EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

27 January 2022
EMA/203365/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Invented name: Senshio

International non-proprietary name: ospemifene

Procedure No. EMEA/H/C/002780/II/0041

Note

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

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List of abbreviations

Abbreviation	Definition
ATC	Anatomical Therapeutic Chemical
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CVE	Cerebrovascular event
DVT	Deep vein thrombosis
EMR	Electronic medical record
ER	Emergency room
EU	European Union
GP	General practitioner
HR	Hazard ratio
HSD	Health Search Database
ICD-9	International Classification of Diseases, Ninth Revision
ICD-10	International Classification of Diseases, 10th Revision
IQR	Interquartile range
ITT	Intention to treat
KM	Kaplan-Meier
MI	Myocardial infarction
NDC	National Drug Code
PASS	Post-authorisation Safety Study
PV	Pharmacovigilance
SD	Standard deviation
SERM	Selective oestrogen receptor modulator
SIDIAP	Information System for the Development of Research in Primary Care
US	United States
VTE	Venous thromboembolism
VVA	Vulvar and vaginal atrophy

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Shionogi B.V. submitted to the European Medicines Agency on 30 June 2021 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication by deletion of information on specific subset of patients for Senshio. This is supported by the submission of the final study report of the imposed non-interventional post-authorisation safety study. As mentioned in Annex IID, this is 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 (RMP), in vulvar and vaginal atrophy (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. As a consequence, sections 4.1 and 4.4 of the SmPC are updated. The Package Leaflet and Annex IID are updated in accordance. Version 2 of the RMP has also been submitted. In addition, the Marketing authorisation holder took the opportunity to update the list of local representatives in the Package Leaflet.

The variation requested amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) 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 MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.
Scientific advice
The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Paula Boudewina van Hennik Co-Rapporteur: N/A

Timetable	Actual dates
Submission date	30 June 2021
Start of procedure:	17 July 2021
CHMP Rapporteur's preliminary assessment report	7 September 2021
PRAC Rapporteur Assessment Report	15 September 2021
PRAC members comments	22 September 2021
Updated PRAC Rapporteur Assessment Report	23 September 2021
PRAC Outcome	30 September 2021
CHMP members comments	4 October 2021
Updated CHMP Rapporteur Assessment Report	7 October 2021
Request for supplementary information and extension of timetable adopted by the CHMP	14 October 2021
MAH's responses submitted to the CHMP	16 November 2021
CHMP Rapporteur Assessment Report	1 December 2021
CHMP members comments	6 December 2021
Updated CHMP Rapporteur Assessment Report	9 December 2021
Request for supplementary information (RSI)	16 December 2021
MAH's responses submitted to the CHMP	21 December 2021
CHMP Rapporteur Assessment Report	12 January 2022
CHMP members comments	17 January 2022
Updated CHMP Rapporteur Assessment Report	20 January 2022
Opinion	27 January 2022

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

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

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

Oestrogen 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 defense against bacterial vaginal and urinary tract infections.

The decline in oestrogen 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).

Claimed therapeutic indication

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

Ospemifene 60 mg/day is the first oral product for VVA with comparable efficacy as shown with vaginal administration of oestrogens, 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 oestrogens is also unknown, and cannot be excluded, this risk is expected to be low due to the low systemic exposure.

Therefore, during the initial marketing authorization procedure, the CHMP considered that, based on the review of data on quality, safety and efficacy, the risk-benefit balance of Senshio was favourable only as second line treatment with the following change in wording of the indication "*treatment of moderate to severe symptomatic vulvar and vaginal atrophy (VVA) in post-menopausal women <u>who are not candidates for local vaginal oestrogen therapy</u> (see section 5.1)*"

Additionally, the by the CHMP recommended granting of the marketing authorisation was subject to the condition of an obligation to complete an imposed non-interventional PASS: An observational retrospective cohort study of ospemifene to assess the incidence of VTE and other safety concerns as agreed in the RMP, 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.

The current variation concerns an extension of the indication of Senshio by deletion of the restriction '*who are not candidates for local vaginal oestrogen therapy*'.

In order to fulfil the obligation, the Applicant submitted, within this variation procedure, the final study report of the imposed non-interventional PASS. The Applicant stated that the results of the PASS will support this update of the SmPC sections 4.1 and 4.4 and warrant a change to the current indication to remove the restriction for "*women who are not candidates for local vaginal oestrogen therapy*". The results of the PASS, and the thereby proposed changes in the SmPC, are assessed in this report.

Epidemiology

Oestrogen deficiency, described as a decline in the levels of circulating oestrogens due to menopause, affects numerous tissues in postmenopausal women, including musculoskeletal, vascular, and urogenital systems leading to a decrease in vaginal lubrication, which is an early hallmark of vulvar and vaginal atrophy (VVA). Symptoms of VVA include vaginal dryness, burning/itching, dyspareunia, vulvar pruritus, bleeding, particularly associated with sexual activity. VVA is also associated with urinary symptoms including urethral discomfort, frequency, haematuria, urinary tract infection, and dysuria. The median age of menopause in Europe is 54 years and in the United States (US) is 51.4 years. In a large online survey of almost 3,500 women ≥45 years of age from the US, 45% of respondents (1,038/2,290) were postmenopausal (mean age = 60 years) and currently or had previously experienced VVA.

For the patients who had never taken hormone therapy or were past users of hormone therapy, 60% were experiencing dryness or dyspareunia and more than 90% reported their symptoms as bothersome.

In addition, a published survey of 1,480 sexually active postmenopausal women reported a prevalence of VVA at 57%.

Current therapies for VVA include local oestrogens and lubricants/moisturisers. Ospemifene is a non-steroidal selective oestrogen receptor modulator (SERM) indicated for the treatment of moderate to severe symptomatic VVA in post-menopausal women who are not candidates for local vaginal oestrogen therapy.

The SERM class of drugs has been associated with an increased risk of VTE, stroke and potentially an increased risk of endometrial cancer. In the ospemifene clinical programme, which followed the Food and Drug Administration Guidance for the Treatment of VVA, no increase in the incidence of VTE or CVE in the ospemifene cohort compared to placebo was observed. This PASS was undertaken to assess the safety of ospemifene in real-world use over a period of five years.

Biologic features

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.

Non-clinical 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)."

Management

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 oestrogen treatment.
- Hormonal treatments: local, low-dose oestrogen 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 (oestradiol 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 oestrogen, treatment options have become limited (Bachmann et. al., 2010). For the indication of 'vulvar and vaginal atrophy' several oestrogen-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 oestrogen 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-oestrogen-based therapy for VVA is therefore of benefit in these patients.

2.1.2. About the product

Ospemifene is an oestrogen receptor (ER) agonist/antagonist, commonly referred to as a selective oestrogen 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 oestrogenic 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.

Ospemifene was authorised in the European Economic Area (EEA) via an EU Centralised Marketing Authorisation, granted by the European Commission (EC) to Shionogi, on 15 January 2015, under the trade name Senshio (EMEA/H/C/002780/0000). Ospemifene was first approved in the US on 26 February 2013 (International Birth Date, IBD) under the trade name Osphena.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

Legal basis

The initial 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.

In order to fulfil the obligation to conduct a category 1, imposed non-interventional PASS in accordance with Article 107n(3) of Directive 2001/83/EC, the MAH, Shionogi Limited, submitted on 16 June 2015 a revised PASS protocol version 6.0 to the EMA for ospemifene (Senshio). This PASS protocol (version 6.0) was assessed and approved by the PRAC under procedure number EMEA/H/C/PSP/0023.2. As the submission of the final results of the imposed PASS as part of this procedure Senshio II/0041 fulfils the requirement under Art.107p(1) of Directive 2001/83/EC, the requested waiver by the MAH for their obligation under Art.107q of Directive 2011/83/EC is endorsed.

The current type II category C.I.6 variation is submitted by the Applicant to report the five-year analysis of the PASS (category 1, imposed non-interventional study). These final results are submitted to support the proposed updates of section 4.1 and 4.4 of the SmPC and EU RMP.

Scientific Advice

No CHMP scientific advice relating to the current PASS has been received.

2.1.4. General comments on compliance with GCP

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

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.3. Clinical aspects

2.3.1. Introduction

Ospemifene is a selective oestrogen receptor modulator (SERM) approved for the indication of "*treatment of moderate to severe symptomatic vulvar and vaginal atrophy (VVA) in post-menopausal women who are not candidates for local vaginal oestrogen therapy"* in the EU in 2015 through centralised procedure EMEA/H/C/002780/0000.

The SERM class of drugs has been associated with an increased risk of VTE, stroke, and potentially an increased risk of endometrial cancer. In the ospemifene clinical programme, submitted in support of the initial MAA, no increase in the incidence of VTE or CVE in the ospemifene cohort compared to placebo was observed.

An imposed non-interventional category 1 PASS has been undertaken to assess the safety of ospemifene in real life over a period of five years, as requested by the CHMP with the marketing authorization. The PASS protocol has been assessed and approved by PRAC under procedure number EMEA/H/C/PSP/0023.2. In total, five annual and interim reports of this study have been submitted by the MAH, which are assessed and approved by the PRAC.

The research question of this study was defined as follows:

What is the risk of VTE in a cohort of postmenopausal women newly prescribed ospemifene relative to:

- a cohort of patients diagnosed with but not treated for VVA (untreated VVA comparison cohort)
- a cohort of postmenopausal women newly prescribed other SERM therapies (SERM comparison cohort) being utilised for oestrogen-deficiency conditions (i.e., non-cancer and non-infertility indications) or breast cancer prevention

The primary objectives of the study were to:

- Compare the incidence of VTE, among postmenopausal women who are newly prescribed ospemifene (ospemifene cohort) to an untreated VVA comparison cohort

- Compare the incidence of VTE, among postmenopausal women who are newly prescribed ospemifene (ospemifene cohort) to that among postmenopausal women newly prescribed other SERM therapies (SERM comparison cohort) being utilised for oestrogen-deficiency conditions (i.e., non-cancer and non-infertility indications) or breast cancer prevention.

The secondary objectives were to:

- Assess other adverse events and off-label use in Europe.

The title of the PASS is:

Safety and Incidence of Side Effects in a Cohort of Postmenopausal Women Prescribed Ospemifene Relative to Patients Diagnosed with but not Treated for Vulvar and Vaginal Atrophy (VVA) and Patients on Selective Oestrogen Receptor Modulators (SERMs) for Oestrogen deficiency Conditions or Breast Cancer Prevention – A Post-Authorisation Safety Study (PASS)

The Applicant has now provided the final report for the PASS. The PASS has been undertaken in Spain and Italy (EU countries where ospemifene was made commercially available) and the US (where ospemifene was launched in 2013 in the US).

Of note, the Applicant submitted in addition to the PASS an Addendum to Clinical Overview section for Senshio (ospemifene), covering safety data of the reporting period from 1st approval in the EU on 15 January 2015 through the DLP of 26 February 2021.

2.4. Clinical efficacy

No new clinical efficacy data have been submitted in this application, which was considered acceptable by the CHMP.

2.5. Clinical safety

PASS – Part 1 - US MarketScan database

Methods

Study design

This PASS was a five-year retrospective cohort study using existing healthcare databases. The safety assessment was conducted in data from the US, where ospemifene was launched in 2013.

The cohorts of interest are described below.

The SERM class of drugs has been associated with increased thromboembolic events; the ospemifene labelling carries the same SERM-class warnings regarding these events. Patients treated with ospemifene were compared with patients treated with other SERMs to assess any differences in the risks of VTE and other adverse outcomes.

Primary and secondary outcomes were identified through the presence of relevant codes in the medical claims. Incidence rates (IR, defined as events per 1,000 person-years [PY]) were calculated for each cohort and compared between ospemifene and untreated VVA, and separately between ospemifene and other SERMs.

Study setting

This was a secondary data analysis using the IBM Watson MarketScan claims database from the US. Medical and pharmacy claims data were obtained from 1 May 2012 to 31 December 2018.

Data sources and Measurement

The IBM Watson (formerly Truven) MarketScan Commercial and Medicare Supplemental Databases provide access to medical and prescription drug claims for privately insured individuals including patients over the age of 65 with Medicare Supplemental coverage.

The Commercial Claims Database represents the inpatient, outpatient, and outpatient prescription drug experience of employees and their dependents. The Medicare Supplemental database contains the healthcare experience of individuals with Medicare Supplemental insurance paid for by their employers. Both the Medicare-covered portion of payment and the employer-paid portion are included in this database. In 2010, there were more than 50 million covered lives in the Commercial Claims and Encounters Database and 4 million in the Medicare Database. The data recorded include disease diagnosis (including date of diagnosis) via International Classification of Diseases, Ninth Revision (ICD-9) and 10th Revision (ICD-10) codes, patient demographics (such as year of birth, gender), pharmacy dispensing of drugs (identifiable via National Drug Codes [NDC]) and dates of laboratory tests.

Since the safety analyses are based on a common biological mechanism linking treatment to outcome, there is in general no reason to expect the relative risks to differ across geographic regions. However, similar to the discussions usually held around the assessment of the risk of VTE with the use of oestrogen containing hormonal contraception in studies performed in the US vs EU, meaningful differences in weight and weight-related baseline characteristics might exist and could impact VTE outcomes. These baseline characteristics from the US might be considered more unfavourable, as compared to EU data, regarding the baseline risk of VTE, as obesity is a known risk factor of VTE.

Bias

Claims data are recorded for billing purposes and may contain inaccurate healthcare information. Medications dispensed may not be taken as prescribed. The database includes information for employed persons and their dependents and is not representative of the unemployed populations of the US. The data come mostly from large employers; medium and small firms may be underrepresented. The study cohorts differ in more ways than drug exposure. Patients with untreated VVA may have reasons for not seeking treatment, such as having other, more urgent conditions requiring medical care. Patients treated with other SERMs are prescribed the treatment for a different indication than for ospemifene; again, the comparator drug users may be more likely to have major health concerns than the ospemifene users. The analyses have made efforts to address these sources of bias through an examination of a wide range of potential confounders of the treatment-outcome association, as well as through several sensitivity analyses varying the analytical approach. Still, the potential exists for residual confounding from factors not available in claims data.

Participants

In the MarketScan database from 1 May 2013 to 2 October 2018, three cohorts of patients were identified:

1. Ospemifene cohort: Postmenopausal patients with at least one dispensing of ospemifene, identified through pharmacy dispensing data

2. Comparator SERM cohort: Postmenopausal patients (treated for oestrogen-deficiency conditions or breast cancer prevention) with at least one dispensing of the SERM therapies raloxifene, bazedoxifene, or tamoxifen (for the reduction in risk of breast cancer in postmenopausal women at high risk of breast cancer)

3. Untreated for VVA cohort: Postmenopausal patients with a new diagnosis of VVA and no dispensing of local or systemic oestrogens

An index date was defined for each patient as the first dispensing of a qualified drug for the two treatment-related cohorts, and first diagnosis of VVA for the untreated for VVA cohort.

Of note, the MAH also investigated the feasibility of including a local oestrogen cohort in this study, but patient counts for post-menopausal women with prescriptions of local oestrogens were found to be low and its use is not well recorded in the healthcare databases used in this study. Although the PI of local oestrogens contain oestrogen class labelling regarding increased risk of VTE, the incidence of VTE during use of vaginally applied oestrogens is not established. Further, vaginally applied oestrogens are often used intermittently and in varying doses, making it difficult to for relative VTE risk comparison with a product with a once-daily oral dosage.

The alternative comparators were considered acceptable by the PRAC. At the time of the PASS protocol assessment by the PRAC (EMEA/H/C/PSP/0023.2), the MAH was asked to include VVA patients treated with a local oestrogen as a comparison cohort, unless they could provide assurance that patients diagnosed with VVA without any treatment actually will be captured in this PASS It should, however, be noted that these groups have its limitations. The reasons for the untreated VVA group not to have obtained a prescribed treatment, and similarly the reasons for half of the ospemifene group not to have a recorded VVA diagnosis, are unknown, but this condition is known to be under-reported in medical practice (Sturdee et al, 2010). Further, the other SERM group, raloxifene in >90% of participants in this cohort, differs from the ospemifene cohort in having a different indication. These limitations have been partly addressed by conducting different sub-analyses.

Inclusion and exclusion criteria

Inclusion criteria for the cohorts were as follows:

- Females
- >54 years of age at index date
- With at least one dispensing of ospemifene, raloxifene, bazedoxifene, or tamoxifen, or with a new diagnosis of VVA within the cohort definition period, defined as 1 May 2013 through 2 October 2018
- Continuous enrolment (medical and pharmacy coverage) from 365 days prior to the index date through one day after the index date (baseline period) in the same treatment cohort

The following exclusion criteria were applied:

1. Any of the following diagnoses in the baseline period: VTE, CVE, myocardial infarction (MI), endometrial hyperplasia, untreated uterine polyps, uterine prolapse, or cancers; or antineoplastic treatment during the baseline period

2. Dispensing of ospemifene, any other SERM, or oestrogen therapy in the baseline period, other than the dispensing of the index therapy on the index date

Cohorts were defined based on the treatment use on the index date. To maximise the size of the ospemifene cohort, patients were selected into this cohort if there was evidence of ospemifene use at any time during the cohort definition period. Patients with no ospemifene dispensing during the cohort

definition period but with a comparator SERM dispensing were assigned to the comparator SERM cohort. Those with a VVA diagnosis and no SERM treatment were assigned to the untreated for VVA cohort. These cohorts indicate the drug exposures on the index date, but some analyses permitted exposure status to change during follow-up, as described in the Data Analysis section.

Treatments and exposure

Ospemifene treatment episodes were defined as continuous use of ospemifene with no more than a 30-day gap. Details regarding the derivation of treatment episodes are as follows:

1. Each dispensing of ospemifene was assumed to last from the date of pharmacy dispensing until the date of dispensing plus days' supply minus one, unless the start date overlapped with a prior dispensing of ospemifene.
2. When the start date of ospemifene occurred prior to the end date of a prior dispensing of ospemifene, the later dispensing was moved to the day after the end of the prior dispensing. Any later dispensing that overlapped were moved similarly. This included multiple dispensing that occur on the same date (i.e., patient received two ospemifene dispensing on the same day).
3. After appending any overlapping dispensing, treatment episodes were defined by linking sequential dispensing of ospemifene that were separated by no more than a 30-day gap (i.e., day of new dispensing minus end date of prior dispensing <30 days).
4. The duration of each treatment episode in days was the end date of the episode minus the start date of the episode plus one. Ospemifene exposure was assumed to be continuous throughout the treatment episode; all person-time during a treatment episode was considered current exposure time, including any <30-day gaps between the appended supply times of two dispensing (i.e., after completion of step 2 above).
5. A new treatment episode started at the first dispensing following a >30-day gap after the end of the most recent supply of ospemifene (i.e., the appended end date, after completion of step 2 above).

Treatment episodes for comparator SERMs were derived using the same approach as for ospemifene. Since the comparator SERMs are not typically used for the same indication as ospemifene, patients were not assumed to have made a treatment switch if they received ospemifene during comparator SERM use, or a comparator SERM during ospemifene use. Both drugs may be used concomitantly, and their treatment episodes were derived independently of one another.

Following creation of the treatment episodes for ospemifene and, separately, for comparator SERM, exposure to ospemifene and to comparator SERM was categorised into blocks of time as follows:

- Current use included the start through end date of a treatment episode as defined above
- Recent use was the first 30 days after the end of the most recent treatment episode
- Past use included all follow-up time more than 30 days after the most recent treatment episode

If a patient received another dispensing of the same drug during recent or past exposure time, the exposure category moved back to current time and proceeded as described above.

The same patient may have had concurrent use of ospemifene and comparator SERM, which was reflected in two separate indicators for current ospemifene and current comparator SERM use. Exposure to the three comparator SERMs (raloxifene, bazedoxifene, or tamoxifen) was considered as a single exposure category, with no differentiation among the three drugs; switching among these three drugs did not lead to a change in exposure category.

For patients in the untreated for VVA cohort, follow-up was categorised into an untreated period, and, for those who initiated treatment with ospemifene or comparator SERM, current, recent, and past treatment periods as for the ospemifene and comparator SERM cohorts. Once ospemifene or a comparator SERM has been initiated, the patient did not return to an untreated state. Discontinuing treatment for more than 30 days led to an exposure category of "past therapy" rather than untreated.

Dosing for ospemifene was examined using the following approach:

1. Values of quantity and days' supply of each dispensing were first checked. The typical duration of a dispensing was assumed to be 30 days, and the typical quantity one tablet per day (30 tablets per dispensing). Any values of daily quantity of >10 tablets per day or <0.1 tablets per day were flagged as unreasonable.
2. For any such daily quantity flagged as unreasonable, the values for quantity dispensed or days' supply were adjusted to the values needed to obtain the standard daily quantity. For example, a dispensing of 20 mg ospemifene tablets at a quantity of 300 tablets with a 30-day supply had the quantity adjusted to 30 tablets, giving a daily quantity of one tablet per day, for a dose of 20 mg rather than an unrealistic 200 mg.
3. The total dose of each ospemifene dispensing was determined by multiplying the quantity of tablets by drug strength.
4. The daily dose was found by dividing the dispensing dose by days' supply.
5. The average monthly dose of ospemifene was estimated by summing the dose of all ospemifene dispensing received at any time by the patient and dividing by the total duration of ospemifene treatment episodes converted to months (i.e., number of days divided by 30.4).
6. The average daily dose was the sum of all daily doses divided by the total number of ospemifene dispensing.
7. The cumulative dose of ospemifene for each patient was the sum of all doses received during the follow-up period.

The same approach was taken to find the daily, monthly, and cumulative dose of comparator SERMs. Because the standard dosages for bazedoxifene and tamoxifen are 20 mg per day, compared to 60 mg per day for ospemifene and raloxifene, the doses of bazedoxifene and tamoxifen were aligned across drugs by multiplying the recorded dose by three prior to analysis.

Objectives and hypotheses

The overall objective of the study was to assess the incidence and risk of various side effects associated with ospemifene use in a real-world population.

<u>The primary objectives of part 1 of the study were to:</u>

- Compare the incidence of VTE among postmenopausal women who are newly prescribed ospemifene (ospemifene cohort) to that among patients diagnosed with but not treated for VVA (untreated for VVA cohort)
- Compare the incidence of VTE among postmenopausal women who are newly prescribed ospemifene (ospemifene cohort) to that among postmenopausal women newly prescribed other SERM therapies (comparator SERM cohort) being utilised for oestrogen-deficiency conditions (i.e., non-cancer and non-infertility indications) or breast cancer prevention

The research hypotheses for this study were:

- In postmenopausal women newly prescribed ospemifene relative to untreated for VVA patients, the hazard ratio (HR) of VTE is not greater than 2.0
- In postmenopausal patients newly prescribed ospemifene relative to postmenopausal patients newly prescribed SERMs for oestrogen-deficiency conditions or breast cancer prevention, the HR of VTE is not greater than 2.0

The secondary objectives of part 1 of the study were to:

- Assess the number and percentage of patients (and time to event) in each cohort with:
    - CVE
    - 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
    - Increased triglycerides
    - Vaginal bleeding
- Assess the number and percentage of patients with uterine diagnostic tests and procedures in each cohort
    - Uterine tests and procedures include: pelvic ultrasound, transvaginal ultrasound, diagnostic and / or surgical hysteroscopy with / without histological evaluation and endometrial biopsy.

Outcomes/endpoints

Patients were followed for outcomes from the day after the index date until the earlier of disenrollment from the health plan or the end of the study data (31 December 2018). The first of each outcome of interest during the follow-up period was examined. The primary analyses examined events occurring during the first continuous treatment episode, as defined in the Exposure section. In the analyses, the outcomes were attributed to exposure periods depending on the current exposure status of the patient at the time of the outcome event, as described in the Data Analysis section.

Primary endpoint:

The primary outcome of the study was the first occurrence during the first treatment episode of VTE, including DVT, pulmonary embolism, and retinal vein thrombosis. An additional analysis examined events during all follow-up time, using an intention-to-treat (ITT) approach.

Secondary endpoints:

The secondary outcomes of the study were the first occurrence of the following events during the follow-up period:

- CVE
- 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
- Increased triglycerides
- Vaginal bleeding
- Uterine diagnostic tests and procedures

Sample size

The study protocol estimated that 8,779 patient-years in the ospemifene cohort would be required to demonstrate non-inferiority at a relative risk of 2.0 with 90% power (as per approved PASS protocol). However, the observed event rates of approximately 11 events per 1,000 person-years (PY) in each of the comparator groups are different from the expected rates for untreated VVA and other SERM of 2.9 and 2.7, respectively, per 1,000 PY used in the original sample size calculation. Those expected rates were generated from clinical trials whose patients are not likely to be representative of our real-world cohorts. Based on the observed background incidence rate (IR) of 11 events per 1,000 PY, a sample size of approximately 2,000 PY in the ospemifene cohort should provide 90% power to assure that the hazard ratio of VTE is not greater than 2.0 compared with the other SERM and untreated VVA cohorts.

Statistical methods

Primary Analyses

Descriptive statistics were employed to summarise patient demographics and baseline characteristics, separately by cohort as defined on the index date. The number and percentage of patients with any use of the study drugs and with time spent untreated for VVA was tabulated, and their total duration of follow-up in any exposure category summarised with the mean, standard deviation (SD), median, and interquartile range (IQR). The total duration of time in each of these categories (i.e., current, recent, and past time with ospemifene and comparator SERM, during both initial and all treatment episodes, as well as untreated time) was also summarised with the mean, SD, median, and IQR. The same statistics are

reported for average daily dose, average monthly dose, and cumulative dose; note that to allow combination among the three comparator SERMs, the transformed (multiplied by three) doses for bazedoxifene and tamoxifen were used.

Occurrence of VTE and each of the secondary outcomes during the first continuous treatment episode (i.e., first episode of ospemifene use for the ospemifene cohort, first episode of comparator SERM use for the comparator SERM cohort, and first episode of untreated time for the untreated for VVA cohort) were described as:

- Number of patients eligible for the outcome (excluding those with the outcome event at baseline)
- Number of patients with the outcome
- Total duration of person-years (PY) of time at risk for the outcome as defined below
- Incidence rate (IR) and 95% confidence interval (CI) for each outcome, calculated as follows: the number of first occurrences of the event in the cohort, during the first continuous treatment episode, was divided by the total aggregate person-time accrued in that cohort at the time of analysis. Person-days for an individual were defined as the total number of days in the treatment episode, ending at the earliest of the date of the initial event, end of the treatment episode, death, end of enrolment in the database, end of the study period, or initiation of oestrogen therapy or other non-comparator SERM (i.e., clomiphene or toremifene). PY were person-days divided by 365. IRs were converted into events per 1,000 PY. Poisson 95% CIs were computed around each IR.

For the primary outcome of VTE of any type, a Kaplan-Meier (KM) plot was constructed to illustrate the time to first event (in days) in each cohort during the first treatment episode. The following statistics are reported:

- Time from index date to event among all patients (KM median would have been produced if there were sufficient number of patients experiencing VTE to estimate a summary measure)
- Time from index date to event among only patients with the event
  - o Mean
  - o SD
  - o Median
  - o IQR

Secondary analyses

Additional, secondary analyses examined the first occurrence of each event during all follow-up time. One secondary analysis linked the incidence of each event to the exposure categories (current, recent, or past ospemifene or comparator SERM) across the cohorts into which patients fell at the time of the event. Because separation into current, recent, and past exposure periods does not allow a view of any lingering effects of a drug after current exposure ends, the exposure periods were also combined. First, current plus recent exposure time were combined, providing a view of the drug exposure period plus a 30-day washout period. Next, current plus recent plus past exposures were combined, showing the total time after start of the drug. Because minimal switching between ospemifene and comparator SERM was observed, an additional secondary analysis was conducted using an ITT approach, examining any event that occurred during the full follow-up period after cohort entry. Tabulations present the following, separately for each exposure category:

- Number of patients eligible for the outcome during the exposure category (i.e., patients with any time in the exposure category prior to or without having experienced the outcome event)
- Number of patients with the outcome during the exposure category
- Total duration of PY of time at risk for the outcome during the given exposure category
- IR and 95% CI for each outcome, calculated as for the first treatment episode, but including in the denominator all time in the exposure category up to the date of the event; patients without the event contributed all time that they spent in the given exposure category

Note that time spent untreated for VVA was not presented in a separate table to parallel the exposure tables for ospemifene and comparator SERM, because the results would be identical to the results for the first continuous treatment episode of untreated for VVA. However, their exposure to ospemifene and/or comparator SERM is presented in the corresponding exposure category.

The age distribution has been found to vary considerably across the treatment groups. As age is also a risk factor for VTE, it may act as a major confounder of the treatment-outcome association. Accordingly, the IR analyses were rerun stratifying by age, and comparative analyses were conducted only within the age-stratified groups. Two age strata were created for patient 54 to 72 years and 73 years and older; the younger group represented approximately 99% of all qualifying ospemifene users. While this age stratification reduced the imbalance in age across treatment groups, the resulting age distribution remained more heavily weighted toward the youngest patients (ages 54 to 59) in the ospemifene cohort, especially relative to the comparator SERM cohort. Hence, further adjustment for age was applied to the outcome models, as described below. For each outcome (i.e., VTE overall and by type) and age group, the median time to event, in days, with 95% CI was calculated. Given that far fewer than 50% of patients experienced the event during follow-up, the median time to event was calculated among patients who had the event; the KM median was not reached. Additionally, since follow-up duration differed markedly among treatment groups, the age-stratified incidence was also examined restricting the follow-up time during the first treatment episode to 90 days, 120 days, and 180 days (i.e., ending at the earlier of the end of the first treatment episode and the given time point of 90, 120, or 180 days).

Separate Cox proportional hazards regression models were used to compare incidence of VTE in patients who were newly prescribed ospemifene vs. other SERM and ospemifene vs. untreated VVA. The older age stratum for ospemifene users was too small to conduct comparative analyses, so Cox models were run only in the younger stratum. Each of the baseline demographic characteristics and resource use variables, as well as the time-varying risk factors (medical conditions and medications) was assessed as a potential confounder in the association between the drug exposure groups and outcomes. Due to concerns regarding residual confounding from age, which may have a non-linear association with the outcome, age was modelled both as a continuous variable and a polynomial transformation (i.e., age-squared).

First, univariable Cox models were constructed for the main study drug exposure variable and other covariates, and an unadjusted HR for each variable calculated. Any covariate that modified the HR for the treatment group comparison by at least 5% was considered for inclusion in the final model. After all such covariates were identified, they were added sequentially to the model, in descending order of confounding strength (i.e., starting from the covariate that changed the HR the most), and removing any covariates that no longer affected the HR for treatment by at least 5%. The models were constructed similarly for the analysis of VTE during the first treatment episode, during all follow-up time (the ITT analysis), and restricting the follow-up time to the first 90 days of the first treatment episode.

Sensitivity Analyses

Three sensitivity analyses were also conducted to further assess the robustness of the comparative analysis results for the outcome of VTE: propensity score matching, an alternate method for selecting

covariates in the Cox models, and a comparison of ospemifene vs. untreated VVA using the VVA diagnosis date as the index date for ospemifene patients.

1. The first sensitivity analysis was conducted using propensity score methods. This analysis considered all patients together without age stratification, as the propensity score permitted balancing on age as well as other potential confounders. First, logistic regression models were constructed with all of the baseline variables as predictors and receipt of ospemifene versus other SERM (and in a separate model, ospemifene versus untreated VVA) as the outcome. From these models, each patient's conditional probability (i.e., propensity) for receiving ospemifene was estimated.

   The propensity scores were used to match patients using a nearest neighbour approach with a maximum difference (calliper) of 0.2 times the SD of the logit of the propensity score. Each ospemifene user was matched to one comparator patient, selecting randomly among comparators when an ospemifene user had more than one closest-matching comparator. The baseline characteristics of the matched groups were examined, and standardised differences calculated to assess the balance between groups on each characteristic. Taking the propensity score matched groups, the IR and Cox models of VTE were rerun. A robust variance estimator was used in the Cox models to account for the matching.

2. The second sensitivity analysis used a backward elimination method to select the covariates for the VTE outcome models. The primary comparative analyses selected only variables that served as confounders of the treatment-outcome association. While such an approach is efficient in estimating the risk associated with treatment as precisely as possible, it prevents a full view of all observed predictors of the outcome.

   Hence, to assess the HR of VTE with simultaneous adjustment for all measured covariates that predicted the outcome at $p<0.05$, this analysis used backward elimination for covariate selection. The variable selection process started with inclusion of all variables in the model. Variables were then removed one at a time and the model fit was recalculated. The variable with the least statistically significant reduction in the overall model fit was kept out of the model. The process stopped when the removal of any remaining variable would result in a statistically significant drop in overall model fit. The models were constructed similarly for the analysis of VTE during the first treatment episode, during all follow-up time (the ITT analysis), and restricting the follow-up time to the first 90 days of the first treatment episode, in patients aged 54 to 72 years only.

3. A final sensitivity analysis following ospemifene users from the VVA diagnosis date was conducted to assess the potential immortal time bias that might occur in the primary analysis. For this analysis, ospemifene users were followed from the date of their first VVA diagnosis rather than from the ospemifene start date, and ospemifene use was treated as a time-varying exposure. Patients with less than one year of baseline enrolment prior to the VVA diagnosis date were excluded. For each ospemifene initiator lacking a VVA diagnosis, two imputed VVA diagnosis dates were created, based on the distribution of time between earliest VVA diagnosis and ospemifene initiation for the patients with the diagnosis. One was calculated by subtracting the median gap duration (which was found to be 10 days) from the ospemifene start date for the undiagnosed patients. The other imputed VVA diagnosis date was set to 30 days prior to ospemifene start. These VVA diagnosis dates served as index dates for two sensitivity analyses, where the baseline and follow-up variables were redefined using the VVA index dates. Cox models of VTE were constructed on all data from the VVA diagnosis forward for all ospemifene and untreated VVA patients. Among ospemifene users, any time prior to ospemifene start was included in the model as untreated time and used in the reference group. Covariate selection was performed using the method described in the primary analysis, and unadjusted and adjusted HRs were estimated.

In conclusion, the primary analysis, using IRs and Kaplan-Meier plots, is considered standard and acceptable. A range of secondary and sensitivity analyses were performed using different (combinations of) exposure categories or periods, an ITT approach, different age subgroups, addition of potential confounders to a Cox regression model, propensity score matching and use of diagnosis instead of first prescription as starting date. Together, these analyses allowed to assess the robustness of the primary results.

Amendment to the Statistical Analysis Plan

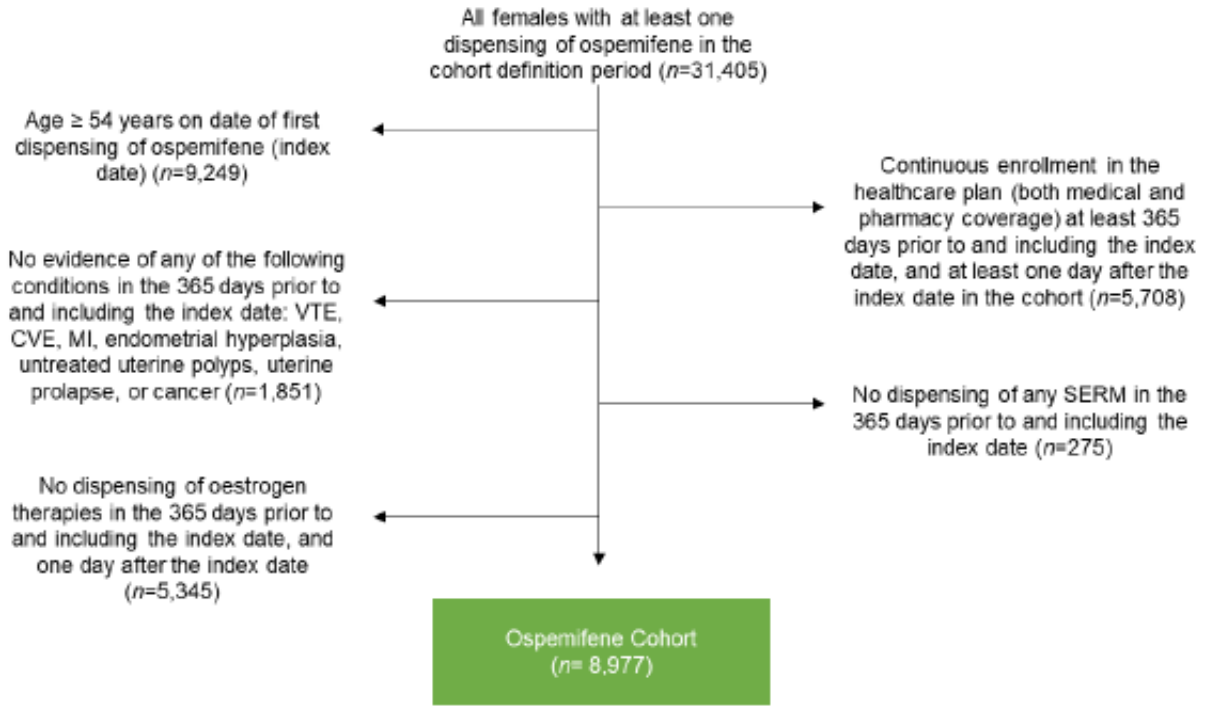
The original statistical analysis plan included an inverse probability of treatment weighted analysis of VTE, with time divided into current, recent, and past exposure to each of the study drugs as well as untreated VVA time, allowing patients to switch among the treatment groups. Minimal switching has been observed, however, calling into question the value of such an analysis. Instead, an analysis of all follow-up time in an ITT approach was added, as well as an analysis censored at 90 days. The former analysis provides a view of the longer-term risk of VTE, whereas the latter allows for more similar exposure durations across groups. The amendment to the SAP was considered by the PRAC and approved.

Results – *Part 1 - US MarketScan database*

Participant flow

From the MarketScan claims data from 1 May 2013 to 2 October 2018, 8,977 patients were included in the ospemifene cohort (Figure 1).

Figure 1: Ospemifene Cohort.



Abbreviations: CVE = cerebrovascular event; MI = myocardial infarction; SERM = selective oestrogen receptor modulator; VTE = venous thromboembolism. For the ospemifene cohort, the index date (date of cohort entry) was defined as the date of first ospemifene dispensing during the cohort definition period.

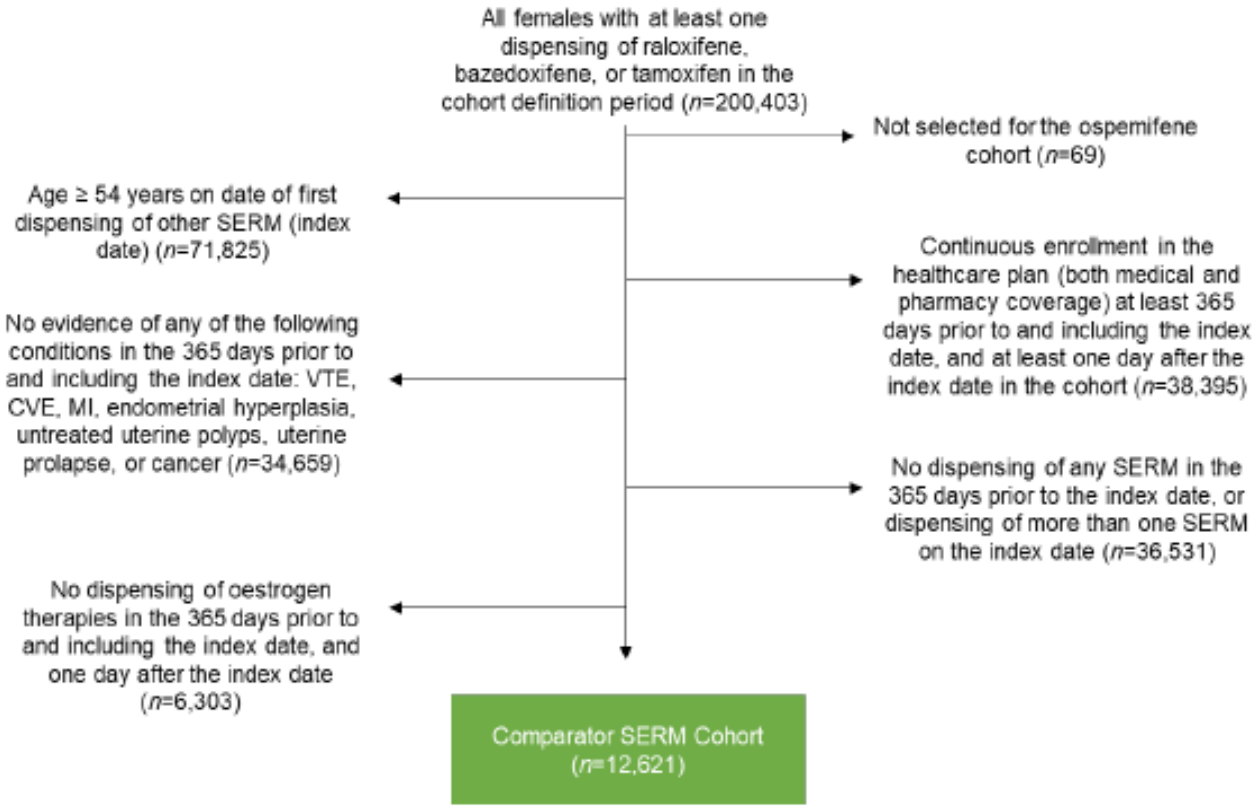
Reasons for exclusion are summarized in Table 1 below:

Table 1: Ospemifene Cohort Study Attrition

Cohort Selection Criteria	Number of Patients Excluded	Number of Patients Remaining
All females with at least one dispensing of ospemifene in the cohort definition period[1]	NA	31,405 (100.0%)
Age ≥54 years on date of first dispensing of ospemifene (index date)	9,249	22,156 (70.5%)
Continuous enrolment in the healthcare plan (both medical and pharmacy coverage) at least 365 days prior to and including the index date, and at least one day after the index date in the cohort	5,708	16,448 (52.4%)
No evidence of any of the following conditions in the 365 days prior to and including the index date: VTE, CVE, MI, endometrial hyperplasia, untreated uterine polyps, uterine prolapse, or cancer	1,851	14,597 (46.5%)
No dispensing of any SERM in the 365 days prior to and including the index date	275	14,322 (45.6%)
No dispensing of oestrogen therapies in the 365 days prior to and including the index date, and one day after the index date	5,345	8,977 (28.6%)
Include in ospemifene cohort	NA	8,977 (28.6%)

A total of 12,621 patients were included in the comparator SERM cohort in the same time period.

Figure 2: Comparator SERM Cohort



Abbreviations: CVE = cerebrovascular event; MI = myocardial infarction; SERM = selective oestrogen receptor modulator; VTE = venous thromboembolism. The index date for the comparator SERM cohort was the first date of a qualifying SERM dispensing during the cohort definition period; qualifying SERMs include raloxifene, bazedoxifene, and tamoxifen for the breast cancer risk reduction in postmenopausal women at high risk for breast cancer (i.e., not for treatment of cancer).

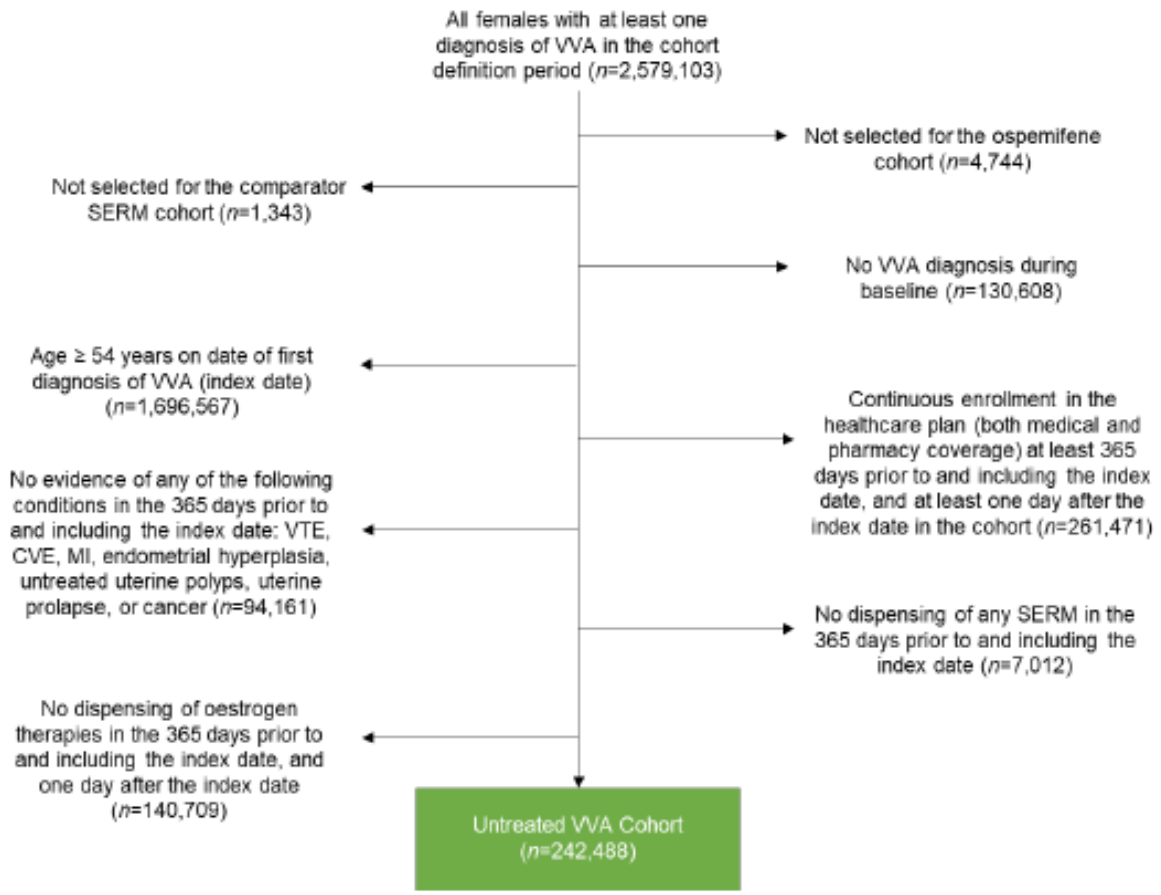
Reasons for exclusion are summarized in Table 2 below:

Table 2: SERM Comparison Cohort Study Attrition

Cohort Selection Criteria	Number of Patients Excluded	Number of Patients Remaining
All females with at least one dispensing of raloxifene, bazedoxifene, or tamoxifen in the cohort definition period[1]	NA	200,403 (100.0%)
Not selected for the ospemifene cohort	69	200,334 (>99.9%)
Age ≥54 years on date of first dispensing of other SERM (index date)	71,825	128,509 (64.1%)
Continuous enrolment in the healthcare plan (both medical and pharmacy coverage) at least 365 days prior to and including the index date, and at least one day after the index date in the cohort	38,395	90,114 (45.0%)
No evidence of any of the following conditions in the 365 days prior to and including the index date: VTE, CVE, MI, endometrial hyperplasia, untreated uterine polyps, uterine prolapse, or cancer	34,659	55,455 (27.7%)
No dispensing of any SERM in the 365 days prior to the index date, or dispensing of more than one SERM on the index date	36,531	18,924 (9.4%)
No dispensing of oestrogen therapies in the 365 days prior to and including the index date, and one day after the index date	6,303	12,621 (6.3%)
Include in comparator SERM cohort	NA	12,621 (6.3%)

A total of 242,488 patients were included in the untreated for VVA cohort in the same time period.

Figure 3: Untreated for VVA Cohort.



Abbreviations: CVE = cerebrovascular event; MI = myocardial infarction; SERM = selective oestrogen receptor modulator; VTE = venous thromboembolism; VVA = vulvar and vaginal atrophy. For the untreated for VVA cohort, the index date was the first date of diagnosis of VVA during the cohort definition period.

Reasons for exclusion are summarized in Table 3 below:

Table 3: Untreated for VVA Comparison Cohort Study Attrition

Cohort Selection Criteria	Number of Patients Excluded	Number of Patients Remaining
All females with at least one diagnosis of VVA in the cohort definition period[1]	NA	2,579,103 (100.0%)
Not selected for the ospemifene cohort	4,744	2,574,359 (99.8%)
Not selected for the comparator SERM cohort	1,343	2,573,016 (99.8%)
No VVA diagnosis during baseline	130,608	2,442,408 (94.7%)
Age ≥54 years on date of first diagnosis of VVA (index date)	1,696,567	745,841 (28.9%)
Continuous enrolment in the healthcare plan (both medical and pharmacy coverage) at least 365 days prior to and including the index date, and at least one day after the index date in the cohort	261,471	484,370 (18.8%)
No evidence of any of the following conditions in the 365 days prior to and including the index date: VTE, CVE, MI, endometrial hyperplasia, untreated uterine polyps, uterine prolapse, or cancer	94,161	390,209 (15.1%)
No dispensing of any SERM in the 365 days prior to and including the index date	7,012	383,197 (14.9%)
No dispensing of oestrogen therapies in the 365 days prior to and including the index date, and one day after the index date	140,709	242,488 (9.4%)
Include in untreated for VVA cohort	NA	242,488 (9.4%)

During the reporting period, the number of patients treated with ospemifene was 8,977 and those treated with comparator SERM 12,621, while untreated VVA patients concerned 242,488 patients.

Cohort selection has been clearly presented by the available data. No new relevant concerns have been revealed from these data.

The safety analyses examining patients entering the cohort included 8,977 new users of ospemifene covering 2,659 person years (PY) in the first continuous treatment episode. The comparator groups included 12,621 new users of a comparator SERM with 6,194 PY, and 242,488 women newly diagnosed with VVA but not treated for the condition, covering 220,920 PY.

The study protocol estimated that 8,779 patient-years in the ospemifene cohort would be required to demonstrate non-inferiority at a relative risk of 2.0 with 90% power. However, the observed event rates of approximately 11 events per 1,000 PY in each of the comparator groups are different from the expected rates for untreated VVA and other SERM of 2.9 and 2.7, respectively, per 1,000 PY used in the original sample size calculation. Those expected rates were generated from clinical trials whose patients are not likely to be representative for the real-world cohorts. Based on the observed background IR of 11 events per 1,000 PY, a sample size of approximately 2,000 PY in the ospemifene cohort should provide 90% power to assure that the hazard ratio of VTE is not greater than 2.0 compared with the other SERM and untreated VVA cohorts. However, it is noted that based on the observed background IR of 11 events per 1,000 PY, a sample size of approximately 2,000 PY in the ospemifene cohort should provide 90% power to assure that the hazard ratio of VTE is not greater than 2.0 compared with the other SERM and untreated VVA cohorts.

Notwithstanding these considerations, the sample size of the ospemifene cohort in this study is in line with that is mentioned in the protocol and is considered sufficient for analysis of the primary hypotheses of this study:

- In postmenopausal women newly prescribed ospemifene relative to untreated for VVA patients, the hazard ratio (HR) of VTE is not greater than 2.0.

- In postmenopausal patients newly prescribed ospemifene relative to postmenopausal patients newly prescribed SERMs for oestrogen-deficiency conditions or breast cancer prevention, the HR of VTE is not greater than 2.0.

Baseline data

Full baseline characteristics are shown in Table 4:

Table 4: Baseline Characteristics of Ospemifene Initiators and Comparators

Characteristic	Ospemifene Cohort (N=8,977)	Comparator SERM Cohort (N=12,621)	Untreated for VVA Cohort (N=242,488)
Age at index date[1], years			
Mean (SD)	59.0 (4.1)	63.7 (8.0)	62.3 (7.5)
Median (IQR)	58 (56–61)	62 (58–67)	60 (57–65)
Age categories, years			
54–59	5,435 (60.5%)	4,328 (34.3%)	105,544 (43.5%)
60–65	3,113 (34.7%)	4,675 (37.0%)	78,901 (32.5%)
66–72	333 (3.7%)	1,785 (14.1%)	32,514 (13.4%)
≥73	96 (1.1%)	1,833 (14.5%)	25,529 (10.5%)
Geographic region			
North East	1,514 (16.9%)	2,593 (20.5%)	66,639 (27.5%)
North Central	1,665 (18.5%)	3,120 (24.7%)	48,116 (19.8%)
South	4,937 (55.0%)	5,091 (40.3%)	87,189 (36.0%)
West	793 (8.8%)	1,670 (13.2%)	38,062 (15.7%)
Unknown	68 (0.8%)	147 (1.2%)	2,482 (1.0%)
Index date, year			
2013	663 (7.4%)	2,931 (23.2%)	52,976 (21.8%)
2014	2,865 (31.9%)	3,623 (28.7%)	69,896 (28.8%)
2015	2,185 (24.3%)	2,395 (19.0%)	47,345 (19.5%)
2016	1,720 (19.2%)	1,917 (15.2%)	31,514 (13.0%)
2017	961 (10.7%)	1,176 (9.3%)	24,899 (10.3%)
2018	583 (6.5%)	579 (4.6%)	15,858 (6.5%)
Index date, month			
January	708 (7.9%)	1,035 (8.2%)	16,835 (6.9%)
February	670 (7.5%)	931 (7.4%)	15,528 (6.4%)
March	864 (9.6%)	931 (7.4%)	17,400 (7.2%)
April	735 (8.2%)	864 (6.8%)	17,496 (7.2%)
May	731 (8.1%)	1,198 (9.5%)	23,132 (9.5%)
June	762 (8.5%)	1,203 (9.5%)	22,893 (9.4%)
July	733 (8.2%)	1,101 (8.7%)	22,755 (9.4%)
August	751 (8.4%)	1,113 (8.8%)	22,838 (9.4%)
September	737 (8.2%)	1,077 (8.5%)	22,503 (9.3%)
October	741 (8.3%)	1,101 (8.7%)	22,448 (9.3%)
November	758 (8.4%)	1,016 (8.1%)	19,616 (8.1%)
December	787 (8.8%)	1,051 (8.3%)	19,044 (7.9%)
Index SERM			
Ospemifene	8,977 (100.0%)	0 (0.0%)	0 (0.0%)
Raloxifene	0 (0.0%)	11,639 (92.2%)	0 (0.0%)

Characteristic	Ospemifene Cohort (N=8,977)	Comparator SERM Cohort (N=12,621)	Untreated for VVA Cohort (N=242,488)
Bazedoxifene	0 (0.0%)	0 (0.0%)	0 (0.0%)
Tamoxifen	0 (0.0%)	982 (7.8%)	0 (0.0%)
Measures of healthcare utilization[2]			
Number of physician visits			
Mean (SD)	9.2 (9.0)	9.8 (9.6)	9.5 (9.1)
Median (IQR)	6 (4–11)	7 (4–13)	7 (4–12)
Number of emergency room visits			
Mean (SD)	0.1 (0.4)	0.1 (0.6)	0.2 (0.6)
Median (IQR)	0 (0–0)	0 (0–0)	0 (0–0)
Any emergency room visit	759 (8.5%)	1,197 (9.5%)	26,606 (11.0%)
Number of hospitalization days			
Mean (SD)	0.0 (0.2)	0.0 (0.2)	0.0 (0.2)
Median (IQR)	0 (0–0)	0 (0–0)	0 (0–0)
Any hospitalization	177 (2.0%)	369 (2.9%)	7,026 (2.9%)
Baseline conditions associated with an increased incidence of VTE[3]			
Atrial fibrillation	78 (0.9%)	246 (1.9%)	6,165 (2.5%)
Transient ischaemic attack	35 (0.4%)	65 (0.5%)	1,552 (0.6%)
Hypertension	3,020 (33.6%)	4,960 (39.3%)	106,774 (44.0%)
Diabetes mellitus	942 (10.5%)	1,416 (11.2%)	40,427 (16.7%)
Atherosclerosis	213 (2.4%)	548 (4.3%)	13,637 (5.6%)
Trauma (within 90 days before index date)	743 (8.3%)	1,221 (9.7%)	20,487 (8.4%)
Surgery (within 90 days before index date)	42 (0.5%)	86 (0.7%)	1,488 (0.6%)
Immobility	176 (2.0%)	283 (2.2%)	5,188 (2.1%)
Congestive heart failure	38 (0.4%)	164 (1.3%)	3,671 (1.5%)
Obesity	678 (7.6%)	814 (6.4%)	25,984 (10.7%)
Chronic obstructive pulmonary disease	216 (2.4%)	599 (4.7%)	9,585 (4.0%)
Rheumatic disease	338 (3.8%)	467 (3.7%)	8,752 (3.6%)
Chronic kidney disease	173 (1.9%)	387 (3.1%)	7,650 (3.2%)
Inflammatory bowel disease	103 (1.1%)	145 (1.1%)	2,343 (1.0%)
Inherited or acquired thrombophilia	6 (0.07%)	13 (0.1%)	449 (0.2%)
Baseline dispensing of medications that potentially modify the incidence of VTE[3]			
Antihypertensives	3,144 (35.0%)	5,146 (40.8%)	102,194 (42.1%)
Antidiabetic agents	775 (8.6%)	1,009 (8.0%)	29,605 (12.2%)
Anticoagulants or anti-thrombolytic therapy	169 (1.9%)	397 (3.1%)	9,140 (3.8%)
Antiarrhythmic therapy	34 (0.4%)	82 (0.6%)	1,596 (0.7%)
Antihyperlipidemic therapy	2,730 (30.4%)	4,605 (36.5%)	80,002 (33.0%)
Progesterone therapy	120 (1.3%)	42 (0.3%)	1,780 (0.7%)
History of study outcome events during baseline[3]			
Pelvic organ prolapse	150 (1.7%)	142 (1.1%)	11,512 (4.7%)

Characteristic	Ospemifene Cohort (N=8,977)	Comparator SERM Cohort (N=12,621)	Untreated for VVA Cohort (N=242,488)
Urinary incontinence	338 (3.8%)	308 (2.4%)	17,950 (7.4%)
Gallbladder events	109 (1.2%)	164 (1.3%)	3,721 (1.5%)
Atrial fibrillation	78 (0.9%)	246 (1.9%)	6,165 (2.5%)
Renal failure	32 (0.4%)	119 (0.9%)	2,425 (1.0%)
Renal adenoma	8 (0.09%)	13 (0.1%)	301 (0.1%)
Liver tumours	1 (0.01%)	6 (0.05%)	114 (0.05%)
Thymic epithelial tumours	0 (0.0%)	0 (0.0%)	7 (0.003%)
Increased triglycerides	2,999 (33.4%)	4,836 (38.3%)	93,680 (38.6%)
Vaginal bleeding	50 (0.6%)	48 (0.4%)	3,088 (1.3%)
Uterine diagnostic tests and procedures	575 (6.4%)	694 (5.5%)	22,189 (9.2%)

Note. Cell entries are n (%) unless otherwise specified. [1]Index date: first dispensing of ospemifene, first dispensing of comparator SERM, or first diagnosis of VVA. [2]183 days prior to and including index date [3]365 days prior to and including index date. Abbreviations: CVE = cerebrovascular event; IQR = interquartile range; NA = not applicable; SD = standard deviation; SERM = selective oestrogen receptor modulator; VTE = venous thromboembolism; VVA = vulvar and vaginal atrophy.

Ospemifene Cohort

Mean age among the 8,977 patients within the ospemifene cohort was 59.0 years (SD: 4.1); the modal age group for ospemifene use was 54 to 59 years (60.5%). The most common year of index date was 2014 (31.9%). Over the 183 days prior to and including index date, the mean number of physician visits was 9.2 (SD: 9.0), 8.5% of the ospemifene cohort visited the emergency room, and 2.0% experienced hospitalisation.

In the 365 days preceding and also including the index date, hypertension was the most frequently seen comorbidity (33.6% of patients), followed by diabetes (10.5% of patients). The most commonly dispensed medication class associated with a potentially modified risk of VTE was antihypertensives, used by 35.0% of the cohort, followed by antihyperlipidemic therapy, used by 30.4% of patients. Of the study outcome events that were not used as exclusion criteria, only increased triglycerides and uterine diagnostic tests/procedures were seen in more than 5% of the ospemifene cohort during the baseline period (33.4% and 6.4%, respectively).

Comparator SERM Cohort

Among the 12,621 patients in the comparator SERM cohort, the mean age was 63.7 years (SD: 8.0), and the modal age group was 60 to 65 (37.0%). The most common index year was 2014 (28.7%). The SERM that qualified patients for inclusion on the index date was raloxifene for 92.2% of patients and tamoxifen for 7.8%; no patients were treated with bazedoxifene.

During the six months prior to the index date, patients had a mean of 9.8 (SD: 9.6) physician visits; 9.5% had an emergency room visit, and 2.9% were hospitalised.

The most common comorbidities and medications dispensed during the one-year baseline period were the same as in the ospemifene cohort: hypertension (39.3%), diabetes (11.2%), antihypertensive medications (40.8%), and antihyperlipidemic therapy (36.5%). Also similar to the ospemifene cohort, increased triglycerides (38.3%) and uterine diagnostic tests and procedures (5.5%) were the most frequent outcome events observed during the baseline period.

Untreated for VVA Cohort

Mean age of the 242,488 patients in the untreated for VVA cohort was 62.3 years (SD: 7.5), and the modal age group was 54 to 59 (43.5%). The most common index year was 2014 (28.8%). During the six months prior to and including the index date, patients had a mean of 9.5 (SD: 9.1) physician visits.

Overall, 11.0% of patients had emergency room visits and 2.9% were hospitalised. The most common comorbidities, medications, and history of outcome events were the same as for both of the treated cohorts: hypertension (44.0%), diabetes (16.7%), antihypertensive medications (42.1%), and antihyperlipidemic therapy (33.0%), increased triglycerides (38.6%), and uterine diagnostic tests and procedures (9.2%).

In the US study, the patients in the ospemifene cohort were younger than patients in the other two cohorts.

Further, there were slight imbalances in the baseline characteristics that may be associated with an increased baseline risk of VTE or CVE. In the ospemifene cohort there were (somewhat) fewer patients having:

- atrial fibrillation (0.9% in the ospemifene cohort compared to 1.9% in the comparator SERM cohort and 2.5% in the untreated VVA cohort)
- hypertension (33.6% in the ospemifene cohort compared to 39.3% in the comparator SERM cohort and 44.0% in the untreated VVA cohort)
- diabetes mellitus (10.5% in the ospemifene cohort compared to 11.2% in the comparator SERM cohort and 16.7% in the untreated VVA cohort)
- atherosclerosis (2.4% in the ospemifene cohort compared to 4.3% in the comparator SERM cohort and 5.6% in the untreated VVA cohort)
- congestive heart failure (0.4% in the ospemifene cohort compared to 1.3% in the comparator SERM cohort and 1.5% in the untreated VVA cohort)
- COPD (2.4% in the ospemifene cohort compared to 4.7% in the comparator SERM cohort and 4.0% in the untreated VVA cohort).

Similarly, the use of antihypertensives, antidiabetic agents, anticoagulants and antihyperlipidemic therapy was less common in the ospemifene cohort compared to the other two cohorts.

These imbalances in baseline characteristics concern common risk factors for CVE which can be expected in the target group of postmenopausal women considered as possible source of bias in this study.

Additionally, it should be noted that in the comparator SERM cohort most (92.2%) patients were on raloxifene, which is favourable for consistency in further analysis. However, there are some differences in patient characteristics comparing the ospemifene and raloxifene group. Particularly patient's age in the raloxifene group (59.0 years) is higher, as compared to the ospemifene group (63.7 years) and also compared to the non-treated group (62.3 years). These differences might affect the incidence of VTEs, cardiovascular and other concomitant diseases.

In summary, on average the patients in the ospemifene cohort were younger than the patients of the other two cohorts and had lower prevalence of some comorbidities that are known risk factors for CVE. These above-mentioned differences in the baseline characteristics between the treatment cohorts should therefore be taken into account in further (sub-)analyses.

Duration of Exposure

Ospemifene Cohort

As per the definition, all 8,977 individuals in the ospemifene cohort were exposed to ospemifene. Within the current use of ospemifene category, the mean duration of use was 129.6 days (SD: 118.1). The mean duration in the recent-use (i.e., the first 30 days after end of a treatment episode) ospemifene category was 27.8 (SD: 21.5) days. The past-use (more than 30 days after end of a treatment episode) ospemifene category had a mean of 143.5 (SD: 164.2) days.

Within the ospemifene cohort, 34 (0.4%) women were treated with comparator SERMs at any time during follow-up. Among these patients, the mean duration of current use of comparator SERMs was 118.0 days (SD: 79.0), of recent use was 14.8 days (SD: 16.8) and of past use was 76.9 days (SD: 120.5).

Ten patients (0.1%) had concurrent exposure to ospemifene and comparator SERM at some time during follow-up.

Comparator SERM Cohort

The mean duration of current use of comparator SERMs in the comparator SERM cohort was 216.7 days (SD: 185.0), with a mean duration of recent use of 21.5 days (SD: 23.9), and of past use of 111.4 days (SD: 176.2).

Twelve (0.10%) women in the comparator SERM cohort received ospemifene at any time during follow-up, with a mean duration of current use of 108.3 days (SD: 106.4). Concurrent use of ospemifene and comparator SERM was seen in six (0.05%) women of the comparator SERM cohort.

Untreated for VVA Cohort

The mean number of days of untreated time in the untreated for VVA cohort was 335.9 days (SD: 216.1). Ospemifene treatment was started during follow-up in 388 (0.2%) patients in the untreated cohort, with current use at a mean of 87.2 days (SD: 91.0). Comparator SERM use was observed during follow-up in 474 (0.2%) of the untreated cohort, with a mean duration of 141.5 days (SD: 143.0) of current use.

Concurrent ospemifene and comparator SERM use was seen in three (0.001%) of patients.

In conclusion, the data on exposure duration show that average duration of ospemifene use was generally twice shorter (129.6 days) than that of comparator SERM use (216.7 days) and far shorter than the untreated time in VVA cohort (335.9 days). The difference in duration of first use between the ospemifene and other SERM is likely due to the difference in indication, i.e. VVA versus prevention or treatment of breast cancer.

Although the risk of VTE is considered to be highest in early use, the shorter duration of exposure could also have impact on the VTE incidence, as the shorter exposure time may overestimate the risk in the ospemifene group. As such, the primary analysis can therefore be considered conservative. Similarly, this may also have such an effect on secondary outcomes.

Dosage of Study Drugs During Follow-up

Ospemifene Cohort

The mean dose of ospemifene at an average daily level, average monthly level, and cumulative dose was 57.6 mg (SD: 5.9); 1,725.9 mg (SD: 216.9); and 7,302.6 mg (SD: 6,615.6). Of the 34 patients in this cohort who also received a comparator SERM during follow-up, the average daily dose of the comparator SERM was 59.8 mg (SD: 5.1).

Comparator SERM Cohort

The mean (SD) daily dose of comparator SERMs was 58.9 mg (6.6); note that tamoxifen doses are reported at three times the actual dose to make the doses comparable with the other study drugs. Average monthly dose of comparator SERMs was 1,765.3 mg (SD: 234.0), and total cumulative dose was 12,674.4 mg (SD: 10,875.6). The 12 patients in this cohort with ospemifene use had a mean daily dose of 58.2 mg (SD: 5.4).

Untreated for VVA Cohort

Among the 388 patients in the untreated for VVA cohort who received ospemifene at any point during follow-up, the mean daily dose was 58.5 mg (SD: 8.0). For the 474 patients who received a comparator SERM, the average daily dose was 58.8 mg (SD: 6.6).

The mean daily and monthly doses were comparable between the ospemifene and the SERM treated groups, while cumulative doses were lower in the ospemifene group, due to longer exposure time.

Outcomes and estimation

Incidence of Outcomes during the First Continuous Treatment Episode

Primary analysis: Incidence of VTE

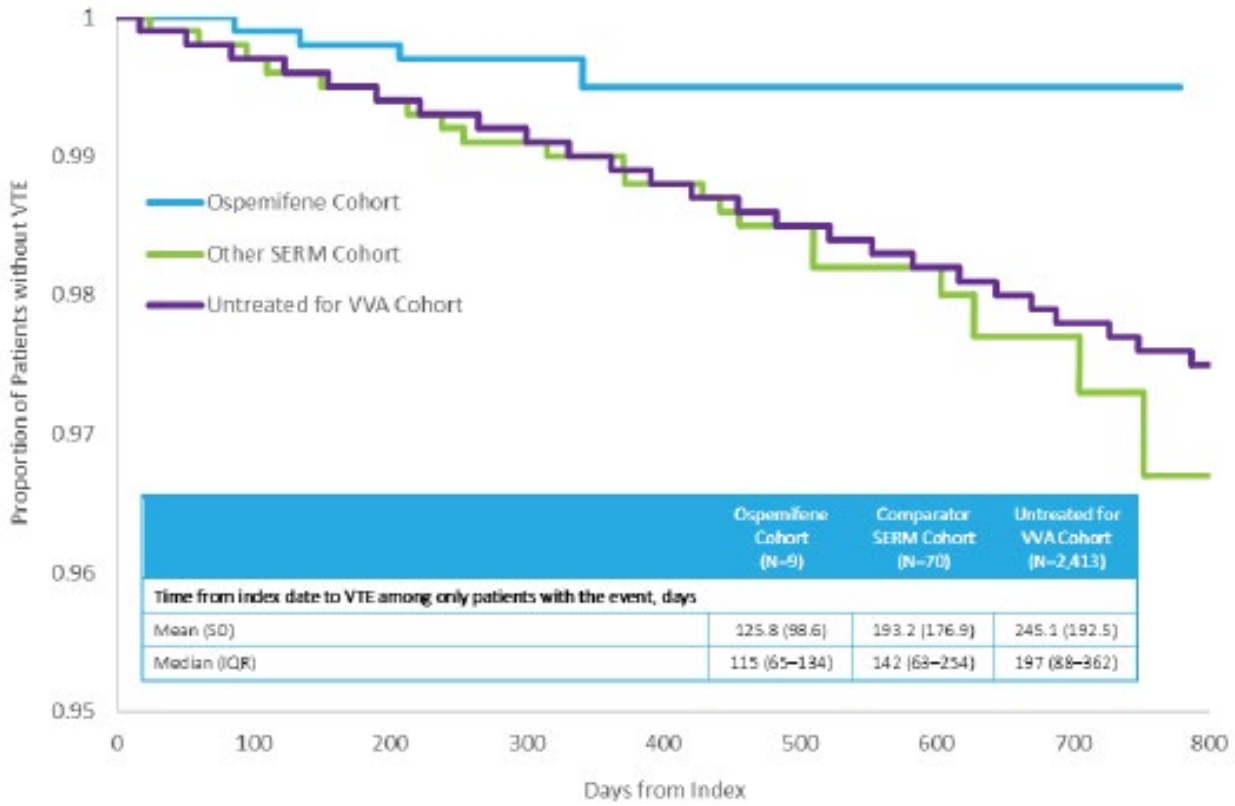
In summary, the incidence of VTE during the first continuous treatment episode was

- 3.39 (95% confidence interval [CI]: 1.55–6.43) events per 1,000 person-years (PY) for ospemifene,
- 11.30 (95% CI: 8.81–14.28) events per 1,000 PY for comparator SERM,
- 10.92 (95% CI: 10.49–11.37) events per 1,000 PY for untreated VVA.

This is further discussed in detail below.

The KM plot (Figure 4) shows these similar event rates for the two comparator cohorts, but a lower rate in the ospemifene cohort.

Figure 4: Kaplan-Meier Plot of Time from Index Date to First VTE Event During First Continuous Treatment Episode



	Ospemifene Cohort (N=9)	Comparator SERM Cohort (N=70)	Untreated for VVA Cohort (N=2,413)
Time from index date to VTE among only patients with the event, days			
Mean (SD)	125.8 (98.6)	193.2 (176.9)	245.1 (192.5)
Median (IQR)	115 (65–134)	142 (68–254)	197 (88–362)

Among patients with at least one VTE, the median time to event was 115 days for ospemifene users, 142 days for comparator SERM users, and 197 days for the untreated VVA patients. These data are presented in Table 5 below:

Table 5: Frequency and Incidence of Study Outcomes During First Continuous Treatment Episode

	Ospemifene Cohort (N=8,977)					Comparator SERM Cohort (N=12,621)					Untreated for VVA Cohort (N=242,488)					All Cohorts (N=264,086)	
	N Patients Eligible for Outcome	n of Eligible Patients with Outcome	Total Duration of Person-years	IR per 1,000 PY (95% CI)	Median (95% CI) Days to Event	N Patients Eligible for Outcome	n of Eligible Patients with Outcome	Total Duration of PY	IR per 1,000 PY (95% CI)	Median (95% CI) Days to Event	N Patients Eligible for Outcome	n of Eligible Patients with Outcome	Total Duration of PY	IR per 1,000 PY (95% CI)	Median (95% CI) Days to Event	N Patients Eligible for Outcome	n of Eligible Patients with Outcome
Primary outcome																	
Any VTE	8,977 (100.0%)	9 (0.1%)	2,658.8	3.39 (1.55 - 6.43)	115.0 (28.0 - 207.0)	12,621 (100.0%)	70 (0.6%)	6,193.9	11.30 (8.81 - 14.28)	141.5 (99.0 - 205.0)	242,488 (100.0%)	2,413 (1.0%)	220,920.2	10.92 (10.49 - 11.37)	197.0 (186.0 - 207.0)	264,086 (100.0%)	2,492 (0.9%)
Deep vein thrombosis	8,977 (100.0%)	8 (0.09%)	2,658.8	3.01 (1.30 - 5.93)	122.0 (65.0 - 341.0)	12,621 (100.0%)	59 (0.5%)	6,196.8	9.52 (7.25-12.28)	145.0 (92.0-208.0)	242,488 (100.0%)	1,967 (0.8%)	221,211.3	8.89 (8.50 -9.29)	197.0 (185.0 - 209.0)	264,086 (100.0%)	2,034 (0.8%)
Pulmonary embolism	8,977 (100.0%)	2 (0.02%)	2,660.0	0.75 (0.09 - 2.72)	46.0 (27.0 - 65.0)	12,621 (100.0%)	16 (0.1%)	6,209.1	2.58 (1.47 -4.18)	215.0 (110.0 - 456.0)	242,488 (100.0%)	542 (0.2%)	222,164.4	2.44 (2.24 -2.65)	196.0 (171.0 - 217.0)	264,086 (100.0%)	560 (0.2%)
Retinal vein thrombosis	8,977 (100.0%)	0 (0.0%)	2,660.0	0.00 (0.00 - 1.13)	NA	12,621 (100.0%)	2 (0.02%)	6,211.3	0.32 (0.04 - 1.16)	78.0 (53.0 - 103.0)	242,488 (100.0%)	83 (0.03%)	222,443.4	0.37 (0.30 - 0.46)	232.0 (159.0 - 289.0)	264,086 (100.0%)	85 (0.03%)
Secondary outcome																	
Cerebrovascular event	8,977 (100.0%)	47 (0.5%)	2,650.1	17.74 (13.03 - 23.58)	50.0 (29.0 - 109.0)	12,621 (100.0%)	182 (1.4%)	6,129.2	29.69 (25.54 - 34.34)	104.5 (77.0 - 133.0)	242,488 (100.0%)	7,373 (3.0%)	217,409.4	33.91 (33.14 - 34.70)	181.0 (176.0 - 188.0)	264,086 (100.0%)	7,602 (2.9%)
Endometrial hyperplasia	8,977 (100.0%)	15 (0.2%)	2,658.0	5.64 (3.16 - 9.31)	28.0 (13.0 - 130.0)	12,621 (100.0%)	12 (0.10%)	6,208.7	1.93 (1.00 - 3.38)	153.5 (28.0 - 414.0)	242,488 (100.0%)	1,467 (0.6%)	221,340.3	6.63 (6.29 - 6.98)	67.0 (57.0 - 74.0)	264,086 (100.0%)	1,494 (0.6%)
Endometrial cancer	8,977 (100.0%)	4 (0.04%)	2,659.7	1.50 (0.41 - 3.85)	21.5 (13.0 - 47.0)	12,621 (100.0%)	5 (0.04%)	6,211.8	0.80 (0.26 - 1.88)	52.0 (42.0 - 491.0)	242,488 (100.0%)	729 (0.3%)	221,958.4	3.28 (3.05 - 3.53)	70.0 (61.0 - 84.0)	264,086 (100.0%)	738 (0.3%)
Pelvic organ prolapse	8,827 (98.3%)	36 (0.4%)	2,605.1	13.82 (9.68 - 19.13)	49.0 (26.0 - 72.0)	12,479 (98.9%)	84 (0.7%)	6,104.4	13.76 (10.98 - 17.04)	99.5 (65.0 - 154.0)	230,976 (95.3%)	3,907 (1.7%)	209,780.7	18.62 (18.04 - 19.22)	126.0 (117.0 - 134.0)	252,282 (95.5%)	4,027 (1.6%)
Urinary incontinence	8,639 (96.2%)	73 (0.8%)	2,541.2	28.73 (22.52 - 36.12)	48.0 (34.0 - 74.0)	12,313 (97.6%)	138 (1.1%)	6,001.9	22.99 (19.32 - 27.16)	105.0 (82.0 - 149.0)	224,538 (92.6%)	6,913 (3.1%)	202,182.2	34.19 (33.39 - 35.01)	133.0 (126.0 - 141.0)	245,490 (93.0%)	7,124 (2.9%)

	Ospemifene Cohort (N=8,977)					Comparator SERM Cohort (N=12,621)					Untreated for VVA Cohort (N=242,488)					All Cohorts (N=264,086)	
Gallbladder events	8,868 (98.8%)	30 (0.3%)	2,624.2	11.43 (7.71 - 16.32)	67.0 (25.0 - 121.0)	12,457 (98.7%)	72 (0.6%)	6,108.2	11.79 (9.22 - 14.84)	78.5 (58.0 - 125.0)	238,767 (98.5%)	3,261 (1.4%)	216,937.3	15.03 (14.52 - 15.56)	170.0 (162.0 - 179.0)	260,092 (98.5%)	3,363 (1.3%)
Atrial fibrillation	8,899 (99.1%)	12 (0.1%)	2,636.7	4.55 (2.35 - 7.95)	58.5 (7.0 - 148.0)	12,375 (98.1%)	66 (0.5%)	6,055.6	10.90 (8.43 - 13.87)	126.0 (95.0 - 225.0)	236,323 (97.5%)	2,374 (1.0%)	215,291.0	11.03 (10.59 - 11.48)	189.5 (181.0 - 202.0)	257,597 (97.5%)	2,452 (1.0%)
Renal failure	8,945 (99.6%)	17 (0.2%)	2,646.3	6.42 (3.74 - 10.29)	57.0 (23.0 - 152.0)	12,502 (99.1%)	66 (0.5%)	6,125.9	10.77 (8.33 - 13.71)	132.0 (81.0 - 181.0)	240,063 (99.0%)	2,111 (0.9%)	219,153.0	9.63 (9.23 - 10.05)	189.0 (178.0 - 200.0)	261,510 (99.0%)	2,194 (0.8%)
Renal carcinoma	8,977 (100.0%)	1 (0.01%)	2,659.3	0.38 (0.01 - 2.10)	72.0 (NA)	12,621 (100.0%)	3 (0.02%)	6,211.3	0.48 (0.10 - 1.41)	157.0 (33.0 - 223.0)	242,488 (100.0%)	190 (0.08%)	222,377.4	0.85 (0.74 - 0.98)	125.5 (100.0 - 167.0)	264,086 (100.0%)	194 (0.07%)
Renal adenoma	8,969 (99.9%)	2 (0.02%)	2,657.1	0.75 (0.09 - 2.72)	252.0 (14.0 - 490.0)	12,608 (99.9%)	5 (0.04%)	6,204.4	0.81 (0.26 - 1.88)	23.0 (11.0 - 345.0)	242,187 (99.9%)	291 (0.1%)	222,015.0	1.31 (1.16 - 1.47)	189.0 (159.0 - 218.0)	263,764 (99.9%)	298 (0.1%)
Liver tumours	8,976 (>99.9%)	4 (0.04%)	2,659.5	1.50 (0.41 - 3.85)	155.0 (56.0 - 314.0)	12,615 (>99.9%)	1 (0.008%)	6,208.4	0.16 (0.00 - 0.90)	124.0 (NA)	242,374 (>99.9%)	206 (0.08%)	222,272.8	0.93 (0.80 - 1.06)	139.0 (119.0 - 182.0)	263,965 (>99.9%)	211 (0.08%)
Thymic epithelial tumours	8,977 (100.0%)	0 (0.0%)	2,660.0	0.00 (0.00 - 1.13)	NA	12,621 (100.0%)	0 (0.0%)	6,212.4	0.00 (0.00 - 0.48)	NA	242,481 (>99.9%)	13 (0.005%)	222,493.1	0.06 (0.03 - 0.10)	217.0 (99.0 - 314.0)	264,079 (>99.9%)	13 (0.005%)
Increased triglycerides	5,978 (66.6%)	347 (5.8%)	1,656.6	209.46 (188.00 - 232.70)	54.0 (41.0 - 63.0)	7,785 (61.7%)	675 (8.7%)	3,509.3	192.35 (178.11 - 207.42)	96.0 (84.0 - 112.0)	148,808 (61.4%)	25,679 (17.3%)	118,704.9	216.33 (213.69 - 218.99)	140.0 (138.0 - 143.0)	162,571 (61.6%)	26,701 (16.4%)
Vaginal bleeding	8,927 (99.4%)	25 (0.3%)	2,642.4	9.46 (6.12 - 13.97)	52.0 (30.0 - 96.0)	12,573 (99.6%)	27 (0.2%)	6,175.2	4.37 (2.88 - 6.36)	80.0 (44.0 - 202.0)	239,400 (98.7%)	2,236 (0.9%)	218,117.0	10.25 (9.83 - 10.69)	76.5 (70.0 - 84.0)	260,900 (98.8%)	2,288 (0.9%)
Uterine diagnostic tests and procedures	8,402 (93.6%)	224 (2.7%)	2,452.9	91.32 (79.75 - 104.10)	20.0 (15.0 - 27.0)	11,927 (94.5%)	235 (2.0%)	5,770.8	40.72 (35.68 - 46.28)	60.0 (44.0 - 80.0)	220,299 (90.8%)	19,779 (9.0%)	186,021.8	106.33 (104.85 - 107.82)	29.0 (28.0 - 30.0)	240,628 (91.1%)	20,238 (8.4%)

Ospemifene Cohort

Primary Outcome of VTE risk

Nine (0.1%) patients in the ospemifene cohort experienced VTE during the first continuous treatment episode over 2,659 PY, including eight patients with DVT and two with pulmonary embolism (note that one patient had both a DVT and a pulmonary embolism, and hence the counts of event types sum to

more than the total number of patients with a VTE). The incidence of VTE was 3.39 (95% CI: 1.55–6.43) events per 1,000 PY.

Secondary Outcomes

Only one of 15 secondary outcomes, increased triglycerides, occurred in more than 5% of the ospemifene cohort during the first continuous treatment episode, at an IR of 209.46 (95% CI: 188.00– 232.70) per 1,000 PY. Uterine diagnostic tests and procedures, the second most common, were recorded for 2.7% of the cohort, at an incidence of 91.32 (95% CI: 79.75–104.10) per 1,000 PY.

No other outcomes occurred in more than 1% of patients in the ospemifene cohort.

Comparator SERM Cohort

Primary Outcome of VTE risk

In the comparator SERM cohort, 70 (0.6%) patients experienced VTE during the first continuous treatment episode over 6,194 PY. The majority of these events were DVT (n=59), followed by pulmonary embolism (n=16), and retinal vein thrombosis (n=2). The incidence of VTE was 11.30 (95% CI: 8.81–14.28) per 1,000 PY, and the incidence of DVT was 9.52 (95% CI: 7.25–12.28) per 1,000 PY.

Secondary Outcomes

The most commonly occurring secondary outcome in the comparator SERM cohort was increased triglycerides, which occurred in 8.7% of patients at an IR of 192.35 (95% CI: 178.11–207.42) per 1,000 PY. Other secondary outcomes that occurred in more than 1% of the cohort were uterine diagnostic tests and procedures (IR: 40.72 per 1,000 PY; 95% CI: 35.68– 46.28), CVE (IR: 29.69 per 1,000 PY; 95% CI: 25.54–34.34), and urinary incontinence (IR: 22.99 per 1,000 PY; 95% CI: 19.32–27.16).

Although comparative analyses were not performed on the secondary outcomes, examination of the 95% CIs between the ospemifene and other SERM cohorts suggests a lower incidence of CVE and atrial fibrillation, and a higher incidence of uterine diagnostic tests and procedures, in the ospemifene group relative to comparator SERM.

Untreated for VVA Cohort

Primary Outcomes of VTE risk

During their continuous episode of untreated time, 2,413 (1.0%) patients in the untreated for VVA cohort experienced VTE, over 220,920 PY, again with the majority of events being DVT (n=1,967). Corresponding IR were 10.92 (95% CI: 10.49–11.37) per 1,000 PY for VTE and 8.89 (95% CI: 8.50–9.29) per 1,000 PY for DVT.

Secondary Outcomes

As in the other cohorts, increased triglycerides were the most frequent secondary outcome, observed in 17.3% of patients at an incidence of 216.33 (95% CI: 213.69–218.99) per 1,000 PY. Several other outcomes were seen in more than 1% of the untreated cohort, including uterine diagnostic tests and procedures (IR: 106.33 per 1,000 PY; 95% CI: 104.85–107.82), urinary incontinence (IR: 34.19 per 1,000 PY; 95% CI: 33.39–35.01), CVE (IR:33.91 per 1,000 PY; 95% CI: 33.14–34.70), pelvic organ prolapse (IR: 18.62 per 1,000 PY; 95% CI: 18.04–19.22), gallbladder events (IR: 15.03 per 1,000 PY; 95% CI: 14.52–15.56), and atrial fibrillation IR: 11.03 per 1,000 PY; 95% CI: 10.59–11.48.

Examination of non-overlapping 95% CIs between the ospemifene and untreated VVA cohorts suggests a lower incidence of both atrial fibrillation and uterine diagnostic tests and procedures in the ospemifene group relative to the untreated VVA cohort.

For the primary outcome VTE, overall, the incidence of VTE was low in the different treatment groups. The IR (i.e. absolute risk rate) of any VTE in the ospemifene patients was 3.39 (95% CI: 1.55–6.43) events per 1,000 PY, and was less than half the absolute rate in both the comparative SERM group with 11.30/1,000 PY (95% CI: 8.81–14.28) and women with untreated VVA with 10.92/1,000 PY (95% CI: 10.49–11.37).

As mentioned earlier, in the comparator SERM cohort most (92.2%) patients were on raloxifene. Of note, in a study of 10,101 postmenopausal women on raloxifene or placebo with documented coronary heart disease or at increased risk for coronary events (i.e. the RUTH study mentioned in section 4.8 of the SmPC of Evista), VTE occurred at a frequency of approximately 2.0 % or 3.88/1,000 PY in the raloxifene group and 1.4 % or 2.70/1,000 PY in the placebo group. The absolute IR found in this group on raloxifene appears to be lower than the SERM cohort in the PASS, but still similar to the IR found for the ospemifene cohort in the current PASS. These data can therefore be considered to support the findings that the absolute IR of ospemifene is not higher as compared to the raloxifene cohort in the PASS and to earlier findings of a raloxifene cohort in the RUTH study.

Further, the figures for DVT were in the same range.

As to the secondary outcomes, IRs of the secondary outcomes were relatively low, with only one outcome (increased triglycerides) occurring in more than 5% (5.8%) of the ospemifene patients with an incidence rate of 209.46/1,000 PY (95% CI: 188.00– 232.70). This outcome was also the most frequent (8.5% and 17.3%, respectively) in both of the comparator cohorts, with 192.35/1,000 PY (95% CI: 178.11–207.42) for the other SERM users and 216.33/1,000 PY (95% CI: 213.69–218.99) for patients who were not treated.

Important to note, regarding CVE, the IR for this risk in the ospemifene patients was 17.74/1,000 PY (95% CI: 13.03–23.58), which was lower than the IR in both the comparative SERM group with 29.69/1,000 PY (95% CI: 25.54–34.34) and women with untreated VVA 33.91/1,000 PY (95% CI: 33.14-34.70). As per an additional analysis, the unadjusted Cox models of the time to a first CVE in the ospemifene cohort compared to the comparator SERM cohort showed a HR of 0.85 (95% CI: 0.59–1.21) and compared the untreated VVA cohort a HR of 0.65 (95% CI: 0.48–0.88).

The differences between the three cohorts appear to be in the same direction as seen for the risk of VTE.

Further, a higher IR of uterine diagnostic tests and procedures with ospemifene relative to other SERM was observed, 2.7% of the cohort, at an incidence of 91.321,000 PY (95% CI: 79.75–104.10) vs 2.0% at an IR of 40.72/1,000 PY (95% CI: 35.68– 46.28) /, respectively. The rate of this outcome was highest in the untreated VVA cohort with 9.0% and an IR of 106.33/1,000 PY (95% CI: 104.85–107.82) suggesting that uterine procedures may be more likely to be performed in women with VVA, which is expected in view of the indication.

Incidence of Outcomes During All Available Follow-up Time (ITT Analysis)

The secondary ITT analysis produced similar results to the primary analysis. During all available follow-up time for each patient, 34 (0.4%) patients in the ospemifene cohort experienced VTE over 7,361 PY. The incidence of VTE was 4.62 (95% CI: 3.20–6.45) events per 1,000 PY. Corresponding IRs for the comparator SERM and untreated VVA cohorts were 11.70 (95% CI: 9.84–13.80) and 10.93 (95% CI: 10.50–11.37), respectively.

As would be expected given the longer follow-up duration in the two treated cohorts, the median time to event was longer than in the primary analysis, at 182 and 195 days for ospemifene and comparator SERM, respectively. Results for the untreated cohort were highly similar to the primary analyses, because

<0.5% of patients in the untreated cohort started treatment with a study drug and were censored in the primary analyses.

These data confirm the earlier findings on the IR of VTE.

Incidence of Outcomes by Exposure Category During Follow-up

The results of the secondary analysis examining event rates during periods of current, recent and past exposure, regardless of cohort assignment, are shortly presented here. The following discussion focuses on the primary outcome only.

Ospemifene Use

Amongst current users of ospemifene, VTE occurred in 14 (0.1%) of 9,373 patients, at an IR of 4.30 (95% CI: 2.35–7.21) per 1,000 PY. The incidence of VTE in recent users of ospemifene was 7.14 (95% CI: 2.32-16.65) per 1,000 PY, and in past users of ospemifene was 4.73 (95% CI: 2.75–7.57) per 1,000 PY.

Comparator SERM Use

Of the patients with current use of a comparator SERM, 87 (0.7%) of 13,119 women experienced VTE, at a rate of 11.41 (95% CI: 9.14–14.08) per 1,000 PY. Corresponding rates of VTE were 22.49 (95% CI: 13.10–36.01) per 1,000 PY with recent comparator SERM use and 10.35 (95% CI: 7.39–14.09) per 1,000 PY with past use.

Also here, in categories of current, recent, and past exposure to ospemifene and comparator SERM, the IR remained in the same range as previously observed.

Frequency and Incidence of VTE by Age Category and Follow-up Window

Among the patients aged 54 to 72 years, the patterns of VTE incidence were similar to the primary analysis, with the ospemifene cohort having a lower incidence than the two comparator cohorts, regardless of follow-up duration. In the ospemifene cohort, only 96 patients were in the age 73 years or older category, none of whom experienced a VTE event during the first continuous treatment episode. In the ITT analysis, only one patient in the ospemifene cohort experienced a VTE event in the older age stratum. In both of the comparator groups, where the older stratum included proportionately larger sample sizes, the incidence of VTE in the older stratum was higher than in the younger stratum of the same cohort.

Fewer than half of the VTE events in each cohort occurred during the first 90 days of the first continuous treatment episode. Incidence of VTE in the younger stratum was lower in this secondary analysis than in the primary analysis for the ospemifene cohort, at 2.63 (95% CI: 0.72–6.73) per 1,000 PY, but largely the same as in the primary analysis for the two comparator cohorts. The rates of VTE varied slightly with extension of the maximum duration to 120 or 180 days, although the general patterns remained the same.

As a conclusion, patterns were similar as previously found and no new relevant signals have been observed.

Main Results: Comparative Analyses of Time to First VTE

In the primary analysis, the unadjusted Cox models of time to first VTE in the women aged 54 to 72 year, shown in Table 6 and Table 7, indicated a lower risk during the first continuous treatment episode with ospemifene compared to other SERM (HR: 0.34, 95% CI: 0.17–0.69) and to untreated VVA (HR: 0.40, 95% CI: 0.21–0.77).

Table 6: Cox Proportional Hazards Model Examining Time to First VTE During First Continuous Treatment Episode, Age 54 to 72 (Ospemifene vs. other SERM)

Characteristic	Univariate Analysis		Final Adjusted Multivariate Analysis	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Treatment				
Ospemifene	0.34 (0.17-0.69)	0.0028	0.40 (0.19-0.82)	0.012
Other SERM	Reference	-	Reference	-
Age				
Age, years	1.08 (1.03-1.14)	0.0027	-	-
Age squared	1.00 (1.00-1.00)	0.0021	1.00 (1.00-1.00)	0.02
Geographic region				
North East	1.18 (0.62-2.27)	0.61	-	-
North Central	1.25 (0.68-2.30)	0.48	-	-
South	Reference		-	-
West	1.03 (0.45-2.38)	0.95	-	-
Unknown	0.00 (0.00-missing value)	0.98	-	-
Number of physician visits				
Counts	1.03 (1.01-1.04)	<0.0001	-	-
Baseline visits (reference is no visits)				
Emergency room visits	2.93 (1.60-5.40)	0.0005	-	-
Inpatient hospitalisations	2.93 (1.06-8.05)	0.038	-	-
Time-varying covariates at follow-up (reference is absence of the time-varying covariates)				
Medical conditions				
Atrial fibrillation	2.54 (0.62-10.39)	0.2	-	-
Transient ischaemic attack	8.69 (2.72-27.75)	0.0003	-	-
Hypertension	1.97 (1.20-3.23)	0.0069	-	-
Diabetes mellitus	2.90 (1.67-5.06)	0.0002	-	-
Atherosclerosis	3.00 (1.36-6.60)	0.0064	-	-
Trauma (in past 90 days)	3.20 (1.77-5.78)	0.0001	-	-
Surgery (in past 90 days)	5.86 (1.43-24.01)	0.014	-	-
Immobility	3.32 (1.33-8.28)	0.01	-	-
Congestive heart failure	0.00 (0.00-missing value)	0.98	-	-
Obesity	1.39 (0.63-3.06)	0.42	-	-
COPD	1.62 (0.59-4.45)	0.35	-	-
Rheumatic disease	1.17 (0.37-3.73)	0.79	-	-
Chronic kidney disease	3.41 (1.37-8.50)	0.0086	-	-
Inflammatory bowel disease	0.00 (0.00-missing value)	0.99	-	-
Inherited or acquired thrombophilia	18.26 (2.51-132.98)	0.0041	-	-

Characteristic	Univariate Analysis		Final Adjusted Multivariate Analysis	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Medications				
Antihypertensives	1.92 (1.18-3.15)	0.0092	-	-
Antidiabetic agents	2.47 (1.32-4.63)	0.0047	-	-
Anticoagulants or anti, thrombolytic therapy	3.49 (1.40-8.70)	0.0073	-	-
Antiarrhythmic therapy	0.00 (0.00-missing value)	0.98	-	-
Antihyperlipidemic therapy	1.66 (1.02-2.71)	0.042	-	-
Progesterone therapy	1.67 (0.23-12.08)	0.61	-	-

Table 7: Cox Proportional Hazards Model Examining Time to First VTE During First Continuous Treatment Episode, Age 54 to 72 (Ospemifene vs. untreated VVA)

Characteristic	Univariate Analysis		Final Adjusted Multivariate Analysis	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Treatment				
Ospemifene	0.40 (0.21-0.77)	0.0065	0.47 (0.24-0.91)	0.025
Untreated	Reference	-	Reference	-
Age				
Age, years	1.06 (1.05-1.07)	<0.0001	-	-
Age squared	1.00 (1.00-1.00)	<0.0001	1.00 (1.00-1.00)	<0.0001
Geographic region				
North East	1.18 (1.05-1.32)	0.0056	-	-
North Central	1.22 (1.08-1.39)	0.0018	-	-
South	Reference	-	-	-
West	0.89 (0.76-1.04)	0.14	-	-
Unknown	0.82 (0.47-1.42)	0.47	-	-
Number of physician visits				
Counts	1.03 (1.03-1.04)	<0.0001	-	-
Baseline visits (reference is no visits)				
Emergency room visits	2.06 (1.83-2.32)	<0.0001	-	-
Inpatient hospitalisations	3.41 (2.88-4.05)	<0.0001	-	-
Time-varying covariates at follow-up (reference is absence of the time-varying covariates)				
Medical conditions				
Atrial fibrillation	3.92 (3.29-4.68)	<0.0001	-	-
Transient ischaemic attack	3.21 (2.47-4.18)	<0.0001	-	-
Hypertension	2.27 (2.05-2.50)	<0.0001	2.09 (1.89, 2.31)	<0.0001
Diabetes mellitus	1.99 (1.80-2.20)	<0.0001	-	-
Atherosclerosis	3.28 (2.91-3.69)	<0.0001	-	-
Trauma (in past 90 days)	2.67 (2.38-3.00)	<0.0001	-	-
Surgery (in past 90 days)	21.65 (19.04-24.62)	<0.0001	-	-
Immobility	3.05 (2.60-3.59)	<0.0001	-	-
Congestive heart failure	5.92 (5.00-7.02)	<0.0001	-	-
Obesity	2.35 (2.12-2.61)	<0.0001	-	-
COPD	3.15 (2.75-3.62)	<0.0001	-	-
Rheumatic disease	2.33 (1.99-2.73)	<0.0001	-	-
Chronic kidney disease	3.51 (3.01-4.10)	<0.0001	-	-
Inflammatory bowel disease	2.02 (1.50-2.73)	<0.0001	-	-
Inherited or acquired thrombophilia	13.76 (10.57-17.92)	<0.0001	-	-

Characteristic	Univariate Analysis		Final Adjusted Multivariate Analysis	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Medications				
Antihypertensives	1.79 (1.63-1.97)	<0.0001	-	-
Antidiabetic agents	1.67 (1.49-1.87)	<0.0001	-	-
Anticoagulants or anti, thrombolytic therapy	5.75 (5.09-6.49)	<0.0001	-	-
Antiarrhythmic therapy	2.99 (2.07-4.31)	<0.0001	-	-
Antihyperlipidemic therapy	1.33 (1.21-1.46)	<0.0001	-	-
Progesterone therapy	1.29 (0.91-1.83)	0.15	-	-

When comparing ospemifene with other SERM, of all of the baseline characteristics and time-varying variables, only age-squared modified the HR for treatment group by more than 5%, and thus was included in the adjusted model as a covariate. The adjusted models confirmed the lower risk of VTE for ospemifene compared with other SERM (HR: 0.40, 95% CI: 0.19–0.82). For the comparison with the untreated VVA cohort, age-squared and hypertension modified the HR for treatment group by more than 5% and were included as covariates. The HR estimate for the comparison with the untreated cohort was 0.47 (95% CI: 0.24–0.91).

The ITT analysis results were similar to the primary analysis for the comparison with other SERM, although age did not act as a confounder in that analysis; the HR for ospemifene was 0.45 (95% CI: 0.30–0.66). In the comparison with the untreated cohort, age-squared and hypertension acted as confounders; the analysis revealed an attenuated effect size for ospemifene exposure, with an adjusted HR of 0.60 (95% CI: 0.43–0.85). Censoring the first continuous treatment episode at day 90 produced a somewhat stronger effect for ospemifene versus comparator SERM than the primary analysis (adjusted HR: 0.29, 95% CI: 0.10–0.88). The comparison with the untreated cohort censoring at day 90 estimated an adjusted HR for ospemifene of 0.37 (95% CI: 0.14–1.00).

Comparative analyses by using Cox models have been performed to calculate the hazard ratio of VTE in ospemifene users versus users of other SERMs and patients who were not treated. The unadjusted Cox models of the time to a first VTE demonstrated a lower risk during the first continuous treatment episode with ospemifene compared to the patients who use of another SERM (HR: 0.34, 95% CI: 0.17–0.69) and to patients with untreated VVA (HR: 0.40, 95% CI: 0.21–0.77).

For the comparison of the ospemifene cohort with the other SERM cohort, age was shown to be the only of the baseline characteristics and time-varying variables that impacted the HR, and thus was included in the adjusted model as a covariate. Also, the adjusted models confirmed the lower risk of VTE for ospemifene compared with other SERMs (HR: 0.40, 95% CI: 0.19–0.82).

When comparing the ospemifene cohort with the untreated VVA cohort, age and hypertension impacted the HR by more than 5% and were included as covariates. The HR estimate for the comparison with the untreated cohort was slightly higher as compared to the unadjusted model with 0.47 (95% CI: 0.24–0.91).

The ITT analysis results were in general similar to the primary analysis for the comparison with other SERMs, but in this analysis 'age' was not a variable that impacted the results.

As expected, the Cox models confirmed the finding that the risk of VTE with ospemifene was not higher (HR <2) compared to a comparator SERM or untreated VVA.

Ancillary analyses

Sensitivity Analysis Using Propensity Score Matching

The propensity score models indicated numerous baseline predictors of treatment group. The logistic regression model of ospemifene treatment versus other SERM showed that age, geographic region, number of physician visits, COPD, antidiabetic agents, and progesterone therapy at baseline were associated with treatment group at $p<0.05$. Predictors of ospemifene versus untreated VVA included age, geographic region, number of physician visits, number of emergency room visits, atrial fibrillation, hypertension, diabetes, atherosclerosis, trauma, congestive heart failure, obesity, rheumatic disease, inflammatory bowel disease, inherited/acquired thrombophilia, antihypertensives, antihyperlipidemic agents, and progesterone therapy at baseline.

Of 8,977 ospemifene users in the overall cohort, 7,547 (84.1%) were successfully matched to a patient from the comparator SERM cohort. The standardised differences for all baseline characteristics were less than 0.10, indicating excellent balance between the matched groups. The age groups, which were a particular concern in the comparison with other SERM, were well balanced, with standardised differences less than 0.03 and identical mean age of 59.6 years and median age of 59 years.

All 8,977 patients from the ospemifene cohort were matched to patients from the untreated for VVA cohort. As with the matching with comparator SERM, the balance after matching with untreated VVA was excellent. Mean and median age were the same between the matched groups (59.0 and 58 years, respectively).

In the subset the ospemifene initiators who were matched to other SERM patients, the incidence of VTE was 3.12 (95% CI: 1.25–6.42) events per 1,000 PY (Table 8). The matched comparator SERM initiators had an incidence of VTE of 8.30 (95% CI: 5.60–11.85) per 1,000 PY. Comparable rates in the matched ospemifene and untreated VVA patients were 3.39 (95% CI: 1.55–6.43) events per 1,000 PY and 5.50 (95% CI: 4.01–7.35) per 1,000 PY, respectively (Table 9).

Table 8: Frequency and Incidence of Study Outcomes During First Continuous Treatment Episode of Ospemifene Initiators and Comparator SERM Initiators After Propensity Score Matching

	Ospemifene Cohort (N=7,547)				Comparator SERM Cohort (N=7,547)			
	n of Eligible Patients with Outcome	Total Duration of Person-years	Incidence Rate per 1,000 person-years (95% CI)	Median (95% CI) Days to Event	n of Eligible Patients with Outcome	Total Duration of Person-years	Incidence Rate per 1,000 person-years (95% CI)	Median (95% CI) Days to Event
Primary Outcome								
Any VTE	7 (0.09%)	2,245.29	3.12 (1.25 - 6.42)	115.0 (27.0 - 341.0)	30 (0.4%)	3,613.91	8.30 (5.60 - 11.85)	109.5 (76.0 - 238.0)
Deep vein thrombosis	6 (0.08%)	2,245.30	2.67 (0.98 - 5.82)	122.0 (65.0 - 341.0)	28 (0.4%)	3,614.66	7.75 (5.15 - 11.20)	109.5 (64.0 - 238.0)
Pulmonary embolism	2 (0.03%)	2,245.98	0.89 (0.11 - 3.22)	46.0 (27.0 - 65.0)	4 (0.05%)	3,622.91	1.10 (0.30 - 2.83)	198.5 (95.0 - 510.0)
Retinal vein thrombosis	0 (0.0%)	2,246.05	0.00 (0.00 - 1.33)	NA	0 (0.0%)	3,623.89	0.00 (0.00 - 0.83)	NA

Table 9: Frequency and Incidence of Study Outcomes During First Continuous Treatment Episode of Ospemifene Initiators and Untreated VVA Patients After Propensity Score Matching

	Ospemifene Cohort (N=8,977)				Untreated for VVA Cohort (N=8,977)			
	n of Eligible Patients with Outcome	Total Duration of Person-years	Incidence Rate per 1,000 person-years (95% CI)	Median (95% CI) Days to Event	n of Eligible Patients with Outcome	Total Duration of Person-years	Incidence Rate per 1,000 person-years (95% CI)	Median (95% CI) Days to Event
Primary Outcome								
Any VTE	9 (0.1%)	2,658.75	3.39 (1.55 - 6.43)	115.0 (28.0 - 207.0)	45 (0.5%)	8,187.08	5.50 (4.01 - 7.35)	190.0 (127.0 - 279.0)
Deep vein thrombosis	8 (0.09%)	2,658.76	3.01 (1.30 - 5.93)	122.0 (65.0 - 341.0)	35 (0.4%)	8,195.59	4.27 (2.97 - 5.94)	176.0 (121.0 - 294.0)
Pulmonary embolism	2 (0.02%)	2,659.95	0.75 (0.09 - 2.72)	46.0 (27.0 - 65.0)	14 (0.2%)	8,204.14	1.71 (0.93 - 2.86)	205.5 (41.0 - 334.0)
Retinal vein thrombosis	0 (0.0%)	2,660.02	0.00 (0.00 - 1.13)	NA	0 (0.0%)	8,215.10	0.00 (0.00 - 0.36)	NA

As the matching of ospemifene users with each comparator group was successful in reducing all standardised differences between baseline variables to less than 0.10, the final Cox models were

univariate models of treatment group (Table 10). These models confirmed the lack of increase in risk of VTE with ospemifene relative to other SERM (HR: 0.42, 95% CI: 0.18–0.96) and to untreated VVA (HR: 0.65, 95% CI: 0.31–1.38).

Table 10: Cox Proportional Hazards Model Examining Effect of Treatment on VTE During First Continuous Treatment Episode, Matched Ospemifene vs. Other SERM and Untreated VVA

Characteristic	Univariate Analysis	
	HR (95% CI)	P-Value
Treatment		
Ospemifene	0.42 (0.18-0.96)	0.041
Other SERM	Reference	-
Treatment		
Ospemifene	0.65 (0.31-1.38)	0.27
Untreated	Reference	-

For the sensitivity analyses, the subsets of the ospemifene cohort were matched to other SERM patients by age, geographic region, number of physician visits, COPD, antidiabetic agents, and progesterone therapy at baseline. The matching was found to be acceptable by the CHMP. Comparable rates in the matched ospemifene and untreated VVA patients were 3.39/1,000 PY (95% CI: 1.55–6.43) and 5.50/1,000 PY (95% CI: 4.01–7.35), respectively. Therefore, matching the baseline data of the three different cohorts did not relevantly impact the outcomes of the study.

The corresponding Cox models confirmed, although with a slightly smaller difference than in the primary model, that the risk of VTE with ospemifene was not higher compared to other SERMs (HR: 0.42, 95% CI: 0.18–0.96) or to untreated VVA (HR: 0.65, 95% CI: 0.31–1.38), as mentioned in the hypotheses (HR<2) of the PASS protocol.

Sensitivity Analysis Using Backward Elimination

As expected, the use of backward elimination to select variables for the Cox models of VTE resulted in models containing more covariates than the primary analysis, while having little impact on the HR for treatment group. In the comparison of ospemifene with other SERM during the first continuous treatment episode, additional predictors of the outcome included baseline emergency room visits (HR: 2.20, 95% CI: 1.17–4.11), transient ischaemic attack (HR: 5.74, 95% CI: 1.78–18.54), diabetes (HR: 2.51, 95% CI: 1.43–4.40), trauma in the past 90 days (HR: 2.63, 95% CI: 1.44–4.82), and inherited or acquired thrombophilia (HR: 8.50, 95% CI: 1.15–62.55), while the adjusted HR for ospemifene versus other SERM was 0.36 (95% CI: 0.18–0.72). The model comparing ospemifene with untreated VVA found that nearly all of the medical conditions and medications assessed were significant predictors of VTE. The strongest predictors were surgery in the past 90 days (HR: 10.17, 95% CI: 8.85–11.70) and inherited or acquired thrombophilia (HR: 6.22, 95% CI: 4.73–8.17). A reduced risk of VTE was found for patients receiving antidiabetic agents (HR: 0.83, 95% CI: 0.70–0.98) and antihyperlipidemic therapy (HR: 0.81, 95% CI: 0.73–0.90). The adjusted HR for ospemifene versus untreated VVA in this model was 0.54 (95% CI: 0.28–1.04).

The models using backward elimination to examine risk of VTE during all follow-up time and censored at day 90 produced similar patterns of additional covariates, while maintaining similar HRs for treatment group to the parallel analyses using the primary model building approach.

Sensitivity Analysis from VVA Diagnosis Date

A VVA diagnosis was recorded at baseline for 4,483 (49.9%) patients from the ospemifene cohort. After setting the index date for ospemifene users to the date of first diagnosis of VVA, if present, or 10 days prior to ospemifene start if missing, and applying the inclusion/exclusion criteria to the new index date, 7,538 (88.4%) of the ospemifene users from the primary cohort were eligible for this sensitivity analysis. The incidence of VTE during episodes of ospemifene use was 4.62 (95% CI: 2.39–8.06) events per 1,000 PY, while the rate of VTE during untreated time was 9.01 (8.60–9.43) events per 1,000 PY. The adjusted Cox model, in which only age-squared served as a confounder, estimated an HR for ospemifene exposure of 0.60 (95% CI: 0.34–1.07).

Replacing the imputed VVA diagnosis date of 10 days prior to ospemifene start with an earlier date (30 days prior to ospemifene start) produced similar results as seen in earlier findings, with an adjusted HR for ospemifene exposure of 0.66 (95% CI: 0.37–1.16).

PASS – part 2 - Off-label use data from EU databases

Introduction – part 2 - Off-label use data from EU databases

The PASS – part 2 has been undertaken in Spain and Italy (EU countries where ospemifene was made commercially available), while PASS – part 1 is undertaken in the US (where ospemifene was launched in 2013 in the US). The US study data have been discussed above. The PASS part 2 off-label use study data from EU databases are assessed below.

Methods – part 2 - Off-label use data from EU databases

Study Design

This was an observational, retrospective database cohort study using secondary databases from Spain and Italy.

Setting

This was a secondary data analysis using the SIDIAP (Information System for the Development of Research in Primary Care) from Spain and the Health Search Database (HSD) from Italy. Within each of the two EU databases, all patients with a prescription for ospemifene were included. No exclusion criteria were applied, as the intent was to examine off-label use in all ospemifene users found in the databases. All diagnoses, treatments, and other indicators of potential off-label use, including hepatic impairment, local/systematic estrogen use or male gender, were examined and the frequency of each summarized.

Study participants

Ospemifene users were identified in SIDIAP from 1 January 2016 to 31 December 2019 and in HSD from 1 October 2015 to 31 December 2019. All patients with a prescription for ospemifene were included. No exclusion criteria were applied, as the intent was to examine off-label use in all ospemifene users found in the databases.

Treatments/exposures

For HSD, exposure to ospemifene was assumed to last from the date of issue of the first prescription to the date of issue of the last prescription, inclusive. For the purpose of this analysis, gaps in ospemifene treatment are considered exposed time. The supply time of the last prescription for each patient is not included in the analysis of off-label use, because a patient who develops a condition that is contraindicated with ospemifene use during the supply time of her final prescription may discontinue ospemifene in response. For patients who receive only one ospemifene prescription, the duration of exposure was therefore considered to be only one day.

For SIDIAP, where the dates of repeat prescriptions were not available, ospemifene exposure was assumed to last from the date of first prescription to the end of exposure noted in the database, truncating at the end date of the study period for patients with no end of exposure indicated.

Objectives

The overall objective of the study was to assess the incidence and risk of various side effects associated with ospemifene use in a real-world population.

The primary objectives apply to part 1 of the PASS, as discussed above.

The secondary objectives that were assessed in this study were:

- Assess off-label use among ospemifene patients resident in the EU (off-label use was not assessed in the US-resident patients):
    - Not diagnosed with VVA
    - Patients with pre-existing gynaecological pathology other than signs of vaginal atrophy, including vaginal bleeding or signs or symptoms of endometrial hyperplasia and endometrial cancer
    - With contradictions for ospemifene such as known or suspected oestrogen-dependent neoplasia, active VTEs, including deep vein thrombosis (DVT), pulmonary embolism and retinal vein thrombosis, arterial thromboembolic disease (such as stroke), or a history of these conditions
    - With breast cancer
    - With sex hormone-dependent malignancy
    - With severe hepatic impairment
    - In pre- and peri-menopausal women
    - In males
- In addition, diagnoses that may lead a woman not to be a candidate for local oestrogen therapy were assessed to evaluate the frequency of these diagnoses and explore the compliance with the restricted EU indication for use of ospemifene. These variables include:
    - History of melanoma
    - History of breast cancer
    - History of endometrial cancer
    - Porphyria

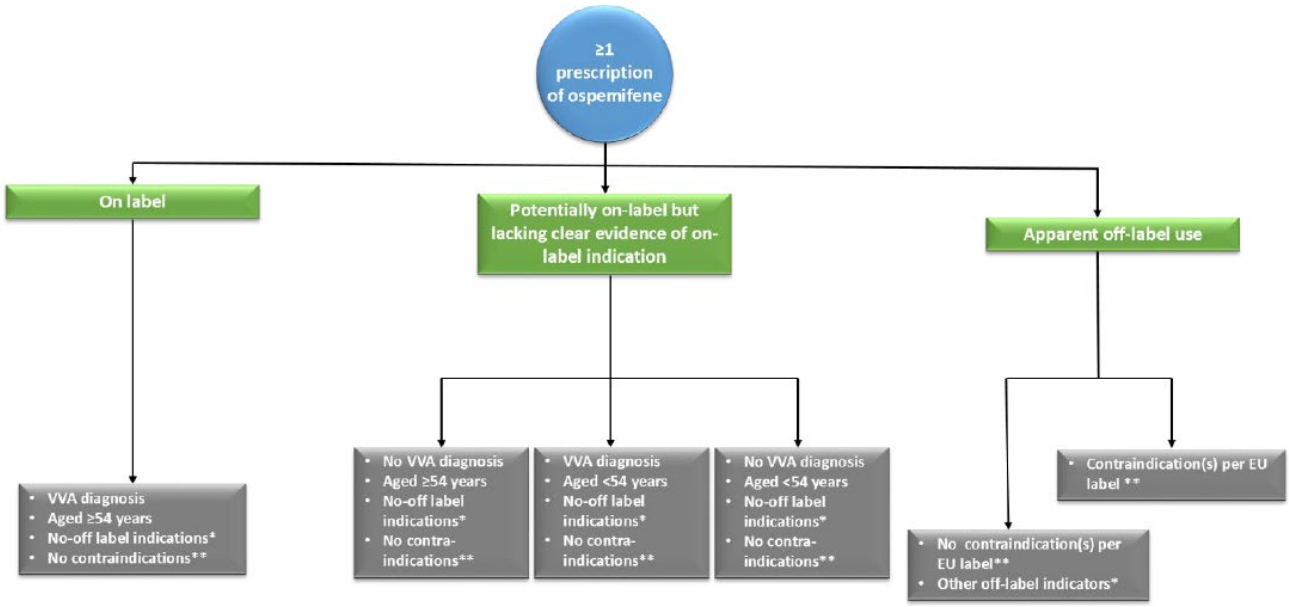
- History of endometriosis
- Dexterity problems, which might be associated with:
    - Parkinson's disease
    - History of stroke

Outcomes/endpoints

The number (and proportion) of patients in the ospemifene cohort were defined for the following groups, as summarized in Figure 5:

- Apparent off-label use
    - Contraindications including VTE, vaginal bleeding, breast cancer diagnosis, sex hormone-dependent malignancy, endometrial hyperplasia, pregnancy, or a treatment associated with one of these contraindications
        - These contraindicated conditions are approximations of the labelled contraindications, in that not all information is available in healthcare databases. The specific labelled contraindications include unexplained vaginal bleeding and suspected or active sex hormone-dependent malignancy.
    - Other off-label indicators, including hepatic impairment, local/systematic oestrogen use or male gender
- Potentially on-label but lacking clear evidence of on-label indication, including patients younger than 54 years or patients without a diagnosis of VVA
    - Not all patients will have a diagnosis of VVA as this condition is often under-reported in healthcare databases. Thus, patients without a VVA diagnosis who were on ospemifene were not strictly considered as off-label usage.
    - Menopausal status is not recorded in either the SIDIAP or HSD databases, and so age 54 or higher was used as a proxy for postmenopausal status. Given that women younger than 54 may be postmenopausal, this age restriction was also not a clear indicator of off-label use.
- On-label use

Figure 5: On-label and Off-label Groups for Ospemifene



Patients were hierarchically assigned to the above groups based on the most severe apparent divergence from the EU label indication for ospemifene. The first group included patients with any of the contraindications to ospemifene (i.e., VTE, vaginal bleeding, breast cancer diagnosis or treatment, sex hormone-dependent malignancy, endometrial hyperplasia, pregnancy, or a related treatment). Among those with none of these contraindications, those with any of the off-label indicators (hepatic impairment, local/systemic oestrogen use, or male gender) formed the second group.

The patients with no contraindications or other off-label indicators, but who either appeared premenopausal (age <54 years) on the index date, or who lacked a VVA diagnosis, were selected into an overarching group of patients who were considered potentially on label but lacking clear evidence of on indication use. This group was further divided into three subgroups: (a) patients aged less than 54 years with no evidence of a VVA diagnosis, (b) patients aged less than 54 years with a recorded diagnosis of VVA, and (c) patients aged at least 54 years with no evidence of a VVA diagnosis.

The remaining patients were considered on-label users of ospemifene. These women had no identifiable contraindications for ospemifene use, no indicators of off-label use, were aged 54 years or greater, and had a recorded VVA diagnosis.

In addition, diagnoses that may lead a woman not to be a candidate for local oestrogen therapy were assessed to evaluate the frequency of these diagnoses and explore the compliance with the restricted EU indication for use of ospemifene. Note that only some of the potential reasons for not using local oestrogen therapy are available in these databases. These variables include:

- History of melanoma
- Porphyria
- History of breast cancer
- History of endometrial cancer
- History of endometriosis
- Dexterity problems, which might be associated with:

- Parkinson's disease
- History of stroke

Data Sources and Measurement

SIDIAP, Spain

The SIDIAP (Information System for the Development of Research in Primary Care) is a general practice electronic medical record (EMR) database with data from almost 6 million patients. The data recorded include disease diagnosis (including date of diagnosis) via ICD-10 codes provided by general practitioners (GP) and in some areas by specialists, patient demographics (such as year of birth, gender, body mass index, date of death), drugs prescribed in primary care (identifiable via Anatomical Therapeutic Chemical [ATC] codes) and drugs dispensed at community pharmacies, dates of laboratory and diagnostic tests with their corresponding results, dates when procedures were requested, specialist referrals, and date of hospital admissions and discharge (along with reasons for admission and discharge). The SIDIAP can be linked to laboratory test records to obtain dates of referrals for laboratory tests outside the primary care practice. Physician notes (stored as free text entered by physicians) can be accessed to obtain test results when these are not coded directly.

In the Spanish healthcare system, the GP acts as gatekeeper to secondary care. The first prescription for this indication is expected to be issued by the specialist (i.e., gynaecologist) and repeat prescriptions to be issued by GPs. SIDIAP contains information on the date the drug was prescribed for the first time and the duration of exposure across all prescriptions; details on dates of repeat prescriptions are not available. Each year, patients may transfer in or out of SIDIAP's coverage area, resulting in patients entering and exiting the SIDIAP database even in years that were analysed previously. In this five-year PASS, each year's data cut assigns a different anonymised identification number to patients, therefore it is not possible to prospectively follow patients through different years. Small discrepancies in patient counts relative to prior years' reports are therefore possible.

Health Search Database, Italy

The Health Search Database (HSD) is a general practice EMR database with data from approximately 2.3% of the Italian population (2.5 million patients and around 1.0 million current active patients, from different Italian regions). The HSD captures data mainly from general practices (GP visits). The data recorded include disease diagnosis (including date of diagnosis) via ICD-9 codes, patient demographics (such as year of birth, gender, body mass index, date of death), drugs prescribed in primary care (identifiable via ATC codes), dates of laboratory and diagnostic tests requested by GPs, and specialist referrals. Data on date of hospital admissions and discharge, and hospital diagnosis are limited because they are only recorded when physicians consider that it is relevant for patient management.

The database does not capture prescription information or procedures from secondary care. After the initial prescription has been prescribed by the gynaecologist, repeat prescriptions are issued by GPs. Just like the SIDIAP database in Spain, patients may be added to or removed from the HSD database in prior years with each successive data extract.

Bias

Both of these EU databases are large and generally representative of their respective populations. While SIDIAP is highly representative of the Catalonian population in terms of geographical, age and sex distributions, it may not be representative of the general Spanish population. Drug exposure dates, especially for repeat prescriptions, may be erroneous, and prescriptions issued in secondary care are not

available. The presence and timing of many of the contraindications to ospemifene are difficult to ascertain in these databases, and most reasons for non-use of local oestrogen therapy are not available.

The analyses have taken a highly conservative approach, including any potential evidence of a contraindication, across the full-time interval from ospemifene start to latest possible end date. Hence, the frequency of contraindications reported here are likely to be overestimates of the true frequency.

Sample size

Sample size calculations were not performed for this secondary objective in Part 2.

Randomisation

N/A.

Blinding (masking)

N/A.

Statistical methods

All data analyses were conducted separately within the two databases. Within each of the patient groups and subgroups for this analysis, and for all ospemifene initiators combined, the frequency distribution (n, %) of each contraindication and other off-label indication was calculated. Age was summarized both as a continuous variable, with the mean, standard deviation, median, and interquartile range, as well as a categorical variable. The distribution of year of index date, and the sum of all PY of ospemifene exposure accumulated to date, were also assessed.

Quality Control

All analyses were assessed and discussed by the project manager and principal investigator, in collaboration with the research lead and analyst from each contributing database. All data queries were resolved prior to finalizing the results.

Results - SIDIAP, Spain

Participant flow

A total of 382 patients were found to be on ospemifene between 1 January 2016 and 31 December 2019 in the SIDIAP database. The number of ospemifene users thus remains limited and data are presented only descriptively.

Outcomes and estimation

Of the 382 patients, 11 patients (2.9%) appeared to have one or more contraindications to ospemifene per the EU label. Contraindications were VTE (n = 1), vaginal bleeding (n = 3), and breast cancer diagnosis (n = 1), with eight patients having treatment associated with a contraindication; some patients

had more than one contraindication, such as breast cancer diagnosis and associated treatment. A total of 81 patients (21.2%) had no contraindication but had another off-label indicator. Most of the patients with an off-label indicator had local/systematic oestrogen use (95.1% of the off-label indicator group), and five patients had hepatic impairment (6.2% of the off-label indicator group). Potentially on-label users included 63 patients (16.5%) who were under 54 years of age and had no VVA diagnosis recorded, 14 patients (3.7%) with a VVA diagnosis but who were under 54 years of age, and 168 patients (44.0%) who were over the age of 54 but had no VVA diagnosis. Among all ospemifene users, 45 patients (11.8%) were over the age of 54 and had a recorded VVA diagnosis without any off-label indicator or contraindication.

The figures are considered low. The quality of the data may be hampered as for more than 50% of women were prescribed on-label ospemifene the diagnosis of VVA was not recorded, potential off-label use seems to be low, as it appears unlikely that ospemifene has been prescribed for another indication than VVA.

Further, use of local or systemic oestrogen therapy was the most commonly observed (95%) off-label indicator from the SIDIAP, Spain data. However, it should be noted that the timing of use of local or systemic oestrogen therapy was not mentioned in the database and, for example, patients for whom the use of local oestrogen therapy was discontinued upon starting ospemifene, which would be an expected pattern of use, and entirely in accordance with the ospemifene label, were now identified as off-label.

Ancillary analyses

The mean age of patients using ospemifene was 59.3 years (SD: 8.4). The mean age of patients using the drug despite a contraindication was 56.3 years (SD: 11.8) which was younger than patients using ospemifene with an off-label indicator (61.1 years, SD: 9.6) and patients with on-label use (mean age 61.5 years, SD: 5.7). There were two patients with a prohibitive indication to oestrogen therapy: one (0.3%) patient had dexterity problems, and one patient (0.3%) had breast cancer.

Numbers were too small to draw any firm conclusions on the slight variation in age between the different groups.

Results - Italy

Participant flow

A total of 218 ospemifene users were found in the HSD database between 1 October 2015 and 31 December 2019. The 2020 interim report erroneously noted that there were 220 ospemifene users but following full quality control checks for the present analyses, the count was confirmed to be 218, which is considered to be limited by the CHMP. Again, data are presented only descriptively.

Outcomes and estimation

Of the 218 ospemifene users, only four (1.8%) had one or more contraindications to ospemifene per EU label; contraindications were vaginal bleeding (one patient), breast cancer (one patient), sex hormone-dependent malignancy (two patients), and/or treatment associated with a contraindication (two patients). Another 21 patients (9.6%) had another off-label indicator, all of whom had local/systematic oestrogen use. Among the patients with no contraindication per EU label and no other off-label indicators, 33 patients (15.1% of total ospemifene users) were under 54 years of age and had no VVA diagnosis, 19 patients (8.7% of total ospemifene users) had a VVA diagnosis but were under 54 years of age whereas

74 patients (33.9% of total ospemifene users) were over the age of 54 but had non VVA diagnosis. The remaining 67 patients (30.7%) appeared to be on-label users of ospemifene.

Use of local or systemic oestrogen therapy was the most commonly observed off-label indicator, but the timing of these therapies in relation to ospemifene remained uncertain. Although quality of the data may be hampered as for more than 50% of women were prescribed on-label ospemifene the diagnosis of VVA was not recorded, potential off-label use seems to be low, as it appears unlikely that ospemifene has been prescribed for another indication than VVA.

Ancillary analyses

The mean age of patients using ospemifene was 58.2 years (SD: 7.0). The mean age of patients using the drug despite a contraindication was 61.3 years (SD: 7.28), compared to a mean age of 58.6 years (SD: 6.16) in patients with other off-label indicators and 61.7 years (SD: 6.4) in patients with on-label use. There was one patient (0.5%) with melanoma and one patient with dexterity problems (0.5%) as a prohibitive indication to oestrogen therapy.

Similarly to the results reported from the Spanish data, numbers were too small to draw any firm conclusions on the slight variation in age between the different groups.

Post marketing experience

Introduction

~~The Applicant submitted, i~~In addition to the final study report of the PASS, an Addendum to Clinical Overview section was provided, ~~for Senshio (ospemifene)~~ covering the reporting period from first approval in the EU on 15 January 2015 through the DLP of 26 February 2021.

This addendum discusses the current benefit-risk balance of ospemifene based on safety and efficacy data accumulated since the initial marketing authorisation of Senshio in the EU and accounts for information previously submitted in PBRERs as well as safety data from all sources, including the completed PASS, and in consideration of the routine risk minimisation measures contained in the RMP version 2.

Summary of the safety data

Worldwide marketing authorisation status

Ospemifene was first approved on 26th February 2013 in the USA for the indication "treatment of moderate to severe dyspareunia, a symptom of VVA, due to menopause", at a dose of 60 mg daily. Ospemifene (60 mg daily) was authorised in the EEA via an EU Centralised Marketing Authorisation, granted by the EC, on 15th January 2015 under the trade name Senshio. In the USA, Osphena was divested to Duchesnay Inc on the 10th March 2017.

Cumulatively, ospemifene has been approved for marketing in a total of 32 countries. Ospemifene is marketed only in Italy, Spain. Outside the EU, ospemifene is only marketed in the UK and in USA, since 2013.

Significant changes to reference safety information

Regarding the safety signal on headache, this signal was analysed in the PSUR #5 (EMEA/H/C/PSUSA/00010340/201708). Headache was added to section 4.8 of the SmPC, with a frequency of 'common'. See for further details below under 'safety signal' evaluation.

Following the assessment of PSUR #7 (PSUSA/00010340/201902), vaginal haemorrhage was added to section 4.8 of the SmPC with the frequency of 'common'. See for further details below under 'safety signal' evaluation.

There were no other safety-related labelling changes that warranted changes to the authorised product information during the reporting period.

Exposure

Exposure in Clinical Trials (Pre-Approval)

Since the Development International Birth Date (DIBD), 697 healthy volunteers (including subjects with hepatic or renal impairment) and approximately 2,772 patients have been enrolled in the ospemifene Shionogi-sponsored clinical programme, of which 2,471 have been exposed to ospemifene.

Exposure in Clinical Trials (Post-Approval)

Based on completed clinical trials (unblinded data) since the IBD (26 Feb 2013), 338 patients have been exposed to ospemifene in Shionogi-sponsored clinical trials.

Exposure in Clinical Trials (Summary)

Overall, 2,809 patients have been exposed to ospemifene in pre-approval and post-approval clinical trials sponsored by Shionogi.

Exposure from Marketing

Based on a once-daily, 60-mg dosage regimen, USA pharmacy distribution data (total prescriptions sold), EU sell out data to pharmacies, as well as USA and EU data from samples (delivered to physicians), the post-marketing exposure of ospemifene was estimated. The cumulative patient exposure to ospemifene from the IBD to 26 Feb 2021 is estimated to be 262,320 patient-years.

Table 11: Summary Estimate of Ospemifene Exposure from 15 Jan 2015 to 26 Feb 2021 Based on Available USA and EU Data

Source	Estimated Patient-Years	
	Interval	Cumulative
Post-marketing USA	20,971	238,255
Post-marketing EU	4,262	24,065

Safety signal evaluation

Since EU approval, there have been three validated safety signals regarding hypersensitivity including rash, headache and uterine polyp.

- Hypersensitivity including rash was identified in May 2014 and a labelling change to the Ospemifene Company Core Data Sheet (CCDS) and EU regional label (SmPC) has been made on 15 Jan 2015. It is considered by the CHMP that this side-effect is currently sufficiently covered in the SmPC of Senshio.
- Headache was classified as a non-important risk after complete signal evaluation; headache was added as an adverse drug reaction (ADR) in the CCDS (effective 30 Oct 2017); the Pharmacovigilance Risk Assessment Committee (PRAC) also accepted the proposal for the addition of headache to the SmPC as part of their assessment of the PBRER (PSUSA-10340-

201708, reporting period 27 Feb 2017-26 Aug 2017) in Feb 2018 and final approval of the SmPC was published by the EC Decision on 28 May 2018. At the time, the MAH conducted a review and identified 167 individual case safety reports, of which there were reports of headache (n=147), migraine (n=15), sinus headache (n=2) and single reports for head discomfort, migraine with aura and exertional headache. There were 11 cases that included a positive de-challenge, with 5 of the cases also showing a positive rechallenge. A strong temporal relationship between ospemifene and headache was seen in many of the cases, which suggested a causal relationship between ospemifene and headache. Section 4.8 of the SmPC was updated, with a frequency of 'common'.

- For uterine polyp, considering the information included in section 4.8 of other SERM (e.g., tamoxifen; toremifene), and available data, the company considered that the identified risk of increase in uterine diagnostic procedures encompasses the risk that ospemifene could, in some instances, accelerate the growth of pre-existing polyps.

  This signal was analysed in the PSUR #8 (EMEA/H/C/PSUSA/00010340/202002) covering the period of 27 February 2019 to 26 February 2020. The MAH concluded that the current evidence supporting a causal association between the development of polyps and the use of ospemifene is too weak to confirm and closed the signal. The MAH's conclusions were endorsed by the PRAC. However, even though there is no clear evidence from post marketing data, since there is an imbalance in reporting rate from clinical trial data, the event continued to be closely monitored was re-evaluated in the following PSUR (EMEA/H/C/PSUSA/00010340/202102). Given the totality of the data and the fact that the risk of uterine polyp is not an important risk (it is addressed under the risk of increase in uterine diagnostic procedures), the conclusion was kept, and uterine polyp will continue to be closely monitored in upcoming PSURs.

RMP – safety specification

VTE

The following summary of VTE data was provided in the Addendum:

Table 12: Cases from clinical studies

Venous Thromboembolic Events	None	**Double-blind Phase 2/3 Placebo-controlled Studies** **Deep vein thrombosis (DVT):** 2 /1695 women (ospemifene) IP (%): 0.118 (95% CI: 0.014 - 0.426) IR (per 1000 PY): 2.92 (95% CI: 0.35, 10.55)	Routine PV activities and additional PV (PASS)
Risk	**Non-Clinical Data**	**Clinical Data**	**Actions**
		1/ 958 women (placebo) IP (%): 0.104 (95% CI: 0.003 - 0.580) IR (per 1000 PY): 3.66 (95% CI: 0.09, 20.41) **All Phase 2/3 Studies** **Deep vein thrombosis (DVT):** 2 /1891 women (ospemifene) IP (%): 0.106 (95% CI: 0.013 - 0.382) IR (per 1000 PY): 2.12 (95% CI: 0.26, 7.67) **Pulmonary Embolism (PE):** There were no cases of PE reported in the ospemifene treated subjects. The 2 subjects with serious adverse events (ADEs) of DVT reported in the ospemifene group discontinued from the study and recovered without sequelae. The most serious complication of DVT occurs when a clot becomes dislodged from a vein, travels to the lung (pulmonary embolism) causing partial to full blockage of the pulmonary artery which can be fatal.	

In the vascular disorders SOC, 90% of the reported ADRs were for hot flush (n=521). Nineteen serious cases of VDT and 16 cases of thrombosis were reported.

Table 13: Cumulative Summary Tabulation of Serious and Non-serious Adverse Reactions from Post-marketing Data Sources

System Organ Class	Preferred Term	Spontaneous Including Competent Authorities (worldwide) and Literature		Total Spontaneous
		Serious Cumulative	Non-Serious Cumulative	Cumulative All
Subtotal		10	37	47
Vascular disorders	Bloody discharge	0	1	1
	Deep vein thrombosis	19	0	19
	Flushing	0	5	5
	Haematoma	0	1	1
	Haemorrhage	0	3	3
	Hot flush	1	520	521
	Hypertension	4	3	7
	Pallor	1	0	1
	Peripheral coldness	0	1	1
	Peripheral embolism	1	0	1
	Post thrombotic syndrome	1	0	1
	Thrombophlebitis	1	0	1
	Thrombophlebitis superficial	0	2	2
	Thrombosis	16	0	16
	Varicose vein	0	1	1
Subtotal		44	537	581

The CHMP concluded that there were no new relevant safety concerns, including safety signals, have been revealed from these data.

Vaginal bleeding

As per the PRAC request made in the preliminary assessment report for PBRER#6, a cumulative review of the important potential risk of vaginal bleeding (uterine/endometrial) due to the cumulative number of cases reported was performed. The analysis did not raise the safety concern of that risk. No additional risks have been added.

The data reviewed during this period and cumulatively did not identify any new safety signals for ospemifene. The risk-benefit profile was assessed qualitatively based on analysis of the periodic and cumulative data; overall, the risk-benefit profile remains positive for ospemifene in this patient population and approved indications.

Following the assessment of PBRER#7 (PSUSA/00010340/201902) ~~5 September 2019~~ and based on the review of data from clinical trials and post-marketing reporting, the PRAC considered that a causal relationship between ospemifene and the adverse reaction vaginal bleeding could not be ruled out. A recommendation was made to update section 4.8 of the SmPC to add vaginal haemorrhage with the frequency of 'common'.

Proposed Re-categorisation of Risks in RMP (Version 2)

Following the results of the PASS, the ospemifene RMP has been updated in accordance with the RMP template rev 2 as per GVP V rev 2. The previously important risks of increase in uterine procedures, VTE, CVE, vaginal haemorrhages, and endometrial cancer, had been characterised and subsequently removed from the list of safety concerns due to low rates of these events in the PASS. Although a potential for these risks could still exist, they no longer require additional pharmacovigilance activity. These risks are now proposed as risks not considered important for inclusion in the list of safety concerns in the RMP but

are to be followed up in upcoming PSUR (see section 2.5.3) They are also seen with other SERMs (with increase in uterine procedures: risk not considered important for inclusion in the safety concerns in the RMP). The available data do not support that the remaining events (i.e. pelvic organ prolapse/urinary incontinence, cholecystitis and gall bladder events, atrial fibrillation, increased triglycerides, liver tumours, thymic epithelial tumours, renal carcinomas and adenomas, renal failure, and off-label use) should be maintained in the list of safety concerns of the RMP as important potential risks.

2.5.1. Discussion on clinical safety

Introduction

Ospemifene is a SERM. The SERM class of drugs has been associated with an increased risk of VTE, stroke, and potentially an increased risk of endometrial cancer. Ospemifene may therefore also have an increased risk of VTE, although so far this has not been reported.

Therefore, during the initial marketing authorization procedure, the CHMP considered that, the risk-benefit balance of Senshio was favourable provided that the medicinal product is only used 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" and with the obligation to complete an imposed non-interventional category 1 PASS, which assesses the incidence of VTE and other safety concerns.

In order to fulfil the obligation, the Applicant submitted, within this variation procedure, the final study report of the PASS.

For further support of this application, the Applicant submitted a clinical overview for Senshio (ospemifene) covering safety data of the reporting period from initial approval in the EU on 15 January 2015 through the DLP of 26 February 2021.

The results of the PASS, the post-marketing experience safety data, and the thereby proposed changes in the SmPC and RMP, have been assessed in this report.

Design and conduct of PASS

The PASS has been undertaken in the US, where ospemifene was launched in 2013. Further, off-label use was evaluated in databases from Spain and Italy, which were the EU countries where ospemifene was made commercially available. The PASS protocol has been assessed and approved by PRAC under procedure number EMEA/H/C/PSP/0023.2.

Part 1 - US MarketScan database

This first part of the PASS was a five-year retrospective cohort study using the existing healthcare MarketScan claims database from the US to assess safety and incidence of side-effects in a cohort of postmenopausal women with VVA prescribed at least one prescription for ospemifene (cohort 1) relative to patients diagnosed with but not treated for VVA (cohort 2) and patients on other SERMs for oestrogen deficiency conditions or breast cancer prevention (cohort 3). The research hypotheses for this study were HR <2.0 of VTE for cohort 1 vs cohort 2 or 3.

The inclusion and exclusion criteria are generally acceptable to identify patients for the three cohorts. The dosing and duration of treatment, the objectives, the primary and secondary endpoints and the proposed sample size, including the non-inferiority margin selected regarding the relative risk of VTE, are in line with the assessment of the protocol as agreed under procedure number EMEA/H/C/PSP/0023.2, and therefore acceptable.

As earlier mentioned, the PASS protocol has been assessed and approved by PRAC. Nevertheless, the study has its limitations. Firstly, this concerns a database with patients from the US only, as use of ospemifene was very limited in the EU. Although there is in general no reason to expect the relative risks to differ across geographic regions, meaningful differences in weight and weight-related baseline characteristics might exist and could impact VTE outcomes, as obesity is a known risk of VTE. These baseline characteristics from the US patients might be considered more unfavourable, as compared to the EU population, regarding the baseline risk of VTE and is similar to the discussions usually held around the assessment of the VTE risk associated with the use of oestrogen containing hormonal contraception in studies performed in the US vs EU. Further, the MAH also investigated the feasibility of including a local oestrogen cohort in this study, but patient numbers for post-menopausal women with prescriptions of local oestrogens were found to be low and its use is not well recorded in the healthcare databases. Such a cohort was therefore not included in the comparisons. Instead, the untreated VVA (cohort 2) and other SERM groups (cohort 3) have been selected for comparison. It should, however, be noted that these groups have its limitations. The reasons for the untreated VVA group not to have obtained a prescribed treatment, and similarly the reasons for half of the ospemifene group not to have a recorded VVA diagnosis, are unknown. Further, the other SERM group (cohort 3) of whom 92% received raloxifene, differs from the ospemifene cohort in having a different indication, i.e. prevention/treatment of breast cancer. These limitations are important to mention, but the impact on the results has been addressed by conducting different sub-analyses.

The primary analysis to assess risk of VTE, using incidence rates (IRs) and Kaplan-Meier plots, is considered standard and acceptable. As mentioned previously, it is acknowledged that the use of claims databases can introduce bias and has its limitations, for which a range of secondary and sensitivity analyses were executed using different (combinations of) exposure categories or periods, an ITT approach, different age subgroups, addition of potential confounders to a Cox regression model, propensity score matching and use of diagnosis instead of first prescription as starting date. Together these analyses will allow to assess the robustness of the primary results.

Part 2 – Spanish and Italian databases for off-label use

The second part of the PASS was an observational, retrospective database cohort study using the SIDIAP database from Spain and the HSD database from Italy (EU countries where ospemifene was made commercially available) to assess off-label use among ospemifene patients who reside in the EU. Within each of the two EU databases, all patients with a prescription for ospemifene were included.

Outcomes of the EU study part 2 were the number (and proportion) of patients in the ospemifene cohort on apparent off-label use, potentially on-label but lacking clear evidence of on-label indication, including patients younger than 54 years or patients without a diagnosis of VVA and on-label use.

Also, this second part of the PASS protocol has been assessed and approved by PRAC.

Results of PASS

Part 1 - US MarketScan database

Baseline data

During the reporting period, the number of patients treated with ospemifene was 8,977 covering 2,659 person-years (PY) in the first continuous treatment episode and those treated with comparator SERM 12,621 with 6,194 PY, while untreated VVA patients concerned 242,488 patients, covering 220,920 PY. The sample size of the ospemifene cohort in this study is in line with that mentioned in the protocol and is considered sufficient for analysis of the primary hypotheses.

The baseline characteristics were mostly sufficiently well distributed across the three cohorts. However, the patients in the ospemifene cohort were on average younger than patients in the other two cohorts. In the ospemifene cohort 60.5% of patients were 54-59 years old, whereas the corresponding percentage in the comparator SERM cohort was 34.9% and in the untreated VVA cohort 43.5%. Further, in the ospemifene cohort there were less patients having atrial fibrillation, hypertension, diabetes mellitus, atherosclerosis, congestive heart failure, COPD. Similarly, the use of antihypertensives, antidiabetic agents, anticoagulants and antihyperlipidemic therapy was less common in the ospemifene cohort, as compared to the other two cohorts. These imbalances in baseline characteristics mostly concern common risk factors for arterial disease, i.e. cardiovascular events (CVE) which can be expected in the target group of postmenopausal women but may have impacted the results of this study.

Additionally, it should be noted that in the comparator SERM cohort most (92.2%) patients were on raloxifene, which is favourable for consistency in further analysis. However, there are some differences in patient characteristics comparing the ospemifene and raloxifene group. Particularly, the patient's age in the raloxifene group (63.7 years) is somewhat higher as compared to the ospemifene group (59.0 years) and also as compared to the non-treated cohort. This might affect the incidence of VTEs, cardiovascular disease and other concomitant diseases.

In summary, the patients in the ospemifene cohort were somewhat younger on average (59.0 years) than the patients of the other two cohorts (63.7 years) and had a lower prevalence of some comorbidities that are known risk factors for CVE. These abovementioned differences in the baseline characteristics between the treatment cohorts should therefore be taken into account in further (sub-)analyses and interpretation thereof.

Exposure and dose

The data on exposure duration show that average duration of ospemifene use was generally twice shorter (129.6 days) than that of comparator SERM use (216.7 days) and far shorter than the untreated time in VVA cohort (335.9 days). Although the risk of VTE is considered to be highest in early use, the shorter duration of exposure could also have impact on the VTE incidence, as the shorter exposure time may overestimate the risk in the ospemifene group. As such, the primary analysis can therefore be considered conservative. Similarly, this may also have such an effect on secondary outcomes.

Primary outcome - Incidence rate (IR) of VTE

Overall, the incidence of VTE was low in the different treatment groups. The IR of VTE during the first continuous treatment episode was 3.39 (95% confidence interval [CI]: 1.55–6.43) events per 1,000 PY for the ospemifene cohort, 11.30/1,000 PY (95% CI: 8.81–14.28) for the comparator SERM cohort, and 10.92/1,000 PY (95% CI: 10.49–11.37) for the untreated VVA cohort.

As mentioned earlier, in the comparator SERM cohort most (92.2%) patients were on raloxifene. Of note, in a study of 10,101 postmenopausal women on raloxifene or placebo with documented coronary heart disease or at increased risk for coronary events (RUTH study mentioned in section 4.8 of the SmPC of Evista), VTE occurred at a frequency of approximately 2.0% or 3.88/1,000 PY in the raloxifene group (vs 1.4% or 2.70/1,000 PY in the placebo group). The absolute IR found in these patients from the RUTH study on raloxifene appears to be lower than the SERM cohort, but still similar to the IR found for the ospemifene cohort in the current PASS. These data can therefore be considered of support for the findings that the absolute IR of ospemifene is not higher as compared to the raloxifene cohort in the PASS and to earlier findings of a raloxifene cohort in the RUTH study.

Further, the figures for DVT were in the same range. For pulmonary embolism, and retinal vein thrombosis cases were too small to draw any firm conclusions.

As expected, no large differences have been observed with the ITT analysis compared to the primary analysis. Also among the subgroup of women aged 54 to 72 years and with different follow-up windows, patterns were similar as previously found and no new relevant signals have been observed. Further, no differences were noted in the categories of current, recent and past exposure to ospemifene and comparator SERM. The IRs remained in the same range as observed earlier and patterns were similar as previously found, and therefore confirm these data.

Primary outcome - Hazard ratio (HR) of VTE

Comparative analyses by using Cox models have been performed to calculate the HR of VTE in ospemifene users versus users of other SERMs and patients who were not treated. The unadjusted Cox models of the time to a first VTE demonstrated a lower risk during the first continuous treatment episode with ospemifene compared to the patients who use of another SERM (HR: 0.34, 95% CI: 0.17–0.69) and to patients with untreated VVA (HR: 0.40, 95% CI: 0.21–0.77).

For the comparison of the ospemifene cohort with the other SERM cohort, age was shown to be the only of the baseline characteristics and time-varying variables to impact the HR and was thus included in the adjusted model as a covariate. Also, the adjusted models confirmed the lower risk of VTE for ospemifene compared with other SERMs (HR: 0.40, 95% CI: 0.19–0.82).

When comparing the ospemifene cohort with the untreated VVA cohort, age and hypertension impacted the HR for VTE by more than 5% and were included as covariates. The VTE HR estimate for the comparison with the untreated cohort was slightly higher as compared to the unadjusted model with 0.47 (95% CI: 0.24–0.91).

The ITT analysis results were in general similar to the primary analysis for the comparison with other SERMs, but age was not a variable that impacted the data.

As expected, the Cox models confirmed the finding that the risk of VTE with ospemifene was not higher (HR <2) compared to patients on other SERMs or untreated patients with VVA.

Sensitivity analyses on VTE risk

Three sensitivity analyses were also conducted to further assess the robustness of the comparative analysis results for the outcome of VTE: propensity score matching, an alternate method for selecting covariates in the Cox models, and a comparison of ospemifene vs. untreated VVA using the VVA diagnosis date as the index date for ospemifene patients.

For the first sensitivity analyses, the patients of the ospemifene cohort were matched to other SERM patients by age, geographic region, number of physician visits, COPD, antidiabetic agents, and progesterone therapy at baseline (propensity score matching), which is acceptable. The incidence of VTE in the ospemifene group was 3.12/1,000 PY (95% CI: 1.25–6.42) vs 8.30/1,000 PY (95% CI: 5.60–11.85) in the matched comparative SERM patients. Comparable rates in the matched ospemifene and untreated VVA patients were 3.39/1,000 PY (95% CI: 1.55–6.43) and 5.50/1,000 PY (95% CI: 4.01–7.35), respectively. Therefore, matching the baseline data of the three different cohorts did not relevantly impact the outcomes of the study. The corresponding Cox models confirmed, although with a slightly smaller difference than in the primary model, that the risk of VTE with ospemifene was not higher compared to other SERMs (HR: 0.42, 95% CI: 0.18–0.96) and to untreated patients with VVA (HR: 0.65, 95% CI: 0.31–1.38), as mentioned in the hypotheses (HR<2) of the PASS protocol.

Further, the sensitivity analyses using backward elimination to select variables for the Cox models of VTE and VVA from diagnosis date maintained similar rates as seen in earlier findings.

Secondary outcomes – IRs on other safety concerns

IRs of the secondary outcomes (CVE, 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, vaginal bleeding) were also relatively low, with only one outcome (increased triglycerides) occurring in more than 5% (5.8%) of the ospemifene patients with 209.46/1,000 PY (95% CI: 188.00– 232.70). This outcome was also the most frequent (8.5% and 17.3%, respectively) in both of the comparator cohorts with 192.35/1,000 PY (95% CI: 178.11–207.42) for the other SERM users and 216.33/1,000 PY (95% CI: 213.69–218.99). Further, a higher IR of uterine diagnostic tests and procedures with ospemifene relative to other SERM was observed: 2.7% in the ospemifene cohort at an IT of 91.32/1,000 PY (95% CI: 79.75–104.10) vs 2.0% at an IR of 40.72/1,000 PY (95% CI: 35.68–46.28), respectively. The rate of this outcome was highest in the untreated VVA cohort with 9.0% and an IR of 106.33/1,000 PY (95% CI: 104.85–107.82) suggesting that such procedures may be more likely to be performed in women with VVA.

Important to note, regarding CVE, the IR for this risk in the ospemifene patients was 17.74/1,000 PY (95% CI: 13.03–23.58), which was lower than the IR in both the comparative SERM group with 29.69/1,000 PY (95% CI: 25.54–34.34) and women with untreated VVA 33.91/1,000 PY (95% CI: 33.14-34.70). The differences between the three cohorts appear to be in the same direction as seen for the risk of VTE.

Part 2 – Spanish and Italian databases for off-label use

Based on data received from the Spanish database, the number of ospemifene users remains limited with only 382 patients. In the 382 patients, 2.9% (n=11 patients) had a contraindication per the EU label indication and 21.2% (n=81 patients) had no contraindication but had another off-label indicator (hepatic impairment, local/systematic oestrogen use or male gender). These figures can be considered low, as the remaining patients are considered to have no contraindication or off-label indicator. However, the quality of the data is hampered (see below), as only 11.8% (n=45) were clearly identifiable in the database as on-label users with diagnosis of VVA. Use of local or systemic oestrogen therapy was the most commonly observed (95%) off-label indicator from the SIDIAP, Spain data.

Also based on data received from the Italian database, the number of ospemifene users remained limited with only 218 patients included until DLP. The proportion of patients with evidence of on-label ospemifene use was higher in Italy (i.e., 30.7%; n=67 patients), as compared to the data in Spain, and 57.8% (n=126 patients) of users had no contraindication or off-label indicator, but were not identifiable as on-label users. Only 1.8% of patients had a contraindication to ospemifene per the EU label, and 9.6% had no contraindication, but had another off-label indicator. Therefore, although the quality of the data is low (see below), potential off-label use points to a low percentage. Also here, use of local or systemic oestrogen therapy was the most commonly observed off-label indicator, but the timing of these therapies in relation to ospemifene remained uncertain.

Of note, although quality of the data may be hampered (as for more than 50% of women were prescribed ospemifene, the diagnosis of VVA was not recorded), potential off-label use seems to be low, because it appears unlikely that ospemifene has been prescribed for another indication than VVA. Further, it should be noted that the timing of use of local or systemic oestrogen therapy was not mentioned in the database and for example cases, for who the use of local oestrogen therapy was discontinued upon starting ospemifene would be an expected pattern of use, and entirely in accordance with the ospemifene SmPC, but are now identified as off-label.

Post-marketing experience safety data (6 years from first approval in EU to DLP)

The cumulative post-marketing exposure is approximately 262,320 patient-years, based on 80,724,426 tablets filled via prescriptions or directly shipped to patients in the USA and tablets distributed in the EU as well as 15,022,447 tablets delivered as samples in the USA and EU.

Based on the post-marketing experience safety data presented in the clinical overview for Senshio (ospemifene) covering the reporting period from first approval in the EU on 15 January 2015 through the DLP of 26 February 2021, there have been three validated safety signals. Two (hypersensitivity and headache) have led to ADR additions in section 4.8 of the SmPC. One is still under assessment. One concern (vaginal bleeding) was reviewed upon PRAC request and has also led to an update of section 4.8 of the SmPC. No new relevant safety concerns, including safety signals and regarding VTE, have been revealed from the available post-marketing data.

RMP version 2 is considered acceptable.

2.5.2. Conclusions on clinical safety

Based on the data from the US database, the IR of VTE during the first continuous treatment episode was 3.39/1,000 PY (95% CI: 1.55–6.43) for the ospemifene cohort vs 11.30/1,000 PY (95% CI: 8.81–14.28) for the comparator SERM cohort, and 10.92/1,000 PY (95% CI: 10.49–11.37) for the untreated VVA cohort.

Comparative analyses by using Cox models (adjusted for age) indicated no increase in risk of VTE for ospemifene versus other SERMs (HR: 0.40, 95% CI: 0.19–0.82), and versus untreated VVA (HR: 0.47, 95% CI: 0.24–0.91).

Also, a low incidence of other investigated safety concerns (CVE, 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, vaginal bleeding), as secondary outcomes, was observed, with no differences between groups except for uterine diagnostic tests, which is expected for patients with VVA.

Overall, although such studies have their limitations, the IRs of VTE and other adverse outcomes with ospemifene use were not higher compared to the IRs with other SERM use and to untreated VVA. This was confirmed by sensitivity analyses, comparative analyses and other study data (RUTH), and all in line with the hypotheses (HR<2) of the PASS.

Further, although data were limited and quality of data may be hampered, potential off-label use of ospemifene use as seen in the EU databases can be considered low.

Also, the post marketing experience safety data reviewed cumulatively did not identify any new safety signals for ospemifene.

Therefore, although such a PASS has its limitations, the provided data do not allow to conclude that there is an increased risk of VTE and other safety concerns in the patients who use ospemifene in comparison to other SERMs and untreated patients with VVA.

2.5.3. PSUR

PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC

and any subsequent updates published on the European medicines web-portal.

Safety concerns to be monitored and reviewed in the upcoming PSURs

Following assessment of the RMP version 2 which was updated according to RMP template rev 2 as per GVP V rev 2, the PRAC and CHMP agreed for the following safety concerns to be removed from the RMP but included in the summary of safety concerns of the PSUR and monitored with gathered new data and reviewed as part of the upcoming PSUR for ospemifene:

- Increase in uterine diagnostic procedures (Important identified risk),
- cerebrovascular events, vaginal bleeding, endometrial cancer (Important potential risks),
- Long term safety, Limited amount of data in the elderly (>65 years-old), Patients with malignancy on mammography or any other kind of malignancy within 10 years (excluding basal cell carcinomas), Severe hepatic impairment (Missing information).

2.6. Risk management plan

The MAH submitted an updated RMP version with this application. The RMP has also been updated according to current revised GVP V Rev 2 template.

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

The PRAC considered that the risk management plan version 2 is acceptable.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 2 with the following content:

Safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

Pharmacovigilance plan

Routine pharmacovigilance is considered sufficient to further characterise the safety concerns of the product.

Risk minimisation measures

Routine risk minimisation measures are considered sufficient to mitigate the safety concerns of the product.

2.7. Update of the Product information

As a consequence of this new indication, section 4.1 Therapeutic indications of the SmPC has been updated. Particularly, the indication is not restricted anymore to women who are not candidates for local vaginal oestrogen therapy. In addition, Annex IID has been updated, as to remove the obligation to conduct post-authorisation measures, following completion of the imposed PASS study. The Package Leaflet has been updated accordingly.

In addition, the list of local representatives in the PL has been revised to amend contact details for the representatives of Germany, United Kingdom (Northern Ireland) and France.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

No full user consultation with target patient groups on the package leaflet has been performed on the basis that the changes to the Package Leaflet in the current procedure have minor impact on the readability of the Package Leaflet. A new user test is therefore not considered necessary.

2.7.2. Additional monitoring

Pursuant to Article 23(3) of Regulation No (EU) 726/2004, Senshio (ospemifene) is removed from the additional monitoring list as the obligation to conduct an imposed PASS study to assess the incidence of venous thromboembolism and other safety concerns has been fulfilled.

Therefore, the statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information, preceded by an inverted equilateral black triangle, is removed from the summary of product characteristics and the package leaflet.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Oestrogen deficiency affects numerous tissues in postmenopausal women, including musculoskeletal, vascular and urogenital systems. The decline in estrogen in postmenopausal women results, among others, 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. Over time these symptoms, especially dyspareunia, can lead to female sexual dysfunction and subsequent emotional distress.

Senshio 60 mg film-coated tablets contain the active substance ospemifene. Ospemifene is a SERM. Like other SERMs, ospemifene acts as an agonist or antagonist on the estrogen receptor in different tissues. The currently claimed indication is for second-line therapy: "Treatment of moderate to severe symptomatic 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.

3.1.2. Available therapies and unmet medical need

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 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 oestrogen treatment.
- Hormonal treatments: Local, low-dose oestrogen 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 (oestradiol 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 oestrogen, treatment options have become limited. For the indication of VVA several oestrogen-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 oestrogen 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-oestrogen-based therapy for VVA could therefore be of benefit in these patients.

3.1.3. Main clinical studies

Ospemifene may have an increased risk of VTE, although so far this has not been reported, as is for other SERMs, similar to systemic HRT with oral oestrogens. Therefore, the CHMP recommended granting of the marketing authorisation, for the indication "treatment of moderate to severe symptomatic vulvar and vaginal atrophy (VVA) in post-menopausal women who are not candidates for local vaginal oestrogen therapy" and with the condition of an obligation to complete an imposed non-interventional category 1 PASS to assess the incidence of VTE and other safety concerns of ospemifene. In order to fulfil this obligation, the Applicant submitted, within this variation procedure, the final study report. The PASS protocol has been assessed and approved by PRAC under procedure number EMEA/H/C/PSP/0023.2.

The PASS has been undertaken in the US, where ospemifene was launched in 2013 (part 1). Further, off-label use was evaluated in databases from Spain and Italy, which were the EU countries where ospemifene was made commercially available (part 2).

Part 1 - US MarketScan database

This first part of the PASS was a five-year retrospective cohort study using the existing healthcare MarketScan claims database from the US to assess safety and incidence of side-effects in a cohort of postmenopausal women with VVA prescribed at least one prescription for ospemifene (cohort 1) relative to patients diagnosed with but not treated for VVA (cohort 2) and patients on SERMs for oestrogen deficiency conditions or breast cancer prevention (cohort 3). The research hypotheses for this study were HR <2.0 of the incidence of VTE (and other side-effects) for cohort 1 vs cohort 2 or cohort 3.

Part 2 – Spanish and Italian databases for off-label use

The second part of the PASS was an observational, retrospective database cohort study using the SIDIAP database from Spain and the HSD database from Italy (EU countries where ospemifene was made commercially available) to assess off-label use among ospemifene patients who reside in the EU. Within each of the two EU databases, all patients with a prescription for ospemifene were included.

3.2. Favourable effects

No relevant information on favourable effects has been submitted and assessed.

In the registrational clinical programme, a statistically significant superiority of ospemifene 60 mg/day compared to placebo was demonstrated for change in vaginal pH, percentage of superficial cells and parabasal cells for 60 mg/day in two pivotal studies. 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. The effect vaginal pH, percentage of parabasal cells and percentage of superficial cells was maintained after 52 weeks.

3.3. Uncertainties and limitations about favourable effects

No relevant information on uncertainties and limitations about favourable effects have been assessed during this procedure.

3.4. Unfavourable effects

Part 1 - US MarketScan database

The primary outcomes of IRs of VTE during the first continuous treatment episode was 3.39/1,000 PY (95% CI: 1.55–6.43) for the ospemifene cohort vs 11.30/1,000 PY (95% CI: 8.81–14.28) for the comparator SERM cohort, and 10.92/1,000 PY (95% CI: 10.49–11.37) for the untreated VVA cohort. Further, the figures for DVT were in the same range.

Comparative analyses by using Cox models (adjusted for age) indicated no increased VTE risk for ospemifene users versus patients on other SERMs (HR: 0.40, 95% CI: 0.19–0.82), and versus untreated patients with VVA (HR: 0.47, 95% CI: 0.24–0.91).

Sub-analyses, such as ITT analyses or adjusted Cox modelling, and sensitivity analyses using propensity score matching, backward elimination to select variables for the Cox models of VTE and VVA from diagnosis date were in line with previously reported IRs and HRs.

As secondary outcomes, a low incidence of other investigated safety concerns was observed between the groups with differences generally in the same range as seen for VTE (e.g. CVE, 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, vaginal bleeding).

Part 2 – Spanish and Italian databases for off-label use

Of the 382 Spanish patients on ospemifene in the SIDIAP database, 2.9% (n=11) of the patients had a contraindication, 21.2% (n=81) patients had no contraindication, but had another off-label indicator (hepatic impairment, local/systematic oestrogen use or male gender), and only 11.8% (n=45) were clearly identifiable in the database as having on-label use.

The proportion of the 218 Italian patients in the HSD database with evidence of a contraindication was 1.8% (n=4), 9.6% (n=21) had no contraindication but had another off-label indicator, and on-label ospemifene use was 30.7% (n=67 patients).

These figures can be considered low and potential off-label use points to a low percentage.

3.5. Uncertainties and limitations about unfavourable effects

Part 1 - US MarketScan database

The study design of the PASS has its limitations. Firstly, the data are derived from a database with patients from the US only. Although there is in general no reason to expect the relative risks to differ across geographic regions, meaningful differences in weight and weight-related baseline characteristics might exist and could impact VTE outcomes, as obesity is a risk factor for VTE. These baseline characteristics from the US patients might be considered more unfavourable, as compared to EU data, regarding the baseline risk of VTE, and similar discussions are usually held around the assessment of the risk of VTE upon oestrogen containing hormonal contraception in studies performed in the US vs EU. Further, the MAH also investigated the feasibility of including a local oestrogen cohort in this study, but patient numbers of post-menopausal women with prescriptions for local oestrogens were found to be low and its use is not well recorded in the healthcare database. Such a comparative cohort was therefore not included. Instead, the untreated VVA (cohort 2) and other SERM groups (cohort 3) have been selected for comparison. It should, however, be noted that these groups have its limitations as well. The reasons for the untreated VVA group not to have obtained a prescribed treatment, and similarly the reasons for half of the ospemifene group not to have a recorded VVA diagnosis, are unknown. Further, the other SERM group (cohort 3) differs from the ospemifene cohort in having a different indication and dosing scheme. These limitations are important to mention but have been adequately addressed by conducting different sub-analyses.

Regarding the baseline characteristics, the patients in the ospemifene cohort were on average somewhat younger (59.0 years) than patients in the other two cohorts (63.7 years and 62.3 years, respectively). Further, in the ospemifene cohort there were less patients having atrial fibrillation, hypertension, diabetes mellitus, atherosclerosis, congestive heart failure, COPD. Similarly, the use of antihypertensives, antidiabetic agents, anticoagulants and antihyperlipidemic therapy was less common in the ospemifene cohort, as compared to the other two cohorts. These imbalances in baseline characteristics mostly concern common risk factors for CVE, which can be expected in the target group of postmenopausal women but may have impacted the results of this study.

Additionally, it should be noted that in the comparator SERM cohort most (92.2%) patients were on raloxifene, and there are some differences in patient characteristics comparing the ospemifene and raloxifene group. Particularly, the patient's age in the raloxifene group is higher as compared to the ospemifene group and also as compared to the non-treated cohort. This may affect the incidence of VTEs, cardiovascular and other concomitant diseases.

Also regarding the exposure duration, it has been shown that the average duration of ospemifene use was generally twice shorter (129.6 days) than of that of comparator SERM use (216.7 days), most likely due to the difference in indication (VVA versus prevention/treatment of breast cancer) and far shorter than the untreated time in VVA cohort (335.9 days). Although the risk of VTE is considered to be highest in early use, the shorter duration of exposure could also have impact on the VTE incidence, as the shorter exposure time may overestimate the risk in the ospemifene group. As such the primary analysis can therefore be considered conservative. Similarly, this may also have such an effect on secondary outcomes.

Further, regarding CVE, the IR for this risk in the ospemifene patients was 17.74/1,000 PY (95% CI: 13.03–23.58), which was lower than the IR in both the comparative SERM group with 29.69/1,000 PY (95% CI: 25.54–34.34) and women with untreated VVA 33.91/1,000 PY (95% CI: 33.14-34.70). The differences in the IRs of CVE between the three cohorts appear to be in the same direction as seen for the risk of VTE.

Part 2 – Spanish and Italian databases for off-label use

From the EU databases, a large proportion of patients were not clearly identifiable in the database as on-label users (Spain 64.2% (n=245 patients); Italy 57.8% (n=126)) and who had no contraindication or off-label indicator.

Further, regarding the off-label use indicator identification, it should be noted that the timing of use of local or systemic oestrogen therapy was not mentioned in the database. Patients, for whom the use of local oestrogen therapy was discontinued upon starting ospemifene would be an expected pattern of use, and entirely in accordance with the ospemifene SmPC, but are now identified as off-label, which could have led to an overestimation of the off-label use proportion in the databases.

3.6. Effects Table

Not applicable for this procedure.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The data of the current PASS show that the IR of VTE was lower (i.e. IR: 3.39/1,000 PY) with the use of ospemifene in postmenopausal women suffering from VVA, as compared to 11.30/1,000 PY (95% CI: 8.81–14.28) for women treated with other SERMs (cohort 2), and 10.92/1,000 PY (95% CI: 10.49–11.37) for those diagnosed with VVA but untreated (cohort 3). The HR was demonstrated to be <2 (i.e. HR adjusted for age: 0.40 (95% CI: 0.19-0.82) and 0.47 (95% CI: 0.24-0.91), for cohort 2 and 3 respectively). These results were also observed with the risk for DVT.

However, although it is only possible to evaluate a relative risk of VTE versus other treatments in an epidemiological study, as the baseline incidence of VTE is very low, it is noted that an epidemiological PASS study has its limitations.

First, the study was performed in the US and not in the EU as the number of women using Senshio in the EU was far too low. However, in the US population the baseline risk of VTE is expected to be more unfavourable, as compared to the baseline risk of VTE in an EU population, since obesity, an established risk factor for VTE, is considered more common. Therefore, the VTE outcomes observed in the current study, based on the US population, are considered higher than to be expected for a study based on the EU population. The outcomes can be considered worst-case-scenario for the EU population. Furthermore, a cohort with a local oestrogen therapy was due to several reasons not included in this study (VTE risk is not established, intermittent use in varying doses, use not well captured in prescription databases). Instead, a three-armed study was set up with a comparison of the ospemifene cohort to patients with untreated VVA and patients using other SERMs. These were considered appropriate alternative comparators and were considered acceptable by the PRAC. A range of secondary and sensitivity analyses were executed to investigate possible impact of any difference in patient populations and exposure duration included in the databases. The results were in the same range as the primary analyses confirming the robustness of the primary results on VTE risk.

Further, a generally lower IR was observed of other investigated safety concerns, such as CVE, 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, vaginal bleeding.

Further, although the quality of data may be hampered, off-label use in ospemifene users as seen in the EU databases points at a low percentage.

The risks with ospemifene are described in the SmPC and are considered manageable by routine risk minimisation, including the risk for VTE. Also, the available post-marketing experience safety database as presented does not give rise to any concern regarding the positive B/R.

3.7.2. Balance of benefits and risks

Although such a PASS has its limitations, the provided data suggest that the risk of VTE with the use of ospemifene in postmenopausal women suffering from VVA is not increased compared to patients on other SERMs for oestrogen deficiency conditions or breast cancer prevention, or to patients diagnosed with but not treated for VVA. As a consequence, the proposed change to section 4.1 is accepted since the previous restriction of use was due to this safety concern. The clinical safety profile and low percentage of off-label use of ospemifene is considered reassuring. The known risks with ospemifene can be managed by routine pharmacovigilance measures. In conclusion, with the submitted data the B/R for Sensio remains positive and the PASS obligation can be considered fulfilled.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

3.8. Conclusions

The overall B/R of Senshio is positive for the amended indication and the PASS obligation can be considered fulfilled.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II and IIIB

Extension of indication by lifting the second line treatment restriction. This is supported by the submission of the final study report of the imposed non-interventional post-authorisation safety study. As mentioned in Annex IID, this is 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 (RMP), in vulvar and vaginal atrophy (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. As a consequence, section 4.1 of the SmPC is updated. The Package Leaflet and Annex IID are updated in accordance. Version 2 of the RMP has also been submitted. In addition, the Marketing authorisation holder took the opportunity to update the list of local representatives in the

Package Leaflet.

The variation leads to amendments to the Summary of Product Characteristics, Annex II D and Package Leaflet and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I, IID and IIIB and to the Risk Management Plan are recommended.