



Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for conjugated estrogens / bazedoxifene acetate

Proprietary Product Name: Duavive

Sponsor: Pfizer Australia Pty Ltd

First round report: April 2016

Second round report: August 2016

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the [TGA website](https://www.tga.gov.au) <<https://www.tga.gov.au>>.

About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent [Product Information \(PI\)](https://www.tga.gov.au/product-information-pi), please refer to the TGA website <<https://www.tga.gov.au/product-information-pi>>.

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List of abbreviations

Abbreviation	Meaning
CE	Conjugated Estrogens
BZA	Bazedoxifene
FDC	Fixed dose combination
MHT	Menopause hormone therapy
MPA	Medroxyprogesterone
VMS	Vasomotor Symptoms
VVA	Vulvar-vaginal Atrophy

1. Introduction

This is an application to register a new fixed dose combination (FDC) medicine. One of the components, bazedoxifene, has not been previously registered in Australia as a mono product. The proposed indication is:

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

The experience treating women older than 65 years is limited.

2. Background

According to the Royal Australian and New Zealand College of Obstetrics and Gynaecology (RANZCOG):¹

the menopause refers to the final menstrual period. A woman is postmenopausal 12 months after her final menstrual period.....The menopause transition commonly starts around 47 years and the average age of natural menopause is 51 years.

Duavive is a FDC of BZA, a SERM, and CE (BZA/CE). BZA has both agonist and antagonist estrogen receptor activity - agonist activity on the skeletal system and antagonist activity in breast and uterine tissues. More specifically, compared to most MHT preparations with CE, in Duavive, the progestogen component has been replaced by BZA.

The first observational studies reporting an association between endometrial cancer (and hyperplasia) and un-opposed estrogen therapy were published in 1975.² As a result, clinicians started prescribing doses of CE at lower doses than the previous standard of 1.25 mg. However, rates of endometrial hyperplasia with CE administered at a lowered dose ranged from 7% with 12 months use to 15% with 24 months use at a CE dose of 0.45 mg CE and 10% with 12 months use to 27% with 24 months use at a CE dose of 0.625 mg.³

MPA was subsequently added to the CE for endometrium protection which proved successful⁴ and the addition of a progestogen/progestin (natural or synthetic progesterone) has become the standard intervention to prevent estrogen induced endometrial stimulation in menopausal therapy. The Women's Health Initiative (WHI) study of 16,608 postmenopausal women reported that CE/MPA 0.625/2.5 mg carried no increased risk of endometrial cancer compared with placebo.⁵

Besides progestogens, an alternative approach for protecting the endometrium against estrogen stimulation in menopausal therapy is a TSEC. This involves combining a SERM with estrogen. Endometrial protection is achieved through modulation of the estrogen receptor. The clinical effect of a TSEC would be the blended tissue specific activities of the SERM and estrogens. An ideal SERM estrogen combination would have the positive attributes of estrogen and fewer of the adverse reactions (for example, stimulation of the endometrium or breast). Not all estrogen SERM combinations reduce endometrial stimulation. For example, oestradiol-raloxifene is associated with endometrial stimulation.⁶

¹ RANZCOG, Management of the menopause, Nov 2014.

² Ziel HK, Finkle WD. Increased risk of endometrial carcinoma among users of conjugated estrogens. *N Engl J Med.* 293: 1167-1170 (1975).

³ Pickar JH, et al. Endometrial Effects of Lower Doses of Conjugated Equine Estrogens and Medroxyprogesterone Acetate: Two-Year Substudy Results. *Fertil Steril.* 80: 1234-1240 (2003).

⁴ Woodruff JD, Pickar JH. *Am J Obstet Gynecol.* 170: 1213-1223 (1994).

⁵ Anderson GL, et al. Effects of estrogen plus progestin on gynecologic cancers and associated diagnostic procedures: the Women's Health Initiative randomized trial. *JAMA* 290: 1739-1748 (2003).

⁶ Stovall DW, et al. The Effects of Combined Raloxifene and Oral Estrogen on Vasomotor Symptoms and Endometrial Safety. *Menopause* 14 (3 Pt 1): 510-517 (2007).

2.1. Provision of overseas evaluation reports⁷

The streamlined process of TGA's evaluation was initiated with a pre-submission meeting.⁸ During this meeting, the sponsor updated TGA about Duavive's overseas regulatory status. This included the EMA evaluation that reflected the critical evaluation of safety, efficacy and quality aspects of Duavive for the treatment of oestrogen deficiency symptoms in post-menopausal women. In CHMP evaluation, from an efficacy perspective, the clinical utility of Duavive in the osteoporosis related indication was considered, and the drug-drug interaction between BZA and CE was also noted. Safety data related to endometrial safety was considered as significant. Subsequently, the adequacy of all these aspects was taken into consideration in their evaluation and final conclusion. Following risk-benefit assessment, EMA approved an indication identical to that submitted for TGA evaluation. Where relevant, the evaluator has considered various aspects of EMA's clinical evaluation in the assessment of this dossier.

In order to ensure patient safety and optimise treatment outcomes, precautionary warnings to health care professionals (HCPs) were included in PIs intended for US, Canada and Switzerland.

Cardiovascular events and endometrial safety were highlighted in those warnings. No similar warnings were proposed to be inserted in to the Australian PI.

2.2. Overview of Phase II and III BZA/CE studies

The following Phase II and III studies were submitted by the sponsor. Pivotal studies, as designated by the sponsor, are highlighted in grey.

Table 1: Overview of Phase II and III BZA/CE studies.

Study	Study Description	FSFV / LSLV	Duration	Treatment groups <i>*Active comparator</i>	Primary endpoints
Study 203 (n = 412)	A Phase II multicentre, double blinded, 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	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	Mean change from baseline to Day 84 in endometrial thickness

⁷ This section is a TGA summary of the wording in the clinical evaluation report, which discussed numerous aspects of overseas evaluation reports and included some information that was commercial-in-confidence.

⁸ TGA guidance at pre-submission meetings is nonbinding and without prejudice.

Study	Study Description	FSFV / LSLV	Duration	Treatment groups *Active comparator	Primary endpoints
Study 303 (n = 3544)	A Phase III multicentre, double blinded, 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	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 / CE 0.625 mg *Raloxifene 60 mg Placebo	Incidence of endometrial hyperplasia at Month 12 Lumbar spine BMD at Month 24 versus placebo
Study 4000 [^] (an ancillary substudy of study 303)	Evaluation of changes in mammographic breast density associated with bazedoxifene acetate / conjugated estrogens, raloxifene, and placebo in postmenopausal women: an ancillary study of protocol 3115A1-303-WW	Jan 09 / Apr 10	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 / CE 0.625 mg *Raloxifene 60 mg Placebo	Mean % change from baseline in breast density within each treatment at 24 month
Study 304 (n = 1083; 523 continued in study extension)	A Phase III 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	12 months + 12 month extension (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	Incidence of endometrial hyperplasia at Month 12 BMD lumbar spine at Month 12 versus placebo
Study 305 (n = 332)	A Phase III multicentre, double blinded, randomised, placebo-controlled, efficacy and safety study designed to demonstrate the	Sep 05 / Feb 07	12 weeks	BZA 20 mg / CE 0.45 mg BZA 20 mg / CE 0.625 mg Placebo	At Weeks 4 and 12: Change in number of hot flushes versus placebo Change in severity score of hot flushes versus placebo

Study	Study Description	FSFV / LSLV	Duration	Treatment groups <i>*Active comparator</i>	Primary endpoints
	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.				
Study 306 (n = 664)	A Phase III multicentre, double blinded, 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	12 weeks	BZA 20 mg / CE 0.45 mg BZA 20 mg / CE 0.625 mg <i>*BZA 20 mg</i> Placebo	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
Study 3307 (n=1886)	A Phase III, multicentre, double blinded, 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	12 months	BZA 20 mg / CE 0.45 mg BZA 20 mg / CE 0.625 mg <i>*BZA 20 mg</i> <i>*CE 0.45 mg</i> / MPA 1.5 mg Placebo	Incidence of endometrial hyperplasia at Month 12 Percent change from Baseline in Lumbar spine BMD at Month 12 versus placebo

FSFV, first subject first visit; LSLV, last subject last visit

The clinical development programme was initiated in 2001 and the last Phase III trial (3307) was finalised in 2011. The pivotal trials were carried out in the United States, Finland, Norway, Italy, Netherlands, Belgium, Poland, Spain, Denmark, Hungary, Brazil, Argentina, Chile, Columbia, Mexico, Australia and New Zealand.

2.3. Regulatory guidelines

There are two relevant EMA Guidelines (adopted by TGA).

Table 2: Overview of Phase II and III BZA/CE studies.

Guideline	Key recommendations
<p>Guideline on clinical investigation of medicinal products for hormone replacement therapy of oestrogen deficiency symptoms in postmenopausal women (EMA/CHMP/021/97 Rev. 1), October 2005</p>	<p>Efficacy</p> <ul style="list-style-type: none"> • The most important oestrogen deficiency symptoms are vasomotor symptoms (hot flushes) and only moderate to severe hot flushes are to be treated by HRT • Primary endpoint for efficacy trials is the frequency of moderate to severe hot flushes • Enrolled subjects should have a minimum of least 5 moderate to severe hot flushes per day at baseline • Placebo-controlled studies are sufficient • Duration of treatment for efficacy symptom evaluation – 3 months • Endometrial safety • Biopsy is the gold standard method for assessing endometrial hypertrophy • Assessment should be done according to predefined and generally accepted criteria • Transvaginal uterine ultrasound should not replace biopsy • Studies of at least 12 month duration are required • The upper limit of the two-sided 95% confidence interval incidence of hyperplasia or more serious endometrial outcomes should not exceed 2% • Other safety • Venous Thromboembolism – careful monitoring recommended • Bleeding <ul style="list-style-type: none"> ○ Minimum duration of 12 months ○ Monitor incidence of amenorrhoea during months 10-12 and % with bleeding and/or spotting in first 3 month and months 10-12. • Breast examination and monitoring required
<p>Guideline on clinical development of fixed combination medicinal products (CHMP/EWP/240/95 Rev.1), February 2009 <i>Of note, currently this GL is under revision</i></p>	<ul style="list-style-type: none"> • It should be clearly stated if the claimed indication is first line, second line therapy or a substitution, and the clinical development should be performed accordingly. • Exploration of interactions between the two substances should be explored • The benefit/risk assessment of the fixed combination should be equal or exceeds that of each substance taken alone • Where there are grounds to expect that a fixed combination product may be substantially more harmful or give rise to much more frequent adverse effects than any individual substances given alone, the applicant should provide evidence that this does not occur in therapeutic use, or that the advantages of the combination e.g. increased efficacy, outweigh such disadvantages.

The FDA offers draft guidance (January 2003) for industry entitled “Estrogen and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms — Recommendations for Clinical Evaluation”. This is relevant to this submission as the sample sizes for studies 303 and 3307 were calculated based on the FDA guidelines for endometrial safety which stipulate that the endometrial hyperplasia observed rate at year 1 should be $\leq 1\%$ with the upper limit of the 1-sided 95% CI less than 4%.

2.4. Australian regulatory history

- No previous submission of CE/BZA combination
- Single agent BZA is not registered in Australia. Single agent BZA (brandname - Conbriza) is registered in the EMA for postmenopausal osteoporosis in women at increased risk of fractures.

2.5. Menopausal Hormone Therapy available in Australia

As listed on the Australian Register of Therapeutic Goods; data from Product Information available on TGA website unless marked otherwise.

Table 3: Menopausal Hormone Therapy available in Australia.

Trade name	Active	Formulat	First	Indication*
Premia continuous	CE and MPA – two strengths: 0.625 mg CE and 2.5 mg or 5 mg MPA.	Tablet	12/06/1997	<p>PREMIA is indicated:</p> <ul style="list-style-type: none"> · as replacement therapy for oestrogen deficiency states associated with the climacteric in women with an intact uterus most commonly manifested by: <ul style="list-style-type: none"> ○ moderate to severe vasomotor symptoms associated with oestrogen deficiency in natural and surgical menopause (sweating, hot flushes). ○ Atrophic vaginitis · for the prevention of postmenopausal osteoporosis in select patients
Premia low ⁹ 0.3/1.5 (information per ARTG)	0.3mg CE and 1.5mg MPA	Tablet	17/06/2002	<p>PREMIA LOW 0.3/1.5 CONTINUOUS is indicated as replacement therapy for oestrogen deficiency states associated with the climacteric in women with an intact uterus most commonly manifested by moderate to severe vasomotor symptoms associated with oestrogen deficiency (sweating, hot flushes).</p>
Premia low ¹⁰ 0.45/1.5 (information per ARTG)	0.45 Combined oestrogens (CE) and 1.5 Medroxyprogesterone acetate (MPA)	Tablet	17/06/2002	<p>PREMIA LOW 0.45/1.5 CONTINUOUS is indicated as replacement therapy for oestrogen deficiency states associated with the climacteric in women with an intact uterus most commonly manifested by moderate to severe vasomotor symptoms associated with oestrogen deficiency (sweating, hot flushes).</p>

⁹ Premia Low has not been supplied for more than 5 years.

¹⁰ Premia Low has not been supplied for more than 5 years.

Trade name	Active Ingredient (s) and dose	Formulation / presentation	First listed on ARTG #	Indication*
Femoston 2/10	Oestradiol and dydrogesterone – two doses per pack: 2mg oestradiol for 14 days and 2mg/10mg dydrogesterone for 14 days	Tablet	08/09/2000	Hormone replacement therapy (HRT) in oestrogen deficiency associated with natural or artificial menopause in women with an intact uterus. Prevention of postmenopausal bone mineral density loss in women.
Femoston 1/10	Oestradiol and dydrogesterone – two doses in single pack: Oestradiol 1mg for 14 days and oestradiol 1mg with dydrogesterone 10mg for 14 days	Tablet	08/05/2014	Hormone replacement therapy (HRT) in oestrogen deficiency associated with natural or artificial menopause in women with an intact uterus. Prevention of postmenopausal bone mineral density loss in women.
Femoston Conti	Oestradiol 1 mg and Dydrogesterone 5 mg	Tablet	30/05/2001	Hormone replacement therapy (HRT) in oestrogen deficiency associated with natural or artificial menopause in women with an intact uterus. Prevention of postmenopausal bone mineral density loss in women.
Trisequens	Oestradiol and norethisterone acetate – three doses in single pack: 12 days 2mg oestradiol, 10 days of 2mg oestradiol/1mg norethisterone acetate and 6 days 1mg oestradiol	Tablet	11/01/2012	Short term symptomatic treatment of oestrogen deficiency associated with natural or artificial menopause
Kliovance	17 β oestradiol 1 mg and norethisterone Acetate 0.5 mg	Tablet	30/08/1999	<ul style="list-style-type: none"> • Short term treatment of menopausal symptoms related to oestrogen deficiency in women more than one year after menopause • For the prevention of postmenopausal bone mineral density loss.
Kliogest	Oestradiol 1mg and norethisterone acetate 2mg	Tablet	17/06/2011	Short term symptomatic treatment of postmenopausal oestrogen deficiency For the prevention of postmenopausal bone mineral density loss

Trade name	Active Ingredient (s) and dose	Formulation / presentation	First listed on ARTG #	Indication*
Angeliq 1/2	Oestradiol 1mg and drospirenone 2mg	Tablet	30/11/2004	Hormone replacement therapy (HRT) for use in the short-term treatment in postmenopausal women with an intact uterus of the climacteric syndrome caused by deficient endogenous oestrogen production due to natural menopause, hypogonadism, castration or primary ovarian failure
Premarin	Combined oestrogens (CE) – two strengths: 0.3mg and 0.625	Tablet	30/03/1995	PREMARIN is indicated as replacement therapy for oestrogen deficiency states associated with climacteric manifested by: <ul style="list-style-type: none"> · moderate to severe vasomotor symptoms associated with the oestrogen deficiency in natural and surgical menopause (sweating, hot flashes). · atrophic vaginitis. PREMARIN is indicated for the prevention of postmenopausal osteoporosis in select patients. Hypoestrogenic states, e.g., female hypogonadism, primary ovarian failure or female castration.
Estrofem	Oestradiol- two strengths: 1mg and 2 mg	Tablet	17/11/2011	Short term symptomatic treatment of oestrogen deficiency due to natural or surgical menopause in hysterectomised postmenopausal women
Zumenon	Oestradiol hemihydrate 2mg	Tablet	08/10/2000	Symptomatic treatment of oestrogen deficiency due to natural or surgical menopause in hysterectomised postmenopausal women.
Progynova	Oestradiol valerate – two strengths: 1mg and 2mg.	Tablet	19/08/1991	Short term treatment of climacteric complaints after the cessation of monthly bleeding, or deficiency symptoms after oophorectomy or radiological castration for non-carcinomatous diseases, such as hot flushes, outbreaks of sweat, sleep disturbances, depressive moods, irritability, headaches, dizziness. PROGYNOVA also has a favourable influence on

Trade name	Active Ingredient (s) and dose	Formulation / presentation	First listed on ARTG #	Indication*
				bladder irritation (a not infrequent occurrence in the climacteric), signs of cutaneous and mucosal involution (particularly in the genital region) which normally occur with advancing age.
Ovestin	Oestriol 1mg	Tablet	20/09/1991	Short-term treatment of menopausal syndrome
Primolut N	Norethisterone 5mg	Tablet	19/08/1991	Dysfunctional bleeding, primary and secondary amenorrhoea, premenstrual syndrome, delay of menstrual period, endometriosis, adjunct to oestrogen hormone replacement therapy.
Provera	Medroxyprogesterone acetate – three strengths: 2.5mg, 5 mg, 10mg [nb. Higher strengths available for Provera, however for different indications]	Tablet	7/01/1993	Adjunct to oestrogen therapy
Ralovera	Medroxyprogesterone acetate – three strengths: 2.5mg, 5 mg, 10mg	Tablet	14/10/1993	Adjunct to oestrogen therapy
Medroxyprogesterone Sandoz	Medroxyprogesterone acetate 10mg	Tablet	19/07/2001	Adjunct to oestrogen therapy in women with an intact uterus.
Livial	Tibolone 2.5 mg	Tablet	19/05/2000 (per ARTG) “TGA approve date” per PI 27/11/2007	<ul style="list-style-type: none"> Short-term treatment of symptoms resulting from the natural or surgical menopause in post menopausal women. Second line therapy for the prevention of bone mineral density loss in postmenopausal women at high risk of future osteoporotic fractures who are intolerant of, or contraindicated for, other medicinal products approved for the prevention of bone mineral density loss.

Trade name	Active Ingredient (s) and dose	Formulation / presentation	First listed on ARTG #	Indication*
Xyvion	Tibolone 2.5 mg	Tablet	14/08/2008	<ul style="list-style-type: none"> · Short-term treatment of symptoms resulting from the natural or surgical menopause in postmenopausal women. · Second line therapy for the prevention of bone mineral density loss in postmenopausal women at high risk of future osteoporotic fractures who are intolerant of, or contraindicated for, other medicinal products approved for the prevention of bone mineral density loss.
Tibogen	Tibolone 2.5 mg	Tablet	9/02/2015	<ul style="list-style-type: none"> · Short-term treatment of symptoms resulting from the natural or surgical menopause in postmenopausal women. · Second line therapy for the prevention of bone mineral density loss in postmenopausal women at high risk of future osteoporotic fractures who are intolerant of, or contraindicated for, other medicinal products approved for the prevention of bone mineral density loss.
Estradot 25, 37.5, 50, 75, 100	Oestradiol- five strengths: 25, 37.5, 50, 75 and 100 µg/day respectively [total dose 0.39mg, 0.585mg, 0.78, 1.17 or 1.56 mg oestradiol respectively]	Patch	05/02/2004	Short term treatment of symptoms of oestrogen deficiency due to the menopause, whether natural or surgically induced.

Trade name	Active Ingredient (s) and dose	Formulation / presentation	First listed on ARTG #	Indication*
Estraderm 25, 50, 100	Oestradiol – three strengths: 25µg, 50µg and 100 µg/24h respectively [total dose 2mg, 4mg and 8mg respectively]	Patch	17/06/1996	Short-term treatment of signs and symptoms of oestrogen deficiency due to the menopause, whether natural or surgically induced. Estraderm 50 and Estraderm 100 may be used for prevention of postmenopausal bone mineral density loss in women with an increased risk of future osteoporotic fractures who are intolerant of, or contraindicated for, other medicinal products approved for the prevention of bone mineral density loss. When prescribed solely for the prevention of postmenopausal bone mineral density loss, therapy should only be prescribed for women who are at high risk of future fracture and who are intolerant of, or contraindicated for, non-oestrogen products approved for prevention of bone mineral density loss.
Estraderm MX 25, 50 75, 100	Oestradiol – four strengths: 25, 50, 75 and 100 µg/day respectively [total dose 0.75 mg, 1.5 mg, 2.25 mg or 3.0 mg oestradiol respectively]	Patch	26/08/1996	Short-term treatment of signs and symptoms of oestrogen deficiency due to the menopause, whether natural or surgically induced. Estraderm MX 50, 75 and 100 may be used for prevention of postmenopausal bone mineral density loss in women with an increased risk of future osteoporotic fractures who are intolerant of, or contraindicated for, other medicinal products approved for the prevention of bone mineral density loss.
Estalis continuous	Oestradiol and norethisterone acetate – two strengths: 50/250 µg/day, 50/140 µg/day	Patch	11/10/1999	<ul style="list-style-type: none"> · For the short-term treatment of symptoms of oestrogen deficiency in menopausal women who have an intact uterus · For prevention of postmenopausal bone mineral density loss in women with an increased risk of future osteoporotic fractures who are intolerant of, or contraindicated for, other medicinal products

Trade name	Active Ingredient (s) and dose	Formulation / presentation	First listed on ARTG #	Indication*
				approved for the prevention of bone mineral density loss.
Estalis Sequi	Oestradiol and norethisterone acetate – single pack includes two doses: oestradiol 50 µg/day and oestradiol / norethisterone 50/250 µg/ day OR oestradiol / norethisterone 50/140 µg/day	Patch	11/03/2008	For the short-term treatment of symptoms of oestrogen deficiency in menopausal women who have an intact uterus.
Climara 25, 50, 75, 100	Oestradiol – four strengths: 25µg/day, 50µg/day, 75µg/day and 100ug/day respectively	Patch	15/11/1996	For short term treatment of signs and symptoms of oestrogen deficiency due to the menopause, whether natural or surgically induced. For the prevention of postmenopausal bone mineral density loss.
Sandrena	0.1% oestradiol – two strengths: 1mg/g and 0.5 mg/g	Gel in single dose sachets	08/04/2003	Short-term treatment of climacteric symptoms after natural or surgical menopause.
Ovestin Cream	Oestriol 1mg/g - single dose is 0.5mg oestriol (0.5g cream)	Cream	16/07/2009	Vulvo-vaginal complaints due to oestrogen deficiency associated with the climacteric and the postmenopause or after ovariectomy: <ul style="list-style-type: none"> · Atrophic vaginitis · Pruritus vulvae · Dyspareunia due to vulvo-vaginal atrophy · As auxiliary therapy in the treatment of vaginal infections · As pre-operative therapy for vulvo-vaginal surgery and during subsequent convalescence · Ulcers in cases of prolapse of the uterus or vagina · To avoid misinterpretation of a cytological smear

Trade name	Active Ingredient (s) and dose	Formulation / presentation	First listed on ARTG #	Indication*
Ovestin Ovula	Oestrinol 0.5mg	Pessary	23/11/1992	Vulvo-vaginal complaints due to oestrogen deficiency associated with the climacteric and the postmenopause or after ovariectomy: <ul style="list-style-type: none"> · Atrophic vaginitis · Pruritus vulvae · Dyspareunia due to vulvo-vaginal atrophy · As auxiliary therapy in the treatment of vaginal infections · As pre-operative therapy for vulvo-vaginal surgery and during subsequent convalescence · Ulcers in cases of prolapse of the uterus or vagina · To avoid misinterpretation of a cytological smear
Vagifem	Oestradiol 25 µg	Modified release pessary	04/07/1991	Indicated for the treatment of atrophic vaginitis due to oestrogen deficiency in postmenopausal women.
Vagifem low	Oestradiol 10 µg	Modified release pessary	19/10/2010	Indicated for the treatment of atrophic vaginitis due to oestrogen deficiency in postmenopausal women.
Mirena	Levonorgestrel releasing 20 µg / 24 hours (total dose: 52mg)	Intrauterine device	24/07/2000	<ul style="list-style-type: none"> · Contraception · Treatment of idiopathic menorrhagia · Prevention of endometrial hyperplasia during oestrogen replacement therapy.

* Not complete indication – disease states only; # ARTG listed information may be different to that contained in PI; Methodology: Searched ARTG for “oestrogen”, “oestradiol”, “medroxyprogesterone”, “dydrogesterone” “norethisterone”, “drospirenone” and “levonorgestrel” then cross referenced with a search in MIMS for hormone replacement products. Medicines listed as export only on ARTG are not included.

Although listed in some clinical guidelines as potential alternatives to MHT,¹¹ use of selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), gabapentin, clonidine and pregabalin would be off-label use for menopausal symptoms in Australia.

2.6. Treatment algorithm

According to RANZCOG:¹²

the principal indication for the use of MHT is to alleviate troublesome menopausal symptoms, the commonest of which are vasomotor symptoms (VMS) followed by muscle

¹¹ Jane FM and Davis SR. Climacteric 2014; 17:5, 564-579; RANZCOG “Menopausal Hormone Therapy Advice”, July 2015.

¹² RANZCOG “Menopausal Hormone Therapy Advice”, July 2015.

and joint aches and pains ... topical low dose oestrogen is preferred for those women whose symptoms are limited to vaginal dryness and dyspareunia.

MHT is not considered to a primary indication for bone protection or the treatment of low mood and libido.¹³ Vulvovaginal atrophy (genitourinary syndrome of menopause) occurs in up to 45% of women in midlife or later¹⁴ and most often presents later in menopause, after VMS symptoms may have abated.¹⁵ Low-dose vaginal oestrogen is an effective treatment for vulvovaginal atrophy.¹⁶

The WHI trial indicated that a combination of conjugated equine oestrogens and medroxyprogesterone MHT is associated with risks such as deep vein thrombosis, arterial thromboembolism (coronary heart syndrome and stroke) and breast cancer.¹⁷ Ovarian cancer is associated with the use of both oestrogen/progestogen combinations and oestrogen only MHT¹⁸ and endometrial cancer is associated with the use of oestrogen alone.¹⁹ The WHI study also showed that a combination of conjugated equine oestrogens and medroxyprogesterone MHT reduces the risk of colorectal cancer, fractures and diabetes.²⁰

Clinical Practice Guidelines recommend a shared, decision-making approach to choose/select the formulation, starting dose, route of administration and how to tailor MHT to each woman's individual situation, risk profile, and treatment goals.²¹

In post-menopausal women for whom MHT is being considered, an oestrogen and progestogen combination is a common starting point in most women with an intact uterus.²² The following treatment algorithm for menopausal hormone treatment is adapted from the RANZCOG endorsed "A Practitioner's Toolkit for Managing the Menopause" focusing on women with an intact uterus.²³

¹³ RANZCOG "Menopausal Hormone Therapy Advice", July 2015.

¹⁴ Manson J and Kaunitz A. NEJM 2016; 374; 9, 803-806.

¹⁵ Stuenkel CA, Davis SR, Gompel A et al. J Clin Endocrinol Metab 2015 100(11): 3975 – 4011.

¹⁶ RANZCOG "Menopausal Hormone Therapy Advice", July 2015.

¹⁷ Manson J, Chlebowski R, Stefanick M et al JAMA 2013; 310 (13): 1353-1368

¹⁸ Supplementary material for Collaborative group on epidemiological studies of Ovarian Cancer Lancet 2015; 385; 1835 – 42.

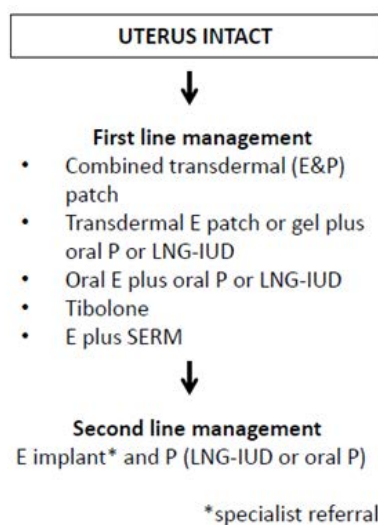
¹⁹ Beral V, Bull D, Reeves G et al. Lancet 2005 365(9470): 1543 - 51

²⁰ Manson J, Chlebowski R, Stefanick M et al JAMA 2013; 310 (13): 1353-1368

²¹ Stuenkel CA, Davis SR, Gompel A et al. J Clin Endocrinol Metab 2015 100(11): 3975 - 4011

²² The North American Menopause Society. Menopause 2015; 22(7); RANZCOG "Menopausal Hormone Therapy Advice", July 2015; Stuenkel C, Davis, S, Gompel A et al. J Clin Endocrinol Metab. 2015; 100(11): 3975 – 4011.

²³ Jane FM and Davis SR. Climacteric 2014; 17:5, 564-579.

Figure 1: Treatment algorithm for menopausal hormone treatment.

E = oestrogen, P = progestogen, LNG-IUD = levonorgestrel intrauterine device, SERM = selective estrogen receptor modulator.

NB. Tibolone is “an alternative to estrogen – progestin therapy.....It is metabolized in the gut and target tissues to metabolites that exhibit estrogenic, progestogenic and androgenic actions. Therefore it alleviates VMS, has favourable mood effects, treats urogenital atrophy and does not activate the endometrium – and therefore does not cause vaginal bleeding” (Jane and Davis, Climacteric, 2014).

The Sponsor has proposed the target population to be “postmenopausal women with a uterus (with at least 12 months since the last menses) for whom treatment with progestogen-containing therapy is not appropriate”. With respect to the proposed population, it is not clear what the Sponsor intends by the wording “for whom treatment with progestogen-containing therapy is not appropriate”; it is not a commonly used phrase in the treatment algorithms consulted.

Within clinical practice guidelines, the concept of second-line treatment (and use in women for whom treatment with progestogen-containing therapy is not appropriate) is not straightforward. For women with a uterus, there are various options that could be discussed as treatment options and considered to relieve moderate-to-severe vasomotor symptoms, including CE/MPA, CE/BZA, CE + micronised progesterone, tibolone, mono-therapy with a natural or synthetic progestogen and topical mono-therapy with CE. That is, there are various types of MHT that can be tailored to each woman’s individual situation, risk profile, and treatment goals.²⁴

Potential non-hormonal options include SSRIs/SNRIs, gabapentin or pregabalin, however these medicines are not registered for these indications.

The Australian Endocrine Therapeutic Guidelines²⁵ notes that symptoms of progestin intolerance include bloating, flatus, irritability, depression and breast tenderness. Options for management proposed include using an alternative progestin, dose or administration route (intrauterine device or transdermal). Jane and Davis²⁶ state that:

progestin therapy may cause lowered mood or irritability. When this occurs, either the dose needs to be reduced or the patient needs to be switched to another progestin. Micronized progesterone may result in less adverse mood effects.

²⁴ Stuenkel C, Davis, S, Gompel A et al. J Clin Endocrinol Metab. 2015; 100(11): 3975 - 4011

²⁵ Oestrogen/progestin hormone replacement [revised Feb 2014] In: eTG [Internet]. Melbourne: Therapeutic Guidelines Limited; November 2015

²⁶ Jane FM and Davis SR. Climacteric 2014; 17:5, 564-579

It has also been noted that some women develop mood side effects and bloating with cyclic progestins in addition to monthly bleeding; impact on mood and bloating is often resolved by switching to a continuous regimen although newly menopausal women may still have breakthrough bleeding.²⁷

Furthermore, for women seeking pharmacological management of moderate-to-severe vasomotor symptoms for whom MHT is contraindicated, or who choose not to take MHT, options include off-label use of selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), gabapentin and pregabalin.²⁸

In countries in which BZA/CE is available, guidelines suggest the following with respect to BZA/CE use:

- The North American Menopause Society (NAMS) indicates that CE/BZA is an option for women with an intact uterus and “especially those with concerns about breast tenderness, breast density, or uterine bleeding”;²⁹
- The Endocrine Society indicates that CE/BZA is an option for relief of vasomotor symptoms and the prevention of bone loss, as well as noting that breast tenderness present with other MHT may be improved with CE/BZA;³⁰
- UpToDate indicates that CE/BZA may be suitable for women with moderate – severe hot flashes who have breast tenderness with standard combination therapy or women who cannot tolerate any type of progestin therapy.³¹

The wording of the proposed Australian indications contains the same caveat as in the approved EU Indications (women for whom treatment with progestogen-containing therapy is not appropriate). However, this caveat does not appear in the FDA Indication. Also, the pivotal clinical trials to establish efficacy and safety did not necessarily recruit women for whom treatment with progestogen-containing therapy is not appropriate. The Sponsor will be asked to further explain the reasoning behind the proposed “second-line” listing (see Questions for Sponsor).

2.7. Formulation and presentation

Duavive is a fixed combination medicine with a modified-release dosage form resulting in the immediate release of bazedoxifene and controlled release of conjugated oestrogen.

No novel excipients are in the product formulation.

3. Pharmacology

The sponsor submitted 20 clinical pharmacology studies – the majority (15) were conducted with BZA alone; combination BZA/CE studies are highlighted in grey.

Table 4: Clinical pharmacology studies.

BZA alone or BZA/CE	Description
<i>Health subject PK and initial tolerability studies</i>	
BZA alone	Ascending single dose
BZA alone	Ascending multiple dose

²⁷ Martin K and Barbieri R Treatment of menopausal symptoms with hormone therapy. Dec 2015 In: UpToDate Online Waltham, MA (accessed February 2016)

²⁸ Jane FM and Davis SR. Climacteric 2014; 17:5, 564-579

²⁹ Manson J, Ames J, Shapiro M et al. Menopause 2015; 22(3)

³⁰ Stuenkel C, Davis, S, Gompel A et al. J Clin Endocrinol Metab. 2015; 100(11): 3975 - 4011

³¹ Martin K and Barbieri R Treatment of menopausal symptoms with hormone therapy. Dec 2015 In: UpToDate Online Waltham, MA (accessed February 2016)

BZA alone or BZA/CE	Description
BZA alone	Mass balance and metabolism of [¹⁴ C] BZA
BZA alone	Dose proportionality
BZA alone	Absolute/Relative bioavailability of BZA
BZA alone	Ascending single dose in Japanese subjects
BZA alone	Ascending single dose in Chinese subjects
BZA alone	Ascending multiple dose in Japanese subjects
BZA alone	Thorough QTc Study
BZA/CE	BZA/CE multiple-dose PK
BZA/CE	Relative bioavailability of BZA monotherapy and BZA/CE combination dosage forms
<i>Intrinsic factor PK studies</i>	
BZA alone	Hepatic impairment
BZA alone	Age and renal impairment
<i>Extrinsic factor PK studies</i>	
BZA alone	Food effect and antacid interaction
BZA alone	Ibuprofen interaction
BZA alone	Azithromycin interaction
BZA alone	Atorvastatin interaction
BZA/CE	Conjugated estrogens interaction
BZA/CE	Effect of BZA on CE PK
BZA/CE	Effect of CE on BZA PK

3.1. Mechanism of action

Duavive is a fixed dose combination of BZA and CE.

CE is well established for the treatment of menopausal symptoms, substituting for loss of oestrogen production and treating symptoms caused by oestrogen deficiency. In women who have no uterus, CE is administered alone. In women who have a uterus, endometrial protection is required and the addition of a progestogen currently fulfils this purpose.

BZA is a selective oestrogen receptor modulator (SERM) which has both agonist and antagonist oestrogen receptor activity. BZA has demonstrated agonist activity on the skeletal system and antagonist activity in breast and uterine tissues. It is proposed that BZA may be combined with CE to treat oestrogen deficient menopausal symptoms and protect the endometrium, instead of a progestogen.

4. Pharmacokinetics

BZA co-administered with CE as individual components does not appear to have an effect on PK of BZA and CE (and vice versa). An *in vitro* study in liver cell extracts showed the metabolism of BZA and the main components of CE (estrone and equilin) do not interfere with each other's metabolic pathways.

As CE has been marketed for decades and its PK is well-established, its individual PK characteristics will not be discussed further in this report.

4.1. BZA alone – summary

Summary is shown in Table 5.

Table 5: BZA alone – summary.

BZA alone	
C_{max}	6.2 +/- 2.2 (ng/ml) in multiple doses of 20 mg/day in healthy postmenopausal women (n = 23)
T_{max}	~2 hours
t_{1/2}	30 hours
Absorption	Linear increase in plasma concentration following single (up to 120mg) and multiple (up to 80mg) daily doses
Distribution	Highly protein bound <i>in vitro</i> (98-99%) Volume of distribution is 14.7 ± 3.9 l/kg (after IV administration 3mg dose)
Metabolism	Major metabolic pathway: glucuronidation by uridine diphosphate glucuronosyltransferase (UGT) enzymes in the intestinal tract and liver Little or no cytochrome P450-mediated metabolism
Excretion	Mainly in faeces; < 1% is eliminated in urine

4.2. BZA/CE fixed dose combination Bioequivalence

Four main bioequivalence studies were performed. These studies compared to-be-marketed formulations of BZA 20 mg / CE 0.625 mg and the BZA 20 mg / CE 0.45 mg to formulations A and B which were used in a number of studies including phase III clinical studies.

The EMA identified that the CE containing formulations contain about 160 components and there was “no regulatory experience within the EU regarding the investigation of bioequivalence of CE-containing formulations”. The EMA’s Pharmacokinetics Working Party determined that it was acceptable that bioequivalence should be proven with respect to the active substance “conjugated oestrogens” based on 2 lead substances, i.e. estrone and equilin as well as total (conjugated and unconjugated) oestrogens (further details available in EPAR).

Regarding bioequivalence, the EPAR concludes that:

bioequivalence of the formulations administered in the clinical studies and the TBM (to be marketed) formulation was adequately demonstrated.

4.3. PK interaction studies

Study B2311065 is a clinical drug-drug interaction study conducted as a post-approval commitment to FDA. This study was not submitted to the EMA prior to approval, however was submitted to the TGA. The study was phase I, open label, two period, fixed sequence, parallel group investigation, designed to estimate the effects of multiple dose administration of itraconazole on the single dose pharmacokinetics of CE/BZA in non-obese (BMI < 30 kg/m²) and obese (BMI ≥ 30 kg/m²). The clinical study report was accepted by the FDA on 25 September 2015.

The European SmPC³² states the following with regards to what appears to be the drug interaction study B23110685:

In vitro and in vivo studies have shown that oestrogens are partially metabolized by cytochrome P450 enzymes, including CYP3A4. However, in a clinical drug-drug interaction study, repeat administration of 200 mg itraconazole, a strong CYP3A4 inhibitor, had minimal impact on the pharmacokinetics of CE (as measured by estrone and equilin) and bazedoxifene when administered with a single dose of CE 0.45 mg/bazedoxifene 20 mg... In a pharmacokinetic study (n=24) BMI appeared to have little impact on systemic exposure to CE and bazedoxifene.

³² 19/11/2015 Duavive: EMEA/H/C/002314-II/0002

4.3.1. Summary of other Pharmacokinetic parameters

Summary is shown in Table 6.

Table 6: Summary of other pharmacokinetic parameters.

Parameter			
t_{max}	~2 hours (administered as BZACE)	~8.5 hours (administered as BZA/CE)	
C_{max} after high fat meal	Unaffected (administered as BZA/CE)	Little or no effect (administered as BZA/CE)	BZA/CE can be administered with or without food. Food effect studies have only been conducted with the 20 mg BZA/0.625 mg CE strength. There is no reason to expect that this would be different for the 20/0.45 strength.
AUC after high fat meal	Increased by 25% (administered as BZA/CE)	Little or no effect (administered as BZA/CE)	
Distribution	Following administration of BZA alone: <ul style="list-style-type: none"> highly bound (98-99%) to plasma proteins in vitro does not bind to sex hormone binding globulin (SHBG) volume of distribution is 14.7 ± 3.9 l/kg (after IV administration 3mg dose) 	Oestrogens are widely distributed throughout the body and circulate in the blood largely bound to SHBG and albumin.	The distribution of CE and BZA after CE/BZA has not been studied.
Metabolism	Following oral administration of 20 mg of radiolabelled BZA in postmenopausal women, BZA is extensively metabolised - glucuronidation is the major metabolic pathway.	CE circulate in different forms in a dynamic manner: 17β-estradiol and estrone is converted to estriol, a urinary metabolite	The metabolism of CE and BZA after CE/BZA has not been studied.
t_{1/2}	~30 hours (administered as BZA/CE)	~ 17 hours (administered as BZA/CE)	Steady state concentrations are achieved by the second week of daily dosing.
Excretion	Faeces (<1% urine)	Urine	

Parameter	BZA	CE component	Note
Dose proportionality	BZA administered alone: linear increase in plasma concentrations as dose was increased	CE administered alone: dose proportional increases in both AUC and C _{max} as dose was increased	
Elderly	In a study of a 20 mg single dose of BZA, AUC increased as age increased	Not reported	No PK data for women older than 75 years.
Renal impairment	Impaired renal function showed little or no influence on BZA pharmacokinetics when administered alone.	Not reported	No PK data for renal impairment.
Hepatic impairment	A study of single agent BZA in women with hepatic impairment showed a 4.3 fold increase in AUC compared with controls	Estrogens may be poorly metabolised in patients with impaired liver function.	No PK data for hepatic impairment.
Race	No significant difference between different races tested (Asian, Black, Hispanic, White)	The oral clearance of baseline-adjusted total estrone versus ethnic origin based on BZA/CE studies showed no difference across these groups.	
Weight	No evidence of an effect alone or in combination	No evidence of an effect alone or in combination	BMI appeared to have little impact on systemic exposure to CE and bazedoxifene in PK study

5. Pharmacodynamics

Descriptions of the PD properties of the BZA/CE combination have been derived from descriptions of both active substances alone.

5.1. Mechanism of Action

- CE active ingredients: primarily the sulphate esters of estrone, equilin sulphates and 17 α / β -estradiol. CE relieves menopausal symptoms by replacing the loss of estrogen in menopausal women.
- Bazedoxifene reduces the risk of endometrial hyperplasia in non-hysterectomised women, induced by estrogens.

Table 7: Summary of PD parameters.

Parameter	Observation
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Parameter	Observation
Endometrial hyperplasia	The effects of CE decrease appear to decrease when combined with increasing doses of BZA
Hot flushes	The effects of CE decrease appear to decrease when combined with increasing doses of BZA 0.3 mg CE has been shown to be effective to preventing hot flushes as part of standard hormone therapy; ³³ however, it was not effective in preventing hot flushes when given in combination with BZA.
QTc prolongation	No indication of QTc prolongation in single agent BZA or CE. There was also no evidence of QTc prolongation based on ECG findings at doses of BZA 20 mg / CE 0.45 mg or BZA 20 mg / CE 0.625 mg in the clinical trials.

6. Clinical efficacy

Please note that the results in the following sections focus on data for the dose of interest – ie. CE/BZA 20 mg / 0.45 mg.

6.1. Phase II dosing trial - Study 203

One Phase II trial was completed – a double blinded study which randomised 412 post menopausal women to one of 11 arms. This study compared the combination of a range of doses of a BZA capsule (5mg, 10mg and 20mg) with a CE tablet (0.3mg or 0.625mg) with active arms of CE alone (0.3mg or 0.625mg), CE 0.625/MPA 2.5mg tablet or placebo. The primary endpoint was endometrial thickness measured by vaginal ultrasound.

Table 8: Phase II dosing trial - Study 203.

Design	N	Intervention	Primary endpoint and key outcomes
<ul style="list-style-type: none"> • Multicentre • Double blinded • Randomised Controlled • Dose finding 	Enrolled: 414 Randomised: 412 Treated: 408 ITT population: 397	Patients were treated for 12 weeks with either: <ol style="list-style-type: none"> 1. BZA 5 mg + CE 0.3 mg 2. BZA 5 mg + CE 0.625 mg 3. BZA 10 mg + CE 0.3 mg 4. BZA 10 mg + CE 0.625 mg 5. BZA 20 mg + CE 0.3 mg 6. BZA 20 mg + CE 0.625 mg 7. BZA 5 mg 8. CE 0.3 mg 9. CE 0.625 mg 10. CE 0.625 mg/MPA 2.5 mg 11. Placebo <p><i>Of note, the intervention for arms 1 – 6 was not a single combination tablet but BZA as a capsule and CE as a tablet</i></p>	Endometrial thickness (mm) measured by transvaginal ultrasound at day 84 Primary comparisons: <ul style="list-style-type: none"> • BZE 20/CE 0.3 vs CE 0.3: -0.98 • SE: 0.49 • 95% CI -1.95 - -0.01) • P Value 0.049 • BZE 20/CE 0.625 vs CE 0.625: -1.95 • SE: 0.54 • 95% CI -3.02 - -0.89) • P Value <0.001 Secondary comparisons: <ul style="list-style-type: none"> • BZA10/CE 0.3 vs CE 0.3: -0.66 • SE: 0.50 • 95% CI -1.64 - 0.33 • P value 0.193 • BZA10/CE 0.625 vs CE 0.625: -1.77 • SE: 0.49 • 95% CI -2.15 - 0.10 • P value 0.019 • BZA5/CE 0.3 vs CE 0.3: 0.03 • SE: 0.51

³³ Utian WH, et al. Relief of vasomotor symptoms and vaginal atrophy with lower doses of conjugated equine estrogens and medroxyprogesterone acetate. *Fertil Steril.* 75: 1065-79 (2001).

Design	N	Intervention	Primary endpoint and key outcomes
			<ul style="list-style-type: none"> 95% CI -0.97 – 1.03 P value 0.953 BZA5/CE 0.625 vs CE 0.625: 0.50 SE: 0.51 95% CI -0.50 – 1.49 P value 0.327

Statistical methodology, selected inclusion and exclusion criteria are shown in Table 9.

Table 9: Statistical methodology, selected inclusion and exclusion criteria.

<ul style="list-style-type: none"> Stratified according to presence or absence of previous HRT Sample size was calculated on the basis of a 2mm difference between the BZA/CE monotherapy group compared to the CE only group with 85% power, two-sided tests at $\alpha = 0.05$ level of significance and an additional 23% patients enrolled to ensure sufficient biopsies. It was subsequently determined that a Fisher's exact test (instead of a logistic regression model) was used to compare the proportion of patients with an endometrial effect due to very low numbers of patients showing any effect. 	<ul style="list-style-type: none"> Post-menopausal women with intact uterus, 40 – 65 years old Last natural menstrual cycle (without exogenous hormone therapy) was to be completed at least 12 consecutive months (but no more than 10 years) before screening Average 4 hot flushes per day within +35% of ideal body weight range by using a nomograph for body mass index (BMI). 	<p>History or active presence of</p> <ul style="list-style-type: none"> Known significant AE with previous exposure to oestrogens Known or suspected oestrogen- dependent neoplasia Endometrial hyperplasia/undiagnosed abnormal genital bleeding within last 90 days/ any clinically significant endometrial abnormality) Hysterectomy Any malignancy (except BCC) unless disease free for > 5 years Thrombophlebitis, thrombosis or thromboembolic disorders Specified cerebrovascular or cardiovascular disease Neuro-ocular disorders Chronic renal or hepatic disease Gallbladder disease (unless cholecystectomy) Hepatitis B or HIV positive <p>Active presence of the following</p> <ul style="list-style-type: none"> Specific Cervical cytological abnormalities Elevated sitting blood pressure (>160 mm HG systolic or >90 mmHg diastolic) or > two antihypertensive medications Liver functions tests > 1.5 times upper limit of normal Elevated cholesterol (7.8 mmol/L) or triglyceride (3.4 mmol/L) Endocrine disease except for controlled thyroid

Statistical methodology	Selected Inclusion criteria	Selected Exclusion criteria
		disease <ul style="list-style-type: none"> Excessive smoking (more than 15 cigarettes per day)

Study objectives are in Table 10.

Table 10: Study objectives.

Primary objectives	Secondary objectives and key outcomes
<p>Explore the effects of the combination of 3 doses (5 mg, 10 mg, and 20 mg) of BZA with 2 doses (0.3 mg and 0.625 mg) of CE on the endometrium (by transvaginal ultrasonography and endometrial biopsy assessment) in postmenopausal women. Primary patient population was ITT population. The primary efficacy variable was the ultrasonographic measurement of endometrial thickness at day 84 (visit 5), using local data (no discrepancy was found with central data). Comparison of treatment groups was done by using ANCOVA model with treatment, pooled centre and previous use of HRT as factors and screening value as a covariate. Primary comparisons were 2 sided at $\alpha = 0.05$ level:</p> <ul style="list-style-type: none"> BZA 20/CE 0.3 vs CE 0.3: BZA 20/CE 0.625 vs CE 0.625: <p>The secondary pairwise comparisons were 2 sided at the $\alpha = 0.05$ level and were presented as:</p> <ul style="list-style-type: none"> BZA 10 mg/Premarin 0.625 mg vs Premarin 0.625 mg BZA 10 mg/Premarin 0.3 mg vs Premarin 0.3 mg BZA 5 mg/Premarin 0.625 mg vs Premarin 0.625 mg BZA 5 mg/Premarin 0.3 mg vs Premarin 0.3 mg <p>Other pairwise comparisons, considered as exploratory, were 2 sided at the $\alpha = 0.05$ level.</p>	<p>Secondary objectives were</p> <ul style="list-style-type: none"> Evaluate the effects of CE/BZA on vaginal bleeding, vaginal maturation index, mastalgia, vasomotor activity, biochemical bone markers, serum lipid levels and coagulation factors Evaluation of safety and tolerability Assess population pharmacokinetic parameters <p>The Secondary efficacy population was a Per-protocol population (excluded some patients).</p> <p>Secondary efficacy variables and outcomes</p> <ul style="list-style-type: none"> Endometrial biopsies – oestrogen effect grade Vaginal smears - Vaginal Maturation Index (VMI): <ul style="list-style-type: none"> CE 0.3 mg: decreased with increasing doses of BZA CE 0.625mg: decreased with increasing doses of BZA In the BZA 20 mg / CE 0.625 mg group an increase of the VMI from baseline to day 84 was observed however very little change was seen over the same period in the BZA 20 mg / CE 0.3 mg group Severity of Hot Flushes (see below) <ul style="list-style-type: none"> CE 0.3 mg: increased BZA dose decreased CE effect CE 0.625 mg: all BZA doses decreased CE effect Lipid panel <ul style="list-style-type: none"> no clear dose-relationship Coagulation panel <ul style="list-style-type: none"> fibrinogen levels: BZA 10 mg / CE 0.625 mg and BZA 20 mg / CE 0.625 mg compared to placebo - statistically significant reduction from baseline prothrombin time/ partial prothrombin time: BZA/CE 0.625 mg combinations were not significantly different from placebo or CE 0.625 mg / MPA 2.5 mg Bone markers <ul style="list-style-type: none"> Consistent with known effects of BZA and CE

Discontinuations: 6% of patients discontinued treatment from the safety population and the most common reason for discontinuation were treatment emergent adverse events (3%).

6.1.1. Results – primary endpoint

The following table shows the endometrial thickness in millimetres at day 84 as measured by transvaginal ultrasound in terms of the primary, secondary and exploratory comparisons.

Table 11: Results – primary endpoint.

Comparison source	Estimate	Standard error	95% CI	p-value
Primary comparisons				
· BZA 20 mg/ CE 0.3 mg vs CE 0.3 mg	-0.98	0.49	(-1.95, -0.01)	0.049
· BZA 20 mg/ CE 0.625 mg vs CE 0.625 mg	-1.95	0.54	(-3.02, -0.89)	<0.001
Secondary Comparisons				
· BZA 10 mg/ CE 0.3 mg vs CE 0.3 mg	-0.66	0.50	(-1.64, 0.33)	0.193
· BZA 10 mg/ CE 0.625 mg vs CE 0.625 mg	-1.77	0.49	(-2.15, -0.20)	0.019
· BZA 5 mg/ CE 0.3 mg vs CE 0.3 mg	0.03	0.51	(-0.97, 1.03)	0.953
· BZA 5 mg/ CE 0.625 mg vs CE 0.625 mg	0.50	0.51	(-0.50, 1.49)	0.327
Exploratory Comparisons				
· BZA 20 mg/ CE 0.625 mg vs placebo	0.60	0.54	(-0.47, 1.67)	0.273
· BZA 10 mg/ CE 0.625 mg vs placebo	1.38	0.50	(0.40, 2.37)	0.006
· BZA 5 mg/ CE 0.625 mg vs placebo	3.05	0.51	(2.04, 4.06)	<0.001
· BZA 5 mg vs placebo	-0.30	0.51	(-1.30, 0.70)	0.551
· CE 0.3 mg vs placebo	0.98	0.51	(-0.03, 1.99)	0.057
· CE 0.625 mg vs placebo	2.55	0.51	(1.54, 3.56)	<0.001
· CE 0.625 mg/MPA 2.5 mg vs placebo	1.34	0.52	(0.32, 2.36)	0.010
· BZA 20 mg/ CE 0.625 mg vs v 0.625 mg/MPA 2.5 mg	-0.74	0.55	(-1.82, 0.33)	0.176
· BZA 10 mg/ CE 0.625 mg vs CE 0.625 mg/MPA 2.5 mg	0.04	0.50	(-0.94, 1.03)	0.934
· BZA 5 mg/ CE 0.625 mg vs CE 0.625 mg/MPA 2.5 mg	1.71	0.51	(0.70, 2.72)	<0.001
· CE 0.625 mg vs CE 0.625 mg/MPA 2.5 mg	1.21	0.51	(0.21, 2.22)	0.018
· BZA 5 mg/CE 0.3 mg vs BZA 5 mg	1.31	0.51	(0.32, 2.31)	0.010
· BZA 5 mg/CE 0.625 mg vs BZA 5 mg	3.35	0.50	(2.36, 4.34)	<0.001
· CE 0.3 mg vs BZA 5 mg	1.28	0.50	(0.29, 2.27)	0.011
· CE 0.625 mg vs BZA 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, centre, and previous hormonal replacement therapy.				

In terms of endometrial protection in patients treated with CE 0.625, 20 mg BZA seems to be more effective than 10 mg BZA. 5 mg BZA provides insufficient endometrial protection.

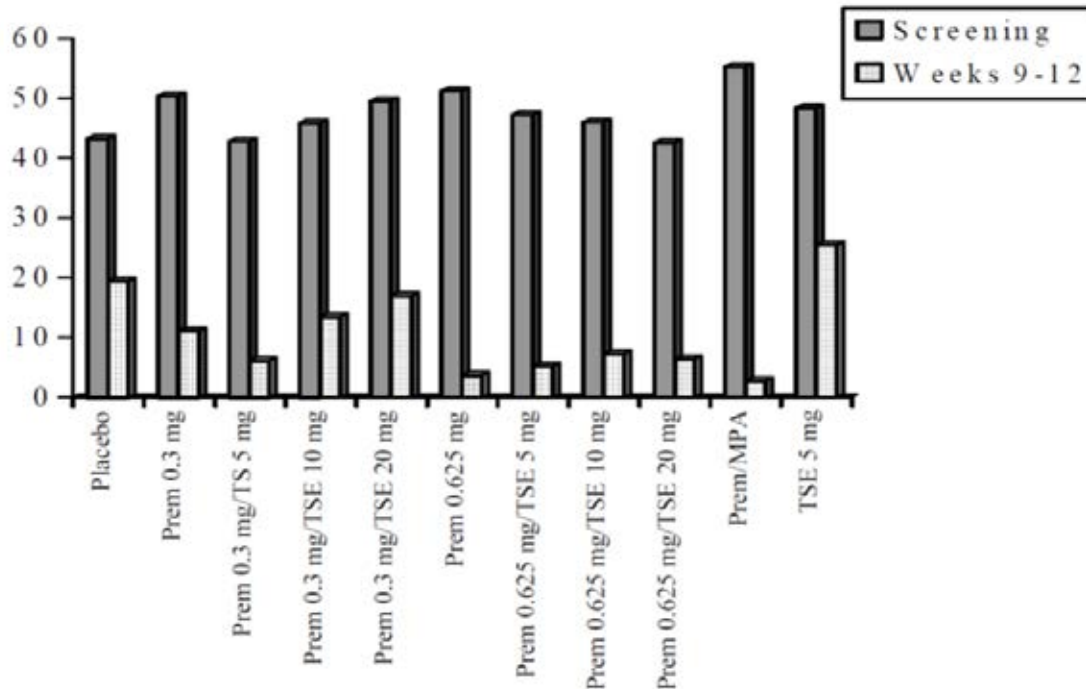
6.1.2. Results – hot flushes (secondary endpoint)

Although a number of different parameters were measured for hot flushes, for the sake of brevity only the weekly number of hot flushes are described in the table and graph below; however, summary statements refer to the data relating to hot flushes as a whole.

- The efficacy of CE 0.3 mg for VMS is considerably compromised by 20 mg BZA, but not by the 10mg dose. However, in study 303, a dose of 10mg BZA provided inadequate endometrial protection in patients treated with 0.45 mg CE therefore 0.3mg CE has not been further investigated.
- There were no statistically significant differences in the number or severity of hot flushes of BZA/CE versus CE alone, however, there was a trend towards more benefit with CE alone.
- Compared with placebo, there were statistically significant differences with all 3 doses of BZA combined with 0.625 CE.
- The combination of 0.625 mg CE with BZA showed no statistically significant differences with respect to number and severity of hot flushes compared with CE 0.625 / 2.5 mg MPA.

- Regarding the dose of 0.625mg CE, the effects of 10mg BZA on VMS decreased relative to 5mg BZA; 10mg BZA and 20 mg BZA effects were comparable.

Figure 2: absolute mean number of hot flushes per week at screening at weeks 9-12 (study report 203).



Note: TSE (tissue selective estrogen) is BZA, Premarin (Prem) is CE, and MPA is medroxy progesterone acetate. Prem/MPA = Premarin 0.625 mg / MPA 2.5 mg.

Table 12: Results – secondary endpoint.

Comparison	Estimate	Standard error	95% CI	p-value
BZA 20 mg/CE 0.3 mg vs CE 0.3 mg	6.18	3.34	(-0.40, 12.75)	0.066
BZA 20 mg/ CE 0.625 mg vs CE 0.625 mg	3.86	3.43	(-2.89, 10.62)	0.261
BZA 10 mg/ CE 0.3 mg vs CE 0.3 mg	3.32	3.40	(-3.37, 10.01)	0.329
BZA 10 mg/ CE 0.625 mg vs CE 0.625 mg	4.15	3.42	(-2.58, 10.87)	0.226
BZA 5 mg/ CE 0.3 mg vs CE 0.3 mg	-3.39	3.43	(-10.13, 3.35)	0.324
BZA 5 mg/ CE 0.625 mg vs CE 0.625 mg	2.05	3.40	(-4.63, 8.73)	0.546
BZA 20 mg/CE 0.625 mg vs placebo	-13.24	3.40	(-19.91, -6.56)	<0.001
BZA 10 mg/CE 0.625 mg vs placebo	-12.95	3.39	(-19.62, -6.28)	<0.001
BZA 5 mg/CE 0.625 mg vs placebo	-15.05	3.37	(-21.67, -8.42)	<0.001
BZA 20 mg/CE 0.625 mg vs CE 0.625 mg/MPA 2.5 mg	5.52	3.47	(-1.31, 12.34)	0.113
BZA 10 mg/CE 0.625 mg vs CE 0.625 mg/MPA 2.5 mg	5.80	3.45	(-0.99, 12.58)	0.094

Comparison	Estimate	Standard error	95% CI	p-value
BZA 5 mg/CE 0.625 mg vs CE 0.625 mg/MPA 2.5 mg	3.70	3.43	(-3.03, 10.44)	0.280

6.2. Phase III trials

Five Phase III studies were submitted; the sponsor indicated that four of five of the studies are considered pivotal (Studies 303, 305, 306 and 3307) and study 304 is considered supportive.

However, 303 and 3307 might be better considered as supportive, rather than pivotal (reasoning given below and highlighted in grey).

Table 13: Phase III trials.

Study number	Primary endpoint	Considered by sponsor to be pivotal?	Status unclear	Comments
303	Endometrial hyperplasia at month 12	Yes	Yes	GCP non-compliant and not taken into account for the assessment of efficacy by EMA
304	Endometrial hyperplasia at month 12	No	No	Not considered to be pivotal by the Sponsor due to bioequivalence issues
305	Vasomotor symptoms - change in baseline at week 4 and week 12 in Average daily number of moderate and severe hot flushes Severity of hot flushes	Yes	No	It is noted that this trial is GCP non-compliant, nevertheless, the data regarding hot flushes was taken into account in the assessment of efficacy of BZA / CE by EMA
306	Vulvar-vaginal atrophy co-primary endpoints at week 12: proportion of superficial cells (vaginal smear) - relating to vaginal maturation (positive outcome is increase) proportion of parabasal cells (vaginal smear) - relating to vaginal maturation (positive	Yes	Yes	The EMA guideline, adopted by the TGA (EMA/CHMP/021/97 Rev.1) states that "the most important oestrogen deficiency symptoms are vasomotor symptoms (hot flushes) ... the proposed primary endpoint for efficacy trials is the frequency of moderate to severe hot flushes". For women with vaginal symptoms only, local treatment is recommended. As this trial primarily assessed the effect of

Study number	Primary endpoint	Considered by sponsor to be pivotal?	Status unclear	Comments
	outcome is decrease) vaginal pH (positive outcome is decrease) the most bothersome VVS symptom (MBS) according to Symptom questionnaire identified at screening (positive outcome is improvement)			BZA/CE on VVA, and systemic treatment is not recommended for patients with VVA only, the TGA considers this trial to be supportive and not pivotal.
3307	Endometrial hypertrophy at month 12	Yes	No	

6.3. Studies accepted as pivotal

6.3.1. Study 305 [Selective Oestrogens Menopause and Response to Therapy – 2 (SMART-2)]

This study was found to be GCP non-compliant; nevertheless, the data regarding hot flushes was taken into account in the assessment of efficacy of BZA / CE.

- Published as Pinkerton JV, Utian WH, Constantine GD et al Menopause 2009;16(6):1116-1124
- Duration of main phase: September 2005 to February 2007
- Participants: 43 sites in the United States

6.3.1.1. Study Design

Study 305 was a placebo controlled, double blinded, randomised phase 3 study.

Table 14: Study 305.

	Criteria
Patients	<p>Selected Inclusion criteria:</p> <ul style="list-style-type: none"> • Generally healthy, postmenopausal, age 40 to less than 65 years with at least 12 months of spontaneous amenorrhea or 6 months of spontaneous amenorrhea with serum FSH > 40 mIU/ml • Intact uterus • Subjects seeking treatment for hot flushes and report a minimum of 7 moderate to severe hot flushes per day or 50 per week at screening • Endometrial biopsy report at screening (with one of specified diagnoses) • Body mass index (BMI) ≤ 34 kg/m² <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • History or active presence of • Known hypersensitivity to oestrogens • Known or suspected oestrogen- dependent neoplasia • Endometrial hyperplasia • Malignancy or treatment for malignancy within the previous 5 years except Basal Cell Carcinoma or Squamous Cell Carcinoma of skin • Breast cancer, melanoma or any gynaecologic cancer • Thrombophlebitis, thrombosis or thromboembolic disorders

	Criteria
	<ul style="list-style-type: none"> • Specified cerebrovascular or cardiovascular disease • Neuro-ocular disorders • Chronic renal or hepatic disease • Gallbladder disease (unless cholecystectomy); Active presence of the following <ul style="list-style-type: none"> • Endocrine disease (except for controlled hypothyroidism or diet controlled diabetes mellitus) • Heavy smoking (more than 15 cigarettes/day) Clinically important abnormalities at screening – eg. <ul style="list-style-type: none"> • Specific cervical cytological abnormalities • Uncontrolled hypertension; those with blood pressure >140 mm HG systolic or >90 mmHg diastolic should be controlled on not > two antihypertensives • Elevated cholesterol (>7.77mmol/L) or triglyceride (>3.39 mmol/L) • Fasting blood glucose > 6.94mmol/L; Receiving medications thought to treat VMS within 4 weeks of screening; Use of oral estrogen-, progestin-, androgen-, or SERM-containing drug products within 8 weeks before screening; use of transdermal hormone products within 8 weeks before screening; use of vaginal hormone products (rings, creams, gels) within 4 weeks before screening; use of intrauterine progestins within 8 weeks before screening; use of progestin implants/injectables or estrogen pellets/injectables within 6 months before screening.
Intervention	BZA 20 mg / CE 0.45 mg BZA 20 mg / CE 0.625 mg For a treatment duration of 12 weeks
Comparator/s	Placebo <i>Of note, a control group treated with oral CE/MPA has not been included</i>
Endpoints	Primary Change from baseline at week 4 and week 12 in the <ul style="list-style-type: none"> • Average daily number of moderate and severe hot flushes • Severity of hot flushes. Secondary <ul style="list-style-type: none"> • Other parameters related to VMS including a responder analysis, reduction in number of mild, moderate and severe hot flushes, the time to reach a 50% decrease from baseline in the number of hot flushes for at least 3 consecutive days and the reduction in daily composite scores • Medical Outcomes Sleep scale • Menopause-specific quality of life (MENQOL) questionnaire • Menopause symptoms-treatment satisfaction questionnaire (MS-TSQ) • Breast pain

6.3.1.2. Measurement of endpoints

Compared with placebo, the change from baseline at week 4 and week 12 in the

- Average daily number of moderate and severe hot flushes
- Severity of hot flushes.

Please note that changes at week 4 are not discussed further here since the European guideline recommends evaluation after 3 months (EMA/CHMP/021/97 Rev. 1).

Hot flushes were defined in the following manner, consistent with the EMA definition:³⁴

- Mild: sensation of heat without sweating.
- Moderate: sensation of heat with sweating, able to continue activity.
- Severe: sensation of heat with sweating, causing cessation of activity.

³⁴ EMA CHMP “Guideline on clinical investigation of medicinal products for hormone replacement therapy of oestrogen deficiency symptoms in postmenopausal women” EMA/CHMP/021/97 rev.1

The average daily number of moderate and severe hot flushes for each week was calculated by dividing the “Sum of the number of moderate and severe hot flushes on each day” by the “Number of days with data”.

The average daily severity of hot flushes for each week was calculated by dividing the “Sum of the daily severity scores” by the “Number of days with data” where the daily severity score was calculated as:

$$\frac{(\text{no. mild hot flushes}) \times 1 + (\text{no. moderate hot flushes}) \times 2 + (\text{no. severe hot flushes}) \times 3}{\text{Total number of hot flushes}}$$

A daily severity score of zero was assigned if no hot flushes were reported to have occurred on that day.

The number and severity (mild, moderate, or severe) of hot flushes were recorded daily on a subject diary card.

6.3.1.3. Modified-intent-to-treat (MITT)

The primary analysis population was the Modified-intent-to-treat (MITT) population with a last-observation-carried-forward (LOCF) approach at all time points. The MITT population included randomised participants who took at least one dose, had recorded at least 5 days of data at baseline and had at least 5 days data for at least one on-therapy week.

6.3.1.4. Minimal clinically important difference (MCID)

For the sample size calculation, the MCID was specified as 3 moderate to severe hot flushes per day.

6.3.1.5. Discontinuations

Of the 133 subjects allocated to the BZA/CE 20/0.45 arm, 6 did not receive BZA/CE 20/0.45 and 14 discontinued for the following reasons (n) - adverse event (5), protocol violation (5), subject request (3), unsatisfactory response (1).

Of the 66 subjects allocated to placebo, 3 did not receive placebo and 10 discontinued for the following reasons (n) - adverse event (6), protocol violation (2), subject request (1), unsatisfactory response (1).

6.3.1.6. Baseline characteristics (of safety population)

See Table 15.

Table 15: Baseline characteristics.

	BZA/CE 20/0.45	BZA/CE 20/0.625	placebo
N =	127	128	63
Characteristic			
Mean age (years)	53.57	53.09	53.62
Mean BMI (kg/m ²)	26.37	26.10	26.03
Mean years since last menstrual period	4.69	4.25	4.84
Mean age at Last natural menstrual period (LMP)	49.42	49.34	49.26
Race (white)	88.19%	82.81%	84.13%

6.3.1.7. Results for primary endpoint (LOCF)

See Table 16.

Table 16: Results for primary endpoint (LOCF).

	BZA/CE 20/0.45	BZA/CE 20/0.625	placebo
N =	122	125	63
Change from baseline in the average daily number of moderate and severe hot flushes at week 12	-7.63	-8.05	-4.92
<i>standard error</i>	0.36	0.35	0.48
<i>p value vs placebo</i>	<0.001	<0.001	
Change from baseline in the average daily severity score at week 12	-0.87	-1.21	-0.26
<i>standard error</i>	0.08	0.08	0.11
<i>p value vs placebo</i>	<0.001	<0.001	

Point estimates of the placebo - subtracted treatment effect of both the average daily number of moderate and hot flushes at week 12 and the severity with 95% confidence intervals were not found within the dossier. These data will be requested from the Sponsor.

6.3.1.8. Selected secondary endpoints

- All secondary endpoints related to VMS and four out of five items of the MOS sleep scale showed statistically significant differences favouring the BZA/CE 0.45/20 group vs. placebo
- MENQOL: statistically significant differences compared with placebo were observed regarding 2 of 5 items in the BZA 20 mg / CE 0.45 mg group at week 12 (see below).

Table 17: Mean (SE) change from baseline in the menopause-specific QoL score at Week 12 (MITT population).

Test	Treatment Group	No. of Pairs	--Adjusted Change--		p-Value vs Placebo
			Mean	SE	
Vasomotor function	BZA 20 mg/CE 0.45 mg	112	-3.27	0.19	<0.001
	BZA 20 mg /CE 0.625 mg	109	-3.81	0.18	
	Placebo	54	-1.58	0.25	
Psychosocial function	BZA 20 mg/CE 0.45 mg	112	-0.89	0.14	0.483
	BZA 20 mg/CE 0.625 mg	109	-1.19	0.13	
	Placebo	54	-0.73	0.19	
Physical function	BZA 20 mg/CE 0.45 mg	112	-1.07	0.11	0.106
	BZA 20 mg/CE 0.625 mg	109	-1.28	0.11	
	Placebo	53	-0.78	0.15	
Sexual function	BZA 20 mg/CE 0.45 mg	111	-1.18	0.16	0.084
	BZA 20 mg/CE 0.625 mg	109	-1.45	0.15	
	Placebo	52	-0.73	0.22	
Total MENQOL score	BZA 20 mg/CE 0.45 mg	111	-1.62	0.11	<0.001
	BZA 20 mg/CE 0.625 mg	109	-1.94	0.11	
	Placebo	52	-1.00	0.15	

ANCOVA: change = treatment + study site + baseline.

Abbreviations: BZA = bazedoxifene; CE = conjugated estrogens; MITT = modified intent-to-treat; No. = number; SE = standard error.

- Breast pain: no statistically significant difference compared with placebo however at all time slots (weeks 1-4, 5-8 and 9-12) there were numerically more patients reporting at least one day of breast pain on the BZA 20mg/CE 0.45mg arm compared to placebo. The largest difference was seen at the 9-12 weeks timeslot: BZA 20mg/CE 0.45mg 10.17% vs 5.36% placebo).

6.3.1.9. Conclusions

BZA 20 mg / CE 0.45 mg was shown to be statistically superior vs. placebo with respect to the co-primary endpoints at week 12 of change from baseline in the average daily number of moderate and severe hot flushes and change from baseline in the average daily severity score of hot flushes. The secondary endpoints also support the efficacy of BZA/CE for hot flushes.

6.3.2. Study 3307 [Selective Oestrogens Menopause and Response to Therapy – 5 (SMART-5)]

This study included an osteoporosis substudy, a breast density substudy and a sleep substudy.

- Published as Pinkerton J, Harvey J, Lindsay R et al J Clin Endocrinol Metab (2014) 99(2): E189 - E198
- Duration of main phase: Jan 2009 – Feb 2011
- Participants: 171 sites in Argentina, Australia, Chile, Colombia, Denmark, Finland, Hungary, Mexico, Norway, New Zealand, Poland and the United States

6.3.2.1. Study Design

Study 3307 was a placebo and active controlled, double blinded, randomised phase 3 study.

Table 18: Study 3307.

	Criteria
Patients	<p><u>Selected Inclusion criteria</u></p> <ol style="list-style-type: none"> 1. Generally healthy, postmenopausal, age 40 to 65 years seeking treatment for menopausal symptoms, with at least: <ul style="list-style-type: none"> • 12 months of spontaneous amenorrhea, or • 6 months of spontaneous amenorrhea with serum follicle-stimulating hormone (FSH) levels > 40 mIU/mL 2. Intact uterus 3. Endometrial biopsy report at screening with protocol specified diagnoses 4. Body mass index (BMI) \leq 34 kg/m² 5. For the sleep substudy, subjects must respond yes to the following questions: <ul style="list-style-type: none"> • Are you very bothered by hot flushes or night sweats? • Do you often awake during sleep time and have trouble falling asleep again? • Do you feel that you often do not get the amount of sleep needed during sleep time? <p><u>Exclusion criteria</u></p> <ol style="list-style-type: none"> 1. History or active presence of <ul style="list-style-type: none"> • Known hypersensitivity to oestrogens • Undiagnosed vaginal bleeding • Known or suspected oestrogen- dependent neoplasia • Endometrial hyperplasia • Malignancy or treatment for malignancy within the previous 5 years except Basal Cell Carcinoma or Squamous Cell Carcinoma of skin • Breast cancer, melanoma or any gynaecologic cancer • Thrombophlebitis, thrombosis or thromboembolic disorders • Specified cerebrovascular or cardiovascular disease • Neuro-ocular disorders • Chronic renal or hepatic disease • Gallbladder disease (unless cholecystectomy) 2. Active presence of any of the following that, in the investigator's judgment will substantially increase the risk associated with the subject's participation in the study: <ul style="list-style-type: none"> • Malabsorption disorders. • Endocrine disease (except for controlled hypothyroidism or diet-controlled diabetes mellitus) • Known alcohol or drug abuse. • Heavy smoking (more than 15 cigarettes per day). 3. Clinically important abnormalities at screening - eg. <ul style="list-style-type: none"> • Specified cervical cytological or endometrial abnormalities • Uncontrolled hypertension; those with sitting blood pressure >140 mmHg systolic or >90 mmHg diastolic should be controlled on not > three antihypertensives • Elevated cholesterol (>7.77mmol/L) or triglyceride (>3.39 mmol/L) • Fasting blood glucose > 6.94mmol/L 4. Use of oral estrogen-, progestin-, androgen-, or SERM-containing drug products within 8 weeks before screening and use of transdermal hormone products within 8 weeks before screening (<i>12 weeks for the osteoporosis substudy</i>); use of vaginal hormone products (rings, creams, gels) within 4 weeks before screening (<i>12 weeks for the osteoporosis substudy</i>); use of intrauterine progestins within 12 weeks before screening; use of progestin implants/injectables or estrogen pellets/injectables within 6 months before screening.

	Criteria
Intervention	<ul style="list-style-type: none"> • BZA 20 mg / CE 0.45 mg • BZA 20 mg / CE 0.625 mg
Comparator/s	<ul style="list-style-type: none"> • BZA 20 mg <i>*not registered in Australia*</i> • CE/MPA 0.45 mg/1.5 mg Placebo
Endpoints	Primary <ul style="list-style-type: none"> • Incidence of endometrial hyperplasia at month 12 Secondary <ul style="list-style-type: none"> • Amenorrhoea and breast tenderness related endpoints Substudies: <ul style="list-style-type: none"> • Osteoporosis substudy primary endpoint: Mean percentage change from baseline at month 12 in the BMD measurement of the lumbar spine. Other osteoporosis related analyses were also done. • Sleep substudy: Medical Outcomes Sleep scale, Menopause-specific quality of life (MENQOL) questionnaire • Breast density substudy: descriptive statistics and mean changes

It is noted that the active comparator CE/MPA 0.45mg/1.5mg is a lower dose MHT and is registered in Australia as Premia low, however is not listed as a currently available product on the Sponsor's website. Thus, the relevance of this active comparator in an Australian context is unclear.

6.3.2.2. Measurement of endpoints

The primary endpoint was the incidence of endometrial hyperplasia at month 12 for all subjects in the efficacy -evaluable (EE) population.

The incidence at month 12 was calculated as:

$$\frac{\text{All subjects in the EE population with biopsy results positive for endometrial hyperplasia during the first 12 months}}{\text{All subjects in the EE population}}$$

The EE analysis population was defined as subjects who were randomly assigned and:

- had taken at least one dose
- at least 2 blinded central pathologists had assessed the screening endometrial biopsy
- had a biopsy during Month 12 or had hyperplasia diagnosed before Month 12
- had no major protocol violations.

Subjects were excluded from the EE analysis population if they had a reading of hyperplasia by any pathologist at baseline, or had biopsies taken after another prohibited hormone medication had been administered. Subjects who had endometrial malignancy were not included in the numerator or denominator of the incidence calculation.

It is noted that 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 analysis of biopsy results should be based on:

- evaluable endometrial biopsies at 1 year - ie. endometrial tissue sufficient for diagnosis
- biopsies with insufficient tissue for diagnosis and endometrial thickness < 5 mm, (considered as atrophic endometrium),
- biopsies with diagnosis of hyperplasia or carcinoma performed during the study, whatever the duration of treatment.

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.

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 should be $\leq 1\%$ 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 (EMA/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%.

6.3.2.3. Discontinuations

See Table 19.

Table 19: Discontinuations.

	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	445	474	230	220	474
Completed	357	393	1856	159	383
Discontinued	88 (19.2)	81 (17.0)	45 (19.6)	61 (27.7)	91 (19.2)
· Adverse event	34 (7.6)	33 (7.0)	16 (7)	31 (14.1)	33 (7)
· Death	0	0	0	0	1
· Investigator request	0	1 (0.2)	1(0.2)	0	0
· Lost to follow up	8 (1.8)	10(2.1)	11 (4.8)	8 (3.6)	0 (1.9)
· Other	6	4	6	2	15
· Protocol violation	8	9	4	9	5
· Subject request	27 (6.1)	18 (3.8)	2 (0.9)	7 (3.2)	16 (3.4)
· Unsatisfactory response (efficacy)	1.1	6 (1.3)	6 (2.6)	4 (1.8)	12 (2.5)

6.3.2.4. Baseline characteristics (safety population)

See Table 20.

Table 20: Baseline characteristics.

	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
N	445	474	230	220	474
Mean age (year)	54.43	53.89	54.07	54.15	54.19
BMI (kg/m ²)	25.81	26.07	26.49	26.23	25.99
Age at last menstrual period	49.74	50.00	50.04	49.93	49.90

	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
Years since last menstrual period	5.2	4.41	4.54	4.73	4.80
Race (white)	397 (89.21%)	435 (91.77%)	207 (90%)	193 (87.73%)	426 (89.87%)

6.3.2.5. Results for primary endpoint

Two definitions for defining cases of endometrial hyperplasia were used - definition 2 is a diagnosis of hyperplasia was based on at least 2 positive diagnoses and is accordance with the EU guidelines (EMA/CHMP/021/97 Rev. 1, 13 October 2005).

Table 21: Results for primary endpoint.

	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
N (MITT)	335	368	169	149	354
Incidence of hyperplasia (%)	1 (0.30)	1 (0.27)	0 (0)	0 (0)	1 (0.28)
CI (upper limit 95% 1 sided)	1.41	1.28	1.76	1.99	1.33
CI (upper limit 95% 2 sided)	1.65	1.50	2.16	2.45	1.56

It is noted that the EPAR assessment of the incidence of endometrial hyperplasia is a different denominator to that contained within the study report - the EPAR considers 314 biopsies to be evaluable and therefore the report states that incidence of endometrial hyperplasia / malignancy at month 12 was 0.32% (95% CI 0.01%; 1.76%). This data does not appear to be in the dossier.

Regarding the analysis of the incidence of endometrial hyperplasia/malignancy, the following issues are noted

- Four pts in the BZA 20/ CE 0.45 group with an endometrial thickness \geq 4mm detected on ultrasound had no biopsy performed at month 12 and a further 8 subjects had neither a biopsy nor ultrasound. In other words, 12 subjects in total in the BZA 20mg/CE 0.45mg group are lacking in biopsy results. This is noteworthy because a small number of missed cases of hyperplasia would change the interpretation of the study from success to failure.
- Only the diagnosis of the endometrial biopsy is reported; no further information is available. This is of note as the non-specific diagnosis of "endometrium, other" was common - 73.76% - 86.49% of all diagnoses of the four pathologists (see Table 15.73 in clinical study report for additional details).

6.3.2.6. Selected Secondary endpoints

- Bone mineral density (BMD): For both BZA/CE doses, there were significant increases in mean percent change from baseline in BMD of lumbar spine at month 12 compared to placebo. BZA/CE 20mg/0.045mg failed the pre-specified non-inferiority test as the upper bound of the 95% CI (0.754) exceeded the pre-specified margin.
- Over a one year treatment period, the cumulative rate of amenorrhoea for BZA/CE was similar to placebo and higher than CE 0.45/MPA 1.5mg.

- Compared to CE 0.45/MPA 1.5mg, the bleeding and spotting profile of the BZA/CE group was significantly better.
- The incidence of subjects reporting breast tenderness was not significantly different between BZA/CE and placebo groups however the CE 0.45/MPA 1.5mg group reported more breast tenderness compared to placebo.
- In terms of the mean percent change of mammographic breast density from baseline, slight decreases in all groups were seen except the CE 0.45/MPA 1.5mg group which showed increased breast density. There were no significant differences between the BZA/CE group and placebo.
- Of the five items measured on the MOS sleep scale, BZA/CE 20mg/0.45mg showed more effectiveness compared to placebo in only one item at 3 months and in two items at 12 months.
- The MENQOL analysis showed some improvements compared to placebo, but not across all tests

6.3.2.7. Conclusions

The incidence of endometrial hyperplasia for BZA 20 mg/CE 0.45 mg was 0.30 with a 95% 2 sided limit of 1.65 based on the definition 2. This is within the reference limit of 2% stated within the EU guideline (EMA/CHMP/021/97 Rev. 1, 13 October 2005). It is noted that the EMA has assessed compliance with the EU guidelines on an incidence of 0.32% (95% CI 0.01 – 1.76%) from 314 evaluable biopsies for BZA 20 mg/CE 0.45 mg, however the TGA has not been able to find the source of this data within the study report.

It is noted that a significant proportion of biopsy results are diagnosed as “endometrial, other”, with no further details available and there are missing biopsy results which may significantly impact the endometrial safety outcomes of this study. Due to these two issues, the EMA has noted that, “currently endometrial safety cannot be concluded” (EPAR).

6.3.3. Summary of primary and secondary outcomes in trials accepted as pivotal for BZA 20 mg / CE 0.45 mg

Table 22 shows a summary of primary and secondary outcomes in trials accepted as pivotal for BZA 20 mg /CE 0.45 mg

Table 22: Summary of primary and secondary outcomes in trials accepted as pivotal for BZA 20 mg /CE 0.45 mg.

Efficacy	Evidence
Vasomotor symptoms <i>According to European guidelines (adopted by the TGA), the most important estrogen deficiency symptom to be treated by MHT are vasomotor symptoms</i>	Study 305 primary endpoint - statistically significant decrease in moderate-severe hot flushes vs placebo (change from baseline: -7.63 average daily number BZA/CE 20/0.45 compared to placebo -4.92; p value < 0.001) Study 305 - all secondary endpoints related to VMS show a statistically significant difference vs placebo
Other estrogen deficient symptoms (all secondary endpoints or substudies)	Bleeding 3307 - cumulative rate of amenorrhea was similar to placebo and sig lower than CE/MPA; bleeding and spotting BZA/CE sig better than CE/MPA
	Breast pain 305 - no difference compared with placebo 3307 - no difference compared with placebo; significantly higher in the CE/MPA group
	Sleep 305 - statistically significance difference vs placebo in most items 3307 - statistically significance difference vs placebo in 2/5 items

Efficacy	Evidence
	<p>QOL 305 - statistically significance difference vs placebo in 2/5 items 3307 - statistically significance difference vs placebo but not vs CE/MPA</p>
	<p>Breast density 3307 - no statistically significance difference vs placebo</p>
	<p>Osteoporosis 3307 - statistically significance increase in mean percent change from baseline in BMD of lumbar spine compared to placebo however failed non-inferiority test</p>
Safety endpoint – endometrial hyperplasia	3307 primary endpoint - incidence of endometrial hyperplasia below the reference limit stipulated by EMA guidelines however there are missing and non-specific biopsy results which may have impacted the final results.

6.4. Supportive studies

6.4.1. Study 303 [Selective Oestrogens Menopause and Response to Therapy – 1 (SMART-1)]

This study was found to be GCP non-compliant and the CHMP has not taken it into account for the assessment of efficacy of BZA / CE.

- Published as: Pickar JH, Yeh I-T, Bachmann, G et al. Fertil Steril 2009; 92(3):1018 - 1024
- Recruitment: Apr 2002 – Dec 2003
- Participation: 94 sites in US, Europe, Brazil

6.4.1.1. Study design

Study 303 was a placebo and active controlled, double blinded, randomised phase 3 study.

Table 23: Study 303.

	Criteria
Patients	<p><u>Inclusion criteria</u></p> <ol style="list-style-type: none"> 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 (with one of specified diagnoses); no evidence of endometrial hyperplasia at screening 5. Last natural menstrual cycle completed at least 12 consecutive months before screening 6. Body mass index (BMI) ≤ 32.2 kg/m² <p><u>Exclusion criteria</u></p> <ul style="list-style-type: none"> · History or active presence of · Known hypersensitivity to oestrogens · Known or suspected oestrogen- dependent neoplasia · Endometrial hyperplasia · Any malignancy within previous 10 years · Breast cancer, melanoma or any gynaecologic cancer · Thrombophlebitis, thrombosis or thromboembolic disorders · Specified cerebrovascular or cardiovascular disease · Neuro-ocular disorders · Chronic renal or hepatic disease · Gallbladder disease (unless cholecystectomy) · Hepatitis B or HIV positive <p>Active presence of the following</p> <ul style="list-style-type: none"> · Specific cervical cytological abnormalities · Elevated sitting blood pressure (>160 mm HG systolic or >100 mmHg diastolic) or $>$

	Criteria
	two antihypertensives <ul style="list-style-type: none"> • Elevated cholesterol (>7.77mmol/L) or triglyceride (>3.39 mmol/L) • Fasting blood glucose > 6.94mmol/L Past HRT <ul style="list-style-type: none"> • No oral estrogen, progestin, androgen, SERM; or transdermal or vaginal hormonal product within 8 weeks of screening • No IUD within 12 weeks • No injectable or pelted hormonal product within 24 weeks
Intervention	<ul style="list-style-type: none"> • BZA/CE 10 mg / 0.45 mg • BZA/CE 20 mg / 0.45 mg • BZA/CE 40 mg / 0.45 mg • BZA/CE 10 mg / 0.625 mg • BZA/CE 20 mg / 0.625 mg • BZA/CE 40 mg / 0.625 mg
Comparator/s	Placebo Raloxifene 60 mg
Endpoints	Primary <ul style="list-style-type: none"> • Incidence of endometrial hyperplasia at month-12 in the efficacy-evaluable population (EEP) <ul style="list-style-type: none"> • Secondary • Endometrial hyperplasia at 6 and 24 months • Change from baseline in the composition of the vaginal epithelium (% parabasal cells, % intermediate cells, % superficial cells) at months 6, 12, 18, and 24 • Change in baseline of number and severity of hot flushes at various time points • Sexual activity • Dyspareunia • Sleep quality and quantity • Breast pain • Bleeding and spotting • The metabolic substudy parameters included bone metabolism markers, coagulation parameters, lipid profile, carbohydrate and other parameters • Osteoporosis substudies (2) - a number of endpoints related to osteoporosis; primary endpoint for BMD was mean percent change from baseline to month 24 in BMD for lumbar spine Ancillary study - study 4000: single blinded radiologists examined the breast density in mammograms taken at baseline and at month 24 from a subset of subjects who had received BZA 20 mg / CE 0.45 mg, BZA 20 mg / CE 0.625 mg, raloxifene, or placebo as part of study 303

6.4.1.2. Measurement of endpoints

Primary

At any given timepoint, incidence of endometrial hyperplasiathis was calculated as the number of women in the EEP with biopsies positive for endometrial hyperplasia, up to and including that timepoint.

EEP (efficacy evaluable population)

This comprised women who took at least one dose of the study drug; had an endometrial biopsy read by central pathologist at screening; had an endometrial biopsy performed at the specified timepoint; or received a diagnosis of endometrial hyperplasia at any earlier timepoint.

Using the EEP is considered preferable to using ITT because EEP results in a larger estimate of the incidence of hyperplasia. ITT could dilute the estimate of the incidence of hyperplasia.

Evaluation of endometrial histology

Endometrial biopsies were done at screening, and at 6, 12, 24 months; or when women withdrew from the study and more than 3 months had elapsed since the previous biopsy; or if the woman experienced heavy bleeding.

All endometrial biopsy samples were centrally evaluated by two blinded pathologists according to standard criteria.³⁵ Disputes were resolved by the third blinded pathologist.

Minimal clinical important difference

An acceptable incidence of hyperplasia was defined as $\leq 2\%$; with a one-sided 95% CI $\leq 4\%$.

6.4.1.3. Discontinuations

These are shown in Table 24.

Table 24: Discontinuations.

	CE 0.625 mg			CE 0.45 mg			Raloxifene 60 mg	Placebo
	BZA 10 mg	BZA 20 mg	BZA 40 mg	BZA 10 mg	BZA 20 mg	BZA 40 mg		
N	430	414	417	430	433	423	423	427
EEP for month 12	340	314	311	320	335	309	298	312
Excluded from EEP	90	100	106	110	98	114	125	115
Discontinuations, n (%)	136 (31.6)	130 (31.4)	136 (32.6)	141 (32.8)	129 (79.8)	142 (33.6)	151 (35.7)	151 (35.4)
Adverse event, n (%)	66 (15.3)	52 (12.6)	49 (11.8)	63 (14.7)	46 (10.6)	43 (10.2)	59 (13.9)	61 (14.3)
Death, n	0	1	1	0	0	1	0	1
Unsatisfactory response - efficacy, n (%)**	2 (0.5)	1 (0.2)	4 (1.0)	0 (0.2)	4 (0.9)	8 (1.9)	9 (2.1)	12 (2.8)
Failed to return (%)	17 (4.0)	8 (1.9)	20 (4.8)	14 (3.3)	18 (4.2)	24 (5.7)	22 (5.2)	13 (3.0)
Subject request unrelated to study	28 (6.5)	36 (8.7)	39 (9.4)	32 (7.4)	34 (7.9)	34 (8.0)	36 (8.5)	33 (7.7)

**Overall p-value 0.002

6.4.1.4. Baseline characteristics, safety population

These are shown in Table 25.

Table 25: Baseline characteristics, safety population.

	CE 0.625 mg			CE 0.45 mg			Raloxifene 60 mg	Placebo
	BZA 10 mg	BZA 20 mg	BZA 40 mg	BZA 10 mg	BZA 20 mg	BZA 40 mg		
Age (mean)	56.36	56.29	56.68	56.84	56.22	56.31	56.54	56.48
BMI (mean)	25.74	25.87	25.66	25.83	25.97	25.57	25.92	25.94
Years since LMP (mean)	7.8	8.10	8.29	7.94	8.11	7.9	8.33	8.36
Age at LMP (mean)	49.08	48.72	48.86	49.44	48.62	48.90	48.71	48.60
Ethnic origin - white %	82.33	82.85	81.77	80.47	81.06	77.30	80.61	79.63

6.4.1.5. Results for primary endpoint (endometrial hyperplasia at month-12)

These are shown in Table 26.

³⁵ Kurman RJ. Blaustein's Pathology of the Female Genital Tract, Springer-Verlag, New York, 1994: 411-437.

Table 26: Baseline characteristics, safety population.

	CE 0.625 mg			CE 0.45 mg			Raloxifene 60 mg	Place bo
	BZA 10 mg	BZA 20 mg	BZA 40 mg	BZA 10 mg	BZA 20 mg	BZA 40 mg		
N	340	314	311	320	335	309	298	312
Cases (%)	13 (3.82) ^a	1 (0.32)	0	3 (0.94)	0	0	0	0
95% CI ^b	2.28, 6.01 ^a	0.02, 1.50	0.00, 0.96	0.26, 2.41	0.00, 1.10 ^c	0.00, 1.19 ^c	0.00, 1.00	0.00,0.9 6

a. Incidence of hyperplasia unacceptable according to study protocol; b. One-sided; c. One-sided 97.5% (pre-specified, to adjust for multiple comparisons)

Similar to study 3307, it is noted that the EPAR assessment of the incidence of endometrial hyperplasia is a different denominator to that contained within the study report - the EPAR considers 294 biopsies to be evaluable with an incidence of endometrial hyperplasia/malignancy at month 12 of 0.00% (95% CI 0.00%; 1.25%). This data does not appear to be in the dossier either and the reason for this is unclear.

6.4.1.6. Selected secondary endpoints

Endometrial hyperplasia

- at 24 months for CE 0.45mg /BZA 0.20mg (n= 293; EE population) incidence 0.34 (n = 1); one-sided 95% CI: 0.02 – 1.61
- EPAR notes that “3 cases of endometrial hyperplasia / malignancy had been detected in the two BZA/CE groups during the second treatment year. This is considered to be a safety signal”. One case occurred on the CE 0.45mg /BZA 0.20mg dose, and the other two on the higher CE dose.³⁶
- Mean change from baseline in average daily number of moderate and severe hot flashes at week 12 for CE 0.45mg /BZA 0.20mg (n= 28 pairs; EE population LOCF): -5.23 (SE 1.05; p value vs placebo 0.022 – ANCOVA with stepdown procedure p <0.001)
- Vaginal atrophy was assessed by assessing the proportion of superficial, intermediate, and parabasal cells in vaginal smears. Desirable results should reflect a higher proportion of superficial and intermediate cells and lower proportion of basal cells. At 6 months, CE 0.45mg /BZA 0.20mg showed an adjusted change of
 - Superficial cells: 4.96% (SE 0.74); p-Value vs placebo 0.511 (n pairs = 230)
 - Intermediate cells: 15.59% (SE 2.16); p-Value vs placebo <0.001 (n pairs = 230)
 - Parabasal cells: -20.52% (SE 2.32); p-Value vs placebo <0.001 (n pairs = 23)

Osteoporosis

- significant increases in lumbar spine BMD from baseline to month 24 in both substudies for all groups except placebo (in which BMD values were decreased). The largest increase in BMD was associated with 10mg BZA; this effect decreased as the dose of BZA was increased and was regardless of the CE dose.

³⁶ Clarification (24 November 2016): Three cases of endometrial hyperplasia/malignancy were detected in the BZA 20 mg/CE 0.45 mg and the BZA 20mg/CE 0.625mg arms during the second treatment year. Two cases occurred on the BZA 20 mg/CE 0.45 mg dose, including one case of malignancy, and one additional case on the higher CE dose. Please also note that reference to a BZA dose of “0.20 mg” is a typographical error and should be read as “20 mg”.

Sleep

- The most effective combinations were either 10mg or 20mg BZA with 0.625 mg CE. The combination of CE 0.45mg and either 10mg or 20mg BZA significantly reduced the time to fall asleep compared with placebo at some, but not all, time points.

Sexual activity

- no significant difference between groups

Dyspareunia

- Numerical decrease in percentage of women with dyspareunia was seen during the study for women for either 10mg or 20mg BZA combined with CE 0.45, although only the 20mg BZA was statistically significant at weeks 9-12. In comparison, there was a slight increase with raloxifene or placebo. Analysis of the Menopause-Specific Quality of Life (MENQOL) questionnaire showed some improvement compared to placebo.

Breast pain

- there were no significant differences between groups.

Bleeding and spotting

- In terms of cumulative amenorrhea, percentages were comparable between groups (including placebo) except for BZA 10 mg /CE 0.625mg for which percentages were lower.

Breast density substudy (study 4000)

- The mean percentage change in breast density between baseline and month 24 for CE 0.45mg /BZA 0.20mg (n = 129) was -0.39 (95% CI -0.69, -0.08) compared to placebo (n = 126) which was -0.42 (95% CI -0.72, -0.11).

6.4.1.7. Conclusions

BZA/CE 20mg/0.45 gave a rate of hyperplasia of <1% at 12 months (and also at 24 months) and a lower dose of BZA (10 mg) was not effective in protecting the endometrium. Three cases of endometrial hyperplasia / malignancy were diagnosed in the second treatment year, one in CE 0.45mg /BZA 0.20mg dose group and two in the CE 0.625mg /BZA 0.20mg group³⁷ – this is a safety signal in the EPAR.

6.4.2. Study 306 [Selective Oestrogens Menopause and Response to Therapy – 3 (SMART-3)]

- This trial was a double blinded, active and placebo controlled study in which the 664 subjects were randomised into 4 arms.
- Interventions: BZA 20 mg / CE 0.45 mg, BZA 20 mg / CE 0.625 mg, BZA 20 mg (not available in Australia)
- Control arm: Placebo
- The co-primary endpoints concerned VVS outcomes at week 12 – proportion of superficial cells and parabasal cells, vaginal pH and the most bothersome symptom.
- Secondary endpoints included other parameters related to VVA plus questionnaires relating to quality of life, menopause symptom improvement and sexual experience.
- Results for Primary co-endpoints: shown in Table 27.

³⁷ Clarification (24 November 2016): Three cases of endometrial hyperplasia/malignancy were detected in the BZA 20 mg/CE 0.45 mg and the BZA 20 mg/CE 0.625 mg arms during the second treatment year. Two cases occurred on the BZA 20 mg/CE 0.45 mg dose, including one case of malignancy, and one additional case on the higher CE dose. Please also note that reference to a BZA dose of “0.20 mg” is a typographical error and should be read as “20 mg”.

Table 27: Study 306: Results for Primary co-endpoints

Change from baseline – LOCF (p value vs placebo)				
	BZA 20 /CE 0.45	BZA 20 /CE 0.625	BZA 20 mg	Placebo
Superficial cells - median	0 (0.005)	1.0 (0.002)	0.0 (0.318)	0.0
Parabasal cells - median	-9.0 (0.001)	-8.0 (<0.001)	3 (<0.001)	0
Vaginal pH - mean	-0.25 (0.116)	-0.50 (<0.001)	0.07 (0.389)	-0.09
Intensity of the Most bothersome symptom	* (0.09)	* (0.048)	* (0.178)	* (n/a)

* Symptoms were graded according to severity of none, mild, moderate and severe at baseline and week 12 – for full comparison of specific scores according to individual severity categories, please see Supportive tables 15.29 and 15.30 in study report.

6.4.2.1. Conclusion

The outcome for the BZA 20 mg / CE 0.45 mg (n = 225) arm was mixed – compared with placebo, there was a positive and statistically significant difference in terms of superficial and parabasal cell markers, however no statistically significant difference in terms of vaginal pH and most bothersome symptom.

6.4.3. Study 304 [Selective Oestrogens Menopause and Response to Therapy – 4 (SMART-4)]

Considered by the Sponsor to be supportive as the formulations were not bioequivalent to the formulations used in study 303 – that is, there was a decrease in bioavailability of BZA of about 20% in the formulations used in this study which impacted endometrial safety.

An outpatient, multicentre, double-blind, randomised, 4-parallel-group, placebo- and active-controlled study in non-hysterectomised postmenopausal women

Interventions: BZA/CE 20 mg / 0.45 mg and 20 mg / 0.625 mg

Control: CE/MPA 0.45 mg/1.5 mg and placebo

The primary endpoints were the incidence of endometrial hyperplasia at month 12 of therapy and in the osteoporosis substudy, the percent change from baseline in BMD of lumbar spine after month 12 of therapy compared with placebo (not discussed further here).

Secondary endpoints included the incidence of endometrial hyperplasia at month 24, cumulative and noncumulative amenorrhea and breast pain; an osteoporosis substudy was also included.

Results for hyperplasia primary endpoint: shown in Table 28.

Table 28: Study 304: results for hyperplasia primary endpoint.

	BZA 20 mg / CE 0.45 mg	BZA 20 mg / CE 0.625 mg	CE 0.45 mg/MPA 1.5 mg	Placebo
N (EE population)	261	273	119	135
Hyperplasia cases (%)	0 (0)	3 (1.10)	0 (0)	0 (0)
95% CI 2 sided	0 - 1.4	0.23 - 3.18	0 - 3.05	0 - 2.7

The EPAR has noted that, “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 (EMA/CHMP/021/97 Rev. 1, 13 October 2005)”.

6.4.3.1. Conclusion

Despite a decrease in bioavailability of BZA of about 20% for the formulations of BZA/CE used in this study the incidence of hyperplasia in the BZA 20 mg / CE 0.45 mg arm remained within the limits stated in the CHMP Guideline on clinical investigation of medicinal products for hormone replacement therapy of oestrogen deficiency symptoms in postmenopausal women (EMA/CHMP/021/97 Rev. 1, 13 October 2005), although it is noted that the higher dose did not fare so well and that the EPAR notes that the evaluable population for this study may not be consistent with the guidelines.

7. Clinical safety

The safety analysis was mainly based on data of the five premarket, phase 3 studies (303, 304, 305, 306, 3307). Data from phase 1 and 2 studies, as well as data from the BZA monotherapy program provided additional data. PSURs for BZA/CE (03 October 2013 to 03 April 2015) and BZA monotherapy (01 April 2009 to 15 October 2014) were also available.

7.1. Premarket data

Overall exposure – total number of subjects (%) beginning each treatment interval: all data up to 2 years for studies 303, 304, 305, 306 and 3307.

Table 29: Overall exposure – total number of subjects (%).

	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)

In terms of active comparators (with cumulative data up to 2 years): 399 subjects were exposed to CE 0.45/MPA 1.5mg, 340 to BZA 20mg and 423 to raloxifene 60 mg.

Data for BZA/CE are sparse beyond 2 years. Data for BZA monotherapy are available out to 7 years (1281 women received BZA and completed all 7 years of study in the phase III -301 study).

7.1.1. Summary of clinical safety data

Most common adverse events:

- No unexpected results when comparing the most common AEs ($\geq 10\%$) reported for BZA/CE 20mg/0.45mg, BZA/CE 20mg/0.625mg and placebo at the time points of 3m, 12 m and 24 m.
- The most common AEs included headache, nasopharyngitis, back pain, arthralgia, pain in extremity, influenza, and myalgia

Treatment emergent adverse events (TEAEs):

- The analysis of TEAEs starts at the active phase of the study from the first dose of double-blind therapy until 30 days after the last dose of study medication All TEAEs:
 - No particular TEAEs noted

Related TEAEs:

- The most common severe drug-related treatment emergent adverse event was headache in all groups
- See EPAR for the incidence of severe, treatment-related (as assessed by investigators) TEAEs reported for > 1 subject in any treatment group (cumulative data up to 2 years)
- The EPAR notes that the original dossier showed that “about 3-4% of women experienced treatment adverse events considered severe and related to therapy by the investigators; there was no clear pattern or significant differences between groups. However GCP inspection findings clearly indicated that the relatedness of AEs has not been adequately assessed and there is considerable underreporting in this regard. Therefore the Applicant [Sponsor] was asked [by the EMA] to provide updated overall numbers of adverse events considered to be related, using a most conservative approach in reassessing relatedness”. According the EPAR, this updated data was deemed acceptable, however, the EPAR further notes that “considerable doubts as relates to the quality of the safety data for BZA/CE remain”.

Adverse Events of Special Interest (AESI):

- Adverse events considered to be potential SERM and CE class effects have been analysed, including venous thromboembolic events (VTE), cardiovascular (CHD) events, cerebrovascular accidents (CVAs) and malignancies.
- Analysis was carried out using a meta-analytic approach as follows:
 - Incidence rates, rate differences, and relative risk versus placebo were first calculated for each study
 - Incidence rates, differences in rate versus placebo, and relative rates were summarised across studies using an inverse variance approach
 - Based on these calculations, each study and endpoint was weighted differently. Poisson variance was done due to large differences in study duration.
 - For studies with no events, the number of such events was inflated by 0.5 events to allow inclusion.
 - The results were presented as incidence rates, risk differences, and relative risks and, of note, the 95% confidence intervals are considered to be ‘nominal’ as they have not been adjusted for multiple comparisons.

Table 30: Summary table of AESI.

AESI	
Venous Thromboembolism	<ul style="list-style-type: none"> • Absolute number of events was 3 events in the BZA/CD 20mg/0.45mg and no events in the 20mg/0.625 group • Insufficient data to assess differences between groups • Identified as an important identified risk in the RMP
Cardiac Adverse Events	<ul style="list-style-type: none"> • Insufficient data to assess risk compared to placebo or CE/MPA • Identified as an important potential risk in the RMP
Cerebrovascular events	<ul style="list-style-type: none"> • Insufficient data to assess risk compared to placebo or CE/MPA • Identified as an important potential risk in the RMP

AESI	
Cancer - specifically breast cancer, ovarian cancer, endometrial cancer, lung cancer, thyroid cancer and skin cancer	<ul style="list-style-type: none"> Some cases of cancer were reported in the BZA/CE groups, including endometrial cancer and ovarian cancer. Thyroid and ovarian cancer events occurred in the phase 3 trial of single agent BZA. Insufficient data to assess risk compared to placebo or CE/MPA Identified as an important potential risk in the RMP
Gynaecological safety	<ul style="list-style-type: none"> Increased number of subjects experiencing AEs relating to endometrium on all BZA/CE arms compared to placebo Statistically significant increase in difference in endometrial thickness vs placebo (measured on TVUS) Ovarian volume not adversely affected in those treated with BZA/CE vs placebo Bleeding pattern favourable for BZA/CE vs placebo, however relatively low dose of MPA was used Endometrial hyperplasia identified as an important <u>potential</u> risk in the RMP
Fractures	<ul style="list-style-type: none"> Incidence of traumatic (but not osteoporotic) fractures slightly higher in those treated with BZA/CE vs placebo. Not identified as safety concern in the RMP
Ocular events	<ul style="list-style-type: none"> Post marketing reports of ocular events associated with BZA monotherapy. The post marketing reports of ocular events listed in PSUR # 9 for BZA (the most recent supplied by the Sponsor) included visual acuity reduced, vision blurred, eyelid oedema, visual impairment, visual field defect, erythema of eyelid, eye inflammation, eye pruritus, retinal vein occlusion, and retinal vein thrombosis (29 ocular events in total during the one year period). No increase in the incidence of ocular adverse events in those treated with BZA/CE vs placebo. Identified as an important potential risk in the RMP

Regarding gynaecological safety, the following points regarding the dataset are noted:

- Safety data from Study 304 have been excluded from the assessment of endometrial safety due to reduced bioavailability of the formulation used in this study
- AEs relating to endometrium are drawn from studies 303, 305, 306, 3307 however per EMA guidelines, safety data from studies 305 and 306 was insufficient as the treatment duration was only 3 months.
- Endometrial thickness, ovarian volume and bleeding pattern conclusions based on single study – 3307.

7.1.2. Summary of other key safety findings

See Table 31.

Table 31: Summary of other key safety findings.

	Findings
Serious Adverse Events (SAEs)	<ul style="list-style-type: none"> No imbalances of death between groups No significant differences identified between BZA 20mg/CE vs placebo however slightly higher numbers of the following events were seen : <ul style="list-style-type: none"> Coronary artery disease Chest pain Cholelithiasis Cholecystitis Abnormal endometrium results Cerebrovascular accident Transient ischaemic attack Deep vein thrombosis

	Findings
Lab findings	<ul style="list-style-type: none"> • Increased Triglycerides <ul style="list-style-type: none"> ○ Increase of approximately 16% at month 12 and 20% at month 24 was seen compared to baseline ○ Identified as an important identified risk in the RMP • Decreases from baseline of calcium, phosphorus and alkaline phosphatase were seen, but few were considered potentially clinically significant. • Compared with placebo, the administration of BZA 20 mg / CE had no clinically relevant influence on the lab parameters of lipid profile, mean fasting glucose levels, fasting insulin, C-reactive protein, plasma homocysteine, liver function, renal function, haemoglobin, haematocrit, platelets, coagulation, or thyroid stimulating hormone
Vital signs	<ul style="list-style-type: none"> • No effects detected
Safety in special populations	<ul style="list-style-type: none"> • No clear or relevant differences detected • Limited data in elderly and women of other than white ethnicity noted
Safety related to drug-drug interactions	<ul style="list-style-type: none"> • Only one drug interaction study was carried out: repeat administration of a strong CYP3A4 inhibitor had minimal impact on the PK of BZA/CE
Discontinuation due to AEs	<ul style="list-style-type: none"> • No clear differences detected across studies, except for those that may be expected such as more subjects discontinued due to hot flush on the placebo arm (1.6% vs 0.7% all BZA/CE) • It is noted that data analyses in the EPAR excluded two GCP non-compliant sites in trial 303. However, per the EPAR: <i>“the provided analyses do not indicate significant differences in the rates of discontinuation due to AEs reanalysis and the original analysis”</i>.

7.2. Post marketing experience

The Duavive dossier contained a number of PSURs that have not been submitted to the EMA. It is presumed that this is because these PSURs were produced after initial BZA/CE submission to the EMA.

7.2.1. BZA/CE Periodic Safety Update Report (PSUR)

7.2.1.1. CE/BZA PSUR #1 (3 Oct 2013 – 3 April 2015)

Ongoing safety concerns as listed by the PSUR with relevant information are as follows.

Table 32: Ongoing safety concerns PSUR #1.

	Risk	Events reported during reporting period
Important identified risks	Venous thromboembolism (VTE)	3 post-marketing cases that reported events encoded to the MedDRA PT Deep vein thrombosis (3). All 3 cases were spontaneously reported and in all 3 cases the event was assessed as serious. One of the 3 cases reported an additional risk factor for thrombotic events, as the event occurred after the patient travelled by air; other two cases lacked significant detail
	Increased Triglycerides	Nil reported
Important potential risks	Arterial thromboembolic events: Cerebrovascular events and myocardial infarction (MI)	Nil reported
	Coronary heart disease (CHD)	Nil reported
	Atrial fibrillation	Nil reported
	New presentation or aggravation of pre-existing renal failure or insufficiency	Nil reported

	Risk	Events reported during reporting period
	Renal carcinoma or adenoma	Nil reported
	Gallbladder disease	Nil reported [Not listed in Core Data Sheet, only RMP]
	Cancers: breast, ovarian, endometrial, lung, thyroid, skin, gastrointestinal and other cancers	One post-marketing case of ductal breast carcinoma following a biopsy post mammography was reported, however little further information is available. One post-marketing case of endometrial cancer was reported; the patient had previously taken other oestrogen/progesterone combinations (had not taken progestin for a year)
	Depression	Two post-marketing cases of depressed mood were reported.
	Ocular events	One post-marketing case was reported - per the PSUR (table 5) "This case involved a [information redacted] female patient with a history of diabetes who received CE/BZA for hot flushes. Approximately 3 weeks after starting CE/BZA she experienced several events (dizziness, balance disorder, headache, neck pain, back pain, and dyskinesia) and commented that 'her vision was all messed up'. CE/BZA was withdrawn (no treatment was reported for the events) and the events of visual impairment, dizziness, balance disorder, and dyskinesia were reported to have resolved (outcome of other events were unknown)."
	Gastro-oesophageal reflux disease (GORD)	Two post-marketing cases of indigestion were reported and both were considered to be non-serious. <i>Note: not in RSI only in RMP</i>
	Endometrial hyperplasia	One post-marketing case of endometrial hypertrophy associated with breakthrough bleeding was reported. Two post-marketing cases of endometrial hyperplasia were reported.
	Drug-drug interactions	Per the PSUR: "A study conducted during the reporting interval investigating the effects of itraconazole, a strong CYP3A4 inhibitor, demonstrated that itraconazole had minimal impact on the pharmacokinetics of CE and bazedoxifene when administered with a single dose of CE/BZA." One post-marketing event was reported in which a patient taking CE/BZA subsequently started ospemifene (a SERM).
	Off-label use	Twenty-three cases reported off-label use: <ul style="list-style-type: none"> • 8 cases of concomitant use of oestrogens • 7 cases of usage in woman without a uterus • 4 cases of off label indication: 2 cases for vaginal dryness, 1 for endometriosis and 1 for 'brain heated' • 2 cases of using a dose above recommended - two tablets daily. • 1 case of administration to male patient • 1 cases of administration to a patient with history of breast cancer
Missing information	Use in elderly patients	Six post-marketing cases involving elderly patients were reported - mean age 71.7 years (range 66 -77 years); all were assessed as non-serious and no MedDRA PT was reported in more than one case.
	Use in hepatic impaired patients	No new safety information identified
	Use in renal impaired patients	No new safety information identified
	Use in patients with malignancy	One case of a patient with a history of breast cancer reported (see also off-label uses) that she had gained 20 pounds because of an unnamed breast cancer drug she was receiving.

	Risk	Events reported during reporting period
	Use in patients with history of cardiovascular disease (including hypertension, hyperlipidemias, arrhythmias, CHD, angina), diabetes or obesity or long-term smoking	9 post-marketing cases of patients with a history of cardiovascular disease or diabetes. One case of increased blood pressure was considered serious however reporting physician did not consider CE/BZA to be causal. Adverse events reported in more than one case included 3 cases of headache, 3 cases of neck pain and 2 cases of dizziness.
	Long-term (> 2 years) safety data on breast protection and gynaecological cancers (endometrial and ovarian in particular)	According to the PSUR, no new significant information was identified

According to the PSUR, no new significant information regarding fatal outcomes, abuse, misuse and drug dependency was identified.

7.2.2. BZA Periodic Safety Update Reports (PSURs) [listed in reverse chronological order]

7.2.2.1. BZA PSUR #9 (17 October 2013 to 16 October 2014)

BZA PSUR #9 is the most recent PSUR submitted in this application and is summarised in the most detail here.

BZA has regulatory approval in 39 countries. The PSUR notes that it is estimated that 6302 subjects have been exposed in the BZA clinical development program and there have been approximately 667 639 patient-years of exposure to BZA from marketing experience.

Table 33: Ongoing safety concerns PSUR #9.

	Risks	
Important identified risks	Venous thromboembolism [VTE; including pulmonary embolism (PE), deep vein thrombosis (DVT) and retinal vein thrombosis (RVT)]	14 post-marketing cases reported VTE events - 7 cases of PE, 6 DVT, 2 pulmonary thrombosis and 1 each of retinal vein occlusion, RVT and venous occlusion (1 each). All 14 cases were assessed as serious. Relevant event outcome: recovered/recovering (7 cases), not recovered at the time of reporting (1), and unknown (2; no cases reporting a fatal outcome).
	Ocular events	29 post-marketing cases of ocular events were reported - 12 cases of visual acuity reduced, 7 vision blurred, 5 eyelid oedema, 4 visual impairment, 2 visual field defect, and 1 each of erythema of eyelid, eye inflammation, eye pruritus, retinal vein occlusion, and retinal vein thrombosis. In 24 cases, the reported ocular events were considered serious. Of the 29 cases in this dataset, 13 cases reported a medical history of ocular events. Relevant event outcome was reported as recovered/recovering (6 cases), not recovered at the time of reporting (1), and unknown (20).
Important potential risks	Ischaemic stroke	Two post-marketing cases potentially involving ischemic stroke are noted - 1 case reported cerebral infarction in a female of an unspecified age and contained insufficient information to allow for a meaningful case assessment. The other case described an 81-year-old female patient with a relevant history of hypertension who experienced cerebral infarction while on bazedoxifene for an unspecified period of time. The patient was hospitalized and the event outcome was reported as resolved with sequelae.
	Atrial fibrillation	Nil reported

	Risks	
Potential risks from non-clinical studies	Renal cell carcinoma and adenoma	Nil reported
	New presentation or aggravation of pre-existing renal failure or insufficiency	Nil reported
Potential risks	Cholecystitis	Nil reported <i>Note: not in reference safety information (RSI), only in RMP</i>
	Increased triglyceride levels	Nil reported
	Cancers	Nil reported
	Depression	Nil reported <i>Note: not in RSI, only in RMP</i>
	Gastroesophageal Reflux Disease (GERD)	Nil reported <i>Note: not in RSI, only in RMP</i>
Important missing information	Use in the elderly	130 post-marketing cases reported involved elderly patients with an age range from 65 to 93 years (4 cases did not provide age). The most commonly recorded Preferred Terms (>3) in the elderly dataset regardless of MedDRA System Organ Class were Hot flush (10 events), Peripheral oedema (9), Rash (8), Breast discomfort (7), Pulmonary embolism (7), Visual acuity reduced (7), Vision blurred (6), Deep vein thrombosis (5), Hyperhidrosis (5), Blood pressure increased, Dyspnoea, and Palpitations (4 each).
	Use in patients with a history of thrombotic/ischemic cardiac disorders	No specific information noted in the PSUR

According to the PSUR, no new significant information regarding fatal outcomes, abuse, misuse and drug dependency was identified.

The PSUR reported that the following events/topics that had been recommended for monitoring and discussion in a previous PSUR and/or assessment report: palpitations, increased blood pressure, QT prolongation, pain in extremity, and skin events. The Sponsor has proposed that routine monitoring occur for these events in future reports unless a new safety issue is identified.

The investigation of thirst was closed as a potential safety signal.

Significant safety changes to RSI:

- addition of information regarding a possibility of an increased metabolism of bazedoxifene by concomitant use of substances known to induce the enzyme uridine diphosphate glucuronosyltransferase (UGT)
- update of frequency category of the adverse drug reactions (ADRs) Rash and Pruritus from not known to common

7.2.2.2. BZA PSUR #8 (17 October 2012 to 16 October 2013)

Of note, the important potential risk of ocular events was upgraded to an important identified risk in response to a request from PRAC following review of the RMP (version 4.0) as ocular events are listed as an adverse reaction in the RSI.

The investigation of increased blood parathyroid hormone, palpitations, uterine haemorrhage as a potential safety signal was closed and determined not to be risks. The investigation of skin events (rash and pruritus) as a safety signal was closed and rash and pruritus was added to the core data sheet as appropriate representative terms for skin events.

7.2.2.3. BZA PSUR #7 (17 April 2012 to 16 October 2012)

No new safety issues identified.

7.2.2.4. BZA PSUR #7 (17 October 2011 to 16 April 2012)

A number of safety related changes were made to the RSI. No new safety issues identified.

7.2.3. Combined Oestrogens

No PSURs were submitted.

7.2.4. Safety signal detection

The EMA Pharmacovigilance Risk Assessment Committee (PRAC) has recently recommended modifications to the Summary of Product Characteristics (SmPC) and Package Leaflet in Europe for post-menopausal MHT products, following the publication of a meta-analysis regarding the risk of ovarian cancer associated with the use of MHT products. The meta-analysis found an increased risk of ovarian cancer in women who had used hormone therapy for menopause.

Of particular note, specific changes were recommended by PRAC for the SmPC and Package Leaflet for Duavive.

7.2.5. RMP

Summary of safety concerns

These are shown in Table 34.

Table 34: Summary of safety concerns.

	Summary
Important identified risks	<ul style="list-style-type: none"> • Venous thromboembolism (VTE) • Increased Triglycerides
Important potential risks	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • 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)

It is unclear why identified risks for CE (eg. arterial thrombotic events, breast cancer) and BZA (ocular events) are only considered to be potential risks for the combination products. A question regarding this has been addressed to the Sponsor.

8. Overall summary

- It appears that the efficacy of CE is decreased when given in combination with BZA; as compared to efficacy of CE when given in combination with MPA. However, no attempt was made to measure this possible decrease in efficacy because the pivotal study for VVS (Study 305) did not include a direct comparison to CE/MPA (or CE/micronised progesterone). This

possible decrease in efficacy of CE with BZA is important because it runs counter to accepted clinical practice guidelines to prescribe CE in the lowest possible dose (and for the shortest period of time). This may mean that women, whose symptoms might be controlled on CE 0.3 mg, are exposed to CE 0.45 mg. This could lead to an increase in known adverse reactions with CE: Arterial Thromboembolism (stroke, acute coronary syndrome), VTE, breast cancer, ovarian cancer, etc.

- Endometrial safety assessment is made on the basis of one pivotal Study 3307. As Study 303 is considered GCP non-compliant, it has not been included for the purposes of endometrial evaluation. Further, although endometrial outcomes were the primary outcome in Phase II dosing Study 203, this was measured by transvaginal ultrasound, which is not recommended as replacement of biopsy in the evaluation of endometrial hypertrophy according to the EMA guidelines.³⁸

In Study 3307, although there were no identified cases of endometrial hyperplasia in the BZA/CE 20/0.45 mg group, a small number of missed cases could mean that the pre-specified acceptable incidence for endometrial hyperplasia according to EMA guidelines (an upper limit of the 2-sided 95% confidence interval of 2%) would not have been met. Specifically it is noted that in Study 3307, 12 of 445 subjects in the BZA/CE 20/0.45 mg group are missing follow up biopsy results.

The use of efficacy-evaluable population (EEP) to analyse endometrial hyperplasia is accepted. That is, EEP provides the appropriate denominator. However, some cases of endometrial hyperplasia might have been missed (numerator underestimated).

- The population of women for whom progestogen containing therapy is “not appropriate” is not a well characterised subset of women suitable for MHT. More specifically, this terminology is somewhat vague and vulnerable to differences in interpretation by both prescribers and women. Relevant issues include:
 - There are already other treatment options for “women for whom treatment with progestogen containing therapy is not appropriate”. Existing options for management include using an alternative progestin, dose or administration route (intrauterine device or transdermal)³⁹ as well as non-progestin containing therapies such as tibolone.⁴⁰
 - Different natural and synthetic progesterones have different effects in different women; intolerance to a specific natural or synthetic progesterone might not apply to all natural and synthetic progesterones, in general.
- The efficacy and safety for the subgroup of women specified in the proposed indication (“women for whom treatment with progestogen containing therapy is not appropriate”) was not directly measured in the Phase III clinical development program. EMA guidelines⁴¹ state that the claimed indication should be clearly identified – for example, first or second line therapy – and the clinical development performed accordingly. Further, the clinical development program does not contain direct data to support the use of Duavive for the proposed Indication. For example, there are no direct data on whether “women for whom treatment with progestogen containing therapy is not appropriate” will tolerate BZA/CE. More specifically, adverse effects which, according to the EPAR,⁴² the sponsor considers to be “specific adverse effects of progestins” (for example, flatulence, depression, mood swings,

³⁸ European Medicines Agency, “Guideline on clinical investigation of medicinal products for hormone replacement therapy of estrogen deficiency symptoms in postmenopausal women (EMA/CHMP/021/97 Rev. 1)”, 13 October 2005.

³⁹ Oestrogen/progestin hormone replacement [revised Feb 2014] In: eTG [Internet]. Melbourne: Therapeutic Guidelines Limited; November 2015.

⁴⁰ Stuenkel CA, et al. Treatment of Symptoms of the Menopause: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab.* 100: 3975-4011 (2015).

⁴¹ European Medicines Agency, “Guideline on clinical development of fixed combination medicinal products (CHMP/EWP/240/95 Rev. 1)”, 19 February 2009.

⁴² European Medicines Agency, European Public Assessment Report: Duavive (oestrogens conjugated / bazedoxifene).

peripheral edema, acne, hirsutism, increased weight) might occur with the same frequency with BZA/CE. Further, there are no direct data on which co-existing conditions (for example, depression, diabetes) are exacerbated by natural or synthetic progestones, but not by BZA/CE.

The EPAR⁴³ refers to a post hoc subgroup analysis of women for whom progestin-containing therapy is not appropriate (including patients with a medical history of diabetes or depression). In other documents related to the EMA submission provided by the Sponsor, the EMA refers to data regarding progestin intolerance in the proposed population. However these documents do not appear to have been provided to the TGA.

- Two of the sponsor designated pivotal trials – Studies 303 and 305 – were found to be GCP non-compliant by EMA. Although data from Study 305 was taken into account for the efficacy evaluation by EMA and TGA, data from Study 303 was not taken into account for the assessment of efficacy.
- Of the four studies (303, 305, 306, 3307) that the sponsor has indicated are pivotal in the letter to the Delegate dated 31 October 2015, it could be argued that only two should be accepted as pivotal: Studies 305 and 3307.
 - Study 303 was GCP non-compliant and due to this, data from study 303 was not taken into account for the assessment of efficacy and is not considered to be pivotal.
 - Study 306 primarily assessed the effect of BZA/CE on VVA. The European guideline states that:⁴⁴

the most important estrogen deficiency symptoms are vasomotor symptoms (hot flushes) ... the proposed primary endpoint for efficacy trials is the frequency of moderate to severe hot flushes.

For women with vaginal symptoms only, local treatment is recommended.⁴⁵ As this trial primarily assessed the effect of BZA/CE on VVA, this trial is considered to be supportive and not pivotal.

- Long-term (>24 months) endometrial safety is unknown. The pivotal study for endometrial safety, Study 3307, measured the incidence of endometrial hyperplasia at month 12. Study 303 followed patients up for 24 months, however due to GCP non-compliance, this trial does not contribute to the efficacy data being evaluated. Nevertheless, it is noted that in study 303, the incidence of endometrial hyperplasia at 24 months for CE 0.45 mg/BZA 0.20 mg (n = 293; EE population) was 0.34 (n = 1) with 95% CI: 0.02-1.61.⁴⁶
- Safety data for the fixed dose combination are sparse beyond 2 years of exposure. This is relevant as the RANZCOG Menopausal Hormone Therapy Advice⁴⁷ notes that “most guidelines recommend using HRT for up to four to five years”. It is also noted that in a study of 3302 women in the US, the median total duration of frequent VMS (≥6 days in the previous 2 weeks) is 7.4 years.⁴⁸

⁴³ European Medicines Agency, European Public Assessment Report: Duavive (oestrogens conjugated / bazedoxifene).

⁴⁴ European Medicines Agency, “Guideline on clinical investigation of medicinal products for hormone replacement therapy of estrogen deficiency symptoms in postmenopausal women (EMEA/CHMP/021/97 Rev. 1)”, 13 October 2005.

⁴⁵ RANZCOG, Management of the menopause, Nov 2014.

⁴⁶ Clarification (24 November 2016): Two cases of endometrial hyperplasia/malignancy occurred on the BZA 20 mg/CE 0.45 mg arm during the second treatment year, including one case of malignancy. Please also note that reference to a BZA dose of “0.20 mg” is a typographical error and should be read as “20 mg”.

⁴⁷ RANZCOG, Menopausal Hormone Therapy Advice, Jul 2015.

⁴⁸ Avis NE, et al. Duration of menopausal vasomotor symptoms over the menopause transition. *JAMA Intern Med.* 175: 531-539 (2015).

- A total of 1585 women were exposed to the BZA 20 mg/CE 0.45 mg dose, 1241 to placebo and 1162 to active comparators. As stated by the EPAR:⁴⁹

due to this limitation in the number of women treated together with the limited treatment duration [as noted above] and missing data in elderly women [as noted below], 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).

Therefore, assessment of the potential additive effects of the combination of BZA/CE on the individual components' safety profiles cannot be made.

- There is limited data in women over the age of 65 years of age. The North American Society Statement on Continuing Use of Systemic Hormone Therapy after age 65 notes that:⁵⁰

vasomotor symptoms persist for an average of 7.4 years and for more than a decade in many women. Moderate to severe vasomotor symptoms have been documented in 42% of women aged 60 to 65 years. Thus, many women will continue to have vasomotor symptoms after age 65, and these symptoms can disrupt sleep and adversely affect health and quality of life.

At the opposite end of the scale, it is noted that BZA/CE was not studied in patients with premature menopause.

9. Clinical questions

1. The evaluator seeks clarification regarding several key aspects of the proposed indication:

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

Specifically:

- The approach for defining the targeted patient population.
- Subgroup analysis to justify the targeted patient population.
- The rationale for second line listing.
- Disparity in the indication across jurisdictions, in terms of the second line listing.

2. The EPAR report⁵¹ states that Study 3307 showed that:

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% (two-sided 95% CI 0.01%; 1.76%) and 0.30% (two-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.

However, this specific data cannot be found in the Study 3307 final study report which indicates that for BZA 20 mg/CE 0.45 mg (n = 335) with one diagnosis of hyperplasia, the hyperplasia rate is 0.30% with an upper limit of 2-sided 95% CI is 1.65.

Similarly, the EPAR⁵² indicates that in Study 303 the incidence for the purposes of assessing endometrial hyperplasia from a regulatory perspective contains a different denominator to that

⁴⁹ European Medicines Agency, European Public Assessment Report: Duavive (oestrogens conjugated / bazedoxifene).

⁵⁰ North American Menopause Society. The North American Menopause Society Statement on Continuing Use of Systemic Hormone Therapy After Age 65. *Menopause* 22: 693 (2015).

⁵¹ European Medicines Agency, European Public Assessment Report: Duavive (oestrogens conjugated / bazedoxifene).

contained within the study report: the EPAR considers 294 biopsies to be evaluable with an incidence of endometrial hyperplasia/malignancy at month 12 of 0.00% (95% CI 0.00%; 1.25%).

Please indicate where the data in the EPAR report is located within the dossier and how it was derived.

3. Due to GCP non-compliance, the results from study 303 were not taken into account for the assessment of BZA/CE efficacy. However the Sponsor indicated that they considered it to be a pivotal study.
 - Given that study 303 is GCP non-compliant and the EMA determined that the data should not be used to demonstrate the endometrial safety of Duavive, why is this listed as a pivotal trial in the Australian dossier?
 - Please summarise why this study was found to be GCP non-compliant
4. Based on the data presented, BZA appears to reduce the efficacy of CE. This is potentially important for safety because it is possible that a higher dose of estrogen is required in a BZA/CE combination compared to CE/progestogen to achieve a similar level of efficacy. Please comment on this concern.
5. For Study 305, please provide the point estimates of the placebo - subtracted treatment effect for the co-primary endpoints with 95% confidence intervals. These were not found within the dossier.
6. It is noted that a number of recognised safety concerns for the individual components of BZA/CE such as arterial thrombotic events, breast cancer, and ovarian cancer for CE and ocular events for BZA have not been listed as an “important identified risk”, only as potential risks. Why are these not listed as “identified” risks for the combination product?
7. Please provide the most recent SmPC for Duavive.

10. Second round evaluation

Evaluator’s question has been reproduced in italics.

10.1. Question 1

1. *The evaluator seeks clarification regarding several key aspects of the proposed indication:*

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

Specifically:

- *The approach for defining the targeted patient population.*
- *Subgroup analysis to justify the targeted patient population.*
- *The rationale for second line listing.*
- *Disparity in the indication across jurisdictions, in terms of the second line listing.*

10.1.1. Evaluator comments

In general, second line indication and subgroup analysis were largely based on scientific interactions between CHMP and the sponsor during the evaluation process and the outcomes of their regulatory approvals; rather than the actual study data. The rationale appears to be the relative safety of CD/BZA to the currently available treatment option (progestin containing

⁵² European Medicines Agency, European Public Assessment Report: Duavive (oestrogens conjugated / bazedoxifene).

HRT) and the unmet need of a subset of the targeted patient group due to tolerability issues with current therapeutic options.

The sponsor has maintained the indication that is approved in EU for the purpose of TGA evaluation. The alternative or “second line” indication appears to be based on the CHMP’s clinical evaluation that specifically noted the absence of clinical data to suggest an advantage over progestin containing HRT products. However, the improved safety and tolerability profile of CD/BZA over progestin containing products were considered. Subsequently, extrapolation of current data was performed and an alternative indication in line with the favourable safety profile was approved by CHMP.

In terms of the endometrial safety and long term risks of VTE, the post hoc subgroup analysis in a defined subpopulation characterised by tolerability issues with progestin containing HRT revealed comparable study endpoints for efficacy, safety and tolerability.

Overall, the evaluator has outstanding concerns regarding these aspects and has referred to the Delegate for further consideration.

The sponsor has stated that the efficacy and safety data were consistent for applications submitted for evaluations across all jurisdictions and also proposed the use of CE/BZA in a first line setting. The sponsor’s response indicates that the disparity in indication was to address the inherent differences in the therapeutic purpose of hormone therapy across these jurisdictions.

Duavive (proposed trade name for TGA approval) is approved in US (3 October 2013) as Duavee and in EU (16 December 2014) as Duavive. Although the approved dosage is the same across these countries at BZA/CE 20 mg/0.45 mg, the approved indications are different. The approved indication in EU was identical to that submitted for TGA approval. Meanwhile, the indication approved by FDA was:

Treatment of the following conditions in women with a uterus:

§ *Treatment of moderate to severe vasomotor symptoms associated with menopause*

§ *Prevention of postmenopausal osteoporosis*

Limitation of Use: Duavee should be used for the shortest duration consistent with treatment goals and risks for the individual woman.

A similar indication was approved by Health Canada.

In terms of other jurisdictions, the sponsor stated that the proposed indication across applications submitted to Medsafe and TGA were identical. However, during the process of evaluation, the evaluator noted disparity in this regards.

The evaluator has outstanding concerns regarding sponsor’s response and has referred to the Delegate for further consideration.

10.2. Question 2

2. *The EPAR report⁵³ states that Study 3307 showed that:*

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% (two-sided 95% CI 0.01%; 1.76%) and 0.30% (two-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.

⁵³ European Medicines Agency, European Public Assessment Report: Duavive (oestrogens conjugated / bazedoxifene).

However, this specific data cannot be found in the Study 3307 final study report which indicates that for BZA 20 mg/CE 0.45 mg (n = 335) with one diagnosis of hyperplasia, the hyperplasia rate is 0.30% with an upper limit of 2-sided 95% CI is 1.65.

Similarly, the EPAR⁵⁴ indicates that in Study 303 the incidence for the purposes of assessing endometrial hyperplasia from a regulatory perspective contains a different denominator to that contained within the study report: the EPAR considers 294 biopsies to be evaluable with an incidence of endometrial hyperplasia/malignancy at month 12 of 0.00% (95% CI 0.00%; 1.25%).

Please indicate where the data in the EPAR report is located within the dossier and how it was derived.

10.2.1. Evaluator comments

According to the Sponsor, additional analysis of studies 303 and 3307 were provided to the EMA following requests from the rapporteurs.

Results from 3307 referred to above were based on a modified Efficacy Evaluable population which excluded endometrial biopsies categorised by at least one of the two central pathologists as either “endometrial tissue insufficient for diagnosis” (with a TVU result of endometrial thickness ≥ 5 mm) or “no tissue/no endometrium”; this resulted in the exclusion of an additional 10, 18 and 12 biopsies from the BZA 20 mg/CE 0.45 mg, BZA 20 mg/CE 0.625mg and placebo groups respectively. This was in addition to an EMA requested modified analysis which excluded subjects with no tissue identified/no endometrium identified or tissue insufficient for diagnosis and endometrium ≥ 5 mm.

This data can be found in “Applicant’s Response to Day 180 Major Objection (MO)-34”.

A similar modified analysis was done for study 303 and the results were included in table 17 of the EPAR and submitted to the EMA in the Applicant’s Response to the Rapporteurs’ Day 180 Response JAR, Major Objection (MO)-11.

It is noted that using the modified analysis proposed by the EMA for study 303, the upper limit of the 95% Confidence Intervals at month 12 for the higher CE dose (BZA/CE 20mg/0.625mg arm) is 2.04 and therefore exceeds 2%, which is outside the EMA guidelines for endometrial safety. This result is in contrast to study 3307. However, the upper limit of the 95% confidence interval for BZA/CE 20mg/0.45mg (ie. the dose strength for which approval is being sought in Australia) remains within the 2% guideline at 1.25%.

At month 24, the upper limit of the 95% confidence interval for BZA 20 mg/CE 0.45 mg, BZA 20 mg/CE 0.625mg and placebo all exceed 2%; although it is acknowledged that the 2% boundary as stipulated by the EMA guidelines is at 12 months.

The following table is from the sponsor’s response to TGA.

⁵⁴ European Medicines Agency, European Public Assessment Report: Duavive (oestrogens conjugated / bazedoxifene).

Table 35: Incidences of endometrial hyperplasia/malignancy at Month 12 and 24 in Study 3115A1-303-US/EU/BR – Modified EE population.

Treatment Time Point	Number of Subjects with Evaluable Biopsies	Number of subjects with endometrial hyperplasia/malignancy	Incidence of endometrial hyperplasia/malignancy (%)	2-sided 95% CI
BZA 20 mg/CE 0.45 mg				
Month 12	294	0	0.00	(0.00, 1.25)
Month 24	229	2 ^b	0.87	(0.11, 3.12)
BZA 20 mg/CE 0.625 mg				
Month 12	271	1 ^c	0.37	(0.01, 2.04)
Month 24	195	2 ^c	1.03	(0.12, 3.66)
Placebo				
Month 12	261	0	0.00	(0.00, 1.40)
Month 24	176	0	0.00	(0.00, 2.07)

^a Modified Efficacy Evaluable (mEE) population: Excluded subjects with at least one biopsy read of no tissue identified/no endometrium identified or tissue insufficient for diagnosis and endometrium ≥ 5 mm or tissue insufficient for diagnosis and no TVU.

^b One subject with endometrial malignancy, one subject with endometrial hyperplasia

^c Two subjects with endometrial hyperplasia (one subject at Month 6, which carried over to Months 12 and 24, and one subject at Month 24)

Summary statement: Issue resolved

10.3. Question 3

3. *Due to GCP non-compliance, the results from study 303 were not taken into account for the assessment of BZA/CE efficacy. However the Sponsor indicated that they considered it to be a pivotal study.*
 - *Given that study 303 is GCP non-compliant and the EMA determined that the data should not be used to demonstrate the endometrial safety of Duavive, why is this listed as a pivotal trial in the Australian dossier?*
 - *Please summarise why this study was found to be GCP non-compliant*

10.3.1. Evaluator comments

The Sponsor has stated that “Whilst the Sponsor acknowledges that the EMA considered Study 303 to be GCP non-compliant, the Sponsor believes that this study should be considered pivotal” for the following reasons:

- Training was provided to relevant staff and procedures for deviations were in place
- A third party auditor engaged by the Sponsor audited 18% of sites and found 42 unreported AEs (1.2%) which were included in the clinical study reports. Other audit findings were considered not significant.
- With particular reference to site 447:
 - the investigator carried out weekly meetings to discuss study related issues
 - missed AEs and endometrial biopsy results found during a Sponsor audit were included in the final Study 303 clinical study report and did not include any SAEs or AEs of special interest
 - FDA also conducted an audit of site 447 however the findings were not considered to impact the validity of the data and study 303 was considered pivotal by the FDA.
- Additional measures such as independent assessment of biopsies and review of subjects where there was a risk of missed endometrial hypertrophy or malignancy was carried out

(eg. no biopsies performed, prolonged bleeding events, excluded subjects with potentially significant transvaginal ultrasound results).

Reasons why the study was found to be GCP non-compliant was not stated clearly in the Sponsor's response. Based on information in the supporting documents referred to by the Sponsor, it appears that the key concerns regarding GCP are related to the following:

- Critical GCP violations resulted in termination of site 326
- Critical and major findings in the GCP inspection of sites 447 and 450, including missing source data and that source data was in possession of the Sponsor
- Missing biopsy results in the clinical database at a number of sites

Summary statement: The Sponsor's explanation has been noted. At this point in time, pending further advice, this is not an issue that would preclude registration.

10.4. Question 4

4. *Based on the data presented, BZA appears to reduce the efficacy of CE. This is potentially important for safety because it is possible that a higher dose of estrogen is required in a BZA/CE combination compared to CE/progestogen to achieve a similar level of efficacy. Please comment on this concern.*

10.4.1. Evaluator comments

In response to this question, the Sponsor has referred to a number of other documents and outcomes including a meta analysis by MacLennon et al, the Sponsor's response to EMA in response to their major objection and literature review by Komm et al. The Sponsor also refers to the outcomes of Study 305.

Key points include the following:

- In terms of efficacy, there is similar reduction of hot flushes on the active arm compared to placebo in both study 305 and the MacLennon et al metanalysis of CE and CE + progesterone: 74.4% for BZA/CE 20/0.45 vs 51.2% placebo and 77% for E+P combinations vs 50.8% placebo respectively. The Sponsor then states that "thus, the notion that BZA appears to reduce the efficacy of CE is hypothetical and deduced based on similar molecular mechanism of action."
- In terms of safety, using data from the Women's Health initiative (WHI) study as external comparators, the incidence of events such as Venous thromboembolism, coronary heart disease, stroke, breast cancer are lower than the "expected" incidence based on extrapolated data from the WHI study (women received either MPA/CE or placebo)

The Sponsor concludes that the efficacy and safety profile for CE/BZA is similar to that of other hormone therapy products prescribed in Europe and that additional safety data is to be collected in two post marketing studies in the US and in Europe.

The response to the TGA's question is noted, however the proposition that BZA decreases efficacy of oestrogen does not appear to be specifically discussed in the Sponsor's response, but rather the discussion focuses on the premise that the safety and efficacy profiles are not dissimilar to what would be expected from other MHT. It is noted that the review referred to by the Sponsor (Komm et al.⁵⁵) indicates that "BZA may antagonize CE-induced cell proliferation without inhibiting other CE activity such as effects on VMS" however this is based on preclinical studies.

Summary statement: The available data are subject to uncertainty; however, at this point in time, pending further advice, this is not an issue that would preclude registration.

⁵⁵ Komm BS, Mirkin S, Jenkins SN. Development of conjugated estrogens/bazedoxifene, the first tissue selective estrogen complex (TSEC) for management of menopausal hot flashes and postmenopausal bone loss. *Steroids*. 2014; 90:71-81.

10.5. Question 5

5. *For Study 305, please provide the point estimates of the placebo - subtracted treatment effect for the co-primary endpoints with 95% confidence intervals. These were not found within the dossier.*

10.5.1. Evaluator comments

Summary statement: Response noted.

10.6. Question 6

6. *It is noted that a number of recognised safety concerns for the individual components of BZA/CE such as arterial thrombotic events, breast cancer, and ovarian cancer for CE and ocular events for BZA have not been listed as an "important identified risk", only as potential risks. Why are these not listed as "identified" risks for the combination product?*

10.6.1. Evaluator comments

The Sponsor has indicated that the above safety concerns have been included as potential safety risks in order to be consistent with the risks identified for the individual components of the fixed dose combination or their respective class effects.

A review of the incidence of breast cancer, ovarian cancer and ocular events from the phase III trials was provided by the Sponsor which showed slightly higher incidence of breast cancer in the CE 0.45mg/BZA 20mg treatment group compared to placebo (0.3% and 0.2% respectively) and a relative risk of 1.11 (95% confidence interval 0.33-3.78). With respect to Ocular events, events were reported by 3.3% of subjects in the CE 0.45mg/BZA 20mg treatment arm compared 4% in the placebo group. No events of ovarian cancer were reported in any of the CE/BZA phase 3 studies. The sponsor also notes that the patients with a history of arterial thromboembolic events were excluded from the phase 3 CE/BZA trials.

The Sponsor has provided two Periodic Safety Update Reports (PSURs) which were not included in the previous dossier.

10.6.1.1. PSUR #3 03-OCT-2015 - 02-APR-2016

In the reporting interval, there were no completed or ongoing CE/BZA trials and the Sponsor has stated that "no new safety information was identified contributing significantly to the risk profile of CE/BZA".

Important identified risks remain the same as previously stated in the round one report as do important potential risks and missing information.

The following information is noted:

- There have been approximately 21,761 patient-years of exposure to CE/BZA from marketing experience since February 2014 (when the product became commercially available in the US).
- During the reporting period, the European SmPC and patient information leaflet (PIL) was updated to include mandated information regarding ovarian cancer.
- The first interim report for the US Post Authorisation Safety study (PASS) was submitted to the EMA on 31 March 2016.
- The Sponsor was requested within the PRAC PSUR assessment report dated 01-April-2016 to comment on the potential impact of higher Body Mass Index (BMI) on CE/BZA efficacy and whether this should be included as an important risk. Following analysis of clinical trial and post marketing data, the Sponsor has concluded that a potential impact of higher BMI on CE/BZA efficacy had not been identified but will continue to monitor with routine pharmacovigilance.

10.6.1.2. PSUR #2 03-APR-2015 - 02-OCT-2015

As stated in the report, no new safety information contributing significantly to the risk profile of CE/BZA was identified. Important identified risks remain the same as previously stated in the round one report as do important potential risks and missing information. No changes to current risk minimisation activities were made.

One safety signal was identified and closed within the reporting period: increased risk of ovarian cancer. As noted for PSUR #3, the European SmPC and PIL have subsequently been updated.

Summary statement: The Sponsor's response has been carefully studied and considered. This is a matter for the delegate to consider with the RMP team when finalising the "Summary of Safety Concerns" for Australia. At this point in time, pending further advice, this is not an issue that would preclude registration.

10.7. Question 7

7. *Please provide the most recent SmPC for Duavive.*

10.7.1. Evaluator comments

It is noted that an updated SmPC has been provided, dated 04/2016.

10.8. Follow-up questions

Follow up questions were sent to the Sponsor; a response was received.

10.8.1. Question 8

8. *The Sponsor has stated that the indication approved in Europe "served as a basis for that submitted to the TGA" in the response to Question 1. The wording is actually almost identical, except for the word "progestogen" in the proposed Australian indication, whereas it is "progestin" in the European indication. Please provide an explanation for this difference.*

10.8.2. Evaluator comments

The Sponsor has stated the following "The British Pharmacopeia lists the action and use of progesterone and progestins such as medroxyprogesterone acetate, levonorgestrel and norethisterone as progestogens. We understand the term progestin refers to synthetic progestational agents. The word "progestogen" in the proposed Australian indication is intended to be synonymous to the word "progestin" in the European indication."

10.8.3. Question 9

9. *Per PSUR #3 03-OCT-2015 - 02-APR-2016, Duavive has been approved in 36 countries but only marketed in 2 countries. Please provide an explanation for this difference.*

10.8.4. Evaluator comments

The Sponsor has stated that "Pfizer's plans for commencement of supply of Duavive are constantly under review. Since publication of PSUR #3, we have commenced marketing of Duavive in the United Kingdom, Italy, Spain and the Netherlands. We are also planning to commence supply of Duavive in New Zealand in the near future."

10.8.5. Question 10

10. *Per PSUR #3 03-OCT-2015 - 02-APR-2016, the first interim report for the US Post Authorisation Safety study (PASS) was submitted to the EMA on 31 March 2016. Please provide a copy of the report and the associated EMA assessment if available.*

10.8.6. Evaluator comments

Copy of both the US PASS first interim analysis report and the associated EMA assessment was received.

The objectives of the US PASS are stated within the report as follows:

- Primary objective: To estimate the incidence and compare the risks of endometrial hyperplasia and endometrial cancer among postmenopausal women initiating either CE/BZA or Estrogen / Progesterin (E + P) Hormone Replacement Therapy (HRT).
- Secondary objective: To estimate the incidence and compare the risks of incurring selected secondary safety endpoints (venous thromboembolism [VTE], myocardial infarction, stroke, breast cancer, ovarian cancer, thyroid cancer, renal cancer and adenoma, gastrointestinal cancer, all cancers, and all-cause mortality) among postmenopausal women initiating CE/BZA or E+P HRT.

At the time of reporting, few events of interest had occurred. Limited follow up of the patients enrolled (median treatment duration across the subsets ranged from 2 – 8 months) and the relatively small numbers of patients likely contributed to this. The following table shows the incidence rates for the primary and secondary outcomes as per 10 000 person years.

Table 36: Incidence of study outcomes and hazard ratios.

	CE/BZA				E+P HRT				Hazard Ratio	95% CI
	Cases	Person-years	Incidence Rate	95% CI	Cases	Person-years	Incidence Rate	95% CI		
New users										
Primary outcomes										
Endometrial cancer	1	169	59.0	1.5 328.9	0	632	0.0	0.0 58.4	NE	
Corrected for PPV (88%)			52.1	0.4 262.4			0.0	0.0 58.4	NE	
Endometrial hyperplasia	0	169	0.0	0.0 217.7	0	631	0.0	0.0 58.5	NE	
Corrected for PPV (80%)			0.0	0.0 217.7			0.0	0.0 58.5	NE	
Secondary outcomes										
Venous thromboembolism	0	169	0.0	0.0 218.0	0	630	0.0	0.0 58.6	NE	
Coronary heart disease	0	168	0.0	0.0 219.4	0	631	0.0	0.0 58.5	NE	
Stroke (including transient ischemic attack)	0	169	0.0	0.0 218.9	0	631	0.0	0.0 58.5	NE	
Breast cancer	0	169	0.0	0.0 217.7	2	632	31.7	3.8 114.3	0.00	0.00 ∞
Ovarian cancer	0	169	0.0	0.0 217.7	1	632	15.8	0.4 88.2	0.00	0.00 ∞
Thyroid cancer	0	169	0.0	0.0 217.7	1	632	15.8	0.4 88.2	0.00	0.00 ∞
Renal cancer	0	169	0.0	0.0 217.7	0	632	0.0	0.0 58.4	NE	
Renal adenoma	0	169	0.0	0.0 217.7	0	630	0.0	0.0 58.5	NE	
Gastrointestinal cancer	0	169	0.0	0.0 217.7	1	632	15.8	0.4 88.2	0.00	0.00 ∞
Cancer (all types)	2	169	118.1	14.3 426.4	11	632	174.1	86.9 311.4	0.68	0.15 3.10
Non-new users, prior E+P HRT										
Primary outcomes										
Endometrial cancer	0	89	0.0	0.0 412.6	0	2,187	0.0	0.0 16.9	NE	
Corrected for PPV			0.0	0.0 412.6			0.0	0.0 16.9	NE	
Endometrial hyperplasia	0	89	0.0	0.0 412.6	0	2,185	0.0	0.0 16.9	NE	
Corrected for PPV			0.0	0.0 412.6			0.0	0.0 16.9	NE	
Secondary outcomes										
Venous thromboembolism	0	88	0.0	0.0 417.3	1	2,156	4.6	0.1 25.8	0.00	0.00 ∞
Coronary heart disease	0	89	0.0	0.0 415.9	1	2,175	4.6	0.1 25.6	0.00	0.00 ∞
Stroke (including transient ischemic attack)	0	88	0.0	0.0 417.8	0	2,158	0.0	0.0 17.1	NE	0.00 ∞
Breast cancer	0	89	0.0	0.0 412.6	18	2,187	82.3	48.8 130.1	0.00	0.00 ∞
Ovarian cancer	0	89	0.0	0.0 412.6	2	2,187	9.2	1.1 33.0	0.00	0.00 ∞
Thyroid cancer	0	89	0.0	0.0 412.6	1	2,187	4.6	0.1 25.5	0.00	0.00 ∞
Renal cancer	0	89	0.0	0.0 412.6	0	2,187	0.0	0.0 16.9	NE	
Renal adenoma	0	88	0.0	0.0 421.2	0	2,181	0.0	0.0 16.9	NE	
Gastrointestinal cancer	0	89	0.0	0.0 412.6	6	2,187	27.4	10.1 59.7	0.00	0.00 ∞
Cancer (all types)	0	89	0.0	0.0 412.6	49	2,187	224.1	165.8 296.2	0.00	0.00 ∞
Non-new users, prior unopposed estrogen										
Secondary outcomes										
Venous thromboembolism	0	19	0.0	0.0 1,943.1	0	24	0.0	0.0 1,548.9		
Coronary heart disease	0	19	0.0	0.0 1,943.1	0	24	0.0	0.0 1,548.9		
Stroke (including transient ischemic attack)	0	19	0.0	0.0 1,943.1	0	24	0.0	0.0 1,548.9		
Breast cancer	0	19	0.0	0.0 1,943.1	0	24	0.0	0.0 1,548.9		
Ovarian cancer	0	19	0.0	0.0 1,943.1	0	24	0.0	0.0 1,548.9		
Thyroid cancer	0	19	0.0	0.0 1,943.1	0	24	0.0	0.0 1,548.9		
Renal cancer	0	19	0.0	0.0 1,943.1	0	24	0.0	0.0 1,548.9		
Renal adenoma	0	19	0.0	0.0 1,943.1	0	23	0.0	0.0 1,581.8		
Gastrointestinal cancer	0	19	0.0	0.0 1,943.1	0	24	0.0	0.0 1,548.9		
Cancer (all types)	0	19	0.0	0.0 1,943.1	2	24	839.8	101.7 3,033.5		

Abbreviations: CE/BZA: conjugated estrogens/bazedoxifene; CI: confidence interval; E+P HRT: estrogen + progesterin, combination hormone replacement therapy; NE: not estimable; PPV: positive predictive value

Note: All IR estimates are presented per 10,000 person-years.

In conclusion, the EMA assessment report indicated that:

Data obtained to date concerning the primary and secondary endpoints are limited. Therefore interpretation of data is not yet possible due to small study size and short follow

up. As the number of patients and the follow-up time increase over time, it is expected to get more data and interpretable results. Additionally, there is one issue to be clarified concerning the rationale for the inclusion of the use of statins in the proposed regression model which is raised.

(Per the Endometrial Cancer and Endometrial Hyperplasia algorithm memo provided by the Sponsor, the patient feature associated with confirmed hyperplasia of “statins after diagnosis” was assigned a co-efficient of 0.42 for proposed the lasso logistic regression model.)

11. Amendments

Clarification footnotes dated 25 October 2016:

- This clarification was added to clarify which arm the non-inferiority test was against, as it was not described in the original report.

Clarification footnotes dated 24 November 2016:

- This clarification was added on 24 November 2016 to amend the information in the clinical evaluation report regarding study 303 and the cases of endometrial hyperplasia/malignancy diagnosed on the BZA 20 mg/CE 0.45 mg and BZA 20 mg/CE 0.625 mg arms in the second treatment year. The original clinical evaluation report states that three cases of endometrial hyperplasia/ malignancy were diagnosed in the second treatment year - one case on the BZA 20 mg/CE 0.45 mg dose and the other two on the higher CE dose. However, as indicated in the Sponsor’s final study report for study 303, two cases occurred on the BZA 20 mg/CE 0.45 mg dose, which included one case of malignancy, and one case on the higher CE dose. This clarification aligns the information in the clinical evaluation report with the data in the proposed product information regarding BZA 20mg/CE 0.45mg. It is also noted the reference to a BZA dose of “0.20 mg” is a typographical error and should be read as “20 mg”.

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