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Relugolix/estradiol/norethisterone acetate (uterine fibroids) –

Benefit assessment according to §35a Social Code Book V[1]

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Relugolix/Estradiol/Norethisteronacetat (Uterusmyome) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.1; Status: 28 January 2022). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

Patient and family involvement

No feedback of persons concerned was received within the framework of the present dossier assessment.

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Table of contents

List of tables[2]

Page

[2] Table numbers start with “2” as numbering follows that of the full dossier assessment.

List of figures

Page

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
BPD	Bleeding and Pelvic Discomfort
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CTCAE	Common Terminology Criteria for Adverse Events
DXA	dual-energy X-ray absorptiometry
E2	estradiol
EMA	European Medicines Agency
EQ-5D	European Quality of Life-5 Dimensions
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IPD	individual patient data
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MBL	menstrual blood loss
MMRM	mixed-effects model with repeated measures
NETA	norethisterone acetate
NRS	numeric rating scale
RCT	Randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SMD	standardized mean difference
SPC	Summary of Product Characteristics
UFS-QoL	Symptom Severity Scale of the Uterine Fibroid Symptom and Quality of Life Questionnaire
VAS	visual analogue scale

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug combination relugolix/estradiol/norethisterone acetate. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 31 August 2021.

Research question

The aim of the present report is the assessment of the added benefit of the drug combination relugolix, estradiol (E2) and norethisterone acetate (NETA) (hereinafter referred to as "relugolix/E2/NETA") in comparison with the appropriate comparator therapy (ACT) in adult patients of reproductive age for the treatment of moderate to severe symptoms of uterine fibroids.

The G-BA's specification of the ACT results in the research question presented in Table 2.

Table 2: Research question of the benefit assessment of relugolix/E2/NETA

Therapeutic indication	**ACT[a]**
Adult patients of reproductive age with moderate to severe symptoms of uterine fibroids	Individual treatment depending on the type and the severity of the symptoms as well as the patient's symptom burden, selecting from: ▪ watchful waiting ▪ symptom-oriented treatment: ▫ progestogens under consideration of the respective approval status (for patients for whom symptomatic treatment of prolonged and/or heavy periods [menorrhagia, hypermenorrhoea] is sufficient) ▫ ulipristal acetate (for patients who have not yet reached menopause and for whom uterine fibroid embolization and/or surgery are not suitable or have failed) ▪ invasive treatment options
a. Presented is the respective ACT specified by the G-BA. b. Because of its contraceptive effect, relugolix/E2/NETA cannot be used in patients with a current desire to have children. After treatment discontinuation, contraception is no longer given [1]. E2: estradiol; G-BA: Federal Joint Committee; NETA: norethisterone acetate	

The company first followed the ACT specified by the G-BA and named individual treatment depending on the type and the severity of the symptoms as well as the patient's symptom burden, taking into account the therapy options named by the G-BA. When retrieving information on relevant studies for the benefit assessment, the company took into account all therapy options mentioned in the ACT.

However, the company subsequently stated that it was critical of the naming of ulipristal acetate as a treatment option due to existing safety concerns regarding the risk of liver damage and due to its currently unclear importance in health care. The present benefit assessment was conducted in comparison with the ACT specified by the G-BA, which means including ulipristal acetate.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) with a minimum duration of 24 weeks were used for the derivation of added benefit.

Study pool and study design

The twin studies LIBERTY 1 and LIBERTY 2 are relevant for the benefit assessment. These are multinational, randomized, double-blind studies on the comparison of relugolix + E2/NETA (free combination) with placebo. Relugolix + E2/NETA is approved as fixed combination; the results of the free combination can be used for the benefit assessment.

Premenopausal women from 18 up to 50 years inclusively with uterine fibroids and associated heavy menstrual bleeding were included. Exclusions included patients with fast-growing uterine fibroids, patients scheduled for gynaecological surgery or ablation procedures for uterine fibroids within 6 months of study inclusion, patients with current osteoporosis or risk factors for developing osteoporosis (e.g. z-score for bone mineral density < -2.0, history of osteoporosis or current/previous other metabolic disorder associated with bone metabolism unless adequately treated) and patients with a haemoglobin level < 8.0 g/dL.

The design of the two studies included a screening phase of up to 13 weeks followed by a 24-week treatment phase with monthly visits, in which patients received relugolix + E2/NETA (according to the Summary of Product Characteristics [SPC] or placebo. In addition to the study medication, the patients in both study arms had the option of taking analgesics for the treatment of uterine fibroid-associated pain and iron supplements for iron deficiency anaemia.

Primary outcome in both studies was the proportion of patients with confirmed clinically relevant reduction of the menstrual blood loss (MBL) volume. Patient-relevant secondary outcomes were outcomes on morbidity, health-related quality of life and adverse events (AEs).

Implementation of the ACT

In the comparator arms of the two studies LIBERTY 1 and LIBERTY 2 placebo was administered. Placebo administration in combination with the allowed concomitant medication in the two studies is considered a sufficient approximation to watchful waiting as a possible treatment option within the ACT. Based on the studies LIBERTY 1 and LIBERTY 2, conclusions for the benefit assessment can only be drawn for patients for whom watchful waiting was best suited on an individual basis within the framework of the ACT. In the present situation, however, uncertainty remains as to whether watchful waiting was the most suitable treatment option for each individual patient in the two studies, or whether another individual treatment option might have been more suitable for some of the patients (ulipristal acetate or

invasive treatment options). Overall, the uncertainty regarding the implementation of the ACT in the studies LIBERTY 1 and LIBERTY 2 did not lead to an exclusion of the studies. However, the uncertainty was considered in the assessment of the certainty of conclusions of the results. Data for patients for whom symptom-oriented treatment (with progestogens or ulipristal acetate) or an invasive treatment option was the best individual choice in the framework of the ACT are not available.

Risk of bias and assessment of the certainty of conclusions

The risk of bias across outcomes was rated as low for both studies. The risk of bias of the results of all relevant outcomes (except for the outcome "discontinuation due to AEs") is high in both studies; for the outcome "discontinuation due to AEs", there is a reduced certainty of conclusions with a low risk of bias.

The limitations described above with regard to the implementation of the ACT in the studies LIBERTY 1 and LIBERTY 2 lead to a reduced certainty of conclusions. Overall, at most hints, e.g. of an added benefit, can therefore be derived on the basis of the studies LIBERTY 1 and LIBERTY 2.

Results

Mortality

Overall survival

No deaths occurred during the course of the studies LIBERTY 1 and LIBERTY 2. There was no hint of an added benefit of relugolix/E2/NETA in comparison with watchful waiting for the outcome "all-cause mortality"; an added benefit is therefore not proven.

Morbidity

Confirmed clinically relevant reduction of the MBL volume

The meta-analysis of the studies shows a statistically significant difference in favour of relugolix + E2/NETA for the outcome "confirmed clinically relevant reduction of the MBL volume at week 24" (at least one confirmed response at week 24). This resulted in a hint of an added benefit of relugolix/E2/NETA in comparison with watchful waiting for this outcome.

Pain (numeric rating scale [NRS])

The meta-analysis of the studies showed a statistically significant difference in favour of relugolix + E2/NETA for the outcome "pain" recorded with the NRS. A standardized mean difference (SMD) was considered to assess the relevance of the result. The 95% confidence interval (95% CI) was fully outside the irrelevance range [−0.2; 0.2]. This was interpreted to be a relevant effect. This resulted in a hint of an added benefit of relugolix/E2/NETA in comparison with watchful waiting for this outcome.

Health status (visual analogue scale of the European Quality of Life-5 Dimensions [EQ-5D VAS])

For the outcome "health status" recorded with the EQ-5D VAS, the meta-analysis of the studies shows no statistically significant difference between the treatment groups for the changes between study start and week 24. This resulted in no hint of an added benefit of relugolix/E2/NETA in comparison with watchful waiting; an added benefit is therefore not proven.

Symptoms (Symptom Severity Scale of the Uterine Fibroid Symptom and Quality of Life Questionnaire [UFS-QoL])

The meta-analysis of the studies showed a statistically significant difference in favour of relugolix + E2/NETA for the outcome “symptoms (symptom severity scale of the UFS QoL). The SMD was considered to assess the relevance of the result. The 95% CI was fully outside the irrelevance range [−0.2; 0.2]. This was interpreted to be a relevant effect. This resulted in a hint of an added benefit of relugolix/E2/NETA in comparison with watchful waiting for this outcome.

Health-related quality of life

Total score of the UFS-QoL

The meta-analysis of the studies showed a statistically significant difference in favour of relugolix + E2/NETA for the outcome “health-related quality of life” recorded with the UFS-QoL. An SMD was considered to assess the relevance of the result. The 95% CI for the total score was fully outside the irrelevance range [−0.2; 0.2]. This was interpreted to be a relevant effect. This resulted in a hint of an added benefit of relugolix/E2/NETA in comparison with watchful waiting for this outcome. In addition to the total score, all 6 subscales of the UFS-QoL also show a consistent positive result in favour of relugolix/E2/NETA compared to watchful waiting.

Side effects

Serious adverse events (SAEs), severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3), discontinuation due to AEs, vasomotor events (AEs), skeletal-related events (SAEs)

The meta-analysis of the studies showed no statistically significant differences between the treatment groups for each of the outcomes "SAEs", “severe AEs (CTCAE grade ≥ 3)”, “discontinuation due to AEs”, "vasomotor events (AEs)", as well as “skeletal-related events (SAEs)”. In each case, this resulted in no hint of greater or lesser harm from relugolix/E2/NETA in comparison with watchful waiting; greater or lesser harm is therefore not proven.

With regard to the informative value of the results on skeletal-related events (SAEs), it is pointed out that the duration of the LIBERTY studies (24 weeks) was too short for a sufficient assessment of skeletal-related events and that long-term data were necessary for this, especially since the approval specifies no time limit for the administration of relugolix/E2/NETA.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

Based on the results presented, the probability and extent of added benefit of the drug relugolix/E2/NETA in comparison with the ACT are assessed as follows:

Patients for whom watchful waiting was best suited on an individual basis within the framework of the ACT

Overall, there are several positive effects of relugolix/E2/NETA compared to watchful waiting within an observation period of 24 weeks for patients for whom watchful waiting is individually best suited in the context of the ACT.

For the outcome "confirmed clinically relevant reduction of the MBL volume", there is a hint of considerable added benefit of relugolix/E2/NETA compared with watchful waiting. In addition, there are further positive effects in the outcome categories "morbidity" and "health-related quality of life". Here, there is a hint of a non-quantifiable added benefit of relugolix/E2/NETA for each of the outcomes "pain" (NRS), "symptoms" (symptom severity scale of the UFS QoL) as well as "health-related quality of life" (total score of the UFS-QoL). The advantages based on these patient-reported outcomes overall support the hint of considerable added benefit shown for the confirmed clinically relevant reduction of the MBL volume. There are neither advantages nor disadvantages for the outcome category "side effects". However, the duration of the LIBERTY studies (24 weeks) is too short for a sufficient assessment of skeletal-related events.

In summary, there is a hint of considerable added benefit of relugolix/E2/NETA compared with watchful waiting for adult patients of reproductive age with moderate to severe symptoms of uterine fibroids, for whom watchful waiting is individually best suited in the context of the ACT.

Patients for whom symptom-oriented treatment (with progestogens or ulipristal acetate) or an invasive treatment option is the best individual choice in the framework of the ACT

The company presented no data versus the ACT for patients for whom symptom-oriented treatment (with progestogens or ulipristal acetate) or an invasive treatment option was the best individual choice in the framework of the ACT. An added benefit is therefore not proven.

Table 3 shows a summary of the probability and extent of the added benefit.

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) "proof", (2) "indication", (3) "hint", or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [2,3].

Table 3: Relugolix/E2/NETA – probability and extent of added benefit

Therapeutic indication	ACT[a]	Probability and extent of added benefit
Adult patients of reproductive age with moderate to severe symptoms of uterine fibroids	Individual treatment depending on the type and the severity of the symptoms as well as the patient's symptom burden, selecting from: ▪ watchful waiting ▪ symptom-oriented treatment: ▫ Progestogens under consideration of the respective approval status (for patients for whom symptomatic treatment of prolonged and/or heavy periods [menorrhagia, hypermenorrhoea] is sufficient) ▫ ulipristal acetate (for patients who have not yet reached menopause and for whom uterine fibroid embolization and/or surgery are not suitable or have failed). ▪ invasive treatment options	Patients for whom watchful waiting is best suited on an individual basis: ▪ hint of considerable added benefit Women for whom symptom-oriented treatment (with gestagens or ulipristal acetate) or an invasive treatment option is the best individual choice: ▪ added benefit not proven
a. Presented is the respective ACT specified by the G-BA. b. Because of its contraceptive effect, relugolix/E2/NETA cannot be used in patients with a current desire to have children. After treatment discontinuation, contraception is no longer given [1]. E2: estradiol; G-BA: Federal Joint Committee; NETA: norethisterone acetate		

The approach for the derivation of an overall conclusion on the added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

2.2 Research question

The aim of the present report is the assessment of the added benefit of the drug combination relugolix, E2 and NETA (hereinafter referred to as "relugolix/E2/NETA") in comparison with the ACT in adult patients of reproductive age for the treatment of moderate to severe symptoms of uterine fibroids.

The G-BA's specification of the ACT results in the research question presented in Table 4.

Table 4: Research question of the benefit assessment of relugolix/E2/NETA

Therapeutic indication	**ACT**[a]
Adult patients of reproductive age with moderate to severe symptoms of uterine fibroids	Individual treatment depending on the type and the severity of the symptoms as well as the patient's symptom burden, selecting from: ▪ watchful waiting ▪ symptom-oriented treatment: ▫ progestogens under consideration of the respective approval status (for patients for whom symptomatic treatment of prolonged and/or heavy periods [menorrhagia, hypermenorrhoea] is sufficient) ▫ ulipristal acetate (for patients who have not yet reached menopause and for whom uterine fibroid embolization and/or surgery are not suitable or have failed). ▪ invasive treatment options
a. Presented is the respective ACT specified by the G-BA. b. Because of its contraceptive effect, relugolix/E2/NETA cannot be used in patients with a current desire to have children. After treatment discontinuation, contraception is no longer given [1]. E2: estradiol; G-BA: Federal Joint Committee; NETA: norethisterone acetate	

The company first followed the ACT specified by the G-BA and named individual treatment depending on the type and the severity of the symptoms as well as the patient's symptom burden, taking into account the therapy options named by the G-BA. When retrieving information on relevant studies for the benefit assessment, the company took into account all therapy options mentioned in the ACT.

However, the company subsequently stated that it was critical of the naming of ulipristal acetate as a treatment option due to existing safety concerns regarding the risk of liver damage and due to its currently unclear importance in health care [4,5].

The background to this is that a risk assessment procedure for ulipristal acetate was initiated by the European Medicines Agency (EMA) in March 2020 [6]. During the procedure, the approval for ulipristal acetate, which covered both preoperative treatment and interval therapy in the present therapeutic indication was suspended until the initiation of the risk assessment procedure. As a result of the risk assessment procedure, ulipristal acetate was re-approved in January 2021, but with a restricted therapeutic indication. Ulipristal acetate is currently only approved for interval therapy in premenopausal women with moderate to severe symptoms for whom surgery is not appropriate or for whom surgery has failed [7,8]. The Committee for Medicinal Products for Human Use [CHMP]) concluded that for the restricted approval population, the benefits of ulipristal acetate in patients without treatment alternatives outweigh the observed risks of use [9]. Based on the EMA assessment, the G-BA considers ulipristal acetate to be a possible approved treatment option within the ACT in patients who have no treatment options and who have a correspondingly high level of suffering [10]. Even though there are safety concerns for ulipristal acetate, it is still an effective treatment option in the

therapeutic indication [11,12], which should in principle be available to patients as a therapeutic option, taking into account the limited therapeutic indication.

The present benefit assessment was conducted in comparison with the ACT specified by the G-BA, which means including ulipristal acetate.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs with a minimum duration of 24 weeks were used for the derivation of added benefit.

2.3 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study lists on relugolix/E2/NETA (status: 27 July 2021)
- bibliographical literature search on relugolix/E2/NETA (last search on 4 June 2021)
- search in trial registries/trial results databases for studies on relugolix/E2/NETA (last search on 4 June 2021)
- search on the G-BA website for relugolix/E2/NETA (last search on 4 June 2021)

To check the completeness of the study pool:

- Search in trial registries for relugolix/E2/NETA (last search on 7 September 2021); see Appendix A of the full report for search strategies

The check did not identify any additional relevant study.

2.3.1 Studies included

The studies listed in the following Table 5 were included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: relugolix/E2/NETA vs. individual treatment

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)	Clinical study report (CSR) (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication and other sources[c] (yes/no [citation])
Study MVT-601-3001 (LIBERTY 1[d])	Yes	No[e]	Yes	Yes [13]	Yes [14,15]	Yes [16,17]
Study MVT-601-3002 (LIBERTY 2[d])	Yes	No[e]	Yes	Yes [18]	Yes [19,20]	Yes [16,17]

a. Study sponsored by the company.
b. References of trial registry entries and any available reports on the study design and/or results listed in the trial registries.
c. Other sources: EPAR.
d. In the following tables, the study is referred to with this abbreviated form.
e. The sponsor of the study was Myovant Sciences GmbH. In March 2020, the company concluded an exclusive licence agreement with the sponsor for the regional clinical development, manufacture and marketing of relugolix/E2/NETA in Europe, the Commonwealth of Independent States including Russia, as well as Latin America, Australia and New Zealand.

E2: estradiol; EPAR: European Public Assessment Report; G-BA: Federal Joint Committee; NETA: norethisterone acetate; RCT: randomized controlled trial

The study pool for the benefit assessment of relugolix/E2/NETA corresponds to that of the company. It includes the two twin studies LIBERTY 1 and LIBERTY 2, which directly compare a free combination of relugolix and E2/NETA directly with placebo. The results of the free combination can be used for the benefit assessment of the fixed combination relugolix/E2/NETA (see also 2.3.2 2.3.2).

The placebo administration in combination with the allowed concomitant medication in the two studies is considered a sufficient approximation to watchful waiting as a possible treatment option within the ACT (see Section 2.3.2, Implementation of the ACT). Based on the studies LIBERTY 1 and LIBERTY 2, conclusions for the benefit assessment can only be drawn for patients for whom watchful waiting was best suited on an individual basis within the framework of the ACT. Data for patients for whom symptom-oriented treatment (with progestogens or ulipristal acetate) or an invasive treatment option was the best individual choice in the framework of the ACT are not available

2.3.2 Study characteristics

Table 6 and Table 7 describe the studies used for the benefit assessment.

Table 6: Characteristics of the studies included – RCT, direct comparison: relugolix + E2/NETA vs. placebo[a] (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and time period of study conduct	Primary outcome; secondary outcomes[b]
LIBERTY 1	RCT, double-blind, parallel-group	Premenopausal women aged 18 to ≤ 50 years with uterine fibroids[c] and associated heavy menstrual bleeding[d, e]	Relugolix + E2/NETA (N = 128) relugolix + placebo (weeks 1–12) followed by relugolix + E2/NETA (weeks 13–24)[f] (N = 132) placebo[a] (N = 128)	Screening: up to 13 weeks treatment: 24 weeks follow-up observation: up to 30 days (or participation in single-arm extension study)	80 centres in Brazil, Italy, Poland, South Africa, United Kingdom, USA 03/2017–04/2019	Primary: clinically relevant reduction of the MBL volume[g] secondary: morbidity, health-related quality of life, AEs
LIBERTY 2	RCT, double-blind, parallel-group	See LIBERTY 1	Relugolix + E2/NETA (N = 126) relugolix + placebo (weeks 1–12) followed by relugolix + E2/NETA (weeks 13–24)[f] (N = 127) placebo[a] (N = 129)	Screening: up to 13 weeks treatment: 24 weeks follow-up observation: up to 30 days (or participation in single-arm extension study)	99 centres in Belgium, Brazil, Chile, Czech Republic, Hungary, Poland, South Africa, USA 05/2017–07/2019	See LIBERTY 1

Table 6: Characteristics of the studies included – RCT, direct comparison: relugolix + E2/NETA vs. placebo[a] (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and time period of study conduct	Primary outcome; secondary outcomes[b]

a. This is considered, with limitations, to be a sufficient approximation to watchful waiting as a possible treatment option within the ACT (individual therapy) (see Section 2.3.2, Implementation of the ACT).

b. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes include only information on relevant available outcomes for this benefit assessment.

c. Confirmed by transvaginal ultrasound within the screening period. At least one uterine fibroid has to meet ≥ 1 of the following criteria (verified by central readout site): subserosal, intramural or < 50% intracavitary submucosal fibroid with a diameter ≥ 2 cm (longest diameter) or multiple small fibroids with a total uterine volume of ≥ 130 cm^3.

d. Evidenced by an MBL volume of ≥ 160 ml within a cycle or ≥ 80 ml per cycle over 2 menstrual cycles, measured by the alkaline haematin method during the screening period.

e. Exclusions included patients with fast-growing uterine fibroids, patients scheduled for gynaecological surgery or ablation procedures for uterine fibroids within 6 months of study inclusion, patients with current osteoporosis or risk factors for developing osteoporosis (e.g. z-score for bone mineral density < -2.0, history of osteoporosis or current/previous other metabolic disorder associated with bone metabolism unless adequately treated) and patients with a haemoglobin level < 8.0 g/dL.

f. In this study arm, patients initially received relugolix monotherapy (relugolix + placebo) for 12 weeks followed by another 12 weeks in which patients received relugolix combination therapy (relugolix + E2/NETA). The arm is irrelevant for the assessment and is not presented in the following tables.

g. Defined as an MBL volume of < 80 ml and at least a 50% reduction in baseline MBL volume in the last 35 days of treatment (measured using the alkaline haematin method).

AE: adverse event; E2: estradiol; MBL: menstrual blood loss; N: number of randomized patients; NETA: norethisterone acetate; RCT: randomized controlled trial

Table 7: Characteristics of the intervention – RCT, direct comparison: relugolix + E2/NETA vs. placebo[a] (multipage table)

Study	Intervention	Comparison
LIBERTY 1, LIBERTY 2	Relugolix, 40 mg, orally (tablet) + E2/NETA 1 mg/0.5 mg, orally (capsule) once daily each (in the morning, on an empty stomach)	Placebo orally (tablet + capsule) once daily each (in the morning, on an empty stomach)
	dose adjustments ▪ dose adjustments of the study medication were not planned; for AEs with CTCAE grade ≥ 3 that could not be improved by adequate medical interventions, interruption of treatment until AEs improved to CTCAE grade ≤ 2	
	Non-permitted pretreatment: ▪ within 6 months before screening: myomectomy, ultrasound-guided laparoscopic radiofrequency ablation or other surgical interventions for uterine fibroids, uterine artery embolization, magnetic resonance-guided focused ultrasound for uterine fibroids, or endometrial ablation for abnormal uterine bleeding **permitted concomitant treatment** ▪ analgesics for the treatment of uterine fibroid-associated pain[b]: ▫ first-line treatment: ibuprofen ▫ second-line treatment: paracetamol or other nonsteroidal anti-inflammatory drugs except ibuprofen ▫ third-line treatment: opioids or opioid-paracetamol combinations ▫ fourth-line treatment: at the investigator's discretion ▪ iron supplements for iron deficiency anaemia[c] **non-permitted concomitant treatment** ▪ hormone preparations (GnRH analogues, antiandrogens, progestogens and progestogen implants, aromatase inhibitors, oestrogens, hormonal contraceptives, selective oestrogen receptor modulators [e.g. tamoxifen], selective progesterone receptor modulators [e.g. ulipristal acetate], herbal products with known hormonal activity) ▪ intrauterine device (e.g. with levonorgestrel or copper) ▪ certain anticonvulsants: phenobarbital, carbamazepine, phenytoin, valproic acid and primidone ▪ before and during the study: drugs for the treatment of the bone density loss[e] (e.g. bisphosphonates, calcitonin, calcitriol, ipriflavone, teriparatide, denosumab) ▪ anticoagulants, fibrinolytic agents (e.g. tranexamic acid) ▪ glucocorticoids (if an oral dose of > 5 mg [prednisone equivalent] was expected every other day during the study) ▪ P-glycoprotein inducers (e.g. rifampicin, St. John's Wort) ▪ moderate and strong p-glycoprotein inhibitors (e.g. amiodarone, itraconazole, verapamil) ▪ surgical interventions to treat the uterine fibroids during the course of the study, unless it was deemed urgent for the patient for safety reasons	

Table 7: Characteristics of the intervention – RCT, direct comparison: relugolix + E2/NETA vs. placebo[a] (multipage table)

Study	Intervention	Comparison
a. This is considered, with limitations, to be a sufficient approximation to watchful waiting as a possible treatment option within the ACT (individual treatment) (see Section 2.3.2, Implementation of the ACT). b. Aim of the recommendation was to standardize analgesic medication as much as possible. Patients were instructed not to use analgesics prophylactically. c. Patients who were found to have microcytic iron deficiency anaemia during the screening period or in the course of the study had to start oral or parenteral iron supplementation and continue this for the entire study period. In this context, microcytic iron deficiency anaemia was defined as a haemoglobin value of ≤ 10 g/dL, a mean corpuscular volume below the lower normal range, and decreased serum iron and ferritin levels. d. After at least one month of use, relugolix/E2/NETA inhibits ovulation in women taking the recommended dose and provides adequate contraception [1]. Before the start of treatment, all hormonal contraceptives must be discontinued. Conclusions on fertility are therefore not possible within the framework of the study. e. Calcium and vitamin D preparations are excluded. CTCAE: Common Terminology Criteria for Adverse Events; E2: estradiol; GnRH: gonadotropin-releasing hormone; NETA: norethisterone acetate; RCT: randomized controlled trial		

The studies LIBERTY 1 and LIBERTY 2 have an identical study design (so-called twin studies) and are described jointly below.

The studies LIBERTY 1 and LIBERTY 2 are multinational, randomized, double-blind studies comparing relugolix + E2/NETA with placebo. Premenopausal women from 18 up to 50 years inclusively with uterine fibroids and associated heavy menstrual bleeding were included. Exclusions included patients with fast-growing uterine fibroids, patients scheduled for gynaecological surgery or ablation procedures for uterine fibroids within 6 months of study inclusion, patients with current osteoporosis or risk factors for developing osteoporosis (e.g. z-score for bone mineral density < -2.0, history of osteoporosis or current/previous other metabolic disorder associated with bone metabolism unless adequately treated) and patients with a haemoglobin level < 8.0 g/dL.

A total of 388 patients in the LIBERTY 1 study and 382 patients in the LIBERTY 2 study were randomly assigned in a 1:1:1 ratio to either treatment with relugolix + E2/NETA or relugolix + E2/NETA (delayed) or placebo. Stratification in both studies was based on geographical region (North America versus rest of the world) and the mean baseline MBL volume (< 225 ml vs. ≥ 225 ml, measured using the alkaline haematin method). In the study arm with the delayed administration of E2/NETA, patients first received relugolix monotherapy for 12 weeks followed by another 12 weeks in which patients were given relugolix combination therapy (relugolix + E2/NETA). This study arm is not relevant for the benefit assessment and is no longer considered hereinafter.

Figure 1 is a schematic presentation of the design of the two studies LIBERTY 1 and LIBERTY 2.

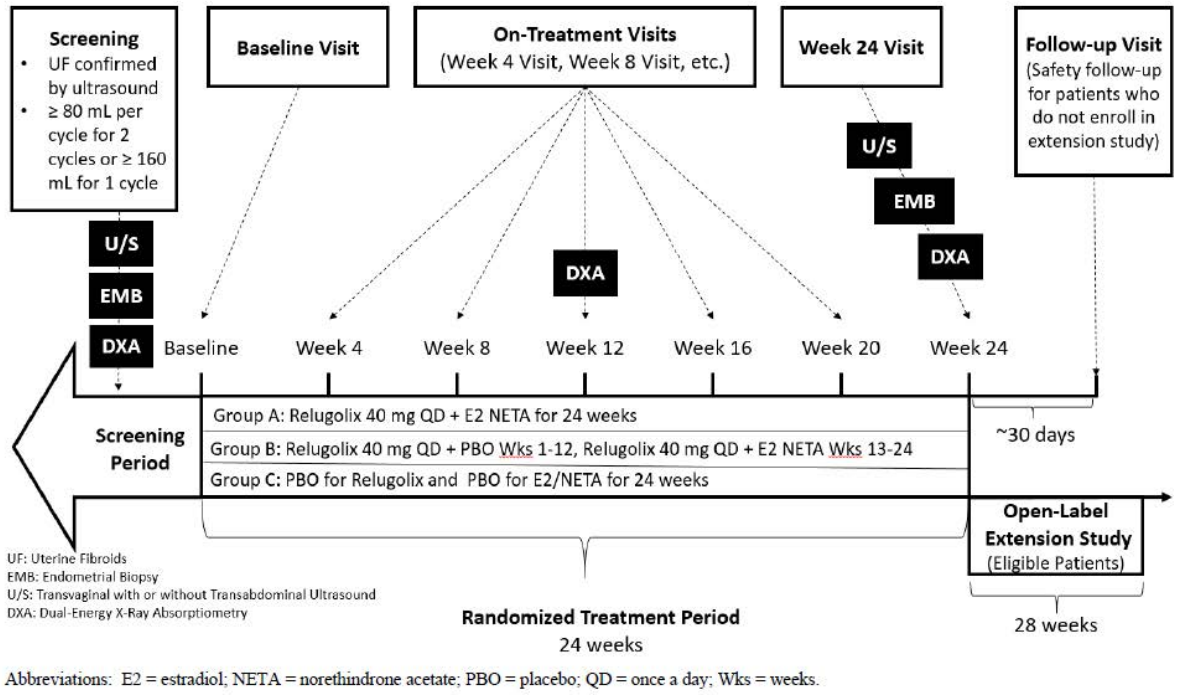

Figure 1: Design of the studies LIBERTY 1 and LIBERTY 2

The design of the two studies included a screening phase of up to 13 weeks followed by a 24-week treatment phase with monthly visits. Under certain circumstances, patients who completed the 24-week treatment phase could participate in a single-arm, open-label extension study (MVT-601-3003 [21]) in which all patients were treated with relugolix + E2/NETA.

The use of relugolix+E2/NETA (or relugolix/E2/NETA) was largely in compliance with the SPC [1]. In the studies, a loose-dose combination consisting of one tablet of relugolix 40 mg and one capsule of E2/NETA 1 mg/0.5 mg was used instead of the approved fixed combination in tablet form (relugolix/E2/NETA [40 mg/1 mg/0.5 mg]) [1]. In the context of the approval [17], the bioequivalence of the fixed combination and the free combination was proven on the basis of the MVT-601-042 study. The results of the free combination can be used for the benefit assessment of the fixed combination relugolix/E2/NETA.

In addition to the study medication, the patients in both study arms had the option of taking analgesics for the treatment of uterine fibroid-associated pain and iron supplements for iron deficiency anaemia (see Table 7).

Primary outcome in both studies was the proportion of patients with clinically relevant reduction of the MBL volume (defined as an MBL volume of < 80 ml and at least 50% reduction of the baseline MBL volume in the last 35 days of treatment, measured using the alkaline haematin method). Patient-relevant secondary outcomes were outcomes on morbidity, health-related quality of life and AEs.

Implementation of the ACT

The G-BA specified an individual treatment depending on the type and the severity of the symptoms as well as the patient's symptom burden as ACT, taking into account several treatment options (watchful waiting, symptom-oriented treatment [progestogens, ulipristal acetate] and invasive treatment options) (see Table 4).

In the comparator arms of the two studies LIBERTY 1 and LIBERTY 2 placebo was administered. Placebo administration in combination with the allowed concomitant medication in the two studies is considered a sufficient approximation to watchful waiting as a possible treatment option within the ACT (for an explanation, see below). Based on the studies LIBERTY 1 and LIBERTY 2, conclusions for the benefit assessment can only be drawn for patients for whom watchful waiting was best suited on an individual basis within the framework of the ACT. Data for patients for whom symptom-oriented treatment (with progestogens or ulipristal acetate) or an invasive treatment option was the best individual choice in the framework of the ACT are not available

Suitability of watchful waiting as treatment option for the study populations investigated

LIBERTY 1 and LIBERTY 2 are placebo-controlled studies. In addition to the study medication, both study arms also included the concomitant administration of analgesics and iron supplements (for details see Table 7). This made it possible to respond to the typical uterine fibroid-associated symptoms of pain as well as iron deficiency anaemia (as a result of severe blood loss) within the study. In relation to this, in the two study arms, approx. 74% (LIBERTY 1) and 73% (LIBERTY 2) of the patients took anti-inflammatory and antirheumatic drugs (predominantly ibuprofen), 54% (LIBERTY 1) and 56% (LIBERTY 2) received anti-anaemic drugs (e.g. ferrous sulphate) and 36% (LIBERTY 1) or 48% (LIBERTY 2) received analgesics (mainly paracetamol, occasionally also opioids). Antifibrinolytics (such as tranexanic acid) were prohibited in the study. These represent an acute therapy for severe bleeding and were only used as pretreatment in individual patients in the studies. Overall, the permitted concomitant medication is considered an adequate implementation of watchful waiting.

In the present situation, however, uncertainty remains as to whether watchful waiting is the most suitable treatment option for all patients in the two studies. A universal treatment algorithm for patients with symptomatic uterine fibroids does not exist and the treatment option chosen depends very much on the personal situation of the women, the subjectively perceived level of suffering and their wish for treatment [22]. Watchful waiting is recommended particularly for patients without symptoms [23-25]. The G-BA also advised the company that watchful waiting was mainly suitable for patients whose symptoms were only mild or did not significantly burden the patient [10]. As also comprehensively stated by the company, a large proportion of the patients in both studies had other symptoms in addition to heavy menstrual bleeding, such as uterine fibroid-related pain (91%), a feeling of tension and pressure in the pelvic area (93%) or fatigue (95%) (see Module 4 A of the full dossier assessment, Section 4.3.1.2.1 of the full dossier assessment). Therefore, uncertainty remains as to whether watchful

waiting was the adequate treatment option for all of these patients or whether another individual treatment option might have been more suitable for some patients. See the section below for more information.

Suitability of the other treatment options specified in the ACT for the study populations investigated

Progestogens

The G-BA defined treatment with progestogens in the framework of an individual treatment as ACT only for those patients for whom symptomatic treatment of prolonged and/or heavy menstrual bleeding is sufficient. The background is that in Germany, progestogens are not approved for the treatment of symptomatic uterine fibroids, but only for the treatment of hypermenorrhoea [26,27]. Uterine fibroids are also a contraindication for the levonorgestrel intrauterine device if they deform the uterine cavity [27]. Due to the limited approval and the fact that a large proportion of the patients had other symptoms in addition to heavy menstrual bleeding (see above), progestogens were not considered a possible treatment option for the patients investigated in the two studies. For the present benefit assessment, the lack of progestogens as a possible treatment option in the two studies is therefore not considered a restriction of an individual treatment for the study population investigated.

Ulipristal acetate

The G-BA defined treatment with ulipristal acetate as part of an individual treatment as an ACT for those patients for whom embolization of uterine fibroids and/or surgery are not suitable or have failed. This corresponds to the approval of ulipristal acetate [7].

According to the study protocol, the use of ulipristal acetate was prohibited in both studies and was thus not available as a possible treatment option for the patients. Approx. 10% of the study participants in the two studies had already had previous surgery due to uterine fibroids, which means that treatment with ulipristal acetate could in principle be an option for these patients. As well as for patients who refuse an invasive procedure (e.g. hysterectomy if they still wish to have a child [9]). It is therefore unclear whether for some patients in the study, due to their distressing symptoms (see above), treatment with ulipristal acetate compliant with the approval would have been better suited to the individual patient than watchful waiting also in the absence of other approved drug therapy alternatives.

However, it should additionally be pointed out that the studies were predominantly conducted in North America (see Table 8) and that ulipristal acetate is not approved in the USA for the therapeutic indication to be assessed. However, the German health care context is decisive for the benefit assessment and ulipristal acetate should therefore principally have been available to the study participants for a complete implementation of the ACT (in the sense of a multicomparator study).

Invasive treatment options

One inclusion criterion of both studies was that no invasive procedures (no gynaecological surgeries or ablation procedures) for the treatment of uterine fibroids were to be planned within 6 months after enrolment in the study and thus for the entire duration of the study. In the course of the study, invasive treatment of uterine fibroids was allowed in exceptional cases when it was urgently needed for the safety of the patients. The study documents show that one patient underwent invasive treatment of the uterine fibroids, i.e. in the form of a hysterectomy, during the course of the study.

For the present benefit assessment, it is assumed that the patients in the study consciously refrained from invasive procedures as a treatment option - at least for the period of study participation - and that such invasive procedures were also not necessarily medically indicated in the course of the study. However, the fact that no invasive therapy was planned at the time of inclusion in the study does not exclude the possibility that an invasive therapy option might have been more suitable on an individual basis for some patients. Analogous to the assessment of ulipristal acetate, invasive therapy options should therefore principally have been available to the study participants for a complete implementation of the ACT (in the sense of a multicomparator study)

Summary

Placebo administration in combination with the allowed concomitant medication in the two studies is considered a sufficient approximation to watchful waiting as a possible treatment option within the ACT. In the present situation, however, uncertainty remains as to whether watchful waiting was the most suitable treatment option for each individual patient in the two studies, or whether another individual treatment option might have been more suitable for some of the patients (ulipristal acetate or invasive treatment options). Overall, the uncertainty regarding the implementation of the ACT in the studies LIBERTY 1 and LIBERTY 2 did not lead to an exclusion of the studies. However, the uncertainty was considered in the assessment of the certainty of conclusions (see Section 2.4.2).

This deviates from the assessment of the company, according to which for the patients in the studies LIBERTY 1 and LIBERTY 2, only watchful waiting could be considered a suitable individual treatment.

Patient characteristics

Table 8 shows the patient characteristics for the studies included.

Table 8: Characteristics of the study populations – RCT, direct comparison: relugolix + E2/NETA vs. placebo[a] (multipage table)

Study characteristic category	LIBERTY 1		LIBERTY 2	
	relugolix/E2/ NETA	watchful waiting	relugolix/E2/ NETA	watchful waiting
	N[b] = 128	N[b] = 127	N[b] = 125	N[b] = 129
Age [years], mean (SD)	43 (5)	42 (6)	42 (5)	42 (5)
Age [years], n (%)				
< 40	30 (23)	36 (28)	32 (26)	42 (33)
≥ 40	98 (77)	91 (72)	93 (74)	87 (67)
Family origin [F/M], n (%)				
Black or African American	59 (46)	65 (51)	62 (50)	74 (57)
White	64 (50)	56 (44)	58 (46)	49 (38)
Other[c]	5 (4)	6 (5)	5 (4)	6 (5)
Region, n (%)				
Europe	23 (18)	26 (20)	18 (14)	16 (12)
North America	98 (77)	98 (77)	93 (74)	96 (74)
Rest of the world[d]	7 (5)	3 (2)	14 (11)	17 (13)
BMI [kg/m^2], mean (SD)	31.4 (7.6)	32.3 (7.5)	31.0 (6.6)	32.1 (7.6)
MBL volume [ml][e], mean (SD)	239.4 (180.3)	218.8 (125.0)	246.7 (186.0)	211.8 (129.9)
MBL volume [ml][e], n (%)				
< 225	84 (66)	85 (67)	80 (64)	86 (67)
≥ 225	44 (34)	42 (33)	45 (36)	43 (33)
Volume of the index uterine fibroid [cm^3], median [min; max]	24.2 [1.5; 989.0]	27.8 [0.8; 1031.2]	29.2 [2.2; 944.0]	31.4 [1.3; 866.5]
Uterus volume [cm^3], median [min; max]	265.2 [56.6; 1580.1]	293.2 [65.5; 2015.1]	274.3 [79.4; 1907.6]	295.9 [58.2; 2625.0]
Classification of the uterine fibroids, n (%)				
Subserosal	30 (23)	36 (28)	20 (16)	22 (17)
Intramural	67 (52)	70 (55)	48 (38)	60 (47)
Submucosal	25 (20)	25 (20)	21 (17)	18 (14)
Unknown	54 (42)	50 (39)	65 (52)	56 (43)
Disease duration of the uterine fibroids, n (%)				
< 1 year	32 (25)	30 (24)	31 (25)	30 (23)
≥ 1 – < 3 years	34 (27)	21 (17)	27 (22)	29 (22)
≥ 3 – < 5 years	19 (15)	21 (17)	19 (15)	16 (12)
≥ 5 – < 10 years	20 (16)	27 (21)	26 (21)	22 (17)
≥ 10 years	23 (18)	26 (20)	22 (18)	30 (23)
Unknown	0 (0)	2 (2)	0 (0)	2 (2)
Previous intervention due to uterine fibroids, n (%)				
Yes	20 (16)	13 (10)	11 (9)	11 (9)
No	108 (84)	114 (90)	114 (91)	118 (91)

Table 8: Characteristics of the study populations – RCT, direct comparison: relugolix + E2/NETA vs. placebo[a] (multipage table)

Study characteristic category	LIBERTY 1		LIBERTY 2	
	relugolix/E2/ NETA	watchful waiting	relugolix/E2/ NETA	watchful waiting
	N[b] = 128	N[b] = 127	N[b] = 125	N[b] = 129
Previous pregnancies, n (%)				
Yes	101 (79)	103 (81)	103 (82)	108 (84)
No	27 (21)	24 (19)	22 (18)	21 (16)
Haemoglobin value [g/dL] – mean (SD)	11.2 (1.6)	11.4 (1.4)	11.3 (1.5)	11.1 (1.6)
UFS-QoL Symptom Severity Scale, MW (SD)	55.7 (20.5)	61.1 (19.0)	59.9 (22.1)	60.1 (19.6)
Maximum NRS score for uterine fibroid-associated pain, n (%)				
< 4	43 (33.6)	31 (24.4)	30 (24.0)	31 (24.0)
≥ 4	84 (65.6)	95 (74.8)	93 (74.4)	95 (73.6)
Unknown	1 (0.8)	1 (0.8)	2 (1.6)	3 (2.3)
Maximum NRS score, mean (SD)[f]	5.4 (3.4)	5.7 (3.1)	5.7 (3.2)	5.7 (2.9)
PGA for uterine fibroid-related function, n (%)				
No restriction at all	10 (8)	7 (6)	6 (5)	9 (7)
Slight restriction	19 (15)	21 (17)	15 (12)	9 (7)
Moderate restriction	28 (22)	26 (20)	38 (30)	42 (33)
Marked restriction	34 (27)	34 (27)	36 (29)	31 (24)
Severe restriction	5 (4)	12 (9)	12 (10)	20 (16)
Unknown	32 (25)	27 (21)	18 (14)	18 (14)
PGA for uterine fibroid-associated symptoms, n (%)				
No restriction at all	0 (0)	2 (2)	2 (2)	4 (3)
Slight restriction	12 (9)	10 (8)	11 (9)	7 (5)
Moderate restriction	36 (28)	36 (28)	32 (26)	37 (29)
Marked restriction	34 (27)	35 (28)	41 (33)	38 (29)
Severe restriction	14 (11)	17 (13)	21 (17)	25 (19)
Unknown	32 (25)	27 (21)	18 (14)	18 (14)
Treatment discontinuation, n (%)	28 (22)[g]	22 (17)[g]	23 (18)[h]	27 (21)[h]
Study discontinuation, n (%)	ND	ND	ND	ND

Table 8: Characteristics of the study populations – RCT, direct comparison: relugolix + E2/NETA vs. placebo[a] (multipage table)

Study characteristic category	LIBERTY 1		LIBERTY 2	
	relugolix/E2/ NETA	watchful waiting	relugolix/E2/ NETA	watchful waiting
	N[b] = 128	N[b] = 127	N[b] = 125	N[b] = 129

a. This is considered, with limitations, to be a sufficient approximation to watchful waiting as a possible treatment option within the ACT (individual treatment) (see Section 2.3.2, Implementation of the ACT).
b. Number of patients who received at least one dose of the study treatment. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
c. Institute's calculation, including: native Americans/Alaskans, several family origins or unknown.
d. Institute's calculation.
e. Measured using the alkaline haematin method.
f. Based on the last 35 days before randomization.
g. In the LIBERTY 1 study, the most common reasons for treatment discontinuation (before reaching the maximum treatment duration of 24 weeks) were withdrawal of consent (7.8% and 5.5%), AEs (5.5% and 3.9%), other reasons (3.9% vs. 0.8%), lack of efficacy (3.1% and 2.3%) and loss to follow-up (0.8% and 3.9%) in the intervention and the comparator arm, respectively.
h. In the LIBERTY 2 study, the most common reasons for treatment discontinuation (before reaching the maximum treatment duration of 24 weeks) were withdrawal of consent (10.3% and 4.7%), loss to follow-up (3.2% and 5.4%), AEs (1.6% and 4.7%), lack of efficacy (1.6% and 0.8%) and other reasons (0.8% vs. 3.9%) in the intervention and the comparator arm, respectively.

AE: adverse event; BMI: body mass index; BPD: Bleeding and Pelvic Discomfort; E2: estradiol; F: female; M: male; MBL: menstrual blood loss; n: number of patients in the category; N: number of patients receiving the study medication; ND: no data; NETA: norethisterone acetate; NRS: numeric rating scale; PGA: Patient Global Assessment; RCT: randomized controlled trial; SD: standard deviation; UFS-QoL: Uterine Fibroid Symptom and Quality of Life Questionnaire

Overall, the characteristics of the patients included were largely comparable both between the studies and between the treatment arms. The mean age of the participants in both studies was about 42 years; most of them were from North America (across arms and studies 76%). Overall, only 16% of the included patients were from Europe. The mean MBL volume per arm ranged from 212 ml to 247 ml and a large proportion of patients had not yet undergone surgery for uterine fibroids. At baseline, 72% of patients across arms and studies had an NRS score ≥ 4, pointing to at least moderate pain [28]. Almost all included patients were at least slightly restricted by uterine fibroid-associated symptoms or slightly restricted in their daily activities. About 20% of the patients discontinued treatment prematurely.

Risk of bias across outcomes (study level)

Table 9 shows the risk of bias across outcomes (risk of bias at study level).

Table 9: Risk of bias across outcomes (study level) – RCT, direct comparison: relugolix + E2/NETA vs. placebo[a]

Study	Adequate random sequence generation	Group allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
LIBERTY 1	Yes	Yes	Yes	Yes	Yes	Yes	Low
LIBERTY 2	Yes	Yes	Yes	Yes	Yes	Yes	Low

a. This is considered, with limitations, to be a sufficient approximation to watchful waiting as a possible treatment option within the ACT (individual treatment) (see Section 2.3.2, Implementation of the ACT).

E2: estradiol; NETA: norethisterone acetate; RCT: randomized controlled trial

The risk of bias across outcomes was rated as low for both studies.

Transferability of the study results to the German health care context

The company stated that the results of the studies LIBERTY 1 and LIBERTY 2 are transferable to the German health care context. The study comparator used, placebo, together with the option to take analgesics for pain and iron supplementation to treat anaemia in both study arms, would be in line with clinical practice. About half of the study population was "white" and more than 90% of the included patients were treated in North America and Europe. Since the vast majority of the patients included were thus treated in countries where the general health care situation is considered comparable to the health care situation in Germany, it can be assumed that the study results are fully transferable to the German health care context.

The company did not provide any further information on the transferability of the study results to the German health care context.

2.4 Results on added benefit

2.4.1 Outcomes included

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

- Mortality
  - All-cause mortality
- Morbidity
  - Confirmed clinically relevant reduction of the MBL volume
  - Pain, recorded with a NRS

- Health status, recorded with the EQ-5D VAS
- Symptoms, recorded with the UFS-QoL

- Health-related quality of life
  - Recorded with the total score of the UFS-QoL
- Side effects
  - Serious AEs (SAEs)
  - Severe AEs (CTCAE grade ≥ 3)
  - Discontinuation due to AEs
  - Skeletal-related events (SMQ osteoporosis/osteopenia (broad search) + user-defined PT compilation of fractures, SAEs)
  - Vasomotor events (PT compilation [hyperhidrosis, heat sensation, hot flush, night sweats, flush], AEs)
  - Further specific AEs, if any

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

Table 10 shows the outcomes for which data were available in the studies included.

Table 10: Matrix of outcomes – RCT, direct comparison: relugolix + E2/NETA vs. placebo[a]

Study	Outcomes											
	All-cause mortality[b]	Confirmed clinically relevant reduction of the MBL volume[c]	Pain (NRS)	Health status (EQ-5D VAS)	Symptoms (Symptom Severity Scale of the UFS-QoL)	Health-related quality of life (total score of the UFS-QoL)[d]	SAEs	Severe AEs (CTCAE grade ≥ 3)	Discontinuation due to AEs	Skeletal-related events (SAEs)[e]	Vasomotor events (AEs)[f]	Further specific AEs[g]
LIBERTY 1	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
LIBERTY 2	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No

a. This is considered, with limitations, to be a sufficient approximation to watchful waiting as a possible treatment option within the ACT (individual treatment) (see Section 2.3.2, Implementation of the ACT).
b. Operationalized via AEs that led to death.
c. MBL volume of < 80 ml and at least a 50 % reduction of the baseline MBL volume measured using the alkaline haematin method, which existed at least since the previous analysis date and until the end of the study (week 24) (referred to as permanent normalization of the MBL volume by the company in Module 4 A of the full dossier assessment).
d. To calculate the QoL total score, the scores of the 6 subscales ("Concern", "Activities", "Energy/Mood", "Control", "Self-Consciousness", "Sexual Function") are added. The subscales are presented as supplementary information in the benefit assessment.
e. Operationalized a priori as SMQ "osteoporosis/osteopenia" (broad search) + user-defined PT compilation of fractures (all PTs termed "fracture" except "tooth fracture" and "penile fracture"). To ensure that no non-patient-relevant AEs are included (e.g. osteopenia [without symptoms]), only the serious AEs are considered. The results on AEs show consistent results.
f. Operationalized a priori via the following 5 PTs: hyperhidrosis, heat sensation, hot flush, night sweats, flush
g. No further specific AEs were identified.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; E2: estradiol; MBL: menstrual blood loss; MedDRA: Medical Dictionary for Regulatory Activities; NETA: norethisterone acetate; NRS: numeric rating scale; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SMQ: Standardized MedDRA Query; UFS-QoL: Uterine Fibroid Symptom and Quality of Life Questionnaire; VAS: visual analogue scale

Notes on the included outcomes and analyses

Morbidity

Confirmed clinically relevant reduction of the MBL volume

The following response criterion was used in the two studies to assess the clinically relevant reduction in MBL volume: MBL volume of < 80 ml and at least a 50% reduction in baseline MBL volume. This was considered adequate to record a clinically relevant reduction in MBL volume.

For this outcome, the company presented analyses on the one-time reduction and the confirmed clinically relevant reduction. The confirmed clinically relevant reduction in MBL volume (referred to by the company as permanent normalization of the MBL volume) [29].

For this operationalization, the company presented several types of analysis (responder frequencies broken down by visits and event time analyses). The relative risk at the end of the study (week 24) was used for the benefit assessment. For this assessment, a patient was considered a responder if she showed a response during the course of the study (by week 20 at the latest) that lasted until the end of the study (response confirmed at least once at week 24).

Additionally, the confirmed amenorrhoea (at week 24) and the reduction in MBL volume (percentage change) were presented as further operationalizations. Moreover, the proportions of responders per visit (weeks 8, 12, 16 and 20) for the outcomes "confirmed clinically relevant reduction in MBL volume" and "confirmed amenorrhoea" are presented to better assess the progress during the study (see Table 21 in Appendix C of the full dossier assessment).

Pain (NRS)

In the studies LIBERTY 1 and LIBERTY 2, patients assessed the maximum intensity of their uterine fibroid-related pain daily by means of an electronic diary. In doing so, they used an NRS to record the pain. On this 11-point scale, a score of 0 corresponds to no pain and a score of 10 corresponds to the worst pain imaginable [28]. For the benefit assessment, the reduction of the maximum NRS score within the last 35 days before a visit based on the entire study population is used (change versus baseline in relation to all visits in the course of the study). Analyses based on continuous data (mean difference compared with baseline) are considered using a mixed-effects model with repeated measures (MMRM).

UFS-QoL

The UFS-QoL is a valid, disease-specific instrument for recording uterine fibroid-associated symptoms and health-related quality of life [30,31]. The questionnaire comprises 37 items, all of which are queried using a 5-point Likert scale. All scales are transformed to values from 0 to 100. The first eight items record typical symptoms in the therapeutic indication (e.g. menstrual complaints, feeling of tension and pressure in the pelvic area, fatigue, increased urinary frequency) and are summarized in the Symptom Severity Scale. For the benefit assessment, the scale is assigned to the outcome category "morbidity" and not - as stated by the company - to health-related quality of life. The remaining 29 items record the disease-specific health-related quality of life and are used to assess the health-related quality of life in the benefit assessment on the basis of the total score. Here, the total score consists of 6 subscales (Concern, Activities, Energy/Mood, Control, Self-consciousness and Sexual Function), which are presented as supplementary information in the benefit assessment. For the benefit assessment, analyses based on continuous data (mean difference compared with baseline) were considered using an MMRM.

For the Symptom Severity Score, the company additionally provided post hoc defined responder analyses for the proportion of patients with an improvement of ≥ 25 points (corresponds to ≥ 25%). These were not used for the benefit assessment. As explained in the *General Methods* of the Institute [2,32], for a response criterion to reflect with sufficient certainty a patient-noticeable change, it should correspond to a predefined value of at least 15% of the scale range of an instrument (in post-hoc analyses exactly 15% of the scale range).

The analyses based on the UFS-QoL (Bleeding and Pelvic Discomfort [BPD] Scale and UFS-QoL Revised Activities Scale) additionally provided by the company do not provide any additional relevant information and were therefore not used for the benefit assessment.

Side effects

Analyses on AEs

In addition to the total rates of AEs and SAEs, the company presented sensitivity analyses in the dossier in which it excludes AEs that, in its view, were already recorded and reported in the context of the patient-relevant efficacy outcomes (change in MBL volume, pain caused by uterine fibroids) (see Module 4 A of the full dossier assessment, Section 4.2.5.4 of the full dossier assessment). The selection was made for the dossier. In doing so, it also excluded events that did not necessarily represent symptoms of the underlying disease (e.g. back pain or diarrhoea). The study protocol of the LIBERTY studies specified that severe MBL should not be recorded as an AE unless it is an event that meets the criteria for classification as a SAE. This is deemed sufficient for the benefit assessment. The total rates on AEs and SAEs were therefore used in the present benefit assessment. In addition, it is pointed out that the sensitivity analyses submitted by the company do not show any deviating result compared to the total rates used in the benefit assessment.

2.4.2 Risk of bias

Table 11 describes the risk of bias for the results of the relevant outcomes.

Table 11: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: relugolix + E2/NETA vs. placebo[a]

Study	Study level	Outcomes										
		All-cause mortality[b]	Confirmed clinically relevant reduction of the MBL volume	Pain (NRS)	Health status (EQ-5D VAS)	Symptoms (Symptom Severity Scale of the UFS-QoL)	Health-related quality of life (QoL total score of the UFS-QoL)	SAEs	Severe AEs (CTCAE grade ≥ 3)	Discontinuation due to AEs	Skeletal-related events (SAEs)[c]	Vasomotor events (AEs)[d]
LIBERTY 1	L	H[e]	H[e]	H[e]	H[e, f]	H[e]	H[e]	H[e]	H[e]	N[g]	H[e]	H[e]
LIBERTY 2	L	H[e]	H[e]	H[e]	H[e, f]	H[e, f]	H[e, f]	H[e]	H[e]	N[g]	H[e]	H[e]

a. This is considered, with limitations, to be a sufficient approximation to watchful waiting as a possible treatment option within the ACT (individual therapy) (see Section 2.3.2, Implementation of the ACT).
c. Operationalized via AEs that led to death.
c. Operationalized a priori as SMQ "osteoporosis/osteopenia" (broad search) + user-defined PT compilation of fractures (all PTs termed "fracture" except "tooth fracture" and "penile fracture").
d. Operationalized a priori via the following 5 PTs: hyperhidrosis, heat sensation, hot flush, night sweats, flush
e. Incomplete observations for potentially informative reasons; (for reasons, see running text below).
f. Large proportion of patients (> 10%) who were not considered in the analysis.
g. Despite the low risk of bias, the certainty of results for the outcome "discontinuation due to AEs" was assumed to be limited (for reasons, see running text below).

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; E2: estradiol; H: high; L: low; MBL: menstrual blood loss; MedDRA: Medical Dictionary for Regulatory Activities; NETA: norethisterone acetate; NRS: numeric rating scale; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SMQ: Standardized MedDRA Query; UFS-QoL: Uterine Fibroid Symptom and Quality of Life Questionnaire; VAS: visual analogue scale

In both studies, the risk of bias of the results of all relevant outcomes was high, except for the outcome "discontinuation due to AEs".

The high risk of bias is mainly due to the fact that in the studies LIBERTY 1 and LIBERTY 2 the proportion of patients with premature treatment discontinuation (before reaching the planned treatment duration of 24 weeks) was high (approx. 20%) in each case (see Table 8) and these patients were not or not completely taken into account in the analysis. With premature treatment discontinuation, the observation period ("early termination visit") for the outcomes presented in the benefit assessment ended, too. AEs were observed until 30 days after the end of treatment, but not until the end of the study. The reasons for discontinuation (mainly withdrawal of consent, AEs, lack of efficacy and loss to follow-up) are potentially informative and also differ in part between the study arms (e.g. "withdrawal of consent", LIBERTY 2: 10.3% [relugolix + E2/NETA] vs. 4.7% [placebo] of the patients). The company provided no information on the responses to the questionnaires used in the studies, which could possibly

allow conclusions to be drawn about the time of the discontinuations. The available information in the study reports (Summary of Exposure) shows that a relevant part of the patients already discontinued in the first half (≙ 12 weeks) of the studies and thus their observation time was significantly shortened. Overall, there is therefore a high risk of bias in the results for all outcomes except “discontinuation due to AEs”.

The risk of bias of each of the results on the outcome "discontinuation due to AEs" was rated as low in both LIBERTY studies. In each case, however, the certainty of results was limited despite the low risk of bias. Premature treatment discontinuation for reasons other than AEs is a competing event for the outcome of discontinuation due to AEs to be recorded. This means that, after discontinuation for other reasons, AEs that would have led to treatment discontinuation may have occurred, but that the criterion "discontinuation" can no longer be applied to them. It cannot be estimated how many AEs this concerns.

Summary assessment of the certainty of conclusions

Irrespective of the aspects described for the risk of bias, the certainty of conclusions of the study results is reduced for the present research question due to the uncertainties described in Section 2.3.2 (regarding the implementation of the ACT). Overall, at most hints, e.g. of an added benefit, can therefore be derived on the basis of the studies LIBERTY 1 and LIBERTY 2.

2.4.3 Results

Table 12 and Table 13 summarize the results of the comparison of relugolix + E2/NETA with placebo in adult patients of reproductive age with moderate to severe symptoms of uterine fibroids. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company’s dossier. The forest plots of the meta-analyses calculated by the Institute can be found in Appendix B of the full dossier assessment. For the outcome “confirmed clinically relevant reduction in MBL volume” and the supplementary outcome “confirmed amenorrhoea”, the proportions of responders at the individual visits during the course of the study are also shown in Appendix C of the full dossier assessment. Tables with the common AEs, SAEs, severe AEs as well as all AEs that led to discontinuation of treatment can be found in Appendix D of the full dossier assessment.

Table 12: Results (mortality, morbidity, side effects) – RCT, direct comparison: relugolix + E2/NETA vs. placebo[a] (multipage table)

Outcome category outcome study	Relugolix + E2/NETA N	 patients with event n (%)	Placebo N	 patients with event n (%)	Relugolix + E2/NETA vs. placebo RR [95% CI]; p-value[b]
Mortality					
All-cause mortality					
LIBERTY 1	128	0 (0)	127	0 (0)	–
LIBERTY 2	126	0 (0)	129	0 (0)	–
Morbidity					
Confirmed clinically relevant reduction of the MBL volume[c]					
LIBERTY 1	128	88 (68.8)	127	15 (11.8)	5.82 [3.57; 9.50]; < 0.001[d]
LIBERTY 2	125	87 (69.6)	129	6 (4.7)	14.96 [6.79; 32.97]; < 0.001[d]
Total					8.40 [5.53; 12.74]; < 0.001[e]
Confirmed amenorrhea (presented as supplementary information)					
LIBERTY 1	*128*	*67 (52.3)*	*127*	*7 (5.5)*	*9.50 [4.54; 19.88][d]*
LIBERTY 2	*125*	*63 (50.4)*	*129*	*4 (3.1)*	*16.25 [6.10; 43.32][d]*
Total					*11.92 [6.61; 21.50][e]*
Side effects					
AEs (supplementary information)					
LIBERTY 1	128	79 (61.7)	127	84 (66.1)	–
LIBERTY 2	126	76 (60.3)	129	76 (58.9)	–
SAEs					
LIBERTY 1	128	7 (5.5)	127	2 (1.6)	3.47 [0.74; 16.40]; 0.172
LIBERTY 2	126	1 (0.8)	129	4 (3.1)	0.26 [0.03; 2.26]; 0.370
Total					1.34 [0.47; 3.84]; 0.584[g]
Severe AEs (CTCAE grade ≥ 3)					
LIBERTY 1	128	7 (5.5)	127	11 (8.7)	0.63 [0.25; 1.58]; 0.341
LIBERTY 2	126	5 (4.0)	129	8 (6.2)	0.64 [0.22; 1.90]; 0.571
Total					0.63 [0.31; 1.28]; 0.200[g]
Discontinuation due to AEs					
LIBERTY 1	128	7 (5.5)	127	5 (3.9)	1.39 [0.45; 4.26]; 0.769
LIBERTY 2	126	3 (2.4)	129	6 (4.7)	0.51 [0.13; 2.00]; 0.500
Total					0.91 [0.39; 2.12]; 0.834[g]
Skeletal-related events (SAEs[h])					
LIBERTY 1	128	1 (0.8)	127	0 (0)	2.98 [0.12; 72.39]; > 0.999
LIBERTY 2	126	0 (0)	129	1 (0.8)	0.34 [0.01; 8.30]; > 0.999
Total					1.01 [0.14; 7.17]; 0.994[g]

Table 12: Results (mortality, morbidity, side effects) – RCT, direct comparison: relugolix + E2/NETA vs. placebo[a] (multipage table)

Outcome category outcome study	Relugolix + E2/NETA		Placebo		Relugolix + E2/NETA vs. placebo
	N	patients with event n (%)	N	patients with event n (%)	RR [95% CI]; p-value[b]
Vasomotor events (AEs[i])					
LIBERTY 1	128	19 (14.8)	127	12 (9.4)	1.57 [0.80; 3.10]; 0.250
LIBERTY 2	126	8 (6.3)	129	5 (3.9)	1.64 [0.55; 4.87]; 0.407
Total					1.59 [0.89; 2.83]; 0.112[g]

a. This is considered, with limitations, to be a sufficient approximation to watchful waiting as a possible treatment option within the ACT (individual treatment) (see Section 2.3.2, Implementation of the ACT).
b. Unless otherwise stated unstratified calculation of RR and CI. The CI is based on a normal distribution approximation; p-value: exact test according to Fisher.
c. MBL volume of < 80 ml and at least a 50% reduction of the baseline MBL volume measured using the alkaline haematin method, which existed at least since the previous analysis date and until the end of the study (week 24) (referred to as permanent normalization of the MBL volume by the company in Module 4 A of the full dossier assessment). Imputation of missing values according to statistical analysis plan, no information on this in Module 4 A of the full dossier assessment. The proportion of responders at the other analysis dates (weeks 8, 12, 16 and 20) are presented as supplementary information in Table 21 of the full dossier assessment.
d. Effect, CI and p-value: Institute's calculation; p-value: unconditional exact test (CSZ method according to [33]).
e. Institute's calculation of the meta-analysis.
f. Amenorrhoea that existed at least since the previous analysis date and until the end of the study (week 24) (referred to as permanent amenorrhoea by the company in Module 4 A of the full dossier assessment). Amenorrhoea was defined as either "no dispensing of menstrual hygiene products at two consecutive visits due to reported amenorrhoea" or "no dispensing of menstrual hygiene products due to absence of menstruation" or "dispensing of menstrual hygiene products with an MBL volume of less than 5 ml". Imputation of missing values according to statistical analysis plan, no information on this in Module 4 A of the full dossier assessment. The proportion of responders at the other analysis dates are presented as supplementary information in Table 21 of the full dossier assessment.
g. From IPD meta-analysis. RR and CI: Cochran-Mantel-Haenszel (CMH) method stratified by study; p-value: CMH test stratified by study.
h. Operationalized as SMQ “osteoporosis/osteopenia” (broad search) + user-defined PT compilation of fractures (all PTs termed "fracture" except “tooth fracture” and “penile fracture”). However, the duration of the LIBERTY studies (24 weeks each) is too short for a sufficient assessment of skeletal-related events.
i. Operationalized using the following 5 PTs: hyperhidrosis, heat sensation, hot flush, night sweats, flush.

AE: adverse event; CI: confidence interval; CMH: Cochran-Mantel-Haenszel; CTCAE: Common Terminology Criteria for Adverse Events; E2: estradiol; IPD: individual patient data; MBL: menstrual blood loss; n: number of patients with (at least one) event; N: number of analysed patients; NETA: norethisterone acetate; PT: preferred term; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SMQ: standardized MedDRA Query

Table 13: Results (morbidity, health-related quality of life, continuous) – RCT, direct comparison: relugolix + E2/NETA vs. placebo[a] (multipage table)

Outcome category outcome study	Relugolix + E2/NETA			Placebo			Relugolix + E2/NETA vs. placebo
	N[b]	values at baseline mean (SD)	change in the course of the study mean[c] (SE)	N[b]	values at baseline mean (SD)	change in the course of the study mean[c] (SE)	MD [95% CI]; p-value[c]
Morbidity							
Reduction of the MBL volume (percentage change, presented as supplementary information)[d]							
LIBERTY 1	*118*	*239.4 (180.3)*	*-78.9 (3.6)*	*120*	*218.8 (125.0)*	*-15.9 (3.5)*	*-63.01 [-72.55; -53.47]; < 0.001*
LIBERTY 2	*116*	*246.7 (186.0)*	*-76.4 (4.5)*	*124*	*211.8 (129.9)*	*-13.9 (4.4)*	*-62.53 [-74.29; -50.77]; < 0.001*
Total[e]							*-63.09 [-70.67; -55.52] < 0.001*
Pain (NRS)[d]							
LIBERTY 1	127	5.4 (3.4)	-2.6 (0.2)	126	5.7 (3.1)	-1.2 (0.2)	-1.42 [-2.06; -0.78]; < 0.001
LIBERTY 2	124	5.7 (3.2)	-2.8 (0.3)	128	5.7 (2.9)	-1.6 (0.3)	-1.24 [-1.92; -0.55]; < 0.001
Total[e]							-1.33 [-1.80; -0.86]; < 0.001 SMD -0.43 [-0.61; -0.26]
Health status (EQ-5D VAS)[f]							
LIBERTY 1	99	75.9 (17.4)	5.1 (2.0)[g]	104	73.5 (18.5)	4.8 (2.0)[g]	0.34 [-5.07; 5.74]; 0.902[g]
LIBERTY 2	100	73.9 (19.3)	7.6 (2.1)[g]	97	75.8 (19.5)	3.2 (2.2)[g]	4.33 [-1.23; 9.90]; 0.126[g]
Total[e]							2.29 [-1.59; 6.17]; 0.247[g]
Symptoms (symptom severity scale of the UFS-QoL)[d]							
LIBERTY 1	113	55.7 (20.5)	-30.2 (2.2)	119	61.1 (19.0)	-10.9 (2.1)	-19.28 [-25.18; -13.38]; < 0.001
LIBERTY 2	115	59.9 (22.1)	-31.1 (2.2)	114	60.1 (19.6)	-12.3 (2.3)	-18.76 [-24.52; -13.01]; < 0.001
Total[e]							-18.94 [-23.05; -14.84]; < 0.001 SMD -0.79 [-0.98; -0.60]
Health-related quality of life							
Total score of the UFS-QoL[f]							
LIBERTY 1	113	38.1 (20.4)	36.2 (2.3)	119	34.3 (20.5)	11.7 (2.2)	24.59 [18.47; 30.71]; < 0.001

Table 13: Results (morbidity, health-related quality of life, continuous) – RCT, direct comparison: relugolix + E2/NETA vs. placebo[a] (multipage table)

Outcome category outcome study	Relugolix + E2/NETA			Placebo			Relugolix + E2/NETA vs. placebo
	N[b]	values at baseline mean (SD)	change in the course of the study mean[c] (SE)	N[b]	values at baseline mean (SD)	change in the course of the study mean[c] (SE)	MD [95% CI]; p-value[c]
LIBERTY 2	115	38.1 (23.3)	33.5 (2.2)	114	36.5 (20.7)	13.2 (2.2)	20.31 [14.72; 25.90]; < 0.001
Total[e]							22.39 [18.25; 26.53]; < 0.001 SMD 0.93 [0.74; 1.12]
Subscale "Concern"[f]							
LIBERTY 1	113	23.0 (18.6)	46.8 (2.6)	119	22.2 (19.3)	13.7 (2.5)	33.11 [26.19; 40.02]
LIBERTY 2	115	24.9 (22.4)	45.4 (2.7)	114	24.9 (20.6)	15.7 (2.8)	29.67 [22.71; 36.63]
Total[e]							31.35 [26.45; 36.24]
Subscale "Activities"[f]							
LIBERTY 1	113	37.8 (23.5)	42.0 (2.5)	119	32.8 (23.1)	13.3 (2.4)	28.67 [22.07; 35.26]
LIBERTY 2	115	37.3 (25.6)	40.0 (2.5)	114	34.5 (21.5)	16.4 (2.5)	23.61 [17.21; 30.02]
Total[e]							26.15 [21.57; 30.73]
Subscale "Energy/Mood"[f]							
LIBERTY 1	113	39.6 (23.8)	33.8 (2.6)	119	36.6 (23.8)	12.3 (2.5)	21.54 [14.77; 28.32]
LIBERTY 2	115	40.7 (28.0)	30.0 (2.4)	114	38.3 (25.3)	13.4 (2.4)	16.55 [10.46; 22.63]
Total[e]							18.99 [14.44; 23.53]
Subscale "Control"[f]							
LIBERTY 1	113	48.9 (26.6)	30.6 (2.6)	119	41.8 (25.8)	11.5 (2.5)	19.15 [12.23; 26.07]
LIBERTY 2	115	48.0 (28.4)	27.1 (2.4)	114	44.4 (26.8)	12.8 (2.5)	14.25 [7.99; 20.51]
Total[e]							16.63 [11.96; 21.30]
Subscale "Self-Consciousness"[f]							
LIBERTY 1	113	38.5 (29.7)	29.3 (2.7)	119	34.2 (27.6)	6.9 (2.6)	22.45 [15.36; 29.54]
LIBERTY 2	115	37.3 (27.5)	27.3 (2.6)	114	37.3 (30.1)	8.9 (2.7)	18.43 [11.64; 25.23]

Table 13: Results (morbidity, health-related quality of life, continuous) – RCT, direct comparison: relugolix + E2/NETA vs. placebo[a] (multipage table)

Outcome category outcome study	Relugolix + E2/NETA			Placebo			Relugolix + E2/NETA vs. placebo
	N[b]	values at baseline mean (SD)	change in the course of the study mean[c] (SE)	N[b]	values at baseline mean (SD)	change in the course of the study mean[c] (SE)	MD [95% CI]; p-value[c]
Total[e]							20.34 [15.41; 25.26]
Subscale "Sexual Function"[f]							
LIBERTY 1	113	44.3 (31.3)	22.4 (2.9)	119	42.8 (31.4)	5.9 (2.8)	16.48 [8.66; 24.31]
LIBERTY 2	115	41.3 (32.1)	19.1 (3.3)	114	44.6 (33.9)	2.7 (3.3)	16.46 [7.99; 24.92]
Total[e]							16.32 [10.56; 22.08]

a. This is considered, with limitations, to be a sufficient approximation to watchful waiting as a possible treatment option within the ACT (individual treatment) (see Section 2.3.2, Implementation of the ACT).
b. Number of patients considered in the analysis for the calculation of the effect estimation; baseline values may be based on higher patient numbers. For pain (NRS), according to the information provided by the company in Module 4 A of the full dossier assessment, three patients for whom no values were available at baseline were included in the analysis for the LIBERTY 2 study. It is unclear how changes were then formed for these 3 patients compared to the start of the study. Due to the small number of patients affected, this has no consequences for the benefit assessment.
c. Unless otherwise stated: change, mean difference, SMD if applicable, CI and p-value from MMRM. Effect presents the difference between the treatment groups of the changes averaged over the course of the study between baseline and the respective time point of measurement.
d. For the outcome "reduction in MBL volume", data at baseline represent absolute values (in ml), while change over the course of the study represents a percentage change. Lower values indicate better symptoms (scale range for pain [NRS] 0 to 10, scale range for the UFS-QoL [Symptom Severity Scale] 0 to 100); negative effects (relugolix + E2/NETA vs. placebo) mean an advantage for relugolix + E2/NETA.
e. From IPD meta-analysis.
f. Higher values indicate a better health status/a better health-related quality of life (scale range 0 to 100 in each case); for the change from baseline, this means that positive values indicate improvement; positive effects (relugolix + E2/NETA vs. placebo) mean an advantage for relugolix + E2/NETA.
g. Change at week 24, mean difference, CI and p-value by analysis of variance (ANOVA). Effect presents the difference between the treatment groups of the changes from the start of the study until week 24.

CI: confidence interval; E2: estradiol; IPD: individual patient data; MBL: menstrual blood loss; MD: mean difference; MMRM: mixed-effects model repeated measures; N: number of analysed patients; NETA: norethisterone acetate; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; SMD: standardized mean difference; UFS-QoL: Uterine Fibroid Symptom and Quality of Life Questionnaire; VAS: visual analogue scale

Overall, based on the available information, at most hints, e.g. of an added benefit, can be determined for all outcomes (see also Section 2.4.2).

Mortality

All-cause mortality

No deaths occurred during the course of the studies LIBERTY 1 and LIBERTY 2. There was no hint of an added benefit of relugolix/E2/NETA in comparison with watchful waiting for the outcome "all-cause mortality"; an added benefit is therefore not proven.

Morbidity

Confirmed clinically relevant reduction of the MBL volume

The meta-analysis of the studies shows a statistically significant difference in favour of relugolix + E2/NETA for the outcome “confirmed clinically relevant reduction of the MBL volume at week 24” (at least one confirmed response at week 24). This resulted in a hint of an added benefit of relugolix/E2/NETA in comparison with watchful waiting for this outcome.

The results of the operationalizations “confirmed amenorrhoea” and “reduction in MBL volume (percentage change)” presented as supplementary information are consistent with the results of the outcome “confirmed clinically relevant reduction of the MBL volume”. The proportions per visit in the course of the study presented as supplementary information also make clear that in a large proportion of patients with a response, the confirmed response (clinically relevant reduction in MBL volume or amenorrhoea) had already occurred at week 12 and then persisted until the end of the study (see Table 21 of the full dossier assessment). In addition, it is pointed out that a large proportion of the patients with confirmed clinically relevant reduction in MBL volume in the intervention arm had amenorrhoea in each case (affects 66% to 75% depending on the visit).

Pain (NRS)

The meta-analysis of the studies showed a statistically significant difference in favour of relugolix + E2/NETA for the outcome “pain” recorded with the NRS. An SMD was considered to assess the relevance of the result. The 95% CI was fully outside the irrelevance range [−0.2; 0.2]. This was interpreted to be a relevant effect. This resulted in a hint of an added benefit of relugolix/E2/NETA in comparison with watchful waiting for this outcome.

Health status (EQ-5D VAS)

For the outcome "health status" recorded with the EQ-5D VAS, the meta-analysis of the studies shows no statistically significant difference between the treatment groups for the changes between study start and week 24. This resulted in no hint of an added benefit of relugolix/E2/NETA in comparison with watchful waiting; an added benefit is therefore not proven.

Symptoms (Symptom Severity Scale of the UFS-QoL)

The meta-analysis of the studies showed a statistically significant difference in favour of relugolix + E2/NETA for the outcome “symptoms (symptom severity scale of the UFS QoL). The SMD was considered to assess the relevance of the result. The 95% CI was fully outside

the irrelevance range [−0.2; 0.2]. This was interpreted to be a relevant effect. This resulted in a hint of an added benefit of relugolix/E2/NETA in comparison with watchful waiting for this outcome.

Health-related quality of life

Total score of the UFS-QoL

The meta-analysis of the studies showed a statistically significant difference in favour of relugolix + E2/NETA for the outcome “health-related quality of life” recorded with the UFS-QoL. The SMD was considered to assess the relevance of the result. The 95% CI for the total score was fully outside the irrelevance range [−0.2; 0.2]. This was interpreted to be a relevant effect. This resulted in a hint of an added benefit of relugolix/E2/NETA in comparison with watchful waiting for this outcome. In addition to the total score, all 6 subscales of the UFS-QoL also show a consistent positive result in favour of relugolix/E2/NETA compared to watchful waiting.

Side effects

SAEs, severe AEs (CTCAE grade ≥ 3), discontinuation due to AEs, vasomotor events (AEs)

The meta-analysis of the studies showed no statistically significant differences between the treatment groups for each of the outcomes "SAEs", “severe AEs (CTCAE grade ≥ 3)”, “discontinuation due to AEs” as well as "vasomotor events (AEs)". In each case, this resulted in no hint of greater or lesser harm from relugolix/E2/NETA in comparison with watchful waiting; greater or lesser harm is therefore not proven.

Skeletal-related events (SAEs)

The meta-analysis of the studies showed no statistically significant difference between treatment groups for the outcome of skeletal-related events (SAEs). This resulted in no hint of greater or lesser harm from relugolix/E2/NETA in comparison with watchful waiting; greater or lesser harm is therefore not proven.

With regard to the informative value of the results, it is pointed out that the duration of the LIBERTY studies (24 weeks) was too short for a sufficient assessment of skeletal-related events and that long-term data were necessary for this, especially since the approval specifies no time limit for the administration of relugolix/E2/NETA. Reduction in bone mineral density was also identified as a relevant risk associated with the administration of relugolix/E2/NETA within the framework of the approval process [17]. Therefore, according to the SPC, a dual-energy X-ray absorptiometry (DXA) scan was to be performed after the first 52 weeks of treatment to exclude the possibility that the patient had an undesirable degree of bone mineral density loss that outweighed the benefit of treatment with relugolix/E2/NETA [1]. The performance of such a DXA scan is recommended for consideration even before the start of treatment in patients with risk factors for the development of osteoporosis. Treatment with relugolix/E2/NETA is contraindicated for patients with known osteoporosis.

2.4.4 Subgroups and other effect modifiers

The following subgroup characteristics were considered in the present assessment:

- Age (< 40/≥ 40)
- Pain (NRS score) at baseline (< 4/≥ 4)
- MBL volume at baseline (< 225 ml/≥ 225 ml)

In the case of homogeneous data in the total population, the company generally presents subgroup analyses in the dossier on the basis of a one-step meta-analysis (based on individual patient data [IPD]). The company stated that, assuming homogeneous data in the total population, information at the individual study level would not provide any additional information relevant to the benefit assessment.

In principle, it is adequate to conduct the subgroup analyses at the meta-analysis level. Nevertheless, at first, it must also be examined whether a meta-analytical summary of the results from the two studies within a subgroup is useful. For the individual outcomes, homogeneous data in the total population do not necessarily mean homogeneous data in the subgroups. However, these considerations regarding heterogeneity between the individual studies per subgroup are not found in the dossier. Therefore, it cannot be assessed whether the meta-analytical summary of the studies per subgroup is useful. However, since the results of the subgroups (assuming homogeneity) are not relevant to the conclusion in the present data situation (see subgroup results presented below), the lack of data on heterogeneity in the subgroups remains without consequence.

Interaction tests are performed when at least 10 patients per subgroup are included in the analysis. For binary data, there must also be at least 10 events in at least 1 subgroup.

Only the results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup results are presented only if there is a statistically significant and relevant effect in at least one subgroup.

Table 14 summarizes the subgroup results of the comparison of relugolix + E2/NETA with placebo in adult patients of reproductive age with moderate to severe symptoms of uterine fibroids.

Table 14: Subgroups (morbidity) – RCT, direct comparison: relugolix + E2/NETA vs. placebo[a]

Outcome characteristic subgroup	Relugolix + E2/NETA			Placebo			Relugolix + E2/NETA vs. placebo
	N[b]	values at baseline mean (SD)	change in the course of the study mean[c] (SD)	N[b]	values at baseline mean (SD)	change in the course of the study mean[c] (SD)	MD [95% CI]; p-value[c]
Pain (NRS)[d]							
Age							
< 40 years	62	6.2 (3.4)	-2.4 (0.3)	76	5.9 (3.2)	-1.8 (0.3)	-0.55 [-1.42; 0.32]; 0.213
≥ 40 years	189	5.4 (3.2)	-2.9 (0.2)	178	5.7 (2.9)	-1.3 (0.2)	-1.60 [-2.14; -1.07]; < 0.001 SMD: -0.52 [-0.73; -0.31]
Total[e]						Interaction:	p-value = 0.040
NRS score at baseline							
< 4	73	1.3 (1.1)	-0.3 (0.3)	61	1.6 (1.2)	0.3 (0.3)	-0.59 [-1.33; 0.15]; 0.117
≥ 4	175	7.3 (2.0)	-3.9 (0.2)	189	7.1 (2.0)	-2.0 (0.2)	-1.81 [-2.27; -1.36]; < 0.001 SMD -0.67 [-0.88; -0.46]
Total[e]						Interaction:	p-value = 0.005
Symptoms (symptom severity scale of the UFS-QoL)[d]							
MBL volume							
< 225 ml	148	55.6 (20.0)	-28.9 (1.8)	156	61.7 (19.3)	-13.2 (1.8)	-15.71 [-20.72; -10.7]; < 0.001 SMD -0.66 [-0.89; -0.43]
≥ 225 ml	80	61.9 (23.2)	-34.0 (2.5)	77	58.3 (19.1)	-8.7 (2.6)	−25.34 [−32.40; −18.29]; < 0.001 SMD -1.06 [-1.39; -0.72]
Total[e]							p-value = 0.029

a. This is considered, with limitations, to be a sufficient approximation to watchful waiting as a possible treatment option within the ACT (individual treatment) (see Section 2.3.2, Implementation of the ACT).
b. Number of patients considered in the analysis for the calculation of the effect estimation; baseline values may be based on higher patient numbers.
c. Unless otherwise stated: change, mean difference, SMD if applicable, CI and p-value per MMRM. Effect presents the difference between the treatment groups of the changes averaged over the course of the study between baseline and the respective time point of measurement.
d. Lower values indicate better symptoms (scale range for pain [NRS] 0 to 10, scale range for the UFS-QoL [Symptom Severity Scale] 0 to 100); negative effects (relugolix + E2/NETA vs. placebo) mean an advantage for relugolix + E2/NETA.
e. From IPD meta-analysis.

CI: confidence interval; E2: estradiol; MBL: menstrual blood loss; MD: mean difference; MMRM: mixed-effects model repeated measures; N: number of analysed patients; NETA: norethisterone acetate; NRS: numeric rating scale; RCT: randomized controlled trial; SD: standard deviation; SMD: standardized mean difference; SSS: Symptom Severity Scale

Morbidity

Pain (NRS)

For the outcome "pain (NRS)", there was a statistically significant interaction for the characteristic "age (< 40 years/≥ 40 years)" and "NRS score (< 4/≥ 4)" at baseline. These effect modifications cannot be assessed without examining for cross-interactions. The derivation of the added benefit was therefore conducted on the basis of the results on the total population.

Symptoms (Symptom Severity Scale of the UFS-QoL)

For the outcome "symptoms (Symptom Severity Scale of the UFS-QoL)", there was a statistically significant interaction for the characteristic "MBL volume (< 225 ml/≥ 225 ml)", with a statistically significant difference in favour of relugolix + E2/NETA compared to placebo for both patients with an MBL volume of < 225 ml and those with an MBL volume ≥ 225 ml. In each case, the 95% CI of the SMD was fully outside the irrelevance range [−0.2; 0.2]. This was interpreted to be a relevant effect in each case. This and also the extent (each not quantifiable) for both subgroups concurred with the result of the total study population. Therefore, the characteristic "MBL volume" is not considered further for the outcome "symptoms (Symptom Severity Scale of the UFS-QoL)".

2.5 Probability and extent of added benefit

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

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.

2.5.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level was estimated from the results presented in Section 2.4 (see Table 15).

Determination of the outcome category for symptom outcomes

For the symptoms outcomes below, it cannot be inferred from the dossier whether they are serious/severe or non-serious/non-severe. The classification for these outcomes is justified.

The outcomes "confirmed clinically relevant reduction of the MBL volume", "pain (NRS)" and "symptoms (Symptom Severity Scale of the UFS-QoL)" were assigned to the outcome category of non-serious/non-severe symptoms/late complications. No information is available which would justify classifying the named outcomes as serious/severe symptoms/late complications.

This deviates from the assessment of the company, which assigned the outcomes "confirmed clinically relevant reduction of the MBL volume" (referred to as permanent normalization of

the MBL volume by the company) and “pain (NRS)” to the outcome category of serious (or severe) symptoms (or late complications) without providing further justification. It assigned the outcome “symptoms (Symptom Severity Scale of the UFS-QoL)” to the outcome category "health-related quality of life” (see Section 2.4.1).

Table 15: Extent of added benefit at outcome level: relugolix/E2/NETA vs watchful waiting[a] (multipage table)

Outcome category outcome	**Relugolix/E2/NETA vs. watchful waiting[a] proportion of events (%) or mean effect estimation [95% CI]; p-value probability[b]**	**Derivation of extent[c]**
Mortality		
All-cause mortality	0% vs. 0% RR: –	Lesser benefit/added benefit not proven
Morbidity		
Confirmed clinically relevant reduction of the MBL volume	68.8% to 69.6% vs. 4.7% to 11.8%[d] RR: 8.40 [5.53; 12.74] RR: 0.12 [0.08; 0.18][e] p < 0.001 probability: hint	Outcome category: non-serious/non-severe symptoms/late complications CI_u < 0.80 added benefit, extent: “considerable”
Pain (NRS)	−2.8 to −2.6 vs. −1.6 to −1.2[d] MD: -1.33 [-1.80; -0.86] p < 0.001 SMD: -0.43 [-0.61; -0.26][f] probability: hint	Outcome category: non-serious/non-severe symptoms/late complications added benefit, extent: “non-quantifiable”
Health status (EQ-5D VAS)	5.1 to 7.6 vs. 3.2 to 4.8[d] MD: 2.29 [–1.59; 6.17] p = 0.247	Lesser benefit/added benefit not proven
Symptoms (Symptom Severity Scale of the UFS-QoL)	-31.1 to -30.2 vs. -12.3 to -10.9[d] MD: -18.94 [-23.05; -14.84] p < 0.001 SMD: -0.79 [-0.98; -0.60][f] probability: hint	Outcome category: non-serious/non-severe symptoms/late complications added benefit, extent: “non-quantifiable”
Health-related quality of life		
Total score of the UFS-QoL	33.5 to 36.2 vs. 11.7 to 13.2[d] MD: 22.39 [18.25; 26.53] p < 0.001 pMD: 0.93 [0.74; 1.12][f] probability: hint	Outcome category: health-related quality of life added benefit, extent: “non-quantifiable”

Table 15: Extent of added benefit at outcome level: relugolix/E2/NETA vs watchful waiting[a] (multipage table)

Outcome category outcome	**Relugolix/E2/NETA vs. watchful waiting[a] proportion of events (%) or mean effect estimation [95% CI]; p-value probability[b]**	**Derivation of extent[c]**
Side effects		
SAEs	0.8% to 5.5% vs. 1.6% to 3.1%[d] RR: 1.34 [0.47; 3.84] p = 0.584	Greater/lesser harm not proven
Severe AEs	4.0% to 5.5% vs. 6.2% to 8.7%[d] RR: 0.63 [0.31; 1.28] p = 0.200	Greater/lesser harm not proven
Discontinuation due to AEs	2.4% to 5.5% vs. 3.9% to 4.7%[d] RR: 0.91 [0.39; 2.12] p = 0.834	Greater/lesser harm not proven
Skeletal-related events (SAEs)	0% to 0.8% vs. 0% to 0.8%[d] RR: 1.01 [0.14; 7.17] p = 0.994	Greater/lesser harm not proven
Vasomotor events (AEs)	6.3% to 14.8% vs. 3.9% to 9.4%[d] RR: 1.59 [0.89; 2.83] p = 0.112	Greater/lesser harm not proven

a. The assessment was based on the two studies LIBERTY 1 and LIBERTY 2, which compared relugolix + E2/NETA with placebo. This is considered to be a sufficient approximation to watchful waiting as a possible treatment option within the ACT (individual treatment, see Table 4) for patients for whom watchful waiting is best suited, however, with limitations (see Section 2.3.2, Implementation of the appropriate comparator therapy)
b. Probability provided if statistically significant differences are present.
c. Depending on the outcome category, estimations of effect size use different limits based on the upper limit of the confidence interval (CI_u).
d. Minimum and maximum proportions of events or minimum and maximum mean changes per treatment arm in the included studies.
e. Institute's calculation; reversed direction of effect to enable use of limits to derive the extent of the added benefit.
f. If the CI for the SMD is fully outside the irrelevance range [−0.2; 0.2], this is interpreted to be a relevant effect. In other cases, the presence of a relevant effect cannot be derived.

AE: adverse event; CI: confidence interval; CI_u: upper limit of the confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; E2: estradiol; MBL: menstrual blood loss; NETA: norethisterone acetate; NRS: numeric rating scale; RR: relative risk; SAE: serious adverse event; SMD: standardized mean difference; UFS-QoL: Uterine Fibroid Symptom and Quality of Life Questionnaire; VAS: visual analogue scale

2.5.2 Overall conclusion on added benefit

Table 16 summarizes the results considered in the overall conclusion on the extent of added benefit.

Table 16: Positive and negative effects from the assessment of relugolix/E2/NETA compared with watchful waiting

Positive effects	Negative effects
Non-serious/non-severe symptoms/late complications ▪ confirmed clinically relevant reduction of the MBL volume: hint of an added benefit - extent: "considerable" ▪ pain (NRS): hint of an added benefit – extent: "non-quantifiable" ▪ symptoms" (symptom severity scale of the UFS-QoL): hint of an added benefit – extent: "non-quantifiable"	–[a]
Health-related quality of life ▪ total score of the UFS-QoL: hint of an added benefit – extent: "non-quantifiable"	
a. Treatment duration in both LIBERTY studies was 24 weeks. Long-term data, which are particularly necessary for the comprehensive assessment of skeletal-related events, are lacking. AE: adverse event; E2: estradiol; MBL: menstrual blood loss; NRS: numeric rating scale; NETA: norethisterone acetate; UFS-QoL: Uterine Fibroid Symptom and Quality of Life Questionnaire	

Based on the studies LIBERTY 1 and LIBERTY 2, conclusions in the present benefit assessment can only be drawn for patients for whom watchful waiting was best suited on an individual basis within the framework of the ACT. Data for patients for whom symptom-oriented treatment (with progestogens or ulipristal acetate) or an invasive treatment option was the best individual choice in the framework of the ACT are not available. The added benefit is therefore derived separately for these two patient groups.

Patients for whom watchful waiting was best suited on an individual basis within the framework of the ACT

Overall, there are several positive effects of relugolix/E2/NETA compared to watchful waiting within an observation period of 24 weeks for patients for whom watchful waiting is individually best suited in the context of the ACT.

For the outcome "confirmed clinically relevant reduction of the MBL volume", there is a hint of considerable added benefit of relugolix/E2/NETA compared with watchful waiting. In addition, there are further positive effects in the outcome categories "morbidity" and "health-related quality of life". Here, there is a hint of a non-quantifiable added benefit of relugolix/E2/NETA for each of the outcomes "pain" (NRS), "symptoms" (symptom severity scale of the UFS QoL) as well as "health-related quality of life" (total score of the UFS-QoL). The advantages based on these patient-reported outcomes overall support the hint of considerable added benefit shown for the clinically relevant reduction of the MBL volume. There are neither advantages nor disadvantages for the outcome category "side effects". However, the duration of the LIBERTY studies (24 weeks) is too short for a sufficient assessment of skeletal-related events.

In summary, there is a hint of considerable added benefit of relugolix/E2/NETA compared with watchful waiting for adult patients of reproductive age with moderate to severe symptoms of uterine fibroids, for whom watchful waiting is individually best suited in the context of the ACT.

Patients for whom symptom-oriented treatment (with progestogens or ulipristal acetate) or an invasive treatment option is the best individual choice in the framework of the ACT

The company presented no data versus the ACT for patients for whom symptom-oriented treatment (with progestogens or ulipristal acetate) or an invasive treatment option was the best individual choice in the framework of the ACT. An added benefit is therefore not proven.

Table 17 summarizes the result of the assessment of the added benefit of relugolix/E2/NETA in comparison with the ACT.

Table 17: Relugolix/E2/NETA – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adult patients of reproductive age with moderate to severe symptoms of uterine fibroids	Individual treatment depending on the type and the severity of the symptoms as well as the patient's symptom burden, selecting from: ▪ watchful waiting ▪ symptom-oriented treatment: ▫ progestogens under consideration of the respective approval status (for patients for whom symptomatic treatment of prolonged and/or heavy periods [menorrhagia, hypermenorrhoea] is sufficient) ▫ ulipristal acetate (for patients who have not yet reached menopause and for whom uterine fibroid embolization and/or surgery are not suitable or have failed). ▪ invasive treatment options	Patients for whom watchful waiting is best suited on an individual basis ▪ hint of considerable added benefit
		Women for whom symptom-oriented treatment (with gestagens or ulipristal acetate) or an invasive treatment option is the best individual choice: ▪ added benefit not proven

a. Presented is the respective ACT specified by the G-BA.
b. Because of its contraceptive effect, relugolix/E2/NETA cannot be used in patients with a current desire to have children. After treatment discontinuation, contraception is no longer given [1].

E2: estradiol; G-BA: Federal Joint Committee; NETA: norethisterone acetate

The assessment described above deviates from that of the company, which derived proof of major added benefit for adult patients of childbearing age with moderate to severe symptoms of uterine fibroids.

The approach for the derivation of an overall conclusion on the added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

References for English extract

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

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