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Relugolix/estradiol/ norethisterone acetate (uterine fibroids 1) –

Addendum to Commission A21-112[1]

Addendum

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
E2	estradiol
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
NETA	norethisterone acetate
NRS	Numerical Rating Scale
SGB	Sozialgesetzbuch (Social Code Book)
UFS-QoL	Uterine Fibroid Symptom and Quality of Life Questionnaire

1 Background

On 11 January 2022, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A21-112 (Relugolix/estradiol/norethisterone acetate – Benefit assessment according to §35a Social Code Book V) [1].

The benefit assessment included the twin studies LIBERTY 1 and LIBERTY 2, which directly compare a free combination of relugolix and estradiol/norethisterone acetate (E2/NETA) with placebo. On the basis of these two studies, conclusions were drawn for those patients for whom watchful waiting is best suited for the individual patient within the framework of the appropriate comparator therapy (ACT) [1].

In its comment, the pharmaceutical company (hereinafter referred to as "the company") submitted supplementary information, which went beyond the information provided in the dossier, to prove the added benefit [2,3]. Therefore, the G-BA commissioned IQWiG with the following assessment of the analyses submitted by the company in the commenting procedure under consideration of the information provided in the dossier:

Responder analysis under consideration of the 15% relevance threshold for the following outcomes:

- symptoms (symptom severity scale of the Uterine Fibroid Symptom and Quality of Life Questionnaire [UFS-QoL]), improvement of symptoms (reduction by ≥ 15 points)
- total score of the UFS-QoL, improvement of health-related quality of life (increase by ≥ 15 points)

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

2 Assessment

The benefit assessment included the twin studies LIBERTY 1 and LIBERTY 2, which directly compare a free combination of relugolix and E2/NETA with placebo. Placebo administration in combination with the allowed concomitant medication in the two studies was 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 were only drawn for patients for whom watchful waiting is best suited on an individual basis within the framework of the ACT. 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 (see text on the "implementation of the ACT" in Section 2.3.1 of dossier assessment A21-112 [1]).

The present addendum assesses the subsequently submitted responder analyses with a relevance threshold of 15% for the outcomes "symptoms (symptom severity scale of the UFS-QoL) and for the total score of the UFS-QoL.

2.1 Subsequently submitted analyses

2.1.1 Risk of bias and certainty of conclusions

Analogous to the continuous analyses in dossier assessment A21-112, the risk of bias for the subsequently submitted responder analyses on the outcomes "symptoms (symptom severity scale of the UFS-QoL) and on the total score of the UFS-QoL is rated as high. This is due to the high proportion (> 10%) of patients who were not considered in the assessment (see number of patients with observed values at week 24 in Module 4 A of the dossier, Table 4-83 and Table 4-139).

Overall, , at most indications, for example of an added benefit, can therefore still be pronounced for the subsequently submitted analyses on the outcomes "symptoms (symptom severity scale of the UFS-QoL)" and on the total score of the UFS-QoL taking into account the uncertainty that still exists with regard to the implementation of the ACT.

2.1.2 Results

The responder analyses on the UFS-QoL subsequently submitted in the commenting procedure are presented in Table 1.

Table 1: Results (morbidity, health-related quality of life) – RCT, direct comparison: vs. placebo

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]
Morbidity					
Symptoms (symptom severity scale of the UFS-QoL)[c]					
LIBERTY 1	128	74 (57.8)	127	39 (30.7)	1.89 [1.39; 2.55]; < 0.001
LIBERTY 2	125	79 (63.2)	129	42 (32.6)	1.96 [1.48; 2.59]; < 0.001
Total[d]					1.92 [1.56; 2.35]; < 0.001
Health-related quality of life					
Total score of the UFS-QoL[e]					
LIBERTY 1	128	70 (54.7)	127	37 (29.1)	1.88 [1.38; 2.58]; < 0.001
LIBERTY 2	125	80 (64.0)	129	41 (31.8)	2.02 [1.52; 2.69]; < 0.001
Total[d]					1.95 [1.58; 2.41]; < 0.001

a. Sufficient approximation to the ACT "individual treatment", but with limitations (see Section 2.3.1 of dossier assessment A21-112 [1] on the implementation of the ACT and Section 2.2.2 of the present addendum).
b. Unless otherwise indicated: RR, CI and p-value were calculated using a Mantel-Haenszel (CMH) method stratified by baseline MBL volume (< 225 ml/≥ 225 ml) and geographical region (North America/rest of the world) (exception: stratification in LIBERTY 1 was not based on geographical region, because less than 15 patients were assigned to the stratum „baseline MBL volume ≥ 225 ml and rest of the world"). However, there is no information as to whether the p-value was calculated for RR or another effect measure.
c. Analyses on the proportion of patients with improvement, defined as a decrease in the score by at least 15 points (corresponds to 15% with a scale range of 0 to 100) after 24-week treatment.
d. Based on a CMH method. The pooled analysis, stratified by study, baseline MBL volume and geographical region, was calculated using one-step IPD meta-analysis based on a fixed-effect model; the p-value was calculated on the basis of a CMH test, stratified by baseline MBL volume and geographical region; however, there is no information as to whether the p-value was calculated for RR or another effect measure.
e. Analyses on the proportion of patients with improvement, defined as an increase in the score by at least 15 points (corresponds to 15% with a scale range of 0 to 100) after 24-week treatment.

CI: confidence interval; CMH: Cochran-Mantel-Haenszel; E2: estradiol; IPD: individual patient data; mITT: modified intention to treat; MBL: menstrual blood loss; n: number of patients with (at least one) event; N: number of patients in the mITT population; NETA: norethisterone acetate; RCT: randomized controlled trial; RR: relative risk

Morbidity

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)".

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 "total score of the UFS-QoL". This resulted in a hint of an added benefit of relugolix/E2/NETA in comparison with watchful waiting for this outcome.

2.1.3 Subgroups and other effect modifiers

No subgroup analyses for the subgroup characteristics considered relevant in the dossier assessment (age, pain at baseline and baseline MBL volume) are available for the subsequently submitted responder analyses.

2.2 Probability and extent of added benefit

Probability and extent of the added benefit at outcome level for the subsequently submitted responder analyses 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 [4].

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.

2.2.1 Assessment of added benefit at outcome level

On the basis of the results presented in Section 2.1 and the assessment of the outcome categories presented below, the extent of the respective added benefit was estimated at outcome level (see Table 2).

Determination of the outcome category

Analogous to the procedure in dossier assessment A21-112 [1], the outcome "symptoms (Symptom Severity Scale of the UFS-QoL)" is assigned to the outcome category of non-serious/non-severe symptoms/late complications and the total score of the UFS-QoL is assigned to the outcome category of health-related quality of life.

Table 2: Extent of added benefit at outcome level: relugolix/E2/NETA vs. individual treatment (patients for whom watchful waiting is best suited[a])

Outcome category **outcome**	**Relugolix/E2/NETA vs. individual treatment[a]** **proportion of events (%)** **effect estimation [95% CI];** **p-value** **probability[b]**	**Derivation of extent[c]**
Morbidity		
Symptoms (symptom severity scale of the UFS-QoL)	57.8% to 63.2% vs. 30.7% to 32.6%[d] RR: 1.92 [1.56; 2.35] RR: 0.52 [0.43; 0.64][e] p < 0.001 probability: hint	Outcome category: non-serious/non-severe symptoms/late complications CIu < 0.80 added benefit, extent: "considerable"
Health-related quality of life		
Total score of the UFS-QoL	54.7% to 64.0% vs. 29.1% to 31.8%[d] RR: 1.95 [1.58; 2.41] RR: 0.51 [0.41; 0.63][e] p < 0.001 probability: hint	Outcome category: health-related quality of life CI_u < 0.75, risk ≥ 5% added benefit, extent: "major"

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 the ACT "individual treatment" for patients for whom watchful waiting is best suited, however, with limitations (see text on the "implementation of the ACT" in Section 2.3.1 of dossier assessment A21-112 [1]and Section 2.2.2 of the present addendum).
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 in each treatment arm in the studies included.
e. Institute's calculation; inverse direction of effect to enable use of limits to derive the extent of the added benefit.

AE: adverse event; CI: confidence interval; CI_u: upper limit of the confidence interval; E2: estradiol; MBL: menstrual blood loss; NETA: norethisterone acetate; RR: relative risk; SAE: serious adverse event; UFS-QoL: UFS-QoL: Uterine Fibroid Symptom and Quality of Life Questionnaire

2.2.2 Overall conclusion on added benefit

Table 3 summarizes the results of the benefit assessment on Commission A21-112 and of the present addendum considered in the overall conclusion on the extent of the added benefit.

Table 3: 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: "**considerable**"	–[a]
Health-related quality of life ▪ total score of the UFS-QoL: hint of an added benefit – extent: "**major**"	
The results presented in **bold** result from the analyses subsequently submitted by the company with its written comments. 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 still 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

The additional responder analyses subsequently submitted for this addendum enable a quantification of the effects for the outcomes “symptoms (symptom severity scale of the UFS-QoL)” and “total score of the UFS-QoL”, whose continuous analyses were classified as non-quantifiable in dossier assessment A21-112.

Overall, after taking into account the results commissioned in the addendum, there are still 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 total score of the UFS-QoL, a hint of major added benefit of relugolix/E2/NETA compared with watchful waiting is shown in the outcome category “health-related quality of life”. In addition, for each of the outcomes “confirmed clinically relevant reduction in MBL volume” as well as “symptoms (symptom severity scale of the UFS-QoL)” there is a hint of considerable added benefit, as well as a hint of non-quantifiable added benefit of relugolix/E2/NETA for the outcome “pain (numerical rating scale [NRS])”. 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.

For the new overall assessment, it is decisive that it became clear in the commenting procedure that, in particular for the more severely affected patients in the studies (according to clinicians, these are patients who had a baseline MBL blood loss of approx. 200 ml), it is very questionable from the clinicians' point of view whether the ACT “watchful waiting” represents an adequate option for the individual patient [5]. It is thus sufficiently unclear which proportion of patients would really have chosen watchful waiting as an option outside the study context. The mean MBL volume per arm in the patients in the study still ranged between 212 ml and 247 ml, and the group of patients with a baseline MBL volume of ≥ 225 ml represented about one third of the study population. It is unclear whether effects of the same magnitude would have been observed in comparison with the other treatment options. For this addendum, there are also no subgroup analyses for the subgroup characteristics considered relevant in the dossier assessment (age, pain at baseline and baseline MBL volume [< 225 ml/≥ 225 ml]) for the subsequently submitted responder analyses. However, the analyses on the characteristic MBL volume would be of particular importance here, as they allow conclusions to be drawn about effect modifications due to disease severity. In the overall consideration of these uncertainties and taking into account the new findings from the commenting procedure, the conclusion of the dossier assessment therefore remains unchanged. Therefore, 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.

2.3 Summary

The data subsequently submitted by the company in the commenting procedure did not change the conclusion on the added benefit of relugolix/E2/NETA from dossier assessment A21-112.

The following Table 4 shows the result of the benefit assessment of relugolix/E2/NETA under consideration of dossier assessment A21-112 and the present addendum.

Table 4: 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 progestogens or ulipristal acetate) or an invasive treatment option is the best individual choice: ▪ added benefit not proven
Results printed in **bold** result from the data additionally analysed for this addendum. 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 [2]. E2: estradiol; G-BA: Federal Joint Committee; NETA: norethisterone acetate		

The G-BA decides on the added benefit.

3 References

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

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