# Fezolinetant for treating vasomotor symptoms associated with the menopause

For projection – contains no confidential information

**Technology appraisal committee C [11 March 2025]**

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**Company:** Astellas Pharma Ltd

# Fezolinetant for treating vasomotor symptoms associated with the menopause (1)

- ✓ **Background and key issues**
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Other considerations
- ❑ Summary

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# Background on vasomotor symptoms associated with menopause

Menopause usually occurs between age 45 and 55 years, average 51 years. Can happen earlier: induced by surgery or medical treatment; an inherited condition; unknown cause

Overall symptoms described in updated NG23, include: urogenital symptoms, effects on mood, musculoskeletal symptoms, memory lapses, sleep disturbance, and vasomotor symptoms (VMS)

VMS include hot flushes and night sweats: feeling heat in the face and upper body, a red or flushed face, rapid heartbeat, sweating and chills as the VMS subsides, and anxiety

- may be mild and infrequent in the early stages of menopause transition (perimenopause)
- post-menopause, average 17 hot flushes and 11 night sweats per week
- on average VMS persist for 7.4 years including 3.4 years post-menopause: estimated 25% may need treatment for moderate/severe VMS
- Severity can be graded as mild to severe (see appendix).

# Equality considerations

Raised during scoping, in submissions and in the NICE clinical guideline 23

- **Sex:** Unmet need for treatment reflects historical lack of innovation in menopause and women's health. Variable provision of menopause services
- **Age:** Younger people affected by premature or induced menopause and abrupt onset VMS
- **Race and ethnicity:** VMS more prevalent and of longer duration, with greater VMS severity and sleep disturbances in Black and Hispanic people
  - Black African and Caribbean people may be less likely to choose HRT.
  - Some ethnic groups: experience menopause earlier; have higher hysterectomy rates; have different cultural values and views on menopause; may have less access to treatment for symptoms.
- **Disability/cancer:** Issue of treatment options for people with breast cancer but neither HRT nor fezolinetant is recommended for people with oestrogen dependent cancer.
- **Social determinants of health inequality:** Higher impact and prevalence of VMS noted to reflect type of work and educational level.
- **Transgender and non-binary people:** Access to appropriate care.



Abbreviations: HRT, hormone replacement therapy; VMS, vasomotor symptoms.

# Clinical and patient perspectives

Fezolinetant is a promising non-hormonal treatment for VMS.

**Submissions from British Menopause Society and clinical expert**

- VMS are the commonest symptoms of menopause in the UK; treatment aims to reduce VMS symptoms that can cause considerable distress and impair quality of life.
- Pathway is well defined; variation in part due to varying experiences of VMS (and other menopausal symptoms) in type, severity, duration and impact of symptoms. Other non-HRT treatments have limited efficacy
- A benefit of treatment would be reduction in number of VMS, number of night sweats and VMS severity.
- Fezolinetant is a promising new treatment for VMS; appears to be tolerable and no significant side effects.

"Non-hormonal alternatives are needed…Some are available [SSRI] but are associated with significant side effects, which means that continuation is low…Fezolinetant does not appear to be associated with significant side effects"

Abbreviations: MHRA, Medicines and Healthcare products Regulatory Agency; SSRI, selective serotonin reuptake inhibitor; VMS, vasomotor symptoms

# Technology (Veoza, Astellas Pharma Ltd)

| | |
|---|---|
| **Marketing authorisation** | • Moderate to severe vasomotor symptoms (VMS) associated with menopause. Granted December 2023 (MHRA) |
| **Mechanism of action** | • Oral neurokinin 3 receptor (NK3R) antagonist. Moderates activity of thermoregulatory centre of the brain to reduce the frequency and severity of vasomotor symptoms. |
| **Contraindications and monitoring** | Not recommended for people with liver disease or known or previous breast cancer or other oestrogen-dependent malignancies.<br>Further to the SmPC, MHRA and company have agreed that liver function tests prior to treatment are needed, monthly for the first 3 months and periodically thereafter based on clinical judgment. |
| **Administration** | Oral (45 mg daily) |
| **Price** | • £44.80 per 28 tablet pack<br>• £584.40 per person each year |

Abbreviations: SmPC summary of product characteristics.

# Key issues: Clinical effectiveness

| | Key issue | ICER impact | Slide |
|---|---|---|---|
| Comparators | • Are non-hormonal treatments relevant comparators? If so, which treatments are used in NHS? | Unknown | Slides 10-11 |
| Population who will have fezolinetant in NHS | • Is the trial population reflective of NHS practice?<br>• Who would have this treatment in clinical practice?<br>  • peri- and postmenopausal people?<br>  • people with mod-severe VMS of any frequency?<br>• How would the risk:benefit profile/ monitoring associated with fezolinetant affect people's choice of treatment? | Unknown | Slides 14-15<br>Slide 18-19 |
| Treatment effect | • What is impact of approach to missing data?<br>• Generalisability of trial data to NHS clinical practice | Unknown | Slide 16<br>Slides 14-15 |

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Abbreviations: ICER, incremental cost-effectiveness ratio

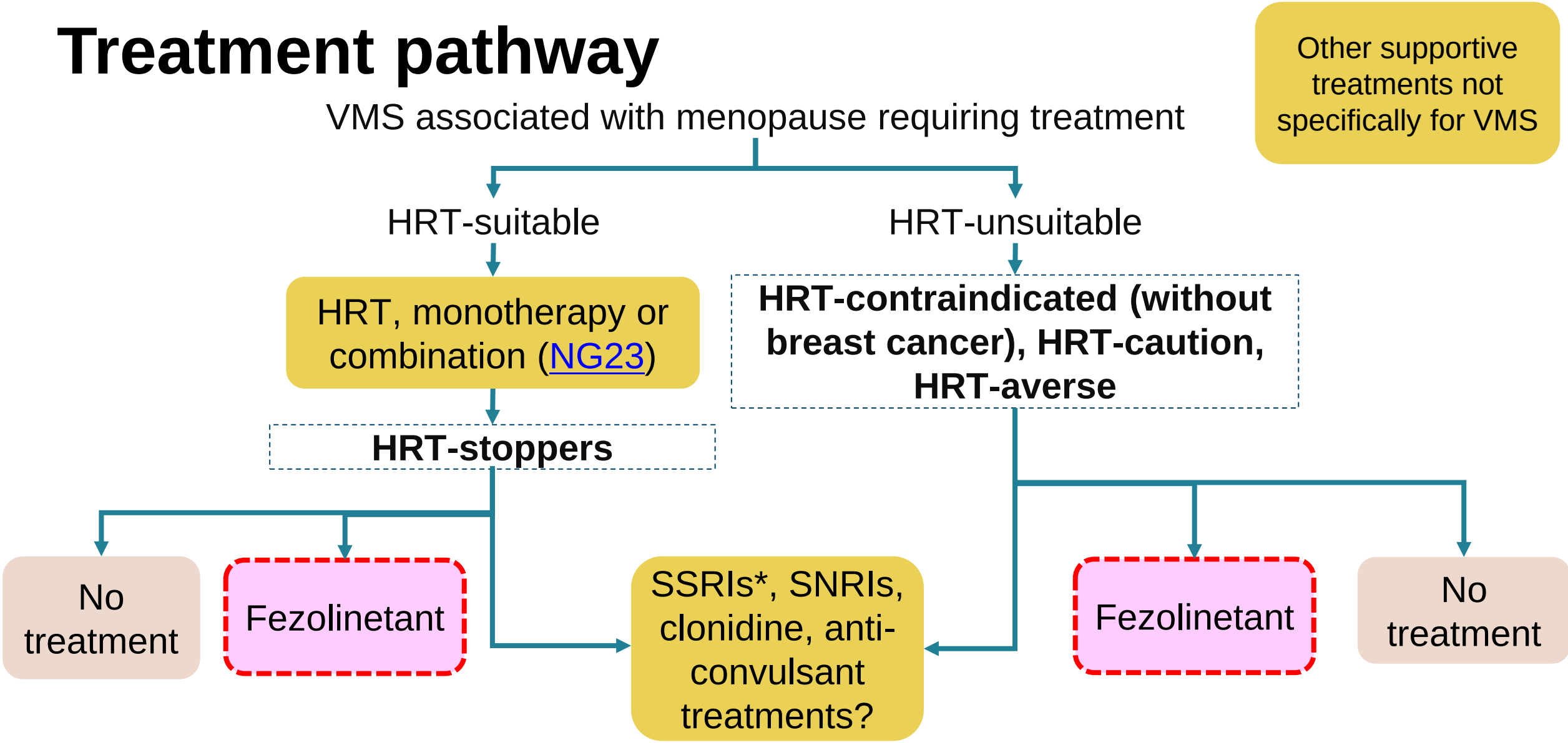
# Key issues: Cost effectiveness

| | Key issue | ICER impact | Slide |
|---|---|---|---|
| Model structure | • Is a model structure with health states based on frequency of daily VMS appropriate and are the cut-offs reasonable? | Unknown | Slides 23-24 |
| Baseline characteristics | • Is the baseline daily VMS frequency applicable to NHS population? | Large | Slide 25-26 |
| Natural history | • Are estimates of natural history plausible?<br>• Appropriate to use the 6-year estimate in model? | Large | Slide 27-28 |
| Modelled placebo effect | • Absolute rather than relative treatment effects applied in the model and limited placebo data applied in the model - is this appropriate? | Large (if extend placebo effect) | Slide 29 |
| Duration of VMS | • Should this be estimated from peri- or post menopause? | Small | Slide 30 |
| Utility values | • Is the adjustment of health state utility values based on clinical opinion appropriate? | Small | Slide 31 |



Abbreviations: ICER, incremental cost-effectiveness ratio, VMS, vasomotor symptoms

# Treatment pathway




* Recommended for those with breast cancer not taking tamoxifen (NG101)

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Abbreviations: HRT, hormone-replacement therapy; SNRI, serotonin and norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; VMS, vasomotor symptoms

# Key issues: Relevant comparators for fezolinetant (1/2)

## Background

- Company positioning: moderate to severe VMS where HRT is 'unsuitable' (HRT-contraindicated, HRT-cautioned, HRT-stopped, HRT-averse); narrower than scope and marketing authorisation.
- Comparators in final scope for people for whom HRT unsuitable: no pharmacological treatment, non-hormonal treatments (anti-depressants, clonidine, anti-convulsants) and nonpharmacological treatments (e.g. CBT).
- Company proposed comparators: no pharmacological treatment.

## Company

- NG23 states non-hormonal treatment should not be used; clinical experts suggest that current alternatives have suboptimal effectiveness and unpleasant side effects, so are not routinely prescribed in UK practice.
- At clarification: company provided an exploratory NMA comparing fezolinetant with paroxetine.

Appendix – decision problem

Abbreviations: HRT, hormone replacement therapy; NG, NICE guideline; NMA, network meta-analysis; VMS, vasomotor symptoms

# Key issues: Relevant comparators for fezolinetant (2/2)

**EAG comments:**

- Focussing on HRT 'unsuitable' is reasonable; excluding HRT as a comparator appropriate.
- Exclusion of non-pharmacological treatments also appropriate; EAG clinical advice agrees these are rarely prescribed in UK practice.
- Current non-hormonal treatments should be considered relevant comparators:
  - NG23 recommendations are based on first line due to superiority of HRT; does not say that non-hormonal treatments should not be prescribed when HRT is unsuitable.
  - alternative treatments are in a similar position to the proposed position for fezolinetant.
  - Clinical advice to EAG: non-hormonal pharmacological treatments are prescribed to 1 in 5 UK people with VMS.
- Company has not provided convincing evidence that other comparators are less effective, i.e. based on a full SLR/NMA; regardless, lower efficacy is not a suitable reason for exclusion. Model structure does not allow relative effects of comparators to be applied.

Are non-hormonal treatments a relevant comparator?
If so, which are used in the NHS?



Abbreviations: EAG, external assessment group; HRT, hormone replacement therapy; NG, NICE guideline; NMA, network meta-analysis; SLR, systematic literature review, VMS, vasomotor symptoms

# Fezolinetant for treating vasomotor symptoms associated with the menopause (2)

- ❑ Background and key issues
- ✓ **Clinical effectiveness**
- ❑ Modelling and cost effectiveness
- ❑ Other considerations
- ❑ Summary

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# Key clinical trials

* See appendix - How severity defined in trial

| | DAYLIGHT | SKYLIGHT 1/2 (identical designs) |
|---|---|---|
| **Population** | Menopausal people aged 40 to 65 years with moderate to severe VMS & deemed **unsuitable for HRT** | Menopausal people aged 40 to 65 years with moderate to severe VMS |
| **Key eligibility criteria** | Minimum average of 7 moderate to severe events of VMS/day in last 10 days prior to randomisation | Minimum average of 7 to 8 moderate to severe VMS/day, or 50 to 60/ week in last 10 days prior to randomisation |
| **Comparison** | Fezolinetant 45 mg vs placebo | Fezolinetant 45 mg or 30 mg vs placebo |
| **Duration** | 24 weeks | 12 weeks, plus a 40-week double-blind uncontrolled extension period |
| **Primary outcome** | Mean change in VMS frequency, from baseline to week 24 | Mean change in VMS frequency and severity from baseline to weeks 4 and 12 |
| **Used in model?** | Yes, including EQ-5D-5L | Data from HRT-unsuitable pre-specified subgroup who had 45mg dose of fezolinetant |

Abbreviations: EQ-5D-5L, European Quality of Life 5 Dimensions 5 Level Version; HRT, hormone replacement therapy; VMS, vasomotor symptoms

# Key issues: Applicability of the trial populations to NHS practice (1/2)

**Background**

- Key trials had narrower populations than would be expected in the NHS.
- Did not recruit people with: perimenopause, chronic diseases, elevated blood pressure, <7 VMS events a day at baseline.

**Company (at clarification)**

- Published literature supports that physiological mechanism underlying VMS is consistent from perimenopause to postmenopause; reasonable to expect similar safety and efficacy outcomes for fezolinetant in both groups.
- EMA/CHMP considered restriction but approved perimenopausal wording on this basis.

Abbreviations: CHMP, Committee for Medicinal Products for Human Use, EMA, European Medicines Agency, VMS, vasomotor symptoms

# Key issues: Applicability of the trial populations to NHS practice (2/2)

**EAG comments**

- Clinical advice:
  - assumption for perimenopause being consistent with post menopause reasonable.
  - proportion of people with hysterectomies in SKYLIGHT trials higher than would be seen in NHS; hysterectomies would cause early menopause and are associated with more severe VMS so may respond differently to treatment than wider population. In SKYLIGHT trials 32% of people had hysterectomy and 22% had ovariectomy. In DAYLIGHT 14% had a hysterectomy and 9% had ovariectomy
- Important to understand whether excluded subgroups will benefit from fezolinetant to the same extent as trial cohorts.
- Particularly concerned about exclusion of lower baseline VMS frequency; SKYLIGHT improvements in VMS frequency with fezolinetant appeared to be driven by the subgroup with 10 or more VMS events a day → Could be an important effect modifier.

Who would have fezolinetant in UK clinical practice?
Are the trial populations generalisable to the NHS?

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Abbreviations: EAG, external assessment group; VMS, vasomotor symptoms

# Key issues: Missing outcome data for continuous efficacy estimates

## Background

- SKYLIGHT 1/2: people who discontinued treatment were not followed-up further.
- DAYLIGHT: people who discontinued treatment continued to be followed-up.
- Company approach: missing trial data assumed to be missing at random (MAR); missing data was considered to be similar to the treatment group mean.

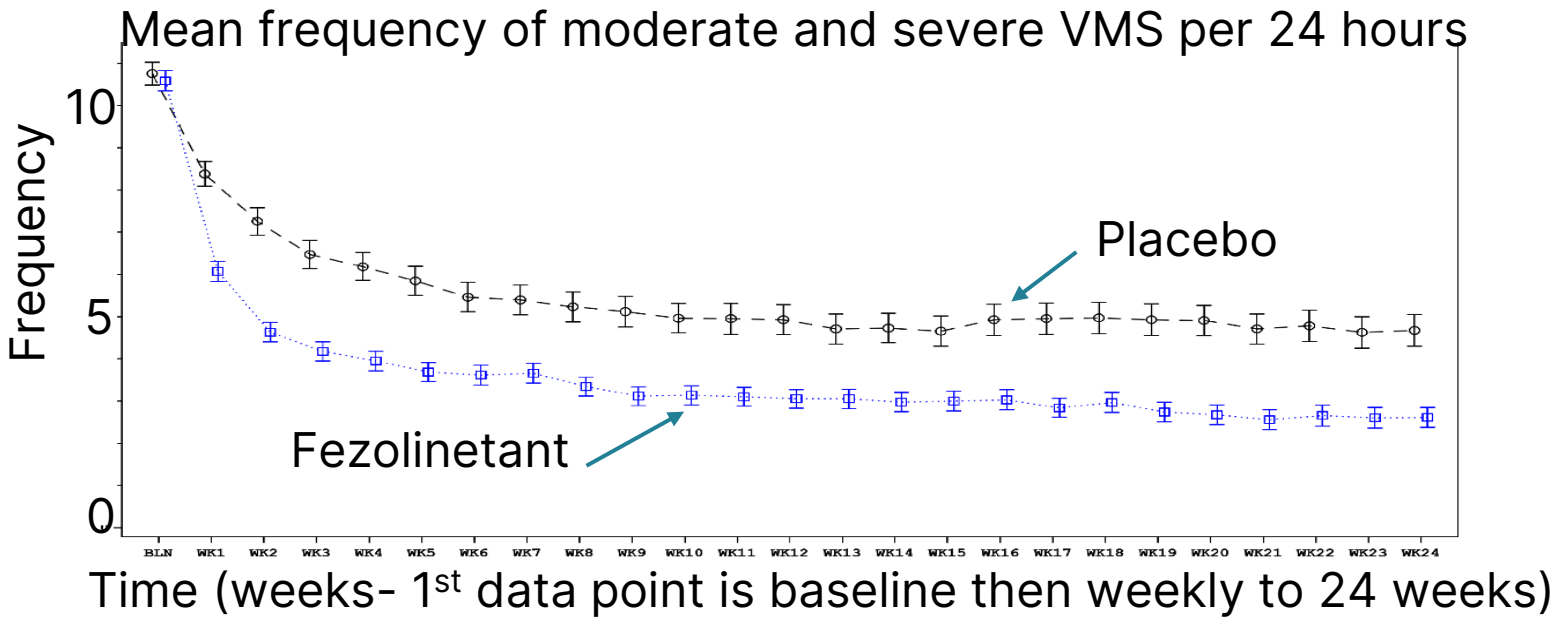
## EAG comments

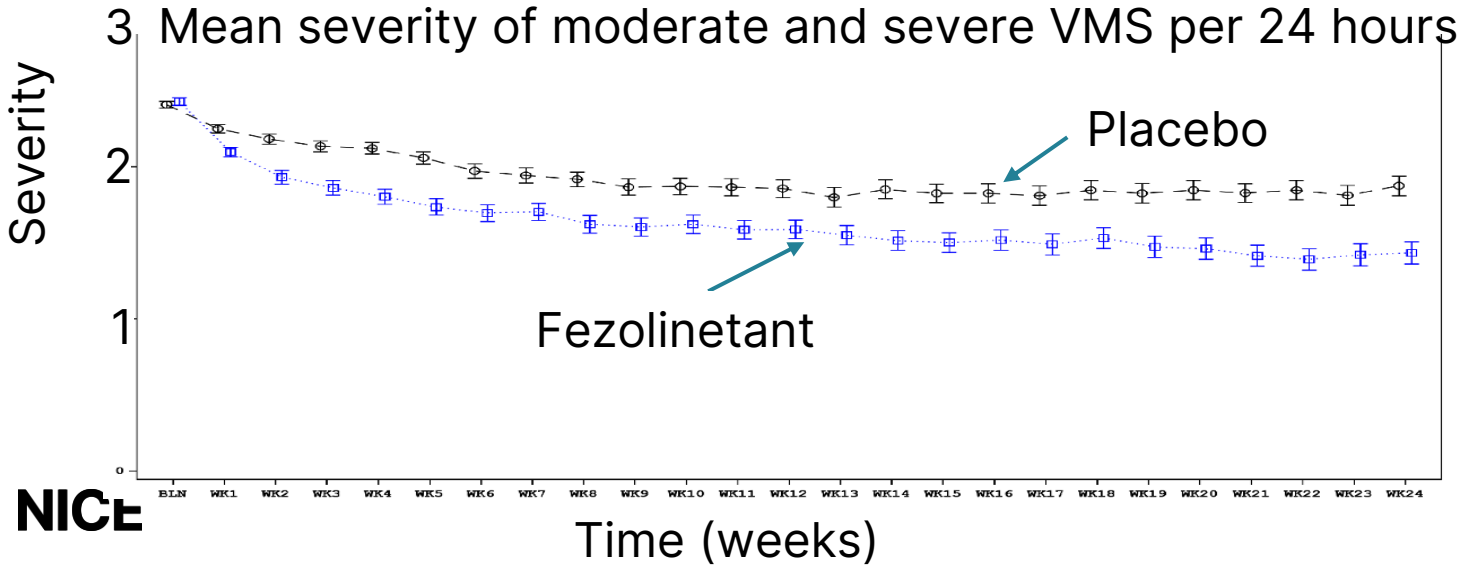
- Lack of follow-up for patients who discontinued in SKYLIGHT 1/2 concerning.
- Patients with missing data are likely to be missing due to discontinuation relating to treatment (e.g. loss of efficacy, adverse events).
- Concerns over reporting clarity for treatment discontinuation, e.g. number of patients who discontinued due to lack/loss of efficacy not reported
- MAR approach unsuitable, over-optimistic and subject to high risk of bias; does not consider that treatment effect likely to attenuate across missing cohort.
    - Would prefer to see alternative scenarios, e.g. baseline values carried forward.



Is the MAR approach appropriate to handle missing data from the key trials?

# Key clinical trial results- summary




- DAYLIGHT (data in graphs) and SKYLIGHT (pooled) showed a statistically significant reduction in VMS frequency and severity
- EAG presented responder analysis for ≥50%, ≥75%, and 100% reduction in VMS frequency showing higher proportion of responders with fezolinetant in each category→ not in model but less at risk of bias due to missing data assumptions than continuous data

See appendix for clinical trial results

# Key Issue: Fezolinetant's safety profile (1/2)

Appendix – safety and discontinuation outcomes

## Background

- Company: fezolinetant and placebo had comparable treatment-related AEs in key trials.
- EAG identified independent analyses of fezolinetant trial data (Douxfils 2023) suggesting significantly higher incidence of neoplasms in fezolinetant arm.
- FDA warning (Sept 2024): rare occurrence of serious liver injury with fezolinetant, based on post-marketing case. Since the company submission and EAG report, the MHRA and company have agreed additional liver function monitoring is required.

## Company (at clarification)

- FDA concluded 50% of malignancy events for fezolinetant were likely due to preexisting malignancy.
- Peto odds ratio method used by Douxfils (2023) not appropriate for rare events.
- NK3R antagonism mechanism for neoplasm development not supported by literature.
- Malignant neoplasms were only observed in SKYLIGHT 4; reanalysis of phase 2/3 studies suggests treatment-related effect of all neoplasm events unlikely.
- Provided cost of a hepatic laboratory test for people taking fezolinetant at in line with FDA recommendations.



Abbreviations: EAG, external assessment group; FDA, Food and Drug Administration; MHRA, Medicines and Healthcare products Regulatory Agency. AE, adverse event

# Key Issue: Fezolinetant's safety profile (2/2)

**EAG comments**

- Acknowledges uncertainty about any association between fezolinetant and neoplasms, but important to note as they are not covered by analyses in the company submission.
- Notes major limitation of Douxfils is combination of studies with different follow up, but EAG's analysis accounting for this supported higher risk.
- Including liver function tests in model has minimal impact on costs.
- Clinicians and patients may need to take these AEs into account when making treatment choices.

**Other considerations (BMS submission and clinical expert statement)**

- Fezolinetant appears to be tolerable and no significant side effects.
- Setting may be secondary care or GP with special interest because of liver function testing

Should liver function tests be included in the model? How will the safety profile of fezolinetant in relation to its benefits affect who chooses this treatment option? What setting will fezolinetant be prescribed in?



Abbreviations: AE, adverse event; BMS, British Menopause Society, EAG, external assessment group.

# **Indirect treatment comparison -** summary *See appendix for NMA detail

- At clarification company provided an ‘exploratory’ NMA and subsequent cost-effectiveness results for fezolinetant versus non-hormonal treatment comparators.

- 15 trials identified; 3 fezolinetant versus placebo and 2 paroxetine (a SSRI) versus placebo trials were included.

- Fezolinetant was more effective than paroxetine for change in moderate/severe VMS frequency.

**EAG comments**

- Additional published NMA (Morga 2023, company sponsored), with searches conducted June 2021 (before DAYLIGHT); showed little evidence to suggest fezolinetant had a clinically meaningful benefit over SSRIs, SNRIs and gabapentin on reducing severe VMS frequency
  - but the NMA had several limitations (primarily high risk of bias from missing data).
- Results from NMA can’t be incorporated into model as does not allow for relative effects.

Abbreviations: NMA, network meta-analysis, SNRI, serotonin and norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; VMS, vasomotor symptoms.

# Fezolinetant for treating vasomotor symptoms associated with the menopause (3)

- ❑ Background and key issues
- ❑ Clinical effectiveness
- ✓ **Modelling and cost effectiveness**
- ❑ Other considerations
- ❑ Summary

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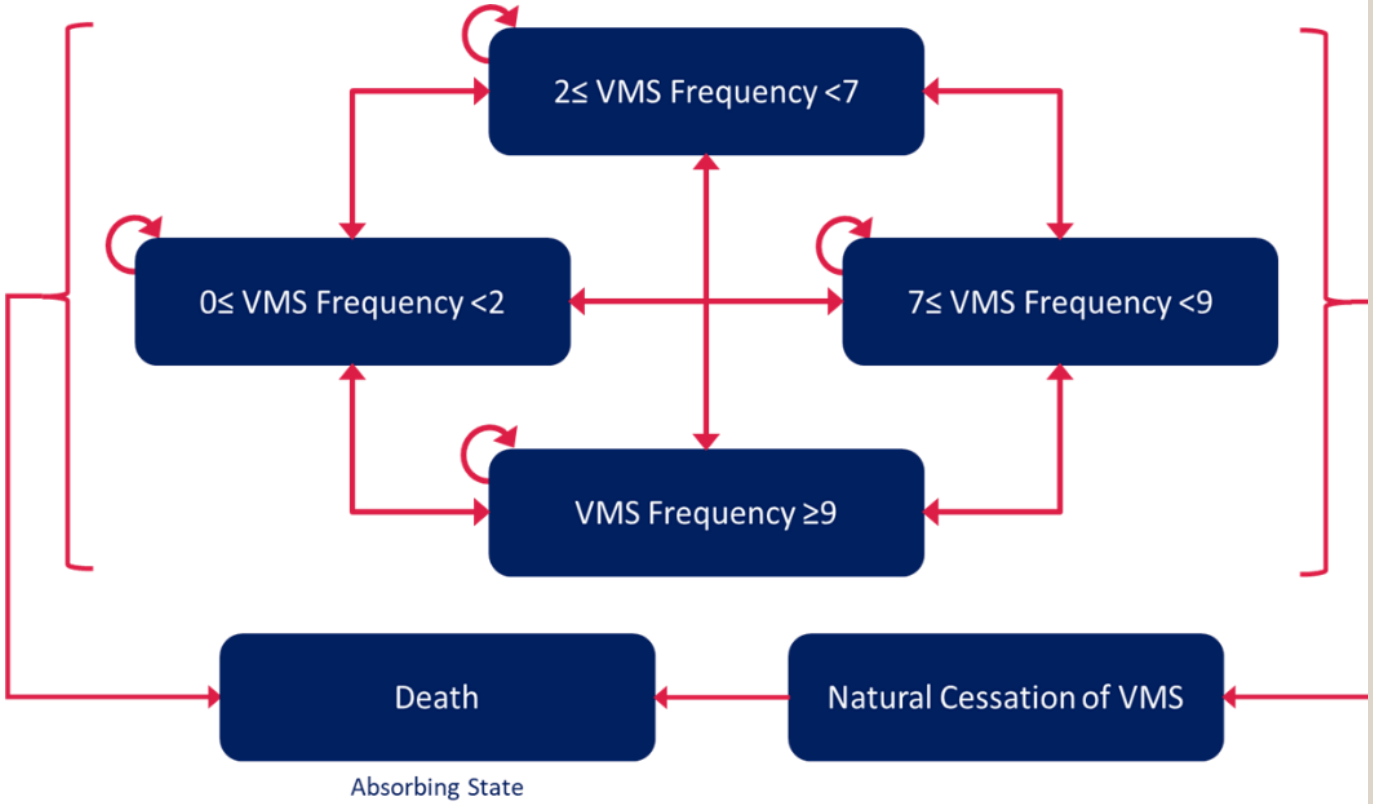
# Company's model overview

Model compares fezolinetant with no active treatment. Health states defined by daily VMS frequency. Accounts for natural cessation of VMS. 10-year time horizon, 4-week cycle length




- All people have VMS ≥ 7 at start
- Modelled cohort average age 51 and post menopausal
- Transition probabilities
  - fezolinetant based on DAYLIGHT to week 24 then pooled SKYLIGHT to week 52, then extrapolation of SKYLIGHT data (while on treatment)
  - no active treatment based on placebo arm in DAYLIGHT (to week 12) then assumed off treatment → natural history
  - Natural history of VMS based on a structured expert elicitation exercise using a hypothetical cohort

Appendix - Summary of how fezolinetant affects costs and QALYs

Abbreviations: VMS, vasomotor symptoms.

# Key Issue: Use of moderate to severe VMS frequency to define model health states.

## Background

- VMS frequency was used to define four VMS health states.
- Company justification: frequency more objective than severity (clinical/patient expert opinion); frequency was a primary endpoint in the key trials
- Correlation analysis at clarification: pooled results from SKYLIGHT 1/2 between [redacted] and [redacted] suggest correlation between frequency and severity .

## EAG comments

- Structure based solely on frequency does not capture impact on severity; clinical advice concerned about using frequency as a proxy for severity (not usual in NHS practice).
- Severity was a primary endpoint in SKYLIGHT 1/2; key secondary outcome in DAYLIGHT.
- Alternative model structure that incorporates severity would more accurately represent the decision problem.
- Notes that treatment discontinuation is independent of VMS frequency health states
- EAG considers the correlation results indicative of moderate to weak correlation.

Is change in frequency of moderate to severe VMS sufficient to capture the impact of change in VMS severity?



Abbreviations: EAG, external assessment group; PSA, probabilistic sensitivity analysis; VMS, vasomotor symptoms.

# Key Issue: Arbitrary cut-off thresholds used to define VMS frequency health states in the model

## Background

- VMS frequency threshold of 7 a day (based on DAYLIGHT eligibility criteria).
- Other cut-offs were based on a statistical analysis of the distribution of average daily VMS frequency in DAYLIGHT and utility values associated with categories of VMS frequency using GEE models (always using 7 as baseline cut-off).
- Cut-offs were chosen if there was a statistically significant difference in utility values between categories; categories validated by clinical experts.

## EAG comments

- Only slight differences observed in utilities for groups 7 to 9 and 2 to 7 VMS events, and CIs overlap substantially.
- Utility values for 7 to 8 and 8 to 9 are higher than utility values between 6 and 7.
- Other GEE models appear to have more favourable p-values, but not enough information for EAG to provide a more detailed assessment.
- Concern over use of utility values to define health states; EQ-5D likely to capture QoL based on other menopause symptoms as well as VMS.

What are the appropriate cut-offs for VMS frequency health states?

Abbreviations: CI, confidence intervals; EAG, external assessment group; EQ-5D, European Quality of Life 5 Dimensions; GEE, generalised estimating equation; QoL, quality of life; VMS, vasomotor symptoms.

# Key Issue: Baseline distribution of moderate to severe VMS frequency

**Background**

- Baseline characteristics in the model based on DAYLIGHT at randomisation: people had minimum of 7 moderate to severe VMS events per day (42% 7 to <9, 58% 9 or more)

**EAG comments**

- Characteristics are narrower than the licensed indication which does not refer to frequency; a minimum of 7 VMS events at baseline inappropriate to represent population who would be likely have fezolinetant in the NHS.
- Baseline distribution in the absence of treatment should be based on elicited values for natural history (see next slide); significant reduction in VMS frequency after 1 year would not be expected.

Is the baseline distribution reflective of people who would receive fezolinetant in NHS practice?



Abbreviations: EAG, external assessment group; VMS, vasomotor symptoms.

# Baseline distribution of moderate to severe VMS frequency

Baseline distribution estimates from DAYLIGHT in the absence of treatment and Year 1 estimates elicited for natural history in the absence of treatment

| Source of estimates | 0 ≤ VMS-F < 2 | 2 ≤ VMS-F < 7 | 7 ≤ VMS-F < 9 | VMS-F ≥ 9 |
|---|---|---|---|---|
| Baseline distribution from DAYLIGHT | 0.00% | 0.22% | 41.81% | 57.96% |
| Year 1 SEE natural history estimates | 16.91% | 47.13% | 17.16% | 18.80% |
| Year 1 clinician-adjusted natural history estimates* | <10% | 30% | 40% | >20% |

*See Appendix for Year 3 and 6 SEE estimates

Abbreviations: SEE, structured expert elicitation; VMS, vasomotor symptoms.

# Key Issue: Uncertainty in the natural history of VMS in the model (1/2)

**Background**

- When people move off treatment, they follow the natural history of moderate-to-severe VMS until cessation, death, or end of model horizon.
- Company did not identify published evidence on natural history.
- Natural history estimated using structured expert elicitation (SEE) with 6 clinical experts;
  - asked to estimate proportion of 1,000 post-menopausal women experiencing different VMS daily frequencies over time (after 1, 3, 6 years), who were not receiving VMS treatment.
- Company notes high uncertainty in the estimates, due to counterfactual nature, and rapid (unrealistic) decline in frequency when applied to DAYLIGHT baseline.
- Proportions further adjusted using additional expert opinion; company used only the 6-year data and assumed linear changes between years 0 to 6 in modelling.

*See Appendix for Year 3 and 6 SEE estimates



Abbreviations: VMS, vasomotor symptoms.

# Key Issue: Uncertainty in the natural history of VMS in the model (2/2)

**EAG comments**

- Natural history in the model is based on postmenopausal people only.
- Company's SLR unlikely to be sufficient to identify natural history studies.
  - Requested specific SLR for natural history at clarification; company said this would be unlikely to resolve uncertainty around SEE estimates.
- Elicitation was not anchored on the baseline distribution of frequency used in the model or DAYLIGHT trial; so baseline distribution and natural history estimates not compatible.
- Approach to only apply year 6 SEE results inappropriate as it suggests either SEE is unreliable or DAYLIGHT not representative of UK practice.
  - SEE suggests more people have less than 7 daily VMS than in model. 1 year SEE estimates should reflect baseline distribution in model
- EAG scenarios show cost-effectiveness results are sensitive to natural history assumptions

How should natural history of moderate to severe VMS be estimated in the model?



Abbreviations: EAG, external assessment group; SEE, structured expert elicitation; SLR, systematic literature review; VMS, vasomotor symptoms.

# Key Issue: Treatment effects used in the model

**Background**

- Company apply absolute changes to frequency from baseline in each arm rather than relative treatment effects
- Fezolinetant arm is informed by trial data whilst on treatment but no active treatment arm is informed by 12 weeks of placebo data, then natural history estimates

**EAG comments**

- Absolute changes not adjusted for the placebo effect from week 12 onwards; placebo effect is lost from week 12 in the 'no active treatment' arm, while absolute changes (including placebo effect) continue in the fezolinetant arm.
- Approach means no active treatment arm sees an abrupt shift in proportion of people in the lower frequency health states to the high frequency health states at week 12 (see Appendix).
- Estimates based on relative treatment effect and applied to natural history would be more appropriate; in absence, placebo effect should be extrapolated for longer .
- EAG scenario extending placebo effect worsens cost effectiveness of fezolinetant.



Abbreviations: EAG, external assessment group; VMS, vasomotor symptoms.

# Key issue Other characteristics of modelled population and impact on modelled VMS duration

## Background

- People in the modelled cohort (based on DAYLIGHT) and SEE study were postmenopausal. Perimenopausal people may also be eligible for fezolinetant within its MA
- Starting age based on average age of menopause onset in the UK (51 years).
- Median duration of VMS 7.4 years is based on a US cohort study of peri- and post-menopausal people (SWAN study).

## EAG comments

- Starting age reasonable, but mismatched with DAYLIGHT cohort (average age 54.5) who are likely to have had VMS for longer.
- Company assumptions of 7.4 year symptom duration → 40% still experiencing moderate-to-severe VMS at end of 10- year model time horizon.
- Postmenopausal subgroup from the US cohort study had VMS duration of 3.4 years; used in EAG base case as more reflective of the modelled cohort, who were post-menopausal. Using EAG preferred assumption → 12% people having VMS at end of  model time horizon

Should modelled duration of VMS be starting from perimenopause or menopause?

Abbreviations: EAG, external assessment group; VMS, vasomotor symptoms.

# Key Issue: Modelled health state utility values are highly uncertain

**Background**

- Utility values based on EQ-5D-5L data mapped to 3L from DAYLIGHT were used to define VMS frequency health states and utility values for each state using GEE models
- Further adjustments were made to decrease utility values in 0-2, 7-9 and >9 health states based on clinical opinion

**EAG comments**

- Company provide limited detail on how the final GEE model to estimate QoL was selected; difficult to assess the appropriateness of the final model.
- Utility values from DAYLIGHT trial are higher in the placebo arm than fezolinetant arm; inverse is observed in SKYLIGHT trials (close to age-adjusted values for general population).
- Adjustment of utility values based on input of only 1 clinical expert highly uncertain.
- EAG scenarios explore different utility values; increases cost-effectiveness results.



Abbreviations: 3L, 3 levels; EAG, external assessment group; EQ-5D, European Quality of Life 5 Dimensions 5 levels; GEE, generalised estimating equation; QoL, quality of life; VMS, vasomotor symptoms.

Abbreviations: HRT, hormone replacement therapy; VMS, vasomotor symptoms.

# Utility values

Additional adjustments were made to health state utility values in company base case. EAG preferred to use unadjusted pooled data from DAYLIGHT and SKYLIGHT trials.

| Health state | Company base case: UK clinician adjusted DAYLIGHT data | DAYLIGHT (scenario) | EAG restricted base case: Pooled DAYLIGHT & SKYLIGHT 1 & 2 (HRT-unsuitable) | Pooled SKYLIGHT 1 & 2 (HRT-unsuitable; scenario) |
|---|---|---|---|---|
| Cessation of VMS | 0.843 | 0.843 | 0.852 | [redacted] |
| 0 ≤ VMS Frequency < 2 | 0.810* | 0.833 | 0.841 | [redacted] |
| 2 ≤ VMS Frequency < 7 | 0.793 | 0.793 | 0.810 | [redacted] |
| 7 ≤ VMS Frequency < 9 | 0.746† | 0.785 | 0.793 | [redacted] |
| VMS Frequency ≥ 9 | 0.710† | 0.747 | 0.773 | [redacted] |

Utility values for VMS cessation of VMS were calculated from the average EQ-5D-5L data of participants who reported a VMS frequency of 0 during any visit, including at baseline
*decreased based on one clinical opinion, †decreased by 5% based on clinical opinion

# Summary of company and EAG base case assumptions

**EAG presents a restricted base case because unable to address key uncertainties in company base case, including:**

- health states based on frequency
- uncertainty around natural history estimates
- modelled cohort characteristics not reflecting who could have fezolinetant in clinical practice and relative treatment effect not being modelled.

Assumptions in company and EAG base case

| Assumption | Company base case | EAG 'restricted' base case |
|---|---|---|
| **placebo effect from DAYLIGHT** | To week 12 | To week 24 |
| **Average duration of VMS** | 7.4 years<br>(includes perimenopause) | 3.4 years<br>(post menopause only) |
| **Source of health state utility values** | DAYLIGHT<br>With further adjustments based on clinical opinion | Combined DAYLIGHT and SKYLIGHT 1&2 (HRT-unsuitable) |

Abbreviations: EAG, external assessment group; HRT, hormone replacement therapy.

# Base case results

| Scenario # | Name | Inc. Costs | Inc. QALYs | ICER, costs/QALY |
|---|---|---|---|---|
| | Company's probabilistic base case results | £1,194.98 | 0.116 | £10,355 |
| | Company's deterministic base case results | £1,199.49 | 0.116 | £10,364.17 |
| **2a** | Increase the placebo effect from week 12 to week 24 | £1,241.87 | 0.107 | £11,621.78 |
| **2a+4a** | Median duration of VMS of 3.4 years | £915.25 | 0.087 | £10,496.77 |
| **2a+4a+5b (EAG restricted* base case)** | Utility values based on pooled DAYLIGHT and SKYLIGHT 1 & 2 (HRT-unsuitable) data (UK) | £915.25 | 0.056 | £16,470.01 |

* EAG unable to address key structural uncertainties in company base case

Abbreviations: EAG, external assessment group; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; HRT, hormone replacement therapy; VMS, vasomotor symptoms.

# EAG deterministic scenario analysis – ICERs over £20,000 (1/2)

**EAG** scenario analyses (deterministic)

| Scenario # | | Name | Inc. Costs | Inc. QALYs | ICER, costs/QALY |
|---|---|---|---|---|---|
| | | Company's base-case results | £1,199.49 | 0.116 | £10,364.17 |
| **Baseline distribution** | 1a | Use Year 1 SEE estimate for baseline distribution | £1,545.00 | 0.045 | £34,308.17 |
| | 1b | Use Year 1 Clinician natural history distribution estimates for baseline distribution | £1,458.71 | 0.064 | £22,641.88 |

Appendix – all EAG scenarios

Abbreviations: EAG, external assessment group; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; HRT, hormone replacement therapy; NMA, network meta-analysis; SEE, structured expert elicitation; VMS, vasomotor symptoms.

# EAG deterministic scenario analysis – ICERs over £20,000 (2/2)

**EAG** scenario analyses (deterministic)

| Scenario # | | Name | Inc. Costs | Inc. QALYs | ICER, costs/QALY |
|---|---|---|---|---|---|
| | | Company's base-case results | £1,199.49 | 0.116 | £10,364.17 |
| **Placebo effect** | 2d | Placebo effect over modelled time horizon, probability of discontinuation of 4.17% per 4-week (per company's base case) | £1,481.50 | 0.054 | £27,191.69 |
| **Natural history study** | 3a | Use Year 1, 3 and 6 SEE estimates for natural history | £1,488.30 | 0.057 | £26,171.46 |

Abbreviations: EAG, external assessment group; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; SEE, structured expert elicitation; VMS, vasomotor symptoms.

# Fezolinetant for treating vasomotor symptoms associated with the menopause (4)

- ❑ Background and key issues
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ✓ **Other considerations**
- ❑ Summary

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# Other considerations

**Severity modifier**

- Not applied.

**Uncaptured benefits**

- No uncaptured benefits raised by stakeholders

**Managed access**

- Not applied – company anticipates routine commissioning.

- Are there any uncaptured benefits?
- how should the equality issues detailed inform the appraisal and are there any other equality issues not already considered?
- What are the uncertainties, and can they be resolved with further data collection?

# Fezolinetant for treating vasomotor symptoms associated with the menopause (5)

- ❑ Background and key issues
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Other considerations
- ✓ **Summary**

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# Key issues revisited: Clinical effectiveness

| | Key issue | ICER impact | Slide |
|---|---|---|---|
| Comparators | • Are non-hormonal treatments a relevant comparator? If so, which treatments are used in NHS? | Unknown | Slides 10-11 |
| Population who will have fezolinetant in NHS | • Is the trial population reflective of NHS practice?<br>• Who would have this treatment in clinical practice?<br>  • peri- and postmenopausal people?<br>  • people with mod-severe VMS of any frequency?<br>• How would the risk to benefit profile/ monitoring associated with fezolinetant affect people's choice of treatment? | Unknown | Slides 14-15<br>Slide 18-19 |
| Treatment effect | • What is impact of missing data approach?<br>• Generalisability of trial data to NHS clinical practice | Unknown | Slide 16<br>Slides 14-15 |

Abbreviations: ICER, incremental cost-effectiveness ratio

# Key issues revisited: Cost effectiveness

| | Key issue | ICER impact | Slide |
|---|---|---|---|
| Model structure | • Is a model structure with health states based on frequency of daily VMS appropriate and are the cut-offs reasonable? | Unknown | Slides 23-24 |
| Baseline characteristics | • Is the baseline daily VMS frequency applicable to NHS population? | Large | Slide 25-26 |
| Natural history | • Are estimates of natural history plausible?<br>• Appropriate to use the 6-year estimate in model? | Large | Slide 27-28 |
| Modelled placebo effect | • Absolute rather than relative treatment effects applied in the model and limited placebo data applied in the model - is this appropriate? | Large (if extend placebo effect) | Slide 29 |
| Duration of VMS | • Should this be estimated from peri- or post menopause? | Small | Slide 30 |
| Utility values | • Is the adjustment of health state utility values based on clinical opinion appropriate? | Small | Slide 31 |



Abbreviations: ICER, incremental cost-effectiveness ratio, VMS, vasomotor symptoms

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

# Supplementary appendix

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# Background on menopause – VMS severity

Return to background
Return to clinical trials

## Definitions of VMS severity (EMA)

| Severity of VMS | Definition |
|---|---|
| Mild | A sensation of heat, without sweating |
| Moderate | A sensation of heat with sweating. You are able to continue with normal activities. |
| Severe | A sensation of heat with sweating. You are not able to continue with normal activities, due to the severity of your symptoms |

## Company approach for calculating severity (combining severity and frequency):

$$\frac{([\text{number of mild VMS/day} \times 1] + [\text{number of moderate VMS/day} \times 2] + [\text{number of severe VMS/day} \times 3])}{\text{Total number of daily (or weekly) mild/moderate/severe VMS}}$$

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**EAG comments**

- Implies an ordering and differential impact across mild/moderate/severe; not validated and may be misleading.

Abbreviations: EAG, Evidence Assessment Group; EMA, European Medicines Agency; VMS, vasomotor symptoms.

# Decision problem (1/2)

| | NICE final scope | Company submission | Company rationale (if different from scope) |
|---|---|---|---|
| Population | People with moderate to severe VMS associated with the menopause. | Menopausal people with moderate to severe vasomotor-predominant symptoms for whom HRT is deemed unsuitable for medical reasons:<br>• HRT-contraindicated<br>• HRT-caution<br>• HRT-stoppers<br>• HRT-averse (corrected at clarification) | Clinical advice to company indicated that HRT would remain treatment of choice, and the fezolinetant would be used where HRT is unsuitable. |
| Intervention | Fezolinetant | No change | NA |

Abbreviations: HRT, hormone replacement therapy; NA, not applicable; VMS, vasomotor symptoms.

# Decision problem (2/3)

| | NICE final scope | Company submission | Company rationale (if different from scope) |
|---|---|---|---|
| Comparator(s) | People for whom HRT is considered suitable:<br>• Hormonal pharmaceutical treatments (such as oestrogen and progestogen combination, or oestrogen alone)<br><br>People for whom HRT is not considered suitable:<br>• No pharmacological treatment<br>• Non-hormonal pharmacological treatments, for example:<br>  • Anti-depressants, such as SSRIs and SNRIs<br>  • Clonidine<br>  • Anti-convulsants, such as gabapentin and pregabalin<br>• Non-pharmacological treatments such as CBT | Menopausal people for whom HRT is not deemed suitable for medical reasons:<br>• No pharmacological treatment | NG23 states “do not routinely offer SSRIs, SNRIs or clonidine as first-line treatment for VMS alone”<br><br>Clinical expert advice:<br>• limited efficacy and unpleasant side effects of current non-hormonal treatments; company suggests would be used at later lines than fezolinetant<br>• CBT and other psychological therapies are not used in clinical practice (also noted in NICE scoping workshop). |

Abbreviations: CBT, cognitive behavioural therapy; HRT, hormone replacement therapy; SNRI, serotonin and norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; VMS, vasomotor symptoms.

# Decision problem (3/3)

| | NICE final scope | Company submission | Company rationale (if different from scope) |
|---|---|---|---|
| Outcomes | The outcome measures to be considered include:<br>• Frequency of VMS<br>• Severity of VMS<br>• Sleep disturbance<br>• Psychological symptoms (anxiety, low mood)<br>• Adverse effects of treatment<br>• Health-related quality of life | No change. | NA |

NICE

Abbreviations: NA, not applicable; VMS, vasomotor symptoms.

# NG23 Menopause: identification and management

## 1.5 Managing symptoms associated with menopause in people aged 40 or over

### Vasomotor symptoms

1.5.1. Offer HRT to people with vasomotor symptoms associated with menopause. **[2015]**

1.5.2. Consider menopause-specific cognitive behavioural therapy (CBT) as an option for vasomotor symptoms associated with menopause:

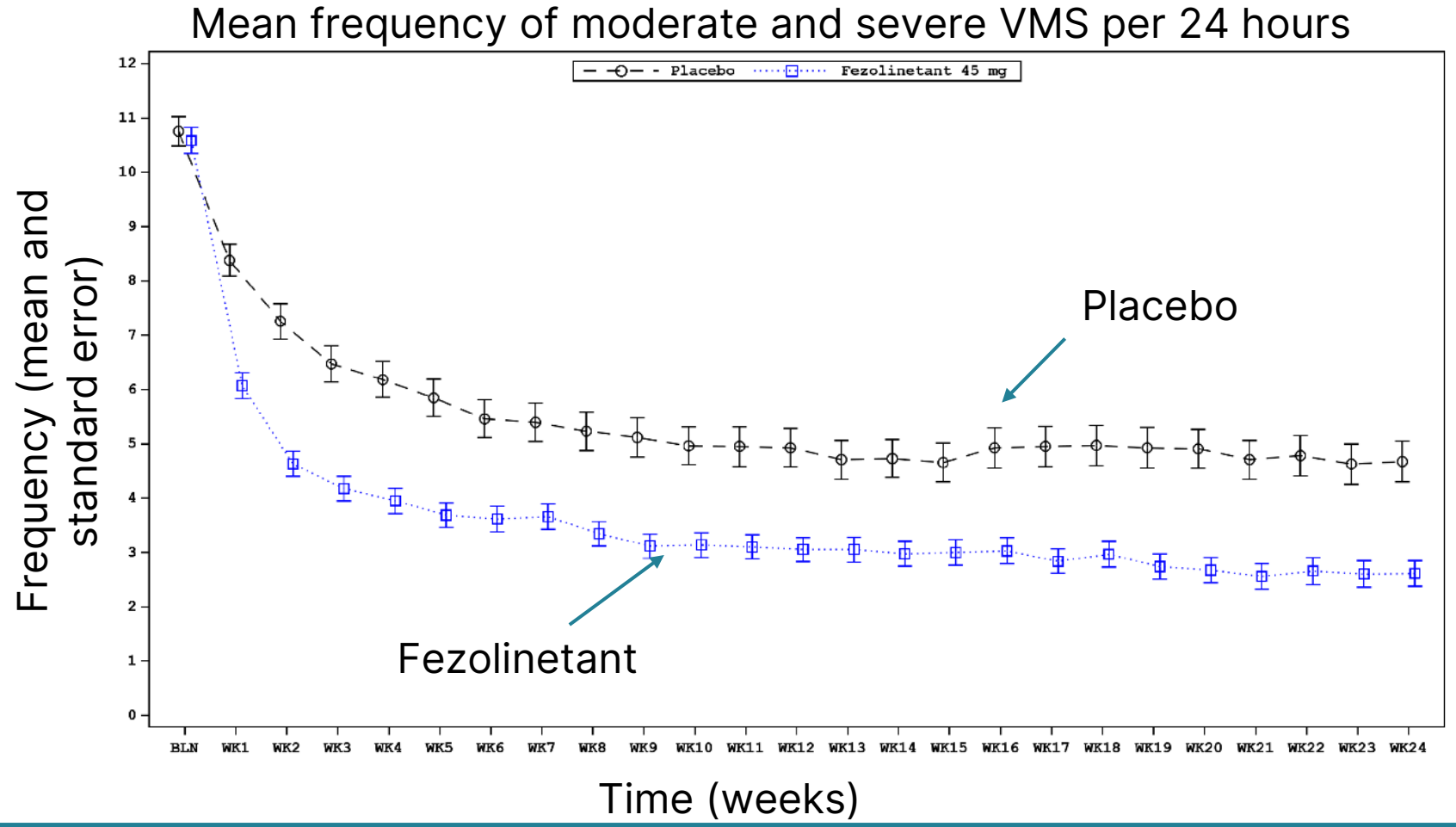
in addition to HRT **or**
for people for whom HRT is contraindicated **or**
for those who prefer not to take HRT. **[2024]**

1.5.3. Do not routinely offer selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs) or clonidine as first-line treatment for vasomotor symptoms alone. **[2015]**

NICE

Abbreviations: HRT, hormone replacement therapy; NG, NICE guideline; VMS, vasomotor symptoms.

# Key clinical trial results (DAYLIGHT) – VMS frequency



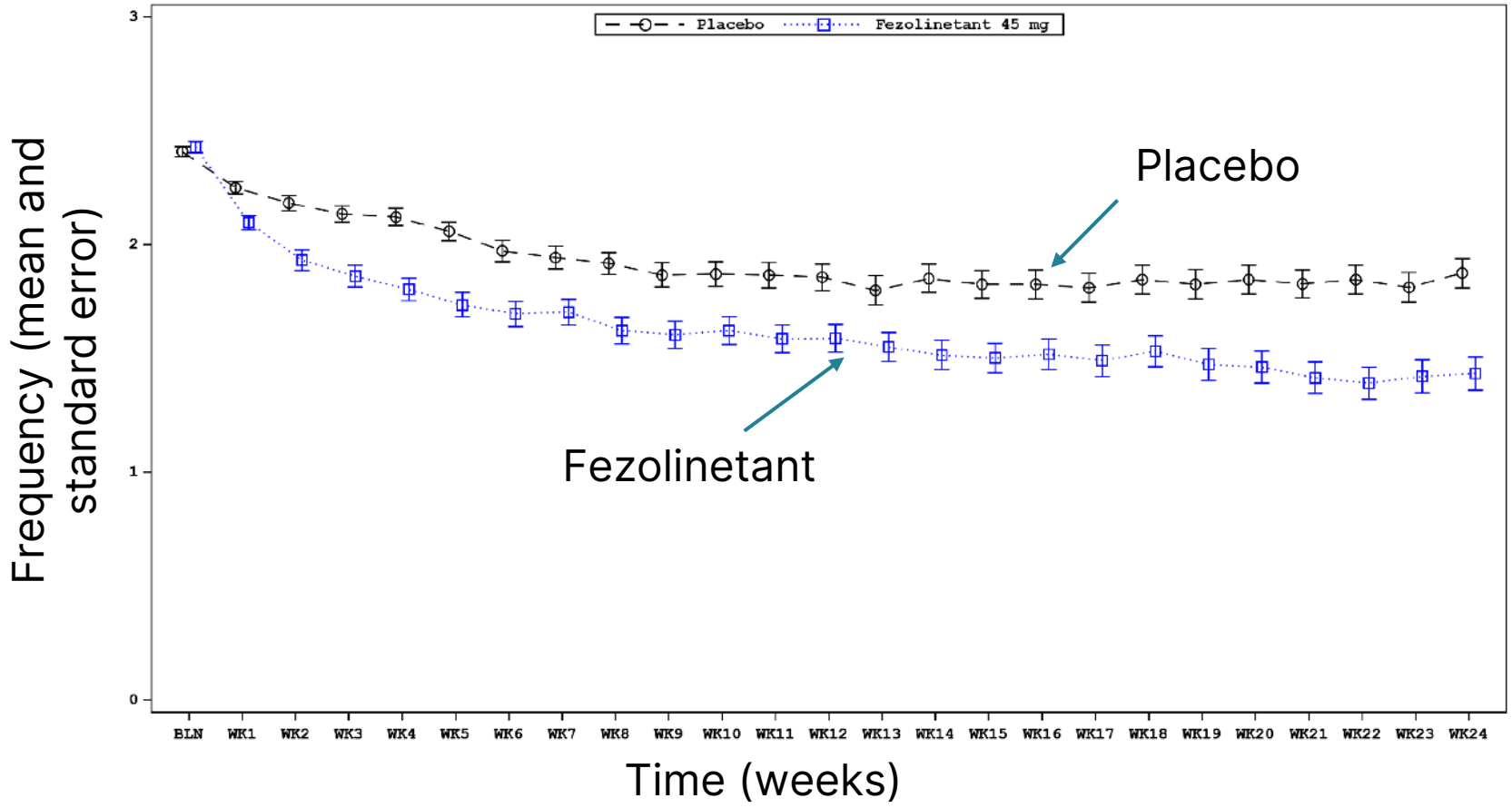

| Difference in LS Means: fezolinetant versus placebo | |
|---|---|
| LS mean (SE) | −1.93 (0.36) |
| p value | <0.001 |

Return to clinical effectiveness section

Abbreviations: LS, least squares; SE, standard error; VMS, vasomotor symptoms.

# Key clinical trial results (DAYLIGHT) – VMS severity

Mean severity of moderate and severe VMS per 24 hours




| Difference in LS Means: fezolinetant versus placebo | |
|---|---|
| LS mean (SE) | −0.39 (0.09) |
| p value | <0.001 |

Return to clinical effectiveness section

Abbreviations: LS, least squares; SE, standard error; VMS, vasomotor symptoms.

# Key clinical trials – VMS frequency (responder analyses)

| Trial | Responders with ≥ 50% Reduction | | Responders with ≥ 75% Reduction | | Responders with 100% Reduction | |
|---|---|---|---|---|---|---|
| | Fez 45mg | Placebo | Fez 45mg | Placebo | Fez 45mg | Placebo |
| DAYLIGHT Week 24 | [redacted] | | [redacted] | | [redacted] | |
| OR (95% CI) | [redacted] | | [redacted] | | [redacted] | |
| DAYLIGHT Week 12 | [redacted] | | [redacted] | | [redacted] | |
| OR (95% CI) | [redacted] | | [redacted] | | [redacted] | |
| SKYLIGHT 1 Week 12 | [redacted] | | 35%* | 13%* | [redacted] | |
| OR (95% CI) | 3.16 (2.04 to 4.94) | | NR | | 3.26 (1.33 to 9.19) | |
| SKYLIGHT 2 Week 12 | [redacted] | | [redacted] | | [redacted] | |
| OR (95% CI) | [redacted] | | [redacted] | | [redacted] | |

*from Morga 2023 NMA

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Abbreviations: CI, confidence intervals; OR, odds ratio; NR, not reported VMS, vasomotor symptoms.

# Key clinical trials – VMS outcomes using different estimand approaches and missing data assumptions

Trial results for VMS outcomes using different estimand approaches and missing data assumptions for discontinuations

| Trial, estimand and missing data assumptions | Difference in LS means: fezolinetant versus placebo | |
|---|---|---|
| | Frequency (SE) | Severity (SE) |
| DAYLIGHT, Week 24 | | |
| Treatment policy, MAR | -1.93 (0.36) | -0.39 (0.09) |
| Treatment policy, Discontinuation-reason based MI & MAR | -1.88 (0.35) | Not analysed |
| Hypothetical policy, MAR | -2.14 (0.36) | -0.43 (0.09) |
| SKYLIGHT 1, Week 12 | | |
| Hypothetical policy, MAR | -2.55 (0.43) | -0.20 (0.08) |
| Hypothetical policy, Discontinuation-reason based MI & MAR | -2.49 (0.44) | -0.20 (0.08) |
| SKYLIGHT 2, Week 12 | | |
| Hypothetical policy, MAR | -2.53 (0.55) | -0.29 (0.08) |
| Hypothetical policy, Discontinuation-reason based MI & MAR | -2.48 (0.55) | -0.28 (0.08) |

Abbreviations: MAR, missing at random; MI, multiple imputations; SE, standard error; VMS, vasomotor symptoms

# Key clinical trials – adverse events (1/2)

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Endometrial hyperplasia, cancer or disordered proliferative endometrium events reported in the CS for DAYLIGHT and SKYLIGHT 1, 2 and 4

| Trial | Placebo | Fezolinetant 45mg |
|---|---|---|
| DAYLIGHT | 2/226 | 1/226 |
| SKYLIGHT 1 | 0/175 | 0/173 |
| SKYLIGHT 2 | 0/167 | 0/167 |
| SKYLIGHT 4 | 0/186 | 1/203 (simple hyperplasia without atypia) |

Neoplasm events reported in the randomised phases of the SKYLIGHT 1, 2 and 4 trials as extracted from the www.clinicaltrials.gov website (Douxfils 2023)

| Trial | Placebo | Fezolinetant 45mg |
|---|---|---|
| SKYLIGHT 1 (12 weeks) | 0/175 | 3/173 |
| SKYLIGHT 2 (12 weeks) | 0/167 | 2/167 |
| SKYLIGHT 4 (52 weeks) | 2/610 | 9/609 |

# Key clinical trials – adverse events (2/2)

Return to main presentation

Liver test[a] elevations from key clinical trials

| n/N (%) | Placebo n/N (%) | Fezolinetant 45mg n/N (%) |
|---|---|---|
| DAYLIGHT | 6/226 (2.7%) | 10/226 (4.4%) |
| SKYLIGHT 1 | 5/175 (2.9%) | 7/173 (4.0%) |
| SKYLIGHT 2 | 0/167 | 3/167 (1.8%) |

[a]Liver tests included ALT, AST, ALP and TBL



Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; ALP, alkaline phosphatase; TBL, total bilirubin

# Key clinical trials - discontinuation

Return to main presentation

Trial discontinuations and missing data at primary endpoints in the key clinical trials

| Trial | Proportion of patients who discontinued trial intervention | | Proportion of patients with missing data at primary endpoints | |
|---|---|---|---|---|
| | Fezolinetant | Placebo | Fezolinetant | Placebo |
| DAYLIGHT | 14%, 5% due to TEAE | 23%, 6% due to TEAE | 22% | 27% |
| SKYLIGHT 1 | 8%, 3% due to TEAE | 13%, 5% due to TEAE | 16% | 21% |
| SKYLIGHT 2 | 7%, 1% due to TEAE | 10%, 1% due to TEAE | 13% | 16% |

In the model For fezolinetant, the per cycle probability of discontinuation of 2.43% was derived from week 0–24 DAYLIGHT data and applied in each model cycle up to week 24. From week 24 onwards, the per cycle probability of discontinuation of [redacted] was sourced from pooled SKYLIGHT 1 and 2 week 24–52 trial data (HRT-unsuitable). This resulted in a median treatment duration with fezolinetant of [redacted] years

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Abbreviations: TEAE, treatment-emergent adverse event

# Indirect treatment comparison - exploratory NMA (1/2)

NMA results demonstrate that fezolinetant is more effective than paroxetine for change in moderate/severe VMS frequency in a fixed effect model

## Background

- At clarification company provided an 'exploratory' network meta-analysis for comparative evidence for fezolinetant versus non-hormonal treatment comparators.
- 15 trials were identified; 3 fezolinetant versus placebo and 2 paroxetine (a SSRI) versus placebo trials were included. Excluded trials of desvenlafaxine (a SNRI) because not licensed in UK and gabapentin because company considered dose above that used in UK clinical practice.

| Comparator | Fezolinetant 45mg versus comparator | | | |
|---|---|---|---|---|
| | Fixed effects | | Random effects | |
| | Treatment difference (mean) | 95% CrI | Treatment difference (mean) | 95% CrI |
| Paroxetine 7.5mg (oral) | [redacted] | [redacted] | [redacted] | [redacted] |

Abbreviations: NMA, network meta-analysis, SNRI, serotonin and norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; VMS, vasomotor symptoms.

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# Indirect treatment comparison - exploratory NMA (2/2)

NMA results demonstrate that fexolinetant is more effective than paroxetine for change in moderate/severe VMS frequency

**EAG comments**

- Methods for the company's exploratory NMA appear appropriate, but reporting is incomplete so could not be validated.
- Fixed effect model fits the data marginally better than random effects
- EAG identified an additional published NMA (Morga 2023), with searches conducted June 2021 (before DAYLIGHT):
  - Included trials of paroxetine 7.5mg (1 trial), desvenlafaxine (6 trials: results for 4 different doses, ranging between 50mg and 200mg) and gabapentin 1800mg (1 trial)
  - NMA showed little evidence to suggest fezolinetant had a clinically meaningful benefit over SSRIs, SNRIs and gabapentin on reducing severe VMS frequency, but the NMA had several limitations (primarily high risk of bias from missing data).

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Abbreviations: EAG, external assessment group; NMA, network meta-analysis SNRI, serotonin and norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; VMS, vasomotor symptoms.

# Company's model overview – additional detail

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- Technology affects **costs** by:
  - Lower healthcare resource with improved health states (since higher moderate to severe VMS has higher costs)

- Technology affects **QALYs** by:
  - Increasing proportion of postmenopausal people moving to lower moderate to severe VMS frequency states over time (which have improved HRQoL than higher frequency states)
  - Use of HRQoL utility values from DAYLIGHT trial adjusted using company clinical expert opinion to ensure higher frequency of moderate to severe VMS have lower HRQoL utility values

- Assumptions with greatest ICER effect:
  - Baseline VMS frequency distribution
  - Adjustment for placebo effect from trials
  - Use of year 1, 3 and 6 SEE estimates for natural history rather than year 6 estimates only
  - Values based on pooled SKYLIGHT 1&2 trials not adjusted using clinical opinion



Abbreviations: HRQoL, health-related quality of life; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; SEE, structured expert elicitation; VMS, vasomotor symptoms.

# Treatment effect – application of placebo effect

Proportion of cohort in VMS frequency health states for no active treatment between week 12 and week 52 in the model.

| | No active treatment | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | On-treatment | | | | Off-treatment | | | |
| Time point | 0 ≤ VMS-F < 2 | 2 ≤ VMS-F < 7 | 7 ≤ VMS-F < 9 | VMS-F ≥ 9 | 0 ≤ VMS-F < 2 | 2 ≤ VMS-F < 7 | 7 ≤ VMS-F < 9 | VMS-F ≥ 9 |
| 12 weeks | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 24 weeks | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 52 weeks | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

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Abbreviations: EAG, external assessment group; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; SEE, structured expert elicitation; VMS, vasomotor symptoms.

# SEE natural history estimates

SEE natural history health state distribution proportions (reproduced from Table 61 of CS)

| Time point | 0 ≤ VMS-F < 2 | 2 ≤ VMS-F < 7 | 7 ≤ VMS-F < 9 | VMS-F ≥ 9 |
|---|---|---|---|---|
| Year 1 | 16.91% | 47.13% | 17.16% | 18.80% |
| Year 3 | 36.77% | 40.34% | 13.36% | 9.53% |
| Year 6 | 48.12% | 33.33% | 12.39% | 6.15% |

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Abbreviations: EAG, external assessment group; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; SEE, structured expert elicitation; VMS, vasomotor symptoms.

# EAG deterministic scenario analysis – all scenarios (1/5)

**EAG** scenario analyses (deterministic)

| Scenario # | | Name | Inc. Costs | Inc. QALYs | ICER, /QALY |
|---|---|---|---|---|---|
| | | Company's base-case results | £1,199.49 | 0.116 | £10,364.17 |
| Baseline distribution | 1a | Use Year 1 SEE estimate for baseline distribution | £1,545.00 | 0.045 | £34,308.17 |
| | 1b | Use Year 1 Clinician Natural History Distribution Estimates for baseline distribution | £1,458.71 | 0.064 | £22,641.88 |

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Abbreviations: EAG, external assessment group; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; SEE, structured expert elicitation; VMS, vasomotor symptoms.

# EAG deterministic scenario analysis – all scenarios (2/5)

**EAG** scenario analyses (deterministic)

| Scenario # | | Name | Inc. Costs | Inc. QALYs | ICER, /QALY |
|---|---|---|---|---|---|
| | | Company's base-case results | £1,199.49 | 0.116 | £10,364.17 |
| Placebo effect | 2a | Increase the placebo effect from week 12 to week 24 | £1,241.87 | 0.107 | £11,621.78 |
| | 2b | No placebo effect at all | £1,149.72 | 0.126 | £9,119.42 |
| | 2c | Placebo effect up to week 52, probability of discontinuation of 4.17% per 4-week (company's base case) | £1,331.62 | 0.088 | £15,126.91 |
| | 2d | Placebo effect over modelled time horizon, probability of discontinuation of 4.17% per 4-week (company's base case) | £1,481.50 | 0.054 | £27,191.69 |

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Abbreviations: EAG, external assessment group; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

# EAG deterministic scenario analysis – all scenarios (3/5)

**EAG** scenario analyses (deterministic)

| Scenario # | | Name | Inc. Costs | Inc. QALYs | ICER, /QALY |
|---|---|---|---|---|---|
| | | Company's base-case results | £1,199.49 | 0.116 | £10,364.17 |
| Natural history study | 3a | Use Year 1, 3 and 6 SEE estimates for natural history | £1,488.30 | 0.057 | £26,171.46 |
| | 3b | Use Year 3 and 6 SEE estimates for natural history | £1,358.54 | 0.083 | £16,333.99 |
| | 3c | Use Year 1,3 and 6 clinician natural history estimates | £1,409.30 | 0.075 | £18,718.94 |
| | 3d | Use Year 3 and 6 clinician natural history estimates | £1,320.08 | 0.093 | £14,246.24 |

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Abbreviations: EAG, external assessment group; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; SEE, structured expert elicitation

# EAG deterministic scenario analysis – all scenarios (4/5)

**EAG** scenario analyses (deterministic)

| Scenario # | | Name | Inc. Costs | Inc. QALYs | ICER, /QALY |
|---|---|---|---|---|---|
| | | Company's base-case results | £1,199.49 | 0.116 | £10,364.17 |
| VMS duration | 4a | Median duration of VMS of 3.4 years | £874.61 | 0.096 | £9,138.54 |
| | 4b | Increase model time-horizon to 20 years when using median duration VMS of 7.4 years | £1,283.00 | 0.115 | £11,118.53 |

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Abbreviations: EAG, external assessment group; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; VMS, vasomotor symptoms.

# EAG deterministic scenario analysis – all scenarios (5/5)

**EAG** scenario analyses (deterministic)

| Scenario # | | Name | Inc. Costs | Inc. QALYs | ICER, /QALY |
|---|---|---|---|---|---|
| | | Company's base-case results | £1,199.49 | 0.116 | £10,364.17 |
| Utility values | 5a | Utility values-DAYLIGHT data (UK) | £1,199.49 | 0.085 | £14,188.67 |
| | 5b | Utility values-Pooled DAYLIGHT & SKYLIGHT 1 & 2 (HRT-unsuitable) pooled data (UK) | £1,199.49 | 0.073 | £16,359.38 |
| | 5c | Utility values- Pooled SKYLIGHT 1 & 2 (HRT-unsuitable) | £1,199.49 | 0.064 | £18,686.20 |

Abbreviations: EAG, external assessment group; HRT, hormone replacement therapy; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year

# Company comparison against paroxetine (exploratory NMA)

Note that because the company model does not model relative treatment effects, the application of NMA data in the model is limited

| Name | Inc. Costs | Inc. QALYs | ICER, costs/QALY |
|---|---|---|---|
| Versus placebo (base case) | £1,199.49 | 0.116 | £10,364 |
| Versus paroxetine (SSRI – exploratory NMA) | £1,366.40 | 0.074 | £18,554 |

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; HRT, hormone replacement therapy; NMA, network meta-analysis; SSRI, selective serotonin reuptake inhibitor; VMS, vasomotor symptoms.