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Key Paper Evaluation

Will elinzanetant, a neurokinin receptor antagonist, have a role in the treatment of hot flashes?

Evaluation of Pinkerton JA, Simon JA, Joffe H et al. Elinzanetant for the treatment of vasomotor symptoms associated with menopause. OASIS 1 and 2 randomized clinical trials. JAMA doi:10.1001/jama.2024.14618

1. Introduction
2. The story so far
3. OASIS 1 and 2 combined
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Abstract

Introduction: The use of hormonal treatment for the vasomotor symptoms (VSM) associated with the menopause is back in favour, as the adverse effects reported in the early 2000s have been dispelled. However, many women are still reluctant to use, or have contraindications to, hormonal therapy. Elinzanetant is a combined neurokinin (NK)-1 and -3 receptor antagonist, being trialled for menopausal symptoms.

Area covered: A combination of OASIS 1 and 2 in the menopause showed that elinzanetant caused a reduction in the frequency and intensity of VSM and may also independently reduce sleep disturbances. Adverse effects were low with elinzanetant.

Expert opinion: Further study is needed to clarify whether elinzanetant reduces sleep disturbance and whether this is due to antagonism at NK-1 receptors. If further studies support OASIS 1 and 2, elinzanetant maybe considered for use in hot flashes associated with the menopause, in subjects where hormonal therapy is contraindicated or not accepted. Fezolinetant, a NK-3 receptor antagonist, has recently been registered for VSM associated with the menopause. Fezolinetant does not have a clear-cut effect on sleep disturbances independent of VMS. Only, if elinzanetant can be shown to independently reduce sleep disturbances, it may have an advantage over fezolinetant.

Key words clinical trial, elinzanetant, fezolinetant, hormonal therapy, menopause, neurokinin receptors, OASIS, vasomotor symptoms (VMS)

1. Introduction

The topic of this key paper evaluation is the combination of two phase 3 clinical trials of elinzanetant in the treatment of vasomotor symptoms (VMS) associated with the menopause [1]. OASIS 1 (NCT05042362) was “A study to learn more about how well elinzanetant works and how safe it is for the treatment of vasomotor symptoms (hot flashes) that are caused by hormonal changes over 26 weeks in women who have been through the menopause” and was performed in the USA [2]. OASIS 2 (NCT05099159) had an identical trial protocol but was performed in Europe [3]. Hot flashes are the main symptom in the menopause and can start prior to the menopause. The menopause is also associated with sleep disturbances and reduced quality of life [4]. Most of these sleep disturbances are directly related to the hot flashes, but some may be independent of the hot flashes [5].

The common treatment for the menopausal symptoms was hormonal until the early 2000s with preparations containing either a combination of the natural hormones progesterone and oestrogen, or oestrogen alone [4]. However, large studies suggesting these treatments caused very small increases in cardiovascular events and breast cancer led to a major decline in their use [4]. Further studies have questioned these findings, and menopausal hormone treatment has returned [4]. For postmenopausal women with contradictions to use of this hormonal treatment (e.g., thromboembolic disease, migraine headache with aura, liver failure, heart disease, and hormone-dependent cancers), the serotonin reuptake inhibitor paroxetine is approved for use [4]. However, paroxetine is not as effective at reducing the frequency and severity of VSM as hormonal treatment [6].

A new approach to treating the symptoms of the menopause is to inhibit the hypothalamic kisspeptin/neurokinin/dynorphin (KINDy) neuron pathway [7]. Oestrogen inhibits this pathway [7]. The reduction in levels of oestrogen with the menopause leads to hypertrophy and hyperactivity of the (KINDy) neuron pathway [7]. The KINDy pathway releases substance P and neurokinin (NK) B onto NK-1 and NK-3 receptors [7]. Hyperactivity of this system upsets thermoregulation and may cause the VMS of the menopause [7]. In addition to contributing to the sleep disturbances in menopause via VMS, the KINDy pathway is involved in the circadian regulation of sleep-wake cycles, and, possibly, mood regulation, which are also disrupted in the menopause [8].

In phase 3 (SKYLIGHT 1 and 2: NCT04003155 and NCT04003142; Studies to find out if fezolinetant helps reduce moderate to severe hot flashes in women going through menopause – 1 and 2), fezolinetant a non-hormonal NK-3 receptor antagonist, was shown to decrease the frequency and severity of VMS in the menopause [9,10]. Fezolinetant (45 mg once daily as Veozah,) has been approved by the US Food and Drug Administration (FDA) for the treatment of moderate to severe VMS associated with the menopause [11].

In addition to blocking NK-3 receptors, elinzanetant (NK-814, BAY3427080) is an antagonist at NK-1 receptors, which are also involved in the KINDy pathway and may have a role in sleep. The next section briefly considers the clinical trials prior to OASIS with elinzanetant, and this is followed by a combined precis of the OASIS 1 (NCT05042362) and 2 (NCT05099159) trials in Section 3. Finally, there is an expert opinion section, which includes a comparison of fezolinetant.

2. The clinical story so far

In NCT02865538 (RELENT-1), Evaluation of the pharmacokinetics and safety of BAY3427080 (NT-814) in post-menopausal women with VSM [12], 76 postmenopausal women with 7-20 moderate to severe hot flashes/day were treated with elinzanetant 50, 100, 150 and 300 mg/daily or placebo [13]. In this phase 2a trial, over 2 weeks, the number and severity of hot flashes were recorded in diaries.

Elinzanetant 100-300 mg reduced the frequency and severity of flashes, and the frequency of waking due to night sweats without causing any serious adverse events [13].

In NCT03596762 (SWITCH-1), a study of BAY3427080 (NT-814) in the treatment of moderate to severe post-menopausal VSM [14], in 180 post-menopausal women with VSM, elinzanetant 40, 80, 120, or 160 mg, and placebo were investigated over 12 weeks [15]. Frequency and severity of hot flashes were recorded in diaries and quality of life was measured on the Menopause-specific Quality-of-life questionnaire intervention (MenQoL-I) [15]. The higher doses of elinzanetant (120 or 160 mg) reduced the frequency and severity of hot flashes, the frequency of night-time awakening secondary to VSM, and improved the quality of life at some weeks [15]. With the small group sizes, there were no obvious adverse effects directly related to elinzanetant [15].

3. OASIS 1 and 2 combined.

The OASIS 1 and 2 trials of elinzanetant in postmenopausal women with hot flashes had identical protocols with the difference being that they were mainly performed in the USA and Europe respectively. The results were similar for both trials, and examples of this at 12 weeks are given in Tables 1 and 2.

Insert Table 1 and 2

To precise the trials, the methods and results are combined as OASIS in the text in the next section.

3.1 Methods and results combined of OASIS 1 and 2 combined (OASIS).

OASIS was a double blind, randomised, placebo-controlled, phase 3 trial. To be enrolled, subjects had to be aged 40-65 years and experience 50 or more moderate to severe VSM over 7 days. Exclusion criteria included abnormal liver function and disordered proliferative endometrium, endometrial hyperplasia, or polyps [1].

About 200 participants were enrolled in each of the 4 groups to give a total of 397 and 399 in the combined placebo and elinzanetant groups. Their mean age was ~ 55 years, most of them were White (~80%), 35-42% had had a hysterectomy and 12-26% an oophorectomy. The participants were randomised to placebo or elinzanetant 120 mg for 12 weeks, and then all participants received elinzanetant for 14 weeks, followed by a 4-week follow-up [1].

The frequency and severity of hot flashes were measured by the electronic hot flash daily diary. Moderate hot flashes were defined as a sensation of heat with sweating allowing continued activity, whereas severe flashes stopped activity. Sleep disturbances were measured on The Patient-Reported Outcomes Measurement Information System Sleep Disturbances Short Form (PROMIS SD SF) 8b total T score. PROMIS SD SF 8b assesses the sleep disturbances of last 7 days including restless sleep, satisfaction with sleep, refreshing sleep, difficulties falling asleep, staying asleep, amount of sleep, and sleep quality. Quality of life was measured on the 29-item Menopause-Specific Quality of Life (MENQOL) questionnaire. The items were in 4 domains: VSM, psychosocial, physical, and sexual [1].

The primary endpoints were mean changes in frequency and severity of moderate-to-severe VMS, to week 4 or 12. At baseline, the participants had a mean of 13.4-16.2 flashes/24 hours, and the frequency was significantly reduced with elinzanetant. At week 4, there was a reduction in frequency of 7.5-8.6 with elinzanetant compared to 4.4-5.6 with placebo, and at week 12, the reduction was 8.7-10 compared to 5.5-7.2 with placebo. Severity of flashes at baseline was 2.5 and this was significantly reduced by ~57% and 66% by elinzanetant 120 mg at 4 and 12 weeks, compared to ~34% and ~44% in the placebo group, respectively [1].

The secondary end points included the mean changes in sleep disturbances measured on the PROMIS SD SF 8b total and T score from baseline score of ~61. Reductions were similar after 4 and 12 weeks and were significantly greater with elinzanetant than placebo. Thus, the reduction was ~11 with elinzanetant, compared to 5 with placebo after 12 weeks [1].

Another secondary end point was reduction from baseline (~4.5) in the MENQOL questionnaire score, which was significantly greater with elinzanetant than placebo. The difference was greater at 12 than 4 weeks, reductions of 1.1 and 1.3 with elinzanetant compared 0.8 and 1 with placebo, after 4 and 12 weeks, respectively. The largest change was in the VMS domain with reductions of 2.9 with elinzanetant compared to 1.6 in the placebo group after 12 weeks [1].

The efficacy of elinzanetant on these primary and secondary outcomes was maintained when treatment was extended from 12 to 26 weeks. Elinzanetant was also efficacious in the placebo group when it was switched to elinzanetant at 12 weeks [1].

After 12 weeks, the percentage of treatment-emergent adverse effects were similar in the elinzanetant and placebo groups. Headache and fatigue were more common with elinzanetant than placebo: headache, ~8% vs 2.55%; fatigue, ~6.2% vs 1.5%. Elinzanetant had no effect on liver enzymes [1].

3.2 Discussion by authors

The authors emphasize that the improvement in the MENQOL (quality of life) scores with elinzanetant were driven by the improvement in VSM. They also emphasised that effects of elinzanetant of a reduction of > 2 VSM/day and a decrease of ≥ 0.9 in MENQOL total score were clinically meaningful, according to previously defined criteria for clinically meaningful [1].

In OASIS, elinzanetant reduced sleep disturbance in the PROMIS SD SF 8b. The authors discuss whether this may be related to blocking NK-1 receptors. NK-1 receptors have been shown to be involved in sleep in healthy male volunteers, with the antagonism improving the quality of sleep. However, NK-1 receptors have not been shown to be involved in sleep in menopausal women. However, the authors suggest that this may be the mechanism whereby elinzanetant improved sleep in OASIS [1].

NK-3 receptor antagonists have previously been shown to elevate liver transaminases, but there was no evidence of this with elinzanetant in OASIS [1].

The limitations to the study given by the authors are that the use of patient reported outcomes (diaries and questionnaires) have previously been shown to contribute to a large placebo effect in VMS, and this was observed in the present study. Secondly, the results of OASIS are limited to the participants of the trials, who were naturally or surgically postmenopausal and predominantly White. Thirdly, despite sleep disturbances being an outcome, participants were not required to have sleep disturbances on enrolment. Thus, the effect of elinzanetant on populations with sleep disturbances associated with the menopause needs to be evaluated [1].

4. Expert opinion

4.1 Limitations to studies with elinzanetant

The limitations given by the authors in the previous section include a large placebo effect in OASIS [1]. To enlarge on this, in RELENT 1, the placebo effect seems to be bigger than that of elinzanetant 50 mg on the frequency and severity of hot flashes [13]. Because of the large placebo effect, although effective, the effects of elinzanetant 100 and 150 mg in reducing flashes were small [13]. In SWITCH-1, the placebo effect on hot flashes was large [15] and like that observed in RELENT 1. Although effective in reducing the frequency of flashes, the effect of elinzanetant (120 and 160 mg) was small

in SWITCH-1 and the effect on severity was not significant [15]. Similar reductions were also observed in the placebo groups in OASIS, the subject of this evaluation (See Table 1) [1]. Similar placebo effects have been observed in studies with fezolinetant (Section 4.5) and hormonal therapy (e.g., [16]). The reasons for the placebo effect are not clear and need investigation.

The added effect with elinzanetant is small in these studies. However, the authors of OASIS consider that even taking the placebo effect into consideration, the effect of elinzanetant is clinically meaningful and like that of fezolinetant and hormonal therapy [1].

As the authors also mention in their discussion, that the results of all clinical trials, cannot be generalised and are only valid for the population enrolled. In OASIS 1 and 2, these were naturally or surgically postmenopausal and predominantly White. Those excluded from enrolled also included abnormal liver function and disordered proliferative endometrium, endometrial hyperplasia, or polyps. Thus, the findings of OASIS do not apply to this group.

4.2 Longer term effects and registration of elinzanetant

RELENT-1 and SWITCH-1 were 2 and 12-week placebo-controlled trial, respectively. Although OASIS 1 and 2 were 26-week trials, only the first 12 weeks were placebo controlled. Thus, the longer-term effects of elinzanetant have not been published in a placebo-controlled trial, including any toxicity. This needs to happen prior to consideration of the wider use of elinzanetant. Fortunately, this has already happened in OASIS 3 (NCT05030584): ‘A study to learn more about how well elinzanetant works and how safe it is for the treatment of VSM (hot flashes) that are caused by hormonal changes over 52 weeks in women who have been through the menopause’ [17]. OASIS-3 has been completed, but the results have not been posted on the clinical trials website [17] or published in a peer reviewed journal.

Bayer have applied to the FDA to have elinzanetant registered for the treatment of hot flashes, associated with menopausal disorders, based on OASIS 1, 2, and 3 [18]. OASIS 1 and 2 are considered in this Key Paper Evaluation. OASIS-3 has been completed, but has not been independently reviewed, which is necessary for registration.

Elinzanetant is also being considered for treatment of hot flashes in other populations. VMS are common in subjects being treated with anti-cancer drugs for hormone-receptor positive breast cancer [19]. Thus, in OASIS-4 (NCT05587296), elinzanetant is being tested in treating hot flashes caused by anti-cancer therapy in women with, or at high risk for developing hormone-receptor positive breast cancer [20].

4.3 Brief comparison with hormonal therapy and paroxetine

As suggested in the Introduction, in postmenopausal women with hot flashes, who do not have a contraindication to hormonal therapy, hormonal therapy is an effective treatment of hot flashes. It will be difficult to compare elinzanetant to hormonal treatment in hot flashes, as the benefit with elinzanetant occur from day 1, whereas the maximal benefit of hormonal treatment is not observed to about 12 weeks [16]. At present, as elinzanetant has not been directly compared to hormonal therapy, it should not be considered as an alternative to hormonal therapy, unless there is a contraindication to hormonal therapy.

An alternative when hormonal therapy is contraindicated in hot flashes, is paroxetine. Paroxetine has been approved by the FDA for the treatment of hot flashes. It has been shown to reduce the frequency and severity of moderate to severe hot flashes in the menopause [21]. However, paroxetine is not considered as effective at reducing the frequency and severity of VSM as hormonal treatment [6]. Elinzanetant has not been compared to paroxetine in the treatment of hot flashes and should be.

4.4 Fezolinetant alone and compared with elinzanetant

4.4.1 Fezolinetant alone

Fezolinetant is a NK-3 receptor antagonist that has been approved by the FDA for the treatment of hot flashes. Fezolinetant does not block NK-1 receptors whereas elinzanetant does. Elinzanetant has not been directly compared to fezolinetant.

The effects of fezolinetant on VSM symptoms were investigated in SKYLIGHT 1 phase 3 clinical trial of 2205 menopausal women who cannot take or do not want to take hormonal treatment (NCT04003155) [22]. The trial was over 12 weeks and showed that fezolinetant reduced the frequency and severity of VSM symptoms ([9], Tables 1 and 2). Fezolinetant also improved the quality of life, measured as the MENQOL questionnaire score, including the VSM domain ([9], Table 2). SKYLIGHT 2 confirmed these findings [10].

There was no clear-cut effect of fezolinetant on sleep disturbances. Thus, measured as a key secondary outcome on the PROMIS SD SG 8b scale, the disturbances were not changed by fezolinetant in SKYLIGHT 1 ([9], Table 2). However, in an exploratory analysis using the PGI-C SD, a participant scale rating the severity of any problems with sleep at night, showed that more subjects in the fezolinetant than placebo group had a positive change [9]. In contrast, in SKYLIGHT 2, fezolinetant at 45 but not 30 mg/day, were significantly improved sleep disturbances, compared to the placebo group, on the PROMIS SD SG 8b scale ([10], Table 2). More participants reported improved sleep on the PGI-C SD for both doses of fezolinetant than in the placebo group [10].

Despite abnormal liver parameters, being an exclusion to enrolment for SKYLIGHT 1, there was a suggestion that fezolinetant might increase liver enzymes, although the effect was transient, and resolved on treatment [9]. Nevertheless, it is recommended that liver enzymes be measured at baseline and monitored during treatment with fezolinetant (at least once in first three months) [23]. In the OASIS trials, subjects with abnormal liver parameters were excluded [1]. At present there is no indication of liver toxicity with elinzanetant, but large and longer studies are needed to confirm this.

SKYLIGHT 2 was a phase 3 clinical trial of fezolinetant in women undergoing the menopause with VMS, which was not limited to menopausal women who cannot take or do not want to take hormonal treatment (NCT04003142, A study to find out if fezolinetant helps reduce moderate to severe hot flashes in women going through menopause) [24]. This data has not been published in a peer-reviewed journal to date, but the results posted on the clinicaltrials website suggest that the effects of fezolinetant were like those reported in SKYLIGHT 1 [24].

4.4.2 Fezolinetant compared with elinzanetant

The evidence from comparing separate clinical trials with different medicines, and variations in protocols will always be weak. For instance, SKYLIGHT 1 and 2 studies with fezolinetant limited enrolments to those menopausal women who cannot take or do not want to take hormonal treatment, whereas the OASIS studies did not. A comparison of the results with elinzanetant and fezolinetant is given in Tables 1 and 2. It is notable that the frequency of hot flashes and sleep disturbances were lower at baseline in SKYLIGHT 1 than the OASIS trials. The effects of elinzanetant and fezolinetant on the frequency of VMS seem similar, but elinzanetant may have a slightly greater effect on severity (Table 1).

Measurements of sleep disturbance on the PROMIS SD SF 8b scale showed smaller lowering effects in the placebo groups in OASIS 1 and 2 than in SKYLIGHT 1 and 2 (Table 2). OASIS 1 and 2 reported significant reductions in sleep disturbances with elinzanetant by 9.0 and 11.3 percentage points (Table

2). Whereas fezolinetant 45 mg was reported to cause a non-significant reduction of 3.4 percentage points in SKYLIGHT 1 and a significant reduction of 7.4 percentage points in SKYLIGHT 2 at 12 weeks (Table 2). This suggests that elinzanetant may have a greater effect on sleep disturbances than fezolinetant. As the exploratory analysis of sleep disturbances with PGI-C SD scale was used in the SKYLIGHT studies, but not the OASIS studies, a comparison between fezolinetant and elinzanetant, on this scale could not be made.

The only way these speculative comparative findings can be proven or not, is in a single **head-to-head** trial comparing the fezolinetant and elinzanetant using the same protocol.

4.5 Is blocking NK-1 receptors contributing to the effect of elinzanetant on sleep?

In OASIS 1 and 2, having sleep disturbances was not a requirement for enrolment. It would be of interest to study the effect of elinzanetant on sleep in a study of menopausal women limited to those who have sleep disturbances.

Whereas fezolinetant only blocks NK-3 receptors, elinzanetant also blocks NK-1 receptors. It is not known whether blocking NK-1 receptors is involved in the benefits of elinzanetant in reducing sleep disturbances associated with the menopause. The receptor/s, NK-1 or -3 involved in the effect of elinzanetant in RELENT-1, SWITCH-1 or OASIS were not identified. **As the receptor was not identified in these trials, it remains hypothetical/speculative as to whether elinzanetant inhibits NK-1 receptors to decrease sleep disturbances.** However, there is some evidence in each of these trials that elinzanetant reduces sleep disturbances, whereas there is no clear evidence that fezolinetant directly reduce sleep disturbances.

4.6 Conclusions

In the menopause, elinzanetant caused a reduction in the frequency and severity of VMS and may also independently reduce sleep disturbances. Further study is needed to clarify whether elinzanetant reduces sleep disturbance independently and whether this is due to antagonism at NK-1 receptors. Fezolinetant, a NK-3 receptor antagonist, has recently been registered for the VSM associated with the menopause. Fezolinetant does not **have a clear-cut effect** on sleep disturbances independent of VMS but may increase liver enzymes. If elinzanetant can be shown to reduce sleep disturbances independently of VMS, and/or have no effect on liver enzymes, it may be favourably to fezolinetant for use in the menopause, and then only in subjects where hormonal therapy is contraindicated or not accepted.

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Table 1. The effects of elinzanetant and fezolinetant on the frequency and severity of Hot Flashes

		Frequency of Hot flashes			Severity of Hot Flashes		
		Baseline	12 wks	Difference	Baseline	12 wks ¹	Difference
OASIS 1	Placebo	14.3	-5.5	-42.2%	2.5	-0.4	-16%
	Elinzanetant	13.4	-8.7	-65.2%	2.6	-0.8	-31%
OASIS 2	Placebo	16.2	-7.2	-45.9%	2.5	-0.5	-20%
	Elinzanetant	14.7	-10.0	-67.0%	2.5	-0.8	-32%
SKYLIGHT 1	Placebo	10.5	-3.6	-34%	2.4	-0.3	-13%
	Fezolinetant 30 mg	10.7	-6.2	-58%	2.4	-0.5	-21%
	Fezolinetant 45 mg	10.4	-6.5	-63%	2.4	-0.5	-21%

1. Estimated from graph in paper

Table 2. The effects of elinzanetant and fezolinetant on Sleep Disturbances and Quality of Life associated with Hot Flashes

		Sleep Disturbances: PROMIS SD SF 8B total T score			Quality of Life: MENQOL VSM domain		
		Baseline	12 wks ¹	Difference	Baseline	12 wks ¹	Difference
OASIS 1	Placebo	60.2	-4 ¹	6.7%	NA	-1.50	
	Elinzanetant	61.0	-10 ¹	16.3%	NA	-2.86	
OASIS 2	Placebo	60.7	-3 ¹	4.9%	NA	-1.64	
	Elinzanetant	61.7	-10 ¹	16.2%	NA	-2.70	
SKYLIGHT 1	Placebo	26.4	-3.2 ¹	12.1%	6.46	-1.31	20.3%
	Fezolinetant 30 mg	26.4	-3.7 ¹	14.0%	6.42	-2.26	35.2%
	Fezolinetant 45 mg	27.1	-4.2 ¹	15.5%	6.35	-2.31	36.4%
SKYLIGHT 2	Placebo	27.4	-3.2	11.7%	NA		
	Fezolinetant 30 mg	27.3	-4.3	15.7%	NA		
	Fezolinetant 45 mg	26.2	-5.0	19.1%	NA		

1. Estimated from graph in paper

NA = not available in paper