COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Bijuva 1 mg/100 mg soft capsules (oestradiol hemihydrate and progesterone)

NL/H/4994/001/DC

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This module reflects the scientific discussion for the approval of Bijuva. The procedure was finalised at 25 February 2021. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

AE	Adverse event
ASMF	Active Substance Master File
BA	Bioavailability
BE	Bioequivalence
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
E2	17β-oestradiol
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
EMA	European Medicines Agency
ER	Oestrogen receptor
ERA	Environmental Risk Assessment
ES	Endometrial safety
FDA	Food and Drug Administration
HRT	Hormone replacement therapy
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MITT-VMS	Modified intent-to-treat vasomotor symptoms
MSDS	Material safety data sheet
NOEL	No observable effect level
OECD	Organisation for Economic Co-operation and Development
P	Progesterone
PDCO	Paediatric Committee
Ph.Eur.	European Pharmacopoeia
PIP	Paediatric Investigation Plan
PL	Package Leaflet
PR	Progesterone receptor
QC	Quality control
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
SSBG	Sex steroid-binding globulin
TSE	Transmissible Spongiform Encephalopathy
USP	United States Pharmacopoeia
UV	Ultraviolet light
VMS	Vasomotor symptom

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Bijuva 1 mg/100 mg soft capsules, from Theramex Ireland Limited.

This concerns an application for Bijuva, which is an oral, fixed-dose combination consisting of a soft capsule containing solubilized estradiol (1 mg as hemihydrate) and micronized progesterone (100 mg).

The product is a continuous combined hormone replacement therapy (HRT) and is indicated for oestrogen deficiency symptoms in postmenopausal women with intact uterus and with at least 12 months since last menses. The experience in treating women older than 65 years is limited.

A comprehensive description of the indications and posology is given in the SmPC.

The application for Bijuva is submitted in accordance with Article 8(3) of Directive 2001/83/EC "Mixed application". The non-clinical part of the dossier in the application (Module 4) consists of bibliographical references only. The clinical part of the dossier in the application (Module 5) consists of a combination of reports of six clinical studies carried out by the MAH and of bibliographical references.

PIP-waiver
According to Article 7 of the Paediatric Regulation, an Article 8(3) application shall be regarded as valid only if it includes either the results of all studies performed and details of all information collected in compliance with an agreed paediatric investigation plan (PIP) or a decision of the European Medicines Agency (EMA) granting a product-specific or a class waiver or a decision of the EMA granting a deferral as also stated in the CMDh Q&A on Paediatric Regulation. The MAH applied for a Class Waiver. The dossier includes a statement from the EMA that the Paediatric Committee (PDCO) is of the view that oestradiol/progesterone (Bijuva) proposed for the indication Hormone replacement therapy (HRT) for oestrogen deficiency symptoms in postmenopausal women falls under the scope of Agency Decision CW/0001/2015, because it is considered to belong to 'All classes of medicinal products for treatment of climacteric symptoms associated with decreased oestrogen levels, as occurring at menopause'. This was considered acceptable and fulfilled the requirements of Articles 7 and 8 of Regulation (EC) No 1901/2006.

Although this is a fixed dose combination of two approved mono-components, the Guideline on clinical development of fixed combination medicinal products (EMA/CHMP/281825/2015) is considered not applicable. This product cannot be used as a substitution therapy, but should be seen as initial therapy in the proposed indication, as the population to be treated and the dose regimen differ from the approved mono components.

The concerned member states (CMS) involved in this procedure were Belgium, Germany, Spain, France, Italy, Luxemburg, Poland and the United Kingdom (Northern Ireland).

The marketing authorisation has been granted pursuant to Article 8(3) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Bijuva is an oval, opaque soft capsule, light pink on one side and dark pink on the other side imprinted '1C1' with white ink.

Bijuva contains as active substances 1 mg of oestradiol (as oestradiol hemihydrate) and 100 mg progesterone. This product contains 0.042 mg allura red (E129), which is an excipient with a known effect.

The capsules are packed in PVC/PE/PCTFE – aluminium blisters.

The excipients are:
Capsule contents – medium chain mono/diglycerides and lauroyl macrogolglycerides 32.

Capsule shell – gelatine (200 bloom), hydrolysed gelatine, glycerine (E442), allura red (E129) and titanium dioxide (E171).

Printing ink – propylene glycol (E1520), titanium dioxide (E171), polyvinyl acetate phthalate, polyethylene glycol (E1521) and ammonium hydroxide (E572).

II.2 Drug Substance

Oestradiol hemihydrate
The first active substance is oestradiol hemihydrate, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a white or almost white, crystalline powder or colourless crystals and is practically insoluble in water. The drug substance is micronized. Particle size distribution and polymorphic form are not critical as the drug substance is dissolved during the manufacturing process of the drug product.

The CEP procedure is used for this active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is

meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The drug substance specification of the drug product manufacturer is largely in accordance with the Ph.Eur. monograph on oestradiol hemihydrate and the CEP and contains additional requirements for identification by Ultraviolet light (UV), microbial limits, residual solvents and particle size. The drug product manufacturer uses a method of the USP for the assay instead of the UV method of the Ph.Eur. This has been justified with the better accuracy of the HPLC method. The drug product manufacturer uses in-house methods for particle size distribution. These methods are based on those of the drug substance manufacturer. Batch analytical data demonstrating compliance with the drug substance specification were provided for four drug substance batches used to manufacture the registration batches at the proposed commercial manufacturing site of the drug product.

Stability of drug substance
The active substance is stable five years if stored in double polyethylene bags placed in fibre drums. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

Progesterone
Progesterone is a known active substance described in the European Pharmacopoeia. The active substance is a white or almost white, crystalline powder or colourless crystals and is practically insoluble in water. The drug substance is micronized. The drug substance exhibits polymorphism. It is present in the thermodynamically more stable form A.

The CEP procedure is used for this active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The drug substance specification of the drug product manufacturer is largely in accordance with the Ph.Eur. monograph on Progesterone and the CEP and contains additional

requirements for residual solvents and particle size. In house methods are used for particle size and palladium. These methods were adequately described and validated.
Batch analytical data demonstrating compliance with the drug substance specification were provided for five drug substance batches used to manufacture the registration batches at the proposed commercial manufacturing site of the drug product.

Stability of drug substance
A re-test period of five years if stored in double polyethylene bags, placed in a polyethylene drum. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

II.3 Medicinal Product

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. Development included Quality by Design elements such as a Quality Target Product Profile and Critical Quality Attributes, but resulted in a conventional description of the manufacturing process without design spaces.
The objective of the formulation development was to develop a novel orally administered immediate release capsule for a fixed dose combination of oestradiol and progesterone identical to the hormones naturally produced in the body in the lowest effective doses. Oestradiol is dissolved in the fill mass while progesterone is suspended.
Overall, formulation development has been adequately explained. The proposed commercial formulation corresponds to the formulation of the batches used in the phase 3 clinical trials.
The dissolution methods for both drug substances used during development and for the batch analysis and stability studies of the registration batches were recently replaced by a rupture test for oestradiol and a new, more discriminatory dissolution method for progesterone as a consequence of a post-approval commitment provided to the Food and Drug Administration (FDA). As a quantitative dissolution test is preferred above the unspecific rupture test, the MAH has therefore reverted back to the previous dissolution test for oestradiol in the current application. For progesterone, the new dissolution method is maintained. The acceptance criteria for both dissolution tests could not be based on pivotal clinical batches as these had expired. It will therefore not be possible to bridge the clinical batches to the commercial product by comparative dissolution testing. This can be accepted as the formulation is the same and the modifications made to the manufacturing process at the commercial site can be considered as minor. The proposed acceptance criteria for both dissolution methods are in accordance with the EMA reflection paper on setting dissolution specifications. The discriminatory power of the dissolution method for progesterone has been shown for various deviations. The dissolution method for oestradiol is discriminatory for changes in the gelatine quality (cross-linking). In general, the manufacturing process development has been adequately described. The clinical batches were manufactured at a different site than the intended commercial manufacturing site. The manufacturing process needed to be optimized after the first campaign at the intended commercial manufacturing site due to content uniformity issues for both active substances and low initial oestradiol assay. The corrective actions (potency adjustments for the amounts of both active substances and improvements

in the transfer of both active substances to the fill mass) will also be used for commercial manufacture.

Manufacturing process

The manufacturing process has been validated according to relevant European/ICH guidelines and includes fill mass manufacturing, gel mass manufacturing, encapsulation, drying, finishing and bulk packaging, and blister and secondary packaging steps. It is regarded as a non-standard process due to the low oestradiol content. Process validation data on the product have been presented for three full-scaled batches in accordance with the relevant European guidelines. Oestradiol assay and content uniformity of both active substances were satisfactory throughout the process.

Control of excipients

The excipients comply with the Ph.Eur., United States Pharmacopoeia (USP) and in-house methods. These specifications are acceptable.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, identification of oestradiol, assay of oestradiol, oestradiol related compounds, rupture test for oestradiol, oestradiol uniformity of dosage units, identification of progesterone, assay of progesterone, progesterone related compounds, progesterone dissolution, water content of fill, and microbial limits. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.

Except for the assay of both drug substances, identical release and shelf life limits are proposed. The proposed drug product specification is acceptable. Analytical methods were adequately described and validated. The methods for related substances of both drug substances were shown to be stability indicating. The risk assessment for elemental impurities was carried out in accordance with ICH guideline Q3D and did not lead to controls for specific elemental impurities in the drug product.. A risk evaluation for nitrosamines was carried out which covered all currently known sources listed in the EMA Q&A. Furthermore, during the board meeting of January 2021 the possible presence of nitrosamines in the dye Allura red was discussed. The risk for unacceptable nitrosamine levels in the drug product contributed by Allura Red was considered very low based on chemical considerations and the very low amount of Allura Red per capsule. No risk has been identified by the MAH.

Batch analytical data from the clinical batches, the registration batches, and three recent production batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for three registration batches stored at 25°C/60% RH (30 months) and 40°C/75% RH (six months) in accordance with applicable European guidelines demonstrating the stability of the product for 24 months. The batches

were stored in the same container closure system which will be used for commercial batches (PVC/PE/PCTFE-Al blisters). No out of specification results were observed at both storage conditions. A decreasing trend is seen for the assay of oestradiol and an increasing trend is seen for oestradiol USP related compound B.

Photostability studies were performed in accordance with ICH Q1B recommendations and showed that the product fades when exposed to light.".

On basis of the data submitted, a shelf life was granted of 24 months. It is supported by results obtained with the intended routine dissolution methods The labelled storage conditions are as follows: "Keep the blister in the outer carton in order to protect from light", with no special temperature storage conditions.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Scientific data and/or certificates of suitability issued by the EDQM for gelatine have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Bijuva has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

III. NON-CLINICAL ASPECTS

III.1 Pharmacology

The pharmacology of the active substances, oestradiol and progesterone, are well-established following decades of use in numerous approved products.
As a class, oestrogens are among the most widely prescribed drugs. oestradiol is the primary female sex hormone and the most potent human oestrogen (Kuhl, 2005). The biological effect of oestrogens including oestradiol is based on interaction with oestrogen receptors (ER), ERα and ERβ, which are ligand-activated transcription factors that alter the synthesis of messenger RNA from target genes (Goodman, 2001). Oestradiol is highly efficacious and selective and is the most potent human oestrogen. Additional signalling mechanisms for oestrogens include cell membrane receptors coupled with G-proteins which can activate intracellular signal cascades (Kuhl, 2005)
Many effects of progesterone are mediated by the progesterone receptor (PR), a member of the nuclear receptor superfamily (Schumacher, 1999). Two isoforms, PRA and PRB, have been cloned (Gruber, 2003). It has been proposed that PRB is the major mediator of gene

transcription activation, whereas PRA provides an inhibitory effect on transcription at PRB as well as the oestrogen and glucocorticoid receptor (Gruber, 2003). PR is known to be expressed in uterus, mammary gland, ovary, fallopian tube (Christow, 2002) and placenta (Shanker, 1997).
The secondary pharmacological effects of oestradiol and other oestrogens are dose-related and are, at least in part, traditionally associated with unopposed oestrogen treatment at large doses without a progestin component. The MAH has not conducted any non-clinical secondary pharmacodynamic studies with Bijuva; however, because Bijuva is an orally administered, combination oestradiol/progesterone product, those secondary pharmacologic effects are not anticipated.

III.2 Pharmacokinetics

The pharmacokinetics of oral oestradiol and progesterone are well-established (Goodman, 2001). Due to the lipophilic nature of oestradiol and progesterone, absorption is generally good across dosing routes with the appropriate formulation.
Oestradiol is extensively bound to plasma proteins in blood, including sex steroid-binding globulin (SSBG) and serum albumin (Goodman, 2001). Due to its size and lipophilic nature, oestradiol readily distributes past the vascular space and into tissues. In general, oestradiol undergoes rapid biotransformation with a half-life of minutes. Oestradiol is metabolized by 17β-hydroxysteroid dehydrogenase to estrone, which is in turn converted by 16α-hydroxylation and 17-keto reduction to estriol, the major urinary metabolite along with a variety of sulphate and glucuronide conjugates. Oestrogens also undergo enterohepatic recirculation by the formation of sulphate and glucuronide conjugates in the liver followed by biliary secretion into the intestine, hydrolysis and then reabsorption by the gut.
After oral administration of progesterone as a micronized soft-gelatine capsule formulation, maximum serum concentration is attained within three hours. Serum progesterone concentrations appear linear and dose proportional following multiple-dose oral administration of progesterone 100 mg over the dose range 100 to 300 mg/day in postmenopausal women (Simon, 1993). Progesterone is approximately 96% to 99% bound to serum proteins, primarily to serum albumin (50% to 54%) and transcortin (43% to 48%). Progesterone is metabolized primarily by the liver, largely to pregnanediols and pregnanolones. Pregnanediols and pregnanolones are conjugated in the liver to glucuronide and sulphate metabolites. Progesterone metabolites which are excreted in the bile may be deconjugated and may be further metabolized in the gut via reduction, dehydroxylation, and epimerization (Goodman, 2001). Progesterone metabolites are eliminated mainly by the kidneys. Progesterone metabolites, which are excreted in the bile, may undergo enterohepatic recycling or may be excreted in the faeces.
In summary, the pharmacokinetics of oestradiol and progesterone in humans is well-established following decades of use in a variety of products via numerous routes of administration.

III.3 Toxicology

The safety profile of oestradiol and progesterone are well-known following decades of use in approved products. The MAH has performed a review on the toxicity of oestradiol and progesterone based on the scientific published literature, as support for the nonclinical section.

Toxicity of oestradiol

In a 90-day repeat study by Biegel et al. (Biegel, 1998a; Biegel, 1998b), male and female rats were administered oestradiol in the diet for an average dose of 0, 0.003, 0.16, 0.61, or 3.7 mg/kg/day. Effects of oestradiol in this study consisted of dose-dependent decreases in body weight and food consumption, minimal to mild non-regenerative anaemia and lymphopenia, and changes in the weights of several organs, including liver, spleen, epididymides, accessory sex organs, and testes in males and spleen, uterus, and ovaries in females. Histopathology revealed diffuse hyperplasia of the pituitary gland, mammary gland hyperplasia in females, cystic ovarian follicles, hypertrophy of the endometrium and endometrial glands in the uterus, degeneration of the seminiferous epithelium, and atrophy of the testes and accessory sex glands.

In genotoxicity studies published by Dhillon and Dhillon (Dhillon, 1995) oestradiol was unable to induce any significant dose-related increase in the mean number of revertants/plate both with and without S9 mix. The actual number of revertants was not provided. A significant increase in the aberration frequencies was observed in a dose- and time-dependent manner without metabolic activation. Six hours of treatment with oestradiol in the presence of S9 mix induced a significant increase in aberration frequencies at the highest doses (10 and 100 µg/mL) as compared to the results obtained without metabolic activation. In human lymphocyte cultures, both chromatid and chromosomal type aberrations were observed. However, the frequency of chromatid-type aberrations was more than chromosomal type. The highest doses of the oestradiol (1.0 and 10 mg/kg) caused a significant increase in the number of micronucleated polychromatic erythrocytes and sister chromatid exchanges as compared to the negative controls.

The carcinogenicity data for oestradiol has been extensively reviewed by working groups convened by the International Agency for Research of Cancer (IARC), considering oestrogen carcinogenic in experimental animals with sufficient evidence, and also carcinogenic to humans (group 1) (IARC 1987; IARC 1979). The MAH has highlighted two mouse (Highman, 1980; Highman, 1978; Welsch , 1977) and one rat study (MacKenzie, 1955) in this application. These studies demonstrate that oestradiol administration in mice can increased the incidences of mammary, pituitary, uterine, cervical, vaginal, testicular, lymphoid and bone tumours. In rats, there was an increased incidence of mammary and pituitary tumours.

A full battery of reproductive toxicity studies with oestradiol in rats have been published (Leighton, 2000). The MAH has highlighted in this application a rat study in Crl:CD rats that encompasses fertility, early embryonic development, and pre- and postnatal development (Biegel, 1998a; Biegel, 1998b). In addition, the MAH has included a rabbit embryofoetal development study (Schofield, 1962).

Oestradiol administered in the feed to female Crl:CD BR rats at doses equal to 0, 0.003, 0.17, 0.69, or 4.1 mg/kg/day and to males at doses equal to 0, 0.003, 0.14, 0.53, or 3.2 mg/kg/day For the three groups with pregnancies, there was no difference in gestation length, however, gestation body weight gain, food consumption, and mean number of implants were affected.

Mean number of live births was significantly decreased in the 0.17 mg/kg/day group compared to control. Parental administration of oestradiol did not affect the anogenital distance in male or female pups. Onset of sexual maturity, as measured by prepubertal separation in males, was significantly delayed in the 0.17 µg/kg/day group. Onset of sexual maturity, as measured by vaginal opening in females, was decreased in both the 0.003 and 0.17 µg/kg/day dosed groups (24/56 female pup were vaginally patent on the day of weaning. The F1 generation was not mated.
In white rabbits, intramuscular oestradiol administration at 15 or 30 µg/animal for 3-6 consecutive days at different times during gestation resulted in 67 and 78% aborted or totally resorbed litters and 4% and 17% of litters with dead foetuses, respectively.

Toxicity of Progesterone
According to the SmPC of Utrogestan oral capsules (micronised progesterone), marketed in Europe since 1981 for HRT, nonclinical data has revealed no special hazard for humans other than those usually described for progesterone, based on conventional studies of safety pharmacology, repeat-dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development (Utrogestan NL SmPC; Utrogestan UK SmPC).
The LD50 of micronized progesterone in the female rat is 327 mg/kg when the hormone is given by intraperitoneal injection, which is equivalent to a dose 50 times higher than that recommended for clinical use in menopausal women (Utrogestan Spanish SmPC; Sitruk-Ware, 2018).
In a 26-week toxicity study, rats were dosed with progesterone orally with 40 or 160 mg/kg/day, or subcutaneously with 4 or 16 mg/kg/day. Oral administration of progesterone led to virtually no effects with no observable effect level (NOEL) of 160 mg/kg/day. Subcutaneous administration revealed effects only at the highest dose of 16 mg/kg/day: in females and males the endocrine target organs (gonads, uterus, prostate) were atrophied and in males the pituitary weight was increased (EMEA/MRL/146/96, 1999). Treatment of dogs for one to 1.5 years with progesterone containing subcutaneous implants (approximately 225, 375, 1125 or 1650 mg/kg) resulted in a slight degree of mammary enlargement, glandular activity and nodule development in the doses equal or above 375 mg/kg (EMEA/MRL/146/96, 1999). Treatment of monkeys for one year with vaginal rings releasing 235 or 1770 µg progesterone/day showed effects on organs of the reproductive system for both dosages. At high dose levels, ovulation was suppressed and widespread atrophy of the uterine mucosal and glandular endometrial epithelium had occurred. An increase in cervical mucus was observed within the lumen of the endocervical canal in a proportion of hormone-treated animals (Wadsworth et al, 1979).
In the Salmonella mutagenicity assay (Ames test), progesterone was not mutagenic. Progesterone did not induce dominant lethal mutations in mice or chromosomal aberrations in rats treated in vivo. It did not induce chromosomal aberrations in cultured human cells, nor chromosomal aberrations or DNA strand breaks in rodent cells. Studies on transformation of rodent cells in vitro were inconclusive: a clearly positive result was obtained for rat embryo cells, a weakly 1987; (Sitruk-Ware, 2018).
The evidence on the carcinogenicity of progesterone has been reviewed by IARC and has designated progesterone to be carcinogenic in experimental animals with sufficient evidence, and possibly carcinogenic to humans (Group 2B) with inadequate evidence (IARC, 1999; IARC

1987; Sitruk-Ware, 2018). Progesterone was tested by subcutaneous and by intramuscular injection in mice, rabbits and dogs, and by subcutaneous implantation in mice. It increased the incidences of ovarian, uterine and mammary tumours in mice. Neonatal treatment with progesterone enhanced the occurrence of precancerous and cancerous lesions of the genital tract and increased mammary tumorigenesis in female mice (IARC, 1979). Dogs treated with progesterone intramuscularly for four years at the doses of 46 or 1140 mg/week, corresponding to approximately one to 25 times the luteal-phase levels for that species, developed a dose-related incidence of mammary-gland nodules (IARC, 1979; Frank et al, 1979) Although limited data were provided on the reproductive toxicity of progesterone, it is clear that progesterone exerts effects on the reproductive system. A Clauberg-McPhail test in rabbits was performed to assess the progestational activity of progesterone after oral administration compared to subcutaneous administration. From this study an oral hormonal NOEL of 3.2 mg/kg/day can be established, while the subcutaneous hormonal NOEL is 0.025 mg/kg/day (EMEA/MRL/146/96, 1999).
Data on teratogenicity/embryotoxicity reveal that no congenital disorders are found after treatment with natural progesterone. Progesterone administered intramuscularly to rats at a dose of 5 mg/day on days 16 to 19 of gestation had no effect, but the same dosage on days 20 to 23 of gestation caused fetal death, which was probably related to the prolonged delay of parturition due to progesterone administration (EMEA/MRL/146/96, 1999).

III.4 Ecotoxicity/environmental risk assessment (ERA)

The use of Bijuva would lead to an increase in current estradiol hemihydrate and progesterone levels found in the environment, therefore an ERA must be submitted. The MAH provided a full ERA, however this was not considered acceptable as it was not in accordance with the current guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00 Corr 2, for the following reasons:

- A complete phase I and II environmental risk assessment has neither been provided for oestradiol nor for progesterone.
- Cited fate or effect data, are insufficient and not appropriate. As already previously mentioned, the data cannot be based on summary data from other regulatory frameworks (eg from material safety data sheet or MSDS, electronic public assessment reports or (E)PARs) without a letter of access from the respective owner. In addition, underlying references from the ERA are not provided and therefore, cited data from literature studies could not be checked (ao for sufficient reliability and (organisation for economic co-operation and development (OECD)-like) design).
- The fact that PNEC values for oestradiol and progesterone were found acceptable by the FDA is not sufficient, for a European procedure, Europe needs to assess the data and form its own conclusion.
- The MAH does not adequately reflect the endocrine modes of action of both active substances. As indicated in the 'Questions and answers on the guideline on the environmental risk assessment of medicinal products for human use', evaluation of a potential endocrine effect on the environment is needed if a direct mechanism of action is affecting reproduction, e.g. for oestrogen receptor agonists, even if in phase I the PECsw value is below the threshold. For further clarification of what is expected

with respect to endocrine active substances can be found in Q12 of the Q&A guidance and the, still draft, revision of the current guideline (EMEA/CHMP/SWP/4447/00 Rev.1).

Therefore, the MAH has committed to submit an new ERA via a variation, taking into account the points above and the current guideline and Q&A, an updated ERA for both compounds, including a full phase I and II assessment covering all aspects with the respective (OECD) study results. This is considered acceptable.

III.5 Discussion on the non-clinical aspects

This product concerns an application in accordance with Article 8(3) of Directive 2001/83/EC "Mixed application". The MAH has only provided an overview with bibliographical references for the non-clinical section, which contains up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required. Finally, the MAH has committed to submit an new ERA via a variation.

IV. CLINICAL ASPECTS

IV.1 Introduction

Oestradiol and progesterone are well-known active substances with established efficacy and tolerability. A clinical overview has been provided, in which the clinical pharmacology, clinical efficacy and safety of both active substances was discussed. The MAH has submitted a total of six clinical studies, which are listed below:

- One single-dose bio-availability (BA) / bioequivalence (BE) studies was conducted: the single-dose study assessed the BA of Bijuva 1 mg E2/100 mg P under fed and fasting conditions. (study 1)
- An additional Phase 1 pharmacokinetics (PK) study of one single dose and multiple doses of 1 mg E2/100 mg P and 0.5 mg E2/100 mg P completed the Phase 1 studies. (study 2)
- A pivotal Phase 3, double-blind, placebo-controlled, randomized, multi-centre study was performed to evaluate the safety and efficacy of oestradiol in combination with progesterone in postmenopausal women with an intact uterus. (study 3)

Finally, the MAH also performed a comparative dissolution study, which assessed the bridging capabilities of the product used in the phase 1 studies and the phase 3 study.

Dissolution study

The formulation used in the phase 3 clinical trial was not manufactured by proposed commercial manufacturer and the formulation used in phase 1 studies TXC16-01 and TXC17-02 was manufactured by the proposed commercial manufacturer. According to the MAH the commercial formulation has the same composition as the formulations used in the phase 3 clinical study. Although the manufacturing sites are not identical, and the manufacturing process was optimized after the site transfer it is supported that both products are comparable. Minor changes were made to resolve low oestradiol assay values and content uniformity issues. As the content of the commercial product is less variable the process optimisations can be accepted.

Dissolution profile comparison was performed between the phase 3 clinical batches manufacturer and the commercial manufacturer using quality control (QC) dissolution tests. The comparative dissolution tests using QC methods and non-QC methods show a similar release of oestradiol and progesterone for both formulations.

Despite some minor manufacturing differences and not fully compliant dissolution test it can be concluded that the quality of the commercial formulation is comparable but less variable than the product used in the phase 3 study. The commercial formulation has been used in the phase 1 studies TXC16-01 (single and multiple dose) and TXC17-02 (food effect). Although no formal bioequivalence study has been performed to support bridging between the phase 3 and commercial formulation, across study comparison of the PK results of the phase 1 study TXC16-01 and phase 3 study TXC12-05 were roughly in line. The bridge between the phase 3 product and proposed commercial product has been established sufficiently.

Analytical/statistical methods

The analytical methods have been adequately validated and are considered acceptable for analysis of the plasma samples. The methods used in these studies for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

The design of the studies are acceptable.

Finally, the MAH submitted a clinical overview in which the clinical pharmacology, clinical efficacy and safety of both active substances was discussed.

IV.2 Pharmacokinetics

Study 1:

Design

A phase 1, open-label, randomized, balanced, single-dose, two-treatment (fed and fasting), crossover, single-centre study was carried out under fasted and high-fat fed conditions to assess the effect of food on the bioavailability of oestradiol/progesterone in 24 healthy postmenopausal female subjects, aged 40-65 years. Each subject received a single dose (oestradiol 1 mg/progesterone 100 mg) of the active substance formulation. For the fasting

group the tablet was orally administered with 240 ml water after a fasting period of at least ten hours. For the fed group, the tablet was orally administered with 240 ml water after a high- fat meal (eggs, bacon, bread, hash browns, milk and butter) they received after a fasting period of at least ten hours. There was one dosing period.

Blood samples were collected at -60, -30, and 0 minutes (the average of which will represent baseline) and then 20, 40, 60, and 90 minutes (±5 minutes), and 2, 3, 4, 6, 8, 12, 18, 24, 36, 48 (±10 minutes), and 72 hours (±2 hours) after administration of the products.

Results
All of the enrolled 24 subjects were eligible for pharmacokinetic analysis.

Table 1. Statistical analysis of baseline-adjusted and unadjusted PK parameters for plasma oestradiol under fed and fasting conditions.

Parameter	**Adjusted geometric mean**		**Adjusted GMR fed/fasting (%)**	**90% CI for adjusted GMR (%)**	**Intra-subject variability**
	Fed	**Fasting**			
Baseline adjusted plasma oestradiol					
AUC_{0-t} (pg·h/mL)	959.32	916.99	104.6	(95.5, 114.6)	18.1
$AUC_{0-\infty}$ (pg·h/mL)	1144.57	1123.41	101.9	(90.8, 114.3)	20.7
C_{max} (pg/mL)	27.71	60.37	45.9	(36.6, 57.5)	46.7
Unadjusted plasma oestradiol					
AUC_{0-t} (pg·h/mL)	1166.12	1172.30	99.5	(92.4, 107.0)	14.5
$AUC_{0-\infty}$ (pg·h/mL)	1670.21	1660.47	100.6	(92.6, 109.2)	14.7
C_{max} (pg/mL)	30.82	64.65	47.7	(38.9, 58.4)	41.7

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
GMR geometric mean ratio
CI confidence interval

Table 2. Statistical analysis of baseline-adjusted and unadjusted PK Parameters for plasma Estrone under fed and fasting conditions

Parameter	**Adjusted geometric mean**		**Adjusted GMR fed/fasting (%)**	**90% CI for adjusted GMR (%)**	**Intra-subject variability**
	Fed	**Fasting**			
Baseline adjusted plasma estrone					
AUC_{0-t} (pg·h/mL)	3320.51	2983.92	111.3	(102.6, 120.7)	16.0
$AUC_{0-\infty}$ (pg·h/mL)	3691.06	3227.13	114.4	(106.2, 123.2)	12.8
C_{max} (pg/mL)	135.25	143.06	94.5	(86.8, 103.0)	17.0
Unadjusted plasma estrone					
AUC_{0-t} (pg·h/mL)	4410.60	4164.68	105.9	(100.0, 112.2)	11.4
$AUC_{0-\infty}$ (pg·h/mL)	5911.95	5463.30	108.2	(101.2, 115.7)	11.5
C_{max} (pg/mL)	150.94	159.45	94.7	(87.7, 102.2)	15.1

$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t}	area under the plasma concentration-time curve from time zero to t hours
C_{max}	maximum plasma concentration
GMR	geometric mean ratio
CI	confidence interval

Table 3. Statistical analysis of baseline-adjusted and unadjusted PK parameters for plasma progesterone under fed and fasting conditions

Parameter	**Adjusted geometric mean**		**Adjusted GMR fed/fasting (%)**	**90% CI for adjusted GMR (%)**	**Intra-subject variability**
	Fed	**Fasting**			
Baseline adjusted plasma progesterone					
AUC_{0-t} (ng·h/mL)	6.45	3.54	182.2	(131.7, 251.9)	70.9
$AUC_{0-\infty}$ (ng·h/mL)	6.72	5.26	127.8	(49.6, 329.6)	57.7
C_{max} (ng/mL)	2.50	0.92	270.9	(188.2, 389.9)	82.0
Unadjusted plasma progesterone					
AUC_{0-t} (ng·h/mL)	6.79	3.54	191.6	(136.9, 268.1)	74.1
$AUC_{0-\infty}$ (ng·h/mL)	6.79	5.30	128.2	(49.8, 330.1)	57.3
C_{max} (ng/mL)	2.53	0.92	274.0	(189.7, 395.8)	83.0

$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t}	area under the plasma concentration-time curve from time zero to t hours
C_{max}	maximum plasma concentration
GMR	geometric mean ratio
CI	confidence interval

Food effect

The pharmacokinetics of a single dose of Bijuva has been characterized with and without food in study TXC17-02. A considerable food effect was observed for progesterone, therefore food intake instructions are considered relevant for the exposure of progesterone and its clinical effects. As a result, the SmPC, PL and Labelling texts state that Bijuva should be taken with food. This statement is based on the food effect observed in PK study TXC17-02.

The MAH did not conduct a bioequivalence study or compare the pharmacokinetic parameters measured in study TXC16-01 to estradiol and progesterone levels of mono preparations reported in literature. This is acceptable for an Article 8(3) mixed application no formal bridge based on pharmacokinetic data is required.

Study 2:

Design

A Phase 1, open-label, parallel-group, randomized study was carried out under fed conditions in 40 healthy postmenopausal female subjects, aged 40-65 years. Each subject received a single dose of one of the two oestradiol/progesterone formulations on the first day of the

study (oestradiol 1 mg/progesterone 100 mg or oestradiol 0.5 mg/progesterone 100 mg). After this single dose the pharmacokinetic parameters assessed. The subjects then received a single dose of the oestradiol/progesterone formulations for six more days, during which the pharmacokinetic parameters were assessed on days six and seven (steady state). The tablets was orally administered with 240 ml water 30 minutes after the evening meal (500 calories). There was one dosing period.

Blood samples were collected at -60, -30, and 0 minutes predose (to estimate baseline) and 20, 40, 60, and 90 minutes (within ±5 minutes of each time point), and 2, 3, 4, 6, 8, 12, 18, and 24 hours (within ±10 minutes of each time point) after administration of the products.

Results
Out of a total of 40 subjects, 37 were eligible for pharmacokinetic analysis. One subject was lost to follow up and two other subjects withdrew on their own accord.

Table 1. Pharmacokinetic parameters for baseline-adjusted serum oestradiol, estrone, and progesterone after single dose concentration (day 1), fed conditions

Dosage strength (oestradiol/progesterone)	**1 mg E2/100 mg P mean (SD)**		**0.5 mg E2/100 mg mean (SD)**	
Oestradiol	**N**		**N**	
AUC_{ttrap} (h·pg/mL)	20	400.5 (157.9)	20	167.8 (100.0)
C_{max} (pg/mL)	20	31.54 (29.70)	20	13.52 (9.320)
t_{max} (h)	20	10.00 (6.786)	20	11.08 (7.197)
Estrone				
AUC_{ttrap} (h·pg/mL)	20	2410 (867.7)	20	1069 (457.1)
C_{max} (pg/mL)	20	152.5 (65.68)	20	67.15 (28.07)
t_{max} (h)	20	11.07 (5.802)	20	11.80 (5.831)
Progesterone				
AUC_{ttrap} (h·ng/mL)	20	14.12 (9.928)	20	10.06 (9.409)
C_{max} (ng/mL)	20	6.48 (6.206)	20	3.73 (3.211)
t_{max} (h)	20	2.23 (1.468)	20	2.52 (1.944)

AUC_{ttrap} area under the plasma concentration-time curve calculated with the trapezoidal method
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
SD standard deviation

Table 2. Mean (SD) trough levels of oestradiol, estrone, and progesterone at steady-state – baseline-adjusted, fed conditions.

	Estradiol (pg/mL)			**Estrone (pg/mL)**			**Progesterone (SD) (ng/mL)**		
Analyte dose	**Day 6 predose**	**Day 7 predose**	**Day 7 24 h postdose**	**Day 6 predose**	**Day 7 predose**	**Day 7 24 h postdose**	**Day 6 predose**	**Day 7 predose**	**Day 7 24 h postdose**

1 mg E2/ 100 mg P	22.85 (12.84)	28.63 (18.14)	24.44 (14.35)	152.6 (79.09)	154.9 (81.42)	157.2 (84.38)	0.14 (0.134)	0.17 (0.154)	0.14 (0.112)
0.5 mg E2/ 100 mg P	10.60 (7.882)	11.41 (9.562)	10.98 (9.940)	65.05 (31.35)	64.75 (32.93)	65.45 (39.17)	0.15 (0.138)	0.15 (0.140)	0.10 (0.079)

h hour
SD standard deviation
E2 17β-oestradiol
P progesterone

Table 3. Pharmacokinetic parameters for oestradiol, estrone, and progesterone at steady state – baseline adjusted, fed conditions.

Dosage strength (oestradiol/progesterone)	**1 mg E2/100 mg P mean (SD)**		**0.5 mg E2/100 mg P mean (SD)**	
Oestradiol	**N**		**N**	
AUC_{τ} (pg·h/mL)	20	772.4 (384.1)	17	386.8 (356.6)
C_{max} (pg/mL)	20	42.27 (18.60)	17	23.95 (16.86)
C_{avg} (pg/mL)	19	33.99 (14.53)	17	16.64 (14.50)
t_{max} (h)	19	4.93(4.97)	17	5.90 (4.44)
t½ (h)	19	26.47 (14.61)	11	28.01 (9.99)
Estrone				
AUC_{τ} (pg·h/mL)	20	4594 (2138)	17	1981 (976.0)
C_{max} (pg/mL)	20	238.5 (100.4)	17	108.0 (48.58)
C_{avg} (pg/mL)	20	192.1 (89.43)	17	82.81 (40.80)
t_{max} (h)	20	5.45 (3.47)	17	8.48 (4.87)
t½ (h)	19	22.37 (7.64)	17	20.46 (5.61)
Progesterone				
AUC_{τ} (ng·h/mL)	20	18.05 (15.58)	17	12.19 (11.01)
C_{max} (ng/mL)	20	11.31 (23.10)	17	4.40 (5.72)
C_{avg} (ng/mL)	20	0.76 (0.65)	17	0.55 (0.45)
t_{max} (h)	20	2.64 (1.51)	17	2.89 (2.29)
t½ (h)	18	9.98 (2.57)	13	8.77 (2.78)

AUC_{τ} area under the plasma concentration-time curve calculated with the trapezoidal method
C_{max} maximum plasma concentration
C_{avg} average plasma concentration
t_{max} time for maximum concentration
t½ half-life time
SD standard deviation
h hour
SD standard deviation
E2 17β-oestradiol
P progesterone

Conclusion
The pharmacokinetics of Bijuva have been appropriately characterized after a single dose and at steady-state under fed conditions. It is agreed that results from this study are most relevant for the SmPC and are in line with recommended conditions in proposed SmPC. The steady state pharmacokinetic parameters for estradiol, estrone, and progesterone are presented in table 6.

IV.2 Clinical efficacy

The efficacy of Bijuva was documented in one pivotal phase 3 clinical trial.

Study 3:

Design
A phase 3, double-blind, placebo-controlled, randomized, multi-centre study to evaluate the safety and efficacy of estradiol in combination with progesterone in postmenopausal women ≥ 12 months of spontaneous amenorrhea with an intact uterus. The design of the study comprised a period of one year to evaluate endometrial safety (ES) in the ES population, in four different dose groups. Efficacy was assessed in the same four different dose groups but also in a placebo group, and was performed in a 12-week substudy, evaluating the decrease in number and severity of hot flushes in women who reported ≥7 moderate to severe hot flushes per day, or ≥50 per week (vasomotor symptom or VMS substudy). The studies (ES and VMS) were performed in 1835 and 766 healthy postmenopausal female subjects, aged 40-65 years, respectively.

The sample size was based on the target that the combination therapy was effective at achieving a ≤ 1% incidence rate of endometrial hyperplasia following 12 months of therapy and that the upper bound of the 95% confidence interval of the estimated incidence rate was ≤ 4%. Approximately 1750 subjects (400 per active treatment group; 150 in the placebo group) were to be enrolled in the overall study. This number of women is considered sufficient to assess endometrial safety in the active treatment groups, in accordance with the EMA guidance on HRT (EMEA/CHMP/021/97, Rev. 1, Oct 2005).

The study evaluated currently approved oral doses of 17β-estradiol (Estrace) and a lower dose of 17β-estradiol along with various progesterone doses that were selected based upon the currently approved dose of progesterone (Prometrium) as well as lower doses. The design of this study is based on current regulatory guidance (FDA Guidance, Jan 2003; European Medicines Agency [EMA] Guidance, 2005).

Four different combinations of oestradiol and progesterone were evaluated in the ES and general safety trial. These four doses were also used in the VMS substudy in order to find the lowest effective dose:

- 1 mg oestradiol/100 mg progesterone
- 0.5 mg oestradiol/100 mg progesterone

- 0.5 mg oestradiol/50 mg progesterone
- 0.25 mg oestradiol/50 mg progesterone

VMS substudy:

Results

Study population

Out of a total of 766 subjects, 726 met the criteria to be included in the population for analysis or modified intent to treat – vasomotor symptom (MITT-VMS). Primary efficacy outcomes were the lowering of both number and severity of moderate and severe VMS.

Co-Primary Efficacy Endpoints

These consisted of the mean change in frequency and severity of moderate to severe VMS from Baseline to Weeks 4 and 12 in an active group compared with placebo.

Baseline values for moderate and severe VMS

Baseline values for VMS had to be identified within all treatment groups to adequately assess changes in VMS values during the VMS substudy, these baselines can be found in table 7. Concluded was that baseline values for the efficacy endpoints of VMS substudy are in line with the inclusion requirement of a minimum frequency of ≥ 50 per week moderate to severe hot flushes in the seven days prior to visit one. The baseline values were similar between the five treatment groups, which is in line with the current HRT Guideline (EMEA/CHMP/021/97, Rev. 1, Oct 2005).

Table 7. Baseline values for co-primary and selected secondary endpoints for MITT-VMS population.

	1 mg E2/ 100 mg P (N=415)	**0.5 mg E2/ 100 mg P (N=424)**	**0.5 mg E2/ 50 mg P (N=421)**	**0.25 mg E2/ 50 mg P (N=424)**	**Placebo (N=151)**
Co-primary efficacy endpoints					
Mean (SD) weekly number of moderate to severe VMS	74.4 (35.26)	72.1 (27.76)	75.9 (28.04)	77.0 (30.42)	72.4 (23.26)
Mean (SD) weekly severity score of moderate to severe VMS	2.54 (0.320)	2.51 (0.249)	2.50 (0.231)	2.51 (0.262)	2.52 (0.246)

SD standard deviation
E2 17β-oestradiol
P progesterone

Frequency of moderate to severe VMS

The *mean change* in VMS values from the previously recorded baseline values are depicted in table 8. By week 12, all doses were statistically significantly different from placebo in reducing the number of moderate to severe VMS ($p \leq 0.002$).

Table 8. Change from baseline and placebo in the mean number of weekly moderate and severe VMS at week four and week 12 (MITT-VMS Population).

	1 mg E2/100 mg P (N=141)	**0.5 mg E2/100 mg P (N=149)**	**0.5 mg E2/50 mg P (N=147)**	**0.25 mg E2/50 mg P (N=154)**	**Placebo (N=135)**
Week 4 (n)	**134**	**144**	**142**	**152**	**126**
Baseline	72.1 (27.80)	72.3 (28.06)	75.2 (27.10)	77.3 (30.51)	72.3 (23.44)
Mean (SD) change from Baseline	-40.6 (30.59)	-35.1 (29.14)	-33.6 (30.64)	-38.9 (31.04)	-26.4 (27.05)
LS Mean (SE) change from placebo	-12.81 (3.30)	-8.07 (3.25)	-4.81 (3.26)	-10.40 (3.22)	---
MMRM P-value vs placebo	< 0.001	0.013	0.141	0.001	---
Week 12 (n)	**124**	**129**	**124**	**135**	**115**
Baseline	72.2 (25.04)	72.8 (28.96)	75.4 (27.08)	76.5 (29.29)	72.2 (22.66)
Mean (SD) change from Baseline	-55.1 (31.36)	-53.7 (31.93)	-50.2 (31.35)	-52.4 (33.90)	-40.2 (29.79)
LS Mean (SE) change from placebo	-16.58 (3.44)	-15.07 (3.39)	-10.79 (3.41)	-11.71 (3.36)	---
MMRM P-value vs placebo	< 0.001	< 0.001	0.002	< 0.001	---

SD standard deviation
E2 17β-oestradiol
P progesterone
LS least square
SE standard error
MMRM mixed model repeated measures

Change in severity scores of moderate to severe VMS

This co-primary efficacy endpoint of the mean change in severity of moderate to severe VMS from baseline to weeks 4 and 12 in an active group compared with placebo was met for the two highest dose groups (1 mg E2/100 mg P and 0.5 mg E2/100 mg P). These results are shown in table 9.

Table 9. Change from baseline and placebo in the mean weekly severity scores of VMS at week 4 and week 12 (MITT-VMS Population)

	1 mg E2/100 mg P(N=141)	**0.5 mg E2/100 mg P(N=149)**	**0.5 mg E2/50 mg P(N=147)**	**0.25 mg E2/50 mg P(N=154)**	**Placebo(N=135)**
Week 4 (n)	**134**	**144**	**142**	**152**	**126**
Baseline	2.54 (0.325)	2.51 (0.248)	2.50 (0.230)	2.51 (0.259)	2.52 (0.249)
Mean (SD) change from Baseline	-0.48 (0.547)	-0.51 (0.563)	-0.40 (0.469)	-0.44 (0.514)	-0.34 (0.386)
LS Mean (SE) change from placebo	-0.13 (0.061)	-0.17 (0.060)	-0.05 (0.060)	-0.10 (0.059)	---
MMRM P-value vs placebo	0.031	0.005	0.401	0.100	---
Week 12 (n)	**124**	**129**	**124**	**135**	**115**
Baseline	2.55 (0.235)	2.51 (0.248)	2.50 (0.235)	2.50 (0.254)	2.52 (0.245)
Mean (SD) change from Baseline	-1.12 (0.963)	-0.90 (0.783)	-0.76 (0.744)	-0.71 (0.806)	-0.56 (0.603)
LS Mean (SE) change from placebo	-0.57 (0.100)	-0.39 (0.099)	-0.24 (0.100)	-0.16 (0.098)	---
MMRM P-value vs placebo	< 0.001	< 0.001	0.018	0.096	---

SD standard deviation
E2 17β-oestradiol
P progesterone
LS least square
SE standard error
MMRM mixed model repeated measures

The outcomes of these additional secondary endpoints were suggestive of a support to the primary efficacy endpoint of decrease in vasomotor symptoms. Key secondary efficacy endpoint was considered the responder analysis. The results showed a higher responder rate of ≥50% and ≥75%, that was statistically significant for all treatment groups compared to placebo at Weeks 4 and 12.

This high 50% and 75% responder rate noted for these product combinations is considered clinically relevant. However, the differences between the active treatment groups are small.

Summarized, a statistically significant and clinically relevant decrease in percentage of moderate to severe VMS was shown as well as a significant decrease in severity of hot flushes against placebo. This outcome was supported by a significantly larger proportion of responders in the active treatment arms who had greater than 50% and 75% reductions in number of VMS at both Week 4 and Week 12. The co-primary efficacy endpoint of the mean change in severity of moderate to severe VMS from Baseline to Weeks 4 and 12 in an active group compared with placebo was met for the two highest dose groups (1 mg E2/100 mg P and 0.5 mg E2/100 mg P).

IV.3 Clinical safety

Study 3:ES study

Design
A phase 3, double-blind, placebo-controlled, randomized, multi-centre study to evaluate the safety and efficacy of estradiol in combination with progesterone in postmenopausal women ≥ 12 months of spontaneous amenorrhea with an intact uterus. The design of the study comprised a period of one year to evaluate endometrial safety (ES) in the ES population, in four different dose groups. Efficacy was assessed in the same four different dose groups but also in a placebo group, and was performed in a 12-week substudy, evaluating the decrease in number and severity of hot flushes in women who reported ≥7 moderate to severe hot flushes per day, or ≥50 per week (vasomotor symptom or VMS substudy). The studies (ES and VMS) were performed in 1835 and 766 healthy postmenopausal female subjects, aged 40-65 years, respectively.

Results
Study population
Out of a total of 1835 subjects included in the ES population, 1255 completed the study and were included for analysis. The number of subjects with evaluable endometrial biopsy at baseline and after 12 months of treatment (n=1255; 280 in 1 mg E2/100 mg P).

Primary safety endpoint
This primary safety endpoint was the incidence of endometrial hyperplasia at 12 months. Endometrial biopsies were performed at screening and at visit 7 (month 12)/end of treatment. There were six subjects who had insufficient tissue for evaluation at baseline (no

endometrium identified/tissue insufficient for diagnosis for both reads) and 574 subjects did not have a post-Baseline biopsy performed after study day 326.

In this phase 3 study, according to the predefined protocol, for the primary safety endpoint, all endometrial biopsies were to be centrally read by three pathologists. Two pathologists, designated by the Sponsor prior to study start, are considered to be the primary pathologists (the pathologists are blinded to this designation). If all three readings were disparate (ie, each fell into a different category – Category 1, 2, or 3), the final diagnosis was based on the most severe of the three readings. This approach is based on the FDA guidance.

The MAH has performed an analysis of endometrial safety taking into taking into account the recommendations of the HRT Guideline (EMEA/CHMP/021/97 Rev. 1.), for a new combination of oestrogen/progestogen (e.g. new administration scheme or new strength) or a new progestogen in a fixed combination:

- Endometrial data collected over at least 12 month duration assessed by endometrial biopsies at baseline and after 12 months of treatment, and/or at the end of treatment if treatment is stopped before the end of study (provided that it is longer than three months). Among women withdrawn from the study, only those treated for longer than three months should have "end of treatment" biopsy.
- Further, under the assumption that the new combination does not increase the frequency of hyperplasia as compared to recently authorised combinations, a sample size of 300 patients treated for one year should provide more than 80% statistical power. For the proposed dose regimens the number of women included varied between 274 and 306.
- For a new HRT combination, a requirement is that the incidence of endometrial hyperplasia should be statistically less than 2% after one year of treatment, i.e. the upper limit of a two-sided 95% confidence interval of the observed frequency of endometrial events should not exceed 2%. For all active doses this was lower, including the proposed dose (1 mg E2/100 mg P), where it was 1.06%.

Based on the results from endometrial biopsies taken at study entry and after 12 months of treatment, no cases of endometrial hyperplasia or endometrial cancer were reported in the ES population in any of the treatment arms in the 12 month phase 3 study.

However, the data initially presented to support endometrial safety were considered inconclusive and insufficient to adequately assess whether the dose regimen selected for marketing (E 1 mg/100 mg P) provides sufficient protection of the endometrium. This was based on the following:

1. Discrepancy noted in incidence of endometrial hyperplasia, i.e. no cases in the endometrial safety analysis for E 1 mg/100 mg P (0/280 (0.00%; 95%CI: 1.06) presented in the study report, but a different analysis (1/281 (0.36%; 95%CI 1.97), was proposed in Section 5.1 of the SmPC.
2. Discrepancy noted in the number of women with biopsy outcome of disordered proliferative endometrium mentioned in the ES analysis and the number included in the SmPC.

3. The outcome of endometrial biopsies taken at 12 months had not been provided.
4. The bleeding pattern observed with the highest dose combination, which is selected for marketing, is less favourable in comparison to the other dose combinations and may also indicate that the progesterone dose in 1 mg E2/100 mg P is too low to adequately suppress oestrogen-induced endometrial growth which could increase risk of endometrial malignancy.
5. A considerable food effect was observed for progesterone which might lead to insufficient exposure needed to protect the endometrium. The study protocol was amended during the phase 3 trial to change the initial dose instruction from intake at bed time into intake with food (evening meal).

The MAH therefore submitted additional data to address these issues, which are discussed below.

Point 1, 2 & 3 Outcome of endometrial biopsies:
The MAH submitted an updated ES analysis that includes the one case of endometrial hyperplasia, utilizing the two-sided confidence interval (table 10). It was shown that the results are in line with requirements for a new HRT, that after one year of treatment, i.e. the upper limit of a two-sided 95% CI of the observed frequency of endometrial events does not exceed 2%. Therefore, the endometrial safety of Bijuva is considered sufficiently substantiated. Further, the wording in SmPC section 5.1 on the risk of endometrial hyperplasia is adapted to reflect the outcome of this new ES analysis.

The MAH provided an additional ES analysis which showed that after 12 months therapy, there were a total of ten cases of endometrial hyperplasia based on the criteria of single most severe pathological diagnosis in women who received E2/P and one case of suspected endometrial malignancy on 1 mg E2/100 mg P. Based on the additional data on discordant endometrial biopsy reads, there were 3 cases of discordant reads identified with worst outcome of endometrial hyperplasia, i.e. the subject who is currently included in the updated analysis on the Bijuva treatment arm (1 mg E2/100 mg P),one subject in the 0.5 mg E2/100 mg P arm, and one subject in the 0.5 mg E2/50 mg P arm (see Table 10).

Table 10. ES analysis including case of hyperplasia.

Population		**1 mg E2/100 mg P**	**0.5 mg E2/100 mg P**	**0.5 mg E2/50 mg P**	**0.25 mg E2/50 mg P**	**Placebo**
ES	Hyperplasia Incidence (%)	1/268 (0.37)	1/288 (0.35)	1/281 (0.36)	0/261 (0.00)	0/85 (0.00)
	Upper Two-sided 95% CI	1.83%	1.70%	1.74%	1.14%	3.46%
E2	17β-oestradiol					
P	progesterone					
ES	endometrial safety					
CI	confidence interval					

Further, as requested, the MAH has provided information regarding the FDA inspection of three sites. According to the information in the FDA clinical review report, "*No corrective action appears to have resulted from these audits. The audit program provides reassurance that trial conclusions were based on valid procedures for data management and analysis, and that the Therapeutics MD's clinical trial program was carried out in accordance with GCP guidelines*." These results sufficiently verify that the process and conduct of the phase 3 study is adequate.

Point 4 (observed bleeding pattern):
The MAH provided additional data regarding irregular bleeding and/or spotting associated with Bijuva (table 11). The percentages of irregular bleeding and/or spotting during the first 3 treatment months and during month 10-12 for all four treatment arms indicate that the incidence of bleeding and/or spotting is 30.1% during the 1st trimester and 17.4% during the 4th trimester. Regarding all 4 dose combinations, Bijuva has relatively highest incidence in comparison with the other 3 dose combinations. However, for comparison, the Applicant has provided the incidence of bleeding/spotting of 4 continuous combined HRTs approved by EU procedure. These percentages indicated that the incidence of bleeding/spotting during Bijuva treatment over 12 months is within the range of that noted with other continuous combined HRTs available in the EU (see Table 12), and are therefore considered acceptable. The percentages of irregular bleeding and/or spotting are included in section 5.1 of the SmPC, in line with the core SmPC for HRT.

Table 11. Irregular bleeding and/or spotting

Time Period	Statistic	1mg E2/100mg P (N=415)	0.5mg E2/100mg P (N=424)	0.5mg E2/50 mg P (N=421)	0.25mg E2/50mg P (N=424)	Placebo (N=151)
Trimester 1	n/M (%)	94/312 (30.1)	77/329 (23.4)	69/334 (20.7)	62/307 (20.2)	11/103 (10.7)
	P-value	<0.001	0.005	0.028	0.036	
Trimester 2	n/M (%)	80/309 (25.9)	42/323 (13.0)	53/325 (16.3)	24/302 (7.9)	5/98 (5.1)
	P-value	<0.001	0.028	0.004	0.501	
Trimester 3	n/M (%)	58/298 (19.5)	41/311 (13)	33/320 (10.3)	20/288 (6.9)	3/97 (3.1)
	P-value	<0.001	0.004	0.024	0.218	
Trimester 4	n/M (%)	49/282 (17.4)	24/304 (7.9)	28/308 (9.1)	20/ 276 (7.2)	5/93 (5.4)
	P-value	0.003	0.501	0.291	0.639	
E2	17β-oestradiol					
P	progesterone					

Table 12. Incidence of bleeding/spotting with HRT products in EU.

Product	Composition	Incidence of bleeding/spotting	
		First 3 months of treatment	During months 10-12 of treatment.
Femoston Conti	1 mg 17β-estradiol (as hemihydrate) and 5 mg dydrogesterone.	15 %	12%
Angelique	1 mg oestradiol (as oestradiol hemihydrate) and 2 mg drospirenone.	59%	27%
Climodien	estradiol valerate 2.0 mg (corresponds to 1.52 mg estradiol), and dienogest 2.0 mg	28-33%	14-17%
Kliovance	Estradiol 1 mg (as estradiol hemihydrate) and norethisterone acetate 0.5 mg.	27%	10%

Point 5 (intake with food increases bioavailability of progesterone):
As observed in pharmacokinetic study 1, there is a considerable food effect for progesterone. This effect led to a protocol amendment during the phase 3 trial, to change the initial dose instruction from intake at bed time into intake with food (evening meal). The amended food intake instructions are relevant for the exposure of progesterone and its clinical effects. As a result, the SmPC, PL and Labelling texts state that Bijuva should be taken with food, see also the results of pharmacokinetic study 1 above.

IV.4 Adverse events (AE)

Overall, the incidence and nature of the AEs reported in this study were consistent with that expected for a HRT product used in this population of postmenopausal women. The adverse events for the proposed dose (1 mg E2/100 mg P) have been included in the SmPC Section 4.8.

IV.5 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Bijuva.

Table 13. Summary table of safety concerns as approved in RMP

Important identified risks	- ATE - VTE
Important potential risks	- None
Missing information	- None

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.6 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies performed with Bijuva. The MAH submitted one pharmacokinetic study that assessed the bioavailability of Bijuva under fasted and high-fed conditions to assess the effect of food on the bioavailability of oestradiol/progesterone. Furthermore, a study under fed conditions assessing the pharmacokinetics of Bijuva, including the pharmacokinetic parameters on days six and seven (steady-state) was performed as well. Additionally, a phase 3 safety and efficacy study investigating endometrial safety and efficacy in patients with vasomotor symptoms was submitted. Risk management is adequately addressed. This medicinal product can be used as an initial therapy for the proposed indication.

V. USER CONSULTATION

The package leaflet (PL) has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PL was English. The test consisted of: a pilot test with two participants, followed by two rounds with ten participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the PL meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Bijuva 1 mg/100 mg soft capsules has a proven chemical-pharmaceutical quality. Based on the review of the data on safety and efficacy, the RMS considers that the benefit-risk balance for Bijuva, as a treatment for oestrogen deficiency symptoms in postmenopausal women with a uterus, and with at least 12 months since last menses is positive.

In the Board meeting of April 2020, issues regarding endometrial safety were discussed, as the data initially presented to support endometrial safety were considered inconclusive and insufficient to adequately assess whether the dose regimen selected for marketing (E 1 mg/100 mg P) provides sufficient protection of the endometrium. Furthermore, issues involving pharmaceutical development, stability, the lack of process validation data, the nitrosamine risk assessment, the clinical overview regarding the pharmacology of oestradiol and progesterone and the wording of the proposed indication were discussed as well. The MAH therefore submitted additional data, which were discussed in the Board meeting of

January 2021. Although these data clarified and solved several uncertainties regarding the endometrial safety, one issue still needed to be further justified as a new endometrial safety analysis was requested and the results needed to be in line with requirements of the EMA HRT guideline for a new HRT. Another topic in the Board meeting concerned possible presence of nitrosamines in the excipient Allura Red. The MAH submitted additional data, which addressed these points adequately. The risk for unacceptable nitrosamine levels in the drug product contributed by Allura Red was considered very low based on chemical considerations and the very low amount of Allura Red per capsule. All issues are considered resolved.

There was no discussion in the CMDh. Agreement between member states was reached during a written procedure. The concerned member states, on the basis of the data submitted, considered that the risk-benefit balance for Bijuva is positive, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 25 February 2021.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

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