20 November 2014
EMA/78875/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Senshio

International non-proprietary name: ospemifene

Procedure No. EMEA/H/C/002780/0000

Note

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

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List of abbreviations

ADR	Adverse drug reaction
AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
ASC-H	Atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion
ASC-US	Atypical squamous cells of undetermined significance
ASMF	Active substance master file
ASM	Active substance manufacturer
AST	Aspartate aminotransferase
ATE	Arterial thromboembolism
AUC	Area under the curve
BCRP	Breast Cancer Resistance Protein
BLQ	Below the limit of quantification
BMI	Body mass index
BrdU	5-bromo-2-deoxyuridine
BSE	Bovine Spongiform Encephalopathy
BSEP	Bile Salt Export Pump
Cmax	Maximum plasma concentration
CI	Confidence interval
CMH	Cochran-Mantel-Haenszel
CMR	Carcinogenic, Mutagenic, Reproductive toxicity
CNS	Central nervous system
CVA	Cardiovascular attack
CYP	Cytochrome P450
DBPC	Double Blind Placebo Controlled
DMBA	Dimethylbenzoanthrasene
DNA	Deoxyribonucleic Acid
DT	Degradation time
DVT	Deep Vein Thrombosis
ED50	50% effective dose
ER	Estrogen receptor
F	Female

FDA	Food and Drug Administration
FSFI	Female Sexual Function Index
FSH	Follicle Stimulating Hormone
GLP	Good laboratory practice
hERG	Human ether-a-go-go-related gene
HI	Hepatic impairment
HPLC	high performance liquid chromatography
HRT	Hormone replacement therapy
HSIL	High-grade squamous intraepithelial lesion
IC50	50% inhibitory concentration
ICH	International conference on harmonisation
IV	Intravenous
K_i	Binding affinity of the inhibitor
LH	Luteinising Hormone
LOD	Limit of detection; Loss on drying
LPS	Lipopolysaccharide
LOQ	Limit of quantification
MBS	Most bothersome symptom
NAS	New active substance
NEC	New chemical entity
NMRI	Nuclear magnetic resonance imaging
NMT	Not more than
NOAEL	No observed adverse effect level
NOEL	No observed effect level
OECD	Organisation for Economic Co-operation and Development
OATP	Organic Anion-Transporting Polypeptide
OVX	Ovariectomised
PASS	Post-authorisation safety study
Pap	Papanicolaou
PBT	Persistence - Bioaccumulation - Toxicity
PE	Pulmonary embolism
PK/PD	Pharmacokinetic / pharmacodynamics
PO	Oral
RH	Relative humidity
RI	Renal impairment
SAP	Statistical Analysis plan
SC	Subcutaneous

SD	Standard deviation
SE	Standard error
SERM	Selective Estrogen Receptor Modulator
SHBG	Serum sex hormone-binding globulin
SOC	System organ class
Tmax	Time of maximum plasma concentration
TEAE	Treatment-emergent adverse event
THF	Tetrahydrofuran
TTC	Threshold of Toxicological Concern
TSE	Transmissible Spongiform Encephalopathies
UDI-6	Urinary distress inventory-6
UGT	Uridine'5 diphospho-glucuronosyl transferase
UTI	Urinary tract infection
UV	Ultraviolet
VTE	Venous thromboembolism
VVA	Vulvar and vaginal atrophy

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Shionogi Limited submitted on 5 March 2013 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Senshio, through the centralised procedure under Article 3 (2) (a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 19 July 2012.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that ospemifene was considered to be a new active substance (refer to sections on New active Substance status for further information).

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision CW/1/2011 on the granting of a class waiver.

Information relating to orphan market exclusivity

Similarity

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

New active Substance status

The applicant requested the active substance ospemifene contained in the above medicinal product to be considered as a new active substance in comparison to the known active substance toremifene (of which ospemifene is a derivative) previously authorised in the Union as Fareston, and claimed that ospemifene differs significantly in properties with regard to safety and efficacy from the already authorised substance.

Scientific Advice

The applicant did not seek scientific advice at the CHMP.

Licensing status

Senshio has been given a Marketing Authorisation in USA on 26 February 2013.

1.2. Manufacturers

Manufacturer(s) responsible for batch release

Penn Pharmaceutical Services Ltd.
23-24 Tafarnaubach Industrial Estate
Tredegar, Gwent NP22 3AA
South Wales
United Kingdom

1.3. Steps taken for the assessment of the product

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

Rapporteur: Pieter de Graeff

Co-Rapporteur: Joseph Emmerich

- The application was received by the EMA on 5 March 2013.
- The procedure started on 27 March 2013.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 14 June 2013. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 14 June 2013.
- During the PRAC meeting on 11 July 2013, the PRAC adopted an RMP Advice and assessment overview.
- During the meeting on 25 July 2013, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 25 July 2013.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 10 January 2014
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 24 February 2014.
- The Rapporteur circulated the Assessment Report on on the claim of new active substance (NAS) status on the 24 February.
- During the PRAC meeting on 6 March 2014, the PRAC adopted an RMP Advice and assessment overview.
- During the CHMP meeting on 20 March 2014, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 23 June 2014.
- During the PRAC meeting on 10 July 2014, the PRAC adopted an RMP Advice and assessment overview.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 17 July 2014.

- During the CHMP meeting on 24 July 2014, the CHMP agreed on a second list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 16 October 2014.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 03 November 2014.
- During the meeting on 20 November 2014, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Senshio.

2. Scientific discussion

2.1. Introduction

Background on vulvar and vaginal atrophy (VVA)

Estrogen deficiency affects numerous tissues in postmenopausal women, including musculoskeletal, vascular and urogenital systems (Archer, 2010).

The vaginal wall has estrogen receptors, mainly in the basal layers of the epithelium, but also in stromal cells and smooth muscle fibers. Estrogen affects the epithelium, connective tissue, and vaginal wall elasticity. Premenopausal estrogen concentrations are associated with a thickened and mature vaginal mucosa, with increased vaginal blood flow, lubrication, and mechanical sensitivity.

Estrogen stimulation also helps produce glycogen in the vaginal epithelial cells, which is metabolized by lactobacilli to produce lactic acid. This lactic acid maintains an acidic environment that keeps vaginal pH levels low (normal range 3.5 to 4.5), which is part of the body's natural defence against bacterial vaginal and urinary tract infections.

The decline in estrogen in postmenopausal women results in a decrease in vaginal lubrication, which is an early hallmark of VVA. Other symptoms of VVA include burning, dyspareunia (vaginal pain associated with sexual activity), loss of vaginal secretions, leukorrhea, vulvar pruritus, a feeling of pressure and bleeding (particularly associated with sexual activity). VVA is also associated with urinary symptoms including urethral discomfort, frequency, hematuria, urinary tract infection, dysuria, and stress incontinence (MacBride et. al., 2010). Over time these symptoms, especially dyspareunia, can lead to female sexual dysfunction and subsequent emotional distress.

Despite the impact of VVA on women's health, this condition is underdiagnosed and undertreated, with only an estimated 20-25% of symptomatic women seeking medical treatment (Archer, 2010).

Treatment Options of VVA

Treatment goals for VVA include alleviating symptoms, reversing or minimizing the physiologic changes, and improving quality of life for the patient. There are:

- Non-hormonal treatments: A number of over-the-counter (OTC) vaginal moisturizer and lubricant products are considered first-line non-hormonal treatments for vaginal dryness. This option can be appropriate for women concerned about hormone use, those with minimal physiologic changes or symptoms, or those who are not candidates for estrogen treatment.

- Hormonal treatments: Local, low-dose estrogen preparations to be applied vaginally are considered first-line pharmacologic treatment (*Royal College of Obstetricians and Gynaecologists Guideline Menopause and Hormone Replacement*). The guideline further states: *"There is no evidence that local vaginal oestrogen treatment is associated with significant risks".* These preparations include: Vagifem 10 mg (estradiol tablets for vaginal application), Estring (estradiol in vaginal ring) and Synapause (estriol ovules for vaginal application).

However, for older women with VVA who prefer oral agents to vaginal products, that no longer complain of vasomotor symptoms or who wish to avoid estrogen, treatment options have become limited (Bachmann et. al., 2010). For the indication of 'vulvar and vaginal atrophy' several estrogen-containing products are registered in Europe, but all these products are indicated for local vaginal application. Also, due to labelling changes following the Women's Health Initiative 2002 study, treatment recommendations on systemic estrogen therapy limit its use to the lowest effective dose for the shortest duration, and primarily for use in women with moderate to severe vasomotor symptoms.

The development of an effective oral non-estrogen based therapy for VVA could therefore be of benefit in these patients.

About the product

The indication claimed by the applicant at initial submission was: *"Treatment of vulvar and vaginal atrophy (VVA) in post-menopausal women (see section 5.1).*"

This was revised to the current indication, which is: "*Treatment of moderate to severe symptomatic vulvar and vaginal atrophy (VVA) in post-menopausal women who are not candidates for local vaginal oestrogen therapy (see section 5.1)".*

The proposed posology is: *"The recommended dose is one 60 mg tablet once daily with food taken at the same time each day."*

The claimed mechanism of action, as stated in 5.1 of the SmPC is: "*Ospemifene's biological actions are mediated through the binding of Ospemifene and its major metabolite to oestrogen receptors. The relative contribution of the metabolite to the pharmacological effect is estimated to be approximately 40%. This binding results in activation of some oestrogenic pathways (agonism) and blockade of other oestrogenic pathways (antagonism). The biological activity profile in humans is predominantly due to the parent compound.*

Nonclinical findings show that Ospemifene and its major metabolite have an oestrogen like effect in the vagina increasing the cellular maturation and mucification of the vaginal epithelium. In the mammary gland, they have a predominantly oestrogen antagonist effect. In bone, Ospemifene has agonist-like activity. In the uterus Ospemifene and its major metabolite have weak partial agonist/antagonist effects. These non-clinical findings are consistent with findings from clinical trials, in which Ospemifene demonstrated benefits on vaginal physiology without apparent oestrogen-like effects on breast tissue (see 5.1 Clinical safety)."

Type of Application and aspects on development

Legal basis

The application was a full, stand-alone application in accordance with Directive 2001/83/EC Article 8(3) as amended for the approval of a new active substance through the centralised procedure.

Scientific Advice

No CHMP scientific advice relating to the Ospemifene development programme has been received. However, several member states have given scientific advice prior to the submission of the marketing authorisation application.

In 2012, Germany and UK gave scientific advice prior to the pre-submission meetings - namely about the daily dose of the medicinal product, its endometrial safety and overall safety profile. During the meeting with BfArM (Germany), a specific concern was raised regarding the lack of active comparator in the pivotal studies conducted. The absence of comparison to standard therapy (local estrogens) was addressed in the assessment of this application.

Development programme

In the EU, no regulatory guidance had been developed - at the time of this report - on the investigation of medicinal products for vulvar and vaginal atrophy. The *"Guideline on Clinical Investigation of Medicinal Products for Hormone Replacement Therapy of Oestrogen Deficiency Symptoms in Postmenopausal Women"* (EMEA/CHMP/021/97) does not specifically address requirements for vaginal atrophy.

The requirements as laid down in the FDA guidance for industry *"Estrogen and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms – Recommendations for Clinical Evaluation"* have been previously accepted in the EU during the authorisation of other products for vaginal atrophy. The development programme for Ospemifene followed the above mentioned FDA guidance.

2.2. Quality aspects

2.2.1. Introduction

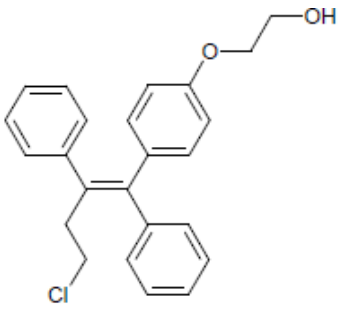
The finished product is presented as immediate release film-coated tablets containing 60 mg of ospemifene as active substance.

Other ingredients are: pregelatinized starch, mannitol (E421), povidone (E1201), sodium starch glycolate Type A, microcrystalline cellulose (E460), colloidal silicon dioxide (E551), magnesium stearate (E578), hypromellose (E464), lactose monohydrate, titanium dioxide (E171), polyethylene glycol (E1521), and triacetin (E1518), as described in section 6.1 of the SmPC.

The product is available in PVC/PVDC aluminium blisters, as described in section 6.5 of the SmPC.

2.2.2. Active Substance

The chemical name of the active substance ospemifene is Z-2-[4-(4-chloro-1,2-diphenylbut-1-enyl) phenoxy]ethanol, corresponding to the molecular formula $C_{24}H_{23}O_2Cl$ and has a relative molecular mass of 378.9. It has the following structure:



The structure of the active substance has been confirmed by elemental analysis, mass spectrometry, infrared spectroscopy, ^{1}H- and ^{13}C-NMR spectroscopy and X-ray, all of which support the chemical structure.
Ospemifene appears as a white to almost white, non-hygroscopic crystalline powder. It is insoluble in water, soluble in ethanol and propanol, very slightly soluble in isopropanol. The partition coefficient was found 4.43 and the pKa was calculated 14.26.
The molecule has two geometrical isomeric forms. The active substance ospemifene is the Z-isomer. Polymorphism was not observed.

Manufacture

The information on the active substance was provided according to the Active Substance Master File (ASMF) procedure.
The active substance is manufactured in four chemical synthetic steps. The material is then dried, micronised and packaged. The manufacture of the Z-isomer is achieved by appropriately selected and controlled reaction conditions. The proposed starting and raw materials used in the synthesis and the intermediates are well-defined and controlled by suitable methods and specifications. The synthesis has been described in sufficient detail and critical process parameters, yields and in-process controls (IPCs) have been reported and are considered satisfactory. The characterisation of the active substance and its impurities is in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities (including genotoxic) and degradation products have been characterised and toxicologically qualified as appropriate. The battery of genotoxicity studies performed has shown that ospemifene itself does not possess a genotoxic potential.

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

Specification

The active substance specification includes appropriate tests and limits for: appearance (visual), identity (IR, UV), assay (HPLC), impurities (HPLC), particle size distribution (laser diffraction), specific surface area (Ph.Eur.), residual solvents (GC), loss on drying (Ph. Eur.), heavy metals (Ph. Eur.), sulphated ash (Ph. Eur.) and microbial limits (Ph. Eur.). The specification limits regarding the potential genotoxic impurities have been set and justified in line with ICH guideline M7.
Batch analysis data from six full scale batches from the proposed manufacturer - three of them micronized at a different site- were provided. In addition another three batches manufactured by a different manufacturer and two smaller batches used in clinical/ toxicological studies have also been provided. Furthermore historical data from older batches were presented too. All the presented results complied with the specifications valid at the time of testing confirming that the manufacturing process is sufficiently robust and produces active substance of consistent quality. Since the specification has been revised during the evaluation it is recommended to update batch analysis data with results from at least three new commercial scale batches tested to the revised specification.

Stability

Stability data on four commercial and three smaller scale batches of active substance from the proposed manufacturer stored in the intended commercial package for up to 60 months under long term conditions at 25 ºC / 60% RH and three commercial and two smaller scale batches for six months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided. Additional data on eight pilot scale batches of active substance from a different manufacturer stored in the intended commercial package for 60 months under long term conditions at 25 ºC / 60% RH and, five pilot scale batches for six months under accelerated conditions at 40 ºC / 75% RH were provided.

The following parameters were tested: assay, impurities and loss on drying. The analytical methods used were the same as for release and were stability indicating as shown by forced degradation studies.

Throughout the stability program all results were within the set specification limits. The amount of impurities did not increase during the storage under ICH long-term or accelerated conditions, and the results of the chromatographic analyses showed no formation of degradation products. From these results, it was also concluded that the particle size distribution remains stable during storage.

Photostability testing following the ICH guideline Q1B was performed on one batch and results suggest that ospemifene is not very sensitive to light.

Results on stress conditions in sample solutions under acidic, basic and oxidizing conditions as well under direct daylight were also provided. The main degradation products detected vary depending on the degradation conditions.

Based on presented stability data, the proposed re-test period and storage conditions for ospemifene are acceptable.

2.2.3. Finished Medicinal Product

Pharmaceutical Development

The aim of the formulation development was to develop an immediate release film-coated tablet containing 60 mg of ospemifene as active substance.

According to the Biopharmaceuticals Classification System (BCS), ospemifene is classified as a Class II substance (low solubility – high permeability). The excipients selected are commonly used Pharmacopoeial grade excipients for the proposed pharmaceutical formulation. The rationale for the selection of excipients in the commercial formulation was presented and is considered satisfactory. The capsule formulation used in early development was replaced by the proposed tablet formulation for phase III clinical studies once the dose and strength were selected.

In order to limit the commercial batches variability only one manufacturing site is proposed. The investigation of the differences in the performance of clinical batches resulted in identifying steps of the manufacturing process and material attributes that critically affect the performance of the product. The investigations have resulted in establishing suitable IPCs and specifications for the active substance and the finished product. Ospemifene is a BCS Class II compound and once dissolved in the small intestine ospemifene is absorbed rapidly, suggesting that the extent and rate of the active substance dissolution in the small intestine will control bioavailability. Hence absorption, once in solution, is assumed to be not rate limiting (based upon Caco-2 cell permeation data). Given ospemifene's extremely low aqueous solubility its saturation solubility in fasted state intestinal conditions is very low. Therefore particle size and specific surface area are critical quality attributes. The investigation of alternative dissolution methods and attempts to establish an *in vitro in vivo* relationship (IVIVR) have resulted in a greater understanding of the factors controlling the bio-

relevant behaviour of the tablets as discussed above. However the methodological approximations made do not allow the use of the IVIVR to raw conclusions on the limits for PS and SSA which are therefore set in a more conservative way from the clinically investigated batches.

Two complimentary quality control dissolution tests will be utilised for routine release of the productand, in combination with other release parameters, will serve to assess product quality of commercial batches. The choice of the methods has been adequately justified. The first method has been found to be discriminating and capable of detecting changes to the manufacturing process that may occur during normal production. Known non-bioequivalent batches observed during development can be distinguished using this method. The second method is proposed to ensure the complete release of ospemifene from the tablet matrix by virtue of the specification. Both methods are intended to be used for batch release and stability testing of the product.

The manufacturing process has been optimised especially with regard to the identified critical step. It is considered that the proposed IPC controls ensure that the manufacture and the quality of the Senshio tablets are under sufficient control. However as an additional reassurance the applicant is recommended to introduce a further IPC of the granulate particle size in order to better characterise and control this intermediate.

The primary packaging is PVC/PVDC - Aluminium. The material complies with Ph.Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product

Senshio film-coated tablets are manufactured via a standard wet granulation process for solid, oral dosage forms. The manufacturing process comprises wet granulation, drying, milling, blending, compression and coating. The manufacturing process has been described in sufficient detail. Critical steps have been identified and appropriate in-process controls are put in place to ensure consistent quality of the product. Successful process validation results have been provided for three full scale batches. In conclusion it is considered that the manufacture is sufficiently robust to provide assurance that the process produces the finished product Senshio film-coated tablets of consistent quality, complying with the designated specification.

Product specification

The finished product release and shelf life specifications include appropriate tests and limits for: appearance (visual), identification (HPLC, UV), assay (HPLC), related substances (HPLC), uniformity of dosage units (Ph. Eur.), dissolution (Ph. Eur.- HPLC) and microbiological quality (Ph Eur).

Batch analysis results of three full scale validation batches were provided. In addition batch analysis results were provided for one pivotal clinical batch, two registration batches and for other earlier clinical batches. All results complied with the specifications valid at the time of testing confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification. Since the finished product specification has been revised during the evaluation it is recommended to update batch analysis data with results from at least three new commercial scale batches tested to the revised specification.

Stability of the product

Stability data on three full scale batches of finished product stored under long term conditions for nine months at 25 ºC / 60% RH and for six months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided. These batches are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing. Stability data on another three smaller scale batches of finished product stored under long term conditions for up to 60 months at 25 ºC / 60% RH and for six months under accelerated conditions at 40 ºC / 75% RH were provided. These batches were packed either in the primary packaging proposed for marketing or in an alternative one not applied for.
Samples were tested for description, water content, assay, related substances, dissolution and microbiological purity. The analytical procedures used are stability indicating. All results complied with the specification at the time of testing.
In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. Results confirmed the product is stable when exposed to light.
Stress studies under temperature, acid hydrolysis, base hydrolysis, light, oxidation and heat were conducted. The typical degradation products for each specific storage condition were identified and it is concluded that the related substances method is sufficiently stability-indicating.

Based on the presented data and extrapolations, the proposed shelf life at the proposed storage conditions as stated in the SmPC is supported.

Adventitious agents

It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The active substance and the finished product are controlled by adequate specifications. Since the active substance and the finished product specifications have been revised during the evaluation it is recommended to update batch analysis data with results from at least three new commercial scale batches of both active substance and finished product tested to the revised specification (see 2.2.6. Recommendations for future quality development). It has been demonstrated that the manufacture of batches of Senshio tablets of consistent quality is under control. Nevertheless, as an additional reassurance the applicant is recommended to introduce within an agreed timeframe a further IPC for a finished product intermediate (see 2.2.6. Recommendations for future quality development). In addition a satisfactory quality control methodology is now in place to ensure the quality of the commercial product. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

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

2.2.6. Recommendation(s) for future quality development

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

- the applicant is recommended to update active substance batch analysis data with results from at least three new commercial scale batches tested to the proposed specification.

- the applicant is recommended to update finished product batch analysis data with results from at least three new commercial scale batches tested to the proposed specification.

- the applicant is recommended to investigate the possibility to test the particle size of the final granulate applying a three-point particle size specification as objective characterization and control of the final granulate.

2.3. Non-clinical aspects

2.3.1. Introduction

Pivotal safety pharmacology and toxicology studies were performed in compliance with GLP.

2.3.2. Pharmacology

Primary pharmacodynamics

In vitro receptor binding

The estimated Ospemifene IC50 for ERα was 476 nM and for ERβ 513 nM; Ki values were 380 and 410 nM respectively. The binding of Ospemifene appears similar to that of Toremifene and Tamoxifen. The competitive binding to ERα and ERβ of the three metabolites 4-hydroxyOspemifene (M-1), 4'-hydroxyOspemifene (M-2) and 4-hydroxy-, side chain carboxylic acid Ospemifene (M-10) is at least as high, or possibly even higher than that of the parent compound.

Ospemifene is a Z-isomer and the E-isomer is present as impurity in the drug. The human plasma Cmax of Ospemifene is about 2 µM, roughly 4 times the estimated IC50 values. However, the unbound fraction is not more than 1-2%, so if corrected for protein binding the IC50 for the ER is far above the human Cmax. Plasma protein binding in the toxicological species was also high (refer to the Pharmacokinetic section): protein binding was 97.0-97.4% in rat plasma and 99.0-99.6% in monkey plasma. The *ex vivo* plasma protein binding of total radioactivity was lower in both species than for Ospemifene, indicating that the metabolites have a lower plasma protein binding than Ospemifene. Based on similar serum protein binding and lower systemic concentrations in humans, in humans the contribution of the metabolite to the overall effect is lower than that of the parent compound.

However, for the laboratory species the situation is different. If it is assumed that for these species serum protein binding of M-1 and parent compound is similar (actual values were not measured). in Particularly in rats and monkeys, based on the similar or higher systemic exposure and similar or higher affinity for the receptor, the contribution of M-1 to the pharmacodynamic effect may be similar or even higher than that of the parent compound - and thus a larger part of the pharmacodynamic effect in these species is due to the pharmacological action of metabolite M-1, compared to humans. The potency of M-1 regarding effects on rat vaginal and uterine tissue, however, was largely similar to that of the parent compound.

In vitro receptor selectivity

Based on limited competitive binding data it was considered possible that both the progesterone receptor and the androgen receptor contribute to effects of Ospemifene, and that the progesterone receptor contributes to effects of metabolites M-1 and M-2.

In vitro receptor activation

In two human cell systems, estrogen-sensitive human breast cancer cells (MCF-7) and human Ishikawa endometrial carcinoma cells, both stably transfected with reporter construct estrogen response element – luciferase (ERE-Luc), Ospemifene and its metabolites M-1 and M-2 showed generally no estrogenic effects, but inhibited transcription in the presence and absence of 17β-estradiol. The antiestrogenic effect of the two metabolites was seen at lower concentrations compared to that of Ospemifene, the parent compound.

In vivo primary pharmacodynamic effect

After oral administration, Ospemifene dose-dependently increased the thickness of the vaginal epithelium of ovariectomised (OVX) rats and relative organ weight of the vagina. However, the histological effect on the vaginal epithelium was different compared to that of 17β-estradiol and 17α-ethinylestradiol. The estrogenic action of Ospemifene was weaker than that of 17β-estradiol and more pronounced compared to that of Raloxifene.

The metabolites M-1 and M-2 appear to be active metabolites, with the potency of M-1 being approximately similar to that of Ospemifene, while the potency of M-2 was somewhat lower. Their relative contributions to the effects of Ospemifene in the OVX rat vagina cannot be accurately defined. The histological effect of both metabolites, if administered separately, was similar to that of Ospemifene.

Secondary pharmacodynamics

In vitro receptor binding of Ospemifene was tested in a panel of 23 receptors. Ospemifene showed IC50 > 1 µM for most of these receptors, except for the histamine H2 receptor (IC50 = 0.56 µM). This result does not preclude secondary pharmacodynamic effects on the tested receptors. The tested receptor screen was limited to receptors found in nervous tissue, and receptor binding of the pharmacodynamically active metabolites of Ospemifene was not tested. However, considering the clinical documentation submitted within the scope of this application, CHMP didn't find it necessary to provide more studies on this issue.

Effect of Ospemifene and Metabolites (and other SERMs) on the Uterus

Effects on the uterus were investigated in three different rat models: the immature, the ovariectomised, and the intact adult rat model.

In the immature rat model three oral daily doses of Ospemifene - or of its metabolites M-1, M-2 and M-3 - increased relative uterine weight and endometrial epithelial cell thickness. The effects of Ospemifene and metabolites were less than those of 17β estradiol and similar to those of Raloxifene.

If combined with17β estradiol, M-1 showed some anti-estrogenic action. Oral administration of Lasofoxifene showed similar effects as Ospemifene, but at lower doses, and also some antiestrogenic activity.

Ovariectomised rats treated orally for periods up to 6 months with Ospemifene showed a dose related increase of relative uterus weight. Metabolites M-1 and M-2 exerted similar effects as the parent compound. No other metabolites were tested. The effects of Ospemifene were similar to those of Raloxifene and Droloxifene. All these effects were lower than those of 17α-ethinylestradiol (oral) or 17β-estradiol (subcutaneous). Ospemifene decreased serum FSH and LH in ovariectomised rats to a similar degree as droloxifene and raloxifene but less than 17β-estradiol and 17α-ethinylestradiol. The ratio LH/FSH was not clearly affected by Ospemifene, droloxifene or raloxifene, but decreased by 17α-ethinylestradiol.

In adult intact rats, oral treatment with Ospemifene for 3 months reduced the relative uterine weight, thus behaving as a partial estrogen receptor antagonist. Raloxifene produced comparable data.

Effects on bone formation and resorption

Effects on several parameters of bone turnover, bone mass density, bone strength, histomorphometry were investigated in in ovariectomised rats in a series of studies, with administration periods ranging from 4 weeks up to 12 months. In a 12 month bone study effects of 1, 5 and 25 mg/kg/day Ospemifene (oral gavage) on bone and bone turnover markers were examined in ovariectomised (OVX) rats. The results from these studies were difficult to interpret due to the effects on body weight, which interacted with effects on bone parameters: OVX rats gain weight faster than sham-controls, which results in stronger bones due to higher body weight load. The decrease of body weight gain caused by Ospemifene treatment, consistent with growth inhibition caused by estrogenic substances, results in weaker bones. Nevertheless it was established that Ospemifene decreased ovariectomy-induced trabecular bone loss. Cortical bone was much less affected by ovariectomy and subsequently Ospemifene effects were not as clear as in trabecular bone. In proximal femur neck, labeled surface and mineralizing surface (% of bone surface) were increased by ovariectomy and dose-dependently decreased by Ospemifene, indicating a diminished bone formation rate in Ospemifene treated rats.

Plasma levels of Ospemifene and M-1 after one year of treatment showed that exposure to the major metabolite M-1 exceeded that of the parent compound to a large extent. Therefore, the observed treatment effect could have been for a large part due to the activity of the metabolite. The results from the shorter lasting studies confirmed the effects found in the 12 month study - Ospemifene treatment can reduce the effect of ovariectomy on bone density and morphometry. However, treatment should start not too long after ovariectomy. If the period between ovariectomy and start of treatment became 4 weeks or longer, no clear treatment effect was observed.

Effects on mammary gland and mammary tumour development

Ospemifene showed anti-estrogenic effects in most studies using two breast cancer cell lines: MCF-7 cells and in ZR-75-1 cells, at concentrations in the range of 1 – 10 µM. Its metabolites M-1 and M-2 showed similar action, but already at lower concentrations. The anti-estrogenic potency of Ospemifene in these studies was lower than that of Raloxifene.

In an *ex vivo* study Ospemifene did not stimulate cell proliferation in human mammary gland primary tissue cultures. At 10 – 100 nM slight anti-proliferative activity - similar to that of Raloxifene but less than Tamoxifen - was observed.

The effect of Ospemifene on BrdU (5-bromo-2-deoxyuridine) labeling, prolactin immunoreactivity and mammary gland lobular structures was evaluated in a series of ovariectomised rat studies.

Ospemifene and other SERMs showed no estrogenic action in the mammary gland of OVX rats, whereas estradiol increased these markers.

In a mouse tumour model - with tumour induction by dimethylbenzanthracene and tumour growth promotion by medroxyprogesterone acetate - Ospemifene prevented the development of mammary tumours, compared to negative control. The mammary tumours in the control mice had a low expression of ERα and no (detectable) expression of ERβ.

In an ovariectomised nude mouse human MCF-7 tumor model, at 1-50 mg/kg/day p.o. Ospemifene effects consisted of very limited inhibition of tumour growth in the presence of estradiol, no effect if estradiol was removed and tumours were small and slight inhibition of tumour shrinkage if estradiol was removed but tumours were large. So, although tumour growth was not promoted in presence or absence of estradiol, regression of tumours in the absence of estradiol was slightly inhibited. The biological significance of the observed small differences is uncertain.

The effect of Ospemifene on Dimethylbenzoanthrasene-induced (DMBA-induced) mammary cancer in rats was studied. Ospemifene treatment showed non-dose dependent antitumor activity at dose levels ranging from 3 to 30 mg/kg, administered for 4 weeks or longer. It was not investigated whether the DMBA induced tumours contained ER or were dependent on estrogenic compounds for their growth. So no conclusion is possible whether the apparent tumour inhibiting potential of Ospemifene was due to its anti-estrogenic properties.

The results of these studies were also consistent with the carcinogenicity studies in rats (refer to Toxicology section), showing lower incidences of mammary tumours.

Effect on vascular wall

The effect of Ospemifene on vascular wall was studied *in vitro* using freshly isolated rat endothelial cells from the aorta and a human vascular smooth muscle cell line. At 10 µM Ospemifene had a slight growth inhibitory effect in rat endothelial cells and a slight stimulatory effect in the human vascular smooth muscle cells. These small effects at a very high concentration were not considered relevant.

Effects on vasomotor symptoms

In a rat model for hot flushes, oral doses of 1 – 100 mg/kg/day Ospemifene dose dependently reduced the magnitude of hot flushes – however, these effects were less effective than those observed with 0.3 mg/kg/day of 17α-ethinylestradiol.

Effects on Cholesterol levels

Ospemifene treatment consistently decreased cholesterol levels in pharmacodynamic studies in rats as well as in repeated dose toxicity studies using mouse, dog and monkey models.

Effects on urodynamics in ovariectomised rats

In an ovariectomised rat model of postmenopausal urodynamic problems, no clear effect of an oral Ospemifene dose of 30 mg/kg/day was observed.

Immunological effects *in vitro*

In two *in vitro* studies on oxidative burst of human leukocytes in whole blood and on TNF-α production by LPS induced monocytes, Ospemifene showed little to no effect on immunological function.

Safety pharmacology programme

Central Nervous System

Six studies were done to investigate effects on the central nervous function. Only a few effects were seen, in two of these studies, at high doses. These were considered not to be of biological significance. The general toxicity studies don't reveal evidence of CNS toxicity (refer to Toxicology section).

Cardiovascular and Respiratory System

Effects of Ospemifene and its metabolite M-1 at concentrations of 0.3, 1, 3, or 30 µM on HERG-1 delayed rectifier currents were shown in transfected HEK 293 cells stably expressing this K^+-channel (GLP study). Ospemifene and its metabolite M-1 exerted significant inhibitory effects on the relative tail current amplitude. In two GLP *in vivo* cardiovascular studies in dogs and monkeys, no effect was found on cardiovascular parameters at single oral doses up to 100 mg/kg in dogs and 1000 mg/kg in monkeys. Further cardiovascular measurements were done in the repeated dose toxicity studies (revealing no evidence of cardiovascular safety issues).

In the dog model, effects on blood gasses and electrolytes, respiratory functions and locomotor activity were also investigated - no effects were observed with Ospemifene.

Other safety pharmacology studies

Single doses of 1, 3, 10, 30 and 100 mg/kg Ospemifene did not affect intestinal motility in NMRI mice (SC route), skeletal muscle tone in NMRI mice (oral route) or kidney function in SD rats (SC route).

2.3.3. Pharmacokinetics

The pharmacokinetics and toxicokinetics have mainly been studied in female mice, rats and Cynomolgus monkeys, although other animal species and males have been used.

Absorption

The solubility of Ospemifene in water is poor and a maximum concentration of 0.4 µg/mL could be dissolved. The studies investigating if Ospemifene and M-1 are substrates for P-glycoprotein and BCRP were performed with an added concentration of 1 µM. Free concentrations of Ospemifene and M-1 were 100 nM and 20.5 nM, respectively. Studies to investgate whether Ospemifene and M-1 are substrates for OATP1B1 and OATP1B3 were also performed with an added concentration of 1 µM - free concentration of Ospemifene was 384 nM while free concentration of M-1 was 697 nM.

While the *in vitro* permeability of Ospemifene was high, the absorption in monkey was low (F of 11% for the radioactivity) and in rat moderate (F is 49% for total radioactivity). After absorption, Ospemifene is subject to extensive first-pass metabolism in the non-clinical species, as indicated by a low oral bioavailability in rat and monkey (both ~3%). In humans, the absorption is higher and the first-pass metabolism is lower. A dose of 2000 mg/kg to the non-clinical species results in a comparable AUC to humans dosed with 1 mg/kg.

Distribution

Ospemifene is rapidly eliminated from the systemic circulation in rats (t½ is ~1 h). In addition, Ospemifene exhibited a low volume of distribution (0.3 L/kg) in rat studies, indicating distribution in total body fluids, while M-1 exhibits a moderate volume of distribution (3.8 L/kg), indicating a high binding to peripheral tissues. The clearance of Ospemifene and M-1 was moderate to high, which is in line with the estimated rapid elimination half-lives. For monkey, no kinetic parameters other than

AUC and Cmax were determined for Ospemifene and M-1. The kinetic data in the non-clinical species indicate that Ospemifene is subject to entero-hepatic recirculation.

In mice and dog, exposure to M-1 is less abundant than to Ospemifene, with metabolic ratios based on AUC values ranging from ~0.2 to 0.8 in mice and ~0.02 in dog; in monkeys, metabolic ratios ranged from 0.9 to 2.0 and in female rats, the metabolic ratio ranged from 0.7 to 2.5 - and tended to decrease with increasing dose.

M-2 was detected in mice and rats in much lower amounts (metabolic ratios between ~0.02 and 0.07). The major non-clinical species were rat and monkey, which had similar metabolic ratios compared to humans. In general, in all non-clinical species and over the investigated dose ranges, systemic exposure to Ospemifene - as well as metabolites M-1 and M-2 - increases in a less than dose proportional manner. The level of less than dose proportionately is greater following multiple dosing and at higher doses. In some instances at high doses, exposure to Ospemifene and M-1 even decreases with increasing dose.

In humans, the plasma protein binding of Ospemifene was 98.6 to >99% and of M-1 was 98.3%. The plasma protein binding of Ospemifene was also high in animal models, and the free fraction varied considerably between species (2.7-3% in rat and 0.4-1% in monkey). Considerable differences were also seen between the plasma protein binding of Ospemifene in non-clinical species and humans. This led CHMP to make a Recommendation for further investigation of the high-protein binding of the compounds, the potential considerable difference in free fraction between species, and the relevance of the active metabolite M-1 (and M-2) – the Applicant has agreed to do so post-authorisation (refer to Conclusions on Non-Clinical aspects).

Based on radioactivity, the blood-to-serum ratio at 5 and 10 minutes after IV administration was 0.96 in rat and 0.49 in monkey, indicating that Ospemifene does not specifically distribute to erythrocytes. After 8h post dose, the blood-to-serum ratio in rats was up to five-fold greater, indicating that the blood-to-serum ratio is considerable higher for the metabolites. In humans, the ratio of AUC0-∞ for total radioactivity in whole blood to serum ranged between 0.57 and 0.83 for individual subjects. Seeing as the blood-to-serum ratio for total radioactivity in rat and monkey was provided, but not specifically for Ospemifene and M-1, CHMP made a Recommendation for the company to provide the blood-to-plasma ratio for Ospemifene (in monkey and rat) and the blood-to-plasma ratio for M-1 (in rat, monkey and human) – the Applicant has commited to do submit these data.

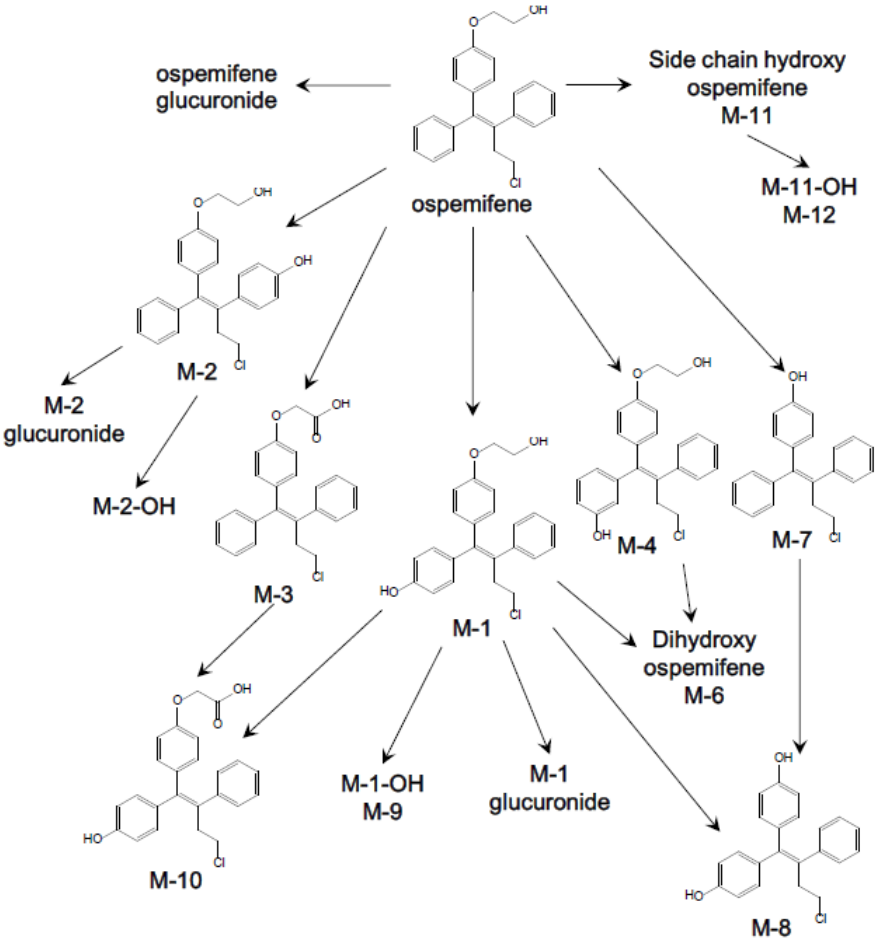
A radioactivity half-life of 60 hours was observed in a rat study with [^{14}C]-radiolabeled Ospemifene. In a previous rat distribution study with the [^{3}H]-radiolabel, a radioactivity half-life of 48-70 hours was seen (thus comparable to the [^{14}C]-radiolabel). In the [^{14}C]-radiolabeled study, no Ospemifene half-life was determined - but half-life was 1-13 hours in the previous rat distribution study. In humans, the radioactivity half-life was 99 hours and for Ospemifene 25 hours. The half-life of radioactivity and Ospemifene is shorter in rat than in humans. Based on the 24 hour distribution data and the calculated half-lives, it can be expected that accumulation could occur in humans in the following organs following repeated dosing: adrenal gland, haderian gland, spleen, liver, skin, female reproductive organ (ovary, oviduct, clitoral gland), cervical lymph node, kidney, fat, bone marrow, and lung.

Metabolism

After absorption, Ospemifene is extensively metabolised. M-1 is the major observed metabolite and is pharmacologically active. In rats, monkeys and humans, respectively 84%, 75% and 79% of the total radioactivity was identified. The formation of M-1 was higher in monkey compared to rat and humans. M-2, M-4 and M-8 were human specific plasma metabolites, although in minor quantities. Metabolite M-10 was present in plasma from monkey and humans, but not in plasma from rat. The

formation of M-3 is higher in the non-clinical species compared to humans. No glucuronide metabolites were observed in plasma from all species. Overall, these results indicate that some interspecies differences occur in metabolite profile, but that the major human metabolite (M-1) is present in the non-clinical species. A total of around 6% of the total radioactivity AUC in humans is present as human specific plasma metabolite.

M-9 is detected as a M-1 hydroxide, M-11 as a metabolite hydroxylated at the side chain of Ospemifene and M-12 as a hydroxy metabolite of M-11 only in *in vitro* studies. Since the chemical structure of M-6 was not identified, M-6 will be described as dihydroxy Ospemifene, but is most likely 3,4-dihydroxy Ospemifene (combination of the hydroxide reaction of M-1 and M-4).



M-1: 4-hydroxyospemifene, formed in humans, rat, cynomolgus monkey
M-2: 4'-hydroxyospemifene, formed in humans, rat, dog, cynomolgus monkey
M-3: carboxylic acid metabolite of Ospemifene, formed in humans. rat, cynomolgus monkey
M-4: 3-hydroxyospemifene, formed in rat, cynomolgus monkey
M-6: dihydroxyospemifene, formed in humans, rat
M-7: Ospemifene without side chain ethanol, formed in rat, cynomolgus monkey
M-8: M-1 without side chain ethanol, formed in cynomolgus monkey
M-9: hydroxy metabolite of M-1, formed in humans
M-10: carboxylic acid metabolite of M-1, formed in humans, rat, cynomolgus monkey
M-11: side chain hydroxylated metabolite of Ospemifene, formed in humans, rat, dog, cynomolgus monkey
M-12: hydroxy metabolite of M-11, formed in humans, rat, dog, cynomologus monkey
The chemical structures of M-6, M-9, M-11 and M-12 were not identified with the authentic compounds, and were just speculated based on the analysis of mass spectrometry.

Figure 1: Proposed metabolic pathway of Ospemifene in non-clinical species and humans

CYP3A4 is the major enzyme involved in the metabolism of Ospemifene – however, 2A6, 2B6, 2C9, and 2C19 are also contribute to a lesser extent. CYP3A4 was identified as the major CYP involved in the formation of M-1 and M-2 and their transformation to other metabolites.

Based on the *in vitro* CYP induction studies in human cryopreserved hepatocytes, it is not expected that Ospemifene or M-1 will lead to CYP induction at clinically relevant systemic concentrations (1.0 µM for Ospemifene and 259 nM for M-1). However, it was unknown if Ospemifene could lead to CYP induction in the intestine, since the maximal intestinal concentration (63 µM) is higher than the concentrations investigated (1-20 µM). Therefore, CHMP made a Recommendation for the Applicant to investigate the CYP induction potential of Ospemifene at clinically relevant concentrations and exclude potential induction potential of CYP3A4 in the intestine – this information can be provided post-authorisation.

Several drug-drug interactions studies were performed by the Applicant. No clinically significant interactions due to a reduced plasma protein binding of warfarin are expected. At clinically relevant maximal organ concentrations (50 × $C_{max,unbound}$ = 50 × 0.014 × 0.785 = 0.55 µg/mL), Ospemifene is not a CYP inhibitor. However, at the maximal intestinal concentration (0.1 × dose/250 mL = 24 µg/mL) Ospemifene could be an inhibitor of 2C9 (IC_{50} of 3.8 µg/mL) in the intestine. Ospemifene was not a CYP inducer at clinically relevant organ concentrations (50 × $C_{max,unbound}$ = 50 × 0.014 × 0.785 = 0.55 µg/mL). The induction potential of Ospemifene was not investigated at clinically relevant intestinal concentrations (0.1 × dose/250 mL = 24 µg/mL). Weak induction was observed at 7.6 µg/mL for CYP3A4, indicating that Ospemifene could lead to a CYP3A4 induction in the intestine. At clinically relevant maximal organ concentrations (50 × $C_{max,unbound}$ = 50 × 0.017 × 0.10 = 0.085 µg/mL), M-1 was not a CYP inhibitor. At clinically relevant maximal organ concentrations (50 × $C_{max,unbound}$ = 50 × 1 × 0.03 µg/mL = 1.5 µg/mL), M-2 was not a CYP inhibitor.

Additionally, Ospemifene and M-1 are glucuronidated to pharmacologically inactive metabolites by UGTs – meaning that drugs that inhibit the CYPs and UGTs involved in the metabolism of Ospemifene could have a potential effect on the efficacy of this product. Since there is a possibility that in humans Ospemifene and M-1 are glucuronidated in the liver and deconjugated in the intestine (as was observed in the non-clinical species), CHMP made a Recommendation for the Applicant to provide information that this is unlikely to occur or provide information on the UGTs involved in the glucuronidation of Ospemifene and M-1 (refer to Conclusions on Non-Clinical aspects).

Ospemifene is not a substrate for P-glycoprotein, BCRP, OATP1B1 and OATP1B3 at clinically relevant systemic concentrations. However, the investigated Ospemifene concentrations are lower than the maximum intestinal concentration (63 µM), and higher concentrations could not be investigated due to solubility problems. The Applicant performed a clinical DDI study with ketoconazole, as an example of a potent inhibitor of CYP3A4 and a moderate inhibitor of P-glycoprotein. An increase in C_{max} and AUC of 40% was observed for Ospemifene when concomitantly administered with ketoconazole. It is therefore unlikely that Ospemifene is a substrate for P-glycoprotein to a clinically relevant extent. It remains unknown if Ospemifene is a substrate for BCRP. However, due to lack of availability of specific BCRP inhibitors, is not feasible to perform a DDI study. Therefore, at CHMP's request, the Applicant added in section 5.2 of the SmPC an quote about the uncertainties around intestinal transport via BCRP and that one should be careful with concomitant use with a BCRP inhibitor.

Ospemifene and M-1 were inhibitors of OCT1, and M-1 also of OATP1B1 (contrary to Ospemifene which did not inhibit OATP1B1). On the other hand, Ospemifene and M-1 weren't inhibitors of P-glycoprotein, BCRP, OATP1B3, OAT1, OAT3 and OCT2 in the *in vitro* inhibition studies. A statement on potential interactions has been included in the SmPC. Currently the clinical consequences of inhibition of these transporters are unknown. To collect more data on potential inhibition of transporters, CHMP made a Recommendation for the Applicant to provide BSEP transporter studies post-marketing (refer to Conclusions on Non-Clinical aspects).

Excretion

Excretion via faeces (either via bile or via direct secretion into the intestine) was determined to be the major route of elimination, while excretion via urine is a minor route in the non-clinical species and in humans. Furthermore, the intestinal flora is most likely involved in the deconjugation of the M-1 and M-2 conjugates back to M-1 and M-2, followed by enterohepatic circulation.

Isomer interconversion

As mentioned previously, Ospemifene is a Z-isomer and the E-isomer is present as impurity in the drug formulation (refer to Pharmacology section). No conversion was observed in the *in vitro* metabolite identification studies, and no studies regarding this issue were performed in non-clinical species. Even though it is unlikely that significant conversion of the Z-isomer to the E-isomer will occur in humans, CHMP has made a Recommendation for the Applicant to provide information on the absence of the conversion (refer also to Clinical section of the report on this issue).

2.3.4. Toxicology

Single dose toxicity

The acute toxicity of Ospemifene is low; no hamsters, minipigs or rats died at single oral doses of 1000, 500 or 2000 mg/kg, respectively - and no drug-related effects were seen. Non-GLP pilot toxicity studies with Ospemifene were performed in mice, rats, hamsters, dogs and monkeys. Ospemifene showed a high tolerability in all animals.

Repeat dose toxicity

In a 4-week study in rats, Ospemifene showed comparable effects as Toremifene and 4-hydroxy-Toremifene, but at higher doses. Uterus atrophy, decreased ovary weight, corpora lutea and endometrial glands, hypertrophy of luminal epithelium, and increased cystic follicles were all related to the SERM-like hormonal activity of Ospemifene. Kidney weight was increased, but no nephrotoxicity was shown.

In mice, Ospemifene was well tolerated up to 2000 mg/kg for 13 weeks (4 – 8 times human exposure). At low or medium doses, oral administration of Ospemifene showed ovarian cysts, uterus cystic dilatation of endometrial glands, reduction of pituitary gland and uterus weight in females and cellular hypertrophy, increased cytoplasmic vacuolation in testis and prostate gland atrophy in males (at high doses). These effects were probably related to the hormonal activity of Ospemifene. Increased liver weight and hepatocellular hypertrophy was shown in males and females and were probably caused by metabolic adaptation.

In rats, Ospemifene was well tolerated up to 2000 mg/kg for 13 weeks (3 times human exposure for parent compound, 8 times human exposure for M1-metabolite), and up to 300 mg/kg for 26 weeks - although food intake and body weight decreased at all doses. At 0.5 –3 mg/kg ovarian and uterus weight decreased, but increased at ≥30 mg/kg. At low doses in females, the following were observed: ovarian cysts and black foci; squamous cell metaplasia of uterus; large follicles; decrease of luteal and endometrial glands; hypertrophy of luminal epithelium; increase of LH, FSH and estradiol and metestrus or abnormal diestrus. At high doses, endometrial hyperplasia was shown. In males, prostate weight decreased and prostate atrophy was shown at low doses. At ≥32 mg/kg seminal vesicle atrophy occurred. These changes in reproductive organs were likely due to disturbances induced in the normal hormonal cycles and hormone levels in fertile animals. Total cholesterol levels were reduced dose-responsively down to maximally 42% of control. At ≥50 mg/kg, males showed higher relative adrenal (up to 100%) and liver weights (up to 48%), possibly related

to metabolic adaptation. The NOAEL after 26 weeks was 300 mg/kg/day, but the NOEL was <0.5 mg/kg/day. Because the toxicity of Ospemifene is principally caused by its pharmacodynamic activity, it is difficult to determine a clear safety margin.

Low exposure in animals when compared to humans was the main issue in all pivotal nonclinical studies, especially in non-human primates. Nevertheless, drug-related hepatic changes in the 39-week oral toxicity study in female monkeys are seen. Liver changes were not only observed in rodents (where they could be an expected species-specific estrogenic effect) but also in monkeys. Based on the available data, it could not be excluded that the enzyme changes seen in monkeys are relevant for humans. However, because no liver toxicity was seen in the histopathological examination of the monkeys, and the lack of any clinical signs regarding increase of ALT in humans, it was concluded that this is unlikely to represent a safety concern for humans.

In dogs, increased alkaline phosphatase, increases in uterine (associated with thickening of the uterus and cervix) and liver weights (up to by 164% or 51%, respectively), decrease in ovarian weight (up to -45%) and cystic uterine endometrial hyperplasia were seen in all treated animals. Ovarian antral follicles were absent in all treated animals and corpora lutea were missing. Centrilobular hepatocellular hypertrophy was observed at 200 mg/kg. NOEL was <80 mg/kg/day and NOAEL was 500 mg/kg/day (2.6 times human exposure). However, dogs were not suitable for the non-rodent chronic toxicity species as only minor amounts of the major human metabolite M-1 is formed.

In female monkeys, Ospemifene caused increased liver weight and ALT level, while serum sex hormone-binding globulin (SHBG) levels were significantly suppressed at all treatments. Estradiol, FSH, progesterone, ovarian and uterine weights, and ovarian, follicular and paraovarian cysts increased. There were no fresh corpora luteae. Endometrial hyperplasia was seen in the uterus. Decidual reaction in endocervix and uterus, inflammatory cell foci, glandular vacuolation and glandular atrophy in mammary glands were seen at low doses after 39 weeks. At higher doses, cervical squamous metaplasia, glycogen storage in liver, increased creatinine and fresh corpora luteae, and epithelial atrophy of the vagina occurred. Most of the findings are considered to be exaggerated pharmacological effects of a compound from the SERM class. Drug-related changes in ALT levels and elevated hepatic glycogen storage may be also related to an estrogen agonistic hepatic activity of the study drug. The NOEL was considered <15 mg/kg/day and the NOAEL was 150 mg/kg/day (ca. 0.6 times human exposure). As mentioned before, since the toxicity of Ospemifene is mainly derived from its pharmacodynamic activity, it is difficult to determine a clear safety margin.

Major human metabolites M-1 and M-2 are formed by the mouse, rat and the cynomolgus monkey. Systemic exposure to Ospemifene and its major metabolites in the repeat dose toxicity studies mostly covered or exceeded exposures achieved in patients following administration of a therapeutic dose of 60 mg. Thus, CHMP was of the opinion that the potential toxicity of Ospemifene and its metabolites was assessed adequately in relevant species.

Genotoxicity

The battery of genotoxicity studies performed showed that Ospemifene does not possess a genotoxic potential.

Carcinogenicity

In male mice, an unexpected in-life finding - swelling of the urogenital and/or abdominal areas - was recorded in animals given Ospemifene, the onset of which occurred in week 3 of dosing (2-year carcinogenicity study). All dose levels (100 – 1500 mg/kg) caused severe abdominal organ herniation

into the scrotal sac, which led to several early deaths in all male groups. The severity of the adverse effect led to cessation of dosing of surviving males in week 14. It should be remarked that this was not observed in the 13-week repeat-dose toxicity study with the same mouse strain and comparable doses (50 – 2000 mg/kg). A study was performed to investigate the age-dependence of the effect, however an explanation for the difference between the 13-week study and the oncogenicity study in male mice was not found. These effects were probably caused by the hormonal actions of SERMs on developing immature mouse hormone-sensitive tissues. Similar hormonal developmental adverse effects in the urogenital area have also been observed before with, for example, Tamoxifen and estrogens. Because Ospemifene is not indicated for male humans, CHMP considered that no further studies were necessary on this issue.

At 100, 400 or 1500 mg/kg/day for 2 years, in female mice there was statistical significant occurrence of adrenal subcapsular cell adenoma, adrenal cortical tumor, liver hepatocellular tumor, ovary adenoma/carcinoma, ovary sex cord/stromal tumor and pituitary adenoma/carcinoma. The exposures were 2.1-, 4.0- and 4.7-fold compared to the intended human exposure.

In male and female rats at 10, 50 and 300 mg/kg/day in the 2-year carcinogenicity study, there was a statistical significant occurrence of liver hepatocellular tumors and thymus epithelial tumors. The majority of the other changes reported for the study (including adrenal and kidney changes) were considered to be adaptive physiological changes, or changes associated with reduced body weight gain. Type of tumors and their incidences were comparable to those seen in the oncogenicity studies with other SERMs. The marked increase in thymic tumors at all dose levels has not been reported during other SERM oncogenicity studies. This effect was probably also due to the antiestrogenic effect of the study drug in this target tissue, which could have been attenuated by the physiological thymic involution (atrophy) process induced by estrogens starting during puberty. The Applicant provided a plausible model for forming of thymomas in Wister rats and presented the following arguments:

- estrogen modulates thymic development and age-related involution,
- estrogen has an atrophic effect and reduces thymic cellularity,
- in an animal model of human thymoma (BUF/Mna rats) inhibition of the oestrogen activity in young (pre-pubertal) animals can promote thymoma development indicating that anti-oestrogenic activity can promote thymic tumor development,
- Ospemifene treatment increased the incidences of thymoma, incidences of thymic atrophy appeared reduced.

Thymomas have not been seen with other SERMs. Much epithelial hyperplasia in Fischer rats was caused by Raloxifene, but no extra (respective to control) epithelial hyperplasia was seen in Wistar rats by Ospemifene. However, Wistar rats are much more sensitive to thymomas then Fischer rats. With regards to malignant tumors, there were only 2 at the high dose (1.2 times intended human exposure based on AUC). There was no increase in the incidence of thymoma in the 2-year mouse. There were no serious treatment-related lesions of the thymus in the repeat dose toxicity studies with rats, dogs and monkeys. Moreover, the Applicant has added thymic epithelial tumours as an Important Potential Risk in the Risk Management Plan and will address this issue in their Post-authorisation safety study (Annex II condition).

A different balance of estrogenic/anti-estrogenic effects between Raloxifene and Ospemifene in different species and/or organs is conceivable, if not probable. Although the suggested mechanism has not been proven yet, a risk for the intended target patients is not very likely.

Compared to human exposure at the clinical dose, the exposure to Ospemifene in rats at week 52 was 0.3-, 1.0- and 1.2-fold. Exposure to the metabolite M-1 was 3.9-, 8.2- and 10.2-fold, and

exposure to M2 was 0.7 fold for 50 mg/kg and 0.95 for 300 mg/kg compared to human exposure. Because of the SERM-like/estrogenic nature of the findings in rodents, it is unlikely that they are relevant for clinical use in postmenopausal women.

Ospemifene did not induce DNA adduct formation in the rat liver.

Reproductive and developmental toxicity

No fertility studies were performed – this was agreed to by CHMP, as Ospemifene is only indicated for post-menopausal women.

Ospemifene did not induce malformations in offspring of rats and rabbits. However, the exposures were far below the intended human exposure. Already a low dose of 0.25 mg/kg caused some dead animals, dystocia, and vaginal bleeding in dams. At 0.05 and 0.25 mg/kg an increased post-implantation loss, an increased number of dead pups at birth and an increased incidence of postnatal loss of pups between days 0 - 4 were observed. The F1 generation showed no clinical signs, and no effects on mating performance and fertility were observed.

The reproductive toxicity may be partly explained by the observed severe reduction in body weight gain, but probably the hormonal properties of Ospemifene were involved in causing the inability to normal delivery. All doses tested are far below the intended human exposure, thus Ospemifene should not be used during pregnancy – it should be kept in mind, however, that Ospemifene is only indicated for post-menopausal women.

Other toxicity studies

Ospemifene is not expected to be phototoxic.

Local Tolerance

Not applicable.

2.3.5. Ecotoxicity / environmental risk assessment

Table 1: Environmental endpoints

Substance (INN / Invented Name): Ospemifene			
CAS-number (if available): 128607-22-7			
PBT screening		Result	**Conclusion**
Bioaccumulation potential – log K_{ow}	OECD123	Log K_{OW} = 5.77	Potentially PBT
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow} = 5.77		
	BCF	1300 and 1708 L/kg	not B
Persistence	OECD 301	Not readily biodegradable	
	OECD 308	degT50 for parent in sediment: 61 and 114 d (20°C). DT50 for metabolite M1 in sediment: >100 and 181 d (20°C)	Parent is P (when T is corrected to 12°C). Metabolite M1 is P and probably vP (when T is corrected to 12°C).
	OECD 307	degT50 parent: 8.9; 18; 6.6 and 6.9 d	substantial mineralisation

					occurred
Toxicity	NOEC algae NOEC crustacean NOEC fish	≥1.2 ≥19 ≥18.7			potentially T
	CMR	Ospemifene is reprotoxic			T
PBT-statement	Ospemifene is not PBT, nor vPvB. Metabolite is M1 more polar (carboxylic acid of parent) than Ospemifene and is therefore not expected to meet the B criterion. M1 is not considered to be PBT, nor vPvB.				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
$PEC_{surface\ water}$, default or refined (e.g. prevalence, literature)	0.3	µg/L			> 0.01 threshold (Y)
Other concerns (e.g. chemical class)		Endocrine disrupting effects in mammals			(Y)
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106	- K_{oc} = 90005; 81419 L/kg (soil) K_{oc} = 16109; 16228 L/kg (sludge)			
Ready Biodegradability Test	OECD 301	Not readily biodegradable			
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50,\ water}$ = 0.6; 1.1 d (parent) $DT_{50,\ water}$ = 5.6; 19 d (metabolite M1) $DT_{50,\ sediment}$ = 114; 61 d (parent) $DT_{50,\ sediment}$ = > 100; 181 d (metabolite) % shifting to sediment = 90%			20°C
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test / *Pseudokirchneriella subcapitata*	OECD 201	NOEC	≥ 1.2	µg/L	
Daphnia sp. Reproduction Test	OECD 211	NOEC	≥ 19	µg/L	
Fish, Early Life Stage Toxicity Test / *Pimephales promelas*	OECD 210	NOEC	≥ 19.6	µg/L	
Fish, Short Term Reproduction Assay / *Pimephales promelas*	OECD 229	NOEC	≥ 18.7	µg/L	
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	≥ 100	mg/L	
Phase IIb Studies					
Bioaccumulation	OECD 305	BCF	1250 and 1587	L/kg	based on total radioactivity, normalised to 5% lipids using worst case lipid content (3.64%)
Aerobic and anaerobic transformation in soil	OECD 307	DegT50 for parent	8.9 18 6.6 6.9	d d d d	determined at 20°C. 14, 13, 18, 22% CO_2 in the four soils at t=120 d.
Soil Micro-organisms: Nitrogen Transformation Test	OECD 216	NOEC	≥2000	mg/kg_{dw}	soil o.c.: 1.0%; result normalised to 2% o.c.
Terrestrial Plants, Growth Test / *Species*	OECD 208	NOEC	p.m.	mg/kg	Test invalid
Earthworm, Acute Toxicity Tests *E. fetida*	OECD 207	LC50	>4.2	mg/kg_{dw}	soil o.c.: 4.8%; result normalised to 2% o.c.
Collembola, Reproduction Test *F. candida*	OECD 232	NOEC	≥0.42	mg/kg_{dw}	soil o.c.: 4.8%; result normalised to 2% o.c.
Sediment dwelling organism / *C. riparius*	OECD 218	NOEC	≥4167	mg/kg_{dw}	sediment o.c.: 2.4%; result normalised to 10% o.c.

As a result of the above results, the available data do not allow to conclude definitively on the potential risk of Ospemifene to the environment.

Regarding the endocrine disrupting mode of action, neither of the chronic fish studies shows any effect up to the solubility limit. Because of this, a full fish life cycle test does not need to be performed.

Ospemifene is persistent and toxic (Toxic to reproduction Cat. 2). However, Ospemifene does not meet the B-criterion and is therefore not PBT, nor vPvB. A PBT assessment of M1 could not be performed since experimental data were lacking, however, the CHMP's opinion is that the B criterion would not be met for M1 - further PBT assessment was therefore considered not necessary.

Risk to groundwater, sediment and sewage treatment plants seem negligible.

Risk assessment for the soil compartment was initiated, however, the submitted toxicity study with plants (OECD 208) is considered invalid as it does not fulfil the test guideline requirements with respect to the number of concentrations tested. A range finding was missing and the concentrations selected as dose-response were too few and spaced too closely together; which did not allow for dose response modelling. In addition, several statistically significant effects were observed that were all disregarded as 'not biologically significant'. A well-established NOEC for plants cannot be derived from this test. The CHMP has made a Recommendtion for the Applicant to repeat the OECD 208 test and to conduct the study according to the guideline – the company has committed to do so and provide the results post-authorisation (refer to the Conclusion on Non-Clinical aspects). A test with three species (1 monocotyledon, 2 dicotyledons) is acceptable.

2.3.6. Discussion on non-clinical aspects

Pharmacology

The provided non-clinical data at receptor level were rather limited. However a large number of *in vivo* studies was provided, confirming that the overall *in vivo* pharmacodynamic profile of Ospemifene and its major metabolite(s) results in a pattern similar to that of known SERMs. Based on the receptor affinity and activation studies, the pharmacokinetic data in the non-clinical *in vivo* studies, and studies in which the major metabolite was tested separately, the pharmacodynamic effect after Ospemifene administration can be concluded to be due to at least the combination of the parent compound and the major metabolite. Other metabolites may contribute to a lower extent, due to lower exposure. Overall, after administration of Ospemifene, the effects in vaginal tissue are estrogen-like (although the histological characteristics are different from those of a pure estrogen), effects in bone tissue resemble those of estrogens (mediation by estrogen receptor not shown), in mammary tissues the effects were mainly anti-estrogenic and in uterine tissue partly agonistic and partly antagonistic. In a hERG assay Ospemifene was clearly positive, but no effects on QT interval or other cardiovascular parameters were found in dog and monkey studies (this will be further addressed in section 2.4 - Clinical aspects).

Pharmacokinetics

Regarding the pharmacokinetics of Ospemifene, the concerns identified were difficulties in solubility of the product in *in vitro* studies, stability of the Z-isomer of Ospemifene, the lack of information on plasma protein binding of the metabolites, comparison of the blood-to-serum ratio of Ospemifene and M-1 in animals and humans, missing information on CYP induction and inhibition, and effects on transporters and UGTs. However, the Applicant has, following CHMP Recommendations, commited to

investigate these issues post-authorisation (please refer to the section “Conclusion on the non-clinical aspects” for a detailed list of Recommendations to be fulfilled.)

Toxicology

Toxicological studies showed mainly the expected effects due to the pharmacodynamic action of a SERM. Clear safety margins on the toxicity of Ospemifene are difficult to establish, because nearly all toxicity is related to the pharmacodynamics of the substance. Risks for induction of tumours or hyperplasia in thymus, uterus and ovaries in postmenopausal women are considered small, but are identified as potential risks in the RMP. In order to better define the potential risks of thymic tumour and endometrial hyperplasia, the Applicant will assess these potential risks in a planned post approval safety study (Annex II condition). CHMP also made a Recommendation for the Applicant to repeat the OECD 208 test and to conduct the study according to the guideline (please refer to the section “Conclusion on the non-clinical aspects”).

2.3.7. Conclusion on the non-clinical aspects

The marketing authorization for Senshio can be granted from a non-clinical point of view.

However, to provide further clarity on some issues of concern, the CHMP considered the following Recommendations to be useful:

Pharmacokinetics

1. The in vitro plasma protein binding data of M-1 in the non-clinical species will be provided post-authorisation for interspecies comparison between non-clinical species and humans. However the protocol should be adapted; the Applicant is requested to investigate a concentration range, e.g. 50 to 200 ng/mL for M1.

2. The blood-to-plasma ratio data for ospemifene in monkey and rat and the blood-to-plasma ratio for M-1 in rat, monkey and human will be provided post-authorisation. However the protocol should be adapted; the Applicant is requested to investigate a concentration range, e.g. 500 to 1200 ng/mL for ospemifene and 50 to 200 ng/mL for M1.

3. The Applicant is requested to investigate the CYP induction potential of ospemifene at clinically relevant intestinal concentrations to exclude potential CYP3A4 induction in the intestine. No CYP induction is expected for ospemifene and M-1 at clinically relevant systemic concentrations.

4. The Applicant will provide BSEP transporter studies post-marketing.

5. It is possible that ospemifene and M-1 are glucuronidated in the liver and deconjugated in the intestine in patients (as was observed in the non-clinical species). The Applicant is requested to provide information that this is unlikely to occur or provide information on the UGTs involved in the glucuronidation of ospemifene and M-1.

6. The Applicant committed to evaluate the inhibition potential of ospemifene and M-1 with regards to the UGT enzymes.

7. The Applicant committed to evaluate the binding of ospemifene SHBG and other plasma circulating proteins in humans.

8. The Applicant committed to evaluate and the conversion of the Z-enantiomer of ospemifene to its E-enantiomer post marketing.

9. The Applicant committed to evaluate the metabolism and excretion of ospemifene and its metabolites using the commercial ospemifene 60 mg under fed conditions in a post-authorization study.

Environmental Risk Assessment

10. The applicant is requested to repeat the OECD 208 test as the submitted study as it did not fulfil the test guideline requirements with respect to the number of concentrations tested and several statistically significant effects that were observed were disregarded as 'not biologically significant'.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant

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

Overview of subjects in clinical development programme

Figure 2 provides an overview on the number of subjects who have been included in clinical trials. In the phase 2 and 3 studies, a total of 1,892 postmenopausal subjects, with and without a uterus, were exposed to at least one dose of Ospemifene. Of the 1,892 subjects in the phase 2 and 3 trials, 1546 (approximately 80%) received the 60 mg or higher dose. Among Ospemifene treated subjects, 1370 had at least 12 weeks exposure, 659 had a least 6 months exposure and 409 subjects had at least 1 year of exposure, with a maximum exposure of 89 weeks.

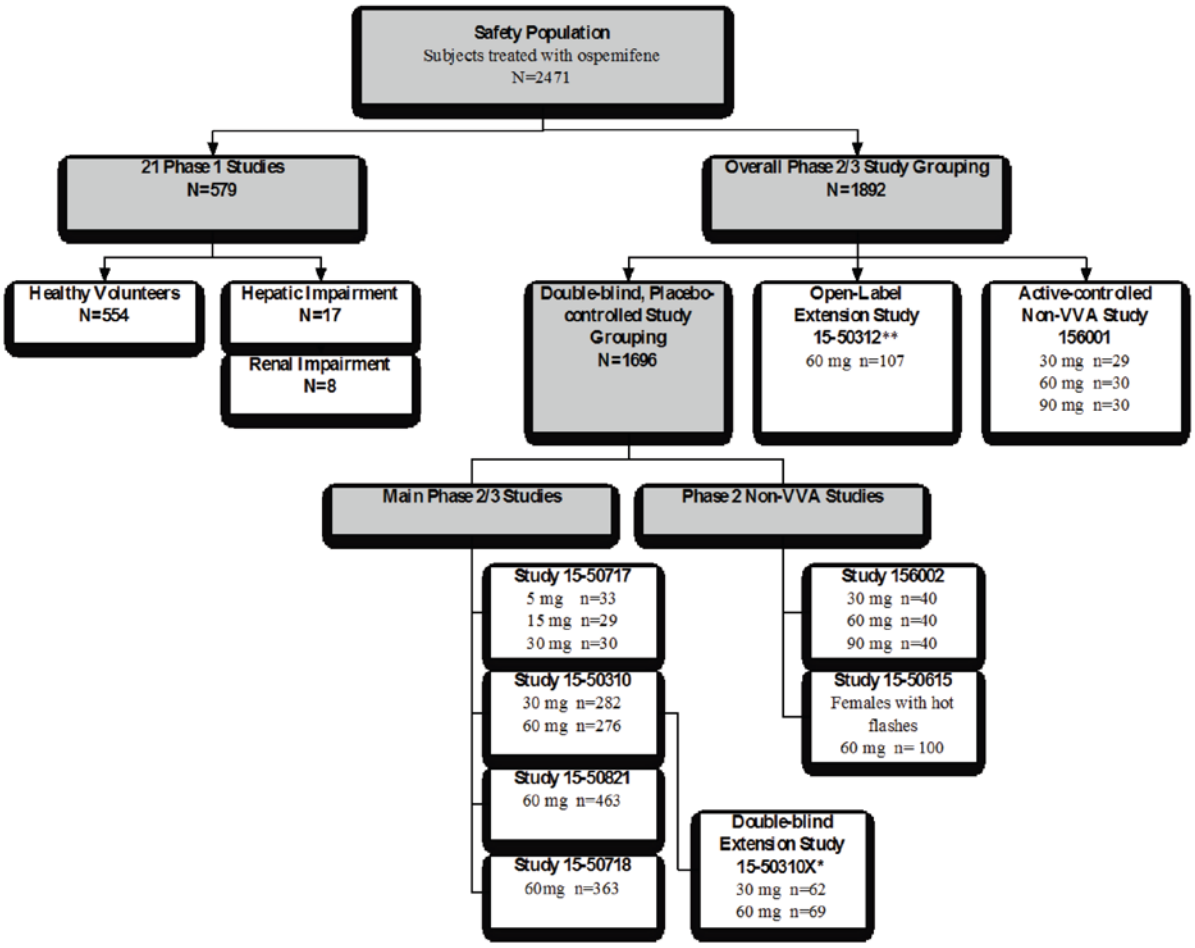


Figure 2: **Overview of number of subjects included in clinical trials**

Tabular overview of clinical studies

The clinical development of Ospemifene includes 21 Phase 1 studies (table 2) and 9 Phase 2/3 studies (table 3). Furthermore a population pharmacokinetic analysis was conducted in a Population PK study using data from Phase 3 studies as well as Phase 1 studies. The dossier also includes 12 in vitro studies using human samples or human cell material. These studies are summarised in table 4.

Table 2: Phase 1 pharmacokinetic studies

Study	population	objectives of the study	Test product(s); Dosage regimen	Number of subjects
15-50927	Healthy postmenopausal women	PK, steady state	Ospemifene 60 mg tablets, multiple doses, PO	12
15-50208	Healthy men	PK, high fat meal	Ospemifene 60 mg tablet single dose, PO	24
15-50208-02	Healthy men who had completed 15-50208	PK,light meal	Ospemifene 60 mg tablet single	12

Study	population	objectives of the study	Test product(s); Dosage regimen	Number of subjects
			dose,PO	
15-50209-01	Healthy postmenopausal women with an intact uterus who completed 1506002	Retrospective survey on effect of food on PK	None	104
1506004 (15-IVQ-001)	Healthy men	BE	Ospemifene 60 mg single dose PO 60 mg tablet vs, 2 x 30 mg capsules or 60 mg solution	23
15-50926	Healthy postmenopausal women	BE, repetitive design	Ospemifene 60 mg tablets Penn vs Manufacturer B batch	24
15-51028	Healthy, fasted post-menopausal women	BE, repetitive design	Ospemifene 60 mg tablets Tablet A (Penn Pharma) vs Tablet B (Manufacturer B)	44
15-51029	Healthy, fed post-menopausal women	BE	Ospemifene 60 mg tablets Tablet A (Penn Pharma) vs Tablet B (Manufacturer B)	28
15-51030	Healthy postmenopausal women	BE	Ospemifene 60 mg tablets Tablet A (Penn Pharma tablet) vs, Tablet B (Manufacturer B), Tablet C (Manufacturer B), Tablet D (Manufacturer B) and Tablet E (Manufacturer B)	29
15-51031	Healthy postmenopausal women	BE	2 single doses of Ospemifene 60 mg tablets given as Tablet A (Penn Pharma tablet) and Tablet B (Manufacturer B)	94
3044001	Healthy men	PK and safety	Ospemifene 10, 25, 50 or 100 mg gelatin capsules; 10, 25, 50, 100, 200, 400, 800 mg single dose PO	28 total: 3 at each dose level and 10 on the highest dose
1506003 (3044002)	Healthy postmenopausal women	PK and safety multiple doses	Ospemifene 25 or 50 mg gelatin capsules; 25, 50, 100 and 200 mg once a day PO	40 total: 8 active and 2 placebo at each of the 4 dose levels
15-50206	Healthy postmenopausal women	ADME	Tritium-labeled Ospemifene in solution; 20.2 MBq in 60 mg single dose PO	6
15-50820	Post-menopausal women with hepatic impairment	PK, hepatic impairment	Ospemifene 60 mg tablet single dose PO	16(7 mild, 2 moderate, and 7 healthy matched control subjects)
15-50920	Post-menopausal women with hepatic impairment	PK renal impairment	Ospemifene 60 mg tablet single dose PO	16 (8 moderate, and 8 healthy matched control subjects)
15-50921	Post-menopausal women with renal impairment	PK renal impairment	Ospemifene 60 mg tablet single dose PO	16 (8 severe, and 8 healthy matched control subjects)
15-50614	Healthy postmenopausal women	DDI S-warfarin -CYP2C9 substrate	Ospemifene 60 mg tablet 12 days plus warfarin 10 mg + vitamin K 5 mg	16
15-50719	Healthy postmenopausal women	DDI omeprazol -YP2C19 and CYP3A4 substrate	Ospemifene 60 mg tablet 7 days plus omeprazole	14
15-50825	Healthy postmenopausal women	DDI bupropion - CYP2B6 substrate	Ospemifene 60 mg tablet 7 days plus bupropion	16
15-50716	Healthy postmeopausal women	DDI rifampicin -potent CYP3A4 inducer ketoconazole -potent CYP3A4 inhibitor	rifampicin 600mg for 5 days plus Ospemifene 60mg ketoconazole 400mg for 4 days plus Ospemifene 60mg	12
15-50823	Healthy postmeopausal women	DDI fluconazole -potent CYP2C9 inhibitor Omeprazole, potent	fluconazole200mg 8 days plus Ospemifene 60mg omeprazole 40mg 8 days plus Ospemifene 60mg	20

Study	population	objectives of the study	Test product(s); Dosage regimen	Number of subjects
		CYP2C19 inhibitor		

Table 3: Phase 2 / 3 studies

Study	Population studied	Objective	Number of subjects
15-50824	Healthy men and women	To evaluate the effects of Ospemifene on the QT interval	Ospemifene 60 mg: 50 240 mg: 50 Placebo: 50 Moxifloxacin : 50
15-50717	Post-menopausal women age 40- 80 with VVA	To evaluate the efficacy and safety of lower doses of Ospemifene in the treatment of vaginal atrophy	Ospemifene 5 mg: 33 15 mg: 29 30 mg: 30 Placebo 34
15-50310	Post-menopausal women age 40- 80 with VVA	To evaluate the efficacy and safety of Ospemifene in the treatment of vaginal atrophy	Ospemifene 30 mg: 282 60 mg: 276 Placebo: 268
15-50310X	Post-menopausal women age 40- 80 with an intact uterus who have completed Protocol 15-50310	To evaluate the long-term safety of Ospemifene in the treatment of vaginal atrophy in post-menopausal women with an intact uterus	Ospemifene 30 mg: 62 60 mg: 69 Placebo: 49
15-50718	Post-menopausal women age 40- 80 with an intact uterus and VVA	To evaluate the efficacy and safety of Ospemifene in the treatment of vaginal atrophy	Ospemifene: 363 Placebo: 63
15-50821	Post-menopausal women age 40- 80 years with moderate-to severe most bothersome VVA symptoms of vaginal dryness or pain associated with sexual activity	To evaluate the efficacy and safety of Ospemifene in the treatment of vaginal atrophy	Ospemifene: 463 Placebo: 456
15-50312	Post-menopausal women age 40- 80 without a uterus who have completed Protocol 15-50310	To evaluate the long-term safety of Ospemifene in the treatment of vaginal atrophy in post-menopausal women without a uterus	301
1506001	Post-menopausal women	To compare the effects of raloxifene and Ospemifene on markers of bone turnover; to compare the tolerability of raloxifene and Ospemifene	118 total: Ospemifene 30 mg: 29 60 mg: 30 90 mg: 30 Raloxifene: 29
1506002	Healthy postmenopausal women with an intact uterus	To determine the effects of Ospemifene on bone, vascular endothelium, lipid metabolism and endometrium	159 total: 40 at each dose level and 39 at placebo
15-50615	Post-menopausal women age 40- 70 with a minimum of 7 moderate, severe or very severe hot flashes per day or 50 per week	To evaluate the efficacy and safety of Ospemifene in the treatment of hot flashes	Ospemifene: 100 Placebo: 98

Table 4: Studies using human biomaterial

Study	Objective	Tested concentrations
15-4302	The potential of Ospemifene to inhibit human CYP enzymes using human liver microsomes	0.1- 1000µM
15-4304	The CYP enzymes metabolizing Ospemifene in liver microsomes	20 µM = 7.6 µg/mL
15-4309	In vitro disappearance and metabolic profile of Ospemifene in human liver homogenate and in liver homogenates of other species, in the presence of cofactors for CYP and UGT	10 and 100 µM = 3.8 and 38 µg/mL
15-4318	The potential of Ospemifene to inhibit human CYP enzymes using N-in-one incubation assay in human liver microsomes	0.01-100 µM =0.0038-38 µg/mL
15-4319	The in vivo metabolism in humans and several other species, using serum samples	samples from study 1506002 (Ospemifene 90mg for 12 weeks)
15-4321	The potential of 4-hydroxy- Ospemifene (M1) to inhibit human CYP enzymes using N-in-one incubation assay in human liver microsomes	0.01-100 µM
15-4324	In vitro disappearance and metabolic profile of M-1 in human liver homogenate, in the presence of cofactors for CYP, UGT, NAT and GST	100 µM
15-4325	The potential of Ospemifene to induce human CYP enzymes using human hepatocytes	0.2-20 µM = 0.076-7.6 µg/mL
15-4326	The potential metabolic drug interactions of Ospemifene and M-1 with exemestane 25 µM (aromatase inhibitor) in human liver microsomes	1-100 µM
15-4328	The contribution of CYP2B6, CYP2C9, CYP2C19 and CYP3A4 to metabolic clearance of Ospemifene in human liver microsomal incubations	0.5, 2 and 10 µM = 0.19, 0.76 and 3.8 µg/mL
15-4332	The potential of 4'-hydroxy- Ospemifene (M2) to inhibit human CYP enzymes using N-in-one incubation assay in human liver microsomes	0.01-100 µM
15-4336	In vitro disappearance and metabolic profile of M-2 in human liver homogenate in the presence of cofactors for CYP, UGT, NAT and GST	5 µM

Pharmacokinetics

Analytical methods

During the development of Ospemifene several analytical methods were used for the analysis of Ospemifene, 4-hydroxy Ospemifene (M1) and 4´-hydroxyOspemifene (M2) in human serum, protein free supernatant and urine. In the early studies, solid phase extraction followed by high performance liquid chromatography (HPLC) with post column photo activation and fluorescence detection was used for the analysis of Ospemifene (and metabolites) in serum. In the more recent studies, LC-MS/MS methods were used for the analysis of Ospemifene in serum and urine. Four different laboratories were involved in the analysis. The analytical methods used in the PK studies were considered to be sufficiently validated and validation reports were provided.

In the human ADME study 15-50206 a tritium labelled form of Ospemifene was used. In this study tritium exchange has been observed.

Pharmacokinetic parameters and statistics

The PK parameters of Ospemifene and its metabolites were evaluated in individual studies using non-compartmental methods. Standard PK parameters were determined and standard statistical analyses were carried out. In most studies the pharmacokinetics were summarized with descriptive statistics. Analysis of variance (ANOVA) models have been used for comparison of two treatments.

Absorption

Absorption and bioavailability

Ospemifene is a lipophilic drug that has a poor aqueous solubility (<0.4µg/ml). The permeability tests with Caco-2 cell monolayers indicated that Ospemifene can be classified as having a high absorption potential. Ospemifene appears to be slowly absorbed by oral route with t_{max} reached 3 to 4 hours after administration under fed conditions. The onset of absorption is rapid, with measurable levels observed 0.5 to 1 hour post dose. However, the extent of absorption and the absolute bioavailability could not be estimated. The Ospemifene C_{max} is approximately 800ng/ml and $AUC_{0-\tau}$ 5500 ng•hr/mL, after once daily repeat doses of 60 mg Ospemifene in the fed state. The main pharmacokinetic parameters of Ospemifene are summarised in table 5.

Table 5: Mean (CV%) PK parameters of Ospemifene and its metabolites after single dose administration and at steady state, under fed conditions, N=12 (Study 15-50927)

Parameter		Ospemifene	4-hydroxyOspemifene	4′-hydroxyOspemifene
C_{max}	Single dose	654 (30.8)	85.7 (44.9)	31.0 (37.8)
(ng/mL)	Steady state	785 (23.1)	102.3 (51.1)	30.1 (41.6)
t_{max}	Single dose	2.8 (2-4)	3.3 (2.5-4)	3.5 (2.5-4)
(hr)	Steady state	3.0 (1-4)	3.8 (1.5-24)	3.5 (2-8)
AUCτ	Single dose	3236 (26.8)	732 (27.4)	297 (30.2)
(ng hr/mL)	Steady state	5448 (19.7)	1435 (41.0)	400 (40.8)
AUC∞ (ng hr/mL)		10433 (32.2)	4577 (39.3)	1091 (37.9)
$t_{½}$ (hr)		29.1 (14.5)	39.3 (21.6)	32.1 (27.3)
CL/F (L/hr)		6.30 (34.2)	NA	NA
Vz/F (L)		258 (27.2)	NA	NA
C_{min} (ng/mL)		93.7 (25.8)	27.8 (40.1)	8.9 (36.9)
C_{av} (ng/mL)		227 (19.7)	59.8 (41.0)	16.7 (40.8)
PTF (%)		311 (25.9)	121 (32.1)	125 (24.8)

A significant food effect was observed for Ospemifene. Both the low- and high-fat breakfasts produced statistically significant increases in C_{max} and exposure of Ospemifene and its active metabolite M-1, when compared to the fasted group. In addition, the variability of the bioavailability is also reduced. Food did not affect t_{max}. The C_{max} and $AUC_{0-72\ h}$ values of Ospemifene were 2.3 and 1.9 fold higher when concomitant administration of a low fat meal was compared to fasted conditions, respectively. The C_{max} and $AUC_{0-72\ h}$ values of 4-hydoxy-Ospemifene were both 1.6 fold higher under fed conditions. High fat food intake enhances AUC and C_{max} by approximately 3.6 fold and 2.8 fold respectively.

The Applicant did not establish the absolute bioavailability of Ospemifene but this has been reflected in the SmPC.

Bioequivalence

The Applicant evaluated the suitability of a capsule formulation and two different tablets, in six bioequivalence studies. Bioequivalence was shown for the Ospemifene tablets by two DP manufacturers including the current commercial manufacturer, Penn Pharma. For the other tablet, bioequivalence was not shown. All pivotal studies used tablets that had been shown to be bioequivalent.

Distribution

In studies 15-50921, 15-50820 and 15-5092, it was shown that Ospemifene is highly (>99%) bound to serum proteins in healthy postmenopausal women, and similar results were observed in patients with renal and hepatic dysfunction. In the ADME study 15-50206 with tritium labeled Ospemifene, the plasma protein binding of total radioactivity was approximately 94%. Binding of Ospemifene and 4-hydroxy-Ospemifene was slightly higher than for total radioactivity, with mean values of approximately 98%. The binding of Ospemifene to SHBG has not been evaluated – however, the CHMP made a Recommendation for the Applicant to evaluate this post-authorisation. A minimal distribution into red blood cells was shown.

Despite being extensively bound to serum protein (>99 %), Ospemifene appears to distribute widely to the extra-vascular compartment. Following oral administration, the mean apparent volume of distribution based on terminal phase is 448 L.

The Applicant has conducted a QWBA study in rats using stable [14C]-Ospemifene. Based on the 24 hour distribution data found in this pre-clinical study and the calculated half-lives, it can be expected that Ospemifene accumulation could occur in humans in the following organs following repeated dosing: adrenal gland, haderian gland, spleen, liver, skin, female reproductive organ (ovary, oviduct, clitoral gland), cervical lymph node, kidney, fat, bone marrow, and lung (refer to Non-Clinical section).

Metabolism and elimination

The apparent elimination half-life of Ospemifene was 25-30 hours. The total clearance by oral route (CL/F) is estimated at approximately 10 L/h. At plasma level, Ospemifene is the predominant entity.

In the ADME studies it was shown that Ospemifene was mainly excreted in the faeces (75%) after oral administration, and approximately 7% of the Ospemifene radioactivity was found in urine. The amount of unchanged Ospemifene that was excreted into the faeces was 39% of the administered dose, and less than 0.2% of the Ospemifene dose is excreted unchanged in urine. In the renal impairment study, hardly any Ospemifene could be detected in the urine samples. Approximately 40% of the total radioactivity in plasma could be identified as Ospemifene or one of the metabolites.

In vitro experiments with human liver microsomes indicated that Ospemifene primarily undergoes metabolism by CYP2C9, CYP3A4 and CYP2C19 enzymes. A total of 7 possible metabolites were detected in humans (refer to figure 1 in the Non-Clinical section of the report). The most abundant metabolite in plasma, representing ~25% of Ospemifene exposure, was M-1 (4-hydroxy Ospemifene). M-2 (4'-hydroxy Ospemifene), M-3 (Ospemifene carboxylic acid), M-4 (3-hydroxy Ospemifene), M-8 (4-hydroxy-O-desalkyl Ospemifene) and M-10 (4-hydroxy Ospemifene carboxylic acid) were also detected in plasma. Their radioactive components in plasma each represented <7% of Ospemifene exposure. Glucuroridation is considered a minor metabolic pathway in humans. The amounts of Ospemifene and M-1 glucuronides excreted in urine and in faeces are small and represent <1% and <5% of the dose administered.

Ospemifene was not a significant P-gp substrate at clinically relevant systemc concentrations.

Based on the large interaction observed with fluconazole (mainly CYP2C9 inhibitor, weak inhibitor of CYP3A4) and the small effect of ketoconazole (strong inhibitor of CYP3A4), CYP2C9 should be considered as the major enzyme and CYP3A4 as a minor enzyme.

The metabolites M1 and M2 are pharmacological active and contribute to the pharmacological effect of Ospemifene for approximately 40%. Therefore the biological activity of Ospemifene (effects and most adverse effects) can be attributed to the cumulative effect of the parent compound and the metabolites M1 and M2.

Dose proportionality and time dependencies

Dose proportionality

Under fed conditions, an almost dose-proportional increase of C_{max} and AUC_{0-T} in the dose range of 60mg to 240 mg was observed. Following oral administration of Ospemifene under the fasted state, C_{max} and AUC_{0-t} increased in a less than dose-proportional manner over this dose range of 25 to 200mg Ospemifene, due to the low solubility of Ospemifene. The pharmacokinetics of Ospemifene over time do not appear to change. Once daily administration resulted in a 2.1 fold accumulation of Ospemifene in serum with an effective half-life of 25 hours.

Inter-conversion

The Applicant did not evaluate if the Ospemifene Z-enantiomer can be converted to its E-enantiomer *in vivo* – however, as previously mentioned, the Applicant commited to evaluate the inter-conversion of the Z to the E-enantiomer post-marketing.

Variability

The intersubject variability of the AUC and C_{max} was 35% and 26% under fed conditions and approximately 50% and 52% under fasting conditions and, respectively. The intra-subject variability of the AUC and C_{max} under fasting conditions was approximately 23% and 43%, respectively. The intra-subject variability has not been tested under fed conditions. No individualization of dose or drug monitoring is needed.

Target population

The Applicant conducted one population PK/PD study to characterize the pharmacokinetics (PK) and pharmacodynamics (PD) of Ospemifene in the target population under fed (analysis 1) and fasting conditions (analysis 2). In analysis 1, a total of 7503 PK blood samples from the 8 studies were analysed, using standard population PK methods. The Applicant selected a two-compartment model with first-order absorption for the Population PK analysis. Age, race, manufacturing sites (Penn Pharmaceuticals [Penn] or Manufacturer B) body weight, BMI, ALB, ALT, BILI, CREAT and CLcr were tested as a covariate on PK parameters of CL/F.

The population PK model appeared to predict the exposure to Ospemifene in the clinical studies properly. Based on this model, it was concluded that none of the tested covariates seemed to have any clinically relevant effect on Ospemifene PK.

Special populations

In patients with severe renal impairment, the Ospemifene exposure was increased by approximately 20%, when compared to healthy matched subjects. The exposure to the major metabolites 4-hydroxy Ospemifene and 4´-hydroxy Ospemifene increased by 20% and 16%, respectively. No studies were conducted in patients with mild and moderate renal insufficiency. Based on these data, the Applicant has added in section 4.2 of the SmPC that no dose adjustment is needed in patients with, moderate or severe renal impairment – this was agreed on by CHMP.

Hepatic impairment studies showed that the exposure of Ospemifene was approximately 30% higher, and the exposure of the main metabolite 4-hydroxy Ospemifene was approximately 70% higher in patients with mild and moderate hepatic impairment, when compared to healthy matched controls. Therefore, no dosage adjustment was considered necessary for patients with mild to moderate hepatic impairment (Child Pugh grade A or B). The effect of severe hepatic impairment on the pharmacokinetics of Ospemifene has not been studied. Therefore, the use of the drug in this subgroup of patients should not be recommended.

The Applicant investigated the influence of age, weight and race on the pharmacokinetics of Ospemifene, and none of these covariates seemed to affect the Ospemifene pharmacokinetics. In the population PK study it was found that body weight was not a significant covariate on the pharmacokinetics of Ospemifene although it was considered a possible statistically significant covariate on the apparent distribution volume of central compartment (V2/F). Based on these data, no dose recommendations for obese and underweighted patients were considered required.

Ospemifene is not indicated in children and adolescents as no PK data are available in these sub-groups.

Pharmacokinetic interaction studies

The potential for drug interactions was evaluated in thirteen in vitro studies and six in vivo studies.

As was previously mentioned, Ospemifene is primarily metabolised by CYP3A4, CYP2C9 and CYP2C19.

When Ospemifene was co-administered with the strong CYP2C9 and moderate CYP3A4 inhibitor fluconazole, a 2.7 fold increase in exposure was observed. Therefore, fluconazole should not be used concomitantly with Ospemifene – this was reflected in section 4.5 of the SmPC. This increase was considered to be due to the inhibition of CYP2C9 and to a lesser extent inhibition of CYP3A involved in Ospemifene metabolism and seemed to suggest that co-administration of Ospemifene with drugs that inhibit both CYP3A and CYP2C9 activity would be expected to increase the drug exposure of Ospemifene significantly and should be avoided.

A mild increase of 40% of the Ospemifene exposure was observed when Ospemifene was co-administered with the potent CYP3A4 inhibitor ketoconazole.

The absorption and metabolism of Ospemifene is not affected to a clinically significant degree (17% increase of AUC) by co-administration of oral omeprazole, a drug that increases gastric pH and is a CYP2C19 inhibitor.

When Ospemifene was co-administered with the potent CYP3A4/CYP2C9 inducer rifampicin, the exposure to Ospemifene decreases by 60% - however, this is not expected to be of clinical relevance. Co-administration of Ospemifene with drugs that induce CYP3A4 or CYP2C9 activity would be expected to decrease significantly the drug exposure of Ospemifene, which may decrease the clinical effect.

In vitro studies have shown that Ospemifene inhibited activities associated with CYP2B6, CYP2C9, CYP2C19, CYP2C8 and CYP2D6, in this order of decreasing potency. Generally, M-1 was a somewhat more potent inhibitor than its parent compound Ospemifene. The CYP induction potential of Ospemifene was also investigated: at 20 µM (7.6 µg/mL), Ospemifene produced a weak induction of CYP2B6- and CYP3A4 mediated activities. The peak serum concentration in postmenopausal women after repeated daily administration of 60 mg Ospemifene does not exceed 3 µM or11367 ng/mL, peaking at approximately 1050 ng/mL. This concentration is clearly lower than the concentrations

inhibiting the enzyme-specific reactions above. Therefore, Ospemifene was considered unlikely to inhibit the metabolism of co-administered drugs metabolised by the hepatic CYP enzymes.

Ospemifene is not a substrate for P-glycoprotein at a concentration of 10 µM (3.8 µg/mL). No other transporter studies were performed with Ospemifene.

Ospemifene treatment did not affect the CYP2C9, CYP2C19, CYP2B6 and 3A4 activity when evaluated using S-warfarin as a CYP2C9 probe substrate, omeprazole as a sensitive CYP2C19 and 3A4 substrate and bupropion as sensitive CYP2B6 substrate, which was consistent with the findings in pre-clinical studies.

Pharmacodynamics

Mechanism of action

Ospemifene (FC-1271a) is an estrogen receptor (ER) agonist/antagonist, commonly referred to as a selective estrogen receptor modulator (SERM) that belongs to the substituted triphenyl chloroethane class of SERM compounds. Its biological actions are mediated through binding to ERs. This binding results in activation of estrogenic pathways in some tissues (agonism) and blockade of estrogenic pathways in others (antagonism). The major target organs of the effects of SERMs include mammary gland, bone, vagina and uterus.

Primary and Secondary pharmacology

In addition to the dose-finding study 15-50717 and three Phase III studies (15-50310, 15-50717 and 15-50310) described in the clinical efficacy section, pharmacodynamic parameters were investigated in the following five studies:

- **15-50842**: Thorough QTc study in healthy males and females.
- **15-06003**: Safety, tolerability and pharmacodynamics during repeated oral administration of Ospemifene (25, 50, 100 and 200 mg/daily) in healthy postmenopausal women.
- **15-06001**: Effect of raloxifene (60 mg/daily) and Ospemifene (30, 60 and 90 mg/daily) on markers of bone turnover in postmenopausal women.
- **15-06002**: Effect of Ospemifene (30, 60 and 90 mg/daily) on bone, vascular endothelium, lipid metabolism and endometrium in postmenopausal women.
- **15-50615**: Efficacy and safety of Ospemifene in treatment of hot flashes in postmenopausal women.

<u>Effects on the vaginal epithelium</u>

Findings on vaginal epithelium are provided from secondary endpoints of the PD studies 15-06001 and 15-06002, as well as from the clinical studies (15-50310, 15-50821 and 15-50718).

- Study **15-06003** was a repeat-dose study in healthy postmenopausal women evaluating 25, 50, 100 and 200 mg doses of Ospemifene administered once daily for 12 weeks. There were 10 subjects per dose level, 8 on active drug and 2 on placebo. The estrogen-like effect on the vaginal epithelium was estimated by karyopyknosis index, assessing parabasal cell layer (index

1), intermediate cell layer (index 2) and superficial cell layer (index 3). All Ospemifene doses differed significantly from placebo for the indices 1 (parabasal cells) and 3 (superficial cells), see table 6 below.

Table 6: Karyopyknosis Index at baseline and after 12 weeks of treatment (mean±SD); Study 15-06003

STUDY GROUP	Visit	N	Karyopyknosis Index		
			1	2	3
25 mg	Baseline	8	39.4±44.3	59.4±44.1	1.3±2.3
	12 weeks	8	7.5±21.2	75.5±22.6	17.0±13.4
50 mg	Baseline	7	82.1±36.5	16.9±34.7	1.0±1.9
	12 weeks	7	0.0±0.0	75.4±17.0	24.6.±17.0
100 mg	Baseline	8	50.0±44.1	45.0±41.7	5.0±4.6
	12 weeks	8	0.6±1.8	80.0±22.2	19.4±22.6
200 mg	Baseline	8	70.0±38.5	29.4±37.2	0.6±1.8
	12 weeks	8	0.0±0.0	76.9±11.6	23.1±11.6
placebo	Baseline	8	38.8±37.7	59.1±36.2	2.1±2.5
	12 weeks	8	54.1±44.0	44.1±42.8	1.8±2.2

- Study 15-06001 compared Ospemifene (30, 60 and 90 mg) with raloxifene (60 mg). This 12 week study was conducted in 119 postmenopausal women. In cervical smears, all Ospemifene groups demonstrated an estrogenic effect on the mucous membranes, as reflected by the percentage shift in Karyopyknosis Index (Table 7 below). Dose response could be observed with increasing Ospemifene dose, although this did not reach statistical significance. In contrast, the raloxifene group had no effect on the index.

Table 7: Karyopyknosis Index at baseline and after 12 weeks of treatment (mean±SD); Study 15-06001

Study group	Visit	N	Karyopyknosis Index		
			1	2	3
30 mg	Baseline	24	51.5±45.4	45.6±42.6	2.9±4.9
	12 weeks	24	6.5±17.1	78.5±20.3	15.0±11.5
60 mg	Baseline	24	34.4±42.8	62.6±41.3	3.0±6.2
	12 weeks	23	8.5±27.4	82.7±26.6	8.8.±10.7
90 mg	Baseline	26	45.1±45.9	51.9±43.2	3.0±5.3
	12 weeks	24	0.8±2.4	84.5±12.0	15.1±11.4
Raloxifene	Baseline	21	32.6±47.3	64.3±45.3	3.1±5.0
	12 weeks	23	31.8±43.6	65.0±42.6	3.2±2.9

- Study **15-06002** was conducted in 160 post-menopausal women. Ospemifene had an estrogen-like effect on vaginal epithelium, as reflected by the changes in the percentage of cells in the parabasal (Index 1), intermediate (Index 2) and superficial (Index 3) layers (Table 8 below). The difference between Ospemifene and placebo was statistically significant in all indices, except for the 30 mg dose in Index 3 ($p = 0.097$).

Table 8: Karyopyknosis Index at baseline and after 12 weeks of treatment (mean±SD); Study 15-06002

Table 21. Karyopyknosis Index at baseline and after 12 weeks of treatment (mean±SD).					
Study group	**Visit**	**N**	**Karyopyknosis Index**		
			1	**2**	**3**
Ospemifene 30 mg	Screening	36	35.1±47.0	59.8±44.5	5.1±9.1
	12 weeks	35	3.5±11.1	86.2±13.7	10.3±9.0
Ospemifene 60 mg	Screening	33	43.6±48.4	52.0±45.1	4.4±6.7
	12 weeks	31	4.2±11.3	83.1±13.9	12.7±9.8
Ospemifene 90 mg	Screening	32	50.2±45.9	47.4±44.0	2.4±3.8
	12 weeks	24	0.3±1.2	86.1±15.1	13.6±15.0
Placebo	Screening	24	46.8±49.3	50.4±46.8	2.8±4.4
	12 weeks	22	69.5±43.0	28.7±41.0	1.8±3.5

Effects on the endometrium

- In study 15-06001 the mean change from Week 12 compared to Baseline was for 30 mg 0.33 mm, 60 mg 0.43 mm, 90 mg 0.52 mm and raloxifene -0.09 mm. Endometrial biopsies showed atrophy in the majority of subjects (83.3% to 95.7% of 12 week samples).
- In study 15-06002 the mean change from Week 12 compared to Baseline was for 30 mg 0.65 mm, 60 mg 0.52 mm, 90 mg 0.39 mm and placebo -0.04 mm. Increases in the number of proliferative changes were observed in all Ospemifene groups. For more details on the endometrium see the section on Clinical Safety.
- No firm conclusions could be drawn on study 15-06003, as the number of women in each group was small (n=8), and the range was wide. However, a weak dose-dependent estrogenic effect was seen on endometrial histology at the 50 mg dose an estrogen effect in one subject, and at the 100 and 200 mg doses in two subjects.

Hormonal assessment

- In study 15-06002 serum FSH, LH, E2 and IGF-1 were measured at Screening, Week 12 and Weeks 14-16 in the Ospemifene 30 mg, 60 mg and 90 mg groups. The LH and FSH concentrations were decreased in a dose-related manner by Ospemifene treatment: 30 mg -6.5 IU/l, 60 mg -9.1 IU/l, 90 mg -12.7 IU/l and placebo -1.6 IU/l. Also a dose-related decrease was observed in IGF-1 concentrations. Ospemifene treatment did not affect E2 concentrations.
- Similarly, in study 15-06001 (60 mg raloxifene and 30 mg, 60 mg and 90 mg Ospemifene) a dose-dependent effect was observed for FSH and SHBG. FSH decreased significantly more with an Ospemifene dose of 90 mg than other dose levels or raloxifene 60 mg. SHBG increased significantly more on all three Ospemifene dose levels compared with raloxifene.
- In study 15-06003 investigating 25 mg, 50 mg, 100 mg and 200 mg Ospemifene, a decrease in FSH and LH levels was observed for the 100 and 200 mg/day dose. Ospemifene had no clear effect on E2 levels at the 60 mg dose, but at high doses (200 mg) estradiol levels could increase - though it should be remarked that the number of subjects evaluated was very small.

QTc prolongation

Study 15-50824 was a Phase 1 study designed to determine the ECG effects of Ospemifene in approximately 200 healthy male and female subjects, between 18 and 45 years of age. The total treatment duration was 7 days, and subjects were randomized to receive placebo daily, Ospemifene 60 mg/day (the proposed therapeutic dose), Ospemifene 240 mg/day (supra-therapeutic dose), or moxifloxacin (as a positive control). The time-averaged QTcI placebo-corrected mean changes from baseline for the Ospemifene 60 mg and 240 mg groups were -2.7 and -3.5 ms, respectively (Figure 3). Neither of the 2 Ospemifene dose groups demonstrated an upper bound that approached or exceeded 10 ms. The data did not raise a signal for any QTc-prolonging effect of Ospemifene, nor on other ECG parameters, including heart rate, PR or QRS interval. Assay sensitivity was reached in that the placebo- corrected QTcI mean change from baseline values for moxifloxacin was +5.4 ms (expected 5-10 ms).

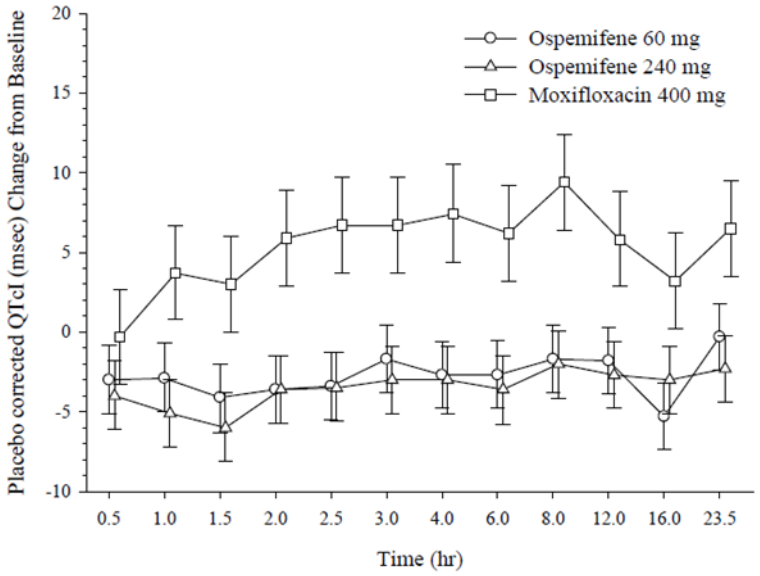


Figure 3: QTcI Placebo-Corrected Change from Baseline at Day 7, Means +/- 2 SEM, ECG Analysis Population

Effects on bone

The effect of Ospemifene activity on bone was assessed with markers of bone formation and reabsorption. The pharmacodynamic studies (1506001, 1506002 and 1506003) suggested an agonistic effect on bone.

In study 1506001, Ospemifene 60 and 90 mg had in some parameters slightly better values when compared to raloxifene 60 mg, but the only significant difference was in the concentrations of the procollagen type I N-terminal propeptide (PINP) - favouring 90 mg/day Ospemifene. These potential beneficial effects of Ospemifene have not been further investigated in clinical Phase 3 studies for an indication of osteoporosis.

Effect on vasomotor symptoms

A placebo-controlled Phase 2 study 15-50615 was conducted in post-menopausal women with vasomotor symptoms. A total of 198 postmenopausal subjects, aged 40 to 70, with a minimum of 7 hot flushes (moderate, severe or very severe) per day or 50 per week, were randomized. For the primary efficacy variable of change in frequency of moderate, severe and very severe vasomotor

symptoms from Baseline to Week 6, the median decrease was significantly greater (p = 0.004) in the Placebo group [-27; CI -32 to -17; Mean (SD) -32.8 (51.9)] compared to the Ospemifene group (-14; CI -21 to -5; Mean (SD) - 10.1 (60.0)]. Also, for the primary efficacy variable of change in severity of moderate, severe and very severe vasomotor symptoms from Baseline to Week 6, the median decrease was significantly greater in the Placebo group (p = 0.005) [-69; CI -85 to -51, Mean (SD) -93.6 (164.9)] compared to the Ospemifene group [-43; CI -64 to -12; Mean (SD) -20.4 (214.4)]. Ospemifene 60 mg/day was not considered to be efficacious in reducing the frequency or severity of vasomotor symptoms in post-menopausal women. Refer also to section "Clinical Safety" for the incidence of hot flushes in the Phase III trials.

Effect on coagulation factors

In study 15-06002, the following coagulation/fibrinolysis parameters were assessed: Fibrinogen, F1+2, TAT, D-Dimer, tPA, Plasminogen Activator Inhibitor (PAI-1). Ospemifene demonstrated a lowering effect on fibrinogen and PAI-1 and no effect on other markers of coagulation/fibrinolysis F1+2, TAT, D-dimer and tPA. The slight differences noted among the list of hemostatic variables could not be used to predict the risk of VTE during use of Ospemifene as none of these are validated surrogate endpoints for the clinical endpoint of VTE.

Effect on lipids

In study 15-06003, Ospemifene treatment demonstrated a decrease in serum LDL variables and an increase in the HDL/LDL ratio - representing a beneficial effect on lipid metabolism. Ospemifene reduced serum LH and FSH with the greatest effect at 100 and 200 mg doses at week 12.

Relationship between plasma concentration and effect

The PK/PD analyses from the pooled data from three Phase 3 studies (15-50310, 15-50821 and 15-50718) did not suggest any meaningful associations between the drug exposures (AUCss or Cmax,ss) of Ospemifene and measures of efficacy indices (percent change of parabasal cells at week 12 from the baseline, percent change of superficial cells at week 12 from the baseline, change of vaginal pH at week 12 from the baseline, and severity of Most Bothersome Symptom [MBS, vaginal dryness or vaginal pain associated with sexual activity]) in the exposure range obtained in these studies.

2.4.2. Discussion on clinical pharmacology

Pharmacokinetics

In the early studies, Ospemifene and metabolite concentrations in serum were determined using HPLC methods with fluorescence detection; in the more recent studies LC-MS/MS methods were used. Because all methods were sufficiently validated and the results of the different studies were more or less comparable, the use of different methods over time was considered acceptable by CHMP. No cross-validation of the different analytical methods used in the PK development program was carried out. The Applicant developed a PK-population model that included "analytical method" as a covariate. Based on the presented population PK data (single dose and multiple dose data), it could be concluded that the analytical methods used in the different studies did not appear to have a significant impact on the pharmacokinetic results. Therefore, CHMP considered the lack of cross-validation of the different analytical methods used in the PK development program could be accepted.

Due to its intrinsic properties (very low solubility and lipophylic nature), the absorption of Ospemifene is highly variable and dependent on food intake. The bioavailability of Ospemifene and its major metabolite 4-hydroxy-Ospemifene increases when Ospemifene is administered concomitantly with food - a light meal enhances the BA of Ospemifene slightly (approximately 10 to 20%), whereas a high fat meal enhances it in a much more marked manner (approximately 100%). In addition, the variability of the bioavailability is also reduced when Ospemifene is administered with food. Ospemifene displays almost dose-proportional pharmacokinetics under fed conditions, in the dose range of 60 to 240 mg. Under the fasted state Ospemifene pharmacokinetics are less than dose-proportional, indicating that the absorption of Ospemifene is limited due its low solubility.

In the SmPC the Applicant recommends to take Ospemifene with food – this advice was supported by the submitted food effect studies, where administration with food led to statistically significantly higher bioavailability of Ospemifene, and also lower inter-subject variability in drug exposure (like mentioned previously). As there were considerable differences between concomitant administration with a light meal or a high fat meal, it is recommended to take Ospemifene at the same time of the day, to keep the nature of food as stable as possible during daily use. The instructions for use are in alignment with the instructions implemented in the pivotal studies, and thus reflect the administration conditions under which Ospemifene has demonstrated clinical efficacy.

The Ospemifene C_{max} is approximately 800ng/ml and AUC_{0-T} 5500 ng•hr/mL, after once daily repeat doses of 60 mg Ospemifene in the fed state. T_{max} can be found approximately 3 hours after administration. Following attainment of the C_{max} the concentration seemed to decline in a biphasic manner, with multiple peaks apparent and a terminal $t_{1/2}$ of 25-30 hours. This could be an indication of enterohepatic cycling of Ospemifene. After administration of multiple doses of Ospemifene a 2.1 fold accumulation was observed, which was in line with the observed long half life.

The Applicant conducted most bioequivalence studies under fasted conditions, which was not considered the most appropriate design for Ospemifene, as its administration is recommended to take place under fed conditions. However, CHMP considered there was no need to repeat the pivotal bioequivalence study - which was also conducted under fasting conditions - as the Applicant still showed bioequivalence despite of the high variability.

No investigation of the absolute BA of Ospemifene was performed. According to the Applicant, the lack of such investigation was justified by the availability of sufficient data showing that the bioavailability of Ospemifene is already complete under fed conditions. Such statement could not be endorsed as the relative bioavailability under fed versus fasting conditions suggests strongly that solubility is a limiting step in the absorption of the drug. Besides, the outcome of the mass-balance

study did not lead to any reliable estimation of absolute bioavailability or the absorbed fraction of the drug. However, as the Applicant reflected the lack of information on the absolute BA in the SmPC, CHMP did not considered necessary to further pursue this issue.

Ospemifene is highly (>99%) bound to serum proteins in healthy postmenopausal women and similar results were also observed in patients with renal dysfunction and hepatic dysfunction. In the ADME study, the plasma protein binding of total radioactivity was approximately 94% and the binding of Ospemifene and 4-hydroxy-Ospemifene was approximately 98%. The difference could possibly be partly explained by the observed tritium exchange in the ADME study.

The human ADME study 15-50206 was conducted to clarify the extent of radioactivity in plasma and excreta. Although an unstable tritium label was used the results were probably likely, seeing as preclinical studies that were conducted in rats showed that the distribution, metabolism and excretion of radioactivity was comparable between stable [14C]Ospemifene and [3H]Ospemifene. Therefore, it could be concluded that the [3H]-exchange in the previous studies has probably not affected the ADME characterisation of the elimination and metabolism of Ospemifene.

Only 40% of the radioactivity could be identified as Ospemifene or one of the metabolites. In the ADME studies it was shown that after oral administration Ospemifene was mainly excreted in the faeces (75%), and approximately 7% of the Ospemifene radioactivity was found in urine. Most of the Ospemifene found in the faeces probably represents unabsorbed Ospemifene. There were no adequate investigations (direct comparison of BA under different food status) with the commercial formulation. However, the CHMP made a Recommendation for the Applicant to evaluate in a post-authorisation study the metabolism and excretion of Ospemifene and its metabolites using the commercial Ospemifene 60 mg under fed conditions; the content of the meal to be coadministered with Ospemifene should be representative for the proposed food intake conditions in the SmPC.

The binding of Ospemifene to SHBG (or other plasma circulating proteins) was not investigated, although phase 1 and phase 2 studies suggested that Ospemifene induces the synthesis of SHBG. Therefore, time dependant PK of Ospemifene could not be excluded. Considering that the drug is intended for long-term use, its main PKs features should be clearly drawn – so, in order to better characterize the PKs of Ospemifene, and following the CHMP Recommendation mentioned previously, the Applicant will investigate the binding potential to SHBG and other main circulating proteins (HSA and AAG).

The consequences of genetic polymorphism on the PK of Ospemifene have not been evaluated in clinical studies. Based on the results of the interaction study with fluconazole, the exposure to Ospemifene is expected to be higher in patients that are poor CYP2C9 metabolisers. Therefore, a warning has been included in the SmPC that Ospemifene should be avoided in patients who are known or suspected to be CYP2C9 poor metabolisers (based on genotyping or previous history/experience with other CYP2C9 substrates). For these patients, it can be expected that the impact of an interaction with a CYP3A4 inhibitor would be larger.

Most clinical pharmacokinetic studies have been conducted in healthy postmenopausal women; however, the pharmacokinetics in women with vaginal atrophy is not expected to be different. Furthermore, a population pharmacokinetic study was conducted to characterise the pharmacokinetics in the postmenopausal women. Based on this study it can be concluded that none of the tested covariates (age, race, manufacturing sites (Penn Pharmaceuticals [Penn] or Manufacturer B) body weight, BMI, ALB, ALT, BILI, CREAT and CLcr) seemed to have any clinically relevant effect on Ospemifene PK. However, the ability to assess the test all covariates appropriately is limited as some subgroups were rather small (e.g. only 21 women >75years and 12 Asian women were included).

A slightly higher exposure to Ospemifene and the M1 and M2 metabolite was observed in patients with severe renal impairment when compared to healthy matched subjects – however, this was not expected to have any clinical consequences.

Although Ospemifene is primarily metabolised by the liver, the two hepatic impairment studies showed that the pharmacokinetics of Ospemifene are only slightly affected by mild and moderate hepatic impairment when compared to healthy matched controls. In patients with moderate hepatic impairment, the exposure of Ospemifene and M1 was approximately 30% and 70% higher, respectively. This higher exposure was not thought to be clinically relevant.

Concomitant administration of fluconazole resulted in a possibly relevant 2.7 fold increase of the Ospemifene exposure and inhibition of the formation of the active metabolite M1 (M1 Cmax was delayed and decreased by 35%) – therefore, it was expected the PD effect of this interaction would be less pronounced than predicted based on PK data of the parent only.

The potential of Ospemifene to inhibit and induce CYP enzymes has been evaluated mainly *in vitro*. Based on these *in vitro* data it was considered unlikely that Ospemifene will affect hepatic CYP metabolism. Weak induction of CYP2B6- and CYP3A4 mediated activities was observed - this could be relevant for the gastrointestinal CYP metabolism. In *in vitro* CYP3A4 assays it was shown that Ospemifene does not affect the metabolism of midazolam or testosterone.

In clinical studies Ospemifene treatment did not affect the CYP2C9, CYP2C19, CYP2B6 and 3A4 activity when evaluated using S-warfarin as a CYP2C9 probe substrate, omeprazole as a sensitive CYP2C19 and 3A4 substrate and bupropion as sensitive CYP2B6 substrate.

Omeprazole was not accepted as a probe drug to investigate the interaction with CYP3A4, although the conversion of omeprazole to omeprazole sulfone is exclusively mediated by CYP3A4 and underestimation of Ospemifene induction potential cannot be excluded. The Applicant is going to conduct an additional drug-drug interaction study (PAS) with midazolam, which is considered an acceptable CYP 3A4 substrate. This study is reflected in the RMP.

The *in vitro* transporter studies that were submitted to were not acceptable (for details see Non-Clinical part of the AR).

The Applicant will evaluate the inhibition potential of Ospemifene and M-1 with regards to the UGT enzymes post-marketing. If *in vitro* data indicate potential UGT inhibition, clinically relevance should be investigated.

Based on the absorption characteristics and the lipophilic nature of Ospemifene, it can be expected that drugs that are used to decrease fat absorption like orlistat (anti-obesity drug) can affect the absorption. The possibility of a potential drug–drug interaction between Ospemifene and orlistat cannot be ruled out and so a warning regarding this interaction was added in the SmPC.

The mechanisms of action of aromatase inhibitors and Tamoxifen may prevent concomitant use with Ospemifene and therefore a contraindication and warning were also included in the SmPC.

Finally, as mentioned in the Non-Clinical section, the company will follow a CHMP Recommendation and evaluate the conversion of the Z-enantiomer of Ospemifene to its E-enantiomer post approval.

Pharmacodynamics

In contrast to the SERM raloxifene, an estrogen effect was observed on the vaginal epithelium for all Ospemifene groups in study 15-06001 (30, 60 and 90 mg).

In study 15-06002 a statistically significant improvement in vaginal epithelium compared to placebo was observed for the 60 mg and 90 mg groups, where an increase in superficial cells and a decrease in parabasal cells was seen; the 30 mg group did not reach statistical significance for an increase in superficial cells. These data were in support of the chosen dose of 60 mg Ospemifene, although the difference in effect between the 30 mg and 60 mg dose was not very large.

Hormonal assessment noted a dose-dependent decrease in LH and FSH concentrations, which demonstrated an estrogen-like effect on the hypothalamic-hypophysis axis. Also, a dose-dependent increase was observed on SHBG levels. E2 concentrations were not affected at the 60 mg dose, but at high dose (200 mg) estradiol levels may increase.

The two pharmacodynamic studies – studies 15-06001 and 15-06002 **-** showed an increase in the *endometrium thickness* – 0.33 to 0.65 mm. Although a dose-dependent effect was observed in study 15-06001 (30, 60, 90 mg), this was not the case for study 15-06002 (30, 60, 90 mg). In addition, in study 15-06002 increases in the number of proliferative changes were observed in all Ospemifene groups compared to placebo. No cystic structures were observed, which is in contrast to the SERM Lasofoxifene (EPAR Fablyn).

The pharmacodynamic studies (15-06001, 15-06002 and 15-06003) suggested an agonistic effect on *bone*, though these potential beneficial effects have not been investigated in clinical Phase 3 studies for an indication osteoporosis.

Study 15-50824 was designed to determine the ECG effects of Ospemifene. The data did not show a signal for any *QTc-prolonging* effect of Ospemifene, which is in contrast with Toremifene (SmPC Toremifene).

Ospemifene was studied in 15-50615 in post-menopausal women with *vasomotor symptoms*. Ospemifene 60 mg/day was not efficacious in reducing the frequency or severity of vasomotor symptoms in post-menopausal women.

The slight differences noted among the list of *hemostatic variables* could not be used to predict the risk of VTE during use of Ospemifene, as none of these are validated surrogate endpoints for the clinical endpoints of VTE. However, the Applicant committed to conduct a PASS-study that follows thromboembolic events to determine the actual thromboembolic risk of Ospemifene 60 mg/daily (Annex II condition).

The PK/PD analyses from the pooled data from three Phase III studies (15-50310, 15-50821 and 15-50718) did not suggest any meaningful associations between the drug exposures (AUCss or Cmax,ss) of Ospemifene and measures of efficacy indices (percent change of parabasal cells, percent change of superficial cells, change of vaginal pH, and severity of Most Bothersome Symptom in the exposure range obtained in these studies.

For more details on endometrium safety, hot flushes and breast safety reference is made to the section on Clinical Safety.

2.4.3. Conclusions on clinical pharmacology

Pharmacokinetics

In general, CHMP considers the pharmacokinetics of Ospemifene in postmenopausal women to have been sufficiently characterised.

There were some minor deficiencies noted, for which the Applicant committed to conduct additional post-authorisation studies (refer to sections to the Conclusions on Non-Clinical aspects for further details). For all these studies an adequate study protocol synopsis was submitted and only for one study some changes to the protocol were recommended by CHMP and agreed with by the Applicant.

Pharmacodynamics

The extensive clinical programme included several well-conducted pharmacodynamic studies to assess primary and secondary pharmacology. The pharmacodynamics profile is expected for a SERM with agonistic and antagonistic estrogenic effects depending on the tissue.

Ospemifene did not result in QTc prolongation, in contrast to the SERM Toremifene (Fareston SmPC). Further, in contrast to the SERM lasofoxifene (EPAR Fablyn) no cystic changes were observed in the endometrium, which is a favourable finding.

The data of studies 15-06001 and 15-06002, showing that the estrogen effect on the vaginal epithelium was more pronounced in the 60 and 90 mg group (in comparison with 30 mg) are in support of the chosen dose of 60 mg Ospemifene - although the difference in effect between the 30 mg and 60 mg dose was not very large.

It is important to remark, however, that as endometrial safety is an issue of concern, the Applicant commited to undertake a post-authorisation safety study that will address this matter (Annex II condition). Endometrial safety will be addressed in further detail on the section regarding Clinical Safety.

2.5. Clinical efficacy

In support of the efficacy of Ospemifene for the treatment of VVA, four double-blind, placebo-controlled clinical studies were submitted (Tables 9.1 and 9.2):

- One Phase 2, 12-week, randomized, double-blind, placebo-controlled dose-ranging study to assess the minimum effective dose of Ospemifene on objective measures of VVA: Study 15-50717
- Three Phase 3 randomized, double-blind, placebo-controlled, parallel-group, multi-center studies:
  - Two 12-week studies: Studies 15-50310 and 15-50821
  - One 52-week study: Study 15-50718

Table 9.1: Randomized Subjects in Efficacy Clinical Studies of Ospemifene in VVA

Study Number	Treatment Duration	Placebo	Ospemifene					All Groups
			5 mg/ day	15 mg/ day	30 mg/ day	60 mg/ day	All	
15-50310	12 weeks	268	--	--	282	276	558	826
15-50717	12 weeks	34	33	29	30	--	92	126
15-50718	52 weeks	63	--	--	--	363	363	426
15-50821 – Dryness Stratum	12 weeks	154	--	--	--	160	160	314
15-50821 – Dyspareunia Stratum	12 weeks	302	--	--	--	303	303	605
Total Subjects		821	33	29	312	1,102	1,476	2,297

Table 9.2: Efficacy Variables in Clinical Studies of Ospemifene in VVA

	Study			
	15-50310	**15-50821**[a]	**15-50718**	**15-50717**
Primary Efficacy				
Change from Baseline to Week 12				
– Vaginal smear MI: % parabasal cells	●	●	●	●
– Vaginal smear MI: % superficial cells	●	●	●	●
– Vaginal pH	●	●	●	●
– Severity of most bothersome VVA symptom: Vaginal dryness	●	●		
– Severity of most bothersome VVA symptom: Vaginal pain associated with sexual activity	●	●		
Secondary Efficacy				
Change from Baseline to Week 4				
– Vaginal smear MI: % parabasal cells	●	●		●
– Vaginal smear MI: % superficial cells	●	●		●
– Vaginal pH	●	●		●
– Severity of most bothersome VVA symptom: Vaginal dryness	●	●		
– Severity of most bothersome VVA symptom: Vaginal pain associated with sexual activity	●	●		
Change from Baseline to Weeks 4 and 12				
– Severity of VVA symptoms in subjects reporting the symptom as moderate or severe at Baseline	●	●		
– Severity of VVA symptoms	●	●		
– Maturation value[b]	●	●		
– Visual evaluation of the vagina	●	●	●[c]	●
– Serum hormone levels	●[c]	●[c]	●[c]	●[c]
– Urinary Distress Inventory-Short Form (UDI-6)	●	●		
– Female Sexual Function Index (FSFI)		●		
% Responders at Week 12[d]	●	●		
Frequency of lubricant application	●	●		
Change from Baseline to Weeks 26 and 52				
– Vaginal smear MI: % parabasal cells			●	
– Vaginal smear MI: % superficial cells			●	
– Vaginal pH			●	
– Visual evaluation of the vagina			●	
– Serum hormone levels			●	

2.5.1. Dose response studies

Study 15-50717

Table 10: Summary of efficacy for trial 15-50717

Title: Efficacy and Safety of Ospemifene in the Treatment of Vulvar and Vaginal Atrophy (VVA) in Postmenopausal Women: A Phase II Dose-Ranging, 12-Week, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study Comparing Oral Ospemifene 5 mg, 15 mg and 30 mg Daily Doses With Placebo	
Study identifier	15-50717
Design	Randomized, Double-Blind, Placebo-Controlled, Parallel-Group

	Duration of main phase:	12 weeks
	Duration of Run-in phase:	not applicable
	Duration of Extension phase:	not applicable
Hypothesis	Superiority	
Treatments groups	**placebo**	12 weeks, 34 subjects
	5 mg Ospemifene	5 mg/daily, 12 weeks, 33 subjects
	15 mg Ospemifene	15 mg/daily, 12 weeks, 29 subjects
	30 mg Ospemifene	30 mg/daily, 12 weeks, 30 subjects

Endpoints and definitions	**Co-Primary endpoint**	Mean change from baseline to Week 12 in vaginal pH
	Co-Primary endpoint	Mean change from baseline to Week 12 in percentage of parabasal cells
	Co-primary endpoint	Median change from baseline to Week 12 in percentage of superficial cells
	Secondary endpoints	- Mean change from baseline to Week 4 in vaginal pH - Mean change from baseline to Week 4 in percentage of parabasal cells - Median change from baseline to Week 4 in percentage of superficial cells
Database lock	11 February 2008	

Results and Analysis

Analysis description	**Primary Analysis**				
Analysis population and time point description	Intent to treat				
Descriptive statistics and estimate variability co-primary endpoints + Effect estimate per comparison	Treatment group (ITT population)	placebo	5 mg	15 mg	30 mg
	Number of subject	N=34	N=33	N=29	N=30
	Change from Baseline to Week 12 in vaginal pH **Mean (SD)**	-0.07 (0.91)	-0.37 (0.83)	-0.95 (1.02)	-1.11 (1.06)
	Mean difference vs. placebo (95% CI) p-value (pairwise comparison, ANCOVA)		-0.285 (-0.705; 0.134) p=0.180	-0.838 (-1.273; -0.404) p<0.001	-1.071 (-1.502; -0.640) p<0.001

	Change from Baseline to Week 12 in percentage parabasal cells **Mean (SD)**	-3.0 (30.2)	-2.8 (33.2)	-24.1 (36.7)	-26.8 (41.1)
	Mean difference vs. placebo (95% CI) p-value (pairwise comparison, ANCOVA)		-2.725 (-16.477; 11.027) p=0.695	-21.566 (-35.785; -7.346) p=0.003	-29.437 (-43.571; -15.303) p<0.001
	Change from Baseline to Week 12 in percentage superficial cells **Median (range)**	0 (-3, 5)	0 (-4, 11)	1 (-5, 30)	1 (-5, 35)
	Median difference vs. placebo (95% CI) p-value (pairwise comparison, CMH)		0 (0; 0) p=0.198	1 (0; 5) p=0.002	1 (0; 4) p=0.018
Analysis description; secondary endpoints	At Week 4, mean changes in vaginal pH were -0.12 for placebo, -0.26 for 5 mg, -0.53 for 15 mg, and -0.78 for 30 mg. The difference in mean change from Screening to Week 4 was statistically significant for 15 mg (p=0.050) and 30 mg (p<0.001). At Week 4, mean percentage of parabasal cells were -0.6% for placebo and 5 mg, -19.7% for 15 mg and -22.0% for 30 mg. The difference in mean change from Screening to Week 4 was statistically significant for 15 mg (p=0.004) and for 30 mg (p<0.001). At Week 4, median changes in percentage of superficial cells were 0% for placebo and 5 mg, 1% for 15 mg, and 2% for 30 mg. The difference in median change from Screening to Week 4 was statistically significant for 15 mg (p=0.011) and 30 mg (p=0.004).				

2.5.2. Main studies

1. Study 15-50310

Table 11: Summary of efficacy for trial 15-50310

Title: Efficacy and Safety of Ospemifene in the Treatment of Vulvar and Vaginal Atrophy (VVA) in Postmenopausal Women: A 12-Week, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study Comparing Oral Ospemifene 30 mg and 60 mg Daily Doses with Placebo	
Study identifier	15-50310
Design	Randomized, Double-Blind, Placebo-Controlled, Parallel-Group

		Duration of main phase:	12 weeks
		Duration of Run-in phase:	not applicable
		Duration of Extension phase:	not applicable
Hypothesis		Superiority	
Treatments groups		**placebo**	12 weeks, 268 subjects
		30 mg Ospemifene	30 mg/daily, 12 weeks, 282 subjects
		60 mg Ospemifene	60 mg/daily, 12 weeks, 276 subjects
Endpoints and definitions	**Co-Primary endpoints**	- Mean change from baseline to Week 12 in vaginal pH - Mean change from baseline to Week 12 in percentage of parabasal cells - Mean change from baseline to Week 12 in percentage of superficial cells - Mean change from baseline to Week 12 in most bothersome VVA symptom (vaginal dryness; vaginal pain associated with sexual activity)	
	Secondary endpoints	- Change from baseline to Week 4 in vaginal pH - Change from baseline to Week 4 in percentage of parabasal cells - Change from baseline to Week 4 in percentage of superficial cells - Percentage of subjects who are responders (Week 12). Defined as 1. Maturation Value increased by at least 10 from Baseline; 2. Vaginal pH decreased by at least 0.5 from baseline; 3. MBS improved by at least 1 point from baseline	
Database lock		19 November 2007	

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat			
Descriptive statistics and estimate variability co-	Treatment group (ITT population)	placebo	30 mg	60 mg

primary endpoints + Effect estimate per comparison	Number of subject	N=268	N=282	N=276
	Change from Baseline to Week 12 in vaginal pH **Mean (SD)**	-0.096 (0.8357)	-0.67 (1.054)	-1.01 (1.053)
	p-value for treatment comparison		P<0.001	P<0.001
	Change from Baseline to Week 12 in percentage parabasal cells **Mean (SD)**	3.98 (35.205)	-21.9 (32.60)	-30.1 (37.93)
	p-value for treatment comparison		P<0.001	P<0.001
	Change from Baseline to Week 12 in percentage superficial cells **Mean (SD)**	2.18 (8.393)	7.78 (12.136)	10.8 (15.66)
	p-value for treatment comparison		P<0.001	P<0.001
	Change from Baseline to Week 12 in most bothersome symptom of Vaginal Dryness **Mean (SD)**	-0.84 (0.996)	-1.22 (0.929)	-1.26 (1.025)
	p-value for treatment comparison (CMH)		P=0.040	P=0.021
	Change from Baseline to Week 12 in most bothersome symptom of Vaginal Pain associated with sexual activity **Mean (SD)**	-0.89 (1.115)	-1.02 (1.132)	-1.19 (1.292)

	p-value for treatment comparison (CMH)		P=0.200	P=0.023
Secondary endpoints	**Mean change from Baseline to Week 4 in vaginal pH** p-value for treatment comparison	-0.18	-0.60 p<0.001	-0.89 p<0.001
	Mean change from baseline to Week 4 in percentage of parabasal cells p-value for treatment comparison	2.75	-18.6 p<0.001	-25.1 p<0.001
	Mean Change from baseline to Week 4 in percentage of superficial cells p-value for treatment comparison	1.29	7.62 p<0.001	9.66 p<0.001
	Mean change from Baseline to Week 4 in most bothersome symptom of Vaginal Dryness p-value for treatment comparison	-0.80	-1.02 p=0.251	-1.03 p=0.203
	Mean change from Baseline to Week 4 in most bothersome symptom of Vaginal Pain associated with sexual activity p-value for treatment comparison	-0.99	-0.99 p=0.968	-1.09 p=0.394

	Percentage of subjects who are responders (Week 12) p-value for treatment comparison	3.4%	20.6% p<0.001	33.7% p<0.001

2. Study 15-50821

Table 12: Summary of efficacy for trial 15-50821

Title: Efficacy and Safety of Ospemifene in the Treatment of Moderate to Severe Vaginal Dryness and Vaginal Pain Associated With Sexual Activity, Symptoms of Vulvar and Vaginal Atrophy (VVA), Associated With Menopause: A 12-Week, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study Comparing Oral Ospemifene 60 mg Daily Dose With Placebo in Postmenopausal Women			
Study identifier		15-50821	
Design		Randomized, Double-Blind, Placebo-Controlled, Parallel-Group	
		Duration of main phase:	12 weeks
		Duration of Run-in phase:	not applicable
		Duration of Extension phase:	not applicable
Hypothesis		Superiority	
Treatments groups		**placebo**	12 weeks, 154 subjects Dryness Stratum, 302 subjects Dyspareunia Stratum
		60 mg Ospemifene	60 mg/daily, 12 weeks, 160 subjects Dryness Stratum,303 subjects Dyspareunia Stratum
Endpoints and definitions	**Co-Primary endpoints**	- Mean change from baseline to Week 12 in vaginal pH - Mean change from baseline to Week 12 in percentage of parabasal cells - Mean change from baseline to Week 12 in percentage of superficial cells - Mean change from baseline to Week 12 in most bothersome VVA symptom (vaginal dryness; vaginal pain associated with sexual activity)	

	Secondary endpoints	- Change from baseline to Week 4 in vaginal pH - Change from baseline to Week 4 in percentage of parabasal cells - Change from baseline to Week 4 in percentage of superficial cells - Change from baseline to Week 4 in severity of the MBS of vaginal dryness and vaginal pain associated with sexual activity - Percentage of subjects who are responders (Week 12). Defined as 1. Maturation Value increased by at least 10 from Baseline; 2. Vaginal pH decreased by at least 0.5 from baseline; 3. MBS improved by at least 1 point from baseline
Database lock		30 July 2009

Results and Analysis

Analysis description	**Primary Analysis**				
Analysis population and time point description	Intent to treat				
Descriptive statistics and estimate variability co-primary endpoints + Effect estimate per comparison	Treatment group (ITT population)	Dryness stratum placebo	Dryness stratum 60 mg	Dyspareunia stratum placebo	Dyspareunia stratum 60 mg
	Number of subject	N=154	N=160	N=302	N=303
	Change from Baseline to Week 12 in vaginal pH **Mean (SD)**	-0.25 (0.068)	-0.95 (0.067) p<0.0001	-0.07 (0.050)	-0.94 (0.050) p<0.0001
	Change from Baseline to Week 12 in percentage parabasal cells **Mean (SD)**	-3.9 (2.18)	-31.7 (2.11) p<0.0001	-0.4 (1.57)	-40.3 (1.56) p<0.0001
	Change from Baseline to Week 12 in percentage superficial cells **Median (Min, Max)**	0.0 (-11, 57)	7.0 (-4, 65) p<0.0001	0.0 (-5, 85)	7.0 (-6, 79) p<0.0001

	Change from Baseline to Week 12 in most bothersome symptom **-3** **-2** **-1** **0** **1**	 9.1% 25.3% 33.8% 28.6% 3.2%	 14.4% 31.9% 24.4% 27.5% 1.9% p=0.0803	 15.6% 23.2% 25.2% 33.8% 2.3%	 22.1% 30.7% 27.1% 18.2% 2.0% p=0.0001
Secondary endpoints	**Change from Baseline to Week 4 in vaginal pH** **Mean (SD)**	-0.23 (0.064)	-0.86 (0.064) p<0.0001	-0.19 (0.049)	-0.84 (0.048) p<0.0001
	Change from Baseline to Week 4 in **percentage parabasal cells** **Mean (SD)**	-2.8 (2.18)	-31.2 (2.15) p<0.0001	-0.8 (1.59)	-37.8 (1.54) p<0.0001
	Change from Baseline to Week 4 in percentage superficial cells **Mean (SD)**	3.6 (1.07)	12.7 (1.05) p<0.0001	1.9 (0.69)	13.0 (0.67) p<0.0001

	Change from Baseline to Week 12 in most bothersome symptom **-3** **-2** **-1** **0** **1**	 5.9% 16.4% 37.5% 39.5% 0.7%	 7.1% 20.1% 43.5% 26.0% 3.2% p=0.1886	 11.8% 22.3% 29.3% 33.1% 3.5%	 13.2% 24.4% 32.9% 26.4% 3.1% p=0.1698
	Percentage of subjects who are responders (Week 12) **strata combined**	Placebo 5.5% (25/456)		60 mg Ospemifene 39.7% (184/463)	

2.5.3. Supportive study

Study 15-50718

Table 13: Summary of efficacy for trial 15-50718

Title: Efficacy and Long-Term Safety of Ospemifene in the Treatment of Vulvar and Vaginal Atrophy (VVA) in Postmenopausal Women: A 52-Week, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study Comparing 60 mg Oral Daily Dose of Ospemifene With Placebo			
Study identifier	15-50718		
Design	Randomized, Double-Blind, Placebo-Controlled, Parallel-Group		
	Duration of main phase: **Duration of Run-in phase:** **Duration of Extension phase:**	52 weeks not applicable not applicable	
Hypothesis	Superiority		
Treatments groups	**placebo**	52 weeks, 63 subjects	
	60 mg Ospemifene	60 mg/daily, 52 weeks, 363 subjects	
Endpoints and	**Co-Primary**	- Mean change from baseline to Week 12 in vaginal pH	

definitions	**endpoints**	- Median change from baseline to Week 12 in percentage of parabasal cells - Median change from baseline to Week 12 in percentage of superficial cells
	Secondary endpoints	- Mean change from baseline to Weeks 52 in vaginal pH - Median change from baseline to Weeks 52 in percentage of parabasal cells - Median change from baseline to Weeks 52 in percentage of superficial cells
Database lock	26 June 2009	

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat		
Descriptive statistics and estimate variability co-primary endpoints + Effect estimate per comparison	Treatment group (ITT population)	placebo	60 mg
	Number of subject	N=63	N=363
	Change from Baseline to Week 12 in vaginal pH **Mean (SD)**	-0.16 (0.952)	-1.22 (0.917)
	Mean difference vs. placebo (95% CI) p-value (ANCOVA)		-1.00 (-1.20; -0.81) p<0.0001
	Change from Baseline to Week 12 in percentage parabasal cells **Median (range/ 95% CI)**	0 (-90, 98/ 0.0, 10.0)	-40 (-100, 75/ -55.0, -30.0)
	Median difference vs. placebo (95% CI) p-value (CMH)		P<0.0001

	Change from Baseline to Week 12 in percentage superficial cells **Median (range/95% CI)** Median difference vs. placebo (95% CI) p-value (CMH)	0 (-5, 28/ 0.0, 0.0)	5 (-5, 60/ 5.0, 7.0) P<0.0001
Secondary endpoints	**Change from Baseline to Week 52 in vaginal pH. Mean (SD)** Mean difference vs. placebo (95% CI) p-value (ANCOVA)	-0.07 (1.210)	-1.30 (0.972) -1.21 (-1.44; -0.98) p<0.0001
	Change from Baseline to Week 52 in percentage parabasal cells. **Median (range/95% CI)** Median difference vs. placebo (95% CI) p-value (CMH)	4 (-60, 97/ 0.0, 11.0)	-45 (-100, 82/ -55.0, -30.0) p<0.0001
	Change from Baseline to Week 12 in percentage superficial cells **Median (range/95% CI)** Median difference vs. placebo (95% CI) p-value (CMH)	0 (-4, 8/ 0.0, 0.0)	2 (-5, 50/ 1.0, 3.0) p<0.0001

2.5.4. Clinical studies in special populations

Modified ITT population analyses

An additional 'Modified ITT' population was defined in order to analyze the efficacy data for the pivotal studies including only subjects who met the inclusion criteria for percent superficial cells, vaginal pH, and MBS. The Modified ITT population included ITT subjects who had ≤5% superficial cells in the maturation index of the vaginal smear at Baseline (defined as the last value taken prior to or on Study Day 1), a vaginal pH >5.0 at Baseline, and moderate or severe vaginal dryness or vaginal pain associated with sexual activity at Randomization that was designated as the most bothersome VVA symptom (Study 15-50821, Dryness Stratum and Dyspareunia Stratum, respectively), or at least one moderate or severe symptom of VVA that was designated as most bothersome at Randomization (Study 15-50310). Overall, mITT results were similar to that seen with ITT population.

Gender, Race, Age

Change from Baseline to Week 12 in the primary endpoints of the four Phase 2 and Phase 3 clinical studies of Ospemifene in VVA was analyzed by subgroups.
The subgroups were age (<65 years, ≥65 years), race (white, black, other), uterine status (intact uterus, Yes/No), prior history of vaginal birth (Yes/No), and previous HRT use (within 6 months prior to first dose of study drug, Yes/No).

Overall, in the subgroup analyses of the effect of age, race, vaginal birth or previous HRT use, there were no significant differences in the efficacy of Ospemifene among categories within subgroups for the endpoints of percentage of parabasal cells, percentage of superficial cells, vaginal pH or severity of the most bothersome VVA symptom of vaginal dryness and vaginal pain associated with sexual activity.

Uterus status

Uterine status (subjects with and without an intact uterus) was chosen as a subgroup because it was unknown whether uterine secretions contribute significantly to the efficacy response to Ospemifene.
Study population in study 15-50310 was stratified by uterine status.
In pooled analyses of clinical trials, the majority of subjects had an intact uterus (55.7% to 90.9%) across treatment groups, with the exception of the Ospemifene 30 mg/day group in which 50% of subjects had an intact uterus, and 50% did not. Overall, the efficacy of Ospemifene on the four primary endpoints was not significantly different among uterine status categories.

None of the subgroup analyses showed any findings of relevance that were different from the findings of the primary analyses in the overall study populations.

Lubricant effect analysis

The clinical studies investigated the effect of lubricant use on efficacy outcomes, as secondary endpoints in studies 15-50310 and 15-50821.

Studies 15-50310 and 15-50821 collected lubricant use data differently; subjects in Study 15-50310 recorded lubricant applications per week in a weekly diary with checkboxes of "None", "1-2 times", and "3 or more times", whereas subjects in Study 15-50821 recorded whether or not lubricant was used each day in a daily diary.

There was a trend toward a lower percentage of women reporting lubricant use in the Ospemifene 60 mg/day group compared to placebo. The percentage of women who reported vaginal lubricant use decreased slightly more in the 60 mg Ospemifene group as compared with placebo after 3 weeks of treatment and over the 12 week study duration.

2.5.5. Analysis performed across trials (pooled analyses AND meta-analysis)

Change in Maturation Index of Vaginal Epithelium: Parabasal cells

In each study, the changes from Baseline to Week 12/LOCF in the percentage of parabasal cells in the Ospemifene 30 mg/day and Ospemifene 60 mg/day groups were significantly different from placebo, indicating greater improvement at Week 12 in the percentage of parabasal cells for subjects in the Ospemifene 30 mg/day, and 60 mg/day groups (Figure 4).

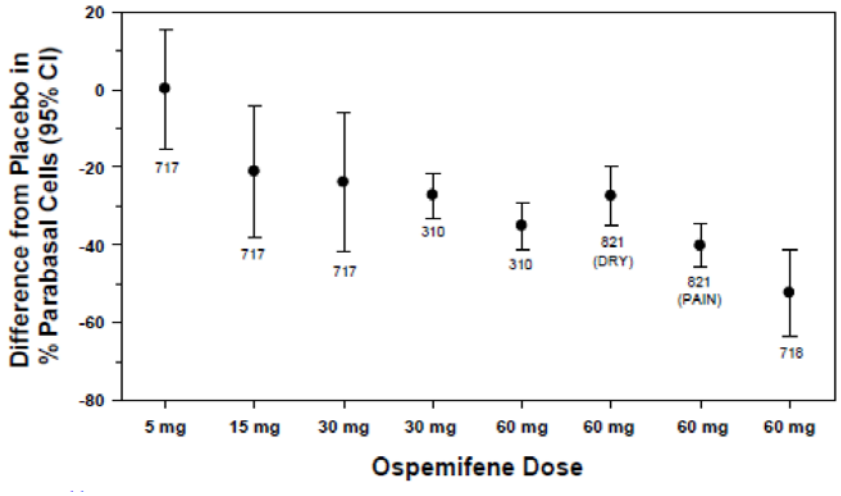


Figure 4: Mean Change from Baseline to Week 12/LOCF in % Parabasal Cells Relative to Placebo by Dose and Study (ITT Population): Studies 15-50310, 15-50717, 15-50718 and 15-50821

Change in Maturation Index of Vaginal Epithelium: Superficial cells

In each study, the changes from Baseline to Week 12/LOCF in the percentage of superficial cells in the Ospemifene 30 mg/day and Ospemifene 60 mg/day groups were significantly different from placebo, indicating greater improvement at Week 12 in the percentage of superficial cells for subjects in the Ospemifene 30 mg/day, and 60 mg/day groups (Figure 5).

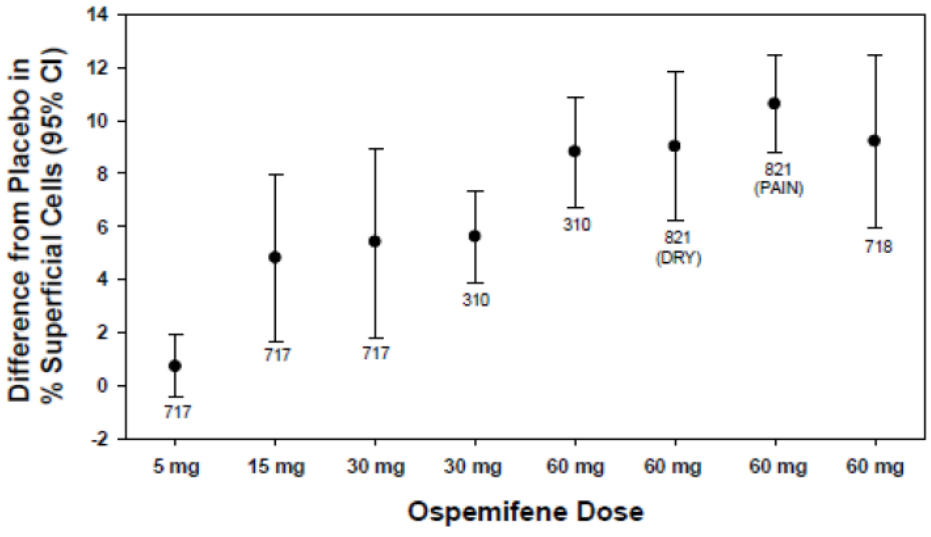


Figure 5: Mean Change from Baseline to Week 12/LOCF in % Superficial Cells Relative to Placebo by Dose and Study (ITT Population): Studies 15-50310, 15-50717, 15-50718 and 15-50821

Change in Vaginal pH

The changes from Baseline to Week 12/LOCF in vaginal pH in the Ospemifene 30 mg/day and Ospemifene 60 mg/day groups were significantly different from placebo, indicating greater improvement at Week 12 in vaginal pH for subjects in both Ospemifene groups. In pooled analyses, there was statistically significant improvement in pH in the 60 mg/day group compared to the 30 mg/day group (Figure 6).

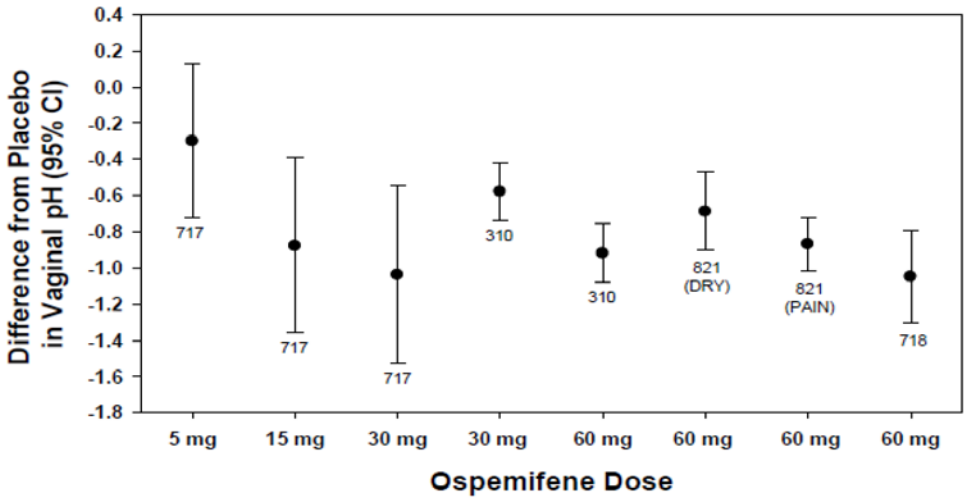


Figure 6: Mean Change from Baseline to Week 12/LOCF in Vaginal pH Relative to Placebo by Dose and Study (ITT Population): Studies 15-50310, 15-50717, 15-50718 and 15-50821

2.5.6. Discussion on clinical efficacy

Design and conduct of clinical studies

Four double-blind, placebo-controlled clinical studies were submitted in support of the efficacy of Ospemifene for the treatment of VVA, one Phase 2 (Study 15-50717) and three Phase 3 studies (studies 15-50310, 15-50821 and 15-50718).

From the three main studies, studies 15-50310 and 15-50821 were considered the most important for efficacy. For the double-blind long-term (52 weeks) study 15-50718, the main objective was long-term safety, however also long-term efficacy data were collected.

Conducting placebo-controlled studies for the indication VVA are in line with the FDA Guidance document 'Estrogen and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms'. This was acceptable since at the time of Opinion there was no guideline in the EU, and FDA requirements have been accepted previously for products for vulvar and vaginal atrophy. Ospemifene was not registered in Europe at the time of this report, and for a new molecular entity two placebo-controlled phase 3 clinical trials are recommended to establish safety and efficacy - according to the FDA Guidance document. These requirements were fulfilled.

Lack of comparator group

No active-comparator group (meaning alternative VVA- treatment group) was included in any phase 2/3 studies. So, in response to Day 120 LOQ and Day 180 LoOI, the Applicant provided an indirect

comparison between Ospemifene and local estrogens (a.o. Vagifem 10 µg, vaginal estradiol preparations).

Dose-finding study

The dose-finding study 15-50717 studying 5 mg/day, 15 mg/day and 30 mg/day Ospemifene was performed 'a posteriori'. Although this could be accepted, it would have been more logical to perform this study before the Phase 3 studies 15-50310, 15-50821 and 15-50781.

Inclusion – and exclusion criteria

Overall, the inclusion and exclusion criteria were acceptable, and in accordance with the FDA Guidance document for studies 15-50310 and 15-50821. For studies 15-50717 and 15-50718, however, the enrolment criteria did not include the parameter "most bothersome symptom of VVA". This parameter should have been included to be in line with the claimed indication.

Co-primary endpoints

The four co-primary efficacy endpoints for studies 15-50310 and 15-50821 were in accordance with the FDA Guidance document.

However, in studies 15-50717 and 15-50718, the co-primary endpoint "*mean change from baseline to Week 12 in the moderate to severe symptom that has been identified by the patients as being the MBS to her*" was not included. It would have been preferred to include this co-primary endpoint also in the European study 15-50718, as there were no data at the time of the report on the change in MBS in the European population. However, a recent international survey (Nappi and Kokot-Kierepa 2010) has shown that subjects from various European countries are not essentially different from those in the USA or Canada with regard to issues related to vaginal atrophy. Therefore, the effect of Ospemifene on MBS in European patients was very likely to be comparable to that seen in subjects of the studies performed in the USA.

Secondary endpoints

A subject was considered a responder if all the following criteria were met:

1) Maturation value increased by at least 10 from Baseline (Screening);

2) Vaginal pH decreased by at least 0.5 from Baseline (Screening);

3) MBS improved (decreased in severity) by at least 1 point from Baseline (Randomization).

As requested in the Day 120 LOQ, the clinical relevance of this responder definition was discussed by the Applicant.

- A change in 1-point improvement (0=None, 1=Mild, 2=Moderate, 3=Severe) was chosen as clinically relevant, as it is perceived by the patient as an improvement, which was considered acceptable.
- The change in pH of 0.5 and improvement in the maturation value by 10 were selected during discussions with the FDA based on a change that is unlikely to be due to chance alone, which was also considered acceptable.

Further, the other secondary endpoints could be used in support of the co-primary endpoints.

Non-hormonal lubricant as needed

The use of lubricant in both groups could make it more difficult to reach statistical significant difference in MBS. In contrast, the European study 15-50718 was performed in accordance with the

initial study design, i.e. without lubricant use in the screening period and the first 12 weeks of the study.

Statistical methods and sample size

In general, the statistical methods used were adequately described and considered acceptable. To replace missing values for the efficacy analyses, the LOCF approach was used.

Number of centers

The number of centers in study 15-50821 was considered high in relation to the number of subjects included. There were a lot of centers with a low number of subjects. This necessitated pooling centers into clusters. The pooling was performed prior to breaking the blinding and was based on geographical location. This was considered acceptable.

Efficacy data and additional analyses

Dose-finding study 15-50717

Both the 15 mg/day and 30 mg/day dose showed statistical significance for the primary efficacy variables, i.e. percentage of parabasal cells, percentage of superficial cells and vaginal pH, compared to placebo. The 5 mg/dose was not statistically significantly different from placebo, and thus could be considered ineffective. The FDA Guidance document recommends that studies identify the lowest effective dose by including an ineffective dose as one of the doses evaluated - this was thereby fulfilled. Based on these results, the Applicant's choice to include 30 mg/day as the lowest dose in the phase III study 15-50310, in addition to a higher dose of 60 mg/day, could be supported.

Demographics, gynaecological history and baseline characteristics

No clinically relevant differences were observed in the demographic characteristic (see also Table 15 in the following section regarding Clinical Safety), gynaecological history and baseline characteristics between treatment groups in the four placebo-controlled studies, nor between the two strata in study 15-50821.

Co-primary efficacy analyses

In study 15-50310, both 30 mg/day and 60 mg/day showed statistical superiority compared to placebo in the ITT population for the co-primary endpoints percentage parabasal cells, percentage superficial cells, vaginal pH and MBS vaginal dryness. For the MBS vaginal pain associated with sexual activity, only the higher dose of 60 mg/day Ospemifene showed superiority.A dose-response effect was seen with the largest difference for the 60 mg/day Ospemifene dose compared to placebo. The PP population showed similar results.

Table 14: Change over time in % patients complaining of MBS by degree of severity (ITT population - LOCF)

	Degree of severity	Ospemifene 60 mg (n=118)			Placebo (n=104)		
		Baseline	4 weeks	12 weeks	Baseline	4 weeks	12 weeks
MBS dryness	None	0.0	19.5	29.7	0.0	15.4	18.3
	Mild	3.4	34.7	36.4	1.0	28.8	30.8
	Moderate	51.7	33.1	22.9	59.6	37.5	28.8
	Severe	44.9	12.7	11.0	39.4	18.3	22.1
		Ospemifene 60 mg (n=120)			Placebo (n=122)		

	Degree of severity	Ospemifene 60 mg (n=118)			Placebo (n=104)		
		Baseline	4 weeks	12 weeks	Baseline	4 weeks	12 weeks
		Baseline	4 weeks	12 weeks	Baseline	4 weeks	12 weeks
MBS dyspareunia	None	3.3	27.5	28.3	1.6	22.1	18.9
	Mild	2.5	24.2	29.2	0.8	17.2	23.0
	Moderate	24.2	17.5	15	27.0	32.0	19.7
	Severe	70.0	30.8	27.5	70.5	28.7	38.5

Also study 15-50821 showed for 60 mg/day statistical significance for percentage parabasal cells, percentage superficial cells and vaginal pH for both the Dryness Stratum and the Dyspareunia Stratum. In line with study 15-50310, for the MBS vaginal pain associated with sexual activity statistical significant superiority was also shown compared to placeboAlthough statistical significant superiority was not met for the MBS vaginal dryness, a trend was observed in favour of Ospemifene compared to placebo. In response to the Day 120 LoQ, the Applicant adequately justified that the improvement over placebo noted for the co-primary efficacy endpoints could be considered clinically relevant, and that the degree of improvement observed with Ospemifene versus placebo was comparable to that observed with Vagifem 10 µg versus placebo.

Further, the Applicant performed an additional descriptive analysis on the primary endpoint outcome based on the medical literature (Ettinger et al, 2008) and discussions with leading European clinicians

The proportion of subjects with clinically relevant MBS outcomes (vaginal dryness and dyspareunia) at Week 12 (see Table 15 below) supported that suggested that not only more patients report benefit with Ospemifene compared to placebo, but also the magnitude of the benefit was greater for Ospemifene.

Table 15: Summary of proportion of subjects with clinically relevant MBS outcomes (vaginal dryness and dyspareunia) at Week 12 (studies 15-50310 and 15-50821: ITT populations, LOCF)

Study	Clinical relevance category	Number (%) of subjects			
		MBS Vaginal dryness		MBS Dyspareunia	
		Ospemifene 60 mg	Placebo	Ospemifene 60 mg	Placebo
15-50310		N=118	N=104	N=120	N=122
	Subjects with **improvement** [a]	88 (74.6%)	60 (57.7%)	82 (68.3%)	66 (54.1%)
	Subjects with **substantial improvement** [b]	50 (42.4%)	28 (26.9%)	49 (40.8%)	36 (29.5%)
	Subjects with **relief** [c]	78 (66.1%)	51 (49.0%)	69 (57.5%)	51 (41.8%)
15-50821		N=160	N=154	N=303	N=302
	Subjects with **improvement** [a]	113 (70.6%)	105 (68.2%)	242 (79.9%)	193 (63.9%)
	Subjects with **substantial improvement** [b]	74 (46.3%)	53 (34.4%)	160 (52.8%)	117 (38.7%)

Subjects with **relief** [c]	99 (61.9%)	82 (53.2%)	191 (63.0%)	143 (47.4%)

[a] Improvement from baseline of ≥1 point on the 4-point scale for MBS (none, mild, moderate and severe).

[b] Improvement from baseline of 2 or 3 points on the 4-point scale for MBS (none, mild, moderate and severe).

[c] Mild or no symptoms at Week 12 (irrespective of baseline severity).

Secondary efficacy analyses

- A significant larger proportion of responders was observed in both pivotal trials in the Ospemifene 60 mg/day group versus placebo.

	Ospemifene	Placebo
Study 15-50310		
N(%) of Responders	33.7% (93/276)	3.4% (9/268)
Study 15-50821		
N(%) of Responders – Strata combined	39.7% (184/463)	5.5% (25/456)
N(%) of Responders – Vaginal dryness as MBS	33.8% (54/160)	7.1% (11/154)
N(%) of Responders – Vaginal pain associated with sexual activity as MBS	42.9% (130/303)	4.6% (14/302)

- The change from baseline to Week 4 was supportive of the co-primary endpoints. An effect was already observed at Week 4. In studies 15-50310 and 15-50821, a statistical significant difference was reached for percentage parabasal cells, percentage superficial cells and vaginal pH The change in MBS did show a trend in favour of the Ospemifene groups, though it was not statistically significant in both studies at Week 4.
- In the secondary endpoint FSFI a difference was seen in pain with a better score in the Ospemifene group compared to placebo, which is in line with the difference observed in the co-primary endpoint MBS vaginal pain associated with sexual activity at Week 12. However, the difference was only small.

Long-term effect

After 52 weeks in study 15-50718, a statistically significant effect was maintained in vaginal pH, percentage of parabasal cells and percentage of superficial cells - however, MBS was not included in this study.

Pooled data of four placebo-controlled efficacy studies

The pooled data showed a similar effect to the one observed in the pivotal efficacy study used for registration of Vagifem 10 for the indication ‘vaginal atrophy’ in terms of improvement in parabasal cells, superficial cells and vaginal pH.

Comparison of improvement in VVA during treatment with Ospemifene over placebo versus improvement in VVA during treatment with Vagifem 10 mcg over placebo

In addition, in response to the D120 LoQ the Applicant identified another relevant study with Vagifem 10 µg (Bachmann et al., 2008).The data show that the efficacy of Ospemifene 60 mg/day is comparable to Vagifem 10 µg (refer to figures 7 to 9).

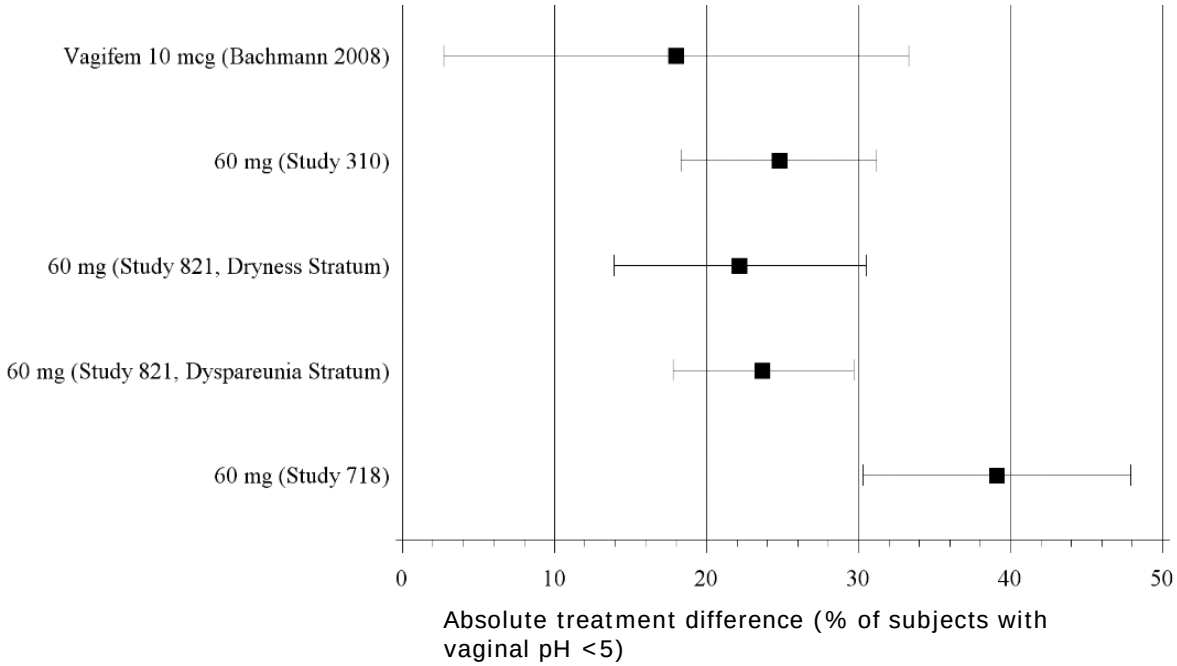


Figure 7. Difference between active arm and placebo in percentage of subjects with vaginal pH<5 at Week 12 (95% CI)

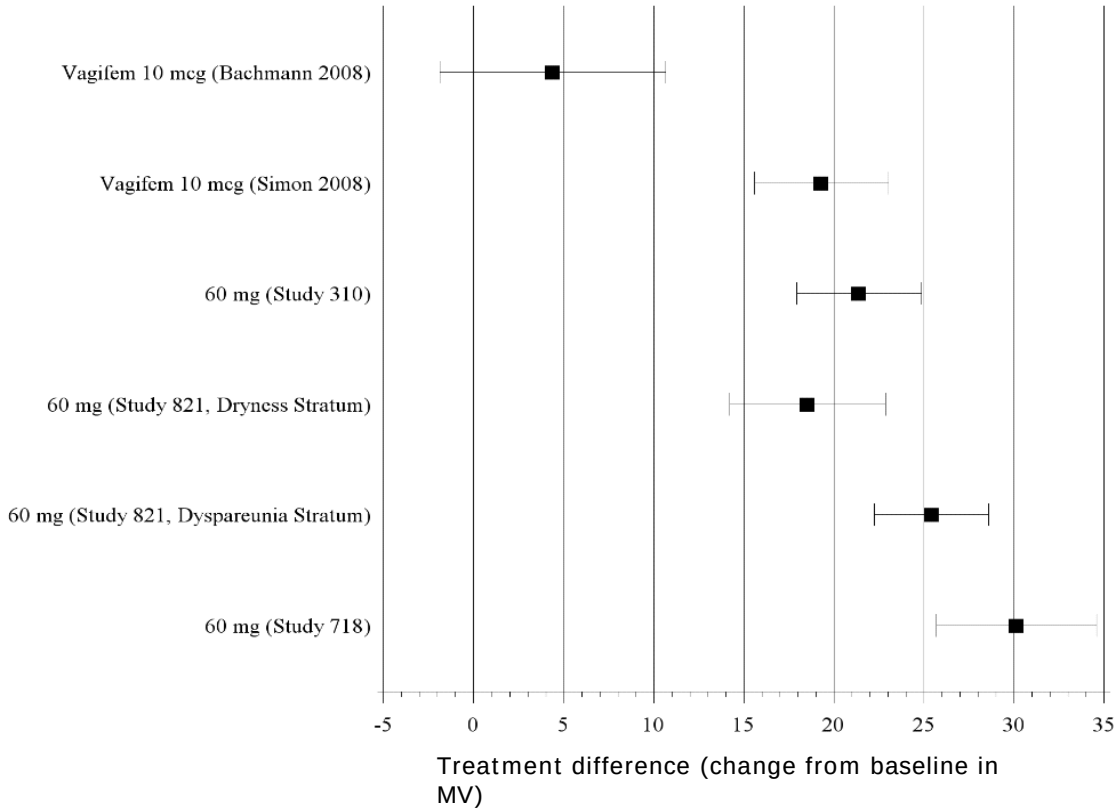


Figure 8. Difference between active arm and placebo in 12-week change in MV (95% CI)

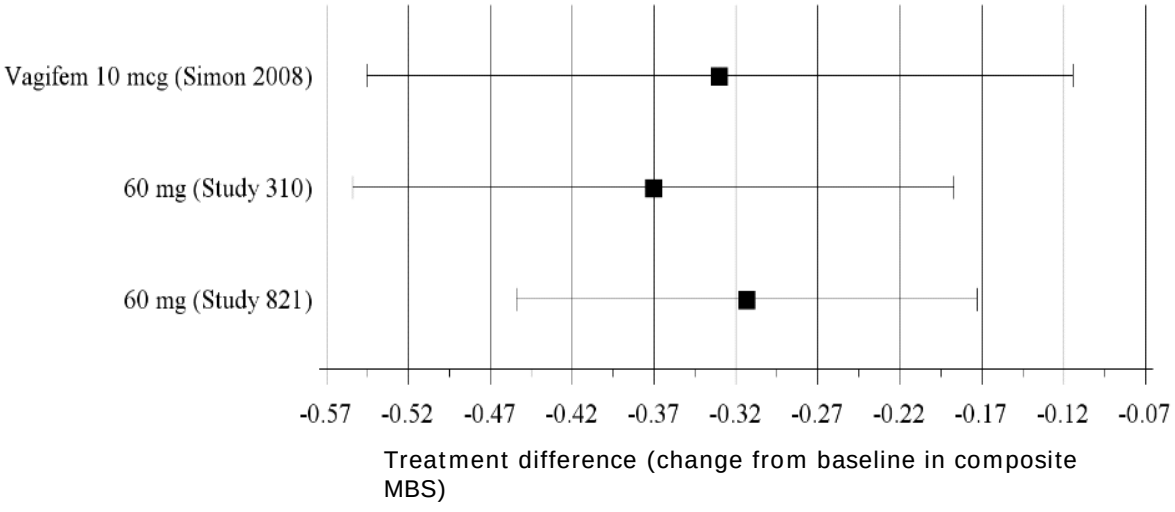


Figure 9: Difference between active arm and placebo in composite MBS at Week 12 (95% CI)

Comparison of improvement in VVA during treatment with Ospemifene over placebo versus improvement in VVA during treatment with oestriol (0.005% oestriol gel, 0.03 mg oestriol, 0.2 mg oestriol vaginally applied (SynapauseR)) and promestriene (10 mg vaginal capsule administered daily) over placebo.

The published efficacy and safety data were not of the same quality for vaginally applied oestriol and promestriene, as for Vagifem 10 µg, but the Applicant compared the available published data to the Ospemifene data. CHMP considered the degree of improvement of Ospemifene versus placebo to be comparable to the degree of improvement versus placebo observed for vaginally applied promestriene and oestriol (refer to Figures 10 and 11).

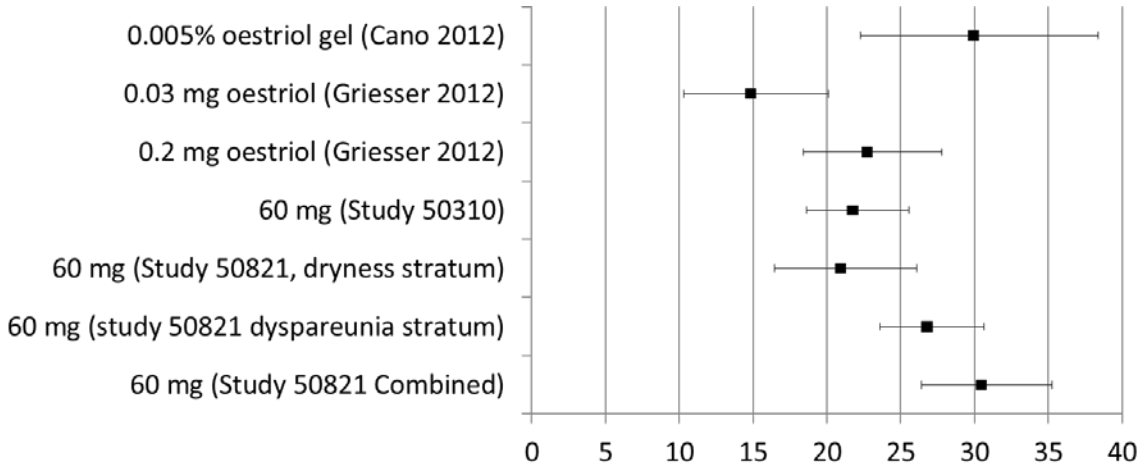


Figure 10: **Difference between active and placebo in mean change from baseline to week 12 in Maturation Value (95% CI), observed cases only.**

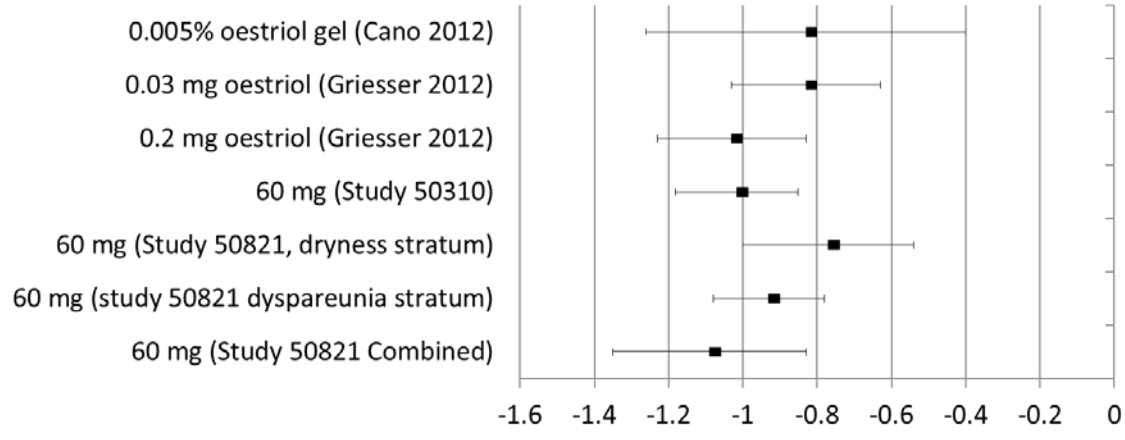


Figure 11: Difference between active and placebo in mean change from baseline to week 12 in pH (95% CI), observed cases only.

2.5.7. Conclusions on the clinical efficacy

The placebo-controlled studies had a good design and were conducted according to the FDA Guidance document.

Although the 30 mg/day dose also showed superiority for vaginal pH, percentage of *superficial cells* and percentage of *parabasal cells* compared to placebo in study 15-50310, the effect of the 60 mg/day dose was 1.4-fold larger for the change in *superficial* and *parabasal* cells and 1.5-fold larger for the change in vaginal pH. Moreover, when looking at the percentage of responders (defined as 1) Maturation value increased by at least 10 from Baseline; 2) Vaginal pH decreased by at least 0.5 from Baseline; 3) MBS improved by at least 1 point from Baseline), the responder-rate was higher for 60 mg Ospemifene (33.7%) compared to 30 mg Ospemifene (20.6%).

For the *MBS vaginal pain associated with sexual activity*, statistical significant superiority was also demonstrated for Ospemifene 60 mg/day, compared to placebo. In contrast, although a strong trend was observed for the *MBS vaginal dryness,* no statistical significant superiority was reached. It should, however, be taken into account that in both 15-50310 and 15-50821 studies the use of a lubricant was allowed as needed, which could make it more difficult to establish a statistically significant difference compared with placebo with regard to MBS vaginal dryness. The efficacy of Ospemifene 60 mg/day was supported by the responder analysis, where significant larger proportion of responders was observed in both pivotal trials in the Ospemifene 60 mg/day group versus placebo. Also, in trial 15-50821, both in the vaginal dryness stratum (33.8% for Ospemifene and 7.1% for placebo) and as in the vaginal pain associated with sexual activity stratum (42.9% for Ospemifene and 4.6% for placebo), a significant higher proportion of responders was identified in the Ospemifene group versus placebo.

Considering that a direct comparison between a systemic and local administration of estrogens was not included in the clinical development, the Applicant provided indirect comparison data of Ospemifene vs local estrogens treatment referring to two publications on the use of Vagifem 10 µg versus placebo (Simon et al 2008 and Bachmann et al 2008). Based on the Applicant's analysis of the data, the degree of improvement observed with Ospemifene 60 mg/day versus placebo was considered comparable to the degree of improvement of Vagifem 10 µg, oestriol (vaginally applied 0.005% oestriol gel, 0.03 mg oestriol, 0.2 mg oestriol) and promestriene (10 mg vaginal capsule administered daily) versus placebo. It was sufficiently demonstrated that the efficacy of Ospemifene versus placebo is comparable to the efficacy of local estrogens versus placebo.

Subgroup analyses of the effect of age, race, vaginal route of birth, or previous HRT use, did not show significant differences in the efficacy of Ospemifene among categories within subgroups for the endpoints of percentage of parabasal cells, percentage of superficial cells, vaginal pH or severity of the most bothersome VVA symptom of vaginal dryness and vaginal pain associated with sexual activity. Therefore, no subgroup could be identified in which the benefit/risks is likely to be different than that of local estrogens.

2.6. Clinical safety

The clinical safety assessment of Ospemifene was based on 30 studies, which included 21 Phase 1 studies and 9 Phase 2/3 studies.

Patient exposure

2471 study participants received at least one dose of Ospemifene. Phase 2 and Phase 3 clinical studies included 1583 subjects with signs and symptoms of VVA, as well as 309 postmenopausal female volunteers with or without vasomotor symptoms associated with menopause. Treatment ranged from six weeks to 64 weeks in duration and evaluated doses of Ospemifene varying from 5 mg/day to 90 mg/day. Four placebo-controlled Phase 2/3 studies included the intended patient population with signs and symptoms of VVA (Table 16).

Table 16. Overall Exposure of Subjects in All Phase 2/3 Studies Grouping

Study	Placebo	Osp 5 mg	Osp 15 mg	Osp 30 mg	Osp 60 mg	Osp 90 mg	All Osp	Raloxifene
Phase 2 Non-VVA Studies								
1506001	--	--	--	29	30	30	89	29
1506002	39	--	--	40	40	40	120	--
15-50615	98	--	--	--	100	--	100	--
Main Studies in VVA								
15-50717	34	33	29	30	--	--	92	--
15-50310	268	--	--	282	276	--	558	--
15-50821	456	--	--	--	463	--	463	--
15-50718	63	--	--	--	363	--	363	--
Extensions Studies in VVA								
15-50312	--	--	--	--	107*	--	107	--
15-50310X	--	--	--	--	--	--	--	--
Total	**958**	**33**	**29**	**381**	**1379**	**70**	**1892**	**29**

Considering only the double blind placebo controlled (DBPC) phase 2/3 studies, 1242 subjects received 60 mg/day Ospemifene with a median duration of exposure to Ospemifene 60 mg of 86 (1, 395) days. The duration of most of these studies was minimum 12 weeks. Of the Ospemifene 60 mg subjects, 384 subjects had at least 24 weeks of exposure, 353 subjects had at least 48 weeks of exposure, and 191 subjects had at least 52 weeks of exposure.
Data regarding long-term safety of Ospemifene 60 mg was considered limited, as only 384 subjects were given Ospemifene 60 mg for more than 6 months and 191 subjects for more than 12 months (DBPC phase 2/3 studies).

Participants were all post-menopausal women. The majority of subjects were 55 to 64 years of age (57% Ospemifene and 59% placebo), with the median age in the overall groups being 59.0 years. The proportion of black or African American women and percentage of subjects from other ethnicity was low compared to white subjects (with 93% Ospemifene subjects and 91% placebo subjects being white).

A total of 396 subjects participating in the DBPC phase 2/3 studies had a BMI ≥30 kg/m2, representing 14.92% of the study population. There was a slightly higher proportion of obese

subjects in the placebo group: 16.8% compared to 13.85% in the Ospemifene group but overall height, weight, and Body Mass Index (BMI) were similar across all groups.

Table 17 includes detailed data on subject demographics from Phase 2/3 studies with Ospemifene:

Table 17: Subject demographics from Phase 2/3 studies with Ospemifene

		Ospemifene	
	Placebo	Osp placebo controlled	All Osp
Characteristics	**N=958**	**N=1696**	**N=1892**
Age, years	**n=958**	**n=1696**	**N=1892**
Mean (SD)	59.1 (6.27)	59.3 (6.42)	59.2 (6.36)
Median (Min, Max)	59.0 (41, 79)	59.0 (40, 80)	59.0 (40, 80)
Age Distribution, n (%)	**n=958**	**n=1696**	**n=1892**
<45 years	8 (0.8)	13 (0.8)	14 (0.7)
45-54 years	212 (22.1)	373 (22.0)	425 (22.5)
55-64 years	563 (58.8)	971 (57.3)	1093 (57.8)
≥65 years	175 (18.3)	339 (20.0)	360 (19.0)
Race, n (%)	**n=956**	**n=1695**	**n=1891**
White	871 (91.1)	1583 (93.4)	1772 (93.7)
Black or African American	49 (5.1)	65 (3.8)	69 (3.6)
Asian	9 (0.9)	17 (1.0)	18 (1.0)
Pacific Islander	0	4 (0.2)	4 (0.2)
Other	27 (2.8)	26 (1.5)	28 (1.5)
Height, cm	**n=958**	**n=1696**	**n=1892**
Mean (SD)	162.4 (6.23)	162.5 (6.23)	162.5 (6.21)
Median (Min, Max)	162.2 (138, 181)	162.6 (132, 183)	162.6 (132, 183)
Weight, kg	**n=958**	**n=1696**	**n=1892**
Mean (SD)	68.69 (12.079)	67.96 (11.605)	67.97 (11.611)
Median (Min, Max)	67.65 (39.6, 118.0)	66.65 (37.6, 113.0)	66.80 (37.6, 113.0)
BMI, kg/m^2	**n=958**	**n=1696**	**n=1892**
Mean (SD)	26.03 (4.191)	25.73 (4.073)	25.73 (4.068)
Median (Min, Max)	25.45 (16.5, 40.8)	25.34 (14.7, 48.6)	25.31 (14.7, 48.6)

Adverse events

A total of 1291/1892 subjects (68.2%) in the all Phase 2/3 grouping reported at least 1 TEAE compared with 1118/1696 (65.9%) in the DBPC group and 518/958 subjects (54.1%) in the placebo group (Table 18). This difference between groups might have been in part due to the greater duration of exposure for the Ospemifene-treated subjects.

Table 18: Overview of Adverse Events: Phase 2/3 Studies

Number (%) of Subjects	Ospemifene DBPC N=1696	All Ospemifene N=1892	Placebo N=958
All Adverse Events	1118 (65.9)	1291 (68.2)	518 (54.1)
Related Adverse Events	516 (30.4)	604 (31.9)	157 (16.4)
Severe Adverse Events	124 (7.3)	169 (8.9)	57 (5.9)
Severe Related Adverse Event	56 (3.3)	79 (4.2)	16 (1.7)
Serious Adverse Events	39 (2.3)	52 (2.7)	17 (1.8)
Related Serious Adverse Events	9 (0.5)	10 (0.5)	1 (0.1)
Deaths	0	0	0
Adverse Events leading to Discontinuation	119 (7.0)	164 (8.7)	36 (3.8)
Related Adverse Events leading to Discontinuation	79 (4.7)	107 (5.7)	17 (1.8)

A breakdown of TEAEs by dose is provided in Table 19.

Table 19: Overview of Treatment-Emergent Adverse Events: Double-blind, Phase 2/3, Placebo-Controlled Studies by Dose

Adverse Event Category	Number (%) of Subjects					
		Ospemifene				
	Placebo N=958	≤15 mg N=62	30 mg N=352	60 mg N=1242	90 mg N=40	All Osp N=1696
Number (%) of Subjects With TEAEs						
All TEAEs	518 (54.1)	28 (45.2)	235 (66.8)	840 (67.6)	15 (37.5)	1118 (65.9)
Treatment-related AEs	157 (16.4)	19 (30.6)	111 (31.5)	378 (30.4)	8 (20.0)	516 (30.4)
Number (%) of Subjects With TEAEs by Maximum Intensity						
All TEAEs						
Mild	213 (22.2)	16 (25.8)	84 (23.9)	330 (26.6)	3 (7.5)	433 (25.5)
Moderate	247 (25.8)	11 (17.7)	122 (34.7)	416 (33.5)	12 (30.0)	561 (33.1)
Severe	57 (5.9)	1 (1.6)	29 (8.2)	94 (7.6)	0	124 (7.3)
Treatment-related AEs						
Mild	90 (9.4)	11 (17.7)	55 (15.6)	178 (14.3)	4 (10.0)	248 (14.6)
Moderate	50 (5.2)	7 (11.3)	40 (11.4)	160 (12.9)	4 (10.0)	211 (12.4)
Severe	16 (1.7)	1 (1.6)	16 (4.5)	39 (3.1)	0	56 (3.3)
Number (%) of Subjects With TEAEs by Causality						
All TEAEs	518 (54.1)	28 (45.2)	235 (66.8)	840 (67.6)	15 (37.5)	1118 (65.9)
None	214 (22.3)	5 (8.1)	73 (20.7)	267 (21.5)	1 (2.5)	346 (20.4)
Unlikely	147 (15.3)	4 (6.5)	51 (14.5)	195 (15.7)	6 (15.0)	256 (15.1)
Possible	129 (13.5)	16 (25.8)	83 (23.6)	259 (20.9)	8 (20.0)	366 (21.6)
Probable	26 (2.7)	3 (4.8)	23 (6.5)	107 (8.6)	0	133 (7.8)
Definite	1 (0.1)	0	5 (1.4)	12 (1.0)	0	17 (1.0)
Number (%) of Subjects with SAEs						
All SAEs	17 (1.8)	0	7 (2.0)	32 (2.6)	0	39 (2.3)
Treatment-related SAEs	1 (0.1)	0	2 (0.6)	7 (0.6)	0	9 (0.5)
Number (%) of Subjects Who Discontinued the Study Due to a TEAE						
All TEAEs	36 (3.8)	4 (6.5)	19 (5.4)	95 (7.6)	1 (2.5)	119 (7.0)
Treatment-related AEs	17 (1.8)	2 (3.2)	12 (3.4)	64 (5.2)	1 (2.5)	79 (4.7)

The most common treatment-related (drug-related) TEAEs (Table 20) reported by patients that participated in all of the DBPC Phase 2/3 studies and who received Ospemifene were: hot flushes (7.5% for Ospemifene and 2.6% for placebo); vaginal discharge (3.7% for Ospemifene and 0.3% for placebo); and headache (3.1% for Ospemifene and 2.4% for placebo).

There was no clear dose-related increase in TEAEs for any of the most common TEAEs considered to be related to treatment, with similar percentages of subjects reporting TEAEs for Ospemifene

≤15 mg/day, 30 mg/day, 60 mg/day, and 90 mg/day. There was no increase in ADRs between the 30 mg and 60 mg Ospemifeme groups (similar proportions of subjects reporting ADRs). However, as the population size was imbalanced in the different treatment groups, no firm conclusions could be drawn regarding the relation between ADR incidence and the administered dose.

Table 20: Summary of Number (%) of Treatment-Related Adverse Events in ≥1% of All Ospemifene-treated Subjects: Phase 2/3 Studies

System Organ Class	Number (%) of Subjects						
		Ospemifene					
	Placebo	≤15 mg	30 mg	60 mg	90 mg	Osp DBPC	All Osp
Preferred Term	N=958	N=62	N=352	N=1242	N=40	N=1696	N=1892
Any Treatment-related AE	157 (16.4)	19 (30.6)	111 (31.5)	378 (30.4)	8 (20.0)	516 (30.4)	604 (31.9)
Investigations	**17 (1.8)**	**1 (1.6)**	**13 (3.7)**	**34 (2.7)**	**0**	**48 (2.8)**	**59 (3.1)**
Weight Increased	5 (0.5)	0	7 (2.0)	11 (0.9)	0	18 (1.1)	22 (1.2)
Musculoskeletal and Connective	**21 (2.2)**	**0**	**9 (2.6)**	**64 (5.2)**	**0**	**73 (4.3)**	**90 (4.8)**
Muscle Spasms	9 (0.9)	0	7 (2.0)	40 (3.2)	0	47 (2.8)	59 (3.1)
Nervous System Disorders	**33 (3.4)**	**5 (8.1)**	**23 (6.5)**	**48 (3.9)**	**4 (10.0)**	**80 (4.7)**	**93 (4.9)**
Headache	23 (2.4)	4 (6.5)	15 (4.3)	30 (2.4)	4 (10.0)	53 (3.1)	63 (3.3)
Reproductive System and Breast	**34 (3.5)**	**5 (8.1)**	**34 (9.7)**	**114 (9.2)**	**2 (5.0)**	**155 (9.1)**	**179 (9.5)**
Vaginal Discharge	3 (0.3)	2 (3.2)	13 (3.7)	47 (3.8)	0	62 (3.7)	67 (3.5)
Genital Discharge	1 (0.1)	2 (3.2)	9 (2.6)	16 (1.3)	2 (5.0)	29 (1.7)	38 (2.0)
Skin and Subcutaneous Tissue	**18 (1.9)**	**2 (3.2)**	**11 (3.1)**	**57 (4.6)**	**3 (7.5)**	**73 (4.3)**	**87 (4.6)**
Hyperhidrosis	6 (0.6)	0	4 (1.1)	20 (1.6)	2 (5.0)	26 (1.5)	34 (1.8)
Vascular Disorders	**27 (2.8)**	**7 (11.3)**	**28 (8.0)**	**95 (7.6)**	**1 (2.5)**	**131 (7.7)**	**169 (8.9)**
Hot Flush	25 (2.6)	6 (9.7)	28 (8.0)	93 (7.5)	1 (2.5)	128 (7.5)	166 (8.8)

Urinary Tract Infection (UTI)

For the TEAE of UTI, higher percentages of subjects experienced this TEAE from 4 weeks to <12 weeks (46/1800 subjects [2.6%] and 19/925 subjects [2.1%], respectively) and from 12 weeks to <26 weeks (30/1370 subjects [2.2%] and 11/568 subjects [1.9%], respectively) than during the preceding duration intervals. This was likely associated with the urine dipstick testing being done at 4 weeks and 12 weeks. When all infective events relating to infections of the urinary tract were taken into account, there are no differences over time with placebo and DBPC Phase 2/3 Ospemifene groups.

Vulvovaginal signs and symptoms

In the DBPC study grouping, 5.4% of 60 mg Ospemifene-treated subjects experienced a TEAE of vulvovaginal infection and 2.6% of placebo subjects. None of these AEs led to discontinuation in the Ospemifene- treatment group.

Vaginal discharge was consistently higher in the Ospemifene group compared to the placebo group: 3.8% 60 mg Ospemifene, 3.7% 30 mg Ospemifene and 0.3% placebo. The Applicant indicated that the recording of the event of vaginal or genital discharge did not appear to differentiate between physiological and pathological discharge. Further, the Applicant indicated that it could be expected that if Ospemifene increases the number of superficial cells and reduces the number of parabasal cells, the vaginal epithelium could return to a state more akin to the early-menopausal cellular state and a physiological vaginal discharge might occur.

Serious adverse events

Thirty-nine (2.3%) patients in the DBPC group experienced a serious adverse event compared to 17 (1.8%) in the placebo group, representing an exposure corrected rate of 57 SAEs/1000 women years exposure on Ospemifene and 62.3 SAEs/1000 women years exposure on placebo.

In response to D120 LoQ, the Applicant provided a list and description of SAEs that occurred with Ospemifene 60 mg during the DBPC clinical programme: in total, with Ospemifene 60 mg, 32 subjects (2.6%) experienced 41 SAEs of them 7 were considered by the sponsor as drug related. In the placebo group, 17 subjects (1.8%) experienced 33 SAEs, from which 1 was considered drug related.

The AEs in the Ospemifene group were CVA, endometrial hyperplasia, ovarian cyst, DVT (two subjects), global amnesia and nausea. The incidences of CVA, DVT and endometrial hyperplasia were not higher than the expected background incidence. A registration file was, however, considered too limited to reliably estimate the incidence of these rare events. As an increased risk of thromboembolic events is a class effect of SERMs, a potential increased risk cannot be excluded. The risk of VTE and endometrial hyperplasia and cancer is separately discussed below in AEs of interest.

Deaths

No deaths occurred during the drug development program for Ospemifene.

Adverse events of special interest

Two of the Major Objections raised during the course of this procedure regarded clinical concerns on endometrial safety and possility of increased risk of VTE events – these will be addressed in the present section. Both concerns were addressed specifically by the Applicant and the overall answers were considered adequate by CHMP.

Endometrial thickness

Subjects that had uterine or vaginal prolapse (Grade 2 or higher) or had clinically significant abnormal gynaecological findings - other than VVA - were excluded. In addition, patients with uterine bleeding of unknown origin, uterine polyps were also excluded due to the weak oestrogen agonist/antagonist effect of Ospemifene on the endometrium. Patients with symptomatic and/or large uterine fibroids (estimated size >3 cm) were likewise excluded.

Uterine safety was monitored by transvaginal ultrasound (TVU) at baseline, during treatment and at the end of study to evaluate endometrial thickness. In addition, endometrial biopsies at baseline and end-of-study to evaluate endometrial histology were carried out, as well as during treatment as needed for subjects with findings of endometrial thickness ≥4 mm or for symptoms of vaginal bleeding. Whenever possible, histopathology of all endometrial polyps was determined per regulatory guidelines, and central expert review of polyp histopathology was performed.

An increase from Baseline to 12 weeks was observed for the mean change in the Ospemifene group (0.474±1.4292 mm); little change was observed for the placebo group (0.040±1.1500 mm). Mean changes were similar across all doses of Ospemifene, with the exception of ≤15 mg/day, in which no mean change from baseline was observed (0.000±0.6281 mm). At 6 months, the mean change from baseline in the Ospemifene group was 0.568±1.6434 mm; little change was observed for the placebo group (0.045±1.2625 mm) for this interval. Mean changes were similar in the Ospemifene 60 mg/day group (0.561±1.6092 mm) and the Ospemifene 30 mg/day group (0.620±1.9000 mm). At 12 months, the mean change from baseline in the Ospemifene group was 0.800±1.6893 mm; little

change was observed in the placebo group (0.069±1.2290 mm) for this interval. Mean changes were 0.814±1.5405 mm in the Ospemifene 60 mg/day group and 0.696±2.5628 mm in the 30 mg/day group. Also, at last observation, incidences of subjects with endometrial thickness ≥5 mm and ≥ 8 mm were higher in Ospemifene 60 mg group compared to placebo group.

Table 21: Endometrial Thickness (Observed Cases) in Study 15-50718

	Placebo N=62		Ospemifene 60 mg N=364	
Endometrial thickness (mm) at:	**Mean (SD)**	**Mean Change from Baseline**	**Mean (SD)**	**Mean Change from Baseline**
Baseline	2.022 (0.8632)		2.057 (0.8350)	
Week 12	2.323 (1.6475)	0.312 (1.5251)	2.512 (1.4899)	0.436 (1.6667)
Week 26	2.215 (1.0085)	0.218 (1.3231)	2.557 (1.4586)	0.511 (1.5901)
Week 52	2.143 (0.9968)	0.167 (1.2523)	2.772 (1.3565)	0.751 (1.5315)

Endometrial histology

In addition to endometrial thickness, endometrial histology was evaluated and findings were reported at baseline, 12 weeks, and 12 months for biopsy findings and at 12 months for the incidence of endometrial hyperplasia and carcinoma.

At 12 months, 317 biopsies were available for evaluation. There were no occurrences of endometrial hyperplasia or carcinoma in any subject who received Ospemifene or placebo. One subject treated with Ospemifene 60 mg daily did have an endometrial biopsy result of simple hyperplasia without atypia. This result occurred approximately 3 months after the subject's last dose of study drug and was recorded as an SAE of endometrial hyperplasia. This equates to an incidence of 0.32% with an upper bound for the 95% CI of 1.74%. In addition, two Ospemifene 60 mg subjects had active proliferation at Week 52.

At 12 months, in the Ospemifene group, the majority of subjects had endometrial biopsy findings that were classified as "tissue insufficient for diagnosis" (16.2%) or "atrophic" (76.3%). Additionally, classifications of "inactive" occurred in 3.4% of Ospemifene-treated subjects and 1.2% of placebo subjects, and classifications of "weakly proliferative" occurred in 2.6% of Ospemifene-treated subjects and no placebo subjects. There was one subject with a diagnosis of "active proliferative" (0.3%) and one subject with a diagnosis of "proliferative pattern, disordered type" (0.3%), both treated with Ospemifene 60 mg/day.

In conclusion, the requirements for assessment of endometrial safety (risk of endometrial hyperplasia/cancer) as laid down in the guideline 'Clinical investigation of medicinal product for hormone replacement therapy of oestrogen deficiency symptoms in postmenopausal women (EMEA/CHMP/021/97 Rev. 1)' have been fulfilled for Ospemifene. Only 1 endometrial biopsy with simple hyperplasia without atypia (approximately 3 months after the subject's last dose of study drug) was observed out of 317 biopsies at 12 months on Ospemifene 60 mg. This single case of case of hyperplasia without atypia equates to an incidence of 0.3% with an upper 95% confidence limit of 1.7%, which is statistically less than 2% after one year of treatment (EMEA/CHMP/021/97 Rev. 1, October 2005). This showed that there was no increase in frequency of hyperplasia in the clinical programme of Ospemifene. No cases of endometrial cancer were observed. Moreover, in contrast to

some other SERMs, no cystic changes in the endometrium were reported in the Ospemifene clinical programme. An increase in endometrial thickness was observed with a mean of 0.81±1.54 mm over 12 months. This increase is also noted with other SERMS, such as lasofoxifene 0.5 mg, for which the mean thickness increased from 0.61 - 1.44 mm (EPAR Fablyn). The data of Ospemifene did not signal a concern that the use of Ospemifene may adversely affect endometrial safety. However, it will be important to follow endometrial safety issues in the proposed PASS-study (Annex II condition).

Vaginal bleeding and spotting

A total of 22 subjects with an intact uterus in the double-blind, Phase 2/3, placebo-controlled studies experienced a vaginal bleeding and spotting-related TEAE: 17 Ospemifene-treated subjects (1.5%) and five placebo subjects (0.9%). The information was collected by direct questioning either by telephone or during the clinical visit. This approach is considered the most conservative way to collect incidence of an adverse event. All episodes of bleeding resolved without further action and without sequelae. The incidences in the Ospemifene and placebo groups were low and comparable.

In the phase 2/3 trials, 9 women without a uterus reported vaginal bleeding. In none of the cases a potential cause of the bleeding was reported, except for one woman who had a gynaecological examination on the previous day, which may have caused bleeding. Some of these women had also reported bleeding in relation with coitus. The data did not suggest that Ospemifene use is causally related to vaginal bleeding in postmenopausal women without a uterus.

Uterine polyps

Uterine polyp related TEAEs were found in 5/1140 Ospemifene subjects (0.4%) and 1/570 placebo subject (0.2%) with an intact uterus. All of these subjects discontinued the study due to the uterine polyp TEAE per protocol. Of all findings, only one event was felt to represent a true polyp (in the placebo group).

Breast safety

Women with a suspicion of malignancy on mammography or a family history of breast cancer of two close relatives were excluded from clinical trials. Mammogram and breast palpation findings were reported for the DBPC studies in which they were performed.

There were two cases of breast cancer reported in placebo subjects (one breast cancer, one carcinoma in situ) in approximately 300 patient years on placebo. In comparison, there were no cases of breast cancer in the 60 mg/day Ospemifene group with 805 patient years of exposure. It should be noted that the duration of exposure to Ospemifene in the DBPC phase 2/3 studies was considered too short and the number of treated subjects is too limited with regard to delay of breast malignancy emergence. Also, the limited safety information on patients with a pre-existing malignancy (due to women with a suspicion of malignancy on mammography or a family history of breast cancer of two close relativesbeing excluded from the pivotal trials), led to incorporation of the following contra-indication: *"Patients with known or suspected breast cancer or undergoing active treatment (including adjuvant therapy) for breast cancer."*

Vasomotor-related TEAEs

178 Ospemifene-treated subjects (11.2%) and 43 placebo subjects (5.0%) had vasomotor-related TEAEs in the DBPC study population. The percentages of the Ospemifene-treated subjects with vasomotor-related TEAEs were similar for the ≤15 mg/day, 30 mg/day, and 60 mg/day groups (around 11%) and smaller for the 90 mg/day group (7.5%). 19 Ospemifene treated subjects discontinued the study due to the vasomotor-related TEAE (1.3%), whereas three placebo subjects (0.3%) discontinued the study due to the vasomotor-related TEAE.

In the Ospemifene 60 mg grouping population, hot flushes were the most common reported AE, were more severe and more subjects had new experiences of hot flushes compared to the placebo group. In addition, hot flushes were the most frequently reported AE leading to discontinuation (1% and 0.3% of discontinued subjects in Ospemifene 60 mg group and placebo group, respectively).

The incidence of hyperhydrosis was low and only marginally higher in the Ospemifene groups compared to placebo. No increase in the incidence of hot flush or hyperhydrosis was observed with increasing doses of Ospemifene up to 60 mg, neither for raw incidences nor after adjustment for exposure. The 15 mg and 90 mg groups were small and, therefore, considered with caution.

Table 22: Hot Flush and Hyperhidrosis Ratio Incidence/Exposure by Dose: DBPC Phase 2/3 Studies Grouping

	Number (%) of Subjects					
		Ospemifene				
Preferred Term	Placebo N=860	≤15 mg N=62	30 mg N=352	60 mg N=1242	90 mg N=40	All Osp N=1696
Hyperhidrosis	9 (0.9)	0	5 (1.4)	24 (1.9)	2 (5.0)	31 (1.8)
Hot Flush	32 (3.3)	6 (9.7)	32 (9.1)	106 (8.5)	1 (2.5)	145 (8.5)
Total	41	6	37	130	3	176
Total Subject-Years of DB Exposure	272.7	13.4	114.3	547.5	8.8	684.1
Hyperhidrosis/exposure	0.03	0	0.04	0.04	0.22	0.04
Hot Flush/exposure	0.12	0.45	0.27	0.19	0.11	0.21
Total/exposure	0.15	0.45	0.32	0.23	0.34	0.26

Cervical safety

Cervical Pap smear was performed at the screening visit, at week 52 or if the subject discontinues after the week 12 visit. Subjects with abnormal finding at screening were excluded. Samples were analysed at a central laboratory and classified according to Bethesda 2001 system for the studies 15-50310, 15-50310X, 1550718 and 15-50721. Of note, Study 15-50718 and Study 15-50310X were the only studies that included Pap smear assessments at 12 months.

DBPC phase 2/3 studies that used Bethesda criteria at 12 months showed that nearly all subjects in the Ospemifene group and the placebo group continued to have Pap smear classified as negative for intraepithelial lesion or malignancy (96.8% and 95.5%, respectively). Diagnoses of ASC-US occurred in 9/401 subjects (2.2%) in the Ospemifene group; none of these subjects had a diagnosis of negative for intraepithelial lesion or malignancy at baseline. Diagnoses of ASC-US occurred in 2/88 subjects in the placebo group. Additionally, 1/401 subject (0.2%) had a diagnosis of ASC-H and 1/401 subject (0.2%) had a diagnosis of LSIL in the Ospemifene group.

Of note, Ospemifene's mode of action suggests an estrogen-like effect in the vagina (increasing the cellular maturation and mucification of vaginal epithelium). In response to the D120 LoQ, the Applicant reviewed the issue of a possible link between oestrogen exposure and development of cervical cancer. The current general opinion is that the occurrence of cervical cancer is closely linked to HPV infection. Oestrogens are implicated in the progression to cervical cancer in infected individuals, but also are suggested to be protective, though evidence is certainly not that robust as shown for endometrial and ovarian cancer. However, it was agreed with the Applicant that there was no evidence to suggest that oestrogen alone, without the presence of a HPV infection, is a risk factor for cervical cancer.

Cardiovascular safety (VTE and ATE)

The data in the registration file of Ospemifene do not show an increased risk of VTE or ATE.

Thromboembolic event	Incidents per thousand women years (95% CI)	
	Ospemifene 60 mg (547.89 women-years)	Placebo (272.95 women-years)
DVT[a]	3.65 (0.44–13.19)	3.66 (0.09–20.41)
Arterial thrombotic event (ATE) [b]	1.83 (0.05–10.17)	3.66 (0.09–20.41)

[a] Includes a subject in the placebo group who reported an AE of 'cerebrovascular accident'. The subject subsequently experienced a DVT, which was not reported as an SAE by the investigator.

[b] Both events were reported as stroke.

However, a registration file is too small to reliably estimate the incidence, as was shown by the wide confidence limits. Of the 5 Ospemifene-treated subjects, 4 discontinued the study due to the CV related TEAE (2 subjects due to cerebrovascular accident and 2 subjects due to deep vein thrombosis).

Table 23: Cardiovascular-related Adverse Events: Double-blind, Placebo-controlled Phase 2/3 Studies Grouping

Preferred Term	2.5.2 Number (%) of Subjects					
		Ospemifene				
	Placebo N=958	≤15 mg N=62	30 mg N=352	60 mg N=1242	90 mg N=40	All Osp N=1696
Any CV-related TEAE	1 (0.1)	0	1 (0.3)	4 (0.3)	0	5 (0.3)
Cerebrovascular Accident	1 (0.1)	0	1 (0.3)	1 (0.1)	0	2 (0.1)
Deep Vein Thrombosis	0	0	0	2 (0.2)	0	2 (0.1)
Cerebral Haemorrhage	0	0	0	1 (0.1)	0	1 (0.1)

Table 24: Cardiovascular-related Adverse Events: Description per Subject

Treatment	Event: Severity / Relation to study drug	Outcome / Study Drug
Ospemifene 30 mg	**Cerebrovascular accident:** - severe in intensity - possibly related to study treatment	Recovered with sequelae / Study discontinuation
Ospemifene 60 mg	**Cerebrovascular accident:** - severe in intensity - possibly related to study drug	Recovered with sequelae / Study discontinuation
Ospemifene 60 mg	**Deep vein thrombosis:** - moderate in severity - possibly related to study drug	Resolved / Study discontinuation
Ospemifene 60 mg	**Cerebral hemorrhage:** - severe in intensity - unlikely related to study drug	Resolved / Study completed
Ospemifene 60 mg	**Deep vein thrombosis**: - moderate in intensity	Resolved / Study discontinuation

Treatment	Event: Severity / Relation to study drug	Outcome / Study Drug
	- probably related to study drug. In the opinion of the sponsor, while study drug may have contributed to the subject's developing a DVT, the relative immobilization from the 8-hour car ride during which her symptoms developed likely played a significant role in the pathogenesis of the event.	
Placebo	**Cerebrovascular accident:** - severe in intensity - unlikely related to study drug	Recovered with sequelae / Study discontinuation

In addition to AE observed in DBPC study results, two cardiovascular/cerebrocascular AEs were reported from 2 subjects from the extension study 15-503 12 (open label uncontrolled study):
I) One subject from Ospemifene 60 mg group had an acute myocardial infarction. She had a previous MI and a significant past history of CVD.
II) One subject from Ospemifene 60 mg had a hemorrhagic stroke/CVA following completion of 12-week parent study 15-50310

Of note, one transient cerebral ischemic attack (TIA) was reported from subject in phase 1 study (single dose, 60 mg Ospemifene).

In the placebo group, only one case of ischemic stroke was reported.

There were no deaths due to stroke.

In addition, before randomization, subjects in phase 2/3 clinical studies were screened for Factor V Leiden (FVL) and excluded in case of positive findings. In response to the D120 LoQ, the Applicant sufficiently explained that based on the estimates of the incidence of VTE (<1/1000 patient years) and proportion of subjects who tested positive for FVL during screening for the Ospemifene trials (3.2%), it is anticipated that despite the increased risk of VTE in FVL carriers, few or no additional VTE cases would have been observed if FVL carriers were included in phase 2/3 trials. It is therefore not expected that the currently provided risk estimation for VTE would have changed relevantly if these 128 patients were included in the trials.

Estrogen receptor modulators are known to increase the risk of venous thromboembolism (VTE, see table below), an increased risk for Ospemifene can therefore not be excluded. The possibility that SERMS also increase risk of ATE (including cerebrovascular events) is less clear; up to now no clear increased risk is noted for other approved SERMs (raloxifene, bazedoxifene, lasofoxifene).

Venous thromboembolism (VTE)

Relative risk versus placebo in registration dossiers (13,000 – 20,000 patient years of exposure):

- Lasofoxifene (Fablyn):	2.13 (95% CI 1.34, 3.39; p=0.0010)
- Bazedoxifene (Conbriza):	1.9
- Raloxifene (Evista):	2.13 (95% CI 1.21, 3.75)

Arterial thromboembolism

Relative risk versus placebo in registration dossiers:

Overall incidence of cerebrovascular adverse events of myocardial infarction did not show a statistically significant increased risk.

Pelvic Organ Prolapse

In the double-blind, Phase 2/3, placebo-controlled studies, a total of 3 subjects reported a pelvic organ prolapse-related TEAE: 2 in the 60 mg Ospemifene-group (0.2%) and 1 in the placebo group (0.1%). None of the pelvic organ prolapse TEAEs led to discontinuation.

Mood and depression

Incidence of mood and depression related AEs was similar between 60 mg Ospemifene treated group and placebo group. No special safety concern regarding mood or depression was raised from the DBPC phase 2/3 studies with Ospemifene.

Sexual functions

Sexual function-related TEAEs were reported in 0.2% of 60 mg Ospemifene-treated subjects and 0.4% of placebo subjects. Of the Ospemifene-treated subjects, three subjects (0.9%) were treated with 30 mg/day and three subjects (0.2%) were treated with 60 mg/day. One subject in the placebo group (0.1%) discontinued the study due to the TEAE (libido decreased).

Vertebral and other fractures

In the double-blind, Phase 2/3, placebo-controlled studies, the percentage of subjects experiencing vertebral or other fracture-related TEAEs was similar between Ospemifene-treated and placebo subjects. 32 subjects reported a vertebral- or other fracture-related TEAE: 18 Ospemifene-treated subjects (1.1%) and 14 placebo subjects (1.5%). Of the Ospemifene-treated subjects with vertebral- or other fracture-related TEAEs, 2 subjects (0.6%) were treated with 30 mg/day, 15 subjects (1.2%) with 60 mg/day, and 1 subject (2.5%) with 90 mg/day. No subjects discontinued the study due to vertebral or other fracture related TEAEs.

Laboratory findings

Coagulation parameters: 15-50718 and 15-50310X were the only studies that included assessment of coagulation parameters at 12 months in the double-blind, Phase 2/3, placebo-controlled study grouping. In addition, coagulation parameter assessments were performed in the Study 15-50312 (open label) at 12 and 15 months.

The following coagulation parameters were evaluated at Baseline and different time points: Activated partial thromboplastin time (aPTT), Fibrinogen, Antithrombin antigen, Protein C Antigen, Protein S Antigen (free). Of note, study 15-50718 did not include assessments of protein S Ag (free).

Pooled results from the DBPC phase 2/3 studies showed, overall, in Ospemifene-treated subjects minor changes for coagulation parameters - and not notably different from changes observed for placebo subjects from Baseline to 12 weeks, 6 months, and 12 months. However, the most relevant coagulation parameters to assess VTE risk were not studied (i.e activated protein C resistance test, d-dimer, F&+2, factor VIII). Although the selection of the evaluated coagulation parameters was in line with the FDA Guidance for Industry (*Guidance for industry: oestrogen and oestrogen/progestin drug products to treat vasomotor symptoms and vulvar and vaginal atrophy symptoms – recommendations for clinical evaluation. January 2003*), the CHMP Guideline (*clinical investigation of steroid contraceptives in women,* EMEA/CPMP/EWP/519/98 Rev 1) of July 2005, recommends to evaluate additional biological variables possibly related to VTE risk and evaluation of these parameters was not taken into account in Ospemifene clinical program.

The clinical chemistry change tables and haematology change tables did not suggest any consistent or disturbing finding in any variable measured. However, none of the haemostatic variables are validated surrogate endpoint for the clinical endpoint of VTE.

Lipids: In the DBPC phase 2/3 studies, lipid-related TEAEs were observed in 27 Ospemifene-treated subjects (1.6%). Among them, 6 (1.7%) received 30 mg Ospemifene and 21 (1.7%) received 60 mg Ospemifene. Also, 2 placebo subjects (2.3%) reported lipid-TEAE.

The most common lipid-related TEAEs in the Ospemifene-treated subjects were hypercholesterolemia and hyperlipidemia. Two Ospemifene-treated subjects (0.1%) and one placebo subject (0.1%) discontinued due to lipid-related TEAE (hyperlipidemia).

Table 25: Lipid-related Adverse Events: DBPC phase 2/3 Studies

	Number (%) of Subjects					
		Ospemifene				
Preferred Term	Placebo N=958	≤15 mg N=62	30 mg N=352	60 mg N=1242	90 mg N=40	All Osp N=1696
Any Lipid-related TEAE	22 (2.3)	0	6 (1.7)	21 (1.7)	0	27 (1.6)
Hypercholesterolaemia	11 (1.1)	0	3 (0.9)	15 (1.2)	0	18 (1.1)
Hyperlipidaemia	2 (0.2)	0	3 (0.9)	4 (0.3)	0	7 (0.4)
Blood Triglycerides Increased	4 (0.4)	0	0	1 (0.1)	0	1 (0.1)
Hypertriglyceridaemia	1 (0.1)	0	0	1 (0.1)	0	1 (0.1)
Blood Cholesterol Increased	5 (0.5)	0	0	0	0	0
Dyslipidaemia	1 (0.1)	0	0	0	0	0

Of interest, unlike exogenous estrogen, the incidence of hypertriglyceridemia did not increase but was the same or lower in the Ospemifene group compared to the placebo group.
Also, in this generally normolipidemic population, LDL-cholesterol decreased from baseline to termination in a dose-dependent manner, with the decrease for Ospemifene 60 mg/day at 12 months being -6.96±18.081%, compared to -2.13±18.427% for placebo. At 12 months, mean HDL cholesterol increased by 2.28±14.951% in the Ospemifene 60 mg/day group compared with -1.91±12.687% for placebo. At 12 months, the changes from baseline in mean triglyceride levels were lower in the Ospemifene 60 mg/day group when compared to the placebo group (13.30±36.115% and 17.63±37.753%, respectively).

Study 15-06002 was a randomized, double blind placebo controlled study designed to compare Ospemifene with placebo, with a special consideration of effects on bone, vascular endothelium, lipid

metabolism and endometrium. In this study, lipids (serum Lp(a), triglycerides, total cholesterol, LDL, HDL, HDL2 cholesterol and LDL-BDC), samples were drawn at screening visit, at 12 weeks and at 14-16 weeks (for LDL-BDC additionally at 4 weeks). In this study, Ospemifene tended to decrease the levels of total cholesterol and LDL, and also LDL-BDC. Ospemifene also increased HDL levels, but HDL2 fraction did not seem to contribute to this increase. After treatment period, total cholesterol, LDL, LDL-BDC and HDL started to return to the pre-treatment levels, further suggesting that the changes in *lipids* were caused by the active treatment. Ospemifene had no effect on Lp(a) levels and a clinically insignificant increase in triglyceride levels was observed with the highest 90 mg dose level.

Overall, from the DBPC phase 2/3 studies, incidence of lipid-related TEAE was comparable between Ospemifene 60 mg group and placebo group; at 12 months, changes from baseline showed a trend to a decrease in LDL- cholesterol in subjects receiving Ospemifene 60 mg, and changes in TG levels were comparable to those in placebo group. Results from the study 15-06002 were consistent with these findings. Altogether, the data suggest that Ospemifene has estrogen-like effect on lipid profile.

Blood chemistry parameters:

In studies 15-50310 and 15-50821 chemistry parameters were evaluated at Screening and at the end of the 12-week treatment period/discontinuation. There were no clinically meaningful changes in mean chemistry values between Baseline and 12 weeks in any treatment group in studies 15-50310 (table 26) and 15-50821 (table 27).

Table 26: Chemistry tests (ALT, AST, CK) – Mean changes from Baseline to Week 12

Test		Ospemifene 30 mg	Ospemifene 60 mg	Placebo
Alanine aminotranferase (ALT)	BL	27.4 ± 10.64	28.4 ± 10.54	28.4 ± 10.19
	W12	25.1 ± 11.44	24.9 ± 9.96	29.6 ± 14.90
	Mean Change from BL	-2.45 ± 9.113	-3.09 ± 8.240	1.25 ± 13.335
Asparate aminotransferase (AST)	BL	25.0 ± 6.10	25.6 ± 6.10	26.1 ± 6.61
	W12	24.8 ± 7.09	25.0 ± 6.14	26.9 ± 9.27
	Mean Change from BL	-0.18 ± 5.504	-0.32 ± 4.715	0.93 ± 8.181
Creatine kinase	BL	91.8 ± 45.71	99.3 ± 63.45	94.2 ± 49.09
	W12	94.8 ± 53.85	95.8 ± 61.85	95.4 ± 56.82
	Mean Change from BL	3.50 ± 45.408	-3.74 ± 55.185	1.40 ± 50.977

BL= Baseline; W12= Week 12

Table 27: Blood Chemistry: Mean change from Baseline to Week 12/LOCF (Strata Combined – ITT Population)

Parameter	Time Point	Ospemifene 60 mg	Placebo
ALT (U/L) Mean ± SD	Baseline	27.7 ± 11.37	27.8 ± 12.27
	Week 12/LOCF	24.5 ± 13.32	27.4 ± 10.86
	Mean Change from Baseline	-3.4 ± 13.44	-0.2 ± 8.90
AST (U/L) Mean ± SD	Baseline	27.2 ± 7.48	27.6 ± 7.46
	Week 12/LOCF	26.6 ± 10.45	27.2 ± 7.09
	Mean Change from Baseline	-0.7 ± 10.14	-0.4 ± 6.41
CK (U/L) Mean ± SD	Baseline	98.4 ± 62.16	103.0 ± 160.96
	Week 12/LOCF	102.4 ± 102.56	102.3 ± 76.45
	Mean Change from Baseline	4.6 ± 99.51	-0.7 ± 174.14

Source: Table 14.3.7.1.3.
Abbreviation: ALT – alanine aminotransferase; AST – aspartate aminotransferase; CK – creatine kinase; ITT – intent-to-treat; LOCF – last observation carried forward; SD – standard deviation.

Hematology: The mean values at termination for each hematology parameter were within the normal range for the Ospemifene and placebo groups. There were no clinically relevant changes from baseline to termination in the mean value of any of the hematology parameters for the Ospemifene and placebo groups.

Urinalysis: There were no trends or clinically meaningful differences among treatment groups for any urinalysis parameters. Although slight changes were observed from Baseline to termination for specific gravity and pH, they were minor. Mean values at termination were within normal ranges and not clinically significant.

Glucose metabolism: In the double-blind, Phase 2/3, placebo-controlled studies, minor changes in fasting glucose were observed for the Ospemifene group from baseline to all post-baseline time points (mean change from baseline to 12 weeks was 0.02±1.074 mmol/L, mean change from baseline to 6 months was -0.01±0.670 mmol/L, and mean change from baseline to 12 months was 0.05±0.590 mmol/L). There were no notable trends across the different doses of Ospemifene.

Vital Signs

Blood pressure and pulse: From DBPC phase 2/3 studies, no notable changes from baseline to termination were observed for systolic and diastolic blood pressure in subjects treated with Ospemifene and subjects treated with placebo (minor mean decrease in systolic and diastolic blood pressure in both Ospemifene and placebo groups).

There was no consistent trend for change in mean pulse rate across all doses of Ospemifene in the double-blind, placebo-controlled Phase 2/3 studies.

Weight: There was a minor increase in weight in both the Ospemifene and placebo groups, with the increase in the placebo group being higher than that in the Ospemifene group. The percentage of subjects experiencing weight-related changes reported as TEAEs was similar between Ospemifene-treated and placebo subjects.

Safety in special populations

Age: The incidence of TEAEs was 64.0% in Ospemifene-treated subjects <65 years and 73.2% in Ospemifene-treated subjects ≥65 years; 55.0% in placebo subjects <65 years and 50.0% in placebo subjects ≥65 years. In response to the D120 LoQ, the Applicant provided a summary of ADRs observed in subjects < 65 years, from 65 – 74 years, from 74 to 85 years and over 85 years, and for each of the mentioned age sub-groups a summary of AEs, AEs leading to discontinuation and SAEs observed. Although the proportion of elderly subjects may be regarded as relatively small, the data did not show any special safety concerns with Ospemifene treatment for VVA in women over the age of 65 years.

Race: The incidence of any TEAE in the all Ospemifene group was similar across the three racial groups, with a slightly higher incidence in Black Ospemifene-treated subjects (66.0% White subjects, 69.2% Black subjects, and 57.4% other subjects). Hot flush was a TEAE reported in higher percentage of white Ospemifene treated subjects (9%) compared to black Ospemifene treated subjects (3.1%) and other subjects (2.1%). However, limited safety data is available from subjects other than white.

Uterine status: included as a subgroup because it would potentially be possible to assess for uterine prolapse, which has been observed with other SERMs. Also, depending on the source of increased lubrication, complaints of vaginal discharge could have differed in subjects with and without a uterus. Results showed that percentage of subjects reporting TEAEs was similar in Ospemifene-treated subjects with and without an intact uterus (66.8% and 64.2%). Also, there were no notable differences between subjects with and without an intact uterus for the incidence of SAEs.

Prior vaginal birth: included as a subgroup because subjects with a prior vaginal birth could potentially have been more prone to pelvic organ prolapse issues. Results showed that percentage of subjects with TEAEs was similar in Ospemifene-treated subjects with and without a prior vaginal birth. Also, the incidence of vaginal discharge in subjects with and without a prior vaginal birth was higher in Ospemifene (4.5% and 4.9%, respectively) than in placebo (0.3% and 0.8%, respectively).

Previous HRT: The percentage of subjects reporting TEAEs was similar in Ospemifene-treated subjects with and without previous HRT use; the incidence of TEAEs was also similar in Ospemifene compared with placebo for subjects with and without previous HRT use. Higher incidence of hot flush was observed for Ospemifene-treated subjects with previous HRT use (12.3%) compared to those without previous HRT use (7.6%). In subjects with and without previous HRT use, the incidence of hot flush was higher in Ospemifene (12.3% and 7.6%, respectively) than in placebo (3.8% and 3.2%, respectively).

Safety related to drug-drug interactions and other interactions

From the clinical program phase 2/3, AEs related to drug-drug interactions had not been mentioned. The Applicant was therefore requested to clarify whether such AEs occurred or not in Ospemifene clinical studies.

- The CYP3A/CYP2C9/CYP2C19 inhibitor fluconazole increased the AUC of Ospemifene by 174% (90% CI 147% to 203%).

- The CYP3A/CYP2C9 inducer rifampicin decreased the AUC of Ospemifene by 58% (90%CI 53% to 63%: Study 15-50716).

- The CYP2C19 inhibitor omeprazole increased the AUC of Ospemifene by 17%.

- Co-administration of ketoconazole, a strong CYP3A inhibitor, increased AUC0-inf of Ospemifene by 42% (90%CI 27% to 60%).

- Ospemifene did not affect the CYP2C9, CYP2C19 and CYP2B6 activity when evaluated using S-warfarin as a CYP2C9 probe substrate, omeprazole as a sensitive CYP2C19 substrate and bupropion as sensitive CYP2B6 substrate.

The interactions with rifampicin, omeprazole and ketoconazole were not expected to be of clinical relevance when taking into account that no meaningful associations between drug exposures (AUCss or Cmax,ss) of Ospemifene and the efficacy PD parameters were detected in the population PK/PD study.

Discontinuation due to adverse events

Phase 2/3, placebo-controlled studies: 119/1696 subjects (7.0%) in the all Ospemifene group and 36/958 subjects (3.8%) of the placebo group; the percentage of subjects that discontinued due to TEAEs was slightly higher in the all Ospemifene group compared with the placebo group. There was no dose-related increase in TEAEs that led to discontinuation; the incidences were 6.5%, 5.4%, 7.6%, and 2.5% for the Ospemifene ≤15 mg/day, 30 mg/day, 60 mg/day, and 90 mg/day groups, respectively.

The most common TEAEs leading to discontinuation in the all Ospemifene group were hot flush (16/1696 subjects [0.9%]), headache (10/1696 subjects [0.6%]), nausea (7/1696 subjects [0.4%]), muscle spasms (7/1696 subjects [0.4%]), and vaginal discharge (6/1696 subjects [0.4%]).

2.6.1. Discussion on clinical safety

The patient exposure was considered adequate. 2471 study participants have received at least one dose of Ospemifene, which fulfils the requirement of at least 1500 participants in the guideline ICH Topic E 1 Population Exposure: The Extent of Population Exposure to Assess Clinical Safety (CPMP/ICH/375/95). The median (min, max) duration of exposure to Ospemifene 60 mg was 86 days with a maximum duration in most DBPC studies of 12 weeks. 191 subjects received 60 mg Ospemifene for more than 52 weeks. Only studies 15-50310X and 15-50718 included subjects for up to 52 weeks. According to the guideline CPMP/ICH/375/95 a number of 300-600 participants for long-term safety is required. However, long-term safety data was limited for an indication for which long-term treatment may likely be prescribed – therefore, on CHMP's request, the Applicant has included a statement at the beginning of section 4.4 that a yearly appraisal should be conducted of the benefits and risks for the individual patient.

In the Clinical package submitted by the Applicant, there was no active-comparator group (alternative VVA treatment group) included in any phase 2/3 studies. In response to the D120 LoQ, the Applicant provided an indirect comparison of Ospemifene to local estrogens, with regard to the benefit-risk ratio.

No clinically relevant differences were present in demographics between the placebo group and the Ospemifene groups. In the Ospemifene groups, the percentage of women with an intact uterus was slightly higher compared to the placebo group. This could be explained by the long-term safety study 50718 in which only women with an intact uterus participated, as the randomization of this study was 1:6 for placebo: Ospemifene, respectively. Proportion of obese subject (BMI≥30 kg/m2) in each group is unknown.

Dose-response relationship

No clear dose-response relationship was observed in TEAEs. The 90 mg dose had the lowest reporting of TEAEs (37.5%). It should however be noted that the number of subjects treated with 90 mg/day was too small to draw firm conclusions. Between the 30 and 60 mg dose/day no differences were observed in % of subjects with TEAEs, severity or causality of TEAEs. Similarly, the number of related TEAEs was similar for 30 mg/day and 60 mg/day, 31.5% and 30.4%, respectively.

The number of subjects who discontinued the study due to a TEAE was only slightly higher for the 60 mg dose compared to the 30 mg dose, 7.6% vs. 5.4%, respectively.

Serious adverse events

The exposure corrected rate for serious adverse events was similar for the Ospemifene and placebo group, 57 SAEs/1000 women years exposure and 62.3 SAEs/1000 women years exposure, respectively.

Adverse events of special interest

Endometrial safety

The requirements for endometrial safety as laid down in the guideline '*Clinical investigation of medicinal product for hormone replacement therapy of oestrogen deficiency symptoms in postmenopausal women (EMEA/CHMP/021/97 Rev. 1)*' were fulfilled. For long-term endometrial safety 363 participants have been studied in the indication VVA, which was considered acceptable. The submitted data of Ospemifene did not signal a concern that the use of Ospemifene may adversely affect endometrial safety – however, these concern will be addressed in the proposed PASS study (Annex II condition).

Endometrial thickness

A small mean increase was observed; 0.814 mm ±1.5405 mm over 12 months. However, this has also been seen with other SERMS, such as lasofoxifene. In comparison, the mean thickness increase with 0.5 mg lasofoxifene ranged from 0.61 - 1.44 mm (EPAR Fablyn). Also, in contrast to lasofoxifene, Ospemifene does not result in cystic changes.

There was no difference in the rate of vaginal bleeding for Ospemifene compared with placebo. Additionally, the bleeding incidence was very low (2.2% for Ospemifene 60 mg vs. 2.6% for placebo). Therefore, it is not expected that Ospemifene 60 mg will lead to an increase in unnecessary gynaecological procedures resulting from vaginal bleeding or spotting.

Endometrial histology findings

- At baseline the majority were as expected for this population, i.e. "atrophic" and "insufficient for diagnosis". In the Ospemifene group more patients were seen with proliferative endometrium at Week 12 and 12 months.

- One case of simple hyperplasia without atypia was observed after 12 months of treatment in Ospemifene 60 mg group that occurred approximately 3 months after the subject's last dose of study drug. The EU criteria were met with 1 case of endometrial hyperplasia out of 317 biopsies at 12 months on 60 mg Ospemifene with an upper 95% confidence limit of 1.7%, which should be statistically less than 2% after one year of treatment (EMEA/CHMP/021/97 Rev. 1, October 2005), showing that there is no increase in frequency of hyperplasia and endometrial cancer in the clinical programme of Ospemifene. Although the data provided did not raise a concern that Ospemifene

adversely affects endometrial safety, it is important to follow endometrial safety issues in the proposed PASS-study.

Cervical safety

Nearly all subjects in the Ospemifene group and the placebo group continued to have Pap smear classified as negative for intraepithelial lesion or malignancy (96.8% and 95.5%, respectively).

Uterine polyps

The small number of polyps seen on TVU had a similar frequency between placebo and Ospemifene treatment.

Vaginal discharge

Vaginal discharge was consistently higher in the Ospemifene group compared to the placebo group: 3.8% 60 mg Ospemifene, 3.7% 30 mg Ospemifene and 0.3% placebo. However, the Applicant indicated that the recording of the event did not appear to differentiate between physiological and pathological discharge and that it might physiological vaginal discharge might be expected to occur seeing as Ospemifene increases the number of superficial cells and reduces the number of parabasal cells.

Vaginal bleeding

For subjects with an intact uterus, the rate of vaginal bleeding per 1000 patient-years is 21.7 (95% CI 10.4, 39.9) for Ospemifene 60 mg and 26.3 (95% CI 8.6, 61.5) for placebo. Outcomes were all non-malignant and included atrophic, inactive or tissue insufficient for diagnosis and one polyp and fibroidone case each. Additionally, the incidence was very low. Therefore it is not expected that Ospemifene 60 mg will lead to an increase in unnecessary gynaecological procedures resulting from vaginal bleeding or spotting.

Breast safety

In the Non-Clinical studies, an antagonistic effect of Ospemifene was observed on breast tissue. Despite this antagonistic effect, women with a suspicion of a malignancy on mammography or a family history of breast cancer of two close relatives were excluded from the clinical trials. The results of obtained seemed to be in support of an anti-oestrogenic effect on breast tissue: there were two cases of breast cancer reported in placebo subjects (one breast cancer, one carcinoma in situ) in approximately 300 patient years on placebo, while there were no cases of breast cancer in the 60 mg/day Ospemifene group with 805 patient years of exposure. This seemed to suggest that the risk of breast cancer in post-menopausal women is unlikely to be increased after limited exposure duration to Ospemifene 60 mg.

Even though the available safety data did not reveal a special safety concern, a contra-indication was incorporated into the SmPC due to the limited safety information on patients with a pre-existing malignancy: *"Patients with known or suspected breast cancer or undergoing active treatment (including adjuvant therapy) for breast cancer."*

Vasomotor symptoms

For Ospemifene the incidence of hot flushes is about 2-fold higher in the Ospemifene group (11.2%) compared to placebo (5.0%). However, the discontinuation due to vasomotor-related AEs was low (1.3%). In comparison, in the Phase 2/3 clinical programme for Lasofoxifene for the treatment of osteoporosis in postmenopausal women, the incidence of hot flushes was also 2-fold higher, i.e. 14.6% in the 0.5 mg/day Lasofoxifene and 6.4% in the placebo group (EPAR Fablyn).

Cerebrovascular events and Deep Venous Thrombosis

The data in the registration file of Ospemifene did not show an increased risk of VTE (3.65 per 1000 patient years for Ospemifene 60 mg (95% CI: 0.44-13.19) vs. 3.66 per 1000 patient years for placebo (95% CI: 0.09–20.41)) or ATE (1.83 per 1000 patient years for Ospemifene 60 mg (95% CI: 0.05-10.17) vs. 3.66 per 1000 patient years (95% CI: 0.09-20.41)).

However, SERMs are known to increase the risk of VTE, and due to the limitations of a registration dossier, the exact incidence could not be reliable estimated, as is shown by the wide confidence limits. Similar uncertainties were present for a possible increased risk of ATE. However, the possibility that SERMS also increase risk of ATE (including cerebrovascular events) is less clear; up to now no clear increased risk is noted for other approved SERMs (Raloxifene, Bazedoxifene, Lasofoxifene).

Discontinuation due to AEs

The discontinuation due to AEs was slightly higher for the Ospemifene group. The reason for continuation varied with the most frequent hot flush (0.9%), nausea (0.4%), muscle spasms (0.4%) and vaginal discharge (0.4%). However, the frequency of these AEs leading to discontinuation is considered low.

Women over 65 years

A higher incidence of AE (not specifically the drug-related) was observed in women over 65 years compared to women below 65 years.

2.6.2. Conclusions on the clinical safety

Overall, the safety profile of Ospemifene was considered acceptable. No increase in risk was observed in breast cancer. The data on VTE and cerebrovascular events provided from the clinical studies did not show a statistically significant increase in this risk versus placebo. However due to the limitations of a registration dossier, the incidence of such rare events cannot be reliably estimated, as is shown by the wide confidence limits. Thus, an uncertainty remains with regard to VTE and possibly ATE risk. An increased risk of VTE is a SERM class effect, although variable rates have been reported for the separate components - Ospemifene may therefore also have an increased risk of VTE. The possibility that SERMS also increase risk of ATE (including cerebrovascular events) is less clear; up to now no clear increased risk is noted in the registration dossiers of approved SERMs (Raloxifene, Bazedoxifene, Lasofoxifene).

The long-term Ospemifene's effect on endometrium is unknown, although the requirements as laid down in the guideline '*Clinical investigation of medicinal product for hormone replacement therapy of oestrogen deficiency symptoms in postmenopausal women (EMEA/CHMP/021/97 Rev. 1)*' were fulfilled. The CHMP is of the opinion that the endometrial data obtained do not give rise to a concern on endometrial safety.

Due to the above uncertainties, the CHMP proposed to include a statement at the beginning of section 4.4 that Ospemifene treatment should be yearly evaluated. A post-authorisation safety study to further investigate VTE, cerebrovascular events, endometrial cancer, increase in uterine diagnostic procedures and long-term safety is endorsed by the CHMP (Annex II condition).

Refer to the section on the Risk Management plan for further details on the measures CHMP considered necessary to address issues related to clinical safety.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system.

Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation, the CHMP considered that the Pharmacovigilance system as described by the Applicant was acceptable.

2.8. Risk Management Plan

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

PRAC Advice

Based on the PRAC review of the Risk Management Plan version 0.4, the PRAC considers by consensus that the risk management system for ospemifene (Senshio) in the treatment of moderate to severe symptomatic vulvar and vaginal atrophy (VVA) in post-menopausal women who are not candidates for local vaginal oestrogen therapy could be acceptable if the applicant implements the changes to the RMP as described in the PRAC endorsed PRAC Rapporteur assessment report.

The CHMP endorsed this advice with one change. This change was the inclusion of 'off-label use' as an important potential risk. The justification for this change is that the proposed indication for prescribing has been changed from a wider, to a more restricted target patient population. However, it may be that prescribing still occurs to a wider patient population. This will be monitored in the imposed PASS.

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

The CHMP endorsed the Risk Management Plan version 1.0 with the following content:

- **Safety concerns**

Table 28: List of safety concerns in the RMP

Summary of safety concerns	
Important identified risks	• Increase in uterine diagnostic procedures
Important potential risks	• Cerebrovascular events • Venous thromboembolic events • Vaginal bleeding • Endometrial cancer (SERM class-effect) • Pelvic Organ Prolapse/Urinary incontinence • Cholecystitis and gallbladder events • Atrial fibrillation • Increased triglycerides • Liver tumours (potential risk from nonclinical finding) • Thymic epithelial tumours (potential risk from non-clinical finding) • Renal carcinoma and adenoma (potential risk from non-clinical findings with other SERMs) • Renal Failure - new presentation oraggravation of pre-existing condition(potential risk from non-clinical findings with other SERMs) • Off label use
Missing information	• Long-term safety information • Patients with pre-existing gynaecological pathology other than signs of vaginal atrophy • Patients with malignancy on mammography or any other kind of malignancy within 10 years (excluding basal cell carcinoma) • Concomitant use with SERMs, oestrogens or other medications with oestrogenic/antioestrogenic actions • Clinical consequences of potential ospemifene over exposure with concomitant use of strong CYP3A and CYP2C9 inhibitors or use of strong CYP3A4 inhibitors in patients known or suspected to be CYP2C9 poor metabolisers. • Risk for lack of efficacy as a consequence of potential under exposure when used concomitantly with CYP2C9 inducers and strong CYP3A inducers • Severe hepatic impairment • Patients with strong susceptibility to allergic reactions • Limited amount of data in the Elderly (≥ 65 years old)

- **Pharmacovigilance plans**

Table 29: Ongoing and planned studies in the Pharmacovigilance development plan

Study / activity type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
A post authorisation safety study to evaluate the incidence of venous thromboembolism and other adverse events, as agreed in the risk management plan, in VVA patients treated with ospemifene as compared to 1) patients newly prescribed SERMs for oestrogen-deficiency conditions or breast cancer prevention and 2) the incidence in untreated VVA patients. This is an observational retrospective cohort study of ospemifene utilising existing databases in Germany, Italy, Spain, and the United States. (Category 1)	Primary Objective: Compare the incidence of VTE, among postmenopausal women who are newly prescribed ospemifene (ospemifene cohort) to that among patients newly prescribed SERMs for oestrogen-deficiency conditions or breast cancer prevention and patients diagnosed with but not treated for VVA (untreated VVA comparison cohort). Secondary Objectives: (1) Assess the number and percentage of patients in each cohort with cerebrovascular events, endometrial hyperplasia, endometrial cancer, pelvic organ prolapse, urinary incontinence, gall bladder events, atrial fibrillation, renal failure, renal carcinoma, renal adenoma, liver tumours, thymic epithelial tumours and increased triglycerides (2) Assess the number and percentage of patients with uterine	Venous thromboembolic events, cerebrovascular events, increase in uterine diagnostic procedures, pelvic organ prolapse, urinary incontinence, cholecystitis/gall bladder events, atrial fibrillation, increased triglycerides, liver tumours, thymic epithelial tumours, renal carcinoma and adenoma, renal failure and endometrial cancer. Off label use. Missing information (through monitoring off-label use): Patients with Pre-existing Gynaecological Pathology other than Signs of Vaginal Atrophy. Severe hepatic impairment. Patients with Malignancy on Mammography or any other kind of Malignancy within	Planned. Draft protocol in Annex 6.	Annual study progress reports and interim reports will be provided for each individual country from 2016 to 2020. Final report (planned): Feb 2021.

Study/activity type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
	diagnostic tests and procedures in each cohort. (3) Assess off-label use among ospemifene patients.	10 years (excluding Basal Cell Carcinoma)		
An Open-Label, One-Sequence Crossover Drug-Drug Interaction Study to Evaluate the Effect of Repeated Doses of Ospemifene on the Pharmacokinetics of the CYP3A4 Substrate, Midazolam, in Postmenopausal Females and an Open-Label Study to Evaluate the Pharmacokinetics in Serum and Excreta of a 60 mg Single Dose of Ospemifene in Postmenopausal Females (Category 3)	Objectives: To determine the effect of multiple-dose ospemifene administration on the pharmacokinetics of midazolam in postmenopausal females. To evaluate the pharmacokinetics of ospemifene in serum, urine and feces after a single dose administration of the commercial tablet in postmenopausal females. To evaluate the safety of ospemifene during multiple-dose administration, and when co-administered with midazolam.	In-vitro studies have shown that ospemifene is a weak inducer of CYP 3A4 and this Phase 1 study is being conducted to investigate the effects of ospemifene on a CYP3A4 substrate midazolam. CYP3A4 induction is not considered to be a safety concern on the basis of the in-vitro data.	Planned	Planned Dec 2016

*Category 1 are imposed activities considered key to the benefit risk of the product.
Category 2 are specific obligations
Category 3 are required additional PhV activity (to address specific safety concerns or to measure effectiveness of risk minimisation measures)

- **Risk minimisation measures**

Table 30: Summary table of Risk Minimisation Measures

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Cerebrovascular events	**SmPC Section 4.4** Advises that a risk of cerebrovascular events has been seen with other SERMs, therefore this finding should be considered when prescribing Senshio for postmenopausal women with a history of stroke or other significant stroke risk factors.	None proposed.
Increase in uterine diagnostic procedures Vaginal bleeding Endometrial cancer (SERM class-effect)	**SmPC Section 4.3** Unexplained vaginal bleeding is contraindicated. Suspected or active sex-hormone dependent malignancy (e.g. endometrial cancer) is contraindicated. Patients with signs or symptoms of endometrial hyperplasia are contraindicated. **SmPC Section 4.4** Advises that in all cases a careful appraisal of the risks and benefits should be undertaken at least annually taking into consideration other menopausal symptoms, effects on uterine and breast tissues, thromboembolic and cerebrovascular risks. Senshio should only be continued as long as the benefit outweighs the risk. Section on endometrial findings warns that if any bleeding or spotting occurs on therapy, or continues after treatment has been discontinued, this should always be investigated, which may include an endometrial biopsy to exclude endometrial malignancy.	None proposed.

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Venous thromboembolic events	**SmPC Section 4.3** Contraindicates active or past history of venous thromboembolic events, including deep vein thrombosis, pulmonary embolism and retinal vein thrombosis. **SmPC Section 4.4** Warns about SERM class risk for venous thromboembolic events. Advises to discontinue Senshio at least 4 to 6 weeks prior to and during prolonged immobilisation. Advises that if a VTE develops after initiating therapy, the drug should be discontinued and that patients should contact their doctors immediately when they experience a potential thromboembolic symptom (e.g. painful swelling of a leg, sudden pain in the chest, dyspnoea).	None proposed.
Pelvic organ prolapse/urinary incontinence	None proposed since no increased risk of pelvic organ prolapse has been identified from the ospemifene clinical trials. This risk is a safety concern observed with some other SERMs.	None proposed
Cholecystitis and gallbladder events	None proposed since no increased risk of cholelithiasis has been identified from ospemifene clinical trials. This risk is a safety concern observed with some other SERMs.	None proposed
Atrial fibrillation	None proposed since no increased risk over the background risk of atrial fibrillation has been identified from ospemifene clinical trials. This risk is a safety concern observed with another SERM.	None proposed

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Increased triglycerides	None proposed since no risk of increased triglycerides has been identified from ospemifene clinical trials. This risk is a safety concern observed with some other drugs from the SERM class.	None proposed
Liver tumours	**SmPC Section: 5.3** Informs that increases in hepatocellular tumours were recorded in rat carcinogenicity studies and that these findings are unlikely to have any clinical relevance in postmenopausal women.	None proposed
Thymic epithelial tumours	**SmPC Section: 5.3** Informs that a clear increase in mostly benign thymic tumours was recorded at all ospemifene dose levels in a 2-year carcinogenicity study in rats and that these findings are unlikely to have any clinical relevance in postmenopausal women.	None proposed
Renal carcinoma and adenoma	None proposed. This risk is based on non-clinical findings with other SERMs.	None proposed
Renal failure-new presentation or aggravation of pre-existing condition	None proposed. This risk is based on non-clinical findings with other SERMs. No TEAEs of renal failure or aggravation of renal failure were reported in ospemifene clinical trials.	None proposed

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Off label use	**SmPC Section 4.1** Describes the therapeutic indication as treatment of moderate to severe symptomatic vulvar and vaginal atrophy (VVA) in post-menopausal women who are not candidates for local vaginal oestrogen therapy. **SmPC Section 4.4** Warns that Senshio may increase the incidence of hot flushes and that it is not effective in reducing hot flushes associated with oestrogen deficiency. In some asymptomatic patients, hot flushes may occur upon beginning therapy. About 1% of subjects discontinued in the Phase 2/3 clinical programme due to hot flushes.	None proposed
Long-term safety information	**SmPC Section 4.4** Advises that in all cases a careful appraisal of the risks and benefits should be undertaken at least annually taking into consideration other menopausal symptoms, effects on uterine and breast tissues, thromboembolic and cerebrovascular risks. Senshio should only be continued as long as the benefit outweighs the risk. **SmPC Section 4.8** The summary of the safety profile describes the duration of treatment in Phase 2 and 3 studies as ranging from 6 weeks to 64 weeks. Most subjects (N=1370) had a treatment period of at least 12 weeks and 409 had at least 52 weeks (1 year) of exposure.	None proposed.

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Patients with pre-existing gynaecological pathology other than signs of vaginal atrophy	**SmPC Section 4.4** Warns that there are limited clinical trial data on the use of Senshio in patients with other gynaecological conditions and recommends that any additional pathology be investigated and treated appropriately.	None proposed.
Patients with malignancy on mammography or any other kind of malignancy within 10 years (excluding basal cell carcinoma)	**SmPC Section 4.3** Patients with suspected breast cancer and patients undergoing active treatment (including adjuvant therapy) for breast cancer are contraindicated. Patients with signs or symptoms of endometrial hyperplasia are contraindicated. Patients with suspected or active sex-hormone dependent malignancy (e.g. endometrial cancer) are contraindicated. **SmPC Section 4.4** Warns that Senshio has not been formally studied in women with a prior history of breast cancer and that no data are available on its concomitant use with agents used in the treatment of early or advanced breast cancer. Therefore Senshio should be used for the treatment of VVA only after the treatment of breast cancer, including adjuvant therapy, has been completed.	None proposed.
Concomitant use with SERMs, oestrogens or other medications with oestrogenic/antioestrogenic actions	**SmPC Section 4.5** Warns that the safety of using (Senshio) concomitantly with oestrogens or other SERMS, such as tamoxifen, toremifene, bazedoxifene and raloxifene, has not been studied and concurrent use is not recommended.	None proposed.

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Clinical consequences of potential ospemifene over exposure with concomitant use of strong CYP3A and CYP2C9 inhibitors.	**SmPC Section 4.4** Warns that caution is recommended when co-administering Senshio with fluconazole. If necessary because of impaired tolerance, ospemifene should be stopped as long as treatment with fluconazole lasts. **SmPC Section 4.5** States that any medicinal products that inhibit both CYP3A4 and CYP2C9 activity (e.g. fluconazole) would be expected to increase the exposure of ospemifene and warns that caution is recommended when co-administering Senshio with fluconazole. Warns that co-administration of Senshio with strong/moderate CYP3A4 inhibitors should be avoided in patients who are known, or suspected to be CYP2C9 poor metabolisers based on genotyping or previous history/experience with other CYP2C9 substrates.	None proposed.
Risk for lack of efficacy as a consequence of potential ospemifene under exposure when used concomitantly with CYP2C9 inducers and strong CYP3A inducers	**SmPC Section 4.5** Warns that co-administration of Senshio with strong CYP3A / CYP2C9 enzyme inducers like carbamazepine, phenytoin, St John's wort and rifabutin would be expected to decrease the exposure of ospemifene, which may decrease the clinical effect.	None proposed.

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Severe hepatic impairment	Information on hepatic impairment included in **SmPC Sections 4.2 and 5.2.** **SmPC Section 4.2** No dose adjustment is necessary for patients with mild to moderate hepatic impairment. Ospemifene has not been studied in patients with severe hepatic impairment, therefore, Senshio is not recommended for use in such patients.	None proposed.
Patients with strong susceptibility to allergic reactions	**SmPC Section 4.3** Hypersensitivity to the active substance or to any of the excipients is contraindicated **SmPC Section 4.8** Post-marketing experience with ospemifene Rash (includes rash erythematous, rash generalised) included as a common adverse reaction. Drug hypersensitivity, Hypersensitivity, Swollen tongue, Pruritus and Urticaria included as uncommon adverse reactions.	None proposed.
Limited amount of data in the elderly (≥ 65 years old)	**SmPC Sections 4.2 and 5.2** No dose adjustment is necessary in elderly patients.	None proposed.

2.9. User consultation

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

3. Benefit-Risk Balance

Benefits

Senshio 60 mg film-coated tablets contain the active substance Ospemifene (also known as FC-1271a), which is a minor metabolite from Toremifene. Ospemifene is a Selective Estrogen Receptor Modulator (SERM). Like other SERMs, Ospemifene acts as an agonist or antagonist on the estrogen receptor in different tissues. The claimed revised indication is: *"Treatment of moderate to severe symptomatic vulvar and vaginal atrophy (VVA) in post-menopausal women who are not candidates for local vaginal oestrogen therapy (see section 5.1)."*

The proposed posology is 60 mg tablet once daily with food.

Vaginal low-dose estrogen preparations are currently considered first-line pharmacologic treatment for the treatment of VVA (Royal College of Obstetricians and Gynaecologists Guideline Menopause and Hormone Replacement). Approved estrogen preparations in Europe are:

- Vagifem 10 microgram (estradiol tablets for vaginal application) approved by decentralised procedure (UK/H/2176/001) and Estring (estradiol-containing vaginal ring) approved by mutual recognition procedure;

- Synapause (estriol ovules/cream for vaginal application) nationally registered.

In Europe no guidance document exists for VVA, though the requirements as laid down in the FDA guidance for industry 'Estrogen and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms – Recommendations for Clinical Evaluation' have been previously accepted in the EU during the authorisation of other products for vaginal atrophy, such as Vagifem 10 µg.

Beneficial effects

In the clinical programme, statistical significant superiority compared to placebo was demonstrated for change in vaginal pH, percentage of superficial cells and parabasal cells for 60 mg/day in pivotal studies 15-50310 and 15-50821. Also for 60 mg/day for the MBS "vaginal pain associated with sexual activity" superiority was shown, whereas the 30 mg/day dose did not show a statistically significant difference compared to placebo in study 15-50310. Despite the use of non-hormonal lubricant, which could be applied by women as needed (making it more difficult to show superiority) in both studies, a statistically significant difference versus placebo was shown for the MBS "vaginal dryness" in study 15-50310, whereas a trend in favour of 60 mg/day was observed in study 15-50821.

The following secondary efficacy endpoints were used to assess clinical relevance further:

- A clear difference was noted in the responder rate. A subject was a responder if all the following criteria were met: 1) Maturation value increased by at least 10 from Baseline; 2) Vaginal pH decreased by at least 0.5 from Baseline; 3) MBS improved by at least 1 point from Baseline. In study 15-50310 the responder rate was 3.4% for placebo, 20.6% for 30 mg/day Ospemifene and 33.7% for 60 mg/day Ospemifene, and in study 15-50821 5.5% for placebo and 39.7% for 60 mg/day Ospemifene.
- The change from Baseline to Week 4 was supportive of the co-primary endpoints (Week 12). Superiority was demonstrated for vaginal pH, percentage parabasal cells and superficial cells. The

change in MBS did show a trend in favour of the Ospemifene groups, but was not statistically significantly superior at Week 4.

- The non-hormonal lubricant use was in both studies 15-50310 and 15-50821 only slightly decreased in the Ospemifene group after 3 to 4 weeks in comparison to the placebo group. For instance, in 15-50821 at Weeks 9-12 in the placebo group 0.7 +/- 1.09 and in the 60 mg group 0.5 +/- 0.86.
- In the validated Female Sexual Function Index questionnaire, a difference was seen in pain with a better score in the Ospemifene group, which is in line with the difference observed in the co-primary endpoint MBS vaginal pain associated with sexual activity at Week 12.

Long-term effect

Also after 52 weeks in the double-blind study 15-50718 a statistically significant effect was maintained in vaginal pH, percentage of parabasal cells and percentage of superficial cells. The most bothersome symptom (MBS) was not included as endpoint.

Extrapolation of data

It would have been preferred to include MBS also in the dose-finding study 15-50717 and in the European study 15-50718, as there are currently no data on the change in MBS in the European population. However, a recent international survey (Nappi and Kokot-Kierepa 2010) has shown that subjects from various European countries are not essentially different from those in the USA or Canada with regard to issues related to vaginal atrophy. Indeed, the effects of treatment for VVA indicated no clear regional geographic differences in the way women in North America and Europe experience the effects of VVA therapy. Therefore, the effect of Ospemifene on MBS in European patients is very likely to be comparable to that seen in subjects of the studies performed in the USA.

Clinical relevance of observed treatment effect

An additional descriptive analysis was performed on the primary endpoint outcome based on the medical literature (Ettinger et al, 2008) and discussions with leading European clinicians.

The proportion of subjects with clinically relevant MBS outcomes (vaginal dryness and dyspareunia) at Week 12 supported that the difference between Ospemifene and placebo is more pronounced in the “substantial improvement” and “relief” categories, therefore suggesting that not only more patients report benefit with Ospemifene compared to placebo, but also the magnitude of the benefit was greater for Ospemifene than with placebo.

Further, in trial 15-50821 both in the vaginal dryness stratum (33.8% for Ospemifene vs. 7.1% for placebo) as in the vaginal pain stratum (42.9% for Ospemifene vs. 4.6% for placebo) a significant higher proportion of responders was identified in the Ospemifene group versus placebo.

Uncertainty in the knowledge about the beneficial effects

Comparison to local vaginally applied therapy

No active-comparator group (alternative VVA- treatment group) was included in any phase 2/3 studies. In the FDA guidance document no active control is required. Similarly, placebo-controlled studies were conducted for Vagifem 10 µg (Simon et al 2008, Bachmann et al 2008) and oestriol gel (Cano et al., 2012), and no active control was requested. In response to the D120 LoQ, the Applicant provided indirect comparison of Ospemifene and local estrogens. In the literature search all publications on local estrogens were included. Two relevant publications for efficacy were identified on Vagifem 10 µg (Simon et al 2008 and Bachmann et al 2008). Based on the Applicant’s analysis, the degree of improvement in women with moderate to severe symptoms of VVA over placebo was

comparable with that noted in public literature for Vagifem 10 µg. In addition, in response to the D180 LoOI, the Applicant adequately discussed the data on vaginally applied oestriol (0.005% oestriol gel, 0.03 mg oestriol, 0.2 mg oestriol tablets) and promestriene (10 mg vaginal capsule administered daily) in comparison to Ospemifene. The degree of improvement of Ospemifene versus placebo was also comparable to the degree of improvement versus placebo observed for vaginally applied promestriene and oestriol.

Risks

Unfavourable effects

2471 study participants have received at least one dose of Ospemifene. For long-term safety 353 subjects had ≥48 weeks of exposure and 191 subjects had ≥52 weeks of exposure, which is acceptable according to the guideline CPMP/ICH/375/95. No clear dose-response relationship was observed, as between the 30 and 60 mg/day doses no differences were observed in % subjects with drug-related TEAEs, and severity or causality of TEAEs. However, due to known side effects of approved SERMs for other indications, special focus is given to possible adverse effects on the endometrium, thromboembolism, vaginal bleeding, breast safety and vasomotor symptoms.

Endometrial thickness
An increase in endometrial thickness was observed with Ospemifene; 0.81±1.54 mm over 12 months. This has also been seen with other SERMS, such as Lasofoxifene. In comparison, the mean thickness increase with 0.5 mg Lasofoxifene ranged from 0.61 - 1.44 mm (EPAR Fablyn). However, in contrast to Lasofoxifene, no cystic changes of the endometrium were observed.

Endometrial histology
The EU criteria laid down in the CHMP NfG on hormonal replacement therapy regarding the investigation of endometrial safety were met: only 1 endometrial biopsy with simple hyperplasia without atypia (approximately 3 months after the subject's last dose of study drug) out of 317 biopsies was observed at 12 months on 60 mg Ospemifene. This equates to an incidence of 0.3% with an upper 95% confidence limit of 1.7%, which should be statistically less than 2% after one year of treatment (EMEA/CHMP/021/97 Rev. 1, October 2005). No cases of endometrial cancer were observed.

Cerebrovascular events and Venous Thromboembolism
SERMs are known to increase the risk of venous thromboembolism (VTE). No increased risk was observed for VTE in the clinical programme: 3.65 per 1000 patient years for Ospemifene 60 mg (95% CI: 0.44-13.19) vs. 3.66 per 1000 patient years for placebo (95% CI: 0.09–20.41). Similarly, no increased risk was observed for cerebrovascular events: 1.83 per 1000 patient years for Ospemifene 60 mg (95% CI: 0.05-10.17) vs. 3.66 per 1000 patient years (95% CI: 0.09-20.41). These data do not indicate a specific concern, but the confidence limits are wide, as a registration file is too limited to reliably estimate the incidence of these rare events. Therefore, the Applicant indicated a commitment to study VTE and cerebrovascular events in a post-authorisation safety study, as proposed in the RMP (Annex II condition).

Vaginal bleeding
Vaginal bleeding incidence was comparable versus placebo: Ospemifene group (1.5%) vs. placebo (0.9%). Outcomes of subsequent endometrial biopsies (required per protocol in case of bleeding and

also recommended in clinical practice, see SmPC recommendations) were all non-malignant and included atrophic, inactive or tissue insufficient for diagnosis and one polyp and fibroidone case each. Therefore, it is not expected that Ospemifene 60 mg will lead to an increase in unnecessary gynaecological procedures resulting from vaginal bleeding or spotting.

Breast safety
The results of the clinical trial seem to be in support of an anti-oestrogenic effect on breast tissue. There were two cases of breast cancer reported in placebo subjects (based on an exposure of about 300 patient years), whereas no cases of breast cancer were observed in the 60 mg/day group (based on exposure of 805 patient years). However, patients with a suspicion of a malignancy on mammography or a family history of breast cancer were excluded from the clinical trials, so data in patients with a prior history of breast cancer are therefore still limited.

Vasomotor symptoms
In total 178 Ospemifene-treated subjects (11.2%) and 43 placebo subjects (5.0%) reported hot flushes, indicating that in Ospemifene-treated women the incidence of hot flushes is about 2-fold higher in the Ospemifene group compared to placebo. However, the discontinuation due to vasomotor-related AEs was low, 1.3% (19 Ospemifene-treated women) versus 0.3% (3 placebo-treated women).

Vulvovaginal symptoms
The proportion of subjects who experienced vulvovaginal adverse events was higher in Ospemifene 60 mg compared to placebo, 5.4% vs. 2.6%, respectively.

Uncertainty in the knowledge about the unfavourable effects

VTE and ATE (CVA) risk
SERMs are known to increase the risk of VTE, up to doubling the rate. Due to the limitations of a registration dossier, the exact incidence of this event could not be reliably estimated, as was shown by the wide confidence limits. Similar uncertainties are present for a possible increased risk of cerebrovascular events. However, the possibility that SERMS also increase risk of cerebrovascular events is less clear; up to the time of this report, no clear increased risk was noted with approved SERMs (Raloxifene, Bazedoxifene, Lasofoxifene). The uncertainty with regard to the possibility of increased VTE risk is of concern – therefore, this will be further investigated in a PASS study (Annex II condition).

Long term safety data
Long-term safety data was limited to 15 months of treatment. Due to the limitation in long-term safety data, and since VVA is more or less considered a chronic indication, CHMP decided that a yearly individual re-evaludation of the need for and risk of continuing therapy is performed.This recommendation has therefore been reflected in the SmPC.

Endometrial safety
The CHMP is of the opinion that endometrial safety evaluations (endometrial thickness increase, endometrial histology and uterine polyps) did not raise a major concern. However, long-term safety data after 12 months is limited. To address this uncertainty on endometrial safety, the Applicant proposes to also follow endometrial safety issues in the proposed PASS-study (Annex II condition).

Benefit-risk balance

Importance of favourable and unfavourable effects

For the indication of 'vulvar and vaginal atrophy' several estrogen-containing products are registered in Europe. All these products are indicated for local vaginal application: Vagifem 10 microgram, Synapause (estriol ovules) and Estring (estradiol in vaginal ring). Both estradiol (oral, patch) and oestriol (oral) are also approved for systemic treatment of hormone suppletion therapy, but these products are not first line in the indication of VVA as these should always be combined with a progestagen to protect the endometrium.
Ospemifene can be taken orally, which can be considered an advantage, as it would be the first oral product for VVA and might increase the medication choice for women in the indication of 'vulvar and vaginal atrophy'.

Superiority versus placebo has been shown for objective endpoints including vaginal pH, percentage of superficial cells and parabasal cells when compared to placebo. Also for the most bothersome symptom (MBS) "vaginal pain associated with sexual activity" superiority has been shown. For MBS "vaginal dryness" superiority was shown in one pivotal trial, whereas in the other trial statistical significance was not reached.
These results on the co-primary efficacy endpoints are further supported by a significant larger proportion of responders in the Ospemifene 60 mg/day group versus placebo: in study 15-50310 33.7% for Ospemifene vs. 3.4% for placebo and in study 15-50821 in the "vaginal pain associated with sexual activity stratum" 42.9% for Ospemifene vs. 4.6% for placebo.
The criteria applied in the responder definition (1.*Maturation Value increased by at least 10 from Baseline; 2.Vaginal pH decreased by at least 0.5 from baseline; 3.MBS improved by at least 1 point from baseline*), were considered adequately justified in terms of clinical relevance. Although the 30 mg/day dose showed superiority compared to placebo in the co-primary endpoints (except for the co-primary endpoint MBS), the effect was more pronounced in the 60 mg/day dose. When looking at the responder rate, the difference became more apparent with 20.6% responders for 30 mg/day Ospemifene and 33.7% for 60 mg/day Ospemifene. The 60 mg/day dose could therefore be supported. Moreover, indirect comparison showed that the degree of improvement observed with Ospemifene versus placebo was comparable to that observed with Vagifem 10 µg, vaginally applied oestriol and promestriene versus placebo.

In addition, the safety profile for the 30 mg/day and 60 mg/day dose appeared to be comparable, and no clear dose-response relationship in ADR incidence was observed for these two doses, which is also in support of the acceptance of the 60 mg/day dose.

The safety profile was in line with what can be expected for a SERM. As to effects on the endometrium, a slight increase in endometrium thickness was noted, which is not a reason for concern. However, endometrial safety will be followed up in the proposed PASS study. No indication of an increased risk in endometrium hyperplasia and cancer was noted. Furthermore, in contrast to Lasofoxifene, no cystic changes are observed in the endometrium, and no additional educational efforts are needed to inform pathologists on the endometrial pattern in users of this product.

The incidence of vaginal bleeding was comparable to placebo, and treatment with Ospemifene is therefore unlikely to result in an increase in additional gynaecological procedures.

In the clinical programme no increased risk was observed for VTE and cerebrovascular events (CVA) compared to placebo. However, a registration file is too limited to reliably estimate the VTE and CVA risk. Therefore the risk of VTE and CVA for Ospemifene could not be reliably estimated. For other SERMs up to now no clear increased risk has been noted for CVA (Raloxifene, Bazedoxifene, Lasofoxifene). A possibly increased risk for CVA is therefore unlikely. However, an increased risk of VTE was observed with other SERMs, and therefore considered a class effect, although variable rates have been reported for the separate components. Ospemifene may possibly also have an increased risk of VTE. Even though the VTE risk of local estrogens is also unknown, this risk is expected to be low due to the low systemic exposure. Taking this into account, the Senshio's indication was modified to "*Treatment of moderate to severe symptomatic vulvar and vaginal atrophy (VVA) in post-menopausal women who are not candidates for local vaginal oestrogen therapy (see section 5.1)".*

SERMs are also known to increase the incidence of hot flushes. This is a disadvantage in comparison to the local treatment of VVA with estrogen preparations. During use of Ospemifene, a 2-fold increase in hot flushes was observed compared to placebo. However, the discontinuation rate (1.3% versus 0.3% in the placebo groups) due to hot flushes was low, suggesting that this adverse event is not of concern.

The safety data obtained did not suggest an increased risk of breast cancer, and non-clinical data suggested predominantly an antagonistic effect on breast tissue. However, patients with a suspicion of a malignancy on mammography or a family history of breast cancer were excluded from the clinical trials. As data in patients with a prior history or undergoing active treatment of breast cancer was therefore limited, CHMP considered these patients should be contra-indicated – this was reflected in the SmPC of the product.

Long-term safety data were limited to 15 months of treatment. In total, 384 subjects were given Ospemifene 60 mg for more than 6 months and 191 subjects for more than 12 months. There is also no information on the long-term safety with local, vaginal treatment of VVA, but due to the low systemic estrogen exposure the long-term safety profile is considered benign. Even so, risks as noted with systemic HRT cannot be excluded, and therefore similar warnings on VTE and ATE are included in the SmPCs of local estradiol products.

Due to these limitations on safety data, the Applicant will conduct a post-authorisation safety study (Annex II condition) to investigate venous thromboembolic events, cerebrovascular events, increase in uterine diagnostic procedures, endometrial cancer, patients with pre-existing gynaecological pathology other than signs of vaginal atrophy, and patients with malignancy on mammography or any other kind of malignancy within 10 years (excluding basal cell carcinoma). This study is considered mandatory to determine the incidence of these adverse events, as the safety data in the registration data was too limited to reliably estimate the risk.

Benefit-risk balance

Regarding the clinical efficacy of Ospemifene, the degree of improvement over placebo in the co-primary endpoints was sufficiently substantiated to be clinically relevant and comparable with that noted in public literature for Vagifem 10 µg, vaginally applied oestriol and promestriene.

Endometrium safety data, assessed according to the recommendations of the NfG for hormone replacement therapies EMEA/CHMP/021/97 Rev. 1., showed no increased incidence of endometrial hyperplasia/cancer. An increased risk for endometrial hyperplasia/cancer was also not observed with

approved SERMs, except for Tamoxifen, which is actually an anti-estrogen. These data did not signal a concern that the use of Ospemifene may adversely affect endometrial safety.

The data in the registration file of Ospemifene did not show an increased risk of VTE or ATE. However, a registration file is too small to reliably estimate the incidence of such rare adverse events, as is shown by the wide confidence limits. For other SERMs up to now no clear increased risk has been noted for CVA. A possibly increased risk for CVA is therefore unlikely. However, an increased risk of VTE is observed with other SERMs, and therefore considered a class effect - although variable rates have been reported for the separate components. Ospemifene may possibly also lead to an increased risk of VTE, similar to systemic HRT with oral oestrogens. Although the VTE risk of local estrogens is also unknown, it is expected to be low due to the low systemic exposure.

Taking this into account the CHMP therefore proposed to use Senshio treatment for women who are not candidates for local vaginal estrogen therapy, i.e. a second-line indication.

Discussion on the benefit-risk balance

With respect to the clinical efficacy:

- The degree of improvement in women with moderate to severe symptoms of VVA over placebo was sufficiently substantiated to be clinically relevant and comparable with that noted in public literature for Vagifem 10 mcg estradiol, and vaginally applied oestriol and promestriene, though the published data of the latter two products was of lower quality.
- Sufficient documentation was provided that VVA can be a clinically important condition with painful physical symptoms in some women having a significant impact on their lives and their relationships with their partners. A reduction in QoL is reported, linked both to the direct impact of the symptoms of VVA and the associated loss of sexual function. For women with moderate to severe symptoms of VVA medical treatment is accepted, in line with the women who participated in the pivotal trials for Ospemifene.
- Ospemifene 60 mg/day is an oral product for VVA with comparable efficacy as vaginally administered estrogens, which increases the treatment choices for women in the indication of VVA. When the woman is dissatisfied with vaginal therapy due to inconvenience, messiness, or partner exposure, there are currently no alternatives available.

With respect to clinical safety:

- The number of drug-related SAEs in the DBPC trials was 7 for Ospemifene 60 mg/day (N=1242) and 1 for placebo (N=958). This is considered low, given the size of the study population. Further, the treatment exposure for the Ospemifene 60 mg/day group was about 2-fold higher with 548 years for Ospemifene 60 mg/day and 273 years for placebo. The 7 SAEs in the Ospemifene group were CVA, endometrial hyperplasia, ovarian cyst, VTE (two subjects), global amnesia and nausea. The incidences of CVA, VTE and endometrial hyperplasia are not higher than the expected background incidence.
- No increased risk of venous and arterial thromboembolism versus placebo was observed in the clinical programme. However, the registration dossier is too limited to reliably estimate the incidence of this rare adverse event. Since VTE is a class effect of SERMs, the risk cannot be completely excluded for Ospemifene. In comparison, also for Vagifem 10 µg an increased risk for VTE cannot be completely excluded.
- Endometrium safety, assessed according to the recommendations of the NfG for hormone replacement therapies EMEA/CHMP/021/97 Rev. 1., showed no increased incidence of endometrial

hyperplasia/cancer. Only 1 endometrial biopsy with simple hyperplasia without atypia out of 317 biopsies was observed at 12 months on 60 mg Ospemifene approximately 3 months after the subject's last dose of study drug. This equates to an incidence of 0.3% with an upper 95% confidence limit of 1.7%, which should be statistically less than 2% after one year of treatment (EMEA/CHMP/021/97 Rev. 1, October 2005). Ospemifene resulted in a slight mean increase in endometrial thickness from 2.1 mm to 2.9 mm, without any cystic changes. These data did not signal a concern that the use of Ospemifene may adversely affect endometrial safety.

Taking into account the above considerations, the following proposal was made:

Ospemifene 60 mg/day would be the first oral product for VVA with comparable efficacy as shown with vaginal administration of estrogens, which could increase the treatment choices for women in the indication of VVA. SERMs are known to increase the risk of VTE, similar to systemic HRT with oral oestrogens. Ospemifene may therefore also have an increased risk of VTE, although so far this has not been reported. Although the VTE risk of local estrogens is also unknown, and cannot be excluded, but this risk is expected to be low due to the low systemic exposure.

The CHMP therefore proposed to use Senshio treatment only as 2nd line treatment for women who are not candidates for local vaginal estrogen therapy. The following change in wording of the indication was proposed:

"Senshio is indicated for the treatment of moderate to severe symptomatic vulvar and vaginal atrophy (VVA) in post-menopausal women who are not candidates for local vaginal estrogen therapy (see section 5.1).

Since VVA is more or less considered a chronic indication, CHMP recommended that a yearly individual re-evaluation of the need for and risk of continuing therapy is performed. A statement at the beginning of section 4.4 of Senshio SmPC reflects this recommendation and is in line with the SmPCs of the vaginally applied estrogens.

"For the treatment of vulvar and vaginal atrophy, Senshio should only be initiated for symptoms that adversely affect quality of life. In all cases, a careful appraisal of the risks and benefits should be undertaken at least annually taking into consideration other menopausal symptoms, effects on uterine and breast tissues, thromboembolic and cerebrovascular risks. Senshio should only be continued as long as the benefit outweighs the risk."

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by majority decision that the risk-benefit balance of Senshio in the "*treatment of moderate to severe symptomatic vulvar and vaginal atrophy (VVA) in post-menopausal women who are not candidates for local vaginal oestrogen therapy (see section 5.1)*"

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

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription

Other conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

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

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

- **Risk Management Plan (RMP)**

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

An updated RMP should be submitted:

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

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

- **Obligation to complete post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
An observational retrospective cohort study of ospemifene to assess the incidence of venous thromboembolism and other safety concerns as agreed in the risk management plan, in VVA patients treated with ospemifene compared to 1) patients newly prescribed SERMs for oestrogen-deficiency conditions or breast cancer prevention, and 2) the incidence in untreated VVA patients.	28/02/2021

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

Not applicable.

New Active Substance Status

Based on the review of data on the non-clinical and clinical properties of the active substance, the CHMP considers that Ospemifene is qualified as a new active substance based on non-clinically significant differences (in pharmacokinetics, estrogenic and cardiac safety) and clinically significant differences (in the cardiac safety).

Divergent positions to the majority recommendation are appended to this report.

Appendix

Divergent positions

Divergent Position

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

Considering the target population and taking into account all the clinical data, we consider the benefit-risk ratio of Senshio in the initially proposed broad indication as well as in the revised second line indication (treatment of moderate to severe symptomatic vulvar and vaginal atrophy (VVA) in post-menopausal women who are not candidates for local vaginal estrogen therapy) negative for the following reasons:

1 - The efficacy of ospemifene is limited. Significant superiority of ospemifene vs. placebo was demonstrated with respect to objective signs of vulvovaginal atrophy such as vaginal pH or maturation of the vaginal epithelium. However, the results were less convincing with respect to subjective symptoms which are the primary reason for treatment of vulvovaginal atrophy in postmenopausal women. In addition, it is noted that the frequency of vasomotor symptoms is doubled with ospemifene, compared to placebo (ospemifene 11.2%, placebo 5.0%) which is considered as particularly unfavourable in the target population of postmenopausal patients.

2 - Regarding the risks, there are concerns with respect to VTE and stroke. VTE is a known adverse event of other SERMs such as raloxifene or bazedoxifene. As expected, the currently available data on ospemifene in this respect are too sparse so that definite conclusions in this respect are currently not possible. Nevertheless, it appears very likely that ospemifene is also associated with an increased risk of VTE which can only be detected post-marketing. In addition, SERMs are possibly also associated with a risk of stroke which might also apply to ospemifene.

Although proliferative effects on mammary gland tissue appear unlikely according to non-clinical results, the effect of ospemifene on ovaries has not been systematically studied and based on non-clinical data available, estrogenic action of ospemifene towards the ovaries appears likely. Since estrogens appear to be associated with ovarian cancer also in humans, the relevance for humans of these animal findings cannot be disregarded. In addition, an increase in mean endometrial thickeness (0.81mm ±1.54) from baseline was observed with Senshio 60 mg tablets and a proliferative effect on endometrium with Senshio long-term treatment cannot be excluded. Of note, the proposed Product Information does not mention any limited treatment duration.

Therefore, the concerns with respect to a possibly increased risk of serious adverse reactions such as VTE and stroke, the endometrial changes and the uncertain relevance of ovary tumour findings in animals as well as the increase in hot flushes associated with ospemifene outweigh the obviously rather small benefit in the treatment of a non-serious condition such as vaginal pain for which established treatment options of topical estrogens are available. The restriction to patients "who are not candidates for local vaginal estrogen therapy", does not change our view as it is considered somewhat artificial and off-label use is very likely in a larger population of postmenopausal women

Overall, for these reasons, we consider that the benefit/risk ratio is negative for Senshio.

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