IQWiG Reports – Commission No. A19-59

Ravulizumab (paroxysmal nocturnal haemoglobinuria) –

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

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Ravulizumab (paroxysmale nächtliche Hämoglobinurie) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 30 October 2019). 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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Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Im Mediapark 8
50670 Köln
Germany

Phone: +49 221 35685-0
Fax: +49 221 35685-1
E-mail: berichte@iqwig.de
Internet: www.iqwig.de

Medical and scientific advice:

No advisor on medical and scientific questions was available for the present dossier assessment.

IQWiG employees involved in the dossier assessment:

- Katharina Wölke
- Lars Beckmann
- Michaela Florina Kerekes
- Stefan Kobza
- Inga Overesch
- Regine Potthast
- Sonja Schiller
- Volker Vervölgyi

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

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy – Fatigue
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
LDH	lactate dehydrogenase
MAVE	major adverse vascular event
MedDRA	Medical Dictionary for Regulatory Activities
PNH	paroxysmal nocturnal haemoglobinuria
pRBC	packed red blood cells
PT	Preferred Term
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics
ULN	upper limit of normal

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 ravulizumab. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as "the company"). The dossier was sent to IQWiG on 1 August 2019.

Research question

The aim of the present report is the assessment of the added benefit of ravulizumab in comparison with eculizumab as appropriate comparator therapy (ACT) in

- adult patients with paroxysmal nocturnal haemoglobinuria (PNH) with haemolysis with clinical symptom(s) indicative of high disease activity,
- adult patients with PNH who are clinically stable after having been treated with eculizumab for at least the past 6 months.

There are 2 research questions for the present assessment, as 2 treatment situations with different treatment goals result from the approved therapeutic indication of ravulizumab. On the one hand, this is treatment of high disease activity with clinical symptoms of haemolysis (for example at first diagnosis or in case of inadequate disease control under therapy); on the other, maintenance of a clinically stable state achieved under prior therapy.

The research questions and the ACT specified by the G-BA for the total therapeutic indication are presented in Table 2.

Table 2: Research questions of the benefit assessment of ravulizumab

Research question	**Subindication**	**ACT[a]**
1	Adult patients with PNH with haemolysis with clinical symptom(s) indicative of high disease activity	Eculizumab[b]
2	Adult patients with PNH who are clinically stable after having been treated with eculizumab for at least the past 6 months	
a: Presentation of the ACT specified by the G-BA. b: It is assumed that supportive measures are conducted both in the intervention and in the comparator arm. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; PNH: paroxysmal nocturnal haemoglobinuria		

The company followed the specification of the G-BA and cited eculizumab as ACT.

The company considered patients with high disease activity and patients who are clinically stable after eculizumab treatment for at least 6 months separately, but did not investigate 2 separate research questions. The company derived the added benefit for the total population of patients with PNH without differentiating between the patient populations. The present assessment was conducted separately for the 2 research questions 1 and 2.

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 the added benefit.

Results for research question 1 – high disease activity

Study pool

The study pool for research question 1 of the present benefit assessment consisted of Study 301.

Study characteristics of Study 301

Study 301 was a randomized, open-label, multicentre, active-controlled, 2-arm parallel-group study. The study included adult patients with PNH who were naive to complement inhibitor treatment prior to study entry. The patients had to have 1 or more of the following PNH-related signs or symptoms indicative of high disease activity within 3 months before screening: fatigue, haemoglobinuria, abdominal pain, shortness of breath (dyspnoea), anaemia (haemoglobin < 10 g/dL), history or presence of a major adverse vascular event (MAVE), dysphagia, or erectile dysfunction, or history of packed red blood cells (pRBC) transfusion due to PNH. In addition, only patients with a lactate dehydrogenase (LDH) level ≥ 1.5 times the upper limit of normal (ULN) were included. The approval also comprises patients with high disease activity despite pretreatment. These patients were not included in Study 301, hence no data are available for them.

A total of 246 patients entered the study and were randomized in a 1:1 ratio either to treatment with ravulizumab (N = 125) or eculizumab (N = 121). Randomization was stratified by the factors LDH level at screening (1.5 to < 3 times the ULN, or ≥ 3 times the ULN) and history of transfusion (0, 1 to 14, or > 14 pRBC units in the year prior to the first dose of the study medication). Duration of the randomized study phase was 26 weeks.

Ravulizumab and eculizumab were administered in compliance with the recommendations of the respective Summaries of Product Characteristics (SPCs).

Transfusion avoidance and haemolysis, operationalized as normalization of LDH levels, were defined as co-primary outcomes in Study 301. Patient-relevant secondary outcomes were outcomes on morbidity and adverse events (AEs).

Supportive therapy in Study 301

The study protocol allowed concomitant treatment if this was deemed necessary by the investigator in the framework of the therapy or for the treatment of AEs. The documentation of

the concomitant medication showed that the extent of supportive measures was comparable in both study arms.

Risk of bias

The risk of bias across outcomes was rated as low for Study 301. The outcome-specific risk of bias was rated as low for the results of the following outcomes: all-cause mortality, MAVEs, transfusion avoidance, serious AEs (SAEs) and meningococcal infection. The risk of bias was rated as high for the results of the outcomes "fatigue (Functional Assessment of Chronic Illness Therapy [FACIT]-Fatigue)" and "discontinuation due to AEs".

Mortality

All-cause mortality

No death occurred in the ravulizumab or in the eculizumab arm of Study 301. There was no hint of an added benefit of ravulizumab in comparison with eculizumab; an added benefit is therefore not proven.

Morbidity

MAVEs

There was no statistically significant difference between the treatment groups for the outcome "MAVEs". As a result, there was no hint of an added benefit of ravulizumab in comparison with eculizumab; an added benefit is therefore not proven.

Fatigue (FACIT-Fatigue)

The responder analysis on the number of patients with improvement by at least 3 points at week 26 was used for the outcome "fatigue", measured with the FACIT-Fatigue. There was no statistically significant difference between the treatment groups. As a result, there was no hint of an added benefit of ravulizumab in comparison with eculizumab; an added benefit is therefore not proven.

Transfusion avoidance

There was no statistically significant difference between the treatment groups for the outcome „transfusion avoidance". As a result, there was no hint of an added benefit of ravulizumab in comparison with eculizumab; an added benefit is therefore not proven.

Health-related quality of life

In Study 301, health-related quality of life was recorded with the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30). It is unclear whether the EORTC QLQ-C30 reflects health-related quality of life of the patients in the present subindication. This has no consequences for the conclusion on the added benefit, as no statistically significant result was shown for any of the investigated domains of the EORTC QLQ-C30. There was no hint of an added benefit of ravulizumab in comparison with eculizumab; an added benefit is therefore not proven.

Side effects

Serious adverse events

There was no statistically significant difference between the treatment groups for the outcome "SAEs". This resulted in no hint of greater or lesser harm from ravulizumab in comparison with eculizumab; greater or lesser harm is therefore not proven.

Discontinuation due to adverse events

No discontinuations due to AEs occurred in Study 301. There was no hint of greater or lesser harm from ravulizumab in comparison with eculizumab; greater or lesser harm is therefore not proven.

Specific adverse events

Meningococcal infection

In the study, the outcome "meningococcal infection" was operationalized using a combination of Medical Dictionary for Regulatory Activities (MedDRA) Preferred Terms (PTs). It is unclear which PTs were considered. No events for this operationalization occurred in the study. In principle, all infections caused by meningococci are relevant for the present benefit assessment. It can be inferred from the study documents that no infection caused by meningococci occurred.

There was no hint of greater or lesser harm from ravulizumab in comparison with eculizumab; greater or lesser harm is therefore not proven.

Results for research question 2 – clinically stable after at least 6 months of eculizumab treatment

Study pool

The study pool for research question 2 of the present benefit assessment consisted of Study 302.

Study characteristics of Study 302

Study 302 was a randomized, open-label, multicentre, active-controlled, 2-arm parallel-group study. The study included adult patients with PNH who had been treated with eculizumab for at least 6 months and were clinically stable. At the time point of screening, the patients had to have an LDH level of ≤ 1.5 times the ULN and the LDH level was not allowed to be > 2 times the ULN in the 6 months prior to the first treatment with the study medication. History of a MAVE during the 6 months prior to the first treatment with the study medication was another exclusion criterion.

A total of 197 patients entered the study and were randomized in a 1:1 ratio either to treatment with ravulizumab (N = 98) or eculizumab (N = 99). Randomization was stratified by the factor "history of transfusion" (transfusion within the year prior to the first dose of the study medication yes or no). Duration of the randomized study phase was 26 weeks.

Ravulizumab and eculizumab were administered in compliance with the recommendations of the respective SPCs.

Primary outcome of Study 302 was haemolysis, operationalized as the mean change in LDH level at the end of the randomized treatment phase (week 26). Patient-relevant secondary outcomes were outcomes on morbidity and AEs.

Supportive therapy in Study 302

The study protocol allowed concomitant treatment if this was deemed necessary by the investigator in the framework of the therapy or for the treatment of AEs. The documentation of the concomitant medication showed that the extent of supportive measures was comparable in both study arms.

Risk of bias

The risk of bias across outcomes was rated as low for Study 302. The outcome-specific risk of bias was rated as low for the results of the following outcomes: all-cause mortality, MAVEs, transfusion avoidance, SAEs and meningococcal infection. The risk of bias was rated as high for the results of the outcomes “fatigue (FACIT-Fatigue)” and “discontinuation due to AEs”.

Mortality

All-cause mortality

No death occurred in the ravulizumab or in the eculizumab arm of Study 302. There was no hint of an added benefit of ravulizumab in comparison with eculizumab; an added benefit is therefore not proven.

Morbidity

MAVEs

No event for the outcome “MAVEs” occurred in the ravulizumab or in the eculizumab arm. There was no hint of an added benefit of ravulizumab in comparison with eculizumab; an added benefit is therefore not proven.

Fatigue (FACIT-Fatigue)

The responder analysis on the number of patients with improvement by at least 3 points at week 26 was used for the outcome “fatigue”, measured with the FACIT-Fatigue. There was no statistically significant difference between the treatment groups. As a result, there was no hint of an added benefit of ravulizumab in comparison with eculizumab; an added benefit is therefore not proven.

Transfusion avoidance

There was no statistically significant difference between the treatment groups for the outcome “transfusion avoidance”. As a result, there was no hint of an added benefit of ravulizumab in comparison with eculizumab; an added benefit is therefore not proven.

Health-related quality of life

In Study 302, health-related quality of life was recorded with the EORTC QLQ-C30. It is unclear whether the EORTC QLQ-C30 reflects health-related quality of life of the patients in the present subindication. This has no consequences for the conclusion on the added benefit, as no statistically significant result was shown for any of the investigated domains of the EORTC QLQ-C30. There was no hint of an added benefit of ravulizumab in comparison with eculizumab; an added benefit is therefore not proven.

Side effects

Serious adverse events

There was no statistically significant difference between the treatment groups for the outcome "SAEs". This resulted in no hint of greater or lesser harm from ravulizumab in comparison with eculizumab; greater or lesser harm is therefore not proven.

Discontinuation due to adverse events

No discontinuations due to AEs occurred in Study 302. There was no hint of greater or lesser harm from ravulizumab in comparison with eculizumab; greater or lesser harm is therefore not proven.

Specific adverse events

Meningococcal infection

In the study, the outcome "meningococcal infection" was operationalized using a combination of MedDRA PTs. It is unclear which PTs were considered. No events for this operationalization occurred in the study. In principle, all infections caused by meningococci are relevant for the present benefit assessment. It can be inferred from the study documents that no infection caused by meningococci occurred.

There was no hint of greater or lesser harm from ravulizumab in comparison with eculizumab; greater or lesser harm is therefore not proven.

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

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

[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 [1,2].

For research question 1, neither effects in favour nor effects to the disadvantage of ravulizumab were shown in Study 301. In summary, there was no hint of an added benefit of ravulizumab versus the ACT eculizumab for patients with PNH with haemolysis with clinical symptom(s) indicative of high disease activity. An added benefit is therefore not proven.

For research question 2, neither effects in favour nor effects to the disadvantage of ravulizumab were shown in Study 302. In summary, there was no hint of an added benefit of ravulizumab versus the ACT eculizumab for patients with PNH who are clinically stable after having been treated with eculizumab for at least the past 6 months. An added benefit is therefore not proven.

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

Table 3: Ravulizumab – probability and extent of added benefit

Subindication	**ACT**[a]	**Probability and extent of added benefit**
Adult patients with PNH with haemolysis with clinical symptom(s) indicative of high disease activity[b]	Eculizumab[c]	Added benefit not proven
Adult patients with PNH who are clinically stable after having been treated with eculizumab for at least the past 6 months		Added benefit not proven
a: Presentation of the ACT specified by the G-BA. b: There were only data for treatment-naive patients with clinical symptom(s) indicative of high disease activity. It remains unclear whether the observed effects can be transferred to pretreated patients with high disease activity. c: It is assumed that supportive measures are conducted both in the intervention and in the comparator arm. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; PNH: paroxysmal nocturnal haemoglobinuria		

The approach for deriving 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 ravulizumab in comparison with eculizumab as ACT in

- adult patients with PNH with haemolysis with clinical symptom(s) indicative of high disease activity,
- adult patients with PNH who are clinically stable after having been treated with eculizumab for at least the past 6 months.

There are 2 research questions for the present assessment, as 2 treatment situations with different treatment goals result from the approved therapeutic indication of ravulizumab. On the one hand, this is treatment of high disease activity with clinical symptoms of haemolysis (for example at first diagnosis or in case of inadequate disease control under therapy); on the other, maintenance of a clinically stable state achieved under prior therapy.

The research questions and the ACT specified by the G-BA for the total therapeutic indication are presented in Table 4.

Table 4: Research questions of the benefit assessment of ravulizumab

Research question	**Subindication**	**ACT[a]**
1	Adult patients with PNH with haemolysis with clinical symptom(s) indicative of high disease activity	Eculizumab[b]
2	Adult patients with PNH who are clinically stable after having been treated with eculizumab for at least the past 6 months	
a: Presentation of the ACT specified by the G-BA. b: It is assumed that supportive measures are conducted both in the intervention and in the comparator arm. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; PNH: paroxysmal nocturnal haemoglobinuria		

The company followed the specification of the G-BA and cited eculizumab as ACT.

The company considered patients with high disease activity and patients who are clinically stable after eculizumab treatment for at least 6 months separately, but did not investigate 2 separate research questions. The company derived the added benefit for the total population of patients with PNH without differentiating between the patient populations. The present assessment was conducted separately for the 2 research questions 1 and 2 (see Section 2.6.2 of the full dossier assessment).

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 the added benefit. This deviates from the inclusion criteria of the company, which, on the one hand, made no restriction regarding study duration and, on the other, also used non-randomized, uncontrolled studies with ravulizumab for the assessment.

2.3 Research question 1 – high disease activity

2.3.1 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 ravulizumab (status: 2 May 2019)
- bibliographical literature search on ravulizumab (last search on 8 May 2019)
- search in trial registries for studies on ravulizumab (last search on 2 May 2019)

To check the completeness of the study pool:

- search in trial registries for studies on ravulizumab (last search on 7 August 2019)

The check identified no additional relevant study.

2.3.1.1 Studies included

The study listed in the following table was included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: ravulizumab vs. eculizumab (research question 1: high disease activity)

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
ALXN1210-PNH-301 (301[b])	Yes	Yes	No
a: Study sponsored by the company. b: In the following tables, the study is referred to with this abbreviated form. RCT: randomized controlled trial; vs.: versus			

The study pool for research question 1 of the present benefit assessment consisted of Study 301. The company did not investigate 2 separate research questions. It presented the results of each of the studies 301 and 302 (included in the present benefit assessment for research question 2, see Section 2.4), and derived an added benefit for the total population of patients with PNH on the basis of both studies, without differentiating between the patient populations.

Further investigations presented by the company unsuitable for the assessment of the added benefit

In Section 4.3.2.3 in Module 4 A of the dossier, the company described 2 further studies on ravulizumab (ALXN1210-PNH-103 and ALXN1210-PNH-201) in addition to the RCTs included by the company (Study 301 and Study 302). Both studies were non-randomized, uncontrolled dose-escalation studies of ravulizumab with 13 and 26 patients with PNH who had

not previously been treated with a complement inhibitor (see Section 2.6.7 of the full dossier assessment for more details). The company provided only a descriptive presentation of the ravulizumab results of these studies and used them as supporting evidence for the derivation of the added benefit. Since the company did not investigate 2 separate research questions, it did not allocate the studies presented as supportive evidence to any research question.

With these studies, the company presented no data relevant for the benefit assessment, as there was no comparison versus the ACT eculizumab. Correspondingly, both studies were not used for the benefit assessment.

Section 2.3.4 contains a reference list for the study included.

2.3.1.2 Study characteristics

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

Table 6: Characteristics of the included study – RCT, direct comparison: ravulizumab vs. eculizumab (research question 1: high disease activity)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
301	RCT, open-label, parallel	Treatment-naive[b] adult patients with PNH[c] and ▪ 1 or more PNH-related signs or symptoms within 3 months before screening ▪ LDH level ≥ 1.5 times ULN at screening ▪ meningococcal vaccination	Ravulizumab (N = 125) eculizumab (N = 121)	Screening: up to 4 weeks Treatment: 26 weeks Follow-up observation: none[e]	123 centres in Argentina, Australia, Austria, Belgium, Brazil, Canada, Czech Republic, Estonia, France, Germany, Italy, Japan, Malaysia, Mexico, Poland, Russia, Singapore, South Korea, Spain, Sweden, Taiwan, Thailand, Turkey, United Kingdom, USA 12/2016–1/2018	Primary: transfusion avoidance, haemolysis Secondary: morbidity, AEs

a: Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes only include information on relevant available outcomes for this benefit assessment.
b: No previous treatment with complement inhibitor.
c: Diagnosed by flow cytometry.
d: Fatigue, haemoglobinuria, abdominal pain, shortness of breath (dyspnoea), anaemia (haemoglobin < 10 g/dL), history or presence of a MAVE, dysphagia, or erectile dysfunction, or history of pRBC transfusion due to PNH.
e: On completion of the randomized treatment phase, all patients had the possibility to enter an extension phase and receive ravulizumab for up to 2 years or until market approval.

AE: adverse event; LDH: lactate dehydrogenase; MAVE: major adverse vascular event; N: number of randomized patients; PNH: paroxysmal nocturnal haemoglobinuria; pRBC: packed red blood cells; RCT: randomized controlled trial; ULN: upper limit of normal; vs.: versus

Table 7: Characteristics of the intervention – RCT, direct comparison: ravulizumab vs. eculizumab (research question 1: high disease activity)

Study	Intervention	Comparison
301	Ravulizumab, IV, weight-based dosing: induction dose on day 1: ▫ ≥ 40 to < 60 kg: 2400 mg ▫ ≥ 60 to < 100 kg: 2700 mg ▫ ≥ 100 kg: 3000 mg maintenance dose on day 15 and then every 8 weeks (day 71, 127): ▫ ≥ 40 to < 60 kg: 3000 mg ▫ ≥ 60 to < 100 kg: 3300 mg ▫ ≥ 100 kg: 3600 mg	Eculizumab, IV induction dose: 600 mg on days 1, 8, 15 and 22 maintenance dose: 900 mg on day 29 and then every 2 weeks (until day 169)
	Pretreatment required: ▪ if haemoglobin level is ≤ 9 g/dL with signs or symptoms of sufficient severity grade, or ≤ 7 g/dL irrespective of the presence of signs or symptoms, transfusion should be administered within 5 days before day 1 (day of the first administration of the study medication)[a] ▪ meningococcal vaccination within 3 years prior to start of the study or immediately at the start of treatment[b] in accordance with local guidelines not allowed: ▪ prior treatment with complement inhibitors **Concomitant treatment** not allowed: ▪ current treatment with other complement inhibitors than the study medication ▪ any investigational therapy ≤ 30 days before day 1 or ≤ 5 half-lives of that investigational therapy (whichever is greater) allowed: ▪ anticoagulants only at a stable dosage of ≥ 2 weeks before day 1 ▪ unrestricted administration of the following drugs was only allowed from Amendment 3[c] to the study protocol: erythropoietin, immunosuppressants, systemic corticosteroids, iron preparations, folic acid	

a: For inclusion in the study, haemoglobin levels after transfusion had to be above the threshold value defined in the study protocol.
b: Patients who initiated intake of the study medication ≤ 2 weeks after meningococcal vaccination received corresponding prophylactic antibiotics until 2 weeks after vaccination.
c: Amendment 3 from 25 January 2017 (shortly after the first treatment of the first patient on 20 December 2016); before that, these drugs were only allowed in case of a stable dose before the start of the study.
IV: intravenous; RCT: randomized controlled trial; vs.: versus

Study 301 was a randomized, open-label, multicentre, active-controlled, 2-arm parallel-group study. The study included adult patients with PNH who were naive to complement inhibitor treatment prior to study entry. The patients had to have 1 or more of the following PNH-related signs or symptoms indicative of high disease activity within 3 months before screening: fatigue, haemoglobinuria, abdominal pain, shortness of breath (dyspnoea), anaemia (haemoglobin < 10 g/dL), history or presence of a MAVE, dysphagia, or erectile dysfunction, or history of pRBC transfusion due to PNH. In addition, only patients with an LDH level ≥ 1.5 times the ULN were included. The ULN was defined as 246 U/L in Study 301. Inclusion of patients without a history of transfusion within the year before the start of the study was limited to 20%.

The approval also comprises patients with high disease activity despite pretreatment [3]. These patients were not included in Study 301, hence no data are available for them.

A total of 246 patients entered the study and were randomized in a 1:1 ratio either to treatment with ravulizumab (N = 125) or eculizumab (N = 121). Randomization was stratified by the factors LDH level at screening (1.5 to < 3 times the ULN, or ≥ 3 times the ULN) and history of transfusion (0, 1 to 14, or > 14 pRBC units in the year prior to the first dose of the study medication). Duration of the randomized study phase was 26 weeks. The patients could then participate in an extension phase, where all study participants received only ravulizumab. Deviating from the company's approach, the data of the extension phase are not relevant for the present benefit assessment, as there was no comparison with the ACT. Hence, all information provided below in the present benefit assessment refer only to the randomized study phase.

Treatment of the patients in both study arms was conducted according to the regimen described in Table 7. Ravulizumab and eculizumab were administered in compliance with the recommendations of the respective SPCs [3,4].

Transfusion avoidance and haemolysis, operationalized as normalization of LDH levels, were defined as co-primary outcomes in Study 301. Patient-relevant secondary outcomes were outcomes on morbidity and AEs.

Supportive therapy in Study 301

According to the guideline, supportive therapy of PNH includes, besides substitution with pRBC, administration of folic acid and, if necessary, vitamin B12, as well as oral iron substitution in case of a deficiency, early and consequent antibiotic therapy of bacterial infections, as well as life-long anticoagulation after a thromboembolic event. According to the guideline, short-term pulse therapy with steroids might under certain circumstances exert a beneficial influence; permanent therapy with steroids is not recommended [5].

The study protocol allowed concomitant treatment if this was deemed necessary by the investigator in the framework of the therapy or for the treatment of AEs. There was a limitation regarding the administration of anticoagulants, which was only allowed if they had already been administered at a stable dosage for at least 2 weeks before the first treatment with the study medication. Since only 3 thromboembolic events occurred in Study 301, however, the limitation of the treatment with anticoagulants during the study had no consequence for the present benefit assessment. Amendment 3 to the study protocol from 25 January 2017 (shortly after the first treatment of the first patient on 20 December 2016), allowed unrestricted administration of erythropoietin, immunosuppressants, systemic corticosteroids, iron preparations, and folic acid, which before were only allowed to be administered in case of stable dosing before the start of the study. The documentation of the concomitant medication showed that the extent of supportive measures was comparable in both study arms (see Table 9).

Table 8 shows the characteristics of the patients in the study included.

Table 8: Characteristics of the study population – RCT, direct comparison: ravulizumab vs. eculizumab (research question 1: high disease activity)

Study Characteristics Category	**Ravulizumab**	**Eculizumab**
	N[a] = 125	N[a] = 121
Study 301		
Age at the first dose of the study medication [years], mean (SD)	45 (15)	46 (16)
Sex [F/M], %	48/52	43/57
Family origin, n (%)		
White	43 (34.4)	51 (42.1)
Black	2 (1.6)	4 (3.3)
Asian	72 (57.6)	57 (47.1)
Other[b]	8 (6.4)	9 (7.4)
Time between diagnosis and start of study [years], mean (SD)	6.7 (8.1)	6.4 (7.5)
LDH level at baseline [U/L], mean (SD)	1633.5 (778.8)	1578.3 (727.1)
LDH 1.5 to < 3 times ULN[c]	18 (14.4)	16 (13.2)
LDH ≥ 3 times ULN[c]	107 (85.6)	105 (86.8)
PNH clone size at baseline [%], mean (SD)		
Total PNH erythrocyte clone size	38.4 (23.7)	38.7 (23.2)
Total PNH granulocyte clone size	84.2 (21.0)	85.3 (19.0)
Total PNH monocyte clone size	86.9 (18.1)	89.2 (15.2)
Number of patients with pRBC/whole blood transfusion within the last 12 months before the first dose of the study medication, n (%)	103 (82.4)	100 (82.6)
Patients with at least one PNH-related accompanying disease before start of the study, n (%)	121 (96.8)	120 (99.2)
Anaemia	103 (82.4)	105 (86.8)
Haematuria or haemoglobinuria	81 (64.8)	75 (62.0)
Aplastic anaemia[d]	41 (32.8)	38 (31.4)
Renal failure	19 (15.2)	11 (9.1)
Myelodysplastic syndrome	7 (5.6)	6 (5.0)
Complication of pregnancy	3 (2.4)	4 (3.3)
Other[e]	27 (21.6)	13 (10.7)
Patients with history of a MAVE, n (%)	17 (13.6)	25 (20.7)
Treatment discontinuation, n (%)	0 (0)	2 (1.7)
Study discontinuation, n (%)	0 (0)	2 (1.7)

a: Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b: Institute's calculation, comprising the following categories: indigenous people of America and Alaska, others, and unknown.
c: LDH stratification groups at randomization, ULN of the LDH level: 246 U/L.
d: It is assumed for Study 301 that PNH and not aplastic anaemia is the dominant disease of these patients (see Section 2.6.4.1 of the full dossier assessment).
e: According to the specification on the case report form: thrombocytopenia, chronic kidney disease, pancytopenia, and other symptoms.

(continued)

Table 8: Characteristics of the study population – RCT, direct comparison: ravulizumab vs. eculizumab (research question 1: high disease activity) (continued)

F: female; LDH: lactate dehydrogenase; M: male; MAVE: major adverse vascular event; n: number of patients in the category; N: number of randomized patients; PNH: paroxysmal nocturnal haemoglobinuria; pRBC: packed red blood cells; RCT: randomized controlled trial; SD: standard deviation; ULN: upper limit of normal; vs.: versus

The characteristics of the patients in Study 301 were largely comparable between the treatment arms. The mean age of the patients was about 46 years, and slightly more than half of them were male. There were minor imbalances between the study arms in the distribution of family origin: 57.6% of the patients in the ravulizumab arm and 47.1% in the eculizumab arm were of Asian family origin, and 34.4% and 42.1% respectively were of white family origin.

The mean LDH level at baseline was about 1600 U/L; more than 85% of the patients had LDH levels ≥ 3 times the ULN. The mean total PNH granulocyte clone size was about 85%, and the mean total PNH erythrocyte clone size was about 38%. In addition, about 83% of the patients had received pRBC/whole blood transfusions within 12 months before start of the study. More than 90% of the patients had at least one PNH-related accompanying disease, e.g. aplastic anaemia in about 32% of the patients (see Section 2.6.4.1 of the full dossier assessment).

In the study, high disease activity was defined, on the one hand, based on the increased LDH level and, on the other, based on the presence of 1 or more PNH-related signs or symptoms within 3 months before screening. The company presented information on the history of symptoms at any time, but not explicitly on symptoms that were present at baseline. However, it can be inferred from the information on patient-reported PNH symptoms that these (mainly fatigue, haemoglobinuria and shortness of breath) were present in a majority of the patients in Study 301 at baseline (see Section 2.6.4.1 of the full dossier assessment).

Only 2 patients in the eculizumab arm discontinued treatment and the study. Reasons for these discontinuations were decision by the investigator and withdrawal of consent by the patient.

Table 9 contains information on concomitant medication that the patients received in the course of the study.

Table 9: Concomitant medication by ATC class in > 5% of the patients in at least one study arm – RCT, direct comparison: ravulizumab vs. eculizumab (research question 1: high disease activity)

Characteristics **Category**	**Ravulizumab**	**Eculizumab**
	N[a] = 125	N[a] = 121
Concomitant medication[b], n (%)		
ACE inhibitors, pure	10 (8.0)	12 (9.9)
Any other therapeutic products	7 (5.6)	9 (7.4)
Anabolic steroids	4 (3.2)	7 (5.8)
Angiotensin II receptor blockers, pure	9 (7.2)	7 (5.8)
Gout medications	7 (5.6)	3 (2.5)
Antihistamines for systemic use	24 (19.2)	37 (30.6)
Anti-inflammatory and antirheumatic products, no steroids	24 (19.2)	28 (23.1)
Anticoagulants	37 (29.6)	40 (33.1)
Anxiolytics	7 (5.6)	5 (4.1)
Bacterial vaccines	32 (25.6)	41 (33.9)
Beta-blockers	13 (10.4)	10 (8.3)
Beta-lactam antibiotics, penicillins	48 (38.4)	47 (38.8)
Blood-glucose lowering drugs, without insulins	4 (3.2)	7 (5.8)
Calcium	5 (4.0)	7 (5.8)
Corticosteroids for systemic use, pure[c]	31 (24.8)	29 (24.0)
Laxatives	7 (5.6)	9 (7.4)
Gastrointestinal therapeutics	7 (5.6)	5 (4.1)
Drugs for gastric ulcer and gastroesophageal reflux disease	36 (28.8)	36 (29.8)
Mucolytics, not in combination with cough medicines	13 (10.4)	15 (12.4)
Hypnotics and tranquilizers	4 (3.2)	10 (8.3)
Additive solutions, intravenously	7 (5.6)	9 (7.4)
Immunosuppressants	12 (9.6)	13 (10.7)
Iron-containing preparations	18 (14.4)	24 (19.8)
Lipid-modifying agents, pure	6 (4.8)	8 (6.6)
Macrolide, lincosamide and streptogramin	2 (1.6)	8 (6.6)
Systemic drugs that reduce swelling or congestion	7 (5.6)	1 (0.8)
Opioids	12 (9.6)	5 (4.1)
Other analgesics or antipyretics	57 (45.6)	38 (31.4)
Other beta-lactam antibiotics	19 (15.2)	13 (10.7)
Potassium	8 (6.4)	6 (5.0)
Propulsives	4 (3.2)	12 (9.9)
Quinolone antibiotics	31 (24.8)	33 (27.3)
Selective calcium channel blockers with mainly vascular effects	15 (12.0)	16 (13.2)
Viral vaccines	10 (8.0)	10 (8.3)
Vitamins A and D, including combinations of both	12 (9.6)	8 (6.6)

(continued)

Table 9: Concomitant medication by ATC class in > 5% of the patients in at least one study arm – RCT, direct comparison: ravulizumab vs. eculizumab (research question 1: high disease activity) (continued)

Characteristics Category	Ravulizumab	Eculizumab
	N[a] = 125	N[a] = 121
Vitamin B complex, including combinations	7 (5.6)	2 (1.7)
Vitamin B12 and folic acid	65 (52.0)	70 (57.9)

a: Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b: Data refer to the concomitant medication during the randomized study phase from the time point of randomization; order adopted from the company without alterations.
c: There is no concrete information on whether this is short-term pulse therapy or long-term therapy.
ACE: angiotensin converting enzyme; ATC: anatomical therapeutic chemical; n: number of patients in the category; N: number of randomized patients; RCT: randomized controlled trial; vs.: versus

There were no important differences between the treatment arms regarding concomitant medication. About 31% of the patients received anticoagulant therapy, about 39% penicillins, about 26% quinolone antibiotics, and about 55% vitamin B12 and folic acid. The use of concomitant interventions was considered adequate in the present benefit assessment.

Risk of bias across outcomes (study level)

Table 10 shows the risk of bias across outcomes (risk of bias at study level).

Table 10: Risk of bias across outcomes (study level) – RCT, direct comparison: ravulizumab vs. eculizumab (research question 1: high disease activity)

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
301	Yes	Yes	No	No	Yes	Yes	Low

RCT: randomized controlled trial; vs.: versus

The risk of bias across outcomes was rated as low for Study 301. This deviates from the assessment of the company, which rated the risk of bias across outcomes as high due to the lack of blinding of patients and treating staff.

Limitations resulting from the open-label study design are described in Section 2.3.2 with the outcome-specific risk of bias.

2.3.2 Results on added benefit

2.3.2.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment (for reasons, see Section 2.6.4.3.2 of the full dossier assessment):

- Mortality
  - all-cause mortality
- Morbidity
  - MAVEs
  - fatigue, measured with FACIT-Fatigue
  - transfusion avoidance
- Health-related quality of life
- Side effects
  - SAEs
  - discontinuation due to AEs
  - meningococcal infection
  - if applicable, further specific AEs

The choice of patient-relevant outcomes deviates from that of the company, which used further outcomes in the dossier (Module 4 A) (see Section 2.6.4.3 of the full dossier assessment).

Table 11 shows for which outcomes data were available in the study included.

Table 11: Matrix of outcomes – RCT, direct comparison: ravulizumab vs. eculizumab (research question 1: high disease activity)

Study	Outcomes							
	All-cause mortality	MAVEs[a]	Fatigue (FACIT-Fatigue)	Transfusion avoidance[b]	Health-related quality of life	SAEs	Discontinuation due to AEs	Meningococcal infection[c]
301	Yes	Yes	Yes	Yes	No[d]	Yes	Yes	Yes

a: Defined as occurrence of one of the following events: thrombophlebitis/deep vein thrombosis, pulmonary embolism, myocardial infarction, transient ischaemic attack (TIA), unstable angina pectoris, renal vein thrombosis, acute peripheral arterial occlusion (PAOD), mesenteric/visceral vein thrombosis or infarction, mesenteric/visceral arterial thrombosis or infarction, hepatic/portal vein thrombosis (Budd-Chiari syndrome), cerebral arterial occlusion/stroke, cerebral vein occlusion, renal artery thrombosis, gangrene (non-traumatic, non-diabetic), amputation (non-traumatic, non-diabetic), dermal thrombosis, other.

b: Defined as the proportion of patients who, in accordance with the guidelines specified in the protocol, did not require transfusion from baseline until day 183 of the randomized study phase (week 26). PRBC transfusion was administered if a patient had an Hb level of ≤ 9 g/dL with clinical signs or symptoms of sufficient severity to justify transfusion, or if a patient had an Hb level of ≤ 7 g/dL irrespective of clinical signs or symptoms.

c: In the study operationalized using a combination of MedDRA PTs; it is unclear which PTs were considered. All infections caused by meningococci are relevant for the present benefit assessment. According to the information in the study documents, there were no such infections (see Section 2.6.4.3.2 of the full dossier assessment).

d: In the study, health-related quality of life was recorded using the EORTC QLQ-C30 questionnaire. It is unclear whether the EORTC QLQ-C30 reflects health-related quality of life of the patients in the present subindication; for reasons, see Section 2.6.4.3.2 of the full dossier assessment. The results are presented as supplementary information in Appendix B of the full dossier assessment.

AE: adverse event; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; FACIT: Functional Assessment of Chronic Illness Therapy; Hb: haemoglobin; MAVE: major adverse vascular event; MedDRA: Medical Dictionary for Regulatory Activities; PAOD: acute peripheral arterial occlusion; pRBC: packed red blood cells; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; TIA: transient ischaemic attack; vs.: versus

2.3.2.2 Risk of bias

Table 12 describes the risk of bias for the results of the relevant outcomes.

Table 12: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: ravulizumab vs. eculizumab (research question 1: high disease activity)

Study		Outcomes							
	Study level	All-cause mortality	MAVEs[a]	Fatigue (FACIT-Fatigue)	Transfusion avoidance[b]	Health-related quality of life	SAEs	Discontinuation due to AEs	Meningococcal infection[c]
301	L	L	L	H[d]	L	–[e]	L	H[d]	L

a: Defined as occurrence of one of the following events: thrombophlebitis/deep vein thrombosis, pulmonary embolism, myocardial infarction, transient ischaemic attack (TIA), unstable angina pectoris, renal vein thrombosis, acute peripheral arterial occlusion (PAOD), mesenteric/visceral vein thrombosis or infarction, mesenteric/visceral arterial thrombosis or infarction, hepatic/portal vein thrombosis (Budd-Chiari syndrome), cerebral arterial occlusion/stroke, cerebral vein occlusion, renal artery thrombosis, gangrene (non-traumatic, non-diabetic), amputation (non-traumatic, non-diabetic), dermal thrombosis, other.
b: Defined as the proportion of patients who, in accordance with the guidelines specified in the protocol, did not require transfusion from baseline until day 183 of the randomized study phase (week 26). PRBC transfusion was administered if a patient had an Hb level of ≤ 9 g/dL with clinical signs or symptoms of sufficient severity to justify transfusion, or if a patient had an Hb level of ≤ 7 g/dL irrespective of clinical signs or symptoms.
c: In the study operationalized using a combination of MedDRA PTs; it is unclear which PTs were considered. All infections caused by meningococci are relevant for the present dossier assessment. According to the information in the study documents, there were no such infections (see Section 2.6.4.3.2 of the full dossier assessment).
d: Lack of blinding in subjective recording of outcomes.
e: In the study, health-related quality of life was recorded using the EORTC QLQ-C30 questionnaire. It is unclear whether the EORTC QLQ-C30 reflects health-related quality of life of the patients in the present subindication; for reasons, see Section 2.6.4.3.2 of the full dossier assessment. The results are presented as supplementary information in Appendix B of the full dossier assessment.

AE: adverse event; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; FACIT: Functional Assessment of Chronic Illness Therapy; H: high; Hb: haemoglobin; L: low; MAVE: major adverse vascular event; MedDRA: Medical Dictionary for Regulatory Activities; PAOD: acute peripheral arterial occlusion; pRBC: packed red blood cells; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; TIA: transient ischaemic attack; vs.: versus

The outcome-specific risk of bias was rated as low for the results of the following outcomes: all-cause mortality, MAVEs, transfusion avoidance and SAEs. The risk of bias was also rated as low for the results of the outcome “meningococcal infection”. Although it is unclear which methods were used in Study 301 to test for meningococcal infection, it is assumed that there is little room for subjective assessment if the specific pathogen is detected. This deviates from the

assessment of the company, which rated the risk of bias for the results of these outcomes as high due to the lack of blinding of patients and outcome assessors.

Due to subjective recording of outcomes and lack of blinding, the risk of bias was rated as high for the results of the outcomes "fatigue (FACIT-Fatigue)" and "discontinuation due to AEs". The result of these assessments concur with the assessment of the company.

Health-related quality of life was recorded in the study using the EORTC QLQ-C30 questionnaire. It is unclear whether the EORTC QLQ-C30 reflects health-related quality of life of the patients in the present subindication (for reasons, see Section 2.6.4.3.2 of the full dossier assessment). The risk of bias is therefore not assessed.

2.3.2.3 Results

Table 13 summarizes the results for the comparison of ravulizumab with eculizumab in patients with PNH with haemolysis with clinical symptom(s) indicative of high disease activity. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier. Common AEs, SAEs and discontinuations due to AEs are listed in Appendix A of the full dossier assessment.

Table 13: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: ravulizumab vs. eculizumab (research question 1: high disease activity)

Study Outcome category Outcome	Ravulizumab		Eculizumab		Ravulizumab vs. eculizumab
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value[a]
Study 301					
Mortality					
All-cause mortality	125	0 (0)	121	0 (0)[b]	–
Morbidity					
MAVEs[c]	125	2 (1.6)[d]	121	1 (0.8)[e]	1.94 [0.18; 21.07]; 0.682
Fatigue (FACIT-Fatigue improvement[f])	125	77 (61.6)	121	71 (58.7)	1.05 [0.86; 1.29]; 0.711
Transfusion avoidance[g]	125	92 (73.6)	121	80 (66.1)	1.11 [0.94; 1.31]; 0.246
Health-related quality of life	No usable data[h]				
Side effects					
AEs (supplementary information)	125	110 (88.0)	121	105 (86.8)	–
SAEs	125	11 (8.8)	121	9 (7.4)	1.18 [0.51; 2.75]; 0.769
Discontinuation due to AEs	125	0 (0)	121	0 (0)	–
Meningococcal infection[i]	125	0 (0)	121	0 (0)	–

(continued)

Table 13: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: ravulizumab vs. eculizumab (research question 1: high disease activity) (continued)

a: Institute's calculation; 95% CI asymptotic; p-value from unconditional exact test (CSZ method according to [6]).
b: One patient died during the extension phase; the reason was lung cancer diagnosed in the extension phase. The symptoms of lung cancer had already occurred during the randomized study phase.
c: Defined as occurrence of one of the following events: thrombophlebitis/deep vein thrombosis, pulmonary embolism, myocardial infarction, transient ischaemic attack (TIA), unstable angina pectoris, renal vein thrombosis, acute peripheral arterial occlusion (PAOD), mesenteric/visceral vein thrombosis or infarction, mesenteric/visceral arterial thrombosis or infarction, hepatic/portal vein thrombosis (Budd-Chiari syndrome), cerebral arterial occlusion/stroke, cerebral vein occlusion, renal artery thrombosis, gangrene (non-traumatic, non-diabetic), amputation (non-traumatic, non-diabetic), dermal thrombosis, other.
d: Both events were deep vein thromboses.
e: Mesenteric vein thrombosis.
f: Patients with an improvement in FACIT-Fatigue total score by at least 3 points at week 26.
g: Defined as the proportion of patients who, in accordance with the guidelines specified in the protocol, did not require transfusion from baseline until day 183 of the randomized study phase (week 26). PRBC transfusion was administered if a patient had an Hb level of ≤ 9 g/dL with clinical signs or symptoms of sufficient severity to justify transfusion, or if a patient had an Hb level of ≤ 7 g/dL irrespective of clinical signs or symptoms. Patients who met these transfusion criteria were included in the group of patients requiring transfusion, regardless of whether they actually received a transfusion or not.
h: In the study, health-related quality of life was recorded using the EORTC QLQ-C30 questionnaire. It is unclear whether the EORTC QLQ-C30 reflects health-related quality of life of the patients in the present subindication; for reasons, see Section 2.6.4.3.2 of the full dossier assessment. The results are presented as supplementary information in Appendix B of the full dossier assessment.
i: In the study operationalized using a combination of MedDRA PTs; it is unclear which PTs were considered. All infections caused by meningococci are relevant for the present benefit assessment. According to the information in the study documents, there were no such infections.

AE: adverse event; CI: confidence interval; CSZ: convexity, symmetry, z score; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; FACIT: Functional Assessment of Chronic Illness Therapy; Hb: haemoglobin; MAVE: major adverse vascular event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least one) event; N: number of analysed patients; PAOD: peripheral arterial occlusive disease; pRBC: packed red blood cells; PT: Preferred Term; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; TIA: transient ischaemic attack; vs.: versus

Based on the available data, at most indications, e.g. of an added benefit, can be determined for the following outcomes: all-cause mortality, MAVEs, transfusion avoidance, SAEs and meningococcal infection; and, due to the high risk of bias, at most hints for the outcomes "fatigue (FACIT-Fatigue)" and "discontinuation due to AEs".

This approach deviates from that of the company. The company derived the added benefit on the basis of a global assessment of all available results of the studies 301 and 302 (including their extension phases) and the results of the non-randomized, uncontrolled studies ALXN1210-PNH-103 and ALXN1210-PNH-201 without differentiating between the patient populations of research questions 1 and 2. The company derived hints of an added benefit for different outcomes. The company based its conclusions on the presence of numerical superiority of ravulizumab versus eculizumab. According to the company, quantification of the added benefit is not possible because there were non-inferiority research questions for most

outcomes in the studies 301 and 302. For this reason, it is not described below to what extent the assessment of individual outcomes deviates from that of the company.

Mortality

All-cause mortality

No death occurred in the ravulizumab or in the eculizumab arm of Study 301. There was no hint of an added benefit of ravulizumab in comparison with eculizumab; an added benefit is therefore not proven.

Morbidity

MAVEs

There was no statistically significant difference between the treatment groups for the outcome "MAVEs". As a result, there was no hint of an added benefit of ravulizumab in comparison with eculizumab; an added benefit is therefore not proven.

Fatigue (FACIT-Fatigue)

The responder analysis on the number of patients with improvement by at least 3 points at week 26 was used for the outcome "fatigue", measured with the FACIT-Fatigue. There was no statistically significant difference between the treatment groups. As a result, there was no hint of an added benefit of ravulizumab in comparison with eculizumab; an added benefit is therefore not proven.

Transfusion avoidance

There was no statistically significant difference between the treatment groups for the outcome "transfusion avoidance". As a result, there was no hint of an added benefit of ravulizumab in comparison with eculizumab; an added benefit is therefore not proven.

Health-related quality of life

In Study 301, health-related quality of life was recorded with the EORTC QLQ-C30. It is unclear whether the EORTC QLQ-C30 reflects health-related quality of life of the patients in the present subindication (for reasons, see Section 2.6.4.3.2 of the full dossier assessment). This has no consequences for the conclusion on the added benefit, as no statistically significant result was shown for any of the investigated domains of the EORTC QLQ-C30. There was no hint of an added benefit of ravulizumab in comparison with eculizumab; an added benefit is therefore not proven.

Side effects

Serious adverse events

There was no statistically significant difference between the treatment groups for the outcome "SAEs". This resulted in no hint of greater or lesser harm from ravulizumab in comparison with eculizumab; greater or lesser harm is therefore not proven.

Discontinuation due to adverse events

No discontinuations due to AEs occurred in Study 301. There was no hint of greater or lesser harm from ravulizumab in comparison with eculizumab; greater or lesser harm is therefore not proven.

Specific adverse events

Meningococcal infection

In the study, the outcome "meningococcal infection" was operationalized using a combination of MedDRA PTs. It is unclear which PTs were considered. No events for this operationalization occurred in the study. In principle, all infections caused by meningococci are relevant for the present benefit assessment. It can be inferred from the study documents that no infection caused by meningococci occurred.

There was no hint of greater or lesser harm from ravulizumab in comparison with eculizumab; greater or lesser harm is therefore not proven.

2.3.2.4 Subgroups and other effect modifiers

The following characteristics were relevant for the present benefit assessment (see also Section 2.6.4.3.4 of the full dossier assessment):

- age at first dose of the study medication (18 to 65 years versus > 65 years)
- sex (female versus male)
- region (North America versus Europe versus Japan versus rest of the Asian-Pacific region versus Latin America)
- history of transfusion within 1 year before the first dose of the study medication (0 pRBC units versus 1 to 14 pRBC units versus > 14 pRBC units)

All subgroup characteristics used in the present benefit assessment were defined a priori, although partly only for the co-primary outcomes of Study 301, partly additionally for some secondary outcomes.

Interaction tests were performed when at least 10 patients per subgroup were included in the analysis. For binary data, there had to be 10 events in at least one 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 only presented if there is a statistically significant and relevant effect in at least one subgroup.

For the outcomes included in the present benefit assessment overall, the company presented subgroup analyses only for the outcome "transfusion avoidance". In accordance with the methods described above, no relevant effect modification was identified for this outcome.

There were subgroup analyses on the mean change at the end of the randomized treatment phase (week 26) for the outcome "fatigue" (measured with the FACIT-Fatigue questionnaire), but not for the responder analysis used for the benefit assessment. It was not possible to calculate interaction tests due to the lack of results on the respective subgroups.

The lack of subgroup analyses has no consequence for the outcomes "all-cause mortality", "MAVEs", "discontinuation due to AEs" and "meningococcal infection", as no or too few results occurred for each of these outcomes.

2.3.3 Probability and extent of added benefit

Probability and extent of the added benefit at outcome level are presented below. The various outcome categories and the effect sizes were taken into account. The methods used for this purpose are explained in the *General Methods* of IQWiG [1].

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.

2.3.3.1 Assessment of the added benefit at outcome level

The extent of the respective added benefit at outcome level was estimated from the results presented in Section 2.3.2 (see Table 14).

Table 14: Extent of added benefit at outcome level: ravulizumab vs. eculizumab (research question 1: high disease activity)

Outcome category **Outcome**	**Ravulizumab vs. eculizumab** **Proportion of events (%)** **Effect estimation [95% CI]; p-value** **Probability[a]**	**Derivation of extent[b]**
Mortality		
All-cause mortality	0% vs. 0%	Lesser benefit/added benefit not proven
Morbidity		
MAVE[c]	1.6% vs. 0.8% RR: 1.94 [0.18; 21.07]; p = 0.682	Lesser benefit/added benefit not proven
Fatigue (FACIT-Fatigue)[d]	61.6% vs. 58.7% RR: 1.05 [0.86; 1.29]; p = 0.711	Lesser benefit/added benefit not proven
Transfusion avoidance[e]	73.6% vs. 66.1% RR: 1.11 [0.94; 1.31]; p = 0.246	Lesser benefit/added benefit not proven
Health-related quality of life		
No usable data[f]	–	Lesser benefit/added benefit not proven
Side effects		
SAEs	8.8% vs. 7.4% RR: 1.18 [0.51; 2.75]; p = 0.769	Greater/lesser harm not proven
Discontinuation due to AEs	0% vs. 0%	Greater/lesser harm not proven
Meningococcal infection[g]	0% vs. 0%	Greater/lesser harm not proven

a: Probability provided if there is a statistically significant and relevant effect.
b: Estimations of effect size are made depending on the outcome category with different limits based on the CI_u.
c: Defined as occurrence of one of the following events: thrombophlebitis/deep vein thrombosis, pulmonary embolism, myocardial infarction, transient ischaemic attack (TIA), unstable angina pectoris, renal vein thrombosis, acute peripheral arterial occlusion (PAOD), mesenteric/visceral vein thrombosis or infarction, mesenteric/visceral arterial thrombosis or infarction, hepatic/portal vein thrombosis (Budd-Chiari syndrome), cerebral arterial occlusion/stroke, cerebral vein occlusion, renal artery thrombosis, gangrene (non-traumatic, non-diabetic), amputation (non-traumatic, non-diabetic), dermal thrombosis, other.
d: Patients with an improvement in FACIT-Fatigue total score by at least 3 points at week 26.
e: Defined as the proportion of patients who, in accordance with the guidelines specified in the protocol, did not require transfusion from baseline until day 183 of the randomized study phase (week 26). PRBC transfusion was administered if a patient had an Hb level of ≤ 9 g/dL with clinical signs or symptoms of sufficient severity to justify transfusion, or if a patient had an Hb level of ≤ 7 g/dL irrespective of clinical signs or symptoms. Patients who met these transfusion criteria were included in the group of patients requiring transfusion, regardless of whether they actually received a transfusion or not.
f: In the study, health-related quality of life was recorded using the EORTC QLQ-C30 questionnaire. It is unclear whether the EORTC QLQ-C30 reflects health-related quality of life of the patients in the present subindication; for reasons, see Section 2.6.4.3.2 of the full dossier assessment. This has no consequences for the conclusion on the added benefit, as no statistically significant result was shown for any of the investigated domains of the EORTC QLQ-C30. The results are presented as supplementary information in Appendix B of the full dossier assessment.
g: In the study operationalized using a combination of MedDRA PTs; it is unclear which PTs were considered. All infections caused by meningococci are relevant for the present benefit assessment. According to the information in the study documents, there were no such infections.

AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; FACIT: Functional Assessment of Chronic Illness Therapy; Hb: haemoglobin; MAVE: major adverse vascular event; MedDRA: Medical Dictionary for Regulatory Activities; PAOD: acute peripheral arterial occlusion; pRBC: packed red blood cells; PT: Preferred Term; RR: relative risk; SAE: serious adverse event; TIA: transient ischaemic attack; vs.: versus

2.3.3.2 Overall conclusion on added benefit

Table 15 summarizes the results considered in the overall conclusion on the extent of added benefit.

Table 15: Positive and negative effects from the assessment of ravulizumab in comparison with eculizumab (research question 1: high disease activity)

Positive effects	Negative effects
–	–
In Study 301, health-related quality of life was recorded with the EORTC QLQ-C30. It is unclear whether the EORTC QLQ-C30 reflects health-related quality of life of the patients in the present subindication. This has no consequences for the conclusion on the added benefit, as no statistically significant result was shown for any of the investigated domains of the EORTC QLQ-C30.	

Study 301 showed neither effects in favour nor effects to the disadvantage of ravulizumab. In summary, there was no hint of an added benefit of ravulizumab versus the ACT eculizumab for patients with PNH with haemolysis with clinical symptom(s) indicative of high disease activity. An added benefit is therefore not proven.

This deviates from the assessment of the company, which derived a non-quantifiable added benefit of ravulizumab in the overall assessment of the results used by the company for the total population of patients with PNH. The company did not provide separate information on the population of patients with high disease activity (research question 1 of the present benefit assessment).

2.3.4 List of included studies

Alexion Pharmaceuticals. ALXN1210 (Ravulizumab) versus eculizumab in complement inhibitor treatment-naïve adult participants with paroxysmal nocturnal hemoglobinuria (PNH): study details [online]. In: ClinicalTrials.gov. 16.05.2019 [Accessed: 15.08.2019]. URL: https://ClinicalTrials.gov/show/NCT02946463.

Alexion Pharmaceuticals. A phase 3, randomized, open-label, active-controlled study of ALXN1210 versus eculizumab in complement inhibitor-naïve adult patients with paroxysmal nocturnal hemoglobinuria (PNH) [online]. In: EU Clinical Trials Register. [Accessed: 15.08.2019]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2016-002025-11.

Alexion Pharmaceuticals. ALXN1210 (ravulizumab) versus eculizumab in complement inhibitor treatment-naïve adult participants with paroxysmal nocturnal hemoglobinuria (PNH): study results [online]. In: ClinicalTrials.gov. 16.05.2019 [Accessed: 15.08.2019]. URL: https://clinicaltrials.gov/ct2/show/results/NCT02946463.

Alexion Pharmaceuticals. A phase 3, randomized, open-label, active-controlled study of ALXN1210 versus eculizumab in complement inhibitor-naive adult patients with paroxysmal nocturnal hemoglobinuria (PNH): study ALXN1210-PNH-301; protocol [unpublished]. 2017.

Alexion Pharmaceuticals. A phase 3, randomized, open-label, active-controlled study of ALXN1210 versus eculizumab in complement inhibitor-naive adult patients with paroxysmal nocturnal hemoglobinuria (PNH): study ALXN1210-PNH-301; statistical analysis plan [unpublished]. 2017.

Alexion Pharmaceuticals. A phase 3, randomized, open-label, active-controlled study of ALXN1210 versus eculizumab in complement inhibitor-naive adult patients with paroxysmal nocturnal hemoglobinuria (PNH): study ALXN1210-PNH-301; clinical study report (primary evaluation period) [unpublished]. 2018.

Alexion Pharmaceuticals. A phase 3, randomized, open-label, active-controlled study of ALXN1210 versus eculizumab in complement inhibitor-naive adult patients with paroxysmal nocturnal hemoglobinuria (PNH): study ALXN1210-PNH-301; Zusatzanalysen [unpublished]. 2019.

Lee JW, Sicre de Fontbrune F, Wong Lee Lee L, Pessoa V, Gualandro S, Fureder W et al. Ravulizumab (ALXN1210) vs eculizumab in adult patients with PNH naive to complement inhibitors: the 301 study. Blood 2019; 133(6): 530-539.

2.4 Research question 2 – clinically stable after at least 6 months of eculizumab treatment

2.4.1 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 ravulizumab (status: 2 May 2019)
- bibliographical literature search on ravulizumab (last search on 8 May 2019)
- search in trial registries for studies on ravulizumab (last search on 2 May 2019)

To check the completeness of the study pool:

- search in trial registries for studies on ravulizumab (last search on 7 August 2019)

The check identified no additional relevant study.

2.4.1.1 Studies included

The study listed in the following table was included in the benefit assessment.

Table 16: Study pool – RCT, direct comparison: ravulizumab vs. eculizumab (research question 2: clinically stable after at least 6 months of eculizumab treatment)

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
ALXN1210-PNH-302 (302[b])	Yes	Yes	No
a: Study sponsored by the company. b: In the following tables, the study is referred to with this abbreviated form. RCT: randomized controlled trial; vs.: versus			

The study pool for research question 2 of the present benefit assessment consisted of Study 302.

The company did not investigate 2 separate research questions. It presented the results of each of the studies 301 (included in the present benefit assessment for research question 1, see Section 2.3) and 302, and derived an added benefit for the total population of patients with PNH on the basis of both studies, without differentiating between the patient populations.

Further investigations presented by the company unsuitable for the assessment of the added benefit

As described under research question 1, the company used 2 further non-randomized, uncontrolled dose escalation studies of ravulizumab for the derivation of the added benefit (ALXN1210-PNH-103 and ALXN1210-PNH-201) in addition to the studies 301 and 302 included by the company.

The studies did not allow to make a comparison versus the ACT eculizumab and were therefore not used for the benefit assessment. Further details can be found in Section 2.3.1 and Section 2.6.7 of the full dossier assessment.

Section 2.4.4 contains a reference list for the study included.

2.4.1.2 Study characteristics

Table 17 and Table 18 describe the study used for the benefit assessment.

Table 17: Characteristics of the included study – RCT, direct comparison: ravulizumab vs. eculizumab (research question 2: clinically stable after at least 6 months of eculizumab treatment)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
302	RCT, open-label, parallel	Clinically stable adult patients with PNH[b] with ≥ 6 months eculizumab pretreatment and ▪ LDH level ≤ 1.5 times ULN at screening ▪ meningococcal vaccination	Ravulizumab (N = 97) eculizumab (N = 98)	Screening: up to 4 weeks Treatment: 26 weeks Follow-up observation: none[c]	49 centres in: Australia, Canada, France, Germany, Italy, Japan, Netherlands, South Korea, Spain, United Kingdom, USA 6/2017–3/2018	Primary: haemolysis Secondary: morbidity, AEs

a: Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes only include information on relevant available outcomes for this benefit assessment.
b: Diagnosed by flow cytometry.
c: On completion of the randomized treatment phase, all patients had the possibility to enter an extension phase and receive ravulizumab for up to 2 years or until market approval.
AE: adverse event; LDH: lactate dehydrogenase; N: number of randomized patients; PNH: paroxysmal nocturnal haemoglobinuria; RCT: randomized controlled trial; ULN: upper limit of normal; vs.: versus

Table 18: Characteristics of the intervention – RCT, direct comparison: ravulizumab vs. eculizumab (research question 2: clinically stable after at least 6 months of eculizumab treatment)

Study	Intervention	Comparison
302	Ravulizumab, IV, weight-based dosing: induction dose on day 1[a]: ▫ ≥ 40 to < 60 kg: 2400 mg ▫ ≥ 60 to < 100 kg: 2700 mg ▫ ≥ 100 kg: 3000 mg maintenance dose on day 15 and then every 8 weeks (day 71, 127): ▫ ≥ 40 to < 60 kg: 3000 mg ▫ ≥ 60 to < 100 kg: 3300 mg ▫ ≥ 100 kg: 3600 mg	Eculizumab, IV maintenance dose: 900 mg on day 1[a] and then every 2 weeks (until day 169)
	Pretreatment required: ▪ eculizumab in compliance with the dosage recommended in the SPC for ≥ 6 months before day 1 ▪ if haemoglobin level is ≤ 9 g/dL with signs or symptoms of sufficient severity grade, or ≤ 7 g/dL irrespective of the presence of signs or symptoms, transfusion should be administered within 5 days before the first administration of the study medication[b] ▪ meningococcal vaccination within 3 years prior to start of the study or immediately at the start of treatment[c] in accordance with local guidelines **Concomitant treatment** not allowed: ▪ treatment with other complement inhibitors than the study medication ▪ any investigational therapy ≤ 30 days before day 1 or ≤ 5 half-lives of that investigational therapy (whichever is greater) allowed: ▪ anticoagulants only at a stable dosage of ≥ 2 weeks before day 1 ▪ further drugs (e.g. erythropoietin, immunosuppressants, systemic corticosteroids, iron preparations, folic acid)	

a: Day 1 of treatment with the study medication is 2 weeks after the last dose of eculizumab.
b: For inclusion in the study, haemoglobin levels after transfusion had to be above the threshold value defined in the study protocol.
c: Patients who initiated intake of the study medication ≤ 2 weeks after meningococcal vaccination received corresponding prophylactic antibiotics until 2 weeks after vaccination.
IV: intravenous; RCT: randomized controlled trial; SPC: Summary of Product Characteristics; vs.: versus

Study 302 was a randomized, open-label, multicentre, active-controlled, 2-arm parallel-group study. The study included adult patients with PNH who had been treated with eculizumab for at least 6 months and were clinically stable. At the time point of screening, the patients had to have an LDH level of ≤ 1.5 times the ULN and the LDH level was not allowed to be > 2 times the ULN in the 6 months prior to the first treatment with the study medication. History of a MAVE during the 6 months prior to the first treatment with the study medication was another exclusion criterion.

A total of 197 patients entered the study and were randomized in a 1:1 ratio either to treatment with ravulizumab (N = 98) or eculizumab (N = 99). One patient in each treatment group withdrew their consent before receiving the first dose of the study medication, however. Thus, all data refer to N = 97 randomized patients in the ravulizumab arm and N = 98 randomized patients in the eculizumab arm. Randomization was stratified by the factor "history of transfusion" (transfusion within the year prior to the first dose of the study medication yes or no). Duration of the randomized study phase was 26 weeks. The patients could then participate in an extension phase, where all patients received ravulizumab. Deviating from the company's approach, the data of the extension phase are not relevant for the present benefit assessment, as there was no comparison with the ACT. Hence, all information provided below in the present benefit assessment refer only to the randomized study phase.

Treatment of the patients in both study arms was conducted according to the regimen described in Table 18. Ravulizumab and eculizumab were administered in compliance with the recommendations of the respective SPCs [3,4].

Primary outcome of Study 302 was haemolysis, operationalized as the mean change in LDH level at the end of the randomized treatment phase (week 26). Patient-relevant secondary outcomes were outcomes on morbidity and AEs.

Supportive therapy in Study 302

The study protocol allowed concomitant treatment if this was deemed necessary by the investigator in the framework of the therapy or for the treatment of AEs. There was a limitation regarding the administration of anticoagulants, which was only allowed if they had already been administered at a stable dosage for at least 2 weeks before the first treatment with the study medication. Since no thromboembolic events occurred in Study 302, however, the limitation of the treatment with anticoagulants during the study had no consequence for the present benefit assessment. The documentation of the concomitant medication showed that the extent of supportive measures was comparable in both study arms (see Table 20).

Table 19 shows the characteristics of the patients in the study included.

Table 19: Characteristics of the study population – RCT, direct comparison: ravulizumab vs. eculizumab (research question 2: clinically stable after at least 6 months of eculizumab treatment)

Study **Characteristics** **Category**	**Ravulizumab**	**Eculizumab**
	N[a] = 97	N[a] = 98
Study 302		
Age at the first dose of the study medication [years], mean (SD)	47 (14)	49 (14)
Sex [F/M], %	48/52	51/49
Family origin, n (%)		
White	50 (51.5)	61 (62.2)
Black	5 (5.2)	3 (3.1)
Asian	23 (23.7)	19 (19.4)
Other[b]	19 (19.6)	15 (15.3)
Time between diagnosis and start of study [years], mean (SD)	12.4 (8.4)	11.9 (9.4)
Duration of eculizumab treatment before first infusion in the study [years], mean (SD)	6.0 (3.5)	5.6 (3.5)
LDH level at baseline [U/L], mean (SD)	228.0 (48.7)	235.2 (49.7)
PNH clone size at baseline [%], mean (SD)		
Total PNH erythrocyte clone size	60.6 (32.5)	59.5 (31.4)
Total PNH granulocyte clone size	82.6 (23.6)	84.0 (21.4)
Total PNH monocyte clone size	85.6 (20.5)	86.1 (19.7)
Number of patients with pRBC/whole blood transfusion within the last 12 months before the first dose of the study medication, n (%)	13 (13.4)	12 (12.2)
Patients with at least one PNH-related accompanying disease before start of the study, n (%)	90 (92.8)	96 (98.0)
Anaemia	64 (66.0)	67 (68.4)
Haematuria or haemoglobinuria	47 (48.5)	48 (49.0)
Aplastic anaemia[c]	34 (35.1)	39 (39.8)
Renal failure	11 (11.3)	7 (7.1)
Myelodysplastic syndrome	3 (3.1)	6 (6.1)
Complication of pregnancy	4 (4.1)	9 (9.2)
Other[d]	14 (14.4)	14 (14.3)
Patients with history of a MAVE, n (%)	28 (28.9)	22 (22.4)
Treatment discontinuation, n (%)	1 (1.0)	3 (3.0)
Study discontinuation, n (%)	1 (1.0)	3 (3.0)

(continued)

Table 19: Characteristics of the study population – RCT, direct comparison: ravulizumab vs. eculizumab (research question 2: clinically stable after at least 6 months of eculizumab treatment) (continued)

a: Number of randomized and treated patients. There is no information on the untreated patients (one in each arm).
b: Institute's calculation, comprising the following categories: indigenous people of America and Alaska, Hawaiians and other Pacific islanders, others, and unknown.
c: It is assumed for Study 302 that PNH and not aplastic anaemia is the dominant disease of these patients (see Section 2.6.4.1 of the full dossier assessment).
d: According to the specification on the case report form: neutropenia, proteinuria, renal function disorder, lymphoid hyperplasia, pancytopenia, thrombocytopenia, iron deficiency, mild aplasia, splenomegaly, grade 1 hepatic cytolysis, and number of other symptoms.
F: female; LDH: lactate dehydrogenase; M: male; MAVE: major adverse vascular event; n: number of patients in the category; N: number of randomized patients; PNH: paroxysmal nocturnal haemoglobinuria; pRBC: packed red blood cells; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

The characteristics of the patients in Study 302 were largely comparable between the treatment arms. The mean age of the patients was about 48 years, and half of them were male. There were minor imbalances between the study arms in the distribution of different family origins: for example, 51.5% of the patients in the ravulizumab arm and 62.2% in the eculizumab arm were of white family origin, and 23.7% and 19.4% respectively were of Asian family origin.

The mean LDH level at baseline was about 232 U/L. The mean total PNH granulocyte clone size was about 83%, and the mean total PNH erythrocyte clone size was about 60%. The patients' mean treatment duration with eculizumab was almost 6 years before the first dose of the study medication. About 13% of the patients had received pRBC/whole blood transfusions within 12 months before start of the study. In these patients, it is unclear whether they were actually stable under eculizumab treatment (see Section 2.6.4.1 of the full dossier assessment). This has no consequence for the present benefit assessment, however, as it concerned fewer than 20% of the patients in the study. More than 90% of the patients had at least one PNH-related accompanying disease, e.g. aplastic anaemia in about 37% of the patients (see Section 2.6.4.1 of the full dossier assessment).

Also for Study 302, the company only presented information on the history of symptoms at any time, but not explicitly on symptoms that were present at baseline (see Section 2.6.4.1 of the full dossier assessment).

One patient in the ravulizumab arm and 3 patients in the eculizumab arm discontinued treatment and the study. The reasons were withdrawal of consent by the patient, lack of efficacy, and pregnancy.

Table 20 contains information on concomitant medication that the patients received in the course of the study.

Table 20: Concomitant medication by ATC class in > 5% of the patients in at least one study arm – RCT, direct comparison: ravulizumab vs. eculizumab (research question 2: clinically stable after at least 6 months of eculizumab treatment)

Characteristics **Category**	**Ravulizumab**	**Eculizumab**
	N[a] = 97	N[a] = 98
Concomitant medication[b], n (%)		
ACE inhibitors, pure	5 (5.2)	4 (4.1)
Other therapeutic products	6 (6.2)	8 (8.2)
Antacids	2 (2.1)	7 (7.1)
Antidepressants	8 (8.2)	8 (8.2)
Antihistamines for systemic use	8 (8.2)	10 (10.2)
Anti-inflammatory and antirheumatic products, no steroids	11 (11.3)	15 (15.3)
Anticoagulants	26 (26.8)	18 (18.4)
Anxiolytics	2 (2.1)	7 (7.1)
Bacterial vaccines	28 (28.9)	29 (29.6)
Beta-blockers	4 (4.1)	10 (10.2)
Beta-lactam antibiotics, penicillins	55 (56.7)	48 (49.0)
Bile therapeutic agents	4 (4.1)	5 (5.1)
Blood-glucose lowering drugs, without insulins	5 (5.2)	3 (3.1)
Calcium	3 (3.1)	6 (6.1)
Corticosteroids for systemic use, pure[c]	9 (9.3)	2 (2.0)
Antitussive drugs, pure	5 (5.2)	8 (8.2)
Drugs that reduce swelling and other preparations for nasal use	5 (5.2)	4 (4.1)
Direct-acting antiviral agents	4 (4.1)	6 (6.1)
Laxatives	5 (5.2)	7 (7.1)
Drugs for gastric ulcer and gastroesophageal reflux disease	14 (14.4)	23 (23.5)
Mucolytics, not in combination with antitussive drugs	7 (7.2)	6 (6.1)
Hormonal contraceptives for systemic use	2 (2.1)	5 (5.1)
Hypnotics and tranquilizers	3 (3.1)	6 (6.1)
Immunosuppressants	5 (5.2)	8 (8.2)
Iron-containing preparations	8 (8.2)	4 (4.1)
Cholesterol-lowering preparations, pure	8 (8.2)	4 (4.1)
Macrolide, lincosamide and streptogramin	4 (4.1)	5 (5.1)
Opioids	8 (8.2)	12 (12.2)
Other analgesics or antipyretics	35 (36.1)	37 (37.8)
Other anti-anaemic preparations	5 (5.2)	9 (9.2)
Other beta-lactam antibiotics	8 (8.2)	5 (5.1)

(continued)

Table 20: Concomitant medication by ATC class in > 5% of the patients in at least one study arm – RCT, direct comparison: ravulizumab vs. eculizumab (research question 2: clinically stable after at least 6 months of eculizumab treatment) (continued)

Characteristics Category	Ravulizumab	Eculizumab
	N[a] = 97	N[a] = 98
Quinolone antibiotics	16 (16.5)	16 (16.3)
Selective calcium channel blockers with mainly vascular effects	4 (4.1)	8 (8.2)
Thyroid preparations	0 (0.0)	8 (8.2)
Topical products for joint and muscle ache	5 (5.2)	3 (3.1)
Viral vaccines	20 (20.6)	18 (18.4)
Vitamins A and D, including combinations of both	5 (5.2)	10 (10.2)
Vitamin B12 and folic acid	61 (62.9)	60 (61.2)

a: Number of randomized and treated patients. There is no information on the untreated patients (one in each arm).
b: Data refer to the concomitant medication during the randomized study phase from the time point of randomization; order adopted from the company without alterations.
c: There is no concrete information on whether this is short-term pulse therapy or long-term therapy.
ACE: angiotensin converting enzyme; ATC: anatomical therapeutic chemical; n: number of patients in the category; N: number of randomized patients; RCT: randomized controlled trial; vs.: versus

There were no important differences between the treatment arms regarding concomitant medication. About 23% of the patients received anticoagulant therapy, about 53% penicillins, about 16% quinolone antibiotics, and about 62% vitamin B12 and folic acid. The use of concomitant interventions was considered adequate in the present benefit assessment.

Risk of bias across outcomes (study level)

Table 21 shows the risk of bias across outcomes (risk of bias at study level).

Table 21: Risk of bias across outcomes (study level) – RCT, direct comparison: ravulizumab vs. eculizumab (research question 2: clinically stable after at least 6 months of eculizumab treatment)

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
302	Yes	Yes	No	No	Yes	Yes	Low

RCT: randomized controlled trial; vs.: versus

The risk of bias across outcomes was rated as low for Study 302. This deviates from the assessment of the company, which rated the risk of bias across outcomes as high due to the lack of blinding of patients and treating staff.

Limitations resulting from the open-label study design are described in Section 2.4.2 with the outcome-specific risk of bias.

2.4.2 Results on added benefit

2.4.2.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment (for reasons, see Section 2.6.4.3.2 of the full dossier assessment):

- Mortality
  - all-cause mortality
- Morbidity
  - MAVEs
  - fatigue, measured with the FACIT-Fatigue
  - transfusion avoidance
- Health-related quality of life
- Side effects
  - SAEs
  - discontinuation due to AEs
  - meningococcal infection
  - if applicable, further specific AEs

The choice of patient-relevant outcomes deviates from that of the company, which used further outcomes in the dossier (Module 4 A) (see Section 2.6.4.3 of the full dossier assessment).

Table 22 shows for which outcomes data were available in the study included.

Table 22: Matrix of outcomes – RCT, direct comparison: ravulizumab vs. eculizumab (research question 2: clinically stable after at least 6 months of eculizumab treatment)

Study	Outcomes							
	All-cause mortality	MAVEs[a]	Fatigue (FACIT-Fatigue)	Transfusion avoidance[b]	Health-related quality of life	SAEs	Discontinuation due to AEs	Meningococcal infection[c]
302	Yes	Yes	Yes	Yes	No[d]	Yes	Yes	Yes

a: Defined as occurrence of one of the following events: thrombophlebitis/deep vein thrombosis, pulmonary embolism, myocardial infarction, transient ischaemic attack (TIA), unstable angina pectoris, renal vein thrombosis, acute peripheral arterial occlusion (PAOD), mesenteric/visceral vein thrombosis or infarction, mesenteric/visceral arterial thrombosis or infarction, hepatic/portal vein thrombosis (Budd-Chiari syndrome), cerebral arterial occlusion/stroke, cerebral vein occlusion, renal artery thrombosis, gangrene (non-traumatic, non-diabetic), amputation (non-traumatic, non-diabetic), dermal thrombosis, other.

b: Defined as the proportion of patients who, in accordance with the guidelines specified in the protocol, did not require transfusion from baseline until day 183 of the randomized study phase (week 26). PRBC transfusion was administered if a patient had an Hb level of ≤ 9 g/dL with clinical signs or symptoms of sufficient severity to justify transfusion, or if a patient had an Hb level of ≤ 7 g/dL irrespective of clinical signs or symptoms.

c: In the study operationalized using a combination of MedDRA PTs; it is unclear which PTs were considered. All infections caused by meningococci are relevant for the present benefit assessment. According to the information in the study documents, there were no such infections (see Section 2.6.4.3.2 of the full dossier assessment).

d: In the study, health-related quality of life was recorded using the EORTC QLQ-C30 questionnaire. It is unclear whether the EORTC QLQ-C30 reflects health-related quality of life of the patients in the present subindication; for reasons, see Section 2.6.4.3.2 of the full dossier assessment. The results are presented as supplementary information in Appendix B of the full dossier assessment.

AE: adverse event; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; FACIT: Functional Assessment of Chronic Illness Therapy; Hb: haemoglobin; MAVE: major adverse vascular event; MedDRA: Medical Dictionary for Regulatory Activities; PAOD: peripheral arterial occlusion; pPRC: packed red blood cells; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; TIA: transient ischaemic attack; vs.: versus

2.4.2.2 Risk of bias

Table 23 describes the risk of bias for the results of the relevant outcomes.

Table 23: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: ravulizumab vs. eculizumab (research question 2: clinically stable after at least 6 months of eculizumab treatment)

Study	Study level	Outcomes							
		All-cause mortality	MAVEs[a]	Fatigue (FACIT-Fatigue)	Transfusion avoidance[b]	Health-related quality of life	SAEs	Discontinuation due to AEs	Meningococcal infection[c]
302	L	L	L	H[d]	L	–[e]	L	H[d]	L

a: Defined as occurrence of one of the following events: thrombophlebitis/deep vein thrombosis, pulmonary embolism, myocardial infarction, transient ischaemic attack (TIA), unstable angina pectoris, renal vein thrombosis, acute peripheral arterial occlusion (PAOD), mesenteric/visceral vein thrombosis or infarction, mesenteric/visceral arterial thrombosis or infarction, hepatic/portal vein thrombosis (Budd-Chiari syndrome), cerebral arterial occlusion/stroke, cerebral vein occlusion, renal artery thrombosis, gangrene (non-traumatic, non-diabetic), amputation (non-traumatic, non-diabetic), dermal thrombosis, other.
b: Defined as the proportion of patients who, in accordance with the guidelines specified in the protocol, did not require transfusion from baseline until day 183 of the randomized study phase (week 26). PRBC transfusion was administered if a patient had an Hb level of ≤ 9 g/dL with clinical signs or symptoms of sufficient severity to justify transfusion, or if a patient had an Hb level of ≤ 7 g/dL irrespective of clinical signs or symptoms.
c: In the study operationalized using a combination of MedDRA PTs; it is unclear which PTs were considered. All infections caused by meningococci are relevant for the present benefit assessment. According to the information in the study documents, there were no such infections (see Section 2.6.4.3.2 of the full dossier assessment).
d: Lack of blinding in subjective recording of outcomes.
e: In the study, health-related quality of life was recorded using the EORTC QLQ-C30 questionnaire. It is unclear whether the EORTC QLQ-C30 reflects health-related quality of life of the patients in the present subindication; for reasons, see Section 2.6.4.3.2 of the full dossier assessment. The results are presented as supplementary information in Appendix B of the full dossier assessment.

AE: adverse event; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; FACIT: Functional Assessment of Chronic Illness Therapy; H: high; Hb: haemoglobin; L: low; MAVE: major adverse vascular event; MedDRA: Medical Dictionary for Regulatory Activities; PAOD: peripheral arterial occlusion; pRBC: packed red blood cells; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; TIA: transient ischaemic attack; vs.: versus

The outcome-specific risk of bias was rated as low for the results of the following outcomes: all-cause mortality, MAVEs, transfusion avoidance and SAEs. The risk of bias was also rated as low for the results of the outcome “meningococcal infection”. Although it is unclear which methods were used in Study 302 to test for meningococcal infection, it is assumed that there is little room for subjective assessment if the specific pathogen is detected. This deviates from the

assessment of the company, which rated the risk of bias for the results of these outcomes as high due to the lack of blinding of patients and outcome assessors.

Due to subjective recording of outcomes and lack of blinding, the risk of bias was rated as high for the results of the outcomes “fatigue (FACIT-Fatigue)” and “discontinuation due to AEs”. The result of these assessments concur with the assessment of the company.

In the study, health-related quality of life was recorded with the EORTC QLQ-C30. It is unclear whether the EORTC QLQ-C30 reflects health-related quality of life of the patients in the present subindication (for reasons, see Section 2.6.4.3.2 of the full dossier assessment). The risk of bias is therefore not assessed.

2.4.2.3 Results

Table 24 summarizes the results for the comparison of ravulizumab with eculizumab in patients with PNH who are clinically stable after having been treated with eculizumab for at least the past 6 months. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company’s dossier. Common AEs, SAEs and discontinuations due to AEs are listed in Appendix A of the full dossier assessment.

Table 24: Results (mortality, morbidity, health-related quality of life, side effects, dichotomous) – RCT, direct comparison: ravulizumab vs. eculizumab (research question 2: clinically stable after at least 6 months of eculizumab treatment)

Study Outcome category Outcome	Ravulizumab		Eculizumab		Ravulizumab vs. eculizumab
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value[a]
Study 302					
Mortality					
All-cause mortality	97	0 (0)	98	0 (0)	–
Morbidity					
MAVEs[b]	97	0 (0)	96	0 (0)	–
Fatigue (FACIT-Fatigue improvement[c])	97	36 (37.1)	98	33 (33.7)	1.10 [0.75; 1.61]; 0.682
Transfusion avoidance[d]	97	85 (87.6)	98	81 (82.7)	1.06 [0.94; 1.19]; 0.529
Health-related quality of life	No usable data[e]				
Side effects					
AEs (supplementary information)	97	85 (87.6)	98	86 (87.8)	–
SAEs	97	4 (4.1)	98	8 (8.2)	0.51 [0.16; 1.62]; 0.253
Discontinuation due to AEs	97	0 (0)	98	0 (0)	–
Meningococcal infection[f]	97	0 (0)	98	0 (0)	–

a: Institute's calculation; 95% CI asymptotic; p-value from unconditional exact test (CSZ method according to [6]).
b: Defined as occurrence of one of the following events: thrombophlebitis/deep vein thrombosis, pulmonary embolism, myocardial infarction, transient ischaemic attack (TIA), unstable angina pectoris, renal vein thrombosis, acute peripheral arterial occlusion (PAOD), mesenteric/visceral vein thrombosis or infarction, mesenteric/visceral arterial thrombosis or infarction, hepatic/portal vein thrombosis (Budd-Chiari syndrome), cerebral arterial occlusion/stroke, cerebral vein occlusion, renal artery thrombosis, gangrene (non-traumatic, non-diabetic), amputation (non-traumatic, non-diabetic), dermal thrombosis, other.
c: Patients with an improvement in FACIT-Fatigue total score by at least 3 points at week 26.
d: Defined as the proportion of patients who, in accordance with the guidelines specified in the protocol, did not require transfusion from baseline until day 183 of the randomized study phase (week 26). PRBC transfusion was administered if a patient had an Hb level of ≤ 9 g/dL with clinical signs or symptoms of sufficient severity to justify transfusion, or if a patient had an Hb level of ≤ 7 g/dL irrespective of clinical signs or symptoms. Patients who met these transfusion criteria were included in the group of patients requiring transfusion, regardless of whether they actually received a transfusion or not.
e: In the study, health-related quality of life was recorded using the EORTC QLQ-C30 questionnaire. It is unclear whether the EORTC QLQ-C30 reflects health-related quality of life of the patients in the present subindication; for reasons, see Section 2.6.4.3.2 of the full dossier assessment. The results are presented as supplementary information in Appendix B of the full dossier assessment.
f: In the study operationalized using a combination of MedDRA PTs; it is unclear which PTs were considered. All infections caused by meningococci are relevant for the present benefit assessment. According to the information in the study documents, there were no such infections.

AE: adverse event; CI: confidence interval; CSZ: convexity, symmetry, z score; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; FACIT: Functional Assessment of Chronic Illness Therapy; Hb: haemoglobin; MAVE: major adverse vascular event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least one) event; N: number of analysed patients; PAOD: peripheral arterial occlusive disease; pRBC: packed red blood cells; PT: Preferred Term; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; TIA: transient ischaemic attack; vs.: versus

Based on the available data, at most indications, e.g. of an added benefit, can be determined for the following outcomes: all-cause mortality, MAVEs, transfusion avoidance, SAEs and meningococcal infection; and, due to the high risk of bias, at most hints for the outcomes "fatigue (FACIT-Fatigue)" and "discontinuation due to AEs".

This approach deviates from that of the company. The company derived the added benefit on the basis of a global assessment of all available results of the studies 301 and 302 (including their extension phases) and the results of the non-randomized, uncontrolled studies ALXN1210-PNH-103 and ALXN1210-PNH-201 without differentiating between the patient populations of research questions 1 and 2. The company derived hints of an added benefit for different outcomes. The company based its conclusions on the presence of numerical superiority of ravulizumab versus eculizumab. According to the company, quantification of the added benefit is not possible because there were non-inferiority research questions for most outcomes in the studies 301 and 302. For this reason, it is not described below to what extent the assessment of individual outcomes deviates from that of the company.

Mortality

All-cause mortality

No death occurred in the ravulizumab or in the eculizumab arm of Study 302. There was no hint of an added benefit of ravulizumab in comparison with eculizumab; an added benefit is therefore not proven.

Morbidity

MAVEs

No event for the outcome "MAVEs" occurred in the ravulizumab or in the eculizumab arm. There was no hint of an added benefit of ravulizumab in comparison with eculizumab; an added benefit is therefore not proven.

Fatigue (FACIT-Fatigue)

The responder analysis on the number of patients with improvement by at least 3 points at week 26 was used for the outcome "fatigue", measured with the FACIT-Fatigue. There was no statistically significant difference between the treatment groups. As a result, there was no hint of an added benefit of ravulizumab in comparison with eculizumab; an added benefit is therefore not proven.

Transfusion avoidance

There was no statistically significant difference between the treatment groups for the outcome "transfusion avoidance". As a result, there was no hint of an added benefit of ravulizumab in comparison with eculizumab; an added benefit is therefore not proven.

Health-related quality of life

In Study 302, health-related quality of life was recorded with the EORTC QLQ-C30. It is unclear whether the EORTC QLQ-C30 reflects health-related quality of life of the patients in the present subindication (for reasons, see Section 2.6.4.3.2 of the full dossier assessment). This has no consequences for the conclusion on the added benefit, as no statistically significant result was shown for any of the investigated domains of the EORTC QLQ-C30. There was no hint of an added benefit of ravulizumab in comparison with eculizumab; an added benefit is therefore not proven.

Side effects

Serious adverse events

There was no statistically significant difference between the treatment groups for the outcome "SAEs". This resulted in no hint of greater or lesser harm from ravulizumab in comparison with eculizumab; greater or lesser harm is therefore not proven.

Discontinuation due to adverse events

No discontinuations due to AEs occurred in Study 302. There was no hint of greater or lesser harm from ravulizumab in comparison with eculizumab; greater or lesser harm is therefore not proven.

Specific adverse events

Meningococcal infection

In the study, the outcome "meningococcal infection" was operationalized using a combination of MedDRA PTs. It is unclear which PTs were considered. No events for this operationalization occurred in the study. In principle, all infections caused by meningococci are relevant for the present benefit assessment. It can be inferred from the study documents that no infection caused by meningococci occurred.

There was no hint of greater or lesser harm from ravulizumab in comparison with eculizumab; greater or lesser harm is therefore not proven.

2.4.2.4 Subgroups and other effect modifiers

The following characteristics were relevant for the present benefit assessment (see also Section 2.6.4.3.4 of the full dossier assessment):

- age at first dose of the study medication (18 to 65 years versus > 65 years)
- sex (female versus male)
- region (North America versus Europe versus Japan versus rest of the Asian-Pacific region)
- history of transfusion within 1 year before the first dose of the study medication (yes versus no)

All subgroup characteristics used in the present benefit assessment were defined a priori, although partly only for the primary outcome of Study 302, partly additionally for some secondary outcomes.

Interaction tests were performed when at least 10 patients per subgroup were included in the analysis. For binary data, there had to be 10 events in at least one 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 only presented if there is a statistically significant and relevant effect in at least one subgroup.

For the outcomes included in the present benefit assessment, the company presented subgroup analyses only for the outcome "transfusion avoidance". In accordance with the methods described, no relevant effect modification was identified for this outcome.

There were subgroup analyses on the mean change at the end of the randomized treatment phase (week 26) for the outcome "fatigue" (measured with the FACIT-Fatigue questionnaire), but not for the responder analysis used for the benefit assessment. It was not possible to calculate interaction tests due to the lack of results on the respective subgroups.

The lack of subgroup analyses has no consequence for the outcomes "all-cause mortality", "MAVEs", "discontinuation due to AEs" and "meningococcal infection", as no results occurred for each of these outcomes.

2.4.3 Probability and extent of added benefit

Probability and extent of the added benefit at outcome level are presented below. The various outcome categories and the effect sizes were taken into account. The methods used for this purpose are explained in the *General Methods* of IQWiG [1].

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.

2.4.3.1 Assessment of the added benefit at outcome level

The extent of the respective added benefit at outcome level was estimated from the results presented in Section 2.4.2 (see Table 25).

Table 25: Extent of added benefit at outcome level: ravulizumab vs. eculizumab (research question 2: clinically stable after at least 6 months of eculizumab treatment)

Outcome category **Outcome**	**Ravulizumab vs. eculizumab** **Proportion of events (%)** **Effect estimation [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
All-cause mortality	0% vs. 0%	Lesser benefit/added benefit not proven
Morbidity		
MAVEs[c]	0% vs. 0%	Lesser benefit/added benefit not proven
Fatigue (FACIT-Fatigue)[d]	37.1% vs. 33.7% RR: 1.10 [0.75; 1.61]; p = 0.682	Lesser benefit/added benefit not proven
Transfusion avoidance[e]	87.6% vs. 82.7% RR: 1.06 [0.94; 1.19]; p = 0.529	Lesser benefit/added benefit not proven
Health-related quality of life		
No usable data[f]	–	Lesser benefit/added benefit not proven
Side effects		
SAEs	4.1% vs. 8.2% RR: 0.51 [0.16; 1.62]; p = 0.253	Greater/lesser harm not proven
Discontinuation due to AEs	0% vs. 0%	Greater/lesser harm not proven
Meningococcal infection[g]	0% vs. 0%	Greater/lesser harm not proven

(continued)

Table 25: Extent of added benefit at outcome level: ravulizumab vs. eculizumab (research question 2: clinically stable after at least 6 months of eculizumab treatment) (continued)

a: Probability provided if there is a statistically significant and relevant effect.
b: Estimations of effect size are made depending on the outcome category with different limits based on the CI_u.
c: Defined as occurrence of one of the following events: thrombophlebitis/deep vein thrombosis, pulmonary embolism, myocardial infarction, transient ischaemic attack (TIA), unstable angina pectoris, renal vein thrombosis, acute peripheral arterial occlusion (PAOD), mesenteric/visceral vein thrombosis or infarction, mesenteric/visceral arterial thrombosis or infarction, hepatic/portal vein thrombosis (Budd-Chiari syndrome), cerebral arterial occlusion/stroke, cerebral vein occlusion, renal artery thrombosis, gangrene (non-traumatic, non-diabetic), amputation (non-traumatic, non-diabetic), dermal thrombosis, other.
d: Patients with an improvement in FACIT-Fatigue total score by at least 3 points at week 26.
e: Defined as the proportion of patients who, in accordance with the guidelines specified in the protocol, did not require transfusion from baseline until day 183 of the randomized study phase (week 26). PRBC transfusion was administered if a patient had an Hb level of ≤ 9 g/dL with clinical signs or symptoms of sufficient severity to justify transfusion, or if a patient had an Hb level of ≤ 7 g/dL irrespective of clinical signs or symptoms. Patients who met these transfusion criteria were included in the group of patients requiring transfusion, regardless of whether they actually received a transfusion or not.
f: In the study, health-related quality of life was recorded using the EORTC QLQ-C30 questionnaire. It is unclear whether the EORTC QLQ-C30 reflects health-related quality of life of the patients in the present subindication; for reasons, see Section 2.6.4.3.2 of the full dossier assessment. This has no consequences for the conclusion on the added benefit, as no statistically significant result was shown for any of the investigated domains of the EORTC QLQ-C30. The results are presented as supplementary information in Appendix B of the full dossier assessment.
g: In the study operationalized using a combination of MedDRA PTs; it is unclear which PTs were considered. All infections caused by meningococci are relevant for the present benefit assessment. According to the information in the study documents, there were no such infections.

AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; FACIT: Functional Assessment of Chronic Illness Therapy; Hb: haemoglobin; MAVE: major adverse vascular event; MedDRA: Medical Dictionary for Regulatory Activities; PAOD: peripheral arterial occlusive disease; pRBC: packed red blood cells; PT: Preferred Term; RR: relative risk; SAE: serious adverse event; TIA: transient ischaemic attack; vs.: versus

2.4.3.2 Overall conclusion on added benefit

Table 26 summarizes the results considered in the overall conclusion on the extent of added benefit.

Table 26: Positive and negative effects from the assessment of ravulizumab in comparison with eculizumab (research question 2: clinically stable after at least 6 months of eculizumab treatment)

Positive effects	**Negative effects**
–	–
In Study 302, health-related quality of life was recorded with the EORTC QLQ-C30. It is unclear whether the EORTC QLQ-C30 reflects health-related quality of life of the patients in the present subindication. This has no consequences for the conclusion on the added benefit, as no statistically significant result was shown for any of the investigated domains of the EORTC QLQ-C30.	

Study 302 showed neither effects in favour nor effects to the disadvantage of ravulizumab. In summary, there was no hint of an added benefit of ravulizumab versus the ACT eculizumab for patients with PNH who are clinically stable after having been treated with eculizumab for at least the past 6 months. An added benefit is therefore not proven.

This deviates from the assessment of the company, which derived a non-quantifiable added benefit of ravulizumab in the overall assessment of the results used by the company for the total population of patients with PNH. The company did not provide separate information on the population of patients who are clinically stable after having been treated with eculizumab for at least the past 6 months (research question 2 of the present benefit assessment).

2.4.4 List of included studies

Alexion Pharmaceuticals. ALXN1210 versus eculizumab in adult participants with paroxysmal nocturnal hemoglobinuria (PNH) currently treated with eculizumab: study details [online]. In: ClinicalTrials.gov. 16.05.2019 [Accessed: 15.08.2019]. URL: https://ClinicalTrials.gov/show/NCT03056040.

Alexion Pharmaceuticals. A phase 3, randomized, open-label, active-controlled study of ALXN1210 versus eculizumab in adult patients with paroxysmal nocturnal hemoglobinuria (PNH) currently treated with eculizumab [online]. In: EU Clinical Trials Register. [Accessed: 15.08.2019]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2016-002026-36.

Alexion Pharmaceuticals. ALXN1210 versus eculizumab in adult participants with paroxysmal nocturnal hemoglobinuria (PNH) currently treated with eculizumab: study results [online]. In: ClinicalTrials.gov. 16.05.2019 [Accessed: 15.08.2019]. URL: https://clinicaltrials.gov/ct2/show/results/NCT03056040.

Alexion Pharmaceuticals. A phase 3, randomized, open-label, active-controlled study of ALXN1210 versus eculizumab in adult patients with paroxysmal nocturnal hemoglobinuria (PNH) currently treated with eculizumab: study ALXN1210-PNH-302; protocol [unpublished]. 2017.

Alexion Pharmaceuticals. A phase 3, randomized, open-label, active-controlled study of ALXN1210 versus eculizumab in adult patients with paroxysmal nocturnal hemoglobinuria (PNH) currently treated with eculizumab: study ALXN1210-PNH-302; statistical analysis plan [unpublished]. 2017.

Alexion Pharmaceuticals. A phase 3, randomized, open-label, active-controlled study of ALXN1210 versus eculizumab in adult patients with paroxysmal nocturnal hemoglobinuria (PNH) currently treated with eculizumab: study ALXN1210-PNH-302; clinical study report (primary evaluation period) [unpublished]. 2018.

Alexion Pharmaceuticals. A phase 3, randomized, open-label, active-controlled study of ALXN1210 versus eculizumab in adult patients with paroxysmal nocturnal hemoglobinuria (PNH) currently treated with eculizumab; study ALXN1210-PNH-302; Zusatzanalysen [unpublished]. 2019.

Kulasekararaj AG, Hill A, Rottinghaus ST, Langemeijer S, Wells R, Gonzalez-Fernandez FA et al. Ravulizumab (ALXN1210) vs eculizumab in C5-inhibitor–experienced adult patients with PNH: the 302 study. Blood 2019; 133(6): 540-549.

2.5 Probability and extent of added benefit – summary

Table 27 summarizes the result of the assessment of the added benefit of ravulizumab in comparison with the ACT.

Table 27: Ravulizumab – probability and extent of added benefit

Subindication	**ACT[a]**	**Probability and extent of added benefit**
Adult patients with PNH with haemolysis with clinical symptom(s) indicative of high disease activity[b]	Eculizumab[c]	added benefit not proven
Adult patients with PNH who are clinically stable after having been treated with eculizumab for at least the past 6 months		Added benefit not proven
a: Presentation of the ACT specified by the G-BA. b: There were only data for treatment-naive patients with clinical symptom(s) indicative of high disease activity. It remains unclear whether the observed effects can be transferred to pretreated patients with high disease activity. c: It is assumed that supportive measures are conducted both in the intervention and in the comparator arm. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; PNH: paroxysmal nocturnal haemoglobinuria		

The approach for deriving 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.

1. Institute for Quality and Efficiency in Health Care. General methods: version 5.0 [online]. 10.07.2017 [Accessed: 04.06.2018]. URL: https://www.iqwig.de/download/General-Methods_Version-5-0.pdf.

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The full report (German version) is published under https://www.iqwig.de/en/projects-results/projects/drug-assessment/a19-59-ravalizumab-benefit-assessment-according-to-35a-social-code-book-v.12495.html.