Relugolix (prostate cancer)

Addendum to Project A22-108 (dossier assessment)[1]

ADDENDUM

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List of abbreviations

Abbreviation	Meaning
AE	adverse event
CNS	central nervous system
CTCAE	Common Terminology Criteria for Adverse Events
EORTC	European Organisation for Research and Treatment of Cancer
EPAR	European Public Assessment Report
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MACE	major adverse cardiovascular event
MedDRA	Medical Dictionary for Regulatory Activities
QLQ-C30	Quality of Life Questionnaire-Core 30
QLQ-PR25	Quality of Life Questionnaire-Prostate 25
PT	Preferred Term
SAP	statistical analysis plan
SGB	Sozialgesetzbuch (Social Code Book)
SMQ	Standardized MedDRA Query

1 Background

On 21 February 2023, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A22-108 (Relugolix – Benefit assessment according to § 35a Social Code Book V) [1].

The commission comprises the following data and analyses of the HERO study submitted by the pharmaceutical company (hereinafter referred to as "the company") in the commenting procedure, taking into account the information provided in the dossier:

- responder analyses with a response criterion of ≥ 10 points for the outcomes of symptoms and health-related quality of life recorded using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) and the EORTC QLQ-Prostate 25 (EORTC QLQ-PR25)
- data on the outcome of major adverse cardiovascular events (MACE)
- analyses of adverse events (AEs)

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 of relugolix in patients with advanced hormone-sensitive prostate cancer used the randomized, controlled, open-label HERO study [2-4], which compared relugolix with leuprorelin. A detailed description of the HERO study can be found in dossier assessment A22-108 [1].

The subpopulation of patients without distant metastasis presented by the company is considered for research question 2 of the benefit assessment, which comprises the patient population with advanced hormone-sensitive prostate cancer who are not candidates for local therapy. It should be noted for this subpopulation in general that there is uncertainty as to whether local therapy would still have been an option for an unknown proportion of patients in this subpopulation (for a detailed explanation, see dossier assessment A22-108 [1]). This uncertainty is taken into account in the certainty of conclusions (see the following sections).

In its comments [5], the company presented further data and analyses on the subpopulation used for research question 2. The data subsequently submitted thus refer exclusively to research question 2 of the present benefit assessment.

2.1 Responder analyses with the response criterion of ≥ 10 points for outcomes recorded with the EORTC QLQ-C30 and EORTC QLQ-PR25

In its dossier, the company presented responder analyses for the time to deterioration by ≥ 15 points for outcomes on symptoms and health-related quality of life recorded with the EORTC QLQ-C30 and EORTC QLQ-PR25. 15 points correspond to 15% of the scale range for all scales of both instruments (with a range 0 to 100). According to the "Answers to frequently asked questions about the benefit assessment procedure" [6] provided by the G-BA, only analyses using the response criterion of 10 points are to be presented in the dossier for analyses of the EORTC QLQ-C30 questionnaire and the corresponding validated supplementary disease-specific modules.

In its comments, the company provided analyses of deterioration by ≥ 10 points for the EORTC QLQ-C30 scales of fatigue and physical functioning and for the EORTC QLQ-PR25 scales of micturition problems and hormonal treatment-related symptoms. For all other scales of the 2 instruments, the company did not subsequently submit any analyses of the deterioration by ≥ 10 points. For these scales, however, a response threshold of 15 points leads to the same change step as a response threshold of 10 points. Analyses with a response threshold of 15 points are therefore identical to analyses with a response threshold of 10 points for these scales. Thus, with the comments and the dossier of the company, analyses that correspond to a response threshold of 10 points are available for all scales of the EORTC QLQ-C30 and EORTC QLQ-PR25.

Risk of bias and certainty of conclusions for the results of the outcomes recorded using EORTC scales

Risk of bias

The risk of bias of the results for the outcomes on symptoms and health-related quality of life recorded using the EORTC QLQ-C30 and EORTC QLQ-PR25 is rated as high due to the lack of blinding in subjective recording of outcomes and due to the unclear proportion of patients included in the analysis. According to the company, all patients in the relevant subpopulation were included in the analyses of the patient-reported outcomes. At the same time, however, the company stated that patients with no baseline value and/or no value in the further course of the study were censored on day 1. Thus, no times of these patients were actually included in the analysis. The exact number of these patients cannot be determined.

The company described in its comments that the number of patients without baseline value at the start of the study can be derived from the analyses of the continuous data. Missing baseline values for the EORTC QLQ-C30 and EORTC QLQ-PR25 scales are only present in fewer than 5% of patients in the relevant subpopulation. However, it remains unclear whether other patients were censored who had a value at baseline but not in the further course of the study. Based on the data on the responses for the outcomes recorded using the EORTC QLQ-C30 and EORTC QLQ-PR25, which were > 85% in relation to the relevant subpopulation at all time points, the number of patients included in the analyses can be estimated as sufficiently large for the analyses to be used for the benefit assessment.

Certainty of conclusions

Due to the high risk of bias and the uncertainty as to whether all patients in the subpopulation presented by the company were no longer candidates for local therapy, the certainty of conclusions is reduced. On the basis of the available information, no more than hints, for example of an added benefit, can therefore be derived for all outcomes recorded using EORTC-QLQ-C30 or EORTC-QLQ-PR25 (for more detailed justification, see benefit assessment A22-108 [1]).

Results for the outcomes of the EORTC scales

Table 1 summarizes the results for the outcomes on symptoms and health-related quality of life recorded using EORTC QLQ-C30 and EORTC QLQ-PR25 from the company's dossier and the analyses for the comparison of relugolix with leuprorelin for research question 2 of the present benefit assessment subsequently submitted in the company's comments. Where necessary, calculations conducted by the Institute are provided in addition to the data presented by the company.

Kaplan-Meier curves on the event time analyses are presented in Appendix A.

Table 1: Results (morbidity, health-related quality of life) – RCT, direct comparison: relugolix vs. leuprorelin – research question 2: patients who are not candidates for local therapy (multipage table)

Study Outcome category Outcome	Relugolix N[a]	Relugolix Median time to event in months [95% CI][b] Patients with event n (%[c])	Leuprorelin N[a]	Leuprorelin Median time to event in months [95% CI][b] Patients with event n (%[c])	Relugolix vs. leuprorelin MD [95% CI]; p-value[d]
HERO					
Morbidity					
EORTC QLQ-C30 – symptoms[e, f]					
Fatigue	ND	2.9 [2.8; 4.7] 304 (71.2)	ND	5.6 [2.9; 8.3] 147 (69.0)	1.14 [0.93; 1.39]; 0.205
Nausea and vomiting	ND	NA 90 (21.1)	ND	NA 47 (22.1)	0.93 [0.65; 1.32]; 0.685
Pain	ND	11.1 [8.5; 11.2] 211 (49.4)	ND	11.2 [10.8; NC] 96 (45.1)	1.14 [0.90; 1.46]; 0.278
Dyspnoea	ND	11.5 [11.5; NC] 138 (32.3)	ND	11.3 [11.2; NC] 78 (36.6)	0.84 [0.63; 1.11]; 0.213
Insomnia	ND	8.5 [8.3; 11.3] 220 (51.5)	ND	11.0 [8.2; NC] 108 (50.7)	1.06 [0.84; 1.34]; 0.628
Appetite loss	ND	NA 99 (23.2)	ND	NA 44 (20.7)	1.11 [0.77; 1.58]; 0.580
Constipation	ND	11.5 [11.5; NC] 146 (34.2)	ND	NA 62 (29.1)	1.16 [0.86; 1.57]; 0.319
Diarrhoea	ND	NA 139 (32.6)	ND	NA 50 (23.5)	1.45 [1.05; 2.00]; 0.026
EORTC QLQ-PR25 – symptoms[e, f]					
Micturition problems	ND	11.1 [8.5; NC] 199 (46.6)	ND	11.3 [11.2; NC] 84 (39.4)	1.28 [0.99; 1.66]; 0.057
Bowel symptoms	ND	NA 94 (22.0)	ND	NA 36 (16.9)	1.31 [0.89; 1.92]; 0.170
Hormonal treatment-related symptoms	ND	3.0 [2.9; 5.5] 308 (72.1)	ND	3.0 [2.8; 5.6] 150 (70.4)	1.05 [0.86; 1.27]; 0.646
Incontinence aid	No suitable data[g]				

Table 1: Results (morbidity, health-related quality of life) – RCT, direct comparison: relugolix vs. leuprorelin – research question 2: patients who are not candidates for local therapy (multipage table)

Study Outcome category Outcome	Relugolix N[a]	Relugolix Median time to event in months [95% CI][b] Patients with event n (%[c])	Leuprorelin N[a]	Leuprorelin Median time to event in months [95% CI][b] Patients with event n (%[c])	Relugolix vs. leuprorelin MD [95% CI]; p-value[d]
Health-related quality of life					
EORTC QLQ-C30[f, h]					
Global health status	ND	11.1 [8.3; 11.2] 215 (50.4)	ND	11.1 [8.5; NC] 101 (47.4)	1.06 [0.84; 1.35]; 0.608
Physical functioning	ND	NA [11.3; NC] 159 (37.2)	ND	NA [11.2; NC] 82 (38.5)	0.96 [0.74; 1.26]; 0.775
Role functioning	ND	11.2 [11.0; NC] 200 (46.8)	ND	11.2 [11.1; NC] 90 (42.3)	1.19 [0.93; 1.52]; 0.176
Emotional functioning	ND	11.5 [11.5; NC] 113 (26.5)	ND	11.7 [NC] 61 (28.6)	0.91 [0.67; 1.25]; 0.561
Cognitive functioning	ND	11.2 [11.0; NC] 198 (46.4)	ND	11.1 [8.3; NC] 103 (48.4)	0.94 [0.74; 1.20]; 0.626
Social functioning	ND	11.2 [11.1; NC] 186 (43.6)	ND	11.2 [9.0; NC] 96 (45.1)	0.93 [0.73; 1.19]; 0.572
EORTC QLQ-PR25[f, h]					
Sexual activity	ND	NA 102 (23.9)	ND	NA 65 (30.5)	0.76 [0.55; 1.03]; 0.078
Sexual functioning	No suitable data[g]				

Table 1: Results (morbidity, health-related quality of life) – RCT, direct comparison: relugolix vs. leuprorelin – research question 2: patients who are not candidates for local therapy (multipage table)

Study Outcome category Outcome	Relugolix N[a]	Relugolix Median time to event in months [95% CI][b] Patients with event n (%[c])	Leuprorelin N[a]	Leuprorelin Median time to event in months [95% CI][b] Patients with event n (%[c])	Relugolix vs. leuprorelin MD [95% CI]; p-value[d]
a. According to the company, all patients of the relevant subpopulation were included in the analysis. At the same time, the company stated that patients with no baseline value and/or no value in the course of the study were censored on day 1. Thus, no times of these patients were actually included in the analysis. The exact number of these patients cannot be determined. Based on the information on the responses, the number of patients included in the analysis is considered to be sufficiently large. b. Institute's conversion from time data to months. c. Percentage refers to the number of patients randomized into this arm. d. HR, CI and p-value: Cox proportional hazards model; stratified by region (North and South America/Europe/Asia/other regions) and age (≤ 75 years/> 75 years). e. Time to first deterioration. A score increase by ≥ 10 points from baseline is deemed a clinically relevant deterioration (scale range of 0 to 100). f. Regarding the analyses of the outcomes on symptoms and health-related quality of life (EORTC QLQ-C30 and EORTC QLQ-PR25), the company stated that it had not taken into account the recording from the 30-day safety follow-up visit, as it only wanted to investigate the effects of the respective treatment. This approach is not appropriate. g. For 56% and 61% of patients, respectively, no recording regarding incontinence aid or sexual functioning was available at baseline. At least this proportion of patients was not included in the analysis. The approach of the company does not ensure that the burden of patients who develop incontinence or become sexually active in the course of the treatment is recorded. h. Time to first deterioration. A score decrease by ≥ 10 points from baseline is deemed a clinically relevant deterioration (scale range 0 to 100). CI: confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; NC: not calculable; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-PR25: Quality of Life Questionnaire-Prostate 25; RCT: randomized controlled trial					

Symptoms (EORTC QLQ-C30 and EORTC QLQ-PR25)

Diarrhoea

A statistically significant difference to the disadvantage of relugolix compared with leuprorelin was shown for the outcome of diarrhoea recorded with the EORTC QLQ-C30. However, the difference is no more than marginal for this outcome in the category of non-serious/non-severe symptoms/late complications. There is no hint of added benefit; an added benefit is therefore not proven for this outcome.

Incontinence aid

No suitable data are available for the outcome of incontinence aid recorded with the EORTC QLQ-PR25. For this outcome, there is no hint of an added benefit of relugolix in comparison with leuprorelin; an added benefit is therefore not proven.

All other symptom outcomes (EORTC QLQ-C30 and EORTC QLQ-PR25)

No statistically significant difference between treatment groups was shown for any of the other symptom outcomes recorded with the EORTC QLQ-C30 and EORTC QLQ-PR25. In each case, there is no hint of an added benefit of relugolix in comparison with leuprorelin; an added benefit is therefore not proven.

Health-related quality of life (EORTC QLQ-C30 and EORTC QLQ-PR25)

Sexual functioning

No suitable data are available for the outcome of sexual functioning recorded with the EORTC QLQ-PR25. For this outcome, there is no hint of an added benefit of relugolix in comparison with leuprorelin; an added benefit is therefore not proven.

All other health-related quality of life outcomes (EORTC QLQ-C30 and EORTC QLQ-PR25)

No statistically significant difference between treatment groups was shown for any of the other health-related quality of life outcomes recorded with the EORTC QLQ-C30 and EORTC QLQ-PR25. In each case, there is no hint of an added benefit of relugolix in comparison with leuprorelin; an added benefit is therefore not proven.

Subgroup analyses for the results of the outcomes recorded using EORTC scales

In its comments, the company did not present any subgroup analyses for the results of the EORTC QLQ-C30 and EORTC QLQ-PR25 scales with a response threshold of 10 points.

However, subgroup analyses for the analyses with a response threshold of 15 points are available in the dossier of the company for all scales of both instruments. No effect modifications were shown for the selected subgroups of age (< 75 years, ≥ 75 years) and Gleason score at baseline (< 8 vs. ≥ 8) for these scales.

However, for the analyses of the scales of fatigue and physical functioning (EORTC QLQ-C30) and the scales of micturition problems and hormonal treatment-related symptoms (EORTC QLQ-PR25) subsequently submitted by the company in its comments, the results with a response threshold of 15 points are not identical to the analyses with a response threshold of 10 points (see above). Therefore, the subgroup analyses presented in the dossier cannot be used for these outcomes. Conclusions on potential subgroup results are therefore not possible for these 4 scales.

2.2 Data on the outcome of MACE

In its dossier, the company presented results for the outcome of MACE, which it assigned to the outcome category of morbidity. As in benefit assessment A22-108 and analogous to the statistical analysis plan (SAP), the outcome is referred to as "MACE" in the present assessment, despite the uncertainties addressed in the present addendum regarding the operationalization of MACE. In Module 4 A, the outcome was defined as a composite outcome with the following individual components:

- any event leading to death
- "nonfatal myocardial infarction", recorded using the Standardized Medical Dictionary for Regulatory Activities Query (SMQ) "myocardial infarction" (broad) excluding fatal events
- "nonfatal central nervous system (CNS) haemorrhages and cerebrovascular conditions", recorded using the SMQ "central nervous system haemorrhages and cerebrovascular conditions" (broad) excluding fatal events

In the dossier, the company also presented results of a sensitivity analysis in which the component "any event leading to death" was replaced by the component "cardiovascular events leading to death". In addition to the results for the composite outcome, the company also presented the results of the 3 individual components.

The recording of MACE events in the HERO study – even if not explicitly named as an outcome in the SAP – is to be considered predefined in the context of the AE recording using events leading to death as well as events recorded using the nonfatal events of the mentioned SMQs. However, the outcome of MACE was not used in benefit assessment A22-108. The reason for this was that it could not be assessed whether the outcome of MACE – in the sense of severe or serious cardiovascular or cerebrovascular events – is represented with sufficient measurement reliability with the operationalization described. Firstly, there was no information on the events that were included in the individual components "nonfatal myocardial infarction" and "nonfatal CNS haemorrhages and cerebrovascular conditions" in the subpopulation presented. Secondly, there was also a lack of information on the respective severity grade of the recorded events, which is necessary for the assessment of a MACE event. Based on the information in the dossier it was thus unclear whether all events included in the analyses of the relevant subpopulation actually represent severe or serious cardiovascular events in the sense of a MACE. However, the adjudication of events included in the outcome, which is usually performed for MACE outcomes, was not performed in the HERO study. Overall, the operationalization of the outcome of MACE in the company's dossier, together with the unclear measurement reliability, especially due to the lack of adjudication, was not suitable to represent patient-relevant severe or serious cardiovascular events [1].

Data and analyses subsequently submitted by the company for the outcome of MACE

In its comments, the company provided further information on the outcome of MACE. On the one hand, the company cited all events included in the outcome of MACE by citing the corresponding verbatim and Preferred Term (PT) according to the Medical Dictionary for Regulatory Activities (MedDRA). On the other, for each event, the company provided information on the severity grade according to the Common Terminology Criteria for Adverse Events (CTCAE) and whether it was a serious event (SAE). In addition, the company's comments included separate analyses that included either only serious or only severe (CTCAE grade ≥ 3) events for the outcome of MACE.

The present assessment uses the outcome of MACE with the component "cardiovascular events leading to death" (referred to by the company as sensitivity analysis). According to the information provided by the company in Module 4 A, the classification as a cardiovascular event was made post hoc by clinical experts on the basis of the documented cause of death. For the present benefit assessment, both analyses of MACE (SAEs and severe AEs) are taken into account. In contrast to the approach adopted by the company, the results on MACE are assigned to the outcome category of side effects.

Risk of bias, certainty of conclusions and quantification of the added benefit for the outcome of MACE

Analogous to the risk of bias of the results for the outcomes of SAEs and severe AEs, the risk of bias of the results for the outcome of MACE (analysed either as SAEs or as severe AEs) is rated as low. Overall, however, the certainty of conclusions is reduced due to the uncertainty as to whether local therapy would no longer have been an option for all patients in the subpopulation presented by the company (for further justification, see benefit assessment A22-108 [1]). For the outcome of MACE, at most hints, e.g. of lesser harm, can therefore be derived on the basis of the available information. With its comments, the company resolved various uncertainties regarding the measurement reliability of the outcome of MACE addressed in dossier assessment A22-108. This concerns, on the one hand, the information on the included events of the individual components recorded via SMQs and, on the other, the information on the severity grade of the events according to CTCAE as well as the classification as serious event. However, implausibilities arise from the information provided by the company on the events included in the outcome and their severity grades. For example, according to information provided by the company in its comments, the event of a CTCAE grade 3 transient ischaemic attack was included in the analyses as a severe AE. However, according to the CTCAE, there is no grade 3 transient ischaemic attack. Due to the implausibility in the documented data, the extent of the outcome is rated as non-quantifiable.

Results

Table 2 summarizes the results from the company's dossier and the analyses subsequently submitted in the comments on the comparison of relugolix with leuprorelin for research question 2 of the present benefit assessment for the outcome of MACE (outcome category of side effects). Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier.

Kaplan-Meier curves on the event time analyses can be found in Appendix B.

Table 2: Results on side effects (MACE) – RCT, direct comparison: relugolix vs. leuprorelin – research question 2: patients who are not candidates for local therapy (multipage table)

Study Outcome category Outcome	Relugolix		Leuprorelin		Relugolix vs. leuprorelin
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value[a]
HERO					
Side effects					
MACE (SAEs)[b]	427	2 (0.5)	213	8 (3.8)	0.12 [0.03; 0.58]; 0.002
Cardiovascular events leading to death[c, d]	427	0 (0)	213	3 (1.4)	0.07 [0.00; 1.38]; 0.015
Nonfatal myocardial infarction[d, e]	427	2 (0.5)	213	1 (0.5)	1.00 [0.09; 10.94]; > 0.999
Nonfatal central nervous system haemorrhages and cerebrovascular conditions[d, f]	427	0 (0)	213	5 (2.3)	0.05 [0.00; 0.82]; 0.001
MACE (severe AEs[g])[h]	427	2 (0.5)	213	6 (2.8)	0.17 [0.03; 0.82]; 0.012
Cardiovascular events leading to death[c, d]	427	0 (0)	213	3 (1.4)	0.07 [0.00; 1.38]; 0.015
Nonfatal myocardial infarction[d, e]	427	2 (0.5)	213	1 (0.5)	1.00 [0.09; 10.94]; > 0.999
Nonfatal central nervous system haemorrhages and cerebrovascular conditions[d, f]	427	0 (0)	213	3 (1.4)	0.07 [0.00; 1.38]; 0.015

a. Institute's calculation: RR, CI (asymptotic), p-value (unconditional exact test, CSZ method according to [7]).
b. Composite outcome consisting of the components of cardiovascular events leading to death, nonfatal myocardial infarction (SAE) and nonfatal central nervous system haemorrhages and cerebrovascular conditions (SAE).
c. According to the information provided by the company in Module 4 A, the classification as a cardiovascular event was made post hoc by clinical experts on the basis of the documented cause of death.
d. An event was considered regardless of whether it was also the qualifying event for the composite outcome.
e. Recorded using the Standardized MedDRA Query (SMQ) "myocardial infarction" (broad) excluding fatal events.
f. Recorded using the SMQ "central nervous system haemorrhages and cerebrovascular conditions" (broad) excluding fatal events.
g. Operationalized as CTCAE grade ≥ 3.
h. Composite outcome consisting of the components of cardiovascular events leading to death, nonfatal myocardial infarction (severe AEs) and nonfatal central nervous system haemorrhages and cerebrovascular conditions (severe AEs).

AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; MACE: major adverse cardiovascular event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least one) event; N: number of analysed patients; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SMQ: Standardized MedDRA Query

In each case, a statistically significant difference in favour of relugolix in comparison with leuprorelin was shown for the composite outcome of MACE considering only SAEs or only severe AEs. There is a hint of lesser harm of relugolix in comparison with leuprorelin for this outcome.

2.3 Subsequent analyses on AEs

In its dossier, the company presented analyses for the outcome of MACE (see Section 2.2). However, the SAP prespecified other categories of AEs besides MACE, mainly using SMQs. With its comments, the company presented the analyses of these prespecified AE analyses for the relevant subpopulation of research question 2 of the benefit assessment. These include:

- osteoporosis/osteopenia SMQ (broad); including all PTs that contained the terms "fracture"; the terms "tooth fracture" and "fracture of penis" were excluded
- torsade de pointes/QT prolongation SMQ (broad)
- drug related hepatic disorder SMQ (narrow)
- hyperglycaemia/new onset diabetes mellitus SMQ (narrow)
- dyslipidaemia SMQ (broad)
- ischaemic heart disease SMQ (broad)
- vasomotor symptoms (comprising the following 5 PTs: hyperhidrosis, flushing, hot flush, night sweat or facial flushing)
- depression and suicide/self-injury SMQ (broad)
- hypersensitivity SMQ (narrow)

Based on the relative risks, no statistically significant difference between treatment groups was shown for any of the AEs subsequently submitted by the company.

2.4 Probability and extent of added benefit (research question 2: patients who are candidates for local therapy)

The probability and extent of added benefit at outcome level are derived 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 [8].

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.

2.4.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level is estimated from the results presented in benefit assessment A22-108 [1] and in the previous sections (see Table 3).

Table 3: Extent of added benefit at outcome level: relugolix vs. leuprorelin (multipage table)

Outcome category **Outcome**	**Relugolix vs. leuprorelin** **Median time to event (months) or proportion of events (%)** **Effect estimation [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Total observation period		
Mortality		
Overall survival	NA vs. NA HR: 0.36 [0.08; 1.62]; p = 0.185	Lesser/added benefit not proven
Shortened observation period		
Morbidity		
Symptoms (EORTC QLQ-C30) – deterioration ≥ 10 points		
Fatigue	2.9 vs. 5.6 HR: 1.14 [0.93; 1.39]; p = 0.205	Lesser/added benefit not proven
Nausea and vomiting	NA vs. NA HR: 0.93 [0.65; 1.32]; p = 0.685	Lesser/added benefit not proven
Pain	11.1 vs. 11.2 HR: 1.14 [0.90; 1.46]; p = 0.278	Lesser/added benefit not proven
Dyspnoea	11.5 vs. 11.3 HR: 0.84 [0.63; 1.11]; p = 0.213	Lesser/added benefit not proven
Insomnia	8.5 vs. 11.0 HR: 1.06 [0.84; 1.34]; p = 0.628	Lesser/added benefit not proven
Appetite loss	NA vs. NA HR: 1.11 [0.77; 1.58]; p = 0.580	Lesser/added benefit not proven
Constipation	11.5 vs. NA HR: 1.16 [0.86; 1.57]; p = 0.319	Lesser/added benefit not proven
Diarrhoea	NA vs. NA HR: 1.45 [1.05; 2.00]; p = 0.026 HR: 0.69 [0.50; 0.95][c]	Outcome category: non-serious/non-severe symptoms/late complications $0.90 \leq CI_u < 1.00$ Lesser benefit/added benefit not proven[d]

Table 3: Extent of added benefit at outcome level: relugolix vs. leuprorelin (multipage table)

Outcome category **Outcome**	**Relugolix vs. leuprorelin** **Median time to event (months) or proportion of events (%)** **Effect estimation [95% CI]; p-value** **Probability[a]**	**Derivation of extent[b]**
Symptoms (EORTC QLQ-PR25) – deterioration ≥ 10 points		
Micturition problems	11.1 vs. 11.3 HR: 1.28 [0.99; 1.66]; p = 0.057	Lesser/added benefit not proven
Bowel symptoms	NA vs. NA HR: 1.31 [0.89; 1.92]; p = 0.170	Lesser/added benefit not proven
Hormonal treatment-related symptoms	3.0 vs. 3.0 HR: 1.05 [0.86; 1.27]; p = 0.646	Lesser/added benefit not proven
Incontinence aid	No suitable data	Lesser/added benefit not proven
Health status (EQ--5D VAS) – deterioration ≥ 15 points		
EQ-5D VAS	NA vs. 11.5 HR: 0.89 [0.65; 1.22]; p = 0.465	Lesser/added benefit not proven
Health-related quality of life		
EORTC QLQ-C30 – deterioration ≥ 10 points		
Global health status	11.1 vs. 11.1 HR: 1.06 [0.84; 1.35]; p = 0.608	Lesser/added benefit not proven
Physical functioning	NA vs. NA HR: 0.96 [0.74; 1.26]; p = 0.775	Lesser/added benefit not proven
Role functioning	11.2 vs. 11.2 HR: 1.19 [0.93; 1.52]; p = 0.176	Lesser/added benefit not proven
Emotional functioning	11.5 vs. 11.7 HR: 0.91 [0.67; 1.25]; p = 0.561	Lesser/added benefit not proven
Cognitive functioning	11.2 vs. 11.1 HR: 0.94 [0.74; 1.20]; p = 0.626	Lesser/added benefit not proven
Social functioning	11.2 vs. 11.2 HR: 0.93 [0.73; 1.19]; p = 0.572	Lesser/added benefit not proven
EORTC QLQ-PR25 – deterioration ≥ 10 points		
Sexual activity	NA vs. NA HR: 0.76 [0.55; 1.03]; p = 0.078	Lesser/added benefit not proven
Sexual functioning	No suitable data	Lesser/added benefit not proven
Side effects		
SAEs	9.4% vs. 12.7% RR: 0.74 [0.47; 1.17]; p = 0.204	Greater/lesser harm not proven
Severe AEs	15.0% vs. 16.4% RR: 0.91 [0.63; 1.33]; p = 0.736	Greater/lesser harm not proven
Discontinuation due to AEs	2.8% vs. 0.5% RR: 5.99 [0.78; 45.73]; p = 0.0502	Greater/lesser harm not proven

Table 3: Extent of added benefit at outcome level: relugolix vs. leuprorelin (multipage table)

Outcome category **Outcome**	**Relugolix vs. leuprorelin** **Median time to event (months) or proportion of events (%)** **Effect estimation [95% CI]; p-value** **Probability[a]**	**Derivation of extent[b]**
MACE		
MACE (SAEs)	0.5% vs. 3.8% RR: 0.12 [0.03; 0.58]; p = 0.002 Probability: "hint"	Outcome category: serious/severe side effects CI_u < 0.75; risk < 5% Lesser harm, extent: "non-quantifiable"
MACE (severe AEs)	0.5% vs. 2.8% RR: 0.17 [0.03; 0.82]; p = 0.012 Probability: "hint"	Outcome category: serious/severe side effects 0.75 ≤ CI_u < 0.90 Lesser harm, extent: "non-quantifiable"

a. Probability provided if there is a statistically significant and relevant effect.
b. Depending on the outcome category, the effect size is estimated using different limits based on the upper limit of the confidence interval (CI_u).
c. Institute's calculation; inverse direction of effect to enable use of limits to derive the extent of the added benefit.
d. The extent of the effect in this non-serious/non-severe outcome was no more than marginal.

AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; MACE: major adverse cardiovascular event; NA: not achieved; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-PR25: Quality of Life Questionnaire-Prostate 25; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; VAS: visual analogue scale

2.4.2 Overall conclusion on added benefit

Table 4 summarizes the results taken into account in the overall conclusion on the extent of added benefit.

Table 4: Positive and negative effects from the assessment of relugolix in comparison with leuprorelin

Positive effects	**Negative effects**
Total observation period	
–	–
Shortened observation period	
Serious/severe side effects ▪ MACE (severe AEs and SAEs): hint of lesser harm – extent: "non-quantifiable", no more than "considerable"	–

AE: adverse event; MACE: major adverse cardiovascular event; SAE: serious adverse event

Overall, with the exception of the outcome of MACE, there are no positive or negative effects for relugolix. For the outcome of MACE, there is a hint of non-quantifiable lesser harm from relugolix. For this outcome, however, there is uncertainty in the measurement reliability due to the lack of adjudication of the events included in the outcome, even after inclusion of the data subsequently submitted by the company. The lack of adjudication was also criticized by the regulatory authority in the European Public Assessment Report (EPAR) [9]. The advantage of relugolix over leuprorelin observed in the HERO study for the outcome of MACE is not sufficient on its own to determine an added benefit for relugolix in comparison with the appropriate comparator therapy. Thus, there is no added benefit of relugolix in comparison with the ACT for patients with advanced hormone-sensitive prostate cancer who are not candidates for local therapy.

The assessment described above deviates from that by the company, which derived an indication of considerable added benefit.

2.5 Summary

The data subsequently submitted by the company in the commenting procedure have not changed the conclusion on the added benefit of relugolix from dossier assessment A22-108.

The following Table 5 shows the result of the benefit assessment of relugolix taking into account the dossier assessment A22-108 and the present addendum.

Table 5: Relugolix – probability and extent of added benefit (multipage table)

Research question	**Therapeutic indication**	**ACT**[a]	**Probability and extent of added benefit**
Patients with advanced hormone-sensitive prostate cancer[b]			
1	Patients who are candidates for local therapy	▪ radical prostatectomy, if necessary in combination with lymphadenectomy or ▪ percutaneous radiotherapy in combination with conventional androgen deprivation[c] or bicalutamide or ▪ percutaneous radiotherapy in combination with HDR brachytherapy (only for patients in clinical category cT3)	Added benefit not proven
2	Patients who are not candidates for local therapy	▪ conventional androgen deprivation[c] or ▪ bicalutamide	Added benefit not proven[d]
3	Patients with PSA recurrence or clinical recurrence after primary local therapy	Individualized treatment[e] selected from ▪ salvage prostatectomy, ▪ percutaneous salvage radiotherapy, and ▪ percutaneous salvage radiotherapy in combination with conventional androgen deprivationc or bicalutamide; taking into account the prior therapy and the risk of progression	Added benefit not proven
Patients with metastatic hormone-sensitive prostate cancer (mHSPC)[f, g]			
4a	Patients who are candidates for combination therapy	▪ conventional androgen deprivation[c] in combination with apalutamide or ▪ conventional androgen deprivation[c] in combination with abiraterone acetate and prednisone or prednisolone (only for patients with newly diagnosed high-risk prostate cancer) or ▪ conventional androgen deprivation[c] in combination with docetaxel with or without prednisone or prednisolone or ▪ conventional androgen deprivation[c] in combination with enzalutamide	Added benefit not proven
4b	Patients who are not candidates for combination therapy	▪ conventional androgen deprivationc	Added benefit not proven

Table 5: Relugolix – probability and extent of added benefit (multipage table)

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
a. Presented is the respective ACT specified by the G-BA. b. It is assumed that there is no distant metastasis (M0). According to the G-BA, it is assumed that, when determining the ACT, the individual therapeutic decision in the target population was made against long-term observation. Watchful waiting is therefore not considered to be an ACT in the present case. c. According to the G-BA, conventional androgen deprivation in the context of the present therapeutic indication means surgical castration or medical castration using treatment with GnRH agonists or GnRH antagonists. The drugs buserelin, leuprorelin, goserelin, triptorelin (GnRH agonists) and degarelix (GnRH antagonist) are considered suitable for the implementation of medical castration in the context of conventional androgen deprivation. In the context of a clinical study, the selection of only one of these drugs (single-comparator study) is considered sufficient. d. The HERO study included only patients with an ECOG PS of 0 or 1. It remains unclear whether the observed effects can be transferred to patients with an ECOG PS of ≥ 2. e. According to the G-BA, for the implementation of individualized therapy in a study of direct comparison, the investigator is expected to have a selection of several treatment options at disposal to permit an individualized treatment decision which considers the listed criteria (multi-comparator study). f. It is assumed that there is distant metastasis (M1). g. According to the G-BA, corresponding to the generally recognized state of medical knowledge, conventional androgen deprivation alone is only indicated for patients with mHSPC for whom a combination therapy – additional therapy to conventional androgen deprivation – is not an option with regard to any comorbidities and the general condition (research question 4b). ACT: appropriate comparator therapy; ECOG PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee; GnRH: gonadotropin-releasing hormone; HDR: high dose rate; mHSPC: metastatic hormone-sensitive prostate cancer; PSA: prostate-specific antigen			

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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Appendix A Kaplan-Meier curves of the analyses of the EORTC QLQ-C30 and EORTC QLQ-PR25 (research question 2: patients who are not candidates for local therapy)

Symptoms

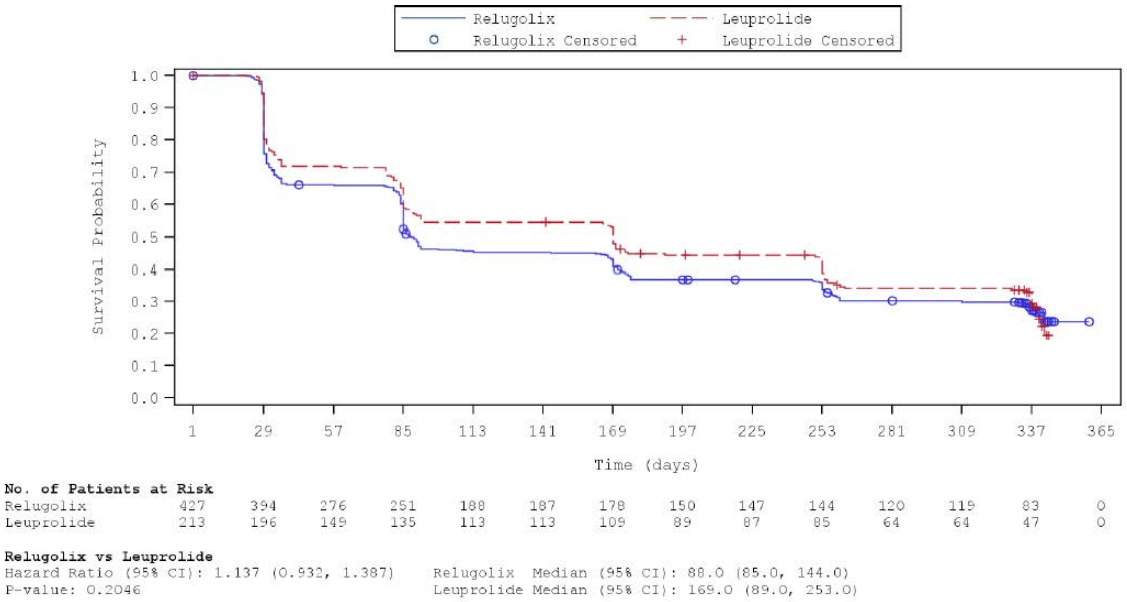

Figure 1: Kaplan-Meier curves for the outcome of fatigue (EORTC QLQ-C30), HERO study, relevant subpopulation (final analysis, database lock: 23 September 2020)

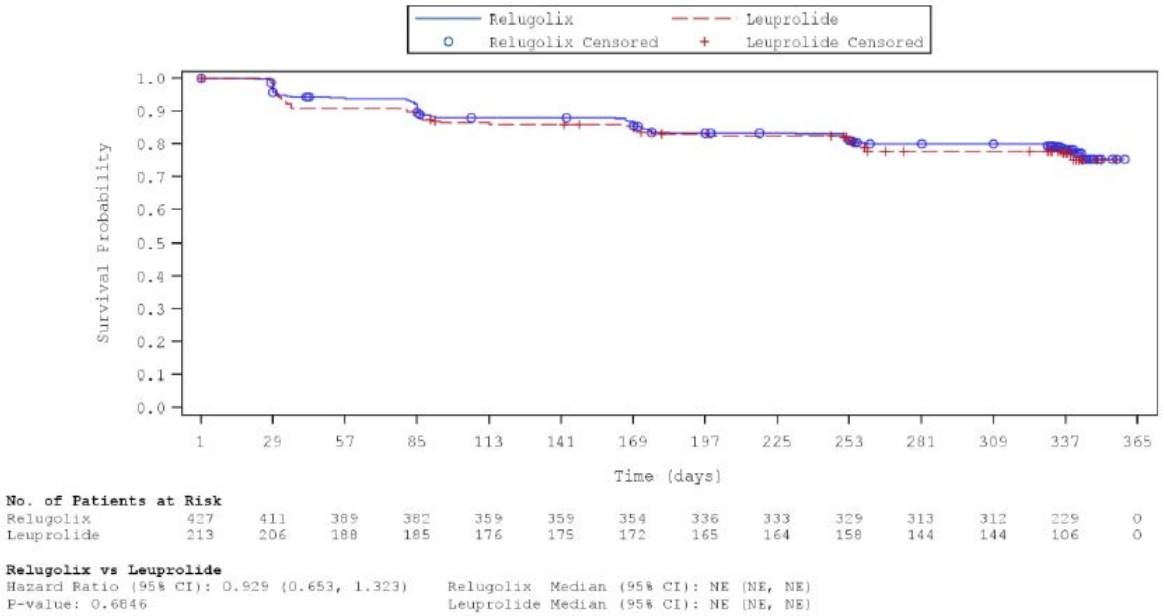

Figure 2: Kaplan-Meier curves for the outcome of nausea and vomiting (EORTC QLQ-C30), HERO study, relevant subpopulation (final analysis, database lock: 23 September 2020)

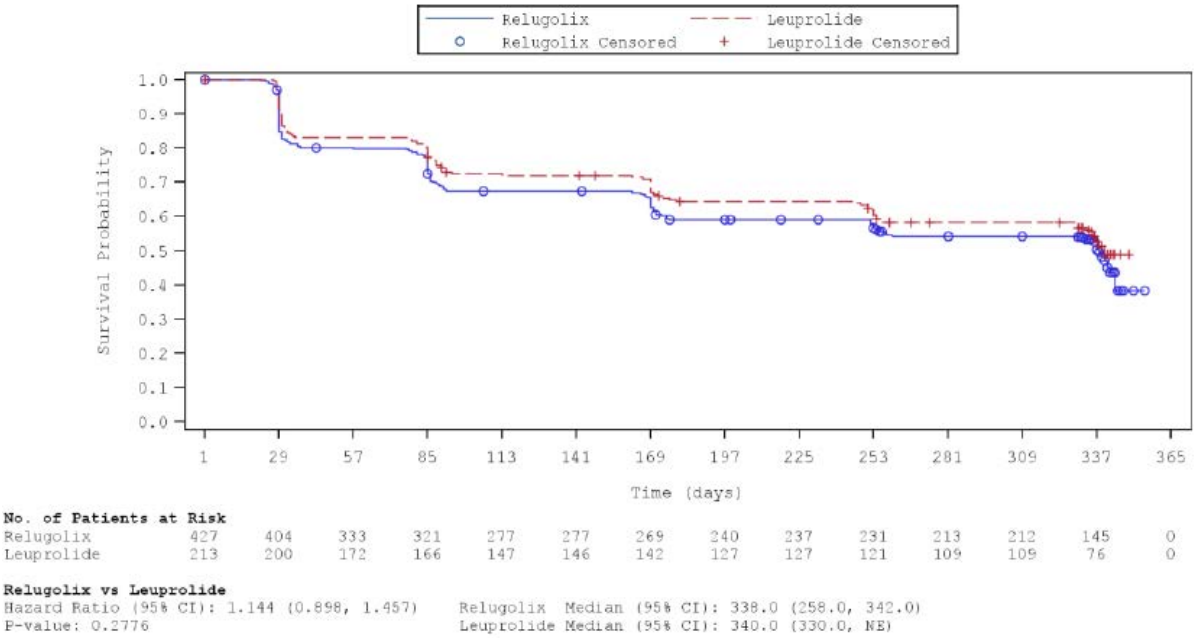

Figure 3: Kaplan-Meier curves for the outcome of pain (EORTC QLQ-C30), HERO study, relevant subpopulation (final analysis, database lock: 23 September 2020)

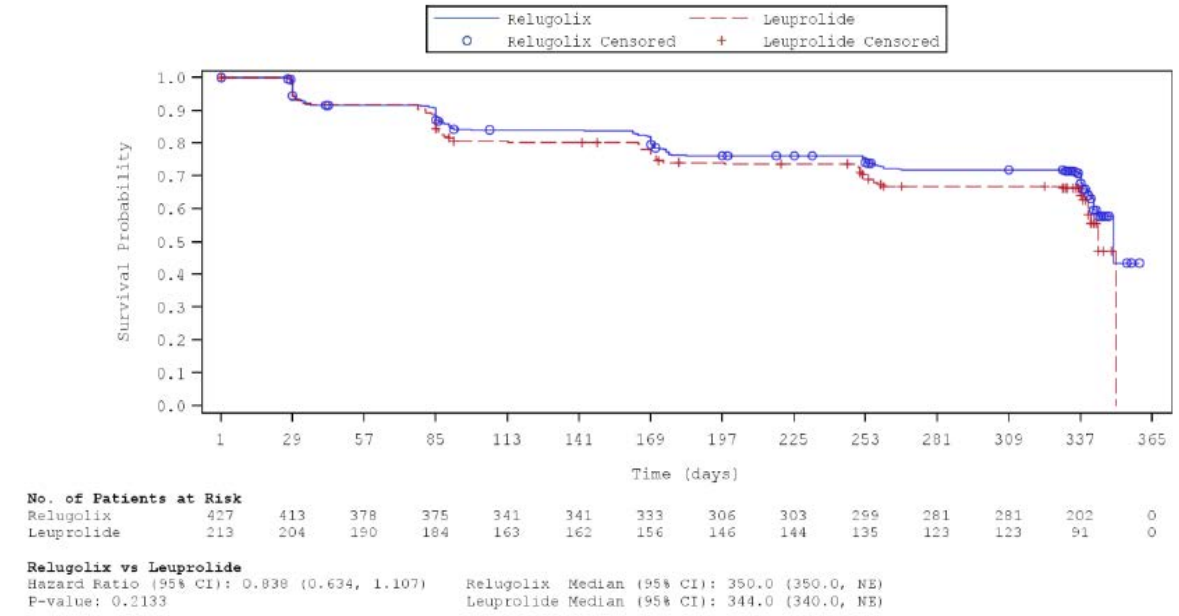

Figure 4: Kaplan-Meier curves for the outcome of dyspnoea (EORTC QLQ-C30), HERO study, relevant subpopulation (final analysis, database lock: 23 September 2020)

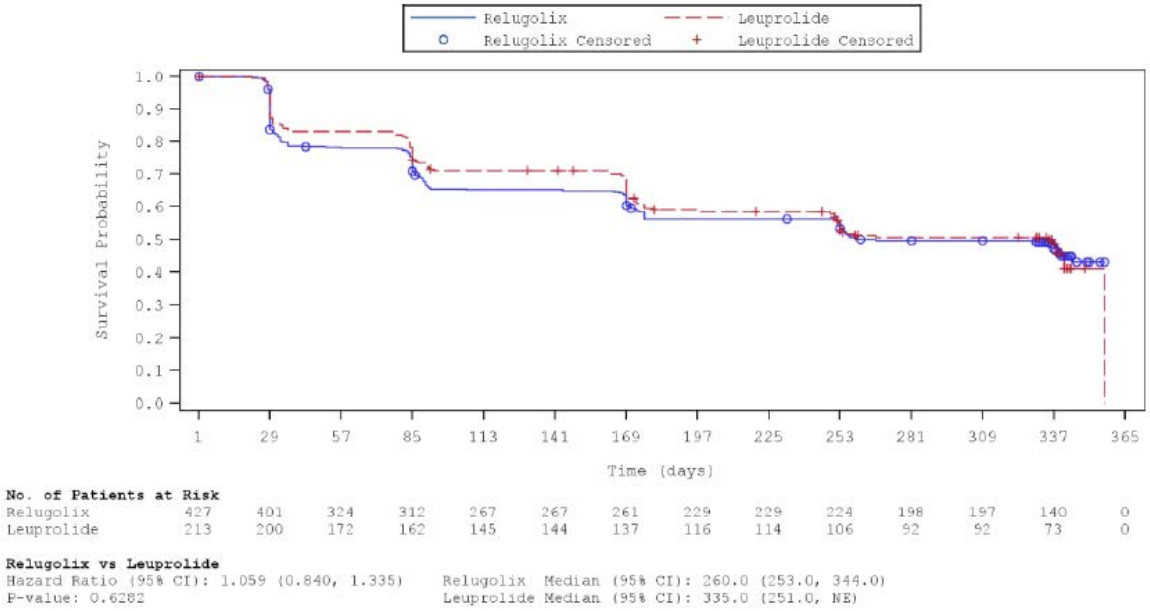

Figure 5: Kaplan-Meier curves for the outcome of insomnia (EORTC QLQ-C30), HERO study, relevant subpopulation (final analysis, database lock: 23 September 2020)

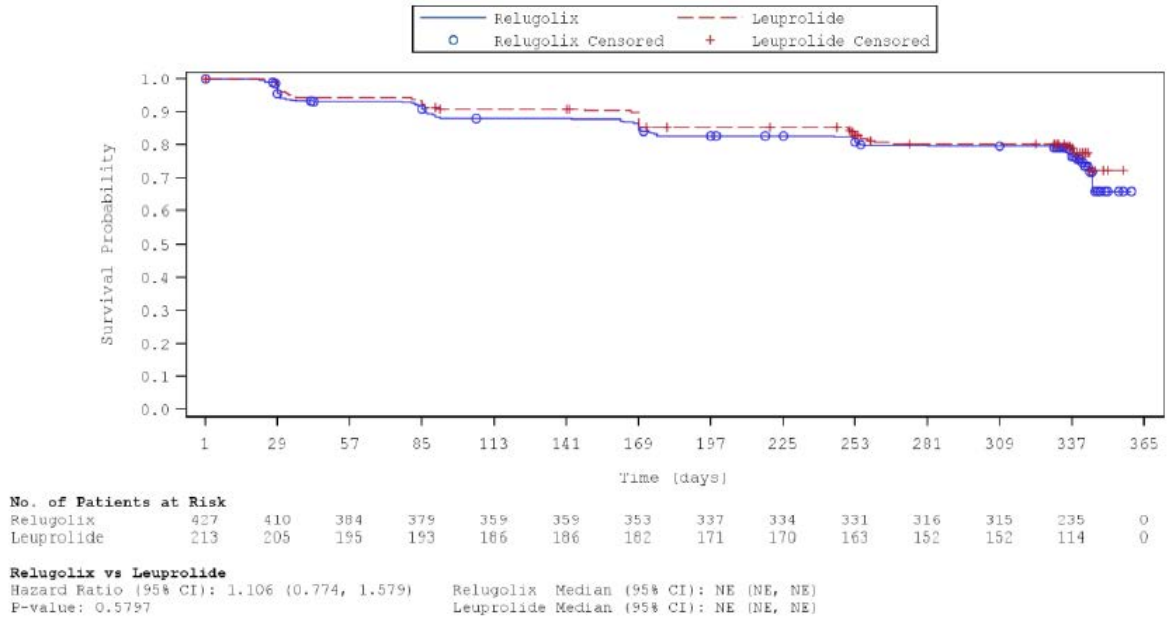

Figure 6: Kaplan-Meier curves for the outcome of appetite loss (EORTC QLQ-C30), HERO study, relevant subpopulation (final analysis, database lock: 23 September 2020)

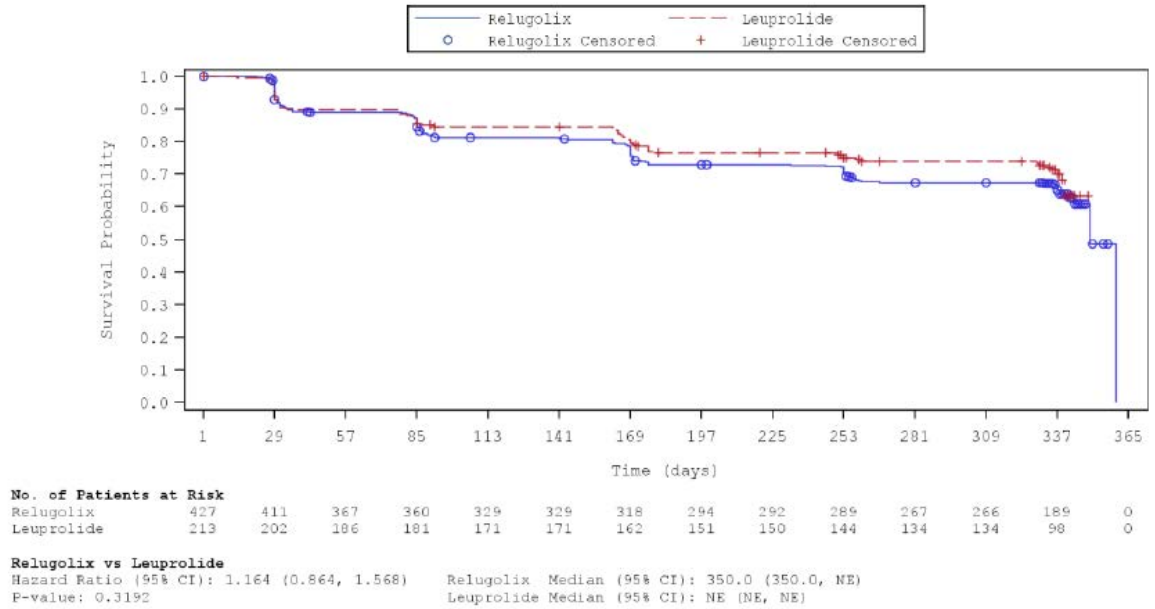

Figure 7: Kaplan-Meier curves for the outcome of constipation (EORTC QLQ-C30), HERO study, relevant subpopulation (final analysis, database lock: 23 September 2020)

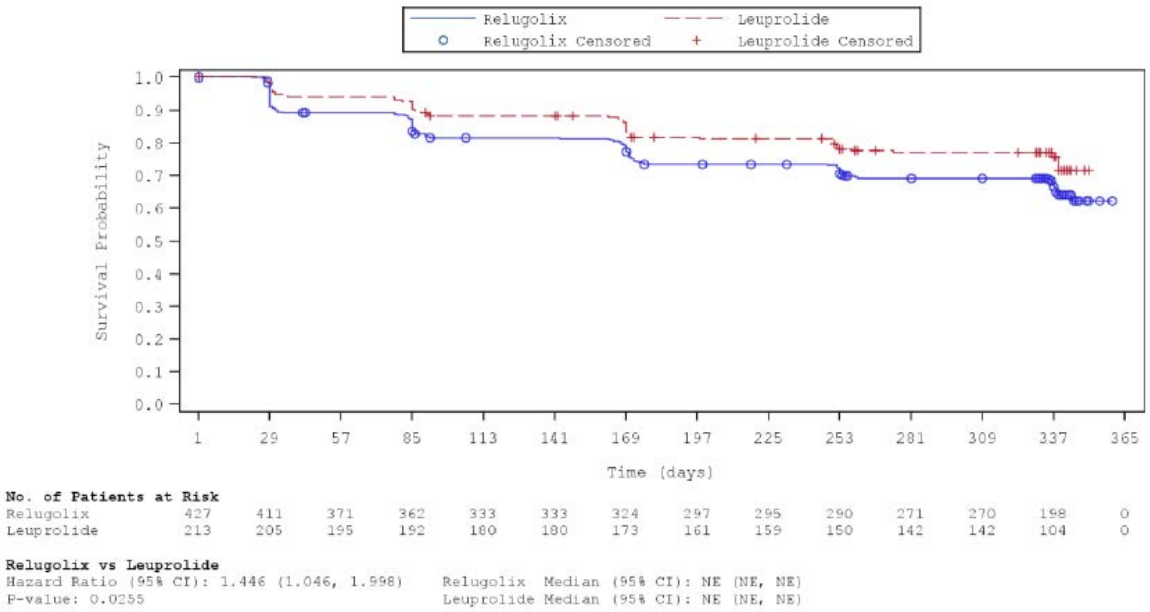

Figure 8: Kaplan-Meier curves for the outcome of diarrhoea (EORTC QLQ-C30), HERO study, relevant subpopulation (final analysis, database lock: 23 September 2020)

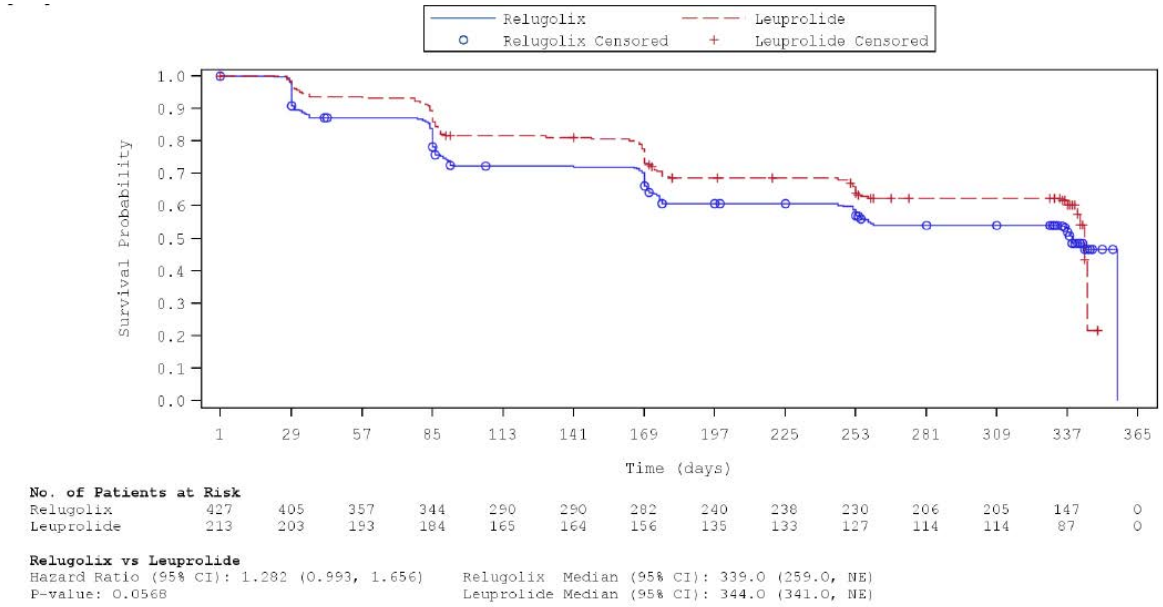

Figure 9: Kaplan-Meier curves for the outcome of micturition problems (EORTC QLQ-PR25), HERO study, relevant subpopulation (final analysis, database lock: 23 September 2020)

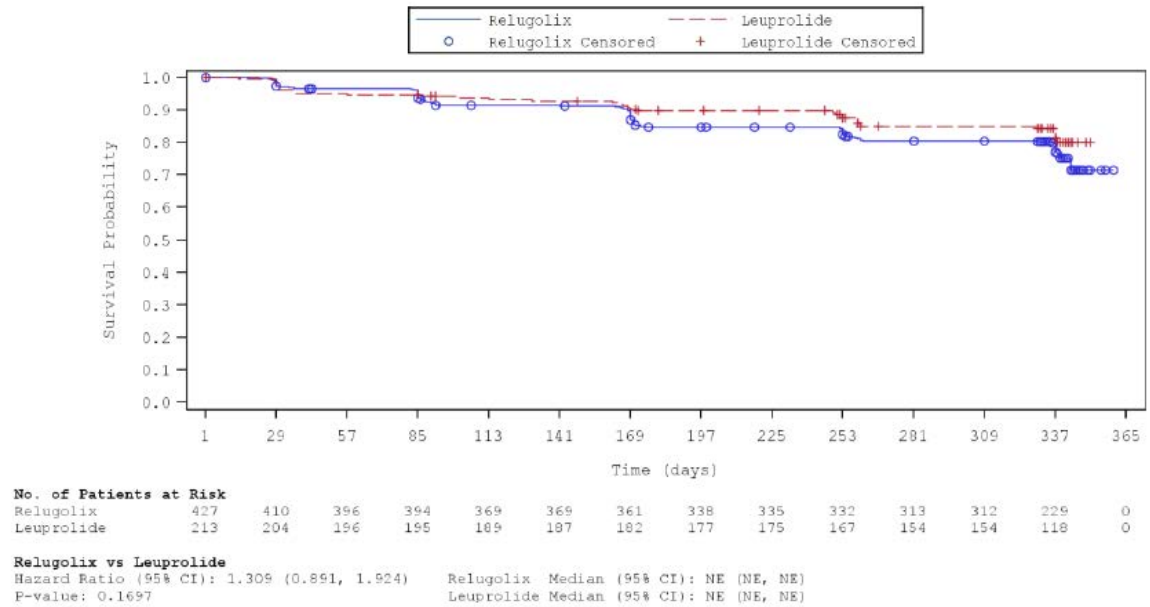

Figure 10: Kaplan-Meier curves for the outcome of bowel symptoms (EORTC QLQ-PR25), HERO study, relevant subpopulation (final analysis, database lock: 23 September 2020)

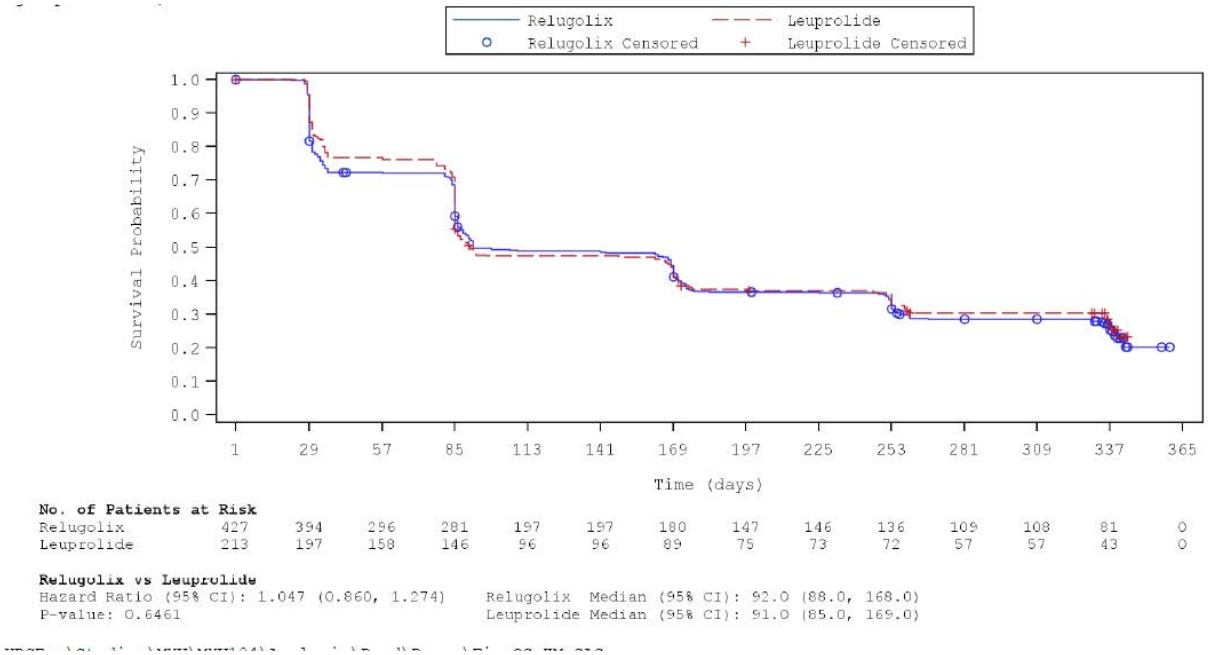

Figure 11: Kaplan-Meier curves for the outcome of hormonal treatment-related symptoms (EORTC QLQ-PR25), HERO study, relevant subpopulation (final analysis, database lock: 23 September 2020)

Health-related quality of life

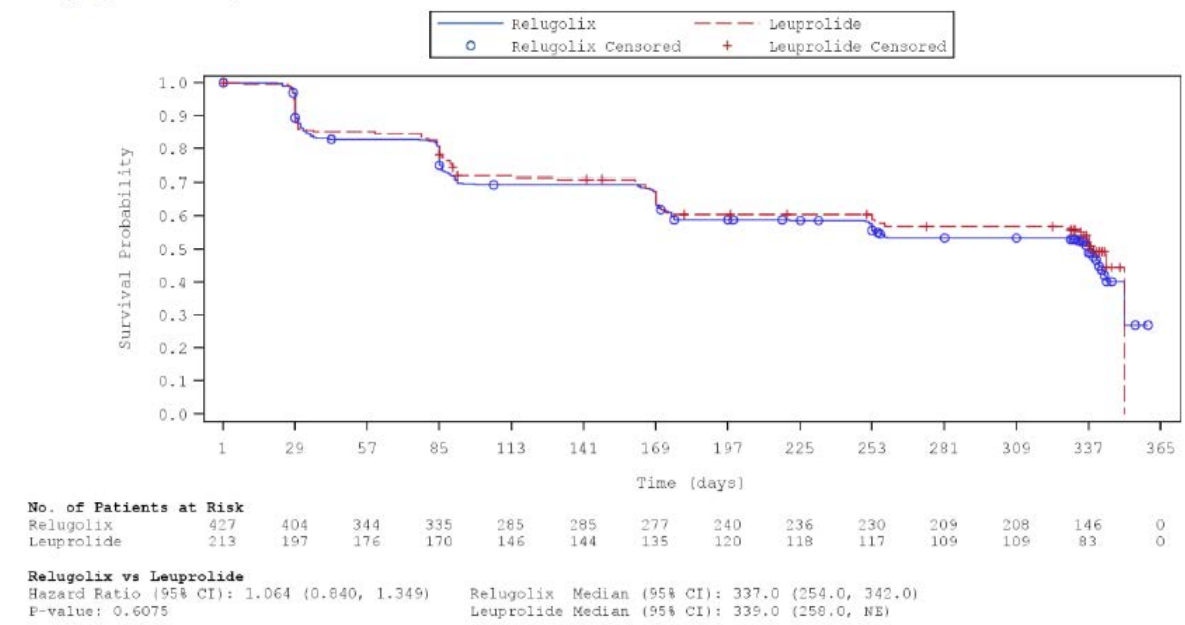

Figure 12: Kaplan-Meier curves for the outcome of global health status (EORTC QLQ-C30), HERO study, relevant subpopulation (final analysis, database lock: 23 September 2020)

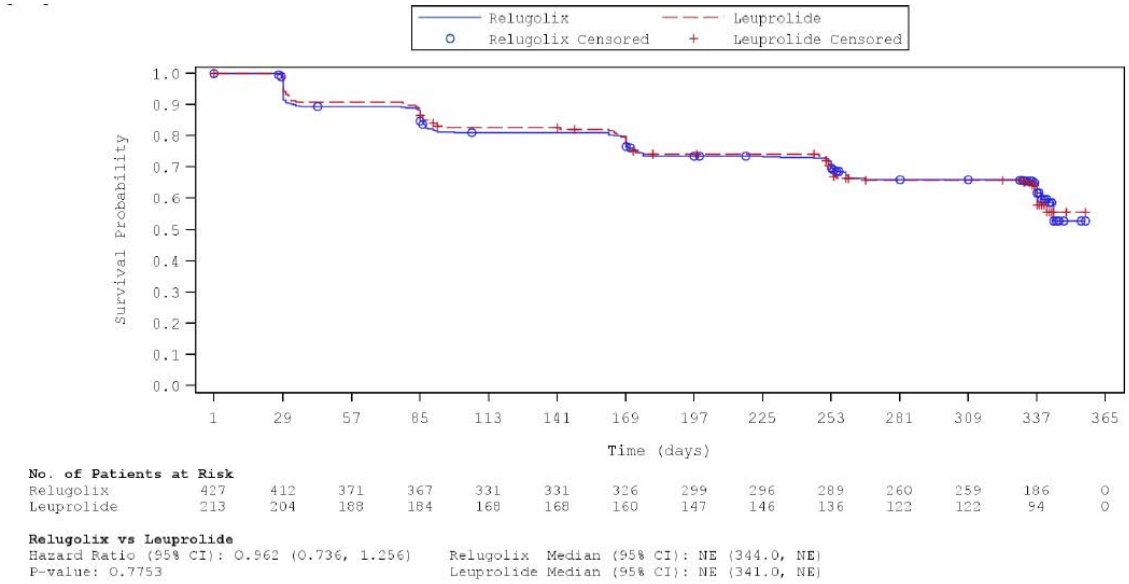

Figure 13: Kaplan-Meier curves for the outcome of physical functioning (EORTC QLQ-C30), HERO study, relevant subpopulation (final analysis, database lock: 23 September 2020)

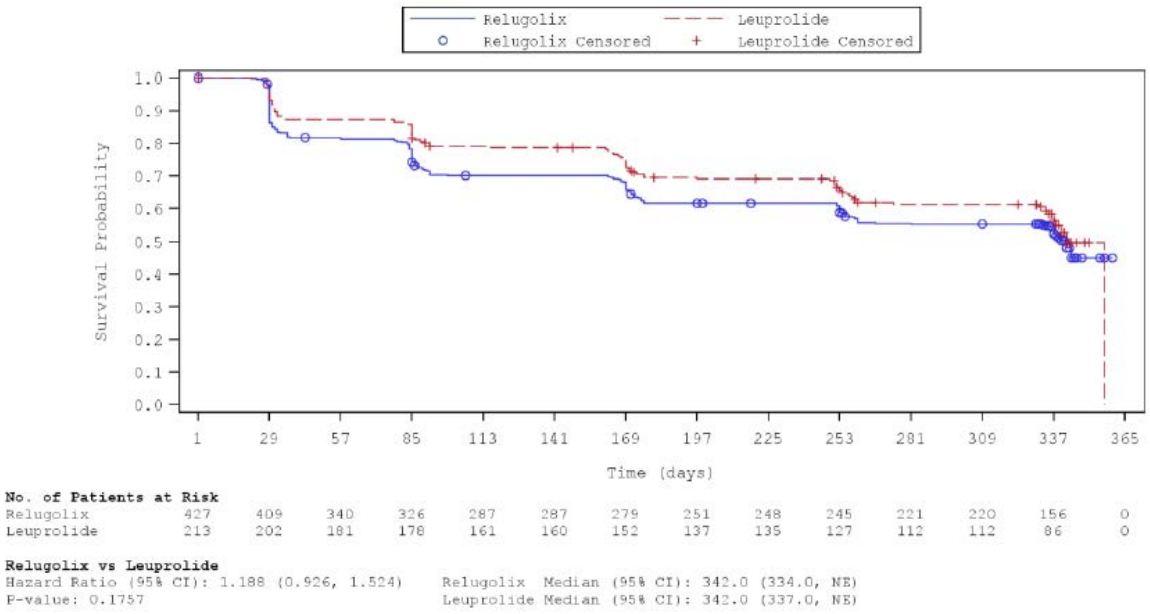

Figure 14: Kaplan-Meier curves for the outcome of role functioning (EORTC QLQ-C30), HERO study, relevant subpopulation (final analysis, database lock: 23 September 2020)

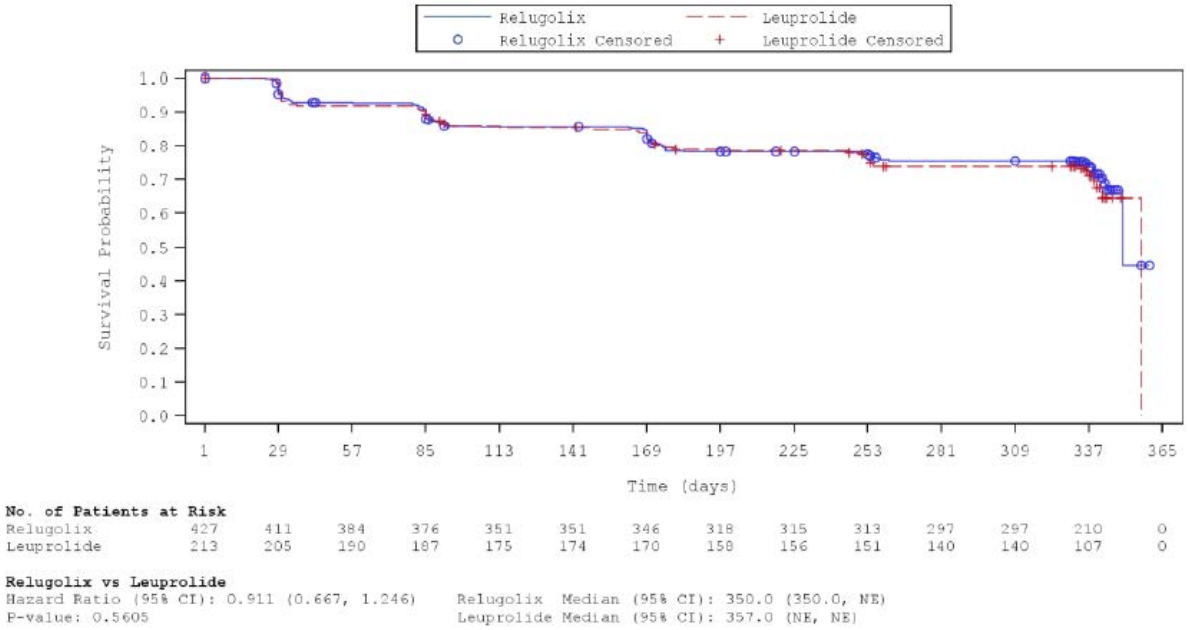

Figure 15: Kaplan-Meier curves for the outcome of emotional functioning (EORTC QLQ-C30), HERO study, relevant subpopulation (final analysis, database lock: 23 September 2020)

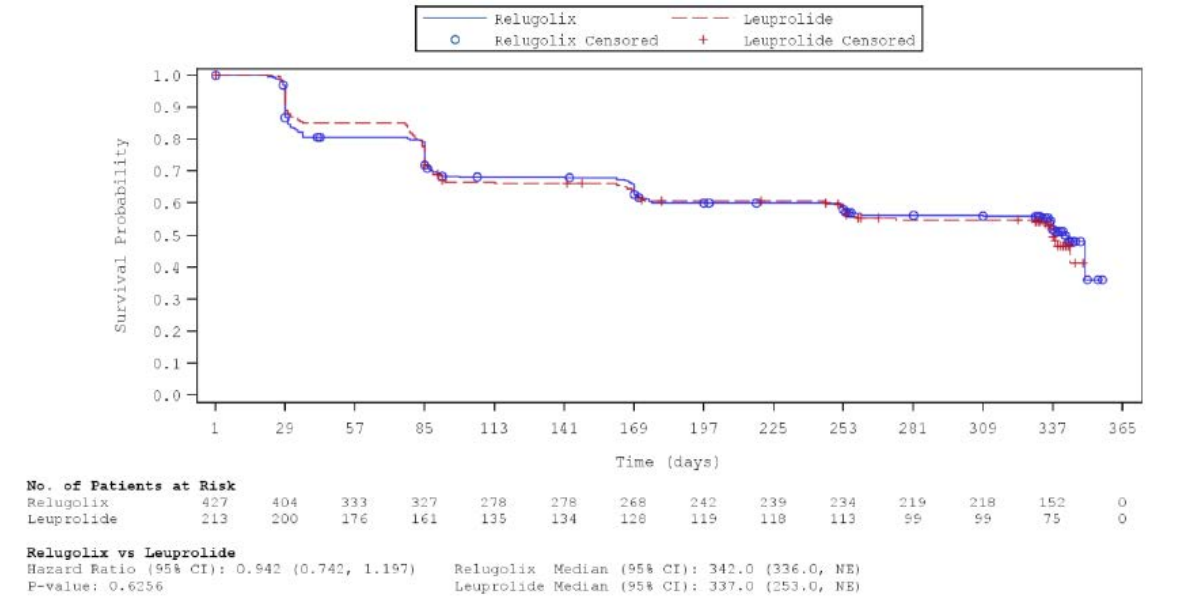

Figure 16: Kaplan-Meier curves for the outcome of cognitive functioning (EORTC QLQ-C30), HERO study, relevant subpopulation (final analysis, database lock: 23 September 2020)

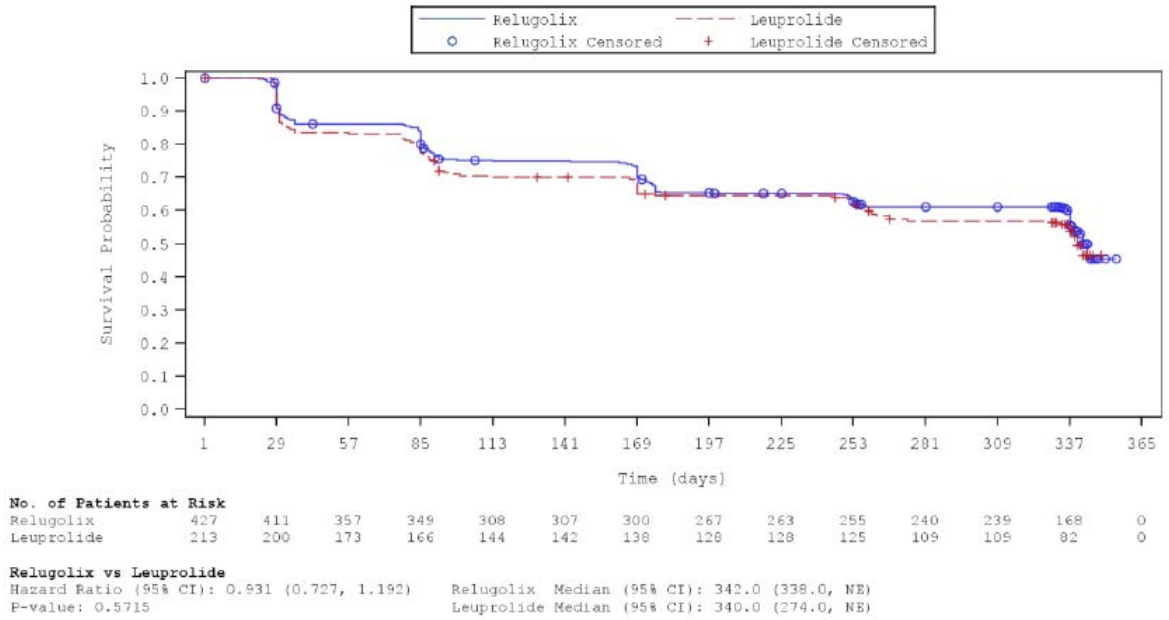

Figure 17: Kaplan-Meier curves for the outcome of social functioning (EORTC QLQ-C30), HERO study, relevant subpopulation (final analysis, database lock: 23 September 2020)

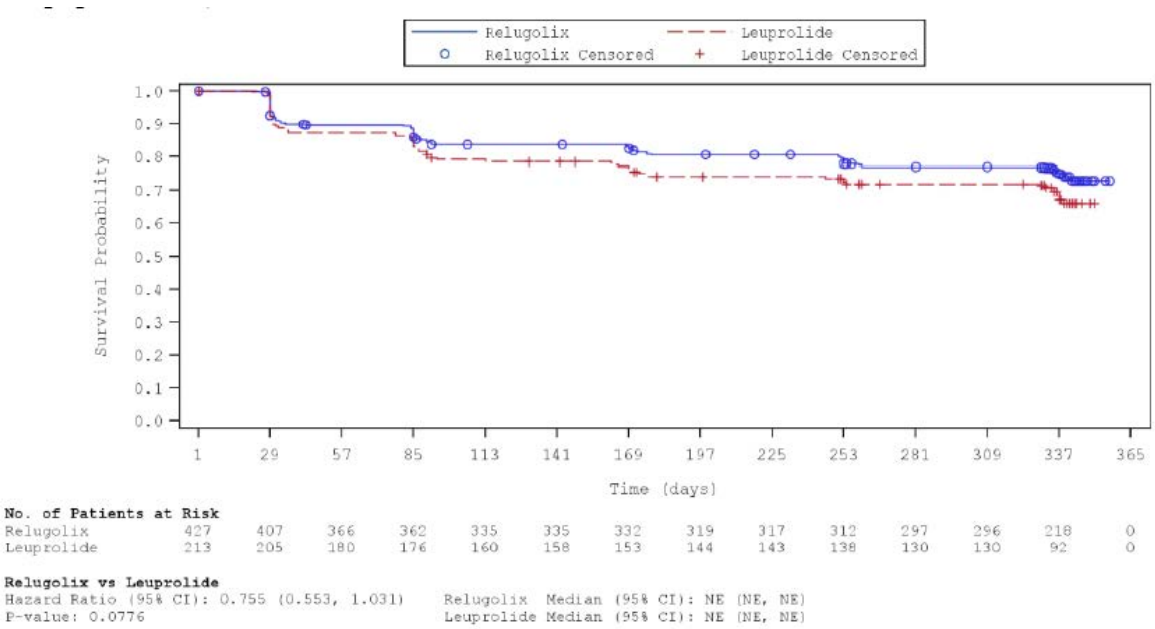

Figure 18: Kaplan-Meier curves for the outcome of sexual activity (EORTC QLQ-PR25), HERO study, relevant subpopulation (final analysis, database lock: 23 September 2020)

Appendix B Kaplan-Meier curves for the outcome of MACE (research question 2: patients who are not candidates for local therapy)

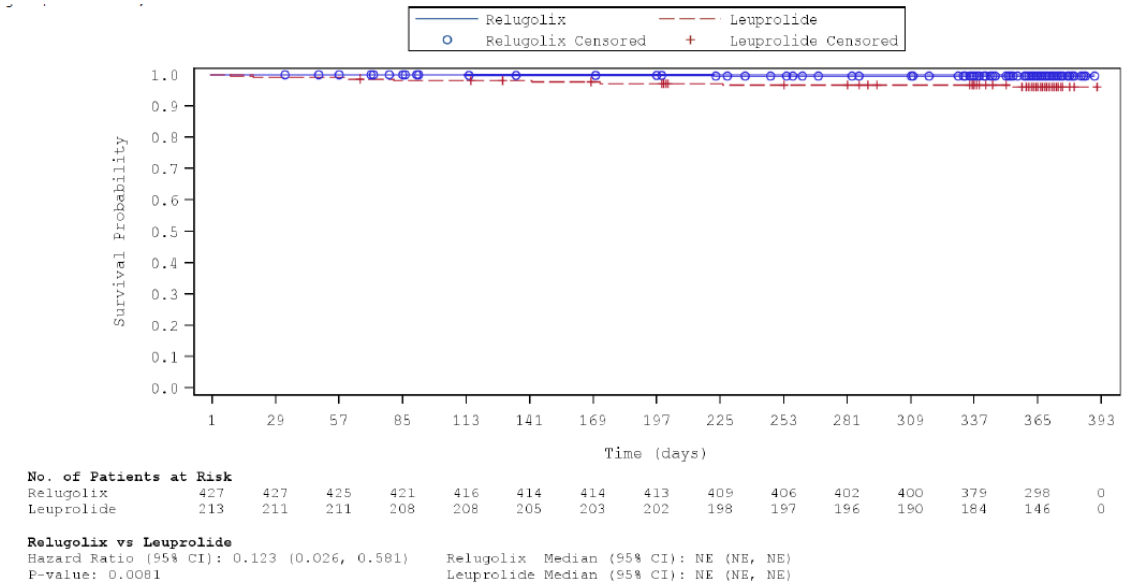

Figure 19: Kaplan-Meier curves for the outcome of MACE (SAEs), HERO study, relevant subpopulation (final analysis, database lock: 23 September 2020)

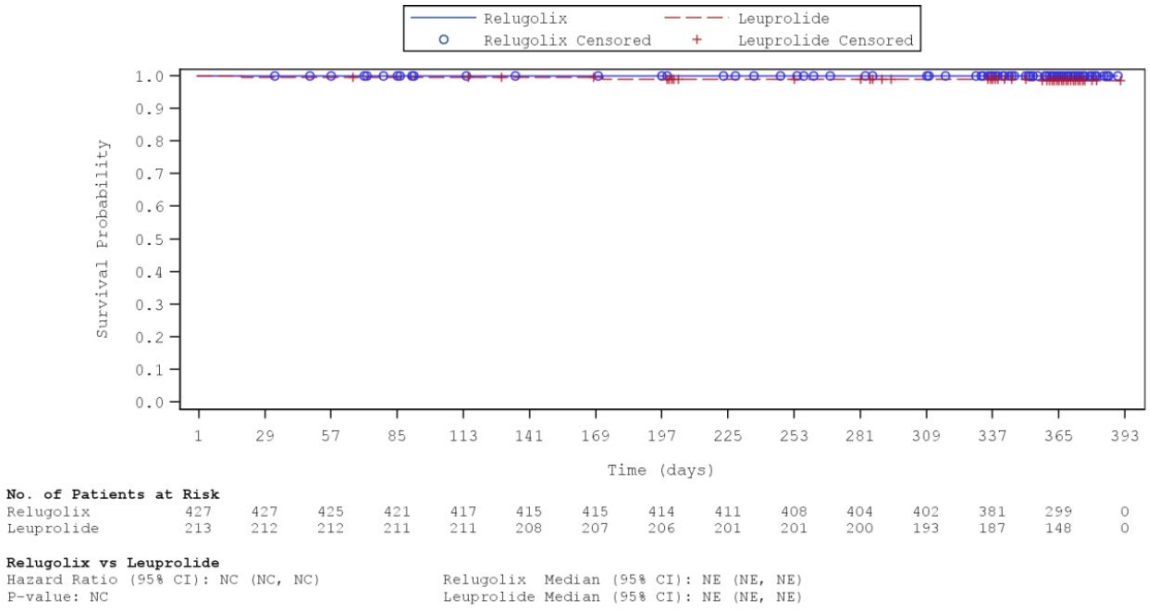

Figure 20: Kaplan-Meier curves for the subcomponent of cardiovascular events leading to death of the outcome of MACE (SAEs) and MACE (severe AEs), HERO study, relevant subpopulation (final analysis, database lock: 23 September 2020)

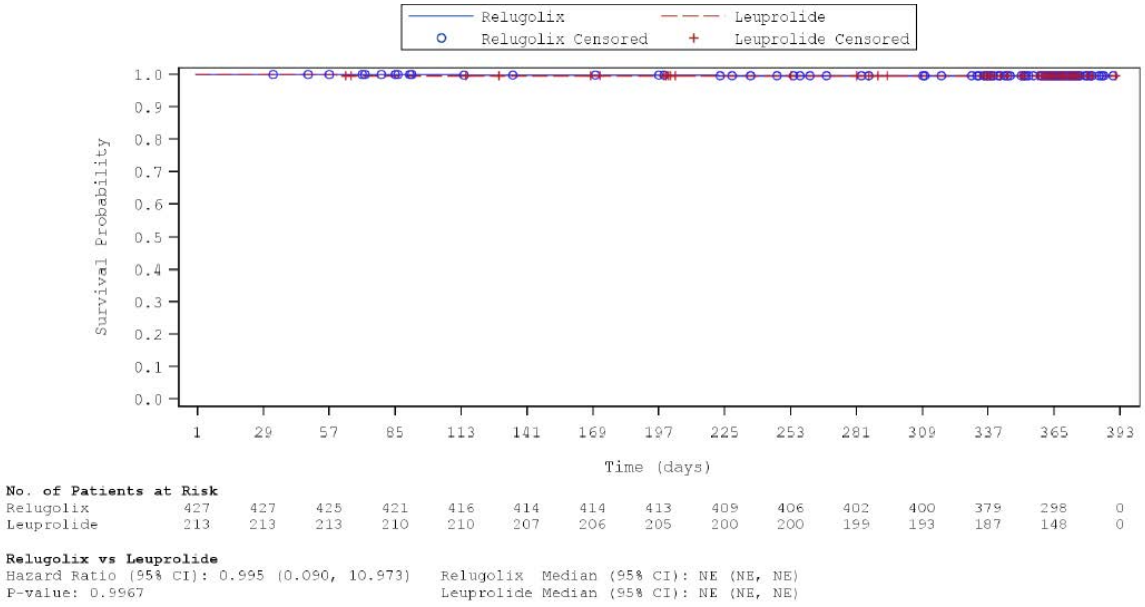

Figure 21: Kaplan-Meier curves for the subcomponent of nonfatal myocardial infarction of the outcome of MACE (SAEs), HERO study, relevant subpopulation (final analysis, database lock: 23 September 2020)

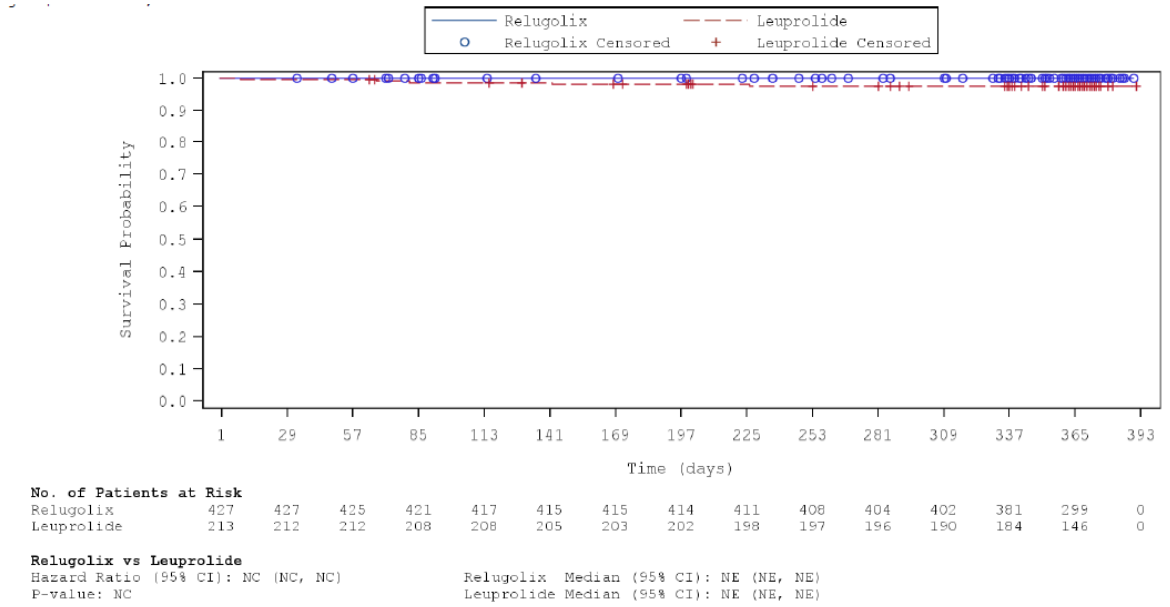

Figure 22: Kaplan-Meier curves for the subcomponent of nonfatal central nervous system haemorrhages and cerebrovascular conditions of the outcome of MACE (SAEs), HERO study, relevant subpopulation (final analysis, database lock: 23 September 2020)

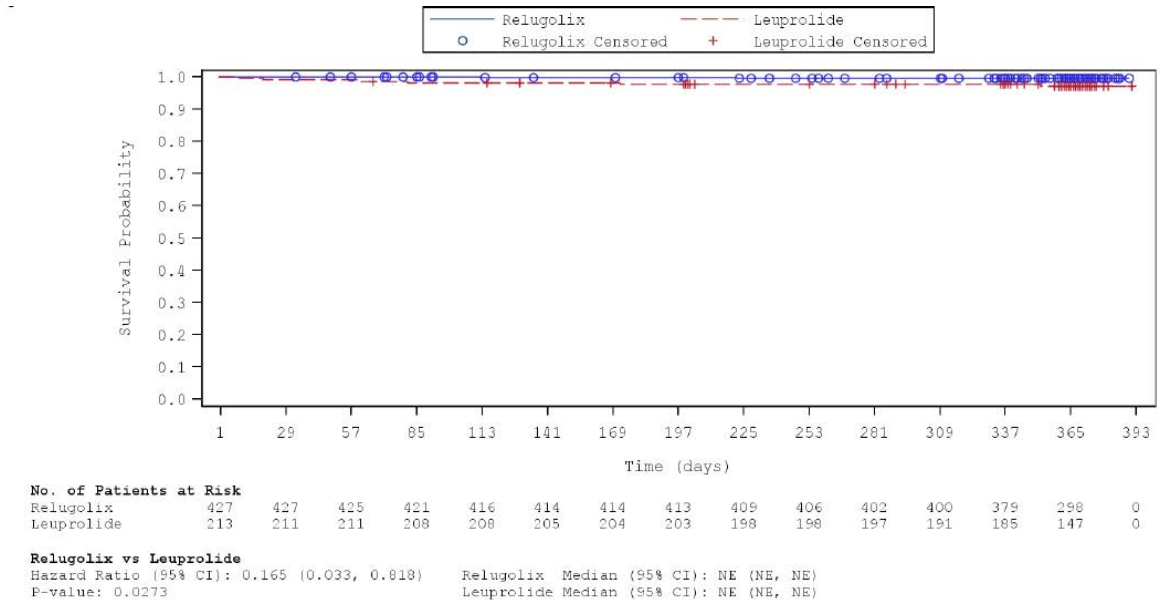

Figure 23: Kaplan-Meier curves for the outcome of MACE (severe AEs), HERO study, relevant subpopulation (final analysis, database lock: 23 September 2020)

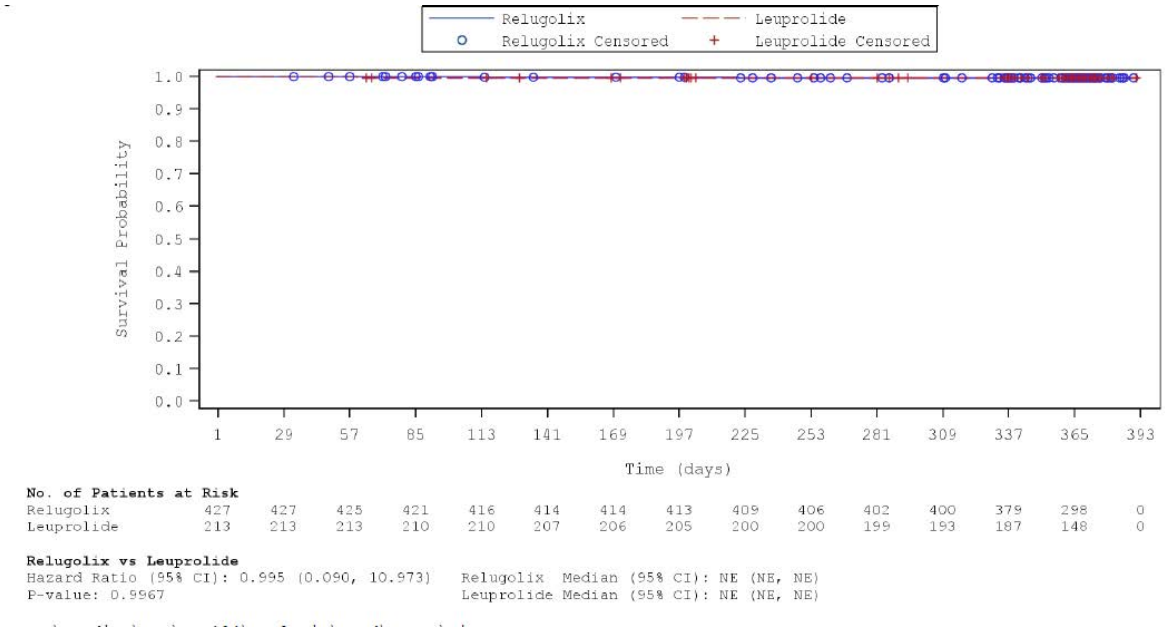

Figure 24: Kaplan-Meier curves for the subcomponent of nonfatal myocardial infarction of the outcome of MACE (severe AEs), HERO study, relevant subpopulation (final analysis, database lock: 23 September 2020)

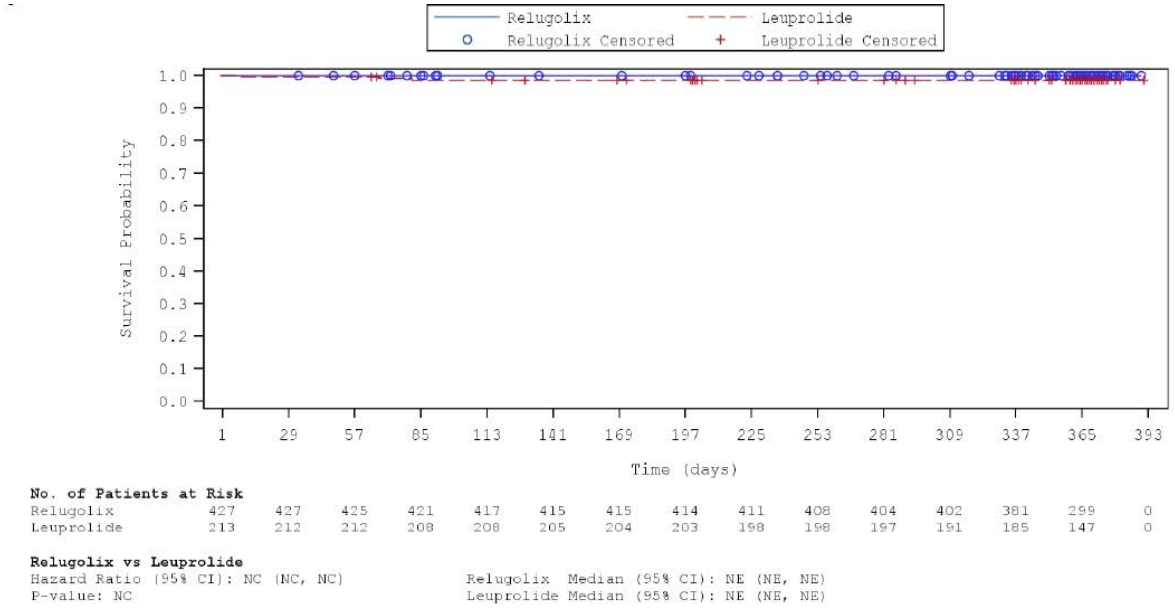

Figure 25: Kaplan-Meier curves for the subcomponent of nonfatal central nervous system haemorrhages and cerebrovascular conditions of the outcome of MACE (severe AEs), HERO study, relevant subpopulation (final analysis, database lock: 23 September 2020)