Fezolinetant (menopausal patients with vasomotor symptoms 1)

Addendum to Project 24-15 (dossier assessment)[1]

ADDENDUM

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
FSFI	Female Sexual Function Index
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MENQOL	Menopause-Specific Quality of Life
PGI-C	Patient Global Impression of Severity Change of Sleep Disturbance
PGI-S	Patient Global Impression of Severity
PHQ	Patient Health Questionnaire
PROMIS	Patient-Reported Outcomes Measurement Information System
RCT	randomized controlled trial
SAE	serious adverse event
SD SF 8b	Sleep Disturbance Short Form 8b
SGB	Sozialgesetzbuch (Social Code Book)
SMQ	Standardized MedDRA Query
SOC	System Organ Class
VAS	visual analogue scale

1 Background

On 11 June 2024, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Project A24-15 (Fezolinetant – Benefit assessment according to § 35a Social Code Book V) [1].

In its comments [2,3], the pharmaceutical company (hereinafter referred to as "the company") presented supplementary information, which went beyond the information provided in the dossier [4], to prove the added benefit. The commission comprises the assessment of the analyses of the DAYLIGHT study (new analyses on the modified analysis population after 24 weeks) presented by the company in the commenting procedure, taking into account the information in the dossier. In addition, the data/information [5,6] subsequently submitted by the company following the oral hearing should be considered.

The responsibility for the present assessment and the assessment result lies exclusively with IQWiG. The assessment is sent to the G-BA. The G-BA decides on the added benefit.

2 Assessment

In the dossier [4], the company used the randomized controlled trials (RCTs) SKYLIGHT 1, SKYLIGHT 2, SKYLIGHT 4 and DAYLIGHT for research question 2 of the benefit assessment of fezolinetant (menopausal patients with moderate to severe vasomotor symptoms for whom hormone replacement therapy is not an option). The analyses were based on patients for whom hormone replacement therapy is not an option according to the company's assessment. As explained in detail in dossier assessment A24-15 [1], the data presented by the company were not included in the benefit assessment. While it was not sufficiently certain for the patient population analysed by the company from the DAYLIGHT and SKYLIGHT 4 studies that at least 80% of the patients corresponded to research question 2, the studies SKYLIGHT 1 and SKYLIGHT 2 with a comparative treatment period of 12 weeks were too short for the assessment of the added benefit of fezolinetant.

In the commenting procedure and following the oral hearing, the company subsequently submitted analyses of a subpopulation for each of the studies DAYLIGHT, SKYLIGHT 1 and SKYLIGHT 2, which exclusively comprised patients with at least 1 of the criteria “contraindication”, “discontinuation of hormone replacement therapy” or “decision against hormone replacement therapy”. Patients with a risk factor for hormone replacement therapy were only considered if one additional criterion of the above criteria was fulfilled. As described in dossier assessment A24-15, the criteria of contraindication, discontinuation of hormone replacement therapy or decision against hormone replacement therapy are considered adequate to delineate the patient population for whom hormone replacement therapy is not an option. Therefore, the analyses presented by the company were used for the benefit assessment. All information stated below is based on the relevant subpopulation. However, because the study duration was too short, the subsequently submitted analyses of the studies SKYLIGHT 1 and SKYLIGHT 2 are still not suitable for the benefit assessment.

For the SKYLIGHT 4 study, the company clarified in the commenting procedure that the proportion of patients with moderate to severe vasomotor symptoms according to the approved therapeutic indication of fezolinetant cannot be quantified, as the frequency and severity of vasomotor symptoms were not recorded in the study. Concurring with the company, the SKYLIGHT 4 study was therefore not included in the benefit assessment.

There are still no data available for research question 1 of the dossier assessment (menopausal patients with moderate to severe vasomotor symptoms for whom hormone replacement therapy is an option).

Concurring with the commission, the analyses of the DAYLIGHT study (new analyses on the modified analysis population after 24 weeks) presented by the company in the commenting

procedure and the data subsequently submitted after the oral hearing are assessed in the following.

Sections 2.1 to 2.7.2 refer exclusively to research question 2 of dossier assessment A24-15. Section 2.8 contains a statement on the added benefit for both research questions.

2.1 Studies included

The study presented in the following Table 1 was included in the benefit assessment.

Table 1: Study pool – RCT, direct comparison: fezolinetant versus watchful waiting

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication and other sources[c] (yes/no [citation])
2693-CL-0312 (DAYLIGHT[d])	No	Yes	No	Yes [7]	Yes [8,9]	No

a. Study sponsored by the company.
b. Citation of the trial registry entries and, if available, of the reports on study design and/or results listed in the trial registries.
c. Other sources: documents from the search on the G-BA website and other publicly available sources.
d. In the following tables, the study is referred to by this acronym.

RCT: randomized controlled trial

The study pool for research question 2 of the benefit assessment of fezolinetant in comparison with the appropriate comparator therapy (ACT) consists of the DAYLIGHT study and differs from the company's study pool, which also includes the studies SYKLIGHT 1 and SKYLIGHT 2. Since regular visits (every 2 to 4 weeks) took place in the placebo-controlled study, this is considered to be a sufficient approximation to the ACT watchful waiting in the present therapeutic indication.

2.2 Study characteristics

A detailed description of the DAYLIGHT study can be found in dossier assessment A24-15.

Patient characteristics

Table 2 shows the characteristics of the patients in the DAYLIGHT study.

Table 2: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: fezolinetant versus watchful waiting

Study characteristic category	Fezolinetant N[a] = 195	Placebo N[a] = 186
DAYLIGHT		
Age [years], mean (SD)	55 (5)	54 (5)
Geographical region, n (%)		
Europe	157 (81)	155 (83)
North America	38 (20)	31 (17)
Smoking status, n (%)		
Smoker[b]	25 (13)	26 (14)
Non-smoker[c]	170 (87)	160 (86)
Time since onset of hot flushes [years], mean (SD)	64.2 (54)	60.7 (52)
Amenorrhoea, n (%)	184 (94)	174 (94)
Time since onset of amenorrhoea [years], mean (SD)	72.9 (61)	56.9 (48)
Oophorectomy , n (%)	20 (10)	17 (9)
Hysterectomy, n (%)	37 (19)	19 (10)
Criterion "HRT[d] is not an option", n (%)		
Contraindication	27 (14)	23 (12)
Discontinuation of HRT	54 (28)	58 (31)
Decision against HRT after a medical consultation	134 (69)	120 (65)
Risk factor[e]	52 (27)	63 (34)
Treatment discontinuation, n (%)[f]	25 (13)	43 (23)
Study discontinuation, n (%)[g]	15 (8)	31 (17)

a. Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b. Includes current smokers.
c. Includes former smokers or patients who have never smoked before.
d. Several criteria per patient are possible.
e. Only includes patients who fulfil at least one other category (contraindication, discontinuation of HRT, decision against HRT after a medical consultation).
f. Common reasons for treatment discontinuation in the intervention vs. control arm were the following (percentages based on randomized patients): withdrawal of consent (11 [5.6%] vs. 24 [12.9%] patients) and AEs (11 [5.6%] vs. 13 [7.0%] patients).
g. Common reasons for study discontinuation in the intervention vs. control arm were the following (percentages based on randomized patients): withdrawal of consent (10 [5.1%] vs. 21 [11.3%] patients) and lost to follow-up (1 [0.5%] versus 6 [3.2%] patients).

HRT: hormone replacement therapy; n: number of patients in the category; N: number of randomized patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation

The demographic and disease-specific characteristics are largely comparable between the DAYLIGHT study arms. There were differences in the time since the onset of amenorrhoea, which was 72.9 months on average for patients in the intervention arm, compared with 56.9

months in the control arm. In addition, the proportion of patients with hysterectomy in the intervention arm was 19%, which was higher than in the control arm (10%).

The proportion of patients with treatment discontinuation was higher in the control arm (23%) than in the intervention arm (13%). The most common reasons for treatment discontinuation were withdrawal of consent and the occurrence of side effects. The proportion of patients with study discontinuation was also notably higher in the control arm (17%) than in the intervention arm (8%).

Risk of bias across outcomes (study level)

Table 3 shows the risk of bias across outcomes (risk of bias at study level).

Table 3: Risk of bias across outcomes (study level) – RCT, direct comparison: fezolinetant versus watchful waiting

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
DAYLIGHT	Yes	Yes	Yes	Yes	Yes	Yes	Low
RCT: randomized controlled trial							

The risk of bias across outcomes for the DAYLIGHT study was rated as low.

2.3 Outcomes included

The following patient-relevant outcomes were to be included in the assessment:

- Mortality
  - All-cause mortality
- Morbidity
  - Reduction of moderate and severe vasomotor symptoms
  - Sleep disturbance, recorded using the Patient-Reported Outcomes Measurement Information System Sleep Disturbance Short Form (PROMIS SD SF) 8b
  - Female sexual functioning, recorded using the Female Sexual Function Index (FSFI)
  - General symptoms of depression and anxiety disorders, recorded using the Patient Health Questionnaire (PHQ)-4

- Health status, recorded with the visual analogue scale (VAS) of the EQ-5D

- Health-related quality of life
  - Menopause-Specific Quality of Life (MENQOL)
- Side effects
  - Serious adverse events (SAEs)
  - Discontinuation due to adverse events (AEs)
  - Neoplasms benign, malignant and unspecified (including cysts and polyps) (System Organ Class [SOC], SAEs)
  - Liver-related examinations, clinical signs and symptoms (Standardized MedDRA Query [SMQ], SAEs)
  - Other specific AEs, if any

The choice of patient-relevant outcomes deviates from that made by the company, which used further outcomes in the dossier (Module 4 A) and in its comments.

Table 4 shows the outcomes for which data are available in the included study.

Table 4: Matrix of outcomes – RCT, direct comparison: fezolinetant versus watchful waiting

Study	Outcomes											
	All-cause mortality[a]	Moderate/severe VMS	Sleep disturbance (PROMIS SD SF 8b)	Female Sexual Function Index (FSFI)	General symptoms of depression and anxiety disorders (PHQ-4)	Health status (EQ-5D VAS)	Health-related quality of life (MENQOL)[b]	SAEs	Discontinuation due to AEs	Neoplasms benign, malignant and unspecified (including cysts and polyps) (SOC, SAEs)	Liver-related examinations, clinical signs and symptoms (SMQ, SAEs)[c]	Other specific AEs
DAYLIGHT	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No[d]

a. Operationalized as AEs that led to death.
b. Operationalized via the 4 individual domains: vasomotor, psychosocial, physical and sexual.
c. Predefined in the study as AESIs.
d. No specific AEs were identified based on the AEs that occurred in the relevant study.

AE: adverse event; AESI: adverse events of special interest; FSFI: Female Sexual Function Index; MedDRA: Medical Dictionary for Drug Regulatory Activities; MENQOL: Menopause-Specific Quality of Life Questionnaire; PHQ: Patient Health Questionnaire; PROMIS: Patient-Reported Outcomes Measurement Information System; RCT: randomized controlled trial; SAE: serious adverse event; SD: Sleep Disturbance; SF 8B: Short Form 8b; SMQ: standardized MedDRA query; SOC: system organ class; VAS: visual analogue scale; VMS: vasomotor symptoms

Notes on outcomes

Responder analyses on the improvement of symptoms and health-related quality of life are adequate

In both its dossier and its comments, the company presents responder analyses on the improvement at Week 24 as well as continuous analyses on the change from baseline for the outcomes in the categories of morbidity and health-related quality of life. The treatment goal in the present therapeutic indication is an improvement in symptoms [10], which is why the analyses of the proportion of patients with an improvement at Week 24 are used in each case.

Vasomotor symptoms

Frequency and severity of vasomotor symptoms (recorded via electronic diary)

In the DAYLIGHT study, patients used an electronic diary to record the severity and time of hot flushes on a daily basis, with sweating being taken into account in terms of severity. A distinction was made between mild, moderate and severe degrees of severity:

- mild: flushing without sweating
- moderate: flushing with sweating, but ability to continue activity
- severe: flushing with sweating that leads to cessation of activity

The company uses the outcomes of frequency and severity of vasomotor symptoms, among others, to derive the added benefit. In this context, the frequency is operationalized as the average number of daily moderate to severe hot flushes in a period of 7 days (or 10 days for the baseline value). Severity was determined as the weekly mean of the weighted average number of daily moderate to severe hot flushes based on the following formula:

$$\frac{([Anzahl\ moderater\ Hitzewallungen\ pro\ Tag * 2] + [Anzahl\ schwerer\ Hitzewallungen\ pro\ Tag * 3])}{Gesamtanzahl\ moderater\ und\ schwerer\ Hitzewallungen\ pro\ Tag}$$

If no moderate or severe hot flushes occurred on a day, the daily value was set to 0. If moderate to severe hot flushes occurred, the daily value was between 2 and 3. Based on the formula, daily values between 0 and 1 are not possible. Values from 0 to 3 can result for the averaged weekly value.

For this benefit assessment, the proportion of patients with a 100% reduction in moderate and severe vasomotor symptoms (at Week 24) compared to baseline is used. This means that the patients no longer had moderate to severe hot flushes at Week 24. This operationalization presented by the company for the frequency of vasomotor symptoms takes into account both the number and the severity of the hot flushes that occurred, so that the severity of the vasomotor symptoms is not considered separately.

In the commenting procedure, the company additionally presented analyses on the frequency and severity of vasomotor symptoms of any severity (mild/moderate/severe). As a supplement, the proportion of patients with a 100% reduction in all vasomotor symptoms compared to baseline is used for this benefit assessment.

Change in vasomotor symptoms (assessed via patient-reported global disease activity [PGI-C VMS])

The PGI-C VMS consists of a single question that asks patients at Week 24 to assess change in hot flushes/night sweat since starting treatment on a 7-point scale (from “much better” to

“much worse”). In its dossier, the company presents post hoc defined responder analyses taking into account patients who assessed their symptoms as "very much better" or "much better" compared to baseline.

The wording of the question chosen by the company for the PGI-C links the two symptoms hot flushes/night sweats with each other, so that when answering the question it may be unclear whether the answer refers to one or to both of the two symptoms asked about. In addition, the responder analysis on the reduction of vasomotor symptoms (see previous section) presented by the company provides a suitable operationalization of the vasomotor symptoms. The outcome of PGI-C VMS is therefore presented as supplementary information.

Insomnia

Patient-Reported Outcomes Measurement Information System (PROMIS) SD SF 8b (sleep disturbance short form 8b)

In the DAYLIGHT study, sleep disturbance were recorded via PROMIS. PROMIS is a valid, generic system consisting of domain-specific instruments for the self-reported and proxy-reported assessment of physical, mental, and social health. In the DAYLIGHT study, the short form of the PROMIS SD SF 8b questionnaire was used for the patient-reported assessment of sleep disturbance. However, the analyses in the dossier were not suitable for the benefit assessment because, contrary to the approach described in the PROMIS manual [11], they were not based on transformed values.

In the commenting procedure, the company presented post hoc responder analyses based on transformed values for the outcome “sleep disturbance” recorded using PROMIS SD SF 8b. As already described in the dossier assessment, there are 2 methods for transforming the raw values according to the PROMIS manuals [11]: firstly, manual transformation using the conversion table in the corresponding manual, and secondly, the so-called "Response Scoring Pattern" using the HealthMeasures Scoring Service [12]. According to the PROMIS manuals, the use of the "Response Scoring Pattern" should be favoured, as it measures more accurately and deals better with missing values. The company did not provide any information on the transformation method used by it.

Responder analyses conducted post hoc with an improvement in the PROMIS SD SF 8b by ≥ 7.14 points were used for the present benefit assessment. This response criterion corresponds to exactly 15% of the scale range (based on transformed values) and can be taken into account according to the General Methods of the Institute [13].

Patient Global Impression of Severity or Change of Sleep Disturbance (PGI-S SD and PGI-C SD)

In the DAYLIGHT study, sleep disturbance was assessed using the PGI-S SD and PGI-C SD in addition to the PROMIS. These each consist of a single question on the severity or on the

change in sleep disturbance. For the PGI-S SD, the patients indicated the severity of their sleep problems at baseline and at Week 24 on a 4-point scale (from "no problems" to "severe problems"). For the PGI-C SD, the patients indicated on a 7-point scale (from "much better" to "much worse") at Week 24 how their sleep problems had changed compared to baseline. Since the PROMIS SD SF 8b is a valid instrument for recording sleep disturbance that covers sleep disturbance in detail across several questions, the PGI-S SD and the PGI-C SD were not used for the benefit assessment.

FSFI

The FSFI was developed to assess sexual functioning in women [14]. The FSFI consists of 19 questions on various aspects of sexuality, which are summarized in 6 domains (desire, arousal, lubrication, orgasm, general satisfaction and pain) and relates to the last 4 weeks. The individual questions are answered on Likert scales from 1 to 5 or 0 to 5, with 0 indicating a lack of sexual activity in the last month. The scale range of the weighted total score is 2 to 36 points.

Responder analyses defined post hoc with an improvement in the FSFI total score of ≥ 5.1 points are used for the present benefit assessment. This response criterion corresponds to 15% of the scale range.

General symptoms of depression and anxiety disorders (PHQ-4)

The PHQ-4 is a short questionnaire on the screening for suspected anxiety and depression [15,16]. The PHQ-4 consists of 2 questions on depression and 2 questions on anxiety disorders and asks about complaints in the last 2 weeks on a 4-point Likert scale. This results in a total score (scale range 0 to 12 points) and the two subscales of anxiety and depression (0 to 6 points each).

Responder analyses defined post hoc with an improvement in the PHQ-4 total score by ≥ 1.8 points are used for the present benefit assessment. This response criterion corresponds to 15% of the scale range.

Activity impairment (recorded using question 6 of the Work Productivity and Activity Impairment [WPAI])

In the DAYLIGHT study, the WPAI questionnaire “hot flushes/night sweats” was used. Question 6 measures the impairment of daily activities in the last 7 days on a scale from 0 to 10. Since the impairment of activity is already reflected by the daily indication of the severity of vasomotor symptoms in the electronic diary (severe hot flushes mean cessation of activity), the analyses on the impairment of activity are not used for the benefit assessment.

Health-related quality of life (MENQOL)

The MENQOL questionnaire was specifically developed to assess the quality of life of menopausal women [17]. The version of the questionnaire used in the DAYLIGHT study comprises a total of 29 items distributed across the 4 domains “vasomotor”, “physical”, “psychosocial” and “sexual”. The questionnaire is completed by the patients themselves and records whether problems have occurred within the last 7 days and, if so, their severity. For the analysis, the result of each item is converted into a scale from 1 to 8 and the domain scores are calculated separately as the mean value of the corresponding items. The value range is therefore also 1 to 8, with higher scores indicating more severe symptoms.

Responder analyses defined post hoc with an improvement in the 4 domain scores by ≥ 1.05 points each are used for the present benefit assessment. This response criterion corresponds to 15% of the subscales’ scale range.

Outcomes in the category of side effects

The analyses presented by the company on SAEs and discontinuation due to AEs contain events of the underlying disease. Based on the AEs at SOC and PT level, the data on the relevant subpopulation subsequently submitted in the commenting procedure and the information on the total population in the study report show that the proportion of underlying disease events is low, meaning that the data are suitable for the benefit assessment.

Notes on the analyses presented

Planned duration of follow-up after treatment

According to the study protocol, after discontinuation of study treatment, morbidity outcomes should continue to be recorded up to Week 24 and outcomes in the side effects category up to Week 27. In the dossier and in the comments, however, the company presented analyses for the outcomes in the side effects category, which included all AEs that occurred after the first application of the study medication and up to 21 days after the last dose of the study medication.

2.4 Risk of bias

Table 5 describes the risk of bias for the events of the relevant outcomes.

Table 5: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: fezolinetant versus watchful waiting

Study		Outcomes											
	Study level	All-cause mortality[a]	Moderate/severe VMS	Sleep disturbance (PROMIS SD SF 8b)	Female Sexual Function Index (FSFI)	General symptoms of depression and anxiety disorders (PHQ-4)	Health status (EQ-5D VAS)	Health-related quality of life (MENQOL)[b]	SAEs	Discontinuation due to AEs	Neoplasms benign, malignant and unspecified (including cysts and polyps) (SOC, SAEs)	Liver-related examinations, clinical signs and symptoms (SMQ, SAEs)[c]	Other specific AEs
DAYLIGHT	L	H[d]	H[e]	H[e]	H[e]	H[e]	H[e]	H[e]	H[d]	H[d]	H[d]	H[d]	–

a. Operationalized via AEs that led to death.
b. Operationalized via the 4 individual domains: vasomotor, psychosocial, physical and sexual.
c. Predefined in the study as AESIs.
d. Incomplete observations for potentially informative reasons.
e. High proportion of patients (> 10%) and large difference between the treatment groups (> 5 percentage points)who were imputed as non-responders.

AE: adverse event; AESI: adverse events of special interest; FSFI: Female Sexual Function Index; H: high; L: low; MedDRA: Medical Dictionary for Drug Regulatory Activities; MENQOL: Menopause-Specific Quality of Life Questionnaire; PHQ: Patient Health Questionnaire; PROMIS: Patient-Reported Outcomes Measurement Information System; RCT: randomized controlled trial; SAE: serious adverse event; SD: Sleep Disturbance; SF 8B: Short Form 8b; SMQ: standardized MedDRA query; SOC: system organ class; VAS: visual analogue scale; VMS: vasomotor symptoms

In the DAYLIGHT study, the risk of bias for the results on all outcomes was rated as high. For the outcomes of morbidity and health-related quality of life, this is due to the high and discrepant proportions of imputed values (non-responder imputation) between treatment arms. For the outcome of all-cause mortality, captured via the recording of AEs, and the side effects outcomes, the risk of bias of the results is rated as high due to incomplete observations for potentially informative reasons. This is due to the different proportions of treatment and study discontinuations between the study arms (see Section 2.2).

2.5 Results

Table 6 summarizes the results comparing fezolinetant with watchful waiting in menopausal patients with moderate to severe vasomotor symptoms for whom hormone replacement therapy is not an option. Where necessary, the data submitted by the company in the comments and after the oral hearing were supplemented by the Institute's calculations.

Table 6: Results (mortality, morbidity, health-related quality of life and side effects, dichotomous) – RCT, direct comparison: fezolinetant vs. watchful waiting (multipage table)

Study (time point) outcome category outcome	Fezolinetant		Placebo		Fezolinetant vs. placebo
	N	patients with event n (%)	N	patients with event n (%)	RR [95% CI]; p-value
DAYLIGHT (Week 24)					
Mortality					
All-cause mortality[a]	195	0 (0)	186	0 (0)	–
Morbidity					
Moderate/severe VMS (reduction by 100%)[b]	195	47 (24.1)	186	19 (10.2)	2.34 [1.43; 3.83]; < 0.001[c]
Mild/moderate/severe VMS (reduction by 100 %)[d] (supplementary information)	*195*	*32 (16.4)*	*186*	*9 (4.8)*	3.38 [1.66; 6.88]; < 0.001[c]
Sleep disturbance (PROMIS SD SF 8b; improvement ≥ 7.14 points)[e]	195	99 (50.8)	185	52 (28.1)	1.74 [1.33; 2.26]; < 0.001[c]
Sexual functioning (FSFI; improvement by ≥ 5.1 points)[f]	195	36 (18.5)	184	33 (17.9)	1.06 [0.69; 1.61]; 0.803[c]
Desire (improvement by ≥ 0.72 points)[g]	195	46 (23.6)	184	30 (16.3)	1.43 [0.95; 2.16]
Arousal (improvement ≥ 0.9 points)[h]	195	51 (26.2)	184	35 (19.0)	1.38 [0.94; 2.01]
Lubrication (improvement ≥ 0.9 points)[h]	195	45 (23.1)	184	42 (22.8)	1.03 [0.71; 1.48]
Orgasm (improvement ≥ 0.9 points)[h]	195	35 (17.9)	184	35 (19.0)	0.97 [0.64; 1.47]
General satisfaction (improvement ≥ 0.8 points)[i]	195	48 (24.6)	184	45 (24.5)	1.08 [0.79; 1.49]
Pain (improvement ≥ 0.9 points)[h]	195	36 (18.5)	184	31 (16.8)	1.13 [0.74; 1.73]

Table 6: Results (mortality, morbidity, health-related quality of life and side effects, dichotomous) – RCT, direct comparison: fezolinetant vs. watchful waiting (multipage table)

Study (time point) outcome category outcome	Fezolinetant N	Fezolinetant patients with event n (%)	Placebo N	Placebo patients with event n (%)	Fezolinetant vs. placebo RR [95% CI]; p-value
General symptoms of depression and anxiety disorders (PHQ-4) (improvement ≥ 1.8 points)[j]	195	71 (36.4)	184	50 (27.2)	1.23 [0.94; 1.62]; 0.137[c]
Anxiety (improvement by ≥ 0.9 points)[k]	195	81 (41.5)	184	63 (34.2)	1.18 [0.94; 1.49][c]
Depression (improvement by ≥ 0.9 points)[k]	195	80 (41.0)	184	54 (29.3)	1.22 [0.94; 1.58][c]
Patient-reported global disease activity (PGI-C VMS)[l] (supplementary information)	*195*	*141 (72.3)*	*186*	*74 (39.8)*	1.82 [1.49; 2.21]; < 0.001[c]
Health status (EQ-5D VAS; improvement by ≥ 15 points)[m]	195	30 (15.4)	184	26 (14.1)	1.09 [0.67; 1.77]; 0.731[c]
Health-related quality of life					
MENQOL (improvement by ≥ 1.05 points)[n]					
Vasomotor	195	136 (69.7)	184	89 (48.4)	1.45 [1.23; 1.73]; < 0.001[c]
Psychosocial	195	94 (48.2)	184	62 (33.7)	1.35 [1.08; 1.69]; 0.009[c]
Physical	195	87 (44.6)	184	54 (29.3)	1.47 [1.14; 1.89]; 0.003[c]
Sexual	195	72 (36.9)	184	47 (25.5)	1.33 [1.02; 1.75]; 0.036[c]
Side effects					
AEs[o] (supplementary information)	195	126 (64.6)	186	111 (59.7)	–
SAEs[o]	195	7 (3.6)	186	6 (3.2)	1.11 [0.38; 3.25]; p = 0.999[p]
Discontinuation due to AEs[o]	195	11 (5.6)	186	13 (7.0)	0.81 [0.37; 1.76]; 0.675[p]
Neoplasms benign, malignant and unspecified (including cysts and polyps) (SOC, SAEs)	195	0 (0)	186	0 (0)	–
Liver-related examinations, clinical signs and symptoms (SMQ, SAEs)[q]	195	2 (1.0)	186	0 (0)	4.77 [0.23; 98.71]; 0.499[p]

Table 6: Results (mortality, morbidity, health-related quality of life and side effects, dichotomous) – RCT, direct comparison: fezolinetant vs. watchful waiting (multipage table)

Study (time point) outcome category outcome	Fezolinetant		Placebo		Fezolinetant vs. placebo
	N	patients with event n (%)	N	patients with event n (%)	RR [95% CI]; p-value
a. Operationalized as AEs that led to death. b. Proportion of patients with a 100% reduction in the average daily frequency of moderate and severe hot flushes compared to baseline. c. RR, 95% CI and p-value based on log-binomial regression with treatment group and smoking status (current vs. former/never) as factors and the baseline value as covariate. Missing values were imputed using non-responder imputation (NRI). d. Proportion of patients with a 100% reduction in the average daily frequency of mild, moderate and severe hot flushes compared to baseline. e. A decrease in the PROMIS SD SF 8b score by ≥ 15% (≥ 7.14 points) compared to baseline is deemed a clinically relevant improvement (scale range based on transformed T-scores 28.9 to 76.5). f. A decrease in the FSFI score by ≥ 15% (≥ 5.01 points) compared to baseline is deemed a clinically relevant improvement (scale range of 2 to 36). g. A decrease in the FSFI score: domain “desire” by ≥ 15% (≥ 7.2 points) compared to baseline is deemed a clinically relevant improvement (scale range of 1.2 to 6). h. A decrease in the FSFI score: domain “arousal/lubrication/orgasm/pain” by ≥ 15% (≥ 0.9 points) compared to baseline is deemed a clinically relevant improvement (scale range of 0 to 6). i. A decrease in the FSFI score: domain “general satisfaction” by ≥ 15% (≥ 0.8 points) compared to baseline is deemed a clinically relevant improvement (scale range of 0.8 to 6). j. A decrease in the PHQ-4 score by ≥ 15% (≥ 1.8 points) compared to baseline is deemed a clinically relevant improvement (scale range of 0 to 12). k. A decrease in the PHQ-4 score: domain “anxiety/depression” by ≥ 15% (≥ 0.9 points) compared to baseline is deemed a clinically relevant improvement (scale range of 0 to 6). l. Proportion of patients with a response categorized as "much better" and "moderately better" compared to baseline. m. An increase in the EQ-5D VAS score by ≥ 15% (≥ 15 points) from baseline is considered a clinically relevant improvement (scale range 0 to 100). n. A decrease in the MENQOL score in the 4 individual domains: vasomotor, psychosocial, physical and sexual by ≥ 15% (≥ 1.05 points) each compared to baseline is deemed a clinically relevant improvement (scale range of 1 to 8). o. Includes events of the underlying disease. p. RR based on unstratified Mantel-Haenszel test, 95% CI based on Wald. p-value based on Fisher exact test. q. Predefined in the study as AESI. AE: adverse event; AESI: AE of special interest; CI: Confidence interval; FSFI: Female Sexual Function Index; MedDRA: Medical Dictionary for Drug Regulatory Activities; MENQOL: Menopause-Specific Quality of Life Questionnaire; n: number of patients with (at least 1) event; N: number of analysed patients; PGI-C: Patient Global Impression of Change; PROMIS: Patient-Reported Outcomes Measurement Information System; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SD: sleep disturbance; SF 8b: Short Form 8b; SMQ: standardized MedDRA query; SOC: System Organ Class; VAS: visual analogue scale; VMS: vasomotor symptoms					

At most hints, e.g. of an added benefit, can be derived for all outcomes.

Mortality

No deaths occurred in the DAYLIGHT study during the course of the study. There is no hint of an added benefit of fezolinetant in comparison with watchful waiting; an added benefit is therefore not proven.

Morbidity

Vasomotor symptoms (moderate/severe)

For the outcome of moderate and severe vasomotor symptoms (100% reduction), there was a statistically significant difference in favour of fezolinetant. There is a hint of an added benefit of fezolinetant in comparison with watchful waiting.

Sleep disturbance (PROMIS SD SF 8b)

A statistically significant difference in favour of fezolinetant was shown for the outcome of sleep disturbance (PROMIS SD SF 8b, improvement by ≥ 7.14 points). There is a hint of an added benefit of fezolinetant in comparison with watchful waiting.

Sexual Functioning (FSFI)

No statistically significant difference between treatment arms was shown for the outcome of female sexual functioning (FSFI, improvement by ≥ 5.1 points). There is no hint of an added benefit of fezolinetant in comparison with watchful waiting; an added benefit is therefore not proven.

General symptoms of depression and anxiety disorders (PHQ-4)

No statistically significant difference between treatment arms was shown for the outcome of general symptoms of depression and anxiety disorders (PHQ-4, improvement by ≥ 1.8 points). There is no hint of an added benefit of fezolinetant in comparison with watchful waiting; an added benefit is therefore not proven.

Health status (EQ-5D VAS)

There is no statistically significant difference between the treatment arms for the outcome "health status" (EQ-5D VAS, improvement by ≥ 15 points). There is no hint of an added benefit of fezolinetant in comparison with watchful waiting; an added benefit is therefore not proven.

Health-related quality of life

MENQOL

For the outcome of health-related quality of life, measured using MENQOL, there was a statistically significant difference in favour of fezolinetant for all 4 domains (vasomotor, psychosocial, physical and sexual; improvement by ≥ 1.05 points in each case). There is a hint of an added benefit of fezolinetant in comparison with watchful waiting.

Side effects

SAEs and discontinuation due to AEs

No statistically significant difference was found between treatment groups for either of the outcomes of SAEs or discontinuation due to AEs. In each case, there is no hint of greater or lesser harm from fezolinetant in comparison with watchful waiting; greater or lesser harm is therefore not proven.

Neoplasms benign, malignant and unspecified (including cysts and polyps) (SOC, SAEs)

For the outcome of benign, malignant and unspecified neoplasms (including cysts and polyps) (SOC, SAEs), no events occurred during the course of the study. There is no hint of greater or lesser harm from fezolinetant in comparison with watchful waiting; greater or lesser harm is therefore not proven.

Liver-related examinations, clinical signs and symptoms (SMQ, SAEs)

There was no statistically significant difference between the treatment arms for the outcome of liver-related examinations, clinical signs and symptoms (SMQ, SAEs). There is no hint of greater or lesser harm from fezolinetant in comparison with watchful waiting; greater or lesser harm is therefore not proven.

2.6 Subgroups and other effect modifiers

The following subgroup characteristics were considered for the present benefit assessment: This is explained below.

For the DAYLIGHT study, the company pre-specified subgroup analyses for the characteristic “age” based on 2 age categories:

- Age category 1 (< 55 years versus ≥ 55 years)
- Age category 2 (≥ 40 to < 46 years versus ≥ ≥ 46 to < 51 years versus ≥ 51 to < 56 years versus ≥ 56 to < 61 years versus ≥ 61 to < 66 years)

In the dossier and in the comments, the company presented subgroup analyses on age category 1. The cut-off value used does not appear to make sense in the present therapeutic indication, which exclusively includes postmenopausal women. On the one hand, the age of the patients included ranges between 40 and 65 years, with a majority of patients included being women between the ages of 50 and 60. On the second hand, the guidelines do not provide any medical or substantive rationale for considering these age categories. The subgroup characteristic “age” is therefore not considered for the present benefit assessment.

Irrespective of the suitability of the cut-off value of 55 years, a statistically significant interaction (p-value < 0.05) between treatment and age was only present for the outcome of

general symptoms of depression and anxiety disorders (PHQ-4). While there was no statistically significant difference between the treatment groups in the age group < 55 years, there was a statistically significant difference in favour of fezolinetant in patients ≥ 55 years.

The characteristic of sex is disregarded because the study population only includes women. No suitable characteristic is available for disease severity.

2.7 Probability and extent of the added benefit

The derivation of probability and extent of added benefit for research question 2 at outcome level is shown below, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the IQWiG General Methods [13].

The approach for deriving an overall conclusion on the added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

2.7.1 Evaluation of added benefit at outcome level

The extent of the respective added benefit at outcome level is estimated from the results presented in Section 2.5 (see Table 7).

Determination of the outcome category for symptom outcomes

Vasomotor symptoms (moderate/severe)

According to the inclusion criteria, all patients in the DAYLIGHT study experienced an average of at least 7 moderate to severe hot flushes per day. Data on the number of vasomotor symptoms broken down by severity are not available. In addition, the distinction between moderate and severe vasomotor symptoms was based solely on whether the activity being performed could be continued or not. However, this information does not allow a differentiated assessment of the extent of the impairment. It should not generally be assumed that all vasomotor symptoms that lead to cessation of an activity are also to be equated with serious/severe symptoms in the context of the benefit assessment. The outcome of moderate and severe vasomotor symptoms was therefore assigned to the outcome category "non-serious/non-severe symptoms/late complications".

Sleep disturbance (PROMIS SR SF 8b)

Based on transformed values, the PROMIS SR SF 8b scale can take values between 28.9 and 76.5, with higher values indicating more pronounced symptoms. A value of 50 corresponds to the mean value of the reference population (with a standard deviation of 10) and is within the normal range [12]. In the DAYLIGHT study, the patients had a baseline value of approx. 59 and are therefore not in the range of severe symptoms. Therefore, this outcome is assigned to the outcome category of non-serious/non-severe symptoms/late complications.

Table 7: Extent of added benefit at outcome level: fezolinetant versus watchful waiting (multipage table)

Outcome category **outcome**	**Fezolinetant vs. placebo** **proportion of events (%)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Mortality		
All-cause mortality	0% vs. 0% RR: –	Lesser/added benefit not proven
Morbidity		
Moderate/severe VMS (reduction by 100%)	24.1% vs. 10.2% RR: 2.34 [1.43; 3.83]; RR: 0.43 [0.26; 0.70][c]; p < 0.001 probability: “hint”	Outcome category: non-serious/non-severe symptoms/late complications CI_u < 0.80; added benefit; extent: “considerable”
Sleep disturbance (PROMIS SD SF 8b; improvement ≥ 7.14 points)	50.8% vs. 28.1% RR: 1.74 [1.33; 2.26]; RR: 0.57 [0.44; 0.75][c]; p < 0.001 probability: “hint”	Outcome category: non-serious/non-severe symptoms/late complications CI_u < 0.80; added benefit; extent: “considerable”
Sexual function (FSFI, improvement by ≥ 5.1 points)	18.5% vs. 17.9% RR: 1.06 [0.69; 1.61]; p = 0.803	Lesser/added benefit not proven
General symptoms of depression and anxiety disorders (PHQ-4, improvement ≥ 1.8 points)	36.4% vs. 27.2% RR: 1.23 [0.94; 1.62]; p = 0.137	Lesser/added benefit not proven
Health status (EQ-5D VAS; improvement by ≥ 15 points)	15.4% vs. 14.1% RR: 1.09 [0.67; 1.77]; p = 0.731	Lesser/added benefit not proven
Health-related quality of life		
MENQOL (improvement by ≥ 1.05 points)		
Vasomotor	69.7% vs. 48.4% RR: 1.45 [1.23; 1.73]; RR: 0.69 [0.58; 0.81][c]; p < 0.001 probability: “hint”	Outcome category: health-related quality of life 0.75 ≤ CI_o < 0.90, added benefit; extent: “considerable”
Psychosocial	48.2% vs. 33.7% RR: 1.35 [1.08; 1.69]; RR: 0.74 [0.59; 0.93][c]; p = 0.009 probability: “hint”	Outcome category: health-related quality of life 0.90 ≤ CI_o < 1.00 added benefit – extent: “minor”

Table 7: Extent of added benefit at outcome level: fezolinetant versus watchful waiting (multipage table)

Outcome category **outcome**	**Fezolinetant vs. placebo** **proportion of events (%)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Physical	44.6% vs. 29.3% RR: 1.47 [1.14; 1.89]; RR: 0.68 [0.53; 0.88][c]; p = 0.003 probability: "hint"	Outcome category: health-related quality of life $0.75 \leq CI_o < 0.90$, added benefit; extent: "considerable"
Sexual	36.9% vs. 25.5% RR: 1.33 [1.02; 1.75]; RR: 0.75 [0.57; 0.98][c]; p = 0.036 probability: "hint"	Outcome category: health-related quality of life $0.90 \leq CI_o < 1.00$, added benefit – extent: "minor"
Side effects		
SAEs	3.6% vs. 3.2% RR: 1.11 [0.38; 3.25]; p > 0.999	Greater/lesser harm not proven
Discontinuation due to AEs	5.6% vs. 7.0% RR: 0.81 [0.37; 1.76]; p = 0.675	Greater/lesser harm not proven
Neoplasms benign, malignant and unspecified (including cysts and polyps) (SAEs)	0% vs. 0% RR: –	Greater/lesser harm not proven
Liver-related examinations, clinical signs and symptoms (SAEs)	1.0% vs. 0% RR: 4.77 [0.23; 98.71]; p = 0.499	Greater/lesser harm not proven

a. Probability provided if there is a statistically significant and relevant effect.
b. Depending on the outcome category, the effect size is estimated using different limits based on the upper limit of the confidence interval (CI_u).
c. Institute's calculation; inverse direction of effect to enable use of limits to derive the extent of the added benefit.

AE: adverse event; CI: Confidence interval; CI_u: upper limit of the confidence interval; FSFI: Female Sexual Function Index; MedDRA: Medical Dictionary for Drug Regulatory Activities; MENQOL: Menopause-Specific Quality of Life Questionnaire; n: number of patients with (at least 1) event; N: number of analysed patients; PHQ: Patient Health Questionnaire; PROMIS: Patient-Reported Outcomes Measurement Information System; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SD: sleep disturbance; SF 8b: Short Form 8b; SMQ: standardized MedDRA query; SOC: System Organ Class; VAS: visual analogue scale; VMS: vasomotor symptoms

2.7.2 Overall conclusion on added benefit

Table 8 summarizes the results taken into account in the overall conclusion on the extent of added benefit.

Table 8: Positive and negative effects from the assessment of fezolinetant in comparison with watchful waiting

Positive effects	Negative effects
Morbidity non-serious/non-severe symptoms/late complications ▪ moderate/severe VMS: hint of an added benefit – extent: “considerable” ▪ sleep disturbance (PROMIS SD SF 8b): hint of an added benefit - extent: “considerable”	–
Health-related quality of life ▪ MENQOL ▫ vasomotor: hint of an added benefit - extent “considerable” ▫ psychosocial: hint of an added benefit – extent: “minor” ▫ physical: hint of an added benefit – extent: “considerable” ▫ sexual: hint of an added benefit – extent: “minor”	–
MENQOL: Menopause-Specific Quality of Life Questionnaire; PROMIS: Patient-Reported Outcomes Measurement Information System; SD: Sleep disturbance; SF 8b: Short Form 8b; VMS: vasomotor symptoms	

Overall, only positive effects were found for fezolinetant in comparison with watchful waiting in several outcomes. For the outcome of moderate and severe vasomotor symptoms, there is a hint of considerable added benefit. For the outcome of sleep disturbance (recorded using PROMIS SD SF 8b), there is also a hint of a considerable added benefit. Regarding health-related quality of life, there were positive effects for the outcome of MENQOL for all 4 domains (vasomotor, psychosocial, physical and sexual) with the extents “low” or “considerable”, each with the probability of a hint.

In summary, for menopausal patients with moderate to severe vasomotor symptoms for whom hormone replacement therapy is not an option, there is a hint of a considerable added benefit versus the ACT of watchful waiting.

2.8 Summary

The data subsequently submitted by the company in the commenting procedure and following the oral hearing change the conclusion on the added benefit of fezolinetant from dossier assessment A24-15 for research question 2 of the benefit assessment: For menopausal patients with moderate to severe vasomotor symptoms for whom hormone replacement

therapy is not an option, there is a hint of a considerable added benefit of fezolinetant compared with watchful waiting.

For research question 1 (menopausal patients with moderate to severe vasomotor symptoms for whom hormone replacement therapy is an option), there is no change compared to dossier assessment A24-15.

Table 9 below shows the result of the benefit assessment of fezolinetant, taking into account dossier assessment A24-15 and the present addendum.

Table 9: Fezolinetant – probability and extent of added benefit

Research question	**Therapeutic indication**	**ACT[a]**	**Probability and extent of added benefit**
1	Menopausal women with moderate to severe vasomotor symptoms for whom hormone therapy is an option and who have decided in favour of hormone replacement therapy after an individual risk-benefit assessment[b]	Treatment of physician's choice choosing from systemic hormone replacement therapy (in women with an intact uterus [oestrogen/gestagen combination] or in women without uterus [only oestrogen])[c]	Added benefit not proven
2	Menopausal women with moderate to severe vasomotor symptoms for whom hormone therapy is not an option, or those who have decided against therapy after individual risk-benefit assessment[b]	Watchful waiting	Hint of considerable added benefit

a. Presented is the respective ACT specified by the G-BA.
b. According to the G-BA, it is assumed that the patients in research questions 1 and 2 are postmenopausal.
c. For the implementation of the ACT for research question 1, a single comparator study is generally not sufficient. The decision on individualized treatment with regard to the comparator therapy should be made before group allocation (e.g. randomization).

G-BA: Federal Joint Committee

The G-BA decides on the added benefit.

3 References

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