June 21, 2021

Submitted electronically to: publiccomments@icer.org
Institute for Clinical and Economic Review (ICER)

Astellas appreciates the opportunity to provide feedback on the Institute for Clinical and Economic Review's (ICER's) draft scoping document for the assessment of fezolinetant for moderate to severe vasomotor symptoms (VMS) associated with menopause, characterized by hot flashes (also called hot flushes) and/or night sweats. Astellas is committed to turning innovative science into medical solutions that bring value and hope to patients and their families. Keeping our focus on addressing unmet medical needs and conducting our business with ethics and integrity enables us to improve the health of people throughout the United States and around the world.

VMS BURDEN AND UNMET NEED

ICER notes in the draft scope that VMS affects up to 80% of women during or after the menopausal transition in the US.[1] While some individuals who are postmenopausal experience no VMS or only mild symptoms, the prevalence of moderate to severe VMS during perimenopause or postmenopause in the United States ranges from 32% to 46%.[2] Women experience a wide range of intensity, frequency, and duration of symptoms associated with menopause. Most women experience an average of four menopausal symptoms —most commonly hot flashes, sleep problems, vaginal dryness, and mood.[3] Menopause-associated VMS have a profound negative impact on key health, quality of life, work productivity, and economic outcomes.[4-8] VMS associated with menopause can impact daily life, such that women with frequent moderate to severe VMS report effects on their sleep (94%), concentration (84%), mood (85%), energy (77%), and sexual activity (61%).[9] VMS are also associated with psychosocial issues including irritability, anxiety, depressed mood, fatigue, and social embarrassment/isolation.[7,10,11] Moreover, the direct and indirect economic burden of VMS increases with the severity of VMS symptoms.[8,12] Astellas welcomes ICER's recognition of the undertreatment of VMS and its impact on women.

Guidelines stress the importance of individualized treatment and shared decision-making between individuals and providers, taking into consideration symptom severity, age, preference, and estimated benefit/risk ratio.[13,14,15]

Menopausal hormone therapy (HT) has been prescribed and used for more than 50 years for the management of menopause symptoms, including VMS.[16] HT is highly effective and benefits are thought to outweigh risks for women with no contraindications who are younger than 60 years of age or less than 10 years post-menopause.[15] However, in practice, many individuals are unsuitable for HT, for example those who are intolerant, contraindicated, or unwilling to take HT for their VMS. Non-hormonal prescription treatment options for women seeking pharmacological management for moderate to severe VMS currently are limited to paroxetine

7.5 mg (BRISDELLE®) (an SSRI – selective serotonin reuptake inhibitor) and off-label use of other SSRIs, serotonin–noradrenaline reuptake inhibitors (SNRIs), anti-epileptic medications (gabapentin, pregabalin), and clonidine. Current non-hormonal treatments have limited efficacy and may be associated with side effects such as nausea, headache, dizziness, fatigue, drowsiness, dry mouth, constipation, weight changes, hypertension, changes in sexual function, and in rare cases, suicidal thoughts.[17]

CLINICAL BENEFIT OF FEZOLINETANT

While most treatments for VMS associated with menopause include hormones such as estrogen, fezolinetant would be a nonhormonal treatment option. Fezolinetant is an investigational selective NK3R antagonist that blocks a specific receptor in the temperature control center of the brain (the hypothalamus) to reduce the frequency and severity of moderate to severe VMS associated with menopause.[18-23] If approved by the U.S. Food and Drug Administration, fezolinetant will provide a new targeted non-hormonal treatment option with a novel MOA for women for whom HT is deemed not appropriate or who prefer not to use HT.

In the Phase 3 SKYLIGHT 1 and 2 trials, women with moderate to severe VMS receiving fezolinetant experienced a statistically significant reduction in the frequency and severity of VMS after 4 and 12 weeks' treatment compared to placebo.[24,25]

The safety and tolerability profile of fezolinetant was confirmed in the 52-week SKYLIGHT 4 trial. SKYLIGHT 4 was a randomized, placebo-controlled, double-blind Phase 3 clinical trial investigating the long-term (52-week) safety of fezolinetant in over 1,800 women seeking treatment for relief of VMS associated with menopause.[26]

SPECIFIC CLARIFICATIONS AND ADDITIONS

Astellas would like to provide the following considerations to inform development of the revised scoping document.

I. Low treatment rates reflect the need for new treatment options for the management of VMS

Although VMS negatively impact women's daily lives and despite the availability of many effective HT options, and several non-hormonal psychotropic pharmacologic agents used on- and off-label, an estimated 60% of women with moderate to severe symptoms seek medical attention and more than 70% of them remain untreated.[8] Women with VMS remain undertreated due to many factors, including contraindications, adverse effects, and the desire to avoid hormonal options.[27]

In a recent observational study of 1,016 women who presented to a United States health care provider with menopausal complaints (including VMS), about 40% of women had no prescription medication documented, and 13% had no treatment of any kind (including over-the-counter treatment) documented. While "considered to have good efficacy" was the primary reason providers prescribed therapy, "lack of efficacy" was the top reason they modified treatment.[28]

II. Importance of shared decision-making and individual preference

Guidelines and professional organizations such as the American College of Obstetricians and Gynecologists (ACOG), North American Menopause Society (NAMS), and Endocrine Society stress an individualized approach to treatment selection with shared decision-making remaining key for women with VMS, considering risk/benefit, goals, and individual preference.[13,14,15]

III. Disproportional impact on historically underserved populations

Astellas agrees with ICER that VMS disproportionally affects women of color, with a higher prevalence of VMS in Black women and a higher median duration of VMS symptoms of 10 years compared with other ethnicities.[3,29] ICER's draft scope states that Hispanic and Chinese women typically have the shortest duration of symptoms. However, results from the Study of Women's Health Across the Nation (SWAN) study, a multiracial/multiethnic observational study of 3,302 women from February 1996 through April 2013, found that Hispanic women had the second longest median duration of VMS (8.9 years), after Black women (10.1 years).[29]

IV. Clarification on inclusion of vaginal symptoms and urinary tract symptoms

In the draft scope, ICER indicates the aim of this assessment is to "evaluate the health and economic outcomes of fezolinetant for vasomotor symptoms associated with menopause." The focus on VMS is appropriate and consistent with the anticipated indication of fezolinetant. We observe that the proposed outcomes of "Other menopausal symptoms" on page 5 of the draft scope extends beyond those associated with VMS to comprehensively include outcomes broadly related to menopause such as vaginal symptoms and urinary tract symptoms. These outcomes are not directly related to VMS and are beyond the scope defined by ICER.

We appreciate the opportunity to provide input on the scoping document. Astellas is dedicated to enabling a future where healthcare innovation is driven by scientific possibility and patient need.

Sincerely,

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REFERENCES

1. ICER. Fezolinetant for Moderate to Severe Vasomotor Symptoms Associated with Menopause. Draft Background and Scope. June 1, 2022. https://icer.org/wp-content/uploads/2022/05/ICER_Menopause_Draft-Scoping-Document_060122.pdf
2. Freeman EW, Sammel MD, Sanders RJ. Risk of long-term hot flashes after natural menopause: evidence from the Penn Ovarian Aging Study cohort. *Menopause.* 2014;21:924-32.
3. Gold EB, Sternfeld B, Kelsey JL, et al. Relation of demographic and lifestyle factors to symptoms in a multi-racial/ethnic population of women 40-55 years of age. *Am J Epidemiol*. 2000;152(5):463-473.
4. Thurston RC. Vasomotor symptoms: natural history, physiology, and links with cardiovascular health. *Climacteric.* 2018;21(2):96-199.
5. Thurston RC. In: Crandall CJ, ed. Menopause Practice: A Clinician's Guide. 6th ed. Pepper Park, OH: North American Society; 2019:43-55.
6. Crandall CJ, Aragaki A, Cauley JA, et al. Associations of menopausal vasomotor symptoms with fracture incidence. *J Clin Endocrinol Metab*. 2015;100(2):524-534.
7. Utian WH. Psychosocial and socioeconomic burden of vasomotor symptoms in menopause: a comprehensive review. Associations of menopausal vasomotor symptoms with fracture incidence. *Health Qual Life Outcomes*. 2005;3:47. doi.org/10.1186/1477-7572-3-47.
8. Sarrel P, Portman D, Lefebvre P. et al. Incremental direct and indirect costs of untreated vasomotor symptoms. *Menopause*. 2015;22(3):260-266.
9. Williams RE, Levine KB, Kalilani L, Lewis J, Clark RV. Menopause-specific questionnaire assessment in US population-based study shows negative impact on health-related quality of life. *Maturitas*. 2009;62:153-9.
10. English M, Stoykova B, Slota C, Doward L, Siddiqui E, Crawford R, et al. Qualitative study: burden of menopause-associated vasomotor symptoms (VMS) and validation of PROMIS sleep disturbance and sleep-related impairment measures for assessment of VMS impact on sleep. *J Patient Rep Outcomes*. 2021;5:37.
11. Savolainen-Peltonen H, Hautamaki H, Tuomikoski P, Ylikorkala O, Mikkola TS. Health-related quality of life in women with or without hot flashes: a randomized placebo-controlled trial with hormone therapy. *Menopause*. 2014;21:732-9.
12. Whiteley J, Wagner J, Bushmakin A, et al. Impact of the severity of vasomotor symptoms on health status, resource use, and productivity. *Menopause*. 2013;20(5):518-524.
13. Stuenkel CA, Davis SR, Anne Gompel, et al. Treatment of symptoms of the menopause: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab.* 2015;100(11):3975-4011.

14. ACOG Practice Bulletin No. 141. Management of menopausal symptoms. *Obstet Gynecol*. 2014;123(1):202-216.

15. Shifren JL, Gass MLS for NAMS. The North American Menopause Society Recommendations for Clinical Care of Midlife Women Working Group. NAMS Clinical Care Recommendations. https://www.menopause.org/publications/clinical-care-recommendations Accessed June 8, 2022.

16. Cagnacci A, Martina Venier M. The controversial history of hormone replacement therapy. *Medicina (Kaunas).* 2019;55(9): 602.

17. Sahni S, Lobo-Romero A, Smith T. Contemporary non-hormonal therapies for the management of vasomotor symptoms associated with menopause: A literature review. *touchREV Endocrinol*. 2021;17(2):133-137.

18. Krajewski-Hall SJ, Blackmore EM, McMinn JR, Rance NE. Estradiol alters body temperature regulation in the female mouse. *Temperature* (Austin, Tex). 2018;5:56-69.

19. Padilla SL, Johnson CW, Barker FD, Patterson MA, Palmiter RD. A neural circuit underlying the generation of hot flushes. *Cell Rep.* 2018;24:271-7.

20. 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;157:752-63.

21. 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. *Proc Natl Acad Sci U S A.* 2012;109:19846-51.

22. Jayasena CN, Comninos AN, Stefanopoulou E, Buckley A, Narayanaswamy S, Izzi-Engbeaya C, et al. Neurokinin B administration induces hot flushes in women. *Sci Rep*. 2015;5:8466.

23. Santoro N, Waldbaum A, Lederman S, Kroll R, Fraser GL, et al.. Effect of the neurokinin 3 receptor antagonist fezolinetant on patient-reported outcomes in postmenopausal women with vasomotor symptoms: results of a randomized, placebo-controlled, double-blind, dose-ranging study (VESTA). *Menopause*. 2020;27:1350-1356.

24. Lederman S, Shapiro CM M, Stute P, et al. SKYLIGHT 1™ Phase 3 study of fezolinetant for treatment of moderate-to-severe vasomotor symptoms associated with menopause. Oral presentation at the American College of Obstetricians and Gynecologists (ACOG) Annual Meeting. May 6-8, 2022. San Diego, California.

25. Johnson KA, Nappi RE, Neal-Perry G, et al. A Phase 3, randomized, placebo-controlled, 12-week, double-blind study, plus a non-controlled extension treatment period, to assess efficacy and safety of fezolinetant, a neurokinin-3 receptor antagonist, in women with moderate-to-severe vasomotor symptoms associated with menopause. Oral presentation at the North American Menopause Society (NAMS) Annual Meeting. September 24, 2021.

26. Astellas announces topline results from long-term Phase 3 safety study of fezolinetant which inform future regulatory filings for the treatment of vasomotor symptoms associated with menopause. March 07, 2022. https://www.astellas.com/us/news/6216.

27. Nappi R, Kroll R, Siddiqui E, et al. Global cross-sectional survey of women with vasomotor symptoms associated with menopause: prevalence and quality of life burden. *Menopause.* 2021;28(8):875-882.

28. DePree B, Houghton K, Shiozawa A, et al. Real-world treatment and resource utilization for menopausal symptoms in the United States. Poster presented at The North American Menopause Society Annual Meeting. September 22-25, 2021. Washington, DC.

29. Avis NE, Crawford SL, Greendale G, et al. Duration of menopausal vasomotor symptoms over the menopause transition. *JAMA Intern Med.* 2015;175(4):531-9.

June 21, 2022

HealthyWomen is pleased to have the opportunity to provide written comments to the Institute for Clinical and Economic Review (ICER) for its assessment of the comparative clinical effectiveness and value of therapies for the vasomotor symptoms (VMS) associated with menopause, a natural process of aging. HealthyWomen wants to ensure appropriate awareness of the impact VMS has on women and the clear need for more treatment options to help women through this critical time in their health journey than those that are currently available.

Founded in 1988, HealthyWomen is the nation's leading nonprofit women's health information source dedicated to educating and empowering women ages 35-64 to make informed decisions about their healthcare. Throughout the years, we have educated healthcare consumers and providers about advances in women's health, from the latest information on diseases and conditions to various milestones pertaining to access to care. We ensure that women have accurate, balanced, evidence-based information so they can participate in shared decision-making with their healthcare providers. We also educate our audience regarding innovations in research and science as well as changes in policy that affect women's access to treatment and care so that women are prepared to self-advocate for better health outcomes.

Experiencing VMS, including night sweats and hot flashes, is a normal occurence for women going through the stages of menopause. It is also a common medical complaint for 80% of both perimenopausal and postmenopausal women. VMS often happens without warning, starting with a sudden increase of heat throughout the body and subsequent sweating and overall discomfort from feeling very hot.

As you are aware from your Draft Scoping Document, VMS is triggered when neurons in the hypothalamus change because of hormonal shifts, like the reduction of estrogen, and can occur both during the day and night. They disrupt a woman's life, functionality and health, impacting sleep, social life, ability to work, concentration, mental health and overall quality of life.

There are some racial and ethnic differences with respect toVMS. Black women report VMS more frequently than Hispanic or white women; Asian women report at the lowest frequency. Black women's symptoms start earlier and last longer but, in, general the symptoms last around 7.4 years on average — though a third of women have them for a decade or longer.

While we know that VMS affects the majority of women of perimenopausal, menopausal and postmenopausal age, frequent and severe symptoms are associated with risk factors such as:

- Overweight or obesity
- Smoking
- Reduced physical activity
- Poor mental health (depression, anxiety, high stress)

Further, some studies have shown that VMS puts women at risk of additional illnesses such as cardiovascular disease. There is also a correlation between VMS frequency and severity and future chronic disease, such as memory or concentration issues or bone health. It is unfortunate that despite the prevalance and impact of VMS, the pathophysiology of them is unclear, though decline in estrogen during menopause clearly plays an important role.

Regardless of the high number of women experiencing VMS, interestingly, many women do not necessarily seek treatment or they choose not to because of the options available. Those who do seek medical help, especially those who have severe symptoms, are often directed to the various forms of menopausal hormone therapy (HT). However, while HT is currently viewed as the most effective option for relieving VMS, many women do not choose to take it. There are various reasons women choose not to do so from not wishing to take something hormonal to having concerns over potential side effects.

Throughout the ages, women have long sought other options to deal with VMS and other aspects of menopause. These efforts can start with eliminating foods from their diet (such as spicy foods, caffeine and alcohol), exercising, practicing yoga, undergoing acupuncture, and trying various herbal therapies, etc., but the results are generally inconclusive and show little significant benefit. While women will keep trying to figure out how to reduce their symptoms, it is clearly evident they want more options and those options need to be accessible and affordable.

HealthyWomen believes time has long since passed for there to be new treatment options to address such a common occurrence for midlife women as VMS during menopause. For those seeking treatment and even those currently under treatment, having an option of a non-hormonal therapy that is evidenced-based and clinically sound could be life-changing, especially if it's accessible and affordable for all women.

Thank you for the opportunity to comment on this important matter.

Sincerely,

Martha Nolan, J.D.

Senior Policy Advisor

Comments on ICER VMS in Menopause Document by Nanette Santoro, MD

1. There is a small proportion of women for whom hot flashes never go away and they are in need of a safe and effective long term treatment option. They will often 'time out' on hormone therapy and reach a point where risks begin to outweigh benefits or they will develop a health condition that is a contraindication to further hormone use. This proportion is variable in different estimates based on different studies. The WHI reported on hot flashes in women one year after stopping the hormone therapy arms of the study and observed that 5% of women over 70 still reported moderate to severe hot flashes (https://pubmed.ncbi.nlm.nih.gov/20505547/). A caveat to interpretation is that the WHI was less likely to recruit very symptomatic women and I suspect the true population number is higher than that.

2. Data from Rachel Williams' Menopause Epidemiology Study indicates that about 60% of women seek health care for menopausal symptoms, and most of that is driven by hot flashes (https://www.sciencedirect.com/science/article/abs/pii/S0378512207002666) so the proportion of women seeking treatment being listed as 20-30% seems low to me.

3. Hispanic women appeared to have a duration of hot flashes that was intermediate between African-American and Non-Hispanic White women in the Study of Womens Health Across the Nation. They did not appear to have a shorter duration similar to that reported by Chinese women in SWAN (https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2110996)

3. Need for a non hormonal alternative for hot flashes is also likely to increase as our knowledge of the genetics of breast and ovarian cancer improves, as many women who have undergone risk reducing surgery to prevent cancer are eligible for hormones, but many are afraid of them and this is a group that stands to benefit from an effective alternative.

Society for Women's Health Research

June 21, 2022

Submitted electronically to publiccomments@icer.org.

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Re: Draft Background and Scope: Fezolinetant for Moderate to Severe Vasomotor Symptoms Associated with Menopause

Dear Dr. Pearson:

The Society for Women's Health Research (SWHR) appreciates the opportunity to provide input to the Institute for Clinical and Economic Review (ICER) on its Draft Scoping Document outlining how it plans to conduct the clinical effectiveness and value assessment of fezolinetant for the vasomotor symptoms (VMS) associated with menopause.

SWHR, a more than 30-year-old national nonprofit organization based in Washington, D.C., is widely recognized as a thought leader in promoting research on biological sex differences in disease and eliminating imbalances in care for women through science, policy, and education.

Through this comment opportunity, SWHR will share a few key points for ICER's consideration. Chiefly, given that menopause exclusively affects women, it will be vital that this assessment take a female-centered approach that reflects this life stage's unique patient experience, including indirect burdens, availability of current and necessary treatment options, and quality of life.

The Burden of VMS Symptoms in Menopausal Women

Approximately 1.3 million women transition into menopause each year, at an average age of 51 in the United States.[1] Each woman's menopause experience is different. Some are likely to experience the transition to menopause with few symptoms, while others may have a variety of symptoms at differencing levels of severity and that last for different periods of time.

Among the most common symptoms associated with menopause is VMS, or hot flashes and night sweats, which are "episodes of profuse heat accompanied by sweating and flushing, experienced predominately around the head, neck, chest, and upper back."[2]

[1] Takahashi TA, Johnson KM. Menopause. Med Clin North Am. 2015 May;99(3):521–534.
[2] Thurston RC, Joffe H. Vasomotor symptoms and menopause: findings from the Study of Women's Health across the Nation. *Obstet Gynecol Clin North Am.* 2011;38(3):489-501. doi:10.1016/j.ogc.2011.05.006

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- **The majority of women (73%) are not treating their menopause symptoms**.[3] Despite the fact that VMS occur during the menopause transition for up to 80% of women in the United States, most are not treating those symptoms.

- **Women of different races and ethnicities may have different experiences with VMS.** The Study of Women's Health Across the Nation (SWAN) reported variations in how long VMS usually last across populations.[4] Time spans ranged from 4.8 years among Japanese women to 10.1 years for African American women. African American women also often report the highest incidence of hot flashes.[5] Research also indicates that Native American women may experience the worst perimenopausal hot flashes of all.

- **There are important quality of life considerations for women experiencing VMS**. Based on SWAN analyses, VMS have been strongly associated with reduced health-related quality-of-life, affecting outcomes including sleep, mood, and cognitive function, and the association was strongest in those with more frequent VMS. Notably, the association did not apply to menopause itself.

Key Considerations in Response to the Fezolinetant Assessment Draft Scoping Document

Menopause is a life stage that exclusively affects women—and one that can have implications for a woman's overall quality of life. Further, it is a highly individualized process; no one woman's symptoms and symptom severity are the same.

Currently, women have extremely limited treatment options for VMS. Those options are even more limited when it comes to non-hormonal therapies. Therefore, it is essential that women be provided with as much choice as possible when it comes to establishing a treatment plan. Given that fezolinetant would be a first-in-class, non-hormonal treatment option for menopause-related VMS, as ICER conducts this assessment, SWHR would encourage the Institute to keep in mind that additional choice alone could be a valuable outcome for a significant portion of this population.

Additionally, SWHR would raise the following points in response to items included in the Draft Scoping Document:

- **Outcomes**. Within the outcomes of interest listed in the Draft Scoping Document are "Other menopausal symptoms," including vaginal symptoms, urinary tract symptoms, sexual function, and "Other patient-reported outcomes," including mood changes. While SWHR appreciates that ICER is thinking about these symptoms—as they are all relevant outcomes in a woman's menopause journey—it has not been suggested that fezolinetant could be used to treat any of these symptoms. Fezolinetant is only being investigated for the treatment of moderate to severe VMS associated with menopause and its long-term safety, as reiterated early in the Draft Scoping Document. Measuring the drug's value against symptoms on

[3] . State of Menopause Survey. Bonafide. https://hellobonafide.com/pages/state-of-menopause Accessed 16 June 2022.
[4] . Avis NE, Crawford SL, Greendale G, et al. Duration of Menopausal Vasomotor Symptoms Over the Menopause Transition. JAMA Intern Med. 2015 Apr;175(4):531-539.
[5] Green R, Santoro N. Menopausal Symptoms and Ethnicity: The Study of Women's Health Across the Nation. Womens Health (Lond). 2009 Mar;5(2):127-133

which it does not claim to work could skew the assessment of the drug and take attention away from the drug's intended purpose.

- **Scope of Comparative Value Analyses**. SWHR is glad that key economic model inputs will include clinical probabilities, quality of life values, and health care costs along with productivity impacts and indirect costs, data permitting.

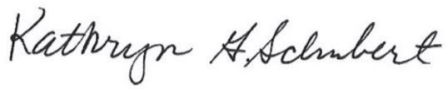
  However, SWHR would note that ICER includes, among the health outcomes against which it is evaluating interventions, quality-adjusted life years (QALYs) and life-years gained. SWHR would again remind ICER that menopause itself is a life stage, not a life-threatening disease or condition, and that fezolinetant is not meant to, nor does it claim to, add years to one's life; its goal is to reduce menopause-related VMS. While research has been conducted into menopause's effect on life expectancy (research shows that age-adjusted mortality is reduced 2% with each year of age at menopause[6]), that research shows life expectancy is related to the menopause stage and not to its symptoms.

- **Direct and Indirect Costs**. SWHR appreciates that ICER will aim to evaluate productivity impacts and other indirect costs of VMS. A 2015 study found that untreated VMS are associated with higher health care utilization, work loss, and cost burden.[7] With respect to productivity, one research study looking at presenteeism (attending work while sick) among peri and postmenopausal women revealed that among women experiencing VMS, women with severe and moderate symptoms had presenteeism rates of 24.28% and 14.3% versus 4.33% in women with mild symptoms. While VMS are not life-threatening, they are disruptive across multiple areas of a woman's life. Considering the patient experience and overall quality of life will be of the utmost importance.

Thank you for your consideration of the above comments. SWHR looks forward to engaging with ICER during this assessment and on future other topics affecting women's health.

If you have questions or need any additional information that would be helpful to inform ICER's value assessment, please contact me at kathryn@swhr.org or Lindsey Horan, Chief Advocacy Officer, at lindsey@swhr.org.

Sincerely,



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[6] Ossewaarde ME, Bots ML, Verbeek AL, Peeters PH, van der Graaf Y, Grobbee DE, van der Schouw YT. Age at menopause, cause-specific mortality and total life expectancy. Epidemiology. 2005 Jul;16(4):556-62. doi: 10.1097/01.ede.0000165392.35273.d4. PMID: 15951675.

[7] Sarrel P, Portman D, Lefebvre P, Lafeuille MH, Grittner AM, Fortier J, Gravel J, Duh MS, Aupperle PM. Incremental direct and indirect costs of untreated vasomotor symptoms. Menopause. 2015 Mar;22(3):260-6. doi: 10.1097/GME.0000000000000320. PMID: 25714236.