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Earlier Treatment of Vulvovaginal Atrophy in Post-Menopausal Women May Improve Treatment Outcomes

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Abstract

Objective: To determine whether early ospemifene treatment, when vulvovaginal atrophy (VVA) symptoms are still moderate rather than severe, leads to greater treatment benefits.

Methods: This post-hoc analysis used the clinical trial data from the two ospemifene pivotal 12-week Phase III trials, which enrolled women with at least one moderate or severe symptom of vaginal dryness or dyspareunia. The participants were split into those with a moderate most bothersome symptom (MBS) and those with a severe MBS, as reported at baseline. The impact of ospemifene treatment on improvement and relief of their MBS was evaluated. The impact of treatment on all VVA symptoms, by baseline severity, was also recorded.

Results: In the first efficacy study, a greater proportion of women with MBS of dyspareunia and vulvar/vaginal itching/irritation at baseline improved if they had moderate rather than severe symptoms. In the second efficacy study, the opposite was observed. When all moderate/severe symptoms at baseline were included in the analysis, there was no difference in improvement based on severity. However, when all symptoms were analysed, more women experienced relief if treatment was started when symptoms were moderate (75%) rather than severe (58%).

Conclusion: Ospemifene improves all moderate or severe VVA symptoms, regardless of baseline severity, but earlier treatment of VVA symptoms, when symptoms are moderate rather than severe, may be associated with greater treatment benefits, as indicated by the higher 'cure' rate in women with moderate VVA symptoms at baseline.

Keywords: Post-menopausal, Genitourinary syndrome, Vulvar and vaginal atrophy, VVA, Vaginal dryness, Dyspareunia, Selective estrogen receptor modulator, Ospemifene

Abbreviations: HCP: Healthcare Professional, MBS: Most Bothersome Symptom, SERM: Selective Estrogen Receptor Modulator, QoL: Quality of Life, VVA: Vulvovaginal Atrophy

Introduction

Vulvovaginal atrophy (VVA) is a component of the genitourinary syndrome of menopause [1] and is associated with decreased estrogenization of the vaginal tissue [2]. Symptoms include vaginal dryness, dyspareunia (vaginal pain associated with sexual activity), vaginal and/or vulvar irritation or itching, dysuria, and vaginal bleeding associated with sexual activity [1,3]. Women with VVA rarely experience only one symptom, with the European Vulvovaginal Epidemiological Survey (EVES) recently reporting an average of five symptoms (range 1-14) [4]. Approximately 50-60% of post-menopausal women experience VVA symptoms [1] and these can adversely impact different aspects of well-being [4,5], such as the quality of sex lives and relationships, self-esteem, and everyday activities [6-8]. Recently, the EVES found that VVA symptoms and their severity correlated strongly with patient quality of life (QoL) [4,9]. Specifically, QoL was significantly lower in women with severe symptoms versus those without severe symptoms in all women, with women with severe urinary symptoms showing the greatest reduction

[9]. Decrements in QoL were particularly evident for emotional well-being, self-concept/body image, and mobility [9]. Importantly, reductions in QoL in women with VVA have been reported to be comparable with those found in serious conditions, such as arthritis, chronic obstructive pulmonary disease, asthma, and irritable bowel syndrome [2].

Unlike hot flushes and night sweats, vaginal atrophic changes do not resolve spontaneously with time, are often progressive, and frequently require treatment [10]. However, some women regard VVA symptoms as manifestations of the natural ageing process and do not seek help [1]. In the Vaginal Health: Insights, Views & Attitudes (VIVA) survey, 42% of post-menopausal women were able to relate VVA symptoms to the menopause, but only 4% of women surveyed attributed their vaginal symptoms to vaginal atrophy [11].

Despite its high prevalence and negative impact on QoL, VVA is not only under-reported by women, but also under-diagnosed and under-treated by healthcare professionals (HCPs) [1]. The European REal women's VIew of treatment options for menopausal Vulvar/Vaginal changEs (REVIVE-EU) survey found that 60% of women on treatment had discussed VVA with their HCP, but only 10% of HCPs had initiated the discussion about VVA symptoms with their patients [12].

The combination of under-reporting, under-diagnosis, and under-treatment may lead to many women presenting with severe VVA symptoms, at an advanced stage of disease. Potentially, this has important consequences, as not only are the symptoms unlikely to improve spontaneously, but the anatomical changes of atrophy will not improve without treatment. Such changes may, sometimes rapidly, lead to vaginal stenosis and more severe consequences, including vaginal occlusion [13].

Also, delaying treatment of vaginal atrophy may lead to vaginal and urinary tract infections (UTIs); increasing vaginal atrophy is associated with increasing overactive bladder symptoms, recurrent UTIs and non-infective cystitis, as well as bacterial vaginosis and thrush infections [14]. Ospemifene, a selective estrogen receptor modulator (SERM), is a novel oral treatment for moderate to severe symptomatic VVA in post-menopausal women who are not candidates for local vaginal oestrogen therapy [15]. Ospemifene is the only SERM which was developed specifically for VVA [16]. Unlike other SERMs, ospemifene has an oestrogenic effect on the vaginal epithelium [17]; after 12 weeks of treatment, an increase from baseline in the percentage of superficial cells has been observed, coupled with a reduction in parabasal cells and vaginal pH [18-20]. Moreover, the improvements in vaginal physiology were accompanied by consistent improvements in the most bothersome symptom (MBS) of vaginal dryness [18,20] or dyspareunia [18,19].

Whilst the need for treatment is clearly demonstrated by the anatomical changes that could be mitigated, it would be of interest to determine whether early treatment also leads to better symptom alleviation. Hence, the aim of this post-hoc analysis was to assess whether early treatment of VVA symptoms, when they are still moderate rather than severe, leads to greater treatment benefits.

Methods

Using the clinical trial data from the two ospemifene pivotal 12-week Phase III trials [18-20], which enrolled women with at least one moderate or severe symptom of vaginal dryness or dyspareunia, the participants were split into two groups: those with a moderate MBS and those with a severe MBS, as reported at baseline (symptom severity was reported by the patient at baseline as 'none', 'mild', 'moderate', or 'severe').

The analysis evaluated the impact of 12 weeks of ospemifene treatment on: improvement (reflecting the percentage of patients who achieved a reduction in severity score of one or more steps [on a 3-step scale], which included patients whose baseline score changed from 'severe' to 'none', 'mild', or 'moderate'; from 'moderate' to 'mild' or 'none'; and from 'mild' to 'none'); relief (reflecting the percentage of patients who had a severity score of 'mild' or 'none' at 12 weeks). In addition, the impact of treatment on all VVA symptoms, by baseline severity, was recorded for all women. This descriptive analysis did not include any formal statistical testing and hence the results are presented as numerical findings.

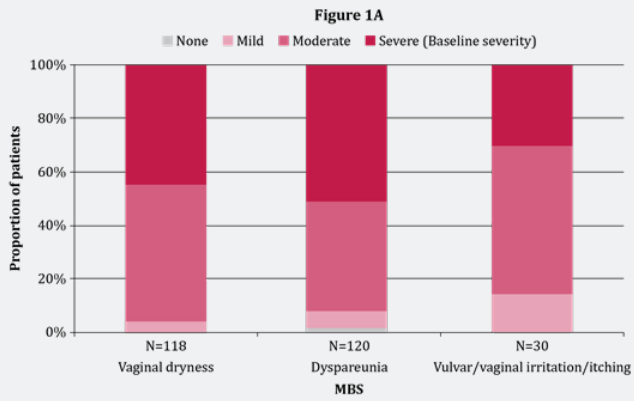

Figure 1A: Baseline severity distribution of the most bothersome symptom (MBS, study 15-50310).

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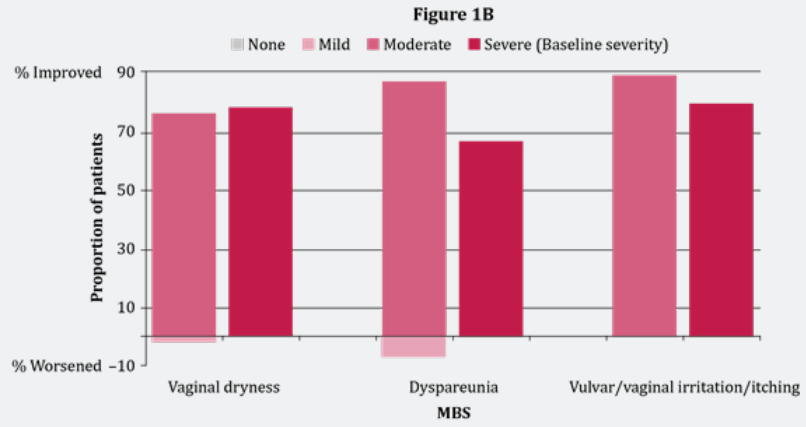

Figure 1B: Impact of baseline severity on improvement after 12 weeks of ospemifene treatment (most bothersome symptom [MBS], study 15-50310).

Results

In the first pivotal efficacy study (15-50310, NCT00276094) [18], all women who selected a VVA symptom as their MBS were enrolled. There were very few women who selected dysuria or post-coital bleeding, so those groups were too small to include in the analysis. In this study, 46% of women selected dyspareunia as the MBS, 39% vaginal dryness, and 13% vulvar/vaginal irritation/itching [18]. The baseline severity distribution of the MBS in the first pivotal efficacy study (15-50310) is presented in Figure 1A. The impact of 12 weeks of ospemifene treatment on improvement, by baseline severity, can be seen in Figure 1B; more women with moderate compared with severe MBS of dyspareunia (86.2% versus 65.5%) or vulvar/vaginal irritation/itching (88.2% versus 77.8%) showed improvement with ospemifene, although the differences were small (no difference for vaginal dryness).

The baseline severity distribution in the second pivotal efficacy study (15-50821, NCT00729469), where only women with an MBS of vaginal dryness [20] or dyspareunia [19] were enrolled, can be seen in Figure 2A. In this study, the improvement after 12 weeks of ospemifene treatment was slightly better in the severe population compared with the population whose MBS was moderate at baseline (vaginal dryness: 76.8% versus 64.1%, dyspareunia: 81.1% versus 77.5%); however, the differences were again small (Figure 2B).The baseline severity distribution of all VVA symptoms is shown in Figure 3A. Comparing the impact of 12 weeks of ospemifene treatment on improvement of all moderate versus all severe symptoms at baseline, revealed only a small difference between the two populations: 75% versus 79% (Figure 3B).

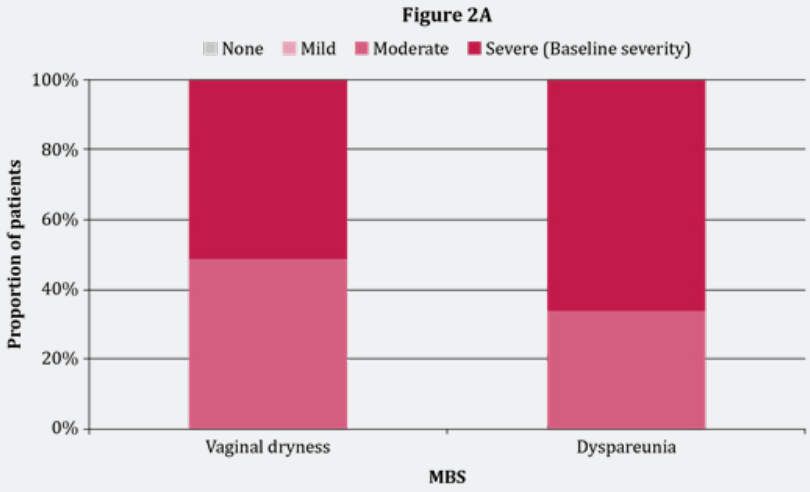

Figure 2A: Baseline severity distribution of the most bothersome symptom (MBS, study 15-50821).

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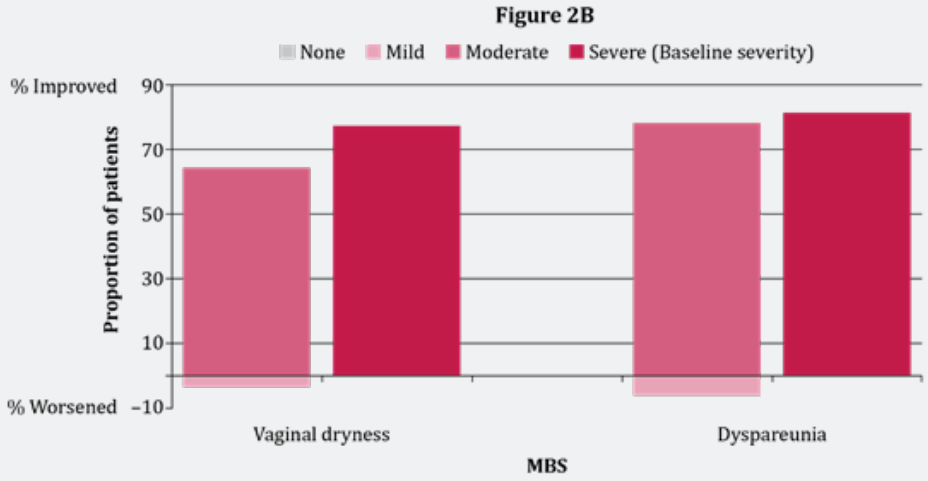

Figure 2B: Impact of baseline severity on improvement after 12 weeks of ospemifene treatment (most bothersome symptom [MBS], study 15-50821).

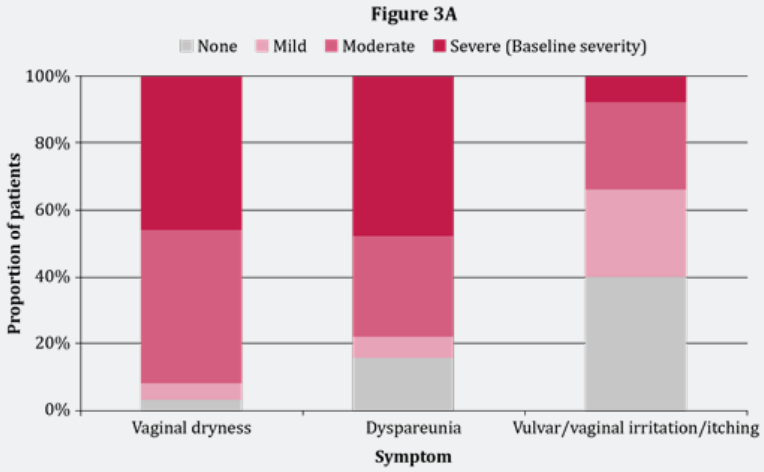

Figure 3A: Baseline severity distribution of all VVA symptoms (studies 15-50821 and 15-50310 combined).

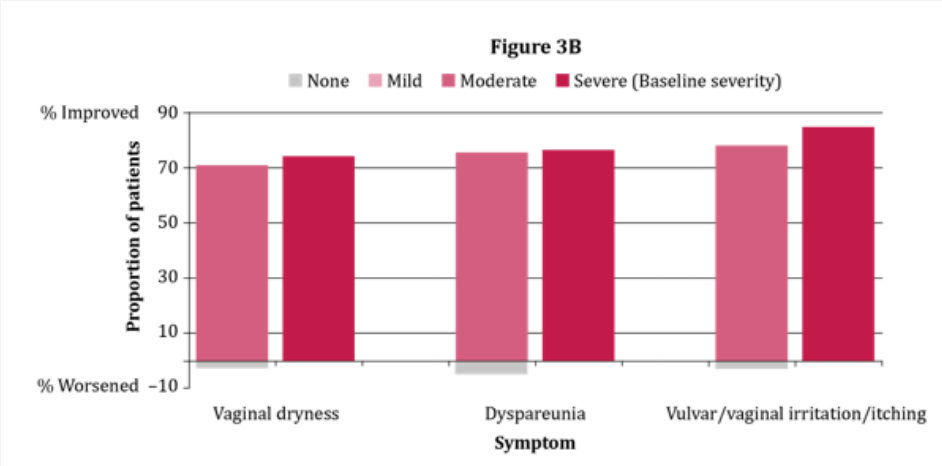

Figure 3B: Impact of baseline severity on improvement of all moderate or severe VVA symptoms after 12 weeks of treatment (studies 15-50821 and 15-50310 combined).

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When we evaluated the impact of 12 weeks of ospemifene treatment on relief (or 'cure'), by baseline severity, the proportion of women who experienced relief after treatment was higher in those women who had moderate MBS at baseline compared with those who had severe MBS and this effect was evident in both pivotal studies (Figure 4A&B). A comparison of the impact of 12 weeks of ospemifene treatment on all moderate or severe symptoms, by baseline severity, also confirmed that the proportion of patients with symptoms that were only mild or non-existent after treatment was higher in patients with symptoms that were moderate at baseline compared with those whose symptoms were severe at baseline; the 'cure' rate in women with moderate symptoms was around 75%, whereas it was 58% in women with severe symptoms (Figure 5).

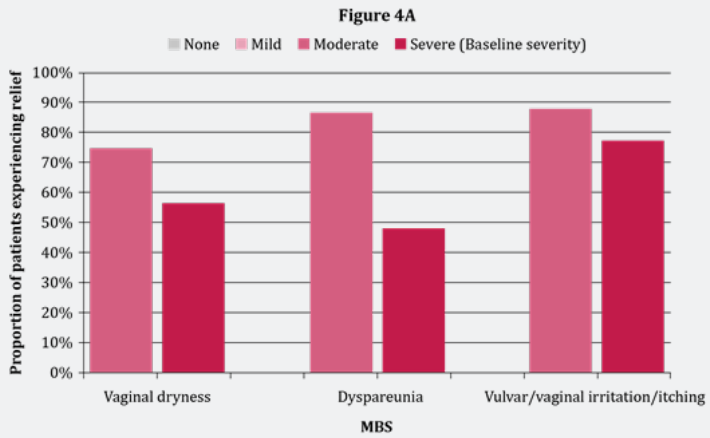

Figure 4A: Impact of baseline severity on relief after 12 weeks of ospemifene treatment (most bothersome symptom [MBS], study 15-50310).

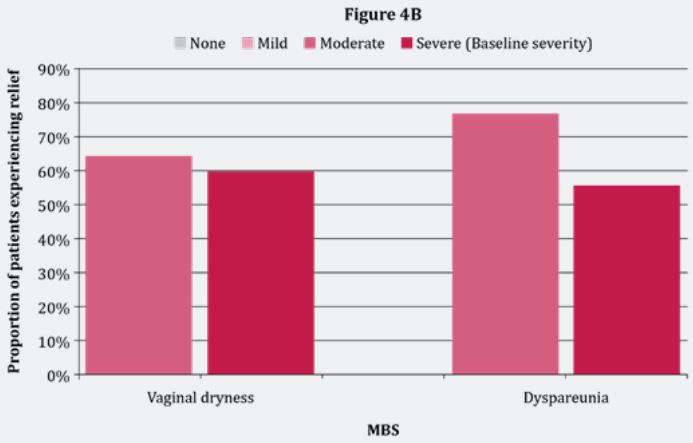

Figure 4B: Impact of baseline severity on relief after 12 weeks of ospemifene treatment (most bothersome symptom [MBS], study 15-50821).

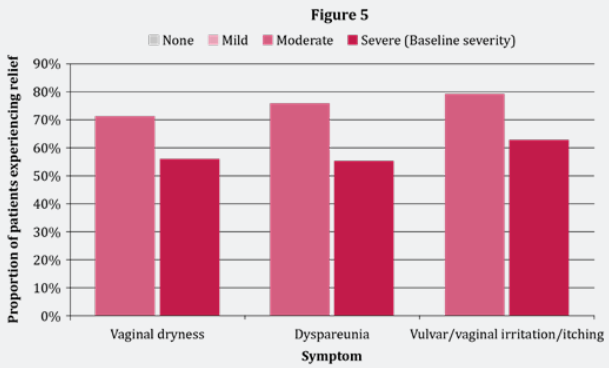

Figure 5: Impact of baseline severity on relief of all moderate or severe VVA symptoms after 12 weeks of treatment (studies 15-50821 and 15-50310 combined).

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Discussion

The current post-hoc analysis showed that in the first ospemifene efficacy study, more women showed greater improvement with moderate MBS of dyspareunia and vulvar/vaginal itching/irritation at baseline than did women whose MBS was severe. In the second efficacy study, this was the other way around (i.e. more women improved in the group with severe MBS at baseline).

Because 79.5% of the women enrolled in the pivotal studies combined had more than one moderate or severe symptom of VVA (two symptoms: 47.3%; three symptoms: 23.5%; four symptoms: 7.1%; five symptoms: 1.6%) [21], selecting one MBS per patient would underestimate the impact of treatment. Therefore, we also considered the effect of early treatment based on all symptoms of VVA. When we compared all moderate or severe symptoms at baseline, there was no impact on improvement based on severity (there was only 4% difference in improvement of all moderate or severe symptoms). Taken together, these results suggest that ospemifene improves all moderate or severe VVA symptoms, regardless of baseline severity.

This is a reassuring finding, as there is no reason to restrict treatment with ospemifene to those women with the most severe symptoms: ospemifene is equally beneficial for women with moderate symptoms. However, our analysis of all symptoms revealed that more women experienced relief of their symptoms if those were treated when moderate rather than severe (17% difference in relief of all moderate or severe symptoms). These findings suggest that earlier treatment of VVA symptoms, when symptoms are moderate rather than severe, may be associated with greater treatment benefits; both because of the higher 'cure' rate and because it prevents the sequelae of ongoing atrophy, which may lead to vaginal stenosis, or even occlusion [13].

Indeed, the International Menopause Society (IMS) recommends that VVA treatment is started early, before irrevocable atrophic changes have occurred, and that it is continued to maintain the benefits [22]. The EVES also concluded that treatment of VVA should be initiated early, before the appearance of significant anatomical changes and despite the absence of obvious VVA signs; the authors stressed that objective gynaecological assessment of VVA was important to help rule out conditions with VVA-type symptoms and for early treatment initiation [4]. The lower QoL in women with severe VVA symptoms that was observed in the EVES may reflect a delay in visiting their doctor, compromising the management of VVA [4]. Most recently, the EVES data were used to evaluate the association between treatments for VVA and symptom frequency and severity, QoL, and sexual functioning in post-menopausal women [23]. Women on VVA treatment presented with more severe symptoms, which suggests that treatment tends not to be initiated when symptoms commence, but when they have become more severe and are causing considerable distress [23]. These findings lead to the same conclusion that the treatment of VVA should ideally be initiated at early stages of the disease, to prevent irreversible changes [23].

Interestingly, a recent study, AN evaluation of GEnitourinary symptoms in perimenopausaL women (ANGEL), has shown that VVA and its symptoms are common across the menopausal transition, with the prevalence ranging from 19.2% among women aged 40-45 years to 53.8% in women aged 52-55 years; hence, early identification of this condition may favour early therapeutic intervention [24]. Direct questioning by HCPs during history taking in peri- and post-menopausal women has been highlighted as an important aspect of VVA diagnosis and management [5,14]. Also, because most women are not familiar with the term 'vaginal atrophy' [11], initiating discussion about the range of possible VVA symptoms may be more useful [14].

Limitations of the present research include the post-hoc nature of the analysis, the lack of formal statistical testing, and the lack of data on the length of time that the women had been suffering with moderate or severe VVA symptoms. Additionally, by not undertaking a prospective analysis, we were more likely to show better results for moderate VVA symptoms, as these would be more easily 'cured' than severe VVA symptoms, because of the lower scores at baseline.

An important strength is the fact that this analysis was based on a large population of women with VVA who had been evaluated in the controlled environment of double-blind randomized controlled trials. Also, this analysis should raise awareness of VVA as a chronic condition with a progressive pathology. Thus, like other chronic conditions, VVA should be promptly diagnosed and treated.

Conclusion

Despite methodological limitations, the present findings suggest that ospemifene improves all moderate or severe VVA symptoms, regardless of baseline severity; however, earlier treatment of VVA symptoms, when symptoms are moderate rather than severe, may be associated with greater treatment benefits, as indicated by the higher 'cure' rate in women with moderate VVA symptoms at baseline.

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Conflicts of Interest

SP has received honoraria or consulting fees from Pfizer, Amgen, MSD, Gynea, Procare Health, Bayer, Lacer, Serelys and Shionogi Europe and has participated in company-sponsored speakers' bureaus for Pfizer, Abbott, Bioiberica, Shionogi Europe, Amgen, Novo Nordisk, Teva, Bayer Healthcare, Serelys, Exeltis and Gedeon Richter. NP has received honoraria for lecturing

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and acting in an advisory capacity for several pharmaceutical companies, including Abbott, Bayer, Besins, Mithra, MSD, Mylan, Novo Nordisk, Pfizer, Se-cure and Shionogi Ltd. RSB has received research funding from Bayer and Procare Health and honoraria from Shionogi Europe, Lacer, Mylan, Theramex and Seid Pharmaceuticals. MP and SD are employees of Shionogi Europe.

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