Single Technology Appraisal

Fezolinetant for treating moderate to severe vasomotor symptoms caused by menopause [ID5071]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Fezolinetant for treating moderate to severe vasomotor symptoms caused by menopause [ID5071]

Contents:

The following documents are made available to stakeholders:

1. **a. Comments on the Draft Guidance from Astellas Pharma Ltd**
   b. Addendum to company evidence submission

2. **Consultee and commentator comments on the Draft Guidance** from:
   a. British Menopause Society
   b. Society for Endocrinology

3. **Comments on the Draft Guidance received through the NICE website**

4. **External Assessment Group critique of company comments on the Draft Guidance**

5. **Addendum from Astellas Pharma Ltd – response to economic modelling requests following the second committee meeting**

6. **External Assessment Group critique of the company's response to the economic modelling requests**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

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Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Monday 28 April 2025. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced.
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	**Astellas Pharma Ltd**

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	Not applicable
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.

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1	**Executive summary** Astellas thanks NICE for the opportunity to comment on the Draft Guidance Document (DGD) and welcomes the appraisal committee's conclusion that: • There is a need for effective treatments to manage vasomotor symptoms (VMS) caused by menopause, both in perimenopause and menopause, and that treatment options are limited when hormone replacement therapy (HRT) is unsuitable, noting that non-hormonal treatments may be used when HRT is unsuitable (DGD Sections 3.1 and 3.2) • It would consider fezolinetant for people with moderate to severe VMS associated with the menopause, for whom HRT is unsuitable (DGD Section 3.3) • Non-pharmacological treatments and HRT were not relevant comparators for people with moderate to severe VMS associated with the menopause, for whom HRT is unsuitable (DGD Section 3.5) • Fezolinetant was clinically effective compared with placebo in reducing daily vasomotor symptom frequency and severity in the trial population (DGD Section 3.6) While Astellas is disappointed with the draft guidance not to recommend fezolinetant for treating moderate to severe VMS caused by menopause, particularly given the significant unmet need among patients for whom HRT is unsuitable, we acknowledge the key issues raised by the committee in the DGD regarding our original submission. **Astellas has now developed a new cost-effectiveness model**, specifically designed to address the key uncertainties identified in the draft guidance and to reflect outcomes that are meaningful to both patients and the NHS. This model was informed by discussions with NICE and the EAG (refer to response letters submitted in May and June 2025), consultations with UK clinical experts, and market research. Astellas believes that this approach provides a robust and reliable basis for evaluating fezolinetant and offers analyses that are well-suited to informing the committee's decision-making. To support a positive recommendation for fezolinetant as a non-hormonal treatment option for moderate to severe VMS in patients for whom HRT is unsuitable in the primary care setting, Astellas focuses its response on the key areas of uncertainty raised in the DGD:

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	• Place in therapy for fezolinetant (primary versus secondary care) (DGD Section 3.4) • Relevant comparators (DGD Section 3.5) • Uncertainty about the size of benefit demonstrated in the clinical effectiveness evidence for fezolinetant in the phase 3 trials and the handling of missing data (DGD Section 3.6) • Generalisability to the NHS population (DGD Section 3.7) • Indirect treatment comparisons (ITCs) with non-hormonal pharmacological treatments and direct incorporation of relative treatments effects from the ITCs into cost-effectiveness analyses (DGD Sections 3.8 and 3.11) • Incorporation of severity in the cost-effectiveness analysis (DGD Section 3.10) • Handling of placebo effect, reliance on natural history of VMS and baseline health state occupancy based on moderate to severe VMS frequency (DGD Section 3.11) • Health state utility values based on EQ-5D data (DGD Section 3.12) • Uncaptured costs of liver monitoring for fezolinetant (DGD Section 3.13) In most cases, the revised cost-effectiveness model aligns with the committee's preferred assumptions. Where deviations remain, Astellas has provided comprehensive justification in the relevant sections of this response. Details of the network meta-analysis (NMA) and the revised model are included in the addendum submitted alongside this response document, which updates and supersedes Section 2.10 and Section 3 of the original company submission. The revised base-case economic analysis following DGD includes the following: **Committee-preferred assumptions:** • Inclusion of non-hormonal pharmacological comparators (see DGD Response Comment 4) • Inclusion of relative treatment effects (see DGD Response Comment 7)

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	• Model structure based on improvement in moderate to severe VMS frequency from baseline (termed 'response') (see DGD Response Comments 5 and 9) • Inclusion of placebo effect, removal of highly uncertain natural history data and need for baseline moderate to severe VMS frequency distribution (see DGD Response Comment 9) • Health state utility values based on EQ-5D data from phase 3 RCTs (see DGD Response Comment 10) • Inclusion of liver monitoring costs for fezolinetant (see DGD Response Comment 11) **Original assumptions (i.e., no revisions made) supported by additional evidence:** • Fezolinetant is expected to be initiated and managed in primary care (see DGD Response Comment 3) • No restrictions to eligibility for fezolinetant based on baseline moderate to severe VMS frequency (see DGD Response Comment 6) • Defining response based solely on reduction in moderate to severe VMS frequency (see DGD Response Comment 8) **Summary of base-case results:** The revised base-case results (probabilistic) following DGD are presented in Table 1. The cost-effectiveness of fezolinetant for the treatment of moderate to severe vasomotor-predominant menopausal symptoms in patients unsuitable for HRT was evaluated against no active treatment and desvenlafaxine, the most relevant comparators. Base-case analyses demonstrated that fezolinetant is cost-effective, with probabilistic ICERs of £10,263 per QALY gained versus no active treatment and £18,053 per QALY gained versus desvenlafaxine – both below the £20,000 per QALY willingness-to-pay threshold. These results were consistent with deterministic results and showed minimal variation in sensitivity analyses. A scenario analysis comparing fezolinetant to paroxetine produced an ICER of £21,619 per QALY gained. Across all probabilistic scenarios, fezolinetant remained cost-effective.

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While comparisons with desvenlafaxine and paroxetine provide additional context, these analyses relied on assumptions that limit generalisability, particularly given that the evaluated SSRI and SNRI formulations or doses are not available in the UK and, as drug classes, are associated with variable efficacy and high discontinuation rates, limiting their applicability to UK clinical practice. As a result, no active treatment reflects the clinical reality for most patients unsuitable for HRT and serves as the most appropriate comparator.

Overall, the evidence demonstrates that fezolinetant represents a cost-effective treatment option for patients with moderate to severe vasomotor-predominant menopausal symptoms for whom HRT is unsuitable.

Table 1: ICERs for the company's revised base-case following DGD (probabilistic)

Treatment	Total			Incremental			ICER
	Costs	LYs	QALYs	Costs	LYs	QALYs	
Fezolinetant	£2,157.08	8.436	7.088	-	-	-	-
No Treatment	£1,664.31	8.436	7.040	£492.77	0.000	0.048	£10,263
Desvenlafaxine	£1,547.11	8.436	7.054	£609.97	0.000	0.034	£18,053

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years.

2

Clinical validation and market research

- A total of 19 UK external experts were consulted through 1:1 engagements and an additional 1,003 UK GPs were consulted via an online survey platform on topics including the DGD key issues and modelling-related questions

In response to the DGD, further clinical validation and market research was conducted by Astellas to validate inputs and assumptions. **A total of 19 UK external experts were consulted through 1:1 engagements and an additional 1,003 UK GPs were consulted via an online survey platform**:

- Three clinical experts during virtual one-hour individual meetings held in August and September 2025, focusing on clinical assumptions in the new cost-effectiveness model[1]

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	• Nine clinical experts during virtual two-hour individual meetings held in August and September 2025, including six GPs (five of whom were British Menopause Society [BMS]-accredited Menopause Specialists), one Menopause Nurse, one Consultant in Obstetrics and Gynaecology, and one BMS-accredited pharmacist[2] • Seven other experts with a professional interest in menopause and women's health during virtual 30- to 45-minute individual meetings held in August and September 2025 to discuss the service implications and patient considerations of introducing a novel treatment for VMS. These included three Menopause Specialist GPs (one of whom was ICB Clinical Lead for Women's Health), a Consultant Gynaecologist, a recently retired Consultant in Community Gynaecology and Reproductive Healthcare, the founder of Menopause Support, and the CEO of Wellbeing of Women[3] • A survey of 1,003 UK-based and regionally representative GPs conducted in August 2025 using the MedeConnect monthly Omnibus survey.[4] Questions were provided by Astellas and independently validated to ensure they were clear, unbiased and compliant with industry guidelines. Research was conducted in line with British Healthcare Business Intelligence Association (BHBIA) guidelines The focus of discussions was the key issues raised in the DGD, and included: • Place in therapy for fezolinetant (primary versus secondary care) • Clinical positioning with other non-hormonal treatments • Liver blood tests and monitoring • Generalisability of the fezolinetant trials to the NHS population • Response definition and timepoint of response assessment The following topics were also covered: • Stopping rules • Quality of life • Adverse events

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	• Resource use • VMS cessation Summary reports of individual interviews and full results of the Astellas-funded GP market research are provided in the reference pack for transparency and completeness. Clinical inputs for the different topics are summarised in the relevant sections of the response below when appropriate.
3	**Place in therapy for fezolinetant (primary versus secondary care) (DGD Section 3.4)** • Feedback from the extensive UK expert consultations was strongly in favour of fezolinetant being initiated and managed in NHS primary care • Results from the GP Omnibus survey show that GPs have high confidence to manage liver monitoring requirements in primary care • Restricting fezolinetant prescribing to secondary care would increase burden on the NHS, undermine the government's 10-Year Health Plan goal of shifting care from hospital to community, and perpetuate equity concerns • 76% of 1,003 UK GPs agreeing that fezolinetant should be prescribed in primary care • Fezolinetant would not significantly impact the provision of primary care services The committee suggested that offering fezolinetant in secondary care may be more appropriate; Astellas acknowledges that this conclusion was mainly driven by the liver monitoring requirements for fezolinetant. In response, Astellas has conducted multiple interviews and market research with UK clinical experts in menopause care to establish the appropriate place in therapy for fezolinetant. **Feedback from the extensive UK expert consultations was strongly in favour of fezolinetant being initiated and managed in NHS primary care**, in line with other treatments for moderate to severe VMS, if recommended.[2-4] Experts emphasised that implementation in primary care would not present a challenge given existing resources, as ordering liver function tests (LFTs) and monitoring liver function is already a routine, non-specialist activity in primary care, typically performed by a health care assistant or phlebotomist.[2-4] The findings from these consultations highlight two key themes described in detail below:

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1. Confidence and capability of primary care to manage liver monitoring requirements

2. Alignment of primary care initiation with NHS priorities and system capacity

Confidence and capability in primary care to manage liver monitoring requirements

Results from the GP Omnibus survey show that GPs have high confidence to manage liver monitoring requirements in primary care. GPs order, on average, 43 liver marker tests per month (Table 2).[4] Moreover, a shown in Table 3, the majority of GPs (Q2a: 90% and Q2b: 87%) would feel "moderately", "very", or "completely" confident in prescribing medicines requiring LFTs and in making clinical decisions based on test results, respectively.[4] This high level of confidence reflects the fact that LFT monitoring is a familiar and well-integrated aspect of routine care in primary practice, supported by clear clinical guidance and systems for test ordering and review.[2] Medicines such as atorvastatin, pioglitazone, and terbinafine already require ongoing liver function monitoring, and clinicians are accustomed to managing these treatments safely and efficiently.[2] Similarly, women prescribed testosterone for menopause typically receive regular blood tests and monitoring throughout treatment, reinforcing the established processes for liver monitoring in primary care.[2]

Unlike several of the non-hormonal treatment options sometimes prescribed for moderate to severe VMS in primary care,[2] fezolinetant does not require dose adjustment, such as titration upon initiation or tapering at treatment discontinuation,[5] which further supports its suitability for initiation in primary care, as complex dosing regimens are often a determining factor in whether a treatment can be prescribed by a GP or requires specialist oversight (see DGD Response Comment 4).

Table 2: Frequency of liver marker blood test orders in UK general practice according to GP Omnibus survey responses (n=1,003)

Q1 - Approximately how many patients do you order liver marker blood tests (liver function tests) for in a typical month, if any?

0	1 - 5	6 - 10	11 - 20	21 - 30	31 - 40	41 - 50	51+	Mean
1%	6%	16%	22%	16%	6%	12%	20%	43

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Table 3: Confidence in clinical decision-making relating to liver marker blood tests in UK general practice according to GP Omnibus survey responses (n=1,003)

Q2 - How confident or not are you to:

(a) Prescribe medicines which require liver marker blood tests (for example but not limited to atorvastatin or pioglitazone)?

Not at all confident	Slightly confident	Moderately confident	Very confident	Completely confident
1%	8%	41%	41%	8%

Footnote: Sum of "moderately", "very", or "completely" confident is 90%

(b) Make clinical decisions on continuation of treatment on the basis of the results of liver marker blood tests (for example but not limited to atorvastatin or pioglitazone)?

Not at all confident	Slightly confident	Moderately confident	Very confident	Completely confident
2%	12%	46%	35%	6%

Footnote: Sum of "moderately", "very", or "completely" confident is 87%

Alignment of primary care initiation with NHS priorities and system capacity

Astellas' position on the place in therapy of fezolinetant is aligned to NHS England's budget impact assessment for fezolinetant which estimated, based on clinical expert advice, that 90–95% of eligible patients would be treated by their local GP. **Restricting fezolinetant prescribing to secondary care would increase burden on the NHS and undermine the government's 10-Year Health Plan goal of shifting care from hospital to community**.

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	These views are supported by feedback from the BMS during the draft scope consultation, which noted that **limiting access to secondary care would perpetuate equity concerns**. Clinical experts and patient group representatives consulted by Astellas consistently emphasised the importance of menopause management in primary care, noting that only complex menopause cases should be referred to secondary care, and not people whose symptoms are limited to moderate to severe VMS.[3] In line with national ambitions to move care towards neighbourhood settings, experts also emphasised the important role of primary care Women's Health Hubs – now established in over 95% of ICS areas – in enabling NHS providers to manage menopause treatment in the most appropriate setting and deliver benefits to patients and the system.[3] In addition, clinical experts highlighted regional disparities in access to secondary care specialist menopause clinics and lengthy waiting times for appointments. GPs in the market research (Q3) estimated a mean UK waiting time of 7.8 months for a patient with moderate to severe VMS to be referred to secondary care, while clinical experts estimated between 9 and 12 months.[2, 4] Current pressures within the secondary care setting, including long waiting lists, are negatively impacting women, particularly those already facing barriers, such as more vulnerable women and those from disadvantaged communities, who have additional challenges in accessing care.[3] Therefore, restricting fezolinetant to secondary care would further exacerbate regional inequalities in access to menopause treatments.[3] Moreover, the Omnibus survey (Q9) strongly supports this with **76% of 1,003 UK GPs agreeing that fezolinetant should be prescribed in primary care**, with the majority (62%) also agreeing that it should be able to be prescribed in secondary care as well.[4] At the committee meeting, a clinical expert advised that the population for whom HRT would be unsuitable would be small. Based on target population estimates from the original budget impact assessment submission, it is expected that the relatively low number of patients eligible for and likely to be prescribed **fezolinetant would not significantly impact primary care services**. *Conclusion* Taken together, the evidence garnered by Astellas consistently supports positioning fezolinetant for use in NHS primary care. Astellas hopes that the extensive feedback provided removes any remaining concerns the committee may have about the appropriateness of initiating fezolinetant in primary care.
4	**Relevant comparators (DGD Section 3.5)** • Non-hormonal pharmacological treatments, in addition to no active treatment, are now included in the revised cost-effectiveness analysis

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- UK clinical experts highlighted limitations in non-hormonal options prescribed in primary care for treating moderate to severe VMS
- SSRIs and SNRIs are described by experts as offering variable efficacy, requiring titration, and being associated with unpleasant adverse effects that cannot be fully captured in the model
- Experts rarely use clonidine because of limited efficacy and poor tolerability, and raised concerns about gabapentin and pregabalin's adverse events and risks associated with their use
- As such, many patients in routine practice do not receive pharmacological therapy for moderate to severe VMS
- No active treatment is the most relevant comparator for estimating the cost-effectiveness of fezolinetant

The committee noted that because non-hormonal treatments are offered in primary care, they should therefore be included as a relevant comparator for fezolinetant if it is offered in primary care. In keeping with the intended place in therapy for fezolinetant in NHS primary care (see DGD Comment Response 3) **non-hormonal pharmacological treatments, in addition to no active treatment, are now included in the revised cost-effectiveness analysis**.

Astellas would like to stress that **UK clinical experts highlighted limitations across non-hormonal pharmacological options prescribed in primary care for treating moderate to severe VMS**.[1, 2]

Selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) were described as offering variable efficacy, requiring both up and down titration over months to minimise adverse effects or withdrawal symptoms, and being associated with high discontinuation rates due to adverse effects that cannot be fully captured in the model (e.g. sexual dysfunction, weight gain, sedation), with some side effects such as loss of libido and emotional dullness potentially persisting long term and not resolving after discontinuation.[1, 2] Experts also noted that many patients are reluctant to use antidepressants because of the stigma associated with a mental health diagnosis being recorded in their clinical notes.[2]

UK clinical experts rarely use clonidine because of limited efficacy and poor tolerability, including risk of rebound hypertension, although it is the only non-hormonal licensed for hot flushes in the UK.[2] Additionally, the **experts raised concerns about gabapentin and pregabalin's adverse events (including sedation, cognitive impairment and weight gain) and risks associated with their potential misuse and dependence**.[2, 6]

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	Given the stigma associated with antidepressants, the side-effect burden and contraindications across drug classes, the need for tapering and frequent monitoring, and high discontinuation rates, **many patients in routine practice do not receive pharmacological therapy for moderate to severe VMS.** No active treatment therefore represents the clinical reality of most patients seeking medical advice for moderate to severe VMS in women who are unsuitable for HRT. Furthermore, challenges in data availability limit the ability to incorporate these comparators adequately in the new cost-effectiveness model (See DGD Response Comment 7). Therefore, **no active treatment is the most relevant comparator for estimating the cost-effectiveness of fezolinetant**.
5	**Uncertainty about the size of benefit demonstrated in the clinical effectiveness evidence for fezolinetant in the phase 3 trials and the handling of missing data (DGD Section 3.6)** • The clinical effectiveness evidence informing the base-case cost-effectiveness analysis has now been based on a responder analysis of change from baseline in moderate to severe VMS frequency • In the base-case, response was defined by a reduction of at least 75% in moderate to severe VMS frequency from baseline because this was clinically meaningful, at low risk of bias, enables indirect comparisons with non-hormonal comparators and implicitly captures severity • A recently published study showed that a reduction of 6.2 VMS episodes per day at Week 12 represents a clinically meaningful improvement, thereby supporting the use of a 75% reduction threshold The committee raised concerns about the uncertainty in the size of benefit associated with fezolinetant, mainly driven by the handling of missing data in the analysis of primary and secondary endpoints of DAYLIGHT and pooled SKYLIGHT 1&2. In response to these concerns, and in alignment with the EAG's preference, **the clinical effectiveness evidence informing the base-case cost-effectiveness analysis has now been based on a responder analysis of change from baseline in moderate to severe VMS frequency**. Additionally, response based on the Patient Global Impressions Scale - Clinical for VMS (PGI-C VMS) endpoint was considered in a scenario analysis (see DGD Response Comment 8). **In the base-case, response was defined by a reduction of at least 75% in moderate to severe VMS frequency from baseline**. This definition was chosen for several reasons:

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- **Clinically meaningful**, since UK clinical experts and patient representatives consulted for the original submission considered change in frequency to be a more objective outcome than measures of severity and that a 75% threshold was clinically meaningful. **A recently published study investigating thresholds for clinically meaningful changes in moderate to severe VMS using patient reported outcome data from pooled SKYLIGHT 1&2 (n=1,022) showed that a reduction of 6.2 VMS episodes per day at Week 12 represents a clinically meaningful improvement, thereby supporting the use of a 75% reduction threshold as a substantial and clinically relevant level of benefit.**[7]

- **Low risk of bias**, since patients with missing data in the phase 3 fezolinetant trials were conservatively treated as non-responders.

- **Enables comparisons with external comparators** outside the fezolinetant phase 3 trials, as proportions of responders defined in this way were also available for other active non-hormonal treatments.

- **Implicitly captures impact on VMS severity**, PGI-C VMS explicitly captures improvements in both VMS frequency and severity and is strongly correlated with moderate to severe VMS frequency with both polyserial and Spearman's rank values of 0.5 at Week 12, exceeding the minimum correlation criterion of >0.37 and meeting the 0.5 cut-off noted by the EAG in its report.[7] This suggests that response according to reduction in VMS frequency also accounts for the impact on VMS severity.

The results of the responder analysis from the phase 3 fezolinetant trials, which is at low risk of bias, demonstrate that fezolinetant is superior to placebo (Table 4). Consistently across the three phase 3 fezolinetant trials and two timepoints, fezolinetant more than doubled the odds of experiencing a 75% reduction in moderate to severe VMS frequency.

Table 4: Responder analyses of change from baseline in frequency of moderate to severe VMS

Trial	Responders with ≥75% reduction	
	Fezolinetant 45mg	Placebo
DAYLIGHT Week 24	106/226 (47%)	67/226 (30%)
	OR (95% CI): 2.10 (1.43 to 3.10)	
DAYLIGHT Week 12	110/226 (49%)	66/226 (29%)
	OR (95% CI): 2.30 (1.56 to 3.40)	

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	SKYLIGHT 1 Week 12	60/174 (35%)	23/175 (13%)
		OR (95% CI): 3.48 (2.05 to 6.06)	
	SKYLIGHT 2 Week 12	66/167 (40%)	35/167 (21%)
		OR (95% CI): 2.48 (1.53 to 4.09)	

Abbreviations: CI: confidence interval; NR: not reported; OR: odds ratio.
Source: Reproduced from EAG Report and SKYLIGHT 1 CSR Table 9.3.3.6.1.

6

Generalisability to the NHS population (DGD Section 3.7)

- UK clinical opinion is that typically patients who seek treatment are those who experience frequent moderate to severe VMS rather than all women who experience VMS
- UK clinical experts considered the fezolinetant trial populations to be generalisable to NHS practice
- Women likely to be seeking treatment are those that are "really desperate and suffering, which would mean a significant number of hot flushes per day"
- "7–8 [hot flushes] per day would generally be the average number that [they] would consider for treatment as opposed to observation"
- Therefore, the clinical and cost-effectiveness results are considered generalisable to the NHS population eligible for fezolinetant

The committee raised concerns that the modelled population may not reflect the NHS population eligible for fezolinetant, as there is no requirement in clinical practice for women to be experiencing ≥7 moderate to severe VMS episodes per day in order to be eligible for treatment.

Feedback from **UK Clinical experts consulted for the DGD response is that typically patients who seek treatment are those who experience frequent moderate to severe VMS**, **rather than all women who experience VMS**. Therefore, **experts considered the fezolinetant trial populations to be generalisable to NHS practice**, noting that the inclusion criteria were appropriate and unlikely to overestimate treatment effects.[1]

While some clinicians assess symptom burden holistically rather than focusing solely on VMS frequency, it was noted that **women likely to be seeking treatment are those that are "really desperate and suffering, which would mean a significant number of hot flushes per day"**.[1] It

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	was also noted that **"7–8 [hot flushes] per day would generally be the average number that [they] would consider for treatment as opposed to observation"**.[1] These views are consistent with the clinical opinion sought by Astellas for the original submission, which indicated that the baseline characteristics of the fezolinetant trials were aligned with NHS clinical practice. Collectively, **these insights support the generalisability of the clinical and cost-effectiveness results to the NHS population eligible for fezolinetant**.
7	**NMAs with non-hormonal pharmacological treatments and direct incorporation of relative treatments effects from the NMAs into cost-effectiveness analysis (DGD Sections 3.8 and 3.11)** • Astellas has conducted a new NMA and included non-hormonal pharmacological treatments in the cost-effectiveness analysis • Desvenlafaxine was selected as the base-case non-hormonal comparator because it was the only non-hormonal comparator with suitable RCT data for the ≥75% VMS reduction endpoint and can be considered equivalent to venlafaxine (when adjusted for dose), which is commonly prescribed off-label in UK clinical practice • A model scenario compares fezolinetant to paroxetine 7.5 mg where efficacy is based on 50% reduction in moderate to severe VMS frequency at Week 12, as efficacy data were not available for the 75% threshold • Missing data in the response NMA were imputed using LOCF to align with comparator studies, minimise methodological heterogeneity and preserve the NMA assumption of homogeneity • The response and discontinuation NMAs were considered methodologically robust and consistent with best practice, providing suitable relative treatment effect estimates to inform the cost-effectiveness analysis As noted in the DGD Response Comment 4 above, **Astellas has conducted a new NMA and included non-hormonal pharmacological treatments in the cost-effectiveness analysis** (see addendum for details). *Selection of comparators was based on eligibility for inclusion and data availability for NMAs* In selecting the non-hormonal pharmacological treatments to include in the NMAs and cost-effectiveness analysis, the primary considerations were their availability and use in NHS clinical practice, as a specific agent or as a class, and whether treatments had RCT evidence on the proportion of

responders to support their efficacy versus placebo. **Desvenlafaxine was selected in the base-case economic analysis (and NMA) as the non-hormonal comparator treatment because**:

- **SNRIs are one of the most commonly prescribed (off-label) non-hormonal treatments for moderate to severe VMS**[1, 2]
- **Desvenlafaxine is the only non-hormonal comparator for which there is RCT evidence versus placebo on the proportion of patients who experienced at least 75% reduction in moderate to severe VMS frequency** (see Section 2.10 of addendum)
- **External evidence indicates that desvenlafaxine 100 mg is a suitable proxy for venlafaxine (SNRI)**, which is a related drug that is prescribed off-label in the UK for this indication but for which no relevant evidence was available, given their interchangeability when adjusted for dose.[8]

A model scenario compares fezolinetant to paroxetine 7.5 mg where efficacy is based on 50% reduction in moderate to severe VMS frequency at Week 12, as efficacy data were not available for the 75% threshold. Paroxetine is an SSRI sometimes prescribed off-label in the UK for moderate to severe VMS. However, it should be noted that paroxetine 7.5 mg is not a dose recommended by the BMS (10–20 mg), which limits the generalisability of the scenario results to the UK setting.[9] For this reason, the results from this scenario analysis should be interpreted with caution.

Other non-hormonal comparators were not included in the economic analysis as studies identified in the SLR were not considered eligible for inclusion in the NMA (see Section 2.10.5 of addendum as well as DGD Response Comment 4).

Handling of missing data in the NMA and economic model

In the response NMA, missing data were imputed using **last observation carried forward (LOCF), which was considered the most appropriate approach given all comparator studies also used LOCF to handle missing data, making it necessary to align with this approach in order to minimise methodological heterogeneity and preserve the NMA assumption of homogeneity**. In contrast, for the base-case economic analysis, patients with missing data for 75% reduction in moderate to severe VMS frequency in the fezolinetant trials were assumed to be non-responders when deriving the responder proportions, in line with the EAG's preference in the DGD. Therefore, while the odds ratio for fezolinetant versus desvenlafaxine from the NMA reflects an LOCF-based imputation (consistent with the comparator studies), it was applied to the fezolinetant response rates derived using non-responder imputation. Furthermore, LOCF was considered to be at low risk of bias because the binary response

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	outcome (≥75% reduction) is less sensitive to missingness than raw VMS frequency, and women who discontinued due to poor response would typically have been classified as non-responders before discontinuation, further limiting bias. Astellas considers **the response and discontinuation NMAs to be methodologically robust and consistent with best practice, providing suitable relative treatment effect estimates to inform the cost-effectiveness analysis**. The results of which demonstrate that patients receiving fezolinetant had higher odds of achieving a response and remaining on treatment compared with placebo or desvenlafaxine (as a proxy for venlafaxine). Full methodological details are included in Section 2.10 of the addendum.
8	**Incorporation of severity in the cost-effectiveness analysis (DGD Section 3.10)** • Feedback from three UK clinical experts and four patient representatives consulted for the original submission was consistent in identifying moderate to severe VMS frequency as the most relevant outcome for patients • Feedback from three UK clinical experts consulted for the DGD response supported the use of moderate to severe VMS frequency in defining response • Experts also noted that the PGI-C VMS aligns closely with how clinicians assess treatment benefit in practice. As such, improvement according to PGI-C VMS was used in a model scenario, showing minimal impact on the cost-effectiveness results (ICER: £11,140/QALY [% Δ from base case: +8.03%] versus no active treatment; £19,661 [+9.42%] versus desvenlafaxine) The committee noted that by not incorporating severity, the cost-effectiveness analysis may not fully capture the benefits of fezolinetant. Astellas acknowledges this concern but highlights inconsistency between the feedback received from UK clinical experts and patient representatives during the original submission, and that provided by patient experts at the first Appraisal Committee Meeting (ACM). **Feedback from three UK clinical experts and four patient representatives consulted for the original submission was consistent in identifying moderate to severe VMS frequency as the most relevant outcome for patients**. Frequency was considered more appropriate than severity because it is an objective measure, whereas severity is inherently subjective. Accordingly, moderate to severe VMS frequency was selected to inform the modelling. In contrast, patient experts at the first ACM suggested that frequency was less important than the severe impact of

	symptoms. These contrasting views serve to reflect the highly variable experience of each person experiencing moderate to severe VMS associated with menopause. As such, to further validate the response definition used in the revised cost-effectiveness analysis, Astellas sought additional feedback from UK clinical experts.[1] **These experts supported the use of moderate to severe VMS frequency**.[1] Furthermore, **the experts also noted that the PGI-C VMS aligns closely with how clinicians assess treatment benefit in practice**, as it incorporates patients' perceptions of their symptoms and the broader impact of treatment.[1] PGI-C VMS is a single-item global PRO, analogous to the Clinical Global Impression (CGI) scales[10], designed to provide a patient's assessment of change in VMS from the start of treatment. The PGI-C VMS asked the following question: ''Compared to the beginning of this study, how would you rate your hot flushes/night sweats now?'' Participants rated change using a seven-point Likert scale: ''much better,'' ''moderately better,'' ''a little better,'' ''no change,'' ''a little worse,'' ''moderately worse,'' and ''much worse.'' **Improvement according to PGI-C VMS was used in a model scenario, showing minimal impact on the results** (ICER: £11,140/QALY [% Δ from base case: +8.03%] versus no active treatment; £19,661 [+9.42%] versus desvenlafaxine) (see Section 3.10.11 of the addendum). One explanation for the minimal impact is the strong correlation that has been observed in a recent study between PGI-C VMS and moderate to severe VMS frequency using data from fezolinetant phase 3 trials.[7] This study reported that, in the pooled SKYLIGHT 1 and SKYLIGHT 2 trials, both polyserial and Spearman's rank values were 0.5 at Week 12, exceeding the minimum correlation criterion of >0.37 and meeting the 0.5 cut-off noted by the EAG in its report for this appraisal. Response according to PGI-C VMS was not used in the base-case economic analysis for three reasons. First, UK clinical experts confirmed that PGI-C VMS is not routinely used in clinical practice in the UK.[1] Second, comparator data for this outcome were unavailable outside the fezolinetant phase 3 trials; therefore, it was not possible to compare PGI-C VMS outcomes between fezolinetant and non-hormonal comparators, as it would increase uncertainty to assume that 75% response outcome generalises to PGI-C VMS response outcome in non-hormonal pharmacological comparators. Third, the use of the 75% response outcome aligns with the EAG's preference (discussed on a call with the EAG after the first ACM) given it is a more objective measure and had a lower likelihood of bias than PGI-C VMS which may be prone to recall bias, in addition to its subjectivity.

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9	**Baseline health state occupancy based on moderate to severe VMS frequency, reliance on natural history of VMS and handling of placebo effect (DGD Section 3.11)** • Astellas acknowledge the committee's concerns and has now developed a *de novo* cost-effectiveness model that is both robust and explicitly addresses these issues: misalignment between the baseline number of events, natural history estimates and approach to placebo adjustment • The model removes the requirement to define baseline distributions across frequency categories, thereby reducing structural assumptions • The model no longer requires natural history estimates of VMS derived through structured expert elicitation (SEE), relying solely on trial data • The model is also not heavily reliant on long-term maintenance of response utilities, as fezolinetant treatment duration is relatively short (median: 11 months, mean: 18 months) and over 50% patients are modelled to achieve VMS cessation within five years • The model accounts for the placebo effect associated with no active treatment by using the utility and response data collected in the phase 3 fezolinetant trials The committee noted that the misalignment between the baseline number of events, natural history estimates and approach to placebo adjustment were all linked and needed to be addressed in a coherent way. **Astellas acknowledge the committee's concerns and has now developed a *de novo* cost-effectiveness model that is both robust and explicitly addresses these three issues**. As detailed in Section 3.2.2 of the addendum, **the revised model removes the requirement to define baseline distributions across frequency categories, thereby reducing structural assumptions**. Instead, health states were defined by response, aligning with the binary responder outcomes of the fezolinetant phase 3 trials, which were judged to be at low risk of bias by the EAG. **The model no longer requires natural history estimates of VMS derived through structured expert elicitation (SEE), relying solely on trial data** and thereby avoiding the introduction of uncertainty via additional assumptions. The responder-based structure captures clinically meaningful changes in moderate to severe VMS frequency over time, while utilities remain constant within health states, given sustained symptom reduction observed through 52 weeks in the pooled SKYLIGHT 1&2 trials and feedback from a UK clinical expert that among 20–25 of their patients treated with fezolinetant for more than 18 months, no evidence of waning was observed.[1] **The model is not heavily reliant on the assumption that**

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	response utilities are maintained over the long term, as the median treatment duration for fezolinetant was approximately 11 months (mean: 18 months) and over 50% of patients were modelled to achieve VMS cessation by around 5 years. **The model also accounts for the placebo effect associated with no active treatment by using the utility and response data collected in the phase 3 fezolinetant trials**, and by assuming that patients who do not receive active treatment nonetheless experience some improvement after the treatment decision point, in line with the response rates and utilities observed for responders and non-responders. Collectively, these refinements ensure that the model is both fit-for-purpose and evidence-based, providing ICERs that are robust and reliable for the committee's decision-making.
10	**Health state utility values based on EQ-5D data (DGD Section 3.12)** • EQ-5D-5L data mapped to EQ-5D-3L was considered most appropriate to inform the cost-effectiveness analysis, in line with the NICE reference case • No adjustment to the EQ-5D-derived utilities was performed, in line with committee feedback The committee suggested that it may be useful to explore health-related quality of life for vasomotor symptoms using a disease-specific tool, such as the Menopause-Specific Quality of Life (MENQOL) measure, to estimate the utility values. Astellas thank the committee for their acknowledgement of the limitations of the EQ-5D data in this condition. However, given the additional uncertainty that would be introduced by using the MENQOL measure with a non-UK value set, it was ultimately decided that **EQ-5D-5L data mapped to EQ-5D-3L would be most appropriate to inform the cost-effectiveness analysis, in line with the NICE reference case**. Unlike the previous cost-effectiveness model, **no adjustment to the EQ-5D-derived utilities was performed, in line with committee feedback.**
11	**Uncaptured costs of liver monitoring for fezolinetant (DGD Section 3.13)** • Feedback from UK clinical experts and insights from the GP Omnibus survey was that fezolinetant would be initiated in primary care despite additional liver monitoring requirements

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	• Costs for additional liver monitoring and liver blood testing, and any subsequent costs in cases of treatment-related liver damage were included in the cost-effectiveness analysis The committee concluded that the modelled costs should include liver blood tests and appointments for liver monitoring and in line with the setting in which fezolinetant is prescribed and monitored. As noted in DGD Response Comment 3, **feedback from UK clinical experts and insights from the GP Omnibus survey was that fezolinetant would be initiated in primary care despite additional liver monitoring requirements**. As such, in the base-case economic analysis, it was assumed that treatment initiation and ongoing management for moderate to severe VMS would be conducted in primary care. Therefore, in line with these views, **costs for additional liver monitoring and liver blood testing, and any subsequent costs in cases of elevated liver enzymes were included in the base-case cost-effectiveness analysis** (described in more detail in the addendum Section 3.5.2).
12	**Conclusion of economic evidence** Given the key issues raised by the committee in the DGD, every effort has been made to develop a *de novo* cost-effectiveness model that is both robust and explicitly addresses key sources of uncertainty in the original submission model. As detailed in Section 3.2.2 of the addendum and in DGD Response Comment 1, the revised model directly incorporates treatment effects for fezolinetant versus relevant comparators (DGD Sections 3.5, 3.8, 3.11); defines health states by treatment response rather than VMS frequency categories, thereby reducing structural assumptions and aligning with binary responder outcomes of the phase 3 trials (DGD Section 3.10); applies a conservative approach to missing data, classifying patients with missing outcomes as non-responders (DGD Section 3.6); accounts for placebo response using trial-based data; no longer relies on natural history estimates of VMS from structured expert elicitation (DGD Section 3.11); and derives utilities directly from EQ-5D data collected in the fezolinetant phase 3 trials (DGD Section 3.11). New model assumptions on the timing of response assessment, the 75% VMS frequency threshold, and the continuation of partial responders were informed by NICE menopause guidelines, trial data, and UK clinical expert opinion, ensuring close alignment with the expected NHS pathway of care. Collectively, these refinements ensure that the model is both fit-for-purpose and evidence-based, providing ICERs that are robust and reliable for the committee's decision-making. The cost-effectiveness of fezolinetant for treatment of moderate to severe vasomotor-predominant menopausal symptoms in patients who are deemed unsuitable for HRT was evaluated versus no active treatment and desvenlafaxine. The base case probabilistic ICERs versus no active

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	treatment (£10,263 per QALY gained) and versus desvenlafaxine (£18,053 per QALY gained) were below the £20,000 per QALY WTP threshold and did not differ meaningfully from the corresponding deterministic ICER (£10,214 per QALY gained and £17,969 per QALY gained, respectively). The probabilistic sensitivity analysis indicated that the base-case results versus no active treatment or desvenlafaxine showed little variation with regard to incremental costs in each iteration. On the effectiveness side, all iterations fell within the northeast quadrant, and more than half the iterations fell below the £20,000 cost-effectiveness threshold, with a modest variation in incremental QALYs gained. A scenario analysis for paroxetine, which required additional assumptions to enable pairwise comparison, produced an ICER of £21,619 per QALY gained. Across all probabilistic scenario analyses, fezolinetant was consistently demonstrated to be cost-effective. Overall, the base case and scenario analyses demonstrate that fezolinetant is a cost-effective treatment for patients with moderate to severe vasomotor-predominant menopausal symptoms who are unsuitable for HRT. While results versus desvenlafaxine and paroxetine provide supportive evidence across relevant alternatives, as noted in Section 3.2.4.2 of the addendum, the analyses for SSRIs and SNRIs required several assumptions that limited generalisability of those results; for example, RCT evidence for SSRIs/SNRIs was available for treatments (desvenlafaxine, proxy for venlafaxine) or doses (paroxetine 7.5 mg) that are not available in the UK. These treatments are associated with variable efficacy, require both up and down titration over months to minimise adverse effects or withdrawal symptoms, and being associated with high discontinuation rates due to adverse effects. Consequently, many patients in routine practice do not receive non-hormonal pharmacological therapy for moderate to severe VMS. No active treatment therefore represents the clinical reality of most patients seeking medical advice for moderate to severe VMS who are unsuitable for HRT and thus the most reliable comparator for estimating the cost-effectiveness of fezolinetant.

Insert extra rows as needed

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- Do not include medical information about yourself or another person from which you or the person could be identified.
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- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

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Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

References

1. Astellas Data on File. Veoza 1:1 HCP Consultations - Meeting Minutes. 2025.
2. Astellas Data on File. MSL 1:1 Consultancy Activities with Menopause KEEs. 2025.
3. Astellas Data on File. 1:1 Menopause Clinical, Patient and System Experts Consultations - Meeting Minutes. 2025.
4. Astellas Data on File. GP Omnibus August 2025. 2025.
5. Electronic medicines compendium (emc). Veoza 45 mg film-coated tablets. Summary of Product Characteristics. Available at: https://www.medicines.org.uk/emc/product/15361/smpc#gref [Accessed: October 2025].
6. NHS England. Handling of gabapentin and pregabalin as Schedule 3 Controlled Drugs in health and justice commissioned services: letter from Kate Davies. London: NHS England; 2019 Available from: https://www.england.nhs.uk/publication/handling-of-gabapentin-and-pregabalin-as-schedule-3-controlled-drugs-in-health-and-justice-commissioned-services/ [Accessed October 2025].

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7. Morga A ZL, Valluri U, Siddiqui E, McLeod L, Bender RH. . Validation and application of thresholds to define meaningful change in vasomotor symptoms frequency: analysis of pooled SKYLIGHT 1 and 2 data. . Advances in Therapy. 2024;41:2845-2858.
8. Drugs & Therapy Bulletin: Factor in the criteria. In: Lagasse C.A, ed. UFHealth Shands Hospital 2013.
9. The British Menopause Society (BMS). BMS Consensus Statements. Non-hormonal-based treatments for menopausal symptoms. Available at: https://thebms.org.uk/publications/consensus-statements/non-hormonal-based-treatments-menopausal-symptoms/ [Accessed 30 January 2024].
10. Busner J, Targum SD. The clinical global impressions scale: applying a research tool in clinical practice. Psychiatry (Edgmont) 2007;4:28-37.

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Single technology appraisal

Fezolinetant for treating vasomotor symptoms associated with the menopause [ID5071]

Addendum to company evidence submission

October 2025

File name	Version	Contains confidential information	Date
ID5071_Fezolinetant_NICE_Addendum_1.0 [CON].docx	1.0	Yes	10th October 2025

Executive Summary

Astellas thanks NICE for the opportunity to comment on the Draft Guidance Document (DGD) and welcomes the appraisal committee's conclusion that:

- There is a need for effective treatments to manage vasomotor symptoms (VMS) caused by menopause, both in perimenopause and menopause, and that treatment options are limited when hormone replacement therapy (HRT) is unsuitable, noting that non-hormonal treatments may be used when HRT is unsuitable (DGD Sections 3.1 and 3.2)
- It would consider fezolinetant for people with moderate to severe VMS associated with the menopause, for whom HRT is unsuitable (DGD Section 3.3)
- Non-pharmacological treatments and HRT were not relevant comparators for people with moderate to severe VMS associated with the menopause, for whom HRT is unsuitable (DGD Section 3.5)
- Fezolinetant was clinically effective compared with placebo in reducing daily vasomotor symptom frequency and severity in the trial population (DGD Section 3.6)

While Astellas is disappointed with the draft guidance not to recommend fezolinetant for treating moderate to severe VMS caused by menopause, particularly given the significant unmet need among patients for whom HRT is unsuitable, we acknowledge the key issues raised by the committee in the DGD regarding our original submission.

Astellas has now developed a new cost-effectiveness model, specifically designed to address the key uncertainties identified in the draft guidance and to reflect outcomes that are meaningful to both patients and the NHS. This model was informed by discussions with NICE and the EAG (refer to response letters submitted in May and June 2025), consultations with UK clinical experts, and market research. Astellas believes that this approach provides a robust and reliable basis for evaluating fezolinetant and offers analyses that are well-suited to informing the committee's decision-making.

To support a positive recommendation for fezolinetant as a non-hormonal treatment option for moderate to severe VMS in patients for whom HRT is unsuitable in the primary care setting, Astellas focuses its response on the key areas of uncertainty raised in the DGD:

- Place in therapy for fezolinetant (primary versus secondary care) (DGD Section 3.4)
- Relevant comparators (DGD Section 3.5)
- Uncertainty about the size of benefit demonstrated in the clinical effectiveness evidence for fezolinetant in the phase 3 trials and the handling of missing data (DGD Section 3.6)
- Generalisability to the NHS population (DGD Section 3.7)
- Indirect treatment comparisons (ITCs) with non-hormonal pharmacological treatments and direct incorporation of relative treatments effects from the ITCs into cost-effectiveness analyses (DGD Sections 3.8 and 3.11)
- Incorporation of severity in the cost-effectiveness analysis (DGD Section 3.10)
- Handling of placebo effect, reliance on natural history of VMS and baseline health state occupancy based on moderate to severe VMS frequency (DGD Section 3.11)

- Health state utility values based on EQ-5D data (DGD Section 3.12)
- Uncaptured costs of liver monitoring for fezolinetant (DGD Section 3.13)

In most cases, the revised cost-effectiveness model aligns with the committee's preferred assumptions. Where deviations remain, Astellas has provided comprehensive justification in the relevant sections of the DGD response form. Details of the network meta-analysis (NMA) and the revised model are described below, updating and superseding Section 2.10 and Section 3 of the original company submission but that the rest of the original submission remains the same.

The revised base-case economic analysis following DGD includes the following:

Committee-preferred assumptions:

- Inclusion of non-hormonal pharmacological comparators (see DGD Response Comment 4)
- Inclusion of relative treatment effects (see DGD Response Comment 7)
- Model structure based on improvement in moderate to severe VMS frequency from baseline (termed 'response') (see DGD Response Comments 5 and 9)
- Inclusion of placebo effect, removal of highly uncertain natural history data and need for baseline moderate to severe VMS frequency distribution (see DGD Response Comment 9)
- Health state utility values based on EQ-5D data from phase 3 RCTs (see DGD Response Comment 10)
- Inclusion of liver monitoring costs for fezolinetant (see DGD Response Comment 11)

Original assumptions (i.e., no revisions made) supported by additional evidence:

- Fezolinetant is expected to be initiated and managed in primary care (see DGD Response Comment 3)
- No restrictions to eligibility for fezolinetant based on baseline moderate to severe VMS frequency (see DGD Response Comment 6)
- Defining response based solely on reduction in moderate to severe VMS frequency (see DGD Response Comment 8)

Summary of base-case results:

The cost-effectiveness of fezolinetant for treatment of moderate to severe vasomotor-predominant menopausal symptoms in patients who are deemed unsuitable for HRT was evaluated versus no active treatment and desvenlafaxine, the most relevant comparators (see DGD Response Comment 4). The base case probabilistic ICERs versus no active treatment (£10,263 per QALY gained) and versus desvenlafaxine (£18,053 per QALY gained) were below the £20,000 per QALY willingness-to-pay (WTP) threshold and did not differ meaningfully from the corresponding deterministic ICER (£10,313 per QALY gained and £17,969 per QALY gained, respectively). The probabilistic sensitivity analysis indicated that the base-case results versus no active treatment or desvenlafaxine showed little variation with regard to incremental costs in each iteration. On the effectiveness side, all iterations fell within the northeast quadrant, and most iterations fell below the £20,000 cost-effectiveness threshold, with a modest variation in incremental QALYs gained. A scenario analysis for paroxetine, which required additional assumptions to enable pairwise comparison, produced an ICER of £21,619 per QALY gained.

Across all probabilistic scenario analyses, fezolinetant was consistently demonstrated to be cost-effective.

Overall, the base case and scenario analyses demonstrate that fezolinetant is a cost-effective treatment for patients with moderate to severe vasomotor-predominant menopausal symptoms who are unsuitable for HRT. While results versus desvenlafaxine and paroxetine provide supportive evidence across relevant alternatives, as noted in Section 3.2.4.2, the analyses for SSRIs and SNRIs required several assumptions that limits generalisability of results; for example, RCT evidence for SSRIs/SNRIs was available for treatments (desvenlafaxine, proxy for venlafaxine) or doses (paroxetine 7.5 mg) that are not available in the UK. As a class, these treatments are associated with variable efficacy, require both up and down titration over months to minimise adverse effects or withdrawal symptoms, and being associated with high discontinuation rates due to adverse effects, limiting their applicability to UK clinical practice. Consequently, many patients in routine practice do not receive non-hormonal pharmacological therapy for moderate to severe VMS. No active treatment therefore represents the clinical reality of most patients seeking medical advice for moderate to severe VMS who are unsuitable for HRT and thus the most reliable comparator for estimating the cost-effectiveness of fezolinetant.

2 Clinical effectiveness

Summary of indirect and mixed treatment comparisons

- A new NMA was conducted in line with best practice to estimate the relative effect of fezolinetant versus non-hormonal pharmacological comparators in efficacy (response) and safety (treatment discontinuation) outcomes that could suitably inform inputs for the cost-effectiveness analysis
- Desvenlafaxine was selected in the base-case response NMA as the non-hormonal comparator because:
    - SNRIs are one of the most commonly prescribed (off-label) non-hormonal treatments for moderate to severe VMS[1, 2]
    - Desvenlafaxine is the only non-hormonal comparator for which there is RCT evidence versus placebo on the proportion of patients who experienced at least 75% reduction in moderate to severe VMS frequency
    - External evidence indicates that desvenlafaxine is a suitable proxy for venlafaxine (SNRI), which is a related drug that is prescribed off-label in the UK for this indication but for which no relevant evidence was available, given their interchangeability when adjusted for dose[3]
- As only one input estimate was required for the economic analysis, the estimate for desvenlafaxine 100 mg was selected over that for desvenlafaxine 50 mg (both clinically relevant doses of desvenlafaxine) on the grounds that desvenlafaxine 100 mg represented the more conservative estimate in comparison to fezolinetant from the relevant comparators. The treatment effect estimate for desvenlafaxine 100 mg was informed by substantially more data than the estimate for desvenlafaxine 50 mg (5 studies versus 1 study)
- Paroxetine 7.5 mg was included only in the discontinuation NMA, as data were not available for the 75% response outcome. This formulation is not available or licensed in the UK, and differs from BMS-recommended doses (10–20 mg)[4], limiting the relevance of the results to UK practice
- Results of the response NMA showed that fezolinetant increased the odds of achieving a ≥75% reduction in VMS frequency by approximately 20% versus desvenlafaxine 100 mg (odds ratio [OR]: 0.84, 95% credible interval [CrI]: 0.35–2.09]). Ranking (median and SUCRA) analyses indicated fezolinetant had a >86% probability of being the top-ranked treatment for achieving a clinically meaningful reduction in moderate to severe VMS frequency
- Fezolinetant demonstrated a lower likelihood of discontinuation compared with desvenlafaxine

100 mg or paroxetine 7.5 mg. Ranking analyses further supported the statistically significant difference between fezolinetant and desvenlafaxine 100 mg and paroxetine 7.5 mg, with fezolinetant demonstrating the lowest likelihood of discontinuation

2.10 Indirect and mixed treatment comparisons

2.10.1 Rationale

To address the committee's preference for the inclusion of non-hormonal pharmacological treatments in the NICE final scope in the decision problem of this appraisal (**DGD Section 3.5 and 3.8 of DGD**), estimates for relative treatment effects of non-hormonal pharmacological comparators of interest versus fezolinetant 45 mg in efficacy (response) and safety (treatment discontinuation) outcomes were required for use in the cost-effectiveness analysis (Section 3). In the absence of direct head-to-head data for the comparative efficacy and safety of fezolinetant versus relevant comparators, indirect treatment comparisons (ITCs) were conducted, specifically network meta-analyses (NMAs).

The NMA was designed in light of the new cost-effectiveness model structure (see Section 3.2.2 for details). In brief, in the new model, patients are stratified according to whether their symptoms improved sufficiently (termed 'responders') at a specific time point, and the probability that patients discontinue treatment depends on whether they responded or not. As such, the NMA focussed on the outcomes of response and treatment discontinuation.

2.10.2 Population

For both response and discontinuation NMAs, the population was aligned with the HRT-unsuitable subpopulation of SKYLIGHT 1&2 and with the patient population of DAYLIGHT; that is, women aged 40–65 years, born female, and seeking treatment or relief from moderate to severe VMS (average of ≥7 hot flashes/day) and falling into at least one category of:

- **HRT contraindicated:** people for whom HRT is contraindicated
- **HRT caution**: people for whom a medical risk assessment of a specific caution has concluded that the risk of HRT outweighs the benefit, for example in people with diabetes or heart disease
- **HRT stopper:** people who have previously taken HRT but can no longer take HRT
- **HRT averse:** people for whom HRT is indicated but do not wish to take HRT

2.10.3 Data sources

Data for Fezolinetant

Aggregate data for fezolinetant were derived from individual patient data (IPD) from the SKYLIGHT 1, SKYLIGHT 2 and DAYLIGHT trials, which included data for placebo, fezolinetant 30mg and fezolinetant 45mg.

Using the Analysis Data Model (ADaM) datasets from the SKYLIGHT 1&2 trials, patients were restricted to only those who were considered unsuitable for HRT (see Section 2.10.2). For each trial, "responder status" was defined based on the percentage reduction in VMS frequency from

baseline at Week 12. Specifically, patients who achieved at least a 50% reduction and those who achieved at least a 75% reduction were identified. Missing data were addressed through last observation carried forwards (LOCF) based on weekly derived response status. This approach was considered appropriate as it aligned with the approach used to derive response rates across all of the comparator trials of interest (see Section 2.10.10). Participants with missing LOCF-defined imputation (i.e., those with missing initial observations) were excluded from the dataset; response and discontinuation were then summarised based on randomised treatment.

Data for Comparators

To identify relevant clinical evidence for inclusion in the response and discontinuation NMAs, the original clinical systematic literature review (SLR) conducted on 25th June 2021, together with SLR updates on 14th June 2023 (SLR Update 1) and 9th April 2024 (SLR Update 2) were leveraged.

A total of 35 publications reporting on 14 unique studies were included, including SKYLIGHT 1&2 and DAYLIGHT. Response was included as an outcome in the original 2021 SLR but was not included as an outcome in the SLR updates. For the outcomes included in the SLR updates, no further relevant publications reporting on outcomes included were identified in the SLR updates beyond those identified in the original SLR (see Section 2.10.13 for further discussion). Full details on the methodology and the results of the SLR, including a full list of search dates, are presented in Appendix D of the original Company Submission.

2.10.4 Excluded studies

Studies were initially excluded from the clinical SLR in line with the eligibility criteria outlined in Appendix D.1.2 of the original Company Submission. Of the remaining studies, additional criteria were applied to exclude those not reporting on comparisons between comparators of interest (see Section 2.10.5) or between a comparator of interest and placebo as the sole comparator.

2.10.5 Interventions

The fezolinetant dosage of interest was fezolinetant 45 mg.

All non-hormonal comparators identified as part of the clinical SLR were considered of interest. These comprised desvenlafaxine (an SNRI) at doses of 50 mg, 100 mg, 150 mg and 200 mg, paroxetine (an SSRI) at a dose of 7.5 mg, gabapentin at a dose of 1800 mg and clonidine at a dose of 0.1 mg. Of these comparators, only clonidine is licensed in the UK for VMS associated with menopause. While licensing status is not a prerequisite for clinical use in the NHS, it is worth noting that desvenlafaxine in particular has not been licensed for *any* indication in the UK. However, it was considered as a proxy for venlafaxine (an SNRI). Venlafaxine is a related drug which has (non-VMS) indications in the UK and which is sometimes prescribed off-label for VMS, but for which no relevant evidence was available from the SLR (see Section 2.10.7).

The doses of paroxetine and desvenlafaxine available included those that might, UK indication notwithstanding, be considered clinically relevant (see Section 2.10.7). However, it should be noted that paroxetine 7.5 mg is not a formulation available in the UK, nor a dose recommended by the BMS, which refers instead to 10–20 mg for the management of VMS.[4] This may limit the generalisability of results to the UK setting.[4] The only doses of gabapentin for which a relevant study was identified in the SLR (BREEZE 1–3), however, were substantially higher than the

recommended dose and dosing schedule by the BMS in the UK (300 mg three times a day) (Table 1).[5] [4] Given this, gabapentin was not considered further as a comparator of interest in this analysis. Final selection of comparators for primary analyses was constrained by data availability for endpoints of interest, described in Section 2.10.7.

Table 1. Details of gabapentin dosage and administration for available studies

Study	Treatment Arm 1		Treatment Arm 2		Control Arm
	Treatment	Dosing Schedule	Treatment	Dosing Schedule	
BREEZE 1	Gabapentin extended-release (G-ER) 1200 mg	G-ER 1200 mg QD (given as two 600-mg tablets)	Gabapentin extended-release (G-ER) 1800 mg	G-ER 1800 mg QD (given as one 600-mg tablet in the morning and two 600-mg tablets in the evening)	Placebo
BREEZE 2	Gabapentin extended release 1200 mg	Two 600 mg tablets QD	Gabapentin extended release 1800 mg	One 600 mg tablet in the morning and two 600 mg tablets in the evening	Placebo
BREEZE 3	Gastroretentive gabapentin	1800 mg QD (1200 mg PM; 600 mg AM). Titration (AM/PM) occurred on days 1 to 3 (0 mg/600 mg), days 4 to 6 (0 mg/1,200 mg), and day 7 (600 mg/1,200 mg)	NR	NR	Placebo

Abbreviations: G-ER: gabapentin extended-release; QD: Once a day; NR: not reported.

2.10.6 Timepoint and endpoints

Endpoints and timepoints were as described below.

Timepoint

The Week 12 timepoint was selected on the basis that 1) this is the recommended timepoint for assessing efficacy and tolerability in clinical practice, as noted in the menopause guideline (NG23);[6] 2) that it was also the timepoint with the most consistent data availability (see section 2.10.8); and 3) was supported by clinical opinion from three UK clinical experts, who all indicated that treatment response would typically be assessed at Week 12 at which point the decision to continue or stop treatment would be made.[1]

Endpoint: Response

Response defined on the basis of percentage reduction in the frequency of moderate to severe VMS was selected in preference to the Patient Global Impressions Scale - Clinical for VMS (PGI-C VMS) for three reasons. First, UK clinical experts confirmed that PGI-C VMS is not routinely

used in clinical practice in the UK.[1] Second, response according to reduction in VMS frequency from baseline was reported for comparators, but not according to PGI-C VMS. Third, while PGI-C VMS explicitly captures perceptions of *VMS severity* and the benefits of treatment more holistically (as noted in DGD Response Comment 8), a strong correlation has been observed in a recent study between PGI-C VMS and moderate to severe VMS frequency.[7] This study reported that, in the pooled SKYLIGHT 1 and SKYLIGHT 2 trials, both polyserial and Spearman's rank values were 0.5 at Week 12, exceeding the minimum correlation criterion of >0.37 and meeting the 0.5 cut-off noted by the EAG in its report.[7] Therefore, this evidence suggests that response according to reduction in the frequency of moderate to severe VMS sufficiently reflects improvements in both VMS frequency and severity.

For the NMA, data were extracted using two response definitions (50% and 75% reduction in moderate to severe VMS frequency) at Week 12 to align with the available definitions and timepoints reported in the identified literature.

The 75% response threshold was prioritised over the 50% threshold for use in the economic analysis. This selection was informed by UK clinical expert opinion, which indicated that a ≥75% reduction from baseline represents a clinically meaningful improvement.[8] During the post-submission stage, the EAG also supported this threshold during a call after the first appraisal committee meeting, considering it to be the most appropriate for capturing meaningful differences in clinical benefit. Furthermore, a recent study investigating thresholds for clinically meaningful changes in moderate to severe VMS established that a reduction of 6.2 VMS episodes per day at Week 12 constitutes a clinically meaningful improvement for patients.[7] The baseline VMS frequency in this study was 11.02 episodes per day (standard deviation: 5.30). Consequently, a 50% reduction equates to approximately 5.5 fewer episodes, which does not reach the established meaningful threshold.[7] In contrast, a 75% reduction exceeds this threshold, indicating a more substantial and clinically relevant improvement. While the study primarily used PGI-C VMS scores to define meaningful benefits, it also demonstrated a strong correlation between these scores and reductions in moderate to severe VMS frequency.[7] Taken together, the above considerations support the case for applying the 75% response criterion rather than the 50% threshold in the economic analysis.

In line with the EAG's preference, the response-based analysis was used to inform efficacy inputs in the economic model. This approach enabled conservative assumptions to be made for those with missing data through non-responder imputation, which the EAG judged as carrying a low risk of bias.

Endpoint: Discontinuation

For the NMA of treatment discontinuation, the endpoint of interest was all-cause treatment discontinuation, assessed at Week 12. Treatment discontinuation was measured as the proportion of patients who discontinued treatment for any reason at this timepoint. Week 12 was selected to align with the response assessment timepoint in the fezolinetant trials and because it was the most consistently reported timepoint across comparator studies. Time-to-event analyses (e.g., hazard ratios for time to treatment discontinuation) were not feasible, as this outcome was not reported for most comparators.

2.10.7 *Feasibility assessment*

Trials included in the response and discontinuation NMAs were assessed for feasibility to evaluate the similarity of patient populations, which involved examining characteristics identified as treatment effect modifiers (TEMs), as determined through a review of subgroup results from the SKYLIGHT and DAYLIGHT studies, published literature, and internal clinical opinion from the Company. Additionally, heterogeneity was explored by reviewing outcome definitions and outcomes observed in placebo arms, to assess the plausibility of the transitivity assumption.

A 2022 feasibility assessment (FA) concluded that the comparison of all desvenlafaxine and paroxetine studies with the full (HRT-suitable and HRT-unsuitable) population of SKYLIGHT 1 and SKYLIGHT 2 did not violate the assumptions of NMA. An NMA (2022) in this population was conducted on this basis.[9] Subsequently, an FA update in 2023, focussing on the HRT-unsuitable subpopulation, determined that it was appropriate to compare the desvenlafaxine and paroxetine studies and the SKYLIGHT 1 and SKYLIGHT 2 HRT-unsuitable subpopulation and the DAYLIGHT population.[10] This FA noted some variation in racial/ethnic composition between trial populations but ultimately considered this insufficient to warrant exclusions of individual studies.[10] Additionally, HRT suitability was not considered a treatment effect modifier based on subgroup results from SKYLIGHT trials (see Table 26 and Table 38 of the original submission).[10] Further details of the 2022 and 2023 FAs are provided in the reference pack. On the basis of this 2023 FA, an additional NMA (2023) was conducted.[11] As all studies included in the present NMAs are a subset of those studies included in the aforementioned FA and/or FA update (Table 2), where analyses were deemed feasible, it was considered appropriate to conduct analyses based on this subset. A full list of included studies, treatment arms and data is provided in Table 4 and Table 5.

Table 2. List of studies included in the present analysis and their inclusion in the original NMA and/or NMA update*

Study included in present analysis[5]	Intervention(s)	Analysis Inclusion		
		Present Analysis	Original 2022 NMA[8]	2023 NMA Update[9]
Archer, 2009a	Desvenlafaxine 100 mg QD Desvenlafaxine 150 mg QD Placebo	Y	Y	Y
Archer, 2009b	Desvenlafaxine 100 mg QD Desvenlafaxine 150 mg QD Placebo	Y	Y	Y
Bouchard, 2012	Desvenlafaxine 100 mg QD Placebo	Y	Y	Y
Pinkerton, 2013a	Desvenlafaxine 100 mg QD Placebo	Y	Y	Y[1]
Pinkerton, 2013b	Desvenlafaxine 100 mg QD Placebo	Y	Y	Y[1]
Simon, 2013	Paroxetine 7.5 mg QD Placebo	Y	Y	Y
Speroff, 2008	Desvenlafaxine 50 mg QD Desvenlafaxine 100 mg QD Desvenlafaxine 150 mg QD	Y	Y	Y

	Desvenlafaxine 200 mg QD Placebo			
SKYLIGHT 1&2 HRT-unsuitable subpopulation + DAYLIGHT	Fezolinetant 45 mg Placebo	Y	-	Y
Archer, 2003	E2 0.75mg (gel) E2 1.5mg (gel) Placebo	N[2]	Y	N[2]
Archer, 2014	E2 0.3mg (oral) Drospirenone 0.5mg/E2 0.5mg (oral) Placebo	N[2]	Y	N[2]
Bachmann, 2007	E2/Levonorgestrel 0.023/0.0075mg (TDS patch) E2 0.014mg (TDS patch) Placebo	N[2]	Y	N[2]
Buster, 2008	E2 3.06mg (TDS spray) E2 4.59mg (TDS spray) E2 1.53mg (TDS spray) Placebo	N[2]	Y	N[2]
Good, 1999	CEE 0.625 mg (oral) CEE 1.25mg (oral) E2 0.05mg (oral) E2 0.1mg (oral)	N[2]	Y	N[2]
Kaunitz, 2020	E2/P4 1/100mg (oral) E2/P4 0.5/100mg (oral) E2/P4 0.5/50mg (oral) E2/P4 0.25/50mg (oral) Placebo	N[2]	Y	N[2]
Landgren, 2005	Tibolone 0.625mg (oral) Tibolone 1.25mg (oral) Tibolone 2.5mg (oral) Tibolone 5mg (oral) Placebo	N[2]	Y	N[2]
Notelovitz, 2000	E2 1mg (oral) E2 0.5mg (oral) Placebo	N[2]	Y	N[2]
Pinkerton, 2009	Bazedoxifene/CEE 20/0.45mg (oral) Bazedoxifene/CEE 20/0.625mg (oral) Placebo	N[2]	Y	N[2]
Prior, 2012	Progesterone 300mg (oral) Placebo	N[2]	Y	N[2]
Rozenbaum, 2002	E2 0.15mg (intranasal spray)	N[2]	Y	N[2]

	E2 0.30mg (intranasal spray) Placebo			
Speroff, 2006	EA 0.45mg (oral) Placebo	N[2]	Y	N[2]
Stevenson, 2010	E2 0.5mg/dydrogesterone 2.5mg (oral) E2 1mg/dydrogesterone 5mg (oral) Placebo	N[2]	Y	N[2]
Utian, 2004	Synthetic conjugated oestrogen 0.3mg (oral) Synthetic conjugated oestrogen 0.625mg (oral) Synthetic conjugated oestrogen 1.25mg (oral) Placebo	N[2]	Y	N[2]
Utian, 2005	CEE 0.625mg (oral) E2 0.78 mg (oral) E2 1mg (oral)	N[2]	Y	N[2]
BREEZE 1	G-ER 1200 mg QD G-ER 1800 mg QD Placebo	N[6]	Y	Y
BREEZE 2	G-ER 1200 mg QD G-ER 1800 mg QD Placebo	N[6]	Y	Y
BREEZE 3	G-GR 1800 mg QD Placebo	N[6]	Y	Y
Sassarini 2012	Clonidine 0.1 mg QD Placebo	N[7]	N[7]	N[7]

Footnote: * Additional studies were included in the previous SLRs and FAs but were excluded from analyses on the basis of study, patient, or outcome reporting characteristics and were consequently not considered to be suitable for the present analysis. [1] As a secondary publication to Pinkerton 2012. [2] Comparator not relevant. [3] Timepoint not relevant. [4] Published after SLR; [5] All references are included in Appendix D of the original company submission; [6] Intervention dose used in trial is higher than used in clinical practice for VMS (BMS recommended dose[4]), but less than the maximum dose for a licensed indication in the UK. [7] Outcomes were not reported at timepoints of interest [8] following feasibility assessment in 2022; [9] following feasibility assessment in 2023.
Abbreviations: FA: feasibility assessment; SLR: systematic literature review.
Abbreviations: CEE: conjugated equine oestrogen; E2: estradiol or 17-beta estradiol; TDS: transdermal; P4: progesterone.

2.10.8 Data availability and comparator selection

Table 3 provides a summary of the availability of data for response and treatment discontinuations for fezolinetant and its relevant comparators at Week 12.

Table 3. Summary of data availability for fezolinetant and its relevant comparators for outcomes of interest at Week 12

Treatment/ comparator	Dose	Time point of interest	Response: Percentage reduction in moderate to severe VMS frequency:	Discontinuations:

			50%	75%	All-cause
Fezolinetant	45 mg	Week 12	✓	✓	✓
Desvenlafaxine (SNRI)	50 mg; 100 mg; 150 mg; 200 mg		✓	✓	✓
Paroxetine (SSRI)	7.5 mg		✓	×	✓

Abbreviations: SNRI: serotonin and norepinephrine reuptake inhibitors; SSRI: Selective serotonin reuptake inhibitor; VMS: vasomotor symptoms.

Response

Data for the selected response outcome (≥75% reduction in moderate to severe VMS frequency at Weeks 12) were only available for desvenlafaxine. Desvenlafaxine is the active metabolite, and a close analogue, of venlafaxine, a treatment licensed in the UK for which no data were identified by the SLR, and considered interchangeable with venlafaxine in practice (when adjusted for dose).[3] Specifically, NICE and other guidelines recommend the use of venlafaxine 75 mg for menopause, which has itself been clinically equated to a desvenlafaxine dose of 50–100 mg.[3] Consequently, to enable analysis of the selected response criterion desvenlafaxine 50 mg and 100 mg were selected as the most appropriate comparators.

Discontinuation

Data were available for both paroxetine and desvenlafaxine for treatment discontinuation at Week 12 and, to facilitate scenario analyses in the economic model, data for both comparators were included.

2.10.9 Networks and connectivity

The networks of studies included in each NMA are presented below in Figure 1 to Figure 4.

Base case

Paroxetine was not included as a comparator for the base case response NMA, as no data were available for the relevant response definition (75% response) at Week 12 (see Table 3). Consequently, this network included only placebo and desvenlafaxine as comparators to fezolinetant 45 mg.

Discontinuation data were available for both desvenlafaxine and paroxetine, so both comparators were included in the network for this endpoint, along with placebo.

Notably, under the recommendation to limit networks to include only relevant comparators, doses of desvenlafaxine other than 50 mg and 100 mg, which were identified as relevant comparators (Section 2.10.8), were not included in the base case networks.[12]

For both base case networks, all available studies could be connected in a network resulting in no exclusions on the basis of connectivity (Figure 1 and Figure 3).

Sensitivity analysis

All doses of desvenlafaxine for which data were available (50, 100, 150 and 250 mg) were included in networks for sensitivity analyses of both response and discontinuation. For both sensitivity networks, all available studies could be connected in a network resulting in no exclusions on the basis of connectivity (Figure 2 and Figure 4).

Figure 1. Network for the response NMA: base case (50–100 mg desvenlafaxine)

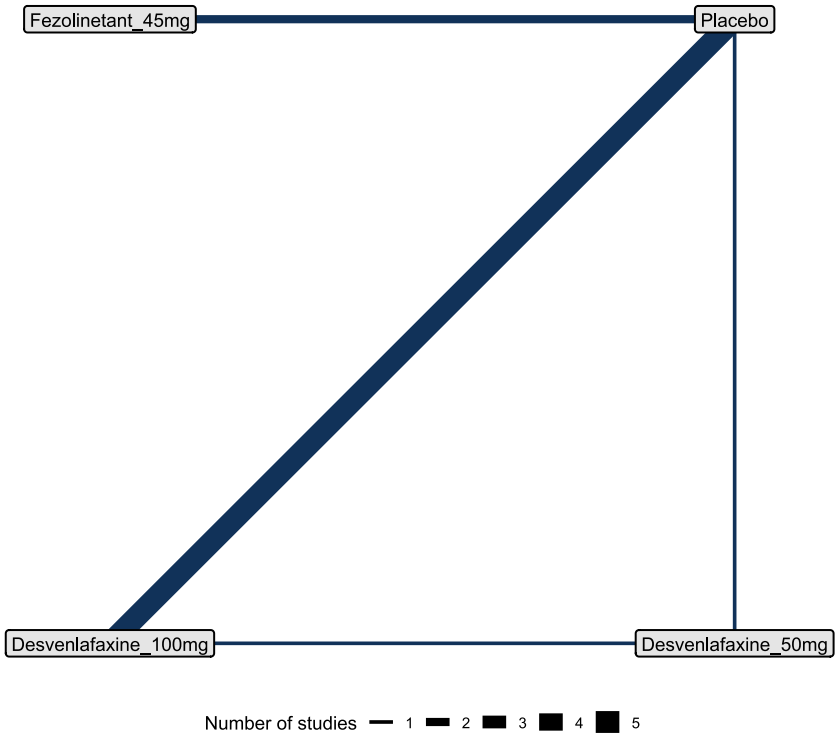


Figure 2. Network for the response NMA: sensitivity analysis (all doses of desvenlafaxine)

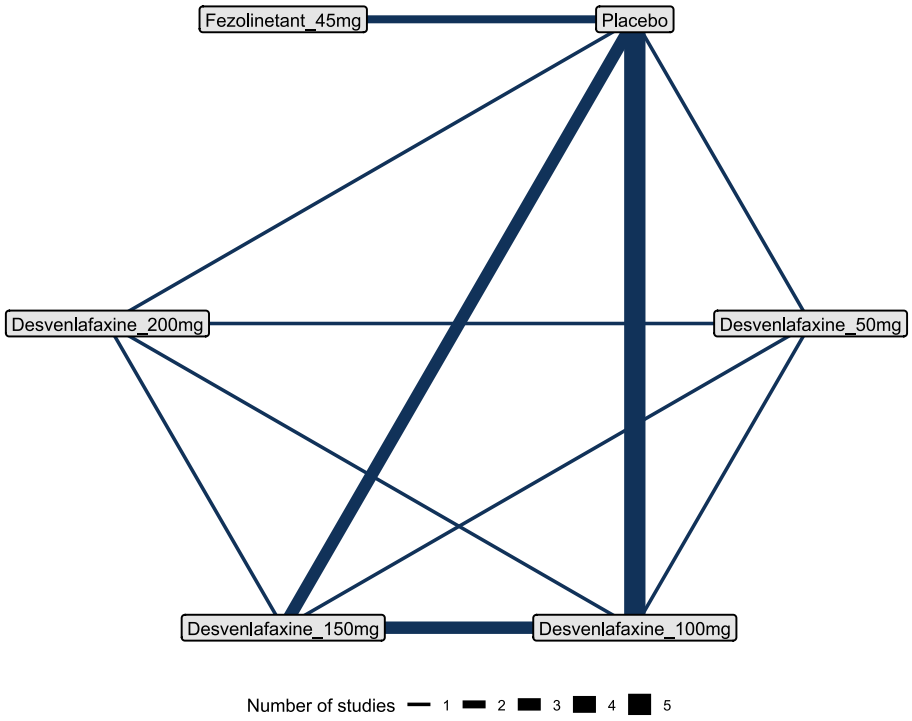


Figure 3. Network for NMA of discontinuation: base case (50–100 mg desvenlafaxine)

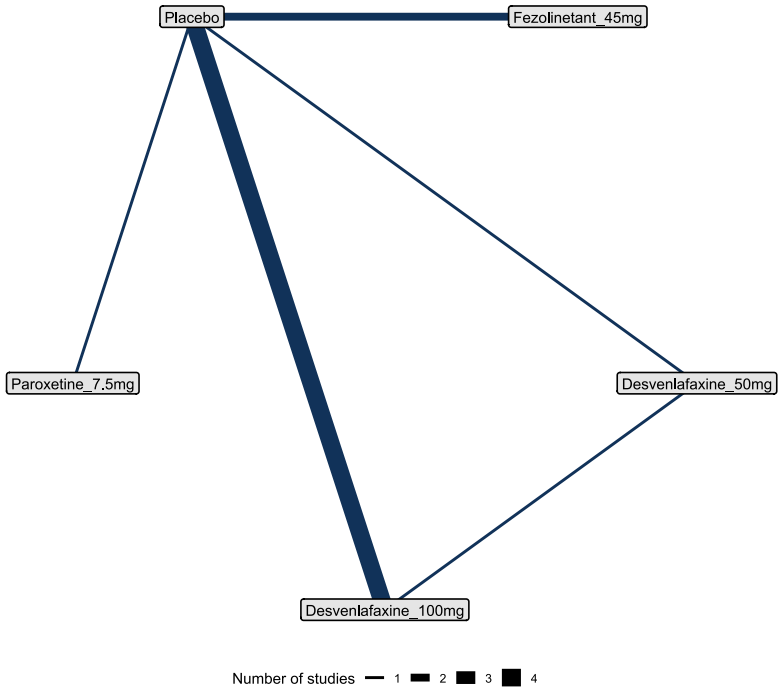
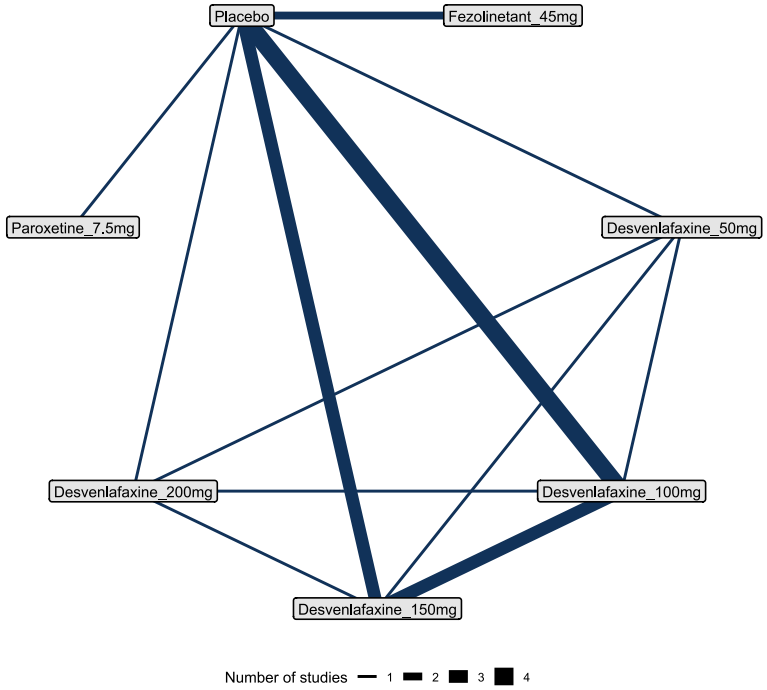


Figure 4. Network for NMA of discontinuation: sensitivity analysis (all doses of desvenlafaxine)



2.10.10 Data used in the NMAs

A summary of trials and input data used in the response and discontinuation NMAs are provided in Table 4 and Table 5, respectively. Input data were the number of patients (n) experiencing the event (response or discontinuation) and the total number of patients (N). For fezolinetant, IPD for SKYLIGHT 1 and SKYLIGHT 2 were pooled naively following the approach taken for previously published analyses of this population (Section 2.10.2) prior to generation of aggregate data.[13, 14] It is noteworthy that Pinkerton 2013a[15] reported a relatively high discontinuation percentage for both desvenlafaxine and placebo (Table 5), but did not report response data and so was not included in the NMA of response.

Table 4: Summary of the trials used to carry out the response NMA

Study	Treatment	Dose	n (%) 75% response	N	OR (95% CI) vs Placebo	Included in base case	Included in sensitivity analysis
Speroff 2008[16]	Desvenlafaxine	50 mg	47 (33.33)	141	1.43 (0.77–2.64)	✓	✓
	Desvenlafaxine	100 mg	73 (50.34)	145	2.89 (1.58–5.29)	✓	✓
	Desvenlafaxine	150 mg	56 (40.88)	137	1.97 (1.07–3.64)	x	✓
	Desvenlafaxine	200 mg	54 (45)	120	2.33 (1.25–4.35)	x	✓
	Placebo	-	20 (25.97)	77	NA	✓	✓

Pinkerton 2013b[17]	Desvenlafaxine	100 mg	76 (41.3)	184	3.16 (1.96–5.09)	✓	✓
	Placebo	-	33 (18.23)	181	NA	✓	✓
Archer 2009b[18]	Desvenlafaxine	100 mg	67 (41.36)	162	1.97 (1.24–3.10)	✓	✓
	Desvenlafaxine	150 mg	65 (45.14)	144	2.29 (1.44–3.66)	x	✓
	Placebo	-	47 (26.4)	178	NA	✓	✓
Archer 2009a[19]	Desvenlafaxine	100 mg	71 (49.65)	143	2.38 (1.47–3.84)	✓	✓
	Desvenlafaxine	150 mg	76 (53.15)	143	2.73 (1.69–4.42)	x	✓
	Placebo	-	44 (29.33)	150	NA	✓	✓
Bouchard 2012[20]	Desvenlafaxine	100 mg	55 (40.15)	137	1.09 (0.68–1.76)	✓	✓
	Placebo	-	57 (38)	150	NA	✓	✓
Pooled SKYLIGHT[a]	Fezolinetant	45 mg	133 (47.33)	281	2.90 (2.03–4.14)	✓	✓
	Placebo		70 (23.65)	296	NA	✓	✓
DAYLIGHT[a]	Fezolinetant	45 mg	124 (54.87)	226	2.25 (1.54–3.28)	✓	✓
	Placebo	-	79 (35.11)	225	1.43 (0.77–2.64)	✓	✓

Footnote: [a] The Company holds IPD on file
Abbreviations: CI, confidence interval; IPD: individual patient data; N: number of patients; NA, not applicable; NMA: network meta-analysis; VMS: Vasomotor symptoms.

Table 5: Summary of the trials used to carry out the discontinuation NMA

Study	Treatment	Dose	N (%) Discontinued	N	OR (95% CI) vs Placebo	Included in base case	Included in sensitivity analysis
Speroff 2008[16]	Desvenlafaxine	50 mg	24 (16.11)	149	1.29 (0.58–2.85)	✓	✓
	Desvenlafaxine	100 mg	34 (21.94)	155	1.88 (0.88–4.05)	✓	✓
	Desvenlafaxine	150 mg	48 (30.57)	157	2.95 (1.40–6.22)	x	✓
	Desvenlafaxine	200 mg	54 (35.76)	151	3.73 (1.77–7.84)	x	✓
	Placebo	-	10 (12.99)	77	NA	✓	✓
Pinkerton 2013b[17]	Desvenlafaxine	100 mg	37 (18.5)	200	1.21 (0.71–2.05)	✓	✓
	Placebo	-	30 (15.79)	190	NA	✓	✓
Pinkerton 2013a[15]	Desvenlafaxine	100 mg	397 (37.24)	1066	1.28 (1.07–1.53)	✓	✓
	Placebo	-	333 (31.65)	1052	NA	✓	✓
Archer 2009b[18]	Desvenlafaxine	100 mg	19 (12.67)	150	1.32 (0.64–2.70)	✓	✓
	Desvenlafaxine	150 mg	25 (16.56)	151	1.80 (0.91–3.57)	x	✓
	Placebo	-	15 (9.93)	151	NA	✓	✓
Archer 2009a[19]	Desvenlafaxine	100 mg	64 (35.16)	182	1.78 (1.12–2.82)	✓	✓
	Desvenlafaxine	150 mg	67 (37.43)	179	1.97 (1.24–3.11)	x	✓
	Placebo	-	42 (23.33)	180	NA	✓	✓
Pooled SKYLIGHT[a]	Fezolinetant	45 mg	17 (5.92)	287	0.60 (0.32–1.13)	✓	✓
	Placebo	-	28 (9.43)	297	NA	✓	✓
DAYLIGHT[a]	Fezolinetant	45 mg	17 (7.52)	226	0.42 (0.23–0.76)	✓	✓
	Placebo	-	37 (16.37)	226	NA	✓	✓

Simon 2013[21]	Paroxetine	7.5 mg	35 (11.78)	297	1.21 (0.72–2.03)	✓	✓
	Placebo	-	30 (9.93)	302	1.29 (0.58–2.85)	✓	✓

Footnote: [a] The Company holds IPD on file.
Abbreviations: CI, confidence interval; IPD: individual patient data; N: number of patients; NA, not applicable; NMA: network meta-analysis.

2.10.11 NMA methodology

Given the availability of data for multiple comparators from multiple studies in all networks (Table 4 and Table 5) and the established sufficient homogeneity of patient populations and outcome definitions to meet statistical assumptions (Section 2.10.7), NMA was the preferred methodology for evidence synthesis.

Base case

The base case NMAs aimed to estimate relative treatment effects comparing fezolinetant 45 mg with desvenlafaxine 50–100 mg for response, and paroxetine 7.5 mg and desvenlafaxine 50–100 mg for discontinuation. The cost-effectiveness model (CEM) required a single relative efficacy estimate for the comparison between desvenlafaxine and fezolinetant. Consequently, class effects models intended to produce a single estimate incorporating both desvenlafaxine 50 mg and 100 mg were explored in addition to simple network models. The following modelling structures were explored:

a. **Simple network analysis:** Each desvenlafaxine dose was treated as a separate treatment arm in each study to generate distinct relative effect estimates for each dose compared to fezolinetant.

b. **Class-effects analysis**: A class-level treatment effect term was introduced in a hierarchical structure, to model multiple desvenlafaxine doses simultaneously and generate a single relative effect estimate compared to fezolinetant. Exchangeable class-effects were assumed, on the basis that treatment effects of doses of the same drug were expected to be different but related. Common class effects were deemed inappropriate because it was not clinically expected for treatment effects of desvenlafaxine 50 and 100 mg to be equivalent for either response or treatment discontinuation.

Across both approaches, fixed and random effects models were evaluated to account for potential heterogeneity in the observed treatment effects across studies.

Sensitivity analysis

As sensitivity analyses, and given the selection of the simple network model, the simple network models were rerun for both endpoints, incorporating an expanded range of desvenlafaxine doses (50 mg, 100 mg, 150 mg, and 200 mg) as comparators (Figure 2 and Figure 4). The objective of these analyses was to evaluate the robustness of the estimated treatment effects for desvenlafaxine 50 mg and 100 mg versus fezolinetant 45 mg within an extended treatment network that includes all dose levels of desvenlafaxine.

NMA implementation

The NMAs were conducted within a Bayesian framework in line with key technical guidance documents (in particular, NICE Decision Support Unit [DSU] Technical Support Documents

[TSDs] 2 and 3). The more modern Stan environment was used for Bayesian modelling, instead of the older BUGS environment included in the NICE guidance.[12, 22] Analyses were performed using the software Stan version 2.37,[23] using the statistical software R version 4.4.3,[24] via the R package *multinma* (version 0.8.1).[25] Stan employs a Hamiltonian Monte Carlo (HMC) sampling algorithm that leverages the derivatives of the posterior density function to efficiently explore the parameter space. This approach typically requires fewer iterations to reach convergence than traditional Markov Chain Monte Carlo (MCMC) methods employed in other software packages, such as OpenBUGs.

As described in Section 2.10.10, the outcomes for response and discontinuation at Week 12 were expressed as the number of patients who experienced the event (n) out of the total number of patients (N) in each treatment group for each study. A binomial likelihood with a logit link was used to model the number of events observed in each treatment arm, as recommended in the NICE DSU TSD 2 (p. 19–20) for NMA of binomial outcomes at the same timepoint.[12] Specifically, let $\mathrm{r_{s,k}}$ denote the number of patients with the event of interest in study s, arm k, out of a total of $\mathrm{n_{s,k}}$ patients. The data were modelled as:

$$r_{s,k} \sim \text{Binomial}(p_{s,k}, n_{s,k})$$
$$logit(p_{s,k}) = \mu_s + \delta_{s,k}$$

where $\mathrm{p_{s,k}}$ is the probability of an event in arm k of study s, μ_s is the study-specific baseline log-odds, and $\mathrm{delta_{s,k}}$ is the relative treatment effect (log-odds ratio) for treatment k relative to the reference treatment within study s. The treatment in the reference arm was set to have $\mathrm{delta_{s,ref}} = 0$ within each study.

- **Fixed-Effect Simple Network Model**

Under a fixed-effect specification, the relative treatment effects were assumed to be the same across studies. The model was parameterised as:

$$\delta_{s,k} = d_{t[k]} - d_{t[\text{ref}]}$$

where $\mathrm{d_t}$ is the log-odds ratio for treatment t relative to a common reference treatment, typically with $\mathrm{d_1} = 0$.

- **Random-Effects Simple Network Model**

In the random-effects model, treatment effects were allowed to vary across studies. Specifically, the relative treatment effects were modelled as:

$$\delta_{\mathrm{s,k}} \sim \text{Normal}\left(\mathrm{d_{t[k]}} - \mathrm{d_{t[ref]}}, \tau^2\right)$$

where τ represents the between-study standard deviation, capturing heterogeneity in treatment effects.

- **Exchangeable Class Effects Model**

In the exchangeable class effects model, individual treatment effects were estimated but assumed to be drawn from a class-specific distribution. Let $\mathrm{c[t]}$ denote the class of treatment t, and θ_c the mean effect for class c. In this case, a single class was specified – desvenlafaxine 50–200 mg. The treatment effects were modelled as:

$$\mathrm{d_t} \sim \text{Normal}\left(\theta_{\mathrm{c[t]}}, \sigma^2\right)$$

where σ^2 represents the within-class variability of treatment effects.

The relative treatment effects were modelled as above for fixed- and random-effects.

Relative treatment effects were estimated with reference to fezolinetant 45 mg. Multinma-default vague priors were specified for all model parameters, as detailed below:

- μ ~ Normal (0,100)
- τ ~ HalfNormal (0, 25)
- θ_c ~ Normal (0,100)
- σ ~ HalfNormal (0, 25)

For each model, four independent chains were run. An initial burn-in period of 20,000 iterations per chain was employed to facilitate convergence diagnostics. These burn-in iterations were subsequently discarded. Posterior samples were then collected from a further 80,000 iterations per chain, with a thinning factor of 1. This sampling configuration was selected based on the automatic optimisation settings provided by the multinma package. Manual adjustments were made to the adapt_delta parameter (increased to 0.995), and the maximum tree depth (increased to N=15), to reduce the occurrence of divergent transitions and enhance the stability of model outputs.

Diagnostics, model selection and results interpretation

Convergence of the models was assessed through multiple approaches. Visual diagnostics included history trace plots, smoothed Kernel density plots of the posterior distributions, and prior versus posterior plots. Autocorrelation plots were also examined to evaluate the dependence between successive iterations of the Markov chains. Additionally, convergence was statistically assessed using the potential scale reduction factor ($\hat{R}$), with values close to 1 indicating adequate convergence.

Model fit statistics were analysed, including the Deviance Information Criterion (DIC), total residual deviance, and the effective number of parameters (pD). Model selection was based on the DIC, with a lower DIC indicating a more preferable model. Clinical significance was also taken into account during the selection process.

Relative treatment effects were extracted from the models versus the reference, which were median of posterior distributions. 95% credible intervals (CrIs) were produced, and the strength of association determined by whether or not the CrIs include the value of no effect (1 for ORs). Ranking parameters were derived for each treatment, including the probability of being the best, median rank, and the mean Surface Under the Cumulative RAnking curve (SUCRA) value.

2.10.12 Results

2.10.12.1. VMS response

All fitted models converged and exhibited appropriate diagnostic characteristics. The results of the NMAs comparing desvenlafaxine at doses of 50 mg and 100 mg with fezolinetant at 45 mg for VMS response are reported in Table 6. All NMA results are given as point estimate (95% CrI).

Base case analysis

The RE simple network and the RE class effect models had the best fit, with almost identical DIC of 29.64 and 29.56, respectively. The estimated desvenlafaxine class effect was characterised by substantial uncertainty in both the class estimate (RE model: 0.68 [0.01, 39.27]) and class effect standard deviation (sigma) (RE model: 3.48 [1.07, 2100.98]), driven by inclusion of only two treatments within the desvenlafaxine class, sparse data for desvenlafaxine 50 mg, and observed meaningful differences in the effects of desvenlafaxine 50 mg versus 100 mg.

As a result of the implausibly wide 95% CrI for the class effects model, which would introduce substantial instability into the CEM, and the absence of clear improvement in model fit versus the RE simple network model, the simple network was selected. According to the model, patients receiving desvenlafaxine 50 mg were estimated to have less than half the odds of achieving a 75% response at Week 12 compared with fezolinetant 45 mg, with credible intervals encompassing parity (OR: 0.46, 95% CrI: 0.14–1.69). For desvenlafaxine 100 mg, the odds were moderately (approximately 84% the odds) lower than fezolinetant 45 mg, with credible intervals encompassing parity (OR: 0.84, 95% CrI: 0.35–2.09). Overall, both desvenlafaxine doses were less likely than fezolinetant 45 mg to achieve the target response, but the credible intervals indicate substantial uncertainty (see Figure 5). Of note, the 95% CrI crossed the point of indifference across both desvenlafaxine doses, which was partly driven by the limited number of studies informing both comparators, especially 50 mg, and partly by the observed variation in relative response across included trials. Notwithstanding the uncertainty in the CrIs, the ranking statistics indicate that fezolinetant 45 mg had the highest probability of being the top-ranked treatment for achieving a 75% response at Week 12, with a SUCRA exceeding 0.86 (over 86%; Table 8). This indicates a very high likelihood that fezolinetant is the top-ranked treatment compared with desvenlafaxine 50 mg, desvenlafaxine 100 mg, and placebo, despite the wide CrIs around the point estimates. These results support the preference of UK clinical experts to use fezolinetant ahead of other non-hormonal treatments for treating moderate to severe vasomotor-predominant menopausal symptoms.[2]

As only one input estimate was required for the CEM, the estimate for desvenlafaxine 100 mg was selected over that for desvenlafaxine 50 mg on the grounds that:

- Desvenlafaxine 100 mg represented the more conservative estimate in comparison to fezolinetant from the relevant comparators.
- The treatment effect estimate for desvenlafaxine 100 mg was informed by substantially more data than the estimate for desvenlafaxine 50 mg (5 studies versus 1 study; Table 4).

Sensitivity analysis

Results of the sensitivity analysis, incorporating all dose levels of desvenlafaxine, were consistent with the primary analysis (Figure 6; Table 7), suggesting that the base case estimates were not sensitive to the exclusion of doses of desvenlafaxine greater than 100 mg.

Table 6. NMA model outputs for VMS response (fezolinetant 45mg reference): primary analysis

Analysis	Model Type	Class Effects	Relative treatment estimates OR (95% CrI). comparator vs. fezolinetant 45 mg	Other parameters; point estimate (95% CrI)	DIC	Favoured primary model	Favoured sensitivity model
Primary	Fixed effects	N	• Desvenlafaxine 50 mg: 0.44 (0.26 ,0.75) • Desvenlafaxine 100 mg: 0.82 (0.58 ,1.15) • Placebo: 0.39 (0.30 ,0.50)	NA	32.46		NA
Primary	Random effects	N	• Desvenlafaxine 50 mg: 0.46 (0.14, 1.69) • Desvenlafaxine 100 mg: 0.84 (0.35, 2.09) • Placebo: 0.39 (0.19 ,0.84)	Tau: 1.43 (1.05, 3.02)	29.64	✓	NA
Primary	Fixed effects	Y; Exchangeable	• Desvenlafaxine 50 or 100 mg: 0.63 (0.01, 44.88) • Placebo: 0.39 (0.30, 0.50)	Sigma: 3.92 (1.19, 2412.16)	32.55		NA
Primary	Random effects	Y; Exchangeable	• Desvenlafaxine 50 or 100 mg: 0.68 (0.01, 39.27) • Placebo: 0.39 (0.19, 0.82)	Tau: 1.43 (1.05, 2.90) Sigma: 3.48 (1.07, 2100.98)	29.56		NA

Abbreviations: CrI; credible interval; DIC: deviance information criterion; NA: not applicable.

Table 7. NMA model outputs for VMS response (fezolinetant 45 mg reference): sensitivity analyses

Analysis	Model Type	Class Effects	Relative treatment estimates OR (95% CrI). • comparator vs. fezolinetant 45 mg	Other parameters; point estimate (95% CrI)	DIC	Favoured primary model	Favoured sensitivity model
Sensitivity	Fixed effects	N	• Desvenlafaxine 50mg: 0.50 (0.30, 0.84) • Desvenlafaxine 100mg: 0.83 (0.59, 1.16) • Desvenlafaxine 150mg: 0.85 (0.58, 1.23) • Desvenlafaxine 200mg: 0.83 (0.49, 1.39) • Placebo: 0.39 (0.30, 0.50)	NA	39.29	NA	
Sensitivity	Random effects	N	• Desvenlafaxine 50mg: 0.52 (0.20, 1.40) • Desvenlafaxine 100mg: 0.84 (0.42, 1.73) • Desvenlafaxine 150mg: 0.86 (0.40, 1.86) • Desvenlafaxine 200mg: 0.85 (0.32, 2.30) • Placebo: 0.39 (0.22, 0.70)	Tau: 1.34 (1.04, 2.14)	36.57	NA	✓

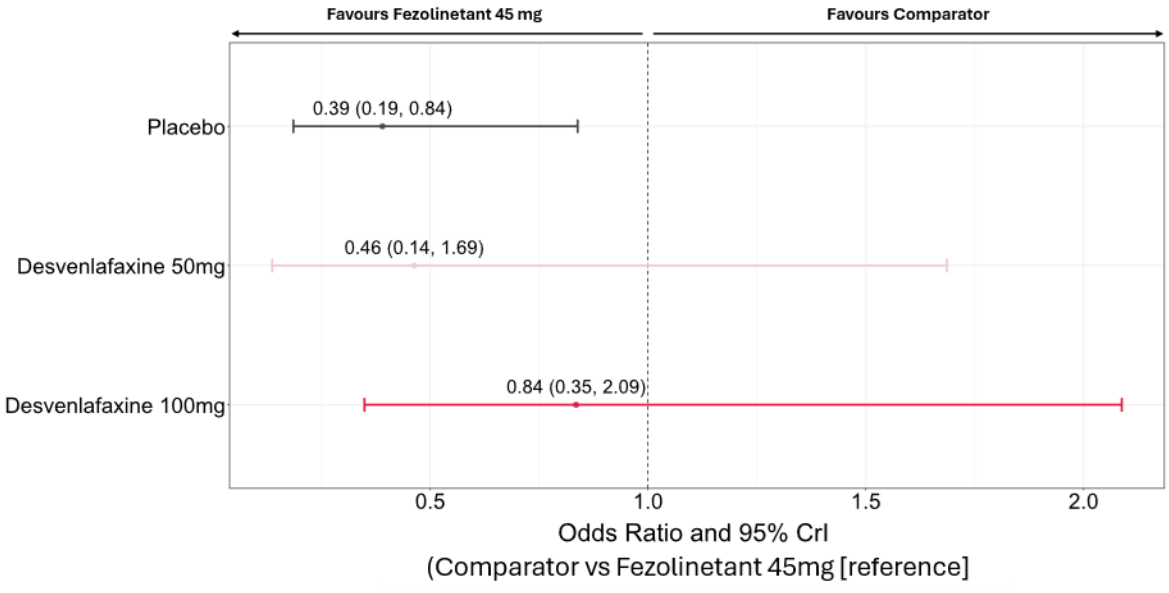
Abbreviations: CrI, credible interval; DIC, deviance information criterion; NA: not applicable.

Table 8. Ranking statistics from the selected model for response

Treatment	Median Rank (lower value is better)	SUCRA (higher is better)
Fezolinetant 45 mg	1	0.86762639
Desvenlafaxine 100 mg	2	0.73327083
Desvenlafaxine 50 mg	3	0.28114028
Placebo	4	0.1179625

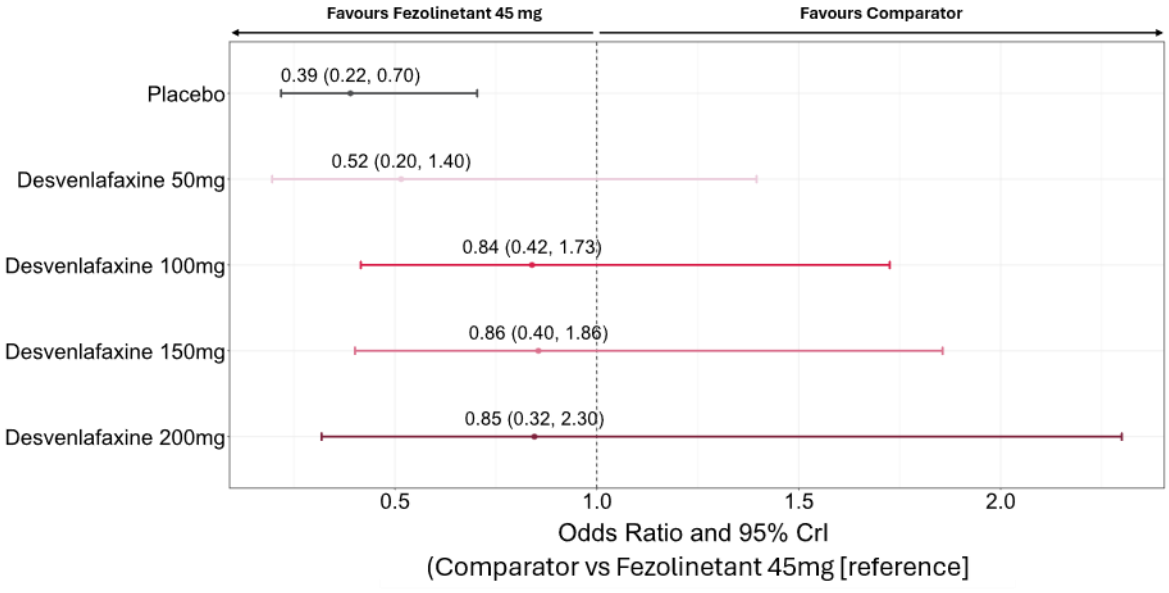
Abbreviations: SUCRA, surface under the cumulative ranking curve.

Figure 5. NMA Results for selected model: primary analysis of response (fezolinetant 45mg reference)



Footnote: results shown for standard random effects model, specified without class effects.

Figure 6. NMA Results for selected model: sensitivity analysis of response (fezolinetant 45mg reference)



Footnote: results shown for standard random effects model, specified without class effects.

2.10.12.2. Discontinuation

All fitted models converged and exhibited appropriate diagnostic characteristics. The results of the NMAs comparing paroxetine 7.5 mg and desvenlafaxine at doses of 50 mg and 100 mg with fezolinetant at 45 mg for discontinuations are reported in Table 9.

Base case analysis

The FE simple network and the FE class effect models had the best model fit, with almost identical DIC values. As with the NMA for response, as observed for the response outcome, the estimated desvenlafaxine class effect for discontinuation was associated with considerable uncertainty, primarily due to the inclusion of only two treatments within the desvenlafaxine class, sparse data for desvenlafaxine 50 mg, and notable differences between desvenlafaxine 50 mg and 100 mg.

As a result of the implausibly wide 95% CrI for the class effects model, which would introduce substantial instability into the CEM, and the absence of clear improvement in model fit versus the RE simple network model, the RE simple network model was selected

According to this model, patients receiving desvenlafaxine 50 mg, desvenlafaxine 100 mg, or paroxetine 7.5 mg were all more likely to discontinue treatment compared with fezolinetant 45 mg. For all three treatments, the CrI excluded parity despite wide CrIs, indicating that the differences were statistically robust. Among these, desvenlafaxine 100 mg showed the largest increase in the likelihood of discontinuation (Figure 7). The SUCRA rankings further supported the statistically significant difference between fezolinetant and all three comparator treatments, with fezolinetant demonstrating the lowest likelihood of discontinuation. These results support the preference of UK clinical experts to use fezolinetant ahead of other non-hormonal treatments for treating moderate to severe vasomotor-predominant menopausal symptoms.[2]

As only one desvenlafaxine input estimate was required for the CEM, the estimate for desvenlafaxine 100 mg was selected over that for desvenlafaxine 50 mg on the grounds that:

- The treatment effect estimate for desvenlafaxine 100 mg was informed by substantially more data than the estimate for desvenlafaxine 50 mg (5 studies versus 1 study; Table 5).
- Consistency with dosage selected for the analysis of 75% VMS response at Week 12 (see Section 2.10.12)

The results for paroxetine informed a scenario analysis within the economic model.

Sensitivity analysis

Results of the sensitivity analysis, incorporating all dose levels of desvenlafaxine, were consistent with the primary analysis (Figure 8; Table 10), suggesting that the base case estimates were not sensitive to the exclusion of doses of desvenlafaxine greater than 100 mg.

Table 9. NMA model outputs for discontinuation (fezolinetant 45mg reference): primary analyses

Analysis	Model Type	Class Effects	Relative treatment estimates OR (95% CrI). comparator vs. fezolinetant 45 mg	Other parameters; point estimate (95% CrI)	DIC	Favoured primary model	Favoured sensitivity model
Primary	Fixed effects	N	• Desvenlafaxine 50 mg: [redacted] • Desvenlafaxine 100 mg: [redacted] • Paroxetine 7.5 mg: [redacted] • Placebo: [redacted]	NA	[redacted]	✓	NA
Primary	Random effects	N	• Desvenlafaxine 50 mg: [redacted] • Desvenlafaxine 100 mg: [redacted] • Paroxetine 7.5 mg: [redacted] • Placebo: [redacted]	Tau: [redacted]	[redacted]		NA
Primary	Fixed effects	Y; Exchangeable	• Desvenlafaxine 50 or 100 mg: [redacted] • Paroxetine 7.5 mg: [redacted] • Placebo: [redacted]	Sigma: [redacted]	[redacted]		NA
Primary	Random effects	Y; Exchangeable	• Desvenlafaxine 50 or 100 mg: [redacted] • Paroxetine 7.5 mg: [redacted] • Placebo: [redacted]	Tau: [redacted] Sigma: [redacted]	[redacted]		NA

Abbreviations: CrI; credible interval; DIC: deviance information criterion; NA, not applicable.

Table 10. NMA model outputs for discontinuation (fezolinetant 45 mg reference): sensitivity analyses

Analysis	Model Type	Class Effects	Relative treatment estimates OR (95% CrI); comparator vs. fezolinetant 45 mg	Other parameters; point estimate (95% CrI)	DIC	Favoured primary model	Favoured sensitivity model
Sensitivity	Fixed effects	N	• Desvenlafaxine 50mg: [redacted] • Desvenlafaxine 100mg: [redacted] • Desvenlafaxine 150mg: [redacted] • Desvenlafaxine 200mg: [redacted] • Paroxetine 7.5 mg: [redacted] • Placebo: [redacted]	NA	[redacted]	NA	✓
Sensitivity	Random effects	N	• Desvenlafaxine 50mg: [redacted] • Desvenlafaxine 100mg: [redacted] • Desvenlafaxine 150mg: [redacted] • Desvenlafaxine 200mg: [redacted] • Paroxetine 7.5 mg: [redacted] • Placebo: [redacted]	Tau: [redacted]	[redacted]	NA	

Abbreviations: CrI, credible interval; DIC, deviance information criterion; NA: not applicable.

Table 11. Ranking statistics from the selected model for discontinuation

Treatment	Median Rank (higher number is better)	SUCRA (lower is better)
Fezolinetant 45 mg	[redacted]	[redacted]
Placebo	[redacted]	[redacted]
Desvenlafaxine 50 mg	[redacted]	[redacted]
Paroxetine 7.5 mg	[redacted]	[redacted]
Desvenlafaxine 100 mg	[redacted]	[redacted]

Abbreviations: SUCRA, surface under the cumulative ranking curve.

Figure 7. NMA Results for base case model selection: primary analysis of discontinuations (fezolinetant 45mg reference)

Footnote: results shown for standard fixed effects model, specified without class effects.

Figure 8. NMA Results for sensitivity model selection: sensitivity analysis of discontinuations (fezolinetant 45mg reference)

Footnote: results shown for standard fixed effects model, specified without class effects.

2.10.12.3. Results Summary

A summary of the key results from the selected models for NMAs of response and of discontinuation is presented in Table 12.

Table 12. Summary of key results from NMAs

Outcome	Model type	Treatment	Relative treatment estimates OR (95% CrI); comparator vs. fezolinetant 45 mg	Other parameters	Summary of Effect Relative to Fezolinetant 45 mg
Response	Random effects; no class effects	Desvenlafaxine 50 mg	0.46 (0.14, 1.69)	Tau: 1.43 (1.05, 3.02)	Odds of response ~54% lower
		Desvenlafaxine 100 mg	0.84 (0.35, 2.09)		Odds of response ~16% lower
		Placebo	0.39 (0.19, 0.84)		Odds of response ~ 61% lower

Discontinuation	Fixed effects; no class effects	Desvenlafaxine 50 mg	[redacted]	NA	Odds of discontinuation ~120% higher
		Desvenlafaxine 100 mg	[redacted]		Odds of discontinuation ~210% higher
		Paroxetine 7.5 mg	[redacted]		Odds of discontinuation ~145% higher
		Placebo	[redacted]		Odds of discontinuation ~100% higher

Abbreviations: NA, not applicable; NMA, network meta-analysis.

2.10.13 Uncertainties in the indirect and mixed treatment comparisons

Whilst response and discontinuation NMAs were conducted in accordance with best practice, there were notable limitations that may introduce uncertainty and/or bias to the results.

The updates to the original SLR did not include response as an outcome of interest. Although no relevant studies additional to those included in the original SLR were included in the SLR update, it is possible that new studies reporting response but not reporting on the VMS frequency and severity outcomes included in the SLR updates may have been excluded. Given that the included outcomes in the SLR update were the most commonly reported outcomes in this context, this was considered to be unlikely. Despite inclusion of randomised evidence only, estimates derived from the NMA, as opposed to head-to-head trials, may have been biased by heterogeneity between the trials. Sources of heterogeneity may include quantified variation in TEMs (such as differences in race and ethnicity, as noted in the 2023 FA update report), and unquantified variation in TEMs not observed at baseline (Section 2.10.7; reference pack).

In the CEM, a single relative effect estimate was required to compare desvenlafaxine with fezolinetant for response and discontinuation. Two doses, 50 mg and 100 mg, were identified as of clinical relevance. Despite exploring class effects models to generate pooled estimates for both desvenlafaxine doses, the presence of classes with very sparse data (particularly for the 50 mg dose of desvenlafaxine, represented by a single study for both outcomes) meant that these models were driven mainly by limited evidence and yielded unstable class effect estimates with implausibly wide credible intervals. As a result, hierarchical models incorporating class effects were deemed unsuitable due to the increased risk of unreliable estimates, and estimates from simple network models were used instead. This limited outputs to estimates for single desvenlafaxine doses; for both outcomes, the estimates from the 100 mg desvenlafaxine dose were selected because they were based on a larger amount of data than the 50 mg dose and were consequently considered to be more robust. This choice led to a more conservative estimate of treatment effect for VMS response, meaning it likely underestimates the true efficacy. Conversely, the selected estimate was more optimistic regarding discontinuation rates.

For the discontinuation NMA, data for paroxetine were sparse (represented by only one study), similar to those for desvenlafaxine 50 mg. Consequently, estimates of relative treatment effect on discontinuation for this comparator, used in scenario analyses for the CEM, are also driven primarily by results from one trial and may also be of limited robustness.

As well as its impact on the ability to estimate class effects, the sparse data for desvenlafaxine 50 mg prevented formal investigation of consistency within the evidence network for both response and discontinuation.

In the response NMA, missing data were imputed using last observation carried forward (LOCF), which was considered the most appropriate approach given all comparator studies also used LOCF to handle missing data, making it necessary to align with this approach in order to minimise methodological heterogeneity and preserve the NMA assumption of homogeneity. For the base-case economic analysis, patients with missing data on 75% reduction in moderate to severe VMS frequency in the fezolinetant trials were assumed to be non-responders when deriving the responder proportions. Therefore, while the odds ratio for fezolinetant versus desvenlafaxine from the NMA reflects an LOCF-based imputation (consistent with the comparator studies), it was applied to the fezolinetant response rates derived using non-responder imputation. On balance, LOCF was considered to be at low risk of bias because the binary response outcome (≥75% reduction) is less sensitive to missingness than raw VMS frequency, and women who discontinued due to poor response would typically have been classified as non-responders before discontinuation, further limiting bias.

3 Cost effectiveness

Summary of the cost-effectiveness analysis

De novo cost-effectiveness model

- A new cost-effectiveness model was developed, specifically designed to address the key uncertainties identified in the draft guidance and to reflect outcomes that are meaningful to both patients and the NHS
- The Markov cohort model comprised six health states, two of which were based on response status at the treatment decision timepoint: On Treatment – Pre-Response Assessment, On Treatment Responder, On Treatment Non-Responder, Off Treatment with VMS (pre-/post-response assessment), VMS cessation and Death
- The revised model structure addresses key issues in the DGD by:
    - Allowing direct incorporation of relative treatment effects for fezolinetant versus comparators
    - Avoiding the need for transition matrices. Health states are defined by response rather than moderate to severe VMS frequency categories, reducing structural assumptions and aligning with the binary outcomes of the phase 3 fezolinetant and comparator trials (with conservative handling of missing data)
    - The response assessment further reduces uncertainty by ensuring that non-responders discontinue treatment, so long-term efficacy is not overestimated. Additionally, incorporation of treatment discontinuation by non-responders avoids overestimation of long-term efficacy
    - The model explicitly accounts for placebo effects by using trial-based response and utility data; therefore, patients receiving no active treatment are assumed to experience some improvement

    - The model no longer relies on natural history estimates from structured expert elicitation, instead drawing solely on trial data to avoid additional assumptions
    - The model is not heavily reliant on the assumption that response utilities are maintained over the long term, as the median treatment duration was approximately 11 months (mean: 18 months) and over 50% of patients were modelled to achieve VMS cessation by around 5 years
- Upon entering the model, all patients started in the 'On Treatment – Pre-Response Assessment' health state. In the active treatment arms (fezolinetant and desvenlafaxine), patients can discontinue treatment (transition to Off Treatment with VMS), experience VMS cessation (transition to VMS Cessation), or die (transition to Dead). In the no active treatment arm, discontinuation was not modelled, as patients were not receiving treatment
- At the response assessment timepoint, patients alive with VMS were classified as responders or non-responders based on predefined response criteria. Responders and partial responders continued treatment, entering the On Treatment Responder or On Treatment Non-Responder states, respectively. Non-responders unsuitable to continue treatment discontinued immediately and moved to Off Treatment with VMS. On Treatment Non-Responders who initially remained on active treatment were modelled to discontinue after a period of sustained non-response
- The model is informed by the DAYLIGHT and SKYLIGHT 1&2 (HRT-unsuitable subpopulation) trials, the NMAs on response and treatment discontinuation, and external evidence

Cost-effectiveness results

- The base case probabilistic ICERs versus no active treatment (£10,263 per QALY gained) and versus desvenlafaxine (£18,053 per QALY gained) were below the £20,000 per QALY willingness-to-pay (WTP) threshold and did not differ meaningfully from the corresponding deterministic ICER (£10,313 per QALY gained and £17,969 per QALY gained, respectively)
- The probabilistic sensitivity analysis indicated that the base-case results versus no active treatment or desvenlafaxine showed little variation with regard to incremental costs in each iteration. On the effectiveness side, all iterations fell within the northeast quadrant, and most iterations fell below the £20,000 cost-effectiveness threshold, with a modest variation in incremental QALYs gained
- Across all probabilistic scenario analyses, fezolinetant was consistently demonstrated to be cost-effective. A scenario analysis for paroxetine, which required additional assumptions to enable pairwise comparison, produced an ICER of £21,619 per QALY gained

Conclusion

- Overall, the base case and scenario analyses demonstrate that fezolinetant is a cost-effective treatment for moderate to severe vasomotor-predominant menopausal symptoms in women unsuitable for HRT. While comparisons versus desvenlafaxine and paroxetine support these findings, the analyses for SSRIs/SNRIs were limited by assumptions and evidence based on non-UK formulations or doses (e.g., desvenlafaxine as a proxy for venlafaxine; paroxetine 7.5 mg). As such, no active treatment best reflects real-world clinical practice and serves as the most appropriate comparator for assessing the cost-effectiveness of fezolinetant

3.1 Published cost-effectiveness studies

As noted in Section B.3.1 of the original company submission, a *de novo* economic SLR was conducted to identify economic evaluations for the treatment of VMS associated with menopause. Across the original SLR (June 2023) and SLR update (April 2024), one study reporting economic evaluation evidence was included, the summary of which is presented in Table 55 of the original company submission.

3.2 Economic analysis

In order to conduct a cost-effectiveness analysis that robustly captures the cost-effectiveness of fezolinetant versus relevant non-hormonal pharmacological comparators in line with the committee's preference in **draft guidance document (DGD) Section 3.5 and 3.8 (Comparators; Relative treatment effects)**, a *de novo* cost-utility model based on response assessment was developed. A detailed overview and justification for the new modelling approach are provided in Section 3.2.2 below.[26]

3.2.1 Patient population

The modelled patient population was patients with moderate to severe VMS for whom HRT is deemed unsuitable, consistent with the committee's conclusion in **DGD Section 3.3 (Population for whom HRT is unsuitable)**.

3.2.2 Model structure

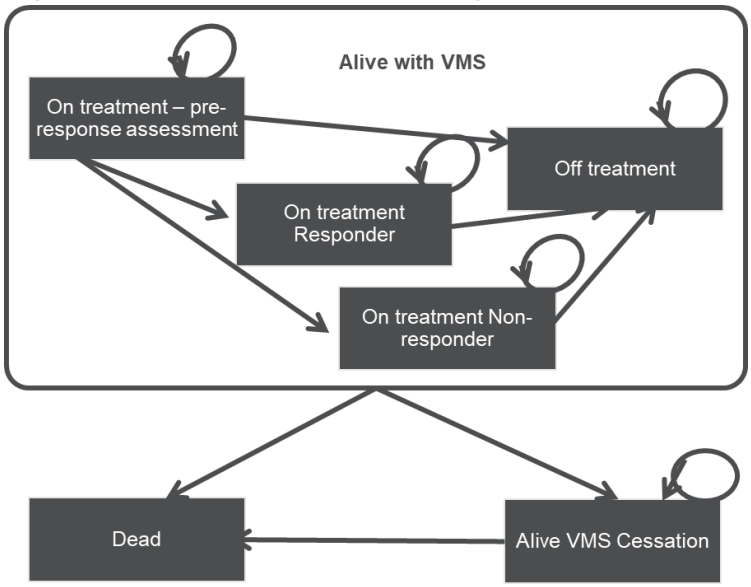
3.2.3 Overview of model structure

The *de novo* cohort Markov model comprised six health states, two of which were based on response status at the treatment decision timepoint (see *Justification for the modelling approach* section below):

- On Treatment Pre-Response Assessment
- On Treatment Responder
- On Treatment Non-Responder
- Off Treatment with VMS (pre-/post-response assessment)
- VMS cessation
- Death

The health state transition diagram is shown in Figure 9.

Figure 9: health state transition diagram



Although the health states are labelled as "On Treatment", these health states refer to no treatment for the no active treatment comparator arm.
Abbreviations: VMS: vasomotor symptoms

Upon entering the model, the cohort starts in the 'On Treatment Pre-Response Assessment' health state. In this state, patients in the active treatment arms (fezolinetant and desvenlafaxine) were at risk of treatment discontinuation (transitioning to 'Off Treatment with VMS'), in addition to the risk of experiencing VMS cessation (transitioning to the 'VMS Cessation' health state), or death (transitioning to the 'Dead' health state). For patients in the no active treatment arm, transitions to 'Off Treatment with VMS' were not modelled, as patients were not receiving any active treatment. Once patients on active treatment experienced VMS cessation or death, they were modelled to discontinue treatment (incurring no further drug costs).

At the treatment decision timepoint, patients alive with VMS and still in the On Treatment – Pre-Response Assessment state were classified as either 'responders' or 'non-responders', based on the response criteria (see *Justification for the modelling approach* section below). In the active treatment arms, responders and non-responders deemed suitable to continue treatment (i.e. partial responders that do not meet the response criteria) transitioned to the 'On Treatment Responder' or 'On Treatment Non-Responder' health state, respectively. Patients in the On Treatment Responder state remained there until treatment discontinuation, VMS cessation, death or the end of the model time horizon. On Treatment Non-Responders were modelled to discontinue treatment after a sustained period of non-response (see *Justification for the modelling approach* section below) and transitioned to the Off Treatment with VMS state; before this point, they were at risk of treatment discontinuation, VMS cessation, or death. The non-responders considered unsuitable to continue treatment at the treatment decision timepoint, stopped treatment immediately and transitioned to the Off Treatment with VMS health state, where they remained until VMS cessation, death or the end of the model time horizon.

For the cohort in the no active treatment arm, the proportion of responder and non-responder at the treatment decision timepoint was modelled based on trial data from the placebo arm of the pooled DAYLIGHT and SKYLIGHT 1&2 (HRT-unsuitable subpopulation) trials. Patients remained in either the On Treatment Responder or On Treatment Non-Responder health states until VMS

cessation, death or the end of the model time horizon. Although the health states are labelled as "On Treatment", for the no active treatment arm, these health states refer to no treatment.

The proportion of responders and non-responders at the treatment decision timepoint across treatment arms in the model were treatment dependent (see Section 3.3.2.1). The probability of treatment discontinuation was both health state- and treatment-dependent (see Section 3.3.2.2), while the probability of VMS cessation (see Section 3.3.2.3) or death (see Section 3.3.2.5) was independent of treatment or health state.

Justification for the modelling approach

1. The new model structure addresses the committee's concerns

The committee's preference was that additional comparators be included in the cost-effectiveness analysis (**DGD Section 3.5, 3.8 and 3.11: Comparators; Relative treatment effects**). In contrast to the original submission model, the current model structure allows direct incorporation of relative treatment effects for fezolinetant versus relevant comparators, avoiding the need to derive 4x4 transition probability matrices from a single treatment effect estimate – an approach that would introduce additional complexity and uncertainty in the cost-effectiveness analysis.

The current model structure also eliminates the need for multiple moderate to severe VMS frequency health states as used in the original submission model (**DGD Section 3.10: Cut-Off thresholds used to define moderate to severe VMS frequency health states**). This removes the requirement to define baseline distributions across frequency categories, thereby reducing structural assumptions (**DGD Section 3.10: Baseline distribution with a moderate to severe VMS frequency**). Instead, health states were defined by response (which represents sufficient improvement in moderate to severe VMS frequency), aligning with the binary responder outcomes of the fezolinetant phase 3 trials. These outcomes were at low risk of bias, as missing data were conservatively handled by classifying patients with missing data as non-responders (**DGD Section 3.6: Handling of missing data**).

The model accounts for the placebo effect associated with no active treatment by using the utility and response data collected in the phase 3 fezolinetant trials, and by assuming that patients who do not receive active treatment nonetheless experience some improvement after the treatment decision point, in line with the response rates and utilities observed for responders and non-responders (**DGD Section 3.11: Data from trials and estimates of natural history)**. The model no longer requires natural history estimates of VMS derived through structured expert elicitation (SEE), relying solely on trial data and thereby avoiding additional assumptions (**DGD Section 3.11: Data from trials and estimates of natural history**). The responder-based structure captures clinically meaningful changes in moderate to severe VMS frequency over time, while utilities remain constant within health states, given sustained symptom reduction observed through 52 weeks in the pooled SKYLIGHT 1&2 trials and feedback from a UK clinical expert that among 20–25 patients treated with fezolinetant for more than 18 months, no evidence of waning was observed.[1] The model is not heavily reliant on the assumption that response utilities are maintained over the long term, as the median treatment duration for fezolinetant was approximately 11 months (mean: 18 months) and over 50% of patients were modelled to achieve VMS cessation by around 5 years.

Lastly, the model uses health state utility values derived directly from the phase 3 fezolinetant trials based on EQ-5D data (**DGD Section 3.11: Health state utilities**).

2. The new model structure reflects the clinical pathway of care

Timepoint of response assessment

In the base case, response was assessed at Week 12. This aligns with NICE menopause guidelines (NG23), which recommend reviewing treatment after 3 months to assess efficacy and tolerability.[6] UK clinical experts further noted that 12 weeks is a suitable assumption that allows sufficient time for the full treatment effect to be observed, and which also aligns with their first in-person follow-up appointment in clinical practice.[1] Two scenarios were considered that examined the impact of a shorter (Week 4) and longer (Week 24) treatment decision timepoint on the cost-effectiveness analysis (Section 3.11.3).

Definition of response

In the base case analysis, response was defined by a reduction of at least 75% in moderate to severe VMS frequency from baseline. This definition was chosen for several reasons. UK clinical experts and patient representatives consulted for the original submission considered change in moderate to severe frequency to be a more objective outcome than measures of severity and that such threshold was clinically meaningful. The outcome was also at low risk of bias, since patients with missing data were conservatively treated as non-responders. Importantly, proportions of responders defined in this way were also available for comparators outside the fezolinetant phase 3 trials, allowing meaningful indirect comparisons. Furthermore, as noted in Section 2.10.6, there is a strong correlation between PGI-C VMS and VMS frequency, suggesting that response according to reduction in the frequency of moderate to severe VMS was considered to sufficiently reflect improvements in both VMS frequency and severity. Finally, a recent study investigating thresholds for clinically meaningful changes in moderate to severe VMS further supports the use of a 75% threshold, indicating that this level of reduction reflects a more substantial and clinically relevant improvement.[7]

In response to further feedback from UK clinical experts consulted during the post-DGD stage, two scenario analyses were also conducted (Section 3.11.3):

- Scenario 1: Response defined as a 50% reduction in VMS frequency. UK clinical opinion highlighted that patients achieving at least this level of improvement would be considered by clinicians to be deriving sufficient benefit and therefore would likely continue on treatment.

- Scenario 2: Response defined according to patients' self-reported scores on the PGI-C VMS tool (a patient-reported measure of perceived improvements in VMS on a 7-point scale ranging from [1] much better to [7] much worse), with values of 1 (much better) or 2 (moderately better) considered to represent treatment response).
  UK clinical experts advised that such judgements closely reflect how clinicians assess treatment benefit in practice, since they incorporate patients' perceptions of their symptoms and the wider impact of treatment.

Response according to PGI-C VMS was not used in the base-case economic analysis for three reasons. First, UK clinical experts confirmed that PGI-C VMS is not routinely used in clinical practice in the UK. Second, comparator data for this outcome were unavailable outside the

fezolinetant phase 3 trials; therefore, it was not possible to compare PGI-C VMS outcomes between fezolinetant and non-hormonal comparators, as it would increase uncertainty to assume that 75% response generalises to PGI-C response in non-hormonal pharmacological comparators. Third, the use of the 75% response outcome aligns with the EAG's preference (discussed on a call with the EAG after the first ACM) given it is a more objective measure and had a lower likelihood of bias than PGI-C VMS which has a recall bias, in addition to its subjectivity.

Partial responders

UK clinical experts noted that, despite the 75% threshold there are a proportion of non-responders who would continue on treatment despite not meeting the response criteria if they had a partial response (at least 50% reduction but less than 75% reduction).[1] As such, in the base case analysis, 50% of non-responders were conservatively modelled to continue treatment at the treatment decision timepoint until 52 weeks when they discontinue treatment. This proportion reflected both UK clinical opinion and observed data from the pooled DAYLIGHT and SKYLIGHT 1&2 trials which showed that approximately half of the women classified as non-responders under the 75% threshold nevertheless achieved a 50% improvement in moderate to severe VMS frequency.

Features of the economic analysis

The key features of the economic analysis and their justifications are presented in Table 13.

Effectiveness measures include life years (LYs) and quality-adjusted life years (QALYs). The incremental cost-effectiveness ratio (ICER) was evaluated in terms of the incremental cost per QALY gained. An annual discount rate of 3.5% was applied for both costs and QALYs. The cost perspective was of the NHS and personal social services (PSS), and the outcomes perspective was all relevant health effects over a 10-year time horizon. A time horizon of 10 years was considered appropriate, given that there is no differential mortality effect between treatment options and the differences in costs and clinical outcomes relate to a relatively short period, in line with the NICE reference case.

Table 13: Features of the economic analysis

	Current evaluation	
Factor	**Chosen values**	**Justification**
Time horizon	10 years	There is no differential mortality effect between treatment options and the differences in costs and clinical outcomes relate to a relatively short period. As such, in line with the NICE reference case, a time horizon shorter than a lifetime was justified. The median/mean treatment duration for fezolinetant in the current model is approximately 11.0/18.4 months. Corresponding to a 61%/57% reduction in treatment duration compared with the original submission model (28.5/42.5 months). Given that the vast majority of cohort are off treatment by the end of the model time horizon, the cost-effectiveness analysis is not sensitive to this assumption.

		This approach was further validated by three UK clinical experts who indicated that a 10-year time horizon was appropriate, given that they expect the vast majority of patients to have discontinued treatment by the 10-year timepoint.[8]
Cycle length	4 weeks	A four-week cycle length was used in the model in line with the clinical assessment timepoints used in SKYLIGHT 1&2 and DAYLIGHT.
Treatment waning effect?	N/A	It is expected that loss of treatment response in patients with moderate to severe VMS is clinically measurable and will therefore lead to treatment discontinuation. Discontinuation was therefore considered a suitable proxy for treatment waning. As noted in Section B.3.3.2.4 of the original submission, 52 weeks of fezolinetant efficacy data from pooled SKYLIGHT 1 and SKYLIGHT 2 trials showed that fezolinetant is effective at both eliciting symptom relief from Day 1 of treatment and maintaining that response up to Week 52, with no indication of treatment waning. UK clinical experts likewise confirmed that waning is not expected, both due to the mechanism of action and their clinical experience with fezolinetant.[1] One expert reported that among 20–25 patients treated with fezolinetant for more than 18 months, no evidence of waning was observed.[1]
Source of utilities	EQ-5D-5L data were collected directly from patients enrolled in pooled fezolinetant trials (DAYLIGHT and SKYLIGHT 1&2)	In line with the NICE reference case.
Source of costs	Healthcare resource unit costs were sourced from PSSRU and NHS costs	In line with the NICE reference case.
Health effects measure	QALYs	In line with the NICE reference case.
Half-cycle correction	Yes	A half-cycle correction was applied to the calculation of LYs, QALYs and costs to account for events that occur part way through a cycle.

Abbreviations: EQ-5D: EuroQoL-5 Dimension; HRQoL: health-related quality of life; LYs: life years; NHS: National Health Service; PSSRU: Personal Social Services Research Unit; QALYs; quality-adjusted life-years; UK: United Kingdom; VMS: vasomotor symptoms.

3.2.4 Intervention technology and comparators

3.2.4.1. Intervention

The intervention assessed in the base case analysis was fezolinetant 45 mg once daily. This was in line with the decision problem and the licensed dose for fezolinetant in moderate to severe

VMS associated with menopause. The dosing schedule for fezolinetant used in the model is also consistent with the fezolinetant 45 mg arm of SKYLIGHT 1&2 and DAYLIGHT.

3.2.4.2. Comparators

As noted in the DGD Response Comment 3, feedback from the extensive UK expert consultations was strongly in favour of fezolinetant being initiated and managed in NHS primary care, in line with other treatments for moderate to severe VMS, if recommended.[2, 27, 28] Experts strongly believed that GPs are suitably placed to handle most patients presenting with bothersome menopausal symptoms and that access to fezolinetant in primary care would reduce disparities in access and may alleviate some of the pressure on specialist menopause clinics, given the long waiting lists currently experienced.[1, 2, 8, 27-29]

The committee's preference was that non-hormonal pharmacological treatments, such as selective serotonin reuptake inhibitors (SSRIs)/serotonin-norepinephrine reuptake inhibitors (SNRIs), should be included as relevant comparators as they are offered to patients in primary care, in addition to no active treatment (**DGD Section 3.5: Comparators**). In two letters submitted to the EAG/NICE in May and June 2025, the place in therapy of fezolinetant and choice of comparators was extensively discussed, noting that if fezolinetant was used in the primary care setting then non-hormonal therapies, such as SSRIs/SNRIs would be considered as comparators. As such, SSRI/SNRI comparators, in addition to no active treatment, were considered in the decision problem of this appraisal.

For the purposes of the base case economic analysis, only two comparators were considered: no active treatment and desvenlafaxine (proxy for venlafaxine), described in more detail below.

Selection of comparators was based on eligibility for inclusion and data availability for ITCs

In selecting the non-hormonal pharmacological treatments to include in the NMAs and hence, the cost-effectiveness analysis, the primary considerations were their availability and use in NHS clinical practice, as a specific agent or as a class, and whether treatments had RCT evidence on the proportion of responders to support their efficacy versus placebo. Desvenlafaxine was selected in the base-case economic analysis (and NMA) as the non-hormonal comparator because:

- SNRIs are one of the most commonly prescribed (off-label) non-hormonal treatments for moderate to severe VMS[1, 2]
- Desvenlafaxine is the only non-hormonal treatment for which there is RCT evidence versus placebo on the proportion of patients who experienced at least 75% reduction in moderate to severe VMS frequency (see Section 2.10.8)
- External evidence indicates that desvenlafaxine 100 mg is a suitable proxy for venlafaxine (SNRI), which is a related drug that is prescribed off-label in the UK for this indication but for which no relevant evidence was available, given their interchangeability when adjusted for dose.[3]

A cost-effectiveness scenario compares fezolinetant to paroxetine 7.5 mg where efficacy is based on 50% reduction in moderate to severe VMS frequency at Week 12, as efficacy data were not available for the 75% threshold (Section 3.11.3). Paroxetine is an SSRI sometimes prescribed off-label in the UK for moderate to severe VMS. However, it should be noted that

paroxetine 7.5 mg is not a dose recommended by the BMS (10–20 mg), which limits the generalisability of the scenario results to the UK setting.[4] For this reason, the results from this scenario analysis should be interpreted with caution.

Other non-hormonal comparators were not included in the economic analysis as studies identified in the SLR were not considered eligible for inclusion in the NMA (see Section 2.10.7).

No active treatment is the most clinically relevant comparator for estimating cost-effectiveness of fezolinetant

Feedback from UK clinical experts highlighted consistent limitations across non-hormonal pharmacological options prescribed in primary care for treating moderate to severe VMS. SSRIs and SNRIs were described as offering variable efficacy, requiring titration, and being associated with high discontinuation rates due to adverse effects (e.g. sexual dysfunction, weight gain, sedation), with some side effects such as loss of libido or emotional dulling potentially persisting long term and not resolving after discontinuation. Experts also noted that many patients are reluctant to use antidepressants because of the stigma associated with a mental health diagnosis being recorded in their clinical notes. Clonidine, although the only non-hormonal licensed for hot flushes in the UK, was regarded as rarely used because of limited efficacy and poor tolerability, including risk of rebound hypertension. Experts raised concerns about gabapentin and pregabalin's adverse events (including sedation, cognitive impairment and weight gain) and risks associated with their potential misuse and dependence.[2, 30]

Taken together, these insights support the inclusion of no active treatment as the most clinically relevant comparator in the primary care setting. Given the stigma associated with antidepressants, the side-effect burden and contraindications across drug classes, the need for tapering and frequent monitoring, and high discontinuation rates, many patients in routine practice do not receive non-hormonal pharmacological therapy for moderate to severe VMS. No active treatment therefore represents the clinical reality of most patients seeking medical advice for moderate to severe VMS who are unsuitable for HRT and thus the most reliable comparator for estimating the cost-effectiveness of fezolinetant.

3.3 Clinical parameters and variables

The model used clinical data primarily sourced from pooled phase 3 fezolinetant trials (SKYLIGHT 1&2 [HRT-unsuitable subpopulation] and DAYLIGHT) (see Appendix E.3 of original submission for pooled results), and relative treatment effects generated in the response and discontinuation NMAs (Section 2.10).

3.3.1 Baseline Characteristics

3.3.1.1. Age

In the base case analysis, the mean starting age of the modelled cohort was 51 years based on the average age of menopause onset in the UK (Table 14).[31] This was considered appropriate in order to align with clinical expert opinion and given that subgroup results demonstrated consistent efficacy across different age groups and non-significant interaction terms (Section B.27 of the original company submission and response to Clarification Question A20).

Scenario analyses were considered which used alternative data sources for the mean age of the starting cohort, such as DAYLIGHT or pooled DAYLIGHT and SKYLIGHT 1&2 (Section 3.11.3).

Table 14: Baseline characteristics of modelled cohort (base case)

Parameter	Value	Source
Mean age, years	51.0	Clinical input; NHS inform: Menopause[31]

Abbreviations: NHS: National Health Service.

3.3.2 Efficacy

3.3.2.1. Response

Response distribution

As noted in Section 3.2.2, response was assessed at Week 12 based on at least a 75% reduction in moderate to severe VMS frequency. At this treatment decision timepoint, the cohort within the On Treatment Pre-Response Assessment health state in the relevant treatment arms of the model was stratified into the Responder and Non-Responder health states based on response rates outlined in Table 15. Patients with missing data for responder status at Week 12 in the fezolinetant trials were imputed as non-responders in line with the EAG's preference (**DGD Section 3.6: Handling of missing data**). The responder percentage for desvenlafaxine was derived using NMA efficacy inputs (Table 17), and for paroxetine based on response rates reported in pooled NCT01101841 and NCT01361308 (scenario analysis, Table 16).[32, 33]

A scenario analyses were conducted using pooled SKYLIGHT 1&2 only or DAYLIGHT only as an alternative response source for fezolinetant and no active treatment (Section 3.11.3).

Table 15: Response (≥75% reduction in moderate to severe VMS frequency at Week 12) distribution for treatments (base case)

Treatment	Responder percentage	Source
Fezolinetant	41.62%	Pooled DAYLIGHT and SKYLIGHT 1&2 (HRT-unsuitable subpopulation)
No active treatment	21.83%	Pooled DAYLIGHT and SKYLIGHT 1&2 (HRT-unsuitable subpopulation)
Desvenlafaxine	37.32%	Calculation, OR applied to the fezolinetant arm

Abbreviations: OR: odds ratio; VMS: vasomotor symptoms.

Table 16: Response (≥50% reduction in moderate to severe VMS frequency at Week 12) distribution for treatments (scenario analysis)

Treatment	Responder percentage	Source
Fezolinetant	62.43%	Pooled DAYLIGHT and SKYLIGHT 1&2 (HRT-unsuitable subpopulation)
No active treatment	40.32%	Pooled DAYLIGHT and SKYLIGHT 1&2 (HRT-unsuitable subpopulation)

Paroxetine	49.57%	Pooled NCT01101841 and NCT01361308.[32, 33] 12-week response rate, where response is defined as 50% reduction in moderate to severe VMS.

Abbreviations: VMS: vasomotor symptoms.

SNRI (desvenlafaxine) efficacy inputs

Table 17: Response NMA inputs (base case)

Treatment	OR versus fezolinetant	SE	95% CrI lower	95% CrI upper	Source
Desvenlafaxine 100mg	0.84	0.44	0.35	2.09	Five studies were identified and included for desvenlafaxine 100mg in the response NMA (Section 2.10). Response outcome was defined as a ≥75% reduction in moderate to severe VMS at Week 12. Missing data for responder status was imputed primarily using last observation carried forwards (LOCF) imputation, to align with the approach taken by comparator trials.

Timepoint of interest in the NMA was Week 12.
Abbreviations: CrI; credible interval; IPD: individual patient data; NMA: network meta-analysis; OR: odds ratio; SE: standard error.

3.3.2.2. Treatment discontinuation

For patients in the On Treatment Pre-Response Assessment health state, the probability of treatment discontinuation was based on pooled DAYLIGHT and SKYLIGHT 1&2 (HRT-unsuitable subpopulation) data for the fezolinetant arm. For the desvenlafaxine arm, the probability of treatment discontinuation was derived by applying NMA-derived OR to the fezolinetant arm of the pooled DAYLIGHT and SKYLIGHT 1&2 trial. For patients on no active treatment, treatment discontinuation was not modelled as patients were not receiving an active treatment from which they may discontinue.

At the treatment decision timepoint (Week 12), 50% of non-responders regardless of treatment arm were modelled to discontinue treatment, while the remaining 50% were modelled to continue treatment but still experience the risk of treatment discontinuation until Week 52, at which point the remaining non-responder patients discontinue treatment and transition to the Off Treatment with VMS health state. As noted in Section 3.2.2, this conservative modelling approach enabled partial responders (those with a 50%–<75% reduction in moderate to severe VMS) to stay on treatment longer in order to reflect the consistent feedback from UK clinical experts that some patients not meeting the response criteria but still experiencing some meaningful benefit would stay on treatment longer but no longer than 52 weeks; and was in line with the observed, pooled data from the DAYLIGHT and SKYLIGHT 1&2 trials which showed that approximately half of the women classified as non-responders under the 75% threshold nevertheless achieved a 50% improvement in moderate to severe VMS frequency.[1] A scenario analysis applying a 100% stopping rule for non-responders at Week 12 was also considered as well as a scenario without a stopping rule for all non-responders (Section 3.11.3).

The four-weekly probabilities of treatment discontinuation used in the base case are outlined in Table 18. The per cycle treatment discontinuation probabilities for desvenlafaxine were derived using outputs from the discontinuation NMA, as outlined in Table 19.

For Week 24 onwards, pooled Week 12–24 data from DAYLIGHT and SKYLIGHT 1 & 2 were used to inform discontinuation probabilities, rather than pooled Week 24–52 data from SKYLIGHT 1 & 2. The latter were considered less reliable because the discontinuation rate for responders was higher than that of non-responders. This lacks face validity since responders are deriving greater benefits from treatment as opposed to non-responders. By Week 24, many non-responders are expected to have already discontinued, so later discontinuations are less closely linked to response status and may be influenced by other factors. Some patients who initially responded may also have chosen to discontinue because their symptoms were no longer disruptive. That said, scenario analyses using the pooled Week 24–52 SKYLIGHT 1&2 data for Week 24+ or DAYLIGHT for fezolinetant discontinuation probabilities showed that the source of discontinuation probabilities had minimal impact on the cost-effectiveness analysis (Section 3.11.3).

Additionally, treatment discontinuation probabilities reported for desvenlafaxine in Bouchard *et al.*, (2012)[20] were considered in a scenario analysis (Section 3.11.3).

Table 18: Per 4-weekly cycle probability of discontinuation (base case)

Treatment	Time period	Response category	Per 4-week probability of discontinuation	Source
Fezolinetant	Pre-response assessment	All patients	[redacted]	Week 0–12: DAYLIGHT and SKYLIGHT 1&2 (HRT-unsuitable subpopulation)[a]
	Week 12–24	Responder	[redacted]	Week 12–24: DAYLIGHT and SKYLIGHT 1&2 (HRT-unsuitable subpopulation).[a] Response outcome was defined as a ≥75% reduction in moderate to severe VMS. Missing data for responder status was imputed primarily using last observation carried forward (LOCF) imputation, to align with the approach taken by comparator trials.
		Non-responder	[redacted]	
	Week 24+	Responder	[redacted]	
		Non-responder	[redacted]	
Desvenlafaxine	Pre-response assessment	All patients	[redacted]	Calculation, OR applied to the fezolinetant arm
	Week 12–24	Responder	[redacted]	
		Non-responder	[redacted]	
	Week 24+	Responder	[redacted]	
		Non-responder	[redacted]	
Paroxetine (scenario analysis)	Pre-response assessment	All patients	[redacted]	Calculation, OR applied to the fezolinetant arm

	Week 12–24	Responder	[redacted]	
		Non-responder	[redacted]	
	Week 24+	Responder	[redacted]	
		Non-responder	[redacted]	

[a] Treatment discontinuation rate was assumed to be constant and estimated using an exponential model based on the observed data.
Abbreviations: OR: odds ratio

SNRI/SSRI (desvenlafaxine and paroxetine) discontinuation inputs

Table 19: Discontinuation NMA inputs (base case)

Treatment	OR versus fezolinetant	SE	95% CrI lower	95% CrI upper	Source
Desvenlafaxine 100mg	[redacted]	[redacted]	[redacted]	[redacted]	Five studies were identified and included for desvenlafaxine 100mg in the discontinuation NMA (Section 2.10)
Paroxetine 7.5 mg (scenario analysis)	[redacted]	[redacted]	[redacted]	[redacted]	One study was identified and included for paroxetine 7.5 mg in the discontinuation NMA (Section 2.10)

Timepoint of interest in the NMA was Week 12.
Abbreviations: CrI; credible interval; IPD: individual patient data; NMA: network meta-analysis; OR: odds ratio; SE: standard error.

3.3.2.3. VMS cessation

The VMS cessation rate was assumed to be constant over the model time horizon and for all interventions and comparators. The transitions to the VMS cessation health state in each model cycle are based on a per cycle probability of VMS cessation (Table 20).

In the base case, per cycle probability of VMS cessation was derived using the median duration of VMS in postmenopausal women reported by Avis *et al.,* (2015).[34] This value was deemed appropriate in order to be consistent with the pooled DAYLIGHT and SKYLIGHT 1&2 (HRT-unsuitable subpopulation) data informing the base case model and was also in line with the EAG's preferred assumption. Despite the consistency of the modelling approach, UK clinical experts instead considered the median duration of VMS of 7.4 years for all women with VMS to be reflective of their clinical experience; as such, a scenario analysis using this estimate is provided (Section 3.11.3).[1]

Table 20: Probability of VMS cessation per cycle (base case)

Source	Median Duration of Symptoms (years)	Duration of Symptoms (SE)	Probability of Symptom Cessation per Cycle
Avis, 2015[34]	3.40	0.34	0.016

Abbreviations: SE: standard error; VMS: vasomotor symptoms.

3.3.2.4. *Safety*

Treatment-specific all-grade AEs were included in the base case, if ≥5% in *any* treatment arm, reflecting a standard modelling approach that captures clinically relevant and frequent events. Risk of AEs for each treatment arm of the model is provided in Table 21.

It is worth noting that the modelling of adverse events for SSRIs and SNRIs is considered conservative, as the full range of adverse events associated with these treatments was not captured. UK clinical expert feedback was that certain adverse effects, including emotional dulling and sexual dysfunction, may persist long term and do not necessarily resolve on treatment discontinuation.[1, 2] In addition, experts highlighted the need to titrate SSRIs/SNRIs on initiation and again upon discontinuation due to the risk of withdrawal symptoms. This titration requirement typically necessitates additional clinical appointments, with associated implications for adverse event management costs, which were not captured in the modelling. The exclusion of these factors therefore represents a conservative assumption with respect to fezolinetant, in terms of the full spectrum of AEs (short and long term) and costs associated with SSRIs/SNRIs.

Table 21: Adverse event probabilities (base case)

Event	Fezolinetant	No active treatment	Desvenlafaxine	Paroxetine (scenario analysis)
Headache	8.85%	0.00%	0.00%	4.27%
Fatigue	5.75%	0.00%	0.00%	3.41%
Asthenia	0.00%	0.00%	8.86%	0.00%
Constipation	0.00%	0.00%	10.76%	0.00%
Dry mouth	0.00%	0.00%	10.13%	0.00%
Nausea	2.65%	0.00%	31.01%	0.00%
Dizziness	2.65%	0.00%	10.76%	0.00%
Insomnia	2.65%	0.00%	6.96%	0.00%
Somnolence	0.00%	0.00%	6.96%	0.00%
Abnormal vision	0.00%	0.00%	5.70%	0.00%
Source	DAYLIGHT. TEAE in ≥5% of patients in any arm, dependent on the SSRI/SNRI comparator[a]	Assumption, given that patients are not receiving an active treatment	Bouchard *et al.*, (2012).[20] TEAE in ≥5% of patients in any arm	Simon et al., (2013).[21] TEAE in ≥5% of patients in any arm[b]

[a] In the scenario analysis versus paroxetine, the risk of nausea, dizziness and insomnia was 0% for each AE in the fezolinetant arm, given that AEs were only modelled if ≥5% in any treatment arms. [b] the higher strength available in the UK (7.5mg is not available) will likely be associated with higher AE probabilities, so AEs are being conservatively modelled
Abbreviations: AE: adverse event; TEAE: treatment-emergent adverse event.

3.3.2.5. *Mortality*

Based on the observed survival of patients in DAYLIGHT, SKYLIGHT 1, SKYLIGHT 2 and SKYLIGHT 4, and the published literature,[35] it was concluded that moderate to severe VMS did not have any meaningful impact on mortality risk. As such, the modelled cohort were therefore assumed to have the same mortality rate as for the general female population in the UK.

Treatments are not expected to affect mortality rate; hence, the same mortality rate is applied irrespective of whether patients are treated for VMS and the specific treatment.

Age-specific mortality rates for females were derived from the National UK life tables for 2019 (published by the Office for National Statistics [ONS]).[36] Mortality rates from 2019 were used in the base case as these data are the latest UK figures available that were not impacted by COVID-19 mortality rates.

3.4 Measurement and valuation of health effects

3.4.1 Health-related quality-of-life data from clinical trials

Arithmetic mean utility values used in the model were derived using all available EQ-5D-5L data collected directly from patients with moderate to severe VMS in the pooled DAYLIGHT and SKYLIGHT 1&2 trials. This is consistent with the NICE reference case.[37] Details on the HRQoL data from the trials and the analysis to inform the model is presented in Section 3.4.5.

3.4.2 Mapping

In line with the NICE reference case, EQ-5D-5L data collected in pooled DAYLIGHT and SKYLIGHT 1&2 were mapped to EQ-5D-3L utility values using the mapping algorithm published by Hernández Alava *et al.* (2023).[38]

3.4.3 Health-related quality-of-life studies

As described in Section B.3.4.3 of the original company submission, an economic SLR was conducted to identify relevant literature published on previous economic evaluations, utility values and key model inputs to inform the cost effectiveness model for fezolinetant. Utility values from the identified study were not used in the cost-effectiveness model, as EQ-5D data were directly available from the pooled phase 3 DAYLIGHT and SKYLIGHT 1&2 trials in the population of relevance to the decision problem of this appraisal.

3.4.4 Adverse reactions

Disutilities associated with AEs noted in Section 3.3.2.4 are provided in Table 22.

AE utility decrements were applied as a one-off upon initiation of treatment, in line with UK clinical expert opinion sought by the manufacturer in TA367 (vortioxetine in depression) which noted that, on average, short-term AEs last for a duration of 3 weeks.[39]

As noted in Section 3.3.2.4, given that long-term AEs and AEs associated with down-titration were not captured for SSRIs/SNRIs, the modelling of AEs is considered conservative.

Scenario analyses were considered which excluded AE disutilities or which assumed a 1-week duration for short-term AEs (Section 3.11.3).

Table 22: AE utility decrements and durations (base case)

Event	Disutility	Duration of AE (days)	Per event QALY Decrement due to AEs	Source

Headache	0.115	21.00	0.007	Sullivan et al., (2004) (disutility)[40] TA367 (duration)[39]
Fatigue	0.085	21.00	0.005	Sullivan et al., (2004) (disutility)[40] TA367 (duration)[39]
Asthenia	0.085	21.00	0.005	Sullivan et al., (2004) (disutility)[40] TA367 (duration)[39]
Constipation	0.065	21.00	0.004	Sullivan 2004, assumed average of GI (disutility) TA367 (duration)
Dry mouth	0.010	21.00	0.001	Revicki and Wood (1998) (disutility)[41] TA367 (duration)[39]
Nausea	0.065	21.00	0.004	Sullivan et al., (2004) (disutility)[40] TA367 (duration)[39]
Dizziness	0.085	21.00	0.005	Sullivan et al., (2004) (disutility)[40] TA367 (duration)[39]
Insomnia	0.129	21.00	0.007	Sullivan et al., (2004) (disutility)[40] TA367 (duration)[39]
Somnolence	0.085	21.00	0.005	Sullivan et al., (2004) (disutility)[40] TA367 (duration)[39]
Abnormal vision	0.050	21.00	0.003	Sullivan et al., (2004) (disutility)[40] TA367 (duration)[39]

Abbreviations: AE: adverse events; QALY: quality-adjusted life years.

3.4.5 Health-related quality-of-life data used in the cost-effectiveness analysis

Utility values for fezolinetant were based on EQ-5D data collected in the fezolinetant arm of the pooled DAYLIGHT and SKYLIGHT 1&2 (HRT-unsuitable subpopulation) trials. In the base case analysis, before the response assessment (i.e., before Week 12), utility values for fezolinetant corresponded to those observed during Weeks 0–12 in the fezolinetant arm of pooled DAYLIGHT and SKYLIGHT 1&2. After the response assessment (i.e., Week 12 onwards), utility values for fezolinetant were stratified by responder status. Specifically, utility values for the responders and non-responders were informed by Weeks 0–52 data from the fezolinetant arm of pooled DAYLIGHT and SKYLIGHT 1&2 to make use of all available data. Utility values for no active treatment were based on EQ-5D data collected in the placebo arm of pooled DAYLIGHT and SKYLIGHT 1&2. Before response assessment, utility values corresponded to Weeks 0–12 data, while after the response assessment, utility values corresponded to the Weeks 0–24 data to make use of all available data.

Given that patients with moderate to severe VMS are expected to derive benefit from active treatment by reducing moderate to severe VMS frequency, utility values should be greater than those for no active treatment. Moreover, NMA evidence (Section 2.10) shows that fezolinetant achieves greater reductions in moderate to severe VMS frequency and a lower odd of all-cause treatment discontinuation compared with other active comparators, while all active comparators provide greater benefit than placebo (a proxy for no active treatment). It is therefore reasonable to assume that the utility values for the fezolinetant arm is higher with fezolinetant than with SSRIs/SNRIs. Accordingly, utility values for desvenlafaxine and paroxetine were derived as the

mean of the fezolinetant and no active treatment arms of the model, in the absence of utility values reported in the desvenlafaxine and paroxetine studies identified in the clinical SLR. A scenario was conducted which set utility values of desvenlafaxine and paroxetine equal to the fezolinetant arm (Section 3.11.3). It is worth noting that the disutilities currently captured in the model primarily reflect short-term adverse events; however, additional longer-term impacts on quality of life, such as emotional blunting, loss of libido, and the psychosocial burden associated with antidepressant use, are not captured. These uncaptured effects are likely to further reduce the overall utility of non-hormonal comparators relative to fezolinetant.

The utility value for the Off Treatment with VMS (pre-response assessment) health state regardless of treatment arm was assumed to be the same as the utility value for the no active treatment arm. In the no active treatment arm after the response assessment, the utility value was derived as the weighted mean of the utility values for the Responder and Non-Responder health states. The utility value for VMS cessation was calculated from the average EQ-5D-5L data (mapped to 3L) among patients that reported a VMS frequency of zero in pooled DAYLIGHT and SKYLIGHT 1&2. No further adjustment was made in the analysis to account for repeated measurements.

To derive required inputs for fezolinetant and no active treatment, generalised linear mixed models were fitted to the DAYLIGHT and SKYLIGHT 1 & 2 (HRT-unsuitable subpopulation) populations with the following specifications:

Model 1: Utility ~ Treatment + Timepoint + (1|Subject ID),

Model 2: Utility ~ Treatment + Timepoint + Response Status + (1|Subject ID),

where (1|Subject ID) denotes the use of a random intercept for Subject ID to control for repeated measures within women. Data were prepared as described in Section 2.10.3, which aligned with existing summaries for SKYLIGHT 1&2 and DAYLIGHT (see reference pack). Missingness in responder status was addressed using LOCF imputation; complete case analysis with respect to other variables was conducted throughout. Estimated mean change from baseline (CfB) utility values for each health state was then derived from derived model coefficients for fezolinetant 45 mg and placebo arms as estimated marginal means (least squares means) averaged across observed timepoints within the relevant window, with their associated standard errors pooled. Further details on these analyses are provided in the statistical analysis plan for responder analyses in the reference pack.[42]

Utility values were estimated by applying mean CfB utility values (Table 23) to the baseline utility derived from the fezolinetant 45 mg and placebo arms of pooled DAYLIGHT and SKYLIGHT 1&2 (Table 24). A summary of the utility values by treatment and response category used in the base case analysis is presented in Table 25. Further details can be found in the 'Utility' tab of the CEM.

Scenario analyses using alternative data sources for utility values were conducted to assess the impact on the cost-effectiveness analysis (Section 3.11.3).

Table 23: Mean change from baseline in utility values (base case)

Treatment	Response category	CfB utility inputs	SE	Source

Fezolinetant	Pre-response assessment	0.047	0.007	Derived using pooled EQ-5D-5L data (double blind period) from fezolinetant 45mg and placebo in the DAYLIGHT and SKYLIGHT 1 & 2 (HRT-unsuitable subpopulation) trials
	Responders	0.059	0.008	
	Non-responders	0.038	0.008	
No active treatment	Pre-response assessment	0.018	0.007	
	Responders	0.035	0.008	
	Non-responders	0.014	0.007	
Desvenlafaxine	Pre-response assessment	0.033	-	Calculation, mean CfB utility across no active treatment and fezolinetant arms.
	Responders	0.047	-	
	Non-responders	0.026	-	
Paroxetine (scenario analysis)	Pre-response assessment	0.033	-	
	Responders	0.047	-	
	Non-responders	0.026	-	

Abbreviations: CfB: change from baseline; SE: standard error.

Table 24: Mean baseline utility value in pooled DAYLIGHT and SKYLIGHT 1&2 (base case)

Time period	Utility	SE	Source
Baseline	0.779	0.156	Derived using pooled EQ-5D-5L data (double blind period) from fezolinetant 45mg and placebo in the DAYLIGHT and SKYLIGHT 1 & 2 (HRT-unsuitable subpopulation) trials.

Abbreviations: SE: standard error.

Table 25: Summary of utility values for cost-effectiveness analysis

Treatment	Response category	Utility value: mean (SE)	95% CI	Reference in submission (section and page number)	Justification
Fezolinetant	Pre-response assessment	0.826 (0.007)	0.812–0.839	Section 3.4.5 and page 46	Analyses of the trial utility data indicate that utility values varied by assigned treatment arm within each health state
	Responder	0.837 (0.008)	0.823–0.852		
	Non-responder	0.816 (0.008)	0.800–0.832		
No active treatment	Pre-response assessment	0.797 (0.007)	0.783–0.811		
	Responder	0.814 (0.008)	0.797–0.830		
	Non-responder	0.792 (0.007)	0.778–0.807		
Desvenlafaxine	Pre-response assessment	0.811 (-)	-		In absence of utility data, values for desvenlafaxine or paroxetine derived as mean of fezolinetant and no active treatment, reflecting NMA evidence of intermediate efficacy when compared with fezolinetant and no active treatment.
	Responder	0.826 (-)	-		
	Non-responder	0.804 (-)	-		
Paroxetine (scenario analysis)	Pre-response assessment	0.811 (-)	-		
	Responder	0.826 (-)	-		
	Non-responder	0.804 (-)	-		
Off Treatment with VMS, Pre-response	N/A	0.797 (0.007)	0.783–0.811		Assumed to be same as no active treatment in line with UK clinical opinion, given that treatment effect is expected to be lost immediately on discontinuation and patient's utility values expected to revert that of patients with moderate to severe VMS receiving no active treatment[1]
Off Treatment with VMS, Post response	N/A	0.797 (-)	-		Weighted average of utility values for responders and

					non-responders in the no active treatment arm. Assumed to be same as no active treatment arm in line with UK clinical opinion, given that treatment effect is expected to be lost immediately on discontinuation and patient's utility values expected to revert that of patients with moderate to severe VMS receiving no active treatment[1]
VMS cessation	N/A	0.852 (0.008)	0.546–1.000		Reflects available data from the phase 3 DAYLIGHT and SKYLIGHT 1&2 trials; specifically, the utility values of patients who reported a moderate to severe VMS frequency of zero in pooled DAYLIGHT and SKYLIGHT 1&2
Adverse events	N/A	See Table 22		Section 3.4.4 and page 46	Captures the impact of clinically important short-term AEs, aligning with the literature and prior TA367

Abbreviations: CI: confidence interval; N/A: not applicable; SE: standard error.
Source: Pooled EQ-5D-5L data from fezolinetant 45mg and placebo arm of in the DAYLIGHT and SKYLIGHT 1 & 2 (HRT-unsuitable subpopulation) trials, with mapping algorithm obtained from Hernández Alava *et al.* (2023).[38]

Utility age adjustment

In line with the NICE reference case, the model applies an age-dependent annual adjustment factor to account for the expected decline in health utility with increasing age, using UK data from Hernandez Alava *et al*., (2022).[43]

3.5 Cost and healthcare resource use identification, measurement and valuation

As noted in Section B.3.5 of the original company submission, a *de novo* economic SLR was conducted to identify economic evaluations for the treatment of VMS associated with menopause. Across the original SLR (June 2023) and SLR update (April 2024), 24 publications reporting on 23 unique studies were included in the SLR. However, due to the health state definitions used in the model and issues with the generalisability of the included studies to UK clinical practice, none of these studies were considered suitable to inform the model base case. As such, UK clinical expert opinion was sought by Astellas to inform healthcare resource use rates by health state in the model.[8]

The following cost categories were considered in the base case model:

- Treatment acquisition costs
- Costs associated with healthcare resource use
- AE costs
- Treatment-specific testing costs

The cost perspective adopted was that of the NHS and PSS.

3.5.1 Intervention and comparators' costs and resource use

Drug acquisition costs included in the model are summarised in Table 26.

The dosing schedule for fezolinetant 45 mg was in line with the licensed posology for fezolinetant in moderate to severe VMS. The dosing regimen used was also consistent with the fezolinetant 45 mg arm of DAYLIGHT, SKYLIGHT 1 and SKYLIGHT 2.

No drug acquisition costs were considered for no active treatment, given that patients are receiving no active treatment in this arm of the model.

The dosing schedule for desvenlafaxine (proxy for venlafaxine) and drug acquisition costs were aligned with the 75 mg modified release formulation of venlafaxine. As noted in Section 3.4.4, UK clinical experts highlighted that patients discontinuing SSRIs/SNRIs often require slow tapering in order to reduce the risk of withdrawal symptoms associated with these treatments. This was not explicitly modelled in the base case analysis; therefore, the additional appointment costs and potential QoL impact associated with tapering were not captured, which represents a conservative assumption with respect to fezolinetant.

No administration costs were considered for active treatments as they can be self-administered orally by patients.

Table 26: Drug cost inputs (base case)

Treatment	Route of administration	Dosing schedule	% receiving treatment	Cost per cycle (£)	Source
Fezolinetant	Oral	45 mg QD	100%	£44.80	BNF
No active treatment	N/A	N/A	100%	£0.00	Assumption
Venlafaxine (in lieu of desvenlafaxine)	Oral	75 mg QD	100%	£1.42	Dosage: Recommended dosing, Astellas Medical Data on File. Cost: NHS Drug Tariff October 2025 (Pack of 56, 75mg venlafaxine tablets)
Paroxetine (scenario analysis)	Oral	7.5 mg QD	100%	£0.95	Dosing: Simon, et al., (2013).[21] Cost: NHS Drug Tariff October 2025 (Pack of 28 10mg paroxetine tablets, AAH pharmaceuticals Ltd)

Abbreviations: BNF: British National Formulary; QD: once daily; N/A: not applicable.

3.5.2 Health-state unit costs and resource use

As noted in Section 3.2.4 and DGD Response Comment 3, feedback from the extensive UK expert consultations was strongly in favour of fezolinetant being initiated and managed in NHS primary care, in line with other treatments for moderate to severe VMS, if recommended.[2, 27, 28] As such, in the base case analysis it was assumed that treatment initiation and ongoing management for moderate to severe VMS would be conducted in primary care.[1, 2, 8]

Health state resource use and costs

A summary of the estimated resource use rates and associated unit costs considered in the base case model are presented in Table 27 and Table 28, respectively.

Healthcare resource use (HCRU) inputs used in the base case analysis were derived using estimates from UK clinical experts consulted for the DGD response.[1] Given that an appointment to assess response would be expected at Week 12 across treatment arms, any associated costs would be anticipated to net out across treatment arms; as such, no Week 12 appointment cost was applied in the base case.

The unit cost for procedures and monitoring related to the management of VMS were obtained using the Personal Social Services Research Unit (PSSRU) Costs of Health and Social Care 2023/2024 and the NHS Schedule of Costs 2021/2022 or 2022/2023.[44, 45]

Table 27: Healthcare resource use by health state (per year, base case)

Resource	Cessation of VMS	Responder	Non-responder
GP visits (first visit)	1.00	1.00	1.00
GP (follow-up visit)	0.00	0.00	2.00
A&E visits	0.00	0.00	0.50
Specialist visit (first visit)	0.00	0.00	1.00
Specialist visit (follow-up visit)	0.00	0.00	0.00

Abbreviations: A&E: Accident and Emergency; GP: general practitioner; VMS: vasomotor symptoms.
Source: UK clinician estimates.[1]

Table 28: Healthcare resource unit costs (base case)

Resource use	Unit Cost (£)	Source
GP visits (first visit)	£55.00	PSSRU, 2023. Cost per GP surgery consultation (10 minutes)
GP visits (follow-up visit)	£55.00	
A&E visit	£158.47	National schedule of NHS costs 2021/22. Code: VB09Z (Emergency Medicine, Category 1 Investigation with Category 1-2 Treatment)
Specialist visit (first visit)	£215.19	National schedule of NHS costs 2021/22: WF01A (Consultant led, non-admitted face-to-face attendance)
Specialist visit (follow-up visit)	£181.26	National schedule of NHS costs 2021/22: WF01B (Consultant led, non-admitted face-to-face attendance)

Abbreviations: A&E: Accident and Emergency; GP: general practitioner; NHS: national health service; PSSRU: personal and social services research unit.

Costs of healthcare resource use were applied on a per cycle basis, converted from annual costs, using the respective health state inputs; a summary of the base case resource costs per health state are presented in Table 29.

Table 29: Resource use costs per health state (base case)[a]

Health state	Resource utilisation cost (yearly)	Cost per cycle (£)
On Treatment Pre-Response Assessment	NA[b]	Fezolinetant: £22.32 No active treatment: £28.45 Desvenlafaxine: £23.65
VMS cessation	£55.00	£4.22
Off Treatment with VMS[c]	£55.00	£4.22
Responder	£55.00	£4.22
Non-responder	£459.43	£35.22

[a] Costs apply to each treatment arm of the model. [b] Not applicable because the On Treatment Pre-Response Assessment takes 12. [c] Cost per cycle in the Off Treatment with VMS health state was based on the weighted average of the responder and non-responder cost per cycle for the no active treatment arm.
Abbreviations: NA: not applicable; VMS: vasomotor symptoms.
Source: UK clinician estimates.[8]

Treatment-specific resource use and costs

In line with the committee's preference, treatment-specific healthcare resource use for liver function tests (LFTs) for fezolinetant (**DGD Sections 3.4 and 3.13: Monitoring requirements; Uncaptured costs**) is now included in the base case analysis (Table 30).

In the base case analysis, LFT costs were applied at Weeks 0 (baseline), 4, 8, 12, 24 and 36. The Summary of Product Characteristics (SmPC) for fezolinetant states that 'LFTs must be performed prior to treatment initiation and monthly during the first three months of treatment, then based on clinical judgement. LFTs must also be performed when symptoms suggestive of liver injury occur'. Accordingly, Weeks 0, 4, 8 and 12 are mandated, with subsequent monitoring dependent on clinical need. Additional LFTs beyond Week 12 were modelled only for patients who are on treatment with fezolinetant and who are experiencing elevated liver enzymes in the first year of treatment, which was observed in 4.42% of patients in the DAYLIGHT trial.

Scenario analyses were conducted which excludes liver monitoring costs, and which includes costs associated with additional appointments due to liver monitoring (Section 3.11.3). In the latter scenario, clinician interviews consistently stated that these are typically conducted by phlebotomists or healthcare assistants (both NHS Band 2) in primary care and take no more than 5–10 minutes. As such, it was conservatively modelled that additional appointments would be conducted by a Band 5 GP practice nurse, at a higher hourly rate, for 7.5 minutes (midpoint of the range).[2]

Table 30: Fezolinetant liver testing costs (base case)

Monitoring services	Unit Cost (£)	Source
Liver Function Test Cost	£1.61	National schedule of NHS costs 2022/23; DAPS04
Liver function test appointment cost (scenario analysis)	£5.88	PSSRU, 2024. Assumption based on 7.5 minutes of GP practice nurse time (£47 per hour).

Abbreviations: NHS: National Health Service.

3.5.3 Adverse reaction unit costs and resource use

All-grade AE management costs were considered in the base case analysis and are presented in Table 31. A scenario analysis excluding AE costs was also conducted to assess the impact on the cost-effectiveness analysis (Section 3.11.3).

Table 31: AE costs

Event	Cost per Event	Source
Headache	£16.50	Calculation based on the assumption that 30% of patients with AEs consult a GP and incur the cost of a GP appointment (£55, Table 28) in line with TA367.[39]
Fatigue	£16.50	
Asthenia	£16.50	
Constipation	£16.50	
Dry mouth	£16.50	
Nausea	£16.50	
Dizziness	£16.50	
Insomnia	£16.50	

Somnolence	£16.50	
Abnormal vision	£16.50	

Abbreviations: AE: adverse event; GP: general practitioner.

3.5.4 Miscellaneous unit costs and resource use

No additional miscellaneous unit costs and resource use were included in the base case analysis.

3.6 Severity

Fezolinetant does not meet the criteria for a severity weight.

3.7 Uncertainty

Not applicable, please refer to Section 3.11 on exploring uncertainty.

3.8 Managed access proposal

It is anticipated that the appraisal will result in routine commissioning and therefore no managed access proposal is required.

3.9 Summary of base-case analysis inputs and assumptions

3.9.1 Summary of base-case analysis inputs

A summary of inputs for the base case analysis is presented in Table 32.

Table 32: Summary of variables applied in the economic model (base case)

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Model characteristics			
Time horizon	10 years	N/A	Section 3.2.2
Cycle length	4 weeks	N/A	
Half-cycle correction	Yes	N/A	
Discount rate (costs)	3.5%	N/A	
Discount rate (benefits)	3.5%	N/A	
Perspective on cost	NHS and PSS	N/A	
Perspective on outcomes	All relevant health effects	N/A	
Age-adjusted utility	Yes	N/A	Section 3.4.5
Mortality risk	General population mortality	N/A	Section 3.3.2.5
Patient Characteristics			

Mean starting age, years	51.0	41.0–61.0 (Normal)	Section 3.3.1
Responder distribution			
Fezolinetant responder distribution	41.62%	25.31%–57.94% (Beta)	Section 3.3.2.1
No Treatment responder distribution	21.83%	13.27%–30.39% (Beta)	
Responder OR, desvenlafaxine	0.84	0.35–2.09 (Log normal)	
Discontinuation			
Desvenlafaxine, Within Trial	[redacted]	[redacted] (Beta)	Section 3.3.2.2
Desvenlafaxine, Week 12–24, Responder	[redacted]	[redacted] (Beta)	
Desvenlafaxine, Week 12–24, Non-Responder	[redacted]	[redacted] (Beta)	
Desvenlafaxine, Week 24+, Responder	[redacted]	[redacted] (Beta)	
Desvenlafaxine, Week 24+, Non-Responder	[redacted]	[redacted] (Beta)	
Fezolinetant, Within Trial	[redacted]	[redacted] (Beta)	
Fezolinetant, Week 12–24, Responder	[redacted]	[redacted] (Beta)	
Fezolinetant, Week 12–24, Non-Responder	[redacted]	[redacted] (Beta)	
Fezolinetant, Week 24+, Responder	[redacted]	[redacted] (Beta)	
Fezolinetant, Week 24+, Non-Responder	[redacted]	[redacted] (Beta)	
Desvenlafaxine OR, Responder Discontinuation	[redacted]	[redacted] (Log normal)	
VMS cessation state transitions			
Median duration of symptoms (years)	3.40	2.73–4.07 (Normal)	Section 3.3.2.3
Utility			
Utility, VMS Cessation	0.852	0.84–0.87 (Normal)	Section 3.4.5
Utility, Baseline	0.779	0.47–1.00 (Normal)	
Utility CfB, Fezo, Pre Timepoint	0.047	0.03–0.06 (Normal)	
Utility CfB, Placebo, Pre Timepoint	0.018	0.00–0.03 (Normal)	
Utility CfB, Fezo, Post Timepoint, Responder	0.059	0.04–0.07 (Normal)	

Utility CfB, Fezo, Post Timepoint, Non-responder	0.038	0.02–0.05 (Normal)	
Utility CfB, Placebo, Post Timepoint, Responder	0.035	0.02–0.05 (Normal)	
Utility CfB, Placebo, Post Timepoint, Non-responder	0.014	0.00–0.03 (Normal)	
Disutility			
One-off AE Disutility, Fezolinetant	0.0013	SE: 0.0001 (Normal)	Section 3.4.4
One-off AE Disutility, No treatment	0.0000	SE: 0.0000 (Normal)	
One-off AE Disutility, Desvenlafaxine	0.0036	SE: 0.0004 (Normal)	
Resource use and costs			
Cost per Cycle, Active Treatment, Cessation of VMS	£4.22	£3.43–£5.08 (Gamma)	Section 3.5.2
Cost per Cycle, Active Treatment, Response	£4.22	£3.43–£5.08 (Gamma)	
Cost per Cycle, Active Treatment, Non-response	£35.22	£28.66–£42.45 (Gamma)	
Cost per Cycle, No Treatment, Cessation of VMS	£4.22	£3.43–£5.08 (Gamma)	
Cost per Cycle, No Treatment, Response	£4.22	£3.43–£5.08 (Gamma)	
Cost per Cycle, No Treatment, Non-response	£35.22	£28.66–£42.45 (Gamma)	
Liver Function Test	£1.61	£1.31–£1.94 (Gamma)	
Patients with Elevated Liver Enzymes	4.42%	3.60%–5.33% (Gamma)	
Liver Function Test appointment cost	£5.88	£4.78–£7.08 (Gamma)	

Abbreviations: CI: confidence interval; N/A: not applicable; OR: odds ratio; SE: standard error.

3.9.2 Assumptions

A list of the assumptions made in the base case analysis and their justifications are provided in Table 33.

Table 33: Model assumptions (base case)

Parameters	Description of base case assumption(s)	Justification
Model structure	Markov cohort model with six health states, two of which were based on response status at the treatment decision timepoint: • On Treatment – Pre-Response Assessment • On Treatment Responder • On Treatment Non-Responder • Off Treatment with VMS (pre-/post-response assessment) • VMS cessation • Death	The revised model structure addresses key issues in the DGD by allowing direct incorporation of relative treatment effects for fezolinetant versus comparators, avoiding the need for transition matrices. Health states are defined by response rather than moderate to severe VMS frequency categories, reducing structural assumptions and aligning with the binary outcomes of the phase 3 fezolinetant and comparator trials (with conservative handling of missing data). The response assessment further reduces uncertainty by ensuring that non-responders discontinue treatment, so long-term efficacy is not overestimated. Additionally, incorporation of treatment discontinuation by non-responders avoids overestimation of long-term efficacy. The model explicitly accounts for placebo effects by using trial-based response and utility data, ensuring that patients receiving no active treatment are assumed to experience some improvement. In addition, the model no longer relies on natural history estimates from structured expert elicitation, instead drawing solely on trial data to avoid additional assumptions. The model is not heavily reliant on the assumption that response utilities are maintained over the long term, as the median treatment duration for fezolinetant was approximately 11 months (mean: 18 months) and over 50% of patients were modelled to achieve VMS cessation by around 5 years. Collectively, by addressing or minimising most of the EAG's key concerns, the revised structure reduces overall decision uncertainty.
Time horizon	10 years	There is no differential mortality effect between treatment options and the differences in costs and clinical outcomes relate to a relatively short period. As such, in line with the NICE reference case, a time horizon shorter than a lifetime was justified. The median/mean treatment duration for fezolinetant in the current model is approximately 11.0/18.4 months. Corresponding to a 61%/57% reduction in treatment duration compared with the original submission model (28.5/42.5 months). Given that the vast majority of cohort are off treatment by the end of the model time

		horizon, the cost-effectiveness analysis is not sensitive to this assumption. This approach was further validated by three UK clinical experts who indicated that a 10-year time horizon was appropriate, given that they expect the vast majority of patients to have discontinued treatment by the 10-year timepoint.[8]
Discount rate	Costs and health effects will be discounted at an annual rate of 3.5%	A discount rate of 3.5% was used in alignment with the NICE reference case.
Cycle length	4-week cycles	A four-week cycle length was used in the model in line with the clinical assessment timepoints used in SKYLIGHT 1&2 and DAYLIGHT.
Efficacy	In the On Treatment Pre-Response Assessment health state, efficacy was modelled based on the impact of treatment on utility values using pooled DAYLIGHT and SKYLIGHT 1&2 (HRT-unsuitable subpopulation) data	Reflects available data from the phase 3 DAYLIGHT and SKYLIGHT 1&2 trials.
	In the post-response assessment phase, efficacy was modelled based on the impact of treatment on the proportion of responders versus non-responders and utility values associated with each response health state and by whether patients are on active treatment or not.	Reflects available data from the phase 3 DAYLIGHT and SKYLIGHT 1&2 trials.
Response	Responder rates for fezolinetant and no active treatment were modelled using pooled DAYLIGHT and SKYLIGHT 1&2 (HRT-unsuitable subpopulation) data	Reflects available data from the phase 3 DAYLIGHT and SKYLIGHT 1&2 trials.
	Responder rate for desvenlafaxine was modelled by applying the NMA-derived response OR to the responder rate in the fezolinetant arm	Reflects available data from the response NMA. Response outcome was defined as a ≥75% reduction in moderate to severe VMS at Week 12. Missing data for responder status was imputed primarily using LOCF imputation, to align with the approach taken by comparator trials, minimise methodological heterogeneity and preserve the NMA assumption of homogeneity.
Treatment discontinuation	All-cause discontinuation probabilities for fezolinetant were modelled based on pooled DAYLIGHT and SKYLIGHT 1&2 (HRT-unsuitable subpopulation) data	Reflects available data from the phase 3 DAYLIGHT and SKYLIGHT 1&2 trials.
	All-cause discontinuation probabilities for desvenlafaxine were modelled by applying the NMA-derived treatment	Reflects available data from the discontinuation NMA.

	discontinuation OR to the corresponding discontinuation probabilities for the fezolinetant arm	
	Patients in either active treatment arm (fezolinetant or desvenlafaxine) could discontinue treatment due to all-cause discontinuation or VMS cessation. Additionally, 50% of non-responders were modelled to continue treatment until Week 52.	Loss of treatment response in patients with moderate to severe VMS is clinically measurable and will therefore lead to treatment discontinuation. As such, the discontinuation rate accounts for loss of response, as well as discontinuation for other reasons, such as adverse events. Consistent with UK clinical feedback,[1] discontinuation rates for the SSRIs/SNRIs were modelled to be greater than those for fezolinetant based on observed data and application of relative treatment effects, given these treatments are associated with unpleasant side effects. The base case assumption that 50% of non-responders discontinue treatment reflects pooled data from the phase 3 DAYLIGHT and SKYLIGHT 1&2 trials. These data indicated that approximately half of the women classified as non-responders under the 75% threshold nevertheless achieved a 50% improvement in VMS frequency. UK clinical experts further noted that such patients would typically stay on treatment until Week 52 in clinical practice.[1]
	Treatment discontinuation was not possible in the no active treatment arm, as patients were modelled to not be receiving any active treatment.	
VMS cessation	The model assumed that there will be a natural resolving and eventual cessation of VMS. Patients in this health state have a separate, higher utility applied to them compared with those in the VMS frequency health states and do not incur any VMS treatment costs. The cessation of VMS state was based on the median duration of symptoms for postmenopausal women reported in Avis *et al.*, (2015)[34], which was used to estimate a probability of symptom cessation per cycle using an exponential model. The VMS cessation rate was assumed to be constant over the time horizon of the model.	Reflects the natural progression of moderate to severe VMS. The source used to derive per cycle VMS cessation rates was aligned with the EAG's preference for the input to reflect the cohort of postmenopausal women informing the pooled DAYLIGHT and SKYLIGHT 1&2 (HRT-unsuitable subpopulation) data.
Health states utilities	Utilities values were treatment-specific as well as health-state dependent.	Reflects available data from the phase 3 DAYLIGHT and SKYLIGHT 1&2 trials.

Adverse events	Adverse events were considered in the model.	The utility impact of AEs has been modelled in line with NICE requirements to capture all aspects of HRQoL associated with treatment.
Mortality risk	Patients were assumed to be at risk of death throughout the model time horizon, irrespective of health state.	Based on safety results from DAYLIGHT, SKYLIGHT 1, SKYLIGHT 2 and SKYLIGHT 4 clinical trials and findings from the published literature,[35] it was concluded that VMS associated with menopause did not have any meaningful impact on mortality risk and therefore age-specific mortality rates for females are applied to all health states over the model time horizon.
Costs	Treatment administration costs were not considered in the model. No treatment acquisition costs were considered for the no active treatment comparator. Costs associated with healthcare resource use were assumed to be dependent on health state as well as treatment specific in the case of testing costs for fezolinetant. Patients in the same health state are assumed to have a consistent level of health on average. Therefore, patients in the same health state are also assumed to have similar healthcare resource utilisation on average.	As patients in the no active treatment were not expected to receive any active pharmacological treatments for moderate to severe VMS, it was assumed that no active treatment administration or acquisition costs would be incurred. All active treatments in the base case analysis can be self-administrated orally by patients, which is assumed to be associated with no administration costs. Healthcare resource use rates were aligned with feedback from UK clinical experts.[1]

Abbreviations: AE: adverse events; HRQoL: health-related quality of life; HRT: hormone replacement therapy; LOCF: last observation carried forward; NMA: network meta-analysis; OR: odds ratio; SNRIs: serotonin–noradrenaline reuptake inhibitors; SSRIs: selective serotonin reuptake inhibitors; VMS: vasomotor symptoms.

3.10 Base-case results

3.10.1 Base-case incremental cost-effectiveness analysis results

A summary of results in the probabilistic base-case analysis and incremental net health benefits (INHB) are presented in Table 34 and Table 35, respectively, with probabilities of cost-effectiveness at willingness-to-pay (WTP) thresholds of £20,000 and £30,000 per QALY shown in Table 36 versus no active treatment and Table 37 versus desvenlafaxine.

The pair-wise probabilistic ICERs were £10,263 per QALY gained for fezolinetant versus no active treatment and £18,053 per QALY gained for fezolinetant versus desvenlafaxine (proxy for venlafaxine), both below the £20,000 WTP threshold. These results demonstrate that fezolinetant is cost-effective in each pair-wise comparison. The INHB for fezolinetant versus both comparators was positive, and fezolinetant had the highest probability of cost-effectiveness across all options. Taken together, these results indicate that fezolinetant is the most cost-effective treatment option in the analysis, with the ICER versus no active treatment representing the most clinically relevant and reliable estimate for decision-making (see Section 3.2.4).

Disaggregated deterministic results of the base case incremental cost-effectiveness analysis are presented in Appendix H.

Table 34: Probabilistic base-case results

Technologies	Total			Incremental			ICER
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	Versus baseline (£/QALY)
Fezolinetant	£2,157.08	8.436	7.088	-	-	-	-
No Treatment	£1,664.31	8.436	7.040	£492.77	0.000	0.048	£10,263
Desvenlafaxine	£1,547.11	8.436	7.054	£609.97	0.000	0.034	£18,053

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years.

Table 35: Incremental net health benefit

Technologies	Total		Incremental		INHB	
	Costs (£)	QALYs	Costs (£)	QALYs	£20,000	£30,000
Fezolinetant	£2,157.08	7.088	-	-	-	-
No Treatment	£1,664.31	7.040	£492.77	0.048	0.02	0.03
Desvenlafaxine	£1,547.11	7.054	£609.97	0.034	0.00	0.01

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years; INHB: incremental net health benefit.

Table 36: Probability of fezolinetant being cost-effective versus no active treatment

Technologies	Probability of cost-effective at £20,000/QALY gained	Probability of cost-effective at £30,000/QALY gained
Fezolinetant	96%	100%
No Treatment	4%	0%

Abbreviations: QALYs: quality-adjusted life years.

Table 37: Probability of fezolinetant being cost-effective versus desvenlafaxine

Technologies	Probability of cost-effective at £20,000/QALY gained	Probability of cost-effective at £30,000/QALY gained
Fezolinetant	60%	88%
Desvenlafaxine	40%	12%

Abbreviations: QALYs: quality-adjusted life years.

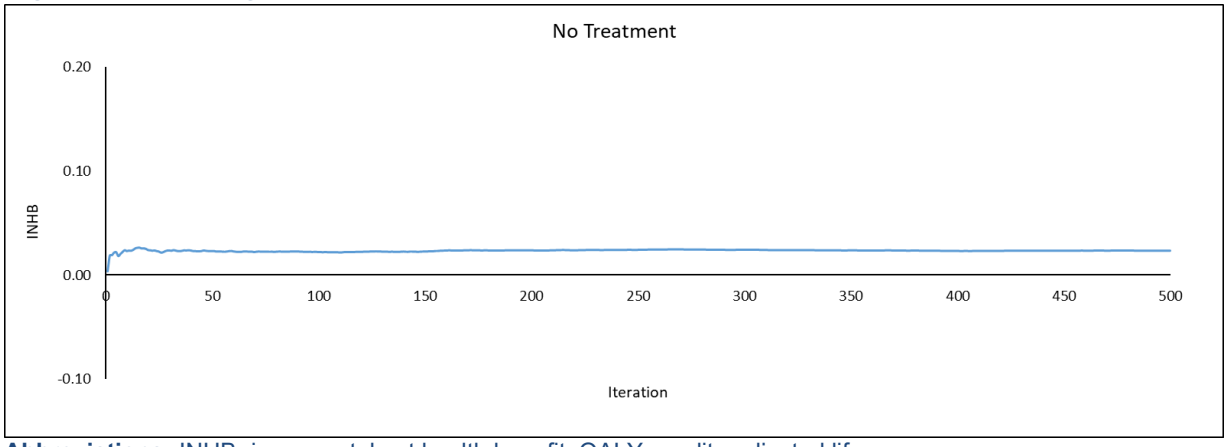
3.11 Exploring uncertainty

To address uncertainty in model inputs and assumptions, several sensitivity analyses were conducted, including PSA (Section 3.11.1), deterministic sensitivity analysis (DSA; Section 3.11.2) and scenario analyses (Section 3.11.3). The PSA was performed to analyse the joint uncertainty of the model parameters, and the DSA and scenario analyses were used to identify model drivers or test alternative data sources.

3.11.1 Probabilistic sensitivity analysis

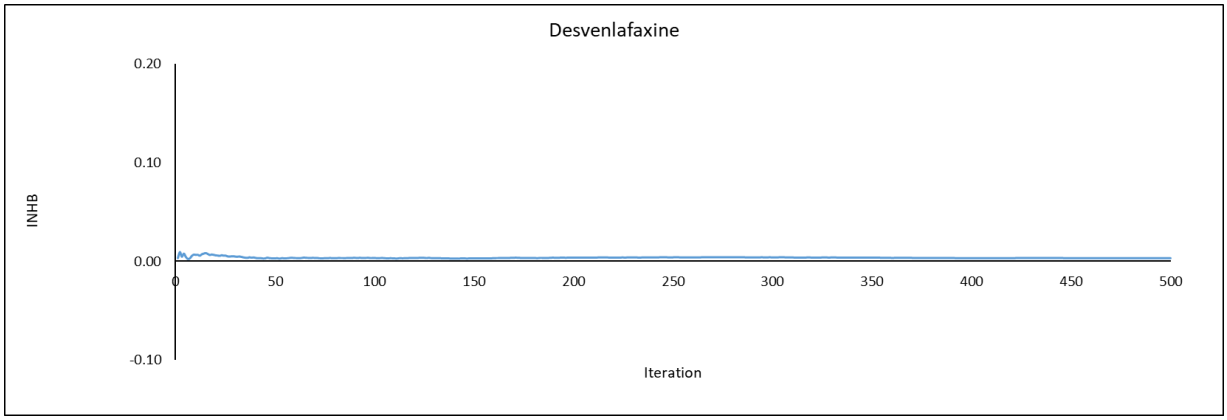
As reflected in the base case results presented in Section 3.10.1, probabilistic sensitivity analyses with 500 iterations were performed to assess the uncertainty associated with model input parameters. Use of 500 iterations was deemed appropriate based on the results of the INHB convergence tests for fezolinetant versus no active treatment and desvenlafaxine, as shown in Figure 10 and Figure 11, respectively.

Figure 10: Convergence plot for INHB versus no active treatment at £20,000/QALY



Abbreviations: INHB: incremental net health benefit; QALY: quality-adjusted life year.

Figure 11: Convergence plot for INHB versus desvenlafaxine at £20,000/QALY



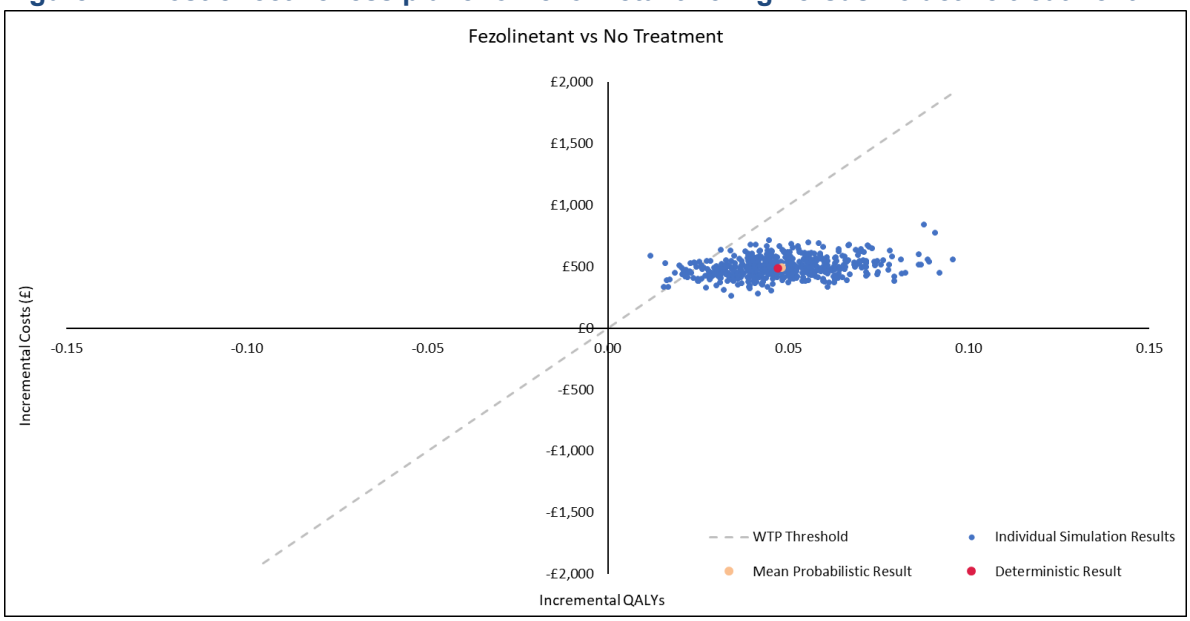
Abbreviations: INHB: incremental net health benefit; QALY: quality-adjusted life year.

The probabilistic base case results are presented in Table 34 and the cost-effectiveness plane scatter plots and cost-effectiveness acceptability curves are presented below for fezolinetant versus no active treatment (Figure 12) and desvenlafaxine (Figure 13).

The results of the cost-effectiveness plane show very little variation with regard to incremental costs in each iteration. On the effectiveness side, all iterations fell within the northeast quadrant, and more than half the iterations fell below the £20,000 WTP threshold, with modest variation in incremental QALYs gained. Additionally, there was overlap between results of the probabilistic and deterministic analyses (Section 3.11.2).

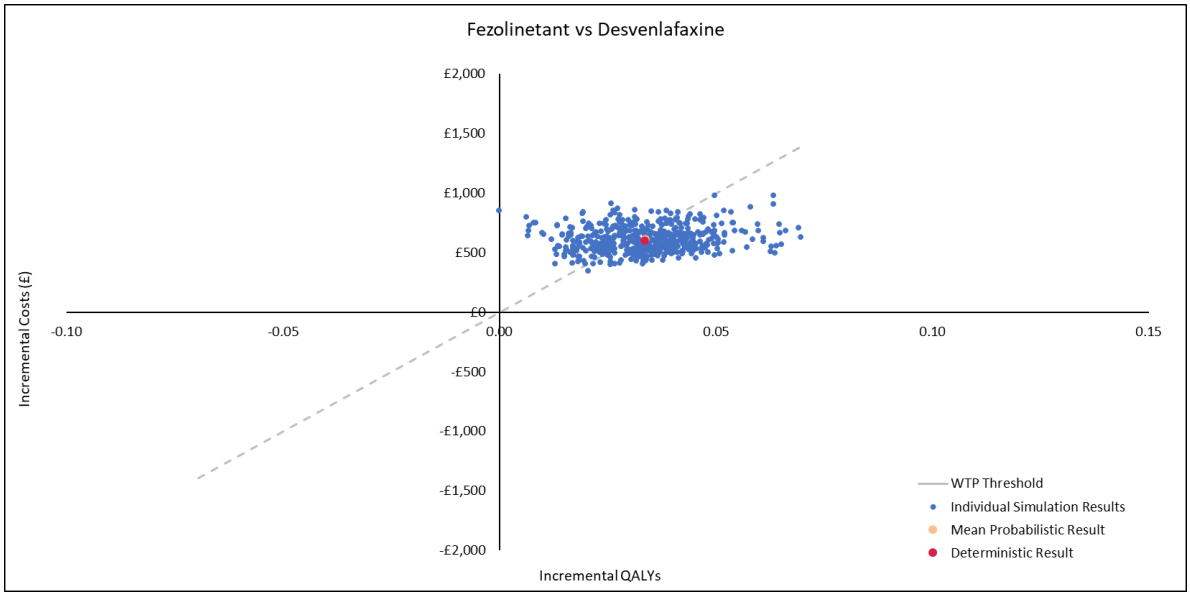
The cost-effectiveness acceptability curves shows that fezolinetant has a higher probability of being cost-effective when compared with no active treatment or desvenlafaxine at both WTP thresholds of £20,000/QALY and £30,000/QALY.

Figure 12: Cost-effectiveness plane for fezolinetant 45 mg versus no active treatment



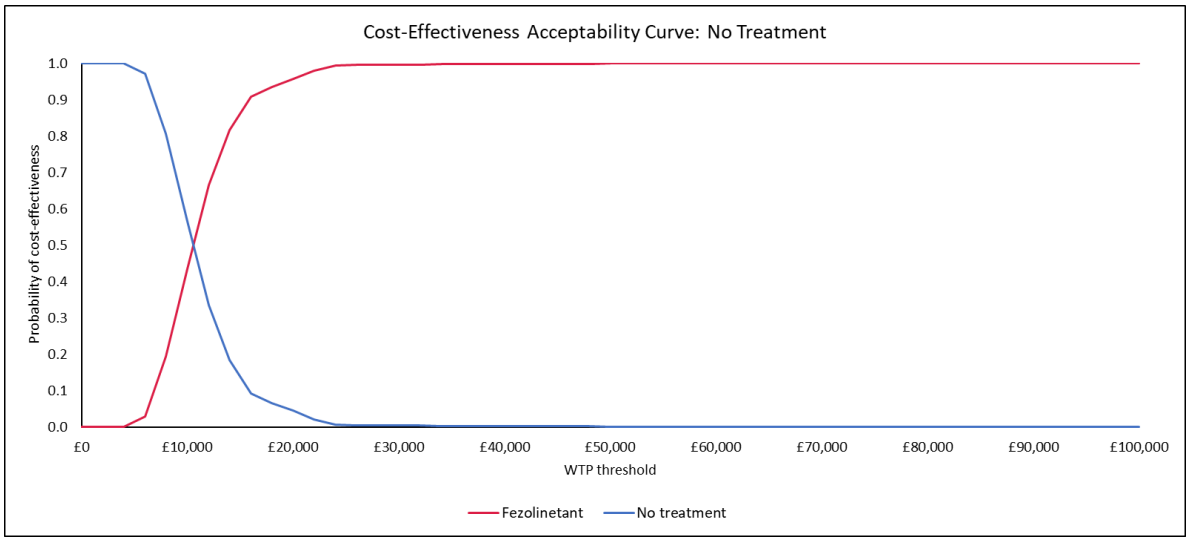
Abbreviations: ICER: incremental cost-effectiveness ratio; WTP: willingness-to-pay.

Figure 13: Cost-effectiveness plane for fezolinetant 45 mg versus desvenlafaxine



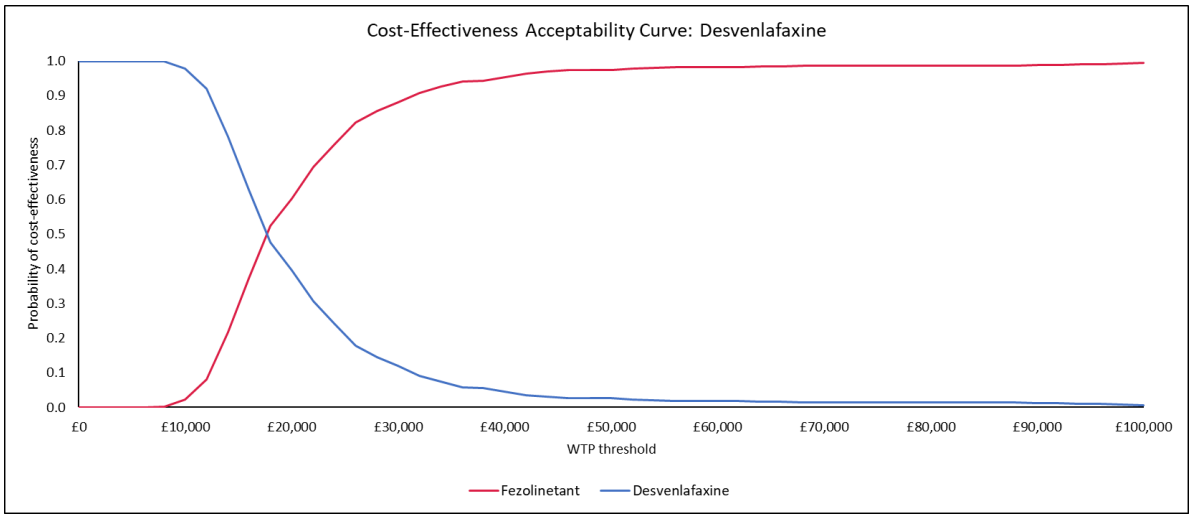
Abbreviations: ICER: incremental cost-effectiveness ratio; WTP: willingness-to-pay.

Figure 14: Cost-effectiveness acceptability curve for fezolinetant 45 mg versus no active treatment



Abbreviations: WTP: willingness to pay.

Figure 15: Cost-effectiveness acceptability curve for fezolinetant 45 mg versus desvenlafaxine



Abbreviations: WTP: willingness to pay.

3.11.2 Deterministic sensitivity analysis

In the DSA, each parameter of interest was changed independently while all others remained at their default base-case values. The following key model inputs were evaluated in the DSA:

- Patient characteristics
- Responder rates
- Treatment discontinuation
- Natural VMS cessation
- HCRU
- Utilities

- AE disutilities and costs

A summary of results in the deterministic base-case analysis and INHB are presented in Table 38 and Table 39, respectively. The deterministic base case results are in close alignment with the probabilistic base case results in Section 3.10.1.

Table 38: Deterministic base-case results

Technologies	Total			Incremental			ICER
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	Versus baseline (£/QALY)
Fezolinetant	£2,160.52	8.449	6.915	-	-	-	-
No Treatment	£1,675.89	8.449	6.868	£484.63	0.000	0.047	£10,313
Desvenlafaxine	£1,558.51	8.449	6.881	£602.01	0.000	0.034	£17,969

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years.

Table 39: Incremental net health benefit

Technologies	Total		Incremental		INHB	
	Costs (£)	QALYs	Costs (£)	QALYs	At £20,000	At £30,000
Fezolinetant	£2,160.52	6.915	-	-	-	-
No Treatment	£1,675.89	6.868	£484.63	0.047	0.02	0.03
Desvenlafaxine	£1,558.51	6.881	£602.01	0.034	0.00	0.01

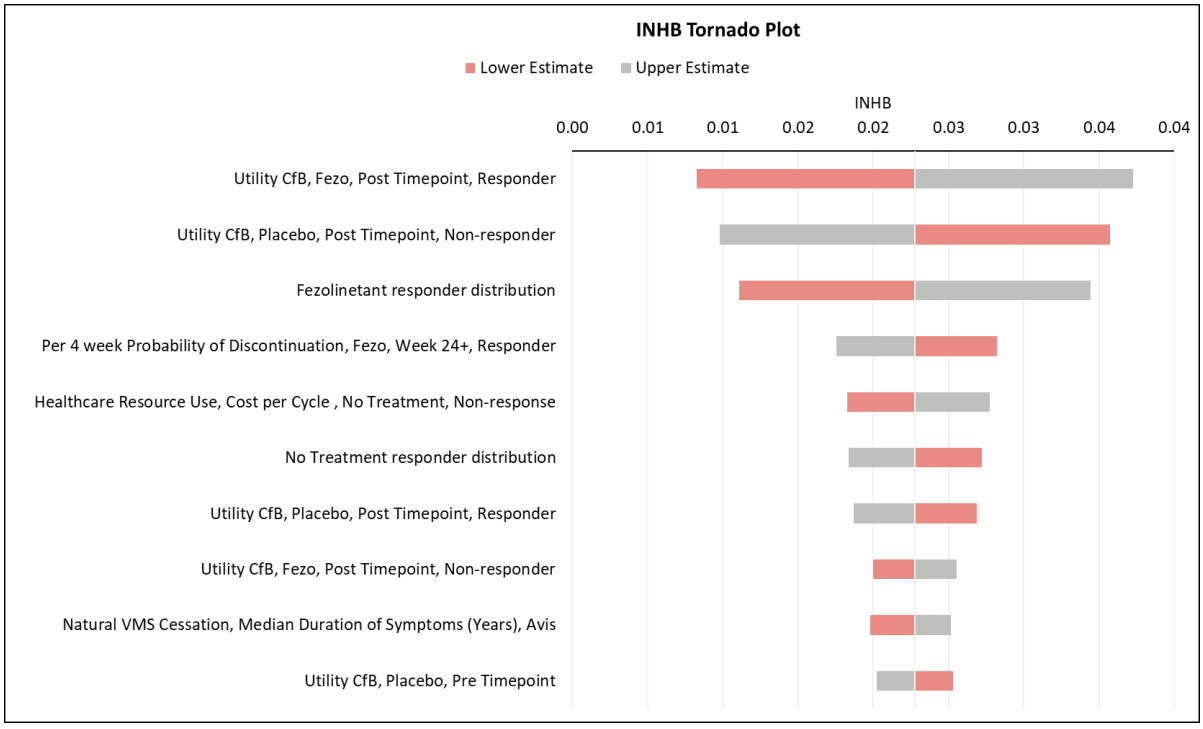
Abbreviations: QALYs: quality-adjusted life years; INHB: incremental net health benefit.

The ten most influential variables in the DSA for the analysis of fezolinetant versus no active treatment and desvenlafaxine are presented as tornado plots in Figure 16 and Figure 17, respectively.

The DSA results showed that the INHB was most sensitive to CfB utility for the fezolinetant Responder health state and no active treatment Non-Responder health state followed by the fezolinetant responder rates. To a lesser extent, INHB was sensitive including the fezolinetant responders treatment discontinuation probability at Week 24+, CfB utility for the no active treatment Responder health state and the no active treatment responder rate. Overall, none of these parameters crossed the point of indifference (i.e., when INHB is zero) for either their lower or upper bound values or had any substantial impact on the cost-effectiveness estimates, showing the model to be largely robust to individual parameter uncertainty.

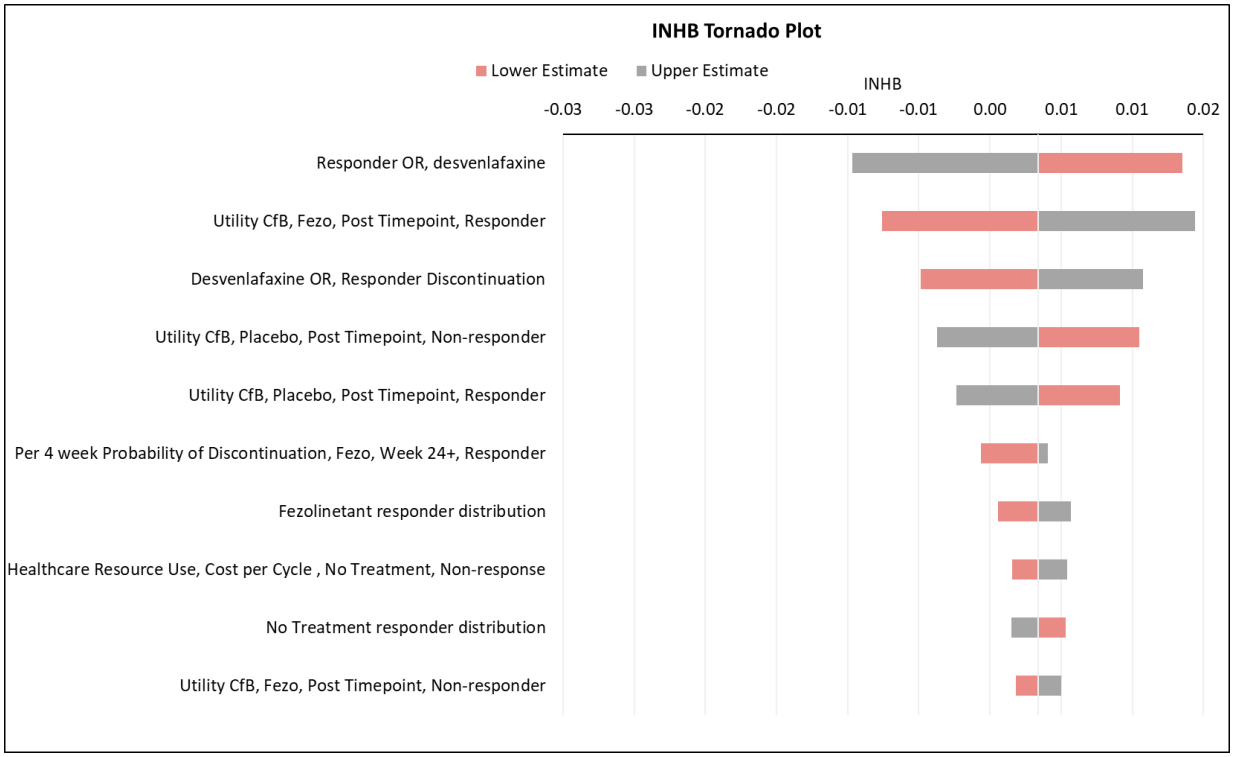
The DSA results for fezolinetant versus desvenlafaxine showed that the INHB was most sensitive to CfB utility for the fezolinetant Responder health state and the Response OR for fezolinetant versus desvenlafaxine. While all ten parameters crossed the point of indifference at either the lower or upper bound, the magnitude of variation was modest, and no parameter had a substantial impact on the overall cost-effectiveness estimates. These results suggest that although fezolinetant could appear less cost-effective under extreme assumptions, such scenarios are unlikely to reflect clinical reality. Importantly, the probabilistic sensitivity analysis, which jointly considers uncertainty across all parameters, consistently supported the cost-effectiveness of fezolinetant, providing reassurance that the base-case conclusions are robust for decision-making.

Figure 16: Tornado diagrams depicting results of fezolinetant versus no active treatment (INHB at £20,000/QALY)



Abbreviations: INHB: incremental net health benefit; VMS: vasomotor symptoms.

Figure 17: Tornado diagrams depicting results of fezolinetant versus desvenlafaxine (INHB at £20,000/QALY)



Abbreviations: INHB: incremental net health benefit; VMS: vasomotor symptoms.

3.11.3 Scenario analysis

A list of the scenario analyses considered in the model and the results for comparisons of fezolinetant versus no active treatment and desvenlafaxine are presented in Table 40 and Table 41, respectively.

Scenarios for fezolinetant versus no active treatment

The model results were robust across a wide range of scenario analyses, with most showing minimal impact on the ICER relative to the base case. The largest driver was the assumption of a no stopping rule for non-responders, which increased the ICER by 65.6%. However, this represents an extreme and clinically implausible scenario, as UK clinical opinion confirms that GPs would discontinue non-responders after the response assessment period.[1] Other scenarios with greater than 9% change in the ICER relative to the base case included alternative response definitions or timepoint and the scenario in which 100% of non-responders discontinued at Week 12. Importantly, across all modelled scenarios, the ICERs versus no active treatment remained below the £20,000 per QALY threshold, confirming the robustness of the base-case conclusions.

Scenarios for fezolinetant versus SSRI/SNRIs

Several scenario analyses were conducted to explore the impact of alternative data sources and assumptions on the base case results. Overall, the model results were generally stable, with most scenarios showing only modest variation in the ICERs and remaining below the £20,000 per QALY threshold, confirming the robustness of the base-case conclusions. For the comparison with paroxetine, to enable inclusion in the economic analysis and to facilitate a

pairwise comparison with fezolinetant, several assumptions were made: 1) response was defined as at least a 50% reduction in moderate to severe VMS frequency, as this was the only outcome available for paroxetine studies identified in the clinical SLR; 2) given that partial responders (see Section 3.2.2) are captured in this definition, a 100% stopping rule was applied to non-responders at the Week 12 treatment decision timepoint; 3) post-response assessment utility values and discontinuation rates derived for the 75% threshold were conservatively assumed to apply in this scenario; and 4) The efficacy is informed by RCT evidence for a dose of paroxetine (7.5 mg) that is not available in the UK or recommended by the BMS (10–20 mg) for treating moderate to severe VMS; additionally, given that recommended doses of paroxetine are expected to be associated with greater AE rates, the impact of paroxetine may be underestimated.[4] This scenario produced an ICER of£21,619 per QALY gained for fezolinetant versus paroxetine

Overall conclusion from scenario analyses

The scenario analyses for fezolinetant versus no active treatment, desvenlafaxine, and paroxetine demonstrated that the model results were robust to alternative data sources and assumptions. Across all scenarios, ICERs remained below the £20,000 per QALY threshold or within the £20,000–£30,000 range considered cost-effective by NICE. While certain assumptions, including no non-responder stopping rule, responder timepoint assessment (Week 24) and definition (50% threshold) had a greater influence on the ICER, none of these scenarios altered the overall conclusion that fezolinetant is a cost-effective treatment option compared with relevant comparators.

Table 40: Summary of scenario analyses and results for fezolinetant versus no active treatment (probabilistic)

Scenario Analysis	Base-case input	Versus no active treatment		
		Incremental costs	Incremental QALYs	ICER (£/QALY)
Base-case (probabilistic)	-	**£485**	**0.05**	**£10,313**
Baseline age				
DAYLIGHT	Mean age of menopause onset in the UK	£492	0.05	£10,276
Pooled DAYLIGHT and SKYLIGHT 1&2 (HRT-unsuitable subpopulation)		£492	0.05	£10,254
Response assessment timepoint				
Week 4	Week 12	£407	0.04	£9,606
Week 24		£579	0.05	£11,645
Response definition				
50% reduction in VMS frequency	75% reduction in VMS frequency	£704	0.06	£11,628
PGI-C response		£697	0.06	£11,140
Response data source				
Pooled SKYLIGHT 1 & 2 (HRT-unsuitable)	Pooled DAYLIGHT and SKYLIGHT 1 & 2 (HRT-unsuitable subpopulation)	£453	0.05	£10,026
DAYLIGHT		£566	0.05	£10,776
Fezolinetant discontinuation rate data source				
DAYLIGHT	Pooled DAYLIGHT and SKYLIGHT 1 & 2 (HRT-unsuitable subpopulation)	£480	0.05	£10,162
Fezolinetant Week 24+ discontinuation rate data source				
Pooled SKYLIGHT 1 & 2 (HRT-unsuitable subpopulation) week 24-52	Pooled DAYLIGHT & SKYLIGHT 1&2 Week 12–24	£491	0.05	£10,340
Utility data source				

DAYLIGHT Pre-response: Week 0–12 (fezolinetant and no treatment) Post response: Week 12–24 (fezolinetant and no active treatment)	Pooled DAYLIGHT and SKYLIGHT 1&2 (HRT-unsuitable subpopulation) Pre-response: Week 0–12 (fezolinetant and no active treatment) Post response: Week 0–52 (fezolinetant) and week 0–24 (no active treatment)	£493	0.05	£10,515
Pooled SKYLIGHT 1 & 2 (HRT-unsuitable subpopulation) Pre-response: Week 0–12 (fezolinetant and no active treatment) Post response: Week 0–52 (fezolinetant) and week 0–12 (no active treatment)		£493	0.05	£9,932
Pooled SKYLIGHT 1 & 2 (HRT-unsuitable subpopulation) Pre-response: Week 0–12 (fezolinetant and no active treatment) Post response: Week 12–52 (fezolinetant) and week 0–12 (no active treatment)		£493	0.05	£10,058
Post responder assessment utility data source				
Pooled DAYLIGHT and SKYLIGHT 1 & 2 (HRT-unsuitable subpopulation) - Week 12–52 (fezolinetant) - Week 0–12 (no active treatment)	Pooled DAYLIGHT and SKYLIGHT 1 & 2 (HRT-unsuitable subpopulation) - Week 0–52: fezolinetant - Week 0–24: no active treatment	£493	0.05	£9,945
Fezolinetant monitoring cost				
Exclude	Include	£487	0.05	£10,137
Additional appointments for liver testing				

Include	Exclude	£502	0.05	£10,464
Adverse events				
Exclude disutilities	Include disutilities	£493	0.05	£9,993
1-week duration of AEs	3-week duration of AEs	£493	0.05	£10,081
Exclude AE costs	Include AE costs	£489	0.05	£10,185
Duration of VMS data source				
Avis *et al.*, (2015): all women with VMS	Avis *et al.*, (2015): postmenopausal women with VMS	£603	0.06	£9,485
Non-responder stopping rule				
No stopping rule	50% of non-responders discontinue treatment at Week 12	£1,149	0.07	£17,076
100% of non-responders discontinue treatment at Week 12	50% of non-responders discontinue treatment at Week 12	£374	0.04	£8,411

Abbreviations: AE: adverse event; HRT: hormone replacement therapy; ICER: incremental cost-effectiveness ratio; OR: odds ratio; QALY: quality-adjusted life years; VMS: vasomotor symptoms.

Table 41: Summary of scenario analyses and results for fezolinetant versus desvenlafaxine (probabilistic)

Scenario Analysis	Base-case input	Versus desvenlafaxine*		
		Incremental costs	Incremental QALYs	ICER (£/QALY)
Base-case (probabilistic)	**-**	**£602**	**0.03**	**£17,969**
Baseline age				
DAYLIGHT	Mean age of menopause onset in the UK	£609	0.03	£18,077
Pooled DAYLIGHT and SKYLIGHT 1&2 (HRT-unsuitable subpopulation)		£609	0.03	£18,040
Response assessment timepoint				
Week 4	Week 12	£521	0.03	£17,773
Week 24		£672	0.04	£18,637
Response definition				

50% reduction in VMS frequency	75% reduction in VMS frequency	£843	0.04	£19,995
PGI-C response		£852	0.04	£19,661
Response data source				
Pooled SKYLIGHT 1 & 2 (HRT-unsuitable subpopulation)	Pooled DAYLIGHT and SKYLIGHT 1 & 2 (HRT-unsuitable subpopulation)	£566	0.03	£17,825
DAYLIGHT		£690	0.04	£18,753
Fezolinetant discontinuation rate data source				
DAYLIGHT	Pooled DAYLIGHT and SKYLIGHT 1 & 2 (HRT-unsuitable subpopulation)	£599	0.03	£17,969
Fezolinetant Week 24+ discontinuation rate data source				
Pooled SKYLIGHT 1 & 2 (HRT-unsuitable subpopulation) week 24-52	Pooled DAYLIGHT & SKYLIGHT 1&2 Week 12–24	£606	0.03	£18,125
Desvenlafaxine discontinuation rate data source				
Bouchard *et al.*, (2012)	OR applied to fezolinetant (NMA)	£519	0.04	£11,975
Fezolinetant utility data source				
DAYLIGHT Pre-response: Week 0–12 Post response: Week 12–24	Pooled DAYLIGHT and SKYLIGHT 1&2 (HRT-unsuitable subpopulation) Pre-response: Week 0–12 Post response: Week 0–52	£610	0.03	£18,516
Pooled SKYLIGHT 1 & 2 (HRT-unsuitable) Pre-response: Week 0–12 Post response: Week 0–52		£610	0.03	£17,460
Pooled SKYLIGHT 1 & 2 (HRT-unsuitable) Pre-response: Week 0–12 Post response: Week 12–52		£610	0.03	£17,688
Fezolinetant post responder assessment utility data source				

Pooled DAYLIGHT and SKYLIGHT 1 & 2 (HRT-unsuitable subpopulation) Week 12–52	Pooled DAYLIGHT and SKYLIGHT 1 & 2 (HRT-unsuitable subpopulation) - Week 0–52: fezolinetant	£610	0.03	£17,476
Desvenlafaxine utility source				
Aligned with fezolinetant utilities	Average of fezolinetant and no active treatment utilities	£610	0.03	£19,470
Fezolinetant monitoring cost				
Exclude	Include	£604	0.03	£17,874
Additional appointments for liver testing				
Include	Exclude	£620	0.03	£18,338
Adverse events				
Exclude disutilities	Include disutilities	£610	0.03	£19,366
1-week duration of AEs	3-week duration of AEs	£610	0.03	£18,908
Exclude AE costs	Include AE costs	£621	0.03	£18,390
Duration of VMS data source				
Avis *et al.*, (2015): all women with VMS	Avis *et al.*, (2015): postmenopausal women with VMS	£758	0.05	£16,634
Non-responder stopping rule				
No stopping rule	50% of non-responders discontinue treatment at Week 12	£1,211	0.05	£24,557
100% of non-responders discontinue treatment at Week 12	50% of non-responders discontinue treatment at Week 12	£509	0.03	£16,160
SSRI comparator				
Paroxetine, 50% moderate to severe VMS frequency reduction, 100% of non-responders discontinue treatment at Week 12	Desvenlafaxine, 75% moderate to severe VMS frequency reduction, 50% of non-responders discontinue treatment at Week 12	£804	0.04	£21,619

Results for the final scenario are versus paroxetine*. **Abbreviations: AE: adverse event; HRT: hormone replacement therapy; ICER: incremental cost-effectiveness ratio; OR: odds ratio; QALY: quality-adjusted life years; VMS: vasomotor symptoms.

3.12 Subgroup analysis

No subgroup analyses were included in the model.

3.13 Benefits not captured in the QALY calculation

See Section B.3.13 of the original company submission.

3.14 Validation

3.14.1 Validation of cost-effectiveness analysis

External Validity

Expert input from health economists and UK clinical experts was sought during the development of the cost-effectiveness model to ensure that the inputs and assumptions reflected UK clinical practice. While the current model was not directly validated by patient representatives, the use of moderate to severe VMS frequency in the response definition was supported by their feedback in the original submission.

Internal model validity

In alignment with best practice, validation of the economic model was conducted by an independent health economist prior to the submission. These quality-control procedures made use of a checklist incorporating key elements of the TECH-VER checklist[46] (for technical and stress test checks) to ensure that the model generated accurate results which were consistent with input data and robust to extreme values. A technical cell by cell verification of formulae, functions and coding was performed as part of this process, as was review of all model calculations, including standalone formulae, equations and Excel macros programmed in Visual Basic for Applications. The correct functioning of the sensitivity and scenario analyses was also reviewed. The stress test ensured that the expected effect is observed when key inputs are varied in the model (e.g. when utilities for all health states for AEs are set to 0, all QALYS should result equal to 0).

3.15 Interpretation and conclusions of economic evidence

Given the key issues raised by the committee in the DGD, every effort has been made to develop a *de novo* cost-effectiveness model that is both robust and explicitly addresses key sources of uncertainty in the original submission model. As detailed in Section 3.2.2, the revised model directly incorporates treatment effects for fezolinetant versus relevant comparators (DGD Sections 3.5, 3.8, 3.11); defines health states by treatment response rather than VMS frequency categories, thereby reducing structural assumptions and aligning with binary responder outcomes of the phase 3 trials (DGD Section 3.10); applies a conservative approach to missing data, classifying patients with missing outcomes as non-responders (DGD Section 3.6); accounts for placebo response using trial-based data; no longer relies on natural history estimates of VMS from structured expert elicitation (DGD Section 3.11); and derives utilities directly from EQ-5D data collected in the fezolinetant phase 3 trials (DGD Section 3.11). New model assumptions on the timing of response assessment, the 75% VMS frequency threshold, and the continuation of partial responders were informed by NICE menopause guidelines, trial data, and UK clinical

expert opinion, ensuring close alignment with the expected NHS pathway of care. Collectively, these refinements ensure that the model is both fit-for-purpose and evidence-based, providing ICERs that are robust and reliable for the committee's decision-making.

The committee raised concerns that the modelled population might not reflect the NHS population eligible for fezolinetant, as there is no requirement in clinical practice for women to be experiencing ≥7 moderate to severe VMS episodes per day in order to be eligible for treatment (DGD Section 3.7). Feedback from UK Clinical experts consulted for the DGD response is that typically patients who seek treatment are those who experience frequent moderate to severe VMS, rather than all women who experience VMS. Therefore, experts considered the fezolinetant trial populations to be generalisable to NHS practice, noting that the inclusion criteria were appropriate and unlikely to overestimate treatment effects.[1] While some clinicians assess symptom burden holistically rather than focusing solely on VMS frequency, it was noted that women likely to be seeking treatment are those that are "really desperate and suffering, which would mean a significant number of hot flushes per day".[1] It was also noted that "7–8 [hot flushes] per day would generally be the average number that [they] would consider for treatment as opposed to observation".[1] These views are consistent with the clinical opinion sought by Astellas for the original submission, which indicated that the baseline characteristics of the fezolinetant trials were aligned with NHS clinical practice. Collectively, these insights support the generalisability of the clinical and cost-effectiveness results to the NHS population eligible for fezolinetant.

The cost-effectiveness of fezolinetant for treatment of moderate to severe vasomotor-predominant menopausal symptoms in patients who are deemed unsuitable for HRT was evaluated versus no active treatment and desvenlafaxine. The base case probabilistic ICERs versus no active treatment (£10,263 per QALY gained) and versus desvenlafaxine (£18,053 per QALY gained) were below the £20,000 per QALY WTP threshold and did not differ meaningfully from the corresponding deterministic ICER (£10,214 per QALY gained and £17,969 per QALY gained, respectively). The PSA indicated that the base-case results versus no active treatment or desvenlafaxine showed little variation with regard to incremental costs in each iteration. On the effectiveness side, all iterations fell within the northeast quadrant, and more than half the iterations fell below the £20,000 cost-effectiveness threshold, with a modest variation in incremental QALYs gained. A scenario analysis for paroxetine, which required additional assumptions to enable pairwise comparison, produced an ICER of £21,619 per QALY gained. Across all probabilistic scenario analyses, fezolinetant was consistently demonstrated to be cost-effective.

Overall, the base case and scenario analyses demonstrate that fezolinetant is a cost-effective treatment for patients with moderate to severe vasomotor-predominant menopausal symptoms who are unsuitable for HRT. While results versus desvenlafaxine and paroxetine provide supportive evidence across relevant alternatives, as noted in Section 3.2.4.2, the analyses for SSRIs and SNRIs required several assumptions that limited generalisability of those results; for example, RCT evidence for SSRIs/SNRIs was available for treatments (desvenlafaxine, proxy for venlafaxine) or doses (paroxetine 7.5 mg) that are not available in the UK. As drug classes, these treatments are associated with variable efficacy, require both up and down titration over months to minimise adverse effects or withdrawal symptoms, and being associated with high discontinuation rates due to adverse effects. Consequently, many patients in routine practice do not receive non-hormonal pharmacological therapy for moderate to severe VMS. No active

treatment therefore represents the clinical reality of most patients seeking medical advice for moderate to severe VMS who are unsuitable for HRT and thus the most reliable comparator for estimating the cost-effectiveness of fezolinetant.

References

1. Astellas Data on File. Veoza 1:1 HCP Consultations - Meeting Minutes. 2025.
2. Astellas Data on File. MSL 1:1 Consultancy Activities with Menopause KEEs. 2025.
3. Drugs & Therapy Bulletin: Factor in the criteria. In: Lagasse C.A, ed. UFHealth Shands Hospital 2013.
4. The British Menopause Society (BMS). BMS Consensus Statements. Non-hormonal-based treatments for menopausal symptoms. Available at: https://thebms.org.uk/publications/consensus-statements/non-hormonal-based-treatments-menopausal-symptoms/ [Accessed 30 January 2024].
5. British National Formulary (BNF). Gabapentin. Available at: https://bnf.nice.org.uk/drugs/gabapentin/ [Accessed: 26 September 2025].
6. National Institute for Health and Care Excellence (NICE). Menopause: diagnosis and management [NG23]. Available at: https://www.nice.org.uk/guidance/NG23 [Accessed September 2025].
7. Morga A ZL, Valluri U, Siddiqui E, McLeod L, Bender RH. . Validation and application of thresholds to define meaningful change in vasomotor symptoms frequency: analysis of pooled SKYLIGHT 1 and 2 data. . Advances in Therapy. 2024;41:2845-2858.
8. Astellas Data on File. UK Individual Expert Validation Meetings Report. 2024.
9. Morga A, Ajmera M, Gao E, et al. Systematic review and network meta-analysis comparing the efficacy of fezolinetant with hormone and nonhormone therapies for treatment of vasomotor symptoms due to menopause. Menopause 2023:10.1097/GME.0000000000002281.
10. Astellas Data on File. AST VMS FA Update Report. 2023.
11. Astellas Data on File. NMA fezolinetant non-HT DAYLIGHT trial. 2023.
12. Dias S, Welton, N.J., Sutton, A.J. & Ades, A.E. . NICE DSU Technical Support Document 2: A Generalised Linear Modelling Framework for Pairwise and Network Meta-Analysis of Randomised Controlled Trials. . 2011;Last updated September 2016.
13. Reame NK. Treating hot flashes in women unsuitable for menopause hormone therapy: more daylight at the end of the tunnel. Menopause 2025;32:483-487.
14. Santoro N, Neal-Perry, G., Stute, P., Blogg, M., Mancuso, S., Morga, A., Ottery, F.D. and Siddiqui, E., . Fezolinetant effect on vasomotor symptoms due to menopause in women unsuitable for hormone therapy. Current Medical Research and Opinion 2025;41:375-384. .
15. Pinkerton JV, Constantine G, Hwang E, et al. Desvenlafaxine compared with placebo for treatment of menopausal vasomotor symptoms: a 12-week, multicenter, parallel-group, randomized, double-blind, placebo-controlled efficacy trial. Menopause 2013;20:28-37.
16. Speroff L GM, Constantine G, Olivier S, Study 315 Investigators. Efficacy and tolerability of desvenlafaxine succinate treatment for menopausal vasomotor symptoms: a randomized controlled trial. Obstetrics & Gynecology 2008;111:77-87.
17. Pinkerton JV CG, Hwang E, Cheng RF, Study 3353 Investigators. Desvenlafaxine compared with placebo for treatment of menopausal vasomotor symptoms: a 12-week, multicenter, parallel-group, randomized, double-blind, placebo-controlled efficacy trial. Menopause. 2013;20(1):28-37.:28-37.
18. Archer DF SL, Constantine GD, Pickar JH, Olivier S. A double-blind, randomly assigned, placebo-controlled study of desvenlafaxine efficacy and safety for the treatment of vasomotor symptoms associated with menopause. American journal of obstetrics and gynecology 2009;200:172-e1.
19. Archer DF DC, Constantine GD, Pickar JH, Olivier S, Study 319 Investigators. . Desvenlafaxine for the treatment of vasomotor symptoms associated with menopause: a double-blind, randomized, placebo-controlled trial of efficacy and safety. American journal of obstetrics and gynecology 2009;200:283-e1.

20. Bouchard P, Panay N, de Villiers TJ, et al. Randomized placebo- and active-controlled study of desvenlafaxine for menopausal vasomotor symptoms. Climacteric 2012;15:12-20.
21. Simon JA, Portman DJ, Kaunitz AM, et al. Low-dose paroxetine 7.5 mg for menopausal vasomotor symptoms: two randomized controlled trials. Menopause 2013;20:1027-1035.
22. Dias S, Sutton, A.J., Welton, N.J., Ades, A.E. . NICE DSU Technical Support Document 3: Heterogeneity: subgroups, meta-regression, bias and bias-adjustment. 2011.
23. Carpenter B, A. Gelman, M. D. Hoffman, D. Lee, B. Goodrich, M. Betancourt, M. Brubaker, J. Guo, P. Li, A. Riddell. . Stan: A Probabilistic Programming Language. Journal of Statistical Software 2017;76
24. . RCT. _R: A Language and Environment for Statistical Computing_. : R Foundation for Statistical Computing, Vienna, Austria. , 2025.
25. Phillippo DM. multinma: Bayesian Network Meta-Analysis of Individual and Aggregate Data. R package version 0.8. , 2025.
26. Beaudoin F, McQueen R, Wright A. Fezolinetant for Moderate to Severe Vasomotor Symptoms Associated with Menopause: Effectiveness and Value; Final Evidence Report. Institute for Clinical and Economic Review 2023.
27. Astellas Data on File. 1:1 Menopause Clinical, Patient and System Experts Consultations - Meeting Minutes. 2025.
28. Astellas Data on File. GP Omnibus August 2025. 2025.
29. Astellas Data on File. UK HRT-unsuitable Consensus Statement. 2024.
30. NHS England. Handling of gabapentin and pregabalin as Schedule 3 Controlled Drugs in health and justice commissioned services: letter from Kate Davies. London: NHS England; 2019 Available from: https://www.england.nhs.uk/publication/handling-of-gabapentin-and-pregabalin-as-schedule-3-controlled-drugs-in-health-and-justice-commissioned-services/ [Accessed October 2025].
31. NHS inform. Menopause. Available at: https://www.nhsinform.scot/healthy-living/womens-health/later-years-around-50-years-and-over/menopause-and-post-menopause-health/menopause. [Accessed: September 2024], 2022.
32. Clinicaltrials.gov. Efficacy/Safety Study of Brisdelle™ (Formerly Known as Mesafem) in the Treatment of Vasomotor Symptoms (VMS) (N30-003), 2015.
33. Clinicaltrials.gov. 24-Week Efficacy & Safety Study of Brisdelle™ (Formerly Known as Mesafem) in the Treatment of Vasomotor Symptoms, 2015.
34. Avis NE, Crawford SL, Greendale G, et al. Duration of menopausal vasomotor symptoms over the menopause transition. JAMA Intern Med 2015;175:531-9.
35. Svartberg J, von Mühlen D, Kritz-Silverstein D, et al. Vasomotor symptoms and mortality: the Rancho Bernardo Study. Menopause 2009;16:888-91.
36. Office for National Statistics (ONS). National life tables: UK. Available at: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/datasets/nationallifetablesunitedkingdomreferencetables [Accessed on 6 June 2024].
37. National Institute for Health and Care Excellence (NICE). NICE health technology evaluations: the manual. NICE process and methods [PMG36].
38. Hernández Alava M, Pudney S, Wailoo A. Estimating the Relationship Between EQ-5D-5L and EQ-5D-3L: Results from a UK Population Study. PharmacoEconomics 2023;41:199-207.
39. National Institute for Health and Care Excellence (NICE). Vortioxetine for treating major depressive episodes [TA367]. Available at: https://www.nice.org.uk/guidance/ta367/ [Accessed: September 2025].
40. Sullivan PW, Valuck R, Saseen J, et al. A comparison of the direct costs and cost effectiveness of serotonin reuptake inhibitors and associated adverse drug reactions. CNS Drugs 2004;18:911-32.
41. Revicki DA, Wood M. Patient-assigned health state utilities for depression-related outcomes: differences by depression severity and antidepressant medications. J Affect Disord 1998;48:25-36.
42. Astellas Data on File. Regression Analyses SAP. 2025.
43. M Hernández Alava SP, A Wailo,. Estimating EQ-5D by age and sex for the UK., 2022.
44. Personal Social Services Research Unit (PSSRU). Unit Costs of Health and Social Care.
45. National Health Service (NHS). 2021/22 National Cost Collection Data Publication.

46. Büyükkaramikli NC, Rutten-van Mölken MPMH, Severens JL, et al. TECH-VER: A Verification Checklist to Reduce Errors in Models and Improve Their Credibility. PharmacoEconomics 2019;37:1391-1408.

Appendices

Appendix B: Identification, selection and synthesis of clinical evidence

B.1 Identification and selection of relevant studies

B.1.4 Summary of trials used for indirect or mixed treatment comparisons

Table 42 summaries details of the trails used for the indirect treatment comparison.

Table 42. Overview of trials used for the indirect treatment comparisons

Study Name	Study Phase and Blinding	Interventions (Sample Size)	Eligible Population	Geography
Speroff 2008	Phase III, Double-blind	• Desvenlafaxine 50mg (N= 149) • Desvenlafaxine 100 mg (N = 155) • Desvenlafaxine 150 mg (N=157) • Desvenlafaxine 200 mg (N=151) • Placebo (N=77)	Healthy postmenopausal women (body mass index 40 kg/m2 or less) who experienced at least seven self-reported moderate to severe hot flushes per day (or 50 or more per week)	US
Pinkerton 2013a [Full study cohort]	Phase III, Double-blind	• Desvenlafaxine 100 mg (N=1066) • Placebo (N=1052)	Postmenopausal women aged 45 years or older with a body mass index of 34.0 kg/m2 or lower who sought treatment for bothersome hot flashes.	US and Canada
Pinkerton 2013b [Efficacy cohort]		• Desvenlafaxine 100 mg (N=200) • Placebo (N=190)		
Archer 2009b	Double-blind	• Desvenlafaxine 100mg (N=150) • Desvenlafaxine 150mg (N=151) • Placebo (N=151)	Postmenopausal women were eligible for enrolment if they were generally healthy, had a body mass index 40 kg/m2 or less, and experienced at least 7 moderate to severe hot flushes per day or 50 or more per week for 2 consecutive weeks at baseline.	US

Archer 2009a	Double-blind	• Desvenlafaxine 100 mg (N=182) • Desvenlafaxine 100mg (N=179) • Placebo (N=180)	Generally healthy, postmenopausal women (body mass index [BMI], ≤ 40 kg/m2) who experienced at least 7 moderate to severe HFs per day (or 50/week) recorded by participants for 7 consecutive days during screening	US
Bouchard 2012	Phase III, Double-blind	• Desvenlafaxine 100 mg (N=158) • Placebo (N=152)	Postmenopausal women aged 40–65 years seeking treatment for hot flushes were eligible for enrolment if they were generally healthy; had completed their last natural menstrual period ≥12 months prior to screening (or had a follicle stimulating hormone (FSH) level >40 mIU/ml).	Europe, South Africa, Mexico
Pooled SKYLIGHT	Phase III, Double-blind	• Fezolinetant 45 mg (N=287) • Placebo (N=297)	Women aged 40–65 years having an average of seven or more moderate to severe hot flashes per day before randomisation and seeking treatment or relief for vasomotor symptoms	US, Canada, Czech Republic, Latvia, Poland, Spain, UK
DAYLIGHT	Phase IIIb, Double-blind	• Fezolinetant 45 mg (N=226) • Placebo (N=226)	Women aged ≥40 to ≤65 years with moderate to severe vasomotor symptoms (VMS) considered unsuitable for hormone therapy (HT) (contraindications, caution, stoppers, or averse)	Belgium, Canada, Denmark, Finland, France, Germany, Hungary, Italy, Netherlands, Norway, Poland, Spain, Sweden, Turkey, UK
Simon 2013	Phase III, Double-blind	• Paroxetine 7.5 mg (N=297) • Placebo (N=302)	Postmenopausal women 40 years or older.	US

B.1.5 Methods and outcomes of studies included in indirect or mixed treatment comparisons

Section 2.10.10 summaries details of the methods and outcomes of the studies used in the indirect treatment comparison.

B.1.6 Methods of analysis of studies included in indirect or mixed treatment comparisons

Table 43 summarises the methods of analysis used for the two outcomes of interest: VMS response and discontinuations, across all studies used in the indirect treatment comparison.

Table 43. Summary of methods of analysis for studies included in indirect treatment comparison

Study Name	VMS Response	Discontinuations
Speroff 2008	Efficacy analyses were carried out on the intent-to-treat population (women who were randomly assigned to a treatment group, received at least one dose of test article, recorded 5 or more days of data for the baseline week, and had data for 5 or more days during at least 1 week in the first 12 on-therapy weeks after the baseline week). Missing data were dealt with using a last-observation-carried-forward approach. Safety and tolerability analyses included all women who were randomly assigned to a treatment group and received at least one dose of test article.	Total discontinuations from any cause. No imputation of missing data.
Pinkerton 2013a [Full study cohort]	Not included in NMA for VMS response	
Pinkerton 2013b [Efficacy cohort]	Missing data were handled using the last-observation-carried-forward approach.	
Archer 2009b	The primary efficacy analysis was carried out on the modified intent-to-treat population, defined as women who were randomly assigned to treatment, received at least 1 dose of desvenlafaxine or placebo, recorded at least 5 days of data during the baseline week and had at least 5 days of on-therapy data for at least 1 on-therapy week. Missing data were dealt with using a last-observation-carried-forward approach.	

Archer 2009a	The primary efficacy analysis was based on the intent-to-treat population (all subjects who were randomly assigned to a treatment group, received ≥ 1 doses of study drug, recorded data for ≥ 5 days of the baseline week, and had VMS data for ≥ 5 days during ≥ 1 weeks in the first 12 weeks on therapy). Missing data were handled using a last-observation-carried-forward approach for the initial 12 weeks of therapy.	
Bouchard 2012	The primary efficacy analyses were based on the intent- to-treat population, which was defined as all women who took at least one dose of study drug, had at least 5 days of baseline efficacy data during 7 consecutive screening days, and at least 5 days of data during the on-therapy phase for at least 1 week of therapy. For the primary efficacy endpoints, the desvenlafaxine and placebo groups were compared using analysis of covariance with treatment group and study site as factors and baseline value as covariate, using the last-observation-carried-forward approach for handling missing data.	
Simon 2013	Not included in the response NMA.	
Pooled SKYLIGHT	Missing data were addressed through last observation carried forwards based on weekly derived response status.	
DAYLIGHT		

Abbreviations: VMS: vasomotor symptoms; NMA: network meta-analysis.

B.1.7 Programming language for indirect or mixed treatment comparisons

All analyses were performed using the software Stan version 2.37,[23] using the statistical software R version 4.4.3,[24] via the R package *multinma* (version 0.8.1).[25]

B.1.8 Risk of bias of studies included in indirect or mixed treatment comparisons

Studies identified for inclusion in the response and discontinuation NMA were leveraged from the clinical SLR; as such, risk of bias assessments can be found in Section D.4 of the original Company Submission.

Appendix H: Clinical outcomes and disaggregated results from the model

H.1 Clinical outcomes from the model

Clinical data from pooled DAYLIGHT and SKYLIGHT 1&2 were used directly in the model, so any differences between the model results and clinical data would be minimal. As such, no clinical outcomes from the model are presented in this Appendix.

H.2 Disaggregated results of the base-case incremental cost-effectiveness analysis

Disaggregated deterministic results from the cost-effectiveness model are presented in Table 44, Table 45 and Table 46.

Table 44: Summary of QALY gain by health state (deterministic)

Health state	QALY fezolinetant	QALY comparator	Increment	Absolute increment	% absolute increment
Versus no active treatment					
On Treatment Pre-Response Assessment	0.15	0.15	0.00	0.00	0%
On Treatment Responder	0.82	0.64	0.18	0.18	4%
On Treatment Non-Responder	0.14	2.23	−2.09	2.09	49%
Off Treatment with VMS	1.96	-	1.96	1.96	46%
VMS cessation	3.85	3.85	0.00	0.00	0%
Total	**6.91**	**6.87**	**0.05**	**4.22**	**100%**
Versus desvenlafaxine					
On Treatment Pre-Response Assessment	0.15	0.14	0.01	0.01	1%
On Treatment Responder	0.82	0.39	0.43	0.43	48%
On Treatment Non-Responder	0.14	0.12	0.02	0.02	2%
Off Treatment with VMS	1.96	2.39	−0.43	0.43	48%
VMS cessation	3.85	3.85	0.00	0.00	0%
Total	**6.91**	**6.88**	**0.03**	**0.89**	**100%**

Abbreviations: QALY, quality-adjusted life year; VMS: vasomotor symptoms.

Table 45: Summary of costs by health state (deterministic)

Health state	QALY fezolinetant	QALY comparator	Increment	Absolute increment	% absolute increment
Versus no active treatment					
On Treatment Pre-Response Assessment	£169.42	£69.80	£99.63	£99.63	4%
On Treatment Responder	£629.39	£43.74	£585.64	£585.64	21%

On Treatment Non-Responder	£184.32	£1,308.37	−£1,124.05	£1,124.05	41%
Off Treatment with VMS	£923.41	-	£923.41	£923.41	34%
VMS cessation	£253.97	£253.97	£0.00	£0.00	0%
Total	**£2,160.52**	**£1,675.89**	**£484.63**	**£2,732.74**	**100%**
Versus desvenlafaxine					
On Treatment Pre-Response Assessment	£169.42	£71.94	£97.48	£97.48	10%
On Treatment Responder	£629.39	£34.77	£594.62	£594.62	59%
On Treatment Non-Responder	£184.32	£72.31	£112.01	£112.01	11%
Off Treatment with VMS	£923.41	£1,125.51	−£202.10	£202.10	20%
VMS cessation	£253.97	£253.97	£0.00	£0.00	0%
Total	**£2,160.52**	**£1,558.51**	**£602.01**	**£1,006.21**	**100%**

Abbreviations: VMS: vasomotor symptoms.

Table 46: Summary of predicted costs by cost category (deterministic)

Cost category	Cost fezolinetant	Cost comparator	Increment	Absolute increment	% absolute increment
Versus no active treatment					
Drug Costs	£784.95	£0.00	£784.95	£784.95	72%
Overall healthcare resource costs (including AE costs)	£1,375.57	£1,675.89	−£300.32	£300.32	28%
Total	**£2,160.52**	**£1,675.89**	**£484.63**	**£1,085.27**	**100%**
Versus desvenlafaxine					
Drug Costs	£784.95	£14.74	£770.21	£770.21	82%
Overall healthcare resource costs (including AE costs)	£1,375.57	£1,543.77	-£168.20	£168.20	18%
Total	**£2,160.52**	**£1,558.51**	**£602.01**	**£938.40**	**100%**

Abbreviations: AE: adverse event; QALY, quality-adjusted life year.

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Fezolinetant for treating moderate to severe vasomotor symptoms caused by menopause [ID5071]
Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Monday 28 April 2025. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	**British Menopause Society**

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	**Astellas Pharma – £2,250** **Exhibition table at BMS 33rd annual scientific conference, 27 & 28 June 2024**
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.

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Fezolinetant for treating moderate to severe vasomotor symptoms caused by menopause [ID5071]
Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Monday 28 April 2025. Please submit via NICE Docs.

1	**Has all of the relevant evidence been taken into account?** The existing evidence excludes women with cancer. Currently there are no comparative trials of Fezolinetant against other non-hormonal treatments. There is a systematic review (Menopause 2024;31(1):p 68-76) but this was sponsored and co-authored by Astellas. Little account is taken of the natural history of vasomotor symptoms and how long they persist. Although relatively short for many women, VMS can last over 10 years in a significant proportion (Avis, N. E., (2015). "Duration of menopausal vasomotor symptoms over the menopause transition." JAMA Intern Med **175**(4): 531-539.
2	**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** In 2023 the Institute for Clinical and Economic Review published an evidence report "Fezolinetant for moderate to severe vasomotor symptoms associated with menopause: Effectiveness and Value" with similar conclusions. Since the manufacturer's submission to NICE in 2024, the MHRA, FDA and EMA have put out information on serious liver injury. The requirement for liver function tests affects the cost calculation. There is uncertainty about the need for ongoing monitoring, which also draws into question the feasibility of prescribing Fezolinetant in primary care. Although most GPs are used to measuring LFTs as changes with medications such as statins and ACE inhibitors are common. These drugs are taken by large numbers of men and women. Also more information is needed regarding the frequency and nature of the liver disease as the FDA appeared to make the decision based on very few cases and comparison with the incidence in the normal population did not appear to be included.
3	**Are the recommendations sound and a suitable basis for guidance to the NHS?** The potential cost to the NHS is very high if Fezolinetant were to be used for the broad indications requested by the manufacturer. Clinical benefit is uncertain and the increased cost associated with liver function tests do not warrant its use in all women with vasomotor symptoms at present. Although there are no head-to-head comparisons, it would appear that HRT is more effective. However, the population most likely to benefit from choice of non-hormonal therapies is the small group of women who cannot take HRT (mainly breast cancer patients) but this population was not addressed in the current application. Women who have had a hormone sensitive cancer are an important group that will suffer without access to Fezolinetant on the NHS. They often get sudden and severe vasomotor symptoms with serious effects on their quality of life. Also, breast cancer patients are often on adjuvant endocrine therapy for 5 to 10 years after initial treatment, giving them further symptoms. Current non-hormonal treatments have variable results and many possible side-effects. Many menopause specialists are getting good results using Fezolinetant off-license in this group of patients.

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	Although the studies on women with breast cancer are not completed yet, the prescribing literature does say this: *Women with previous breast cancer or other oestrogen-dependent malignancies and no longer on any oncologic treatment have not been included in the clinical studies. A decision to treat these women with Veoza should be based on a benefit-risk consideration for the individual.* Some of these women will stop their adjuvant endocrine treatment due to vasomotor symptoms, whereas this could be avoided with the option of Fezolinetant. Sadly, some of these women will then go on to develop a new primary breast cancer or secondary breast cancer, leading to a high cost to the NHS for further treatment. For most, vasomotor symptoms persist throughout treatment with endocrine therapy but will stop relatively rapidly when it is completed.
4	**Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation.** An alternative menopause-specific treatment for women unable to take HRT which does not work through estrogen/progestogen has been long-awaited. Now that such a therapy is regulator-approved, it should be accessible to suitable women to address menopause symptoms and reduce menopause health inequalities. Without NICE approval, this new treatment option will only be available privately to those women who can afford to purchase the drug, furthering health inequalities. Cost-effectiveness of Fezolinetant based only on those women unable to take HRT means the treatment could be initiated in primary care. Furthermore, the duration of treatment trajectories within the NICE appraisal may be overestimated. Fezolinetant provides an effective direct treatment alternative for this group of women, many of whom have complex underlying health issues. Such women could be initiated on Fezolinetant in specialist women's health or secondary care settings, with subsequent prescribing and review in primary care. Rather than an "all or nothing approach", this approach would favour inclusivity and an invaluable treatment option for vulnerable women currently excluded from adequate menopause support.
5	We are concerned that the committee did not have a GP or menopause specialist on it, which is regrettable given that the aim of this drug is to treat one of the commonest symptoms of menopause. The model design used by Astellas had considerable patient and consultant input. Frequency of hot flushes is used, rather than severity as is recommended in the Core Outcomes Sets for Menopause, as it will permit comparison with other drugs and will facilitate a Nested Metanalysis. Severity is quite hard to define and there are many different instruments to assess it.

NICE National Institute for Health and Care Excellence

Fezolinetant for treating moderate to severe vasomotor symptoms caused by menopause [ID5071]
Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Monday 28 April 2025. Please submit via NICE Docs.

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about funding from the company and links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into one response. We cannot accept more than one set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- In line with the NICE Health Technology Evaluation Manual (sections 5.4.4 to 5.4.21), if a comment contains confidential information, it is the responsibility of the responder to provide two versions, one complete and one with the confidential information removed (to be published on NICE's website), together with a checklist of the confidential information. Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please submit a second version of your comments form with that information replaced with asterixis and highlighted in black.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

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NICE National Institute for Health and Care Excellence

Fezolinetant for treating moderate to severe vasomotor symptoms caused by menopause [ID5071]
Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Monday 28 April 2025. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	**Society for Endocrinology**

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NICE National Institute for Health and Care Excellence

Fezolinetant for treating moderate to severe vasomotor symptoms caused by menopause [ID5071]
Draft guidance comments form

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	Astellas have funded a real world data study in menopause management interventions in 2024.£75,000 Astellas have funded an event titled Women's Health Summit in 2024 and 2025. £50,000 included a sponsored symposium at both events. Astellas have not had any involvement in the protocol and dataset for the study or the programme for the event. These events have now run in 2024/5 and the study is going for data collection into 2027. Bayer have funded a real world data study in menopause management interventions in 2024 £37,500. Bayer have not had any involvement in the protocol or dataset for the study, and the study is ongoing to data collection into 2027.
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted] on behalf of menopause experts within the Society for Endocrinolgy – these comments were collated and then checked by these members.

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	The current draft NICE guidance does not scrutinise the nuanced evidence available. It fails to acknowledge the significant gaps in evidence across menopause research and treatments, including HRT, which favour socially advantaged women and effectively widen menopause health inequalities.

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Fezolinetant for treating moderate to severe vasomotor symptoms caused by menopause [ID5071]
Draft guidance comments form

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	An alternative menopause-specific treatment for HRT-unsuitable women, which does not work through estrogen/progestogen, has been long-awaited. Now that such a therapy is regulator-approved, it should be accessible to suitable women to address menopause symptoms and reduce menopause health inequalities. Without NICE approval, this new treatment option will only be available privately to those women who can afford to purchase the drug, furthering health inequalities. Health inequalities relating to all aspects of women's health and menopause are ongoing and remain largely unaddressed. Existing menopause/HRT research significantly under-represents minority ethnic groups, those with complex comorbidities and socioeconomic disadvantage. There is no high-quality data to show that HRT is safe in these and other groups of women. Many such women may have increased cardiometabolic and cancer risks with HRT (1) and may be averse to using HRT or have greater side effects with it. Positioning HRT as the only direct menopause treatment available, therefore, means, purportedly, that the most vulnerable women have no viable direct menopause treatment options. Without a menopause-specific treatment alternative, HRT-unsuitable women may suffer significant health, societal and economic disadvantages, fuelling wider women's health inequalities. Antidepressants do not address the underlying cause of menopause symptoms directly, and many women find them ineffective, develop intolerable side effects or are averse to their use. Offering antidepressants as the only HRT alternative medication for menopause symptoms, where effective options are available, is a non-inclusive and unacceptable approach. The cost-effectiveness of Fezolinetant has been assessed based on all HRT-unsuitable women having treatment initiated in primary care. Furthermore, the duration of treatment trajectories within the NICE appraisal may be overestimated. Fezolinetant provides an effective direct treatment alternative for HRT-unsuitable women. Many HRT-unsuitable women have complex underlying health issues. Such women could be initiated on Fezolinetant in specialist women's health or secondary care settings, with subsequent prescribing and review in primary care. Rather than an "all or nothing approach", this approach would favour inclusivity and an invaluable treatment option for vulnerable women currently excluded from adequate menopause support. The current draft guidance recommendations are unfair and discriminatory. They do not provide an effective targeted treatment option for HRT-unsuitable women in any health setting, even though a regulator-approved option is available. The current guidance risks some women using HRT by default, who may later come to harm from it. It denies these women an effective menopause-specific treatment that has a mechanism of action that does not work through estrogen/progestogen. The Society for Endocrinology is working on a National data registry and prospective research entitled "Patient-reported Outcomes for Menopause Management Interventions Study" (PROMMIS), looking at the quality of life of women undergoing menopause management interventions, which may help address natural history data in the future.

NICE National Institute for Health and Care Excellence

Fezolinetant for treating moderate to severe vasomotor symptoms caused by menopause [ID5071]
Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Monday 28 April 2025. Please submit via NICE Docs.

	1. Mukherjee A, Davis SR. Update on Menopause Hormone Therapy; Current Indications and Unanswered Questions. Clin Endocrinol (Oxf). 2025 Jan 29. doi: 10.1111/cen.15211. Epub ahead of print. PMID: 39878309.

Insert extra rows as needed

Checklist for submitting comments

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- Do not include medical information about yourself or another person from which you or the person could be identified.
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Single Technology Appraisal

Fezolinetant for treating moderate to severe vasomotor symptoms caused by menopause [ID5071]

Comments on the draft guidance received through the NICE website

Name	[redacted]
Role	
Other role	
Organisation	No
Location	
Conflict	No
Notes	
Comments on the DG:	

- **Has all of the relevant evidence been taken into account?**

One issue raised in the recommendation is regarding comparisons to existing treatments:
There is a recent meta-analysis by Morga et al (PMID: 38016166) that demonstrates the benefit of fezolinetant over SSRIs/gabapentin. There are no direct meta-analyses comparing fezolinetant to CBT but I would anticipate a superiority. You could ask the company to look into this.

Another issues is regarding the natural history of hot flushes:
-In terms of natural history of hot flushes where the document says that there is not enough information, please see PMID: 25686030 that contains a wealth of info. I would think that in the first instance, given that the median duration of symptoms is 7.4y, you could recommend trial of weaning off fezolinetant from 7 years at latest.

- **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?**

-It is always difficult to quantify economic. I have seen at first hand the transformations that this class of medication has on women and would suggest that the panel invite patients who are on it to discuss the impact on them so they can see it first hand.
-I think NICE could ask for further discounts on the price although it does not seem too expensive at £44/m.
-Furthermore, HFs result in reduced work productivity and I have seen this with a secretary who had such bad HF that she had to periodically stop work. Therefore, there may be additional economic benefits with increased productivity that have not been included from what I can see. HF in the workplace is a very topical and previously ignored issue.

- **Are the recommendations sound and a suitable basis for guidance to the NHS?**

It is excellent that NICE are carefully considering providing access to this transformative medicine on the NHS.
I have clearly seen patients lives transformed by Fezolinetant and other NK3R antagonists.

Moderate-severe hot flushes affect around 50% of postmenopausal women, primarily during the menopausal transition. 20% report that they are unbearable and this impacts their QoL as well as their work output severely. They typically last up to 7 years.

There are at least 10% of postmenopausal women who cannot for one reason or other take HRT (Napi et al 2021), which is the undisputed first line treatment. I see this dilemma and issue frequently.

Other options such as SSRIs, CBT, herbs are weakly effective. In fact a recent meta-analysis (Morga et al, Menopause 2024) shows clear superiority for Fezolinetant over SSRIs and gabapentin in frequency reduction.

Hence there is a clear need for an effective second line that Fezolinetant provides.
I think the assessment from the panel is reasonable overall but there are issues that are overblown and seem to have prevented the recommendation.

-In terms of checking LFTs, the protocol is similar to LFT checking that is advised in primary care on starting statins (which are started by many more patients). One approach would be for Fezolinetant to be started in secondary care with care then taken over by GPs. However, I think with time GPs should become quite ok with starting it as no more complex than statins.
-While appreciating the need for data in patients with less than 7 HF/day, this was not done in all the P3 trials as 7 HF/day was an FDA requirement. However, it can be extrapolated that would be effective and lesser baseline frequencies with equally mod/severe symptoms. this is based on the mechanism of action. Alternatively one approach would be to recommend for those having 7+ HF/day to start with until further data available.
-In terms of natural history of hot flushes, this data is contained in PMID: 25686030.

Given the urgent need to improve Women's Health as an identified national priority, I hope that NICE will continue to fairly assess NK3R antagonists as they can be transformative for patients.

- **Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful**

discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

If finally approved, NICE would need to consider including the population of transmen who go through biological menopause (unless on gender-reassigning treatment).

It is excellent that NICE are carefully considering providing access to this transformative medicine on the NHS.
I have clearly seen patients lives transformed by Fezolinetant and other NK3R antagonists.
I do hope to be able to provide this treatment in future under the NHS as many women are currently unable to access it.

There are some minor issues with the recommendation but I think it is a good first step to hopefully securing approvals for a much-needed EFFECTIVE second line treatment for these debilitating symptoms.

Conflict: I was involved in the early studies for this class of compound and have given talks on their discovery and mechanism of action for Astellas.

Name	[redacted]
Role	
Other role	
Organisation	No
Location	
Conflict	No
Notes	
Comments on the DG:	

- **Has all of the relevant evidence been taken into account?**

No

- **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?**

NO. There are many women including breast cancer and family history of breast cancer patients who cannot take HRT. Fezolinetant is a good non hormonal option for these women. Your statement that most women can take HRT is incorrect. Also the statement about cost viability does not take into account the cost to the women with VMS ie QOL, inability to work, function, exercise due to insomnia, these women are leaving work due to the VMS. It seems that NOCE just feel VMS are a few flushes, not so, and there is NO mention of the inc CVD risk with VMS.

Your statement that Fezolinetant can't be considered for breast cancer patients as not licensed is nonsense. Virtually all the non hormonal options for breast cancer patients including SSRI and SNRI that you are recommending are NOT licensed.

- **Are the recommendations sound and a suitable basis for guidance to the NHS?**

NO, where on earth can we access CBT on NHS- nowhere!

- **Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?**

Why have Newson Health had a part of this consultation - page 320 Committee pages thanking Dr Sarah Glynn. Newson Health are very anti Fezolinetant and give HRT to all- this is NOT an unbiased view.

Name	[redacted]
Role	
Other role	
Organisation	No
Location	
Conflict	No
Notes	
Comments on the DG:	

I am so disapointed with this decision. This is a real kick in the teeth for cancer sufferers.
I had 17 years of hellish hot flushes that really affected my whole life. Then I was so happy to be able to have fezolineant privately, it changed my life completely. I've been eagerly awaiting the decision to make this wonderful drug available through the nhs.
I am upset, disappointed and angry
And it's clear this decision was made by a man. Womens health is so neglected. If this was to help men it would be passed immediately.

Name	[redacted]
Role	
Other role	
Organisation	No
Location	
Conflict	No

Notes	
Comments on the DG:	

- **Has all of the relevant evidence been taken into account?**

Yes.

- **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?**

No.

- **Are the recommendations sound and a suitable basis for guidance to the NHS?**

No.

- **Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?**

No.

I'm submitting my concerns to you NICE on the decision to NOT recommend Fezolinetant.

I am a GP and we deserve options to treat VMS - they are not just a few flushes. They have significant impact on QOL, which I can personally give testament to. They contribute to insomnia, brain fog, anxiety, fatigue, making it harder to exercise and make positive lifestyle choices, and also increase risk of cardiovascular disease - a point NICE fails to acknowledge.

NICE states the usual treatment for VMS is HRT, but there are many women, in which HRT is contraindicated, and many who also choose not to take it such as high risk family history of breast cancer.

NICE states it is not possible to reliably estimate whether Fezolinetant is better than other options - but other options for the most part are unlicensed and can come with significant side effects- including weight gain, low libido, bone thinning, fluid retention, headache, arrhythmia, permanent inability to orgasm, worsening GSM, cognitive impairment and drug withdrawal issues - to name a few!

They suggest CBT can be offered to those that can't take HRT- perhaps they haven't attempted themselves to access this under the NHS? Much easier said than done!

They say Veoza can’t be considered in women with breast cancer as not licensed in this group, and helpfully suggest we could use SSRI or SNRI instead. However, all other non hormonal treatments are unlicensed for menopause symptoms apart from clonidine which is no longer recommended.

Please review this decision.

Name	[redacted]
Role	
Other role	
Organisation	No
Location	
Conflict	No
Notes	
Comments on the DG:	

- **Has all of the relevant evidence been taken into account?**

Not entirely. While the guideline rightly states that HRT should be considered the first line treatment for VMS in the majority of women, it does not sufficiently acknowledge the proportion of women who either cannot use HRT or who choose not to use it, for example due to a strong family history of breast cancer. This group has not been given enough consideration when reviewing the treatment options. Ultimately, a preparation which is non hormonal should be leapt upon when it comes to women's health and the dirth of available options in this day and age is unacceptable.

- **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?**

Partially, but there are inconsistencies. The economic reasoning for not recommending Veoza (due to uncertainty around how VMS symptoms change over time and how treatments impact symptom severity) is noted. However, this same uncertainty applies to HRT and other pharmacological treatments which are still recommended. Additionally, the guideline suggests CBT when HRT is not suitable, yet access to CBT within the NHS is extremely limited, making this recommendation unrealistic for many women. Furthermore, the guideline states that Veoza cannot be considered for women with a history of breast cancer because it is not licensed for this use, but goes on to recommend SSRIs and SNRIs, which are also unlicensed for VMS — apart from clonidine, which the North American Menopause Society (NAMS) actually advises against. The BMS (British Menopause Society) has mistakenly cited NAMS as recommending clonidine, and this error needs correcting.

- **Are the recommendations sound and a suitable basis for guidance to the NHS?**

There are concerns about the objectivity and balance of the recommendations. Notably, the contribution from Newson Health (acknowledged on page 320 of the committee notes) may represent a conflict of interest, given their policy of recommending HRT for all women, potentially introducing bias. Furthermore, dismissing Veoza based on a perceived lack of comparative benefit without fully considering the significant side effects associated with SSRIs, SNRIs, and clonidine (which are recommended) undermines the reliability of the guidance.

- **Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?**

Yes. By heavily prioritising HRT and offering CBT as an alternative without considering the real-world accessibility issues, the guidelines risk disadvantaging women who cannot use HRT and who cannot easily access psychological therapies. This may amount to indirect discrimination against groups including women with certain medical conditions (e.g., breast cancer survivors) or from lower socio-economic backgrounds where private CBT access is not possible. Special care must be taken to ensure these women have viable, evidence-based treatment options.

Name	[redacted]
Role	
Other role	
Organisation	No
Location	
Conflict	No
Notes	
Comments on the DG:	

Due to having a ER+ breast cancer when I was 40 I am unable to have HRT.
I am now 49 and having peri menopausal symptoms. The night hot flushes are awful and debilitating, waking me many times throughout the night. This is having a really negative effect on my daily life. I have tried every natural thing I can to stop the night flushes, nothing has worked.
I do not want to take an anti depressant as I am not depressed and do not want the many side effects that come with taking an AD.
I have been on veozah for a few months and they work brilliantly. My hot flushes completely subsided and I sleep.
They have literally improved my life.

It's so unfair for anyone who is unable to have HRT, that there is nothing to help.
I'm on many Facebook groups, trying to find a solution for hot flushes and so many women find veozah helps.

Name	[redacted]
Role	
Other role	
Organisation	No
Location	
Conflict	No
Notes	
Comments on the DG:	

Although this medication is currently only suitable for a small number of women until the breast cancer trials are published. It still has a place for women who have menopause vasomotor symptoms and can not take HRT. There is current only one licensed option clonadine which does not have good effectiveness. This means those women who can not take HRT are often put on off licence medication, having this as an alternative medication that is designed for the symptoms would give practitioners an alternative to offer women

Name	[redacted]
Role	
Other role	
Organisation	No
Location	
Conflict	No
Notes	
Comments on the DG:	

- **Section 3.15: Conclusion**

As a lay person, I cannot comment on the technicalities of the evidence. However, I am a patient who had my severe and disruptive vasomotor symptoms treated very effectively with HRT, BUT then had to stop the HRT due to breast cancer. The vasomotor symptoms immediately returned as severely as before. Following the cancer treatment I have had a private prescription of Fezolinetant (and the liver tests etc). Fezolinetant had an immediate effect on my symptoms. And while not as effective as HRT, it has removed the massively disruptive impact that lack of sleep has, and reduced the severity and number of events. Without Fezolinetant I would not be able to fulfil my job effectively.

For patients like me, who have no other choice, it seems entirely unfair that the recommendation is not to recommend treatment with Fezolinetant because patients who have a choice or are less impacted have not been sufficiently included in the study.

At the very least, Fezolinetant should be used to treat cancer patients with moderate to severe vasomotor systems caused by menopause.

Name	[redacted]
Role	
Other role	
Organisation	Menopause Alliance
Location	
Conflict	No
Notes	

Comments on the DG:

- **Section 1.1: Recommendations**

  "Fezolinetant should not be used to treat moderate to severe vasomotor symptoms caused by menopause."

"As a menopause advocate working directly with underserved communities, I have witnessed firsthand the urgent need non-hormonal treatment options for managing menopause symptoms.

Fezolinetant offers a much-needed alternative for women who cannot or choose not to take HRT. However, the women I serve currently have no access to this treatment because of the high private costs, which creates an unacceptable inequality in health outcomes.

We strongly urge NICE to prioritize equitable access to fezolinetant by recommending its funding on the NHS. Making this drug less accessible would disproportionately impact women from low-income, ethnic minority, and marginalized backgrounds — communities already at greater risk of being underserved in healthcare.

Improving access to fezolinetant would significantly enhance quality of life, reduce health disparities, and offer hope to women who currently have no suitable treatment options."

- **Section 1.2: Recommendations**

Without making fezolinetant accessible, women who can't have HRT are left with almost no good options, deepening existing health inequalities. Many women are unable to take hormone therapy due to medical reasons or personal choice, yet non-hormonal alternatives are extremely limited. Fezolinetant offers a vital option to improve symptoms like hot flushes and

night sweats, which can severely impact quality of life, mental health, and daily functioning. Ensuring fair access to this treatment is essential to providing inclusive, equitable menopause care for all women.

- **Section 3.1: Menopause and vasomotor symptoms**

Menopause and perimenopause can be profoundly disabling for some women, significantly impacting their ability to work, maintain relationships, manage their mental health, and cope with everyday activities. Symptoms such as severe hot flushes, sleep disturbances, anxiety, depression, and cognitive difficulties are not just inconvenient — they can be life-altering. For too long, the serious effects of menopause and perimenopause have been overlooked or minimized. It is encouraging that these experiences are now being acknowledged and understood more widely, but much more needs to be done to ensure that women receive the support, treatment options, and understanding they deserve across all areas of life, including healthcare, workplaces, and communities.

- **Section 3.2: Treatment pathway**

HRT is a lifeline for many women, helping them manage the often devastating effects of menopause. However, there are many women who cannot take HRT due to medical reasons or personal choice, and they equally need medical support. Their needs are just as important as those who can use hormone therapy. At present, there are very few effective options available for these women, leaving many to suffer without adequate treatment. Access to fezolinetant on the NHS could be a vital lifeline for them. We urge you to consider the needs of women from lower-income backgrounds and diverse communities, who are often the most affected by lack of access and health inequalities. Everyone deserves the chance to manage their menopause symptoms with dignity and support.

- **Section 3.5: Relevant comparators**

In my direct experience working with women from lower socio-economic backgrounds and diverse ethnic communities, there is often little interest or trust in CBT as a support option for menopause. Many of the women I support dismiss CBT straight away, either because they do not see it as relevant to their symptoms or because they prefer practical, medical solutions to manage what are, for them, very physical and disruptive experiences. This highlights the urgent need for alternative medical treatments to be made available and accessible — therapies that these communities are more likely to engage with and benefit from.

- **Section 3.15: Equality**

The needs of ethnic minority women and other underserved communities must be prioritised, particularly in light of the ongoing inequalities within the healthcare system. These inequalities continue to disadvantage and disable many women today, leaving them without the support and treatments they

urgently need during menopause and perimenopause. It is crucial to recognise that failing to address these gaps will only deepen the long-term health disparities faced by these communities — disparities that already result in poorer health outcomes, reduced quality of life, and increased mental health challenges. We strongly urge decision-makers to prioritise the needs of these women, ensuring that new treatments and interventions are made accessible and inclusive. Addressing menopause care through an equity lens is essential to creating a fairer, healthier future for all women.

Name	[redacted]
Role	
Other role	
Organisation	Menopause Support CIC
Location	
Conflict	No
Notes	

Comments on the DG:

- **Has all of the relevant evidence been taken into account?**

The evaluation does not appear to recognise the significant number of women who either cannot, or choose not to use HRT. It would appear that there has not been enough consideration given to the impact on quality of life and long term health outcomes of these patients.

- **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?**

The economic reasoning for not recommending fezolinetant indicates that there is no robust evidence to show how hot flushes change over a period of time. Surely, this also applies to all other prescribed treatment options, which are currently recommended.

- **Are the recommendations sound and a suitable basis for guidance to the NHS?**

I don't believe that the recommendations fully consider the truly debilitating effects of hot flushes on those who cannot use HRT and prefer not to use unlicensed options or have tried them and have not been able to tolerate them. To deprive the patients who have been patiently waiting for a licensed alternative to HRT and unlicensed options, potentially risks not only their short and long term health but will undoubtedly have effects on the mental and emotional health of others. Those who have been in the fortunate position to be able to pay privately for fezolinetant have described it as a life saver that has drastically improved their quality of life. It is simply unjust to deny those not in a position to pay for the treatment to experience a poorer quality of life. I would also point out that there are many menopause

specialists who have been eagerly anticipating having another treatment option available for their NHS patients, who they wish to be able to help but find themselves with limited options.

- **Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?**

It is important to be aware that many women choose not to use hormone based treatments on the basis of culture or religion. Making the decision not to make fezolinetant available via the NHS would limit the available treatment options for these women.

Please also consider the socioeconomic discrimination that not recommending fezolinetant for use in the NHS would create. We are aware of many women who would like the option to try this treatment but who would be unable to access it if it is not made available via the NHS.

The advice to offer CBT instead of fezolinetant has provoked dismay amongst some of our community, who were hoping to have a licensed treatment option available to them. Some feel that it is insulting to suggest that CBT will help to manage their debilitating hot flushes and night sweats. Others are upset to be told to try CBT when there is a possible treatment option that is simply out of reach for them, as they can't afford private care, where some have already accessed fezolinetant. Some have already tried CBT but not found it helpful. Others have asked where they will access CBT and just how long they will have to wait for an appointment. Some, who have the intersection of menopause and neurodiversity are aware that CBT may not be an option for them, with a smaller number who have already had a negative experience.

As a support organisation for many thousands of women it is clear that there is a significant proportion of women who can't use HRT for medical reasons, or choose not to use it for personal or cultural reasons. The evaluation does not seem to have taken this into account.

The evaluation indicates that there is no robust evidence to show how hot flushes change over a period of time and this is a reason for not recommending fezolinetant. If this is the case how is it that other management options can be recommended to manage hot flushes. This does not appear to make sense.

Having worked with a number of BMS menopause specialists, it is clear that there is a concern about the increased risk of cardiovascular disease associated with unmanaged vasomotor symptoms. I could not see where this was addressed in the evaluation process.

The evaluation suggests that Fezolinetant cannot be used for breast cancer patients as it is not licensed for that use. As I understand it, the majority of non hormonal options suggested, and currently prescribed to this cohort of patients are not licensed for that use either so this does not make sense. As I understand it the only licensed option is Clonodine, which many menopause specialists and doctors no longer prescribe to their patients.

It is clear that those who have been advised not to use HRT, due to a previous medical health diagnosis, often hormone dependent cancer, will often look to manage their symptoms with over the counter products. Not everyone is aware that there can be interactions or contraindications with some of these products, which can potentially cause harm. We must provide choice for these patients with licensed, regulated options.

Name	[redacted]
Role	
Other role	
Organisation	No
Location	
Conflict	No
Notes	
Comments on the DG:	

- **Has all of the relevant evidence been taken into account?**

Yes but further studies pending evaluating the use of this medication in women with cancer who would be the main group where this medication would be invaluable.

- **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?**

No - choice for women who are unable to have or have side effects with hormone replacement therapy is key. At the moment there is only one licensed non-hormonal therapy, clonidine, which, in clinical experience, is not particularly effective for treating VMS. This treatment offers choice and benefit has clearly been demonstrated. In my clinical practice, the patients who have used this medication not only experience a significant reduction (if not complete abolition) of symptoms, but also reduced severity in their VMS. This postively impacts quality of life, function and enables women to continue working. The cost of evaluating a women with postmenopausal bleeding as a result of HRT use needs to be balanced with the cost of this medication in any evaluations. With more women using HRT at above licensed doses and experiencing bleeding, this treatment is an excellent alternative.

Name	[redacted]
Role	
Other role	
Organisation	No
Location	
Conflict	No
Notes	
Comments on the DG:	

- **Has all of the relevant evidence been taken into account?**

This guidance currently excludes women with breast or ovarian cancer who can't take HRT and for whom this drug is potentially a life changing medication. The HIGHLIGHT 1 trial data will be crucial to looking at the impact in this group.

Myself and many other BC survivors who can't take HRT are being prescribed Veoza privately following discussion about the balance of risk (when no clinical trial data from cancer patients is currently available).

I feel this is a really important area for NICE to consider, and if the decision is made to not recommend it generally, the question about whethjer it should be recommended in patients who have had breast or ovarian cancer should be assessed separately when the data from the HIGHLIGHT 1 trial is available.

Personally, I tracked my symptoms and went from having 5-6 episodes at night (causing significantly disturbed sleep) as well as 8-10 per day (significantly impacting on life/work etc) to having 1-2 per night and 1-2 per day and none of the VMS were as severe as they had been before. I recognise this is anecdoatal, but I believe there are a lot of post BC patients who have similar stories.

- **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?**

I think they are reasonable summaries of the evidence as it stands at the moment.

- **Are the recommendations sound and a suitable basis for guidance to the NHS?**

I am disappointed it is not being recommended as an option that could be tried for women with VMS who can't take HRT. There are many and varied reasons why the other options (SSRIs primarily) may not be suitable and again, for women on Tamoxifen, these are not an option anyway.

- **Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful**

discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Generally the options for women with these debilitating symptoms (who can't take HRT) are limited and this is discriminatory in itself, as it adversely affects women and those with underlying conditions (eg cancer) which means HRT is not an option. Patients who have had cancer are protected by the equlity act (as classed as disabled after this diagnosis) and should be prioritised in any future consultations about the use of this drug.

Name	[redacted]
Role	
Other role	
Organisation	Forward Slash Films
Location	
Conflict	No
Notes	
Comments on the DG:	

- **Has all of the relevant evidence been taken into account?**

While the committee has considered the available clinical trial data and stakeholder input, there remains a significant gap in evidence for a key population — people with breast cancer or other oestrogen-dependent cancers, for whom HRT is contraindicated. Although fezolinetant has not been studied in this group, its non-hormonal mechanism of action offers a potentially safer alternative to hormone-based therapies, and it could address a well-recognised unmet clinical need.

In the absence of direct trial data, it may be appropriate to consider access to fezolinetant for the broader population of individuals who are unable or unwilling to take HRT, particularly given the severe impact vasomotor symptoms can have on quality of life. Enabling access while collecting real-world evidence in these groups — with appropriate clinical oversight and risk assessment — would be a pragmatic interim approach that balances patient need with ongoing safety evaluation.

- **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?**

Somewhat - however, they may underrepresent the potential value of fezolinetant for individuals with significant unmet needs, particularly those who cannot take HRT.

- **Are the recommendations sound and a suitable basis for guidance to the NHS?**

The recommendations are based on a cautious interpretation of the available clinical and economic evidence and reflect NICE's established principles for ensuring value for money in NHS treatments. However, given the significant unmet need among those who cannot take HRT — particularly people with oestrogen-dependent cancers or those who are HRT-averse — the decision not to recommend fezolinetant may limit access to a potentially beneficial treatment.

While the limitations of the current evidence base are acknowledged, fezolinetant has shown clinical benefit in reducing the frequency and severity of vasomotor symptoms. In the absence of alternative non-hormonal options with similar efficacy and with appropriate safeguards (e.g. real-world monitoring, specialist prescribing), it may be reasonable to allow conditional access for specific patient groups while further evidence is gathered.

Therefore, while the recommendations are methodologically sound, a more flexible, patient-centred approach — particularly for those with few or no other options — could better support the NHS in meeting diverse patient needs during this interim period of evidence development.

- **Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?**

Yes. While the recommendation not to use fezolinetant is based on clinical and economic uncertainty, it may disproportionately impact several protected groups:

Sex: The recommendation affects a treatment for menopause, which exclusively impacts women and some trans men and non-binary people. Denying access to a non-hormonal option may exacerbate existing health inequalities in women's health.

Disability: People with oestrogen-dependent cancers (often classed as a disability under the Equality Act) are explicitly excluded from HRT and may have no suitable alternative. This recommendation may limit symptom relief for individuals already living with or recovering from cancer.

Gender reassignment: Trans men and non-binary people experiencing menopause symptoms may already face barriers to accessing appropriate care. Limiting access to a non-hormonal treatment may compound these challenges.

Race: Evidence suggests that vasomotor symptoms are often more severe and longer-lasting in Black and Hispanic women. A lack of treatment options

for those unable to use HRT may disproportionately affect these groups, particularly where uptake or trust in HRT is lower.

To ensure equity, it may be necessary to consider mechanisms for conditional access or research inclusion for underserved groups, alongside strengthened efforts to gather evidence in diverse populations. Without this, there is a risk that the recommendation could contribute to systemic inequalities in menopause care.

- **Section 3.6: Generalisability to the NHS population**

I think the assessment from patient experts that severity is somehow more impactful than frequency of vasomotor symptoms is incredibly subjective. In our documentary research where we spoke extensively with women impacted by menopause symptoms, I remember one teacher in particular who was experiencing 30-40 episodes of hot flushes per day - it was the frequency of these which impacted her to the point that she had to leave her job because she could no-longer function in a classroom environment. In our experience severity and frequency are different drivers of the scale of impact, and one individual's experience of which is more impactful will vary hugely from another's.

Name	[redacted]
Role	
Other role	
Organisation	No
Location	
Conflict	No
Notes	
Comments on the DG:	

- **Has all of the relevant evidence been taken into account?**

Yes

- **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?**

Yes

- **Are the recommendations sound and a suitable basis for guidance to the NHS?**

Yes

- **Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful**

discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

no but NICE should be mindful that many menopause societies and menopause specialists have conflicts of interests as they have received funding by Astellas who manufacture fezolinetant

This is really well written and considers the current research and also lack of research in the group most likely to be prescribed this medication - women with breast cancer.

Women take HRT to improve many symptoms, not just vasomotor symptoms. They also take HRT to improve future health - for example to lower future risk of osteoporosis. There is no evidence that fezolinetant will reduce risk of future diseases.

Since this draft was written, the FDA have put a black box warning to this drug in view of its potential adverse effects on liver function and this is important - clearly regular monitoring of liver function is needed.

Long term risks of blocking neurokinin receptors for mental and physical health are unknown which is a concern.

Although the draft commented that published analyses of the fezolinetant trial data (Douxfils 2023), suggested an
increased incidence of neoplasms in the fezolinetant arm. Although it is hard to know if this risk is real or not, it needs to be considered and people need to know that fezolinetant blocks kisspeptin which is a protein that reduces metastatic spread of cancer.

Long term studies on this drug in women with a history of breast cancer need to be undertaken to assess future risks and potential benefits.

Also there needs to be studies comparing fezolinetant with gold standard treatment - HRT - in women.

It is encouraging that NICE have done such a detailed and evidence based draft guidance consultation for this medication.

It could be damaging and harmful for many women if fezolinetant was available on NHS/

Name	[redacted]
Role	
Other role	
Organisation	No

Location	
Conflict	No
Notes	

Comments on the DG:

I strongly disagree with the recommendation that Fezolinetant / Veoza should not be used to treat menopause symptoms.

I am a breast cancer survivor who is no longer able to take HRT to help with menopause symptoms. I take tamoxifen and will do so for 10 years.

I have extensively researched the options available to me to help with debilitating hot flashes. It is not recommended to take antidepressants/SSRIs when taking Tamoxifen and I am also opposed to taking a serious medication like this when I am not suffering with depression.

My GP recommended I find someone who would prescribe a private prescription for Veoza. I pay £80 per month. This is a huge amount to pay monthly for medication however since starting to take it I now sleep through the night for the first time in over a year. a year!! Can you imagine not sleeping through the night for more than an hour or two at a time for a year? Can you imagine how powerless you feel when there is no solution available to you?

So much is taken away from you when you have had cancer. You will never be the same person that you were before. On top of all of that you will put onto a pretty unpleasant drug, Tamoxifen or Letrozole, and have to white knuckle through menopause with nothing to help with the symptoms. You can’t even have camomile tea as it is a contraindication. Veoza is a drug that really works and could be beneficial for so many people who have been through a lot. I understand that they are not that many of us but there are still a lot! With no other decent solutions I can’t understand how you can’t make it available to us.

Name	[redacted]
Role	
Other role	
Organisation	No
Location	
Conflict	No
Notes	

Comments on the DG:

I would like to share my personal experience with Veozah, which has been a crucial part of my treatment since the summer of 2024. After undergoing a total hysterectomy for ovarian cancer in 2022, I found myself suffering from debilitating hot flushes, experiencing them up to three times an hour. These

symptoms significantly disrupted my daily life and were exacerbated by the letrozole I take to prevent cancer recurrence.

I have explored numerous alternatives, including yoga, herbal remedies, dietary changes, and caffeine elimination, but none have provided the relief I found with Veozah. As my cancer is estrogen-receptive, HRT is not an option for me, which makes access to effective non-hormonal treatments like Veozah essential.

Veozah has transformed my quality of life, allowing me to manage my symptoms effectively. It is crucial that we advocate for its availability, as it is a vital option for patients like me who cannot rely on traditional hormone therapies. I urge decision-makers to consider the real-life implications of their recommendations and recognize the necessity of Veozah for those suffering from severe hot flushes.

Our voices matter, and together, we can push for more inclusive treatment options that address the unique needs of individuals facing similar challenges. Thank you for considering the importance of access to Veozah in managing menopausal symptoms.

Name	[redacted]
Role	
Other role	
Organisation	Your Menopause by Harley Street at Home
Location	
Conflict	No
Notes	

Comments on the DG:

- **Has all of the relevant evidence been taken into account?**

While we appreciate the extensive evidence review carried out, we are concerned that some relevant real-world perspectives from the lived experience of women may not have been fully captured.

Your Menopause by Harley Street at Home is an independent organisation supporting over 75,000 women and 6,000 healthcare professionals with evidence-based menopause information and guidance. Through our community, we frequently hear from women experiencing severe vasomotor symptoms who are unable or unwilling to take Hormone Replacement Therapy (HRT). In a recent survey of over 500 women in our network who preferred not to use HRT, none had been advised about prescribable non-hormonal treatment options — leaving them to seek out unlicensed and often costly alternatives without clinical support.

Women’s voices are crucial and must be reflected in evaluations. The reality is that many women are already benefiting from fezolinetant worldwide, and

their experience represents an important form of emerging evidence. It would be a disservice to overlook this.

- **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?**

We respectfully suggest that the modelling used in the UK may not fully capture the breadth of benefit offered by fezolinetant — particularly the indirect but significant improvements in sleep, cognition, emotional wellbeing, and quality of life that result from effective treatment of vasomotor symptoms. These knock-on benefits can have wide-ranging impacts on women's ability to work, care for dependents, and participate in society.

The clinical and economic evidence submitted is broadly in line with that used in multiple regions where reimbursement has already been granted. It may not be perfect, but it is currently the best available, and reflects a robust and pragmatic basis for decision-making. Rejecting fezolinetant on the grounds of imperfect modelling risks halting progress in women's health innovation.

- **Are the recommendations sound and a suitable basis for guidance to the NHS?**

No — in our view, the current recommendation not to make fezolinetant available via NHS reimbursement is deeply flawed. It risks creating an inequitable two-tier system where women who can afford private care benefit from a safe, effective treatment, while others are left with no supported alternative.

We have consistently advocated for the HRT Prescription Prepayment Certificate because of the significant cost barrier prescription charges create. Fezolinetant, if left only to private prescribing, will remain unaffordable to many. Access to non-hormonal treatment options should not be a privilege reserved for the few.

We urge NICE to reconsider and provide clear, equitable access to fezolinetant via NHS services.

- **Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?**

es — failure to approve fezolinetant for NHS reimbursement risks disproportionately affecting women from lower-income groups and those unable to access private menopause care. This recommendation could also disadvantage women who, for cultural, religious, medical, or personal reasons, do not wish to use HRT. The absence of accessible, evidence-

based non-hormonal treatment options leaves these women without safe, supported care.

Below are quotes from women in our community whose voices deserve to be heard:

“My hot flushes were happening 10–15 times a day — I was struggling to function at work. I couldn’t present to my colleagues without fear of a hot flush overwhelming me. After just a few days of starting treatment with fezolinetant, the frequency and severity of the flushes reduced so much — they were barely noticeable.”
[redacted], Bristol

“I’ve never wanted to take HRT. My mum had breast cancer and it’s just not a risk I’m willing to take — my kids are still only young. Knowing there’s a drug that’s safe, works, and that I can only access via private prescription leaves me wondering what I paid National Insurance for all these years.”
[redacted], Northamptonshire

“There’s been so much work in the last few years to give women a voice about their health and menopause — it’s such a kick in the teeth to see new treatments being developed and yet again women being denied access.”
[redacted], Bexley

NICE has a responsibility not only to assess evidence, but also to help tackle the long-standing inequities in women’s health. Making fezolinetant available through the NHS is a vital step in the right direction.

Name	[redacted]
Role	
Other role	
Organisation	No
Location	
Conflict	No
Notes	
Comments on the DG:	

- **Has all of the relevant evidence been taken into account?**

I feel not as many women have VMS for years (can go into decades) these women haven't been accounted for.

- **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?**

No in regards to cost effectiveness as this doesn't take into account the cost (and personal) implications of women who can't carry out their usual activities of living work, society etc due to their VMS.

I do agree that it will be a small proportion of women who have tired or can't/ don't want HRT, and have tried all other non HRT options and have and currently using all diet lifestyle and strategies including CBT.

- **Are the recommendations sound and a suitable basis for guidance to the NHS?**

no as what I have read is all based on presuming that Fezolinetant will be started in primary care. Usually if women have tried everything and still VMS they should according to NICE 2024 Management of Menopause guidelines be referred to secondary care.

- **Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?**

I couldn't see any apart from personal choice of women being carefully considered. Of course prescribing Fezolinetant would be a clinical decision with shared decision making.

It wasn't clear though that the patient population that you consulted with was a diverse age range. Why I mention this is that the patients that I have seen that would benefit from this drug are the over 60's with severe VMS who seem to have symptoms for years. Of course if they were younger the benefits of HRT would outweigh the risks but with age and possible chronic condition now it doesn't. If your cohort of patient were all under 60 this group would not have been represented.

Name	[redacted]
Role	
Other role	
Organisation	No
Location	
Conflict	No
Notes	
Comments on the DG:	

- **Are the recommendations sound and a suitable basis for guidance to the NHS?**

I feel there is far too much emphasis on comparing fezolinetant to SSRIs — these are poor comparators, typically prescribed only because there are virtually no other options available. This reflects the broader, longstanding failure to invest adequately in women's health research, particularly for those for whom HRT is not a safe choice. How much longer must we continue denying these women access to treatments that could meaningfully improve their lives, while simply telling them to "cope"? The economic impact of untreated vasomotor symptoms in the workplace has also been completely overlooked. In my clinical experience, many women find the vasomotor symptoms of menopause more debilitating than their breast cancer treatment itself. We urgently need effective, accessible options to support them — and we need them now.

I am extremely disappointed by this decision. My role involves supporting women for whom HRT is not a safe option. These women already have very limited alternatives — most of which are unlicensed for treating their symptoms and carry significant side effects. For too long, their needs have been overlooked. The development of this medication represents a critical and long-overdue step toward providing them with a safe, effective, and reasonable choice. Dismissing its value for money, particularly for women whose vasomotor symptoms are profoundly debilitating, does not reflect the reality I see every day in clinical practice.

- **Section 3.1: Menopause and vasomotor symptoms**

  “or uterus”

removal of uterus alone does not generally result in menopause (unless ovarian blood supply has been compromised)

- **Section 3.2: Treatment pathway**

  “NG101 recommends SSRIs for people with breast cancer for relieving menopause symptoms, particularly hot flushes, but not for people taking tamoxifen”

The guideline recommends considering these as an option. Some SSRI/SNRIs can be used alongside tamoxifen - notably venlafaxine, escitalopram, citalopram

- **Section 3.3: Population for whom HRT is unsuitable**

  “an individual risk assessment is advised for people who have had breast cancer or other oestrogen-dependent cancers because there is no clinical trial data to determine its safety of clinical effectiveness in these groups. The committee agreed there is a particular unmet need for people with breast cancer or other oestrogen-dependant cancers who are experiencing vasomotor symptoms caused by menopause but acknowledged that fezolinetant would not be used in this group”

As a BMS-registered menopause specialist and breast specialist, I — along with many colleagues across the UK — run menopause clinics specifically for women with breast cancer. Currently, every option we offer for managing vasomotor symptoms involves off-label prescribing. After careful, informed discussions, a number of women have chosen to use fezolinetant, fully understanding the limitations due to the lack of trial data in breast cancer patients. Their treatment options are extremely limited, and having fezolinetant available as a supported option is, in my view, absolutely essential to improving their quality of life.

- **Section 3.4: Monitoring requirements and implications for prescribing setting**

  "The committee concluded that offering fezolinetant in secondary care may be more appropriate."

There are many GPs now who have done extra training in menopause care and would likely be able to support this. Many medications have tests performed in primary care, so I believe it is unlikely to add a hugely significant additional burden, especially given your previous statement that the number of women likely to take it is small (and they are most likely going to have other health conditions - the main reason they cannot have HRT - so may well be having blood monitoring anyway eg diabetes)

- **Section 3.5: Relevant comparators**

  "But the EAG did not agree with the exclusion of non-hormonal treatments such as SSRIs as comparators, stating that lower efficacy is not a suitable reason for exclusion. It also stated that NG23 recommendations on the use of these treatments were based on the first-line superiority of HRT, and do not say that they should not be used when HRT is unsuitable. Also, clinical advice to the EAG suggested that non-hormonal treatments are prescribed to about 1 in 5 people with vasomotor symptoms in NHS practice. Clinical experts and patient experts at the meeting also confirmed that these treatments can be offered."

One in five women are prescribed non-hormonal options largely due to poor training around HRT use, and because, at present, there are no better alternatives. It is important to highlight that SSRIs are not licensed to treat vasomotor symptoms and carry significant side effects, many of which can be particularly detrimental to menopausal women — for example, worsening libido, an issue that is already common during menopause. In my opinion, SSRIs are a poor comparator for fezolinetant; in my experience as a menopause specialist, they are often ineffective. I believe there is currently no true comparator for fezolinetant.

- **Section 3.7: Generalisability to the NHS population**

> “The committee was concerned by the exclusion of people with fewer than 7 vasomotor symptoms per day because they would be included in the NHS population, and it had not been demonstrated that fezolinetant is clinically effective in these people”

This critique feels excessively harsh toward the study design, which I suspect was largely dictated by external requirements. I would also argue that the underlying pathophysiology of vasomotor symptoms remains the same, regardless of their frequency. Based on the science behind the development of fezolinetant, it is highly likely that it would also be effective for women experiencing fewer than seven flushes per day. In my clinical experience, women often underestimate the number of hot flushes they have unless formally asked to diarise them.

- **Section 3.8: Indirect treatment comparison**

None of these drugs actually have a licence to treat vasomotor symptoms

- **Section 3.10: Company's modelling approach**

> “The committee noted the patient experts' experiences that frequency was less of a consideration than the severe impact of symptoms”

I would argue that the frequency impacts on how 'severe' a woman's experience of vasomotor symptoms is - they are not discrete entities

- **Section 3.10: Company's modelling approach**

> “Clinical advice to the EAG was that using frequency as a proxy for severity was a concern and not usual NHS practice”

I disagree. Most of the women I treat feel they can manage some vasomotor symptoms to a certain degree and often tell me that if they could reduce the number of time per day that they happen, this would dramatically improve their quality of life

- **Section 3.11: Data from trials and estimates of natural history**

I cannot understand why such importance has been put on the estimates of natural history of hot flushes. It is widely accepted that women will struggle for a number of years - I do not see the need to provide systematic review evidence to show this

- **Section 3.13: Uncaptured costs**

> “any subsequent costs in cases of treatment-related liver damage”

Evidence so far suggests all liver changes resolved on discontinuation of treatment, so this seems very unlikely

Name	[redacted]
Role	
Other role	
Organisation	No
Location	
Conflict	No
Notes	
Comments on the DG:	

Hi.
I have been taking Veoza for a year and have been extremely helpful with my menopause symptoms! Massively reduced my hot flushes! Please reconsider it going on the NHS
Thanks Veronica

Name	[redacted]
Role	
Other role	
Organisation	No
Location	
Conflict	No
Notes	
Comments on the DG:	

- **Has all of the relevant evidence been taken into account?**

Yes, all the evidence has been taken into account regarding Fezolinetant. However, the consultation misses the vital part about problems related to use of unlicensed medications currently to treat moderate to severe VM symptoms of menopause in individuals who do not wish to and cannot take HRT for medical or personal reasons. The burden of problems in this group has not been factored-in in these recommendations adequately.

- **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?**

No, the use of Fezolinetant will be for a niche group of women and not every woman experiencing mild to severe VMS. This selected group of women who will take this medication for personal or medical reasons will not be replacing women who will pursue HRT or other non-pharmaceutical treatments for VMS. The impression that large numbers of women will use this medication appears incorrect.

- **Are the recommendations sound and a suitable basis for guidance to the NHS?**

No. As a menopause specialist caring for women on the NHS and private sector for 15 years, these recommendations are a missed opportunity to provide women with a useful licensed option for treatment of moderate to severe VMS. I wish there was a member amongst the committee who sees patients on a day to day basis who suffer from severe VMS and cannot take HRT or unlicensed alternatives due to cancer or background medical conditions a to understand how much this drug could make a difference for many and without waiting on long waiting lists to be seen by specialists.

Many women who do not or cannot take HRT are treated with alternatives which are unlicensed and have significant side effect profiles. The cost saving for NHS in the long-run from avoiding complications from either HRT (bleeding etc) or unlicensed medications side effects will be significant.
As far as testing for liver enzymes - there are many medications we use in endocrine and GP settings which need renal or liver monitoring and this not an additional huge burden at all.
The waiting times and demands on hospital menopause services are huge and ever increasing and restricting this drug to secondary care initiation will be denying women a useful option for variable length of time and completely unfair. The drug has been developed over decades of research on NK receptors and one would not expect more than a year's data for a new medication following first RCTs. Future real world data will guide its place amongst treatment options.

- **Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?**

Nil

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	No
Notes	
Comments on the DG:	

Has all of the relevant evidence been taken into account?

This is hard for me to comment on as I am not a medical professional but from a societal and economic perspective, this decision seems to ignore the

enormous impact an additional treatment, such as Fezolinentant would have for those unable to take bio-identical HRT. We have been working in this space for the past five years and have observed a huge severe unmet need for VMS amongst those with contraindications to HRT. Veozah offers an effective route for patients trying to live their life normally. Astellas has conducted significant studies with a robust sample to prove effectiveness of this treatment for a significant number of patients. By approving this drug, it paves the way for investment for effective treatments for those impacted by menopausal symptoms. Denying Veozah as a treatment on the NHS, dampens future investment in women's health (with other innovation coming behind it, such as from Bayer) - a sector which is grossly underserved. There has been such little innovation in this space for a long time and so the ruling not to include it as a treatment is not only incredibly disappointing but damaging to the chances of future innovation to improve menopause symptoms. It feels like there is a political motivation for only promoting bio-identical HRT because of cost to the NHS but you can't put a price on improving the quality of life for individuals. £44.80/ month seems a small price to pay for improving lives. In addition, not including a non-hormonal treatment on the NHS encourages unregulated treatment from unregulated clinics, creating risk and vulnerability for people unable to take HRT (as well as being charged a small fortune for unnecessary hormone testing).

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

We are an organisation that has been working with thousands of women impacted by hot flushes / VMS and have conducted several nationwide proprietary quantitative studies exploring menopause symptom management, as well as the effectiveness of current medical treatments available via the NHS. Our research study with Kantar Insights with a sample of 1000 women aged 35-60 years in the UK, May 2022, showed that 86% on SSRIs and SNRIs describe their symptoms as severe or unbearable. Our research showed that these are not effective treatments for the majority of women trying to manage VMS.

Through our training using MenoVests, proprietary research, and observations on the impact of hot flushes has shown the profound impact VMS can cause for people, psychologically and cognitively, as well as physically. This impacts not just the individuals but the ecosystem they operate within and everyone within it. Not being able to manage VMS impacts the economy, community, family and workplace relationships. Any life improved by the treatment of Fezolinetant is value for money.

Are the recommendations sound and a suitable basis for guidance to the NHS?

There is much focus in the media on the benefits of HRT which we welcome, as well as the recent introduction to the NICE guidelines on CBT. Whilst it’s positive to see the uptake of HRT increase year on year, it can create a feeling of hopelessness for those who this treatment is unsuitable.

Having alternatives to HRT, such as Fezolinetant available on the NHS is essential, so women are given accessible options to manage their VSM.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

There have been various studies to show that women of colour experience VMS more severely and for longer, post-menopause than white women. By denying women of colour an alternative to HRT on the NHS, this decision will unintendedly create unlawful discrimination.

Further, our research conducted in May 2022 with Kantar Insights, a global research agency with a nationally rep sample of 1000 women aged 35-60 years, found that 56% found bio-identical HRT had some positive effect. However, 44% of the sample found HRT had no significant improvement to their symptoms or made it worse. Our study found that VMS was made worse for those with neurodiversity, living with a disability, and exposed to trauma or stress (past or current). For those with contraindications to HRT, the majority found SSRIs and SNRIs were ineffective to help manage VMS. We believe that this decision is discriminating against these groups and the marginalised.

Name	[redacted]
Role	
Other role	
Organisation	Nottingham Clinical Trials Unit
Location	
Conflict	1. NIHR grant 133461 Oxybutynin or venlafaxine for hot flushes in women who cannot or choose not to use hormone replacement therapy: randomised trial and economic evaluation (the BLUSH trial) 2. Discussion with Astellas regarding use of fezolinetant within an investigator initiated research programme for polycystic ovary syndrome. 3. Discussion with Bayer regarding use of elinzanetant within an investigator initiated research programme for menopausal vasomotor symptoms. No further commitment from Bayer until it has received marketing approval in UK.
Notes	
Comments on the DG:	
• **Section 1.1: Recommendations**	

We agree with this conclusion

- **Section 1.2: Recommendations**

NICE should recommend fezolinetant be available within the context of research, and that the NHS considers it use as a NHS treatment costs under the AcoRD guidance.

- **Section 1.3: Recommendations**

We agree with the rationale for the recommendation

- **Section 2: Information about fezolinetant**

No comments, factual information.

- **Section 3.1: Menopause and vasomotor symptoms**

Menopause before the age of 40 is called premature ovarian insufficiency (POI) and can be iatrogenic, genetic or of unknown cause. POI should be out of scope for this class of drugs, as HRT is indicated for bone and heart protection.

- **Section 3.2: Treatment pathway**

We agree/ no comment.

- **Section 3.3: Population for whom HRT is unsuitable**

The definitions of the 4 categories are helpful but do not reflect the marketing authorisation (MA), which allows for all women with moderate to severe VMS. We agree with the clinical expert that there are few women with an absolute contraindication for HRT, as defined by the first category. Nonetheless, the number of women for whom HRT is unsuitable is not insubstantial.<BLUSH surveys>

- **Section 3.4: Monitoring requirements and implications for prescribing setting**

Fezolinentant should ultimately be prescribed in primary care, but the requirement for liver function tests (LFTs) has introduced an extra burden and cost on GPs that might limit the offer. Thus secondary care or GPs with special interests in menopause seem more appropriate setting at this time. However, with long waiting lists for menopause clinics, restricting to secondary care may introduce local or regional disparities in access to fezolinetant. GPs might need to consider alternatives to HRT whilst waiting for the referral, if symptoms cannot be tolerated.

- **Section 3.5: Relevant comparators**

We strongly agree with the EAG that non-hormonal treatments should be considered as a comparator, and that HRT is not an appropriate comparator. Non-hormonal treatments are available and are prescribed by menopause experts in secondary care. Prescribing data is hard to obtain as the non-hormonal treatments are used for other indications.

However, a comparison of oxybutynin versus other NICE recommendation non-hormonal treatment has been commissioned by the NIHR, reflecting the lack of comparative evidence amongst existing non-hormonal treatments. This trial is currently suspended due to oxybutynin supply problems.

We therefore disagree that if fezolinetant is only offered in secondary care, this should be alongside or as an alternative to non-hormonal treatments, not after these have been tried.

- **Section 3.6: Clinical trials**

The company appear to have followed FDA guidance for industry for hormonal drug products for VMS and vulvo-vaginal atrophy (2003). These recommend that only post-menopausal women with a minimum of 7 moderate to severe hot flushes per days are included. They also recommend mean change in frequency and severity of symptoms, separately, from baseline to a timepoint, with 12 weeks suggested as the ideal trial duration.

We agree that the assumption of missing at random for VMS as a continuous measure is not valid and that a range of imputations (best case, worst case etc) could be used. The responder analysis is inherently less efficient use of data.

- **Section 3.7: Generalisability to the NHS population**

The restrictive inclusion criteria are as a result of adherence to the FDA guidance but we agree this results in trial results that are not reflective of the NHS population seeking treatment. An emphasis on the impact of hot flushes would be more appropriate. Whilst the SKYLIGHT/ DAYLIGHT trials will not have captured this using a validated tool such as the HFRDIS, they will have the data to derive a hot flush score: a simple index where a mild flush is scored as 1, moderate as 2 and severe as 3. This will incorporate severity and has been used in many other RCTs of treatments of VMS rendering it a suitable outcome for network meta-analysis.

We are less confident than the EAG that the efficacy of fezolinetant would be equivalent for perimenopausal and post-menopausal people. There will be no trial data in the former, due to the eligibility criteria, but the mechanism of action suggests neurokinin-B inhibitors will cause a decrease in luteinizing hormone and endogenous oestrogen. Whilst not an outcome

under consideration here, neurokinin-B inhibitors may improve abnormal bleeding that is a common feature of perimenopause.
We too note the higher proportion of trial participants who have undergone a hysterectomy with or without oophorectomy compared to the general age matched population. This will skew the trial population to having more VMS at trial entry. Whether a more generalisable population would encounter a floor effect in the decrease of VMS can only be speculated.
We would also like to note the strong placebo effect. Using the response threshold of a reduction of 6.6 hot flushes by 12 weeks, 62% of the placebo group were responders (Morga 2024).

- **Section 3.8: Indirect treatment comparison**

We are disappointed that the company did not include the network meta-analysis that they had commissioned (Monga 2023), but this reflects their argument that the no treatment is the rightful comparator. NICE has provided a thorough critique of the NMA, including the absence of the DAYLIGHT trial, risk of bias of the included trials, the lack of clarity about how heterogeneity and inconsistency have been considered and the apparent differences between fixed and random effect models. We agree that the NMA results should be viewed with caution due to methodological limitations, but also concur that there is little evidence to support clinical benefits of fezolinetant over non-hormonal treatments.

- **Section 3.9: Adverse events**

We agree that the data does not suggest any increase in treatment related serious effects such as neoplasms, but long-term use has not been subject to real world evaluation. The data on liver injury is emerging and again, the impact of long-term use has yet to be seen. The potential for long-term liver functioning tests should be included in the economic model.

- **Section 3.10: Company's modelling approach**

We agree with the EAG's critique of the economic analysis. We again suggest using a composite score of frequency x severity.
We also agree with the critique of the economic evaluation conducted by Institute for Clinical and Economic Review. The model structure for the ICER economic model appears to be more intuitive that the severity gradings of the company model.

- **Section 3.11: Data from trials and estimates of natural history**

We agree it is inappropriate for an asymmetrical reversion to the expert elicitation of VMS symptoms after 12 weeks for the placebo/ no treatment arm when the fezolinetant arm used trial data, given the strong placebo effect initially seen. We agree there is a need for better information regarding the natural history of VMS. These data could be available from symptom tracking apps, albeit from a self selected population, and further research is certainly warranted.

We also question the 7.4 year time horizon. In a follow-up of a cohort who had participanted in a ovarian screening study, 15,000 women aged 54- 65 years were mailed a symptom questionnaire, 10,418 returned completed questionnaires; and 90% had previously had HFs/NSs. Despite being on average 10 years postmenopausal, 54% experienced HFs/NSs (frequency of 33 per week with mean problem rating 4/10) that persisted across the age range.(Hunter 2012). This suggests that VMS symptoms are more prevalent in the 54-65 year age band than has been assumed previously.

- **Section 3.12: Health state utilities**

We acknowledge that EQ-5D-3L is the preferred measure for deriving utilities for NICE TAs, but agree that it is frequently insensitive to subtle but important facets of quality of life. Research to create and validate utilities from valid menopause-specific questionnaires is essential. Although this was attempted within the ICER review, further validation work is needed. We agree that calibrating utilities based on the opinion of one clinician is inappropriate.

- **Section 3.13: Uncaptured costs**

We agree that liver function monitoring costs need to be included in the model before any recommendation can be made, as they model does not reflect MHRA guidance. We would suggest that in modelling different settings, a third setting representing the Women's Health Hubs is considered, to reflect the NHS strategy for women's health.

- **Section 3.14: Acceptable ICER**

We agree with the summary.

- **Section 3.15: Equality**

The Committee is aware of differences in the experience of VMS according to ethnicity, and also that there are different cultural attitudes to menopause, and hence treatment seeking behaviour. Given NICE has not recommended fezolinetant, there are no equity issues. However, if it is subsequently recommended, the setting in which it is prescribed might influence equitable access to the drug. With regards to trans people, a personalised approach to offering fezolinetant would be required, dependent on whether they had undergone medical/ surgical transition and their use of gender affirming hormones.

- **Section 3.16: Conclusion**

We suggest that regardless of the final decision, NICE includes a research recommendation for more randomised data for fezolinentant compared with non-hormonal medical treatments, using frequency and severity of VMS as

well as menopause specific quality of life and impact of VMS as outcome measures.

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EAG ADDENDUM

Review of the company's response to Consultation on the Draft Guidance Document: Fezolinetant for treating vasomotor symptoms associated with the menopause [ID5071]

Produced by
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Declared competing interests of the authors

None.

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

Note on the text

All commercial-in-confidence (CON) data have been highlighted in blue and underlined.

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List of abbreviations

AE	Adverse event
BMS	British Menopause Society
CHE	Centre for Health Economics
CRD	Centre for Reviews and Dissemination
CrI	Credible interval
DG	Draft guidance
DGD	Draft guidance document
EAG	External Assessment Group
EAR	External assessment report
EQ-5D	EuroQoL Group's 5 dimension questionnaire
HRT	Hormone replacement therapy
ICER	Incremental cost-effectiveness ratio
INHB	Incremental net health benefit
LFT	Liver function test
LOCF	Last-observation-carried-forward
LYG	Life year gain
MENQOL	The Menopause-specific quality of life questionnaire
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
OR	Odds ratio
PGI-C	Patient Global Impressions Scale - Clinical
QALY	Quality-adjusted life year
SE	Standard error
SEE	Structured expert elicitation
SNRI	Serotonin and norepinephrine reuptake inhibitors
SSRI	Selective serotonin reuptake inhibitor
UK	United Kingdom
VMS	Vasomotor symptoms
SmPC	Summary of Product Characteristics

1 OVERVIEW OF THE COMPANY'S RESPONSE TO THE DRAFT GUIDANCE DOCUMENT

The company provided 12 comments in response to the Consultation of the Draft Guidance Document (DGD). Comment 1 is an executive summary of the company's response to the key areas of uncertainty raised in the DGD, while comment 12 presents the conclusions of the economic evidence. The external assessment group (EAG) will not provide a critique of these two comments as the content is covered under the response to the other comments. Comment 2 provides a summary of the company's clinical validation with external experts and market research. The EAG considers the company's validation process to be comprehensive, and no specific critique points for comment 2 are required that are not covered under the EAG's response to other comments. The remaining comments 3 to 11 are discussed below. These relate to:

- Place in therapy for fezolinetant (primary versus secondary care) (comment 3, DGD Section 3.4).
- Relevant comparators (comment 4, DGD Section 3.5).
- Uncertainty about the size of benefit demonstrated in the clinical effectiveness evidence for fezolinetant in the phase 3 trials and the handling of missing data (comment 5, DGD Section 3.6).
- Generalisability to the NHS population (comment 6, DGD Section 3.7).
- Network meta-analyses (NMAs) with non-hormonal pharmacological treatments and direct incorporation of relative treatments effects from the NMAs into cost-effectiveness analysis (comment 7, DGD Sections 3.8 and 3.11).
- Incorporation of severity in the cost-effectiveness analysis (comment 8, DGD Section 3.10).
- Baseline health state occupancy based on moderate to severe vasomotor symptom (VMS) frequency, reliance on natural history of VMS and handling of placebo effect (comment 9, DGD Section 3.11).
- Health state utility values based on EuroQoL Group's 5 dimension questionnaire (EQ-5D) data (comment 10, DGD Section 3.12).
- Uncaptured costs of liver monitoring for fezolinetant (comment 11, DGD Section 3.13).

The EAG provides a critical evaluation of the company's response to the draft guidance (DG) where the company has either provided additional evidence or has made a comment where additional clarification is required from the EAG. The company also presented a new model structure, with new base case and scenario analyses following DG. The EAG's critique should be read in conjunction with the company's DG response document[1] and the Evidence Assessment Report (EAR).

2 CRITIQUE OF THE COMPANY'S COMMENTS IN RESPONSE TO THE DRAFT GUIDANCE DOCUMENT

2.1 Comment 3: Place in therapy for fezolinetant (primary versus secondary care) (DGD Section 3.4)

In the draft guidance, the appraisal committee concluded that offering fezolinetant in secondary care may be more appropriate than offering it in primary care, given that liver function monitoring is needed before treatment, monthly for the first 3 months after treatment, then periodically based on clinician discretion. Liver function tests must also be done when there are symptoms suggestive of liver damage and the committee noted uncertainty about the follow-up testing protocol after 3 months. The committee also heard from clinical experts that managing liver monitoring within primary care would have a large impact in terms of appointments and incur additional costs.

In response, the company stated that feedback from their UK expert consultations was strongly in favour of fezolinetant being initiated and managed in primary care settings. This was based on feedback from clinical experts which highlighted regional disparities in access to secondary care specialist menopause clinics and long waiting times for appointments, and that implementation in primary care would not present a challenge given existing resources. The company also reported that its commissioned survey of 1,003 UK GPs found that 76% agreed that (a hypothetical equivalent of) fezolinetant should be prescribed in primary care, although 62% also thought that fezolinetant should be prescribed in secondary care (when responding to the same question). The company also commented that restricting fezolinetant prescribing to secondary care would increase burden on the NHS and undermine the government's 10-Year Health Plan goal of shifting care from hospital to community. Stakeholder comments from clinical experts and patient group representatives emphasised the importance of menopause management in primary care and Women's Health Hubs, noting that only complex menopause cases should be referred to secondary care, and not people whose symptoms are limited to moderate to severe VMS.

The EAG notes that other GP survey question results showed that:

- Most GPs are either very confident (35%) or moderately confident (46%) in making clinical decisions based on the results of liver function tests.
- Half of GPs don't refer any of their patients with moderate to severe VMS to secondary care; the
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- waiting time is 6 months when they do refer.
- Two-thirds of GPs thought they would be either very likely, or fairly likely, to prescribe a 'hypothetical product', aligning with fezolinetant's license and safety/efficacy evidence.

The uncertainty surrounding whether fezolinetant should be prescribed in primary or secondary care settings was supported by web comments from stakeholders. The British Menopause Society (BMS) commented that: "*Women could be initiated on Fezolinetant in specialist women's health or secondary care settings, with subsequent prescribing and review in primary care. Rather than an "all or nothing approach", this approach would favour inclusivity and an invaluable treatment option for vulnerable women currently excluded from adequate menopause support"*. Similarly, a comment from the Nottingham clinical trials unit noted that: "*Fezolinetant should ultimately be prescribed in primary care, but the requirement for liver function tests (LFTs) has introduced an extra burden and cost on GPs that might limit the offer. Thus, secondary care or GPs with special interests in menopause seem a more appropriate setting at this time. However, with long waiting lists for menopause clinics, restricting to secondary care may introduce local or regional disparities in access to fezolinetant*."

The EAG's clinical adviser thought that although fezolinetant could be used in either primary or secondary care, GPs are accustomed to monitoring LFTs so it would be expected that fezolinetant would usually be initiated in primary care.

2.2 Comment 4: Relevant comparators (DGD Section 3.5)

The committee concluded that non-hormonal pharmacological treatments were relevant comparators. The company's response noted that many patients in routine practice do not receive pharmacological therapy for moderate to severe VMS and that no active treatment "*represents the clinical reality of most patients seeking medical advice for moderate to severe VMS in women who are unsuitable for [hormone replacement therapy] HRT*" and "*is the most relevant comparator for estimating the cost-effectiveness of fezolinetant*".

The EAG notes that these conclusions are not supported by results from the company's GP survey results, submitted as part of its DG response (reported in the document "GP Omnibus August 2025 Liver testing and VMS"). Question 7 of that survey asked: "*Of those ^Q6_Total^ patients that consult with you in a typical three-month period for moderate to severe VMS symptoms who are unsuitable for HRT, how many are prescribed the following non-hormonal pharmacological treatments for VMS*?" The results for Question 7 indicated that patients were much more likely to be prescribed a non-hormonal pharmacological treatment than to receive no treatment.

This was supported by the answers the EAG's adviser gave to questions about the use of non-hormonal pharmacological treatments for treating VMS in the NHS. She stated that Selective serotonin reuptake inhibitors (SSRIs) or serotonin and norepinephrine reuptake inhibitors (SNRIs) are used; specifically fluoxetine, paroxetine, venlafaxine, sertraline or citalopram, although discontinuation rates are very high. This statement was supported by reference to two studies published in 2025: a UK survey study of menopause care in 1195 women with a history of breast cancer reported that 46% had been treated with an antidepressant for menopausal symptoms,[2] and a retrospective cohort study in women receiving endocrine therapy for breast cancer treatment/prevention reported that only 19% of women in the UK will still be taking an antidepressant for menopausal symptoms at 6 months.[3]

The EAG's adviser also considered clonidine to be less effective than the antidepressants, although the UK survey study of menopause care in women with a history of breast cancer found that 6.4% had been prescribed clonidine at some point.[2] The EAG's adviser is reluctant to prescribe gabapentin and pregabalin for VMS due to concerns about the adverse effects, although she noted that the UK survey found that 9.3% of women with a history of breast cancer had been prescribed either gabapentin or pregabalin for menopausal symptoms.[2]

The EAG therefore concludes that although no active treatment is a relevant comparator for some patients in this appraisal, non-hormonal pharmacological treatments are the most relevant comparator, based on the evidence presented by the company and clinical advice received by the EAG.

2.3 Comment 5: Uncertainty about the size of benefit demonstrated in the clinical effectiveness evidence for fezolinetant in the phase 3 trials and the handling of missing data (DGD Section 3.6)

The committee concluded that there was uncertainty about the size of the benefit of fezolinetant in reducing daily vasomotor symptom frequency and severity because of the methods the company used to handle missing data. In response to this the company has presented clinical effectiveness evidence based on a responder analysis of change from baseline in moderate to severe VMS frequency. Analyses of response data based on the Patient Global Impressions Scale - Clinical for VMS (PGI-C VMS) endpoint were also presented in a scenario analysis.

For the company's base-case, response was defined by a reduction of at least 75% in moderate to severe VMS frequency from baseline. The EAG's adviser thought that this outcome reflects clinically meaningful improvements in moderate to severe VMS frequency across NHS patients likely to receive fezolinetant and that the choice of a 75% versus 50% threshold is subjective, given that a 50% reduction will be clinically significant for some patients. The EAG considers use of the 75% threshold as being most appropriate, given that in the CS the company stated that UK clinical expert opinion

indicated that a 75% reduction from baseline is a clinically meaningful improvement. The EAG notes that in the fezolinetant trials, Week 12 odds ratios tended to increase a little moving from lower to higher thresholds (50%, 75%, 100%, see EAR Table 10). The EAG also notes that these results are relevant to the specific trial populations, which, to be eligible for inclusion, had to have minimum numbers of VMS events within certain timeframes, e.g. ≥ 7 moderate to severe VMS events per day. It therefore remains unclear how applicable the responder outcome results are to the cohort of NHS patients who have fewer VMS events (than the trial cohorts). For example, it could be more difficult to achieve a 50% reduction from 4 to 2 events, than a reduction from 8 to 4 events, especially given the baseline VMS frequency subgroup effect (see comment 6). The EAG notes that across the DAYLIGHT, SKYLIGHT 1 and SKYLIGHT 2 trials, just under 20% of screened patients were excluded based on the criterion requiring a minimum average of seven moderate to severe VMS events per day as recorded in the electronic diary during the last 10 days prior to randomisation.

The EAG considers the PGI-C VMS response outcome to have limited reliability, given that it relies on just a single question asking for a comparison of symptoms 'now', compared to the start of the study. This makes it prone to being affected by recall bias and by subjectivity in how 'now' is interpreted. Although it is not formally used in practice, the EAG's adviser noted that patients are asked about symptoms in a similar way to the PGI-C VMS question, since patients typically come back to the GP at three months, so would be comparing symptoms then to how they felt three months previous.

2.4 Comment 6: Generalisability to the NHS population (DGD Section 3.7)

The company sought to allay concerns about VMS frequency restrictions in the fezolinetant trial populations by seeking the views of clinical experts. The company concluded that the clinicians' views were that patients who seek treatment are typically those who experience frequent moderate to severe VMS, so the trial results were generalisable to the NHS population likely to be treated with fezolinetant.

The EAG notes that the clinicians also commented that overall quality of life and how women feel, may also be used to assess the need for treatment, rather than relying solely on the frequency of hot flushes. There is no requirement (in the marketing authorisation) for a minimum number of VMS events per day for patients to be treated with fezolinetant. The EAG reiterates its concerns that it is plausible that fezolinetant might not be as effective in the full NHS population, given the baseline VMS frequency subgroup effect seen in the pooled SKYLIGHT trial analyses. This suggested a significantly smaller effect in the subgroup of patients with VMS frequencies lower than the median at baseline (the treatment effect was a mean difference of -1.36) vs the subgroup with VMS frequencies higher than the median at baseline (mean difference -3.66). The EAG remains concerned

that the company did not investigate whether a similar effect was seen in the subsequent DAYLIGHT trial, given the evidence from the SKYLIGHT trials that this could be an effect modifier. This may be a particularly important issue for the subgroup of patients seeking treatment who have few, but severe, VMS events. Additionally, the EAG reiterates concerns that the effectiveness of fezolinetant remains uncertain in patients with chronic diseases, and patients with elevated blood pressure, since large numbers of these patients were excluded from the trials. The safety profile of fezolinetant in these patients is also not known.

2.5 Comment 7: NMAs with non-hormonal pharmacological treatments and direct incorporation of relative treatments effects from the NMAs into cost-effectiveness analysis (DGD Sections 3.8 and 3.11)

The company conducted new NMAs which include non-hormonal pharmacological treatments and results are now included in the revised cost-effectiveness analyses. However, evidence limitations precluded full inclusion of all relevant comparators in the NMAs and economic model. Desvenlafaxine was the only non-hormonal pharmacological comparator considered in the company's base case as a proxy for venlafaxine (which is used in the NHS). Efficacy and discontinuation data were included in the company's NMAs. A scenario analysis also includes a comparison of fezolinetant to paroxetine 7.5 mg. However, as efficacy data for paroxetine based on response measured as a 75% reduction in moderate to severe VMS frequency at week 12 were not available, efficacy data based on a 50% reduction were used instead (see Section 2.3 for EAG comments on response outcome definition).

As noted in Section 2.2, the EAG considers SSRIs, SNRIs, gabapentin, pregabalin and clonidine as relevant comparators, based on both clinical advice and recent evidence As no head-to-head studies of fezolinetant compared to any of these treatments are available, the company carried out NMAs to estimate relative effects of fezolinetant versus desvenlafaxine and paroxetine for the efficacy (response) and safety (discontinuation) outcomes, to align with the inputs required in the economic model. The EAG agrees with this choice of evidence synthesis method. However, the lack of inclusion of evidence on gabapentin and clonidine in the company's NMAs (and consequently in the economic model) is a limitation. The EAG acknowledges that the only study comparing clonidine did not report appropriate outcomes, however the reasons given by the company for not including the available evidence on gabapentin are less convincing. The EAG provides more detailed comments on data sources and selected interventions for inclusion in the NMAs in Sections 2.5.1 and 2.5.2.

2.5.1 Data sources for the NMA

Aggregate-level response and discontinuation data for the comparison of fezolinetant to placebo were derived from the individual participant data in the SKYLIGHT 1, SKYLIGHT 2 and DAYLIGHT

trials. Data for the two SKYLIGHT trials were pooled. Only participants considered unsuitable for HRT were included.

To identify relevant evidence on response and discontinuation for comparators, the company used results from their original submission systematic review (carried out on 2021) and subsequent updates (2023 and 2024), as reported in the original company submission. However, response was only included as an outcome for the original review and not for the updates, so it is possible that studies reporting response but not the other outcomes required in the review updates, may have been missed (section 2.10.13 of the company's addendum to the DG response[4]). Given the limited evidence the company included in the NMAs, this could be a limitation.

The systematic literature review identified evidence on the following non-hormonal comparators: desvenlafaxine (an SNRI) at doses of 50 mg, 100 mg, 150 mg and 200 mg, paroxetine (an SSRI) at a dose of 7.5 mg, gabapentin at a dose of 1800 mg and clonidine at a dose of 0.1 mg.

Whilst desvenlafaxine is not licensed for any condition in the UK and is therefore not used in the NHS, the company noted that it can be considered as a proxy for venlafaxine (SNRI), a related drug which is sometimes prescribed off-label for VMS, but for which no evidence was found in the company's systematic review. The company considered evidence for desvenlafaxine 100 mg was the best proxy for the dose of venlafaxine that would be used in the NHS for VMS, as it represents a more conservative estimate of the relative effect compared to fezolinetant and is informed by more evidence in the NMAs. The EAG's clinical adviser considered this appropriate.

The company's systematic review only identified evidence on paroxetine 7.5 mg, although the dose recommended by the BMS for management of VMS is higher, at 10-20 mg. In addition, response (defined as reduction of at least 75% in moderate to severe VMS frequency from baseline) was not reported in the paroxetine study. It was therefore only included in the company's base case discontinuation (and associated sensitivity analyses) NMA. An additional scenario analysis was conducted using response defined as a reduction of at least 50% in moderate to severe VMS frequency from baseline, so that the paroxetine evidence could be included. However, details of the methods used for this analysis were not presented. From the results used in the economic model, the EAG infer that desvenlafaxine was not included in the scenario NMA, likely due to data on response defined as reduction of at least 50% in moderate to severe VMS frequency from baseline not being available in desvenlafaxine studies. Assuming the NMA followed the same methodology used for the outcome of response defined 75% reduction, the EAG consider it appropriate. However, because of the reduced dose of paroxetine included in the company's NMAs, the effectiveness of paroxetine compared to fezolinetant for VMS in the NHS is likely to be underestimated and its acceptability may be overestimated.

Three studies provided evidence on gabapentin compared to placebo all using doses higher than that used in clinical practice for VMS (BMS recommended dose), although still less than the maximum dose for a licensed indication in the UK: BREEZE 1 and 2 used 1200 mg, BREEZE 3 used 1800 mg per day, whilst the BMS recommended dose is for 900 mg per day (Table 2 of the company's addendum to the DG response[4]). However, it is unclear whether the effectiveness of 900 mg per day differs sufficiently from the effectiveness of 1200 mg per day, to justify exclusion of this evidence from the NMA. In addition, as noted in section 3.3.1 of the EAR, doses up to 3600 mg are allowed for other conditions, suggesting that 1200 mg is not considered an unsafe dose. The EAG further notes that evidence from a lower than recommended dose of paroxetine was included in the company's NMA, and gabapentin evidence was included in a published NMA sponsored by the company[5] and in the company's previous 2022 and 2023 NMAs (which used different outcomes), as described in Table 2 of the company's addendum to the DG response.[4] It is therefore unclear why evidence on gabapentin could not be considered in the NMA provided in the company's response to DG, acknowledging the possible overestimation of effectiveness.

No evidence at the relevant timepoints was available for the only study comparing clonidine to placebo.[6] Therefore, no evidence on this comparator could be included in the NMAs.

2.5.2 Interventions included in the NMA

Following the company's NMA feasibility assessment, the interventions included in the company's base case NMA for response were: placebo, fezolinetant 45 mg, desvenlafaxine 100 mg and desvenlafaxine 50 mg (Figure 1 of the company's addendum to the DG response[4]). Interventions included in the company's base case NMA for discontinuation were: placebo, fezolinetant 45 mg, desvenlafaxine 100 mg, desvenlafaxine 50 mg and paroxetine 7.5 mg (Figure 3 of the company's addendum to the DG response[4]).

Sensitivity analyses were conducted by also including studies (and arms) of all doses of desvenlafaxine in both the response and discontinuation networks. This added evidence on desvenlafaxine 150 mg and 200 mg to the base case networks (Figures 2 and 4 of the company's addendum to the DG response,[4] respectively).

Data included in the NMAs of response and discontinuation are displayed in Tables 4 and 5 of the company's addendum to the DG response,[4] respectively. No details were provided for the effectiveness network considering response defined as at least 50% improvement in moderate to severe VMS frequency from baseline.

2.5.3 NMA Methodology

The company's base case NMA model estimated the relative effects of desvenlafaxine 50 mg and 100 mg compared to fezolinetant as separate nodes (termed a "simple NMA"), with the 100 mg effect used as a proxy for the venlafaxine dose used in NHS practice. The company also explored class models to estimate the effect of desvenlafaxine 50-100 mg as a single class, which were not considered appropriate. The EAG agrees with this assessment and will focus the critique on the simple NMA (where interventions are considered as separate nodes).

Fixed (common) effect and random effects NMA models were fitted for response and discontinuation and for both the company base case and sensitivity analysis (dose-expanded) networks, in accordance with guidance in the NICE Decision Support Unit Technical Support Documents 2 and 3,[7, 8] using the *multinma* R package.[9] The EAG considers this appropriate in principle, although we were unable to reproduce analyses as the NMA code provided did not have the accompanying data files. It is therefore unclear whether placebo or fezolinetant was the reference treatment in the *multinma* package implementation. The company's addendum to the DG response[4] appears to suggest that fezolinetant was the reference treatment in the analysis. This may be the reason for the issues encountered with divergent transitions (Section 2.10.11, page 19, of the company's addendum to the DG response[4]), which typically reflect slower model convergence. This may have been alleviated by using placebo as the reference treatment in the analysis, as it is a better connected node in the network. However, the company adjusted the relevant *multinma* parameters to achieve reliable estimates so the EAG agree that NMA results obtained are appropriate.

The company provide results and model fit statistics for all fitted models. The EAG considers that random effects models are more appropriate for all networks, given the study differences identified in the company's feasibility assessment which, whilst not precluding NMAs, suggest the assumption of a common effect being estimated by all studies within a comparison may not hold. Therefore, despite comparable model fit for the fixed and random effects models for the discontinuation outcome in the company's sensitivity analysis NMA (network extended to include all doses of desvenlafaxine, Table 10 of the company's addendum to the DG response[4]), the estimated between-study heterogeneity is moderate and the random effects model should still be preferred.

In addition, due to data sparsity (few studies included per pairwise comparison in the network) the between-study heterogeneity estimates are very uncertain for the company's base case NMAs of response and discontinuation, which adds to the uncertainty in the relative effect estimates. The use of "external" (but still relevant) evidence to better estimate the between-study heterogeneity is recommended in TSD2[7] (Section 6.2). The EAG therefore considers that results from the sensitivity analysis networks with the additional evidence on all desvenlafaxine doses are preferable as they can

more reliably estimate the between-study heterogeneity which avoids adding additional uncertainty to the relative effect estimates. The odds ratios from the reduced and dose-extended (sensitivity analysis) networks are very similar, but the 95% credible intervals (CrIs) are narrower, indicating more precisely estimated relative effects (Tables 6, 7, 9 and 10 of the company's addendum to the DG response[4]) which more appropriately reflect the remaining uncertainty in the relative effects for inclusion in the economic model.

No details were provided for the scenario analysis which considered response defined as at least 50% improvement in moderate to severe VMS frequency from baseline (to allow inclusion of paroxetine 7.5 mg in the network) so it is unclear whether a fixed or random effects model was used.

In the response NMA, missing data were imputed using last observation carried forward (LOCF). The EAG acknowledges that the company had to adopt this approach to make the results of the fezolinetant studies more comparable to the other studies in the network, given that all the comparator trials reported results based on LOCF. In the economic model, the NMA odds ratio for fezolinetant versus desvenlafaxine, based on LOCF imputation, was applied to fezolinetant response rates derived using a more conservative imputation method, where missing data for the response outcome were assumed to be non-responders. This mixing of methods, while done for pragmatic reasons (aligning the odds ratio with comparator studies), introduces a potential inconsistency; however, the EAG considers it a reasonable assumption given the constraints with the data.

2.5.4 NMA results

The EAG's preferred NMAs were those using random effects models and including all doses of desvenlafaxine (company's sensitivity analysis networks). The EAG agrees with the company that the best proxy for the relative effect of fezolinetant compared to venlafaxine is given by the comparison to desvenlafaxine 100 mg. The EAG would have preferred to include evidence from studies of gabapentin compared to placebo in the NMA, using the results of the lowest daily gabapentin dose (1200 mg) as a proxy for its effectiveness on the NHS.

Results from the random effects NMA for response (dose-extended network, Table 7 and Figure 6 of the company's addendum to the DG response[4]) suggest that although the odds ratio (OR) for response of fezolinetant compared to placebo suggests a benefit of treatment with fezolinetant (OR = 0.39, 95% CrI 0.22 to 0.70), there is no evidence of a difference in effectiveness of fezolinetant compared to desvenlafaxine 100 mg (used as a proxy for venlafaxine, OR = 0.84, 95% CrI 0.42 to 1.73) or compared to any other desvenlafaxine dose included in the network.

Results from the random effects NMA for discontinuation (dose-extended network, Table 10 and Figure 8 of the company's addendum to the DG response[4]) suggest that the odds of discontinuation on

fezolinetant are lower than on placebo, paroxetine and desvenlafaxine 100 mg. However, it should be noted that the 95% CrI for the OR of discontinuation on fezolinetant compared to desvenlafaxine 50 mg includes no effect. If the lower dose of desvenlafaxine is assumed to best represent the discontinuation that would be seen on venlafaxine in the NHS, then there is no evidence of a benefit of fezolinetant on discontinuation.

2.6 Comment 8: Incorporation of severity in the cost-effectiveness analysis (DGD Section 3.10)

The company's original model structure incorporated health states based solely on VMS frequency, failing to capture the impact of VMS severity. As outlined in DGD Section 3.10, the committee noted that by not incorporating severity, which was a separate outcome in the trials, the model may not be fully capturing the benefits of fezolinetant. The committee also heard from patient experts that frequency was less of a consideration than the severe impact of symptoms (DGD Section 3.7). Consequently, the committee concluded that the model structure, with health states based on VMS frequency, was inappropriate for decision making.

The company's response to the issues raised in DGD Section 3.10 is covered under comment 8, with further details of the new model structure, in which health states are now defined by response (corresponding to the binary responder outcomes of the fezolinetant trials) provided under comment 9. The company acknowledges the committee's concerns regarding the relative importance of VMS frequency and severity; however, it highlights that feedback received from 3 UK clinical experts and 4 patient representatives consulted for the original submission was consistent in identifying moderate to severe VMS frequency as the most relevant outcome for patients, which was further supported with additional feedback from 3 clinical experts supporting the use of moderate to severe VMS frequency in defining response in the new model structure.

The EAG is supportive of the company's new approach that uses moderate to severe VMS frequency to define response within the model structure (see Section 2.9 Comment 9). The EAG's primary concern with the original model structure was the emphasis placed on movement between arbitrary cut-off thresholds used to define the moderate to severe VMS frequency health states in the model. These thresholds were based on statistical analyses of utility values associated with different frequency thresholds (and the EAG had raised concerns regarding the method used to identify them), rather than on an efficacy outcome derived from the trials. The use of a responder outcome to define health states overcomes the original frequency threshold concerns; however, it doesn't fully address the committee's concern that the model is failing to capture the impact of VMS severity.

The company argues that severity is inherently subjective; therefore, moderate to severe VMS frequency should be selected as an objective outcome to inform the modelling. To incorporate

patient's perception of their symptoms and the broader impact of treatment, the company presents a modelled scenario analysis where response to treatment is defined according to the PGI-C VMS tool. This was not used in the company's base case analysis for three reasons: (1) PGI-C VMS is not routinely used in clinical practice in the UK; (2) comparator data for PGI-C VMS were unavailable outside of the fezolinetant trials; and (3) the EAG's preference for the use of the 75% response outcome as a more objective measure with a lower likelihood of bias than PGI-C VMS (which may be prone to recall bias). The EAG's clinical advisor confirmed that the PGI-C VMS tool is not routinely used in clinical practice; however, the components of it are indirectly applied when individuals are asked about their feelings regarding symptoms. The EAG supports the company's rationale for including the assessment of improvement according to the PGI-C VMS in a scenario analysis rather than the base case.

2.7 Comment 9: Baseline health state occupancy based on moderate to severe VMS frequency, reliance on natural history of VMS and handling of placebo effect (DGD Section 3.11)

As noted above, the committee concluded in DGD Section 3.10 that the original model structure did not adequately capture the health states relevant to people with moderate to severe VMS. In DGD Section 3.11, the committee decided that the outputs of the structured expert elicitation (SEE), which was used to estimate the natural history of VMS, were not fit for purpose because the baseline distribution of VMS frequency from DAYLIGHT was not defined to the experts, and the resulting elicited distributions lacked face validity. Furthermore, the committee identified that a model structure that did not allow for the inclusion of relative treatment effects and limited the trial data used to 12 weeks in the 'no treatment' arm was highly problematic. Consequently, the committee concluded that the misalignment between the baseline number of events, natural history estimates and approach to placebo adjustment were all linked and needed to be addressed in a coherent way.

In response to the DG, the company developed a *de novo* cost-effectiveness model specifically to address these three core issues. Details of this new model structure and the parameters used to inform it are reported in the company's addendum to the DG response.[4] The EAG provides a summary and critique of the new model structure and parameters, and how these changes overcome the committee's core issues.

2.7.1 New model structure

The company provided a *de novo* cohort Markov model that included six health states, two of which were based on response status at the treatment decision timepoint of Week 12 (see Figure 9 of company's addendum to the DG response[4]): (1) On treatment Pre-Response Assessment, (2) On

Treatment Responder, (3) On Treatment Non-Responder, (4) Off Treatment with VMS (pre-/post-response assessment), (5) Alive VMS Cessation, and (6) Dead.

The cohort starts in the 'On treatment Pre-Response Assessment' health state. Individuals in the active treatment arm are at risk of treatment discontinuation (transitioning to 'Off Treatment with VMS'), in addition to the risk of experiencing VMS cessation (transitioning to the 'Alive VMS Cessation' health state, incurring no further treatment), or death (transitioning to the 'Dead' health state). Individuals in the no active treatment arm, are at risk of experiencing VMS cessation or death.

At Week 12, individuals alive with VMS are classified as either 'responders' or 'non-responders' based on the response criteria. In the active treatment arm, responders enter the 'On Treatment Responder' health state and continue treatment until discontinuation, VMS cessation, death or the end of the model time horizon. For non-responders, 50% immediately discontinue treatment (and transition to the 'Off Treatment with VMS' state), while the remaining 50% enter the 'On Treatment Non-Responder' state to capture partial response to treatment. Individuals in the 'On Treatment Non-Responder' health state continue treatment until they stop at Week 52, while remaining at risk of treatment discontinuation, VMS cessation, or death. In the no active treatment arm, the cohort is categorised into responders and non-responders at Week 12; however, the cohort remains on no active treatment regardless of their response status.

All individuals are at a risk of natural VMS cessation or death, which does not differ by treatment arm.

EAG critique

As discussed previously, the EAG's primary concern with the original model structure was the underlying assumptions used to define arbitrary cut-off thresholds for moderate to severe VMS frequency health states in the model. This in turn led to the core issues arising from the misalignment between the baseline frequency of events and the natural history estimates used in the original model. The EAG considers that the new model structure addresses these core issues by eliminating the need to define a baseline distribution across frequency categories in the model. Instead, health states are now defined based on a percentage reduction in moderate to severe VMS frequency at Week 12 from baseline. This Week 12 timepoint for response assessment aligns with the NICE menopause guideline (NG23[10]), which recommends 3 months to assess efficacy and tolerability of treatments, and was supported by the EAG's clinical advisor. Therefore, the EAG considers the response assessment timepoint at Week 12 appropriate.

A primary concern with the new model structure is that it now creates a misalignment with the utility values used for the health states. This misalignment stems from a structural difference between the

treatment arms: the active treatment arm includes an additional health state, 'On Treatment Non-Responder', to represent partial responders, whereas this specific state is not included in the no active treatment arm. In the company's base case, response was defined as a reduction of at least 75% in moderate to severe VMS frequency from baseline. For the active treatment arm, non-responders were split such that 50% discontinued treatment immediately, transitioning to the 'Off treatment with VMS' state, while 50% continued treatment until Week 52. The continuing 50% were placed in the 'On Treatment Non-Responder' state, where partial response was specifically defined as at least 50% reduction but less than 75% reduction in VMS frequency. Consequently, the utility values for the health states in the active treatment arm should be separated by response status into three distinct groups: (i) responders (who achieve ≥ 75% reduction), (ii) partial responders (who achieve ≥ 50% but less than 75% reduction), and (iii) non-responders (who do not achieve 50% reduction). However, the utility values are not separated by response status in this way (see Comment 10, Section 2.8). Instead, the utility values are only separated into responders and non-responders, using the ≥ 75% reduction criterion. Furthermore, the exclusion of a partial responders' health state in the no active treatment arm creates a discrepancy. Specifically, the utility values for the no active treatment arm are based on a weighted average of responders (who achieve ≥ 75% reduction) and non-responders (who do not achieve 75% reduction), which results in a structure that differs from the active treatment arm, with three categories of response and a lower response threshold for the non-responders.

One way to overcome the misalignment between the structural difference across arms and the utility values in the model, is to change the primary response criterion to at least a 50% reduction in moderate-to-severe VMS frequency from baseline, provided that outcomes for partial responders who achieve ≥ 50% reduction are meaningful to patients. This criterion change would effectively capture the partial responders without the need to incorporate an additional health state in the model for 12 months, as both responders and partial responders continue on treatment. It appears that the only reason the company incorporated the additional 'On treatment Non-Responder' health state was to limit the duration of treatment for these partial responders to one year (Week 52). However, the EAG notes that the company has not provided justification for this assumption of treatment discontinuation at Week 52 for partial responders. The EAG's clinical advisor did not support this 52-week stopping rule, suggesting that treatment is likely to continue beyond one year if partial responders maintain a benefit from the treatment.

2.7.2 Treatment effectiveness and extrapolation

The new model includes three elements relating to treatment effectiveness and extrapolation of effects over the long-term: (i) short-term efficacy based on a distribution of response from the pooled DAYLIGHT and SKYLIGHT 1&2 (HRT-unsuitable subpopulation) at Week 12; (ii) long-term treatment effect and discontinuation rates; and (iii) VMS cessation and mortality.

2.7.2.1 Response assessment at Week 12

In the company's base case analysis, response was defined at Week 12 as at least a 75% reduction in moderate to severe VMS frequency from baseline. This criterion was informed by pooled data for fezolinetant and no active treatment from the DAYLIGHT and SKYLIGHT 1&2 (HRT-unsuitable subpopulation) trials. The justification for choosing this specific definition is detailed under Section 2.3 (Comment 5). To determine the responder percentage for desvenlafaxine 100mg, the OR from the NMA (mean OR of 0.84, with 95% CrI: 0.35 to 2.09) was applied to the fezolinetant data.

Several scenario analyses were conducted by altering four key parameters: the response definition, the assessment timepoint, the source of evidence, and the inclusion of the comparator paroxetine. Two alternative response definitions were considered: (i) ≥ 50% reduction in VMS frequency and (ii) response defined according to patients' self-reported scores on the PGI-C VMS tool, with values of 1 (much better) or 2 (moderately better) on the 7-point scale considered to represent treatment response. For the response definition based on ≥ 50% reduction, the comparator paroxetine was included only in this specific scenario, and the company did not provide results from an updated NMA for all treatments including desvenlafaxine (instead the company applied the OR for desvenlafaxine based on the NMA for the response outcome of ≥ 75% reduction). Two different timepoints for response assessment were considered: (i) Week 4 and (ii) Week 24, while alternative sources of evidence for fezolinetant and no active treatment were used to inform the criterion: (i) pooled SKYLIGHT 1&2 data only or (ii) DAYLIGHT data only.

Table 1 summarises the Week 12 response percentages for fezolinetant and its comparators, for both the company's base case (using the ≥ 75% reduction in VMS frequency definition) and a scenario analysis (using the ≥ 50% reduction definition).

Table 1 Summary of Week 12 response percentages used in the company's base case analysis and scenario analysis with paroxetine

Response definition	Treatment	Responder percentage	Source
75% reduction (company base case)	Fezolinetant	41.62%	Pooled DAYLIGHT and SKYLIGHT 1&2 (HRT-unsuitable subpopulation)
	No active treatment	21.83%	
	Desvenlafaxine 100mg	37.32%	Calculation, mean OR (0.84) applied to the fezolinetant arm based on NMA with 75% reduction from baseline. Details about response input in NMA are in Table 17, company's addendum to DG response.[4]

Response definition	Treatment	Responder percentage	Source
50% reduction (scenario analysis)	Fezolinetant	62.43%	Pooled DAYLIGHT and SKYLIGHT 1&2 (HRT-unsuitable subpopulation)
	No active treatment	40.32%	
	Desvenlafaxine 100mg	58.12%	Calculation, mean OR (0.84) applied to the fezolinetant arm based on NMA **with 75% reduction** from baseline
	Paroxetine 7.5mg	49.57%	Pooled NCT01101841 and NCT01361308.[11, 12]

Abbreviations: OR: odds ratio, VMS: vasomotor symptoms.

EAG critique

The EAG's clinical advisor confirmed that a ≥ 75% reduction in moderate to severe VMS frequency reflects a clinically meaningful improvement in symptoms. However, the EAG's clinical advisor noted that she wouldn't necessarily prioritise the ≥ 75% reduction over a ≥ 50% reduction in VMS frequency, as the 50% threshold may be considered very meaningful to some people. Therefore, the EAG considers both definitions (≥ 75% reduction and ≥ 50% reduction) relevant for evaluating the cost-effectiveness of fezolinetant. This view is further supported by the company's base case, which already includes a partial response state (≥ 50% reduction but less than 75% reduction) for 50% of non-responders, acknowledging the clinical significance of the ≥ 50% threshold. However, the EAG has two concerns regarding the approach used to model partial responders in the active treatment arms (fezolinetant and desvenlafaxine): (i) the proportion of partial responders is uncertain, and (ii) the utility values assigned to partial responders and non-responders needs to align with the corresponding response criterion used.

The EAG considers the company's decision to include the assessment of improvement based on PGI-C VMS only within a scenario analysis to be appropriate (as outlined in Section 2.6, Comment 8). The EAG places less importance on scenarios altering the assessment time point and source of data, given that Week 12 is the appropriate efficacy time point (per NG23), and the pooled DAYLIGHT and SKYLIGHT 1&2 (HRT-unsuitable subpopulation) data are the most relevant evidence for fezolinetant due to similarities in trial design and inclusion criteria across the phase 3 trials.

The revised model addresses the committee's concerns regarding the placebo effect and relative effects from the NMA. The placebo effect associated with no active treatment is accounted for by using the response data (and utility values, see Section 2.8, Comment 10) from the fezolinetant trials, which shows a probability of improvement at Week 12 for individuals who do not receive active treatment, in line with the response rates (and utilities) observed for responders and non-responders. The model also appropriately incorporates relative treatment effects from the NMA.

2.7.2.2 Long-term treatment effect and discontinuation rates

The effect of treatment observed at Week 12 for responders is assumed to be maintained throughout the modelled time horizon of 10 years, provided individuals remain on treatment. Consequently, the treatment discontinuation rates are considered a proxy for modelling treatment waning and the loss of response over time in the company's model.

Prior to the Week 12 response assessment time point, the probability of treatment discontinuation was based on pooled Week 0-12 data from DAYLIGHT and SKYLIGHT 1&2 (HRT-unsuitable subpopulation) for the fezolinetant arm. For the desvenlafaxine arm, the probability of treatment discontinuation was derived by applying the NMA-derived OR (mean OR = [redacted], with 95% CrI [redacted] to [redacted]) to the fezolinetant arm. Similarly, for the scenario with paroxetine the NMA-derived OR (mean OR = [redacted], with 95% CrI [redacted] to [redacted]) was applied to the fezolinetant arm. Treatment discontinuation was not modelled for the no active treatment arm because individuals in this arm were not receiving an active therapy that could be stopped.

After the Week 12 response assessment, the long-term discontinuation rates for fezolinetant were informed by pooled Week 12–24 data from the DAYLIGHT and SKYLIGHT 1&2 (HRT-unsuitable subpopulation) trials. These rates were separated by response status (responders and non-responders). Although data were available from the SKYLIGHT 1&2 trials up to Week 52 (only DAYLIGHT trial data available up to Week 24), the company chose not to use the pooled Week 24–52 data from SKYLIGHT 1&2 to inform long-term discontinuation rates from Week 24 onwards. The company justified the exclusion of Week 24–52 data from SKYLIGHT 1&2 on the basis that this data was considered less reliable because the discontinuation rate for responders was unexpectedly higher than that of non-responders. The company did undertake scenario analyses using (i) the pooled Week 24–52 SKYLIGHT 1&2 data for Week 24+ and (ii) DAYLIGHT only for fezolinetant discontinuation probabilities, which indicated that the source of discontinuation probabilities had a minimal impact on the cost-effectiveness results.

For the comparators, the probability of treatment discontinuation beyond Week 12 was derived by applying the NMA-derived OR for discontinuation to the fezolinetant arm data (as per the approach used prior to Week 12).

Table 2 summarises the 4-weekly cycle probabilities of treatment discontinuation used in the company's base case analysis and the scenario analysis utilising pooled Week 24–52 SKYLIGHT 1&2 data.

Table 2: Summary of the 4-weekly cycle probabilities of treatment discontinuation

Treatment	Time period	Response category	Per 4-week probability of discontinuation	Source
Company base case analysis				
Fezolinetant	Pre-response assessment	All patients	[redacted]	Week 0–12: DAYLIGHT and SKYLIGHT 1&2 (HRT-unsuitable subpopulation)[a]
	Week 12+	Responder	[redacted]	Week 12–24: DAYLIGHT and SKYLIGHT 1&2 (HRT-unsuitable subpopulation).[a] Response outcome was defined as a ≥75% reduction in moderate to severe VMS. Missing data for responder status was imputed primarily using last observation carried forward (LOCF) imputation, to align with the approach taken by comparator trials.
		Non-responder	[redacted]	
Desvenlafaxine	Pre-response assessment	All patients	[redacted]	Calculation, OR ([redacted]) applied to the fezolinetant arm. Details about response input in NMA are in Table 19, company addendum to DG response.
	Week 12+	Responder	[redacted]	
		Non-responder	[redacted]	
Company scenarios				
Fezolinetant	Week 24+	Responder	[redacted]	Week 24 -52: SKYLIGHT 1&2 [a] discontinuation analysis on long term data for patients randomized to fezolinetant only. Responder status is based on the LOCF 75% reduction in baseline frequency definition at 24 weeks.
		Non-responder	[redacted]	
Paroxetine	Pre-response assessment	All patients	[redacted]	Calculation, OR ([redacted]) applied to the fezolinetant arm. Details about response input in NMA are in Table 19, company addendum to DG response.
	Week 12+	Responder	[redacted]	
		Non-responder	[redacted]	

[a] Treatment discontinuation rate was assumed to be constant and estimated using an exponential model based on the observed data.

Abbreviations: OR: odds ratio

EAG critique

The company's revised modelling no longer requires long-term natural history estimates of VMS (in the absence of treatment) derived through structured expert elicitation. This change resolves the core issue associated with the previous model, which was the misalignment between the baseline frequency of events, the natural history estimates, and the approach to placebo adjustment.

The EAG notes that the long-term effectiveness of treatment in the model is now predominantly driven by the treatment discontinuation rates, which are used to reflect the loss of response over time. The company's approach to modelling discontinuations for the active treatment arms up to Week 12 and between Week 12 and Week 24 (using trial data for fezolinetant and the NMA for comparators) is appropriate. However, the EAG has two concerns: (i) the non-responder discontinuation rate is derived from a response definition of ≥ 75% reduction, but it is applied in the model to partial responders who achieve ≥ 50% but less than 75% reduction in moderate to severe VMS; and (ii) there is significant uncertainty regarding the discontinuation rates for both fezolinetant and desvenlafaxine beyond Week 24.

Despite the availability of discontinuation data from SKYLIGHT 1&2 up to Week 52, the company applies the pooled Week 12–24 data from DAYLIGHT and SKYLIGHT 1&2 (HRT-unsuitable subpopulation) to model long-term discontinuations beyond Week 24 for fezolinetant. The company justified this choice by arguing that the later data lacked face validity. They stated that these later discontinuations are less likely to be linked to response status and may be influenced by other factors. They also stated that some participants who initially responded may have chosen to discontinue because their symptoms were no longer disruptive. The EAG considers these to be important arguments that should not be dismissed, as it would be inappropriate to continue people on treatment (thereby adding unnecessary costs and potential risks) if their symptoms were no longer disruptive and treatment was no longer required. The company's model is structured such that discontinuation rates serve as a proxy for the loss of response over time. Therefore, if later discontinuations are less likely to be linked to response status and more influenced by other factors, this suggests that the use of earlier discontinuation rates (Week 12-24) as a proxy for loss of response or treatment waning over the longer time horizon may be unsuitable.

Figure 1 shows the proportion of the cohort on fezolinetant and desvenlafaxine over the modelled time horizon of 10 years in the company's base case analysis. During the initial pre-response assessment period (Week 0-12), there is a relatively high probability of discontinuation compared to later periods. At the Week 12 response assessment, responders continue on treatment. However, 50% of non-responders (i.e., partial responders in the model) also continue treatment up to Week 52, with a higher probability of discontinuing than the responders. The company assumes that at Week 52, all partial responders immediately discontinue treatment (these partial responders represent [redacted] of the cohort still on fezolinetant at that time, and [redacted] for desvenlafaxine), regardless of whether they are still benefiting from treatment. This assumption results in the steep decline observed in Figure 1 at Week 52. From Week 52 onwards, approximately [redacted] of the cohort remaining on fezolinetant have a relatively low probability of discontinuation ([redacted] per 4-week cycle) over the remaining 10-year

model time horizon, while approximately [redacted] remain on desvenlafaxine ([redacted] per 4-week cycle discontinuation probability).

The EAG's clinical advisor expressed concern that the long-term proportion of people continuing fezolinetant treatment shown in Figure 1 may be overestimated due to the low modelled discontinuation rates. Our advisor indicated that patients receiving treatment are reviewed annually for menopausal symptoms, consistent with NG23 guidance, and she would expect that as VMS frequency improves, people would discontinue treatment. Therefore, the EAG considers that extrapolating the low discontinuation rates from the Week 12–24 fezolinetant trial data over the longer term is unlikely to be appropriate.

Figure 1 Proportion of the cohort on fezolinetant and desvenlafaxine over the modelled time horizon of 10 years in the company's base case analysis

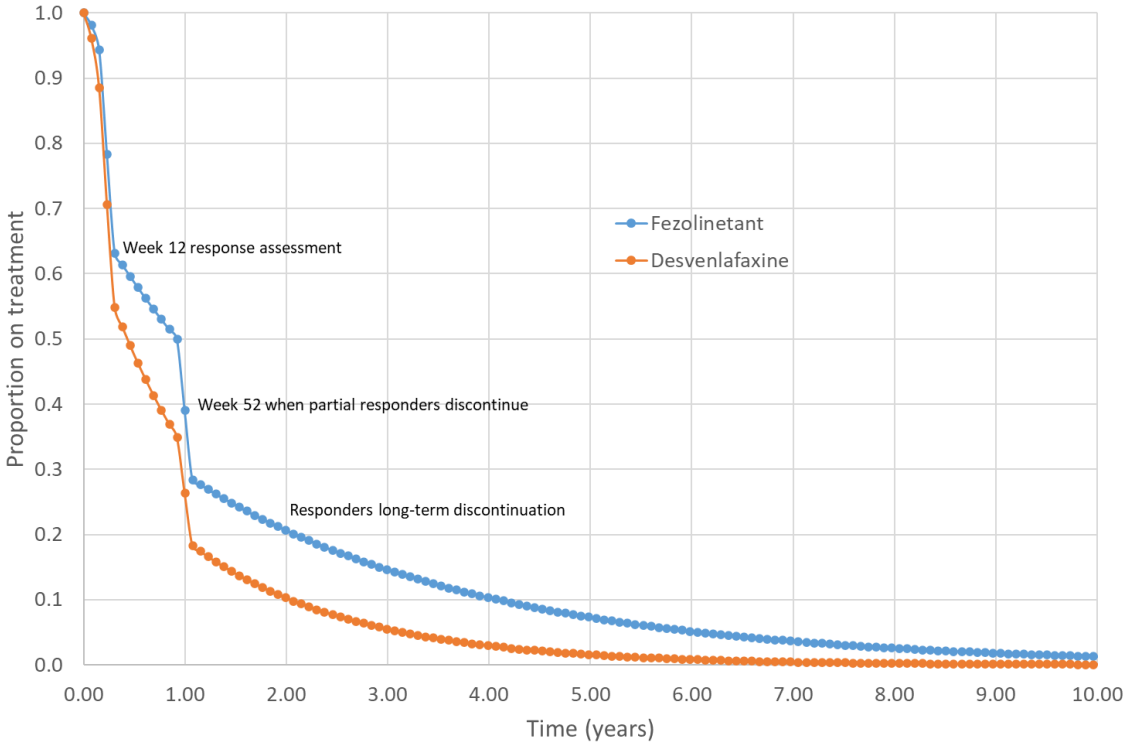

Table 3 summarises the proportion of the cohort in each health state for fezolinetant, desvenlafaxine and no active treatment in the company's base case analysis. After the one-year time point, when partial responders ('On treatment - Non responder') immediately discontinue treatment, [redacted] of people in the fezolinetant arm remain on treatment. This proportion steadily declines over the modelled time horizon: [redacted] by year 2, [redacted] by year 5 and [redacted] by year 10. The mean time on fezolinetant is approximately [redacted] years. For desvenlafaxine, [redacted] of people remain on treatment after the one-year time point. This proportion steadily declines over the modelled time horizon to

[redacted] by year 2, [redacted] by year 5 and [redacted] by year 10. The mean time on desvenlafaxine is approximately [redacted] months ([redacted] years). For the no active treatment arm, individuals are not on-treatment but are distributed across the responder and non-responder health states (rather than the 'Off treatment with VMS' state) to account for the placebo effect and the anticipated higher adherence in the fezolinetant trials.

Given the absence of evidence for fezolinetant beyond one year, the long-term projections of time on treatment are uncertain. The EAG's clinical advisor noted the findings of a retrospective cohort study (Saadedine et al., 2025[3]) of women with breast cancer and endocrine therapy-related menopausal symptoms (a key group of patients for whom HRT is unsuitable). This study showed very low continuation rates with available treatments, irrespective of the medication prescribed as first therapy. Specifically, among UK women prescribed antidepressants (including SSRIs and SNRIs) for menopausal symptoms (including VMS), 19% remained on treatment at 6 months, dropping to 12% at one year and 6% at 2 years, while continuation rates for other treatments were even lower. These real-world continuation rates are approximately [redacted] lower than the continuation rates modelled for desvenlafaxine in the company's base case analysis. This significant difference may suggest that the discontinuation rates derived for desvenlafaxine in the model are underestimated. Consequently, the discontinuation rates used for the reference fezolinetant arm (the data to which the NMA estimates were applied to derive desvenlafaxine's discontinuation rates) may be too low. Thus, the EAG considers the long-term discontinuation rates to be uncertain.

Table 3 Proportion of cohort distributed across health states over time in company's base case

Fezolinetant						
Timepoint	**Pre-response assessment**	**Responder**	**On treatment - Non responder**	**Off treatment (with VMS)**	**VMS Cessation**	**Dead**
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4 weeks	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8 weeks	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12 weeks	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24 weeks	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
52 weeks	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Desvenlafaxine						
Timepoint	**Pre-response assessment**	**Responder**	**On treatment - Non responder**	**Off treatment (with VMS)**	**VMS Cessation**	**Dead**
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

4 weeks	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8 weeks	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12 weeks	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24 weeks	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
52 weeks	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No active treatment						
Timepoint	**Pre-response assessment**	**Responder**	**On treatment - Non responder**	**Off treatment (with VMS)**	**VMS Cessation**	**Dead**
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4 weeks	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8 weeks	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12 weeks	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24 weeks	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
52 weeks	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

2.7.2.3 VMS cessation and mortality

The model includes a VMS cessation health state to capture the natural resolution of VMS in menopausal people, which is independent of treatment. Transitions to this state in each model cycle are based on a per-cycle probability of VMS cessation. In the company's original submission, the probability of VMS cessation was derived from the median duration of VMS of 7.4 years reported by Avis et al., (2015)[13] and was assumed to be constant over the modelled time horizon. In Section 4.2.6.4 of the EAR, the EAG expressed concerns that the median duration of 7.4 years for moderate to severe VMS was too high for the company's modelled base case population of postmenopausal people (starting age 51 years at the onset of menopause). This high duration was derived from a study that tracked women over a long follow-up period, from pre-menopause or early perimenopause through to postmenopause. Furthermore, the EAG questioned the assumption of a constant rate of VMS cessation over time.

In the company's updated model, the per cycle probability of VMS cessation was derived using the median duration of VMS of 3.4 years in postmenopausal women reported by Avis et al., (2015)[13] (Table 20 of the company's addendum to the DG response[4]).

The model assumes that moderate to severe VMS does not have an impact on the risk of mortality. Therefore, the modelled cohort is assumed to have the same mortality rate as the general female population in the UK, which was derived from age-specific mortality rates for females from the National UK lifetables for 2019.

EAG critique

The median VMS duration of 3.4 years from the subset of women who were postmenopausal at VMS onset (Avis et al., 2015[13]) is consistent with the EAG's preferred assumption outlined in the EAR. This revised assumption results in approximately [redacted] of people still experiencing VMS in the model by year 10. To ensure the model fully captures the natural cessation of VMS in almost all postmenopausal people, the EAG considers extending the modelled time horizon to 20 years to be appropriate. However, the EAG does not expect this extension from 10 to 20 years to have any material impact on the cost-effectiveness results because the majority of people have discontinued treatment by year 10. The assumption of a constant rate of VMS cessation over time remains uncertain, but the EAG considers this assumption to be reasonable.

All-cause mortality is estimated based on National Life Tables for the UK. The model assumes menopausal people do not have an increased risk of death due to moderate to severe VMS, which the EAG considers to be appropriate.

In summary, the company's revised model overcomes the committee's core issues outlined in DGD Section 3.11. However, the revised modelling approach introduces two new uncertainties regarding the long-term projections: (1) the long-term discontinuation rates for fezolinetant and its comparator treatments, and (2) the proportion of partial responders who continue treatment and the duration of their continued treatment.

2.8 Comment 10: Health state utility values based on EQ-5D data (DGD Section 3.12)

In the company's original submission, utility values for the VMS frequency health states were derived from EQ-5D-5L data collected in the DAYLIGHT trial, which was subsequently mapped to EQ-5D-3L scores. The company then made subsequent adjustments to decrease the utility values for some of the VMS frequency health states. This adjustment was informed by the opinion of one clinical expert to recognise the insensitivity of the EQ-5D instrument to accurately measure symptom improvements in menopause. In DGD Section 3.12, the committee stated that altering EQ-5D values based on input from a single clinical expert was inappropriate. The committee acknowledged that EQ-5D is NICE's preferred measure for health-related quality of life, but recognised that there are circumstances when EQ-5D may not be the most appropriate measure. Therefore, the committee suggested that it may be useful to explore a disease specific tool, such as the Menopause-Specific Quality of Life (MENQOL)

measure, to more accurately estimate the utility values, while acknowledging the limitation that there is no UK value set for the MENQOL.

In the company's response to the DG, the company thanked the committee for acknowledging the limitations of EQ-5D data to capture symptom improvements in the menopause. The company maintained that the EQ-5D data from the fezolinetant trials was the most appropriate source to inform the cost-effectiveness analysis, in line with the NICE reference case, due to the additional uncertainty that would be introduced by using the MENQOL measure with a non-UK value set. However, the company accepted the committee's feedback that it was inappropriate to adjust the EQ-5D-derived utility values and, therefore, no adjustment is made in the revised model.

In the updated model, utility values for fezolinetant were derived from EQ-5D data collected in the fezolinetant arm of the pooled DAYLIGHT and SKYLIGHT 1&2 (HRT-unsuitable subpopulation) trials. In the base case analysis, utility values before the Week 12 response assessment corresponded to the Weeks 0–12 data. After Week 12, fezolinetant utility values were stratified by responder status (responders and non-responders) and were informed by Weeks 0–52 data, utilising all available data. Similarly, utility values for no active treatment were based on EQ-5D data from the placebo arm of the pooled trials. Before the response assessment, values correspond to Weeks 0–12 data, while after the assessment, the values correspond to Weeks 0–24 data, again making use of all available information. For no active treatment, the utility value was derived as the weighted mean of the utility values for the responder and non-responder health states.

In the absence of reported utility values for desvenlafaxine and paroxetine in the company's systematic literature review, the company assumed that the utility values for these treatments should be greater than those for no active treatment but less than fezolinetant. This was justified by the NMA, which showed that fezolinetant achieves a better response rate and a lower odds of all-cause treatment discontinuation compared to other active comparators, while all active comparators showed a better response rate than placebo. Thus, the company derived the utility values for desvenlafaxine and paroxetine by taking the mean of the fezolinetant and no active treatment arms of the model.

The utility value for the 'Off Treatment with VMS' health state (both pre- and post-response assessment) was assumed to be a weighted average of utility values for responders and non-responders in the no active treatment arm. The utility value for the VMS cessation state was derived from the average EQ-5D score among participants in the pooled fezolinetant trials who reported a VMS frequency of zero.

The model accounts for short-term adverse events (AEs) by applying a one-off utility decrement at treatment initiation, reflecting an average AE duration of 3 weeks. The specific AE probabilities for

fezolinetant, desvenlafaxine, and the paroxetine scenario analysis are listed in Table 21 of the company's addendum to the DG response,[4] while the associated utility decrements and durations are detailed in Table 22. The one-off AE disutilities included in the model for fezolinetant, desvenlafaxine, and paroxetine are 0.0013, 0.0036 and 0.0004, respectively.

Table 4 summarises the health state utility values used in the model.

Table 4 Summary of the utility values used in the model (reproduced from Table 25 of company's addendum)

Treatment	Heath state	Utility value: mean (SE)	95% CI	Source
Fezolinetant	Pre-response assessment	0.826 (0.007)	0.812–0.839	Week 0-12: Pooled DAYLIGHT and SKYLIGHT 1 & 2 (HRT-unsuitable)
	Responder	0.837 (0.008)	0.823–0.852	Week 0-52: Pooled DAYLIGHT and SKYLIGHT 1 & 2 (HRT-unsuitable)
	On treatment non-responder (partial responders)	0.816 (0.008)	0.800–0.832	
No active treatment	Pre-response assessment	0.797 (0.007)	0.783–0.811	Week 0-12: Pooled DAYLIGHT and SKYLIGHT 1 & 2 (HRT-unsuitable)
	Responder	0.814 (0.008)	0.797–0.830	Week 0-24: Pooled DAYLIGHT and SKYLIGHT 1 & 2 (HRT-unsuitable)
	Non-responder	0.792 (0.007)	0.778–0.807	
Desvenlafaxine or paroxetine (scenario analysis)	Pre-response assessment	0.811 (-)	-	Mean of the fezolinetant and no active treatment utility values
	Responder	0.826 (-)	-	
	On treatment non-responder (partial responders)	0.804 (-)	-	
Treatment-independent	Off treatment with VMS (pre- and post-response assessment)	0.797 (0.007)	0.783–0.811	Assumed to be a weighted average of utility values for responders and non-responders in the no active treatment arm.
Treatment-independent	Natural cessation of VMS	0.852 (0.008)	0.546–1.000	Pooled data (double blind period) from fezolinetant 45mg and placebo in the DAYLIGHT and SYKLIGHT 1 & 2 (HRT-unsuitable population)

Abbreviations: CI: confidence interval; HRT: Hormone replacement therapy; SE: standard error; VMS: Vasomotor symptoms.

EAG critique

The EAG considers the approach used by the company to derive EQ-5D utility values based on the pooled DAYLIGHT and SKYLIGHT 1&2 (HRT-unsuitable subpopulation) to be reasonable for the

fezolinetant and no active treatment arms. However, the company has stratified the utility values by responder status (responders and non-responders) in relation to the ≥ 75% reduction response criterion, but the model structure for the active treatment arms include three distinct groups based on achieving different response criterion: responders (≥ 75% reduction), partial responders (≥ 50% reduction but less than 75%), and non-responders (who did not achieve 50% reduction). The company has applied the responders utility value to the 'On Treatment Responders' health state, but has applied the non-responders utility value to the partial responders 'On Treatment Non-Responder' health state, while the utility value for the Week 12 non-responders, who do not meet the 50% reduction response criterion, is based on a weighted average of utility values for responders and non-responders in the no active treatment arm (using a ≥ 75% reduction response criterion).

For the no active treatment arm, a weighted average of utility values for responders and non-responders is carried through the model, which effectively accounts for the placebo effect observed in the fezolinetant trials.

The EAG also has a concern about the approach used to derive utility values for desvenlafaxine and paroxetine. In the absence of reported utility values for these comparators, the company used the mean of the fezolinetant and no active treatment arms, stratified by responder status. This approach effectively means that the company is applying treatment-dependent utility values for responders and non-responders (where the non-responders correspond to partial responders achieving ≥ 50% but < 75% reduction in moderate to severe VMS frequency), despite the same criterion being used to define response across all arms. The EAG's clinical advisor also considered that the utility values should be independent of the treatment received if individuals have met the same response criterion.

The EAG considers that the only plausible reason to apply treatment-dependent utility values by response status is when the treatment itself impacts health-related quality of life independently of the response criterion. This may be justified if the treatments cause significant, non-overlapping AEs, or the health-related quality of life is strongly correlated with time on treatment. The EAG notes that the company has not made a strong case for treatment-specific utility values for responders and partial responders. While the company justified the utility differences based on NMA results for response outcome and all-cause treatment discontinuation rates, the EAG notes that these differences are already reflected in the model through the distinct percentages achieving response status and long-term all-cause treatment discontinuation rates by treatment arm, respectively. The EAG also notes that treatment-specific differences in short-term AEs are separately incorporated in the model as utility decrements. However, the EAG considers that there may be a case for treatment differences based on longer-term impacts on quality of life associated with SSRIs/SNRIs that are not captured in the model. In the absence of evidence supporting the longer-term impacts on quality of life for non-hormonal comparators relative to fezolinetant, the EAG's preference is to apply the same utility

values. Specifically, the utility values used for fezolinetant responders and partial responders is used for the equivalent desvenlafaxine and paroxetine health states. This approach also aligns with the company's modelling of resource use, which is applied by responder health state and is independent of the active treatment received.

The EAG considers it reasonable to apply a treatment-specific difference in utility within the pre-response assessment category. Since this health state represents a weighted average of both future responders and non-responders up to Week 12, taking an average of the fezolinetant and no active treatment arms is considered appropriate to capture the average utility during this initial phase.

A further EAG concern relates to the utility value used for the 'Off Treatment with VMS' health state, which is the health state that captures individuals when they discontinue active therapy. For this state (both pre- and post-response), the company applied the mean utility value of 0.797 corresponding to the weighted average of responders and non-responders in the no active treatment arm of the fezolinetant trials. The EAG considers this a reasonable assumption for the pre-response assessment period. However, in the post-response assessment period, this approach results in a differential utility between two similar groups: (1) individuals off-treatment with VMS in the 'Off Treatment with VMS' health state for the active therapy arms (fezolinetant, desvenlafaxine and paroxetine), who are assigned a mean utility of 0.797; and (2) non-responders, who are off-treatment with VMS, in the no active treatment arm, who are assigned a lower mean utility value of 0.792 corresponding to the placebo arm of the trials. This inconsistency stems from the difference in model structure between the active treatment arm and the no active treatment arm, and the misalignment between the modelled health states and the categorisation of utility values from the trial data. To correct this, the utility values from the trial need to be estimated for the distinct groups of people used to define the health states in the model.

In summary, the company maintains the view that the EQ-5D data from the fezolinetant trials represent the most appropriate source of utility values for the model, thereby adhering to the NICE reference case and avoiding the uncertainty of non-UK value sets. The company addressed the committee feedback outlined in DGD Section 3.11 by making no adjustments to the EQ-5D-derived utility values. However, the revised modelling approach introduces two new issues related to the utility values: (1) the use of treatment-specific utility values for responder status across the active treatment arms, and (2) the appropriate utility values to use for the distinct health states in the model, where the EQ-5D trial data has not been categorised in the same way and using the appropriate response criterion. The company did not explore alternative health-related quality of life utility values for VMS using a disease-specific tool, as suggested by the committee.

2.9 Comment 11: Uncaptured costs of liver monitoring for fezolinetant (DGD Section 3.13)

The committee concluded that the modelled costs should include liver blood tests (LFTs) and appointments for liver monitoring and be in line with the setting in which fezolinetant is prescribed and monitored. In the company's DGD Response Comment 3, the company positioned fezolinetant for use in NHS primary care, despite the need for additional liver monitoring requirements. The company justified this choice based on the results from the GP Omnibus survey, which showed that GPs have high confidence to manage liver monitoring requirements.

In line with the Summary of Product Characteristics (SmPC) for fezolinetant, the company included LFT costs at Week 0 (baseline) and Weeks 4, 8 and 12 during the first three months of treatment. Beyond this initial period, additional LFT costs were included at Weeks 24 and 36 only for people who experience elevated liver enzymes during the first year of treatment, which was observed in 4.42% of participants from the DAYLIGHT trial. The subsequent monitoring at Weeks 24 and 36 is intended to reflect the SmPC wording after the first three months of treatment, which mandates that, based on clinical judgement, *'LFTs must also be performed when symptoms suggestive of liver injury occur'*.

A scenario analysis was conducted which includes costs associated with additional nurse appointments for liver testing (Table 5). Table 6 summarises the unit costs of fezolinetant liver function tests and appointments used in the base case and scenario analysis.

Table 5 Resource use frequency for liver function test appointments used in the company's scenario analysis, by responder status

Model Cycle	Week	Responder	Non-responder	Notes
0	0	0.00	0.00	Included in first GP visit
1	4	1.00	0.00	Included in follow-up GP visit for non-responders
2	8	1.00	0.00	Included in follow-up GP visit for non-responders
3	12	1.00	1.00	-
6	24	1.00	1.00	-
9	36	1.00	1.00	-

Table 6 Unit costs of fezolinetant liver function tests and appointments

Monitoring services	Unit Cost (£)	Source
Liver Function Test Cost	£1.61	National schedule of NHS costs 2022/23; DAPS04
Liver function test appointment cost (scenario analysis)	£5.88	PSSRU, 2024. Assumption based on 7.5 minutes of GP practice nurse time (Band 5, £47 per hour).

Abbreviations: NHS: National Health Service.

EAG critique

Fezolinetant is associated with a risk of drug-induced liver injury and should be avoided in patients with known liver disease or those at a higher risk of liver disease. Importantly, monitoring should be maintained until LFTs have normalised. The SmPC reinforces this by specifying that liver function testing should be repeated monthly during the first three months of treatment, and then afterwards based on clinical judgement of need. Therefore, it is appropriate to include LFTs and monitoring in the analysis.

The EAG notes that in its base case, the company has only included LFT costs, and not the costs of additional nurse appointments for liver testing (these were included only in a scenario analysis). The EAG considers it appropriate to include both LFT costs and nurse appointments for liver testing in the base case because it is unclear if additional nurse time is required for testing.

The EAG's clinical advisor stated that LFTs are likely to be carried out annually for people on fezolinetant due to the lack of long-term safety data for the drug. Furthermore, NG23 recommends that each treatment for menopausal symptoms be reviewed annually. Therefore, the EAG expects that LFTs are carried out annually while individuals remain on treatment; however, annual LFT are unlikely to require an additional test appointment as it would be undertaken as part of the annual medication review. The EAG notes that LFT costs and any additional nurse time required has minimal impact on the cost-effectiveness of fezolinetant due to their low cost (Table 6).

3 CRITIQUE OF THE COMPANY'S REVISED COST-EFFECTIVENESS ANALYSES

3.1 Company's base case results

The committee had been unable to determine a plausible cost-effectiveness estimate for the population with moderate to severe VMS for whom HRT is unsuitable, a conclusion based on the company's

original submission. Consequently, the company has now presented revised base case results following the DG, based on the updated cost-effectiveness analysis.

A summary of the company's probabilistic base-case results is presented in the company's addendum to the DG response:[4] Table 34 shows the results in terms of the incremental cost-effectiveness ratio (ICER), and Table 35 presents the results in terms of incremental net health benefits (INHB). The pair-wise probabilistic ICERs were £10,263 per quality-adjusted life year (QALY) gained for fezolinetant versus no active treatment and £18,053 per QALY gained for fezolinetant versus desvenlafaxine (proxy for venlafaxine).

The company did not present the deterministic base case results. Therefore, Table 7 shows the results of the company's deterministic analysis. The EAG includes these results because it will make interpretation of the impact of changes in scenarios easier to explore, by explicitly removing the uncertainty in the mean estimates inherent in the probabilistic analysis.

Table 7 Summary of the company's deterministic and probabilistic base case results (pairwise comparison with fezolinetant)

Deterministic							
Technologies	**Total**			**Incremental**			**ICER (£/QALY)**
	Costs (£)	**LYG**	**QALYs**	**Costs (£)**	**LYG**	**QALYs**	
Fezolinetant	£2,160.52	8.449	6.915	-	-	-	-
No Treatment	£1,675.89	8.449	6.868	£484.63	0.000	0.047	£10,313
Desvenlafaxine	£1,558.51	8.449	6.881	£602.01	0.000	0.034	£17,969
Probabilistic							
Technologies	**Total**			**Incremental**			**ICER (£/QALY)**
	Costs (£)	**LYG**	**QALYs**	**Costs (£)**	**LYG**	**QALYs**	
Fezolinetant	£2,157.08	8.436	7.088	-	-	-	-
No Treatment	£1,664.31	8.436	7.040	£492.77	0.000	0.048	£10,263
Desvenlafaxine	£1,547.11	8.436	7.054	£609.97	0.000	0.034	£18,053

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years.

3.2 Company's scenario analyses results

A summary of the company's probabilistic scenario analyses and results is presented in the company's addendum to the DG response:[4]: Table 40 shows the ICER results for fezolinetant compared to no active treatment, and Table 41 presents the ICER results for fezolinetant compared to desvenlafaxine. The results for the scenario with paroxetine as a comparator are also included in Table 41 of the company's addendum to the DG.

The EAG validated and confirmed the results of the company's scenario analyses by producing the corresponding deterministic results.

Table 8 shows the results of the company's deterministic scenario analyses for fezolinetant versus no active treatment, while Table 9 shows the results for fezolinetant versus desvenlafaxine (including the scenario with paroxetine as a comparator).

Across the comprehensive list of scenario analyses, most scenarios showed minimal impact on the ICER results relative to the base case. The scenario with the largest impact was the assumption of a no stopping rule for non-responders (i.e., the percentage of non-responders discontinuing active treatment at Week 12 was set to 0%), which increased the company's base case deterministic ICER from £10,313 to £17,286 for fezolinetant vs. no active treatment, and from £17,969 to £24,638 for fezolinetant vs. desvenlafaxine. The alternative response definitions (≥ 50% reduction in VMS frequency and PGI-C VMS) and the assessment timepoint of Week 24 increased the ICER to around £11,600 per QALY gained for fezolinetant vs. no active treatment, and to around £19,700 per QALY gained for fezolinetant vs. desvenlafaxine. Aligning the desvenlafaxine utility values with those of fezolinetant increased the company's deterministic base case ICER from £17,969 to £25,548 for fezolinetant compared to desvenlafaxine.

For the comparison of fezolinetant with paroxetine, the probabilistic ICER was £21,619 per QALY gained (deterministic ICER, £20,541 per QALY). However, the company noted the limitations of this comparison, which incorporated several assumptions: (i) response was defined as at least a 50% reduction in moderate to severe VMS frequency because it was the only outcome available for the paroxetine studies; (ii) a 100% stopping rule was applied to non-responders at the Week 12 assessment timepoint, given that partial responders were captured in the ≥ 50% reduction threshold; (iii) the utility values in this scenario are based on a ≥ 75% reduction threshold; and (iv) efficacy outcomes are based on evidence for a dose of paroxetine (7.5 mg) that is not available in the UK or recommended for treating moderate to severe VMS.

Table 8 Summary of the company's deterministic scenario analyses and results for fezolinetant versus no active treatment

Scenario Analysis	Base-case input	Versus no active treatment		
		Incremental costs	Incremental QALYs	ICER (£/QALY)
Base-case (deterministic)	**-**	**£485**	**0.05**	**£10,313**
Baseline age				
DAYLIGHT	Mean age of menopause onset in the UK	£484	0.05	£10,373
Pooled DAYLIGHT and SKYLIGHT 1&2 (HRT-unsuitable subpopulation)		£484	0.05	£10,325
Response assessment timepoint				
Week 4	Week 12	£400	0.04	£9,683
Week 24		£573	0.05	£11,647
Response definition				
50% reduction in VMS frequency	75% reduction in VMS frequency	£691	0.06	£11,641
PGI-C response		£686	0.06	£11,160
Response data source				
Pooled SKYLIGHT 1 & 2 (HRT-unsuitable)	Pooled DAYLIGHT and SKYLIGHT 1 & 2 (HRT-unsuitable subpopulation)	£443	0.04	£10,097
DAYLIGHT		£554	0.05	£10,811
Fezolinetant discontinuation rate data source				
DAYLIGHT	Pooled DAYLIGHT and SKYLIGHT 1 & 2 (HRT-unsuitable subpopulation)	£468	0.05	£10,243
Fezolinetant Week 24+ discontinuation rate data source				
Pooled SKYLIGHT 1 & 2 (HRT-unsuitable subpopulation) week 24-52	Pooled DAYLIGHT & SKYLIGHT 1&2 Week 12–24	£484	0.05	£10,385
Utility data source				
DAYLIGHT Pre-response: Week 0–12 (fezolinetant and no treatment) Post response: Week 12–24 (fezolinetant and no active treatment)	Pooled DAYLIGHT and SKYLIGHT 1&2 (HRT-unsuitable subpopulation) Pre-response: Week 0–12 (fezolinetant and no active treatment)	£485	0.05	£10,590

Pooled SKYLIGHT 1 & 2 (HRT-unsuitable subpopulation) Pre-response: Week 0–12 (fezolinetant and no active treatment) Post response: Week 0–52 (fezolinetant) and week 0–12 (no active treatment)	Post response: Week 0–52 (fezolinetant) and week 0–24 (no active treatment)	£485	0.05	£9,989
Pooled SKYLIGHT 1 & 2 (HRT-unsuitable subpopulation) Pre-response: Week 0–12 (fezolinetant and no active treatment) Post response: Week 12–52 (fezolinetant) and week 0–12 (no active treatment)		£485	0.05	£10,116
Post responder assessment utility data source				
Pooled DAYLIGHT and SKYLIGHT 1 & 2 (HRT-unsuitable subpopulation) - Week 12–52 (fezolinetant) - Week 0–12 (no active treatment)	Pooled DAYLIGHT and SKYLIGHT 1 & 2 (HRT-unsuitable subpopulation) - Week 0–52: fezolinetant - Week 0–24: no active treatment	£485	0.05	£9,989
Fezolinetant monitoring cost				
Exclude	Include	£479	0.05	£10,184
Additional appointments for liver testing				
Include	Exclude	£494	0.05	£10,517
Adverse events				
Exclude disutilities	Include disutilities	£485	0.05	£10,037
1-week duration of AEs	3-week duration of AEs	£485	0.05	£10,127
Exclude AE costs	Include AE costs	£481	0.05	£10,234
Duration of VMS data source				
Avis *et al.*, (2015): all women with VMS	Avis *et al.*, (2015): postmenopausal women with VMS	£590	0.06	£9,561
Non-responder stopping rule				
No stopping rule	50% of non-responders discontinue treatment at Week 12	£1,130	0.07	£17,286

100% of non-responders discontinue treatment at Week 12	50% of non-responders discontinue treatment at Week 12	£366	0.04	£8,391

Abbreviations: AE: adverse event; HRT: hormone replacement therapy; ICER: incremental cost-effectiveness ratio; OR: odds ratio; QALY: quality-adjusted life years; VMS: vasomotor symptoms.

Table 9 Summary of the company's deterministic scenario analyses and results for fezolinetant versus desvenlafaxine

Scenario Analysis	Base-case input	Versus desvenlafaxine*		
		Incremental costs	Incremental QALYs	ICER (£/QALY)
Base-case (deterministic)	**-**	**£602**	**0.03**	**£17,969**
Baseline age				
DAYLIGHT	Mean age of menopause onset in the UK	£601	0.03	£18,072
Pooled DAYLIGHT and SKYLIGHT 1&2 (HRT-unsuitable subpopulation)		£601	0.03	£17,994
Response assessment timepoint				
Week 4	Week 12	£515	0.03	£17,782
Week 24		£669	0.04	£18,466
Response definition				
50% reduction in VMS frequency	75% reduction in VMS frequency	£832	0.04	£19,792
PGI-C response		£842	0.04	£19,482
Response data source				
Pooled SKYLIGHT 1 & 2 (HRT-unsuitable subpopulation)	Pooled DAYLIGHT and SKYLIGHT 1 & 2 (HRT-unsuitable subpopulation)	£554	0.03	£17,681
DAYLIGHT		£678	0.04	£18,586
Fezolinetant discontinuation rate data source				
DAYLIGHT	Pooled DAYLIGHT and SKYLIGHT 1 & 2 (HRT-unsuitable subpopulation)	£582	0.03	£17,552
Fezolinetant Week 24+ discontinuation rate data source				
Pooled SKYLIGHT 1 & 2 (HRT-unsuitable subpopulation) week 24-52	Pooled DAYLIGHT & SKYLIGHT 1&2 Week 12–24	£600	0.03	£18,135

Scenario Analysis	Base-case input	Versus desvenlafaxine*		
		Incremental costs	Incremental QALYs	ICER (£/QALY)
Desvenlafaxine discontinuation rate data source				
Bouchard *et al.*, (2012)	OR applied to fezolinetant (NMA)	£519	0.04	£12,310
Fezolinetant utility data source				
DAYLIGHT Pre-response: Week 0–12 Post response: Week 12–24	Pooled DAYLIGHT and SKYLIGHT 1&2 (HRT-unsuitable subpopulation) Pre-response: Week 0–12 Post response: Week 0–52	£602	0.03	£18,463
Pooled SKYLIGHT 1 & 2 (HRT-unsuitable) Pre-response: Week 0–12 Post response: Week 0–52		£602	0.03	£17,392
Pooled SKYLIGHT 1 & 2 (HRT-unsuitable) Pre-response: Week 0–12 Post response: Week 12–52		£602	0.03	£17,619
Fezolinetant post responder assessment utility data source				
Pooled DAYLIGHT and SKYLIGHT 1 & 2 (HRT-unsuitable subpopulation) Week 12–52	Pooled DAYLIGHT and SKYLIGHT 1 & 2 (HRT-unsuitable subpopulation) - Week 0–52: fezolinetant	£602	0.03	£17,391
Desvenlafaxine utility source				
Aligned with fezolinetant utilities	Average of fezolinetant and no active treatment utilities	£602	0.02	£25,548
Fezolinetant monitoring cost				
Exclude	Include	£596	0.03	£17,789
Additional appointments for liver testing				
Include	Exclude	£612	0.03	£18,256
Adverse events				
Exclude disutilities	Include disutilities	£602	0.03	£19,298
1-week duration of AEs	3-week duration of AEs	£602	0.03	£18,834

Scenario Analysis	Base-case input	Versus desvenlafaxine*		
		Incremental costs	Incremental QALYs	ICER (£/QALY)
Exclude AE costs	Include AE costs	£613	0.03	£18,307
Duration of VMS data source				
Avis *et al.*, (2015): all women with VMS	Avis *et al.*, (2015): postmenopausal women with VMS	£738	0.05	£16,343
Non-responder stopping rule				
No stopping rule	50% of non-responders discontinue treatment at Week 12	£1,202	0.05	£24,638
100% of non-responders discontinue treatment at Week 12	50% of non-responders discontinue treatment at Week 12	£499	0.03	£16,000
SSRI comparator				
Paroxetine, 50% moderate to severe VMS frequency reduction, 100% of non-responders discontinue treatment at Week 12	Desvenlafaxine, 75% moderate to severe VMS frequency reduction, 50% of non-responders discontinue treatment at Week 12	£777	0.04	£20,541

*Results for the final scenario are versus paroxetine. **Abbreviations:** AE: adverse event; HRT: hormone replacement therapy; ICER: incremental cost-effectiveness ratio; OR: odds ratio; QALY: quality-adjusted life years; VMS: vasomotor symptoms.

4 EAG ADDITIONAL ANALYSES

4.1 EAG's exploratory analyses using company's base case

Table 10 provides a summary of the EAG's exploratory analyses using the company's base case, while Table 11 and Table 12 present the corresponding deterministic and probabilistic results of the EAG's scenarios, respectively.

Table 10 Summary of EAG's exploratory analyses using company's base case

Exploratory analysis number	Company's base-case assumption	EAG scenario	Justification for EAG assumption
1: Extended dose NMA	Restricted dose NMA for VMS response (Figure 5 of company's addendum to DG response) and fixed effect model for discontinuation (Figure 7 of company's addendum to DG response)	Extended dose NMA for VMS response (Figure 6 of company's addendum to DG response) and random effects model for discontinuation (Table 10 random effects model of company's addendum to DG response)	Evidence on all doses should be included to more reliably estimate between-study heterogeneity. The random effects models are more appropriate for all networks to mitigate concerns that the common effect assumption may not hold.
2: Stopping rule for partial responders	Partial responders (50% of the non-responders at Week 12) stop treatment at Week 52	No stopping rule at Week 52 for partial responders	The Week 52 stopping rule for partial responders appears to be arbitrary as no justification has been provided. The EAG's clinical advisor suggested that treatment is likely to continue beyond one year if partial responders maintain a benefit from the treatment.
3: Utility values by response status and treatment arm	Treatment-specific utility values for responders and non-responders for active treatment	Treatment-independent utility values for responders and partial responders (desvenlafaxine = fezolinetant)	The EAG prefers using the same utility values across active treatments for equivalent responder and partial responder health states. This is because treatment-dependent utility values are only justified when the treatment itself impacts quality of life independent of the response status, and no evidence has been provided to support this. Differences in adverse events by treatment are applied separately as treatment-specific utility decrements.
4: Costs of liver function testing for fezolinetant	LFT costs	LFT costs and additional nurse appointments for liver testing	The EAG considers it appropriate to include both LFT costs and nurse appointments for liver testing in the base case because it is unclear if additional nurse time is required for testing.

Table 11 Deterministic results of EAG scenario analyses

#	Name	Option	Costs	QALYs	Inc. Costs	Inc. QALYs	ICER, / QALY
	Company's base-case results	Fezolinetant	£2,160.52	6.91	-	-	-
		No Treatment	£1,675.89	6.87	£484.63	0.047	£10,313
		Desvenlafaxine	£1,558.51	6.88	£602.01	0.034	£17,969
1	Extended dose NMA	Fezolinetant	£2,160.52	6.91	-	-	-
		No Treatment	£1,675.89	6.87	£484.63	0.047	£10,313
		Desvenlafaxine	£1,556.54	6.88	£603.97	0.033	£18,128
2	No stopping rule at Week 52 for partial responders	Fezolinetant	£2,430.36	6.92	-	-	-
		No Treatment	£1,675.89	6.87	£754.47	0.055	£13,802
		Desvenlafaxine	£1,574.53	6.88	£855.83	0.040	£21,352
3	Treatment-independent utility values for responders and partial responders (desvenlafaxine = fezolinetant)	Fezolinetant	£2,160.52	6.91	-	-	-
		No Treatment	£1,675.89	6.87	£484.63	0.047	£10,313
		Desvenlafaxine	£1,558.51	6.89	£602.01	0.026	£23,116
4	Include additional nurse appointments for liver testing	Fezolinetant	£2,170.12	6.91	-	-	-
		No Treatment	£1,675.89	6.87	£494.24	0.047	£10,517
		Desvenlafaxine	£1,558.51	6.88	£611.61	0.034	£18,256

Table 12 Probabilistic results of EAG scenario analyses

#	Name	Option	Costs	QALYs	Inc. Costs	Inc. QALYs	ICER, / QALY
	Company's base-case results	Fezolinetant	£2,158.21	7.10	-	-	-
		No Treatment	£1,669.35	7.05	£488.86	0.047	£10,310
		Desvenlafaxine	£1,551.60	7.06	£606.60	0.034	£18,037
1	Extended dose NMA	Fezolinetant	£2,158.21	7.10	-	-	-
		No Treatment	£1,669.35	7.05	£488.86	0.047	£10,310
		Desvenlafaxine	£1,542.30	7.06	£615.90	0.033	£18,772
2	No stopping rule at Week 52 for partial responders	Fezolinetant	£2,432.67	7.10	-	-	-
		No Treatment	£1,669.35	7.05	£763.31	0.055	£13,756
		Desvenlafaxine	£1,571.32	7.06	£861.35	0.040	£21,352
3	Treatment-independent utility values for responders and partial responders (desvenlafaxine = fezolinetant)	Fezolinetant	£2,158.21	7.10	-	-	-
		No Treatment	£1,669.35	7.05	£488.86	0.047	£10,310
		Desvenlafaxine	£1,551.60	7.07	£606.60	0.026	£23,412

4	Include additional nurse appointments for liver testing	Fezolinetant	£2,167.79	7.10	-	-	-
		No Treatment	£1,669.35	7.05	£498.43	0.047	£10,512
		Desvenlafaxine	£1,551.60	7.06	£616.18	0.034	£18,322

4.2 EAG's preferred base case results

The EAG's preferred assumptions include the following changes to the company's base case:

- Use of the extended dose NMA for response and discontinuation.
- No stopping rule at Week 52 for partial responders.
- Treatment-independent utility values for responders and partial responders for active treatments, i.e., the utility values for desvenlafaxine responders and partial responders are equivalent to those for fezolinetant responders and partial responders.
- Inclusion of additional nurse appointments for liver testing.

Table 13 and Table 14 show the cumulative impact of the EAG's preferred assumptions on the company's base case for the deterministic and probabilistic analysis, respectively.

Table 13 Deterministic results using EAG's preferred assumptions with cumulative impact

#	Name	Option	Costs	QALYs	Inc. Costs	Inc. QALYs	ICER, / QALY
	Company's base-case results	Fezolinetant	£2,160.52	6.91	-	-	-
		No Treatment	£1,675.89	6.87	£484.63	0.047	£10,313
		Desvenlafaxine	£1,558.51	6.88	£602.01	0.034	£17,969
1	Extended dose NMA	Fezolinetant	£2,160.52	6.91	-	-	-
		No Treatment	£1,675.89	6.87	£484.63	0.047	£10,313
		Desvenlafaxine	£1,556.54	6.88	£603.97	0.033	£18,128
1+2	+ No stopping rule at Week 52 for partial responders	Fezolinetant	£2,430.36	6.92	-	-	-
		No Treatment	£1,675.89	6.87	£754.47	0.055	£13,802
		Desvenlafaxine	£1,572.79	6.88	£857.57	0.040	£21,503
1+2+3	+ Treatment-independent utility values for responders and partial responders (desvenlafaxine = fezolinetant)	Fezolinetant	£2,430.36	6.92	-	-	-
		No Treatment	£1,675.89	6.87	£754.47	0.055	£13,802
		Desvenlafaxine	£1,572.79	6.89	£857.57	0.031	£28,090
1+2+3 +4	+ Include additional nurse appointments for liver testing **[EAG base case]**	Fezolinetant	£2,439.96	6.92	-	-	-
		No Treatment	£1,675.89	6.87	£764.08	0.055	£13,977
		Desvenlafaxine	£1,572.79	6.89	£867.17	0.031	£28,404

Table 14 Probabilistic results using EAG's preferred assumptions with cumulative impact

#	Name	Option	Costs	QALYs	Inc. Costs	Inc. QALYs	ICER, / QALY
	Company's base-case results	Fezolinetant	£2,158.21	7.10	-	-	-
		No Treatment	£1,669.35	7.05	£488.86	0.047	£10,310
		Desvenlafaxine	£1,551.60	7.06	£606.60	0.034	£18,037
1	Extended dose NMA	Fezolinetant	£2,158.21	7.10	-	-	-
		No Treatment	£1,669.35	7.05	£488.86	0.047	£10,310
		Desvenlafaxine	£1,542.30	7.06	£615.90	0.033	£18,772
1+2	+ No stopping rule at Week 52 for partial responders	Fezolinetant	£2,432.67	7.10	-	-	-
		No Treatment	£1,669.35	7.05	£763.31	0.055	£13,756
		Desvenlafaxine	£1,562.90	7.06	£869.76	0.039	£22,040
1+2+3	+ Treatment-independent utility values for responders and partial responders (desvenlafaxine = fezolinetant)	Fezolinetant	£2,432.67	7.10	-	-	-
		No Treatment	£1,669.35	7.05	£763.31	0.055	£13,756
		Desvenlafaxine	£1,562.90	7.07	£869.76	0.029	£29,884
1+2+3 +4	+ Include additional nurse appointments for liver testing **[EAG base case]**	Fezolinetant	£2,442.24	7.10	-	-	-
		No Treatment	£1,669.35	7.05	£772.89	0.055	£13,929
		Desvenlafaxine	£1,562.90	7.07	£879.34	0.029	£30,213

4.3 Alternative scenario to the EAG's preferred base case

The EAG considers the company's Week 52 stopping rule for partial responders to be arbitrary, with no justification provided in the company's addendum to the DG response. Consequently, the EAG's preferred base case removes the stopping rule. However, to address the impact of uncertainty regarding continued treatment in partial responders, the EAG presents an alternative scenario to the EAG's preferred base case where the arbitrary Week 52 stopping rule is retained.

Table 15 shows the results of the alternative scenario to the EAG's preferred base case, retaining the Week 52 partial responder stopping rule and including only scenarios 1, 3, and 4 of the EAG's base case.

Table 15 Results of an alternative scenario to the EAG's preferred base case, retaining the Week 52 partial responder stopping rule (deterministic and probabilistic analysis)

#	Name	Option	Costs	QALYs	Inc. Costs	Inc. QALYs	ICER, / QALY
Deterministic							
1+3+4	Extended dose NMA + Treatment-independent utility values for responders and partial responders (desvenlafaxine = fezolinetant) + Include additional nurse appointments for liver testing	Fezolinetant	£2,170.12	6.91	-	-	-
		No Treatment	£1,675.89	6.87	£494.24	0.047	£10,517
		Desvenlafaxine	£1,556.54	6.89	£613.58	0.026	£23,801
Probabilistic							
1+3+4	Extended dose NMA + Treatment-independent utility values for responders and partial responders (desvenlafaxine = fezolinetant) + Include additional nurse appointments for liver testing	Fezolinetant	£2,167.79	7.10	-	-	-
		No Treatment	£1,669.35	7.05	£498.43	0.047	£10,512
		Desvenlafaxine	£1,542.30	7.07	£625.48	0.025	£25,253

4.4 Conclusions of the cost effectiveness evidence

The company provided a new decision model to compare the cost-effectiveness of fezolinetant against either no active treatment or desvenlafaxine (used as a proxy for venlafaxine) in postmenopausal people who have moderate to severe VMS frequency of $\geqslant$ 7 per day and are deemed unsuitable for HRT. A scenario analysis was also included, comparing fezolinetant to paroxetine. While comparisons with desvenlafaxine and paroxetine were provided, the company maintains the view that no active treatment remains the most appropriate comparator. This is due to two factors: the evaluated SSRI and SNRI formulations or doses are not available in the UK, and the analysis for these comparators relies on assumptions that may limit their generalisability to UK clinical practice.

The committee concluded that non-hormonal pharmacological treatments were relevant comparators. The EAG also noted the results of the company's GP survey (Question 7), submitted as part of its DG response, which indicated that people are significantly more likely to be prescribed a non-hormonal pharmacological treatment than no active therapy. This was further supported by the EAG's clinical advisor who stated that SSRIs, SNRIs and other pharmacological treatments are used; specifically,

fluoxetine, paroxetine, venlafaxine, sertraline, citalopram and, to a lesser extent, clonidine. Therefore, the EAG concludes that although no active treatment is a relevant comparator for some people, non-hormonal pharmacological treatments are the most relevant comparator for the target population.

The company positioned fezolinetant for use in primary care. However, the appraisal committee considered that offering fezolinetant in secondary care may be more appropriate, based on the need for liver function tests and ongoing monitoring requirements associated with the drug. The EAG noted that the results of the company's GP survey showed that most GPs are either very confident (35%) or moderately confident (46%) in making clinical decisions based on LFT results, while half of the surveyed GPs don't refer any patients with moderate to severe VMS to secondary care (where the median waiting time for a specialist appointment is 6 months). The EAG's clinical advisor supported the view that GPs are accustomed to monitoring LFTs, suggesting that fezolinetant could therefore be initiated in primary care.

The efficacy evidence informing the company's cost-effective analysis was based on a response outcome assessed at Week 12, where response was defined by a reduction of at least 75% in moderate to severe VMS frequency from baseline, along with treatment discontinuation rates. Pooled data from the DAYLIGHT and SKYLIGHT 1&2 (HRT-unsuitable subpopulation) trials was used for the fezolinetant and no active treatment arms, while evidence from the NMA that included non-hormonal pharmacological treatments was applied to the fezolinetant data to derive efficacy estimates for desvenlafaxine in the company's base case. In general, the EAG supports the company's efficacy response criterion of ≥ 75% reduction in moderate to severe VMS frequency at Week 12 as a clinically meaningful improvement in symptoms. However, the long-term efficacy and duration of active treatments (fezolinetant and desvenlafaxine), which are determined by the discontinuation rates, remain uncertain.

The revised model structure and new approach to modelling adequately addresses the committee's core issues, including concerns related to the previously modelled health states, the misalignment between baseline VMS frequency and the natural history estimates, the prior absence of relative treatment effects, the inappropriate adjustment made to utility values, and the uncaptured costs associated with liver monitoring.

A primary concern with the new model structure is that it now creates a misalignment with the utility values used for the modelled health states. For the active treatment arms, non-responders at Week 12 were split 50:50 such that 50% discontinued treatment immediately, while 50% continued treatment until Week 52 (partial responders). However, the NMA outcomes were not categorised into three distinct categories for (i) responders (who achieve ≥ 75% reduction), (ii) partial responders (who achieve ≥ 50% but less than 75% reduction), and (iii) non-responders (who do not achieve 50%

reduction), nor were the utility values separated by response status in this way. Instead, the utility values were separated into responders and non-responders, using the ≥ 75% reduction criterion. Further, the exclusion of a partial responders' health state in the no active treatment arm results in a model structure that differs from the active treatment arms. The Week 52 stopping rule for partial responders in the company's base case also appears to be arbitrary.

The revised modelling approach introduces a new issue related to the utility values, where treatment-specific utility values by responder status is used across the active treatment arms (fezolinetant and desvenlafaxine). The EAG considers it appropriate to use the same utility values across active treatments for equivalent responder and partial responder health states (noting that an equivalent utility value is already incorporated for non-responders in the company's base case). This is because treatment-dependent utility values are only justified when the treatment itself impacts quality of life independent of the response status, and no evidence has been provided by the company to support this. The EAG noted that differences in adverse events by treatment that might support treatment-specific utility values are already incorporated separately as utility decrements.

The modelled assumptions with the largest impact on the cost-effectiveness results are those relating to: (i) the use of no stopping rule at Week 52 for partial responders, and (ii) the treatment-independent utility values for responders and partial responders in the active treatment arms. With these assumptions included, in addition to additional nurse appointments for liver testing and use of the extended dose NMA for response and discontinuation, the EAG's preferred base case ICER increases from the company's base case ICER of £10,313 to £13,977 per QALY gained for fezolinetant relative to no active treatment, and from £17,969 to £28,404 per QALY gained for fezolinetant relative to desvenlafaxine.

Whilst the EAG notes an important misalignment between the new model structure and the utility values used for the modelled health states, the EAG does not believe that this misalignment would materially impact the ICER results for fezolinetant relative to its comparators.

5 REFERENCES

1. Astellas Pharma Ltd. *Fezolinetant for treating moderate to severe vasomotor symptoms associated with the menopause [ID5071]. Draft guidance comments form [Unpublished]*. In. Company evidence submission to NICE October 2025: Astellas Pharma Ltd; 2025. p. 21.

2. Glynne S, Reisel D, Kamal A, Newson L. Patient experience of menopause care after breast cancer in the UK: a cross-sectional study. *Menopause* 2025;**32**:396–408. Available from: https://www.ncbi.nlm.nih.gov/pubmed/39933042

3. Saadedine M, Banks V, Dinkel-Keuthage C, Janssenswillen C, Lavallee M, Moeller C, et al. Treatment patterns in women with breast cancer and endocrine therapy-related menopausal symptoms: a cohort study from the United States, United Kingdom, and Germany. *Menopause* 2025. Available from: https://www.ncbi.nlm.nih.gov/pubmed/40891646

4. Astellas Pharma Ltd. *Fezolinetant for treating vasomotor symptoms associated with the menopause [ID5071]. Addendum to company evidence submission. [Unpublished, confidential]* In. Company evidence submission to NICE October 2025: Astellas Pharma Ltd; 2025. p. 88.

5. Morga A, Ajmera M, Gao E, Patterson-Lomba O, Zhao A, Mancuso S, et al. Systematic review and network meta-analysis comparing the efficacy of fezolinetant with hormone and nonhormone therapies for treatment of vasomotor symptoms due to menopause. *Menopause* 2023;**31**:68–76.

6. Sassarini J, Fox H, Ferrell W, Sattar N, Lumsden MA. Hot flushes, vascular reactivity and the role of the α-adrenergic system. *Climacteric* 2012;**15**:332–8.

7. Dias S, Welton NJ, Sutton AJ, Ades AE. *NICE DSU technical support document 2: a generalised linear modelling framework for pairwise and network meta-analysis of randomised controlled trials (updated September 2016)*. Sheffield: Decision Support Unit, ScHARR, University of Sheffield; 2011.

8. Dias S, Welton NJ, Sutton AJ, Caldwell DM, Lu G, Ades AE. *NICE DSU technical support document 3: heterogeneity: subgroups, meta-regression, bias and bias-adjustment*. Sheffield: Decision Support Unit, ScHARR, University of Sheffield; 2011.

9. Phillippo D, Perren SJ. *multinma: Bayesian network meta-analysis of individual and aggregate data*. 2020. Available from: https://cran.r-project.org/web/packages/multinma/index.html [accessed 20 November 2025].

10. National Institute for Health and Care Excellence (NICE). Menopause: diagnosis and management [NG23]. Available at: https://www.nice.org.uk/guidance/NG23 [Accessed September 2024]. 2024.

11. Noven Therapeutics. *24-Week efficacy & safety study of brisdelle™ (formerly known as mesafem) in the treatment of vasomotor symptoms*. ClinicalTrials.gov. Bethesda (MD): National Library of Medicine (US); 2015. Available from: https://clinicaltrials.gov/study/NCT01101841 [accessed 15th November 2024].

12. Noven Therapeutics. *Efficacy/safety study of brisdelle™ (formerly known as mesafem) in the treatment of vasomotor symptoms (VMS) (N30-003)*. ClinicalTrials.gov. Bethesda (MD): National Library of Medicine (US); 2015. Available from: https://clinicaltrials.gov/study/NCT01361308 [accessed 15th November 2024].

13. Avis NE, Crawford SL, Greendale G, Bromberger JT, Everson-Rose SA, Gold EB, et al. Duration of menopausal vasomotor symptoms over the menopause transition. *JAMA Intern Med* 2015;**175**:531–9.

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Single technology appraisal

Fezolinetant for treating vasomotor symptoms associated with the menopause [ID5071]

Results from additional economic modelling requests following ACM2

January 2026

File name	Version	Contains confidential information	Date
ID5071_Fezolinetant_ NICE_Post-ACM2 Model Updates_ [CON].docx	1.0	Yes	30th January 2026

1 Introduction

Following the second NICE Appraisal Committee Meeting (ACM2) regarding fezolinetant for treating moderate to severe vasomotor symptoms (VMS) associated with menopause, the appraisal committee requested a number of updates to the cost-effectiveness model. In response, Astellas has implemented these requests and summarised the resulting model changes in Table 1 below.

Updated model inputs and results from the revised cost-effectiveness model are summarised in the sections below.

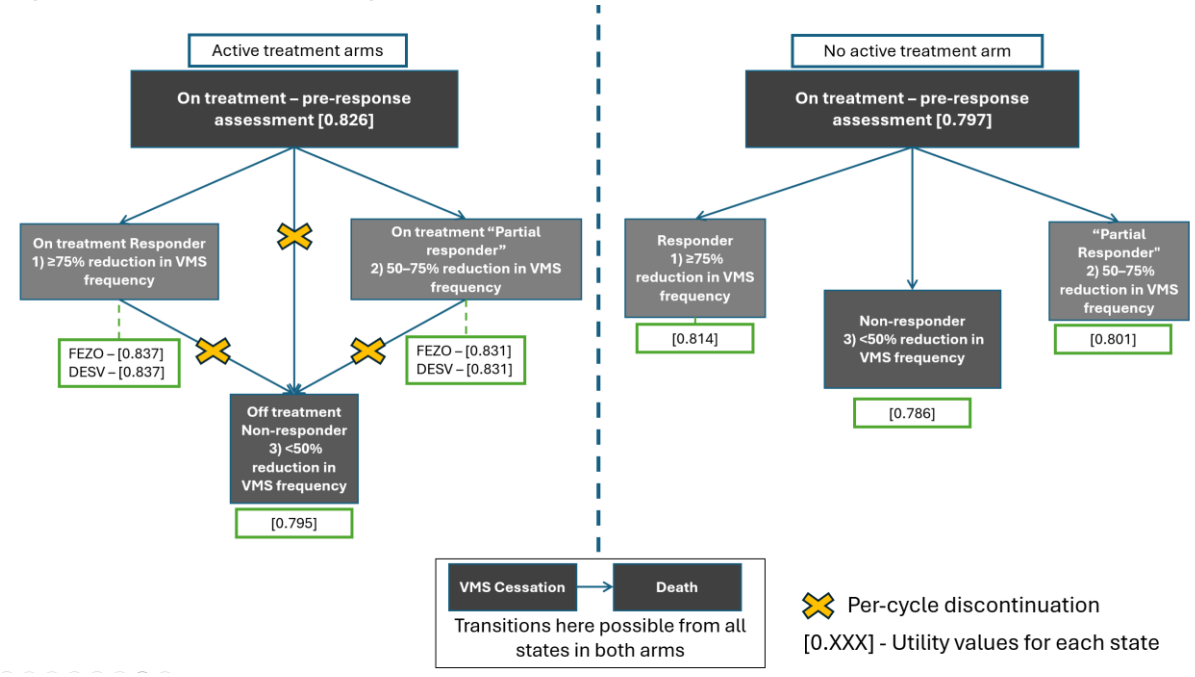
Table 1: Summary of model updates requested by the appraisal committee

Request from the appraisal committee	Updates made to the CEM
The use of the EAG's preferred base-case assumptions post-ACM2. This includes: • Use of the extended dose random effects NMA for response and discontinuation • No stopping rule at week 52 for partial responders • Treatment-independent utility values for responders/non-responders for active treatments • Inclusion of additional nurse appointments for liver testing	The model has been updated to use the preferred base-case assumptions, as implemented by the EAG.
Inclusion of an ICER that is provided separately for both comparators and a weighted ICER between no active treatment and desvenlafaxine, with scenarios basing the proportion receiving no active treatment on either the GP Omnibus Survey (Astellas data on file)[1] or the Glynne *et al.*, (2025)[2] paper noted by the EAG.	The model has been updated to calculate a weighted ICER as requested, using the EAG preferred Glynne *et al.*, 2025[2] (41.5%) as the base case (Section 0) and including a scenario using the GP Omnibus Survey[1] (31.10%) for the proportion of patients receiving no active treatment (Section 4).
Include an additional 'advice and guidance' cost for a proportion of patients receiving fezolinetant, representing the cost associated with a primary care clinician seeking advice from another clinician (usually a specialist) to inform patient care without the need for a formal appointment or referral.	This has been included in the model with a cost of £20 (General Practice Requests for Advice and Guidance, 2025/26).[3] The use of 30% as the proportion of patients was suggested by the appraisal committee as the starting point, therefore, this has been used in the base case. A threshold analysis was included in the 'Resource Use' tab of the revised CEM. This analysis explores the weighted ICER results when the proportion of patients receiving 'advice and guidance' cost is varied in 10% increments, from 10% to 100%.
Updating the model to remove the misalignment of the partial responder states between active treatment (i.e., fezolinetant and desvenlafaxine) and no active treatment arms by including partial responders in the no active treatment arm, deriving the proportion of partial responders from trial data, and removing the	An update was made to the model to include a new explicit 'partial responder' health state for all treatment arms, defined as women who report between 50% and 75% reduction in moderate to severe VMS. A visual representation of this update is illustrated in Figure 1.

partial responder stopping rule at Week 52 as per the EAG's preferred base-case assumption.	Analysis of the trial data was performed to obtain the responder distribution, discontinuation rates and health state utilities to use for this new health state. Given that the proportion of partial responders for fezolinetant and no active treatment was based on trial data, a conservative assumption was made to assume an equal proportion of partial responders between fezolinetant and desvenlafaxine. Alternative assumptions used to derive this proportion are tested in the scenario analyses (Section 4).

Abbreviations: CEM: cost-effectiveness model; EAG: External Assessment Group; GP: general practitioner; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; VMS: vasomotor symptoms.

Figure 1: Updated modelling approach for health states and utilities



Abbreviations: DESV: desvenlafaxine; FEZO: fezolinetant; VMS: vasomotor symptoms.

The health state utilities used for partial and non-responders in the latest version of the CEM were re-analysed from the trial data to align with the updated definitions of these health states (between 50% and 75% reduction in VMS frequency for partial responders and <50% reduction in VMS frequency for non-responders). Further details on these utilities are provided in the section 2.1.3 below. Utility values for pre-response assessment, VMS cessation and death health states remain unchanged.

2 Updated model inputs

This section only presents the revised model inputs and assumptions required to implement the changes requested by the appraisal committee following ACM2. Hence, inputs and assumptions which have not changed are not included in this section.

2.1.1 Responder distribution

Table 2: Responder distribution

Treatment	Responder (≥75% reduction in VMS)	Partial responder (<75% and ≥50% reduction in VMS	Non-responder (<50% reduction in VMS	Source
Fezolinetant	41.62%	20.81%	37.57%	Pooled DAYLIGHT and SKYLIGHT 1&2 (HRT-unsuitable subpopulation)
No active treatment	21.83%	18.49%	59.68%	Pooled DAYLIGHT and SKYLIGHT 1&2 (HRT-unsuitable subpopulation)
Desvenlafaxine	37.46%	20.81%	41.73%	Calculation, OR applied to the fezolinetant arm; partial responder % was assumed equal to fezolinetant

Abbreviations: HRT: hormone-replacement therapy; OR: odds ratio; VMS: vasomotor symptoms.

2.1.2 Treatment discontinuation

The model was updated to include discontinuation rates specific to partial responders from week 12 onwards (following response assessment). These were derived using the same methods and regression models used to generate the responder discontinuation rates already included in the model. Further details of the regression analyses used can be found in the statistical analysis plan provided in the reference pack.[4]

Table 3: Per 4-weekly cycle probability of discontinuation for partial responders

Treatment	Time period	Probability of discontinuation for partial responders	Per 4-week probability of discontinuation for partial responders	Source
Fezolinetant	Week 12–24	[redacted]	[redacted]	Week 12–24: DAYLIGHT and SKYLIGHT 1&2 (HRT-unsuitable subpopulation). Responder status is based on the LOCF 75% reduction in baseline frequency definition at 12 weeks. Partial responders are defined as women with between 75% and 50% reduction in VMS frequency[a]
	Week 24+	[redacted]	[redacted]	
Desvenlafaxine	Week 12–24	[redacted]	[redacted]	Calculation. OR applied to the fezolinetant treatment discontinuation rate for Week 12–24 and Week 24+
	Week 24+	[redacted]	[redacted]	

[a] Treatment discontinuation rate was assumed to be constant and estimated using an exponential model based on the observed data.
Abbreviations: HRT: hormone-replacement therapy; LOCF: last observation carried forward; OR: odds ratio.

2.1.3 *Utilities*

Updated response-based fezolinetant utility values were informed by EQ-5D data collected in the fezolinetant arms of the DAYLIGHT (Weeks 0–24) and SKYLIGHT 1&2 (Weeks 0–52) trials to make use of all available data. Updated response-based no active treatment utility values were informed by EQ-5D data collected in the placebo arms of the DAYLIGHT (Weeks 0–24) and SKYLIGHT 1&2 (Weeks 0–12) trials. To derive required inputs for fezolinetant and no active treatment, generalised linear mixed models were fitted to the DAYLIGHT and SKYLIGHT 1 & 2 (HRT-unsuitable subpopulation) populations with the following specifications:

Model 1: Utility ~ Treatment + Timepoint + (1|Subject ID),

Model 2: Utility ~ Treatment + Timepoint + Response Status + (1|Subject ID),

where (1|Subject ID) denotes the use of a random intercept for Subject ID to control for repeated measures within women. Missingness in responder status was addressed using LOCF imputation; complete case analysis with respect to other variables was conducted throughout. Estimated mean change from baseline (CfB) utility values for each health state was then derived from derived model coefficients for fezolinetant 45 mg and placebo arms as estimated marginal means (least squares means) averaged across observed timepoints within the relevant window, with their associated standard errors pooled. Further details on these analyses are provided in the statistical analysis plan for responder analyses in the reference pack.[4]

The CfB utility inputs based on response status, and resulting utility values for each health state, are presented in Table 4 below.

Table 4: Mean change from baseline in utility values

Treatment	Response category	Calculated utility	CfB utility inputs	SE	Source
Fezolinetant	Responder	0.837	0.059	0.008	Derived using pooled EQ-5D-5L data (double blind period) from fezolinetant 45mg and placebo in the DAYLIGHT and SYKLIGHT 1 & 2 (HRT-unsuitable population) trials, with mapping algorithm obtained from Alava *et al.*, (2023)[5]
	Partial responder	0.831	0.052	0.009	
No active treatment	Responder	0.814	0.035	0.008	
	Non-responder (50% response definition)	0.786	0.007	0.008	
	Partial responder	0.801	0.022	0.009	
Desvenlafaxine	Responder	0.837	0.059	-	
	Partial responder	0.831	0.052	-	

Note: Non-responder values for active treatments are not reported in this table as the model uses the weighted average of the no active treatment utilities for the off treatment non-responder health state, as per the original ACM2 model.
Abbreviations: CfB: change from baseline; HRT: hormone-replacement therapy; SE: standard error.

3 Results

A summary of the updated probabilistic and deterministic results and incremental net health benefits (INHB) for the revised CEM are presented in Table 5, Table 6, and Table 7 respectively. The probabilistic base-case results are in close alignment with the deterministic results. The probabilistic and deterministic weighted ICERs were £16,166 per QALY gained and £15,549 per QALY gained, respectively, both below the Committee's preferred £25,000/QALY ICER threshold.

These results show a reduction in the pairwise probabilistic ICERs versus desvenlafaxine and no active treatment when compared with the EAG-preferred probabilistic ICERs ahead of ACM2 (no treatment: £9,828 (new) versus £13,929 (old) per QALY gained and desvenlafaxine: £25,424 (new) versus £30,213 (old) per QALY gained). This is mostly driven by a reduction in incremental costs for fezolinetant versus no active treatment and desvenlafaxine, as discussed below.

Firstly, the proportion of partial responders derived from the trial is below the previous assumption of 50% of <75% 'non-responders' and so a reduced proportion of women incur fezolinetant treatment acquisition costs post response assessment. This also has the impact of decreasing incremental costs via the reduction in fezolinetant treatment acquisition costs relative to no active treatment and desvenlafaxine.

Secondly, in the previous model, partial responders for fezolinetant and desvenlafaxine were modelled within the 'non-responder' health state. It was assumed 50% of non-responders would remain on treatment as 'partial responders' and as such would incur the relevant treatment costs whilst also incurring non-responder resource use costs. As the non-responder resource use costs are higher than resource use costs for responders, this cohort of women ultimately incurred relatively high costs. In the updated model, partial responders are modelled separately and are assumed to incur 'on treatment, responder' resource use costs, which are comparatively lower (as their symptoms are controlled, fewer HCP consultations are sought). As a result, the total resource use costs across all treatments have decreased, but the reduction in fezolinetant resource use costs is greater than for no active treatment and desvenlafaxine, due to the lower proportion of non-responders ultimately retaining the high resource use costs for fezolinetant versus each comparator. A scenario is provided in Section 4 that explores the use of the average of the responder/non-responder resource use cost for partial responders, which has a minimal impact on the ICER.

While the utility values used for the partial and non-responder health states were updated for this analysis, the overall impact on the incremental QALYs for fezolinetant versus both comparators is small. Nonetheless, a scenario exploring the impact of setting the partial responder utility to equal the non-responder utility is also included in Section 4, with a small impact on the ICER.

Overall, these results demonstrate that fezolinetant remains a cost-effective treatment and that the updates made to the model do not have a material impact on the results. Results from the probabilistic sensitivity analysis (PSA) and deterministic sensitivity analysis (DSA) are presented in Appendix A and Appendix B, respectively.

Table 5: Probabilistic base-case results

Technologies	Total			Incremental			ICER
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	Versus baseline (£/QALY)
Fezolinetant	£1,997.25	8.436	7.126	-	-	-	-
No Treatment	£1,395.26	8.436	7.065	£601.99	0.000	0.061	£9,828
Desvenlafaxine	£1,240.96	8.436	7.096	£756.30	0.000	0.030	£25,424
Weighted Comparator (No treatment/desvenlafaxine)	£1,305.00	8.436	7.083	£692.26	0.000	0.043	£16,166

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years.

Table 6: Deterministic base-case results

Technologies	Total			Incremental			ICER
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	Versus baseline (£/QALY)
Fezolinetant	£1,993.24	8.449	6.920	-	-	-	-
No Treatment	£1,403.51	8.449	6.860	£589.73	0.000	0.060	£9,840
Desvenlafaxine	£1,261.59	8.449	6.888	£731.66	0.000	0.031	£23,270
Weighted Comparator (No treatment/desvenlafaxine)	£1,320.49	8.449	6.877	£672.76	0.000	0.043	£15,549

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years.

Table 7: Incremental net health benefit (probabilistic)

Technologies	Total		Incremental		INHB	
	Costs (£)	QALYs	Costs (£)	QALYs	£25,000	£35,000
Fezolinetant	£1,997.25	7.126	-	-		
No Treatment	£1,395.26	7.065	£601.99	0.061	0.04	0.04

Desvenlafaxine	£1,240.96	7.096	£756.30	0.030	0.00	0.01
Weighted Comparator (No treatment/desvenlafaxine)	£1,305.00	7.08	£692.26	0.043	0.02	0.02

Abbreviations: LYG: life years gained; QALYs: quality-adjusted life years; INHB: incremental net health benefit.

4 Scenario analysis

Scenario analyses were conducted to evaluate the impact of alternative assumptions following updates to the model post-ACM2. Results from the additional scenarios are presented in Table 8. The scenario analyses explored demonstrate that the ICER remains cost-effective (i.e. below the Committee's preferred £25,000/QALY ICER threshold) when considering a range of different assumptions tested for the updated model.

Table 8: Summary of scenario analyses and results for fezolinetant versus no active treatment and desvenlafaxine (deterministic)

Scenario		No treatment			Desvenlafaxine			Weighted comparator		
		Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Base case		£590	0.06	£9,840	£732	0.03	£23,270	£673	0.04	£15,549
1	Desvenlafaxine partial responder %: Assumed equivalent to fezolinetant ratio of non-responders to partial responders	£590	0.06	£9,840	£735	0.03	£23,723	£674	0.04	£15,690
2	Desvenlafaxine partial responder %: Assumed equivalent to fezolinetant ratio of responders to partial responders	£590	0.06	£9,840	£728	0.03	£22,657	£670	0.04	£15,355
3	Source for % receiving no treatment (weighted ICER): GP Omnibus Survey (31.10%)	£590	0.06	£9,840	£732	0.03	£23,270	£688	0.04	£17,059
4	100% of patients associated with Advice and Guidance cost	£604	0.06	£10,073	£746	0.03	£23,715	£687	0.04	£15,873
5	Partial responders resource use: Assumed equal to average of	£533	0.06	£8,898	£774	0.03	£24,617	£674	0.04	£15,581

	responders and non-responders									
6	Partial responder utility: Assumed equal to non-responder utility	£590	0.06	£9,631	£732	0.03	£27,363	£673	0.04	£16,387

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years.

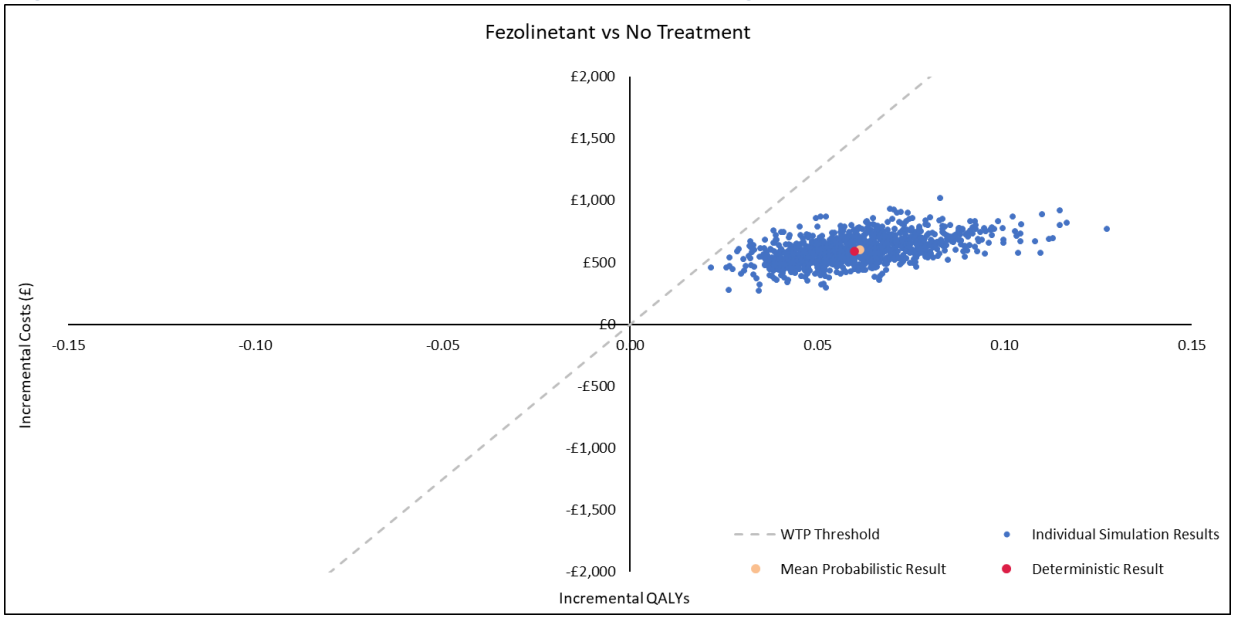
References

1. Astellas Data on File. GP Omnibus August 2025, 2025.
2. Glynne S, Reisel D, Kamal A, et al. Patient experience of menopause care after breast cancer in the UK: a cross-sectional study. Menopause 2025;32:396-408.
3. NHS England. Enhanced Service Specification – General Practice Requests for Advice and Guidance 2025/26, 2026.
4. Astellas Data on File. Regression Analyses SAP. 2026.
5. Hernández Alava M, Pudney S, Wailoo A. Estimating the Relationship Between EQ-5D-5L and EQ-5D-3L: Results from a UK Population Study. PharmacoEconomics 2023;41:199-207.

Appendices

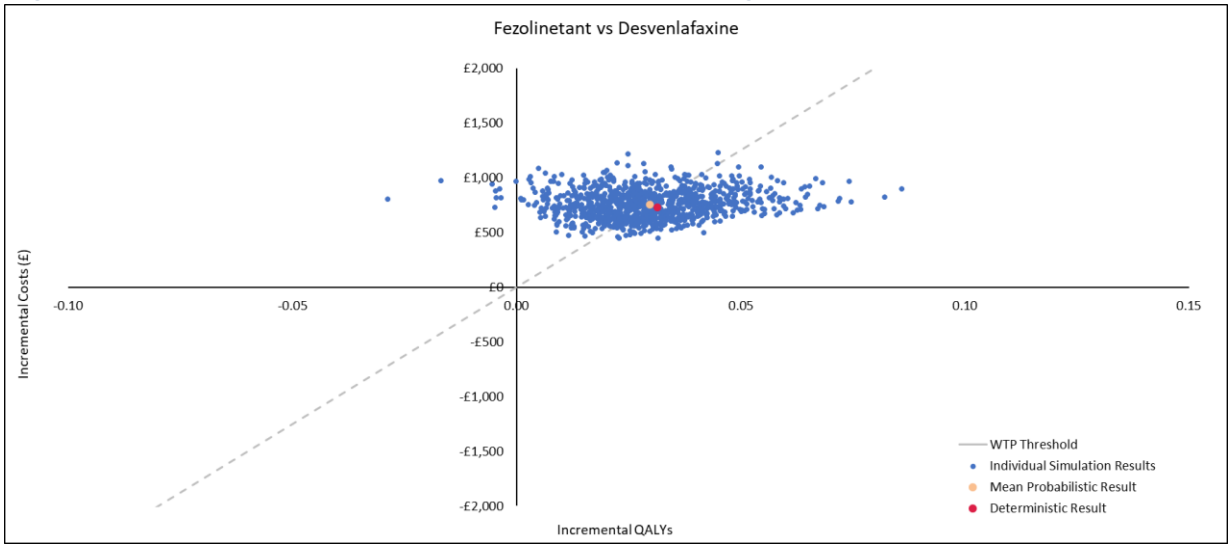
Appendix A Probabilistic Sensitivity Analysis

Figure 2: Cost-effectiveness plane for fezolinetant 45 mg versus no active treatment



Abbreviations: ICER: incremental cost-effectiveness ratio; WTP: willingness-to-pay.

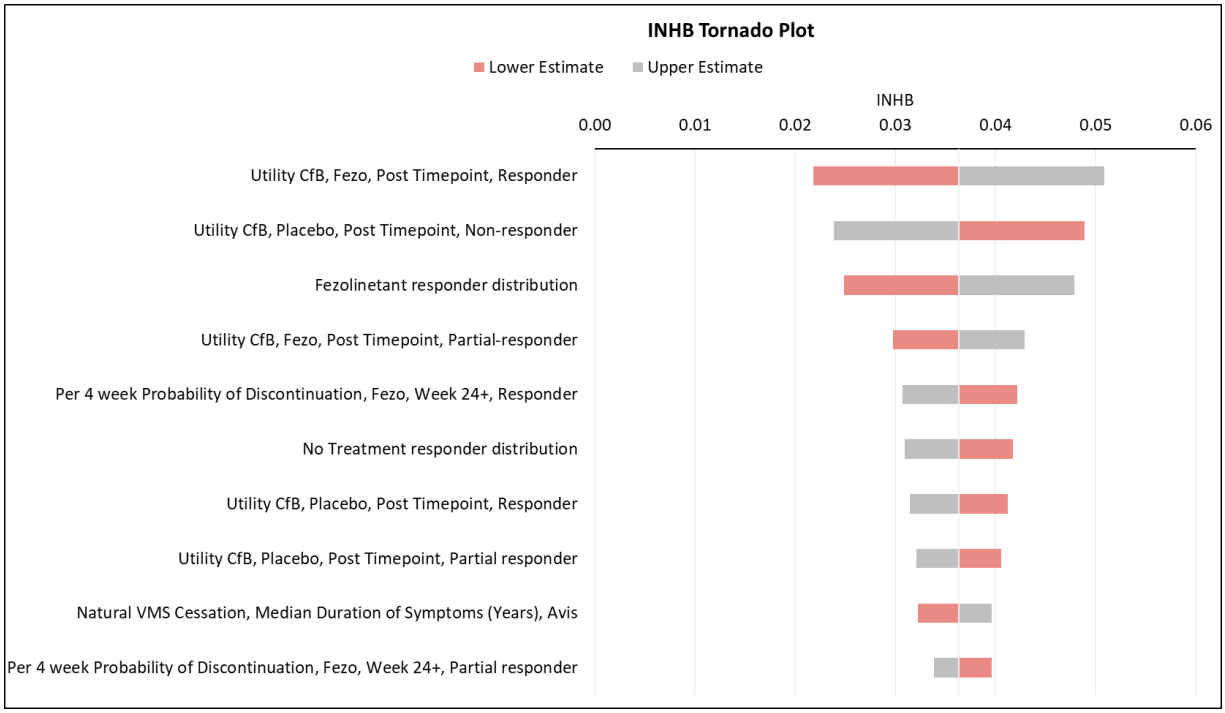
Figure 3: Cost-effectiveness plane for fezolinetant 45 mg versus desvenlafaxine



Abbreviations: ICER: incremental cost-effectiveness ratio; WTP: willingness-to-pay.

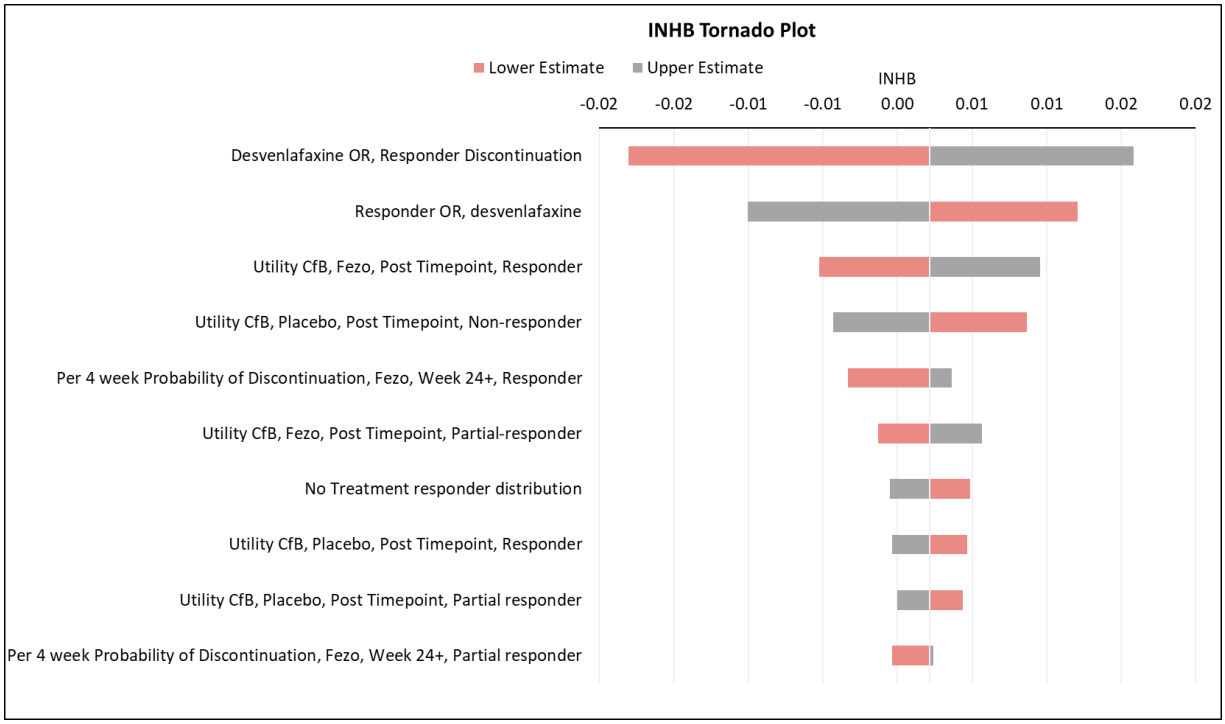
Appendix B Deterministic Sensitivity Analysis

Figure 4: Tornado diagrams depicting results of fezolinetant versus no active treatment (INHB at £25,000/QALY)



Abbreviations: INHB: incremental net health benefit; VMS: vasomotor symptoms.

Figure 5: Tornado diagrams depicting results of fezolinetant versus desvenlafaxine (INHB at £25,000/QALY)



Abbreviations: INHB: incremental net health benefit; VMS: vasomotor symptoms.

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EAG ADDENDUM

Review of the company's response to second NICE Appraisal Committee Meeting (ACM2) requests: Fezolinetant for treating vasomotor symptoms associated with the menopause [ID5071]

Produced by
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None.

Rider on responsibility for report

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1 OVERVIEW OF THE COMPANY'S RESPONSE TO ACM2

The company provides updated analyses and results following the second NICE Appraisal Committee Meeting (ACM2) requests for additional economic modelling. The committee requested the following:

- **The EAG's preferred base case assumptions**: extended dose random effects NMA for response and discontinuation, no stopping rule at week 52 for partial responders, treatment-independent utility values for response in the active treatment arms, and additional nurse appointments for liver testing.
- **Advice and guidance in primary care**: for a proportion of patients an additional cost representing the cost to the NHS for using "advice and guidance" service should be included in the fezolinetant arm only. Scenarios exploring a maximum proportion for which this service could be used, and fezolinetant remain cost effective would support decision making.
- **Modelling partial responders**: partial responders should be included in the non-active treatment arm – same model structure should be used across all treatment arms.
- **Proportion of partial responders**: determined using trial data for fezolinetant and non-active treatment (placebo). Fezolinetant trial data can be applied as an assumption to other active treatments for the proportion of partial responders.
- **Weighted ICER**: cost-effectiveness results to be provided separately for both comparators as well as a weighted ICER. Proportion of active treatment for weighted ICER determined using (1) Glynne et al., (2025) data and (2) the company's GP Omnibus survey results.

The company has updated its economic model to incorporate all the above considerations. Table 1 of the company's response document summarises the company's updates to the model. The EAG has reviewed the company's analyses and implementation within the electronic version of the model, as detailed in the following sections.

2 REVIEW OF THE COMPANY'S RESPONSE TO ACM2

2.1 EAG's preferred base case assumptions

Following ACM2, the model was updated with the EAG's preferred assumptions. The EAG confirms that the company's revised base case now includes these changes.

2.2 Advice and guidance in primary care

The company has included an additional 'advice and guidance' cost (£20) for a proportion of patients receiving fezolinetant (30%). The £20 cost for specialist Advice and Guidance stems from the Enhanced Service introduced in April 2025 (Enhanced Service Specification – General Practice

Requests for Advice and Guidance 2025/26), where the Item of Service (IoS) fee per request for prereferral advice and guidance is £20. The company also varies the proportion of patients in the fezolinetant arm requiring this service from 10% to 100%, in 10% increments, to assess the impact on the weighted ICER results.

The approach used by the company to cost advice and guidance seems reasonable to cover the GP time spent managing treatment with fezolinetant in primary care; however, it doesn't cover the time and cost of the specialist-led service providing the advice and guidance.

At the unit price of £20 per prereferral advice and guidance for 30% of people receiving fezolinetant, the total cost of fezolinetant increases by an average of £6. This increase reaches a maximum of £20 in the company's model when the service is utilised for everyone who receives fezolinetant. The EAG is concerned that this cost may not be reflecting the true cost to the NHS for using the "advice and guidance" service because it is not covering the cost of the specialist time (although some of this cost may be potentially offset by fewer referrals), or reflecting the use of the service for people who do not ultimately receive fezolinetant treatment.

2.3 Modelling partial responders and proportion of partial responders

Responder distribution

The company has updated the model structure to include partial responders in the 'no active treatment' (NAT) arm, following the same approach used for the active treatment arms. The proportion of partial responders for the fezolinetant and NAT arms is based on pooled data from the DAYLIGHT and SKYLIGHT 1&2 (HRT-unsuitable subpopulation) trials at week 12 for the fezolinetant and placebo arms, respectively. In the absence of data for the desvenlafaxine arm, the proportion of partial responders is set equal to the fezolinetant arm. Table 2 of the company's response document summarises the distribution of responders (≥75% reduction in VMS frequency), partial responders (<75% and ≥50% reduction in VMS frequency) and non-responders (<50% reduction in VMS frequency) across the treatment arms. Of note, the proportion of partial responders in the placebo arm (18.49%) is just below the proportion in the fezolinetant arm (20.81%), which suggests that when modelling partial responders in the active treatment arm it is appropriate to model partial responders in the NAT arm to fully capture the placebo effect from the trials. The benefit of including partial responders in the model structure is contingent upon the difference in utility values and resource use between partial responders and non-responders.

Response-based utility values

The health state utility values for partial responders and non-responders have been updated by re-analysing the fezolinetant trial data to align with these health state definitions, while all other utility values remain unchanged. The approach used to derive utility values for partial responders and non-

responders from the trial data remains consistent with the methodology used to calculate responder utilities. For the active treatment arms, the utility values are treatment-independent (aligned with the EAG's preferred base case assumption). Table 1 summarises the response-based utility values used in the company's revised model and compares these to the utility values used in the company's model presented at ACM2 (referred to as "previous model" hereinafter) in order to aid understanding of the impact of the utility changes on the cost-effectiveness results. Notably, while the proportion of partial responders is similar across arms in the revised model, the utility difference is larger. In the active treatment arm, the mean utility for partial responders is close to that of responders (a difference of 0.006). Conversely, in the NAT arm, there is a much larger difference of 0.013 between responders and partial responders, suggesting that partial responders in the NAT arm do not experience as much quality of life relative to responders, or those on active treatment. Thus, the expected impact is a greater QALY difference between the active and NAT arms in the revised model.

Second, the mean utility difference for non-responders between treatment arms is significantly larger in the revised model compared to the previous model. Previously, in the active treatment arm, the non-responder utility value was based on a weighted average of utility values for responders and non-responders derived from the placebo arm (using the 75% response criterion). It is now based directly on the utility for non-responders (<50% reduction in VMS frequency) within the fezolinetant trial arm itself, while the NAT arm is informed by the placebo arm of the trials. The resulting impact is a larger difference between treatment arms for non-responder utility. This change results in a higher QALY gain for the active treatment arm relative to the NAT arm compared to the previous model.

Table 1 Summary of the response-based mean utility values used in the company's revised and previous models

	Revised model			Previous model*		
Response category	**Fezolinetant/ Desvenlafaxine**	**No active treatment**	**Difference between arms**	**Fezolinetant/ Desvenlafaxine**	**No active treatment**	**Difference between arms**
Responder	0.837	0.814	0.023	0.837	0.814	0.023
Partial responder	0.831	0.801	0.030	0.816	0.792	0.024
Non-responder	0.808	0.786	0.022	0.797	0.792	0.005

* Company's model at ACM2 under the revised health state definitions. Previously, in the active treatment arms, the non-responder utility value represented a 50% to 75% reduction in VMS frequency (now defined as partial responders), while those with a <50% reduction were assigned the 'Off Treatment with VMS' utility value, which aligns with the non-responder category under the revised health state definitions. Previously, the no active treatment arm lacked a dedicated partial responders health state; consequently, these individuals were assigned the utility value of non-responders from the placebo arm of the trials.

Response-based resource use

The resource use by response-based health state has not been updated in the company's revised model. In the previous model, resource use rates and associated unit costs (GP visits, GP follow-up visits, A&E visits and Specialist visits, first and follow-up) were separated by responder and non-

responder, where non-responders incurred higher resource use costs than responders. Previously, it was assumed that 50% of non-responders would remain on treatment as 'partial responders' until week 52 and as such would incur the relevant treatment costs whilst also incurring non-responder resource use costs. Conversely, in the company's revised model, partial responders are now modelled to incur responder resource use costs while on treatment (and their resource use only reverts to non-responders upon discontinuation, consistent with the approach used for responders). Given that the non-responder resource use costs are significantly higher than those for responders (£459.43 vs. £55 per annum), the revised model shows a substantial reduction in costs for partial responders compared to the previous model. The overall cost difference between treatment arms is now driven by the relative proportions of partial responders and their respective discontinuation rates.

The EAG considers it reasonable to assume that partial responders do not require the same high level of resource use as non-responders because their symptoms are better controlled as supported by their higher mean utility values. Conversely, since their symptoms are not as well-controlled as those of responders, their resource use is likely to fall between the two groups (responders and non-responders). The company explored a scenario using the average cost of responder and non-responder resource use for the partial responder health state; while this had a minimal impact on the cost-effectiveness results, the EAG views this scenario a more appropriate reflection of resource use costs for partial responders.

Treatment discontinuation rates

The model now includes discontinuation rates specific to partial responders (those with a 50%–75% reduction in VMS frequency) from week 12 onwards, while retaining the original responder discontinuation rates. The approach used is consistent with the methodology used previously to generate the responder discontinuation rates, where fezolinetant trial data was used to inform the fezolinetant arm, while the rate for desvenlafaxine is derived by applying the NMA-sourced odds ratio for all-cause treatment discontinuation at week 12. Table 3 of the company's response document summarises the 4-weekly cycle probability of discontinuation. The EAG is satisfied that this has been appropriately implemented for partial responders, following the same methodology applied to responders.

2.4 Weighted ICER

The committee requested cost-effectiveness results for each comparator (NAT and desvenlafaxine) individually, alongside a weighted ICER. For the latter, the proportion of active treatment is to be informed by (1) Glynne et al. (2025) data and (2) the results of the company's GP Omnibus survey. For the base case, the proportions of active treatment were informed by Glynne et al. (2025). In this UK survey of menopause care in 1195 women with a history of breast cancer, a total of 699 women

(58.5%) were offered treatment for menopausal symptoms, implying that 41.5% received no active treatment. Consequently, the company's base case ICER is weighted using these proportions (41.5% receiving NAT and 58.5% receiving desvenlafaxine). Additionally, a scenario analysis was conducted using the company's GP Omnibus survey, which suggests that 31.1% of HRT-unsuitable people receive NAT.

The weighted ICER is correctly calculated as the weighted average of the incremental costs divided by the weighted average of the incremental effects rather than simply weighting the ICERs for each treatment vs. fezolinetant.

3 REVIEW OF THE COMPANY'S REVISED COST-EFFECTIVENESS ANALYSES

3.1 Revised base case results and scenarios

The company's revised base case results are presented in Tables 5, 6 and 7 of the company's response document, while results of the company's scenario analyses are presented in Table 8. The EAG has validated the changes made to the electronic version of the model and is satisfied that they have been implemented appropriately and the results reported are accurate.

Table 2 presents the company's revised base case results and shows the cumulative impact of several changes:

- **EAG preferred base case assumptions**: Starting with the preferred assumptions from ACM2.
- **Advice and Guidance costs**: Adding advice and guidance costs to the fezolinetant arm.
- **Model structure**: Refining the treatment of partial responders; specifically, the inclusion of partial responders in the NAT arm, updated trial-based response distributions, response-based health state utility values, discontinuation rates, and resource use associated with partial responders.

Table 2 Summary of the company's revised base case showing the cumulative impact of changes (deterministic analysis)

Name	Option	Costs	QALYs	Inc. Costs	Inc. QALYs	ICER, / QALY
EAG base case assumptions at ACM2 [ACM2 BC]	Fezolinetant	£2,433.24	6.922	-	-	-
	No Treatment	£1,675.89	6.868	£757.36	0.054	£13,903
	Desvenlafaxine	£1,571.20	6.894	£862.05	0.028	£30,628
	Weighted comparator, 41.5% NAT	£1,614.64	6.883	£818.60	0.039	£20,951
	Weighted comparator, 31.10% NAT	£1,603.76	6.886	£829.49	0.036	£22,830
+ Advice and guidance cost (additional cost of £20 for fezolinetant for 30% of people)	Fezolinetant	£2,439.24	6.922	-	-	-
	No Treatment	£1,675.89	6.868	£763.36	0.054	£14,013
	Desvenlafaxine	£1,571.20	6.894	£868.05	0.028	£30,842
	Weighted comparator, 41.5% NAT	£1,614.64	6.883	£824.60	0.039	£21,105
	Weighted comparator, 31.10% NAT	£1,603.76	6.886	£835.49	0.036	£22,995
+ Modelling partial responders in both arms and using trial data to inform partial responder inputs **[Company's revised base case]**	Fezolinetant	£1,993.24	6.920	-	-	-
	No Treatment	£1,403.51	6.860	£589.73	0.060	£9,840
	Desvenlafaxine	£1,261.59	6.888	£731.66	0.031	£23,270
	Weighted comparator, 41.5% NAT	£1,320.49	6.877	£672.76	0.043	£15,549
	Weighted comparator, 31.10% NAT	£1,305.73	6.880	£687.52	0.040	£17,059

The company's revised base case results show a reduction in the pairwise and weighted ICERs compared to the EAG's preferred base case assumptions at ACM2. The inclusion of additional advice and guidance costs to the fezolinetant arm has minimal impact on the results because only a prereferral advice and guidance fee of £20 is included for a proportion of people. The main change on the cost-effectiveness results is from refining the modelling of partial responders. There are two key changes that have a large impact on the total costs across all arms:

- The proportion of partial responders from the pooled fezolinetant trials is lower than the proportion assumed at ACM2. In the company's previous model, it was assumed that 50% of non-responders (<75% reduction in VMS frequency) were partial responders in the fezolinetant arm. Using the updated trial-based estimates for partial responders (<75% and ≥50% reduction in VMS frequency) results in a reduction from 29.19% to 20.81% of partial responders in the fezolinetant arm and an increase from 0% to 18.49% in the NAT arm (as previously not modelled), while the change in the desvenlafaxine arm is a reduction from

31.27% to 20.81% (i.e. assumed the same as fezolinetant). This change lowers drug acquisition costs in the active treatment arms due to fewer people on treatment post-response assessment, while NAT acquisition costs remain unaffected. Thus, reducing the incremental difference in costs between fezolinetant and NAT, and fezolinetant and desvenlafaxine.

- The resource use costs for partial responders have been updated to match those of responders, whereas in the previous model costs of partial responders equated to those of non-responders. This change substantially reduces the total costs across all arms because the annual resource use cost for responders is £55, compared to £459.43 previously assigned to non-responders. Table 3 presents an exploratory analysis illustrating the impact of reverting these resource use costs back to non-responder levels, while using the company's refined model structure for partial responders and holding all other changes constant (i.e., using the updated trial-based response distributions, health state utility values and discontinuation rates). In this exploratory scenario, total costs across all treatment arms increase to levels closer to the EAG preferred base case at ACM2 (Table 2). Consequently, in the company's revised base case, total resource use costs have substantially decreased across all treatments. Fezolinetant has a greater reduction compared to NAT or desvenlafaxine, which is driven by the lower percentage of partial responders in the revised analyses.

The revised health state utility values result in lower total QALYs for all arms. The incremental difference is greater for fezolinetant than for NAT or desvenlafaxine, due to:

- A slightly larger difference in utility values for non-responders and partial responders between fezolinetant and NAT relative to the previous model.
- The updated distribution (percentage) of partial responders in the revised analyses.

Despite these shifts, the overall impact on incremental QALYs for fezolinetant against both comparators is minimal.

Table 3 Exploratory scenario demonstrating the impact on costs of reverting the resource use of partial responders from responder to non-responder levels

Name	Option	Costs	QALYs	Inc. Costs	Inc. QALYs	ICER, / QALY
Company's revised base case with partial responder resource use costs reverted back to non-responder levels	Fezolinetant	£2,322.46	6.920	-	-	-
	No Treatment	£1,675.89	6.860	£646.58	0.060	£10,788
	Desvenlafaxine	£1,560.10	6.888	£762.36	0.031	£24,246
	Weighted comparator, 41.5% NAT	£1,608.15	6.877	£714.31	0.043	£16,510
	Weighted comparator, 31.10% NAT	£1,596.11	6.880	£726.35	0.040	£18,022

Of the company's scenario analyses, the EAG considers Scenario 5 (Table 8 of the company's response document) to be the most relevant. In this scenario, resource use costs for partial responders are calculated as a weighted average of responder and non-responder costs. This differs from the company's revised base case, which equates them with responders, and the previous model, which equated them with non-responders (as shown in Table 3 above). The EAG considers it reasonable to assume that partial responders do not require the same high level of resource use as non-responders, but conversely, since their symptoms are not as well-controlled as those of responders, their resource use is likely to fall somewhere between these two groups. Therefore, the EAG considers the weighted average scenario as the most relevant, representing the EAG preferred base case post-ACM2 (Table 4).

Table 4 EAG preferred base case post-ACM2

Name	Option	Costs	QALYs	Inc. Costs	Inc. QALYs	ICER, / QALY
EAG preferred base case post-ACM2	Fezolinetant	£2,073.00	6.92	-	-	-
	No Treatment	£1,539.70	6.86	£533.30	0.060	£8,898
	Desvenlafaxine	£1,298.98	6.89	£774.02	0.031	£24,617
	Weighted comparator, 41.5% NAT	£1,398.88	6.88	£674.12	0.043	£15,581
	Weighted comparator, 31.10% NAT	£1,373.84	6.88	£699.16	0.040	£17,348