Health Technology Briefing
January 2022

Fezolinetant for treating vasomotor symptoms associated with menopause

Company/Developer	Astellas Pharma Ltd

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 26671	NICE ID: 10275	UKPS ID: 648929

Licensing and Market Availability Plans

Currently in phase III clinical trials.

Summary

Fezolinetant is currently in development for the treatment of vasomotor symptoms associated with the menopause. Vasomotor symptoms are characterised by hot flushes and night sweats caused by a loss of thermoregulatory control due to a decrease in oestrogen levels during menopause. These symptoms have been linked to problems with sleep, quality of life and depression, and the discomfort that they cause is the main menopause-related reason that women seek medical attention. The current standard of care for vasomotor symptoms associated with the menopause is hormone replacement therapy (HRT). However, HRT has been linked to several safety and tolerability concerns, resulting in many women being unable or unwilling to use it. There is, therefore, considerable need for a safe, effective non-hormonal therapy for menopause-related vasomotor symptoms.

Fezolinetant is a protein that that is aimed at treating vasomotor symptoms because it moderates activity in the thermoregulatory centre of the brain. Fezolinetant is administered orally and has been shown to have comparable efficacy to HRT in controlling vasomotor symptoms. If licensed it would provide a non-hormonal alternative treatment to women who cannot or are reluctant to use HRT.

Proposed Indication

Women suffering from vasomotor symptoms associated with menopause.[1]

Technology

Description

Fezolinetant (ESN364) is a selective neurokinin-3 receptor (NK3R) antagonist that blocks neurokin B (NKB) binding on the kisspeptin/neurokinin/dynorphin (KNDy) neuron to moderate neuronal activity in the thermoregulatory centre in the hypothalamus.[2] KNDy neurons serve as the GnRH pulse generator, recognized for regulating sex hormone levels over the phases of the menstrual cycle.[3] However, KNDy neurons also integrate neuroendocrine control of various other functions including thermoregulation, circadian rhythms, and sleep, and evidence has shown that they could play a role in the generation of hot flushes.[3,4] KNDy neurons are stimulated by NKB and inhibited by oestrogen as part of the feedback mechanism that supports female reproductive endocrinology and fertility.[5,6] It has therefore been proposed that the drop in oestrogen levels during menopause and the consequent unregulated KNDy neuron activity could be a key driver in vasomotor symptoms.[5]

Fezolinetant is in development for the treatment of vasomotor symptoms associated with menopause and is taken orally as a tablet once daily.[1] In a phase II clinical trial (NCT03192176), fezolinetant was given at orally in tablets of 15, 30, 60 or 90mg once daily for a period of 12 weeks.[7]

Key Innovation

Current standard of care treatment for vasomotor symptoms associated with menopause is hormone replacement therapy (HRT) treatments. However HRT has been linked to a number of different risks including venous thromboembolism, breast cancer and stroke.[8] Whilst it has been shown that most potential increased risks are small and usually outweighed by the benefits of HRT, many women and doctors are still reluctant to use HRT due to safety and tolerability concerns.[9]

Phase II clinical trials showed fezolinetant 30 and 45mg administered once-daily demonstrated a statistically significant reduction from baseline in the frequency and severity of moderate to severe vasomotor symptoms at weeks 4 and 12 versus placebo. Results also showed that improvement in vasomotor symptom frequency and severity greater than placebo was observed through the 12-week placebo-controlled period.[10] These results indicate that fezolinetant might be the first non-hormone treatment for vasomotor symptoms that has efficacy similar to HRT, making it an option for women who cannot or do not want to take hormones.[11]

Regulatory & Development Status

Fezolinetant does not currently have Marketing Authorisation in the EU/UK for any indication.

Patient Group

Disease Area and Clinical Need

The menopause is a natural part of ageing that usually occurs between 45 and 55 years of age, as a woman's oestrogen levels decline. In the UK, the average age for a woman to reach the menopause is 51 years.[12] Most women will experience vasomotor symptoms, such as hot flushes, when going through the

menopause. Hot flushes are often described as a sudden feeling of heat that seems to come from nowhere and spreads throughout the body. Women may also experience sweating, palpitations and flushing of the face. Some women only have occasional hot flushes that do not really bother them, while others can have many a day and find them uncomfortable, disruptive, and embarrassing. Hot flushes can start a few months or years before a woman's periods stop and usually continue for several years after the last period. Hot flushes are thought to be caused by changes in your hormone levels affecting your body's temperature control.

Approximately 25% of menopausal women experience problematic vasomotor symptoms that may need treatment.[13] Using this figure and 2018 population data from the Office for National Statistics it can be estimated that approximately 1,280,420 women in the UK between the ages of 45 and 55 may experience problematic vasomotor symptoms.[14] However, most women do not seek medical intervention so the true prevalence of these symptoms is thought to be much higher, with studies showing up to 80% of menopausal women may experience vasomotor symptoms.[3,15,16]

Recommended Treatment Options

NICE currently recommends HRT to menopausal women experiencing vasomotor symptoms after discussing the short-term and longer-term benefits and risks. The choice of HRT preparations offered are as follows:[8]

- Oestrogen and progestogen to women with a uterus
- Oestrogen alone to women without a uterus

Clinical Trial Information

Trial	**Skylight4; NCT04003389, 2019-000275-16;** A Randomized, Placebo-controlled, Double-blind Phase 3 Clinical Study to Investigate the Long-Term Safety of Fezolinetant in Women Suffering from Vasomotor Symptoms (Hot Flashes) Associated with Menopause **Phase III** – Active, not recruiting **Location(s):** 4 EU countries, UK, US, Canada and Ukraine **Primary Completion Date:** January 2022
Trial Design	Randomised, parallel assignment, double-blinded, placebo-controlled
Population	N=1,833; aged 40 to 65 years old; female; confirmed as menopausal and seeking treatment for vasomotor symptoms associated with menopause
Intervention(s)	Either low dose fezolinetant or high dose fezolinetant oral tablet once a day
Comparator(s)	Matched placebo
Outcome(s)	Primary outcomes: • Frequency of Adverse Events (AE) [Time frame: Up to 55 weeks] • Severity of Adverse Events [Time frame: Up to 55 weeks] • Percentage of participants with endometrial hyperplasia [Time frame: Up to 52 weeks] • Percentage of participants with endometrial cancer [Time frame: Up to 52 weeks] See trial record for full list of other outcomes

Results (efficacy)	-
Results (safety)	-

Trial	**Skylight1; NCT04003155, 2018-003528-35;** A Phase 3, Randomized, Placebo-controlled, 12-week Double-blind Study, followed by a Non-Controlled Extension Treatment Period, to Assess the Efficacy and Safety of Fezolinetant in Women Suffering from Moderate to Severe Vasomotor Symptoms (Hot Flashes) Associated with Menopause **Phase III** – Completed **Location(s):** 4 EU countries, UK, US and Canada **Study Completion Date:** August 2021
Trial Design	Randomized, parallel assignment, double-blinded, placebo-controlled
Population	N=527; aged 40 to 65 years old; female; confirmed as menopausal and seeking treatment for vasomotor symptoms associated with menopause
Intervention(s)	Either low dose fezolinetant or high dose fezolinetant oral tablet once a day
Comparator(s)	Matched placebo
Outcome(s)	Primary outcomes: • Mean change in the frequency of moderate or severe vasomotor symptoms (VMS) from baseline to week 4 [Time frame: baseline to week 4] • Mean change in the frequency of moderate to severe VMS from baseline to week 12 [Time frame: baseline to week 12] • Mean change in the severity of moderate to severe VMS from baseline to week 4 [Time frame: baseline to week 4] • Mean change in the severity of moderate to severe VMS from baseline to week 12 [Time frame: baseline to week 12] See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Trial	**Skylight2, NCT04003142, 2018-003529-27;** A Phase 3, Randomized, Placebo-controlled, 12-week Double-blind Study, followed by a Non-Controlled Extension Treatment Period, to Assess the Efficacy and Safety of Fezolinetant in Women Suffering from Moderate to Severe Vasomotor Symptoms (Hot Flashes) Associated with Menopause **Phase III** – Completed **Location(s):** 4 EU countries, UK, US and Canada **Study Completion Date:** April 2021
Trial Design	Randomized, parallel assignment, double-blinded, placebo-controlled
Population	N=501; aged 40 to 65 years old; female; confirmed as menopausal and seeking treatment for vasomotor symptoms associated with menopause

Intervention(s)	Either low dose fezolinetant or high dose fezolinetant oral tablet once a day
Comparator(s)	Matched placebo
Outcome(s)	Primary outcomes: • Mean change in the frequency of moderate to severe VMS from baseline to week 4 [Time frame: baseline to week 4] • Mean change in the frequency of moderate to severe VMS from baseline to week 12 [Time frame: baseline to week 12] • Mean change in the severity of moderate to severe VMS from baseline to week 4 [Time frame: baseline to week 4] • Mean change in the severity of moderate to severe VMS from baseline to week 12 [Time frame: baseline to week 12] See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Trial	NCT03192176; A Randomized, Placebo-Controlled, Double-Blind, Dose-Ranging, Phase 2b Study to Investigate the Efficacy of ESN364 in Postmenopausal Women Suffering From Vasomotor Symptoms (Hot Flashes) **Phase II** – Completed **Location(s):** US **Study Completion Date:** September 2018
Trial Design	Randomized, parallel assignment, double-blinded
Population	N=356; aged 40 to 65 years old; female; at least 50 moderate to severe vasomotor symptoms per week
Intervention(s)	Either 15, 30, 60 or 90mg fezolinetant oral tablet twice a day
Comparator(s)	Matched placebo
Outcome(s)	Primary outcomes: • Change From Baseline (CFB) in the mean frequency of moderate to severe VMS at week 4 [Time frame: Baseline and week 4] • CFB in the mean frequency of moderate to severe VMS at week 12 [Time frame: Baseline and week 12] • CFB in the mean severity of moderate to severe VMS at week 4 [Time frame: Baseline and week 4] • CFB in the mean severity of moderate to severe VMS at week 12 [Time frame: Baseline and week 12] See trial record for full list of other outcomes.
Results (efficacy)	See trial record
Results (safety)	See trial record

Estimated Cost

The cost of fezolinetant is not yet known.

Relevant Guidance

NICE Guidance

- NICE guideline in development. Menopause: diagnosis and management (GID-NG10241). Expected date of publication: August 2023.
- NICE guideline. Menopause: diagnosis and management (NG23). November 2015.
- NICE quality standard. Menopause (QS143). February 2017.
- NICE interventional procedure guidance in development. Removal, preservation and subsequent re-implantation of ovarian tissue to delay the menopause (GID-IPG10170). Expected date of publication: To be confirmed.
- NICE interventional procedure guidance. Transvaginal laser therapy for urogenital atrophy (IPG697). May 2021.

NHS England (Policy/Commissioning) Guidance

No relevant guidance identified.

Other Guidance

- Primary Care Women's Health Forum. Menopause - Guidance on management and prescribing HRT for GPs. 2020.[17]
- Royal College of Nursing. Menopause: RCN guidance for nurses, midwives and health visitors. 2020.[18]
- NICE evidence summary. Oestrogen deficiency symptoms in postmenopausal women: conjugated oestrogens and bazedoxifene acetate (ES3). 2016.[19]

Additional Information

References

1 Clinicaltrials.gov. *A Study to Find Out How Safe Long-term Treatment With Fezolinetant is in Women With Hot Flashes Going Through Menopause (Skylight 4). Trial ID: NCT04003389*. 2019. Available from: https://clinicaltrials.gov/ct2/show/NCT04003389 [Accessed 7 December 2021].

2 Astellas Pharma Ltd. *Astellas Announces Positive Topline Results from Two Phase 3 Pivotal Global Trials of Fezolinetant for the Nonhormonal Treatment of Vasomotor Symptoms in Postmenopausal Women.* 2021. Available from: https://www.astellas.com/en/news/16701 [Accessed 7 December 2021].

3 Depypere H, Lademacher C, Siddiqui E, Fraser GL. Fezolinetant in the treatment of vasomotor symptoms associated with menopause. *Expert Opinion on Investigational Drugs*. 2021;30(7):681-94. Available from: https://doi.org/10.1080/13543784.2021.1893305.

4 Mittelman-Smith MA, Williams H, Krajewski-Hall SJ, McMullen NT, Rance NE. Role for kisspeptin/neurokinin B/dynorphin (KNDy) neurons in cutaneous vasodilatation and the

estrogen modulation of body temperature. *Proceedings of the National Academy of Sciences*. 2012;109(48):19846-51. Available from: https://doi.org/10.1073/pnas.1211517109.

5 Depypere H, Timmerman D, Donders G, Sieprath P, Ramael S, Combalbert J, et al. Treatment of Menopausal Vasomotor Symptoms With Fezolinetant, a Neurokinin 3 Receptor Antagonist: A Phase 2a Trial. *The Journal of Clinical Endocrinology & Metabolism*. 2019;104(12):5893-905. Available from: https://doi.org/10.1210/jc.2019-00677.

6 Ruka KA, Burger LL, Moenter SM. Both Estrogen and Androgen Modify the Response to Activation of Neurokinin-3 and κ-Opioid Receptors in Arcuate Kisspeptin Neurons From Male Mice. *Endocrinology*. 2016;157(2):752-63. Available from: https://doi.org/10.1210/en.2015-1688.

7 Clinicaltrials.gov. *A Dose-ranging Study of the Efficacy of ESN364 in Postmenopausal Women Suffering Vasomotor Symptoms (Hot Flashes)*. *Trial ID: NCT03192176*. 2017. Available from: https://clinicaltrials.gov/ct2/show/NCT03192176 [Accessed 7 December 2021].

8 NICE. *Menopause: diagnosis and management* (*NG23)*. Last Update Date: 2019. Available from: https://www.nice.org.uk/guidance/ng23/resources/menopause-diagnosis-and-management-pdf-1837330217413 [Accessed 7 December 2021].

9 National Health Service. *Hormone replacement therapy (HRT): Benefits and risks.* 2019. Available from: https://www.nhs.uk/conditions/hormone-replacement-therapy-hrt/risks/ [Accessed 7 December 2021].

10 Astellas Pharma Ltd. *Astellas to Present Fezolinetant 12-Week Findings from Phase 3 SKYLIGHT 2™ Trial in Oral Session at The North American Menopause Society 2021 Annual Meeting.* 2021. Available from: https://www.astellas.com/en/news/17176 [Accessed 7 December 2021].

11 Healio. *Nonhormonal therapy reduces moderate to severe menopausal hot flashes.* 2021. Available from: https://www.healio.com/news/endocrinology/20210927/nonhormonal-therapy-reduces-moderate-to-severe-menopausal-hot-flashes [Accessed 7 December 2021].

12 National Health Service. *Menopause: Overview.* 2018. Available from: https://www.nhs.uk/conditions/menopause/ [Accessed 7 December 2021].

13 Hickey M, Szabo RA, Hunter MS. Non-hormonal treatments for menopausal symptoms. *BMJ*. 2017;359:j5101. Available from: https://doi.org/10.1136/bmj.j5101.

14 Office for National Statistics. *UK population pyramid interactive.* 2021. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/articles/ukpopulationpyramidinteractive/2020-01-08 [Accessed 23 December 2021].

15 Palacios S, Henderson VW, Siseles N, Tan D, Villaseca P. Age of menopause and impact of climacteric symptoms by geographical region. *Climacteric*. 2010;13(5):419-28. Available from: https://doi.org/10.3109/13697137.2010.507886.

16 Thurston RC, Joffe H. Vasomotor symptoms and menopause: findings from the Study of Women's Health across the Nation. *Obstetrics and gynecology clinics of North America*. 2011;38(3):489-501. Available from: https://doi.org/10.1016/j.ogc.2011.05.006.

17 Primary Care Women's Health Forum. *Menopause - Guidance on management and prescribing HRT for GPs* Last Update Date: Available from: https://pcwhf.co.uk/wp-content/uploads/2021/02/Prescribing-HRT-3.pdf [Accessed 9 December 2021].

18 Royal College of Nursing. *Menopause: RCN guidance for nurses, midwives and health visitors* Last Update Date: Available from: https://www.rcn.org.uk/professional-development/publications/rcn-menopause-guidance-for-nurses-midwives-and-health-visitors-uk-pub-0093326 [Accessed 9 December 2021].

19 NICE. *Oestrogen deficiency symptoms in postmenopausal women: conjugated oestrogens and bazedoxifene acetate.* 2016. Available from:

https://www.nice.org.uk/advice/es3/chapter/Key-points-from-the-evidence [Accessed 23 December 2021].

NB: This briefing presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.