EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 October 2014
EMA/CHMP/383987/2014
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Duavive

International non-proprietary name: ESTROGENS CONJUGATED / BAZEDOXIFENE

Procedure No. EMEA/H/C/002314/0000

Note

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

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List of abbreviations

AC	Adjudication Committee
ADR	adverse drug reaction
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
API	Active pharmaceutical ingredient
ASM	Active Substance Manufacturer
ASMF	Active Substance Manufacturer File
ASEX	Arizona sexual experience
AST	aspartate aminotransferase
AUC	Area under the concentration-time curve
BI-RADS	Breast Imaging and Reporting Data System
BMC	Bone mineral content
BMD	Bone mineral density
BMI	Body mass index
BR	Brazil
BSA	body surface area
BTM	Bone turnover marker
BUN	blood urea nitrogen
BZA	Bazedoxifene
BZA/CE	Bazedoxifene/conjugated estrogens
CAS	Chemical Abstracts Service
CE	Conjugated estrogens
CEDL	Conjugated Estrogens Desiccation with Lactose
cp	centipoise
CHD	coronary heart disease
CHF	congestive heart failure
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CL/F	Apparent oral clearance
CMH	Cochran-Mantel-Haenszel
CHMP	Committee for Proprietary Medicinal Products for Human Use

CO	Clinical Overview
COSTART	Coding Symbols for a Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	Contract Research Organisation
CSR	Clinical study report
CTx	C-telopeptide
CVA	Cerebrovascular accident
CVE	cerebrovascular event
CVEAC	Cerebrovascular Event Adjudication Committee
CYP	Cytochrome P450
DB	Double blind
DSC	differential scanning calorimetry
DP	Drug product
DS	Drug substance
DVT	deep vein thrombosis
DXA	Dual-energy x-ray absorptiometry
ECG	Electrocardiogram
EE	Efficacy evaluable
EMA	European Medicines Agency
EMAS	European Menopause and Andropause Society
ESI	electrospray ionisation
ET	Estrogen therapy
EU	European Union
FDA	Food and Drug Administration
FSFV	First subject first visit
FSH	Follicle stimulating hormone
FT	Fourier transform
FPM	finished product manufacturer
GC	Gas Chromatography
GC-MS	Gas Chromatography coupled to mass spectrometry
GCP	Good Clinical Practice
GL	Global
GMP	Good manufacturing practice
Hct	hematocrit
HDL	high-density lipoprotein

HOPE	Women's Health Osteoporosis Progestin Estrogen Study
HPLC	high pressure liquid chromatography
HPMC	Hydroxypropyl methylcellulose
HRT	Hormone replacement therapy
HT	Hormone therapy
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
INR	international normalized ratio
INT	Interaction
IR	Infrared
IRB	Institutional Review Board
ISAP	Integrated Statistical Analysis Plan
ISE	Integrated Summary of Effectiveness
ISS	Integrated Summary of Safety
JP	Japanese Pharmacopoeia
JPE	Japanese Pharmaceutical Excipient
KF	Karl Fischer
LDL	low-density lipoprotein
LDPE	low-density polyethylen
LOCF	Last observation carried forward
LOD	limit of detection
LOQ	limit of quantitation
LS	Lumbar spine
LSLV	Last subject last visit
MAA	Marketing Authorisation Application
MBS	Most bothersome symptom
MedDRA	Medical Dictionary for Regulatory Activities
MENQOL	Menopause-Specific Quality of Life
MI	Myocardial infarction
MITT	Modified intent-to-treat
MOS	Medical Outcomes Study
MPA	Medroxyprogesterone acetate
MRA	Mutual Recognition Agreement
MRI	magnetic resonance imaging
MS	mass spectrometry

MS-TSQ	Menopause Symptoms – Treatment Satisfaction Questionnaire
MW	molecular weight
NA	Not applicable
NCI	National Cancer Institute
NDA	New Drug Application
NMT	Not More Than
OC	Observed cases
OOS	out of specifcation
OP	osteoporosis
OSS	Osteoporosis substudy
OSSI	osteoporosis prevention I Substudy
OSSII	osteoporosis prevention II and metabolic substudy
P1NP	Procollagen type 1 N-propeptide
PAI-1	plasminogen activator inhibitor 1
PAP	Papanicolaou
PBO	Placebo
PCI	potentially clinically important
PCUD	Preserved Condensed Urine, Desiccated
PE	Pulmonary embolus
Ph.Eur.	European Pharmacopoeia
PI	Product information
PKWP	Pharmacokinetics working party
PMU	Pregnant Mare's Urine
PNP	Premarin new process
PP	Per protocol
RLX	Raloxifene
QOL	Quality of life
QTc	corrected QT interval
QTcB	Bazett's corrected QT interval
QTcF	Fridericia corrected QT interval
QTcN	Population corrected QT interval
RMC	Risk Management Committee
RMP	Risk management plan
RR	Relative Risk
RVT	Retinal vein thrombosis

SAE	serious adverse event
SAP	Statistical analysis plan
SCE	Summary of Clinical Efficacy
SCS	Summary of Clinical Safety
SD	Standard deviation
SE	Standard error
SERM	Selective estrogen receptor modulator
SEY	subject exposure years
SGOT	serum glutamic oxaloacetic transaminase (AST)
SGPT	serum glutamic pyruvic transaminase (ALT)
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SNRI	Serotonin-norepinephrine reuptake inhibitor
SSRI	Serotonin-specific reuptake inhibitor
t1/2	Half-life
TBM	To be marketed
TCEC	total conjugated estrogens content
TEAE	treatment-emergent adverse event
TH	Total hip
TIA	transient ischemic attack
Tmax	Time to maximum plasma concentration
TSEC	tissue-selective estrogen complex
TTC	threshold of toxicological concern
TVU	Transvaginal ultrasound
TX	Treatment
UL	Upper limit
ULN	upper limit of normal
US	United States
USP	US Pharmacopeia
USP/NF USP	Pharmacopeia/ National Formulary
UV	Ultraviolet
VLDL	very low-density lipoprotein
VMI	Vaginal maturation index
VMS	Vasomotor symptoms
VSs	vital signs

VTE	venous thromboembolic event
VVA	Vulvar–vaginal atrophy
Vz/F	Apparent volume of distribution
WEY	Women years of exposure
WHI	Women's Health Initiative
WMI	Wyeth Medica Ireland Ltd
W-Y	Women-Years
WW	World-wide
XRD	x-ray diffraction
YSM	Years since menopause

1. Background information on the procedure

1.1. Submission of the dossier

The Applicant Pfizer Limited submitted on 26 June 2012 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Duavive, 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 EMA/CHMP on 18 March 2010.

The Applicant initially applied for the following indication: The treatment of oestrogen deficiency symptoms in postmenopausal women. The treatment of osteoporosis in postmenopausal women at increased risk of fracture. Duavive is indicated in postmenopausal women with a uterus (with 12 months since the last menses). When determining whether to use DUAVIVE 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 sections 4.4 and 5.1).

The legal basis for this application refers to:

Article 10(b) of Directive 2001/83/EC – relating to applications for new fixed combination products.

The application submitted is a new fixed combination medicinal product.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/155/2010 on the granting of a product-specific waiver for the 'treatment of postmenopausal osteoporosis' and an EMA Decision CW/1/2011 on the granting of a class waiver regarding the 'treatment of climacteric symptoms associated with decreased oestrogen levels, as occurring at menopause'.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the Applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific Advice

The Applicant received Scientific Advice from the CHMP on 31 May 2001 and 15 November 2001. The Scientific Advice pertained to non-clinical and clinical aspects of the dossier.

Licensing status

Duavive has been given a Marketing Authorisation in the United States of America on 03 Oct 2013, South Korea on 25 July 2014.

A new application has also been filed in other countries.

1.2. Manufacturers

Manufacturer responsible for batch release

Pfizer Ireland Pharmaceuticals
Little Connell
Newbridge
Co.Kildare
Ireland

1.3. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP:

Rapporteur: Harald Enzmann Co-Rapporteur: Christian Schneider

- The application was received by the EMA on 26 June 2012.
- The procedure started on 18 July 2012.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 5 October 2012. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 9 October 2012
- During the meeting on 15 November 2012, 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 16 November 2012.
- The Applicant submitted the responses to the CHMP consolidated List of Questions on 15 January 2014.
- The Rapporteurs circulated the Joint Assessment Report on the Applicant's responses to the List of Questions to all CHMP members on 17 February 2014.
- During the CHMP meeting on 20 March 2014, the CHMP agreed on a list of outstanding issues to be addressed in writing and by the Applicant.
- The Applicant submitted the responses to the CHMP List of Outstanding Issues on 23 May 2014.
- During the CHMP meeting on 26 June 2014, a 2nd List of Outstanding issues was adopted by the CHMP.
- The Applicant submitted the responses to the CHMP 2nd List of Outstanding Issues on 26 August 2014.
- During the CHMP meeting on 24 September 2014 the Applicant provided an oral explanation.
- During the meeting on 23 October 2014, 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 Duavive.

2. Scientific discussion

2.1. Introduction

This application concerns a fixed dose combination (FDC) of bazedoxifene acetate (BZA), a selective oestrogen receptor modulator (SERM), and conjugated oestrogens (CE) (BZA/CE).

Loss of oestrogen production in women during menopause results in a state of oestrogen deficiency, which has been associated with multiple symptoms, including vasomotor symptoms (VMS), symptoms of vulvar-vaginal atrophy (VVA), and difficulties with sleep, mood, memory, and sexual activity. In addition, oestrogen deficiency has further been associated with loss of bone mass, which often leads to osteoporosis. The only hormone

replacement therapy (HRT) treatment option currently approved to address postmenopausal symptoms in women with a uterus is progestin containing HRT which has been associated with vaginal bleeding, breast pain / tenderness, and increases in breast density. The combination of BZA with CE is considered by the Applicant to provide an alternative treatment option to progestin containing HRT.

BZA has been approved in the EU as Conbriza® and in Japan as Viviant® for the treatment of postmenopausal osteoporosis in women at increased risk of fracture, and has also been approved in a number of other countries for the prevention or treatment of postmenopausal osteoporosis.

CE are obtained from natural sources and are a mixture of sodium estrone sulphate, sodium equilin sulfate, and concomitant components, sodium sulfate conjugates, 17α-dihydroequilin, 17α-estradiol, and 17β-dihydroequilin. CE is a well-established therapy for the treatment of oestrogen deficiency symptoms (EDS) in postmenopausal women, available in the US since 1942 and in the EU since the early 1950s but due to established risks HRT should be administered in the lowest effective dose for the shortest duration and should only be continued as long as the benefit in alleviation of severe symptoms outweighs the risks of HRT. With regard to prevention of osteoporosis, the therapeutic indication within the EU was limited to patients who are intolerant of or contraindicated to other medicinal products approved for the prevention of osteoporosis. CE is administered as a monotherapy in hysterectomised patients. In women with an intact uterus, a progestin has to be added in order to prevent the increased risk of endometrial carcinoma associated with oestrogen alone HRT. Combinations of CE and MPA are approved and available in some EU countries.

BZA has both tissue selective oestrogen receptor agonist and antagonist activity, with agonist activity on the skeletal system and antagonist activity in breast and uterine tissues. The multiple oestrogens in CE have tissue selective oestrogen receptor agonist activity. Measured outcomes are supposed to be a result of a composite of the components' effects distinct from BZA and CE single effects.

The developmental rationale for the combination was based on the assumption that BZA would inhibit proliferative effects of CE on the endometrium reducing the incidence of irregular uterine bleeding and prevent oestrogenic stimulatory effects of CE in breast tissue thus not inducing breast pain / tenderness or changes in breast density associated with traditional progestin-containing hormone therapy (HT), while established benefits of oestrogen therapy (ET) for the treatment of postmenopausal EDS are maintained with the fixed combination therapy. The Applicant considered the fixed combination therapy of BZA/CE as an alternative to current HRT (i.e. oestrogen plus progestin [E+P]) by offering benefits of replacing oestrogen, while reducing side effects and risks associated with oestrogen plus progestin use.

The Applicant initially applied for the following indication:

Duavive is indicated for:
- The treatment of oestrogen deficiency symptoms in postmenopausal women.
- The treatment of osteoporosis in postmenopausal women at increased risk of fracture.
Duavive is indicated in postmenopausal women with a uterus (with 12 months since the last menses). When determining whether to use DUAVIVE 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 sections 4.4 and 5.1).

Two strengths were initially included in this application: BZA/CE 20 mg / 0.45 mg as well as 20 mg / 0.625 mg.

During the procedure the MAH withdrew the indication for the treatment of osteoporosis in postmenopausal women at increased risk of fracture and the higher strength BZA/CE 20 mg / 0.625 mg.

At the end of the procedure the following indication was granted a positive Opinion by the CHMP:

Treatment of oestrogen deficiency symptoms in postmenopausal women with a uterus (with at least 12 months since the last menses) for whom treatment with progestin-containing therapy is not appropriate.

The experience treating women older than 65 years is limited.

The recommended dose for DUAVIVE is 0.45 mg conjugated oestrogens (CE) and 20 mg bazedoxifene taken as a single oral tablet, once daily.

2.2. Quality aspects

2.2.1. Introduction

Duavive is presented as a fixed-dose combination tablet containing conjugated oestrogens and bazedoxifene acetate as active substances corresponding to 0.45 mg / 20 mg of conjugated oestrogens and bazedoxifene respectively. Duavive is a modified release tablet.

Other ingredients are lactose monohydrate, microcrystalline cellulose, powdered cellulose, hypromellose 2208, magnesium stearate, calcium phosphate, sucrose, hydroxypropylcellulose, hypromellose 2910 (E464), macrogol 400, sucrose monopalmitate, titanium dioxide (E171), iron oxide red (E172), ascorbic acid, hydroxyethylcellulose, povidone (E1201), polydextrose (E1200), maltitol liquid, poloxamer 188, isopropyl alcohol and propylene glycol (E1520), as described in section 6.1 of the SmPC.

The product is available in PVC/Aclar/PVC/Alu blister, as described in section 6.5 of the SmPC.

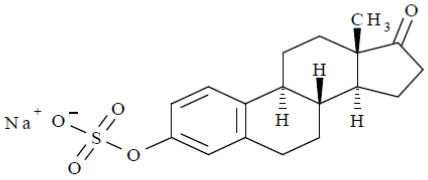
2.2.2. Active Substance

Conjugated Oestrogens

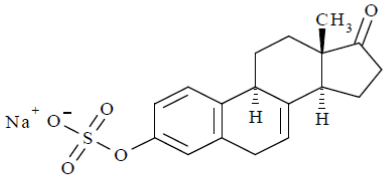
General information

The “active substance” Conjugated Oestrogens is a mixture of different estrogenic substances isolated from pregnant mare’s urine. Conjugated oestrogens is a known entity which is monographed in the European Pharmacopoeia. The main components are estrone sulphate (NES) and equiline sulphate (NEQS) and they are accompanied by other chemical closely related substances. A classification and differentiation is given as primary components, concomitant components, other components and signal impurities as per the Ph Eur. Their structural formulae are shown below.

1.1 Primary Components

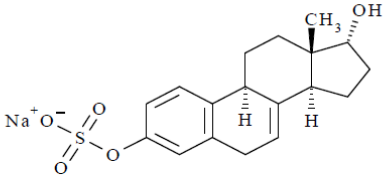


Sodium Estrone Sulphate

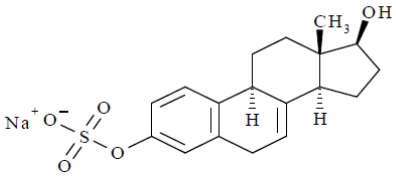


Sodium Equilin Sulphate

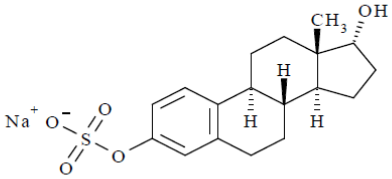
1.2 Concomitant Components



Sodium 17α-Dihydroequilin Sulphate

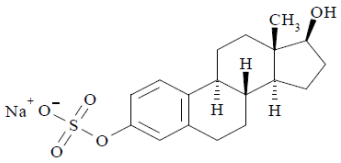


Sodium 17β-Dihydroequilin Sulphate

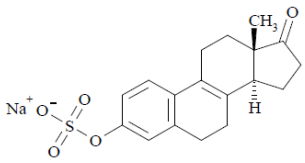


Sodium 17α-Estradiol Sulphate

1.3 Other Components

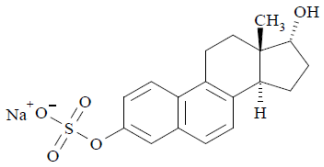


Sodium 17β-Estradiol Sulphate

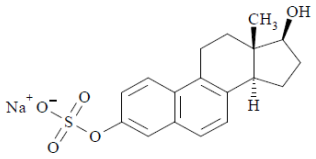


Sodium 8,9-Didehydroestrone Sulphate

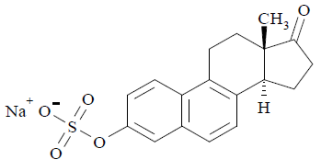
1.4 Signal Impurities



Sodium 17α-Dihydroequilenin Sulphate



Sodium 17β-Dihydroequilenin Sulphate



Sodium Equilenin Sulphate

The European Pharmacopoeia specifies that the mixture of conjugated oestrogens is dispersed in a suitable powdered diluent. The active substance used in Duavive has been designed as Conjugated Oestrogens Desiccation with Lactose (CEDL) which meets the requirements for Conjugated Oestrogens (CE) in the Ph Eur. The chemical names, molecular formulae and relative molecular mass are presented in the table below:

Table 1. Chemical names, molecular formulae and relative molecular mass of Defined Components in conjugated oestrogens

Description	Chemical Name	Molecular Formulae	relative molecular mass
Conjugated Oestrogens Primary Components			
Sodium Estrone Sulfate (NES)	17-oxoestra-1,3,5(10)-trien-3-yl sodium sulfate	$C_{18}H_{21}NaO_5S$	372.4
Sodium Equilin Sulfate (NEQS)	17-oxoestra-1,3,5(10),7-tetraen-3-yl sodium sulfate	$C_{18}H_{19}NaO_5S$	370.4
Concomitant Components			
Sodium 17α-Dihydroequilin Sulfate	17α-hydroxyestra-1,3,5(10),7-tetraen-3-yl sodium sulfate	$C_{18}H_{21}NaO_5S$	372.4
Sodium 17β-Dihydroequilin Sulfate	17β-hydroxyestra-1,3,5(10),7-tetraen-3-yl sodium		372.4

	sulfate		
Sodium 17α-Estradiol Sulfate	17α-hydroxyestra-1,3,5(10)-trien-3-yl sodium sulfate	$C_{18}H_{21}NaO_5S$	374.4
Other Components			
Sodium 17β-Estradiol Sulfate	17β-hydroxyestra-1,3,5(10)-trien-3-yl sodium sulfate	$C_{18}H_{23}NaO_5S$	374.4 370.4
Sodium 8,9-Didehydroestrone Sulfate (*)	17-oxoestra-1,3,5(10),8-tetraen-3-yl sodium sulfate	$C_{18}H_{23}NaO_5S$	
Signal Impurities			370.4
Sodium 17α-Dihydroequilenin Sulfate	17α-hydroxyestra-1,3,5(10),6,8-pentaen-3-yl sodium sulfate	$C_{18}H_{19}NaO_5S$	370.4
Sodium 17β -Dihydroequilenin Sulfate	17β-hydroxyestra-1,3,5(10),6,8-pentaen-3-yl sodium sulfate		368.4
Sodium Equilenin Sulfate	17-oxoestra-1,3,5(10),6,8-pentaen-3-yl sodium sulfate	$C_{18}H_{19}NaO_5S$	
		$C_{18}H_{19}NaO_5S$	
		$C_{18}H_{17}NaO_5S$	

(*) May also be referred to as Sodium Δ8,9 Dehydroestrone Sulfate

It appears as a pale yellow-brown coloured, hygroscopic, amorphous powder, soluble in water. Since CEDL comprises a mixture of active estrogenic substances isolated from natural sources, extensive information on its physical characteristics is not available. The components of the conjugated oestrogens have several stereocenters. The manufacturing process only consists of extraction of the conjugated oestrogens from urine and mixing with excipients. There are no manufacturing steps which would alter the natural occurring isomerism of the components.

The active substance is packaged in material which comply with the EC directive 2002/72/EC and EC 10/2011.

Manufacture, characterisation and process controls

The manufacturing process does not involve any chemical steps. The active substance, defined as conjugated oestrogens desiccation with lactose (CEDL), is manufactured by extraction of pregnant mare's urine (PMU) and by further processing with excipients it to yield CEDL which is then milled analysed and packed into LDPE containers.

PMU is collected during a predetermined period of the gestation of pregnant mares. Two methods of preservation of PMU are currently proposed. However, since one of them involves the use of an organic solvent and since it is possible to completely avoid its use, it is recommended that this option is removed (see 2.2.6. Recommendations for future quality development).The manufacturing process is designed to minimise the potential for increase in bioburden.

The process has been described in sufficient detail and suitable IPCs have been provided. The in-process tests are predominantly product-related tests, however, it has been shown that oestrogen composition is consistent between the incoming PMU and the bulk intermediate PCUD and throughout the PCUD manufacturing process which is considered as reflecting a controlled, validated manufacturing process. The characterisation of the

active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances and the Ph Eur. Potential and actual impurities were well discussed with regards to their origin and characterised.

Appropriate validation data covering the entire complex manufacturing process have been provided. Control of manufacture has been adequately addressed by risk assessment, which was employed to classify manufacturing process parameters and to identify critical steps in the manufacture of PCUD and CEDL, and by assessing the potential impact they may have on product quality and process robustness.

Specification

The active substance specification includes tests and limits for: appearance (visual), identification (Ph. Eur., GC), total Conjugated Oestrogens content (Ph. Eur. or GC), assay of CE primary components (Ph. Eur. or GC), assay of Concomitant Components (Ph. Eur. or GC), impurities (Ph. Eur. or GC), free steroids (Ph. Eur.), residual solvents (GC) and moisture (KF). The specification is considered appropriate and complying with the requirements of the respective EP monograph. Additional tests and adequate limits for moisture and residual solvents (including the preservative solvent) have been set. The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines.

Batch results of eight production batches of active substance CEDL manufactured by the proposed manufacturer together with data from another 17 historical batches have been submitted. The results are within the specifications and the consistency of active substance quality is sufficiently confirmed.

Stability

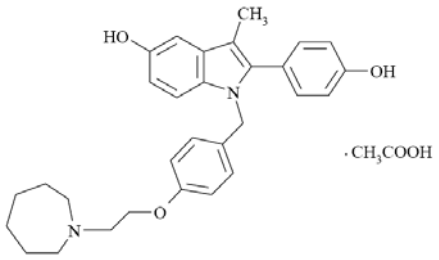
Stability data on seven production batches of CEDL from the proposed manufacturer, three of them stored in the intended commercial package, for up to 24 months under long term refrigerated conditions (2°C – 8°C) and for up to six months under accelerated conditions at 25 ºC / 60% RH according to the ICH guidelines were provided. The parameters tested were the same as for release with the omission of tests for residual solvents and identification. The analytical methods used were the same as for release and were stability indicating.
Stability data for the three batches which have been stored in the proposed EU compliant bag are comparable to the data for batches packed into a different material. All the tested parameters for all batches have met the specification during stability studies. No significant loss in content of any of the ten single oestrogen-sulfate derivatives of the active substance complex (conjugated oestrogens) was observed under the long term refrigerated or even under the accelerated conditions. No trends were observed.

The stability results indicate that the active substance manufactured by the proposed manufacturer is sufficiently stable. The stability results justify the proposed shelf-life and storage conditions in the proposed container.

Bazedoxifene

General information

The chemical name (IUPAC) of the active substance bazedoxifene acetate 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 has molecular mass of 530.65. It has the following structure:



It appears as a white to tan non-hygroscopic crystalline powder. It exists in at least three crystalline

polymorphic forms which can be differentiated with DSC. The route of synthesis is reported to yield only form I. It does not show any optical activity.

Bazedoxifene solubility in water is largely pH dependent showing plateau of approx. 0.5 mg/ml below pH 5.

The active substance is packaged in material which comply with the EC directive 2002/72/EC and EC 10/2011.

Manufacture, characterisation and process controls

Bazedoxifene acetate (BZA) is synthesised in four main chemical steps followed by micronisation, using well defined starting materials with acceptable specifications. Two alternate routes have been adequately described, differing only in step two. The remaining steps for both processes are identical. The starting materials are considered acceptable taking into account the subsequent process steps and the fact that they have been characterised and quality controls in place are considered adequate. The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised. The polymorphism of bazedoxifene has been thoroughly investigated and it has been shown that the process consistently yields the desired form.

The manufacturing in-process controls (IPCs), control of materials, critical steps and intermediates are well defined and adequate to ensure consistent manufacture.

The manufacturing process has been qualified at commercial scale. A validation plan and summary report of a prospective validation has been provided in adequate detail.

The information on the active substance was provided according to the Active Substance Master File (ASMF) procedure.

Specification

The drug substance specification includes tests and limits 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), particle size (laser diffraction) and polymorphic forms (DSC, XRD). The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with the ICH guidelines. The polymorphic purity specifications are set in line with Decision Tree #4 in ICH Q6A. Particle size limits have been also sufficiently justified.

Batch analysis data are provided for eight commercial scale batches 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. Additional results from historical batches of various batch sizes were also presented. The results are within the specifications and consistent from batch to batch.

Stability

Stability studies on three commercial scale batches of active substance manufactured with process 2 and nine pilot scale batches according to process 1, all by the proposed manufacturer and stored in the intended commercial primary package were conducted. Results for up to 36 months under long term conditions (5 ± 3 °C /ambient humidity) and intermediated conditions (25 ºC / 60% RH) and for six months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were presented.

The following parameters were tested*:* appearance, water, impurities, assay and polymorphic form II.

The analytical methods used were the same as for release and were stability indicating. No significant changes are observed.

Additional supportive stability studies on twelve batches packaged in double LDPE bags in HDPE containers, including batches manufactured according to process 1 and process 2 using alternate drying equipment and micronised at the proposed site were initiated to evaluate the use of three types of dryers. An additional twelve batches were placed on stability in order to investigate polymorphic form conversion. These batches include batches manufactured according to process 1 and process 2, using alternate drying equipment, micronised at the proposed site and packaged in double LDPE bags in HPPE containers.

Furthermore, stability results of three industrial lots of unmicronised BZA show no significant changes when stored at 5°C or 25°C/ 60% RH for 36 months. The proposed holding time for storage/ transport of unmicronised bulk substance is accepted.

Photostability testing was also performed on one industrial scale batch following the ICH guideline Q1B. Results do not indicate any significant concern regarding photostability under the conditions tested. Results on stress conditions: heat, oxidative, acidic, basic and light conditions revealed significant degradation after treatment with light, hydrogen peroxide and basic solution.

In conclusion, the data collected to date under all studied conditions support the proposed retest period, storage conditions and packaging material for both the unmicronised and micronised active substance.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

Duavive is a modified release film-coated tablet, designed to provide an immediate release of BZA in combination with a controlled release of CE. The development was based on the Applicant's experience with the current marketed CE mono-product. The composition and manufacturing process of the mono-product tablet has been updated. The proposed product consists of the updated core tablet of the mono-product with the additional BZA active substance coated around the tablet core. The tablet consists of four layers. The tablet core contains the conjugated oestrogens and is coated with an inert filler is identical to the current CE mono-product. This coated tablet is further coated with an active coating containing the other active substance BZA. The two outer layers are colour coating and clear coating. The choice of the excipients has been satisfactorily justified and their function in this modified release formulation has been adequately described.

Their quality is compliant with Ph Eur standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

Conjugated oestrogens is a well-known mixture of water-soluble estrogenic substances described in Ph Eur. The composition of CEDL has remained consistent over the many years of manufacture of the current CE mono-product.

The acetate salt of bazedoxifene was chosen due to its physicochemical properties. Those with impact on drug development were solubility, permeability, solid state properties including polymorphism, chemical stability and particle size. BZA has low solubility; however it is highly soluble at gastric pH. Permeability is high implying a potential for high bioavailability, hence BZA is classified as a BCS class II compound. Crystalline BZA is micronised in order to improve the dissolution rate. The impact of particle size on drug product was evaluated. Solubility, intrinsic dissolution and conversion of the different polymorphs were also studied. It was concluded that tablets spiked with low levels of potential polymorphic impurities exhibited similar dissolution profiles as unspiked tablets and that no conversion of the polymorphic form occurs under the manufacturing conditions used or during storage under ICH conditions; therefore polymorphism is only controlled in the BZA release specifications.

Two dissolution methods have been developed; one for each substance. For the BZA dissolution method the discriminatory power regarding BZA particle size was studied on pilot as well as commercial scale batches. The dissolution method was shown to be discriminatory with regard to the particle size distribution.

Although there is no evidence to suggest that the ratio of the amorphous form of BZA to the crystalline active substance form is critical to bioavailability, the proposed dissolution method has been shown to be biorelevant since it has sufficient discriminatory power to detect non-bioequivalent batches and thus provides a measure of holistic control. In addition, PK data from multiple clinical studies support the above conclusion. Moreover the probability of bioequivalent batches passing the dissolution specification has been calculated and it is concluded that the probability that a non-bioequivalent batch would meet the proposed specification is negligible.

The dissolution method for the CE was based on the already developed method for the current marketed CE mono-product, for which for which a Level A in-vitro/in-vivo correlation (IVIVC) had been established. However, as the proposed CE dissolution method for Duavive was different to the one upon which the IVIVC had been based, a new level A IVIVC has been developed based on the new commercial dissolution method and suitable formulation variants, thereby demonstrating the biorelevance of the CE dissolution method for Duavive tablets.

In conclusion the chosen dissolution methods and conditions have been sufficiently justified and in addition the development of an IVIVC for CE and a discriminating dissolution method for BZA is described in detail.

Development of the proposed formulation and manufacturing process has been described in sufficient detail. Elements of Quality by Design (such as design of experiments) have been applied to development of the manufacturing process; however, no design space is claimed. During the development programme, there were several changes made to manufacturing equipment, scale and sites. Manufacturing process development of the different clinical and the proposed commercial formulation was focused on maintaining equivalency of the quality attributes of the product while addressing the site to site changes in the manufacturing equipment. Each unit operation was evaluated to develop process understanding and determine appropriate ranges for the process. The following quality attributes of the BZA/CE tablets were identified and investigated regarding influence through process parameters: content uniformity, dissolution profile, strength and ID for both active substances as well as impurities, moisture, antioxidant, appearance, and microbial attributes. Control charts and DOE data were provided for the evaluated process parameters. Equivalency of the CE tablet core manufactured by different sites during the development was established by comparing critical quality attributes and including a statistical evaluation (f2) of dissolution profiles.

Finally during scale-up and transfer of the process to the commercial site, the BZA exposure was studied in vivo. The optimisation of the BZA coating process and the level of excipients in the active coating ensured the desired dissolution profile and the corresponding in vivo PK performance. Thus, comparability of both sites regarding consistent quality has been demonstrated.

Duavive tablets are packaged in a PVC/Aclar/PVC/Alu blister, which is then sealed in an aluminium foil laminate pouch. The material complies with the EP requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of the following main steps: preparation of the CE core tablets coated with the inert filler suspension and preparation of the finished tablets.

The CE core tablets are manufactured by mixing CEDL with tablet core excipients, wet granulation and drying, lubrication and compression. The finished tablets are manufactured by coating the CE core tablets by the inert filler, followed by active BZA coating. The BZA coated tablets are subsequently coated first with a colour and finally with a clear coating. The manufacturing process is considered to be a non-standard process because the content of the conjugated oestrogens is below 2% and also because the tablets are modified release. Intermediates and critical steps have been properly identified. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

The manufacturing process has been validated using three production scale batches which have been produced in the same manufacturing facilities and process as for the batches intended for marketing. The results are compliant with specifications. It can be concluded that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

Product specification

The finished product release specifications include appropriate tests and limits for appearance (visual), identification of CE (GC), identification of BZA (HPLC, UV), assay for total CE and NEQS to NES ratio (GC), CE potency (GC), assay for BZA (HPLC), Uniformity of Dosage Units for CE and BZA (HPLC), BZA related substances (HPLC), ascorbic acid (HPLC), water content (Ph Eur), dissolution for CE (Ph Eur-HPLC), dissolution for BZA (Ph Eur-UV) and microbial limits (Ph Eur).

The proposed release specification limit for total Conjugated Oestrogens assay was set upon the statistical analysis of a large number of CE related products and from 27 batches of Duavive and of the current marketed CE mono-product stored at 25 ºC/60 % RH for up to 36 months. The limit is considered acceptable; nevertheless, it should be reviewed upon availability of more data from Duavive tablets (see 2.2.6. Recommendations for future quality development).

The proposed shelf-life limit for BZA assay was predicated upon the statistical analysis from 14 recently manufactured batches and is considered acceptable; the lower limit for shelf life should be re-evaluated upon availability of more data from Duavive tablets. (see 2.2.6. Recommendations for future quality development).

Batch analysis results are provided for three production scale batches. Results confirm the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data of three production scale batches of Duavive tablets stored under long term conditions for up to 36 months at 25 ºC / 60% RH, up to 12 months at 30°C/75% RH and for six months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided. The stability batches were packed in the primary packaging proposed for marketing.

Samples were tested according to ICH guidance for appearance, BZA assay and related substances, total CE, sum of equilin and estrone, ratio equilin/estrone, equilin, estrone, degradation products of the conjugated oestrogens, water content, dissolution of CE and BZA, ascorbic acid and a leak test. Initially and after 12, 24 and 36 months, polymorphism and microbiological quality were additionally tested. All parameters tested remained within the limits set and there were no significant changes in assay of active substance, as well as in any other parameter tested. The analytical procedures used were the same as for release and are stability indicating.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. No significant changes were observed in any of the attributes that were monitored; therefore, it is concluded that the Duavive tablets are not light sensitive and no precautionary packaging or labelling is required.

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

Adventitious agents

The only excipient derived from animal sources is lactose monohydrate. Suppliers of lactose confirm it is produced from milk from healthy animals in the same condition as those used for human consumption according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents.

Satisfactory information has been provided regarding the implemented herd health system for the oversight of the PMU ranches, where the starting material is collected and this has been substantiated by specific information. Virus safety of the drug substance is exclusively based on virus inactivation/ removal capacity of the manufacturing process. Enveloped as well as non-enveloped viruses representing a broad range of physical-chemical characteristics have been included in the virus validation studies. The panel of model viruses chosen for the validation study is thus considered appropriate. The validity of the claimed virus reduction has been supported by adequate data.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Duavive film-coated tablets is a fixed dose combination of two active substances formulated in a special type of dosage form that allows immediate release of bazedoxifene and prolonged release of the conjugated oestrogens. Information on development, manufacture and control of both active substances has been presented in a satisfactory manner. Key aspects of both active substances in relation to the safety and clinical performance of the product were taken into account during the design and development of the product and have been satisfactorily addressed. In this context it is also recommended that the manufacture of CE is updated post-authorisation by the appropriate variation procedure(s) as discussed above. Elements of Quality by Design have been applied to development of the manufacturing process confirming the Applicant's enhanced understanding of the manufacturing process however no design space is claimed. Sufficient information on the development, manufacture and control of this modified release product is also presented with emphasis on the consistency of product quality and clinical performance. It is expected that when data from more product batches become available that certain specification limits should be reviewed in the light of a larger dataset. The results of tests carried out indicate consistency and uniformity of important quality product characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

At the time of the CHMP opinion, there were a number of minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Sufficient information has been presented to give reassurance on viral/TSE safety.

2.2.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

1. The Applicant should provide a post-authorisation variation to remove the organic solvent from the proposed manufacturing process of CE and replace with refrigeration of PMU.
2. The Applicant should critically review the limits for TCEC during release and shelf life upon the availability of a significant body of data. Data should be provided via an appropriate variation if needed at the latest by the time of renewal.
3. The Applicant should critically review the lower shelf-life limit for bazedoxifene upon the availability of a significant body of data. Data should be provided via an appropriate variation if needed at the latest by the time of renewal.

2.3. Non-clinical aspects

2.3.1. Introduction

In nonclinical studies, bazedoxifene (BZA), either alone or in combination with conjugated oestrogens (CE) or 17β estradiol (17β E2), was administered as the acetate salt, and doses are expressed in terms of the free base, bazedoxifene. For the oral gavage studies, the vehicle used was 1% polysorbate 80 and 0.5% methylcellulose in purified water. In studies where bazedoxifene was administered in combination with CE or 17β E2, the vehicle for the oestrogens was 0.5% methylcellulose and purified water.

2.3.2. Pharmacology

Primary pharmacodynamic studies

According to the intended use (combination of CE and BZA, in postmenopausal women without addition of a progestin) the Applicant tried to demonstrate in the non-clinical primary PD programme that BZA does not interfere with the desired effects of CE on bone and in regard to hot flushes but prevents or at least attenuates the undesired (proliferative) effects of CE on uterus and breasts. At the time of the evaluation of this application the combination of a SERM with an oestrogen was not in therapeutic use in the EU. In order to justify this new approach, the Applicant also intended to show that BZA differs from other SERMs pharmacologically in a relevant way. Most of the PD studies were explorative in character, investigating for example changes in the gene expression profile which does not allow immediate conclusions for the therapeutic use of the BZA/CE combination. Nevertheless, a 1-year study in an OVX rat osteopenia model was also conducted in which the effects of CE and BZA, alone and in combination on bone were extensively studied. Effects on uterus were also determined, albeit much less extensive, e.g. without histology. In vivo effects of the BZA/CE combination on the mammary gland were investigated to a limited extent only.

The following table summarises the PD studies performed with CE and BZA in combination and provided a short description of the outcome.

Table 1: PD studies performed with CE and BZA in combination

Type of Study	Test System	Method of Admin.	Report No.	Salient findings
In Vitro Studies Bazedoxifene/CE				
Multiplexed Estrogen Receptor α/Cofactor Assay	Cell Free	NA	RPT-70486	The ten most abundant estranes found in CE were tested alone or in combination with 4-hydroxytamoxifen, RAL, LAS and BZA for their selectivity of peptide recruitment by oestrogen receptor □ (ER □). The results suggest that the estranes induce unique conformations of the receptor and that the addition of SERMs to the estrane mix reveals differences in potency among the SERMs. The clinical relevance of these observations is unknown.
Cell Proliferation and Expression Profiling	MCF-7 Cells	NA	RPT-68444	Three different SERMs, BZA, RAL and LAS), alone or in combination with CE, induced changes in gene expression in MCF7 human breast cancer cells (measured on whole genome DNA arrays). Each treatment induced a slightly different pattern. The clinical relevance of these changes is unknown.
In Vivo Studies Bazedoxifene/CE				

Type of Study	Test System	Method of Admin.	Report No.	Salient findings
In Vitro Studies Bazedoxifene/CE				
Immature Rat Uterine Model: Microarray Gene Analysis and Uterine Wet Weight	Immature Rats	Oral	RPT-68443	Three different SERMs, BZA, RAL and LAS), alone or in combination with CE, induced changes in gene expression in the immature rat uterus (measured on whole genome DNA arrays). Each treatment induced a slightly different pattern. The clinical relevance of these changes is unknown.
Mouse Mammary Gland Morphology and Estrogen-Responsive Gene Expression	OVX Mice	Oral	RPT-73139	Mammary gland morphology and amphiregulin (AREG) expression in the mammary gland were followed. E2 als well as 3 and 10 mg/kg CE markedly induced AREG. RAL, LAS and BZA markedly attenuated the CE effect (not tested with E2), most pronounced for BZA (used in a dose of 2 mg/kg). Morphology was shown as one whole mount photomicrograph per treatment but was not quantified or statistically evaluated so that firm conclusions are not possible.
Hot Flush (Vasomotor Instability) Model	Adult Rats	Oral	GTR-34887	Hot flush was mimicked by the rise in tail skin temperature in response to naxolone-precipitated opioid withdrawal. CE and EE suppressed this model hot flush; BZA from 0.1 to 10 mg/kg partly reversed the effect of CE (not tested with EE) with no clear dose-dependency.
Venous Thromboembolism Mouse Model	OVX Mice	SC	RPT-80571	Femoral vein thrombosis was induced by ferric chloride. The comparator treatment CE+MPA diminished the time to vessel occlusion. CE alone had no statistical significant effect. Although BZA numerically reversed the CE effect, no firm conclusions can be drawn due to the lack of statistical significance.
6-Week Ovariectomised Rat Osteopenia Model, CE (0.5 mg/kg) and Bazedoxifene	Mature, OVX Rats	Oral	GTR-35197	Co-administration of CE with all BZA doses protected from OVX-induced bone loss; the maximal effect of the combination appeared to plateau between 0.3 and 1 mg/kg BZA with a slight attenuation of the effects with the high dose. 1 mg/kg BZA completely blocked the uterine stimulatory activity of CE (0.5 mg/kg)
6-Week Ovariectomised Rat Osteopenia Model, CE (Full Dose Response)	Mature, OVX Rats	Oral	RPT-44690	Effective doses of CE in respect to prevention of bone loss, uterine weight increase and serum cholesterol increase were established to allow conduct of meaningful combination studies
6-Week Ovariectomised Rat Osteopenia Model, CE (2.5 mg/kg) and Bazedoxifene; µCT	Mature, OVX Rats	Oral	RPT-46970	CE in combination with 3 SERMs (RAL, LAS BZA) was tested in respect to bone, uterine weight and serum cholesterol. Effects on bone were comparable with all SERMs combined with CE. Of the 3 SERMs tested, BZA attenuated CE-induced uterine weight gain to the largest extent.
1-Year Ovariectomised Osteopenia Model, Bazedoxifene/CE (GLP)	Rats	Oral (Gavage)	RPT-58143	OVX Rats were treated with CE and ascending doses of BZA. Several bone parameters were determined including BMD, mechanical stability and biochemical turnover markers. BZA and CE counteracted OVX-induced bone loss; there was no additive effect. BZA attenuated CE-induced uterine weight gain.

RAL=raloxifene; LAS= lasofoxifene; MPA= medroxyprogesterone acetate; EE= ethinyl estradiol; E2= estradiol

BZA/CE effect on rat hot flush model

In a rat hot flush model based on naloxone-precipitated morphine withdrawal, CE at 10 mg/kg and 30 mg/kg doses, suppressed the hot flush (rise in tail skin temperature following naloxone withdrawal) in rats. When CE (10 mg/kg) was co-administered with BZA at 0.1, 0.3, 1.0, 3.0, 10.0 mg/kg, BZA antagonized CE's suppression of the tail skin temperature rise to some extent in two experiments. There was no clear dose dependency.

BZA/CE effect on rat uterus

Uterine weight was determined in most in vivo PD studies, in mice and rats. CE (or another oestrogen) increased uterine weight as expected. BZA counteracted this effect dose-dependently. Full antagonism was seen in mice at 10 mg/kg BZA. In rat studies, lower doses were employed, leading to incomplete inhibition of the oestrogen-induced increase in uterine weight. Other uterine parameters (e.g. histology, endometrium proliferation) were not studied in the PD studies.

BZA/CE effect on rat mammary gland

One PD study in rats aimed to investigate the effects of BZA, CE and the combination thereof on rat mammary gland in vivo. However, rather untypical parameters were determined, such as expression of the gene amphiregulin and qualitative evaluation of whole mounts of the mammary gland. No histology data and no proliferation markers were obtained. Thus, although the CE effect on amphiregulin expression was counteracted by BZA, this study only allows limited conclusions in respect to breast safety of the BZA/CE combination. The Applicant also presented in vitro data, obtained with the human breast cancer cell line MCF-7. BZA at 1 nM was able to virtually completely counteract the proliferative effect of CE on these cells. This is reassuring, but extrapolation from tumour cells in vitro to neoplastic disease in vivo is difficult.

BZA/CE effect on bone

Bone effects were examined in a six week and in a one year study in OVX rats. The design of the 1-year study (RPT-58143) can be summarised as follows:

Animals in Groups 1 to 7 underwent surgical procedures; animals in 6 of these groups were ovariectomised at the age of approximately 6 months (OVX Groups 2 to 7) and animals in one group (Group 1) served as Sham controls, while animals in Group 8 served as baseline controls. Bazedoxifene and/or CE was administered orally by gavage to female Sprague-Dawley CD® (Crl:CD® (SD)BR) rats (24/group) once daily for at least 52 consecutive weeks. Bazedoxifene and CE were administered either separately at 0.3 or 2.5 mg/kg/day, respectively, or in combination at dosages of 0.1, 0.3, and 1.0 mg/kg/day of BZA with 2.5 mg/kg/day of CE. Control groups received the vehicle consisting of 1.0% Polysorbate 80, NF (Tween 80) and 0.5% methylcellulose in deionized water. Dosing of animals was initiated the day after ovariectomy was performed. A baseline group of animals was euthanized at the end of the acclimation period. These animals were used to provide additional perspective for histomorphometric evaluation and biomechanical tests. Evaluations for compound-related effects were based on mortality, clinical observations, body weight, food consumption, clinical chemistry, urinalysis, biochemical markers of bone turnover, hormones, bone densitometry consisting of duel energy x-ray absorptiometry (DXA) and quantitative computed tomography (pQCT), organ weights, macroscopic examinations, histomorphometry, and biomechanical testing.

The main finding was that BZA did not inhibit the desirable CE effects on bone (and vice versa) but there was no additive effect of BZA and CE on the bone. BZA in the doses tested (up to 1 mg/kg) inhibited CE-induced uterine weight gain, but not completely. In the six week study (OVX rat), 3 mg/kg BZA slightly inhibited the CE-induced increase in trabecular bone density. Taken together, BZA did not inhibit desired bone effects at doses up to 1 mg/kg but slightly inhibited the desired CE effect on experimental hot flushes and could not fully prevent CE-induced increase in uterine weight. The effect of BZA, CE and the combination on the mammary gland was not studied sufficiently.

Secondary pharmacodynamic studies

No specific secondary PD studies were performed with the BZA/CE combination. Effects of these compounds on other organs beside bone (the intended target) were investigated within the frame of the primary PD studies and are therefore described in the primary PD section above.

Safety pharmacology programme

No safety pharmacology studies were performed with the combination BZA/CE. CE is well-established, and the risks are known from clinical experience. Safety pharmacology of BZA was studied previously, yielding no findings of concern. From the molecular mechanism of action it is not expected that the combination of CE and BZA would reveal fundamentally different effects that were not observed with the individual compounds alone. Hence, omission of safety studies with the combination was considered acceptable by the CHMP.

Pharmacodynamic drug interactions

PD interactions between CE and BZA (and other SERMs) were extensively studied in the primary PD studies as described in the respective section above. No other PD interaction studies were performed.

The lack of further PD interaction studies was considered acceptable by the CHMP. PD interactions of oestrogens and SERMs with other compounds (e.g. progestins) are established and are not expected to be fundamentally different when CE and BZA are combined. Furthermore, it is not intended to combine BZA/CE with drugs capable of PD interaction.

2.3.3. Pharmacokinetics

The pharmacokinetic properties of the individual components of the BZA/CE combination are well known. The Applicant conducted an *in vitro* study in liver cell extracts to demonstrate that the metabolic pathways of BZA and estrone and equilin (main constituents of CE) essentially do not interfere with each other. No *in vivo* interaction study in animals was provided. Plasma levels of BZA after administration of BZA alone and in combination with CE were determined clinically.

2.3.4. Toxicology

Single dose toxicity

No single-dose studies with the BZA/CE combination were performed.

Repeat dose toxicity

Four (4) repeated-dose toxicology studies were performed with the BZA/CE combination, two in rats and two in monkeys. One study in each species was of shorter duration (1 month) whereas the other had the full duration required for a new substance intended for long-term use, namely 6 month plus 3 months recovery in rats and 9 months in monkeys. The findings of the shorter studies are in line with the observations in the longer studies described below.

6-Month with 3-Month Recovery, Rats

BZA and CE were administered individually by gavage to female S-D rats (30/group) at BZA/CE dosages of 0/0, 3/0.33, 12/1, or 60/3 mg/kg/day for 6 months.

An increased incidence (compared with controls) of alopecia occurred at a dosage of 60/3 mg/kg/day during the dosing period and persisted during the recovery period and was attributed to the estrogenic activity of BZA/CE. During the dosing period, test-article-related, but not dose-related, decreases (25% to 27%) in mean body-weight gains were associated with slight decreases (7% to 9%) in mean body weight at week 27 in all treated groups, compared with the control group. Test-article-related, but not dose-related, slight decreases (6% to 9%) in mean food consumption also occurred over the course of the study in all treated groups. These effects were reversible after the 3-month test-article-free recovery period. There were no test-article-related ophthalmoscopic effects or alterations in haematology parameters. There were no noteworthy test-article-related changes in clinical chemistry parameters or organ weights, with the exception of the uterus, as described below.

Decreases (12% to 24%) in absolute and relative (to body and brain) mean weights of the uterus at ≥12/1 mg/kg/day were observed. Microscopic changes included an increased incidence of slight to marked cystic follicular arrest of the ovary, an increased incidence of slight to moderate microscopic dilatation of the uterine lumen (≥12/1 mg/kg/day), slight or mild squamous metaplasia of the uterine endometrial epithelium, and slight or mild atrophy of the uterus. Based on vaginal morphology at final necropsy, animals in all treated groups were predominantly in the estrous phase of their cycle. At recovery necropsy (week 39), diestrus occurred with slightly increased incidence in rats in all treated groups.

After the 3-month test-article-free recovery period (week 39), cystic follicular arrest of the ovary resolved completely; uterus weights returned to normal, but dilatation of the uterine lumen, squamous metaplasia of the uterine endometrial epithelium, and atrophy (ie, reduced overall diameter of the uterine horns) of the uterus did not resolve at 60/3 mg/kg/day, and there was a modest shift toward diestrus in all treated groups. Slight to moderate lobular hyperplasia of the mammary gland occurred with a dose-related increased incidence in all treated groups at the recovery necropsy (week 39). Lobular hyperplasia of the mammary gland occurred with low incidence at final necropsy (week 26), but was not considered test article related.

9-Month, Monkeys

BZA and CE were administered individually by gavage to female cynomolgus monkeys (5/group) at BZA/CE dosages of 0/0, 7.5/0.1, 33.5/0.45, or 150/2 mg/kg/day daily for 9 months. Mean liver weights (absolute and relative to body and brain) were increased 19% to 20% in monkeys given 150/2 mg/kg/day. No macroscopic or microscopic correlates were observed for the increased weights and there were no clinical chemistry changes in liver enzymes. The increased liver weights and absence of any macroscopic or microscopic observations were comparable to the effects seen at dosages up to 300 mg/kg/day in a 9-month toxicity study in monkeys given BZA alone.

Mean ovary weights (absolute and relative to body and brain) were increased 18% to 32%, 71% to 78%, and 179% to 193% in monkeys given 7.5/0.1, 33.5/0.45, or 150/2 mg/kg/day of BZA/CE, respectively, when compared with controls and correlated microscopically with the presence of slight to moderate cystic follicles, which was slightly more severe at 150/2 mg/kg/day of BZA/CE. These findings have been observed in previous repeat dose toxicity studies in monkeys with BZA alone.

Mean uterus weights (absolute and relative to body and brain) were decreased 75% to 79% in monkeys at all dosages of BZA/CE when compared with controls and correlated microscopically with moderate to marked atrophy and macroscopically to a small uterus. Marked atrophy of the cervix and moderate to marked atrophy of vaginal epithelium occurred in monkeys given ≥7.5/0.1 mg/kg/day of BZA/CE when compared with controls.

The severities of this lesion in these organs were similar at all dosages of BZA/CE and are similar in magnitude to the effects seen after administration of BZA alone.

Cystic follicles in the ovary and atrophy of the uterus, vagina, and cervix have been observed in previous toxicity studies in monkeys with BZA alone.

Genotoxicity

Bazedoxifene was tested for genotoxicity in a battery of in vitro (AMES, mouse lymphoma assay, and chromosome aberration test in CHO cells) and in vivo (mouse micronucleus) assays. All studies were performed according to GLP and gave negative results. Therefore bazedoxifene is regarded as devoid of any genotoxic potential. Published studies on genotoxicity of CE revealed no significant increase in induced mutations or chromosome aberrations.

Carcinogenicity

No carcinogenicity studies with the BZA/CE combination were performed. It is known that certain tumours of hormone-sensitive tissue depend on estrogenic stimulation, in animals as well as in humans. The underlying mechanism is not genotoxic. BZA is intended to mitigate proliferative effects of oestrogens (in particular CE) on uterus and breasts. Data from PD and repeated-dose toxicology studies support this intention. Therefore, there is no hint that BZA could increase the carcinogenic potential of oestrogens. Furthermore, rodents are very sensitive towards oestrogens, and the relevance of rodent findings for humans is unclear in case of oestrogens. In consequence, carcinogenesis studies with the combination BZA/CE were not considered necessary. This was agreed by the CHMP.

Reproduction Toxicity

Reproductive and developmental toxicity of BZA alone were evaluated in separate fertility studies for male and female rats and embryotoxicity studies in rats and rabbits. Toxicokinetic parameters were obtained within each study. No study on pre- and postnatal development was performed. Male fertility was not impaired by BZA treatment up to a dose of 300 mg/kg/day, the highest dose studied. BZA treatment of female rats resulted in cessation of estrous cycles and a reduced number of implantations at all dosages. Accordingly, a NOAEL for reproductive parameters in females was not identified. Adverse reproductive effects of BZA were consistent with the pharmacologic activity. 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 BZA resulted in foetal ventricular septum defects, anomalies in skeletal development and fetuses 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, BZA 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.

No reproductive and developmental toxicity studies were performed with the combination BZA/CE. As announced in the *Guideline of Non-clinical-development of fixed combinations of medical products EMEA/CHMP/SWP/258498/2005*, when single components have been adequately tested and the reproductive/developmental toxicity profiles of the compounds are sufficiently characterised, additional studies with the combination may not be warranted.

Toxicokinetic data

Humans

The following human PK data of BZA (20 mg/d, administered along with 0.45 mg CE) and estrone (as a representative component of CE) were obtained from the repeated dose study 3115A1-1138-US in healthy postmenopausal women (for details see clinical AR). Data were obtained on study Day 1 (not shown here) and Day 10, see tables below.

Table 2: Table 2 of Summary of Clinical Pharmacology (shortened): Bazedoxifene Pharmacokinetic Parameters Following Administration of BZA 20 mg / CE 0.45 mg on Day 10 (Steady-State): Study 3115A1-1138-US (N=24)

Treatment		Cmax (ng/mL)	tmax (h)	Cmin (ng/mL)	AUC0-24h ng·h/mL)
Day 10 (steady-state)	Mean ± SD	6.93 ± 3.87	2.5 ± 2.1	1.76 ± 1.05	70.8 ± 34.2

Table 3: Table 2-5 of Summary of Clinical Pharmacology (shortened): Total Estrone Adjusted for Baseline Pharmacokinetic Parameters Following Administration of BZA 20 mg / CE 0.45 mg on Day 10 (Steady-State)): Study 3115A1-1138-US (N=24)

Treatment		Cmax (ng/mL)	tmax (h)	Cmin (ng/mL)	AUC0-24h ng·h/mL)
Day 10 (steady-state)	Mean ± SD	2.57 ± 0.76	6.5 ± 1.6	0.88 ± 0.41	35.4 ± 11.8

Rats

TK data are taken from the pivotal (6 month) rat repeated dose toxicity study and were obtained at study week 26. BZA and main components of the CE mixture were analysed; estrone is shown because this compound was also measured in humans. Note that BZA is expressed as **ng** whereas estrone is given in **pg**.

Table 4: Table 5.10-1 of study report RPT-50335: BZA Mean (±SE) Pharmacokinetic Parameters Week 26

BZA/CE Dosage (mg/kg/day)	Cmax (ng/mL)	tmax (hr)	AUC0-24 (ng·hr/mL)
3/0.33	20.3±9.5	2	97.8±24.5
12/1	25.0±9.0	2	299±51
60/3	111±23	2	966±166

Table 5: Table 5.10-2 of study report RPT-50335: Mean (±SE) Pharmacokinetic Parameters of Unconjugated Estrone - Week 26

Unconjugated Oestrogen	BZA/CE Dosage (mg/kg/day)	Cmax (pg/mL)	Tmax (hr)	AUC0-24 (pg·hr/mL)
Estrone	3/0.33	189±31	2.0	660±108
	12/1	277±52	2.0	2243±272
	60/3	822±84	2.0	4714±475

Monkeys

TK data are taken from the pivotal (9 month) monkey repeated dose toxicity study and were obtained at study week 39. BZA and main components of the CE mixture were analysed; estrone is shown because this compound was also measured in humans.

Table 6: TK data week 39 of monkey study RPT-50336 (from Toxicology Tabulated Summary)

Dosage Groups (mg/kg/day)	Analyte	Steady-State AUC0-24 (ng•h/mL) (Mean±SD)	Cmax (ng/mL)
7.5/0.1	Bazedoxifene	477 ± 109	36.3 ± 17.1
	Estrone	8.53 ± 3.78	550 ± 241
33.5/0.45	Bazedoxifene	1320 ± 183	92.5 ± 23.1
	Estrone	26.22 ± 9.76	1495 ± 506
150/2	Bazedoxifene	4081 ± 1249	212 ± 56
	Estrone	59.19 ± 14.34	3471 ± 1342

Local Tolerance

N/A

Other toxicity studies

No other studies were performed.

2.3.5. Ecotoxicity/environmental risk assessment

Both bazedoxifene and estrone / 17β-dihydroequilin (conjugated oestrogens) are considered for the environmental risk assessment of Duavive®. For bazedoxifene a phase I and phase II Tier A assessment was provided by the Applicant. Based on the available data it was assessed that bazedoxifene is not classified as PBT nor expected to bioaccumulate. The data provided by the Applicant do allow concluding that bazedoxifene is unlikely to present a risk to the environmental compartments surface water, groundwater and sediment as well as wastewater microorganisms. No final conclusion is possible on the potential risk of bazedoxifene to the terrestrial environment. Both for estrone and 17β-dihydroequilin a phase II environmental risk assessment has been initiated. This assessment will be based on the tier A testing, including experimental determination of log D values to perform PBT classification and fish full life cycle evaluation. No conclusion on the potential risk of estrone and 17β-dihydroequilin to the environment is possible yet.

The Applicant committed to provide an updated ERA for bazedoxifene and conjugated oestrogens by end of first quarter 2015. This ERA report will include study reports and missing data of PBT and terrestrial risk assessment of bazedoxifene as well as experimentally determined log Kow of estrone and 17β-dihydroequilin and results from long-term fish test.

Summary of main study results of bazedoxifene (version May 2014)

The ERA of bazedoxifene cannot be concluded because the evaluation is not complete.

Substance (INN/Invented Name): bazedoxifene			
CAS-number (if available): 198481-33-3			
PBT screening		Result	**Conclusion**
Bioaccumulation potential - log K_{ow}	OECD107	Log D = 4.98 (pH 7.8)	Potential PBT: Yes
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow} (log D)	4.98	not B
	BCF	98	
Persistence	DT50 or ready biodegradability		P/not P
Toxicity	NOEC or CMR	7.9 µg/L	not T

PBT-statement :	The compound is not considered as PBT nor vPvB.				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	0.1	µg/L			>0.01 threshold: Yes
Other concerns (e.g. chemical class)		Endocrine disrupting properties			Yes
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106, OECD 308	$K_{oc\ sludge}$ = 10,288 $K_{oc\ soil}$ = 5,661-8,853 $K_{oc\ sediment}$ = 3,310-3,960			$K_{oc\ sediment}$ derived from OECD 308
Ready Biodegradability Test	OECD 301	–			–
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	Aerobic $DT_{50,\ water}$ = 4.1 / 6.4 d (SFO= $DT_{50,\ sediment}$ = no data $DT_{50,\ whole\ system}$ = 4.9 / 13.7 d (SFO) % shifting to sediment = >10% Anaerobic $DT_{50,\ water}$ = 9.4 / 19.2 d (SFO) $DT_{50,\ sediment}$ = no data $DT_{50,\ whole\ system}$ = 7.8 / 17.1 d (FOMC) % shifting to sediment = >10%			Normalized to 12°C
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/ *Pseudokirchneriella subcapitata*	OECD 201	$EC_{10\ growth\ rate}$	17	µg/L	Mean measured concentration
		$EC_{10\ yield}$	7.8	µg/L	Mean measured concentration
Daphnia sp. Reproduction Test	OECD 211	NOEC	1,100	µg/L	Mean measured concentration
Fish, Early Life Stage Toxicity Test/ *Pimephales promelas*	OECD 210	NOEC	860	µg/L	Mean measured concentration
Fish, Full Life Cycle Toxicity Test/ *Pimephales promelas*	US EPA OPPTS 850.1500	NOEC	14	µg/L	Mean measured concentration
Activated sludge respiration inhibition	OECD 209	EC_{15}	8,600	µg/L	Nominal concentration
Phase IIb Studies					
Bioaccumulation in fish	OECD 305	BCF steady state	98	L/kg	Normalized to 5% lipids
Sediment dwelling organism Test/ *Chironomus riparius*	OECD 218	NOEC	85	mg/kg	Spiked sediment, mean measured concentration

Summary of main study results of conjugated oestrogens - estrone / 17β-dihydroequilin (version May 2014)

The ERA of conjugated oestrogens cannot be concluded because the evaluation is not complete.

Substance (INN/Invented Name): –			
CAS-number (if available): –			
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	0.0031	µg/L	>0.01 threshold: No
Other concerns (e.g. chemical class)		Endocrine disrupting properties	Yes

2.3.6. Discussion on non-clinical aspects

The Applicant's intention of the PD programme was to demonstrate suitability of the BZA/CE combination for prevention or treatment of osteoporosis and hot flushes and to avoid undesirable, proliferative actions on breast and uterus. Probably because combinations of oestrogens and SERMs are currently uncommon in therapy and because endometrial protection is to date mainly performed by adding a progestin instead of a SERM, the Applicant also aimed to demonstrate that BZA is more suitable for this purpose than other SERMs. Therefore, in many studies BZA was compared to raloxifene and lasofoxifene. In several studies gene expression profiles were investigated; however, the relevance of these results for therapeutic use of BZA/CE is unknown because the physiological meaning of the observed changes is unknown. Nevertheless, standard bone parameters and uterine weight was also investigated in studies with up to one year duration. It turned out that BZA at suitable doses is indeed able to increase BMD and bone stability together with CE and simultaneously to attenuate the CE-induced uterine weight gain. However, CE-induced uterine proliferation was not completely blocked by the BZA doses used. On the other hand, as revealed in one mouse study, higher doses of BZA may also interfere with the bone-saving effect of CE so that the possibility of increasing the BZA dose for better uterine protection is limited.

Although some of the PD studies performed were rather extensive, the data obtained on breast and uterine effects of BZA/CE appear incomplete. Uterine effects were only determined as weight gain (or gene expression in the whole uterus) but the clinically most important target tissue, the endometrium was not investigated in the PD studies. Information on endometrial histology can be derived from the repeated-dose toxicology studies (see below). However, more specific investigations like morphometry or determination of proliferation markers at doses relevant for the desired bone effect were not performed, and much higher doses of BZA were used in the toxicity studies.

The same concerns also apply for the mammary gland. Apart from effects on gene expression, the relevance of which is not fully clear, no quantifiable effects of BZA/CE on the breast and in particular on mammary gland histology and proliferation were determined. The presented data suggest that BZA could protect the mammary gland from undesired estrogenic effects. This would be highly favourable because this probably cannot be achieved by the standard combination partner of CE, a progestin. On the other hand, in the 6 month repeated-dose toxicity study in rats, mammary gland hyperplasia was observed with the BZA/CE combination even if the BZA dose used was much higher than in the PD studies. Therefore, determination of relevant quantitative standard parameters (e.g. weight, histomorphometry, proliferation markers) to characterise BZA's action on the mammary gland, in particular in respect to proliferation, would have been desirable. The Applicant has sponsored studies in monkeys to address these concerns, where BZA and CE alone and in combination were administered to ovariectomised cynomolgus monkeys. The dose levels were 2.5 mg/kg/day for BZA and 0.03 mg/kg/day for CE, which according to the authors correspond to the target human combination treatment of 20 mg/day for BZA and 0.45 mg/day for CE. Two resulting publications (Ethun et al., 2012, Menopause 19: 1242-1252, and Ethun et al., 2013, Menopause 20: 777-784) conclude that BZA at the target human equivalent dose fully antagonizes the proliferative and transcriptional effects of CE on the macaque endometrium while having no oestrogen agonist activity when given alone. Lumbar bone mineral density was not negatively affected by the chosen BZA/CE dose ratio as compared to the effect of CE alone. BZA antagonized the proliferative and transcriptional effects of CE in the normal postmenopausal nonhuman primate breast. However, mammary gland proliferation was higher with the BZA/CE combination than with BZA alone. This means that addition of CE to BZA, as intended, may alter the established benefit/risk profile of BZA alone.

Monkey data are considered more relevant for humans than rodent data so that no further rodent studies are requested.

Taken together, the non-clinical PD programme has shown that the approach of combining BZA and CE may be feasible but some points remain open from a non-clinical point of view. At least in the non-clinical studies, no BZA dose could be identified that did not impair the desired CE effects on bone and hot flushes and simultaneously provided full uterine protection. The situation in humans may be different but this conclusion could only be reached if confirmed by the assessment of the results of the clinical trials. Effects on the mammary gland are much more easily to study non-clinically than clinically. This information was not provided by the Applicant, however it was agreed that on the other hand, the relevance of the non-clinical findings for humans remains unclear.

The pharmacokinetic properties of the individual components of the BZA/CE combination are well known. The Applicant conducted an in vitro study in liver cell extracts to demonstrate that the metabolic pathways of BZA and estrone and equilin (main constituents of CE) essentially do not interfere with each other. No in vivo interaction study in animals was provided. Plasma levels BZA and estrone after administration of each compound alone vs. in combination, were determined clinically. Thus, an additional in vivo PK interaction study in animals is not considered necessary because no additional relevant information is expected.

The Applicant has conducted repeated-dose toxicology studies of the combination in two species, for up to 9 months in non-rodents (monkeys) and up to 6 months (plus recovery) in rodents (rats). The pharmacodynamic and toxicological properties of both components of the combination are known and from this no increased toxicity of the combination is expected. This expectation was confirmed by the outcome of the repeated dose studies which were performed with a sufficient number of animals and used sufficiently high doses for meaningful conclusions. In rats, which are known to be very sensitive towards oestrogens, the estrogenic effects of CE dominated the findings with the combination. Vice versa, in monkeys oestrogens have less pronounced effects so that in the combination study in this species the BZA effects dominated. All observed effects could be related to the hormonal properties of the test compounds; no unexpected toxicities were observed.

Mammary gland lobular hyperplasia was observed following cessation of treatment with doses giving rise to clinically relevant plasma exposure levels. The Applicant ascribes the mammary gland lobular hyperplasia to a prolactin rebound effect. This finding was not made in the repeat-dose toxicity studies conducted with bazedoxifene. It is acknowledged that post-menopausal women naturally have a lower prolactin level than pre-menopausal women. The effects observed in the nonclinical studies were ascribed to the ovarian functional state in the young cycling animals, whereas the post-menopausal women will have quiescent ovaries. In the clinical studies, breast-related adverse event was comparable between the control and treated groups.

Since no histological evaluation was performed in the PD studies, some information on the pharmacodynamics of the BZA/CE combination may be derived from the toxicology studies. Oestrogens (but not BZA) are known to induce hyperplasia of the mammary gland, and this effect was also observed with the BZA/oestrogen combination in rats. Hence, BZA was not able to (fully) counteract the estrogenic effects on the breast in this species. The matter is not fully clear since in the 1-month study mammary hyperplasia was only observed with the E2/BZA combination but not with the BZA/CE combination. It is not known whether the E2 dose used was stronger estrogenic than the CE dose used because CE and E2 were not tested alone. In the 6-month study, mammary hyperplasia was most pronounced after recovery, which could indicate a sort of rebound effect. It is not known whether a similar rebound effect could occur in humans. Regarding the endometrium, atrophy was observed in the 1-month study as desired, but the 6-month study revealed squamous metaplasia of unknown significance. In monkeys, no hyper- or metaplasia was observed in the mammary gland or endometrium with

the BZA/CE dose ratio tested. It is expected that the dose ratio of BZA and CE is critical for the resulting effects. A sufficiently high BZA dose is probably able to counteract all undesired effects of CE on breast and uterus, but the question remains whether the desired effects of CE in respect to bone and hot flush remain largely unaffected under these circumstances.

It should be noted that the dose ratio of BZA/CE used was markedly different in the PD and toxicology studies so that comparison of the findings is difficult. Whereas in the large rat PD study (RPT-58143) the BZA dose was much lower than the CE dose (per mg/kg), the opposite is true for the toxicology studies. In fact, the high BZA dose in the toxicity studies led to a much higher exposure (AUC) ratio of BZA vs. CE (measured as estrone) in the steady state in animals than in humans (the ratio was up to around 200 in mice, up to around 70 in monkeys and was 2 in humans). Thus, the anti-estrogenic effect of BZA addition to CE was considerably overestimated in the toxicity studies. It can be expected that much more pronounced proliferation of mammary gland tissue and perhaps also proliferation of the endometrium would have been observed if the BZA dose would have been reduced to around one hundredth in rats to match the human therapeutic exposure ratio. It would have been desirable to see PD and toxicology data (including histopathology and proliferation markers) with the same BZA and CE doses leading to a similar exposure ratio as observed in humans. The Applicant explained that dose selection in the PD studies was based on the different sensitivity of humans and rodents towards oestrogens. On the other hand, dose selection in the toxicology studies was only based on exposure multiples. However, if different sensitivity is known, this should also be regarded when selecting the doses for the toxicology studies. Thus, the new information that can be derived from the BZA/CE combination studies in rodents remains limited.

No other toxicology studies were performed but the toxicology programme is considered sufficient for a fixed combination of known authorised substances. Performing repeated dose studies of rather long duration in two species is justified by the fact that BZA and CE are not used as free combination so that clinical experience with the combination is lacking.

Ecotoxicity / Environmental Risk Assessment

The Environmental Risk Assessment of bazedoxifene and estrone / 17β-dihydroequilin cannot be concluded until the Applicant will provide the missing data and the revised ERA. It was agreed that this will be done post-authorisation by 31 March 2015.

2.3.7. Conclusion on the non-clinical aspects

The Applicant submitted pharmacodynamic studies *in vitro* and *in vivo*, aiming to demonstrate that (rather low) doses of BZA added to CE do not affect the desired effects of CE in models of hot flush and osteoporosis. On the other hand, it should be demonstrated that the undesired (proliferative) effects of CE on the uterus and mammary gland can be blocked by addition of BZA. However, it could not be shown that BZA at a suitable dose leaves the desired CE effects completely unaffected but fully blocks the undesired effects. Proliferative effects of the BZA/CE combination on bone and uterus were not investigated with appropriate methods so that no firm conclusions can be drawn, e.g. no histology was performed and no proliferation markers were determined. Although histology data are available from toxicology studies, comparison is not possible because in the toxicology studies much more BZA was administered compared to CE than in the PD studies. This approach is questionable because thereby no toxicological information is available for BZA/CE ratios for which the desired bone effect was demonstrated. By increasing the BZA dose as done in the toxicology studies a rather complete inhibition of mammary gland and endometrium proliferation is easily to achieve but the effect on bone is questionable and was not tested in the toxicology studies. Vice versa, the dose ratio BZA/CE used in the PD

study supports the desired bone effects but could lead to mammary or endometrial proliferation which was not sufficiently tested in these studies. Clarkson has addressed this in a report from 2012 compiled of publications (published or intended for publication), where the effect of bazedoxifene acetate and conjugated equine oestrogens administrated alone and in combination on coronary artery atherosclerosis, bone and breast/endometrial health of surgically postmenopausal monkeys. Whereas the described effects on bone, endometrium and coronary arteries gave no cause for concern, it appeared as if addition of CE increases cell proliferation in the mammary gland. Thus, the effect of BZA/CE in regard to breast cancer remains uncertain; an increased proliferation due to addition of CE to BZA cannot be excluded.

Ecotoxicity / Environmental Risk Assessment

The assessment of the environmental risk of both bazedoxifene and estrone / 17â-dihydroequilin (conjugated oestrogens) cannot be completed. The Applicant committed to provide missing data, study reports as well as a revised ERA by end of first quarter 2015.

The CHMP considers the following measures necessary to address the non-clinical issues:

Description of post-authorisation measure	
Ecotoxicity / Environmental Risk Assessment	**Due date**
Provision of missing data, study reports as well as a revised ERA for all active ingredients.	31 March 2015

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

The CHMP was of the view that GCP inspections should be triggered for at least one of the pivotal trials for each part of the applied indication, i.e. treatment of oestrogen deficiency symptoms and treatment of osteoporosis. In addition, a GCP inspection of the bioanalytical site was recommended in the context of the analysis of the oestrogen plasma levels (free and total) as both the performance of study sample analysis and the in-study validation are considered insufficient.

Therefore a request for GCP inspection was adopted by the CHMP in November 2012 for:

- the bioanalytical part of the pivotal studies **3115A1-1139-US** and **3115A1-1142-US**, as well as at:
- for study **303** (study centres that enrolled 889 and 307 subjects) and
- for study **305** (study centre that enrolled 26 subjects)

in order to provide further product specific information.

The Applicant conducted a routine GCP investigator site auditing programme. In 2010 the Applicant reviewed the outcome of these Sponsor conducted audits and engaged a third party to conduct post-study investigator site assessments of the Phase 3 studies that had been completed at that time. The third-party GCP assessments

were conducted from January through June 2011 and encompassed Studies 303, 304, 305, and 306. Study 3307 was ongoing at that time with no critical issues reported from GCP audits. Fifty-three (53) clinical investigator sites, representing 18% of the total of 293 sites were audited; site selection was determined using a statistical sampling approach, taking into account geographical distribution of sites and review of risk factors including adverse event rates, screen failure rates, subject discontinuations, and subject completer rates. This third party GCP assessment did not identify any significant systemic findings.

EMA GCP inspection of study 303 and study 305

The inspected investigator sites 447 and 450 of trial 303 contributed 889 and 307, respectively, out of 3,544 subjects, about 35% of the total trial population. Thus the inspection findings from these sites have a high relevance for the acceptability of the entire study data of trial 303. The missing source data for 197 subjects from sites 447 and 450 and 3 other sites denote a major concern as the validity of the study data is considered corrupted. This is further aggravated by the Sponsor not having an adequate overview of the trial conduct at the two sites i.e. about serious non-compliances. The available archived source data at the two investigator sites were under the sole control of the Sponsor. With regard to endometrial safety, the results of the GCP inspection of the two sites of study 303 and of the Sponsor inspection referring to the study conduct in general and more specifically to handling of endometrial biopsies are relevant. It is noted that the biopsies were sent from the clinical sites to the Sponsor and then to the pathologists. The reports of the pathologists were sent from the pathologist to the Sponsor and then to the clinical site. Thus, all biopsies as well as all reports from pathologists were in the possession of the Sponsor. This is not acceptable. Taking into account further critical and major findings related to study conduct and reporting it is agreed with the Inspectors that data from this study cannot be used to demonstrate the endometrial safety of BZA 20 mg / CE 0.45 mg and BZA 20 mg / CE 0.625 mg.

The second study investigating endometrial safety in terms of incidence of hyperplasia / malignancy at 12 months was study 3307. No GCP inspection with regard to this study was performed by European inspectors, but further clarification as regards the handling of endometrial biopsies in this study was provided from the Applicant. The CHMP agreed that a GCP inspection of this study is not considered necessary.

With regard to the demonstration of efficacy of BZA/CE in the treatment of hot flushes, study 305 is pivotal. As a result of the GCP inspection, this study was also classified as not GCP-compliant. Nevertheless, the analyses regarding hot flushes described in the study report are considered valid and are taken into account for the assessment of efficacy.

As regards adverse events relatedness to study medication was incorrectly assessed by the investigators of the two sites from study 303 and the data of the clinical study report on the basis of these assessments are incorrect; the assessment was clearly shifted to ‘not related’. Considering that comparable findings occurred for the investigator site inspection of trial 305, the deficiencies as regards adverse event reporting seem to be a systematic deficiency, not involving only the two sites from study 303. There were also concerns in relation to the quality of safety data reported in relation to the adverse event ‘hypertension’ and ‘adverse event related subjects’ withdrawal’. The Sponsor’s re-monitoring at sites 447 and 450 did not remedy the systematic failures in relation to adverse event reporting. Measures at the Sponsor site to ensure quality in the evaluation of the safety profile for the product were also not sufficient. The CHMP agreed with the Inspectors that at this stage it is not realistically possible to remedy this finding. The findings are considered relevant for the benefit / risk assessment, since the study 303 data cannot be used to demonstrate the endometrial safety and adequate

validity of the adverse event reporting has not been shown. Despite this limitation the analyses regarding hot flushes are considered valid and were taken into account for the assessment of efficacy.

EMA GCP inspections of bioanalytical site

The GCP inspection of the bioanalytical site was focused on the verification of the bioanalytical data reported in the Marketing Authorisation Application for the pivotal studies 3115A1-1139-US and 3115A1-1142-US. The inspection revealed 2 major and 1 minor GCP finding. The two major findings observed were related to the method validation for the determination of the oestrogens; only within run, but no between-run precision and accuracy was tested for LLOQ. A possible matrix effect for haemolysed and hyperlipidaemic samples was not investigated. Selectivity Testing was only performed with plasma from two different individuals. Long Term Stability data and data for Stock Solution stability were provided only post inspection. The stability data and documentation provided (investigations from 1995 / 1996 and 2001) were considered not acceptable to reflect the technical, scientific, and documentary standards valid for the trials performed in 2008 and 2009 at the inspected laboratory (Finding MA1). The matrix effect was not tested although the composition of the plasma for the blank samples (obtained by aphaeresis) differed (different dilution and Na-Heparin content) from the composition of the subject plasmas in the two inspected trials (obtained by a vacutainer system) (Finding MA2). Due to these findings the validity of the bioanalytical method could not be concluded and thus these findings were considered relevant for the benefit / risk assessment. In course of the GCP inspection procedure the Applicant was requested to address these findings by submission of additional supporting validation test results. The results of these investigations have been provided after close of the GCP inspection and were considered sufficient to address the GCP major findings. There was one outstanding point for clarification regarding the between-run precision and accuracy at LLOQ for 17β-Dihydroequilin, 17β-Δ8,9 Dehydroestradiol, Δ8,9 Dehydroestrone, and Equilin which has been adequately addressed.

- Tabular overview of clinical studies

Table 9: Studies Clinical Pharmacology

Type of Study Study Number	Description
Healthy Subject Pharmacokinetic and Initial Tolerability Studies	
3068A1-100-US	Ascending Single Dose (CSR-34914)
3068A1-101-US	Ascending Multiple Dose (CSR-35054)
3068A1-103-US	Mass Balance and Metabolism of [^{14}C]Bazedoxifene (CSR-35055)
3068A1-108-US	Dose Proportionality (CSR-45814)
3068A1-111-EU	Absolute/Relative Bioavailability of Bazedoxifene (CSR-40533)
3068A1-114-JA	Ascending Single Dose in Japanese Subjects (CSR-56881)
3068A1-123-CI	Ascending Single Dose in Chinese Subjects (CSR-40532)
3068A1-124-JA	Ascending Multiple Dose in Japanese Subjects (CSR-56882)
3068A1-131-US	Thorough QTc Study (CSR-62492)
3115A1-1138-US	BZA/CE Multiple-Dose Pharmacokinetics (CSR-78662)
3115A1-1136-US	Relative Bioavailability of Bazedoxifene Monotherapy and BZA/CE Combination Dosage Forms (CSR-78946)
Intrinsic Factor Pharmacokinetic Studies	
3068A1-112 EU	Hepatic Impairment (CSR-43639)
3068A1-121-US	Age and Renal Impairment (CSR-51806)
Extrinsic Factor Pharmacokinetic Studies	
3068A1-102-FR	Food Effect and Antacid Interaction (CSR-52314)
3068A1-106-SP	Ibuprofen Interaction (CSR-37791)
3068A1-125-EU	Azithromycin Interaction (CSR-56919)
3068A1-126-EU	Atorvastatin Interaction (CSR-50676)
3115A1-101-US	Conjugated Estrogens Interaction (CSR-46455)
3115A1-1134-US	Effect of Bazedoxifene on Conjugated Estrogens Pharmacokinetics (CSR-77064)
3115A1-1135-US	Effect of Conjugated Estrogen on Bazedoxifene Pharmacokinetics (CSR-77048)

Studies with the prefix 3068A1 were conducted with bazedoxifene; studies with the prefix 3115A1 were conducted using BZA/CE.

Table 10: Overview of Phase 2 and Phase 3 BZA/CE Clinical Studies

Study	Study Description	FSFV	LSLV
Study 203	A Phase 2 multicentre, DB, randomised, controlled, dose finding pilot study to evaluate the effect of the combination of CE with BZA on the estrogenic stimulation of the endometrium in healthy postmenopausal women	Jun 99	Apr 00
Study 303*	A Phase 3 multicentre, DB, randomised, placebo- and active-controlled safety and efficacy study evaluating the effect of 6 combinations of BZA/CE on the incidence of endometrial hyperplasia and the efficacy in preventing osteoporosis in postmenopausal women	Apr 02	Jan 06
Study 304	A Phase 3 multicentre, DB, randomised, placebo- and active-controlled efficacy and safety study evaluating BZA 20 mg / CE 0.45 mg and BZA 20 mg / CE 0.625 mg for endometrial safety and the prevention of osteoporosis.	Oct 05	Aug 08
Study 305	A Phase 3 multicentre, DB, randomised, placebo-controlled, efficacy and safety study designed to demonstrate the efficacy of BZA 20 mg / CE 0.45 mg and BZA 20 mg / CE 0.625 mg in the treatment of moderate to severe VMS.	Sep 05	Feb 07
Study 306	A Phase 3 multicentre, DB, randomised, placebo- and active-controlled efficacy and safety study designed to assess the efficacy of BZA 20 mg / CE 0.45 mg and BZA 20 mg / CE 0.625 mg in VVA.	Oct 05	Mar 07
Study 3307	A Phase 3, multicentre, DB, randomised, placebo- and active-controlled efficacy and safety study evaluating BZA 20 mg / CE 0.45 mg and BZA 20 mg / CE 0.625 mg for endometrial safety and the prevention of osteoporosis.	Jan 09	Feb 11
Study 4000	Evaluation of changes in mammographic breast density associated with bazedoxifene acetate/conjugated oestrogens, raloxifene, and placebo in postmenopausal women: an ancillary study of protocol 3115A1-303-WW	Jan 09	Apr 10

* Study 303 (3115A1-303-US/EU/BR) also included Study 4000 (3115A1-4000-WW), an ancillary substudy of Study 303 that evaluated changes in mammographic breast density associated with BZA/CE, raloxifene, and placebo in postmenopausal women.
Abbreviations: BZA=bazedoxifene; CE=conjugated oestrogens; DB=double-blind; FSFV=first subject first visit; LSLV=last subject last visit; VMS=vasomotor symptoms; VVA=vulvar-vaginal atrophy
Source: 5.3.5.1, Study 203, CSR-35419, 5.3.5.1, Study 303, CSR-64104; 5.3.5.1, Study 304, CSR-68285 and CSR-73414; 5.3.5.1, Study 305, CSR-67461; 5.3.5.1, Study 306, CSR-67466; 5.3.5.1, Study 3307, CSR-81040.

Table 11: Overview of Phase 3 BZA Clinical Studies

Study (CSR)	Study Description	FSFV	LSLV
Study 300	A multicentre, double-blind, randomised, placebo- and raloxifene-controlled study to assess the safety and efficacy of BZA (TSE-424) in the prevention of postmenopausal osteoporosis.	Jun 01	Jul 04
Study 301	A multicentre, double-blind, randomised, placebo- controlled, calcium and vitamin D supplemented Phase 3 study of BZA acetate for reduction of fracture risk in postmenopausal women with osteoporosis.	Dec 01*	Nov 06** Nov 08** Sep 10**

* In Study 301, FSFV for CSR-39808 and CSR-74587 was in Dec 2001 while in CSR-81179 first subject was screened in Oct 2001 and randomised in Dec 2001.
** LSLV was Nov 2006, Nov 2008 and Sep 2010 for CSR-39808, CSR-74587 and CSR-81179, respectively.
BZA=bazedoxifene; DB=double-blind; FSFV=first subject first visit; LSLV=last subject last visit
Source: 5.3.5.4, Study 300, CSR-39807, and 5.3.5.4, Study 301, CSR-39808, CSR-74587, CSR-81179

Tab 12: Summary of Pivotal Phase 3 Clinical Studies of Bazedoxifene/Conjugated Oestrogens

Study	Duration	Treatment Groups	Active Comparator	Primary Endpoints	Secondary Endpoints	Substudies
303 (n*= 3544)	24 months	BZA 10 mg / CE 0.45 mg BZA 20 mg / CE 0.45 mg BZA 40 mg / CE 0.45 mg BZA 10 mg / CE 0.625 mg BZA 20 mg / CE 0.625 mg BZA 40 mg /	Raloxifene 60 mg	Incidence of endometrial hyperplasia at Month 12 Lumbar spine BMD at Month 24 versus placebo	Incidence of endometrial hyperplasia at Months 6 and 24 Lumbar spine BMD at Months 6 12, and 18 versus placebo and versus raloxifene 60 mg Total hip, femoral neck, trochanter and intertrochanteric area BMD at Months 6, 12, 18 and 24 versus placebo and versus raloxifene 60 mg Change in BTMs at Months 6,	OSS I [a] OSS II[b]

Study	Duration	Treatment Groups	Active Comparator	Primary Endpoints	Secondary Endpoints	Substudies
		CE 0.625 mg Raloxifene 60 mg Placebo			12, and 24 versus placebo and versus raloxifene 60 mg Changes from baseline in the proportion of vaginal superficial, parabasal and intermediate cells versus placebo and versus raloxifene 60 mg Change in number and severity of hot flushes versus placebo and versus raloxifene 60 mg Amenorrhea (cumulative and noncumulative) versus placebo and versus raloxifene 60 mg Breast pain versus placebo and versus raloxifene 60 mg Dyspareunia versus placebo and versus raloxifene 60 mg Sleep parameters versus placebo and versus raloxifene 60 mg	
305 (n*= 332)	12 weeks	BZA 20 mg / CE 0.45 mg BZA 20 mg / CE 0.625 mg Placebo	NA	At Weeks 4 and 12: • Change in number of hot flushes versus placebo • Change in severity score of hot flushes versus placebo	Percentage of responders Mean change from baseline in percentage of days of Breast pain versus placebo Mean change from baseline at Week 12 for Sleep parameters versus placebo	NA
306 (n*= 664)	12 weeks	BZA 20 mg / CE 0.45 mg BZA 20 mg / CE 0.625 mg BZA 20 mg Placebo	BZA 20 mg	At Week 12: Severity of Most Bothersome VVA Symptom versus placebo Change in vaginal pH versus placebo Change in % of vaginal superficial and parabasal cells versus placebo	Individual VVA symptoms vaginal dryness versus placebo and versus BZA 20 mg vaginal itching or irritation versus placebo and versus BZA 20 mg Dyspareunia versus placebo and versus BZA 20 mg	NA
3307 (n*= 1886)	12 months	BZA 20 mg / CE 0.45 mg BZA 20 mg / CE 0.625 mg BZA 20 mg CE 0.45 mg / MPA 1.5 mg Placebo	CE 0.45 mg / MPA 1.5 mg BZA 20 mg	Incidence of endometrial hyperplasia at Month 12 Percent change from Baseline in Lumbar spine BMD at Month 12 versus placebo	Total hip BMD at Month 12 versus placebo, versus BZA 20 mg, and versus CE 0.45 mg/MPA 1.5 mg Percent change from Baseline in Lumbar spine, total hip BMD at Month 6 versus placebo, versus BZA 20 mg, and versus CE 0.45 mg/MPA 1.5 mg For the Osteoporosis Substudy: Change in BTMs at	OSS Breast density Sleep

Study	Duration	Treatment Groups	Active Comparator	Primary Endpoints	Secondary Endpoints	Substudies
					Months 6 and 12 versus placebo, versus BZA 20 mg, and versus CE 0.45 mg/MPA 1.5 mg Amenorrhea (cumulative and noncumulative) versus placebo, versus BZA 20 mg, and versus CE 0.45 mg/MPA 1.5 mg Breast tenderness versus placebo, versus BZA 20 mg, and versus CE 0.45 mg/MPA 1.5 mg For Breast Density Substudy: Percent change in Breast density versus placebo, versus BZA 20 mg, and versus CE 0.45 mg/MPA 1.5 mg For Sleep Substudy: Change from Baseline for Sleep parameters versus placebo, versus BZA 20 mg, and versus CE 0.45 mg/MPA 1.5 mg	
4000 (n*= 507)	24 months	BZA 20 mg / CE 0.45 mg BZA 20 mg / CE 0.625 mg Raloxifene 60 mg Placebo	Raloxifene 60 mg	mean % change from baseline in breast density within each treatment at 24 month		ancillary trial to study 303

n* Number of subjects randomised
a Study 303 Osteoporosis Prevention Substudy I (women >5 YSM).
B Study 303 Osteoporosis Prevention Substudy II and Metabolic Substudy (women ≤5 YSM).
BZA= bazedoxifene; BMD=bone mineral density; BTM=bone turnover marker; CE=conjugated oestrogens; MPA=medroxyprogesterone acetate; NA=not applicable; OSS=osteoporosis substudy; VVA=vulvar vaginal atrophy; YSM=years since menopause.
Source: 5.3.5.1, Study 303, CSR-64104; 5.3.5.1, Study 305, CSR-67461; 5.3.5.1, Study 306, CSR-67466; and 5.3.5.1, Study 3307, CSR-81040.

Table 13: Summary of Supportive Phase 3 Clinical Study of Bazedoxifene/Conjugated Oestrogens

Study	Duration	Treatment Groups	Active comparator	Primary Endpoints	Secondary Endpoints
304 (n*=1083) **304 Extension** (n**=523)	12 months 12 months[a] (Total 24 months)	BZA 20 mg/ CE 0.45 mg BZA 20 mg/ CE 0.625 mg CE 0.45 mg/ MPA 1.5 mg Placebo	CE 0.45 mg /MPA 1.5 mg	• Incidence of endometrial hyperplasia at Month 12 • BMD lumbar spine at Month 12 versus placebo	• Percent change in BMD total hip, and other hip sites at Month 12 versus placebo and versus CE 0.45 mg / MPA 1.5 mg • Amenorrhea (cumulative and noncumulative) versus placebo and versus CE 0.45 mg / MPA 1.5 mg • BTMs at Month 6 and 12 versus placebo and versus CE 0.45 mg / MPA 1.5 mg • Breast pain versus placebo and versus CE 0.45 mg / MPA 1.5 mg • Incidence of endometrial hyperplasia at Month 24 • Percent change from Baseline in BMD of Lumbar spine, total hip, and other hip sites at Month 24 versus placebo and versus CE 0.45 mg / MPA 1.5 mg

n* Number of subjects randomised
n** Number of subjects that continued in the study extension
a Study 304 extension was a 12 month study added by protocol amendment with the objective to collect additional efficacy and safety data for an additional 12 months after the initial 12 month study; total duration of Study 304 was 24 months.
BZA= bazedoxifene; BMD=bone mineral density; BTM=bone turnover marker; CE=conjugated oestrogens; MPA=medroxyprogesterone acetate
Source: 5.3.5.1, Study 304, CSR-68285 and 5.3.5.1, Study 304, CSR-73414.

Table 14: Summary of Phase 2 Clinical Study of Bazedoxifene/Conjugated Oestrogens

Study	Duration	Treatment Groups	Active comparator	Primary Endpoints	Secondary Endpoints
203 n*=412	84 Days	BZA 5 mg + CE 0.3 mg BZA 5 mg + CE 0.625 mg BZA 10 mg + CE 0.3 mg BZA 10 mg + CE 0.625 mg BZA 20 mg + CE 0.3 mg BZA 20 mg + CE 0.625 mg BZA 5 mg CE 0.3 mg CE 0.625 mg CE 0.625 mg/MPA 2.5 mg Placebo	BZA 5 mg CE 0.3 mg CE 0.625 mg CE 0.625 mg /MPA 2.5 mg	• Mean change from baseline to Day 84 in endometrial thickness	• Percentage of patients with change in endometrial glandular mitosis (endometrial biopsies) • Change in vaginal maturation index from baseline to Day 84 • Change in the number and severity of hot flushes from baseline over 4 week periods as specified in the study protocol • Change in bone turnover markers from baseline to Day 84 • Change in lipid parameters from baseline to Day 84 • Change from baseline to Day 84 in coagulation parameters and homocysteine • Incidence of vaginal bleeding

n* Number of subjects randomised
BZA= bazedoxifene; CE=conjugated oestrogens; MPA=medroxyprogesterone acetate
Source: 5.3.5.1, Study 203, CSR-35419

2.4.2. Pharmacokinetics

General PK

The PK of BZA is well investigated as shown in the SmPC and EPAR of bazedoxifene. The submission of the dossier for DUAVIVE does not provide relevant new data except the newly submitted interaction studies 3115A1-1134-US and -1135-US. The new information is that bazedoxifene co-administered with Premarin have no effect on PK of BZA and CE (and vice versa) so that the effects seen in study 3115A1-101-US seems to be an effect of the formulation of the fixed combination product, in this case and in concrete Formulation A.

The PK of CE is well established (see SmPC of CE containing products approved nationally within the EU [Premarin in most countries, Climopax in Germany]). The Applicant submitted a comprehensive overview on PK data of CE monotherapy summarising the available study data and literature.

Bioequivalence

Four (4) main bioequivalence studies in fasted state were performed comparing the BZA 20 mg / CE 0.625 mg and the BZA 20 mg / CE 0.45 mg to-be-marketed formulations to clinical formulations A and B which were used in several clinical studies including phase III. For the 2 initially proposed strengths, the 80-125% acceptance ranges for bioequivalence for BZA and the analysed total, i.e. conjugated and unconjugated, oestrogens (i.e. total estrone, estrone adjusted for baseline, equilin, 17β-estradiol, 17β-estradiol adjusted for baseline, Δ-dehydroestrone, 17β-Δ-dehydroestradiol) were met.

However, the active substance CE is an extract from mare´s urine and thus a biological product containing a not fully characterised mixture of about 160 components. Currently there appears to be no regulatory experience

within the EU regarding the investigation of bioequivalence of CE-containing formulations. Proof of bioequivalence between the formulation of BZA/CE used in the clinical studies and the TBM formulation is critical for this application. Therefore the Pharmacokinetics working party (PKWP) was involved with regard to the concept and methodological issues regarding proof of bioequivalence regarding CE. The PKWP agreed that the concept to demonstrate bioequivalence with respect to the active substance “conjugated oestrogens” based on 2 lead substances, i.e. estrone and equilin, is acceptable. It was also agreed that bioequivalence should be demonstrated with respect to total (conjugated and unconjugated) oestrogens and that demonstration of BE with respect to free (unconjugated) oestrogens is not required (for details see Section 1, *Questions to be posed to additional experts* above).

Based on results of a food-effect programme for the mono-components and the combination product C_{max} increases up to 44% and AUC up to 25% for BZA single dose and steady state. For CE both C_{max} and AUC differed (decreased or increased) up to 22%. It is agreed with the MAH that even though one of the food-effect studies with the combination product used a formulation not bioequivalent with the TBM product, the results are in line with previous food-effect studies supporting the overall effect of food on the BZA/CE formulation. In addition, the pivotal studies (conducted with formulations bioequivalent to the TBM formulation) mimicked the real-life situation as no specific recommendations were given regarding administration with or without food. It should be noted that the food-effect studies have only been conducted with the 20 mg BZA / 0.625 mg CE combination. With regards to the CE components no safety issues are expected as the other suggested dosage includes 0.45 mg of CE thus a smaller dose than investigated in the food-effect studies. With regard to BZA 20 mg / CE 0.45 mg intake with food is not expected to result in lack of effect of the CE component as that the ratio of fed state to fasting state for AUC_T and AUC_{inf} were 0.87-1.06 for estrone (total and unconjugated estrone; adjusted and unadjusted) and 0.85-1.06 for equilin, supporting that food does not alter the exposure in clinically relevant ways.

Bioanalytical methods for CE

With regard to the bioanalytical methods used for the determination of total and free oestrogens, the bioanalytical method for the determination of the free (unconjugated) oestrogens is not considered valid. Only the determination of the total (conjugated and unconjugated) oestrogens can be accepted as valid, which however is considered sufficient. The justification for basing the decision with respect to bioequivalence on total oestrogens only is that these are considered as sensitive with respect to detection of formulation-specific differences and that AUC of total oestrogens seems to reflect the amount of oestrogens absorbed from the tablet formulation.

Furthermore, there was one remaining other concern. The shelf life / retest period of almost all of the reference standards used for the bioanalytical determination of oestrogens (free and total) in the study plasma samples was expired prior to study sample analysis. Furthermore, characterization / identification of the working reference standards has not been described for most of the reference standards. However, these issues have been adequately resolved now.

As mentioned in section 2.4 above two GCP major findings related to the method validation for the determination of the oestrogens were identified during the GCP inspection of the bioanalytical site inVentiv, Princeton, New Jersey, USA. In the course of the GCP inspection procedure the Applicant was requested to address these findings by submission of additional supporting validation test results. The results of these investigations have been provided after close of the GCP inspection and were considered sufficient to address the GCP major findings. One outstanding point for clarification regarding the between-run precision and

accuracy at LLOQ for 17β-Dihydroequilin, 17β-Δ Dehydroestradiol, Δ Dehydroestrone, and Equilin was later adequately addressed by the Applicant.

Conclusion regarding bioequivalence

In conclusion, bioequivalence of the formulations administered in the clinical studies and the TBM formulation was adequately demonstrated. No relevant effect of intake with food compared to intake in the fasting state on the bioavailability of CE and BZA is expected.

Absorption

After a single dose of BZA/CE, BZA, and baseline-adjusted total estrone were absorbed with a t_{max} of approximately 2 hours and 8.5 hours, respectively. When single doses of CE 0.625 mg / BZA 20 mg were administered with a high-fat meal, BZA C_{max} was unaffected, but AUC increased by approximately 25%. Food had little or no effect on the exposure of conjugated oestrogens. BZA/CE can be administered with or without food.

Following administration of BZA alone, a linear increase in plasma concentrations for single doses from 0.5 mg up to 120 mg and multiple daily doses from 1 mg to 80 mg was observed. The absolute bioavailability of BZA is approximately 6%. Conjugated oestrogens are soluble in water and are well-absorbed from the gastrointestinal tract after release from the medicinal product formulation. Oestrogen dose proportionality was assessed in two studies of CE. Dose-proportional increases in both AUC and C_{max} were observed across the dose range from 0.3 mg to 0.625 mg of CE for total (conjugated plus unconjugated) equilin, total estrone adjusted for baseline, and unconjugated estrone adjusted for baseline.

Distribution

The distribution of CE and BZA after administration of BZA/CE has not been studied. Following intravenous administration of a 3 mg dose of BZA alone, the volume of distribution is 14.7 ± 3.9 l/kg. BZA is highly bound (98%-99%) to plasma proteins in vitro, but does not bind to sex hormone binding globulin (SHBG). The distribution of exogenous oestrogens is similar to that of endogenous oestrogens. Oestrogens are widely distributed in the body and are generally found in higher concentrations in the sex hormone target organs. Oestrogens circulate in the blood largely bound to SHBG and albumin.

Metabolism and Elimination

The metabolic disposition of CE and BZA, after administration of BZA/CE, has not been studied. Exogenous oestrogens are metabolised in the same manner as endogenous oestrogens. Circulating oestrogens exist in a dynamic equilibrium of metabolic interconversions. 17β-estradiol is converted reversibly to estrone, and both can be converted to estriol, which is the major urinary metabolite. In postmenopausal women, a significant proportion of the circulating oestrogens exists as sulfate conjugates, especially estrone sulfate, which serves as a circulating reservoir for the formation of more active oestrogens. The metabolic disposition of BZA in postmenopausal women has been determined following oral administration of 20 mg of radiolabeled BZA. BZA is extensively metabolised in women. Glucuronidation is the major metabolic pathway. Little or no cytochrome P450-mediated metabolism is evident. BZA-5-glucuronide is the major circulating metabolite. The concentrations of these glucuronides are approximately 10-fold higher than those of unchanged BZA in plasma.

After a single dose of BZA/CE, baseline-adjusted total estrone (representing conjugated oestrogens) is eliminated with a half-life of approximately 17 hours. BZA is eliminated with a half-life of approximately 30 hours. Steady-state concentrations are achieved by the second week of once-daily administration. Conjugated oestrogens components, 17β-estradiol, estrone, and estriol are excreted in the urine along with glucuronide and sulfate conjugates. The clearance of BZA is 0.4 ± 0.1 L/h/kg based on IV administration. The major route of excretion of radiolabeled BZA is the faeces and less than 1% of the dose is eliminated in urine.

Dose proportionality and time dependencies

Following administration of BZA alone, a linear increase in plasma concentrations for single doses from 0.5 mg up to 120 mg, and multiple daily doses from 1 mg to 80 mg was observed.

CE are soluble in water and are well-absorbed from the gastrointestinal tract after release from the drug formulation. Oestrogen dose proportionality was assessed in two studies of CE. Dose-proportional increases in both AUC and C_{max} were observed across the dose range from 0.3 mg to 0.625 mg of CE for total (conjugated plus unconjugated) equilin, total estrone adjusted for baseline, and unconjugated estrone adjusted for baseline.

A drug will exhibit time independent PK when single-dose PK data accurately predicts the PK data observed following multiple doses. Specifically, the exposure (AUC) observed over the dosing interval once the drug has achieved steady state systemic concentrations following multiple dosing (AUC_{ss}) should be similar to the AUC_{inf} observed following a single dose of the drug.

Special populations

Elderly

The pharmacokinetics of BZA/CE have not been evaluated in women over 75 years of age. The PK of a 20 mg single-dose of BZA were evaluated in a study in 26 healthy postmenopausal women. On average, compared to women 51 to 64 years of age (n=8), women 65 to 74 years of age (n=8) showed a 1.5-fold increase in AUC and women >75 years of age (n=8) showed a 2.6-fold increase in AUC. This increase is most likely attributable to age-related changes in hepatic function.

Renal impairment

The pharmacokinetics of BZA/CE have not been evaluated in patients with renal impairment. Limited clinical data (n=5) for BZA are available in subjects with moderate renal impairment (creatinine clearance < 50 ml/min). A single 20 mg dose of BZA was administered to these subjects. Negligible (<1%) amounts of BZA are eliminated in urine. Impaired renal function showed little or no influence on bazedoxifene pharmacokinetics.

Hepatic impairment

The pharmacokinetics of BZA/CE have not been evaluated in women with hepatic impairment. The disposition of a single 20 mg dose of BZA was compared in women 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, women with hepatic impairment showed a 4.3-fold increase in AUC compared with controls. Safety and efficacy have not been evaluated further in women with hepatic insufficiency. Use of BZA/CE in this population is contraindicated.

Gender

Pharmacokinetics were investigated in postmenopausal women so that a gender effect cannot be assessed.

Race

The clearance of BZA was not appreciably different among the different race groups (Asian, Black, Hispanic, White). Population pharmacokinetic analyses showed no significant effect of ethnic origin on CL/F or V/F. A similar analysis of baseline-adjusted total estrone oral clearance versus ethnic origin based on BZA/CE studies proved that there is no difference in the oral clearance across these groups.

Weight

No evidence of an effect of body weight on the pharmacokinetics (clearance) of BZA was found in the clinical programme investigating monotherapy. The same applies to trials performed with the BZA/CE fixed combination. The same applies on estrone.

Pharmacokinetic interaction studies

No interaction studies have been performed with BZA/CE fixed combination. However, the interactions of the components of DUAVIVE with one another have been investigated. Two (2) more recent trials allow the conclusion that the impact of BZA on CE PK and vice versa is minor and clinically irrelevant. Based on this conclusion it is not very likely that the fixed combination will interact with other substances (and vice versa) differently than its single components.

2.4.3. Pharmacodynamics

Mechanism of action

BZA/CE pairs conjugated oestrogens (CE) with the selective oestrogen receptor modulator (SERM), bazedoxifene. The active ingredients of CE are primarily the sulphate esters of estrone, equilin sulphates and 17α/β-estradiol. These substitute for the loss of oestrogen production in menopausal women, and alleviate menopausal symptoms. As oestrogens promote the growth of the endometrium, unopposed oestrogens increase the risk of endometrial hyperplasia and cancer. The addition of bazedoxifene reduces the oestrogen-induced risk of endometrial hyperplasia in non-hysterectomised women.

Primary and Secondary pharmacology

Pharmacodynamic (PD) properties of this fixed dose combination of CE and BZA have mainly been described by referring to the PD properties of both active substances. The PD properties for bazedoxifene monotherapy have been described and are available from the EPAR of bazedoxifene. With regard to the PD properties of the CE, the Applicant submitted a comprehensive overview of monotherapy summarising the available study data and literature.

The pharmacodynamics of various biomarkers seen with the treatment of BZA as monotherapy was evaluated in a multiple ascending dose study (3068A1-101-US).

No sign of QTc prolongation was seen when subjects were treated with BZA alone in the moxifloxacin controlled study 3068A1-131-US. With regard to CE, there are no indications of QTc prolongation in the literature or in

PSURS for CE products. In studies investigating BZA 20 mg / CE 0.45 mg and BZA 20 mg / CE 0.625 mg there was also no evidence of QTc prolongation based on ECG findings.

For the fixed dose combination the Applicant has provided results of a population PD model based on data from Phase 2 trial 203 as well as from Phase 3 trials 300 (BZA mono), 303, and 304 together with historical data from the HOPE trial for CE (Utian WH et al., 2001). The model includes data for the key PD endpoints rate of endometrial hyperplasia and changes in BMD evaluated in Phase 3 trials. Overall, the population PK/PD model development, except of the data handling regarding the handling of outliers and the splitting into different datasets, seems adequate. Results of the model indicate that for a CE dose of 0.45 mg BZA AUC values of less than 10 µg/L*h were associated with a risk of hyperplasia that was greater than 1%. For a CE dose of 0.625 mg BZA AUC values of less than 30 µg/L*h were associated with a risk of hyperplasia that was greater than 1%. Subjects receiving BZA from formulation C had lower AUC values and therefore a higher probability of hyperplasia than subjects receiving the same 40 mg dose with formulation A due to the reduced relative bioavailability of BZA from this formulation. The model based evaluation of spine and hip BMD suggests an effect of BZA in reducing the progression of BMD loss. For the spine BMD model the effect of BZA dose was found to be important but differences in exposure due to formulation are unlikely to have been noted due to the short duration of therapy. Over longer treatment intervals, however, the efficacy of formulation C would be expected to be less than formulation A.

Phase 2 and Phase 3 trials used PD effects as primary and secondary endpoints. The available data indicate that there is a relevant PD interaction between the two active substances CE and BZA. For the prevention of hot flushes the lowest dose of CE of 0.3 mg (e.g. SPC Climopax in DE; Utian WH et al., 2001) effective in hormone replacement therapy (HRT) was not effective to prevent hot flushes in the fixed combination of CE with BZA. As regards bone mineral density (BMD) while in BZA monotherapy programme (Study 300) 20 mg BZA was more effective on BMD than 10 mg, the effect on BMD appears to be most pronounced with the fixed combination of BZA/CE containing 10 mg of BZA and attenuating with increasing doses of BZA. As regards genetic differences in PD response no significant differences in exposure and subsequent differences in response due to poor metaboliser status of one of the metabolizing enzymes is to be expected.

2.4.4. Discussion on clinical pharmacology

Pharmacokinetics of BZA have been well investigated and the current submission does not provide relevant new data except for the newly submitted interaction studies 3115A1-1134-US and -1135-US. Conbriza co-administered with Premarin has no effect on PK of BZA and CE and vice versa; the effects seen in Study 3115A1-101-US seem to be due to the formulation. The known food effect of BZA has been confirmed for the combination. Pharmacokinetics of CE are also well established and a comprehensive overview was provided within this procedure.

As regards the bioequivalence studies provided for the 2 proposed dose strengths the 80-125%-acceptance ranges for bioequivalence for BZA and the analysed CE were met. However, the active substance CE is an extract from mare´s urine and thus a biological product containing a not fully characterised mixture of about 160 components. The CHMP noted that there was no regulatory experience within the EU regarding the investigation of bioequivalence of CE-containing formulations. However, proof of bioequivalence between the formulation of BZA/CE used in the clinical studies and the TBM formulation was considered critical for this application. Therefore, the PKWP was asked to provide a response to two questions.

CHMP questions to PKWP

Is it an acceptable approach to demonstrate bioequivalence of conjugated oestrogens based on two "lead substances", i.e. the most abundant components estrone and equilin?

Summary of the PKWP Response

Based on Ph.Eur monograph, CE is considered an active substance consisting of 169 components (based on observed HPLC-MS analysis). The Ph.Eur monograph states 10 components to represent >91.5 % by mass of overall CE. Accordingly, based on specifications possible content variability is limited. The potency for any given dose strength of CE monotherapy is based on the 3 most abundant components estrone, equilin, and sodium 17alpha-dihydroequilin. Taking the mean percentage, estrone and equilin represent 83.5 %, i.e. more than 80% of the administered dose. The components used for bioequivalence evaluation were selected based on a pragmatic approach, i.e. those having a large quantity of the mixture and were quantifiable in plasma samples hence allowing calculation of relevant PK parameter (AUC and C_{max}) for bioequivalence decision. Based on currently available data it does not seem feasible to identify components that are most relevant with respect to the pharmacodynamic / clinical response. Oestrogens from CE are eliminated in near-parallel fashion with terminal half-lives generally ranging from 10 to 20 hours. For the purpose of bioequivalence only pre-specified compounds should be quantified that have been judged most relevant for the comparison of formulations.

In conclusion, the bioequivalence approach employed for the most abundant ('lead') CE components is considered pragmatic but reasonable. This is supported by data that shows that baseline adjusted total estrone and total equilin appear to translate formulation-related PK differences.

Sufficiently sensitive bioanalytical methods for determination of unconjugated oestrogens are not available. Is it acceptable to take only total (unconjugated and conjugated) oestrogens into consideration for determination of bioequivalence of formulations containing conjugated oestrogens?

Summary of the PKWP Response

Conjugated oestrogens are water-soluble and are well-absorbed from the gastrointestinal tract. However, bioavailability is low due to first-pass metabolism in the small intestine and liver. Following oral administration, many of the conjugates are hydrolysed already in the mucosa of the stomach and the small intestine; however, the unconjugated oestrogens are quickly re-conjugated in the liver following absorption. Furthermore, exogenous oestrogens are reported to be metabolised in the same manner as endogenous oestrogens. Published data indicate that complex metabolic processes result in a dynamic equilibrium of circulating conjugated and unconjugated estrogenic forms. From biopharmaceutics perspective the Applicant's position is agreed that it is reasonable to base bioequivalence decisions on total rather than unconjugated oestrogens since the tablets contain predominantly sulphated conjugates of oestrogens. Conjugates may thus be considered the 'parent compound'. The unconjugated oestrogens are available in plasma in rather small amounts. Moreover, it has been demonstrated that total oestrogens (baseline adjusted) could identify formulation related differences in bioavailability. However, some limitations are expected regarding rate parameter of total oestrogens since they may not describe pure absorption but include biotransformation processes.

In conclusion, the PKWP agreed that the concept using lead substances for demonstration of bioequivalence for the active substance "conjugated oestrogens" which is a mixture of numerous known und some unknown substances is acceptable. In addition, the PKWP agreed that BE can be demonstrated with respect to total

(conjugated and unconjugated) oestrogens. For the full advice from the PKWP see Appendix 1: PKWP Responses to Questions posed by the CHMP.

Based on the available PK data for the mono-components as well as the combination product and taking also into account that in the pivotal studies no specific recommendations were given regarding administration with or without food, a clinically relevant food effect on BZA 20 mg / CE 0.625 mg is not expected. It should be noted that the food-effect studies have only been conducted with the 20 mg BZA / 0.625 mg CE combination. With regard to BZA 20 mg / CE 0.45 mg, intake with food is not expected to decrease the effect of the CE component, based on the ratio of fed to fasting state of AUC_T and AUC_{inf} for estrone and equilin.

PD properties of this FDC of CE and BZA have mainly been described by referring to the PD properties of both active substances. The PD properties for BZA monotherapy have been described and are available from the EPAR of BZA. A description and discussion on the PD properties of CE has been provided within current dossier.

For the FDC the Applicant has provided results of a population PD model. Overall, the model development seems adequate. The model based evaluation of spine and hip BMD suggests an effect of BZA in reducing the progression of BMD loss. For the spine BMD model the effect of BZA dose was found to be important, but differences in exposure due to formulation are unlikely to have been noted due to the short duration of therapy.

Phase 2 and Phase 3 trials used PD effects as primary and secondary endpoints and the available data indicate that the effects of CE decrease when CE is combined with increasing doses of BZA with regard to hot flushes as well as effects on endometrium. As regards genetic differences in PD response no significant differences in exposure and subsequent differences in response due to poor metaboliser status of one of the metabolising enzymes is to be expected.

2.4.5. Conclusions on clinical pharmacology

In summary, due to the lack of pharmacokinetic interaction of BZA on CE and vice versa, PK statements for the proposed BZA/CE SmPC can be based on the SmPC of Conbriza and Premarin and related trade names. As regards bioequivalence the 80-125%-acceptance range for bioequivalence was met for BZA and the measured CEs for the 2 initial proposed tablet strengths used in the provided studies vs. the TBM formulation. Thus, bioequivalence was adequately demonstrated. No relevant effect of intake with food compared to intake in the fasting state on the bioavailability of CE and BZA is expected.

The PD properties of BZA/CE have mainly been described by referring to the PD properties of both active substances. The Applicant has also provided results of a population PD model; the model based evaluation of spine and hip BMD suggests an effect of BZA in reducing the progression of BMD loss. For the spine BMD model the effect of BZA dose was found to be important, but differences in exposure due to formulation are unlikely to have been noted due to the short duration of therapy. Furthermore, the available data indicate that with regards to hot flushes as well as endometrium the effects of CE decrease when CE is combined with increasing doses of BZA. As regards genetic differences in PD response no significant differences in exposure and subsequent differences in response due to poor metaboliser status of one of the metabolising enzymes is to be expected.

The CHMP considers the following measures necessary to address the issues related to pharmacology:

Description of post-authorisation measure	
MEA	**Due date**
Submission of the CSR of the ongoing DDI study to	

Description of post-authorisation measure	
evaluate the effect of the strong CYP3A4 inhibitor, itraconazole, on the pharmacokinetics of conjugated oestrogens (CE) 045mg/BZA 20mg.	Apr 2015

2.5. Clinical efficacy

The BZA/CE clinical development programme consists of data summarised from 26 clinical trials, 20 Phase 1, 1 Phase 2, and 5 Phase 3 studies, of which 4 are considered pivotal.

The Phase 1 programme assessed the pharmacokinetics of BZA/CE in generally healthy postmenopausal women and consisted mainly of bioavailability/bioequivalence, food effect, and drug interaction studies.

Study 203 was the only Phase 2 trial; doses of 5 mg, 10 mg, and 20 mg for BZA and 0.3 mg and 0.625 mg for CE were investigated. Based on these data, the Applicant considered the 0.3 mg CE dose not to be effective for the treatment of moderate to severe vasomotor symptoms (VMS) and vulvar and vaginal atrophy symptoms (VVA).

The BZA/CE Phase 3 programme comprised the 5 studies 303, 304, 305, 306, and 3307; as for the tablets used during trial 304 bioequivalence to the finally to be marketed medicinal product could not be established, data from this trial are considered supportive only. In all these trials BZA/CE was administered as a single tablet in contrast to the Phase 2 dose ranging study. As the dose of 0.3 mg CE was not considered effective based on Study 203, the Applicant choose a dose of 0.45 mg CE as lowest dose in the Phase 3 programme; this dose was identified as effective to treat moderate to severe VMS in the Women's Health Osteoporosis Progestin Estrogen (HOPE) Study (Utian et al., 2001) and investigated this together with a dose of 0.625 mg CE. The Applicant considers the availability of 2 dose strengths of CE in the FDC of BZA/CE consistent with current treatment guidelines for HRT (*North American Menopause Society, 2012; Sturdee DW et al., 2011; Climacteric medicine: European Menopause and Andropause Society (EMAS) 2004/2005 position statements on peri- and postmenopausal hormone replacement therapy, 2005*) by allowing healthcare providers to tailor the dose to a woman's individual needs and to treat women with the lowest dose effective for their symptoms, as well as to modify the dose according to response to treatment. The doses of BZA in the first Phase 3 study 303 were 10 mg, 20 mg, and 40 mg.

The clinical development programme was initiated in 2001, in accordance with regulatory guidelines that were in effect at that time ([1]*FDA HRT Working Group; Guidance for Industry: Clinical evaluation of combination estrogen / progestin-containing drug products used for hormone replacement therapy of postmenopausal women. Mar 1995*; *[2] Division of Reproductive and Urologic Drug Products, United States Department of Health and Human Services, CDER, FDA. Guidance for Industry (draft): Estrogen and estrogen / progestin drug products to treat vasomotor symptoms and vulvar and vaginal atrophy symptoms-recommendations for clinical evaluation, Jan 2003*; *[3] CHMP Guideline on clinical investigation of medicinal products for hormone replacement therapy of oestrogen deficiency symptoms in postmenopausal women (EMEA/CHMP/021/97 rev. 1), Oct 2005*; [4] *Division of Metabolic and Endocrine Drug Products, FDA. Guidelines for preclinical and clinical evaluation of agents used in the prevention or treatment of postmenopausal osteoporosis, Apr 1994*; [5] *CHMP Note for guidance on postmenopausal osteoporosis in women. (CPMP/EWP/552/95 rev 1), Jan 2001*; *[6] CHMP Guideline on clinical investigation of medicinal products for hormone replacement therapy of oestrogen*

deficiency symptoms in postmenopausal women (EMEA/CHMP/021/97 rev. 1), Oct 2005). The last Phase 3 study 3307 was finalised in 2011.

As regards osteoporosis the fixed combination was initially developed for the prevention of osteoporosis in postmenopausal women in accordance with the CHMP Note for guidance in effect in 2001 (*CHMP Note for guidance on postmenopausal osteoporosis in women, Jan 2001 (CPMP/EWP/552/95 rev 1)*). During the clinical development of BZA/CE the CHMP guideline on primary osteoporosis was revised *(CHMP Guideline on the Evaluation of Medicinal Products in the Treatment of Primary Osteoporosis, November 2006 (CPMP/EWP/552/95 Rev 2, Effective 31 May 2007*)); only an indication for the "treatment of osteoporosis in postmenopausal women at increased risk of fracture" should now generally be considered. However, prevention is merged into the treatment indication, since the goal of therapy is to prevent fractures. The current guideline accepts under defined circumstances that for compounds having demonstrated anti-fracture efficacy for a specific formulation, demonstration of non-inferiority for changes in BMD in a study of a minimum of 1 year duration may be an acceptable surrogate marker for applying for an extension of the indication for a new formulation. The Applicant acknowledged that this approach does not directly apply to the new proposed fixed combination, but argues that given the similarity of the pharmacologic activity of the two components, both of which have individually shown efficacy for reduction of fracture risk, the demonstration of comparable effects on changes in BMD and other surrogate endpoints associated with fracture risk, such as bone turnover markers (BTMs), supports the indication for treatment of osteoporosis in postmenopausal women for BZA/CE. Implications of the revision to the guidance were discussed during EU national agency scientific advice consultations in 2008 and 2010.

Per the current *EU CHMP guideline for the clinical investigation of medicinal products for therapy of oestrogen deficiency symptoms, in postmenopausal women (EMEA/CHMP/021/97 rev. 1), Oct 2005* the most important symptoms guiding treatment in postmenopausal women are considered to be VMS (hot flushes).

2.5.1. Dose response study

Study 203

Study 203 was a phase 2, multicentre, double-blind, randomised, controlled, dose finding study of BZA paired with CE on the estrogenic stimulation of the endometrium in healthy postmenopausal women conducted in the EU. Eleven dose groups were studied: 5 mg, 10 mg, and 20 mg BZA each in combination with 0.45 mg CE and 0.626 mg CE; 0.3 mg, 0.625 mg CE monotherapy, 0.625 mg CE / 2.5 mg MPA, and placebo. Patients were treated for 12 weeks. The primary efficacy variable was endometrial thickness measured by transvaginal ultrasound (TVUS) at day 84. Secondary endpoints included change from baseline in the number of subjects presenting oestrogen related changes in the endometrium (glands and stroma), percent change from baseline in VMI, percent change from baseline in number and severity of hot flushes, and change from baseline in bone markers. Bleeding / spotting and breast tenderness were also investigated.

Four hundred fourteen (414) patients were enrolled, 412 patients were randomised, and 408 patients were treated. Of these, 397 patients had at least one post-baseline evaluation of endometrial thickness and constituted the ITT population. With regard to demographic and baseline characteristics the study groups were comparable.

Endometrial thickness

The results of comparisons between treatment groups are displayed in the following table:

Table 15: Transvaginal ultrasonography: endometrial thickness (mm) at day 84 (ITT)

Comparisons Source	Estimate	Standard Error	95% CI	p-Value
Primary Comparisons				
TSE-424 20 mg/Premarin 0.3 mg Vs Premarin 0.3 mg	-0.98	0.49	(-1.95, -0.01)	0.049
TSE-424 20 mg/Premarin 0.625 mg Vs Premarin 0.625 mg	-1.95	0.54	(-3.02, -0.89)	<0.001
Secondary Comparisons				
TSE-424 10 mg/Premarin 0.3 mg Vs Premarin 0.3 mg	-0.66	0.50	(-1.64, 0.33)	0.193
TSE-424 10 mg/Premarin 0.625 mg Vs Premarin 0.625 mg	-1.77	0.49	(-2.15, -0.20)	0.019
TSE-424 5 mg/Premarin 0.3 mg Vs Premarin 0.3 mg	0.03	0.51	(-0.97, 1.03)	0.953
TSE-424 5 mg/Premarin 0.625 mg Vs Premarin 0.625 mg	0.50	0.51	(-0.50, 1.49)	0.327
Exploratory Comparisons				
TSE-424 20 mg/Premarin 0.625 mg Vs placebo	0.60	0.54	(-0.47, 1.67)	0.273
TSE-424 10 mg/Premarin 0.625 mg Vs placebo	1.38	0.50	(0.40, 2.37)	0.006
TSE-424 5 mg/Premarin 0.625 mg Vs placebo	3.05	0.51	(2.04, 4.06)	<0.001
TSE-424 5 mg Vs placebo	-0.30	0.51	(-1.30, 0.70)	0.551
Premarin 0.3 mg Vs placebo	0.98	0.51	(-0.03, 1.99)	0.057
Premarin 0.625 mg Vs placebo	2.55	0.51	(1.54, 3.56)	<0.001
Premarin 0.625 mg/MPA 2.5 mg Vs placebo	1.34	0.52	(0.32, 2.36)	0.010
TSE-424 20 mg/Premarin 0.625 mg Vs Premarin 0.625 mg/MPA 2.5 mg	-0.74	0.55	(-1.82, 0.33)	0.176
TSE-424 10 mg/Premarin 0.625 mg Vs Premarin 0.625 mg/MPA 2.5 mg	0.04	0.50	(-0.94, 1.03)	0.934
TSE-424 5 mg/Premarin 0.625 mg Vs Premarin 0.625 mg/MPA 2.5 mg	1.71	0.51	(0.70, 2.72)	<0.001
Premarin 0.625 mg Vs Premarin 0.625 mg/MPA 2.5 mg	1.21	0.51	(0.21, 2.22)	0.018
TSE-424 5 mg/Premarin 0.3 mg Vs TSE-424 5 mg	1.31	0.51	(0.32, 2.31)	0.010
TSE-424 5 mg/Premarin 0.625 mg Vs TSE-424 5 mg	3.35	0.50	(2.36, 4.34)	<0.001
Premarin 0.3 mg Vs TSE-424 5 mg	1.28	0.50	(0.29, 2.27)	0.011
Premarin 0.625 mg Vs TSE-424 5 mg	2.86	0.50	(1.87, 3.84)	<0.001

Note: CI = confidence interval; MPA = medroxy progesterone acetate; ITT = intent-to-treat.
The following model was used for the comparisons: baseline from local site, treatment, center, and previous hormonal replacement therapy.

BZA 5 mg in combination with the two doses of CE did not decrease endometrial thickness compared to the respective dose of unopposed CE.

The addition of BZA 10 mg to CE 0.3 mg resulted in an endometrial thickness at day 84 not statistically different from 0.3 mg CE alone and numerically higher, but not statistically significantly different from placebo. The addition of 10 mg BZA to CE 0.625 mg resulted in an endometrial thickness at day 84 statistically significantly lower than with CE 0.625 mg alone, comparable to CE 0.625 mg / MPA 2.5 mg and statistically significantly higher compared to placebo.

BZA 20 mg in combination with the two doses of CE led to a statistically significantly lower endometrial thickness at day 84 compared to the respective dose of unopposed CE. In combination with CE 0.3 mg, this dose of BZA led to an endometrial thickness at day 84 comparable to placebo. In combination with 0.625 mg CE this dose of BZA led to an endometrial thickness at day 84 numerically higher than placebo, but numerically lower than CE 0.625 mg / MPA 2.5 mg. These differences however were not statistically significant.

Regarding estrogenic effects in endometrial biopsies there was a considerable increase of about 20 to 25% in the percentage of patients with significant or marked effects from baseline to day 84 in the BZA 5 mg / CE 0.625 mg group and the CE 0.625 mg indicating that endometrial protection was insufficient in these groups. In all other BZA/CE groups and CE groups the number of patients with significant or marked effects increased by 1 or 2 from baseline to day 84, while in the BZA 5 mg group this number remained unchanged and in the CE/MPA group this number decreased from 1 to 0. However, based on the low number of patients per group, no definite conclusions can be drawn.

VMS

For CE 0.3 mg the effect on hot flushes decreased with increasing doses of BZA. Efficacy on VMS seems unlikely with a dose of 20 mg BZA.

For CE 0.625 mg effects on VMS decreased to some extent with BZA 10 mg compared to the BZA 5 mg while between BZA 10 mg and BZA 20 mg, the effects were comparable. However, with all 3 doses of BZA the decrease of VMS can be considered as clinically relevant.

VMI

The effect on VMI decreased with increasing doses of BZA for CE 0.3 mg as well as CE 0.625 mg. In the BZA 20 mg / CE 0.625 mg group an increase of the VMI from baseline to day 84 was still observed while the VMI did hardly change in this time interval in the BZA 20 mg / CE 0.3 mg group.

Markers of bone metabolism

Results for biochemical markers of bone metabolism were in line with known effects of BZA and CE.

Lipid parameters

As regards parameters of lipid metabolism there was no clear dose-relationship.

Coagulation parameters

While BZA 10 mg / CE 0.625 mg and BZA 20 mg / CE 0.625 mg showed a statistically significant reduction from baseline in fibrinogen levels compared to placebo, BZA/CE 0.625 mg combinations were not significantly different from placebo or CE 0.625 mg / MPA 2.5 mg as regards prothrombin time, or partial prothrombin time.

Conclusions

Taking all results into account it can be concluded that a dose of 5 mg BZA is insufficient for endometrial protection with regard to both doses of CE. A dose of 5 mg BZA was not further studied in phase III studies. A dose of 20 mg BZA seems to be more effective for endometrial protection in patients treated with CE 0.625 mg than a dose of 10 mg BZA. However, 10 mg as well as 20 mg BZA were further studied in combination with CE 0.45 mg and CE 0.625 mg in phase III study 303.

The efficacy of CE 0.3 mg for VMS as well as for VVA is considerably compromised by 20 mg BZA. Regarding the combination BZA 10 mg / CE 0.3 mg a clinically relevant efficacy on VMS and VVA might be preserved. However, in study 303 a dose of 10 mg BZA was clearly insufficient for endometrial protection in patients treated with 0.45 mg CE. Thus, it is agreed that a dose of 0.3 mg CE in combination with BZA was not further investigated in phase III studies.

For CE 0.625 mg, effects on VMS decreased to some extent with BZA 10 mg compared to the BZA 5 mg while between BZA 10 mg and BZA 20 mg the effects were comparable. However, with all 3 doses of BZA the statistically significant differences vs. placebo were observed.

No statistically significant differences with respect to number and severity of hot flushes were observed between the different combinations of BZA/CE compared with the same doses of CE as monotherapy. However, numerically the effects were somewhat greater in the CE monotherapy groups except for the comparison BZA

5 mg / CE 0.3 mg vs. CE 0.3 mg. For CE 0.625 mg / BZA 5 mg, CE 0.625 mg / BZA 10 mg and 20 mg no statistically significant differences with respect to number and severity of hot flushes were observed vs. CE 0.625 / 2.5 mg MPA. However, numerically the effects were somewhat greater in the CE/MPA group.

With regard to CE 0.3 mg the effect on VMI appeared to be highest in the CE 0.3 mg monotherapy group and decreased numerically with increasing BZA doses. With regard to CE 0.625 mg similar effects were observed in all BZA/CE groups and the CE 0.625 mg monotherapy group while the effect in the placebo group appeared to be lower. It is also noted that the effect on the VMI appeared to be higher with CE 0.625 mg / MPA 2.5 mg, compared to all combinations of BZA/CE. Statistical significance was not tested regarding these comparisons.

Results for biochemical markers of bone metabolism were in line with known effects of BZA and CE. As regards parameters of lipid metabolism there was no clear dose-relationship. As regards coagulation parameters while BZA/CE 10 mg / 0.625 mg and 20 mg / 0.625 mg showed a statistically significant reduction from baseline in fibrinogen levels compared to placebo, BZA/CE 0.625 mg combinations were not significantly different from placebo or CE/MPA 0.625 mg / 2.5 mg as regards prothrombin time or partial prothrombin time.

2.5.2. Main studies

The Applicant has provided data from 4 pivotal Phase 3 studies, studies 303, 305, 306, and 3307 to support the submission for registration of BZA 20 mg / CE 0.45 mg and BZA 20 mg / CE 0.625 mg. These studies evaluated efficacy and safety of BZA/CE compared to placebo or active comparators.

Study 303

Study 303 'A double-blind, randomised, placebo- and active-controlled safety and efficacy study of bazedoxifene / conjugated oestrogens combinations in postmenopausal women' is a Phase 3 multicentre, double-blind, randomised, outpatient, 8-parallel-group placebo- and active-controlled dose-ranging study evaluating efficacy and safety of 6 combinations of BZA/CE (BZA 10 mg, 20 mg, 40 mg; CE 0.45 mg, 0.625 mg) over 2 years of therapy.

Methods

Study Participants

The study was conducted between April 2002 and January 2006 and enrolled generally healthy, non-hysterectomised postmenopausal women, aged 40 to 75 years having normal endometrial biopsy results at screening. Inclusion Criteria were: 1. Generally healthy, postmenopausal, age 40 to 75 year; 2. Serum follicle-stimulating hormone (FSH) concentration ≥ 30 mIU/mL and serum 17β-estradiol concentration ≤ 183.5 pmol/L (50 pg/mL) at screening; 3. Intact uterus; 4. Endometrial biopsy report at screening; 5. Last natural menstrual cycle completed at least 12 consecutive months before screening, more than 5 years before screening in Osteoporosis Prevention I Substudy (study groups C and D), and not more than 5 years before screening in Osteoporosis Prevention II and Metabolic Substudy (study groups E and F); 6. Body mass index (BMI) ≤ 32.2 kg/m^2; 7. Likely being compliant and having a high probability of completing the study by investigator's opinion; 8. IRB approved written informed consent signed and dated before screening; 9. In Osteoporosis Substudies lumbar spine scans at screening differ by < 5% and total hip scans at screening by < 7.5% at baseline; 10. In Osteoporosis Prevention Substudies participants had to have a bone mineral density (BMD) T-score at lumbar spine or total hip between -1 and -2.5 incl. and at least one of the following risk factors: a. Family history of osteoporosis; b. Early menopause (≤ 40 years); c. Current history of smoking; d. Past history of excessive

alcohol use; e. Diet low in calcium; f. Inactive lifestyle; g. Thin or small frame (weight < 50 kg or BMI < 18 kg/m^2); h. Caucasian or Asian.

Treatments

Subjects were randomly assigned to receive 1 of the 6 BZA/CE doses (10 mg / 0.625 mg, 20 mg / 0.625 mg, 40 mg / 0.625 mg, 10 mg / 0.45 mg, 20 mg / 0.45 mg, 40 mg / 0.45 mg), raloxifene 60 mg, or placebo. Subjects were to take 1 capsule orally once daily on a continuous regimen for 2 years. Subjects were also to maintain a consistent daily intake of dietary and supplemental calcium and vitamin D during the treatment period, with a total daily calcium intake of approximately 1000 to 1600 mg. At the randomization visit, each subject's daily calcium intake (dietary plus supplemental) was assessed and subjects requiring additional supplementation were provided Caltrate 600 + D in open-label market packages as required.

Objectives

The primary objective was to evaluate the effects of BZA/CE on the incidence of endometrial hyperplasia in postmenopausal women after 1 year of treatment. The secondary objective was to evaluate the efficacy of BZA/CE in preventing osteoporosis after 2 years of therapy. Additional objectives were to evaluate the effects on safety (including mammography), metabolic parameters (including lipids, serum bone markers, carbohydrates, and coagulation factors), vaginal atrophy, uterine bleeding, vasomotor symptoms, and quality-of-life indices.

Outcomes/endpoints

The primary endpoint of this study was the incidence of endometrial hyperplasia after 1 year of therapy. The main secondary endpoint was the mean percent change from baseline in BMD of the lumbar spine after 2 years of therapy. The chosen primary and secondary endpoints are adequate to investigate the defined objectives. However, as regards the main secondary endpoint, mean percent change from baseline in BMD of the lumbar spine after 2 years of therapy, osteoporosis prevention was assessed in the Osteoporosis Prevention Substudy I (women >5 YSM with BMD, T-score between -1 and -2.5, at least 1 additional risk factor for osteoporosis) and Osteoporosis Prevention Substudy II (women ≥1 and ≤5 YSM, at least 1 additional risk factor for osteoporosis) as required by the regulatory guidance on prevention of postmenopausal osteoporosis that were in effect at the time the study was designed and initiated. Thus the study is primarily designed as a dose-ranging study and the osteoporosis prevention indication is assessed only in a substudy and the present study cannot be considered as a pivotal main study for the osteoporosis treatment indication. It has to be considered that the relevant CHMP guideline on postmenopausal osteoporosis in women has been revised during the clinical development programme. While revision 1, effective since 2001, considered an indication of prevention of osteoporosis, revision 2, effective since May 2007, does no longer have a specific prevention indication. However, prevention of osteoporosis is contained in the treatment indication since the goal of therapy is to prevent fractures. Since for both components of this fixed combination anti-fracture efficacy has been established, BMD together with other markers of bone turnover is considered an adequate surrogate marker.

Sample size

The sample size calculation with regard to endometrial protection in this study was based on US guidance documents only. According to the current version of the *CHMP Guideline on clinical investigation of medicinal products for hormone replacement therapy of oestrogen deficiency symptoms in postmenopausal women*, the

upper limit of the 2-sided 95% CI of the incidence of hyperplasia should be ≤2%, to conclude to an established endometrial safety.

The sample size calculation with respect to osteoporosis was adequate, as well as randomisation and blinding. Overall, the statistical methods were acceptable.

Randomisation

Participants were randomised at visit 2B after washout, all screening, and baseline procedures being completed. The randomization schedule for packaging and labelling was generated by the Clinical Biostatistics Section of Wyeth Research. Allocation of subjects to treatment groups proceeded using of a computerized randomization/enrolment interactive voice recognition system (IVRS) accessible by phone and randomization and package number were recorded on the CRF.

Blinding (masking)

Both study drug and active comparator were provided as single tablets, over-encapsulated for blinding to match placebo capsules. Reasons for and date of any unblinding were to be documented on the CRF and in the source documents.

Statistical methods

The primary endpoint for proof of efficacy in this study was the incidence of endometrial hyperplasia after 1 year of therapy, and the primary analysis population was the efficacy evaluable (EE) population for month 12 defined as subjects who had taken at least 1 dose of test article, had an endometrial biopsy at screening, an endometrial biopsy within 30 days before or after the time point of interest or were diagnosed with hyperplasia at any time prior to the time point, and had no major protocol violations. An acceptable rate of hyperplasia was defined as an observed rate of 2% or less with a 1-sided 95% upper CI limit of 4% or less. The 1-sided CIs were examined using a step-down procedure to correct for the multiplicity of treatment groups. Comparisons to placebo and raloxifene were done by examining 95% CIs for pairwise differences in hyperplasia rates.

Results

Participant flow

A total of 10,511 subjects were screened for enrolment in the study, and 3,544 were randomly assigned to the 8 treatment groups. A total of 147 randomly assigned subjects did not take a test article and are not included in any analyses. The remaining 3,397 subjects took at least 1 dose and are included in the safety analyses. Among the 3397 subjects dosed, 2539 (75%) were included in the EE population for the primary efficacy analysis incidence of endometrial hyperplasia at month 12, 73% in the placebo and 77% and 76% in the BZA/CE 20 mg / 0.45 mg and 20 mg / 0.625 mg groups, respectively. A total of 1454 subjects participated in the Osteoporosis Prevention I substudy (OSS I, women > 5 years post-menopausal, Groups C and D) and 1295 (89%) of these were included in the MITT population for the primary analysis of percent change from baseline in lumbar spine BMD. A total of 861 dosed subjects participated in the Osteoporosis Prevention II and Metabolic substudy (OSS II, women ≤ 5 years post-menopausal, Groups E and F) and 783 (91%) were included in the MITT population.

Table 16: Primary Analysis Populations [Number (%) of Subjects]

	CE 0.625 mg		
	BZA 10 mg	BZA 20 mg	BZA 40 mg
Safety Population (Dosed Subjects)	430	414	417
EE Population (month 12), Endometrial Hyperplasia	340 (79)	314 (76)	311 (75)
Osteoporosis Prevention I Substudy (Groups C & D)	183	173	182
MITT Population, Lumbar Spine BMD	166 (91)	159 (92)	161 (88)
Osteoporosis Prevention II Substudy (Groups E & F)	113	105	105
MITT Population, Lumbar Spine BMD	102 (90)	96 (91)	96 (91)

	CE 0.45 mg					
	BZA 10 mg	BZA 20 mg	BZA 40 mg	Raloxifene 60 mg	Placebo	Total
Safety Population (Dosed Subjects)	430	433	423	423	427	3397
EE Population (month 12), Endometrial Hyperplasia	320 (74)	335 (77)	309 (73)	298 (70)	312 (73)	2539 (75)
Osteoporosis Prevention I Substudy	186	182	176	188	184	1454
MITT Population, Lumbar Spine BMD (Groups C & D)	167 (90)	160 (88)	159 (90)	164 (87)	159 (86)	1295 (89)
Osteoporosis Prevention II Substudy	104	111	108	107	108	861
MITT Population, Lumbar Spine BMD (Groups E & F)	95 (91)	101 (91)	97 (90)	97 (91)	99 (92)	783 (91)

Safety Population = includes subjects who were randomised and took at least 1 dose of test article.
EE = efficacy evaluable (endometrial hyperplasia): includes subjects who took at least 1 dose of test article; and had endometrial biopsy readings at screening and on treatment for the specified time point, or had hyperplasia anytime prior to the time point. Subjects also had to meet other evaluability criteria and have no major protocol violations.
MITT = modified intent-to-treat (BMD, lumbar spine): includes subjects who took at least 1 dose of test article, had lumbar spine BMD values at baseline and at least 1 value on-therapy or within 60 days of last dose of test article.
BMD = bone mineral density.
Source: /Compounds/PF-05/PF-05212370/Clinical/III/3115A1-303/Tables and Figures:/BIOPSY /3115-303 EE4_BIOP12 (09SEP10 18:18);/303_DOSED_QUALSITES/3115-303: MITT4_BMD_V1_CD (22MAY06 08:53); and MITT4_BMD_V1_EF (22MAY06 08:54)

The overall rate of discontinuation from the study was similar across treatment groups (29.8% to 35.7%, overall p-value = 0.610, Chi-square). For each group, the most frequent reason for withdrawal was AE, followed by subject request unrelated to the study. As regards withdrawal due to AEs, please see also safety assessment below. For most discontinuation reasons, the incidence of withdrawal was similar across groups with no significant differences (p >0.05, Chi-square). The only exception was the incidence of withdrawals due to unsatisfactory response, which was significantly different among groups (p = 0.002, Chi-square) and higher among subjects treated with placebo (12; 2.8%) and raloxifene (9; 2.1%) than for the other groups. The rate of protocol violations leading to discontinuation was low. Overall, protocol deviations appear to have been adequately addressed and dealt with by the Applicant. It is agreed that no major impact on study results are to be expected.

There were no significant differences among groups regarding baseline characteristics, but the population consisted of mainly younger postmenopausal women and the number of women with other than white ethnicity is sparse. Considering the populations for the Osteoporosis Prevention I and II substudies, women in Substudy II were generally younger (mean age approximately 52 years) than those in Substudy I (mean age approximately 59 years). Similarly, the mean number of years since the last menstrual period was 11.14 years for Substudy I as compared with 2.99 years for Substudy II, and 8.10 years for the overall population. Based on BMD data for lumbar spine, the mean T-score at baseline was -1.47 for women in Substudy I and -0.83 for those in Substudy II. In addition, the incidence of elevated systolic and diastolic blood pressure at baseline was greater among women in Substudy I than in Substudy II.

Recruitment

This trial was conducted between April 2002 and January 2006.

Conduct of the study

The original protocol for sites in the US was dated 07 Jan 2002 and was amended once.

Baseline data

Subjects were generally healthy, non-hysterectomised postmenopausal women, ranging in age from 40 to 75 years, with a mean age of 56.5 years. Body mass index (BMI) ranged from 16.2 to 35.7 kg/m² with a mean of 25.8 kg/m², and approximately 59.0% of subjects had BMI ≥ 25 kg/m². The mean number of years since the last menstrual period for these subjects was 8.1, and the mean age at the time of the last menstrual period was 48.9 years. Baseline characteristics were similar across treatment groups, and there were no statistically significant differences among treatment groups for any baseline characteristics, except for maternal history of fracture (p = 0.043, Chi-Square), which was approximately 7% overall and ranged from 4% to 10%. Overall, there were no significant differences among groups regarding baseline characteristics. However, the population consisted of mainly younger postmenopausal women and the number of women with other than white ethnicity is sparse.

Numbers analysed

A total of 3397 subjects were randomly assigned and took at least 1 dose. The numbers analysed for the primary and secondary analyses are summarised below. The primary analysis population for endometrial hyperplasia was the EE population for month 12, while secondary analyses were conducted using data from the MITT population.

Table 3.2.16: Number (%) of Subjects in the EE and MITT Populations for Endometrial Hyperplasia

	Conjugated Estrogens 0.625 mg			Conjugated Estrogens 0.45 mg			Raloxifene	
Population/ Reason Excluded[a]	BZA 10 mg N = 430	BZA 20 mg N = 414	BZA 40 mg N = 417	BZA 10 mg N = 430	BZA 20 mg N = 433	BZA 40 mg N = 423	60 mg N = 423	Placebo N = 427
EE population for month 12	340 (79)	314 (76)	311 (75)	320 (74)	335 (77)	309 (73)	298 (70)	312 (73)
Excluded subjects	90 (21)	100 (24)	106 (25)	110 (26)	98 (23)	114 (27)	125 (30)	115 (27)
MITT population	380 (88)	368 (89)	362 (87)	366 (85)	373 (86)	358 (85)	355 (84)	363 (85)
Excluded subjects	50 (12)	46 (11)	55 (13)	64 (15)	60 (14)	65 (15)	68 (16)	64 (15)

EE = efficacy evaluable (endometrial hyperplasia): includes subjects who took at least 1 dose of test article; and had endometrial biopsy readings at screening and on treatment for the specified time point, or had hyperplasia anytime prior to the time point. Subjects also had to meet other evaluability criteria and have no major protocol deviations.
MITT = modified intent-to-treat (endometrial hyperplasia): includes subjects who took at least 1 dose of test article and had screening data and on treatment for the specified time point.
a. A subject may have been excluded for more than 1 reason.
Source: /Compounds/PF-05/PF-05212370/Clinical/III/3115A1-303/Tables and Figures/BIOPSY/3115-303: EE4_BIOP12 (09SEP10 18:18); and MITT4_BIOP(09SEP10 18:23).

Outcomes and estimation

Endometrial hyperplasia

The following results regarding endometrial hyperplasia / malignancy were reported:

Table 17: Incidence of Endometrial Hyperplasia / malignancy at Months 12 and 24 (Efficacy Evaluable Population)

					Confidence interval	
Treatment	Timepoint	N evaluable biopsies	N endometrial hyperplasia / malignancy	Incidence of hyperplasia/ malignancy (%)	Lower limit	Upper limit
BZA 20 mg / CE 0.45 mg	Month 12	294	0	0.00	0.00	1.25
	Month 24	229	2	0.87	0.11	3.12
BZA 20 mg / CE 0.625 mg	Month 12	271	1	0.37	0.01	2.04
	Month 24	195	2	1.03	0.12	3.66

[a] 1-sided 95% confidence interval
[b] prespecified 1-sided 97.5% confidence interval per stepwise procedure, to adjust for multiple comparisons (CE 0.45mg combined with BZA 40 mg and 20 mg)

It is noted that even in this GCP non-compliant study, 3 cases of endometrial hyperplasia / malignancy had been detected in the two BZA/CE groups during the second treatment year. This is considered as a safety signal. In addition, it is noted that at month 12, the upper limit of the 2-sided 95% CI of the incidence of endometrial hyperplasia / malignancy was above the reference limit of 2% stated in the CHMP HRT Guideline in the BZA 20 mg / CE 0.625 mg group.

Bone mineral density

The MITT analysis of the main secondary endpoint mean percent change from baseline in BMD of the lumbar spine after 2 years of therapy showed significant increases in lumbar spine BMD from baseline to month 24 in both substudies for all groups except placebo were BMD values decreased. Increases in BMD were most pronounced with the lowest dose of BZA of 10 mg attenuating with increasing doses of BZA. In the elder group of women >5 years postmenopausal effects were more pronounced with BZA/CE containing either 10 or 20 mg BZA, but not 40 mg, compared to raloxifene 60 mg; in the younger women ≤5 years postmenopausal BMD increases were more pronounced with all doses of BZA/CE. However, results were only marginally significant for BZA/CE 20 mg / 0.45 mg in the elder women and for both BZA 40 mg / CE in younger women.

Table 18: BMD of Lumbar Spine - Adjusted Mean % Change From Baseline to Month 24: MITT Population, LOCF (Substudy I, Women > 5 Years From Last Menstrual Period)

Treatment Group[a]	N	Adjusted Mean % Change		p-Value Within Group[b]	p-Value vs Raloxifene[b]	p-Value vs Placebo[b]
		Mean	SE			
CE 0.625 mg with:						
10 mg BZA	166	2.38	0.29	<0.001***	<0.001***	<0.001***
20 mg BZA	159	1.96	0.30	<0.001***	0.002**	<0.001***
40 mg BZA	161	1.10	0.29	<0.001***	0.357	<0.001***
CE 0.45 mg with:						
10 mg BZA	167	2.42	0.29	<0.001***	<0.001***	<0.001***
20 mg BZA	160	1.57	0.29	<0.001***	0.040*	<0.001***
40 mg BZA	159	0.78	0.29	0.008**	0.900	<0.001***
Raloxifene 60 mg	164	0.73	0.29	0.012*		
Placebo	159	-1.51	0.29	<0.001***		

N = number of subjects with both a baseline and at least 1 on-therapy BMD value for lumbar spine.
a. Treatment groups are listed in order of analysis per stepwise procedure
b. ANCOVA percent change = treatment + site + baseline + years since menopause
* = p<0.05; ** = p<0.01; *** = p<0.001
SE = standard error.
Source: /Compounds/PF-05/PF-05212370/Clinical/III/3115A1-303/Tables and Figures/303_NDA_2006 /bmd_itt_locf_ancova_sub1_final_06 (19MAY06).

Table 19: BMD Lumbar Spine - Adjusted Mean % Change From Baseline to Month 24: MITT, LOCF (Substudy II, Women ≥ 1 Year and ≤ 5 Years From Last Menstrual Period)

Treatment Group[a]	N	Adjusted Mean % Change		p-Value Within Group[b]	p-Value vs Raloxifene[b]	p-Value vs Placebo[b]
		Mean	SE			
CE 0.625 mg with:						
10 mg BZA	102	2.61	0.35	<0.001***	<0.001***	<0.001***
20 mg BZA	96	1.80	0.36	<0.001***	0.001**	<0.001***
40 mg BZA	96	1.15	0.36	0.001**	0.046*	<0.001***
CE 0.45 mg with:						
10 mg BZA	95	2.33	0.36	<0.001***	<0.001***	<0.001***
20 mg BZA	101	1.69	0.35	<0.001***	0.001**	<0.001***
40 mg BZA	97	1.32	0.35	<0.001***	0.018*	<0.001***
Raloxifene 60 mg	97	0.15	0.35	0.678		
Placebo	99	-1.92	0.35	<0.001***		

N = number of subjects with both a baseline and at least 1 on-therapy BMD value for lumbar spine.
a. Treatment groups are listed in order of analysis per stepwise procedure.
b. ANCOVA percent change = treatment+site+baseline+years since menopause.
* = p<0.05; ** = p<0.01; *** = p<0.001
SE = standard error.
Source: Compounds/PF-05/PF-05212370/Clinical/III/3115A1-303/Tables and Figures/303_NDA_2006/bmd_itt_locf_ancova_sub2_final_06 (19MAY06).

Figure 1: BMD Lumbar Spine - Adjusted Mean % Change From Baseline to Month 24: MITT Population, LOCF (Substudy I, Women > 5 Years From Last Menstrual Period)

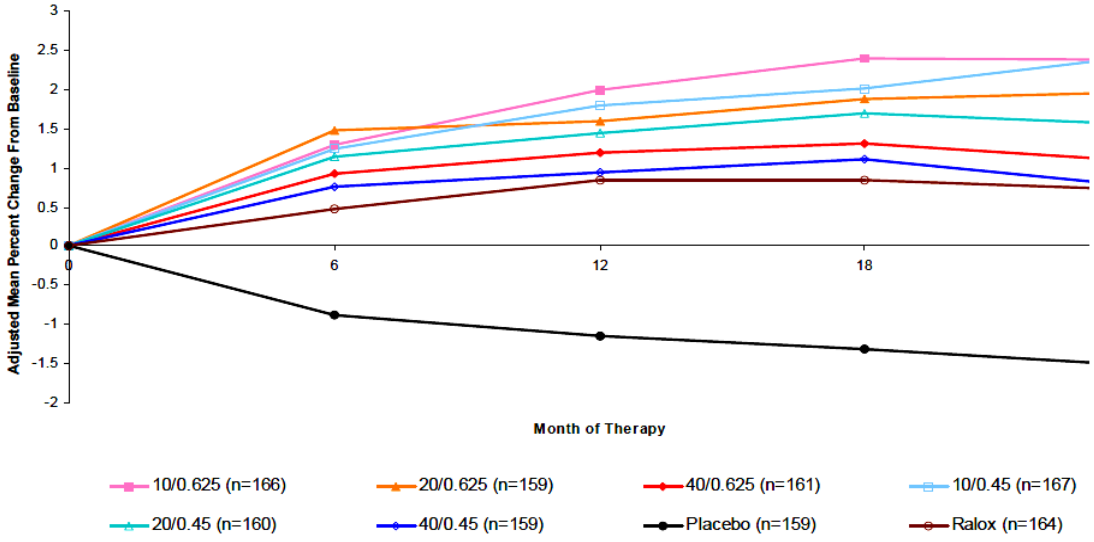
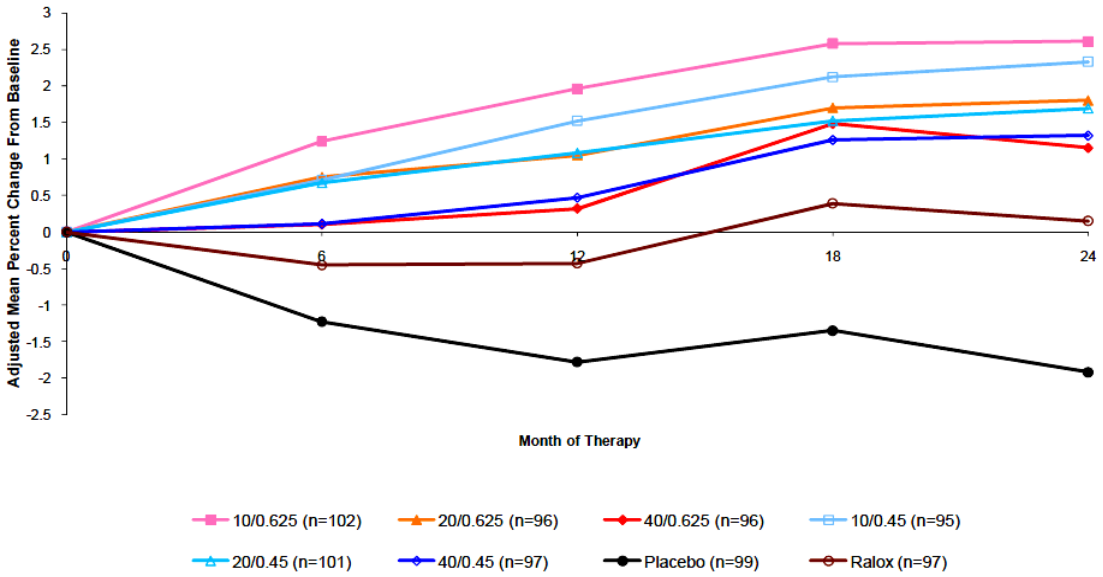


Figure 2: BMD Lumbar Spine - Adjusted Mean % Change From Baseline to Month 24: MITT Population, LOCF (Substudy II, Women ≥ 1 Year and ≤ 5 Years From Last Menstrual Period)



The responder analysis was in line with these findings; in both substudies, consistent with the primary analysis, responder rates tended to be higher with higher doses of conjugated oestrogens and lower doses of BZA. Thus, in general higher doses of CEs induced larger increases in BMD, while increases in the BZA dosage attenuated the effects of CEs.

At total hip women > 5 years (OSS I)and women ≤ 5 years (OSS II) post-menopausal treated with BZA/CE had significant increases in total hip BMD from baseline to month 24 compared to a decrease in BMD in the placebo group. Increases were numerically larger for all BZA/CE groups than for raloxifene in OSS I and in OSS II were significant for all BZA/CE groups except 20 mg / 0.625 mg and 40 mg / 0.45 mg.

Results from the EE and Completer analyses of BMD were consistent with results from the primary analysis.

Serum markers of bone metabolism were determined for subjects participating in OSS II. At all time-points and for all BZA/CE doses the median percent changes from baseline in serum concentrations of C-telopeptide and osteocalcin were significantly greater than for placebo, indicating a decrease in bone turnover.

The efficacy analyses of height used data from the EE populations pooled from both substudies. Data analysed for month 12 and 24 showed little effect on change in height with BZA/CE or raloxifene.

Other endpoints

Efficacy on hot flushes (VMS) was evaluated in a subpopulation of 216 postmenopausal women who were experiencing a minimum of 7 moderate to severe hot flushes per day or 50 or more per week at baseline. All dose of BZA/CE except BZA/CE 40 mg / 0.625 mg induced a greater reduction in the number of moderate to severe hot flushes than placebo at week 4 and week 12.

In the vulvar-vaginal atrophy (VVA) subpopulation as with effects on BMD the lowest doses of BZA tested, 10 mg, together with higher doses of CE were most effective as regards measures of vaginal atrophy. The applied dose of BZA/CE 20 mg / 0.45 mg was not significantly more effective than placebo in increasing the mean proportion of superficial cells from baseline. It is also noted that the differences between BZA 20 mg / CE

0.45 mg and BZA 20 mg / CE 0.625 mg with respect to mean change from baseline in proportion of superficial cells and parabasal cells were numerically small. The clinical relevance seems doubtful. It was not tested whether the difference between the two dose groups was statistically significant. This issue is further discussed with regard to the pivotal study regarding VVA (study 306 below).

As regards quality of sleep, fixed combination with BZA 10 mg or 20 mg and 0.625 mg CE were most effective. As regards sexual activity there were no significant differences between groups while for dyspareunia there was a trend for a decrease in the percent of women with dyspareunia with BZA/CE combinations containing 10 mg or 20 mg BZA versus an increase with raloxifene or placebo. Analysis of the Menopause-Specific Quality of Life (MENQOL) questionnaire showed some improvements compared to placebo again especially with doses of 10 mg BZA. There were no significant differences in the incidence of breast pain between groups. The percentages of women with cumulative amenorrhea were comparable between groups including placebo with the exception of BZA/CE 10 mg / 0.625 mg were percentages were lower.

In conclusion while in the analysis of the primary endpoint of endometrial hyperplasia the lowest dose of BZA, 10 mg, was not sufficiently effective, the most efficacious dose as regards osteoporosis is the lowest dose of 10 mg with effects attenuating with increasing the dose of BZA. Importantly study 303 was classified as GCP non-compliant and should not be taken into account for the assessment of efficacy of BZA / CE.

Summary of main study 303

The following table summarises the efficacy results from study 303 supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment.

Table 3.2.25: Summary of efficacy for trial 303

Title: A DOUBLE-BLIND, RANDOMISED, PLACEBO- AND ACTIVE¬CONTROLLED SAFETY AND EFFICACY STUDY OF BAZEDOXIFENE/CONJUGATED OESTROGENS COMBINATIONS IN POSTMENOPAUSAL WOMEN		
Study identifier	Protocol 3115A1-303-US/EU/BR, CSR-64104	
Design	Multicentre, double-blind, randomised, outpatient, 8-parallel-group, placebo- and active-controlled dose-ranging study; including two substudies (Substudy I in women >5 years postmenopausal; substudy II in women >1 year and ≤5 years postmenopausal)	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	April 2002 – January 2006 not applicable not applicable
Hypothesis	Other: Non comparative, specific requirements regarding confidence intervals	
Treatments groups	BZA 10 mg/CE 0.625 mg	number randomised not specified, number dosed 430
	BZA 20 mg/CE 0.625 mg	number randomised not specified, number dosed 414

	BZA 40 mg/CE 0.625 mg		number randomised not specified, number dosed 417
	BZA 10 mg/CE 0.45 mg		number randomised not specified, number dosed 430
	BZA 20 mg/CE 0.45 mg		number randomised not specified, number dosed 433
	BZA 40 mg/CE 0.45 mg		number randomised not specified, number dosed 423
	Raloxifene 60 mg		number randomised not specified, number dosed 423
	Placebo		number randomised not specified, number dosed 427
Endpoints and definitions	Primary endpoint	incidence of endometrial hyperplasia	to demonstrate an acceptable rate of hyperplasia after 1 year of treatment
	Secondary endpoint	mean percent change from baseline at month 24 in BMD of anteroposteri or lumbar spine	to evaluate efficacy of BZA/CE in preventing osteoporosis after 2 years of therapy in two osteoporosis substudies with women either ≤ or >5 years postmenopausal
	Secondary endpoint	mean percent change from baseline at month 6, 12 and 18 in BMD of anteroposteri or lumbar spine	to evaluate efficacy of BZA/CE in preventing osteoporosis after 2 years of therapy in two osteoporosis substudies with women either ≤ or >5 years postmenopausal
	Other	mean percent change from baseline at month 6, 12, 18, and 24 in BMD of hip	to evaluate efficacy of BZA/CE in preventing osteoporosis after 2 years of therapy in two osteoporosis substudies with women either ≤ or >5 years postmenopausal
	Other	mean percent change from baseline at month 12 and 24 in BMD of distal radius	to evaluate efficacy of BZA/CE in preventing osteoporosis after 2 years of therapy in two osteoporosis substudies with women either ≤ or >5 years postmenopausal

	Other	serum markers bone metabolism	to evaluate efficacy of BZA/CE in preventing osteoporosis after 2 years of therapy in two osteoporosis substudies with women either ≤ or >5 years postmenopausal
	Other	Height	to evaluate efficacy of BZA/CE in preventing osteoporosis after 2 years of therapy in two osteoporosis substudies with women either ≤ or >5 years postmenopausal
	Other	vaginal atrophy	to evaluate change from baseline in vaginal epithelium
	Other	Diary parameters of menopausal symptoms (hot flushes, sexual activity, dyspareunia, sleep) and side effects of hormone treatment (breast pain, bleeding, spotting)	to evaluate change from baseline per each 28 day period on treatment

Database lock	not identified in study report, see LoQ			
Main Results and Analysis				
Analysis description	Primary Analysis: Endometrial Hyperplasia			
Analysis population and time point description	Efficacy evaluable (EE) population month 12 (taken at least 1 dose, endometrial biopsy at screening and within 30 days before or after time point of interest or diagnosed with hyperplasia at any time prior to time point, no major protocol violations)			
Descriptive statistics and estimate variability	Treatment group	BZA/CE 10 mg / 0.45 mg	BZA/CE 10 mg / 0.625 mg	BZA/CE 20 mg / 0.45 mg
	Number of subjects	320	340	335
	Incidence of Hyperplasia (%)	3 (0.94)	13 (3.82)	0 (0)
	CI	(0.26-2.41)	(2.28-6.01)	(0.00-1.01)
	Treatment group	BZA/CE 20 mg / 0.625 mg	BZA/CE 40 mg / 0.45 mg	BZA/CE 40 mg / 0.625 mg
	Number of subjects	314	309	311

	Incidence of Hyperplasia (%)	1 (0.32)	0 (0)	0 (0)
	CI	(0.02-1.50)	(0.00-1.19)	(0.00-0.96)
	Treatment group	Raloxifene 60 mg	Placebo	
	Number of subjects	298	312	
	Incidence of Hyperplasia (%)	0 (0)	0 (0)	
	CI	(0.00-1.00)	(0.00-0.96)	
Analysis description	Main Secondary Analysis: % Change in BMD from Baseline at Lumbar Spine, Substudy I (Women >5 Years Postmenopausal)			
Analysis population and time point description				
Descriptive statistics and estimate variability	Treatment group	BZA/CE 10 mg / 0.45 mg	BZA/CE 10 mg / 0.625 mg	BZA/CE 20 mg / 0.45 mg
	Number of subjects	167	166	160
	Mean % change from baseline (SE)	2.42 (0.29)	2.38 (0.29	1.57 (0.29)
	p-value vs raloxifene	<0.001	<0.001	0.040
	p-value vs placebo	<0.001	<0.001	<0.001
	Treatment group	BZA/CE 20 mg / 0.625 mg	BZA/CE 40 mg / 0.45 mg	BZA/CE 40 mg / 0.625 mg
	Number of subjects	159	159	161
	Mean % change from baseline (SE)	1.96 (0.30)	0.78 (0.29)	1.10 (0.29)
	p-value vs raloxifene	0.002	0.900	0.357

	p-value vs placebo	<0.001	<0.001	<0.001
	Treatment group	Raloxifene 60 mg	Placebo	
	Number of subjects	164	159	
	Mean % change from baseline (SE)	0.73 (0.29)	-1.51 (0.29)	
	p-value vs raloxifene	N/A	N/A	
	p-value vs placebo	N/A	N/A	
Analysis description	Main Secondary Analysis: % Change in BMD from Baseline at Lumbar Spine, Substudy II (Women >1 Year and ≤5 Years Postmenopausal)			
Analysis population and time point description				
Descriptive statistics and estimate variability	Treatment group	BZA/CE 10 mg / 0.45 mg	BZA/CE 10 mg / 0.625 mg	BZA/CE 20 mg / 0.45 mg
	Number of subjects	95	102	101
	Mean % change from baseline (SE)	2.33 (0.36)	2.61 (0.35)	1.69 (0.35)
	p-value vs raloxifene	<0.001	<0.001	0.001
	p-value vs placebo	<0.001	<0.001	<0.001
	Treatment group	BZA/CE 20 mg / 0.625 mg	BZA/CE 40 mg / 0.45 mg	BZA/CE 40 mg / 0.625 mg
	Number of subjects	96	97	96
	Mean % change from baseline (SE)	1.80 (0.36)	1.32 (0.35)	1.15 (0.36)
	p-value vs raloxifene	0.001	0.018	0.046
	p-value vs placebo	<0.001	<0.001	<0.001
	Treatment group	Raloxifene 60 mg	Placebo	
	Number of subjects	97	99	

	Mean % change from baseline (SE)	0.15 (0.35)	-1.92 (0.35)	
	p-value vs raloxifene	N/A	N/A	
	p-value vs placebo	N/A	N/A	

Study 4000

This was an ancillary study that examined the mammograms taken at baseline and at month 24 from a subset of subjects who completed study 303, the primary study, and who had received BZA 20 mg / CE 0.45 mg, BZA 20 mg / CE 0.625 mg, RAL, or placebo in this study. A single radiologist performed the quantifications of breast density in pairs. The radiologist was blinded to the time sequence (baseline versus month 24), treatment assignment, and subject information.

Breast density was determined by using software developed by Byng et al. The digitized mammogram was displayed on a workstation monitor. The skin and pectoral muscle lines were first drawn to define the total breast area. Then a histogram computed the density (in pixels) of the outlined breast. To obtain the percentage of breast occupied by breast tissue, the following formula was used:

$$\%\ Density = \frac{Number\ of\ pixels\ corresponding\ to\ breast\ tissue}{Number\ of\ pixels\ representing\ the\ total\ breast\ area} \times 100$$

Results

The study population consisted of 132, 111, 129, and 135 subjects in the BZA 20 mg / CE 0.45 mg, BZA 20 mg / CE 0.625 mg, RAL 60 mg and placebo groups, respectively. A total of 22 subject´s data were excluded from the breast density analysis because of protocol deviations (mammogram not technically acceptable for reading or missing mammogram at baseline or at month 24). The main results are summarised in the following table:

Table 20: Summary of breast density measurements at baseline and month 24

Treatment Group	BZA 20 mg/ CE 0.45 mg (N=129)	BZA 20 mg/ CE 0.625 mg (N=105)	Raloxifene 60 mg (N=125)	Placebo (N=126)
Baseline				
N	129	105	125	126
Mean (SD)	26.47 (20.63)	25.29 (20.22)	27.18 (21.72)	26.10 (19.44)
Median	21.20	18.00	23.40	22.90
25%, 75% Quartiles	9.80, 37.20	9.00, 38.50	7.00, 42.80	10.70, 36.80
Min, Max	1.70, 86.80	1.10, 89.00	1.40, 83.00	0.60, 86.90
Month 24				
N	129	105	125	126
Mean (SD)	26.08 (20.22)	25.24 (20.16)	26.95 (21.47)	25.69 (19.57)
Median	21.60	18.30	22.90	22.45
25%, 75% Quartiles	9.10, 36.80	8.50, 38.50	7.30, 42.80	10.20, 36.50
Min, Max	1.10, 86.10	1.50, 91.80	1.60, 82.90	0.60, 88.50
% Change from Baseline				
N	129	105	125	126
Mean (SD)	-0.39 (1.75)	-0.05 (1.68)	-0.23 (1.76)	-0.42 (1.72)
95% CI for Mean	(-0.69, -0.08)	(-0.38, 0.27)	(-0.54, 0.08)	(-0.72, -0.11)
Median	-0.30	-0.10	-0.30	-0.35
95% CI for Median	(-0.60, 0.10)	(-0.40, 0.30)	(-0.50, 0.10)	(-0.70, -0.10)
25%, 75% Quartiles	-1.50, 0.70	-0.80, 1.00	-1.00, 0.90	-1.40, 0.50
Min, Max	-7.80, 3.40	-7.10, 4.70	-7.50, 4.60	-5.70, 6.30

Abbreviations: BZA=bazedoxifene; CE=conjugated estrogens; CI=confidence interval; Max=maximum; Min=minimum; SD=standard deviation.
Source: /CLINICAL R&D/CLINICAL PROGRAMMING SAS REPORTS/3115A1/4000/4000_REPORTS_2010/3115-4000 BRST4_ALL – 26AUG10 09:28

The conclusion in the study report that this study has shown that, in healthy postmenopausal women with a mean age of 56 years, BZA/CE treatment did not affect age-related changes in mammographic breast density was not fully agreed by the CHMP. The decrease in breast density seemed numerically less pronounced with BZA 20 mg / CE 0.625 mg, compared to BZA 20 mg / CE 0.45 mg and placebo. Thus, an unfavourable effect of BZA/CE, in particular regarding BZA 20 mg / CE 0.625 mg, on breast density cannot be excluded, even taking into account that this was a GCP non-compliant study.

Study 305

Study 305 was a Phase 3, multicentre, double-blind, randomised, 3-parallel-group placebo-controlled study designed to evaluate the safety and efficacy of BZA 20 mg / CE 0.45 mg and BZA 20 mg / CE 0.625 mg for the treatment of VMS (oestrogen deficiency symptom indication), conducted in the US.

Methods

Study Participants

In brief, the study enrolled generally healthy women with an intact uterus, aged 40 to 65 years, with at least 12 months of spontaneous amenorrhea or 6 months of spontaneous amenorrhea, and who had a serum follicle-stimulating hormone level > 40 mIU/mL. In addition, the women had to be seeking treatment for hot flushes and report at screening a minimum of 7 moderate to severe hot flushes per day or 50 per week.

Treatments

Subjects were randomly assigned to receive BZA 20 mg / CE 0.45 mg, BZA 20 mg / CE 0.625 mg or placebo for a treatment duration of 12 weeks. No control group treated with CE combined with a progestin such as MPA was included.

Objectives

The primary objective was to assess the safety and efficacy of 2 doses of BZA/CE compared with placebo for the treatment of moderate to severe VMS associated with menopause. The secondary objectives were to assess the effect of BZA/CE on breast pain and to assess the results from the Medical Outcomes Study (MOS) sleep scale.

Outcomes/endpoints

The primary efficacy variables were the change from baseline at week 4 and week 12 in the average daily number of moderate and severe hot flushes and the severity of hot flushes. Secondary endpoints included further parameters related to VMS, self-administered questionnaires MOS sleep scale, MENQOL, and MS-TSQ as well as the presence of breast pain. The primary analysis population was the MITT population, defined as subjects who were randomly assigned test article, had taken at least 1 dose of test article, had recorded at least 5 days data at the baseline week and had at least 5 days data for at least 1 on-therapy week, with LOCF approach.

Sample size

A sample size of 104 subjects per group for the BZA/CE treatment groups and 52 subjects for the control group was to provide greater than 90% power to detect a difference of 3 hot flushes between a BZA/CE treatment group and placebo with a 0.05 two-sided significance level (standard deviation [SD] = 4.8). A total of 130 subjects in each BZA/CE treatment group and 65 subjects in each control group were to be enrolled to have allowed for up to 20% of the subjects being excluded from the analysis.

Randomisation

Subjects were allocated to treatment groups through the use of a CORE system that was accessible 24 hours a day.

Blinding (masking)

The study used a double-blind design. Test article were be supplied as 2 doses of bazedoxifene/CE capsules and matching placebo capsules.

Statistical methods

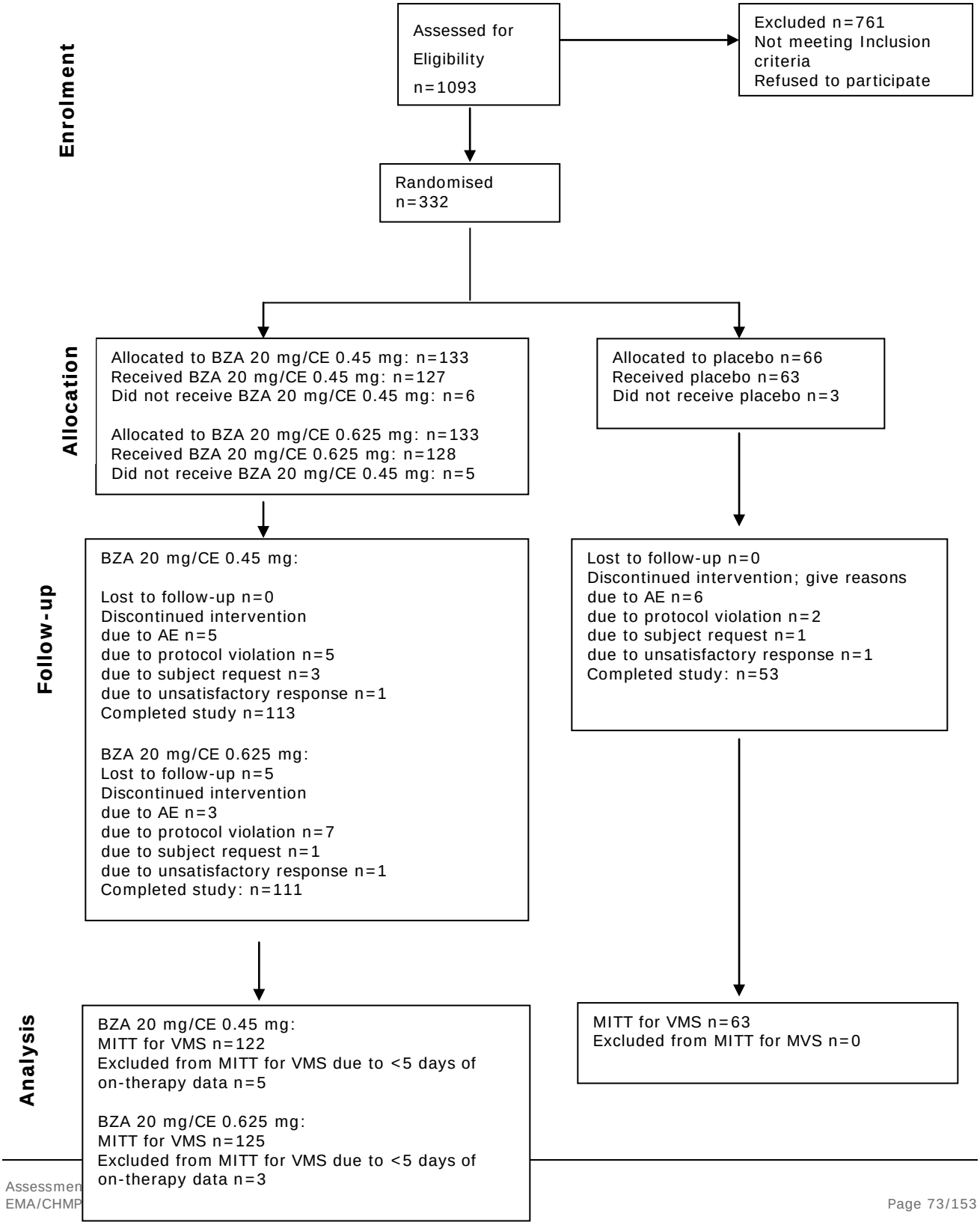
Three populations were defined for the efficacy endpoints:

(1) Modified-intent-to-treat (MITT) population for analysis of hot flushes (the MITT population with LOCF approach was considered to be the primary analysis population at week 4 and week 12), (2) Per-Protocol (PP) population (3) Safety population for analysis of hot flushes included all subjects who were randomly assigned and took at least 1 dose of test article.

The reduction of the average daily number and severity of hot flushes was compared between BZA/CE dose groups and placebo using an analysis of covariance (ANCOVA) with treatment and study site as factors and baseline value as a covariate plus treatment by study site interaction. Pairwise comparisons between the BZA/CE groups and placebo were made using a t-test based on the least square means and pooled error terms obtained from the ANCOVA.

Results

Participant flow



Protocol violations which led to study discontinuation included criteria for hot flushes not met (n=5), endometrial thickness >4 mm or not measurable (n=4), non-compliance with medication or diary cards (n=2), subject meeting exclusion criterion 4c with respect to TVUS (n=1), subject meeting exclusion criterion 4c and not meeting inclusion criterion 4 with respect to endometrial biopsy (n=1), and subject randomised in error (n=1).

Conduct of the study

The study protocol is dated 19 July 2005. There were no protocol amendments.

Baseline data

The 3 study groups were comparable regarding baseline characteristics.

Outcomes and estimation

With regard to all primary endpoints, statistically significant differences favouring BZA 20 mg / CE 0.45 mg and BZA 20 mg / CE 0.625 mg vs. placebo were found in the analysis using the LOCF approach which was prespecified in the protocol. The results are displayed in the following tables.

Table 21: Mean change from baseline in the average daily number of moderate and severe hot flushes at week 4 and week 12 (LOCF, OC)

			--Adjusted Change--		
Treatment	Time Slot	No. of Pairs	Mean	SE	p-Value vs Placebo
LOCF					
BZA 20 mg/CE 0.45 mg	Week 4	122	-5.90	0.42	< 0.001
	Week 12	122	-7.63	0.36	< 0.001
BZA 20 mg/CE 0.625 mg	Week 4	125	-6.60	0.41	< 0.001
	Week 12	125	-8.05	0.35	< 0.001
Placebo	Week 4	63	-2.84	0.56	--
	Week 12	63	-4.92	0.48	--
OC					
BZA 20 mg/CE 0.45 mg	Week 4	119	-5.91	0.43	< 0.001
	Week 12	109	-7.96	0.39	< 0.001
BZA 20 mg/CE 0.625 mg	Week 4	123	-6.53	0.41	< 0.001
	Week 12	109	-8.16	0.38	< 0.001
Placebo	Week 4	61	-2.79	0.57	--
	Week 12	53	-5.22	0.54	--

ANCOVA: change = treat + study site + baseline.
Abbreviations: BZA = bazedoxifene; CE = conjugated estrogens; LOCF = last observation carried forward; MITT = modified intent-to-treat; No. = number; OC = observed case; SE = standard error.
Source: CLINICAL R&D/CLINICAL BIOSTATISTICS SAS REPORTS/3115A1/305/FINAL_21MAR2007_htm/3115-305: IN_HF3_LMB and IN_HF3_OMB, 22MAR07 13:15.

Table 22: Mean change from baseline in the average daily severity score hot flushes at week 4 and week 12 (LOCF, OC)

Treatment	Time Slot	No of Pairs	–Adjusted Change– Mean	SE	p-Value vs Placebo
LOCF					
BZA 20 mg/CE 0.45 mg	Week 4	122	-0.58	0.07	< 0.001
	Week 12	122	-0.87	0.08	< 0.001
BZA 20 mg/CE 0.625 mg	Week 4	125	-0.64	0.06	< 0.001
	Week 12	125	-1.21	0.08	< 0.001
Placebo	Week 4	63	-0.09	0.09	–
	Week 12	63	-0.26	0.11	–
OC					
BZA 20 mg/CE 0.45 mg	Week 4	119	-0.58	0.07	< 0.001
	Week 12	109	-0.92	0.09	< 0.001
BZA 20 mg/CE 0.625 mg	Week 4	123	-0.64	0.07	< 0.001
	Week 12	109	-1.23	0.08	< 0.001
Placebo	Week 4	61	-0.11	0.09	–
	Week 12	53	-0.34	0.12	–

ANCOVA: change = treat + study site + baseline.
Abbreviations: BZA = bazedoxifene; CE = conjugated estrogens; LOCF = last observation carried forward; MITT = modified intent-to-treat; No = number; OC = observed case; SE = standard error.
Source: CLINICAL R&D/CLINICAL BIOSTATISTICS SAS REPORTS/3115A1/305/FINAL_21MAR2007_htm/3115-305: IN_HF1_LMB and IN_HF1_OMB, 22MAR07 13:15.

With regard to missing values, sensitivity analyses were submitted raising no concerns as regards the validity of the results. However, the difference between BZA 20 mg / CE 0.625 mg and BZA 20 mg / CE0.45 mg at week 12 with regard to number (-0.42) as well as severity of hot flushes (-0.34) is small. Statistical significance was not tested.

With regard to all secondary endpoints related to VMS and most items of the MOS sleep scale, statistically significant differences favouring the 2 BZA/CE groups vs. placebo were observed. Regarding MENQOL, statistically significant differences vs. placebo at week 12 (MITT) were observed regarding all 5 criteria in the BZA 20 mg / CE 0.625 mg group, and regarding 2 of 5 items in the BZA 20 mg / CE 0.45 mg group. With regard to breast pain, the differences vs. placebo were not statistically significant for both BZA/CE groups.

However, the differences between BZA 20 mg / CE 0.45 mg and BZA 20 mg / CE 0.625 mg with respect to efficacy in the treatment of hot flushes are in most cases numerically small and of questionable clinical relevance.

It is also noted that no CE /progestin control group was included in this study pivotal for the efficacy in the treatment of hot flushes. According to the results of phase 2 study 203, BZA obviously decreases the efficacy of CE on VMS. A control group treated with oral CE/MPA should have been included in order to investigate in more detail to which extent the efficacy of CE in the combination BZA/CE is decreased and how the benefit risk balance of BZA/CE compares to the currently established treatment of hot flushes with an oestrogen / progestogen combination.

Summary of main study 305

The following table summarises the efficacy results from study 305 supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections and Overview).

Table 3.3.30: Summary of efficacy for trial 305

Title: A DOUBLE-BLIND, RANDOMISED, PLACEBO-CONTROLLED, EFFICACY AND SAFETY STUDY OF BAZEDOXIFENE/CONJUGATED OESTROGENS COMBINATIONS FOR TREATMENT OF VASOMOTOR SYMPTOMS ASSOCIATED WITH MENOPAUSE

Study identifier	Protocol No.: 3115A1-305-US Pfizer Study No.: B2311046		
Design	Phase 3, multicenter, double-blind, randomised, 3-parallel-group placebo-controlled study.		
	Duration of main phase: Duration of Extension phase:		27.09.2005 to 02.02.2007 (study start and end) not applicable
Hypothesis	Superiority vs. placebo		
Treatments groups	BZA 20 mg/CE 0.45		BZA 20 mg/CE 0.45, duration of treatment 12 w, randomised n=133
	BZA 20 mg/CE 0.625		BZA 20 mg/CE 0.625, duration od treatment 12 w, randomised n=133
	placebo		placebo, duration od treatment 12 w, randomised n=66
Endpoints and definitions	Co-primary:	change from baseline in the average daily number of moderate and severe hot flushes at weeks 4 and 12; change from baseline in the average daily severity score at weeks 4 and 12.	Severity score for mild hot flush= 1, for moderate hot flush=2, for severe hot flush =3 The daily severity score was calculated by multiplying the number of mild, moderate and severe hot flushes by 1, 2 and 3, respectively. These values were added and then divided by the total number of hot flushes. The average daily severity of hot flushes was calculated as: $\frac{\text{Sum of the daily severity scores}}{\text{Number of days with data}}$
	Secondary:	further endpoints related to hot flushes	responder analysis (responders defined as subjects who reached at least a 50% or a 75% decrease from baseline in the number of hot flushes for moderate and severe hot flushes and for mild, moderate, and severe hot flushes); reduction in the number of mild, moderate, and severe hot flushes; reduction in the daily composite score; time to reach a 50% decrease from baseline in the number of hot flushes for at least 3 consecutive days; examination of hot flushes by age subgroups;
		breast pain	percent of days with breast pain during each 4 week interval; proportion of subjects reporting at least one day of breast pain during each 4 week interval;
		self-administered health outcomes questionaires	MENQOL, MOS sleep scale, Subject satisfaction)
Database lock	not stated in the study report		
Results and Analysis			
Analysis description	**Primary Analysis**		

Analysis population	mITT (LOCF)			
Descriptive statistics and estimate variability	Treatment group	BZA 20 mg / CE 0.45	BZA 20 mg / CE 0.625	placebo
	Number of subject	122	125	63
	Co-primary endpoint: change from baseline in the average daily number of moderate and severe hot flushes at weeks 4	-5.90	-6.60	-2.84
	standard error	0.42	0.41	0.56
	p value vs. placebo	<0.001	<0.001	
	Co-primary endpoint: change from baseline in the average daily number of moderate and severe hot flushes at week 12	-7.63	-8.05	-4.92
	standard error	0.36	0.35	0.48
	p value vs. placebo	<0.001	<0.001	
	Co-primary endpoint: change from baseline in the average daily severity score at weeks 4	-0.58	-0.68	-0.09
	standard error	0.07	0.06	0.09
	p value vs. placebo	<0.001	<0.001	
	Co-primary endpoint: change from baseline in the average daily severity score at weeks 12	-0.87	-1.21	-0.26
	standard error	0.08	0.08	0.11
	p value vs. placebo	<0.001	<0.001	
	Secondary endpoint: Responder (75%) at week 4	39.34%	53.60%	6.35
	OR vs. placebo (95%CI)	13.36 (4.28; 41.74)	25.30 (8.08; 79.18)	
	Secondary endpoint: Responder (75%) at week 12	66.66%	72.80%	
	OR vs. placebo (95%CI)	5.23 (2.57; 10.64)	9.59 (4.60; 20.00)	

	Secondary endpoint: reduction in the daily composite score;	statistically significantly greater decreases from baseline compared to placebo beginning at week 3 and 2 for the BZA 20 mg / CE 0.45 mg group and the BZA 20 mg / CE 0.625 mg group, respectively		
	Secondary endpoint: median time to reach a 50% decrease from baseline in the number of hot flushes for at least 3 consecutive days p value vs. placebo	15 days 0.001	14 days <0.001	30 days
	percent of days with breast pain during week 9-12 (change from baseline) p value vs. placebo	-2.5 not reported	0.8 not reported	0.5
	proportion of subjects reporting at least one day of breast pain during week 9-12	10.17% 0.39	9.09% 0.55	5.36%
Notes	Responder rates (50%) at week 4 and 12 were also statistically significantly higher in the 2 BZA/CE groups, compared to placebo MENQOL, MOS sleep scale, Subject satisfaction)			

Study 306

Study 306 was a Phase 3, multicentre, double-blind, randomised, outpatient, 4-parallel-group placebo- and active-controlled study designed to assess the efficacy of BZA 20 mg / CE 0.45 mg and BZA 20 mg / CE 0.625 mg compared with placebo and BZA 20 mg for the treatment of VVA. The study was conducted in the US.

Methods

Study Participants

Generally healthy women, 40 to 65 years of age, who had an intact uterus and were postmenopausal, were enrolled. At screening, all subjects had to have a vaginal cytological smear showing ≤ 5% superficial cells, vaginal pH > 5.0; and had to self-identify on the Symptom Questionnaire at least 1 moderate to severe vulvar / vaginal symptom that was most bothersome to them (vaginal dryness, irritation / itching, or pain with intercourse).

Treatments

Subjects were randomly assigned to receive BZA 20 mg / CE 0.45 mg, BZA 20 mg / CE 0.625 mg, BZA 20 mg or placebo for the duration of a treatment of 12 weeks.

Objectives

The primary objective was to compare the efficacy and safety of 2 doses of BZA/CE (BZA 20 mg / CE 0.45 mg and BZA 20 mg / CE 0.625 mg) with those of placebo at 12 weeks for the treatment of moderate to severe vulvar/vaginal atrophy associated with menopause. The secondary objectives were to assess the efficacy and safety of 2 doses of BZA/CE compared with placebo at 4 weeks for the treatment of moderate to severe vulvar/vaginal atrophy associated with menopause; to provide descriptive vulvar/vaginal atrophy data comparing BZA/CE with BZA alone at 4 and 12 weeks; and to assess the effect of 2 doses of BZA/CE on changes at 4 and 12 weeks in each vulvar/vaginal symptom (vaginal dryness, vaginal and/or vulvar irritation/itching, and vaginal pain associated with sexual activity).

Outcomes / endpoints

The co-primary endpoints for vulvar / vaginal atrophy were the increase in superficial cells, decrease in parabasal cells, lowering of vaginal pH, and improvement in the most bothersome symptom at week 12.

Secondary efficacy endpoints included the proportion of vaginal intermediate cells by vaginal smear, and individual symptoms from the Symptom Questionnaire (i.e., dryness, itching, or pain with intercourse). A responder analysis was also conducted. Responders were defined as subjects who had 1 or more of the following at the week 12 (LOCF) evaluation: vaginal superficial cells > 5%, vaginal pH < 5, or improvement of their Most Bothersome Symptom by at least 1 category from baseline. Other secondary efficacy variables included the Arizona Sexual Experiences Scale (ASEX); the Menopause-Specific Quality of Life (MENQOL) questionnaire; and the Menopause Symptoms-Treatment Satisfaction Questionnaire (MS-TSQ).

Vaginal maturation (VM) was assessed by determination of the proportion of superficial, parabasal, and intermediate cells in samples of vaginal epithelium obtained from vaginal smears. Results were read centrally and remained blinded to the investigators and to the subjects for the duration of the study.

The Symptom Questionnaire collected information on 3 vulvar / vaginal symptoms: dryness of the vagina, itching or irritation of the vagina or vulva, and pain with intercourse. Subjects were to rate the intensity of each symptom (rated as none, mild, moderate, or severe) experienced during the past week. At screening only, the subject was to indicate the moderate or severe symptom that bothered her most. This symptom was identified as the subject's "Most Bothersome Symptom" for the remainder of the study. Diaries were used to capture intake of medication and symptoms / complaints.

Sample size

A total of 152 subjects in each BZA/CE treatment group and 76 subjects in each control group were needed to detect a 5% difference between groups in the percentage of superficial cells (assuming standard deviation [SD] of 11%), with 90% power; 190 and 95 subjects, respectively, would ensure adequate numbers of subjects for the analysis even if up to 20% of the subjects were excluded from the analysis because of missing data. Because the goal was to show statistical significance at the 0.05 level for the 4 co-primary endpoints, the sample size was increased to 215 for each BZA/CE group and 110 for each control group to ensure that at least 172 and 88, respectively, were available for inclusion in the analyses.

Randomisation

Subjects were allocated to treatment groups through the use of a CORE system that was accessible 24 hours a day.

Blinding (masking)

The study used a double-blind design. Test article was supplied as 2 doses of BZA/CE (BZA 20 mg / CE 0.45 mg and BZA 20 mg / CE 0.625 mg), BZA 20 mg, and matching placebo. Both study drug and active comparator were provided as single tablets, over-encapsulated for blinding to match placebo capsules.

Statistical methods

For all efficacy variables except for MS-TSQ, the primary efficacy population was the modified-intent-to-treat population (MITT), defined as all subjects who were randomised, took at least 1 dose of test article, had a baseline value, and had at least 1 on-therapy value for the parameter being analysed, using an LOCF approach

Results

Participant flow

The disposition of patients is displayed in the table below.

Table 23: Disposition of subjects and primary analysis populations

	BZA 20 mg/ CE 0.45 mg	BZA 20 mg / CE 0.625 mg	BZA 20 mg	Placebo	Total
Randomly assigned	225	221	110	108	664
Test article not used	6	3	0	3	12
Safety population [a]	219 (100.0)	218 (100.0)	110 (100.0)	105 (100.0)	652 (100.0)
Most bothersome symptom					
Excluded from MITT	2 (< 1)	5 (2)	5 (5)	6 (6)	18 (3)
MITT population	217 (99)	213 (98)	105 (95)	99 (94)	634 (97)
Vaginal maturation					
Excluded from MITT	9 (4)	9 (4)	10 (9)	7 (7)	35 (5)
MITT population	210 (96)	209 (96)	100 (91)	98 (93)	617 (95)
Vaginal pH					
Excluded from MITT	2 (< 1)	5 (2)	4 (4)	4 (4)	15 (2)
MITT population	217 (99)	213 (98)	106 (96)	101 (96)	637 (98)
Discontinued study	14 (6.4)	18 (8.3)	11 (10.0)	8 (7.6)	51 (7.8)
Completed study	205 (93.6)	200 (91.7)	99 (90.0)	97 (92.4)	601 (92.2)

MITT=modified intent to treat: includes subjects who took at least 1 dose of test article, had a baseline value and at least 1 on-therapy value for endpoint.

a. Safety population included all randomly assigned subjects who took at least 1 dose of test article.

Source: /CLINICAL R&D/CLINICAL PROGRAMMING SAS REPORTS/3115A1 BAZEDOXIFENE-CE/306/306_NDA_CDRs_2007/306_DOSED_QUALSITES/3115-306: MITT4_MBS (05APR07 09:57); MITT4_VMI (05APR07 09:58); MITT4_VPH (05APR07 09:58); CPP5_D (04APR07 14:37); and /CLINICAL R&D/CLINICAL PROGRAMMING SAS REPORTS/3115A1 BAZEDOXIFENE-CE/306/306_NDA_CDRs_2007/306_NODOSE_QUALSITES/3115-306 DEMO5 (05APR07 15:56).

Conduct of the study

A total of 100 subjects (15.3%) had protocol violations. Seven patients were withdrawn from the study due to protocol violations: hyperplasia in endometrial biopsy (n=1), endometrial thickness in TVUS >4 mm (n=1), vaginal maturation index exclusionary (n=1), subject receiving exclusionary co-medication (n=1), insufficient vaginal smear material at screening (n=1), and non-compliance with medication or diary cards (n=2).

Baseline data

The 3 study groups were comparable regarding demographic baseline characteristics. With respect to baseline data for primary endpoints, vaginal smears and vaginal pH were comparable in the 4 study groups. Regarding the type and severity of the MBS, the data were similar in the two BZA/CE groups, with pain with intercourse being clearly the most frequent MBS. In the BZA group and the placebo group, vaginal dryness and pain with intercourse were stated as MBS almost equally frequently.

Outcomes and estimation

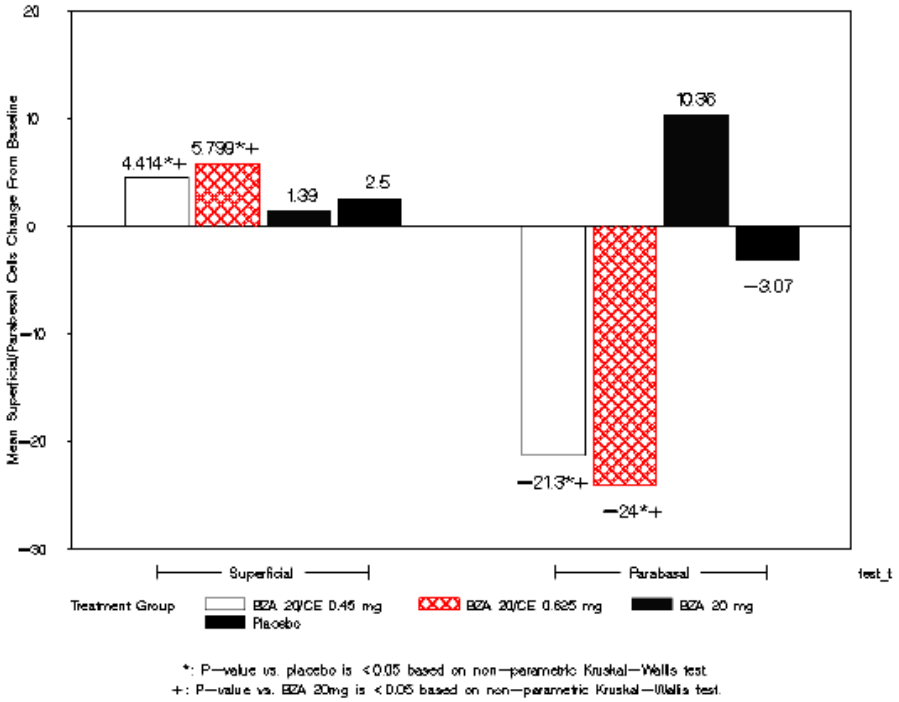
The results regarding the primary endpoints superficial and parabasal cells and vaginal pH are displayed in the tables and figure below.

Table 24: Median Change From Baseline in Percentage of Vaginal Superficial and Parabasal Cells at Week 12 - Nonparametric Analysis, MITT Population (LOCF and OC) (study report, p. 45):

Treatment	No. of Pairs	Change From Baseline Min	Q1	Median	Q3	Max	Overall p-Value	p-Value vs. Placebo	p-Value vs. BZA 20 mg	p-Value Within Group
LOCF										
Superficial Cells										
BZA 20 mg/CE 0.45 mg	210	-31.0	0.0	0.0	7.0	73.0	< 0.001	0.005	< 0.001	< 0.001
BZA 20 mg/CE 0.625 mg	209	-28.0	0.0	1.0	7.0	90.0		0.002	< 0.001	< 0.001
BZA 20 mg	100	-6.0	0.0	0.0	1.0	41.0		0.318		0.065
Placebo	98	-5.0	0.0	0.0	3.0	34.0				< 0.001
Parabasal Cells										
BZA 20 mg/CE 0.45 mg	210	-100.0	-50.0	-9.0	0.0	100.0	< 0.001	0.001	< 0.001	< 0.001
BZA 20 mg/CE 0.625 mg	209	-100.0	-57.0	-8.0	0.0	100.0		< 0.001	< 0.001	< 0.001
BZA 20 mg	100	-100.0	0.0	3.0	29.0	100.0		< 0.001		0.002
Placebo	98	-89.0	-16.0	0.0	2.0	98.0				0.160
Observed cases										
Superficial Cells										
BZA 20 mg/CE 0.45 mg	174	-31.0	0.0	1.0	9.0	73.0	< 0.001	0.002	< 0.001	< 0.001
BZA 20 mg/CE 0.625 mg	163	-6.0	0.0	1.0	7.0	90.0		0.008	< 0.001	< 0.001
BZA 20 mg	81	-6.0	0.0	0.0	1.0	19.0		0.548		0.035
Placebo	80	-5.0	0.0	0.0	3.0	34.0				< 0.001
Parabasal Cells										
BZA 20 mg/CE 0.45 mg	174	-100.0	-49.0	-9.5	0.0	96.0	< 0.001	0.001	< 0.001	< 0.001
BZA 20 mg /CE 0.625 mg	163	-100.0	-59.0	-10.0	0.0	100.0		< 0.001	< 0.001	< 0.001
BZA 20	81	-100.0	-5.0	0.0	28.0	100.0		0.007		0.029
Placebo	80	-89.0	-16.0	0.0	1.5	98.0				0.244

Abbreviations: Min = minimum; Max = maximum; Q1 = first quartile; Q3 = third quartile
Non-parametric 1-way Kruskal-Wallis test for between group comparisons and signed-rank test for within group comparisons.
Source: CLINICAL R&D/CLINICAL BIOSTATISTICS SAS REPORTS/3115A1 BAZEDOXIFENE-CE/306/FINAL_APR2007/3115-306: ALT_SUP (30 APR07, 15:22); ALT_PAR (30 APR07, 15:22); ALT_SUP_OM (30 APR07, 15:22); ALT_PAR_OM (30 APR07, 15:22)

Figure 3: Mean change from baseline in percentage of vaginal superficial and parabasal cells at week 12 (MITT, LOCF)



Source: CLINICAL R&D/CLINICAL BIOSTATISTICS SAS REPORTS/ 3115A1 BAZEDOXIFENE-CE/306/FINAL__APR2007_HTM/3115-306 IN_SUP_PAR_BAR (01JUN2007).

Table 25: Adjusted Mean Change From Baseline in Vaginal pH at Week 12 - ANCOVA Analysis, MITT Population (LOCF and OC)

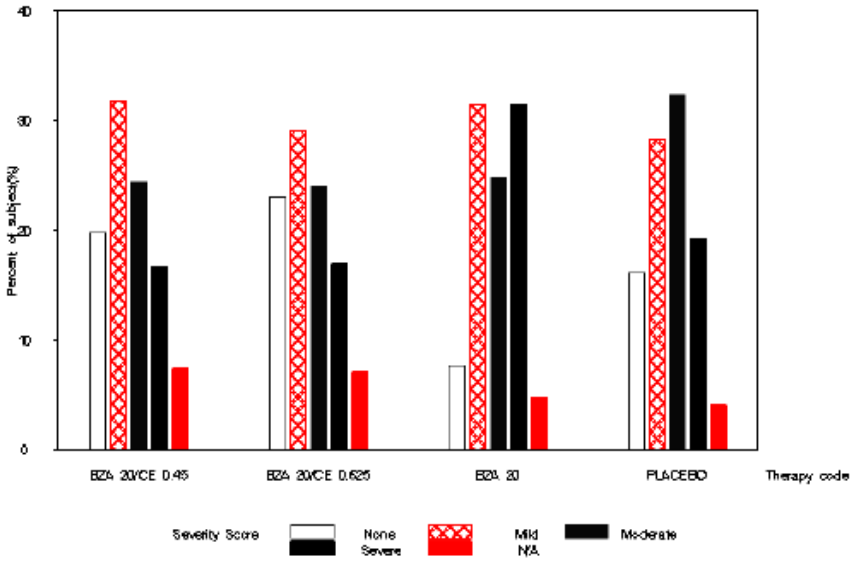
Treatment	No. of Pairs	Adjusted Change Mean	SE	p-Value Within Group	p-Value vs Placebo	p-Value vs BZA 20 mg
LOCF						
BZA 20 mg/CE 0.45 mg	217	-0.25	0.06	<0.001	0.116	<0.001
BZA 20 mg/CE 0.625 mg	213	-0.50	0.06	<0.001	<0.001	<0.001
BZA 20 mg	106	0.07	0.08	0.389	0.146	
Placebo	101	-0.09	0.08	0.253		
Observed cases						
BZA 20 mg/CE 0.45 mg	201	-0.24	0.06	<0.001	0.136	<0.001
BZA 20 mg/CE 0.625 mg	196	-0.46	0.06	<0.001	<0.001	<0.001
BZA 20 mg	94	0.14	0.08	0.109	0.058	
Placebo	92	-0.09	0.09	0.303		

ANCOVA = analysis of covariance; LOCF = last observation carried forward; MITT = modified intent-to-treat; OC = observed cases.
ANCOVA: change = treatment + study site + baseline
Source: CLINICAL R&D/CLINICAL BIOSTATISTICS SAS REPORTS/ 3115A1 BAZEDOXIFENE-CE/306/FINAL_APR2007_HTM/3115-306: IN_PH_LMB (18APR07 11:06); IN_PH_OMB (18APR07 11:06).

Table: 26: Analysis of Most Bothersome Symptom at Week 12, MITT Population (LOCF)

Treatment	Severity Category	N	(%)	p-Value[a] Overall	p-Value[a] vs Placebo	p-Value[a] vs BZA 20 mg
LOCF						
BZA 20 mg/CE 0.45 mg	None	43	19.82	0.002	0.090	0.002
	Mild	69	31.80			
	Moderate	53	24.42			
	Severe	36	16.59			
	N/A[b]	16	7.37			
BZA 20 mg/CE 0.625 mg	None	49	23.00		0.048	< 0.001
	Mild	62	29.11			
	Moderate	51	23.94			
	Severe	36	16.90			
	N/A	15	7.04			
BZA 20 mg	None	8	7.62		0.178	
	Mild	33	31.43			
	Moderate	26	24.76			
	Severe	33	31.43			
	N/A	5	4.76			
Placebo	None	16	16.16			
	Mild	28	28.28			
	Moderate	32	32.32			
	Severe	19	19.19			
	N/A	4	4.04			

Figure 4: Percentage of subjects with most bothersome symptom – data by severity at week 12



P-value of overall comparison is 0.002.
P-value of comparing BZA 20/CE 0.625 vs. Placebo is 0.048. P-value of comparing BZA 20/CE 0.45 vs. Placebo is 0.09

Source: CLINICAL R&D/CLINICAL BIOSTATISTICS SAS REPORTS/3115A1 BAZEDOXIFENE-CE/306/FINAL_APR2007_HTM/MBS_BAR.bmp.

With regard to vaginal maturation statistically significant differences favouring both BZA/CE groups vs. placebo were found in the nonparametric analysis in the MITT population using the LOCF approach which had been prespecified as the primary analysis in the study protocol in case data were not normally distributed. With regard to vaginal pH, the difference vs. placebo was statistically significant only in the BZA 20 mg / CE 0.625 mg group, not in the BZA 20 mg / CE 0.45 mg group.

For BZA, differences vs. placebo were not statistically significant regarding superficial cells and vaginal pH while regarding parabasal cells even a significant increase vs. baseline was observed.

With regard to MBS, a statistically significant difference favouring BZA 20 mg / CE 0.625 mg vs. placebo was found in the parametric analysis in the MITT population using the LOCF approach which had been prespecified as the primary analysis in the study protocol. Regarding the lower dose strength BZA 20 mg / CE 0.625 mg and BZA 20 mg monotherapy, the difference vs. placebo was not statistically significant.

With regard to the issue of missing values, additional sensitivity analyses using different methods for replacing missing values were performed supporting the results reported in the study report.

No comparison of BZA/CE vs. CE/progestin is possible based on this study as no CE/progestin control group was included. It seems that BZA negatively affects the efficacy of CE on VVA. It is assumed that the efficacy of BZA/CE in the treatment of VVA is lower than the efficacy if CE/progestin. A control group treated with either a local oestrogen or with oral CE/MPA should have been included in order to investigate the decrease of the efficacy of CE when it is administered in combination with BZA in the treatment of vulvovaginal atrophy in more detail.

A formal comparison of BZA 20 mg / CE 0.45 mg vs. BZA 20 mg / CE 0.65 mg regarding primary endpoints was not planned. The numerical differences between BZA 20 mg / CE 0.625 mg and BZA 20 mg / CE0.45 mg with regard to change from baseline at week 12 regarding superficial cells and parabasal cells as well as with regard

to MBS at week 12 are small. Statistical significance was not tested. Thus, the higher dose strength applied for appears to be insufficiently justified for the treatment of vulvovaginal atrophy as already discussed above with respect to the treatment of hot flushes.

Regarding secondary endpoints, statistically significant differences vs. placebo were observed with regard to responder rates at week 12 and mean change from baseline in the proportion of vaginal intermediate cells at week 12 and proportion of patients with no dryness of the vagina at week 12. Regarding itching / irritation of the vagina and pain wit intercourse no statistically significant differences were observed.

Statistically significant differences favouring BZA/CE were observed with regard to some but not all items of ASEX Scores, MENQOL, and MS-TSQ. In particular with regard to itching / dryness of the vagina and dyspareunia at week 12 the results were numerically somewhat inferior to placebo in the BZA 20 mg / CE 0.45 mg group and similar to placebo in the BZA 20 mg / CE 0.625 mg group.

As was already observed with respect to primary endpoints, the differences between BZA 20 mg / CE 0.45 mg and BZA 20 mg / CE 0.625 mg are numerically small; statistical significance was not tested.

Summary of main study 306

The following table summarises the efficacy results from the main study 306 supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections and Overview).

Table 3.2.39: Summary of efficacy for trial 306

Title: A DOUBLE-BLIND, RANDOMISED, PLACEBO- AND ACTIVE-CONTROLLED EFFICACY AND SAFETY STUDY OF BAZEDOXIFENE/CONJUGATED OESTROGENS COMBINATIONS FOR TREATMENT OF MODERATE TO SEVERE VULVAR/VAGINAL ATROPHY (VVA) IN POSTMENOPAUSAL WOMEN		
Study identifier	Protocol No.: 3115A1-306-WW Pfizer Study No.: B2311047)	
Design	Phase 3, multicenter, double-blind, randomised, outpatient, 4-parallel-group placebo- and active-controlled study	
	Duration of main phase: Duration of Extension phase:	Study start: 11 Oct 2005, study end 12 Mar 2007 not applicable
Hypothesis	Superiority vs. placebo	
Treatments groups	BZA 20 mg/CE 0.45 mg	BZA 20 mg/CE 0.45, duration of treatment 12 w, randomised n=225
	BZA 20 mg/CE 0.625 mg	BZA 20 mg/CE 0.625, duration of treatment 12 w, randomised n=221
	BZA 20 mg	BZA 20 mg, duration of treatment 12 w, randomised n=110
	placebo	placebo, duration of treatment 12 w, randomised n=108

Endpoints and definitions	Co-Primary	Mean change from baseline in percentage of vaginal superficial and parabasal cells and vaginal pH at week 12, improvement in the most bothersome symptom at week 12	
	Secondary	further endpoints related to vaginal smears and symptoms of VVA, self-administered health outcomes questionaires	proportion of vaginal intermediate cells; responder analysis, with responders defined as subjects who had 1 or more of the following at the week 12 (LOCF) evaluation: vaginal superficial cells > 5%, vaginal pH < 5, or improvement of their Most Bothersome Symptom by at least 1 category from baseline; individual symptoms from the Symptom Questionnaire (i.e., dryness, itching, or pain with intercourse); ASEX MENQOL MS-TSQ
Database lock	not stated in the study report		

Results and Analysis

Analysis description	**Primary Analysis**				
Analysis population	MITT, LOCF				
Descriptive statistics and estimate variability	Treatment group	BZA 20 mg / CE 0.45	BZA 20 mg / CE 0.625 mg	BZA 20 mg	placebo
	Primary endpoint: Median change from baseline in percentage of vaginal superficial cells at week 12				
	number of pairs	210	209	100	98
	point estimate	0.0	1.0	0.0	0.0
	p value vs. placebo	0.005	0.002		
	Primary endpoint: Median change from baseline in percentage of vaginal parabasal cells at week 12 (mean)				
	number of pairs	210	209	100	98
	point estimate	-9.0	-8.0	3.0	0.0
	p value vs. placebo	0.001	<0.001		

	Primary endpoint: Mean change from baseline in vaginal pH at week 12 number of pairs point estimate p value vs. placebo	 217 -0.25 0.116	 213 -0.50 <0.001	 106 0.07	 101 -0.09
	Primary endpoint: improvement in the most bothersome symptom at week 12 number of pairs	not statistically significantly superior vs. placebo (p=0.090)	statistically significantly superior vs. placebo (p=0.048)		
	Secondary endpoint: Responder rate at week 12 (%) n point estimate p value vs. placebo	 217 78.34 0.027	 213 81.22 0.005	 106 57.55 0.201	 101 66.34
	Secondary endpoint: Vulvar/vaginal symptom questionnaire Dryness of vagina itching/irritation of vagina pain with intercorse	 statistically significant greater improvement vs. placebo no statistically significant difference vs. placebo no statistically significant difference vs. placebo			
	Self-administered questionaires ASEX MENQOL MS-TSQ	 statistically significant difference vs. placebo only regarding ease of lubrication, not regarding other individual item scores statistically significant differences vs. placebo regarding most scores statistically significant differences vs. placebo regarding some questions			

Study 3307

Study 3307 ‘A double-blind, randomised, placebo-and active-controlled efficacy and safety study of the effects

of bazedoxifene / conjugated oestrogens combinations on endometrial hyperplasia and prevention of osteoporosis in postmenopausal women' was a Phase 3 outpatient, multicentre, double-blind, randomised, placebo- and active-controlled study conducted between January 2009 and February 2011.
The trial consisted of a main study and included 3 substudies, i.e. osteoporosis (OSS), sleep, and breast density substudies.

Methods

Study Participants

It included generally healthy postmenopausal women with an intact uterus aged between 40 to 65 years. The inclusion and exclusion criteria are acceptable, but as the study excluded women above the age of 65 years this adds to the sparsity of data in the elderly and thus in the overall clinical programme.

Treatments

Participants received either BZA/CE 20 mg / 0.45 mg, BZA/CE 20 mg / 0.625 mg, BZA 20 mg, CE/MPA 0.45 mg/1.5 mg, or placebo.

Objectives

The primary objectives of this study were to investigate the endometrial safety of both BZA 20 mg / CE doses and the effect in preventing postmenopausal osteoporosis in the OSS after 1 year of therapy. Secondary objectives included comparison of effects on BMD between BZA/CE and BZA 20 mg, the effect of BZA/CE versus placebo and BZA 20 mg on bone turnover markers (BTM), the effect of BZA/CE versus placebo and CE/MPA on uterine bleeding / spotting and on breast tenderness, noninferiority of BZA/CE to placebo on quantitative changes in mammographic breast density, and the effect of BZA/CE versus placebo on sleep parameters in a subset of women with bothersome VMS at baseline.

Outcomes / endpoints

For the main endpoints endometrial hyperplasia was assessed by endometrial biopsies performed at screening and after 1 year of therapy; biopsies were analysed by central readings by 2 or 3 pathologists, depending on whether there was a disagreement between first two assessments. BMD measurements of the lumbar spine were performed by DXA expand scan at least twice during screening, once at Month 6, and twice during Month 12. BTM osteocalcin, C-telopeptide, and procollagen type 1 N-propeptide (P1NP) were measured at Month 3, Month 6 and Year 1. The Sleep substudy was analysed using the medical outcomes study (MOS) Sleep Scale. Breast Density was obtained by digital mammography performed at baseline and at Week 52 or at Week 26 for patients who withdrew early from the study. The chosen endpoints are adequate to investigate the defined objectives. In particular, the evaluation of endometrial biopsies is in accordance with the *CHMP Guideline on clinical investigation of medicinal products for hormone replacement therapy of oestrogen deficiency symptoms in postmenopausal women (EMEA/CHMP/021/97 Rev. 1)*. As mentioned for Study 303 the relevant *CHMP guideline on postmenopausal osteoporosis in women* has been revised during the clinical development programme. While revision 1, effective since 2001, considered an indication of prevention of osteoporosis, revision 2, effective since May 2007, does no longer have a specific prevention indication. Nevertheless, prevention of osteoporosis is contained in the treatment indication since the goal of therapy is to prevent fractures. In contrast to Study 303, however this trial was started (January 2009) long after revision 2 came into

effect (May 2007). As with trial 303 aspects regarding the prevention of osteoporosis have only been investigated in a substudy of trial 3307 and are thus not considered pivotal for this indication.

Sample size

The sample size calculation was based on the endometrial hyperplasia endpoint. The FDA recommended in January 2003 draft guidance on oestrogen products that the endometrial hyperplasia observed rate at year 1 had to be ≤ 1% with the upper limit of the 1-sided 95% CI less than 4%. The sample size of 300 subjects having at least 1 year follow-up in each BZA/CE group was sufficient for population rates up to 0.5%. The *EMA/CHMP Guideline on clinical investigation of medicinal products for hormone replacement therapy of oestrogen deficiency symptoms in postmenopausal women (EMEA/CHMP/021/97 Rev. 1, Oct 2005)* recommends that the upper limit of a 2-sided 95% CI of the observed incidence of endometrial hyperplasia should not exceed 2%. Sample size calculation was judged adequate by the CHMP.

Randomisation

The randomization was to be stratified by whether or not a subject participated in the OSS. The randomization ratio for the main study and the OSS was 2:2:1:1:2 (BZA/CE 20 mg/0.45 mg, 20 mg/0.625 mg, BZA 20 mg, CE/MPA 0.45 mg/1.5 mg, placebo).

Blinding (masking)

Blinding was accomplished by over-encapsulating the BZA/CE, BZA and CE/MPA tablets in capsules that matched the placebo capsules.

Statistical methods

The incidence of endometrial hyperplasia or malignancy at Month 12 for each treatment group was calculated for the EE population (primary analysis population) as: I = A / B, where I = incidence at Month 12 evaluation, A = all subjects in the EE population with biopsy results positive for endometrial hyperplasia or malignancy during first 12 months, and B = all subjects in the EE population defined as subjects randomly assigned and at least 1 dose of the test article taken, having screening endometrial biopsy with readings by at least 2 blinded central pathologists, having had a biopsy during Month 12, or hyperplasia diagnosed before Month 12, and having had no major protocol violations. For all groups the incidence of endometrial malignancy at 12 months and the associated exact 1-sided and 2-sided 95% CI were calculated with an acceptable hyperplasia rate of 1% or less with an upper 1-sided 95% confidence limit of 4% or less.

Results

Participant flow

Four thousand seven hundred seventy four (4774) women were screened. There were 2888 screen failures and thus 1886 women were randomly assigned; 43 of these did not take any test article and are not included in any analyses. The remaining 1843 subjects took at least one dose and are included in the safety analyses.

Figure 5: Disposition of Subjects

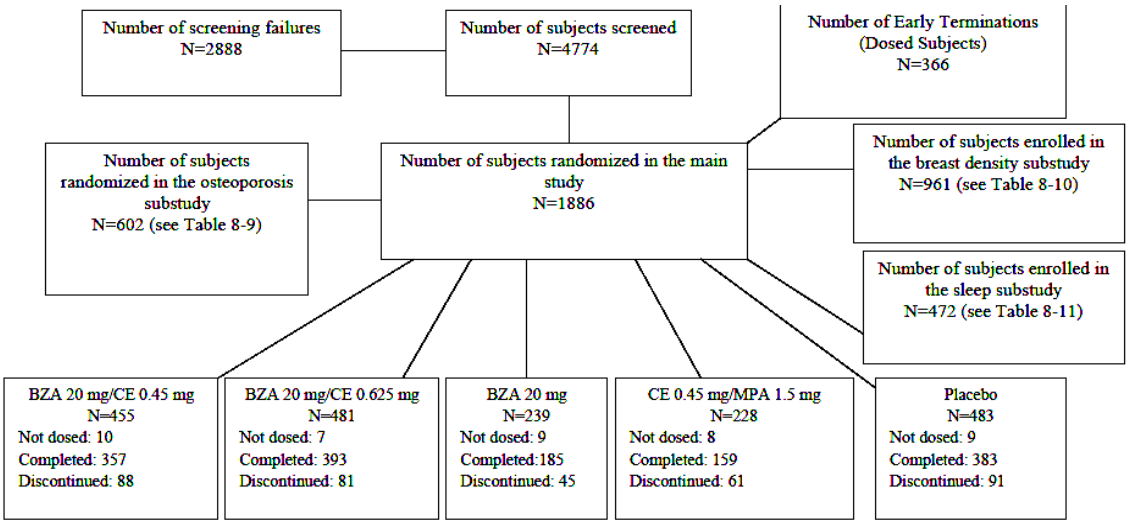
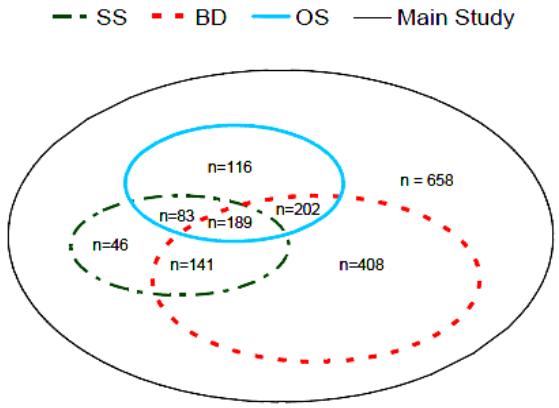


Figure 6 Subject's Allocation to Main Study and Substudies



Total in Main Study: 1843
Total in SS 459
BD 940
OS 590
SS=sleep substudy; BD=breast density substudy; OS=osteoporosis substudy; n=number of subjects.
Source: CLINICAL R&D/CLINICAL Biostatistics SAS Reports/3115A1 Bazedoxifene-CE/3307 graphic V5

Overall, discontinuations in the main study were comparable between BZA/CE 20 mg / 0.45 mg (19.8%), and 20 mg / 0.625 mg groups (17.1%), BZA 20 mg group (19.6%), and placebo (19.2%), but discontinuations were higher in the CE/MPA 0.45 mg / 1.5 mg group (27.7%). Differences were even more pronounced in the osteoporosis substudy. Rates ranged from about 15% in the BZA/CE 20 mg / 0.625 mg to 27% in the CE/MPA group, about 25% discontinued in the BZA 20 mg monotherapy group. A literature review however showed that the overall rate of discontinuation in study 3307 was consistent with overall rates observed in studies with SERMs in women with PMO and as regards the influence of the differences on the interpretation of the BMD data a conservative approach was used for the primary analysis of these data (LOCF) and a set of sensitivity analyses (BOCF, MMRM, CDC, JC) was consistent with the primary analysis, indicating that the differential drop-out rates across groups have no significant influence on the evaluation of the BMD efficacy results. As regards numbers analysed for the primary analysis only 75% in the placebo and 75% and 78% in the BZA/CE 20 mg / 0.45 mg and 20 mg / 0.625 mg groups, respectively, have been included. The percent of women included was even lower in the CE/MPA group with 68%.

Conduct of the study

The original protocol was issued on 20 Nov 2008. Two protocol amendments were implemented following the first visit of the first subject. Protocol Amendment 1 was issued on 08 May 2009 and Protocol Amendment 2 was issued on 08 Jun 2010.

Protocol deviations occurred, but these appear to have been adequately addressed and dealt with by the Applicant. It is agreed that no major impact on study results are to be expected. There were no significant differences among groups regarding baseline characteristics, but the population investigated was even younger than in trial 303 and the number of women with other than white ethnicity again was low.

Baseline data

Overall, there were no significant differences among groups regarding baseline characteristics. However, the population investigated was even younger than in trial 303 and the number of women with other than white ethnicity again is low.

Numbers analysed

Among the 1843 randomised subjects who took at least 1 dose, 1375 (75%) and 1465 (79%) were included in the EE and MITT populations, respectively, for the endometrial hyperplasia analyses. Overall, 1477 (78.3%) subjects completed the study. For the primary analysis only 75% in the placebo and 75% and 78% in the BZA/CE 20 mg/0.45 mg and 20 mg/0.625 mg groups, respectively, have been included. The percent of women included was even lower in the CE/MPA group with 68%.

Outcomes and estimation

Endometrial hyperplasia

Two definitions for defining cases of endometrial hyperplasia were used. For Definition 1 endometrial hyperplasia was assumed if at least 1 pathologist determined hyperplasia. For definition 2 a diagnosis of hyperplasia was based on at least 2 positive diagnosis.

It is reported that at month 12, 324 of 445 dosed subjects in the BZA 20 mg / CE 0.45 mg group and 351 of 474 dosed subjects in the BZA 20 mg / CE 0.625 mg group had evaluable biopsies. Using definition 2 which is in accordance with the CHMP Guideline on clinical investigation of medicinal products for hormone replacement therapy of oestrogen deficiency symptoms in postmenopausal women (EMEA/CHMP/021/97 Rev. 1, 13 October 2005), one case of endometrial hyperplasia in each of these 2 groups is reported at month 12. No endometrial carcinomas were observed in this study. Based on 314 and 333 evaluable biopsies in the BZA 20 mg / CE 0.45 mg group and the BZA 20 mg / CE 0.625 mg group, respectively, the incidence of endometrial hyperplasia / malignancy at month 12 was 0.32% (95% CI 0.01%; 1.76%) and 0.30% (2-sided 95% CI 0.01; 01.66%), respectively. Thus, the upper limit of the 2-sided 95% confidence interval of the incidence of endometrial hyperplasia was below the reference limit of 2% stated in the CHMP HRT Guideline in each of the two groups.

Nevertheless, the following issues with regard to the analysis of the incidence of endometrial hyperplasia / malignancy in study 3307 are considered as not reassuring:

Only the diagnosis of the endometrial biopsy, not a more detailed description of the macroscopic and microscopic findings by the pathologists is available. Thus, more detailed information on cases diagnosed as

"endometrium, other" could not be provided by the Applicant and no further assessment in this respect is possible.

In addition, in study 3307, concerns remain with regard to 4 patients in the BZA 20 mg / CE 0.45 mg in whom no biopsy was performed at month 12 and endometrial thickness was ≥4 mm. It is acknowledged that the Applicant reported that these 4 patients had refused a biopsy. In addition, in 8 patients of the BZA 20 mg / CE 0.45 mg group neither a biopsy nor TVUS was performed. In 4 patients, no reasons are given. In the other 4 subjects, biopsy and TVUs were refused or the patient had moved. In summary, in 12 patients of the BZA 20 mg / CE 0.45 mg group, the outcome with respect to endometrial histology cannot be considered as reassuring. As already stated above, a very low number of additional cases of hyperplasia would change the outcome of the study from success to failure.

Thus, currently endometrial safety cannot be concluded.

Bone mineral density

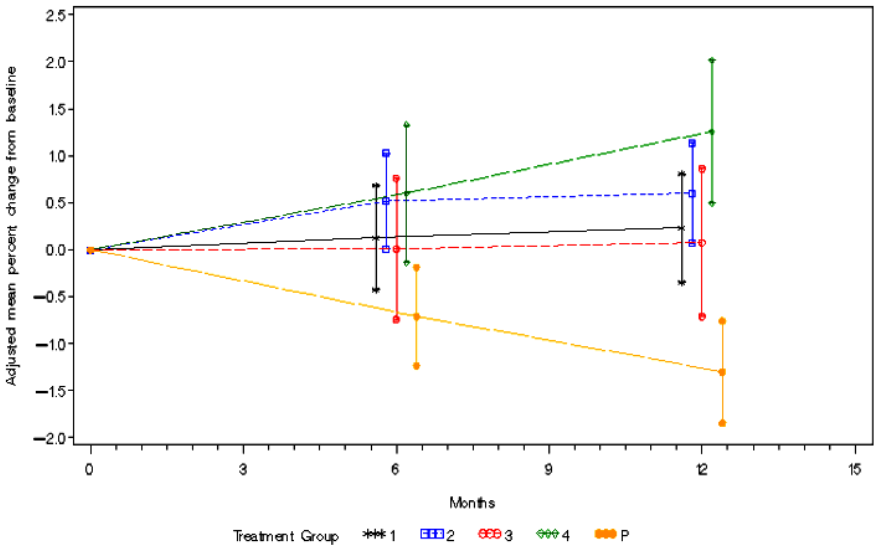
For both BZA/CE doses there were significant increases in mean percent change from baseline in BMD of lumbar spine at Month 12 and Month 6 (secondary) compared to placebo as well as well as in total hip BMD at Month 12. Changes in BMD were not statistically significant between BZA monotherapy, BZA/CE, and CE/MPA groups, but effects were most pronounced with CE/MPA.

Table 27: Adjusted Mean Percentage Changes From Baseline to Month 6 and Month 12 in the Bone Mineral Density of the Lumbar Spine (MITT Population, LOCF)

			Adjusted % Change		Adjusted Difference vs.Placebo		p-value			
Treatment	Time slot	N	Mean	SE	Mean	95% CI	Within Group	Vs. placebo	Vs. BZA 20 mg	Vs. CE 0.45/ MPA 1.5 mg
BZA 20 mg/CE 0.45 mg	Month 6	115	0.12	0.28	0.80	(0.139, 1.470)	0.666	0.017	0.781	0.227
	Month 12	119	0.24	0.29	1.51	(0.822, 2.201)	0.423	<0.001	0.710	0.017
BZA 20 mg/CE 0.625 mg	Month 6	136	0.51	0.26	1.19	(0.556, 1.830)	0.051	<0.001	0.231	0.756
	Month 12	139	0.60	0.27	1.87	(1.209, 2.533)	0.029	<0.001	0.234	0.107
BZA 20 mg	Month 6	55	0.00	0.39	0.68	(-0.154, 1.521)	0.998	0.109		0.202
	Month 12	56	0.07	0.40	1.34	(0.471, 2.215)	0.867	0.002		0.018
CE 0.45 mg/MPA 1.5 mg	Month 6	58	0.64	0.37	1.32	(0.499, 2.147)	0.087	0.001		
	Month 12	59	1.30	0.39	2.57	(1.717, 3.432)	<0.001	<0.001		
Placebo	Month 6	135	-0.68	0.27			0.011			
	Month 12	139	-1.28	0.28			<0.011			

N=number of subjects.
Ancova model: percentage change from baseline=treatment+region +baseline BMD+years since menopause.
BZA=bazedoxifene; CE=conjugated oestrogens; CI=confidence interval; LOCF=last observation carried forward; MITT=modified intent-to-treat; MPA=medroxyprogesterone acetate; SE=standard error.
Source: CLINICAL R&D/CLINICAL PROGRAMMING SAS REPORTS/3115A1/3307/OSS Interim Analysis 2010/3115-3307 BMD_ML_ANCOVA_LS 16DEC2010 12:37; CLINICAL R&D/CLINICAL PROGRAMMING SAS REPORTS/3115A1/3307/Additional STAT Analysis/3115-3307 bmd_ML_ancova_bza_prempro_ls. 03MAY2011 11:42

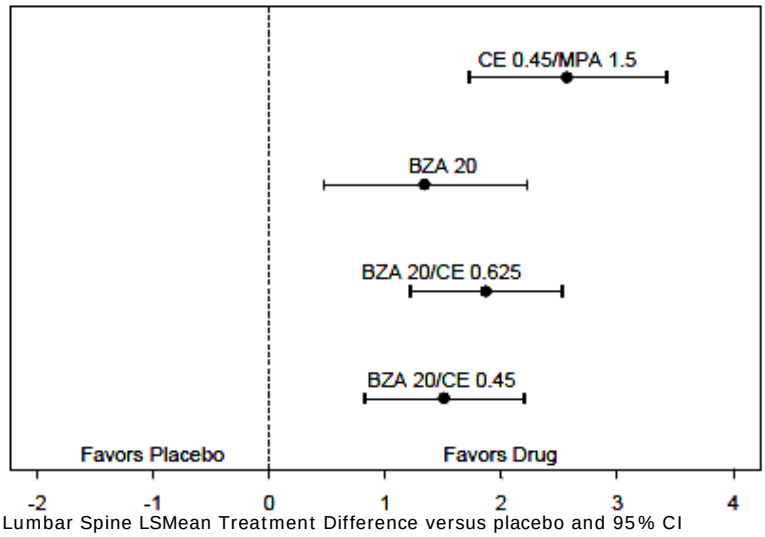
Figure 7: Adjusted Percent Change From Baseline in Lumbar Spine Bone Mineral Density at Month 6 and Month 12 (MITT Population, LOCF)



1: BZA 20 mg/CE 0.45 mg 2: BZA 20 mg/CE 0.625 mg 3: BZA 20 mg
4: CE 0.45 mg/MPA 1.5 mg P: Placebo

ANCOVA=analysis of covariance BMD=Bone mineral density; BZA=bazedoxifene; CE=conjugated oestrogens; CI=confidence interval; LOCF=last observation carried forward; MITT=modified intent-to-treat; MPA=medroxyprogesterone acetate; YSM=year since menopause.
Source: CLINICAL R&D/CLINICAL PROGRAMMING SAS REPORTS/3115A1/3307/Final Reports March 18/3115-3307 BMD_ML_GRAPH_IS GIF 7 APR2011 13:16.

Figure 8: Change From Baseline in the Lumbar Spine ANCOVA Model-Based Comparisons to Placebo.



Lumbar Spine LSMean Treatment Difference versus placebo and 95% CI
ANCOVA=analysis of covariance; BZA=bazedoxifene; CE=conjugated oestrogens; CI=confidence interval; MPA=medroxyprogesterone acetate.
Source: CLINICAL R&D/CLINICAL BIOSTATISTICS SAS Reports/3115A1 Bazedoxifene-CE/3307 Spine Forest.

Table 28: Adjusted Mean Percentage Changes From Baseline in the Bone Mineral Density of the Total Hip at Month 6 and Month 12 (MITT Population, LOCF)

			Adjusted % change		Adjusted Difference vs. Placebo		p-value			
Treatment	Time slot	N[a]	Mean	SE	Mean	95% CI	Within group	vs. placebo	vs. BZA 20 mg	vs. CE 0.45 mg/ MPA 1.5 mg
BZA 20 mg/ CE 0.45 mg	Month 6	117	0.43	0.18	1.32	(0.901, 1.742)	0.017	<0.001	0.706	0.920
	Month 12	119	0.50	0.20	1.21	(0.756, 1.671)	0.011	<0.001	0.936	0.478
BZA 20 mg/ CE 0.625 mg	Month 6	136	0.66	0.17	1.56	(1.152, 1.962)	<0.001	<0.001	0.209	0.435
	Month 12	139	0.89	0.18	1.60	(1.164, 2.044)	<0.001	<0.001	0.160	0.534
BZA 20 mg	Month 6	55	0.32	0.25	1.22	(0.685, 1.750)	0.190	<0.001		0.680
	Month 12	56	0.47	0.27	1.19	(0.610, 1.769)	0.078	<0.001		0.499
CE 0.45 mg/ MPA 1.5 mg	Month 6	57	0.45	0.24	1.35	(0.823, 1.875)	0.058	<0.001		
	Month 12	59	0.71	0.26	1.42	(0.854, 1.994)	0.006	<0.001		
Placebo	Month 6	134	-0.90	0.17			<0.001			
	Month 12	139	-0.72	0.18			<0.001			

a. Number of pairs.
Ancova model: percentage change from baseline=treatment+region +baseline BMD+years since menopause.
N=number of subjects.
BZA=bazedoxifene; CE=conjugated oestrogens; CI=confidence interval; LOCF=last observation carried forward; MITT=modified intent-to-treat; MPA=medroxyprogesterone acetate; SE=standard error.
Source: CLINICAL R&D/CLINICAL PROGRAMMING SAS REPORTS/3115A1/3307/OSS Interim Analysis 2010/3115-3307 BMD_ML_ANCOVA_TH 16DEC2010 12:37; CLINICAL R&D/CLINICAL PROGRAMMING SAS REPORTS/3115A1/3307/Additional STAT Analysis /3115-3307. BMD_ML_ANCOVA_BZA_PREMPRO_TH 03MAY2011 11:42

The analyses of the BMD of the lumbar spine at Month 12 in the MITT population observed cases (OC) and in the PP population were consistent with the results from the primary analyses. In the BMD responder analysis the lumbar spine responder rates were significantly greater for both BZA/CE and the CE/MPA group compared to placebo at Month 12 ($p \leq 0.001$). Differences for BZA 20 mg / CE compared to BZA 20 mg at Month 12 were not statistically significant ($p=0.323$ and 0.101, respectively). The total hip responder rates were significantly greater for all treatment groups compared with placebo at Month 12, but total hip responder rates were not statistically significant different between BZA 20 mg / CE and BZA 20 mg at Month 12 ($p=0.740$ and 0.127, respectively).

The non-inferiority analysis for BMD showed non-inferiority of BZA/CE 20 mg / 0.625 mg to BZA 20 mg but no superiority, whilst BZA/CE 20 mg / 0.45 mg failed the pre-specified non-inferiority criterion.

Others

The cumulative rate of amenorrhea was similar to placebo in both the BZA/CE treatment groups over a 1 year treatment period, while it was significantly lower with CE/MPA treatment. The bleeding and spotting profile of both BZA/CE groups was significantly better than that for the CE/MPA group. There was no significant difference in the incidence of subjects reporting breast tenderness between BZA/CE and placebo groups, while it was significantly higher in the CE/MPA group. There were no significant differences between both BZA/CE groups and placebo in mean percent change of mammographic breast density from baseline with slight decreases in all groups, while breast density increased in the CE/MPA group. As regards quality of sleep BZA/CE 20 mg / 0.625 mg appeared to be effective on more items in the MOS sleep scale than 20 mg / 0.45 mg. The MENQOL analysis showed some improvements compared to placebo, these appear to be more pronounced with higher doses of CE.

In summary, endometrial safety can currently not be concluded based on study 3307. As regards treatment of postmenopausal osteoporosis the investigated doses of BZA/CE of 20 mg / 0.45 mg and 20 mg / 0.625 mg appear not to have an advantage over the active comparators BZA 20 mg and CE/MPA; changes in BMD were

not statistically significant between BZA monotherapy, BZA/CE, and CE/MPA groups, but effects were most pronounced with CE/MPA. These results, in conjunction with the efficacy data seen in study 303, question the suitability of the proposed fixed dose combination of BZA with CE for the treatment of postmenopausal osteoporosis.

Summary of main study 3307

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment.

Table 3.2.49: Summary of efficacy for trial 3307

Title: A DOUBLE-BLIND, RANDOMISED, PLACEBO-AND ACTIVE-CONTROLLED EFFICACY AND SAFETY STUDY OF THE EFFECTS OF BAZEDOXIFENE/CONJUGATED OESTROGENS COMBINATIONS ON ENDOMETRIAL HYPERPLASIA AND PREVENTION OF OSTEOPOROSIS IN POSTMENOPAUSAL WOMEN.			
Study identifier	Protocol 3115A1-3307-WW, CSR-81040		
Design	Multicentre, double-blind, randomised, outpatient, 5-parallel-group, placebo- and active-controlled dose-ranging study including three substudies [breast density, osteoporosis substudy (women ≤5 years postmenopausal); sleep substudy]		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		January 2009 to February 2011 not applicable not applicable
Hypothesis	Other: Non comparative, specific requirements regarding confidence intervals		
Treatment groups	BZA/CE 20 mg/0.45 mg		number randomised 455, number dosed 445
	BZA/CE 20 mg/0.625 mg		number randomised 481, number dosed 474
	BZA 20 mg		number randomised 239, number dosed 230
	CE/MPA 0.45 mg/1.5 mg		number randomised 228, number dosed 220
	Placebo		number randomised 483, number dosed 474
Endpoints and definitions	Primary endpoint	incidence of endometrial hyperplasia at Month 12	to demonstrate an acceptable rate of endometrial hyperplasia after 1 year of treatment (<1%)
	Secondary endpoint (osteoporosis substudy)	mean % change from baseline at month 12 in BMD of lumbar spine	to evaluate efficacy of BZA/CE in preventing osteoporosis after 1 year of therapy in women ≤5 years postmenopausal
	Other (osteoporosis substudy)	mean percent change from baseline at month 6 in BMD of lumbar spine	to evaluate efficacy of BZA/CE in preventing osteoporosis after 1 year of therapy in women ≤5 years postmenopausal
	Other (osteoporosis substudy)	mean percent change from baseline at month 6 and 12 in BMD of total hip	to evaluate efficacy of BZA/CE in preventing osteoporosis after 1 year of therapy in women ≤5 years postmenopausal

	Other (osteoporosis substudy)	% change in serum markers bone metabolism month 3, 6, and 12	to evaluate efficacy of BZA/CE in preventing osteoporosis after 1 year of therapy in women ≤5 years postmenopausal
	Other	% subjects with cumulative amenorrhea day 1 to 354	to assess effect of BZA/CE vs. placebo and CE/MPA on uterine bleeding/spotting
	Other (breast density substudy)	% change in breast density month 12	to assess effect of BZA/CE vs. placebo and CE/MPA on breast tenderness and to demonstrate noninferiority of BZA/CE to placebo on quantitative changes in mammographic breast density in postmenopausal women at Year 1
	Other (sleep substudy)	change from baseline in sleep parameters (MOS Sleep Scale) in women with bothersome VMS at week 13	to assess effect of BZA/CE vs. placebo on sleep parameters in women with bothersome VMS at baseline
Database lock	not identified in study report, see LoQ		

Main Results and Analysis

Analysis description	**Primary Analysis: Endometrial Hyperplasia Definition 1 (at least 1 pathologist positive)**			
Analysis population and time point description	Efficacy evaluable (EE) population month 12 (taken at least 1 dose, endometrial biopsy at screening and within 30 days before or after time point of interest or diagnosed with hyperplasia at any time prior to time point, no major protocol violations)			
Descriptive statistics and estimate variability	**Treatment group**	**BZA/CE 20 mg / 0.45 mg**	**BZA/CE 20 mg / 0.625 mg**	**BZA 20 mg**
	Number of subject	335	368	169
	Incidence of Hyperplasia (%)	1 (0.30)	2 (0.54)	0 (0)
	CI (Upper Limit, 95% 1-sided)	1.41	1.28	1.76
	CI (Upper Limit, 95% 2-sided)	1.65	1.50	2.16
	Treatment group	**CE/MPA 0.45 mg / 1.5 mg**	**Placebo**	
	Number of subject	149	354	
	Incidence of Hyperplasia (%)	0 (0)	3 (0.85)	
	CI (Upper Limit, 95% 1-sided)	1.99	1.33	
	CI (Upper Limit, 95% 2-sided)	2.45	1.56	
Analysis description	**Primary Analysis: Endometrial Hyperplasia Definition 2 (at least 2 pathologist positive)**			
Analysis population and time point description	Efficacy evaluable (EE) population month 12 (taken at least 1 dose, endometrial biopsy at screening and within 30 days before or after time point of interest or diagnosed with hyperplasia at any time prior to time point, no major protocol violations)			
Descriptive statistics and estimate variability	**Treatment group**	**BZA/CE 20 mg / 0.45 mg**	**BZA/CE 20 mg / 0.625 mg**	**BZA 20 mg**
	Number of subject	335	368	169

	Incidence of Hyperplasia (%)	1 (0.30)	1 (0.27)	0 (0)
	CI (Upper Limit, 95% 1-sided)	1.41	1.28	1.76
	CI (Upper Limit, 95% 2-sided)	1.65	1.50	2.16
	Treatment group	**CE/MPA 0.45 mg / 1.5 mg**	**Placebo**	
	Number of subject	149	354	
	Incidence of Hyperplasia (%)	0 (0)	1 (0.28)	
	CI (Upper Limit, 95% 1-sided)	1.99	2.45	
	CI (Upper Limit, 95% 2-sided)	1.33	1.56	
Analysis description	**Main Secondary Analysis: Month 12 % Change in BMD from Baseline at Lumbar Spine**			
Analysis population and time point description	MITT, LOCF			
Descriptive statistics and estimate variability	**Treatment group**	**BZA/CE 20 mg / 0.45 mg**	**BZA/CE 20 mg / 0.625 mg**	**BZA 20 mg**
	Number of subjects	119	139	56
	Mean % change from baseline (SE)	0.24 (0.29)	0.60 (0.27)	0.07 (0.40)
	Adjusted difference vs. placebo (95% CI)	1.51 (0.822, 2.201	1.87 (1.209, 2.533)	1.34 (0.471, 2.215)
	P-value vs. BZA 20 mg	0.710	0.234	N/A
	P-value vs. CE/MPA 0.45 mg/1.5 mg	0.017	0.107	0.018
	Treatment group	**CE/MPA 0.45 mg / 1.5 mg**	**Placebo**	
	Number of subjects	59	139	
	Mean % change from baseline (SE)	1.30 (0.39)	-1.28 (0.28)	
	Adjusted difference vs. placebo (95% CI)	2.57 (1.717, 3.432)	N/A	
	p-value vs. BZA 20 mg	N/A	N/A	
	p-value vs. CE/MPA 0.45 mg/1.5 mg	N/A	N/A	

Clinical studies in special populations

The Applicant did not conduct clinical trials in special populations which acceptable since both active substances are well known and approved.

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

Pooled analyses or meta-analyses across trials with respect to the entire study populations were not performed.

Supportive studies

Study 300

Study 300 has already been assessed in the BZA monotherapy programme (see: EPAR Conbriza EMEA/H/C/000913). It was a 5-arm, outpatient, multicentre, double-blind, randomised, placebo- and raloxifene controlled study in postmenopausal women and 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 CHMP Guideline on Osteoporosis.*

BMD was preserved in BZA 20 mg and raloxifene 60 mg-treated subjects, while significant loss in BMD was observed in patients receiving placebo. The increase in LS BMD with BZA 20 mg and raloxifene 60 mg, compared with placebo, was significant at 6 months (1.14% and 1.26%, respectively) and was maintained through 2 years (1.41% and 1.49%, respectively). The effect of BZA on BMD at other skeletal sites was similar.

Study 301

Study 301 as well has already been assessed in the BZA monotherapy programme (see: EPAR Conbriza EMEA/H/C/000913). It was a 4-arm, outpatient, multicentre, double-blind, randomised, placebo- and raloxifene controlled study over 3 years in postmenopausal osteoporotic women. Treatment groups included BZA 20 mg and 40 mg, raloxifene 60 mg, and placebo. It was considered the main pivotal trial for the monotherapy programme. Inclusion and exclusion criteria and primary endpoint were mainly in line with *Revision 1 of the CHMP 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 was due to ethical considerations regarding the placebo-control included in this study, which was considered to be a valid argument. The study evaluated the incidence of new vertebral fractures over 3 years in the core study with two 2-year double-blind, placebo controlled extensions. The BZA 40 mg dose was decreased to 20 mg after approximately 4 years. The raloxifene group was discontinued during the first 2-year extension.

Overall there was a significant reduction in the incidence of new vertebral fractures after 3 years of treatment with BZA 20 mg and raloxifene 60 mg compared to placebo. The reduction in the incidence of vertebral fracture was similar among BZA and raloxifene groups. The treatment effect was similar among those with and without prevalent vertebral fractures. After 5 years of treatment the incidence of new vertebral fractures remained lower in the BZA 20 mg group (4.49%) compared to placebo (6.82%) with a relative risk reduction of 36% (p=0.014). After 7 years of treatment, the incidence of new vertebral fractures remained lower in the BZA 20 mg group (7.64%) compared to placebo (9.90%) with a relative risk reduction of 30% (p=0.022).

The incidence of non-vertebral osteoporosis-related fractures was similar among BZA 20 mg (5.68%), raloxifene 60 mg (5.87%), and placebo (6.26%) groups. In a post-hoc analysis, the 10-year fracture probability as an index of baseline fracture risk was determined. The mean 10-year fracture probability of a major osteoporotic fracture for the entire study population was 11%. In subjects treated with BZA, the incidence of fractures was related to the baseline fracture risk: the higher the fracture risk, the greater the benefit with BZA treatment. In subjects with 10-year fracture probabilities at or above 16%, BZA was associated with a significant decrease in the risk of all clinical fractures. In a post-hoc analysis, the relative risk of non-vertebral fractures in BZA-treated subjects decreased with increased fracture probability. In subjects with a fracture probability of 20% or greater (n = 618) the risk of non-vertebral fractures in BZA-treated subjects was decreased by 55% (95% CI: 18-76) compared to placebo-treated subjects.

The increase in LS BMD compared with placebo with BZA 20 mg and raloxifene 60 mg was significant at 6 months (1.02% and 1.29%, respectively) and was maintained through 3 years (1.32% and 2.08%, respectively). The effect of BZA on BMD at other skeletal sites was similar. The increases in BMD relative to placebo remained statistically significant at all skeletal sites throughout the 5 years of treatment with BZA. After 7 years of treatment with BZA the increases in BMD relative to placebo remained statistically significant at the femoral neck, femoral trochanter, and total hip. The increase from baseline in lumbar spine BMD at 7 years in the BZA 20 mg group was not statistically greater than in the placebo group.

Study 304

Study 304 'A double-blind, randomised, placebo- and active-controlled efficacy and safety study of bazedoxifene / conjugated oestrogens combinations for prevention of endometrial hyperplasia and prevention of osteoporosis in postmenopausal women' was an outpatient, multicentre, double-blind, randomised, 4-parallel-group, placebo- and active-controlled (CE/MPA 0.45 mg/1.5 mg) study in non-hysterectomised postmenopausal women designed to assess the effect of BZA/CE 20 mg / 0.45 mg and 20 mg / 0.625 mg on the incidence of endometrial hyperplasia and efficacy in preventing postmenopausal osteoporosis after 1 year of therapy, conducted between October 2005 and August 2007.

Study 304 is considered as supportive only as the formulations of BZA 20 mg / CE 0.45 mg and BZA 20 mg / CE 0.625 mg administered in this study were not bioequivalent to the BZA/CE formulations used in study 303 (geometric mean ratio of 82% for AUC, 90% CI 75% - 90%).

The study enrolled healthy, postmenopausal, non-hysterectomised women aged 40 to <65 years.

Before data were analysed the protocol of the original 1-year study (CSR 68285) was amended to add a 1-year extension study (CSR-73414). Not all subjects participating in the original study were eligible for the extension since the amendment was implemented after some subjects had already completed and not all sites participated in the extension. Participants in the BZA/CE groups initially received Formulation B and were later switched to Formulation C. Data from bioequivalence studies performed showed that Formulation C is not bioequivalent to Formulations A and B and thus data from trial 304 are considered supportive only.

The Primary objectives were to assess the effect of BZA/CE on the incidence of endometrial hyperplasia and in preventing postmenopausal osteoporosis after 1 year of therapy. Secondary objectives were to provide descriptive BMD data for BZA/CE versus the active comparator and to assess the effect on uterine bleeding or spotting and breast pain. The objective of the 1-year study extension was to obtain additional efficacy and safety data.

The primary endpoints were the incidence of endometrial hyperplasia at Year 1 of therapy and in the osteoporosis substudy the percent change from baseline in BMD of lumbar spine after 1 year of therapy compared with placebo. Secondary endpoints were percent change from baseline in the BMD of lumbar spine at Month 24, percent change from baseline in the BMD of total hip, the incidence of endometrial hyperplasia at Month 24, cumulative and noncumulative amenorrhea, bone metabolism markers, and breast pain. The numbers of subjects per group and study period are given in the table below.

Table 29: Number of Subjects

Treatment Groups	Number of Subjects*	
	Original Study	Study Extension
BZA 20 mg / CE 0.45 mg	361	168
BZA 20 mg / CE 0.625 mg	349	177
CE 0.45 mg / MPA 1.5 mg	179	84
Placebo	172	94

* Included all randomly assigned subjects who took at least 1 dose of test article
Abbreviations: BZA=bazedoxifene; CE=conjugated oestrogens; MPA=medroxyprogesterone acetate
Source: 5.3.5.1, Study 304, CSR-68285, Table 8-1 and CSR-73414, Table 8-2

Results

The incidence of endometrial hyperplasia at Month 12 is given in the table below.

Table 30: Incidence of Endometrial Hyperplasia at Month 12 (EE* Population)

Treatment	Month	Number of subjects	Number of hyperplasia	Hyperplasia rate (%)	95% CI (2-sided)	
					LL	UL
BZA 20 mg / CE 0.45 mg	12	261	0	0.00	0.00	1.40
BZA 20 mg / CE 0.625 mg	12	273	3	1.10	0.23	3.18
CE 0.45 mg/MPA 1.5 mg	12	119	0	0.00	0.00	3.05
Placebo	12	135	0	0.00	0.00	2.70

* EE analysis population defined as subjects randomly assigned and tooking at least 1 dose of test article, had screening endometrial biopsy with readings by at least 2 blinded central pathologists, had a biopsy during Month 12, or had hyperplasia diagnosed before Month 12 and had no major protocol violations.
BZA=bazedoxifene; CE=conjugated oestrogens; EE=efficacy evaluable; LL=lower limit; MPA=medroxyprogesterone; UL=upper limit
Source: PF-05212370/Clinical/III/3115A1-304/Tables and Figures/additional analysis/3115-304_INTERIM2007_hyper_rate_ee_yr1_1_2sideci.rtf 08APR2008

At Year 2 in the study extension in the BZA/CE 20 mg / 0.45 mg group, the endometrial hyperplasia rate was 0% with an upper limit of the 2-sided 95% CI of 2.78%, while in the 20 mg / 0.625 mg group the endometrial hyperplasia rate was 4.93% with an upper limit of the 2-sided 95% CI of 9.89%. In addition, after 2 years there were 2 cases of endometrial malignancy in the BZA 20 mg / CE 0.625 mg.

It is noted that a decrease in bioavailability of BZA of about 20% for the formulations of BZA/CE used in this study, compared to the formulations used in study 303, considerably compromised the endometrial safety, at least regarding the higher dose. In addition, with respect to BZA 20 mg / CE 0.45 mg, it appears questionable whether the number of subjects in the EE population is the population of subjects with evaluable biopsies as defined in the *CHMP Guideline on clinical investigation of medicinal products for hormone replacement therapy of oestrogen deficiency symptoms in postmenopausal women (EMEA/CHMP/021/97 Rev. 1, 13 October 2005)*. However, as this study is considered as supportive only, this issue is not further discussed.

Changes from baseline in BMD at lumbar spine at month 12 showed significant increases for both doses compared to placebo, but were significantly lower than with CE/MPA. At total hip changes in BMD were comparable with the exception that the difference between CE/MPA and BZA/CE 20 mg / 0.625 mg was not statistically significant (p=0.057). Results from the 1 year study extension were in line with those from the main study, as were results of the responder analyses performed. In conclusion data from trial 304 indicate that the anti-osteoporotic efficacy of both BZA/CE fixed combinations used in this trial was inferior to that seen with CE/MPA 0.45 mg/1.5 mg. Overall changes in markers of bone turnover were in line with changes seen in BMD.

The cumulative rate of amenorrhea was higher in both BZA/CE groups than in the CE/MPA group at all time periods. There were no significant differences in the percentages of subjects reporting at least 1 day of breast pain between BZA/CE groups and placebo, while these were significantly higher in the CE/MPA versus placebo at most time points.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Study 203 was a phase 2, multicentre, double-blind, randomised, controlled, dose finding study of BZA paired with CE on the estrogenic stimulation of the endometrium in healthy postmenopausal women conducted in the EU. Eleven (11) dose groups were studied: doses of 5 mg, 10 mg, and 20 mg BZA were studied each in combination with 0.45 mg CE and 0.626 mg CE; 0.3 mg, 0.625 mg CE monotherapy; 0.625 mg CE / 2.5 mg MPA and placebo. Patients were treated for 12 weeks. The primary efficacy variable was endometrial thickness measured by TVUS at day 84. Secondary endpoints included change from baseline in the number of subjects presenting oestrogen related changes in the endometrium (glands and stroma), endpoints related to VMS and VVA, bleeding / spotting, and breast tenderness.

Study 303 investigated six (6) fixed dose combinations of BZA/CE, BZA 10, 20, and 40 mg, each in combination with either 0.625 mg or 0.45 mg CE; it included 2 osteoporosis substudies. The rate of discontinuation was comparable between groups. For the primary analysis only 73% in the placebo and 77% and 76% in the BZA/CE 20 mg / 0.45 mg and 20 mg / 0.625 mg groups, respectively, have been included. The rate of protocol violations leading to discontinuation was low. Protocol deviations occurred, but these appear to have been adequately addressed and dealt with by the Applicant. It is agreed that no major impact on study results are to be expected.
Overall, there were no significant differences among groups regarding baseline characteristics. However, the population consisted of mainly younger postmenopausal women and the number of women with other than white ethnicity is sparse. Importantly, study 303 was classified as GCP non-compliant.

Study 305 was a Phase 3, multicentre, double-blind, randomised, 3-parallel-group, placebo-controlled study designed to evaluate the safety and efficacy of BZA 20 mg / CE 0.45 mg and BZA 20 mg / CE 0.625 mg for the treatment of VMS (oestrogen deficiency symptom indication). The study was conducted in the USA. In brief, the study enrolled generally healthy postmenopausal women with an intact uterus, aged 40 to 65 years, seeking treatment for hot flushes and reporting at screening a minimum of 7 moderate to severe hot flushes per day or 50 per week. The treatment duration was 12 weeks. The primary objective was to assess the safety and efficacy of 2 doses of BZA/CE compared with placebo for the treatment of moderate to severe VMS associated with menopause. The secondary objectives were to assess the effect of BZA/CE on breast pain and to assess the results from the Medical Outcomes Study (MOS) sleep scale. An active comparator was unfortunately not included.
With regard to the conduct of the study, it is noted that in a GCP inspection the study was classified as GCP non-compliant. Nevertheless, the data regarding efficacy of BZA/CE in the treatment of hot flushes were correctly reported and in particular the MITT analyses regarding hot flushes can be taken into account for assessment of BZA/CE.

Study 306 was a Phase 3, multicentre, double-blind, randomised, outpatient, 4-parallel-group placebo- and active-controlled study designed to assess the efficacy of BZA 20 mg / CE 0.45 mg and BZA 20 mg / CE 0.625 mg compared with placebo and BZA 20 mg for the treatment of VVA. The study was conducted in the USA. Generally healthy postmenopausal women, 40 to 65 years of age, with an intact uterus and with signs and symptoms of VVA were enrolled. Subjects were randomly assigned to receive BZA 20 mg / CE 0.45 mg, BZA 20 mg / CE 0.625 mg, BZA 20 mg, or placebo. The treatment duration was 12 weeks. The co-primary endpoints for vulvar / vaginal atrophy were the increase in superficial cells, decrease in parabasal cells, lowering of vaginal pH, and improvement in the most bothersome symptom at week 12. Secondary efficacy endpoints included

further endpoints related to vaginal smear and symptoms of VVA, including a responder analysis, with responders defined as subjects who had 1 or more of the following at the week 12 (LOCF) evaluation: vaginal superficial cells > 5%, vaginal pH <5, or improvement of their Most Bothersome Symptom by at least 1 category from baseline. Other secondary efficacy variables included the self-administered questionnaires (ASEX, MENQOL, MS-TSQ). Diaries were used to capture intake of medication and symptoms / complaints. For all efficacy variables except for MS-TSQ, the primary efficacy population was the modified-intent-to-treat population (MITT), defined as all subjects who were randomised, took at least 1 dose of test article, had a baseline value, and had at least 1 on-therapy value for the parameter being analysed, using an LOCF approach.

Study 3307 consisted of a main study and included 3 substudies (osteoporosis (OSS), sleep, breast density). The study included healthy, postmenopausal female subjects aged between 40 to 65 years. Participants received BZA/CE 20 mg / 0.45 mg, BZA/CE 20 mg / 0.625 mg, BZA 20 mg, CE/MPA 0.45 mg / 1.5 mg, or placebo. The rate of discontinuation was not comparable between groups. For the overall analysis, the rate of discontinuation was about 28% in the CE/MPA group, versus about 20% in all other groups except BZA/CE 20 mg / 0.625 mg (about 17%). These differences were even more pronounced in the osteoporosis substudy. Rates ranged from about 15% in the BZA/CE 20 mg / 0.625 mg to 27% in the CE/MPA group; about 25% discontinued in the BZA 20 mg monotherapy group. For the interpretation of the BMD data a conservative approach was used for the primary analysis of these data (LOCF) and a set of sensitivity analyses (BOCF, MMRM, CDC, JC) was consistent with the primary analysis, indicating that the differential drop-out rates across groups have no significant influence on the evaluation of the BMD efficacy results. For the primary analysis only 75% in the placebo and 75% and 78% in the BZA/CE 20 mg / 0.45 mg and 20 mg / 0.625 mg groups, respectively, have been included. The percent of women included was even lower in the CE/MPA group with 68%. Protocol deviations occurred, but these appear to have been adequately addressed and dealt with by the Applicant. It is agreed that no major impact on study results is to be expected. Overall, there were no significant differences among groups regarding baseline characteristics. However, the population investigated was even younger than in trial 303 and the number of women with other than white ethnicity again is low.

Efficacy

Oestrogen Deficiency Symptoms

VMS

In dose-finding study 203 it was observed that CE 0.3 mg was statistically significantly superior to placebo only in combination with 5 mg BZA, but not with 10 mg or 20 mg BZA. A dose of 0.3 mg CE was not further studied in phase 3 studies. CE 0.625 mg in combination with 5 mg, 10 mg, or 20 mg BZA was statistically significantly superior to placebo regarding VMS. No statistically significant differences with respect to number and severity of hot flushes were observed between the different combinations of BZA/CE, compared with the same doses of CE as monotherapy. However, numerically the effects were somewhat greater in the CE monotherapy groups except for the comparison BZA 5 mg / CE 0.3 mg vs. CE 0.3 mg. For CE 0.625 mg / BZA 5 mg, CE 0.625 mg / BZA 10 mg and 20 mg, no statistically significant differences with respect to number and severity of hot flushes were observed vs. CE 0.625 / 2.5 mg MPA. However, numerically, the effects were somewhat greater in the CE/MPA group.

In study 305, the pivotal study regarding VMS, statistically significant superiority of BZA 20 mg / CE 0.45 mg and of BZA 20 mg / CE 0.625 mg vs. placebo was shown with respect to the co-primary endpoints change from baseline in the average daily number of moderate and severe hot flushes at week 4 and week 12 and change from baseline in the average daily severity score of hot flushes at week 4 and 12. At week 12 the mean change

from baseline in the average daily number of moderate and severe hot flushes was -7.63, -8.05, and -4.92 in the BZA 20 mg / CE 0.45 mg, the BZA 20 mg / CE 0.625 mg, and the placebo group, respectively. At week 12 the mean change from baseline in the average daily severity score of hot flushes was -0.87, -01.21, and -0.26 in the BZA 20 mg / CE 0.45 mg, the BZA 20 mg / CE 0.625 mg, and the placebo group, respectively. Regarding secondary endpoints the results also support the conclusion that both dose strengths of BZA/CE are more effective than placebo for hot flushes.

The differences between BZA 20 mg / CE 0.625 mg and BZA 20 mg / CE 0.45 mg at week 12 with regard to number as well as severity of hot flushes were small. A formal comparison of the 2 dose strengths of BZA/CE regarding the primary endpoints had not been pre-specified.

With regard to secondary endpoints statistically significantly more subjects experienced a 75% reduction from baseline in the number of moderate and severe hot flushes at week 4 and 12 in the BZA 20 mg / CE 0.625 mg group (53.60% and 72.80%, respectively) compared to BZA 20 mg / CE 0.45 mg (39.34% and 60.66%, respectively). Regarding other secondary endpoints such as subjects with ≥50% decrease in average daily number of hot flushes at week 12 vasomotor function domain of MENQOL, median time to 3 consecutive days of 50% reduction from baseline, and sleep-related endpoints the results were mostly very similar in the BZA 20 mg / CE 0.45 mg and the BZA 20 mg / CE 0.625 mg group. No CE/progestin control group was included in this study.

Study 303, was classified as GCP non-compliant and is not taken into account for the assessment of efficacy of BZA/CE in the treatment of hot flushes.

VVA

In study 203, with regard to CE 0.3 mg the effect on VMI appeared to be highest in the CE 0.3 mg monotherapy group and decreased numerically with increasing BZA doses. With regard to CE 0.625 mg, similar effects were observed in all BZA/CE groups and the CE 0.625 mg monotherapy group while the effect in the placebo group appeared to be lower. It is also noted that the effect on the VMI appeared to be higher with CE 0.625 mg / MPA 2.5 mg, compared to all combinations of BZA/CE. Statistical significance was not tested regarding these comparisons.

In study 306, the pivotal study regarding VVA, statistically significant differences favouring BZA 20 mg / CE 0.625 mg vs. placebo were found with regard to all 4 co-primary endpoints increase in superficial cells and decrease in parabasal cells, decrease in vaginal ph, and improvement in MBS at week 12. Regarding BZA 20 mg / CE 0.45 mg the differences vs. placebo at week 12 were statistically significant only regarding superficial and parabasal cells, not regarding vaginal pH and MBS. For BZA alone, differences vs. placebo were not statistically significant regarding superficial cells, vaginal ph, and MBS while regarding parabasal cells even a significant increase vs. baseline was observed. No CE/progestin control group was included in this study.

The investigation of VVA is acknowledged as additional evidence in the oestrogen deficiency symptoms indication, although not mandatory according to European guidance. It is also noted that also in this study, no CE / progestin control group was included.

Study 303 was classified as GCP non-compliant and should not be taken into account for the assessment of efficacy of BZA/CE in the treatment of VVA.

Treatment of Osteoporosis

Data on surrogate parameters of postmenopausal osteoporosis were collected in substudies of pivotal trials 303 and 3307 only; they evaluated effects on BMD for the prevention of osteoporosis as main secondary endpoint. Study 303 included 2 osteoporosis substudies, while Study 3307 included 1 osteoporosis substudy. Women in the Substudy I of Study 303 had to be >5 years postmenopausal, have a BMD T-score at the lumbar spine or total hip between -1 and -2.5 (inclusive), and have at least 1 risk factor for osteoporosis; those in the Substudy II had to be at least 1 year and ≤5 years postmenopausal and have at least 1 risk factor for osteoporosis. The osteoporosis substudy of Study 3307 had similar requirements for inclusion and exclusion as Study 303 Substudy II.

The Applicant initially designed the clinical programme for the prevention of osteoporosis in postmenopausal women evaluated by improvements in BMD and changes in BTMs in accordance with the *CHMP Note for Guidance on Postmenopausal Osteoporosis in Women, revision 1*, effective from January 2001. This guideline has been revised during the clinical development programme; revision 2, effective since May 2007, does no longer have a specific prevention indication. However, prevention of osteoporosis is contained in the treatment indication since the goal of therapy is to prevent fractures. Since for both components of this fixed combination anti-fracture efficacy has been established, BMD together with BTMs are considered adequate surrogate markers.

Study 303 was classified as GCP non-compliant and should not be taken into account for the assessment of efficacy of BZA/CE as regards osteoporosis. The MITT analysis of the main secondary endpoint mean percent change from baseline in BMD of the lumbar spine after 2 years of therapy showed significant increases in lumbar spine BMD from baseline to month 24 in both substudies (women >5 and ≤5 years postmenopausal) for all groups except placebo were BMD values decreased. All groups with BZA/CE had mean percent changes in lumbar spine BMD from baseline to month 24 significantly different from placebo. Independent of the dose of CE the effect was most pronounced with the lowest dose of 10 mg BZA, attenuating with increasing dose of BZA. This trend was also seen in BMD of total hip and the other hip areas. In the group of women >5 years postmenopausal effects were more pronounced with BZA/CE containing either 10 or 20 mg BZA, but not 40 mg, compared to raloxifene 60 mg; in women ≤5 years postmenopausal BMD increases were more pronounced with all doses of BZA/CE. However, results were only marginally significant for BZA/CE 20 mg / 0.45 mg in the elder women and for BZA 40 mg / CE in younger women. The responder analysis was in line with these findings; in both substudies, consistent with the primary analysis, responder rates tended to be higher with higher doses of conjugated oestrogens and lower doses of BZA. Thus, in general higher doses of CEs induced larger increases in BMD, while increases in the BZA dosage attenuated the effects of CEs. As regards changes in BMD the results clearly favour the BZA 10 mg dose groups. Nevertheless for BZA/CE combinations containing 20 mg of BZA effects on BMD at lumbar spine were more pronounced than with raloxifene 60 mg while in the BZA monotherapy clinical programme, effects of BZA 20 mg on BMD were comparable to that seen with raloxifene 60 mg (EPAR Conbriza 2009).

Study 3307 is the only clinical trial with valid data as regards osteoporosis. In the osteoporosis substudy in postmenopausal women with a baseline T-score ≥-2.5 both BZA/CE groups showed a significant increase in lumbar spine and total hip BMD compared with decreases observed in the placebo group after 1 year of therapy. For both BZA/CE doses there were significant increases in mean percent change from baseline in BMD of lumbar spine at Month 12 and Month 6 (secondary) compared to placebo as well as in total hip BMD at Month 12. Changes in BMD were not statistically significant between BZA monotherapy, BZA/CE, and CE/MPA groups, but effects were most pronounced with CE/MPA. The non-inferiority analysis for BMD showed non-inferiority of

BZA/CE 20 mg / 0.625 mg to BZA 20 mg but no superiority, whilst BZA/CE 20 mg / 0.45 mg failed the pre-specified non-inferiority criterion in comparison to BZA monotherapy. Findings in the analysis of bone turnover markers were in line with the observed changes in BMD.

Overall there was no additive or synergistic effect on skeletal endpoints of the fixed combination of BZA with CEs.

2.5.4. Conclusions on the clinical efficacy

Oestrogen Deficiency Symptoms

Vasomotor symptoms are considered as the most important oestrogen deficiency symptoms in accordance with *Guideline on clinical investigation of medicinal products for hormone replacement therapy of oestrogen deficiency symptoms in postmenopausal women (EMEA/CHMP/021/97 rev. 1, 13 Oct 2005).* The current standard therapy is systemic administration of an oestrogen in hysterectomised patients and an oestrogen combined with a progestin in non-hysterectomised patients. In addition VVA also occurs in postmenopausal women. However, if treatment is intended for VVA only the treatment option of choice is topical oestrogen.

In the therapeutic indication treatment of oestrogen deficiency syndrome in postmenopausal women with a uterus BZA is intended for endometrial protection as oestrogens alone increase the risk of endometrial carcinoma in non-hysterectomised patients. Usually, in this population an oestrogen is combined with a progestin for endometrial safety. This is the first application submitted in the centralised procedure in the EU for a fixed combination of an oestrogen and a SERM.

Both dose strengths of BZA/CE initially applied for are statistically significantly superior to placebo in the treatment of hot flushes. Based on the available data regarding treatment of hot flushes from the phase 2 study 203, the phase 3 study 3307, and a historical comparison vs. the HOPE study investigating different dosages of CE and CE/MPA it is concluded that the efficacy of CE in this regard is decreased in the combination BZA/CE compared to the combination CE/MPA. This decrease cannot be quantified as unfortunately a CE/MPA active control group was not included in study 305 which is considered as pivotal with respect to treatment of hot flushes. The Applicant argues that the decrease in efficacy is outweighed by better tolerability in terms of less breast pain, a more favourable bleeding pattern, and lack of effect on mammographic breast density.

Comparisons of the effects of the 2 dose strengths of BZA/CE initially applied for on hot flushes were not prespecified in the submitted studies. In the pivotal study 305, the results regarding number of hot flushes which is the recommended primary endpoint according to the *CHMP HRT Guideline (EMEA/CHMP/021/97 Rev. 1, 13 October 2005)* were similar with the two dosages. Regarding the co-primary endpoint “severity of hot flushes” the difference between the two dosages was numerically small. With regard to secondary endpoints some statistical significant differences favouring the higher dose, e.g. regarding 75% responder rate, were noted, while regarding other secondary endpoints such as vasomotor function scale of MENQOL, median time to 3 consecutive days of 50% reduction from baseline, or sleep outcomes the results were largely similar with the two doses. Thus, an increased efficacy of BZA 20 mg / CE 0.625 mg compared to BZA 20 mg / CE 0.45 mg was not demonstrated in the pivotal study.

With regard to VVA statistically significant differences vs. placebo were shown for BZA 20 / CE 0.45 mg only regarding increase in superficial cells and decrease in parabasal cells, not regarding vaginal pH and the most bothersome symptom. For BZA 20 / CE 0.625 mg statistically significant differences vs. placebo were shown with regards to all these 4 co-primary endpoints. Regarding treatment of VVA there is a consensus that topical

low dose oestrogens should be used (see e.g. de Villiers TJ et al.: Global consensus statement on menopausal hormone therapy. Climacteric 2013; 16: 203-204; Panay N et al.: The 2013 British Menopause Society and Women´s Health Concern recommendations on hormone replacement therapy. Menopause Int 19; 2013: 59-68). Topical oestrogens have proven efficacious for VVA and are associated with lower systemic exposure as compared to oestrogens. Thus, with regard to the therapeutic indication "oestrogen deficiency symptoms in postmenopausal women", efficacy of BZA/CE in the treatment of VMS is of primary interest.

In summary with regard to hot flushes, the endpoint of primary interest, efficacy of both dose strengths initially applied for vs. placebo was shown. However, the available data indicate that the efficacy of CE in the treatment of oestrogen deficiency syndrome is decreased in the combination BZA/CE compared to CE/MPA. In addition, superior efficacy of the higher dose strength BZA 20 mg / CE 0.625 mg compared to the lower dose BZA 20 mg / CE 0.45 mg has not been demonstrated. Consequently, the Applicant has withdrawn the higher dose strength BZA 20 mg / CE 0.625 mg from the current application.

Treatment of Osteoporosis

Generally higher doses of CEs induced larger increases in BMD while increases in the BZA dosage attenuated the effects of CEs. As regards changes in BMD the results clearly favour the BZA 10 mg dose groups. Nevertheless, for BZA/CE combinations containing 20 mg of BZA effects on BMD at lumbar spine were more pronounced than with raloxifene 60 mg while in the BZA monotherapy clinical programme, effects of BZA 20 mg on BMD were comparable to that seen with raloxifene 60 mg (*EPAR Conbriza EMEA/H/C/000913*). However, these results are based on study 303 which was classified as GCP non-compliant and should therefore not be taken into account for the assessment of efficacy of BZA/CE.

For the investigated doses of BZA/CE 20 mg / 0.45 mg and 20 mg / 0.625 mg no additive or synergistic effect on skeletal endpoints of the FDC over the active comparators BZA 20 mg and CE/MPA has been shown in trial 3307; changes in BMD were not statistically significant between BZA monotherapy, BZA/CE, and CE/MPA groups, but effects were most pronounced with CE/MPA. It should be taken into account that the data for the active comparator CE/MPA are limited to the lower possible dose of CE of 0.45 mg instead of 0.625 mg. This dose is not licensed in some member states of the EU. Data on a direct comparison with CE/MPA containing 0.625 mg have not been provided, but even more pronounced effects on BMD might be expected with this combination. In a FDC both components should contribute to the effect of the combination but the doses of BZA/CE 20 mg / 0.45 mg and 20 mg / 0.625 mg did not appear to be more efficacious compared to monotherapy with BZA 20 mg or CE/MPA.

In conclusion, the added value of the FDC over the mono-components for the proposed indication of treatment of osteoporosis, even considering proposed revised wording during the procedure, has not been shown and is lacking adequate justification. The required long-term treatment for this indication is not considered to be in line with the Core SmPC for Hormone Replacement Therapy products. Furthermore results are only based on substudies of the clinical trials 303 and 3307; these substudies are not considered pivotal. In addition, study 303 was classified as GCP non-compliant and should not be taken into account for the assessment of efficacy of BZA/CE leaving only 1 trial delivering valid data for the assessment of efficacy of the BZA/CE in osteoporosis. In consequence the Applicant has withdrawn the osteoporosis treatment claim from the current procedure.

2.6. Clinical safety

The safety analysis is based on data of the five Phase 3 studies 3115A1-303-US/EU/BR, 3115A1-304-WW, 3115A1-305-US, 3115A1-306-WW, and 3115A1-3307-WW as well as additional supportive data from Phase 1 and Phase 2 studies. This includes 20 Phase 1 studies all of which were conducted in healthy postmenopausal women and a single Phase 2 study (Study 203) in healthy postmenopausal women experiencing moderate to severe VMS.

Patient exposure

The safety population consisted of all subjects who were randomly assigned and received at least 1 dose of test article. For the safety analyses the overall safety population including all data up to 2-years of treatment was comprised of all subjects enrolled in the 5 Phase 3 studies 303, 304, 305, 306, and 3307. Details of the five different study groupings provided by the Applicant and the exposure per group is given in the following table.

Table 31: Safety Population Grouping in Summary of Clinical Safety From all Phase 3 Studies

Safety Population Exposure Time Points	Studies in Population	Treatment Group	N[a]
3-Month			
	303,304, 305, 306, and 3307	BZA 20 mg / CE 0.45 mg	1585
		BZA 20 mg / CE 0.625 mg	1583
		BZA 20/CE[b]	3168
		All BZA/CE[c]	4868
		Placebo	1241
		CE 0.45 mg / MPA 1.5 mg	399
		BZA 20 mg	340
		Raloxifene 60 mg	423
1-Year			
	303, 304, and 3307	BZA 20 mg / CE 0.45 mg	1239
		BZA 20 mg / CE 0.625 mg	1237
		BZA 20/CE[b]	2476
		All BZA/CE[c]	4176
		Placebo	1073
		CE 0.45 mg / MPA 1.5 mg	399
		BZA 20 mg	230
		Raloxifene 60 mg	423
		Total in Safety Population	6301
Cumulative Data up to 2-Year			
	303,304, 305, 306, and 3307	BZA 20 mg / CE 0.45 mg	1585
		BZA 20 mg / CE 0.625 mg	1583
		BZA 20/CE[b]	3168
		All BZA/CE[c]	4868
		Placebo	1241
		CE 0.45 mg / MPA 1.5 mg	399
		BZA 20 mg	340
		Raloxifene 60 mg	423
		Total in Safety Population	7271

Safety Population Exposure Time Points	Studies in Population	Treatment Group	N[a]
Studies of 3 Months Duration			
	305, 306	BZA 20 mg / CE 0.45 mg	346
		BZA 20 mg / CE 0.625 mg	346
		BZA 20 mg / CE[b]	692
		Placebo	168
		BZA 20 mg	110
		Total in Safety Population	970
VMS Populations[d]			
	305, subpopulation of 303 with VMS	BZA 20 mg / CE 0.45 mg	150
		BZA 20 mg / CE 0.625 mg	157
		BZA 20 mg / CE[b]	307
		All BZA/CE[c]	407
		Placebo	96
		Raloxifene 60 mg	24
		Total in Safety Population	527

BZA = bazedoxifene; CE = conjugated oestrogens; VMS = vasomotor symptoms.
Number of subjects who took at least 1 dose of test article.
This group is the combined subjects for the BZA 20 mg / CE 0.45 mg plus the BZA 20 mg / CE 0.625 mg groups.
Includes the 6 combinations: BZA 10 mg / CE 0.45 mg, BZA 20 mg / CE 0.45 mg, BZA 40 mg / CE 0.45 mg, BZA 10 mg / CE 0.625 mg, BZA 20 mg / CE 0.625 mg, and BZA 40 mg / CE 0.625 mg treatment groups.
Includes data from Study 305 and a subpopulation of Study 303 with at least 7 moderate to severe hot flushes per day or 50 per week at baseline. The number of subjects is similar for each time point.
Source: Group D1, demo04_ag.htm

Additionally, safety data from the BZA monotherapy programme has been included (Phase 3 studies 301-WW [3-year core, two 2-year double-blind extensions], 300-GL [2 year], 303-AP; Phase 2 studies 200-BR, 204-US/CA, 205-CN, 207-JA; 18 Phase 1 studies).

A summary of the number of subjects exposed to study medication for up to 2 years in the 5 Phase 3 studies is presented by group in the following table.

Table 32: Overall Exposure - Number (%) of Subjects Beginning Each Treatment Interval: All Data Up to 2-Year for Studies 303, 304, 305, 306, 3307

	Treatment				
Treatment Interval	BZA 20/CE 0.45 n=1585	BZA 20/CE 0.625 n=1583	BZA 20/CE n=3168	All BZA/CE n=4868	Placebo n=1241
Week 12	1468 (93)	1466 (93)	2934 (93)	4526 (93)	1156 (93)
Week 25-28	1089 (69)	1097 (69)	2186 (69)	3655 (75)	934 (75)
Week 53-56	536 (34)	539 (34)	1075 (34)	2372 (49)	451 (36)
Week 101-104	440 (28)	428 (27)	868 (27)	1999 (41)	360 (29)
Week 105+	67 (4)	78 (5)	145 (5)	341 (7)	72 (6)

BZA = bazedoxifene; CE = conjugated oestrogens.
n represents the total number of subjects beginning each treatment interval.
Study durations were different across studies and thus percentages do not solely reflect dropout rates
Source: Modified from 2.7.4 BZA/CE Summary of Clinical Safety, Table 1-8.

Overall, more than 1,000 women have been exposed to the fixed dose combinations of BZA/CE with 20 mg BZA for more than 1 year and more than 850 have been exposed for 2 years. Data for the fixed dose combination are sparse beyond 2 years of exposure except for BZA monotherapy where data for up to 7 years are available.

Adverse events

A full picture over the safety of the BZA/CE combinations was hampered by the Applicant's data presentation in the Clinical Overview and Summary of Clinical Safety which only included comparisons with placebo given that the dossier contains 3 studies with active comparators, namely studies 306 (BZA), 303 (raloxifene), and 3307 (CE/MPA and BZA). The evaluation of the safety therefore focused on the BZA 20 mg / CE 0.45 mg and BZA

20 mg / CE 0.625 mg, and placebo findings. Further data regarding adverse events were provided during this procedure for raloxifene and CE/MPA.

Most common adverse events

The analysis of the most common AEs (≥ 10%) did not reveal any unexpected findings. Details are given in the following table:

Table 33: Most common AEs (≥ 10%) in the Different Analysis Sets

AE	Analysis	BZA/CE 20 mg / 0.45 mg	BZA/CE 20 mg / 0.625 mg	Placebo
		N (%)	N (%)	N (%)
Headache	2 years	479 (30.2)	480 (30.3)	396 (31.9)
	1 Year	299 (24.1)	299 (24.2)	302 (28.1)
	3 month	299 (18.9)	290 (18.3)	251 (20.2)
Nasopharyngitis	2 years	299 (18.9)	274 (17.3)	184 (14.8)
	1 Year	202 (16.3)	182 (14.7)	128 (11.9)
	3 month			
Back pain	2 years	300 (18.9)	321 (20.3)	234 (18.9)
	1 Year	190 (15.3)	215 (17.4)	160 (14.9)
	3 month			
Arthralgia	2 years	274 (17.3)	285 (18.0)	239 (19.3)
	1 Year	175 (14.1)	188 (15.2)	184 (17.1)
	3 month			
Pain in extremity	2 years	196 (12.4)	192 (12.1)	178 (14.3)
	1 Year	126 (10.2)	126 (10.2)	122 (11.4)
	3 month			
Influenza	2 years	182 (11.5)	(159; 10.0).	(134; 10.8),
	1 Year	131 (10.6)		
	3 month			
Myalgia	2 years	181 (11.4)		127 (10.2)
	1 Year			
	3 month			

The AE profile for the Studies 305 and 306 combined was similar to the overall AE data from the integrated 3 months treatment duration data as well as for the VMS subpopulation (Study 305, Study 303 subpopulation) for all time points.

Treatment-emergent adverse events

The analysis of treatment emergent adverse events (TEAEs) included the active phase of the study from the first dose of double-blind therapy through 30 days after the last dose of study medication.

According to the original dossier about 3 to 4% of women experienced treatment emergent adverse events considered severe and related to therapy by the investigators; there were no clear pattern or significant differences in treatment emergent adverse events between groups. However, the GCP inspection findings clearly indicated that the relatedness of AEs has not adequately been assessed and that there is considerable underreporting in this regard. Therefore the Applicant was asked to provide updated overall numbers of adverse events considered to be related, using a most conservative approach in reassessing relatedness. It was agreed that the Applicant has taken a sufficiently conservative approach to report the safety profile in the proposed

SmPC for BZA/CE. No further improvement in the quality of the safety data reporting is expected from further analyses and updates. Considerable doubts as relates to the quality of the safety data for BZA/CE remain and will be considered in the benefit-risk evaluation.

Table 34: Treatment-Emergent Adverse Events Reported for ≥ 5% of Subjects in any Treatment Group - Number (%) of Subjects: Cumulative Data up to 2-Year for Studies 303, 304, 305, 306, 3307

	Treatment				
System Organ Class[a] Preferred Term	BZA 20/CE 0.45 n=1585	BZA 20/CE 0.625 n=1583	BZA 20/CE n=3168	All BZA/CE n=4868	Placebo n=1241
Any Adverse Event	1334 (84.2)	1342 (84.8)	2676 (84.5)	4250 (87.3)	1053 (84.9)
Gastrointestinal disorders					
Abdominal pain	89 (5.6)	94 (5.9)	183 (5.8)	362 (7.4)	58 (4.7)
Abdominal pain upper	100 (6.3)	89 (5.6)	189 (6.0)	392 (8.1)	53 (4.3)
Constipation	74 (4.7)	76 (4.8)	150 (4.7)	268 (5.5)	55 (4.4)
Diarrhoea	107 (6.8)	79 (5.0)	186 (5.9)	311 (6.4)	67 (5.4)
Dyspepsia	90 (5.7)	73 (4.6)	163 (5.1)	304 (6.2)	67 (5.4)
Nausea	118 (7.4)	90 (5.7)	208 (6.6)	332 (6.8)	60 (4.8)
Infections and infestations					
Influenza	161 (10.2)	137 (8.7)	298 (9.4)	616 (12.7)	122 (9.8)
Nasopharyngitis	248 (15.6)	232 (14.7)	480 (15.2)	739 (15.2)	154 (12.4)
Sinusitis	98 (6.2)	99 (6.3)	197 (6.2)	329 (6.8)	91 (7.3)
Upper respiratory tract infection	120 (7.6)	118 (7.5)	238 (7.5)	423 (8.7)	90 (7.3)
Urinary tract infection	91 (5.7)	79 (5.0)	170 (5.4)	321 (6.6)	71 (5.7)
Musculoskeletal and connective tissue disorders					
Arthralgia	202 (12.7)	220 (13.9)	422 (13.3)	854 (17.5)	192 (15.5)
Back pain	226 (14.3)	256 (16.2)	482 (15.2)	880 (18.1)	171 (13.8)
Muscle spasms	137 (8.6)	115 (7.3)	252 (8.0)	427 (8.8)	70 (5.6)
Myalgia	130 (8.2)	119 (7.5)	249 (7.9)	473 (9.7)	99 (8.0)
Pain in extremity	163 (10.3)	153 (9.7)	316 (10.0)	585 (12.0)	148 (11.9)
Nervous system disorders					
Headache	324 (20.4)	323 (20.4)	647 (20.4)	1162 (23.9)	278 (22.4)
Psychiatric disorders					
Insomnia	87 (5.5)	65 (4.1)	152 (4.8)	295 (6.1)	93 (7.5)
Respiratory, thoracic and mediastinal disorders					
Cough	91 (5.7)	92 (5.8)	183 (5.8)	330 (6.8)	69 (5.6)
Oropharyngeal pain	69 (4.4)	62 (3.9)	131 (4.1)	281 (5.8)	50 (4.0)
Vascular disorders					
Hypertension	61 (3.8)	50 (3.2)	111 (3.5)	246 (5.1)	45 (3.6)

BZA = bazedoxifene; CE = conjugated oestrogens.
Classifications of adverse events are based on the Medical Dictionary for Regulatory Activities (MedDRA).
a: Totals for the number of Subjects at a higher level are not necessarily the sum of those at the lower levels since a subject may report two or more different adverse events within the higher level category.
Source: AE4_TEAE_AS_AD_4G_5% - 25JUN11 21:02

The most common severe drug-related treatment emergent adverse event was headache in all groups; as to be expected for hormone replacement therapy hot flush occurred more frequently in the placebo group.

Table 35: Treatment-related Treatment-Emergent Adverse Events Considered to be Severe in >1 Subject in any Treatment Group - Number (%) of Subjects: Cumulative Data up to 2-Year

	Treatment				
System Organ Class [a] Preferred Term	BZA 20 / CE 0.45 n=1585	BZA 20 / CE 0.625 n=1583	BZA 20/CE n=3168	All BZA/CE n=4868	Placebo n=1241
Any Adverse Event[b]	1334 (84.2)	1342 (84.8)	2676 (84.5)	4250 (87.3)	1053 (84.9)
All Severity / Related	391 (24.7)	384 (24.3)	775 (24.5)	1351 (27.8)	310 (25.0)
Severe / Related	47 (3.0)	53 (3.3)	100 (3.2)	204 (4.2)	40 (3.2)
Cardiac disorders					
Palpitations	1 (0.1)	1 (0.1)	2 (0.1)	3 (0.1)	0

System Organ Class [a] Preferred Term	Treatment: BZA 20 / CE 0.45 n=1585	BZA 20 / CE 0.625 n=1583	BZA 20/CE n=3168	All BZA/CE n=4868	Placebo n=1241
Gastrointestinal disorders					
Abdominal distension	0	0	0	2 (0.0)	1 (0.1)
Abdominal pain	1 (0.1)	2 (0.1)	3 (0.1)	7 (0.1)	2 (0.2)
Abdominal pain upper	1 (0.1)	2 (0.1)	3 (0.1)	9 (0.2)	0
Constipation	0	4 (0.3)	4 (0.1)	4 (0.1)	1 (0.1)
Diarrhoea	1 (0.1)	0	1 (0.0)	3 (0.1)	1 (0.1)
Dyspepsia	1 (0.1)	0	1 (0.0)	4 (0.1)	0
Nausea	2 (0.1)	1 (0.1)	3 (0.1)	7 (0.1)	0
General disorders and administration site conditions					
Chest pain	0	2 (0.1)	2 (0.1)	2 (0.0)	2 (0.2)
Fatigue	1 (0.1)	1 (0.1)	2 (0.1)	2 (0.0)	0
Irritability	0	2 (0.1)	2 (0.1)	2 (0.0)	0
Oedema peripheral	2 (0.1)	0	2 (0.1)	3 (0.1)	1 (0.1)
Pain	1 (0.1)	0	1 (0.0)	2 (0.0)	0
Hepatobiliary disorders					
Cholecystitis	1 (0.1)	0	1 (0.0)	2 (0.0)	0
Cholelithiasis	1 (0.1)	0	1 (0.0)	3 (0.1)	0
Infections and infestations					
Sinusitis	0	0	0	2 (0.0)	0
Investigations					
Alanine aminotransferase increased	0	0	0	2 (0.0)	0
Aspartate aminotransferase increased	0	0	0	2 (0.0)	0
Blood triglycerides increased	2 (0.1)	0	2 (0.1)	4 (0.1)	0
Metabolism and nutrition disorders					
Hypertriglyceridaemia	2 (0.1)	2 (0.1)	4 (0.1)	10 (0.2)	0
Musculoskeletal and connective tissue disorders					
Arthralgia	0	1 (0.1)	1 (0.0)	4 (0.1)	0
Back pain	0	1 (0.1)	1 (0.0)	3 (0.1)	0
Muscle spasms	2 (0.1)	4 (0.3)	6 (0.2)	11 (0.2)	3 (0.2)
Myalgia	0	1 (0.1)	1 (0.0)	2 (0.0)	0
Pain in extremity	2 (0.1)	2 (0.1)	4 (0.1)	6 (0.1)	0
Nervous system disorders					
Dizziness	0	0	0	3 (0.1)	0
Headache	7 (0.4)	8 (0.5)	15 (0.5)	31 (0.6)	7 (0.6)
Migraine	1 (0.1)	4 (0.3)	5 (0.2)	5 (0.1)	3 (0.2)
Paraesthesia	0	1 (0.1)	1 (0.0)	2 (0.0)	0
Somnolence	2 (0.1)	0	2 (0.1)	2 (0.0)	0
Transient ischaemic attack	0	0	0	4 (0.1)	0
Psychiatric disorders					
Anxiety	1 (0.1)	0	1 (0.0)	2 (0.0)	0
Depression	0	2 (0.1)	2 (0.1)	3 (0.1)	0
Insomnia	0	2 (0.1)	2 (0.1)	2 (0.0)	1 (0.1)
Libido increased	1 (0.1)	1 (0.1)	2 (0.1)	2 (0.0)	0
Reproductive system and breast disorders					
Breast pain	5 (0.3)	0	5 (0.2)	5 (0.1)	1 (0.1)
Endometrial hyperplasia	0	1 (0.1)	1 (0.0)	8 (0.2)	0
Uterine haemorrhage	1 (0.1)	0	1 (0.0)	2 (0.0)	1 (0.1)
Uterine polyp	1 (0.1)	0	1 (0.0)	2 (0.0)	0
Vaginal haemorrhage	0	0	0	5 (0.1)	1 (0.1)
Vulvovaginal dryness	1 (0.1)	1 (0.1)	2 (0.1)	5 (0.1)	0
Skin and subcutaneous tissue disorders					
Alopecia	0	1 (0.1)	1 (0.0)	2 (0.0)	0
Hyperhidrosis	1 (0.1)	0	1 (0.0)	2 (0.0)	0
Night sweats	0	1 (0.1)	1 (0.0)	2 (0.0)	3 (0.2)
Rash	1 (0.1)	0	1 (0.0)	2 (0.0)	0
Vascular disorders					
Hot flush	3 (0.2)	5 (0.3)	8 (0.3)	13 (0.3)	11 (0.9)

Note: Treatment relationship and severity were assessed by the investigator.

Classifications of adverse events are based on the Medical Dictionary for Regulatory Activities (MedDRA).
a. Totals for the number of Subjects at a higher level are not necessarily the sum of those at the lower levels since a subject may report two or more different adverse events within the higher level category.
b. For each subject, adverse events are reported for the highest drug relationship within the highest severity (first priority) observed.
Source: AE4_TEAE_SEV_AS_AD_4G - 25JUN11 21:57

Adverse events of special interest

Because of the known SERM and CE class effects relevant AEs have been analysed; this included venous thromboembolic events (VTE), cardiovascular (CHD) events, cerebrovascular accidents (CVAs), and malignancies. Post-hoc an independent adjudication committee was initialised to review the AEs of special interest VTEs, CHD, and CVA.

The Applicant chose to use a meta-analytic approach to summarise these safety events. Incidence rates, rate differences, and relative risk versus placebo were first calculated for each study, then the incidence rates, differences in rate versus placebo, and relative rates were summarised across studies using an inverse variance approach, which resulted in a different weight for each study and endpoint. Poisson variance was selected for weighting based on large differences in study duration. To allow inclusion of the studies with no events, the number of such events was inflated by 0.5 events. Results are presented as incidence rates, risk differences, and relative risks. The 95% CIs presented are 'nominal' without adjustment for multiple comparisons.

Venous Thromboembolic Events (VTE)

VTEs were defined as any venous thrombosis involving a deep peripheral vein (DVT), any pulmonary embolus, or any other serious vein thrombosis (e.g. retinal vein thrombosis).

The number of women exposed and the number of events per group do not allow to assess differences per group. The absolute number of events in the clinical trial for this marketing application was 3 events in the BZ/CE 20 mg / 0.45 mg and none in the 20 mg / 0.625 mg group. The issue has to be followed post-authorisation.

Details on the incidence rates, risk differences and relative risks of VTEs as well as a comparison to historical data from the WHI trial are shown in the tables below.

Table 36: Frequency and Rate per 1000 Women-Years and Risk Difference Compared with Placebo for Venous Thromboembolic Events That Began On Treatment or Post Treatment: Cumulative Data up to 2-Years

Treatment Group	Subjects	Number of Events	Total Exposure W-Y	Incidence Rate[a] Per 1000 W-Y (95% CI)	Risk Difference[a] From Placebo Per 1000 W-Y (95% CI)	Relative Risk[a] to Placebo (95% CI)
Venous Thromboembolic Events (including DVT, PE, RVT and Other venous thromboembolic events)						
BZA 20/CE 0.45	1585	3	1605	0.30 (0.00,2.02)	-0.18 (-3.25, 2.88)	0.86 (0.18, 4.14)
BZA20/CE 0.625	1583	0	1604	0.00 (0.00,1.54)	-0.69 (-3.56, 2.18)	0.50 (0.09, 2.65)
BZA 20/CE	3168	3	3209	0.15 (0.00,1.02)	-0.24 (-2.78, 2.29)	0.43 (0.09, 2.07)
All BZA/CE[b]	4868	6	5843	0.69 (0.00,1.49)	0.07 (-2.45, 2.6)	0.48 (0.13, 1.77)
Placebo	1241	1	1326	0.59 (0.00,2.89)		

BZA = bazedoxifene; CE = conjugated oestrogens; CI = confidence interval; DVT=Deep vein thrombosis; PE=Pulmonary embolism; RVT=Retinal vein thrombosis; W-Y= Women-years.
a. Incidence rate, relative risk and risk difference from cumulative meta-analysis with inverse variance weighting (e/t2 for incidence rate; (e1/t12 + e2/t22) for risk difference; and (1/ e1 + 1/ e2) for relative risk.
b. All BZA/CE = BZA 10 mg / CE 0.45 mg, BZA 20 mg / CE 0.45 mg, BZA 40 mg / CE 0.45 mg, BZA 10 mg / CE 0.625 mg, BZA 20 mg / CE 0.625 mg, BZA 40 mg / CE 0.625 mg.
Source: 2.7.4, BZA/CE Summary of Clinical Safety, Table 2-23.

Since VTE is considered a known risk for BZA as well as CE, the Applicant has identified VTE as an important identified risk in the RMP and is proposing the addition of VTE as a Warning in the PI as well as a contraindication for women with "Active or past history of venous thromboembolism (deep venous thrombosis, pulmonary embolism, and retinal vein thrombosis)".

Cardiac Adverse Events

Based on the number of women exposed, the duration of treatment, and the lack of data in elderly women the available data do not allow to assess whether the risk of cardiac events for women treated with BZA 20 mg / CE compared to placebo or to historical data for CE/MPA from the WHI trial is increased. While a possible increase in the incidence of cardiac events for women treated with CE/MPA has been identified, the data provided for the registration of bazedoxifene monotherapy did not demonstrate an increased risk with either BZA 20 mg or 40 mg compared to placebo. The issue is reflected as an important potential risk in the RMP.

Cerebrovascular Events

Based on the number of women exposed, the duration of treatment, and the lack of data in elderly women the provided data do not allow to assess whether the incidence of cerebrovascular events for women treated with BZA 20 mg / CE compared to placebo or to historical data for CE/MPA from the WHI trial is increased. Cerebrovascular AEs were not increased with BZA monotherapy (Studies 300 and 301), while in the CE-alone substudy of the WHI Study there was an increased risk of ischemic stroke due to hormone therapy compared to placebo. The issue was considered to be an important potential risk and included in the RMP.

Cancer

Regarding the clinical trials investigating BZA/CE the duration of exposure is too short and the number of women exposed is too small to draw any conclusions regarding a possible risk of cancer, including breast cancer or ovarian cancer, associated with the fixed combination therapy of BZA 20 mg / CE.

For BZA monotherapy an increased risk of breast cancer has not been reported based on the available data. CE/MPA combination therapy has been associated with an increase in the risk of breast cancer (Chlebowski RT et al.: JAMA 2003; 289: 3243-3253). CE alone did not increase the risk of breast cancer compared to placebo in the WHI study (Stefanick ML et al.: JAMA 2006; 295: 1647-1657) while an increase in breast cancer risk with oestrogen alone was observed in the Million Women Study (Million Women Study Collaborators: Lancet 2003; 362: 419-427). Thus, data regarding the risk of breast cancer associated with CE monotherapy are not consistent. It should be noted that from the data available with respect to mammographic breast density in patients treated with BZA/CE, no conclusions regarding the risk of breast cancer can be drawn. The effect of BZA/CE on the risk of breast cancer is currently unknown and as such was included as important potential risk in the RMP.

As regards endometrial cancer no increase in risk was reported with BZA monotherapy; based on the available data while for conjugated oestrogens the risk of endometrial hyperplasia and carcinoma is increased when they are administered alone for prolonged periods. Endometrial hyperplasia and endometrial cancer are included as important potential risks in the RMP of BZA/CE.

Also in study 301 there were 5 cases of ovarian carcinoma with BZA 20 mg monotherapy versus no cases in the placebo group and 5 cases of thyroid cancer versus 1 case in the placebo group over the 7 years study period. No occurrence of ovarian cancer was reported for subjects in the BZA/CE 20 mg / 0.45 mg, 20 mg / 0.625 mg, or placebo groups. Ovarian cancer was reported in 2 of 4868 patients in all BZA/CE groups. Long-term use of oestrogen-only HRT is associated with a slightly increased risk of ovarian cancer. The effect of BZA/CE on the risk of ovarian cancer is currently unknown and hence included as important potential risk in the RMP.

Based on the available data overall the Applicant proposed to predefine breast cancer, ovarian cancer, endometrial cancer, lung cancer, thyroid cancer, and skin cancer as potential risks in the RMP. This was endorsed.

Gynaecological Safety

In contrast to other safety analyses safety data from Study 304 have been excluded from the assessment of endometrial safety. This is acceptable since the bioavailability of BZA from the formulation used in trial 304 was reduced as compared to the TBM formulation and in combination with 0.625 mg CE no adequate endometrial protection was achieved.

The following table presents the number and percentage of subjects who had AEs related to the endometrium excluding cancer reported during or after treatment in the four Phase 3 studies 303, 305, 306, and 3307, excluding study 304 data.

Table 37: Number (%) of Subjects Experiencing Selected Adverse Events Related to the Endometrium (Excluding Cancer) That Began On Treatment or Post Treatment - Cumulative Data up to 2-Year for Studies 303, 305, 306, 3307

	Treatment				
System Organ Class Preferred Term	BZA 20/CE 0.45 n=1224	BZA 20/CE 0.625 n=1234	BZA 20/CE n=2458	All BZA/CE n=4158	Placebo n=1069
Any Adverse Event	17 (1.4)	23 (1.9)	40 (1.6)	105 (2.5)	7 (0.7)
Investigations	0	0	0	1 (0.0)	0
Biopsy endometrium abnormal	0	0	0	1 (0.0)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps**, excluding cancer**)	0	0	0	2 (0.0)	0
Endometrial adenoma	0	0	0	2 (0.0)	0
Reproductive system and breast disorders	17 (1.4)	23 (1.9)	40 (1.6)	103 (2.5)	7 (0.7)
Endometrial disorder	2 (0.2)	2 (0.2)	4 (0.2)	11 (0.3)	0
Endometrial hyperplasia	2 (0.2)	4 (0.3)	6 (0.2)	35 (0.8)	2 (0.2)
Endometrial hypertrophy	3 (0.2)	8 (0.6)	11 (0.4)	19 (0.5)	2 (0.2)
Uterine polyp	11 (0.9)	10 (0.8)	21 (0.9)	43 (1.0)	4 (0.4)
Uterine, pelvic and broad ligament disorders	0	0	0	1 (0.0)	0
Uterine polyp	0	0	0	1 (0.0)	0

BZA = bazedoxifene; CE = conjugated oestrogens.
Classifications of adverse events are based on the Medical Dictionary for Regulatory Activities (MedDRA).
a. Totals for the number of Subjects at a higher level are not necessarily the sum of those at the lower levels since a subject may report two or more different adverse events within the higher level category.
Source: AE4_OTPT_ENDO_3033053063307_AD_4G - 20OCT11 16:11

It is noted that 1 case of endometrial malignancy was observed in the BZA 20 mg / CE 0.45 mg group of study 303. It should also be noted that the treatment duration of 3 months in study 305 and 306 was not sufficient for the investigation of endometrial safety as per EMA Guideline on HRT.

The results regarding endometrial thickness measured by TVUS from study 3307 which had a treatment duration of 1 year, are displayed below (results from study 303 are not displayed as this study was GCP non-compliant):

Table 38: Mean Changes From Baseline in Transvaginal Ultrasonography Findings at Month 12 and Follow- up in study 3307 (from tab. 10-37 of the study report, p. 258)

Parameter Treatment Data Analysis Interval[b]	N[c]	----Baseline---- Mean	SD	----Change --- Mean	SD	-----Adjusted[a]---- Mean	SE
Endometrium total thickness (mm)							
BZA 20 mg/CE 0.45 mg	445	2.51	0.89				
Month 12	356	2.53	0.89	0.17*	0.08	0.17*	0.08
Follow-up	12	2.67	0.90	0.87	1.00	0.95	0.48
BZA 20 mg/CE 0.625 mg	474	2.52	0.91				
Month 12	389	2.53	0.93	0.50***	0.09	0.51***	0.08
Follow-up	14	2.64	0.63	0.39	0.24	0.43	0.45
BZA 20 mg	230	2.45	0.80				
Month 12	183	2.46	0.81	0.12	0.08	0.09	0.11
Follow-up	6	2.28	0.92	0.18	0.45	-0.10	0.69
CE 0.45 mg/MPA 1.5 mg	220	2.46	0.82				
Month 12	157	2.48	0.84	0.79***	0.18	0.78***	0.12
Follow-up	10	2.61	0.78	-0.04	0.23	-0.02	0.53
Placebo	474	2.53	0.87				
Month 12	380	2.54	0.88	0.08	0.07	0.09	0.08
Follow-up	13	2.57	0.80	0.38	0.27	0.37	0.46

a. Adjusted means of change account for unbalance among treatments with respect to all other effects in model. Adjusted means should be interpreted with caution for small sample sizes.
b. All analyses are done independently by data analysis interval using data with non-missing baseline values.
c. The number of subjects with matching baseline.
Statistical significance at the 0.05, 0.01, and 0.001 levels is denoted by *, **, and ***, respectively.
Standard model of analysis: change=baseline treatment.
Abbreviations: BZA=bazedoxifene; CE=conjugated estrogens; MPA=medroxyprogesterone acetate; SD=standard deviation; SE=standard error

Thus, at month 12 statistical significant increases in endometrial thickness vs. baseline were reported in the BZA 20 mg / CE 0.45 mg group, the BZA 20 mg / CE 0.625 mg group and the CE 0.45 mg / MPA 1.5 mg group. All these increases were statistically significantly higher compared to the change vs. baseline in the placebo group.

Table 39: Number (%) of Subjects With Transvaginal Ultrasonography Results of Potential Clinical Importance (On-Therapy) up in study 3307 (from tab. 10-33 of the study report, p. 254)

Category Test (Units)	Overall p-Value[a]	BZA 20 mg /CE 0.45 mg	BZA 20 mg /CE 0.625 mg	BZA 20 mg	CE 0.45 mg /MPA 1.5 mg	Placebo
Total	0.194	77/385 (20.0)	102/418 (24.4)	40/195 (20.5)	51/182 (28.0)	88/408 (21.6)
Endometrial thickness (mm)	0.035*	45/384 (11.7)	64/417 (15.3)	16/195 (8.2)	31/181 (17.1)	6/405 (11.4)
Increase from baseline >3	0.009**	10/384 (2.6)	27/417 (6.5)	3/195 (1.5)	9/181 (5.0)	12/405 (3.0)
Increase from baseline >5	0.021*	4/384 (1.0)	10/417 (2.4)	0/195	5/181 (2.8)	2/405 (0.5)
Endometrial thickness >4	0.028*	44/384 (11.5)	64/417 (15.3)	16/195 (8.2)	31/181 (17.1)	45/405 (11.1)
Endometrial thickness >8	0.069	3/384 (0.8)	8/417 (1.9)	0/195	4/181 (2.2)	2/405 (0.5)

a. P-value for 5x2 contingency table based on Chi-square test.
b. Right and left ovarian volumes were combined.
Statistical significance at the 0.05, 0.01, and 0.001 levels is denoted by *, **, and ***, respectively.
Abbreviations: BZA=bazedoxifene; CE=conjugated estrogens; MPA=medroxyprogesterone acetate.

Statistical significance of the differences between each of the active treatment groups vs. placebo or between the different active treatment groups vs. each other was not tested. Numerically, the proportion of patients with TVUS findings of potential clinical importance regarding endometrial thickness results was higher in the BZA 20 mg / CE 0.625 mg group and the CE 0.45 mg / MPA 1.5 mg group, compared to the BZA 20 mg / CE 0.45 mg and the placebo group.

Ovarian volume was not adversely affected by BZA/CE 20 mg / 0.45 mg or 20 mg / 0.625 mg. The incidence of ovarian cysts was 6.8%, 9.1%, 10.6% and 12.0% in the BZA 20 mg / CE 0.45 mg group, the BZA 20 mg / CE 0.625 mg group, the CE 0.45 mg / MPA 1.5 mg group and the placebo group, respectively, in study 3307.

With regard to the bleeding pattern, the following results are available from study 3307: The percentage of subjects with amenorrhea from month 1 to 3 was 93.44%, 90.38%, 64.81%, and 92.13% in the BZA 20 mg / CE 0.45 mg group, the BZA 20 mg / CE 0.625 mg group, the CE 0.45 mg / MPA 1.5 mg group, and the placebo group, respectively. The percentage of subjects with amenorrhea from month 10 to 12 was 96.51%, 94.89%, 79.17%, and 93.40% in the BZA 20 mg / CE 0.45 mg group, the BZA 20 mg / CE 0.625 mg group, the CE 0.45 mg / MPA 1.5 mg group and the placebo group, respectively.

Thus, in the population included in study 3307 the bleeding pattern in the two BZA/CE groups was similar to placebo and more favourable compared to CE 0.45 mg / MPA 1.5 mg. However, it is noted that the dose of 1.5 mg MPA is low and that no comparison of the products applied for vs. CE 0.625 mg / MPA 2.5 mg or CE 0.625 mg / MPA 5 mg was provided. In addition the population of study 3307 was not selected based on a minimum frequency / severity of hot flushes and is therefore not identical with a population to be treated for VMA.

Fractures

Although differences are small adverse events of bone fracture occurred more often in patients treated with any combination of BZA and CE than with placebo. The Applicant provided additional analyses of the adverse events of bone fracture by summarising all potential osteoporotic fractures occurring ≥ 120 days after first dose of treatment considering the bone remodelling cycle of approximately 120 days. These analyses do not show clinically relevant differences between BZA/CE groups and placebo. When further subtracting potentially traumatic fractures confirmed by review of patient narratives for each fracture potentially osteoporotic fractures were equally distributed across treatment groups.

Table 40: Number (%) of Subjects With Adverse Events of Bone Fracture That Began on Treatment or Post Treatment - Cumulative Data up to 2-Years

System Organ Class [a] Preferred Term	Treatment: BZA 20/CE 0.45 n=1585	BZA 20/CE 0.625 n=1583	BZA 20/CE n=3168	All BZA/CE n=4868	Placebo n=1241
Any fracture adverse event					
Injury, poisoning and procedural complications	34 (2.1)	33 (2.1)	67 (2.1)	121 (2.5)	23 (1.9)
Ankle fracture	5 (0.3)	4 (0.3)	9 (0.3)	17 (0.3)	5 (0.4)
Avulsion fracture	0	1 (0.1)	1 (0.0)	1 (0.0)	0
Cervical vertebral fracture	0	0	0	0	1 (0.1)
Clavicle fracture	1 (0.1)	0	1 (0.0)	3 (0.1)	0
Compression fracture	0	0	0	1 (0.0)	0
Facial bones fracture	0	1 (0.1)	1 (0.0)	1 (0.0)	0
Femoral neck fracture	0	0	0	0	0
Fibula fracture	1 (0.1)	1 (0.1)	2 (0.1)	3 (0.1)	1 (0.1)
Foot fracture	12 (0.8)	9 (0.6)	21 (0.7)	37 (0.8)	8 (0.6)
Fracture	0	1 (0.1)	1 (0.0)	6 (0.1)	2 (0.2)
Fractured coccyx	0	1 (0.1)	1 (0.0)	1 (0.0)	0
Fractured sacrum	1 (0.1)	0	1 (0.0)	1 (0.0)	0
Hand fracture	1 (0.1)	2 (0.1)	3 (0.1)	8 (0.2)	1 (0.1)
Humerus fracture	0	0	0	1 (0.0)	1 (0.1)
Lower limb fracture	0	0	0	3 (0.1)	1 (0.1)
Open fracture	0	0	0	1 (0.0)	0
Pelvic fracture	0	1 (0.1)	1 (0.0)	1 (0.0)	0
Pubic rami fracture	1 (0.1)	0	1 (0.0)	1 (0.0)	0
Radius fracture	0	3 (0.2)	3 (0.1)	5 (0.1)	1 (0.1)
Rib fracture	5 (0.3)	3 (0.2)	8 (0.3)	13 (0.3)	2 (0.2)
Spinal compression fracture	0	0	0	1 (0.0)	0
Sternal fracture	0	0	0	1 (0.0)	0
Stress fracture	1 (0.1)	0	1 (0.0)	1 (0.0)	0
Thoracic vertebral fracture	0	1 (0.1)	1 (0.0)	1 (0.0)	0
Tibia fracture	1 (0.1)	0	1 (0.0)	1 (0.0)	0
Ulna fracture	0	0	0	1 (0.0)	0
Upper limb fracture	3 (0.2)	2 (0.1)	5 (0.2)	9 (0.2)	3 (0.2)
Wrist fracture	4 (0.3)	5 (0.3)	9 (0.3)	15 (0.3)	2 (0.2)
Musculoskeletal and connective tissue disorders	0	0	0	1 (0.0)	0
Pathological fracture	0	0	0	1 (0.0)	0

BZA=bazedoxifene acetate; CE=conjugated oestrogens.
Classifications of adverse events are based on the Medical Dictionary for Regulatory Activities (MedDRA).
a. Totals for the number of Subjects at a higher level are not necessarily the sum of those at the lower levels since a subject may report 2 or more different adverse events within the higher level category.
Source: AE4_OTPT_FRAC_AS_AD_AG - 20OCT11 20:23

Ocular Events

Since there have been post-marketing reports of ocular events associated with BZA monotherapy ocular events have been specifically assessed. Treatment with a fixed combination of BZA/CE did not result in an increase in the incidence of ocular adverse events compared to placebo.

Serious adverse event / deaths / other significant events

The analysis of deaths did not reveal an imbalance between groups.

A consolidated presentation and discussion of serious adverse events occurring in the BZA/CE 20 mg / 0.45 mg and 20 mg / 0.625 mg versus both BZA 20 mg and CE/MPA was not included in the Summary of Clinical Safety but contained in supportive tables in the annex and the design of these tables was not considered very

informative. However, the analysis of these data did not indicate relevant differences between active treatment groups as regards serious adverse events and thus no further information was requested.

Overall there are currently no significant differences identified in the incidence of serious adverse events between BZA 20 mg / CE and placebo, although small imbalances with low absolute numbers occurred. Serious adverse events of coronary artery disease, chest pain, cholecystitis, cholelithiasis, abnormal endometrium results, cerebrovascular accident, transient ischaemic attack, and deep vein thrombosis occurred more often with active treatment than with placebo.

Table 41: Number (%) of Subjects Reporting Serious Adverse Events: Cumulative Data up to 2-Years

	Treatment				
System Organ Class Preferred Term	**BZA 20 / CE 0.45 n=1585**	**BZA 20 / CE 0.625 n=1583**	**CE/MPA n=399**	**BZA 20 n=340**	**Placebo n=1241**
Any Adverse Event[a]	64 (4.0)	62 (3.9)	20 (5.0)	5 (1.5)	57 (4.6)
Cardiac disorders	2 (0.1)	5 (0.3)	0	0	4 (0.3)
Coronary artery disease	0	3 (0.2)	0	0	0
Myocardial infarction	2 (0.1)	1 (0.1)	0	0	2 (0.2)
Gastrointestinal disorders	4 (0.3)	7 (0.4)	1 (0.3)	1 (0.3)	4 (0.3)
General disorders and administration site conditions	3 (0.2)	6 (0.4)	2 (0.5)	1 (0.3)	4 (0.3)
Chest pain	1 (0.1)	4 (0.3)	0	0	0
Non-cardiac chest pain	2 (0.1)	1 (0.1)	1 (0.3)	1 (0.3)	2 (0.2)
Hepatobiliary disorders	5 (0.3)	3 (0.2)	1 (0.3)	0	3 (0.2)
Cholecystitis	3 (0.2)	1 (0.1)	1 (0.3)	0	0
Cholelithiasis	3 (0.2)	1 (0.1)	0	0	1 (0.1)
Investigations	1 (0.1)	2 (0.1)	0	0	3 (0.2)
Alanine aminotransferase increased	0	1 (0.1)	0	0	1 (0.1)
Aspartate aminotransferase increased	0	1 (0.1)	0	0	1 (0.1)
Biopsy endometrium abnormal	1 (0.1)	1 (0.1)	0	0	0
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	17 (1.1)	13 (0.8)	7 (1.8)	3 (0.9)	17 (1.4)
Basal cell carcinoma	3 (0.2)	6 (0.4)	4 (1.0)	1 (0.3)	4 (0.3)
Breast cancer	1 (0.1)	0	0	0	1 (0.1)
Malignant melanoma	2 (0.1)	2 (0.1)	0	0	3 (0.2)
Squamous cell carcinoma	1 (0.1)	0	1 (0.3)	0	2 (0.2)
Squamous cell carcinoma of skin	2 (0.1)	1 (0.1)	1 (0.3)	1 (0.3)	2 (0.2)
Uterine leiomyoma	2 (0.1)	0	0	0	0
Nervous system disorders	4 (0.3)	3 (0.2)	1 (0.3)	0	3 (0.2)
Cerebrovascular accident	0	1 (0.1)	0	0	0
Transient ischaemic attack	1 (0.1)	0	0	0	0
Psychiatric disorders	2 (0.1)	1 (0.1)	3 (0.8)	0	2 (0.2)
Renal and urinary disorders	4 (0.3)	1 (0.1)	0	0	1 (0.1)
Stress urinary incontinence	2 (0.1)	0	0	0	1 (0.1)
Urinary incontinence	1 (0.1)	0	0	0	0
Reproductive system and breast disorders	3 (0.2)	1 (0.1)	2 (0.5)	0	1 (0.1)
Endometrial hyperplasia	0	0	0	0	1 (0.1)
Ovarian cyst	1 (0.1)	0	0	0	0
Uterine polyp	0	0	0	0	0
Vaginal haemorrhage	0	0	0	0	0
Vascular disorders	5 (0.3)	2 (0.1)	2 (0.5)	0	1 (0.1)
Deep vein thrombosis	3 (0.2)	0	1 (0.3)	0	1 (0.1)
Hypertension	0	1 (0.1)	0	0	0

AE = adverse event; BZA = bazedoxifene; CE = conjugated oestrogens.
Classifications of adverse events are based on the Medical Dictionary for Regulatory Activities (MedDRA).
a. Totals for the number of Subjects at a higher level are not necessarily the sum of those at the lower levels since a subject may report 2 or more different adverse events within the higher level category.
Source: Excerpts from supportive table 1.46. page 5480 ff

Laboratory findings

Treatment with BZA 20 mg / CE had no clinically relevant influence on the lipid profile, C-reactive protein, plasma concentrations of homocysteine, mean fasting glucose levels, fasting insulin, parameters of liver or renal function, haemoglobin, haematocrit, or platelet counts, coagulation parameters, or thyroid stimulating hormone compared to placebo. Treatment with BZA 20 mg / CE 0.45 mg and BZA 20 mg / CE 0.625 mg was associated with an increase in serum triglycerides from baseline of approximately 16% and 20% at months 12 and 24, respectively; this is adequately reflected in the PI. Decreases from baseline in serum calcium, phosphorus, and alkaline phosphatase values were observed in all groups including placebo at all scheduled time points, but there were few occurrences of potentially clinically important decreases in calcium or phosphorus.

With respect to the coagulation system the Applicant has investigated several coagulation parameters to evaluate potential changes that might result in a higher risk for thromboembolic complications. Currently available data about patients with abnormal coagulation laboratory results during on- and post-therapy time periods do not show an association of the thromboembolic risk with the changes observed in the parameters of coagulation or fibrinolysis. Resistance to activated protein C or resistance to other markers for venous thromboembolism have not been measured which has to be reflected in the uncertainty of the knowledge about the unfavourable effects.

Vital Signs

The available data do not indicate an influence of treatment with a fixed combination of BZA/CE compared to placebo on changes in vital signs or blood pressure.

Safety in special populations

No clear pattern or clinical relevance of differences in adverse events in special populations between BZA 20m mg / CE and placebo treated women has been seen in the data provided. However, the amount of data in the elderly as well as in women of other than white ethnicity is very limited and thus no definite conclusion as regards age and ethnicity can be drawn. “Use in elderly patients” was included as missing information in the RMP.

Immunological events

N/A

Safety related to drug-drug interactions and other interactions

No drug interaction studies were conducted with BZA/CE, which was considered acceptable.

Discontinuation due to AEs

The validity of the assessment of discontinuations due to AEs has been questioned for the investigated sites of study 303 in the GCP inspection report. The Applicant has therefore provided updated analyses of discontinuation due to AEs including analyses of relative frequencies calculated without data from investigator sites 447 and 450 of trial 303 together with a discussion of possible differences in relative frequencies as requested. The Applicant has also conducted an additional analysis of AEs leading to discontinuation for the integrated data from all 5 Phase 3 studies (Studies 303, 304, 305, 306 and 3307) after excluding data from sites

447 and 450. The provided analyses do not indicate significant differences in the rates of discontinuation due to AEs re-analyses and the original analyses.

Table 42: Adverse Events Leading to Discontinuation From Study in ≥3 Subjects in Any Treatment Group: Cumulative Data up to 2 years for Study 303 (Excluding Sites 447 and 450)

		---------- CE 0.625 mg ----------			---------- CE 0.45 mg ----------				
Body System[a] Adverse Event	Overall P-value	BZA 10 mg n=283	BZA 20 mg n=266	BZA 40 mg n=271	BZA 10 mg n=283	BZA 20 mg n=284	BZA 40 mg n=275	Raloxifene n=274	Placebo n=281
Any Adverse Event	0.369	51 (18.0)	36 (13.5)	37 (13.7)	41 (14.5)	31 (10.9)	38 (13.8)	43 (15.7)	47 (16.7)
Body as a whole	0.567	7 (2.5)	9 (3.4)	5 (1.8)	6 (2.1)	5 (1.8)	7 (2.5)	4 (1.5)	11 (3.9)
Asthenia	0.002**	0	4 (1.5)	0	0	0	0	0	1 (0.4)
Headache	0.247	2 (0.7)	3 (1.1)	1 (0.4)	0	1 (0.4)	3 (1.1)	1 (0.4)	5 (1.8)
Cardiovascular system	0.030*	9 (3.2)	9 (3.4)	9 (3.3)	6 (2.1)	6 (2.1)	15 (5.5)	17 (6.2)	18 (6.4)
Coronary artery disorder	0.028*	3 (1.1)	1 (0.4)	0	0	0	0	0	0
Hypertension	0.013*	1 (0.4)	4 (1.5)	0	0	0	2 (0.7)	0	0
Vasodilatation	<0.001***	1 (0.4)	1 (0.4)	3 (1.1)	5 (1.8)	4 (1.4)	8 (2.9)	17 (6.2)	16 (5.7)
Metabolic and nutritional	0.116	5 (1.8)	2 (0.8)	4 (1.5)	10 (3.5)	1 (0.4)	3 (1.1)	5 (1.8)	5 (1.8)
Hypercholesteremia	0.029*	0	0	0	3 (1.1)	0	0	0	1 (0.4)
SGOT increased	0.337	1 (0.4)	0	0	1 (0.4)	0	1 (0.4)	3 (1.1)	1 (0.4)
SGPT increased	0.337	1 (0.4)	0	0	1 (0.4)	0	1 (0.4)	3 (1.1)	1 (0.4)
Weight gain	0.388	1 (0.4)	1 (0.4)	1 (0.4)	4 (1.4)	0	1 (0.4)	1 (0.4)	1 (0.4)
Musculoskeletal system	0.003**	1 (0.4)	0	1 (0.4)	5 (1.8)	2 (0.7)	2 (0.7)	2 (0.7)	9 (3.2)
Arthralgia	0.028*	0	0	0	3 (1.1)	0	0	1 (0.4)	0
Osteoporosis	0.027*	0	0	1 (0.4)	0	0	0	0	3 (1.1)
Nervous system	0.659	8 (2.8)	6 (2.3)	6 (2.2)	3 (1.1)	8 (2.8)	3 (1.1)	4 (1.5)	6 (2.1)
Depression	0.509	2 (0.7)	1 (0.4)	4 (1.5)	1 (0.4)	1 (0.4)	2 (0.7)	0	2 (0.7)
Urogenital system	<0.001***	21 (7.4)	8 (3.0)	6 (2.2)	7 (2.5)	8 (2.8)	2 (0.7)	5 (1.8)	5 (1.8)
Breast pain	0.111	1 (0.4)	0	1 (0.4)	0	3 (1.1)	0	0	3 (1.1)
Endometrial hyperplasia	<0.001***	7 (2.5)	1 (0.4)	0	2 (0.7)	0	0	0	0
Vaginal hemorrhage	<0.001***	6 (2.1)	1 (0.4)	0	0	2 (0.7)	0	0	0

[a] Body system totals for the number of subjects are not necessarily the sum of the individual AEs, since a subject may report two or more different AEs in the same body system. Also, some of the preferred terms under the body system are not included in this table because of the cut-off used for this table (≥3 subjects in any treatment group).
Overall P-value: Refers to No. of Subjects data. P-value for Chi-Square.
Statistical significance at the .05, .01, .001 levels is denoted by *, **, *** respectively.
Abbreviations: SGOT=Serum glutamic oxaloacetic transaminase (aspartate aminotransferase); SGPT=serum glutamic-pyruvic transaminase (alanine aminotransferase).
Note: Four of the AEs listed in the text as differing significantly in incidence among the treatment groups (migraine, flatulence, endometrial neoplasia, and urticaria) are not included in this table because of the cut-off used for this table (≥3 subjects in any treatment group).
Source: Module 5.3.5.1: Study 3115A1-303-US/EU/BR (CSR-64104), Report AE5_W_R – 17SEP10 17:59

Table 43: Adverse Events Leading to Discontinuation From Study in ≥3 Subjects in Any Treatment Group: Cumulative Data up to 2 years for Study 303 (for All Sites)

Body System[a] Adverse Event	Overall P-value	CE 0.625 mg: BZA 10 mg n=430	CE 0.625 mg: BZA 20 mg n=414	CE 0.625 mg: BZA 40 mg n=417	CE 0.45 mg: BZA 10 mg n=430	CE 0.45 mg: BZA 20 mg n=433	CE 0.45 mg: BZA 40 mg n=423	Raloxifene n=423	Placebo n=427
Any Adverse Event	0.283	67 (15.6)	53 (12.8)	50 (12.0)	63 (14.7)	47 (10.9)	46 (10.9)	60 (14.2)	62 (14.5)
Body as a whole	0.554	9 (2.1)	15 (3.6)	11 (2.6)	15 (3.5)	10 (2.3)	10 (2.4)	12 (2.8)	18 (4.2)
Abdominal pain	0.652	4 (0.9)	1 (0.2)	4 (1.0)	7 (1.6)	3 (0.7)	3 (0.7)	4 (0.9)	4 (0.9)
Asthenia	0.002**	0	5 (1.2)	0	0	0	0	1 (0.2)	2 (0.5)
Back pain	0.355	1 (0.2)	0	1 (0.2)	3 (0.7)	0	1 (0.2)	0	1 (0.2)
Chest pain	0.540	2 (0.5)	1 (0.2)	0	0	1 (0.2)	1 (0.2)	3 (0.7)	2 (0.5)
Headache	0.224	3 (0.7)	4 (1.0)	1 (0.2)	1 (0.2)	2 (0.5)	3 (0.7)	2 (0.5)	7 (1.6)
Pain	0.461	3 (0.7)	1 (0.2)	3 (0.7)	0	2 (0.5)	0	2 (0.5)	1 (0.2)
Cardiovascular system	0.045*	11 (2.6)	14 (3.4)	11 (2.6)	9 (2.1)	8 (1.8)	19 (4.5)	19 (4.5)	22 (5.2)
Coronary artery disorder	0.081	3 (0.7)	2 (0.5)	0	0	0	0	0	1 (0.2)
Hypertension	0.002**	1 (0.2)	5 (1.2)	0	0	0	3 (0.7)	0	0
Vasodilatation	<0.001***	1 (0.2)	1 (0.2)	4 (1.0)	5 (1.2)	4 (0.9)	9 (2.1)	18 (4.3)	16 (3.7)
Digestive system	0.789	4 (0.9)	5 (1.2)	8 (1.9)	5 (1.2)	6 (1.4)	5 (1.2)	9 (2.1)	8 (1.9)
Abdominal distension	0.401	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)	0	2 (0.5)	4 (0.9)	1 (0.2)
Nausea	0.094	0	1 (0.2)	1 (0.2)	2 (0.5)	2 (0.5)	0	5 (1.2)	4 (0.9)
Metabolic and nutritional	0.113	9 (2.1)	6 (1.4)	5 (1.2)	11 (2.6)	1 (0.2)	3 (0.7)	7 (1.7)	6 (1.4)
Hypercholesteremia	0.086	0	1 (0.2)	0	3 (0.7)	0	0	0	1 (0.2)
Hyperlipemia	0.131	1 (0.2)	4 (1.0)	2 (0.5)	2 (0.5)	0	1 (0.2)	0	0
Peripheral edema	0.138	5 (1.2)	0	2 (0.5)	1 (0.2)	1 (0.2)	0	2 (0.5)	3 (0.7)
SGOT increased	0.343	1 (0.2)	0	0	1 (0.2)	0	1 (0.2)	3 (0.7)	1 (0.2)
SGPT increased	0.343	1 (0.2)	0	0	1 (0.2)	0	1 (0.2)	3 (0.7)	1 (0.2)
Weight gain	0.467	1 (0.2)	2 (0.5)	1 (0.2)	4 (0.9)	0	1 (0.2)	2 (0.5)	1 (0.2)
Musculoskeletal system	0.044*	3 (0.7)	3 (0.7)	2 (0.5)	8 (1.9)	5 (1.2)	3 (0.7)	3 (0.7)	11 (2.6)
Arthralgia	0.127	2 (0.5)	1 (0.2)	0	4 (0.9)	0	1 (0.2)	1 (0.2)	0
Bone disorder	0.191	0	1 (0.2)	1 (0.2)	1 (0.2)	3 (0.7)	1 (0.2)	0	4 (0.9)
Osteoporosis	0.026*	0	0	1 (0.2)	0	0	0	0	3 (0.7)
Nervous system	0.427	9 (2.1)	10 (2.4)	8 (1.9)	3 (0.7)	10 (2.3)	4 (0.9)	6 (1.4)	8 (1.9)
Depression	0.637	3 (0.7)	2 (0.5)	5 (1.2)	1 (0.2)	2 (0.5)	3 (0.7)	1 (0.2)	2 (0.5)
Urogenital system	<0.001***	27 (6.3)	8 (1.9)	6 (1.4)	12 (2.8)	12 (2.8)	3 (0.7)	6 (1.4)	7 (1.6)
Breast pain	0.018*	1 (0.2)	0	1 (0.2)	0	4 (0.9)	0	0	4 (0.9)
Endometrial hyperplasia	<0.001***	11 (2.6)	1 (0.2)	0	4 (0.9)	0	0	0	0
Vaginal hemorrhage	0.002**	6 (1.4)	1 (0.2)	0	1 (0.2)	3 (0.7)	0	0	0

[a] Body system totals for the number of subjects are not necessarily the sum of the individual AEs, since a subject may report two or more different AEs in the same body system. Also, some of the preferred terms under the body system are not included in this table because of the cut-off used for this table (≥3 subjects in any treatment group).
Overall P-value: Refers to No. of Subjects data. P-value for Chi-Square.
Statistical significance at the .05, .01, .001 levels is denoted by *, **, *** respectively.
Note: Two of the AEs listed in the text as differing significantly in incidence among the treatment groups (migraine and urticaria) are not included in this table because of the cut-off used for this table (≥3 subjects in any treatment group).
Abbreviations: SGOT=Serum glutamic oxaloacetic transaminase (aspartate aminotransferase); SGPT=serum glutamic-pyruvic transaminase (alanine aminotransferase).
Source: Module 5.3.5.1: Study 3115A1-303 (CSR-64104), Supportive Table 15.98

Table 44: Adverse Events Leading to Discontinuation From Study in ≥5 Subjects in Any Treatment Group: Cumulative Data up to 2 years for Studies 303 (Excluding Sites 447 and 450), 304, 305, 306, and 3307

System Organ Class[a] Preferred Term	Treatment				
	BZA 20/CE 0.45 n=1436	BZA 20/CE 0.625 n=1435	BZA 20/CE n=2871	All BZA/CE n=3983	Placebo n=1095
Any Adverse Event	116 (8.1)	118 (8.2)	234 (8.2)	401 (10.1)	113 (10.3)
Cardiac disorders	5 (0.3)	6 (0.4)	11 (0.4)	20 (0.5)	2 (0.2)
Coronary artery disease	0	2 (0.1)	2 (0.1)	5 (0.1)	0
Palpitations	0	2 (0.1)	2 (0.1)	5 (0.1)	1 (0.1)
Gastrointestinal disorders	19 (1.3)	18 (1.3)	37 (1.3)	54 (1.4)	8 (0.7)
Abdominal distension	1 (0.1)	4 (0.3)	5 (0.2)	10 (0.3)	0
Abdominal pain	2 (0.1)	3 (0.2)	5 (0.2)	9 (0.2)	0
Dyspepsia	2 (0.1)	4 (0.3)	6 (0.2)	7 (0.2)	1 (0.1)
Nausea	7 (0.5)	2 (0.1)	9 (0.3)	11 (0.3)	4 (0.4)
General disorders and administration site conditions	11 (0.8)	11 (0.8)	22 (0.8)	32 (0.8)	10 (0.9)
Chest pain	2 (0.1)	2 (0.1)	4 (0.1)	5 (0.1)	1 (0.1)
Fatigue	3 (0.2)	4 (0.3)	7 (0.2)	7 (0.2)	1 (0.1)
Oedema peripheral	2 (0.1)	0	2 (0.1)	6 (0.2)	3 (0.3)
Pain	3 (0.2)	1 (0.1)	4 (0.1)	5 (0.1)	0
Investigations	13 (0.9)	13 (0.9)	26 (0.9)	47 (1.2)	8 (0.7)
Alanine aminotransferase increased	1 (0.1)	1 (0.1)	2 (0.1)	5 (0.1)	1 (0.1)
Blood pressure increased	0	3 (0.2)	3 (0.1)	5 (0.1)	0
Weight increased	3 (0.2)	5 (0.3)	8 (0.3)	15 (0.4)	5 (0.5)
Musculoskeletal and connective tissue disorders	15 (1.0)	14 (1.0)	29 (1.0)	45 (1.1)	25 (2.3)
Arthralgia	2 (0.1)	1 (0.1)	3 (0.1)	6 (0.2)	4 (0.4)
Back pain	4 (0.3)	3 (0.2)	7 (0.2)	12 (0.3)	5 (0.5)
Muscle spasms	5 (0.3)	3 (0.2)	8 (0.3)	9 (0.2)	5 (0.5)
Myalgia	2 (0.1)	2 (0.1)	4 (0.1)	5 (0.1)	1 (0.1)
Osteoporosis	0	1 (0.1)	1 (0.0)	2 (0.1)	5 (0.5)
Nervous system disorders	11 (0.8)	19 (1.3)	30 (1.0)	46 (1.2)	12 (1.1)
Headache	2 (0.1)	8 (0.6)	10 (0.3)	16 (0.4)	7 (0.6)
Transient ischaemic attack	1 (0.1)	0	1 (0.0)	5 (0.1)	0
Psychiatric disorders	11 (0.8)	12 (0.8)	23 (0.8)	39 (1.0)	12 (1.1)
Anxiety	3 (0.2)	4 (0.3)	7 (0.2)	8 (0.2)	1 (0.1)
Depression	3 (0.2)	5 (0.3)	8 (0.3)	16 (0.4)	4 (0.4)
Insomnia	2 (0.1)	3 (0.2)	5 (0.2)	7 (0.2)	3 (0.3)
Reproductive system and breast disorders	12 (0.8)	18 (1.3)	30 (1.0)	59 (1.5)	13 (1.2)
Breast pain	3 (0.2)	2 (0.1)	5 (0.2)	7 (0.2)	3 (0.3)
Endometrial hyperplasia	0	3 (0.2)	3 (0.1)	12 (0.3)	0
Vaginal haemorrhage	3 (0.2)	2 (0.1)	5 (0.2)	9 (0.2)	1 (0.1)
Skin and subcutaneous tissue disorders	10 (0.7)	6 (0.4)	16 (0.6)	29 (0.7)	8 (0.7)
Alopecia	2 (0.1)	1 (0.1)	3 (0.1)	7 (0.2)	2 (0.2)
Rash	2 (0.1)	2 (0.1)	4 (0.1)	6 (0.2)	0
Vascular disorders	20 (1.4)	13 (0.9)	33 (1.1)	54 (1.4)	22 (2.0)
Hot flush	11 (0.8)	6 (0.4)	17 (0.6)	33 (0.8)	20 (1.8)
Hypertension	3 (0.2)	5 (0.3)	8 (0.3)	9 (0.2)	1 (0.1)

[a] System Organ Class (SOC) totals for the number of subjects are not necessarily the sum of the individual AEs, since a subject may report two or more different AEs in the same SOC. Also, some of the preferred terms under the SOC are not included in this table because of the cut-off used for this table (≥5 subjects in any treatment group).

Note: Classifications of adverse events are based on the Medical Dictionary for Regulatory Activities (MedDRA).

Source: Module 5.3.5.3: Supportive Tables to the BZA/CE Summary of Clinical Safety, Report AE4_W_AS_AD_AG_R - 21MAR14 17:57

Table 45: Adverse Events Leading to Discontinuation From Study in ≥5 Subjects in Any Treatment Group: Cumulative Data up to 2 years for Studies 303, 304, 305, 306, and 3307 (for All Sites)

System Organ Class[a] Preferred Term	Treatment				
	BZA 20/CE 0.45 n=1585	BZA 20/CE 0.625 n=1583	BZA 20/CE n=3168	All BZA/CE n=4868	Placebo n=1241
Any Adverse Event	132 (8.3)	135 (8.5)	267 (8.4)	493 (10.1)	128 (10.3)
Cardiac disorders	7 (0.4)	8 (0.5)	15 (0.5)	26 (0.5)	4 (0.3)
Coronary artery disease	0	3 (0.2)	3 (0.1)	6 (0.1)	0
Palpitations	1 (0.1)	2 (0.1)	3 (0.1)	6 (0.1)	1 (0.1)
Tachycardia	2 (0.1)	1 (0.1)	3 (0.1)	5 (0.1)	1 (0.1)
Ear and labyrinth disorders	1 (0.1)	3 (0.2)	4 (0.1)	5 (0.1)	2 (0.2)
Vertigo	1 (0.1)	3 (0.2)	4 (0.1)	5 (0.1)	1 (0.1)
Gastrointestinal disorders	23 (1.5)	20 (1.3)	43 (1.4)	79 (1.6)	14 (1.1)
Abdominal distension	1 (0.1)	4 (0.3)	5 (0.2)	10 (0.2)	1 (0.1)
Abdominal pain	2 (0.1)	3 (0.2)	5 (0.2)	10 (0.2)	0
Abdominal pain upper	7 (0.4)	1 (0.1)	8 (0.3)	21 (0.4)	5 (0.4)
Constipation	1 (0.1)	1 (0.1)	2 (0.1)	5 (0.1)	1 (0.1)
Dyspepsia	2 (0.1)	4 (0.3)	6 (0.2)	8 (0.2)	1 (0.1)
Nausea	7 (0.4)	2 (0.1)	9 (0.3)	12 (0.2)	7 (0.6)
General disorders and administration site conditions	12 (0.8)	15 (0.9)	27 (0.9)	44 (0.9)	12 (1.0)
Chest pain	3 (0.2)	4 (0.3)	7 (0.2)	9 (0.2)	1 (0.1)
Fatigue	3 (0.2)	4 (0.3)	7 (0.2)	7 (0.1)	2 (0.2)
Malaise	1 (0.1)	2 (0.1)	3 (0.1)	5 (0.1)	0
Oedema peripheral	2 (0.1)	0	2 (0.1)	9 (0.2)	4 (0.3)
Pain	3 (0.2)	1 (0.1)	4 (0.1)	6 (0.1)	0
Investigations	13 (0.8)	14 (0.9)	27 (0.9)	52 (1.1)	8 (0.6)
Alanine aminotransferase increased	1 (0.1)	1 (0.1)	2 (0.1)	5 (0.1)	1 (0.1)
Blood pressure increased	0	3 (0.2)	3 (0.1)	5 (0.1)	0
Mammogram abnormal	0	1 (0.1)	1 (0.0)	5 (0.1)	0
Weight increased	3 (0.2)	6 (0.4)	9 (0.3)	16 (0.3)	5 (0.4)
Metabolism and nutrition disorders	0	3 (0.2)	3 (0.1)	11 (0.2)	1 (0.1)
Hypertriglyceridaemia	0	3 (0.2)	3 (0.1)	5 (0.1)	0
Musculoskeletal and connective tissue disorders	18 (1.1)	17 (1.1)	35 (1.1)	60 (1.2)	27 (2.2)
Arthralgia	2 (0.1)	2 (0.1)	4 (0.1)	11 (0.2)	4 (0.3)
Back pain	4 (0.3)	3 (0.2)	7 (0.2)	13 (0.3)	5 (0.4)
Muscle spasms	5 (0.3)	4 (0.3)	9 (0.3)	10 (0.2)	5 (0.4)
Myalgia	3 (0.2)	2 (0.1)	5 (0.2)	7 (0.1)	1 (0.1)
Osteoporosis	2 (0.1)	2 (0.1)	4 (0.1)	7 (0.1)	7 (0.6)
Pain in extremity	0	2 (0.1)	2 (0.1)	6 (0.1)	2 (0.2)
Nervous system disorders	12 (0.8)	21 (1.3)	33 (1.0)	54 (1.1)	15 (1.2)
Headache	3 (0.2)	9 (0.6)	12 (0.4)	20 (0.4)	9 (0.7)
Paraesthesia	2 (0.1)	2 (0.1)	4 (0.1)	5 (0.1)	0
Transient ischaemic attack	1 (0.1)	0	1 (0.0)	5 (0.1)	0
Psychiatric disorders	13 (0.8)	14 (0.9)	27 (0.9)	46 (0.9)	13 (1.0)
Anxiety	3 (0.2)	5 (0.3)	8 (0.3)	9 (0.2)	1 (0.1)
Depression	4 (0.3)	6 (0.4)	10 (0.3)	21 (0.4)	4 (0.3)
Insomnia	3 (0.2)	3 (0.2)	6 (0.2)	8 (0.2)	3 (0.2)
Reproductive system and breast disorders	15 (0.9)	18 (1.1)	33 (1.0)	71 (1.5)	15 (1.2)
Breast pain	4 (0.3)	2 (0.1)	6 (0.2)	8 (0.2)	4 (0.3)
Endometrial hyperplasia	0	3 (0.2)	3 (0.1)	18 (0.4)	0
Vaginal haemorrhage	3 (0.2)	2 (0.1)	5 (0.2)	9 (0.2)	1 (0.1)
Skin and subcutaneous tissue disorders	10 (0.6)	6 (0.4)	16 (0.5)	33 (0.7)	8 (0.6)
Alopecia	2 (0.1)	1 (0.1)	3 (0.1)	7 (0.1)	2 (0.2)
Rash	2 (0.1)	2 (0.1)	4 (0.1)	6 (0.1)	0

System Organ Class[a] Preferred Term	Treatment				
	BZA 20/CE 0.45 n=1585	BZA 20/CE 0.625 n=1583	BZA 20/CE n=3168	All BZA/CE n=4868	Placebo n=1241
Vascular disorders	20 (1.3)	16 (1.0)	36 (1.1)	65 (1.3)	24 (1.9)
Deep vein thrombosis	3 (0.2)	0	3 (0.1)	5 (0.1)	1 (0.1)
Hot flush	11 (0.7)	6 (0.4)	17 (0.5)	35 (0.7)	20 (1.6)
Hypertension	3 (0.2)	6 (0.4)	9 (0.3)	11 (0.2)	1 (0.1)

[a] System Organ Class (SOC) totals for the number of subjects are not necessarily the sum of the individual AEs, since a subject may report two or more different AEs in the same SOC. Also, some of the preferred terms under the SOC are not included in this table because of the cut-off used for this table (≥5 subjects in any treatment group).
Note: Classifications of adverse events are based on the Medical Dictionary for Regulatory Activities (MedDRA).
Source: Module 5.3.5.3: Supportive Tables to the BZA/CE Summary of Clinical Safety, Supportive Table 1.70

Post marketing experience

Due to the late introduction of BZA into the market, post marketing exposure to BZA is low. The Applicant did not provide any information on the available extensive post marketing experience with CE.

2.6.1. Discussion on clinical safety

The increased risks of administration of oestrogens in hysterectomised women and of oestrogen / progestin combination therapy in non-hysterectomised women, in particular during long-term treatment, are well-known, mainly based on the WHI studies and the Million Women Study. With oestrogens as well as oestrogen / progestin combination therapy, the risk of VTE is increased compared to placebo. The increase in risk is higher with CE/MPA vs. placebo compared to CE vs. placebo (*Cushman M et al.: JAMA 2004; 292: 1573-1580; Curb JD et al.: Arch Intern Med 2006; 166: 772-780*). The risk of coronary artery disease is slightly increased with oestrogen / progestin combination therapy compared to placebo, while regarding oestrogens alone no increase was observed (*Manson JE et al.: NEJM 2003; 349: 523-534; Hsia J et al.: Arch Intern Med 2006; 166: 357-365*). Both oestrogens alone as well as oestrogen / progestin combination therapy are associated with an up to 1.5-fold increase in the risk of ischemic stroke (*Wassertheil-Smoller S et al.: JAMA 2003; 289: 2673-2684; The Women's health Initiative Steering Committee: JAMA 2004; 291: 1701.1712*). Combined oestrogen-progestin therapy is associated with an increased risk of breast cancer. Regarding oestrogens alone no increased risk was reported in the WHI study while observational studies showed a small increase in risk (*Chlebowski RT et al.: JAMA 2003; 289: 3243-3253; Stefanick ML et al.: JAMA 2006; 295: 1647-1657*). The risk of ovarian cancer is slightly increased with oestrogen-only HRT and possibly also with oestrogen-progestin HRT. There is also some evidence that the risk of dementia is increased in women starting oestrogen-only or oestrogen / progestin HRT after the age of 65 years. Further adverse reactions of oestrogen / progestin HRT include gallbladder disease, erythema nodosum, and erythema multiforma. All these increased risks regarding oestrogens alone and in combination with progestins are reflected in the *CMDh Core SPC for hormone replacement therapy products, CMDh/131/2003/ Rev. 3, December 2009*.

The safety analysis of current application is mainly based on data of the five Phase 3 studies 303, 304, 305, 306, and 3307. Overall, 4868 women have been exposed to BZA/CE at any dose and 3168 women received BZA/CE doses with 20 mg of BZA, 1585 BZA/CE 20 mg / 0.45 mg and 1583 20 mg / 0.625 mg, while 1241 women received placebo, 340 BZA 20 mg monotherapy, 423 raloxifene 60 mg, and 399 CE/MPA 0.45 mg / 1.5 mg. Additionally, safety data from the BZA monotherapy programme have been included. About 850 women have been exposed to the FDC of BZA/CE with 20 mg BZA for 2 years. Data for the FDC are sparse beyond 2 years of exposure; only for BZA monotherapy data are available for up to 7 years.

The analysis of the most common AEs occurring in more than 10% of patients did not reveal any unexpected findings. About 3 to 4% of women experienced treatment emergent adverse event (TEAE) considered severe and related to therapy by the investigators; there were no clear pattern or significant differences in TEAE between groups. However, the validity of the relatedness of AEs to BZA/CE treatment is questioned due to the serious GCP inspection findings. The most common severe drug-related TEAE was headache in all groups. As expected when comparing placebo with HRT, hot flushes occurred more frequently in the placebo group.

Because of the known SERM and CE class effects relevant AE have been specifically analysed; this included venous thromboembolic events (VTE), cardiovascular (CHD) events, cerebrovascular accidents (CVAs), and malignancies. Post-hoc, an independent adjudication committee was initialised to review the AEs of special interest VTEs, CHD, and CVA. Considering the number of women exposed, the lack of data in elderly women, and the duration of treatment, the available safety data for BZA/CE do not allow to assess whether the incidence of these rare adverse events is increased in women treated with BZA 20 mg / CE compared to placebo or to historical data for CE/MPA.

As regards VTE there were only 3 events in the BZA/CE 20 mg / 0.45 mg and none in the 20 mg / 0.625 mg group. Resistance to activated protein C or resistance to other markers for venous thromboembolism have not been measured which adds to the uncertainty of the knowledge about the unfavourable effects. As regards cardiac events a possible increase in the incidence of cardiac events for women treated with CE/MPA has been identified, while the data provided for the registration of bazedoxifene monotherapy did not demonstrate such an increased risk with either BZA 20 mg or 40 mg compared to placebo. The incidence of cerebrovascular events was not increased with BZA monotherapy (Studies 300 and 301) as compared to placebo and in the CE-alone substudy of the WHI study in women aged 50 to 59 years, there was no increased risk of ischemic stroke due to hormone therapy. Regarding breast cancer, there is an increase in risk associated with CE/MPA combination therapy and possibly also with CE monotherapy. Regarding ovarian carcinoma, there were 5 cases of ovarian carcinoma with BZA 20 mg monotherapy versus no cases in the placebo group in study 301. Ovarian cancer was reported in 2 out of 4868 patients in all BZA/CE groups. Long-term use of oestrogen-only HRT is associated with a slightly increased risk of ovarian cancer. With BZA monotherapy 5 cases of thyroid cancer occurred versus 1 case in the placebo group over the 7 years study period in study 301. Based on the available data overall the Applicant proposes to predefine VTE and increased triglycerides as important identified risks and CVA, CHD, breast cancer, ovarian cancer, endometrial hyperplasia and cancer, lung cancer, thyroid cancer, and skin cancer as important potential risks in the RMP. This was endorsed by the PRAC and the CHMP.

As regards endometrial safety from study 203 it can be concluded that a dose of 5 mg BZA is insufficient for endometrial protection with regard to both doses of CE; a dose of 5 mg BZA was not further studied in phase III studies.

Regarding study 303 a GCP inspection was performed, with the result of GCP non-compliance. There were major and critical findings in particular regarding the handling and reporting of endometrial biopsies. Nevertheless, at month 24, 2 cases of endometrial hyperplasia / malignancy had been detected in the BZA 20 mg / CE 0.45 mg group as well as in the BZA 20 mg / CE 0.625 mg group.

In study 3307 one case of endometrial hyperplasia was observed at month 12 each in the BZA 20 mg / CE 0.45 mg and the BZA 20 mg / CE 0.625 mg group. No endometrial carcinomas were observed in this study. The upper limit of the 2-sided 95% confidence interval of the incidence of endometrial hyperplasia was below 2% in each of the two groups. It was noted that only the diagnosis of the endometrial biopsy, not a more detailed description of the macroscopic and microscopic findings by the pathologists is available. Thus, more detailed information on cases diagnosed as “endometrium, other” could not be provided by the Applicant and no further assessment in this respect is possible. In addition, in study 3307 concerns remain with regard to 4 patients in the

BZA 20 mg / CE 0.45 mg in whom no biopsy was performed at month 12 and endometrial thickness was ≥4 mm. It is acknowledged that the Applicant reported that these 4 patients had refused a biopsy. In addition, in 8 patients of the BZA 20 mg / CE 0.45 mg group neither a biopsy nor TVUS was performed. For 4 patients of these patients no reasons are given, while for the other 4 subjects biopsies and TVUS were refused or the patient had moved. Nevertheless the amount of missing data was considered not unusual for a study of this size.
Regarding endometrial thickness measured by TVUS at month 12 statistical significant increases in endometrial thickness vs. baseline were reported in the BZA 20 mg / CE 0.45 mg group, the BZA 20 mg / CE 0.625 mg group, and the CE 0.45 mg / MPA 1.5 mg group in study 3307. All these increases were statistically significant higher compared to the change vs. baseline in the placebo group. Numerically the proportion of patients with TVUS findings of potential clinical importance regarding endometrial thickness results was higher in the BZA 20 mg / CE 0.625 mg group and the CE 0.45 mg /MPA 1.5 mg group compared to the BZA 20 mg / CE 0.45 mg and the placebo group. (For details regarding endometrial thickness see paragraph *Gynaecological Safety* below).
In summary endometrial safety of BZA 20 mg / CE 0.45 mg and BZA 20 mg / CE 0.625 was considered to be sufficiently demonstrated.

Ovarian volume or the incidence of ovarian cysts do not appear to be adversely affected by BZA/CE.

With regard to the bleeding pattern, in the population included in study 3307, the bleeding pattern in the two BZA/CE groups was similar to placebo and more favourable compared to CE 0.45 mg / MPA 1.5 mg. However, it is noted that the dose of 1.5 mg MPA is low and that no comparison of the products applied for vs. CE 0.625 mg / MPA 2.5 mg or CE 0.625 mg / MPA 5 mg was provided. In addition, the population of study 3307 was not selected based on a minimum frequency / severity of hot flushes and is therefore not identical with a population to be treated for VMS.

Although differences are small adverse events of bone fracture occurred more often in patients treated with any combination of BZA and CE than with placebo. The Applicant provided additional analyses of the adverse events of bone fracture by summarising all potential osteoporotic fractures occurring ≥120 days after first dose of treatment considering the bone remodelling cycle of approximately 120 days. These analyses do not show clinically relevant differences between BZA / CE groups and placebo. When further subtracting potentially traumatic fractures confirmed by review of patient narratives for each fracture potentially osteoporotic fractures were equally distributed across treatment groups.

The analysis of deaths did not reveal an imbalance between groups.

A consolidated presentation and discussion of SAEs other than death occurring in the BZA/CE 20 mg / 0.45 mg and 20 mg / 0.625 mg versus both BZA 20 mg and CE/MPA was missing in the Summary of Clinical Safety but contained in supportive tables in the annex. This analysis did not indicate relevant differences between active treatment groups as regards SAEs. Overall, there were no significant differences in the incidence of SAEs between BZA 20 mg / CE and placebo, although small imbalances with low absolute numbers occurred. SAEs of CAD, chest pain, cholecystitis, cholelithiasis, abnormal endometrium results, cerebrovascular accident, transient ischaemic attack, and deep vein thrombosis occurred more often with active treatment than with placebo. Treatment with a fixed combination of BZA and CE did not result in an increase in the incidence of ocular adverse events compared to placebo.

As regards laboratory findings treatment with BZA 20 mg / CE had no clinically relevant influence on the lipid profile, C-reactive protein, plasma concentrations of homocysteine, mean fasting glucose levels, fasting insulin, parameters of liver or renal function, haemoglobin, haematocrit, or platelet counts, coagulation parameters, or thyroid stimulating hormone compared to placebo. Decreases from baseline in serum calcium, phosphorus, and

alkaline phosphatase values were observed in all groups including placebo at all scheduled time points, but there were few occurrences of potentially clinically important decreases in calcium or phosphorus. With respect to the coagulation system the Applicant has investigated several coagulation parameters to evaluate potential changes that might result in a higher risk for thromboembolic complications. Currently available data about patients with abnormal coagulation laboratory results during on- and post-therapy time periods do not show an association of the thromboembolic risk with the changes observed in the parameters of coagulation or fibrinolysis. Resistance to activated protein C or resistance to other markers for venous thromboembolism have not been measured which has to be reflected in the uncertainty of the knowledge about the unfavourable effects. The available data also do not indicate an influence of treatment with a fixed combination of BZA and CE compared to placebo on changes in vital signs or blood pressure.

No clear pattern or clinical relevance of differences in adverse events in special populations between BZA 20 mg / CE and placebo treated women has been seen in the data provided. However, the amount of data in the elderly as well as in women of other than white ethnicity is very limited and thus no definite conclusion as regards age and ethnicity can be drawn.

No drug interaction studies were conducted with BZA/CE which is considered acceptable based on the known PK of the components of this FDC.

A GCP inspection of trials 303 and 305 revealed critical findings as regards the safety assessment for BZA/CE. For details regarding the inspection findings please refer to the GCP section in the Introduction to the Clinical Aspects. The validity of the assessment of discontinuations due to AEs has been questioned for the investigated sites of study 303 in the GCP inspection report. The Applicant has therefore provided updated analyses of discontinuation due to AEs including analyses of relative frequencies calculated without data from investigator sites 447 and 450 of study 303. The provided analyses do not indicate significant differences in the rates of discontinuation due to AEs re-analyses and the original analyses. Adverse events of hot flush and osteoporosis leading to discontinuation occurred more often with placebo than with active treatment.

2.6.2. Conclusions on the clinical safety

Although the Applicant has provided an extensive dataset comparing BZA/CE with placebo, these data do not allow for an assessment of rare adverse events known to be relevant for BZA or CE/MPA. Furthermore, relevant data for a direct comparison in the provided clinical trials to either BZA or CE as monotherapy is limited as well as data in women above 65 years of age or beyond 2 years of treatment. Comparisons to HRT and BZA monotherapy are based on historical data and the BZA licensing dossier.

The known SERM and CE class effects include venous thromboembolic events (VTE), cardiovascular (CHD) events, cerebrovascular accidents (CVAs), and malignancies. Considering the number of women exposed, the lack of data in elderly women, and the duration of treatment the available safety data for BZA/CE do not allow to assess whether the incidence of these rare adverse events is increased in women treated with BZA 20 mg / CE compared to placebo or to historical data for CE/MPA. It was agreed to address these issues in the RMP.

As expected when comparing HRT with placebo, hot flushes occurred more frequently in the placebo group; adverse events “hot flush” and “osteoporosis leading to discontinuation” occurred more often with placebo than with active treatment. Although differences are small adverse events of bone fracture occurred more often in patients treated with any combination of BZA and CE than with placebo; additional analyses of these adverse events revealed that potentially osteoporotic fractures were equally distributed across treatment groups. As regards SAEs small imbalances with low absolute numbers occurred; serious adverse events of CAD, chest pain,

cholecystitis, cholelithiasis, abnormal endometrium results, CVA, TIA, and deep vein thrombosis occurred more often with active treatment than with placebo.

Due to the late introduction of BZA into the market, post marketing exposure to BZA is low.

For the assessment of endometrial safety data from two studies were provided. However, study 303 is not considered GCP-compliant, in particular regarding the investigation of endometrial safety. Nevertheless, in this study 1 case of endometrial hyperplasia was observed in year 1 in the two BZA/CE groups while 3 cases of endometrial hyperplasia / malignancy were detected during the second year of treatment in the two BZA/CE groups.
In study 3307, the upper limit of the 2-sided 95% confidence interval of the incidence of endometrial hyperplasia was below 2% in each of the two BZA/CE groups. In 12 of 445 and 11 of 474 patients in the BZA 20 mg / CE 0.45 mg and the BZA 20 mg / CE 0.625 mg group, respectively, no reassuring outcome with regard to endometrial safety is available. In 4 and 3 patients in the BZA 20 mg / CE 0.45 mg and the BZA 20 mg / CE 0.625 mg group, respectively, no biopsy was performed at month 12 and endometrial thickness was ≥4 mm. Nevertheless, the amount of missing data was considered not unusual for a study of this size. With regard to endometrial thickness, study 3307 is considered most relevant as the treatment duration was 1 year. At month 12, statistically significant increases from baseline were observed in the CE 0.45 mg / MPA 1.5 mg group (0.79 mm). These increases were statistically significant higher than in the placebo group (0.08 mm). However, it can also be stated that the increase with BZA 20 mg / CE 0.45 mg was numerically lower than with CE 0.45 mg / MPA 1.5 mg. In summary, the endometrial safety of BZA 20 mg / CE 0.45 mg was considered as sufficiently demonstrated by the CHMP.

In conclusion, considering the number of women exposed, the lack of data in elderly women, and the duration of treatment the available safety data do not allow to assess whether there is an additive effect of the fixed combination of BZA and CEs on the incidence of adverse events known for either of these active substances. However, the CHMP agreed that despite the validity of the safety data was corrupted based on the serious GCP inspection findings the available data from study 3307 permitted to conclude that the endometrial safety of BZA 20 mg / CE 0.45 mg was sufficiently demonstrated. The important possible and identified risks of this combination will be further investigated and missing information collected as per agreed RMP for this product and also within the requested DUS and PASS studies.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The Applicant has provided documents that set out a detailed description of the system of pharmacovigilance (Version 3.1 dated 26 April 2012). A statement signed by the Applicant and the qualified person for pharmacovigilance, indicating that the Applicant has the services of a qualified person responsible for pharmacovigilance and the necessary means for the notification of any adverse reaction occurring either in the Community or in a third country has been provided.

The CHMP considered that the Pharmacovigilance system as described by the Applicant fulfils the requirements as described in Volume 9A of the Rules Governing Medicinal Products in the EU and provides adequate evidence that the Applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

In conclusion, the CHMP considered that the Pharmacovigilance system as described by the Applicant fulfils the legislative requirements.

2.8. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 2.3 could be acceptable if the Applicant implements the changes to the RMP as described in the PRAC advice.

The CHMP endorsed this advice without changes.

The Applicant implemented the changes in the RMP as requested by the PRAC and CHMP.

The CHMP endorsed the Risk Management Plan version 2.6 with the following content:

Summary of safety concerns

Important identified risks	• Venous thromboembolism (VTE) • Increased Triglycerides
Important potential risks	• Arterial thromboembolic events: Cerebrovascular events and myocardial infarction (MI) • Coronary heart disease (CHD) • Atrial fibrillation • New presentation or aggravation of pre-existing renal failure or insufficiency • Renal carcinoma or adenoma • Gallbladder disease • Cancers: breast, ovarian, endometrial, lung, thyroid, skin, gastrointestinal and other cancers. • Endometrial hyperplasia. • Depression • Ocular events • Gastroesophageal reflux disease (GERD) • Drug-drug interactions • Off-label use
Missing information	• Use in elderly patients • Use in hepatic impaired patients • Use in renal impaired patients • Use in patients with malignancy • Use in patients with history of cardiovascular disease (including hypertension, hyperlipidaemias, arrhythmias, CHD, angina), diabetes or obesity or long-term smoking • Long-term (>2 years) safety data on breast protection and gynaecological cancers (endometrial and ovarian in particular)

Pharmacovigilance plan

Ongoing and planned studies in the PhV development plan

Study / Activity Type, Title and Category (1-3)	**Objectives**	**Safety Concerns Addressed**	**Status (Planned / Started)**	**Date for Submission of Final Study Report (Planned or Actual)**
US PASS: Active surveillance of BZA/CE using US healthcare data. **Category 3**	To estimate the incidence of VTE, CHD, MI, stroke, breast cancer, ovarian cancer, endometrial hyperplasia and endometrial cancer among postmenopausal women initiating BZA/CE treatment or those initiating E+P treatment.	• VTE • CHD • MI • Stroke • Breast cancer • Endometrial hyperplasia • Endometrial cancer • Ovarian cancer	Planned	Final study report to be submitted following accumulation of 4 years of post-US launch data (31 March 2019).

Study / Activity Type, Title and Category (1-3)	Objectives	Safety Concerns Addressed	Status (Planned / Started)	Date for Submission of Final Study Report (Planned or Actual)
EU Drug utilisation Study **Category 3**	The study will provide information on the characteristics of users in real-world clinical care following approval and launch of the product Among patients initiating BZA/CE or E+P therapy: • Describe their baseline and historical characteristics such as age, cardiovascular risk factors, history of a CVD event, history of breast, ovarian or endometrial cancers, other selected medical comorbidities, prior use of oestrogen/progestin therapy, indication for use, and other current or recent drug therapies. • Where possible, describe and compare the pattern of use during follow-up. Summarize the average prescribed dose, prescribed • days supply per prescription (Rx), number of prescriptions, and the duration of continuous treatment. • Estimate the proportion that may have been prescribed the product outside the specifications of the product label as determined by age of the patient, prescribed dose, or recorded indication.	• Use in patients with history of cardiovascular disease or diabetes. • Off-label use.	Planned	Final study report to be submitted following accumulation of 3 years of post-launch data (31 March, 2019).

The final protocol for the PASS, which will be conducted in the US as a post-authorisation commitment to the EMA, is planned for submission by 26 January 2015 for PRAC/CHMP review and approval. The DUS final protocol is planned to be submitted for review within 2 months following the EU approval.

Risk minimisation measures

Summary table of Risk Minimisation Measures

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Important Identified Risks		
Venous thromboembolic events (VTE)	**Routine Activity:** Risk minimisation actions will consist of communication in the Summary of Product Characteristics (SmPC) and Package Leaflet (PL). SmPC Section 4.3 Contraindications: 'Active or past history of venous thromboembolism (deep venous thrombosis, pulmonary embolism, and retinal vein thrombosis)' or 'Known thrombophilic disorders (e.g. protein C, protein S, or antithrombin deficiency)'. SmPC Section 4.4 Special Warnings and Precautions: 'If VTE develops after initiating therapy, or is suspected, DUAVIVE should be discontinued immediately.' In addition, risk factors for thromboembolic disorders are listed as conditions that need supervision. Advice is given in this section in case of prolonged immobilisation, and regarding screening for thrombophilic disorders. SmPC Section 4.8 'Undesirable Effects: VTEs are listed as rare adverse reaction in women treated with DUAVIVE.' In addition, data from clinical studies for CE/BZA, BZA, and CE are provided in Sections 4.8 and 5.1. The PL warns patients that CE/BZA may increase the risk of blood clots and not to take it if they have or have ever had a blood clot in a vein, such as in the legs, the lungs or eyes, or clotting disorder, to stop taking CE/BZA if they develop signs of a blood clot, to take special care if immobile for some time, to move around periodically on long trips, and to speak with a doctor if planning surgery or if any of the listed risk factors apply. Special care is advised if the patient has a family history of blood clots. Blood clots are listed as rare side effects.	None proposed.
Increased triglycerides	Risk minimisation actions will consist of communication in the SmPC and PL. SmPC Section 4.4 Special Warnings and Precautions: 'Women with pre-existing hypertriglyceridaemia should be followed closely during treatment with oestrogens, since rare cases of large increases of plasma triglycerides leading to pancreatitis have been reported with oestrogen therapy in this condition. DUAVIVE has not been studied in women with baseline triglyceride levels >300 mg/dL (>3.4 mmol/L). In clinical trials of up to 2 years duration, DUAVIVE was associated with an increase from baseline in the concentration of serum triglycerides of approximately 16% at month 12 and 20% at month 24. Annual monitoring of serum triglycerides should therefore be considered.' The PL warns patients to take special care if they have a high level of fat (triglycerides) in their blood.	None proposed.

Important Potential Risks		
Arterial thromboembolic events [cerebrovascular events and myocardial infarction (MI)]	Risk minimisation actions will consist of communication in the SmPC and PL. SmPC Section 4.3 Contraindications: 'Active or past history of arterial thromboembolic disease (e.g., myocardial infarction, stroke).' SmPC Section 4.4 Special Warnings and Precautions: 'Should a stroke occur or be suspected, DUAVIVE should be discontinued immediately.' In addition, certain risk factors for CVE and/or MI including hypertension, diabetes, and migraine (or severe headache) are listed as conditions that need supervision. A significant increase in blood pressure, or new onset of migraine-type headache are given as reasons for immediate withdrawal of CE/BZA. The PL states that CE/BZA should not be taken if the patient has or has recently had a disease caused by blood clots in the arteries, such as a heart attack, stroke or angina. The PL also warns patients to take special care if they have high blood pressure, and to stop taking CE/BZA if they experience a large increase in blood pressure. The PL recommends that the patient consult their doctor if they have any concerns about their risk factors for stroke.	None proposed.
Coronary heart disease (CHD)	Risk minimisation actions will consist of communication in the SmPC and PL. CHD is a risk factor for arterial thromboembolic events. Arterial thromboembolic events are adequately described in the SmPC and PL as described above. SmPC Section 4.4 Special Warnings and Precautions: 'There is no evidence from randomised controlled trials of protection against myocardial infarction in women with or without existing CAD who received oestrogen-only therapy. Randomised controlled data found no increased risk of CAD in hysterectomised women using oestrogen-only therapy'. In addition, certain potential risk factors for CHD including hypertension and diabetes are listed as conditions that need supervision.	None proposed.
Atrial fibrillation	Atrial fibrillation is a risk factor for arterial thromboembolic events. Arterial thromboembolic events are adequately described in the SmPC and PL as described above. Risks associated with atrial fibrillation per se will be further characterised through routine pharmacovigilance activities to determine if risk minimisation activities are required.	None proposed.

2.9. Product information

New presentation and aggravation of pre-existing renal failure or insufficiency	Risk minimisation actions for the aggravation of pre-existing renal failure or insufficiency consist of the following statements in the SmPC and PL: SmPC Section 4.2 Posology and Method of Administration: 'The pharmacokinetics of CE/BZA have not been evaluated in patients with renal impairment. Use in this population is therefore not recommended. SmPC Section 4.4 Special Warnings and Precautions: Patients with terminal renal insufficiency should be closely monitored, since it is expected that the level of circulating oestrogens components of CE/BZA will be increased. Use in this population is not recommended. SmPC Section 5.2 Pharmacokinetic Properties: 'The pharmacokinetics of CE/BZA have not been evaluated in patients with renal impairment.' In the PL patients are warned that they may require additional monitoring if they have kidney problems. Risks will be further characterised through routine pharmacovigilance activities to determine if further risk minimisation activities are required.	None proposed.
Renal carcinoma and adenoma	Risk minimisation actions will consist of communication in the SmPC. SmPC Section 5.3 Pre-clinical Safety Data: 'Renal cell carcinomas were observed in an 18-month bone efficacy study in aged ovariectomised cynomolgus monkeys. 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.' BZA, administered orally to monkeys at dosages of 0, 0.2, 0.5, 1, 5, or 25 mg/kg/day, resulted in exposure ratios of 0.05 to 16.3 times, and dose ratios, based on surface area (mg/m^2), of approximately 0.2 to 24 times the clinical dose of 20 mg, respectively.'	None proposed.
Gallbladder disease	Risk minimisation actions will consist of communication in the SmPC and PL. SmPC Section 4.4 Special Warnings and Precautions: 'Cases (<1%) of cholecystitis have been reported in CE/BZA clinical trials. A 2- to 4-fold increase in the risk of gallbladder disease requiring surgery in postmenopausal women receiving oestrogens has been reported.' Close supervision of patients with existing cholelithiasis is advised. SmPC Section 4.8: Undesirable Effects: Cholecystitis is listed as an uncommon adverse reaction.' The PL warns that patients should take special care if they have gallstones. Gallbladder disease is listed as an uncommon side effect.	None proposed.

Breast, ovarian and endometrial cancers	Risk minimisation actions will consist of communication in the SmPC and PL. SmPC Section 4.3 Contraindications: Known, suspected, or past history of breast cancer; Known, past or suspected oestrogen-dependent malignant tumours (e.g., endometrial cancer); Undiagnosed genital bleeding; Untreated endometrial hyperplasia.' SmPC Section 4.4 Special Warnings and Precautions: Risk factors for oestrogen-dependent tumours, e.g., 1st degree heredity for breast cancer, leiomyoma (uterine fibroids) or endometriosis, and a history of endometrial hyperplasia are listed as conditions that need supervision. Advice is also given with respect to breast examination and investigations, and in case of break-through bleeding or spotting after some time on therapy. Risks for breast, ovarian and endometrial cancers are described in SmPC Section 4.8. The PL states that CE/BZA should not be taken if the patient has or has had breast cancer or cancer which is sensitive to oestrogens, or is suspected of having those, or if the patient has had unexplained vaginal bleeding or endometrial hyperplasia. In addition, the PL states that special care should be taken if the patient has endometriosis or a family history of breast cancer or cancer of the lining of the uterus. It is also recommended that patients taking CE/BZA regularly check their breasts for changes.	None proposed.
Lung, thyroid, Skin gastrointestinal tract and other cancers	None. Risks will be further characterised through routine pharmacovigilance activities to determine if risk minimisation activities are required.	None proposed.

Endometrial hyperplasia	Risk minimisation actions will consist of communication in the SmPC and PL. SmPC Section 4.3 Contraindications: CE/BZA is contraindicated in patients with known, past or suspected oestrogen-dependent malignant tumours (e.g. endometrial cancer), undiagnosed genital bleeding and untreated endometrial hyperplasia. SmPC Section 4.4 Special warnings and precautions for use: History of endometrial hyperplasia is listed as a condition that needs supervision. The following advice is also added in SmPC Section 4.4 Endometrial hyperplasia and carcinoma In women with an intact uterus, the risk of endometrial hyperplasia and carcinoma is increased when oestrogens are administered alone for prolonged periods. The reported increase in endometrial cancer risk among oestrogen-only users varies from 2- to 12-fold greater compared with non-users, depending on duration of treatment and oestrogen dose. After stopping treatment risk may remain elevated for at least 10 years Women taking DUAVIVE should not take additional oestrogens as this may increase the risk of endometrial hyperplasia and endometrial carcinoma. The addition of bazedoxifene in CE/BZA reduces the risk of endometrial hyperplasia which may be a precursor of endometrial carcinoma. Break-through bleeding and spotting may occur during treatment. If break-through bleeding or spotting appears after some time on therapy, or continues after treatment has been discontinued, the reason should be investigated, which may include endometrial biopsy to exclude endometrial malignancy. The PL states that CE/BZA should not be taken if the patient has or has had breast cancer or cancer which is sensitive to oestrogens, or is suspected of having those, or if the patient has had unexplained vaginal bleeding or endometrial hyperplasia. In addition, the PL states that special care should be taken if the patient has endometriosis or a family history of cancer of the lining of the uterus.	None proposed.
Depression	None. Risks will be further characterised through routine pharmacovigilance activities to determine if risk minimisation activities are required.	None proposed.
Ocular events	None. Risks will be further characterised through routine pharmacovigilance activities to determine if risk minimisation activities are required.	None proposed.
Gastroesophageal reflux disease (GERD)	None. Risks will be further characterised through routine pharmacovigilance activities to determine if risk minimisation activities are required.	None proposed.

Drug-drug interactions	Risk minimisation actions will consist of communication in the SmPC and PL. SmPC Section 4.5 Interaction with other Medicinal Products: 'No interaction studies have been performed with DUAVIVE.' Conjugated oestrogens 'The metabolism of oestrogens may be increased by concomitant use of substances known to induce active substance-metabolising enzymes, specifically cytochrome P450 enzymes, such as anticonvulsants (e.g., phenobarbital, phenytoin, carbamazapine) and anti-infectives (e.g.' rifampicin, rifabutin, nevirapine, efavirenz). Ritonavir and nelfinavir, although known as strong inhibitors, by contrast exhibit inducing properties when used concomitantly with steroid hormones. Herbal preparations containing St John's wort (*Hypericum perforatum*) may induce the metabolism of oestrogens. Clinically, an increased metabolism of oestrogens may lead to decreased effect and changes in the uterine bleeding profile. Inhibitors of CYP3A4, such as erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir and grapefruit juice, may increase plasma concentrations of oestrogens and may result in adverse reactions.' SmPC Section 4.5 Interaction with other Medicinal Products: Bazedoxifene 'Bazedoxifene undergoes metabolism by uridine diphosphate glucuronosyltransferase (UGT) enzymes in the intestinal tract and liver (see Section 5.2). The metabolism of bazedoxifene may be increased by concomitant use of substances known to induce UGTs, such as rifampin, phenobarbital, carbamazepine, and phenytoin, potentially leading to decreased systemic concentrations of bazedoxifene. A reduction in bazedoxifene exposure may be associated with an increased risk of endometrial hyperplasia. If break-through bleeding or spotting appears after some time on therapy, or continues after treatment has been discontinued, the reason should be investigated, which may include endometrial biopsy to exclude endometrial malignancy (see section 4.4)'.	None proposed.
Off-label use	Risk minimisation actions will consist of communication in the SmPC and PL, as regards approved indication for use and contraindications.	None proposed.

Missing Information		
Use in elderly patients	Risk minimisation actions will consist of communication in the SmPC and PL. SmPC Section 4.2 Posology and Method of Administration: 'DUAVIVE has not been studied in women over 75 years of age.' 'Based on available data no dosage adjustment is necessary based on age.' SmPC Section 5.1 Pharmacodynamic Properties: 'CE/BZA was not studied in women aged 75 or older. Of the total number of women in Phase 3 clinical trials who received CE/BZA 20 mg, 2.4% (n=77) were >65 years. No overall differences in safety or effectiveness were observed between women aged ≥65 years and younger women but greater sensitivity of some older individuals cannot be ruled out.' SmPC Section 5.2 Pharmacokinetic Properties: 'The pharmacokinetics of CE/BZA have not been evaluated in women over 75 years of age.' 'The pharmacokinetics of a 20 mg single-dose of bazedoxifene were evaluated in a study in 26 healthy postmenopausal women. On average, compared to women 51 to 64 years of age (n=8), women 65 to 74 years of age (n=8) showed a 1.5-fold increase in AUC, and women >75 years of age (n=8) showed a 2.6 fold increase in AUC. This increase is most likely attributable to age-related changes in hepatic function.'	None proposed.
Use in patients with renal impairment	Risk minimisation actions will consist of communication in the SmPC and PL. SmPC Section 4.2 Posology and Method of Administration: 'The pharmacokinetics of CE/BZA have not been evaluated in patients with renal impairment. Use in this population is not recommended.' SmPC Section 4.4 Special Warnings and Precautions: Patients with terminal renal insufficiency should be closely monitored, since it is expected that the level of circulating oestrogens components of CE/BZA will be increased. Use in this population is not recommended. SmPC Section 5.2 Pharmacokinetic Properties: 'The pharmacokinetics of CE/BZA have not been evaluated in patients with renal impairment.' In the PL patients are warned that they may require additional monitoring if they have kidney problems.	None proposed.

Use in patients with hepatic impairment	Risk minimisation actions will consist of communication in the SmPC and PL. SmPC Section 4.2 Posology and Method of Administration: 'The safety and efficacy of CE/BZA have not been evaluated in patients with hepatic impairment. Use in this population is contraindicated.' SmPC Section 4.3 Contraindications: 'Acute liver disease, or a history of liver disease as long as liver function tests have failed to return to normal.' SmPC Section 4.4 Special Warnings and Precautions of the SmPC: 'CE/BZA has not been studied in patients with impaired liver function or past history of cholestatic jaundice. Oestrogens may be poorly metabolised in women with impaired liver function. For women with a history of cholestatic jaundice associated with past oestrogen use or with pregnancy, caution should be exercised, and in the case of recurrence, CE/BZA should be discontinued.' 'Close supervision is advised for patients with liver disorders (e.g., liver adenoma).' 'CE/BZA should be withdrawn in the case of jaundice or deterioration in liver function.' SmPC Section 5.2 Pharmacokinetic Properties: 'The pharmacokinetics of CE/BZA have not been evaluated in women with hepatic impairment.' The PL states that patients who have or have ever had liver disease and whose liver function tests have not returned to normal should not take CE/BZA. Special care is recommended for patients with a liver disorder, such as a benign liver tumour. Also, patients who develop jaundice during treatment should stop taking CE/BZA.	None proposed.
Use in patients with malignancy	Risk minimisation actions will consist of communication in the SmPC and PL. SmPC Section 4.3 Contraindications: Known, suspected, or past history of breast cancer; known, past or suspected oestrogen-dependent malignant tumours (e.g., endometrial cancer); Undiagnosed genital bleeding. These contraindications are also listed in the PL.	None proposed.

Use in patients with a history of cardiovascular disease (including hypertension, hyperlipidaemias, arrhythmias, CHD, angina), diabetes or obesity or long-term smoking	Missing information acknowledged or pertinent contraindications (eg. history of arterial thromboembolic disease) in the SmPC and PL. SmPC Section 4.3 Contraindications: 'Active or past history of arterial thromboembolic disease (e.g., myocardial infarction, stroke).' SmPC Section 4.4 Warnings and Precautions: 'CE/BZA has not been studied in women with baseline triglyceride levels >300 mg/dL (>3.4 mmol/L). Annual monitoring of serum triglycerides should therefore be considered.' Hypertension and diabetes are listed as conditions that need supervision. Obesity is listed as a risk factor for VTE. Smoking and an irregular heart beat are listed as risk factors for stroke in the PL, and the PL advises that special care should be taken in patients with a high level of fat in their blood. Obesity is listed as a risk factor for VTE in the PL, and hypertension and diabetes are listed in the PL as conditions that need special care.	None proposed.
Long term (>2 years) safety data on breast protection and gynaecological cancers (endometrial and ovarian in particular)	Risk minimisation actions will consist of communication in the SmPC and PL. The maximum 2 year duration of clinical studies with CE/BZA is acknowledged in the SmPC Sections 4.4, 4.8 and 5.1. SmPC Section 4.4 Special Warnings and Precautions: Data are provided regarding the association of breast, ovarian and endometrial cancer and duration of oestrogen-only therapy.	None proposed.

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the Applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

Benefits

Beneficial effects

Effect on oestrogen deficiency symptoms

In the phase 3 study pivotal for the treatment of VMS (study 305), BZA 20 mg / CE 0.45 mg as well as BZA 20 mg / CE 0.625 mg were statistically significant more effective than placebo with respect to reduction of the number and severity of hot flushes.

In this study, statistically significant superiority of BZA 20 mg / CE 0.45 mg and of BZA 20 mg / CE 0.625 mg vs. placebo was shown with respect to the co-primary endpoints change from baseline in the average daily number of moderate and severe hot flushes at week 4 and week 12 and change from baseline in the average daily severity score of hot flushes at week 4 and 12. At week 12 the mean change from baseline in the average daily number of moderate and severe hot flushes was -7.63, -8.05, and -4.92 in the BZA 20 mg / CE 0.45 mg, the BZA

20 mg / CE 0.625 mg, and the placebo group, respectively. At week 12 the mean change from baseline in the average daily severity score of hot flushes was -0.87, -01.21, and -0.26 in the BZA 20 mg / CE 0.45 mg, the BZA 20 mg / CE 0.625 mg, and the placebo group, respectively. Results regarding secondary endpoints related to VMS in this pivotal study support this conclusion.

Available data suggest that the efficacy of conjugated oestrogens (CE) for the treatment of hot flushes is decreased in the fixed dose combination of BZA/CE, compared to the combination CE/MPA. Unfortunately, this question was not studied due to lack of an active CE/MPA control group in study 305.

The investigation of VVA is acknowledged as additional evidence in the oestrogen deficiency symptoms indication, although not mandatory according to European guidance.

A superior efficacy of the higher dose strengths BZA 20 mg / CE 0.625 mg compared to the lower dose strength BZA 20 mg / CE 0.45 mg was not convincingly shown. Following concerns expressed by the CHMP, the Applicant has withdrawn the higher dose strength BZA 20 mg / CE 0.625 mg during this application.

Osteoporosis

In both trials with osteoporosis substudies (studies 303 and 3307), the fixed dose combinations of BZA 20 mg / CE 0.45 mg and BZA 20 mg / CE 0.625 mg led to significant increases in BMD of the lumbar spine and total hip after 1 or 2 years of therapy compared to a decrease in BMD with placebo in women >5 and ≤5 years postmenopausal. The mean percent changes in lumbar spine BMD from baseline to Month 12 or 24 were statistically significant different from placebo. However, study 303 was classified as GCP non-compliant and could not be taken into account for the assessment of efficacy of BZA/CE.

In study 303 investigating different doses of BZA (10 mg, 20 mg, 40 mg) in combination with CE, independent of the dose of CE the effect was most pronounced with the lowest dose of 10 mg BZA, attenuating with increasing doses of BZA. This trend was also seen in BMD of total hip and the other hip areas. The responder analysis was in line with these findings. For BZA/CE combinations containing 20 mg of BZA, effects on BMD at lumbar spine were more pronounced than with raloxifene 60 mg.

Serum markers of bone metabolism were determined in a subset of women participating in these trials. At all time-points and for all BZA/CE doses the median percent changes from baseline in serum concentrations of bone turnover markers (BTMs) were significantly greater than for placebo, indicating a decrease in bone turnover.

Uncertainty in the knowledge about the beneficial effects

General

In the pivotal studies, formulations other than the to be marketed (TBM) formulation were used. Thus, proof of bioequivalence between study formulations and the TBM formulation was required. With regard to BZA, bioequivalence was adequately demonstrated.

CE is an extract from pregnant mare´s urine and thus a naturally occurring product containing a not fully characterised mixture of at least 160 components. Of these, 10 substances are listed in Ph. Eur. For proof of bioequivalence, the 2 most abundant oestrogens in CE, estrone and equilin, were selected. In addition, some further oestrogens were measured in the 4 most relevant bioequivalence studies. Thus, components for demonstration of BE were obviously selected based on a pragmatic approach, selecting components which comprise the largest part of the mixture and which can be quantified by currently available bioanalytical methods.

With regard to the total (conjugated and unconjugated) oestrogens prespecified for the analysis of bioequivalence, the 80%-125% acceptance range was met. It is noted that with regard to unconjugated oestrogens, the bioanalytical methods were of insufficient sensitivity. Therefore, only results regarding total oestrogens can be taken into account for bioequivalence.

The Pharmacokinetics Working Party (PKWP) of the CHMP was involved regarding the concept and methodological issues regarding proof of bioequivalence of CE as there was no previous regulatory experience within the EU in this regard. The PKWP agreed that the concept to demonstrate bioequivalence with respect to the active substance "conjugated oestrogens" based on 2 lead substances, i.e. estrone and equilin, is acceptable. It was also agreed that bioequivalence should be demonstrated with respect to total (conjugated and unconjugated) oestrogens and that demonstration of BE with respect to free (unconjugated) oestrogens is not required.

Consequently, bioequivalence between the formulations used in the clinical studies and the TBM formulations was considered adequately demonstrated.

Oestrogen deficiency symptoms

With regard to hot flushes and VVA, superiority vs. placebo was shown for BZA 20 mg / CE 0.625 mg and BZA 20 mg / CE 0.45 mg although regarding the lower dose strengths statistically significant superiority vs. placebo was not demonstrated for all primary endpoints of the phase 3 study regarding VVA (study 306). In addition, the pivotal study regarding treatment of VMS (study 305) was classified as GCP non-compliant. Nevertheless, the results regarding hot flushes can be taken into account for the assessment of efficacy.

Comparisons between the 2 dose strengths applied for with respect to efficacy in the treatment of oestrogen deficiency symptoms had not been prespecified in the pivotal studies and thus, no confirmatory analyses are available in this respect.

There is a concern that the efficacy of CE in the combination BZA/CE is decreased compared to the combination CE/MPA. Unfortunately, in phase 3 studies investigating the efficacy of BZA/CE in the treatment of oestrogen deficiency symptoms no CE/MPA control group was included. Thus, for the comparison of efficacy of BZA/CE vs. CE/MPA, data from a phase 2 study (203), from a phase 3 osteoporosis study (3307), and published data on CE/MPA had to be taken into account.

With respect to treatment of VVA, it is noted that in the pivotal study a control group treated with a topical oestrogen preparation is also missing.

In addition, few patients >65 years of age were included in the clinical trials. Thus, experience in this age group is limited. BZA/CE was also not studied in patients with oestrogen deficiency symptoms due to premature menopause.

With regard to the efficacy of BZA 20 mg / CE 0.45 mg in patients for whom treatment with progestin-containing therapy is not appropriate, a post-hoc subgroup analysis including patients with a medical history of diabetes or depression was provided.

Osteoporosis

In contrast to BZA monotherapy (*see published EPAR for Conbriza*) where changes in BMD from baseline are more pronounced with increasing doses of BZA, in the available data with BZA/CE this relation is opposite. Furthermore, in study 3307 for both doses of BZA/CE changes in BMD were not statistically significant between

BZA monotherapy, BZA/CE, and CE/MPA groups, but effects were most pronounced with CE/MPA. The non-inferiority analysis for BMD showed non-inferiority of BZA/CE 20 mg / 0.625 mg to BZA 20 mg but no superiority, whilst BZA/CE 20 mg / 0.45 mg even failed the pre-specified non-inferiority criterion.

As regards the active comparator CE/MPA only the lower dose strength containing 0.45 mg CE has been included in the pivotal trials, while data on a comparison of changes in BMD from baseline with 0.625 mg CE containing products are missing. From the available data, it has to be expected that differences between the CE/MPA containing 0.625 mg of CE compared to the applied dose strengths of BZA/CE would be even more pronounced.

The data supporting the osteoporosis indication are solely based on surrogate parameters referencing to established anti-fracture efficacy of both components. In general, this approach is endorsed. However, data are only derived from substudies within the pivotal trials; the pivotal trials 303 and 3307 have not been designed as osteoporotic trials and the populations in the substudies have not been selected on the basis of risk factors for osteoporosis. Furthermore, study 303 was classified as GCP non-compliant and should not be taken into account for the assessment of efficacy of BZA/CE leaving only data from 1 trial for the assessment of the efficacy of BZA/CE as regards treatment of osteoporosis.

Risks

Unfavourable effects

BZA/CE

About 3 to 4% of women experienced treatment emergent adverse events (TEAEs) considered severe and related to therapy by the investigators. There was no clear pattern or significant differences in TEAEs between groups. The most common severe drug-related TEAE was headache in all groups.

Endometrial safety was investigated in study 303 and 3307. Study 303 was classified as GCP non-compliant, which was agreed by the CHMP. Nevertheless, the cases of endometrial hyperplasia / malignancy detected after treatment duration of 24 months raise concerns regarding endometrial safety during long-term treatment and this is included as important potential risk in the RMP. There were statistically significant increases in endometrial thickness compared to placebo at Month 12 vs. baseline in the BZA 20 mg / CE 0.45 mg group, the BZA 20 mg / CE 0.625 mg group and the CE 0.45 mg / MPA 1.5 mg group in study 3307. As regards increases in endometrial thickness in terms of an increase from baseline >3 mm or >5 mm as well as an endometrial thickness >4 mm or >8 mm, numerically, the proportion of patients was higher in the BZA 20 mg / CE 0.625 mg group and the CE 0.45 mg / MPA 1.5 mg group compared to the BZA 20 mg / CE 0.45 mg and the placebo group.

Regarding breast cancer, there is an increase in risk associated with CE/MPA combination therapy and possibly also with CE monotherapy. Regarding ovarian carcinoma, there were 5 cases of ovarian carcinoma with BZA 20 mg monotherapy versus no cases in the placebo group in study 301. Ovarian cancer was reported in 2 out of 4868 patients in all BZA/CE groups. Long-term use of oestrogen-only HRT is associated with a slightly increased risk of ovarian cancer. With BZA alone, 5 cases of thyroid cancer occurred versus 1 case in the placebo group over the 7 years study period in study 301. Ovarian volume or the incidence of ovarian cysts does not appear to be adversely affected by BZA/CE.

With regard to breast density, the claim of the Applicant that BZA 20 mg / CE 0.45 mg and BZA 20 mg / CE 0.625 mg demonstrated similar changes in mammographic breast density compared to placebo is not agreed due to the fact that the non-inferiority limit vs. placebo was not sufficiently justified and that in study 4000 a

decrease in mammographic breast density was observed in the placebo group after 2 years, but not in the BZA 20 mg / CE 0.625 mg group. However, it is acknowledged that no increase from baseline in mammographic breast density was observed with BZA 20 mg / CE 0.45 mg and BZA 20 mg / CE 0.625 mg. Therefore, a warning in this respect, as included in the SmPC of other HT products, especially of oestrogen / progestogen fixed combinations, is not required. Breast pain / tenderness was less frequent in patients treated with BZA 20 mg / CE 0.45 mg and BZA 20 mg / CE 0.625 mg, compared to CE 0.45 mg / MPA 1.5 mg.

The assessment of vaginal bleeding and spotting based on subject's diaries did not reveal a safety signal. Spotting was less frequent and the rate of amenorrhea was higher in patients treated with BZA 20 mg / CE 0.45 mg and BZA 20 mg / CE 0.625 mg, compared to CE 0.45 mg / MPA 1.5 mg.

The analysis of deaths and serious adverse events other than death did not indicate relevant differences between active treatment groups. While there were no significant differences in the incidence of serious adverse events between BZA 20 mg / CE and placebo, small imbalances with low absolute numbers occurred. Serious adverse events of coronary artery disease, chest pain, cholecystitis, cholelithiasis, abnormal endometrium results, cerebrovascular accident, transient ischaemic attack, and deep vein thrombosis occurred more often with active treatment than with placebo.

BZA 20 mg / CE had no clinically relevant influence on the lipid profile, C-reactive protein, plasma concentrations of homocysteine, mean fasting glucose levels, fasting insulin, parameters of liver or renal function, haemoglobin, haematocrit, or platelet counts, coagulation parameters or thyroid stimulating hormone compared to placebo. Decreases from baseline in serum calcium, phosphorus, and alkaline phosphatase values were observed in all groups including placebo at all scheduled time points, but there were few occurrences of potentially clinically important decreases in calcium or phosphorus. The available data also do not indicate an influence of treatment with a fixed combination of BZA and CEs compared to placebo on changes in vital signs or blood pressure.

No clear pattern or clinical relevance of differences in adverse events in special populations between BZA 20 mg / CE and placebo treated women has been seen in the data provided. Overall, discontinuations due to adverse events were equally distributed across groups. Adverse events of hot flush and osteoporosis leading to discontinuation occurred more often with placebo than with active treatment.

CE

The increased risks of VTE, stroke, myocardial infarction, ovarian cancer, and possibly also dementia associated with oestrogen-only HRT are well-known.

BZA

The safety profile of BZA is mainly in line with the known safety profile of drugs in the SERM class. AE of special interest are venous thromboembolic events (VTE), cardiovascular events, cerebrovascular AE, vasodilatation, reproductive disorders including breast disorders, and leg cramps. BZA monotherapy over 7 years was associated with a numerical increase in ovarian and thyroid cancer versus placebo.

Uncertainty in the knowledge about the unfavourable effects

Endometrial safety in terms of incidence of endometrial hyperplasia / malignancy was studied in studies 303 and 3307.

A GCP inspection of 2 investigator sites (447 and 450) of trial 303 contributing about 35% of the total trial population revealed critical findings as regards the safety assessment for BZA/CE. The critical findings relate to missing source data for 197 subjects from these sites together with evidence of missing source data from other sites, no adequate overview of the trial conduct at the two sites i.e. about serious non-compliances by the Sponsor, incorrectly assessed relatedness of adverse events to study medication by investigators (with a clear shift to 'not related') also seen in the GCP inspection of trial 305 and thus appearing to be a systematic deficiency, concerns regarding the quality of safety data on the adverse event 'hypertension', and adverse event related subjects' withdrawal / discontinuation. The Sponsor's re-monitoring at sites 447 and 450 did not remedy the systematic failures in relation to adverse event reporting and at this stage it does not appear to be realistically possible to remedy this finding. Study 303 was classified as GCP non-compliant in a GCP inspection and therefore cannot be used to justify the endometrial safety of BZA/CE. Nevertheless, 3 cases of endometrial hyperplasia / malignancy were observed during year 2 in the two BZA/CE groups of this study.

In study 3307, only the diagnosis of the endometrial biopsy, not a more detailed description of the macroscopic and microscopic findings by the pathologists is available. Thus, more detailed information on cases diagnosed as "endometrium, other" could not be provided and no further assessment in this respect is possible. In addition, in study 3307 in 4 patients in the BZA 20 mg / CE 0.45 mg group no biopsy was performed at Month 12 and endometrial thickness was ≥4 mm. In addition, in 8 patients of the BZA 20 mg / CE 0.45 mg group neither a biopsy nor TVUS was performed.

Although about 1580 women have been exposed to either dose of BZA/CE numbers in the active control groups are only 340 for BZA 20 mg, 423 for raloxifene 60 mg, and 399 CE/MPA 0.45 mg / 1.5 mg. Due to this limitation in the number of women treated together with the limited treatment duration and missing data in elderly women the data set does not allow the safety assessment of rare AEs known to be relevant class effects for CE or BZA (e.g. VTE or cancer). Thus, it cannot be concluded whether the FDC of BZA/CE has additive effects on the risk profiles known for both single components; no definite conclusions on VTE, cardiac, or cerebrovascular AEs as well as on the risk of cancer can be drawn. Therefore these risks were included as important identified or potential risks in the agreed version of the RMP. Furthermore, as regards VTEs resistance to activated protein C or resistance to other markers for venous thromboembolism have not been measured. The CHMP agreed that it is likely that at least most risks known for the individual components apply to this FDC.

In addition, there is an increase in risk for breast cancer associated with CE/MPA combination therapy and possibly also with CE monotherapy. A study in monkeys revealed that CE may increase the proliferation rate of mammary gland cells when added to BZA in doses corresponding to the intended human therapeutic dose. Thus, the possibility that the BZA/CE combination leads to an increased breast cancer risk as compared to BZA alone cannot be excluded and breast cancer was included in the RMP as important potential risk.

The interpretation of unfavourable effects in elderly women as well as in women of other than white ethnicity is limited by the low number of women in these groups. Due to the late introduction of BZA into the market, post marketing exposure to BZA is low and the limited data currently do not add to the interpretation of risks involved with BZA treatment. In addition, the PASS requested at the time of marketing authorisation of BZA so far did not deliver relevant data due to considerable limitations of the chosen databases and the late introduction into market.

The increased risks in particular of long-term administration of CE alone or CE combined with a progestin are well-known. How these risks are modified when CE is combined with BZA is currently unknown and this was included as missing information into the RMP.

Although the bleeding pattern in the two BZA/CE groups investigated was similar to placebo and more favourable compared to CE 0.45 mg / MPA 1.5 mg the dose of 1.5 mg MPA used in this trial is low and no comparison of the products applied for vs. CE 0.625 mg / MPA 2.5 mg or CE 0.625 mg / MPA 5 mg was provided.

Benefit-risk balance

Importance of favourable and unfavourable effects

Oestrogen deficiency symptoms

Generally, oestrogen deficiency symptoms may adversely affect quality of life but are not associated with serious long-term sequelae. Nevertheless, there is a population of postmenopausal women who experience severe and frequent VMS, often also negatively affecting sleep, and for whom effective treatment is required. Thus, hot flushes are considered as the most important endpoint regarding efficacy with regards to oestrogen deficiency symptoms. This is in accordance with the *EMA Guideline on clinical investigation of medicinal products for hormone replacement therapy of oestrogen deficiency symptoms in postmenopausal women (EMEA/CHMP/021/97 rev. 1), Oct 2005*, which recommends the number of moderate and severe or hot flushes as the primary endpoint.

With regard to safety, endometrial safety is considered as a very important issue.

In the treatment of oestrogen deficiency symptoms, BZA/CE is expected to be used for long-term therapy of several years in many patients. Therefore, potential serious risks associated with long-term use such as VTE or stroke are considered as very important.

Efficacy regarding VVA is considered as less important as there is a consensus that local vulvovaginal symptoms should preferably be treated with topical oestrogens. Thus, BZA 20 mg / CE 0.45 mg as well as BZA 20 mg / CE 0.625 mg would not be considered as suitable treatment options in patients with VVA only.

The bleeding pattern, breast pain, and mammographic breast density are taken into account by the Applicant for the benefit risk evaluation. Irregular bleeding and breast pain are not in itself serious events associated with adverse long-term sequelae but may be of importance for individual patients. These adverse effects should be taken into account for the benefit-risk evaluation, but are not considered as more important than other non-serious adverse effects.

Mammographic breast density is also an effect to be considered as with oestrogen / progestogen combinations an increase in breast density is observed. An increase in mammographic breast density is expected to adversely affect the detection of breast cancer in mammograms. However, no conclusions regarding the risk of breast cancer can be drawn, based on a lack of increase in mammographic breast density.

Osteoporosis

As regards unfavourable effects, the use of HRT or SERMs including BZA is amongst others associated with the occurrence of AEs of VTE, coronary heart disease (CHD), cancer, and hot flushes. Especially cardiovascular as well as cancer related events carry a significant burden for both the individual patient and the society. The relevant AEs are both potential life threatening and disabling and are therefore considered as important.

The effect on osteoporosis could be important as postmenopausal osteoporosis is a common, systemic skeletal disorder. In general for medicinal products with known anti-fracture activity it can be assumed that increases in BMD will reduce the risk of osteoporotic fracture. However, changes in BMD have only unequivocally been

demonstrated in comparison to placebo, while in comparison to the active comparators BZA 20 mg alone or CE/MPA they were not convincing. In particular, as no contribution of CE to the effects of BZA/CE on BMD was demonstrated, the efficacy in the treatment of osteoporosis is considered as unimportant. No additive or synergistic effects of the FDC compared to BZA monotherapy or CE/MPA therapy has been demonstrated. Furthermore, while the HRT Core EU SmPC limits the use of these medicinal products to the shortest duration possible, use of BZA for the treatment of postmenopausal osteoporosis would be required over long time-periods.

Benefit-risk balance

Discussion on the benefit-risk balance

Oestrogen deficiency symptoms

The efficacy of both dose strengths of BZA/CE vs. placebo in the treatment of oestrogen deficiency symptoms has been demonstrated in pivotal study 305. In this study, statistically significant superiority of BZA 20 mg / CE 0.45 mg and of BZA 20 mg / CE 0.625 mg vs. placebo was shown with respect to the co-primary endpoints change from baseline in the average daily number of moderate and severe hot flushes at Week 4 and Week 12 and change from baseline in the average daily severity score of hot flushes at Week 4 and 12.

However, taking all data into account, superior efficacy of BZA 20 mg / CE 0.625 mg vs. BZA 20 mg / CE 0.45 mg was not sufficiently demonstrated. According to the literature, a dose dependent increase in the efficacy of hormone therapy in the treatment of hot flushes is established. As the risks associated with CE are considered as dose-dependent, the higher dose strength BZA 20 mg / CE 0.625 mg was insufficiently justified. Therefore, the Applicant has withdrawn the higher dose strength BZA 20 mg / CE 0.625 mg from the application during the procedure.

The available data also indicate that the efficacy of CE in the treatment of VMS is decreased in the combination BZA/CE, compared to the combination of CE/MPA. Unfortunately, a CE/MPA active control group was not included in the studies pivotal for the treatment of oestrogen deficiency symptoms so that the decrease in efficacy cannot be quantified. In addition, the lack of data regarding possible risks in particular during long-term administration of several years, which is expected in the treatment of oestrogen deficiency symptoms, also has to be taken into consideration. No conclusions can be drawn from the clinical trials in this respect, as the sample size and the treatment duration were not adequate to investigate these risks. In particular, the CHMP did not feel reassured with regards to the number of adverse events classified as low/similar to placebo in clinical studies. In particular, it was noted that BZA alone as well as CE alone are associated with an increased risk of VTE. In addition, stroke is a known risk of CE and a potential risk of BZA. Thus, there is a concern that the incidence of VTE and possibly also stroke will be increased with the combination of BZA/CE. That is why these risks were included as identified or potential risks in the agreed version of the RMP. Furthermore the results of the PASS and the DUS studies should provide further information regarding safety of this product.

In addition, the risk of breast cancer associated with BZA/CE is currently unknown. With regard to mammographic breast density, it is acknowledged that no increase from baseline in mammographic breast density was observed with BZA 20 mg / CE 0.45 mg and BZA 20 mg / CE 0.625 mg. Therefore, a warning in this respect as included in the SmPC of other HT products, especially of oestrogen / progestogen fixed combinations, is not required. However, no conclusions such as no increase in the risk of breast cancer can be drawn, based on a lack of increase in mammographic breast density as mammographic breast density is no established surrogate endpoint in this respect. Data from monkeys are not fully reassuring in regard to mammary gland proliferation.

CE was able to increase proliferation markers even in the presence of BZA. Thus, the breast safety of BZA/CE remains uncertain and is addressed in the agreed version of the RMP.

In study 3307 investigating primarily the efficacy of BZA/CE for osteoporosis, the rates of amenorrhea were higher in the BZA 20 mg / CE 0.45 mg group and the BZA 20 mg / CE 0.625 mg group, compared to CE 0.45 mg / MPA 1.5 mg. In addition, breast pain was less frequent in patients treated with both dose strengths of BZA/CE, compared to CE/MPA.

Endometrial safety was considered by the CHMP of particular importance. Study 303 is not considered GCP-compliant, in particular regarding the investigation of endometrial safety. Nevertheless, in this study no cases of endometrial hyperplasia was observed in year 1 in the BZA 20 mg / CE 0.45 mg group while 2 cases of endometrial hyperplasia / malignancy were detected during the second year of treatment in the BZA 20 mg / CE 0.45 mg group. In study 3307, the upper limit of the 2-sided 95% confidence interval of the incidence of endometrial hyperplasia was below the reference limit of the *EMA Guideline on clinical investigation of medicinal products for hormone replacement therapy of oestrogen deficiency symptoms in postmenopausal women (EMEA/CHMP/021/97 rev. 1), Oct 2005* of 2% in each of the two BZA/CE groups. In 12 of 445 patients in the BZA 20 mg / CE 0.45 mg no reassuring outcome with regard to endometrial safety is available. In 4 patients in the BZA 20 mg / CE 0.45 mg no biopsy was performed at month 12 and endometrial thickness was ≥4 mm. As already stated above, this amount of missing data was considered not unusual for a study of this size. Regarding endometrial thickness measured by TVUS statistically significant increases vs. placebo were observed in the BZA 20 mg / CE 0.45 mg group and the BZA 20 mg / CE 0.625 mg group at month 12 in study 3307.

Taking into account that:

- the efficacy of BZA/CE combination vs. placebo in the treatment of oestrogen deficiency symptoms has been demonstrated in the pivotal for VMS treatment trial,
- the efficacy of CE in the treatment of VMS is decreased in the combination with BZA,
- the available data indicate that efficacy of the BZA/CE combination is lower as compared to the CE/MPA combination (no CE/MPA arm in the pivotal 305 study)

and also considering identified risks such as VTE and potential risks such as stroke, endometrial hyperplasia and others, the Applicant proposed for BZA 20 mg / CE 0.45 mg a more narrow therapeutic indication:

Treatment of oestrogen deficiency symptoms in postmenopausal women with a uterus (with at least 12 months since the last menses) for whom treatment with progestin-containing therapy is not appropriate. The experience treating women older than 65 years is limited.

Taking into account that endometrial safety as well as other safety issues will be further addressed in RMP as well as in DUS and PASS studies, the benefit-risk balance of this more narrow therapeutic indication was considered as positive.

Osteoporosis

It is acknowledged that BZA/CE demonstrated relevant increases in BMD from baseline and that for both components anti-fracture efficacy has been established. However, while the Applicant has provided data on an adequate effect of both doses of BZA/CE on changes in BMD from baseline compared to placebo, these effects appear to be less than those seen with the active control of CE 0.45 mg / MPA 1.5 mg, although this is probably not even the most efficacious dose of CE/MPA. In addition, BZA/CE did not show superiority to BZA 20 mg in changes of BMD from baseline and for the BZA 20 mg / CE 0.45 mg dose even failed the pre-specified non-inferiority criterion. Furthermore, while with BZA effects on BMD increase with increasing dose, the opposite

effect has been seen with BZA/CE were the lowest doses of BZA 10 mg / CE showed the most pronounced increases with attenuating effects with increasing the dose of BZA indicating relevant pharmacodynamic interactions between both components.

The fixed combination of BZA/CE has no superior efficacy on BMD compared to BZA monotherapy and appears to have inferior efficacy to CE/MPA.

Furthermore, the duration of use for HRT has been limited to the shortest duration possible due to the adverse effects seen with this therapy. The data provided by the Applicant do not justify considering the risk profile of the new proposed combination of BZA/CE to be different from that seen with CE/MPA treatment as regards relevant AEs limiting the duration of use.

While there was no added value shown for the fixed-dose combination of BZA/CE over the mono-components in the treatment of postmenopausal osteoporosis, there are important potential life threatening and disabling unfavourable effects associated with its use. It is not possible to determine how the incidence of these unfavourable effects with BZA/CE compares to the rates observed with other forms of the hormone replacement therapy or with SERMs.

In consequence, the Applicant has withdrawn an osteoporosis related indication.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety, and efficacy, the CHMP considers by majority decision that the risk-benefit balance of Duavive in the:

Treatment of oestrogen deficiency symptoms in postmenopausal women with a uterus (with at least 12 months since the last menses) for whom treatment with progestin-containing therapy is not appropriate.

The experience treating women older than 65 years is limited.

is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreeed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

Divergent position to the majority recommendation is appended to this report.

Appendix

DIVERGENT POSITION

Divergent Position

The undersigned members of CHMP did not agree with the CHMP's opinion recommending the granting of a Marketing Authorisation for Duavive. The reasons for divergent opinion were as follows:

Some CHMP members considered that the benefit risk balance of Duavive is negative for the following reasons:

The available data indicate that the efficacy of conjugated oestrogens (CE) in the treatment of VMS is decreased in the combination with bazedoxifene (BZA), compared to the combination CE/medroxprogesterone acetate (MPA). Unfortunately, a CE/MPA active control group was not included in the studies pivotal for the treatment of oestrogen deficiency symptoms so that the decrease in efficacy could not be quantified. However, it is concluded that a higher dose of CE will be required for the treatment of oestrogen deficiency symptoms in the combination BZA/CE compared to the combination CE/MPA.

Taking into account the well-known risks of CE/MPA or more generally of oestrogen / progestogen HRT and the current consensus that oestrogens for the treatment of oestrogen deficiency symptoms should be administered at the lowest possible dose an increase in the dose of CE seems hardly acceptable and is considered as a safety concern.

Endometrial safety is of particular importance. Study 303 is not considered GCP-compliant, in particular regarding the investigation of endometrial safety. Nevertheless, in this study no cases of endometrial hyperplasia was observed in year 1 in the BZA 20 mg/CE 0.45 mg group while 2 cases of endometrial hyperplasia / malignancy were detected during the second year of treatment in the BZA 20 mg/CE 0.45 mg group. This finding is considered as a risk signal, raising concerns regarding safety during long-term treatment.

In study 3307, the upper limit of the 2-sided 95% confidence interval of the incidence of endometrial hyperplasia was below the reference limit of the CHMP HRT Guideline of 2% in each of the two BZA/CE groups. Nevertheless, there are concerns with respect to the analysis of endometrial safety, based on this study. In 12 of 445 patients in the BZA 20 mg / CE 0.45 mg no reassuring outcome with regard to endometrial safety is available. In 4 patients in the BZA 20 mg / CE 0.45 mg no biopsy was performed at month 12 and endometrial thickness was ≥4 mm. As already stated above, a very low number of additional cases of hyperplasia would change the outcome of the study from success to failure.

The applicant proposes to conduct a PASS in the US, in particular to address concerns around endometrial safety in a post-marketing setting. A PASS to be conducted in the EU is not considered to be able to provide additional information regarding the safety issues of interest within a reasonable timeframe.

In addition, the lack of data regarding possible risks in particular during long-term administration of several years which is expected in the treatment of oestrogen deficiency symptoms has also to be taken into consideration. No conclusions can be drawn from the clinical trials in this respect as the sample size and the treatment duration were not adequate to investigate these risks. In particular, it is noted that BZA alone as well as CE alone are associated with an increased risk of VTE. In addition, stroke is a known risk of CE and a potential risk of BZA. The risk of breast cancer associated with BZA/CE is currently unknown.

Taking also into account:

- that different progestogens have different activities and therefore, intolerance to a specific progestin cannot be extrapolated to progestins in general,

- that other treatment options exist for postmenopausal women with VMS who experienced adverse effects during treatment with a specific combined oestrogen progestin regimen,

- that no data are available with respect to the benefits and risks of BZA 20 mg/CE 0.45 mg in the subgroup of postmenopausal patients intolerant of progestins,

- that in particular, it is unknown whether patients discontinuing combined oestrogen progestin hormone therapy due to adverse effects will tolerate BZA 20 mg/CE 0.45 mg better,

- that adverse effects such as flatulence, depression, mood swings, peripheral oedema, acne, hirsutism and increased weight, considered by the applicant as specific adverse effects of progestins, were observed in study 3307 in the BZA 20 mg/CE 0.45 mg group and the CE 0.45 mg/MPA 1.5 mg group with comparable frequency, and

- that it remains unknown which co-morbid conditions will be exacerbated by progestins, but not by BZA/CE,

- that depression should not be considered as such a co-morbid condition because the depression score was similar with CE/MPA and placebo in the WHI study (Hays et al. 2003) and depression occurred with similar frequency in patients treated with CE/MPA or BZA/CE in study 3307,

- that diabetes should not be considered as such a co-morbid condition as the risk of diabetes was decreased in patients treated with CE/MPA compared to placebo in the WHI study (Margolis et al. 2004) and fasting glucose was similar with CE/BZA, CE/MPA and placebo in study 3307,

- that BZA/CE was not investigated in a population of postmenopausal women with diabetes or depression,

the benefit risk balance of BZA 20 mg/CE 0.45 mg in the therapeutic indication applied for is considered negative.

London, 23 October 2014

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Harald Enzmann (Germany)

…….……

Pierre Demolis (France)

…….……

Radka Montoniová (Czech Republic)