Clinical relevance of the effect of ospemifene (Senshio®) on the Most Bothersome Symptoms of VVA

Context
Ospemifene is a novel oral Selective Oestrogen Receptor Modulator (SERM). The 60 mg, film-coated tablet is licensed in the U.S. for the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause and is marketed under the trade name Osphena®. The same dose has recently been approved in Europe under the trade name Senshio® for the treatment of moderate to severe symptomatic vulvar and vaginal atrophy (VVA) in post-menopausal women who are not candidates for local vaginal oestrogen therapy. It is a new treatment in a therapy area that hasn't seen any significant developments for more than 50 years. The development program included two pivotal efficacy trials and was based on the FDA guidance for industry "Estrogen and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms - Recommendations for Clinical Evaluation", the only guidelines which exist for this indication. These guidelines stipulate three objective co-primary endpoints and one patient reported outcome (PRO). The objective endpoints are: the mean change from baseline to week 12 in the vaginal maturation index (VMI, percentage parabasal and superficial cells) and the vaginal pH. The patient reported outcome is the mean change in the moderate to severe symptom of VVA that has been identified by the patient as being the most bothersome to her. In both pivotal efficacy studies, the mean change in VMI and vaginal pH at both 4 and 12 weeks was statistically significantly better in the ospemifene group than the placebo group. The severity of the most bothersome symptom is expressed as none, mild, moderate or severe. These grades of severity were given a score (none=0, mild=1, moderate=2 and severe=3) and the mean change from baseline was expressed as a number. Ospemifene was statistically significantly better then placebo on the most bothersome symptom of dyspareunia in both trials (1.19 vs. 0.89 and 1.5 vs 1.2 resp.) and on dryness in one trial (1.26 vs. 8.84). However, this scoring system is not commonly used in clinical practice and it was considered helpful for practising clinicians to have a description of the primary efficacy results with Senshio® that were more clinically relevant.

Objective
To explore clinically relevant differences of the effect of ospemifene on the severity of the Most Bothersome Symptom (as identified by the patient) due to vulvar and vaginal atrophy (VVA) in postmenopausal women compared with placebo.

Methods
Following a literature review and discussions with other experts in the field, we defined three assessments which we considered clinically relevant: improvement (a reduction of 1 or more units on the four-point scoring system) and relief (severity score of mild/none after 12 weeks). We also included 'substantial improvement', defined as a reduction of two or three units on the four point scoring system. The latter was added because it more accurately reflects the effect of ospemifene on the population with moderate or severe symptoms (a change of 2 or 3 units is, by default, only possible in this population), and it reduces the potential for any changes due to the natural variability of the severity and/or the effect seen with placebo or lubricant. It also allows comparing the improvement seen with ospemifene compared to placebo and the magnitude of improvement as well.

Patients
The patients were postmenopausal women, aged 40-80 years, with the following criteria of VVA: (1) 5% or less superficial cells on the vaginal smear (maturation index), (2) vaginal pH >5.0, (3) at least one moderate or severe symptom of VVA, or moderate to severe vaginal dryness or vaginal pain associated with sexual activity, selected as most bothersome symptom. A total of 739 women were randomised to ospemifene and 724 to placebo in both studies combined. In both studies, the women in all treatment groups were supplied with a non-hormonal lubricant (K-Y® Jelly, McNeil-PPC, Inc., NJ) and were instructed to use as needed.

Main outcome measures
Percentage of women demonstrating improvement, substantial improvement or relief.

Results
The rate of discontinuation was low in both studies: 84.8% of women taking ospemifene 60 mg/day and 85.8% of women taking placebo completed the first study; 89.8% of women taking ospemifene 60 mg/day and 88.4% of women taking placebo completed the second study. After 4 weeks of treatment, the frequency of lubricant application decreased slightly in the ospemifene group with no change in the placebo group (both studies), while the frequency of sexual activity remained consistent in both treatment groups (only recorded in the second study).

In both studies the percentage of subjects demonstrating improvement, substantial improvement and relief were higher in the ospemifene treated groups than in the placebo groups for vaginal dryness and dyspareunia. The percentage of subjects showing improvement in vaginal dryness on ospemifene vs. placebo was 74.6% vs. 57.7% (p=0.0077) and 70.6% vs. 68.2% (n.s.) in the first respectively the second study. For substantial improvement these figures were 42.2% vs. 26.9% (p=0.0161) and 46.3% vs. 34.4% (p=0.0327) and for relief they were 66.1% vs. 49.0% (p=0.0101) and 61.9% vs. 53.2% (n.s.).

For dyspareunia, the percentage of subjects showing improvement on ospemifene vs. placebo was 68.3% vs. 54.1% (0.0231) and 79.9% vs.64.0% (p<0.0001) in the first respectively the second study. For substantial improvement these figures were 40.8% vs. 29.5% (n.s.) and 52.8% vs. 38.7% (p=0.0005) and for relief they were 57.5% vs. 41.8% (p=0.0146) and 63.0% vs. 42.5% (p=0.0001).

The difference between the treatment groups is most pronounced in the substantial improvement and relief categories - indicating that not only did more patients report benefit with ospemifene compared to placebo, but the magnitude of the benefit was greater for ospemifene than placebo and patients receiving ospemifene were more likely to experience relief of their most bothersome symptoms of VVA at Week 12.

The difference with placebo was already observed at 4 weeks and continued to increase up to 12 weeks as confirmed by an increase in the relative improvement over placebo from week 4 to 12 in all three measures of efficacy.

Conclusions
This analysis provides a clinically meaningful description of the efficacy of ospemifene on vaginal dryness and dyspareunia as a result of VVA, based on the (co-)primary endpoints of the pivotal efficacy studies. Ospemifene efficacy was observed from 4 weeks onwards and continued to increase over the 12 weeks of the study compared to baseline and placebo. Not only was ospemifene superior to placebo
for the effect on improvement, but the more pronounced effect on substantial improvement and relief indicates that the magnitude of improvement in symptoms (severe to mild, severe to none, moderate to none) is consistent with a significant effect on VVA.

This analysis provides informative and clinically relevant data that will enable gynaecologists and their patients to assess the effectiveness that patients can expect to achieve when they are prescribed ospemifene (Senshio® or Osphena®) for the improvement of their VVA symptoms.

References