Crovalimab
(paroxysmal nocturnal haemoglobinuria)

Benefit assessment according to §35a SGB V[1]

EXTRACT

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

Patient and family involvement

The questionnaire on the disease and its treatment was answered by Ulrike Göbel.

IQWiG thanks the respondent and the organization Aplastische Anämie & PNH e. V. (Aplastic Anaemia & PNH) for participating in the written exchange and for their support. The respondent and Aplastische Anämie & PNH e. V. were not involved in the actual preparation of the dossier assessment.

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Part I: Benefit assessment

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

I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
C5	complement component 5
CTCAE	Common Terminology Criteria for Adverse Events
DGHO	Deutsche Gesellschaft für Hämatologie und Onkologie (German Society for Haematology and Medical Oncology)
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
FACIT	Functional Assessment of Chronic Illness Therapy
FDA	Food and Drug Administration
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IL40	Item List 40
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
LDH	lactate dehydrogenase
MAVE	major adverse vascular event
MMRM	mixed-effects model with repeated measures
PGIS	Patient Global Impression of Severity
PNH	paroxysmal nocturnal haemoglobinuria
pRBC	packed red blood cells
PT	Preferred Term
QLQ-AA/PNH	Quality of Life Questionnaire-Aplastic Anaemia/Paroxysmal Nocturnal Haemoglobinuria
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SMQ	Standardized Medical Dictionary for Regulatory Activities Query
SNP	single nucleotide polymorphism
SPC	Summary of Product Characteristics
TEAE	treatment emergent adverse event
TIA	transient ischaemic attack
ULN	upper limit of normal
VAS	visual analogue scale

I 1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) has commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug crovalimab. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 13 September 2024.

Research question

The aim of this report is to assess the added benefit of crovalimab in comparison with eculizumab or ravulizumab as the appropriate comparator therapy (ACT) in adult and paediatric patients 12 years of age or older with a weight of 40 kg and above

- with paroxysmal nocturnal haemoglobinuria (PNH) with high disease activity, characterized by clinical symptoms of haemolysis
- with PNH who have been treated with a complement component 5 (C5) inhibitor for ≥ 6 months and are clinically stable.

The research questions presented in Table 2 result from the ACT specified by the G-BA.

Table 2: Research questions of the benefit assessment of crovalimab

Research question	Therapeutic indication	ACT[a]
1	Adult and paediatric patients 12 years of age or older with a weight of ≥ 40 kg with paroxysmal nocturnal haemoglobinuria (PNH) with high disease activity, characterized by clinical symptoms of haemolysis[b, c]	**Eculizumab** or ravulizumab[d]
2	Adult and paediatric patients 12 years of age or older with a weight of ≥ 40 kg with PNH who have been treated with a C5 inhibitor for ≥ 6 months and are clinically stable[b]	**Eculizumab** or ravulizumab[d]

a. Presented is the respective ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company according to the inclusion criteria in Module 4 A Section 4.2.2 is printed in **bold**.
b. The presented therapeutic indication is assumed to include only patients requiring therapy who have PNH and clinical symptoms of haemolysis. Patients with concomitant bone marrow failure – including in the context of aplastic anaemia – are disregarded in this assessment. For the present therapeutic indication, allogeneic stem cell transplantation is assumed not to be indicated at the time point of treatment with crovalimab. In addition, when determining the ACT, it is assumed that patients do not have a medical indication to switch treatment to C3 inhibition at the time of treatment with crovalimab.
c. In patients who remain symptomatic despite treatment with a C5 inhibitor, continuing inadequate therapy when optimization options exist does not constitute the ACT. Any dose modifications which may be needed in the treatment with eculizumab or ravulizumab are assumed to be exhaustively covered by way of adjustments to the dosing interval.
d. Supportive measures in accordance with the generally accepted state of medical knowledge are assumed to be conducted both in the intervention arm and in the control arm.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; PNH: paroxysmal nocturnal haemoglobinuria

In the present benefit assessment, the following terms are used for the research questions:

Research question 1: high disease activity

Research question 2: clinically stable after at least 6 months of treatment with a C5 inhibitor

The company followed the G-BA's specification for both research questions and chose eculizumab as ACT in each case.

While the company considered separately patients with high disease activity versus patients who are clinically stable after at least 6 months of treatment with a C5 inhibitor, it did not investigate the 2 research questions separately. The company derived the added benefit for the total population of patients with PNH without differentiating between the patient populations. Concurring with the G-BA's specification, the present assessment was conducted separately for 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 deriving any added benefit.

Research question 1: high disease activity

Study pool and study design

COMMODORE 2 study

The COMMODORE 2 study was included in the benefit assessment for research question 1. COMMODORE 2 is a randomized, open-label, multicentre, active-controlled non-inferiority study. The study included patients with PNH who were naive to C5 complement inhibitor treatment prior to study entry. The prerequisite for participation in the study was the presence of one or more PNH-related signs or symptoms in the 3 months prior to screening and a lactate dehydrogenase (LDH) level of ≥ 2 times upper limit of normal (ULN) as a sign of high disease activity.

An exclusion criterion for participation in the study was a haemoglobin value ≤ 7 g/dL, or between > 7 g/dL and ≤ 9 g/dL with concurrent signs and symptoms of anaemia (angina pectoris, faint, dizziness, confusion, severe or worsening dyspnoea, severe or worsening fatigue, stroke, transient ischaemic attack [TIA], or new onset or worsening heart failure) within 5 days prior to the first dose of study medication. In these cases, however, a packed red blood cell (pRBC) transfusion could be given to allow patients to meet the haemoglobin eligibility criterion.

The COMMODORE 2 study comprises 3 study arms with a total of 210 patients. In 2 of these arms, adult patients with a weight of 40 kg and above were randomly allocated in a 2:1 ratio to treatment with crovalimab (N = 135) or eculizumab (N = 69). Duration of the randomized study phase was 24 weeks. The patients could then participate in an extension phase, where all study participants received only crovalimab. The results of this extension phase are not relevant for the present benefit assessment, as there was no comparison with the ACT. It is therefore not presented below.

Patients under the age of 18 (N = 6) were not randomized, but all patients in this age group received treatment with crovalimab (non-randomized study arm). This study arm is therefore not presented below.

Only adult patients were included in the randomized study arms, meaning that there is no randomized comparison of crovalimab with eculizumab for patients under the age of 18 years. The company presented no additional comparative data for this age group, so that an assessment of the added benefit of crovalimab for this patient group is not possible.

The dosage of crovalimab and eculizumab essentially corresponded to the specifications in the respective Summary of Product Characteristics (SPC).

In the study, transfusion avoidance and haemolysis control, the latter operationalized as LDH ≤ 1.5 times ULN from Week 5, were defined as co-primary outcomes. Patient-relevant secondary outcomes were outcomes on morbidity and adverse events (AEs).

Definition of high disease activity

Patients included in the COMMODORE 2 study had to have one or more PNH-related signs or symptoms in the 3 months prior to screening and an LDH level of over 2 times ULN (see above). Neither the SPC for crovalimab nor the current German Society for Haematology and Medical Oncology (DGHO) guideline provide a precise definition of high disease activity. The definition applied by the company fulfils the criterion from the SPC to depict disease activity based on symptoms and largely corresponds to the criteria for high disease activity applied in the International PNH Registry. It is therefore considered an adequate definition of high disease activity in the present benefit assessment.

The information provided in the dossier on the patients' symptoms relates to the period of 3 months before randomization, so that specific information on symptoms at baseline is missing. However, the event numbers of various PNH-related symptoms reported in Module 4 A show that a large proportion of patients experienced symptoms during this period. Against this background, it is also not considered critical that transfusions were rated as a symptom in the definition of the study population, especially since transfusions are usually given because of symptoms.

Supportive therapy

The study protocol does not impose any restrictions with regard to concomitant supportive medication. On the contrary, the investigators were required to provide supportive treatment to the patients in accordance with local standards of care, insofar as they considered it indicated. The documentation of the concomitant medication shows that supportive measures were used to a comparable extent in both study arms.

Data cut-offs

The present benefit assessment uses the prespecified primary data cut-off of the COMMODORE 2 study dated 16 November 2022.

Risk of bias

The risk of bias across outcomes was rated as low for the COMMODORE 2 study. The outcome-specific risk of bias was rated as low for the results of the outcomes of all-cause mortality, major adverse vascular events (MAVEs), serious AEs (SAEs), severe AEs and infections (AEs). Due to subjective recording of outcomes in the presence of lack of blinding, the risk of bias

was rated as high for the results of the outcomes of transfusion avoidance, fatigue, health status, discontinuation due to AEs, and type III hypersensitivity reactions (AEs). For the patient-reported outcomes of fatigue and health status, there was also a high proportion of patients not included in the analysis (over 10%).

Results

Mortality

All-cause mortality

The results on all-cause mortality are based on data on fatal AEs. No statistically significant difference between treatment groups was found for the outcome of all-cause mortality. There is no hint of an added benefit of crovalimab in comparison with eculizumab; an added benefit is therefore not proven.

Morbidity

Transfusion avoidance

No statistically significant difference between treatment groups was found for the outcome of transfusion avoidance. There is no hint of an added benefit of crovalimab in comparison with eculizumab; an added benefit is therefore not proven.

MAVE

No statistically significant difference between treatment groups was found for the outcome of MAVE. There is no hint of an added benefit of crovalimab in comparison with eculizumab; an added benefit is therefore not proven.

Fatigue (recorded using the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue)

No statistically significant difference between treatment groups was found for the outcome of fatigue (recorded using the FACIT-Fatigue). There is no hint of an added benefit of crovalimab in comparison with eculizumab; an added benefit is therefore not proven.

Health status (recorded using the EQ-5D visual analogue scale [VAS])

No statistically significant difference between treatment groups was found for the outcome of health status (recorded using the EQ-5D VAS). There is no hint of an added benefit of crovalimab in comparison with eculizumab; an added benefit is therefore not proven.

Symptoms (recorded using the Patient Global Impression of Severity [PGIS])

No suitable data are available for the outcome of symptoms (recorded using the PGIS). There is no hint of an added benefit of crovalimab in comparison with eculizumab; an added benefit is therefore not proven.

Health-related quality of life

No suitable data are available for health-related quality of life. There is no hint of an added benefit of crovalimab in comparison with eculizumab; an added benefit is therefore not proven.

Side effects

SAEs

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

Severe AEs

No statistically significant difference between treatment groups was found for the outcome of severe AEs with Common Terminology Criteria for Adverse Events (CTCAE) grade ≥ 3. There is no hint of greater or lesser harm from crovalimab in comparison with eculizumab; greater or lesser harm is therefore not proven.

Discontinuation due to AEs

No statistically significant difference was found between treatment groups for the outcome of discontinuation due to AEs. There is no hint of greater or lesser harm from crovalimab in comparison with eculizumab; greater or lesser harm is therefore not proven.

Specific AEs: type III hypersensitivity reaction (AEs)

No events occurred in either treatment group for the outcome of type III hypersensitivity reaction (AEs). There is no hint of greater or lesser harm from crovalimab in comparison with eculizumab; greater or lesser harm is therefore not proven.

Specific AEs: injection site reactions and infusion related reactions

No suitable data are available for the specific AEs of injection site reactions and infusion related reactions. In each case, there is no hint of greater or lesser harm from crovalimab in comparison with eculizumab; greater or lesser harm is therefore not proven.

Specific AEs: infections (AEs)

No statistically significant difference between treatment groups was found for the outcome of infections (AEs). There is no hint of greater or lesser harm from crovalimab 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]

On the basis of the results presented, the probability and extent of added benefit of the drug crovalimab in comparison with the ACT is assessed as follows:

The COMMODORE 2 study showed neither positive nor negative effects for crovalimab in comparison with eculizumab. In summary, there is no hint of an added benefit of crovalimab versus eculizumab for patients with PNH with high disease activity, characterized by clinical symptoms of haemolysis. An added benefit is therefore not proven.

Research question 2: clinically stable after at least 6 months of treatment with a C5 inhibitor

Study pool and study design

COMMODORE 1 study

The COMMODORE 1 study was included in the benefit assessment for research question 2. COMMODORE 1 is a randomized, open-label, multicentre, active-controlled study. The original objective of the study was to prove the non-inferiority of crovalimab compared with eculizumab. For this purpose, approximately 200 patients were to be included in the randomized study arms. However, randomization was stopped prematurely due to the slow recruitment of patients, which meant that only around 45% (N = 89) of the study's recruitment target was achieved. The primary analysis then took place in parallel with the COMMODORE 2 study on 16 November 2022. Due to the smaller sample size than originally planned, there was no non-inferiority testing and all primary and secondary efficacy outcomes were only exploratory.

The study included patients with PNH who had received eculizumab for at least 6 months and were clinically stable at baseline. Stable disease was defined by an LDH value that did not exceed the ULN by more than 1.5 times at baseline and no MAVE in the past 6 months before enrolment.

An exclusion criterion for participation in the study was a haemoglobin value ≤ 7 g/dL, or between > 7 g/dL and ≤ 9 g/dL with concurrent signs and symptoms of anaemia (angina

[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].

pectoris, faint, dizziness, confusion, severe or worsening dyspnoea, severe or worsening fatigue, stroke, TIA, or new onset or worsening heart failure) within 5 days prior to the first dose of study medication. In these cases, however, a pRBC transfusion could be given to allow patients to meet the haemoglobin eligibility criterion.

The COMMODORE 1 study has 3 study arms, in which a total of 127 patients were included until randomization was discontinued. In 2 of these arms, adult patients with a weight of 40 kg and above were randomly allocated in a 1:1 ratio to treatment switch to crovalimab (N = 45) or continuation of ongoing treatment with eculizumab (N = 44). Duration of the randomized study phase was 24 weeks. The patients could then participate in an extension phase, where all study participants received only crovalimab. The results of this 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. The third study arm consists of several patient cohorts who were treated with crovalimab in the study. These patients were not randomized, as this study arm was intended as a descriptive analysis arm. As there is no randomized comparison with the ACT, and some of the patient groups included here are not covered by the therapeutic indication, this study arm is no longer presented below.

Only adult patients were included in the randomized study arms, meaning that there is no randomized comparison of crovalimab with eculizumab for patients under the age of 18 years. The company presented no additional comparative data for this age group, so that an assessment of the added benefit of crovalimab for this patient group is not possible. Furthermore, no patients who had been previously treated with ravulizumab were included in the randomized study arms.

The dosage of crovalimab and eculizumab largely corresponded to the specifications in the respective SPC.

In the COMMODORE 1 study, the LDH value at Week 25 was originally planned as the primary outcome. After the premature end of recruitment, the primary outcome was changed to AEs. Patient-relevant secondary outcomes were recorded in the outcome category of morbidity.

Definition of clinically stable disease under treatment with eculizumab

In the COMMODORE 1 study, stable disease was defined by an LDH value that did not exceed the ULN by more than 1.5 times at baseline and no MAVE in the past 6 months before enrolment. Patients with haemoglobin values ≤ 7 g/dL, or between > 7 g/dL and ≤ 9 g/dL with concurrent signs and symptoms of anaemia (see above) were excluded from the study. It can be assumed that the criteria applied in the COMMODORE 1 study are generally suitable for including a predominantly clinically stable patient population. However, it is not clear from the information provided in the dossier how many patients had PNH symptoms at baseline,

but it can be concluded from the baseline values of the patient-reported symptom questionnaires that at least some of the patients had a symptom burden. However, as treatment with C5 inhibitors cannot cure PNH, it is not to be expected that patients with stable disease under prior eculizumab treatment were symptom-free. It should be noted, however, that approximately 23% of patients in the COMMODORE 1 study had received transfusions in the year prior to the start of the study. It is therefore not possible to fully assess whether these patients were actually stable on eculizumab. However, since the information relates to the past 12 months (and not just the required minimum treatment duration of 6 months with eculizumab), it is assumed that fewer than 20% of the study population had received a transfusion in the past six months before the start of the study. This therefore has no consequence for the present benefit assessment.

Supportive therapy

The information provided for the COMMODORE 2 study applies to the implementation of supportive therapy.

Study course and data cut-offs

Randomization for the COMMODORE 1 study was stopped prematurely on 2 November 2022 due to slow recruitment. The sample size required to fulfil the study objective of demonstrating non-inferiority of crovalimab versus eculizumab was not achieved. The COMMODORE 1 study was therefore unable to prove the non-inferiority of crovalimab. On the one hand, in the course of this change, protocol Amendment 6 of 28 September 2022 brought forward the primary data cut-off to 16 November 2022 to synchronize it with the primary data cut-off of the COMMODORE 2 study. On the other hand, all efficacy outcomes were converted to exploratory outcomes, while tolerability became the new primary outcome.

According to the company, 2 data cut-offs and an analysis for the Food and Drug Administration (FDA) (Day 120 safety update) are available for the COMMODORE 1 study. In Module 4 A, the company presented analyses on all outcomes whose time points coincided with the Day 120 safety update for the FDA of 31 May 2023. This analysis is a regular part of the approval procedure in the FDA assessment process. The company justified its choice by stating that, due to the premature recruitment stop at the time of the primary data cut-off, not all patients had yet completed the randomized study phase, which was the case on 31 May 2023. In the described specific data situation, the company's approach is appropriate. In addition, this analysis is more in line with the original study design than the earlier data cut-off date of 16 November 2022. This benefit assessment uses the analysis with data as at 31 May 2023.

Risk of bias

The risk of bias across outcomes was rated as high for the COMMODORE 1 study. This is due to incomplete observations occurring in the outcome of all-cause mortality, for which no reasons were given in the company's dossier and which are therefore potentially informative. In addition, it remains unclear for the other outcomes to what extent the incomplete observations of the patients (potentially informative reasons) led to missing values.

The risk of bias for the results of all outcomes was rated as low. One reason for this is the high risk of bias across outcomes. For the results of the outcomes of transfusion avoidance, fatigue, health status, discontinuation due to AEs, and type III hypersensitivity reactions (AEs), the subjective recording of outcomes in the presence of lack of blinding also contributes to the high risk of bias. For the patient-reported outcomes of fatigue and health status, there was an additional large difference between treatment groups (> 5 percentage points) regarding the proportion of patients who were not considered in the analysis.

Results

Mortality

All-cause mortality

The results on all-cause mortality are based on data on fatal AEs. No events for the outcome of all-cause mortality occurred in the COMMODORE 1 study. There is no hint of an added benefit of crovalimab in comparison with eculizumab; an added benefit is therefore not proven.

Morbidity

Transfusion avoidance

No statistically significant difference between treatment groups was found for the outcome of transfusion avoidance. There is no hint of an added benefit of crovalimab in comparison with eculizumab; an added benefit is therefore not proven.

MAVE

No statistically significant difference between treatment groups was found for the outcome of MAVE. There is no hint of an added benefit of crovalimab in comparison with eculizumab; an added benefit is therefore not proven.

Fatigue (recorded using the FACIT-Fatigue)

No statistically significant difference between treatment groups was found for the outcome of fatigue (recorded using the FACIT-Fatigue). There is no hint of an added benefit of crovalimab in comparison with eculizumab; an added benefit is therefore not proven.

Health status (recorded using the EQ-5D VAS)

No statistically significant difference between treatment groups was found for the outcome of health status (recorded using the EQ-5D VAS). There is no hint of an added benefit of crovalimab in comparison with eculizumab; an added benefit is therefore not proven.

Health-related quality of life

No suitable data are available for health-related quality of life. There is no hint of an added benefit of crovalimab in comparison with eculizumab; an added benefit is therefore not proven.

Side effects

SAEs

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

Severe AEs

A statistically significant difference between treatment groups to the disadvantage of crovalimab was found for the outcome of severe AEs. There is a hint of greater harm from crovalimab in comparison with eculizumab.

Discontinuation due to AEs

No events occurred for the outcome of discontinuation due to AEs in the COMMODORE 1 study. There is no hint of greater or lesser harm from crovalimab in comparison with eculizumab; greater or lesser harm is therefore not proven.

Specific AEs: type III hypersensitivity reaction (AEs)

A statistically significant difference between treatment groups to the disadvantage of crovalimab was found for the outcome of type III hypersensitivity reaction (AEs). However, the difference is no more than marginal for this outcome in the category of non-serious/non-severe side effects. There is no hint of greater or lesser harm from crovalimab in comparison with eculizumab; greater or lesser harm is therefore not proven.

Specific AEs: injection site reactions and infusion related reactions

No suitable data are available for the outcomes of injection site reactions and infusion related reactions. In each case, there is no hint of greater or lesser harm from crovalimab in comparison with eculizumab; greater or lesser harm is therefore not proven.

Specific AEs: infections (AEs)

No statistically significant difference between treatment groups was found for the outcome of infections (AEs). There is no hint of greater or lesser harm from crovalimab 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

On the basis of the results presented, the probability and extent of added benefit of the drug crovalimab in comparison with the ACT is assessed as follows:

In the COMMODORE 1 study, a hint of greater harm of minor extent was shown for the outcome of severe AEs. At the same time, there were no positive effects of crovalimab compared with eculizumab. In summary, there is a hint of lesser benefit of crovalimab versus eculizumab for adult patients with PNH who have been treated with a C5 inhibitor for ≥ 6 months and are clinically stable.

No data are available from the COMMODORE 1 study for the assessment of the added benefit of crovalimab compared with eculizumab for the treatment of paediatric patients 12 years of age or older who have been treated with a C5 inhibitor for ≥ 6 months and are clinically stable. An added benefit of crovalimab compared with eculizumab is therefore not proven for paediatric patients 12 years of age or older.

Probability and extent of added benefit, patient groups with therapeutically important added benefit – summary

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

Table 3: Crovalimab – probability and extent of added benefit

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
1	Adult and paediatric patients 12 years of age or older with a weight of ≥ 40 kg with paroxysmal nocturnal haemoglobinuria (PNH) with high disease activity, characterized by clinical symptoms of haemolysis[b, c]	**Eculizumab** or ravulizumab[d]	Added benefit not proven[e]
2	Adult and paediatric patients 12 years of age or older with a weight of ≥ 40 kg with PNH who have been treated with a C5 inhibitor for ≥ 6 months and are clinically stable[b]	**Eculizumab** or ravulizumab[d]	▪ Adults: hint of lesser benefit[f] ▪ Paediatric patients 12 years of age or older: added benefit not proven[f]

a. Presented is the respective ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company according to the inclusion criteria in Module 4 A Section 4.2.2 is printed in **bold**.
b. The presented therapeutic indication is assumed to include only patients requiring therapy who have PNH and clinical symptoms of haemolysis. Patients with concomitant bone marrow failure – including in the context of aplastic anaemia – are disregarded in this assessment. For the present therapeutic indication, allogeneic stem cell transplantation is assumed not to be indicated at the time point of treatment with crovalimab. In addition, when determining the ACT, it is assumed that patients do not have a medical indication to switch treatment to C3 inhibition at the time of treatment with crovalimab.
c. In patients who remain symptomatic despite treatment with a C5 inhibitor, continuing inadequate therapy when optimization options exist does not constitute the ACT. Any dose modifications which may be needed in the treatment with eculizumab or ravulizumab are assumed to be exhaustively covered by way of adjustments to the dosing interval.
d. Supportive measures in accordance with the generally accepted state of medical knowledge are assumed to be conducted both in the intervention arm and in the control arm.
e. Data from randomized trials are only available for patients aged ≥ 18 years. It remains unclear whether the observed effects can be transferred to patients aged 12 to 17 years.
f. No data from randomized trials are available for patients who were pretreated with ravulizumab.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee

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

I 2 Research question

The aim of this report is to assess the added benefit of crovalimab in comparison with eculizumab or ravulizumab as the ACT in adult and paediatric patients 12 years of age or older with a weight of 40 kg and above

- with PNH with high disease activity, characterized by clinical symptoms of haemolysis
- with PNH who have been treated with a C5 inhibitor for ≥ 6 months and are clinically stable.

The research questions presented in Table 4 result from the ACT specified by the G-BA.

Table 4: Research questions of the benefit assessment of crovalimab

Research question	Therapeutic indication	ACT[a]
1	Adult and paediatric patients 12 years of age or older with a weight of ≥ 40 kg with paroxysmal nocturnal haemoglobinuria (PNH) with high disease activity, characterized by clinical symptoms of haemolysis[b, c]	**Eculizumab** or ravulizumab[d]
2	Adult and paediatric patients 12 years of age or older with a weight of ≥ 40 kg with PNH who have been treated with a C5 inhibitor for ≥ 6 months and are clinically stable[b]	**Eculizumab** or ravulizumab[d]

a. Presented is the respective ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company according to the inclusion criteria in Module 4 A Section 4.2.2 is printed in **bold**.
b. The presented therapeutic indication is assumed to include only patients requiring therapy who have PNH and clinical symptoms of haemolysis. Patients with concomitant bone marrow failure – including in the context of aplastic anaemia – are disregarded in this assessment. For the present therapeutic indication, allogeneic stem cell transplantation is assumed not to be indicated at the time point of treatment with crovalimab. In addition, when determining the ACT, it is assumed that patients do not have a medical indication to switch treatment to C3 inhibition at the time of treatment with crovalimab.
c. In patients who remain symptomatic despite treatment with a C5 inhibitor, continuing inadequate therapy when optimization options exist does not constitute the ACT. Any dose modifications which may be needed in the treatment with eculizumab or ravulizumab are assumed to be exhaustively covered by way of adjustments to the dosing interval.
d. Supportive measures in accordance with the generally accepted state of medical knowledge are assumed to be conducted both in the intervention arm and in the control arm.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; PNH: paroxysmal nocturnal haemoglobinuria

In the present benefit assessment, the following terms are used for the research questions:

Research question 1: high disease activity

Research question 2: clinically stable after at least 6 months of treatment with a C5 inhibitor

The company followed the G-BA's specification for both research questions and chose eculizumab as ACT in each case.

While the company considered separately patients with high disease activity versus patients who are clinically stable after at least 6 months of treatment with a C5 inhibitor, it did not investigate the 2 research questions separately. The company derived the added benefit for the total population of patients with PNH without differentiating between the patient populations. Concurring with the G-BA's specification, the present assessment was conducted separately for 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. RCTs with a minimum duration of 24 weeks were used for deriving any added benefit. This departs from the inclusion criteria used by the company, which applied no restrictions of study duration.

I 3 Research question 1 – high disease activity

I 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 list on crovalimab (status: 1 July 2024)
- bibliographical literature search on crovalimab (last search on 1 July 2024)
- search in trial registries/trial results databases for studies on crovalimab (last search on 1 July 2024)
- search on the G-BA website for crovalimab (last search on 1 July 2024)

To check the completeness of the study pool:

- search in trial registries for studies on crovalimab (last search on 30 September 2024); for search strategies, see I Appendix A of the full dossier assessment

The check did not identify any additional relevant study.

I 3.1.1 Studies included

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

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

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication (yes/no [citation])
COMMODORE 2	Yes	Yes	No	Yes [3]	Yes [4-6]	Yes [7]

a. Study sponsored by the company.
b. Citation of the trial registry entries and, if available, of the reports on study design and/or results listed in the trial registries.

CSR: clinical study report; G-BA: Federal Joint Committee; RCT: randomized controlled trial

The study pool for research question 1 of the present benefit assessment consists of the COMMODORE 2 study. The company did not investigate 2 separate research questions. It presented the results of each of the studies COMMODORE 2 and COMMODORE 1 (included in the present benefit assessment for research question 2, see Section I 4), and derived a

conclusion on the added benefit for the total population of patients with PNH on the basis of both studies, without differentiating between the patient populations.

I 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: crovalimab vs. eculizumab (research question 1: high disease activity) (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
COMMODORE 2	RCT, open-label, parallel	Adult and paediatric[b] patients ≥ 40 kg weight with PNH[c] and ▪ without pretreatment with a C5 complement inhibitor ▪ with one or more PNH-related signs or symptoms[d] in the 3 months prior to screening, and ▪ LDH level ≥ 2 times ULN at screening	Crovalimab (N = 135) eculizumab (N = 69) Additionally: non-randomized arm with patients < 18 years crovalimab (N = 6)[e]	Screening: up to 4 weeks Treatment ▪ randomized for 24 weeks, then possible transition to open-label extension phase with crovalimab treatment of all patients for a maximum of 5 years ▪ non-randomized crovalimab arm: 24 weeks, then further treatment possible for a maximum of 5 years Follow-up: 46 weeks for crovalimab[f], 10 weeks for eculizumab	67 centres in Argentina, Brazil, China, France, Germany, Greece, Hong Kong, Japan, Lithuania, Malaysia, Mexico, Netherlands, Philippines, Poland, Portugal, Romania, Singapore, Spain, Sweden, South Korea, Taiwan, Thailand, Turkey, Ukraine, United Kingdom 10/2020–ongoing Data cut-offs: 16 November 2022 (primary data cut-off) 12 March 2024 (not prespecified)	Primary: transfusion avoidance, haemolysis control Secondary: morbidity, AEs

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

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
a. Primary outcomes include information without taking into account the relevance for this benefit assessment. Secondary outcomes include only information on relevant available outcomes for this benefit assessment. b. Paediatric patients were only included in the non-randomized arm. c. Diagnosed by flow cytometry, with clone size ≥ 10% (granulocytes or monocytes). d. Fatigue, haemoglobinuria, abdominal pain, shortness of breath (dyspnoea), anaemia (haemoglobin < 10 g/dL), history of a MAVE including thrombosis, dysphagia, or erectile dysfunction; or history of pRBC transfusion due to PNH. e. The arm is irrelevant for the assessment and is disregarded in the following tables. f. The original follow-up period for patients treated with crovalimab was 24 weeks; with protocol version 6, a telephone visit after 46 weeks was added to this follow-up period. 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						

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

Study	Intervention	Comparison
COMMODORE 2	Crovalimab, based on weight: ≥ 40 kg to < 100 kg: Initial dose: ▪ Week 1: ▫ Day 1: 1000 mg IV ▫ Day 2: 340 mg SC ▪ Weeks 2, 3 and 4: 340 mg SC, once a week Maintenance dose: ▪ From Week 5: 680 mg SC, every 4 weeks[a] ≥ 100 kg: Initial dose: ▪ Week 1: ▫ Day 1: 1500 mg IV ▫ Day 2: 340 mg SC ▪ Weeks 2, 3 and 4: 340 mg SC, once a week Maintenance dose: ▪ From Week 5: 1020 mg SC, every 4 weeks	Eculizumab Initial dose: ▪ Weeks 1 to 4: 600 mg IV, once a week Maintenance dose: ▪ From Week 5: 900 mg IV, every 2 weeks
	Dose adjustment: ▪ in case of weight changes by ≥ 10% from the last visit if the weight is above or below the threshold of 100 kg ▪ increase in maintenance dose permitted in case of at least 2 intravascular haemolysis events within 24 weeks, or persistent intravascular haemolysis with LDH ≥ 2 x ULN on 3 consecutive measurements for ≥ 4 weeks, provided at least one symptom of intravascular haemolysis was present (in each case without identifiable trigger) ▪ additional crovalimab doses as rescue therapy in case of signs or symptoms of PNH possible at the discretion of the investigator	▪ dose adjustment not permitted during the course of the study

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

Study	Intervention	Comparison
	Pretreatment Required: ▪ vaccination against *Neisseria meningitidis* serotypes A, C, W and Y < 3 years prior to first dose of study drug, against serotype B in accordance with local guidelines; if vaccinated < 2 weeks before study start or after first dose of study drug, additional antibiotic prophylaxis should be given ▪ vaccination against *Haemophilus influenzae* type B and *Streptococcus pneumoniae* according to national recommendations; if vaccinated < 2 weeks before study start or after first dose of study drug, additional antibiotic prophylaxis should be given Allowed: ▪ if haemoglobin ≤ 7 g/dL, or > 7 and ≤ 9 g/dL with concomitant symptoms of anaemia: pRBC transfusion could be given within 5 days before the first dose of study drug to allow patients to meet the haemoglobin eligibility criterion ▪ supportive therapy e.g. with immunosuppressants, corticosteroids, iron supplements, anticoagulants, erythrocyte-stimulating agents in a stable dose for ≥ 28 days before the first dose of study drug Not allowed: ▪ any complement inhibitors ▪ allogeneic stem cell transplantation at any time prior to study inclusion **Concomitant treatment** Allowed: ▪ immunosuppressants, corticosteroids, iron supplements, folic acid; other concomitant therapies possible, but require documentation ▪ medication for the treatment of infusion related symptoms (acetaminophen, ibuprofen, diphenhydramine, H2 receptor antagonists, etc.) ▪ The investigators were required to provide supportive treatment to the patients in accordance with local standards of care, insofar as this was indicated. Not allowed: ▪ other complement inhibitors, investigational treatments	
a. Self-administration of SC injections was permitted starting at Week 9, after confirmation of proficiency by the study staff. IV: intravenous; LDH: lactate dehydrogenase; PNH: paroxysmal nocturnal haemoglobinuria; pRBC: packed red blood cells; RCT: randomized controlled trial; SC: subcutaneous; ULN: upper limit of normal		

Description of the COMMODORE 2 study

COMMODORE 2 is a randomized, open-label, multicentre, active-controlled study. The objective of the study was to prove the non-inferiority of crovalimab compared with eculizumab. The study included patients with PNH who were naive to C5 complement inhibitor treatment prior to study entry. The prerequisite for participation in the study was the presence of one or more PNH-related signs or symptoms in the 3 months prior to screening and an LDH level of ≥ 2 times ULN as a sign of high disease activity. Fatigue, haemoglobinuria,

abdominal pain, shortness of breath (dyspnoea), anaemia (haemoglobin < 10 g/dL), history of a MAVE including thrombosis, dysphagia, erectile dysfunction, or history of pRBC transfusion due to PNH were considered PNH-related symptoms. Patients with high disease activity despite prior treatment with a C5 inhibitor were not included in the COMMODORE 2 study. No data are available for these patients.

An exclusion criterion for participation in the study was a haemoglobin value ≤ 7 g/dL or between > 7 g/dL and ≤ 9 g/dL with concurrent signs and symptoms of anaemia (angina pectoris, faint, dizziness, confusion, severe or worsening dyspnoea, severe or worsening fatigue, stroke, TIA, or new onset or worsening heart failure) within 5 days prior to the first dose of study medication. In these cases, however, a pRBC transfusion could be given to allow patients to meet the haemoglobin eligibility criterion. According to the SPCs, administration of crovalimab and eculizumab is not linked to a haemoglobin value requirement [8,9]. The procedure in the study seems appropriate, as the guideline recommends transfusions as a supportive measure for the treatment of haemolysis in PNH [10]. In addition, the procedure in the study essentially corresponds to the criteria specified for pRBC in the current cross-sectional guideline on therapy with blood components and plasma derivatives [11]. However, it is not clear from the company's dossier how many patients received a transfusion shortly before the start of the study.

The COMMODORE 2 study comprises 3 study arms with a total of 210 patients. In 2 of these arms, adult patients with a weight of 40 kg and above were randomly allocated in a 2:1 ratio to treatment with crovalimab (N = 135) or eculizumab (N = 69). Randomization was stratified based on most recent LDH level before screening (≥ 2 to ≤ 4 times ULN, or > 4 times ULN) and number of pRBC transfusions within 6 months prior to randomization (0 units, > 0 to ≤ 6 units, > 6 units). Duration of the randomized study phase was 24 weeks. The patients could then participate in an extension phase, where all study participants received only crovalimab. The results of this 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.

Patients under the age of 18 (N = 6) were not randomized, but all patients in this age group received treatment with crovalimab (non-randomized study arm). This study arm is therefore not presented below. Only adult patients were included in the randomized study arms, meaning that there is no randomized comparison of crovalimab with eculizumab for patients under the age of 18 years. The company presented no additional comparative data for this age group, so that an assessment of the added benefit of crovalimab for this patient group is not possible.

Treatment of the patients in the 2 randomized study arms was conducted according to the regimen described in Table 7. The dosage of crovalimab and eculizumab essentially

corresponded to the specifications in the respective SPC [8,9]. However, it should be noted that there was an option for weight-independent dose escalation and administration of additional single doses as rescue therapy in the crovalimab arm, which is not provided for in the SPC of crovalimab. In the eculizumab arm, however, no dose adjustment was permitted; according to the SPC for eculizumab, there is the option of shortening the dosing interval by 2 days if signs and symptoms of intravascular haemolysis occur. However, the information in the study documents indicate that there were only individual cases of a dose increase or rescue therapy in the crovalimab arm (4 out of 135 patients [3%] received rescue therapy, 2 out of 135 patients [1.5%] received an additional dose). It is not clear from the dossier for how many patients a shortening of the dosing interval in the eculizumab arm might have been appropriate. A total of 10 out of 69 patients (14.5%) in the eculizumab arm had breakthrough haemolysis during the course of the study. In the 2 phase 3 studies on ravulizumab, about half of all patients with breakthrough haemolysis under eculizumab treatment had an increased concentration of free C5 at the end of the dosing interval, which was due to insufficient concentrations of eculizumab and thus insufficient C5 inhibition by eculizumab [12]. It is therefore unclear for how many of the patients with breakthrough haemolysis in the eculizumab arm an adjustment of the dosing interval would actually have been an option. Therefore, the different procedures in the study arms have no consequences for the benefit assessment of crovalimab.

In the COMMODORE 2 study, transfusion avoidance and haemolysis control, the latter operationalized as LDH ≤ 1.5 times ULN from Week 5, were defined as co-primary outcomes. Patient-relevant secondary outcomes were outcomes on morbidity and AEs.

Definition of high disease activity

Patients included in the COMMODORE 2 study had to have one or more PNH-related signs or symptoms in the 3 months prior to screening and an LDH level of over 2 times ULN (see above). Neither the SPC for crovalimab nor the current DGHO guideline provide a precise definition of high disease activity [8,10]. The definition applied by the company fulfils the criterion from the SPC to depict disease activity based on symptoms and largely corresponds to the criteria for high disease activity applied in the International PNH Registry [13]. It is therefore considered an adequate definition of high disease activity in the present benefit assessment.

The information provided in the dossier on the patients' symptoms relates to the period of 3 months before randomization, so that specific information on symptoms at baseline is missing. However, the event numbers of various PNH-related symptoms reported in Module 4 A show that a large proportion of patients experienced symptoms during this period (see Table 8). For example, 84% and 91% of patients had fatigue. With a mean value of around 36 points at baseline, there was also an increased symptom burden for the outcome of fatigue, recorded using the FACIT-Fatigue, compared with the general population (mean value

of 43.5 according to [14]). Furthermore, dyspnoea occurred in approx. 21% of patients and abdominal pain in 16%; haemoglobinuria was seen in 58% and 65% of patients respectively. Against this background, it is also not considered critical that transfusions were rated as a symptom in the definition of the study population, especially since transfusions are usually given because of symptoms [11].

Supportive therapy in COMMODORE 2

According to the current PNH guideline, besides pRBC substitution, supportive therapy for PNH includes administration of folic acid and vitamin B12 (if necessary) as well as oral or intravenous substitution of iron in the event of a deficiency, early and consistent antibiotic therapy for bacterial infections, and long-term or lifelong anticoagulation after thrombosis [10].

The study protocol does not impose any restrictions with regard to concomitant supportive medication. On the contrary, the investigators were required to provide supportive treatment to the patients in accordance with local standards of care, insofar as they considered it indicated. The documentation of the concomitant medication shows that supportive measures were used to a comparable extent in both study arms (see I Appendix B of the full dossier assessment).

Data cut-offs

According to information provided by the company in Module 4 A, 2 data cut-offs are available for the COMMODORE 2 study:

- Data cut-off on 16 November 2022: prespecified primary data cut-off after the last patient had completed the randomized treatment phase
- Data cut-off on 12 March 2024: non-prespecified data cut-off for publication purposes

The company additionally stated that as of 31 May 2023, the 120-day safety update was prepared as part of the approval procedure for the FDA. The present benefit assessment uses the prespecified primary data cut-off of the COMMODORE 2 study. This concurs with the company's approach.

Patient characteristics in COMMODORE 2

Table 8 shows the patient characteristics of the included study.

Table 8: Characteristics of the study population and study/treatment discontinuation – RCT, direct comparison: crovalimab vs. eculizumab (research question 1: high disease activity) (multipage table)

Study **Characteristic** **Category**	**Crovalimab** **N[a] = 134**	**Eculizumab** **N[a] = 69**
COMMODORE 2		
Age [years], mean (SD)	40 (15)	42 (16)
Sex [F/M],%	43/57	49/51
Family origin, n (%)		
Asian	86 (64)	51 (74)
Black or African American	3 (2)	1 (1)
Caucasian	44 (33)	16 (23)
Unknown	1 (< 1)	1 (1)
Time between diagnosis and study start [years], median [min; max]	2.6 [0.0; 48.5]	2.9 [0.0; 31.0]
Patients with a history of PNH-relevant conditions, n (%)		
Aplastic anaemia	52 (39)	26 (38)
Myelodysplastic syndrome	6 (5)	6 (9)
Renal insufficiency	11 (8)	6 (9)
Patients with history of a MAVE, n (%)	20 (15)	10 (15)
PNH clone size (%) at baseline, mean (SD)		
PNH clone size (%) erythrocytes	29.1 (17.4)	43.2 (24.9)
PNH clone size (%) granulocytes	55.2 (26.9)	61.7 (29.5)
PNH clone size (%) monocytes	84.8 (16.1)	88.1 (15.8)
LDH value (x ULN) at baseline, mean (SD)	7.6 (3.4)	7.8 (3.5)
LDH level prior to randomization, n (%)		
≥ 2 to ≤ 4 x ULN[b]	22 (18)	10 (16)
> 4 x ULN[b]	110 (82)	59 (84)
Haemoglobin value (g/L) at baseline, mean (SD)	87.2 (14.1)	99.7 (87.9)
Number of units of pRBC transfused within 6 months prior to randomization, n (%)		
0	33 (25)	17 (25)
> 0 to ≤ 6	67 (50)	34 (49)
> 6	34 (25)	18 (26)
Number of units of pRBC transfused within 12 months prior to randomization, median [min; max]	3.5 [0.0; 43.5]	3 [0.0; 41.0]
PNH-related signs or symptoms in the 3 months prior to screening, n (%)		
Abdominal pain	21 (15.7)	11 (15.9)
Anaemia	108 (80.6)	57 (82.6)
Dysphagia	8 (6.0)	2 (2.9)

Table 8: Characteristics of the study population and study/treatment discontinuation – RCT, direct comparison: crovalimab vs. eculizumab (research question 1: high disease activity) (multipage table)

Study **Characteristic** **Category**	**Crovalimab** **N[a] = 134**	**Eculizumab** **N[a] = 69**
Erectile dysfunction	13 (9.7)	4 (5.8)
Fatigue	112 (83.6)	63 (91.3)
Haemoglobinuria	78 (58.2)	45 (65.2)
MAVE (including thrombosis)	9 (6.7)	5 (7.2)
Dyspnoea	29 (21.6)	14 (20.3)
Treatment discontinuation (randomized treatment phase), n (%)[c]	6 (4.5[d])	1 (1.4[d])
Study discontinuation (total study duration), n (%)	7 (5.2)	2 (2.9)

a. Number of randomized patients who received at least one dose of the respective treatment and for whom at least one valid LDH value was available from the central laboratory, which was determined after the first IV infusion as part of the planned treatment.
b. Discrepancy regarding the specification as a stratification factor: 24 vs. 11 patients are specified for the stratification factor of ≥ 2 to ≤ 4 x ULN, 110 vs. 58 patients for > 4 x ULN.
c. 95.6% vs. 98.6% of patients completed treatment as planned.
d. Institute's calculation.

F: female; LDH: lactate dehydrogenase; M: male; MAVE: major adverse vascular event; max: maximum; min: minimum; 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

The patient characteristics in the COMMODORE 2 study were largely comparable between the study arms.

The mean age of the patients was 41 years, and the majority (approximately 68%) were of Asian family origin. Patients were diagnosed with PNH a median of 2.6 or 2.9 years ago, and around 15% had already experienced a MAVE since their diagnosis. Almost 40% had a history of aplastic anaemia. As these patients were eligible for inclusion in the study and thus for treatment with C5 inhibitors, it is assumed that stem cell transplantation was not indicated in these cases and that PNH requiring treatment was the main focus. This patient group is therefore covered by the therapeutic indication of crovalimab.

The mean LDH value at baseline was 7.7 times higher than the ULN. The mean haemoglobin value was 87 g/L and 100 g/L respectively. Half of the patients had received 1 to 6 units of pRBC transfusion within 6 months prior to randomization, and a further 25% had received more than 6 units. Within the last 12 months, the median number of units of pRBC transfused was 3.5 and 3 respectively.

During the randomized treatment phase, 6 patients versus 1 patient (4.5% versus 1.4%) discontinued treatment. For the study discontinuations, data are only available for the entire duration of the study including the extension phase; the total number of discontinuations is 7 and 2 patients (5.2% versus 2.9%).

Risk of bias across outcomes (study level)

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

Table 9: Risk of bias across outcomes (study level) – RCT, direct comparison: crovalimab 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			
COMMODORE 2	Yes	Yes	No	No	Yes	Yes	Low
RCT: randomized controlled trial							

The risk of bias across outcomes was rated as low for the COMMODORE 2 study. Limitations resulting from the open-label study design are described in Section I 3.2.2 under outcome-specific risk of bias.

Transferability of the study results to the German health care context

The company described in Module 4 A of the dossier that the results of COMMODORE 2 and COMMODORE 1 are transferable to the German health care context. To justify this, it stated on the one hand that half of the study centres were in European countries and that the proportion of Caucasian study participants in both studies was representative at 29.6% and 73.3% respectively. On the other, it stated that the mean age in the 2 studies was comparable to the mean age of disease onset according to the analysis of the German population of the International PNH Registry and that the sex ratio corresponded to the distribution in the German patient population.

According to the company, the comparator eculizumab corresponds to the PNH therapy established in Germany for haemolytic, symptomatic patients according to the guideline recommendation. The company added that the administration of the supportive therapies recommended in the guideline was permitted and consistently implemented in the COMMODORE studies.

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

I 3.2 Results on added benefit

I 3.2.1 Outcomes included

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

- Mortality
  - all-cause mortality
- Morbidity
  - transfusion avoidance
  - MAVE
  - fatigue, measured with the FACIT-Fatigue
  - health status, measured with the EQ-5D VAS
  - symptoms, measured with the PGIS
- Health-related quality of life
- Side effects
  - SAEs
  - severe AEs (CTCAE grade ≥ 3)
  - discontinuation due to AEs
  - type III hypersensitivity reactions (Preferred Term [PT] type III immune complex mediated reaction, AEs)
  - injection site reactions
  - infusion related reactions
  - infections (System Organ Class [SOC] infections and infestations, AEs)
  - other specific AEs, if any

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

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

Table 10: Matrix of outcomes – RCT, direct comparison: crovalimab vs. eculizumab (research question 1: high disease activity)

Study	Outcomes														
	All-cause mortality[a]	Transfusion avoidance[b]	MAVE[c]	Fatigue (FACIT-Fatigue)	Health status (EQ-5D VAS)	Symptoms (PGIS)	Health-related quality of life	SAEs	Severe AEs[d]	Discontinuation due to AEs	Type III hypersensitivity reactions[e]	Injection site reactions	Infusion related reactions	Infections[f]	Other specific AEs
COMMODORE 2	Y	Y	Y	Y	Y	No[g]	No[g]	Y	Y	Y	Y	No[g]	No[g]	Y	No[h]

a. The results on all-cause mortality are based on the information on fatal AEs.
b. Defined as the proportion of patients who were pRBC transfusion-free from baseline through Week 25 and did not require transfusion per protocol-specified guidelines.
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 thrombosis, gangrene (non-traumatic, non-diabetic), amputation (non-traumatic, non-diabetic), dermal thrombosis, other.
d. Severe AEs are operationalized as CTCAE grade ≥ 3 events.
e. Operationalized as AEs with the MedDRA PT type III immune complex mediated reaction.
f. Operationalized as AEs of the MedDRA SOC infections and infestations.
g. No suitable data available; for the reasoning, see Section I 3.2.1 of the present benefit assessment.
h. No further specific AEs were identified based on the AEs occurring in the relevant study.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; FACIT-Fatigue: Functional Assessment of Chronic Illness Therapy-Fatigue; Hb: haemoglobin; MAVE: major adverse vascular event; MedDRA: Medical Dictionary for Regulatory Activities; PGIS: Patient Global Impression of Severity; PNH: paroxysmal nocturnal haemoglobinuria; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class; VAS: visual analogue scale; Y: yes

Notes on included outcomes

The COMMODORE 2 study described here is relevant for research question 1. Besides, the COMMODORE 1 study is relevant for research question 2 of the present benefit assessment presented in Section I 4. As the selection and operationalization of the outcomes are largely identical, they are described together for both studies below, where applicable. Factors that also apply to the COMMODORE 1 study are designated as such.

Transfusion avoidance

In the COMMODORE 2 study (as in COMMODORE 1), transfusion avoidance was defined as the proportion of patients who were pRBC transfusion-free from baseline through Week 25 and did not require transfusion per protocol-specified guidelines. A pRBC transfusion was

given in the studies if a patient had an Hb value of ≤ 9 g/dL with symptoms or signs of sufficient severity to warrant a transfusion at the investigator's discretion. Typical symptoms of anaemia justifying transfusion included angina pectoris, faint, drowsiness, confusion, severe or worsening dyspnoea, severe or worsening fatigue, stroke, TIA, or new or worsening heart failure. Patients with an Hb value ≤ 7 g/dL were given a pRBC transfusion regardless of clinical signs or symptoms. This procedure is largely in line with the recommendations of the cross-sectional guideline by the German Medical Association on therapy with blood components and plasma derivatives [11].

In Module 4 A of the dossier, the company justified the patient relevance of the outcome with the risks for late complications from pRBC administration, based on the 2021 haemovigilance report by the Paul Ehrlich Institute and the publications by Gilliss 2011 and Müller 2015 [15-17]:

- occurrence of acute allergic transfusion reactions, most of which of grade III/IV severity, which could lead to death in individual cases
- occurrence of haemolytic transfusion reactions caused by antibodies directed against erythrocytes, with associated symptoms such as fever, shortage of breath, hypotension, tachycardia, and pain in the kidney area
- occurrence of transfusion-related volume overload (hypervolaemia), which can cause shortness of breath, tachycardia, hypertension, transfusion-related dyspnoea and transfusion haemosiderosis
- infections due to bacterial or viral contamination of the pRBC

The company's argument that late complications can be prevented by avoiding transfusions is understandable, and transfusion avoidance is considered patient relevant.

Symptoms, recorded using the PGIS

The PGIS is a single-item scale that patients use to assess the severity of PNH-associated symptoms within the last 14 days. In the COMMODORE 2 study, the PGIS was only recorded at baseline and then again at Week 33. At this point, the randomized study phase had already been completed for 8 weeks, and crovalimab treatment had been possible for patients from the comparator arm since then. The PGIS results are therefore unusable for the benefit assessment. The outcome was not recorded in the COMMODORE 1 study.

Infusion related reactions

According to the company's Module 4 A, infusion related reactions were presented as selected AE and it is described that the definition/recording in the electronic documentation form was carried out at the discretion of the investigator.

The protocols of COMMODORE 2 and COMMODORE 1 describe that infusion related reactions were defined as AEs that occurred within 24 hours after administration of the study medication and which, in the opinion of the investigator, were related to the drug administration. The study documents show that primarily the diagnosis of an infusion related reaction (e.g. via the PTs “infusion related reaction” or “anaphylactic reaction”) and not the underlying individual symptoms were to be recorded. However, the underlying symptoms had to be recorded in a separate documentation form in addition to the diagnosis.

The aforementioned operationalization for infusion related reactions is not used for the benefit assessment for the reasons explained below.

In the intervention arm, the first dose of crovalimab is administered intravenously and the subsequent doses subcutaneously, while eculizumab in the comparator arm is administered only intravenously. However, based on the information in the study documents, it remains unclear whether infusion related reactions in COMMODORE 2 and COMMODORE 1 were actually recorded equally in both arms. In the case of the different forms of administration used in the arms, an aggregated analysis of all symptomatic AEs potentially relevant for infusion related reactions would generally be required, regardless of the form of administration, to obtain the necessary comparative data for this outcome for the benefit assessment. Specific AEs that represent infusion related reactions should either be predefined or refer to content-based compilations based on publications or compilations of the Medical Dictionary for Regulatory Activities system (e.g. Standardized Medical Dictionary for Regulatory Activities Query [SMQ]) and be recorded in both study arms. This allows taking these events into account in the benefit assessment even if they occurred in studies comparing subcutaneously and intravenously administered drugs. For this reason, the data presented are not suitable for the benefit assessment.

Another limitation for the interpretation of the results is that the COMMODORE 2 study (as the COMMODORE 1 study) provided no specific criteria (e.g. a predefined PT list) for the investigator assessment of whether an AE was to be classified as infusion related reaction. In certain data constellations, e.g. in the presence of marked effects (see dossier assessment A21-60 [18]), it is nevertheless conceivable to derive greater or lesser harm based on such an operationalization. Such a data constellation is not present in these 2 studies, however.

Overall, the data presented for the outcome of infusion related reactions are therefore not suitable for the benefit assessment.

Furthermore, based on the information in the study documents, it is also likely that the individual symptoms underlying the diagnosis of infusion related reaction were recorded in a separate documentation form as described, but that these were not taken into account in the AE analyses of the treatment emergent adverse events (TEAEs) according to SOC and PT. This

can be seen, for example, in the event numbers for the symptom of headache in the COMMODORE 2 study. These are higher in the analysis of the symptoms for infusion related reactions than shown in the AE analysis of the TEAEs for this PT (18 versus 6 and 11 versus 3). Thus, individual PTs, which frequently occurred as infusion related events, were probably not fully taken into account in the analyses according to SOC and PT. This may complicate the interpretability of the results for common PTs/SOCs, namely for PTs/SOCs that frequently occur infusion related. Thus, the analysis of infusion related reactions only allows a conclusion to be drawn about the AEs assessed by the physicians to be related to an infusion. An additional analysis of all symptomatic AEs (TEAEs including infusion related events) that occurred during the course of the study is missing, but would be necessary. It is not possible to add up both rates, as a patient may have experienced both an infusion related and a non-infusion related event. However, since the event rates for symptoms that led to classification as infusion related reaction mostly only affected individual patients in COMMODORE 2 and COMMODORE 1, the impact on the interpretability of the results on common PTs/SOCs is considered negligible.

Injection site reactions

According to the company's Module 4 A, injection site reactions were presented as selected AE and it is described that the definition/recording in the electronic documentation form was carried out at the discretion of the investigator.

The protocols of COMMODORE 2 and COMMODORE 1 describe that injection site reactions were defined as AEs that occurred within 24 hours after administration of the study medication and which, in the opinion of the investigator, were related to the drug administration. The study documents show that primarily the diagnosis of an injection site reaction (e.g. via the PT "injection site reaction") and not the underlying individual symptoms were to be recorded. However, the underlying symptoms had to be recorded in a separate documentation form in addition to the diagnosis.

The aforementioned operationalization for injection site reactions is not used for the benefit assessment for the same reasons already described above for the operationalization of the outcome of infusion related reactions. This concerns uncertainties as to whether these reactions were recorded equally in both study arms, no adequate operationalization for a comparison of different administration forms and the lack of concrete criteria for a classification as injection site reaction (e.g. predefined PT lists).

Overall, the data presented for the outcome of injection site reactions are therefore not suitable for the benefit assessment.

Furthermore, based on the information in the study documents, it is likely also for injection site reactions that the symptoms underlying the diagnosis were recorded in a separate

documentation form as described, but that these were not taken into account in the AE analyses of the TEAEs according to SOC and PT.

Notes on other outcomes presented by the company

Breakthrough haemolysis, recorded via the occurrence of symptoms in the presence of elevated LDH

The company included the outcome of breakthrough haemolysis in its benefit assessment. In COMMODORE 2 and COMMODORE 1, breakthrough haemolysis was defined as at least one new or worsening symptom or sign of intravascular haemolysis (fatigue, haemoglobinuria, abdominal pain, dyspnoea, anaemia [haemoglobin < 10 g/dL], a MAVE, dysphagia, or erectile dysfunction) in the presence of elevated LDH ≥ 2 x ULN (after prior reduction to ≤ 1.5 x ULN on treatment).

Although the symptoms associated with breakthrough haemolysis are patient relevant, the present operationalization of this outcome links the recording of these symptoms with the presence of elevated LDH. This does not ensure that all symptoms that can occur in the context of breakthrough haemolysis are actually recorded in full, decoupled from the LDH value (see also dossier assessment on ravulizumab [19]). In addition, the symptom of anaemia (haemoglobin < 10 g/dL) included in the operationalization presented by the company, for example, which in the presence of elevated LDH can be assessed as breakthrough haemolysis, is not necessarily patient relevant, as it is based exclusively on the measurement of the haemoglobin value. Noticeable symptoms caused by the anaemia would be patient relevant, however. The outcome is therefore not included in the present benefit assessment. Regardless of this, no statistically significant effects for the outcome were shown in either study.

Scales for measuring health-related quality of life and PNH-related symptoms

European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) functional scales

In COMMODORE 2 and COMMODORE 1, the company used the EORTC QLQ-C30 scales of physical functioning, role functioning and global health status/quality of life to depict health-related quality of life. Further scales, such as the remaining functional scales of emotional functioning, cognitive functioning and social functioning, as well as the symptom scales were not recorded in the studies.

The approach of the company is not appropriate. On the one hand, the validity of the EORTC QLQ-C30 in the present therapeutic indication is unclear. As already described in benefit assessment A19-59 on ravulizumab, there are different assessments in the literature as to whether the EORTC QLQ-C30 reflects health-related quality of life and morbidity of patients in the present therapeutic indication [19-21]. The company presented no further documents

on the validity of the EORTC QLQ-C30 in the therapeutic indication of PNH. Irrespective of this, according to the manual [22] the EORTC questionnaires are generally validated in full with all scales, and must therefore also be recorded and presented in full. According to EORTC specifications, it would also be possible to use and analyse only the functional scales of the EORTC QLQ-C30, as these are validated as a separate questionnaire, EORTC QLQ-F17 [23]. However, in addition to the 3 scales recorded by the company in COMMODORE 2 and COMMODORE 1, this also includes the scales on emotional functioning, cognitive functioning and social functioning. The scales presented by the company therefore do not fully reflect health-related quality of life. They are therefore not used for the present benefit assessment.

EORTC Item List 40 (IL40)

In COMMODORE 2 and COMMODORE 1, the company used a list of items to record disease-specific symptoms, which included several scales from the EORTC Item Library. This is the IL40 item list with 6 scales for the symptoms of dysphagia, chest pain, abdominal pain, dyspnoea, headache, and erectile dysfunction. The company presented the results in Module 4 A of the dossier as “supportive analyses” and did not use them to derive the added benefit. In its dossier, the company did not state whether the scales in the IL40 item list were compiled by the EORTC or whether it compiled them itself from the EORTC Item Library. According to the company, the IL40 item list is used to record PNH-related symptoms.

Neither the EORTC QLQ-C30 questionnaire nor the EORTC QLQ-F17 were fully recorded in the studies, so that the company analysed the item list in isolation. However, this does not comply with the EORTC guideline on the use of item lists. According to the information in the EORTC Item Library User Guidelines, the item lists can be used to support symptom recording with a core questionnaire such as the EORTC QLQ-C30 or the QLQ-F17 and, if necessary, a disease-specific module, if indication-specific symptoms or specific side effects are not sufficiently taken into account in the core modules. Isolated use without the recording of a core questionnaire such as the EORTC QLQ-C30 or the QLQ-F17 is not intended [24]. Furthermore, the users of the Item Library are responsible for compiling and validating the item lists, so it cannot be generally assumed that an item list is valid in a particular therapeutic indication. In the guideline, the EORTC explicitly points out that item selection must be driven by theoretical and empirical evidence and must involve patients and experts. However, the company did not provide any information on the generation and validation of the item list in its dossier. As described above, it also remains unclear whether this is an item list compiled by the EORTC. The IL40 symptom scales are therefore not included in the present benefit assessment.

Health-related quality of life, measured using the Quality of Life Questionnaire-Aplastic Anaemia/Paroxysmal Nocturnal Haemoglobinuria (QLQ-AA/PNH)

In the COMMODORE 2 study, the QLQ-AA/PNH questionnaire was only recorded at baseline and then again at Week 33. At this point, the randomized study phase had already been

completed for 8 weeks, and crovalimab treatment had been possible for patients from the comparator arm since then. The QLQ-AA/PNH results are therefore unusable for the benefit assessment. The outcome was not recorded in the COMMODORE 1 study.

I 3.2.2 Risk of bias

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

Table 11: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: crovalimab vs. eculizumab (research question 1: high disease activity)

Study	Study level	Outcomes														
		All-cause mortality[a]	Transfusion avoidance[b]	MAVE[c]	Fatigue (FACIT-Fatigue)	Health status (EQ-5D VAS)	Symptoms (PGIS)	Health-related quality of life	SAEs	Severe AEs[d]	Discontinuation due to AEs	Type III hypersensitivity reactions[e]	Injection site reactions	Infusion related reactions	Infections[f]	Other specific AEs
COMMODORE 2	L	L	H[g]	L	H[g, h]	H[g, h]	–[i]	–[i]	L	L	H[j]	H[g]	–[i]	–[i]	L	–

a. The results on all-cause mortality are based on the information on fatal AEs.
b. Defined as the proportion of patients who were pRBC transfusion-free from baseline through Week 25 and did not require transfusion per protocol-specified guidelines.
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 thrombosis, gangrene (non-traumatic, non-diabetic), amputation (non-traumatic, non-diabetic), dermal thrombosis, other.
d. Severe AEs are operationalized as CTCAE grade ≥ 3.
e. Operationalized as AEs with the MedDRA PT type III immune complex mediated reaction.
f. Operationalized as AEs of the MedDRA SOC infections and infestations.
g. Lack of blinding in the presence of subjective recording of outcomes.
h. High proportion of patients excluded from the analysis (> 10%).
i. No suitable data available; for the reasoning, see Section I 3.2.1 of the present benefit assessment.
j. Lack of blinding in the presence of subjective decision on treatment discontinuation.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; FACIT-Fatigue: Functional Assessment of Chronic Illness Therapy-Fatigue; H: high; Hb: haemoglobin; L: low; MAVE: major adverse vascular event; MedDRA: Medical Dictionary for Regulatory Activities; PGIS: Patient Global Impression of Severity; PNH: paroxysmal nocturnal haemoglobinuria; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class; VAS: visual analogue scale

The outcome-specific risk of bias was rated as low for the results of the outcomes of all-cause mortality, MAVE, SAEs, severe AEs and infections (AEs).

Due to subjective recording of outcomes in the presence of lack of blinding, the risk of bias was rated as high for the results of the outcomes of transfusion avoidance, fatigue, health status, discontinuation due to AEs, and type III hypersensitivity reactions (AEs). For the patient-reported outcomes of fatigue and health status, there was also a high proportion of patients not included in the analysis (over 10%).

I 3.2.3 Results

Table 12 summarizes the results for the comparison of crovalimab with eculizumab in patients with PNH with high disease activity, characterized by clinical symptoms of haemolysis. Where necessary, IQWiG calculations are provided to supplement the data from the company's dossier. Despite the small sample size, the company used an asymptotic test (Wald test) for the side effect outcomes, but an exact test (convexity, symmetry, z-score [CSZ] test) leads to more valid results and is therefore considered more adequate [25]. Thus, the Institute conducted its own calculations.

Common AEs, SAEs and discontinuations due to AEs are listed in I Appendix E of the full dossier assessment.

Table 12: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: crovalimab vs. eculizumab (research question 1: high disease activity) (multipage table)

Study Outcome category	Crovalimab		Eculizumab		Crovalimab vs. eculizumab
Outcome	**N**	**Patients with event n (%)**	**N**	**Patients with event n (%)**	**RR [95% CI]; p-value**
COMMODORE 2					
Mortality					
All-cause mortality[a]	134	1 (0.7)	69	1 (1.4)	0.51 [0.03; 8.11]; 0.736[b]
Morbidity					
Transfusion avoidance[c]	134	88 (65.7)	69	47 (68.1)	0.96 [0.79; 1.18]; 0.790[d]
MAVE[e]	134	0 (0.0)	69	1 (1.4)	0.17 [0.01; 4.19]; 0.173[d]
Fatigue (FACIT-Fatigue – improvement[f])	128	55 (43.0)	66	23 (34.8)	1.23 [0.84; 1.81]; 0.322[d]
Health status (EQ-5D VAS – improvement[g])	127	31 (24.4)	68	17 (25.0)	0.98 [0.58; 1.63]; 0.964[d]
Symptoms (PGIS)	No suitable data[h]				
Health-related quality of life	No suitable data[h]				
Side effects					
AEs (supplementary information)	135	105 (77.8)	69	55 (79.7)	–
SAEs	135	14 (10.4)	69	9 (13.0)	0.80 [0.36; 1.74]; 0.615[i]
Severe AEs[j]	135	24 (17.8)	69	17 (24.6)	0.72 [0.42; 1.25]; 0.309[i]
Discontinuation due to AEs	135	1 (0.7)	69	1 (1.4)	0.51 [0.03; 8.05]; 0.736[i]
Type III hypersensitivity reaction[k] (type III immune complex mediated reaction [PT, AEs])	135	0 (0.0)	69	0 (0.0)	–
Injection site reactions[l]	No suitable data[h]				
Infusion related reactions[l]	No suitable data[h]				
Infections[l, m] (infections and infestations [SOC, AEs])	135	32 (23.7)	69	25 (36.2)	0.65 [0.42; 1.01]; 0.061[i]

Table 12: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: crovalimab vs. eculizumab (research question 1: high disease activity) (multipage table)

Study Outcome category Outcome	Crovalimab N	Crovalimab Patients with event n (%)	Eculizumab N	Eculizumab Patients with event n (%)	Crovalimab vs. eculizumab RR [95% CI]; p-value
a. The results on all-cause mortality are based on the information on fatal AEs. In the crovalimab arm, another patient died on Study Day 2. According to the company, the reason was a myocardial infarction that had already occurred before the administration of crovalimab. As no data on the LDH value was recorded for the patient after the start of the study, she is not included in the primary analysis population. b. Institute's calculation of RR, CI (asymptotic) and p-value (unconditional exact test, CSZ method according to [25]); since the observation periods in both treatment arms are comparable, the RR is used for the benefit assessment. c. Defined as the proportion of patients who were pRBC transfusion-free from baseline through Week 25 and did not require transfusion per protocol-specified guidelines. d. Institute's calculation of RR, CI (asymptotic) and p-value (unconditional exact test, CSZ method according to [25]); the company presented p-values for the effect measure of weighted risk reduction; these are not relevant for the benefit assessment. e. 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, 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. f. A score increase by ≥ 8 points from baseline to Week 25 is considered a clinically relevant improvement (scale range: 0 to 52). g. A score increase by ≥ 15 points from baseline to Week 25 is considered a clinically relevant improvement (scale range: 0 to 100). h. See Section I 3.2.1 of the present dossier assessment for the reasoning. i. Institute's calculations, p-value unconditional exact test (CSZ method according to [25]). j. Operationalized as CTCAE grade ≥ 3. k. Predefined as AE of special interest (AESI) according to the study protocol. l. Presented in the study as "selected AE". m. Including no cases of meningococcal meningitis. AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; FACIT-Fatigue: Functional Assessment of Chronic Illness Therapy-Fatigue; Hb: haemoglobin; LDH: lactate dehydrogenase; MAVE: major adverse vascular event; n: number of patients with (at least one) event; N: number of analysed patients; PGIS: Patient Global Impression of Severity; PNH: paroxysmal nocturnal haemoglobinuria; PT: Preferred Term; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SOC: System Organ Class; ULN: upper limit of normal; VAS: visual analogue scale					

Based on the available information, at most indications, e.g. of an added benefit, can be determined for the outcomes of all-cause mortality, MAVE, SAEs, severe AEs, and infections (AEs); and, due to the high risk of bias, at most hints for the outcomes of transfusion avoidance, fatigue, health status, discontinuation due to AEs, and type III hypersensitivity reactions (AEs).

Mortality

All-cause mortality

The results on all-cause mortality are based on data on fatal AEs. No statistically significant difference between treatment groups was found for the outcome of all-cause mortality. There is no hint of an added benefit of crovalimab in comparison with eculizumab; an added benefit is therefore not proven.

Morbidity

Transfusion avoidance

No statistically significant difference between treatment groups was found for the outcome of transfusion avoidance. There is no hint of an added benefit of crovalimab in comparison with eculizumab; an added benefit is therefore not proven.

MAVE

No statistically significant difference between treatment groups was found for the outcome of MAVE. There is no hint of an added benefit of crovalimab in comparison with eculizumab; an added benefit is therefore not proven.

Fatigue (recorded using the FACIT-Fatigue)

No statistically significant difference between treatment groups was found for the outcome of fatigue (recorded using the FACIT-Fatigue). There is no hint of an added benefit of crovalimab in comparison with eculizumab; an added benefit is therefore not proven.

Health status (recorded using the EQ-5D VAS)

No statistically significant difference between treatment groups was found for the outcome of health status (recorded using the EQ-5D VAS). There is no hint of an added benefit of crovalimab in comparison with eculizumab; an added benefit is therefore not proven.

Symptoms (recorded using PGIS)

No suitable data are available for the outcome of symptoms (recorded using PGIS) (see Section I 3.2.1 for reasons). There is no hint of an added benefit of crovalimab in comparison with eculizumab; an added benefit is therefore not proven.

Health-related quality of life

No suitable data are available for the outcome of health-related quality of life (see Section I 3.2.1 for reasons). There is no hint of an added benefit of crovalimab in comparison with eculizumab; an added benefit is therefore not proven.

Side effects

SAEs

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

Severe AEs

No statistically significant difference between treatment groups was shown for the outcome of severe AEs. There is no hint of greater or lesser harm from crovalimab in comparison with eculizumab; greater or lesser harm is therefore not proven.

Discontinuation due to AEs

No statistically significant difference was found between treatment groups for the outcome of discontinuation due to AEs. There is no hint of greater or lesser harm from crovalimab in comparison with eculizumab; greater or lesser harm is therefore not proven.

Specific AEs

Type III hypersensitivity reactions (AEs)

No events occurred in either treatment group for the outcome of type III hypersensitivity reaction (AEs). There is no hint of greater or lesser harm from crovalimab in comparison with eculizumab; greater or lesser harm is therefore not proven.

Injection site reactions and infusion related reactions

No suitable data are available for the specific AEs of injection site reactions and infusion related reactions (see Section I 3.2.1 for reasons). In each case, there is no hint of greater or lesser harm from crovalimab in comparison with eculizumab; greater or lesser harm is therefore not proven.

Infections (AEs)

No statistically significant difference between treatment groups was found for the outcome of infections (AEs). There is no hint of greater or lesser harm from crovalimab in comparison with eculizumab; greater or lesser harm is therefore not proven.

I 3.2.4 Subgroups and other effect modifiers

The following subgroup characteristics are taken into account in the present benefit assessment:

- sex (male versus female)
- age (< 65 years versus ≥ 65 years)

- pRBC transfusions within 6 months prior to randomization (0 units versus > 0 to ≤ 6 units versus > 6 units)

The aforementioned subgroup analyses were predefined in the COMMODORE 2 study for the coprimary outcomes of transfusion avoidance and haemolysis control as well as for the outcome of change in LDH levels until Week 25. The characteristic of pRBC transfusions within 6 months prior to randomization was also a stratification factor for randomization. For the characteristic of age, an additional subgroup < 18 years was originally planned in the study design. However, since only 2 patients from this age group were included in the randomized study arms, the company assigned them to the subgroup < 65 years.

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

In accordance with the described methods, no relevant effect modification was identified for the outcomes for which suitable data are available.

I 3.3 Probability and extent of added benefit

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

I 3.3.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level is estimated from the results presented in Section I 3.2 (see Table 13).

Table 13: Extent of added benefit at outcome level: crovalimab vs. eculizumab (research question 1: high disease activity) (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Crovalimab vs. eculizumab** **Proportion of events (%)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
All-cause mortality	0.7 vs. 1.4 RR: 0.51 [0.03; 8.11]; p = 0.736	Lesser/added benefit not proven
Morbidity		
Transfusion avoidance	65.7 vs. 68.1 RR: 0.96 [0.79; 1.18]; p = 0.790	Lesser/added benefit not proven
MAVE	0 vs. 1.4 RR: 0.17 [0.01; 4.19]; p = 0.173	Lesser/added benefit not proven
Fatigue (FACIT-Fatigue – improvement)	43.0 vs. 34.8 RR: 1.23 [0.84; 1.81]; p = 0.322	Lesser/added benefit not proven
Health status (EQ-5D VAS – improvement)	24.4 vs. 25.0 RR: 0.98 [0.58; 1.63]; p = 0.964	Lesser/added benefit not proven
Symptoms (PGIS)	No suitable data	Lesser/added benefit not proven
Health-related quality of life	No suitable data	Lesser/added benefit not proven
Side effects		
SAEs	10.4 vs. 13.0 RR: 0.80 [0.36; 1.74]; p = 0.615	Greater/lesser harm not proven
Severe AEs	17.8 vs. 24.6 RR: 0.72 [0.42; 1.25]; p = 0.309	Greater/lesser harm not proven
Discontinuation due to AEs	0.7 vs. 1.4 RR: 0.51 [0.03; 8.05]; p = 0.736	Greater/lesser harm not proven
Type III hypersensitivity reactions (AEs)	0 vs. 0 RR: –[c]	Greater/lesser harm not proven
Injection site reactions	No suitable data	Greater/lesser harm not proven
Infusion related reactions	No suitable data	Greater/lesser harm not proven
Infections (AEs)	23.7 vs. 36.2 RR: 0.65 [0.42; 1.01]; p = 0.061	Greater/lesser harm not proven

Table 13: Extent of added benefit at outcome level: crovalimab vs. eculizumab (research question 1: high disease activity) (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Crovalimab vs. eculizumab** **Proportion of events (%)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
a. Probability provided if there is a statistically significant and relevant effect. b. Depending on the outcome category, estimations of effect size are made with different limits based on the upper limit of the confidence interval (CI_u). c. An effect estimation (including confidence interval and p-value) was not carried out as no events occurred. AE: adverse event; CI: confidence interval; CI_u: upper limit of the confidence interval; FACIT-Fatigue: Functional Assessment of Chronic Illness Therapy-Fatigue; MAVE: major adverse vascular event; PGIS: Patient Global Impression of Severity; RR: relative risk; SAE: serious adverse event; VAS: visual analogue scale		

I 3.3.2 Overall conclusion on added benefit

Table 14 summarizes the results taken into account in the overall conclusion on the extent of added benefit.

Table 14: Positive and negative effects from the assessment of crovalimab in comparison with eculizumab (research question 1: high disease activity)

Positive effects	**Negative effects**
–	–
No suitable data are available on the outcomes of symptoms (measured using the PGIS), health-related quality of life, and the specific AEs of injection site reactions and infusion related reactions.	
AE: adverse event; PGIS: Patient Global Impression of Severity	

The COMMODORE 2 study showed neither positive nor negative effects for crovalimab in comparison with eculizumab. In summary, there is no hint of an added benefit of crovalimab versus eculizumab for patients with PNH with high disease activity, characterized by clinical symptoms of haemolysis. An added benefit is therefore not proven.

This concurs with the assessment of the company, which also derived no added benefit across research questions.

I 4 Research question 2: clinically stable after at least 6 months of treatment with a C5 inhibitor

I 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 list on crovalimab (status: 1 July 2024)
- bibliographical literature search on crovalimab (last search on 1 July 2024)
- search in trial registries/trial results databases for studies on crovalimab (last search on 1 July 2024)
- search on the G-BA website for crovalimab (last search on 1 July 2024)

To check the completeness of the study pool:

- search in trial registries for studies on crovalimab (last search on 30 September 2024); for search strategies, see I Appendix A of the full dossier assessment

The check did not identify any additional relevant study.

I 4.1.1 Studies included

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

Table 15: Study pool – RCT, direct comparison: crovalimab vs. eculizumab (research question 2: clinically stable after at least 6 months of treatment with a C5 inhibitor)

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication (yes/no [citation])
COMMODORE 1	Yes	Yes	No	Yes [26]	Yes [27-29]	Yes [30]

a. Study sponsored by the company.
b. Citation of the trial registry entries and, if available, of the reports on study design and/or results listed in the trial registries.

CSR: clinical study report; RCT: randomized controlled trial

The study pool for research question 2 of the present benefit assessment consists of the COMMODORE 1 study.

The company did not investigate 2 separate research questions. It presented the results of each of the studies COMMODORE 2 (included in the present benefit assessment for research question 1, see Section I 3) and COMMODORE 1, and derived a conclusion on the added benefit for the total population of patients with PNH on the basis of both studies, without differentiating between the patient populations.

I 4.1.2 Study characteristics

Table 16 and Table 17 describe the study used for the benefit assessment.

Table 16: Characteristics of the included study – RCT, direct comparison: crovalimab vs. eculizumab (research question 2: clinically stable after at least 6 months of treatment with a C5 inhibitor) (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
COMMODORE 1	RCT, open-label, parallel	Adult patients ≥ 40 kg weight with PNH[b], ▪ treated with eculizumab for ≥ 6 months in compliance with the approval, and ▪ clinically stable (LDH ≤ 1.5 x ULN) at screening	Crovalimab (N = 45) eculizumab (N = 44) Additionally: non-randomized crovalimab arm[c] with patients ▪ < 18 years with previous eculizumab therapy (N = 1) ▪ ≥ 18 years with previous ravulizumab therapy (N = 21) ▪ ≥ 18 years with previous eculizumab therapy at a higher dose than specified in the SPC (N = 10) ▪ ≥ 18 years with C5 SNP and poorly controlled haemolysis under eculizumab (N = 6) ▪ ≥ 18 years with previous eculizumab therapy in compliance with the SPC for ≥ 6 months and LDH ≤ 1.5 x ULN (N: ND)[d]	Screening: up to 4 weeks treatment: ▪ randomized for 24 weeks, then possible transition to open-label extension phase with crovalimab treatment of all patients for a maximum of 5 years ▪ non-randomized crovalimab arm: 24 weeks, then further treatment possible for a maximum of 5 years Follow-up: 46 weeks for crovalimab[e], 10 weeks for eculizumab	70 centres in Belgium, Brazil, Canada, Czech Republic, Germany, Estonia, France, Greece, Hong Kong, Hungary, Ireland, Italy, Japan, Netherlands, Poland, Portugal, Saudi Arabia, Singapore, South Korea, Spain, Sweden, Taiwan, Turkey, United Kingdom, United States 9/2020 – ongoing Data cut-offs: 16 November 2022 (primary analysis) Day-120 safety update from 31 May 2023 for the FDA 12 March 2024 (not prespecified)	Primary[f]: ▪ originally: LDH level until Week 25 ▪ changed: AEs Secondary: morbidity

Table 16: Characteristics of the included study – RCT, direct comparison: crovalimab vs. eculizumab (research question 2: clinically stable after at least 6 months of treatment with a C5 inhibitor) (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
a. Primary outcomes include information without taking into account the relevance for this benefit assessment. Secondary outcomes include only information on relevant available outcomes for this benefit assessment. b. Diagnosed by flow cytometry, with clone size ≥ 10% (granulocytes or monocytes). c. The arm is irrelevant for the assessment and is disregarded in the following tables. d. The cohort of patients ≥ 18 years with previous eculizumab therapy in compliance with the SPC for ≥ 24 weeks and LDH ≤ 1.5 x ULN was introduced with the stop of randomization on 2 November 2022. e. The original follow-up period for patients treated with crovalimab was 24 weeks; with protocol version 6, a telephone visit after 46 weeks was added to this follow-up period. f. The original primary outcome was changed to safety and tolerability with Amendment 6 to the study protocol, as the necessary sample size was not reached due to insufficient recruitment, and recruitment was subsequently stopped on 2 November 2022. AE: adverse event; FDA: Food and Drug Administration; LDH: lactate dehydrogenase; MAVE: major adverse vascular event; N: number of randomized patients; PNH: paroxysmal nocturnal haemoglobinuria; SNP: single nucleotide polymorphism; RCT: randomized controlled trial; ULN: upper limit of normal						

Table 17: Characteristics of the intervention – RCT, direct comparison: crovalimab vs. eculizumab (research question 2: clinically stable after at least 6 months of treatment with a C5 inhibitor) (multipage table)

Study	Intervention	Comparison
COMMODORE 1	Crovalimab, based on weight: ≥ 40 kg to < 100 kg: Initial dose: ▪ Week 1: ▫ Day 1: 1000 mg IV ▫ Day 2: 340 mg SC ▪ Weeks 2, 3 and 4: 340 mg SC, once a week Maintenance dose: ▪ From Week 5: 680 mg SC, every 4 weeks[b] ≥ 100 kg: Initial dose: ▪ Week 1: ▫ Day 1: 1500 mg IV ▫ Day 2: 340 mg SC ▪ Weeks 2, 3 and 4: 340 mg SC, once a week Maintenance dose: ▪ From Week 5: 1020 mg SC, every 4 weeks	Eculizumab Maintenance dose: 900 mg IV, every 2 weeks[a]
	Dose adjustment: ▪ in case of weight changes by ≥ 10% from the last visit if the weight is above or below the threshold of 100 kg ▪ increase in maintenance dose permitted in case of at least 2 intravascular haemolysis events within 24 weeks, or persistent intravascular haemolysis with LDH ≥ 2 x ULN on 3 consecutive measurements for ≥ 4 weeks, provided at least one symptom of intravascular haemolysis was present (in each case without identifiable trigger) ▪ additional crovalimab doses as rescue therapy in case of signs or symptoms of PNH possible at the discretion of the investigator	▪ dose adjustment not permitted during the course of the study

Table 17: Characteristics of the intervention – RCT, direct comparison: crovalimab vs. eculizumab (research question 2: clinically stable after at least 6 months of treatment with a C5 inhibitor) (multipage table)

Study	Intervention	Comparison
	Pretreatment Required: ▪ eculizumab in compliance with the dosage recommended in the SPC for ≥ 6 months before Day 1 ▪ vaccination against *Neisseria meningitidis* serotypes A, C, W and Y < 3 years before study start, against serotype B in accordance with local guidelines; if vaccinated < 2 weeks before study start, additional antibiotic prophylaxis should be given ▪ vaccination against *Haemophilus influenzae* type B and *Streptococcus pneumoniae* according to national recommendations; if vaccinated < 2 weeks before study start or after first dose of study drug, additional antibiotic prophylaxis should be given Allowed: ▪ if haemoglobin ≤ 7 g/dL, or > 7 and ≤ 9 g/dL with concomitant symptoms of anaemia: pRBC transfusion could be given within 5 days before the first dose of study drug to allow patients to meet the haemoglobin eligibility criterion ▪ supportive therapy e.g. with immunosuppressants, corticosteroids, iron supplements, anticoagulants, erythrocyte-stimulating agents in a stable dose for ≥ 28 days before the first dose of study drug Not allowed: ▪ allogeneic stem cell transplantation at any time prior to study inclusion **Concomitant treatment** Allowed: ▪ immunosuppressants, corticosteroids, iron supplementation, folic acid; other concomitant therapies possible, but require documentation ▪ medication for the treatment of infusion related symptoms (acetaminophen, ibuprofen, diphenhydramine, H2 receptor antagonists, etc.) ▪ The investigators were required to provide supportive treatment to the patients in accordance with local standards of care, insofar as this was indicated. Not allowed: ▪ other complement inhibitors, investigational treatments	

a. Information according to Module 5 of the dossier; in contrast, an induction period of 4 weeks is indicated in some places in Module 4 A. However, this does not seem plausible in the present situation.
b. Self-administration of SC injections was permitted starting at Week 9, after confirmation of proficiency by the study staff.

IV: intravenous; LDH: lactate dehydrogenase; PNH: paroxysmal nocturnal haemoglobinuria; pRBC: packed red blood cells; RCT: randomized controlled trial; SC: subcutaneous; ULN: upper limit of normal

Description of the COMMODORE 1 study

COMMODORE 1 is a randomized, open-label, multicentre, active-controlled study. The original objective of the study was to prove the non-inferiority of crovalimab compared with eculizumab. For this purpose, approximately 200 patients were to be included in the randomized study arms. However, randomization was stopped prematurely due to the slow

recruitment of patients, which meant that only around 45% (N = 89) of the study's recruitment target was achieved. The primary analysis then took place in parallel with the COMMODORE 2 study on 16 November 2022. Due to the smaller sample size than originally planned, there was no non-inferiority testing and all primary and secondary efficacy outcomes were only exploratory.

The study included patients with PNH who had received eculizumab for at least 6 months and were clinically stable at baseline. Stable disease was defined by an LDH value that did not exceed the ULN by more than 1.5 times at baseline and no MAVE in the past 6 months before enrolment. An exclusion criterion for participation in the study was a haemoglobin value ≤ 7 g/dL, or between > 7 g/dL and ≤ 9 g/dL with concurrent signs and symptoms of anaemia (angina pectoris, faint, dizziness, confusion, severe or worsening dyspnoea, severe or worsening fatigue, stroke, TIA, or new onset or worsening heart failure) within 5 days prior to the first dose of study medication. In these cases, however, a pRBC transfusion could be given to allow patients to meet the haemoglobin eligibility criterion. According to the SPCs, administration of crovalimab and eculizumab is not linked to a haemoglobin value requirement [8,9]. The procedure in the study seems appropriate, as the guideline recommends transfusions as a supportive measure for the treatment of haemolysis in PNH [10]. In addition, the procedure in the study essentially corresponds to the criteria specified for pRBC in the current cross-sectional guideline on therapy with blood components and plasma derivatives [11]. However, as the information in the dossier refers to a period of 12 months before randomization, it is unclear how many patients received a transfusion shortly before the start of the study.

The COMMODORE 1 study has 3 study arms, in which a total of 127 patients were included until randomization was discontinued. In 2 of these arms, adult patients with a weight of 40 kg and above were randomly allocated in a 1:1 ratio to treatment switch to crovalimab (N = 45) or continuation of ongoing treatment with eculizumab (N = 44). Randomization was stratified according to pRBC transfusion within 12 months prior to randomization (yes versus no). Duration of the randomized study phase was 24 weeks. The patients could then participate in an extension phase, where all study participants received only crovalimab. The results of this 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.

The third study arm consists of several patient cohorts who were treated with crovalimab in the study. These patients were not randomized, as this study arm was intended as a descriptive analysis arm. The study arm includes one patient under 18 years of age, patients with ravulizumab pretreatment, with eculizumab treatment at a higher dose than recommended in the SPC, with C5 single nucleotide polymorphism (SNP) and poorly

controlled haemolysis under eculizumab, as well as other patients with previous eculizumab therapy in compliance with the SPC for ≥ 24 weeks and LDH ≤ 1.5 times ULN; the latter could be included in this cohort after the end of randomization. As there is no randomized comparison with the ACT, and some of the patient groups included here are not covered by the therapeutic indication, this study arm is no longer presented below.

Only adult patients were included in the randomized study arms, meaning that there is no randomized comparison of crovalimab with eculizumab for patients under the age of 18 years. The company presented no additional comparative data for this age group, so that an assessment of the added benefit of crovalimab for this patient group is not possible. Furthermore, no patients who had been previously treated with ravulizumab were included in the randomized study arms.

Treatment of the patients in both study arms was conducted according to the regimen described in Table 17. The dosage of crovalimab and eculizumab largely corresponded to the specifications in the respective SPC [8,9]. However, it should be noted that there was an option for weight-independent dose escalation and administration of additional single doses as rescue therapy in the crovalimab arm, which is not provided for in the SPC of crovalimab. In the eculizumab arm, however, no dose adjustment was permitted; according to the SPC for eculizumab, there is the option of shortening the dosing interval by 2 days if signs and symptoms of intravascular haemolysis occur. However, it can be inferred from the information in the study documents that a dose increase or rescue therapy in the crovalimab arm only took place in individual cases. It is not clear from the dossier for how many patients a shortening of the dosing interval in the eculizumab arm might have been appropriate. A total of 5 out of 42 patients (11.9%) in the eculizumab arm had breakthrough haemolysis during the course of the study. In the 2 phase 3 studies on ravulizumab, about half of all patients with breakthrough haemolysis under eculizumab treatment had an increased concentration of free C5 at the end of the dosing interval, which was due to insufficient concentrations of eculizumab and thus insufficient C5 inhibition by eculizumab [12]. It is therefore unclear for how many of the patients with breakthrough haemolysis in the eculizumab arm an adjustment of the dosing interval would actually have been an option. Therefore, the different procedures in the study arms have no consequences for the benefit assessment of crovalimab.

In the COMMODORE 1 study, the LDH value at Week 25 was originally planned as the primary outcome. After the premature end of recruitment (see above), the primary outcome was changed to AEs. Patient-relevant secondary outcomes were recorded in the outcome category of morbidity.

Definition of clinically stable disease under treatment with eculizumab

In the COMMODORE 1 study, stable disease was defined by an LDH value that did not exceed the ULN by more than 1.5 times at baseline and no MAVE in the past 6 months before enrolment. Patients with haemoglobin values ≤ 7 g/dL, or between > 7 g/dL and ≤ 9 g/dL with concurrent signs and symptoms of anaemia (see above) were excluded from the study. It can be assumed that the criteria applied in the COMMODORE 1 study are generally suitable for including a predominantly clinically stable patient population. However, it is not clear from the information provided in the dossier how many patients had PNH symptoms at baseline, but it can be concluded from the baseline values of the patient-reported symptom questionnaires that at least some of the patients had a symptom burden. However, as treatment with C5 inhibitors cannot cure PNH, it is not to be expected that patients with stable disease under prior eculizumab treatment were symptom-free. It should be noted, however, that approximately 23% of patients in the COMMODORE 1 study had received transfusions in the year prior to the start of the study. It is therefore not possible to fully assess whether these patients were actually stable on eculizumab. However, since the information relates to the past 12 months (and not just the required minimum treatment duration of 6 months with eculizumab), it is assumed that fewer than 20% of the study population had received a transfusion in the past six months before the start of the study. This therefore has no consequence for the present benefit assessment.

Supportive therapy in COMMODORE 1

According to the current PNH guideline, besides pRBC substitution, supportive therapy for PNH includes administration of folic acid and vitamin B12 (if necessary) as well as oral or intravenous substitution of iron in the event of a deficiency, early and consistent antibiotic therapy for bacterial infections, and long-term or lifelong anticoagulation after thrombosis [10].

The study protocol does not impose any restrictions with regard to concomitant supportive medication. On the contrary, the investigators were required to provide supportive treatment to the patients in accordance with local standards of care, insofar as they considered it indicated. The documentation of the concomitant medication shows that supportive measures were used to a comparable extent in both study arms (see I Appendix B of the full dossier assessment).

Study course and data cut-offs

As mentioned above, randomization for the COMMODORE 1 study was stopped prematurely on 2 November 2022 due to slow recruitment. The sample size required to fulfil the study objective of demonstrating non-inferiority of crovalimab versus eculizumab was not achieved. The COMMODORE 1 study was therefore unable to prove the non-inferiority of crovalimab. On the one hand, in the course of this change, protocol Amendment 6 of 28 September 2022

brought forward the primary data cut-off to 16 November 2022 to synchronize it with the primary data cut-off of the COMMODORE 2 study. On the other hand, all efficacy outcomes were converted to exploratory outcomes, while tolerability became the new primary outcome.

According to information provided by the company in Module 4 A, 2 data cut-offs and an analysis for the FDA are available for the COMMODORE 1 study:

- Data cut-off on 16 November 2022: primary data cut-off brought forward due to the early recruitment stop; the primary data cut-off was originally planned after the last patient had completed the randomized treatment phase
- Day 120 safety update for the FDA of 31 May 2023 [31]
- Data cut-off on 12 March 2024: non-prespecified data cut-off for publication purposes

In Module 4 A, the company presented analyses on all outcomes whose time points coincided with the Day 120 safety update for the FDA (31 May 2023). This analysis is a regular part of the approval procedure in the FDA assessment process. The company justified its choice by stating that, due to the described premature recruitment stop at the time of the primary data cut-off, not all patients had yet completed the randomized study phase, which was the case on 31 May 2023. In the described specific data situation, the company's approach is appropriate. In addition, this analysis is more in line with the original study design than the earlier data cut-off date of 16 November 2022. This benefit assessment uses the analysis with data as at 31 May 2023.

Patient characteristics in COMMODORE 1

Table 18 shows the patient characteristics of the included study.

Table 18: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: crovalimab vs. eculizumab (research question 2: clinically stable after at least 6 months of treatment with a C5 inhibitor) (multipage table)

Study **Characteristic** **Category**	**Crovalimab** **N[a] = 44**	**Eculizumab** **N[a] = 42**
COMMODORE 1		
Age [years], mean (SD)	45 (16)	50 (15)
Sex [F/M],%	55/45	50/50
Family origin, n (%)		
Asian	9 (21)	7 (17)
Black or African American	2 (5)	1 (2)
Caucasian	33 (75)	30 (71)
Unknown	0 (0)	4 (10)
Time between diagnosis and study start [years], median [min; max]	6.6 [0.0; 26.8]	10.4 [0.8; 26.5]
Patients with a history of PNH-relevant conditions, n (%)		
Aplastic anaemia	15 (34)	15 (36)
Renal insufficiency	7 (16)	7 (17)
Patients with history of a MAVE, n (%)	10 (23)	9 (21)
PNH clone size (%) at baseline, mean (SD)		
PNH clone size (%) erythrocytes	50.1 (30.9)	54.7 (32.8)
PNH clone size (%) granulocytes	54.9 (28.5)	61.7 (29.7)
PNH clone size (%) monocytes	80.8 (22.1)	86.6 (21.7)
LDH value (x ULN) at baseline, mean (SD)	1.1 (0.3)	1.0 (0.2)
Haemoglobin value (g/L) at baseline, mean (SD)	109.7 (20.0)	107.3 (17.7)
Patients with pRBC transfusion within 12 months prior to randomization, n (%)[b]	10 (23)	10 (24)
Number of units of pRBC transfused within 12 months prior to randomization, n (%)		
0	33 (76.7)	32 (76.2)
> 0 to < 4	4 (9.3)	2 (4.8)
≥ 4 to < 14	4 (9.3)	5 (11.9)
≥ 14	2 (4.7)	3 (7.1)
Number of units of pRBC transfused within 12 months prior to randomization, median [min; max]	0 [0.0; 14.0]	0 [0.0; 24.0]
Treatment discontinuation (randomized treatment phase), n (%)[c, d]	ND	ND
Study discontinuation (total study duration), n (%)[e]	2 (4.5)	1 (2.4)

Table 18: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: crovalimab vs. eculizumab (research question 2: clinically stable after at least 6 months of treatment with a C5 inhibitor) (multipage table)

Study Characteristic Category	Crovalimab N[a] = 44	Eculizumab N[a] = 42
a. Number of randomized patients who received at least one dose of the respective treatment and for whom at least one valid LDH value was available from the central laboratory, which was determined after the first IV infusion as part of the planned treatment. b. Discrepancy regarding the specification as stratification factors: 12 vs. 10 patients with pRBC transfusion are specified for the stratification factor. c. 2.2% vs. 4.5% of randomized patients never started treatment. d. No information for the analysis at the time of the Day 120 safety update (31 May 2023); at the data cut-off on 16 November 2022, 0 vs. 2 (4.8%) patients discontinued treatment before Week 24. Over the entire duration of the study, 2 (4.5) vs. 5 (11.9) patients discontinued treatment until the analysis on 31 May 2023. e. No information is available in the dossier for the randomized study phase. F: female; LDH: lactate dehydrogenase; M: male; MAVE: major adverse vascular event; max: maximum; min: minimum; 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		

The patient characteristics in the COMMODORE 1 study were largely comparable between the study arms. The mean age of the patients was 48 years, and the majority (approximately 73%) were of Caucasian family origin.

Patients were diagnosed with PNH a median of 6.6 or 10.4 years ago, and around 22% had already experienced a MAVE since their diagnosis. About 35% had a history of aplastic anaemia. As all these patients had been pretreated with eculizumab for at least 24 weeks before enrolment, it is assumed that stem cell transplantation at study start was not indicated and that PNH requiring treatment was the main focus. This patient group is therefore covered by the therapeutic indication of crovalimab.

The mean LDH level at baseline was close to the ULN. The mean haemoglobin value was approximately 108 g/L. Around 23% of patients had received at least one pRBC transfusion in the 12 months prior to the start of the study; around 5% and 7% in the respective study arm had received 14 or more units of pRBC.

For the analyses of the Day 120 safety update of 31 May 2023, no information is available on how many patients had discontinued treatment during the randomized study phase. At the same analysis date, the total number of study discontinuations for the entire duration of the study was 2 patients versus 1 patient (4.5% versus 2.4%).

Risk of bias across outcomes (study level)

Table 19 shows the risk of bias across outcomes (risk of bias at study level).

Table 19: Risk of bias across outcomes (study level) – RCT, direct comparison: crovalimab vs. eculizumab (research question 2: clinically stable after at least 6 months of treatment with a C5 inhibitor)

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			
COMMODORE 1	Yes	Yes	No	No	Yes	No[a]	High

a. High proportion of censoring for potentially informative reasons early on in the course of the study (see Kaplan-Meier curves for all-cause mortality, Figure 1 in the full dossier assessment). The reasons for these censorings are not comprehensible, as they are not due to study discontinuations (see Table 18).

RCT: randomized controlled trial

The risk of bias across outcomes was rated as high for the COMMODORE 1 study. The Kaplan-Meier curves for all-cause mortality show that a total of 10 (20.7%) versus 15 (35.7%) patients were censored during the course of the study, i.e. incompletely observed (see I Appendix C of the full dossier assessment). On the one hand, this is an overall high proportion of patients with incomplete observations; on the other, more patients with incomplete observations were already recorded from Week 9 onwards (2 versus 3) than the total number of patients who discontinued the study (see Table 18). Reasons for the incomplete observations occurring in the outcome of overall survival are not provided in the company's dossier, and are therefore potentially informative.

It remains unclear for the other outcomes to what extent the incomplete observations of the patients (potentially informative reasons) led to missing values.

Transferability of the study results to the German health care context

The company's information on the transferability of the study results refers to both research questions. They are described in Section I 3.1.2 of the present benefit assessment.

I 4.2 Results on added benefit

I 4.2.1 Outcomes included

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

- Mortality

- all-cause mortality

- morbidity
  - transfusion avoidance
  - MAVE
  - fatigue, measured using the FACIT-Fatigue
  - health status, measured using the EQ-5D VAS
- health-related quality of life
- Side effects
  - SAEs
  - severe AEs (CTCAE grade ≥ 3)
  - discontinuation due to AEs
  - type III hypersensitivity reactions (PT type III immune complex mediated reaction, AEs)
  - injection site reactions
  - infusion related reactions
  - infections (SOC infections and infestations, AEs)
  - other specific AEs, if any

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

Table 20 shows the outcomes for which data were available in the included study.

Table 20: Matrix of outcomes – RCT, direct comparison: crovalimab vs. eculizumab (research question 2: clinically stable after at least 6 months of treatment with a C5 inhibitor)

Study	Outcomes													
	All-cause mortality[a]	Transfusion avoidance[b]	MAVE[c]	Fatigue (FACIT-Fatigue)	Health status (EQ-5D VAS)	Health-related quality of life	SAEs	Severe AEs[d]	Discontinuation due to AEs	Type III hypersensitivity reactions[e]	Injection site reactions	Infusion related reactions	Infections[f]	Other specific AEs
COMMODORE 1	Y	Y	Y	Y	Y	No[g]	Y	Y	Y	Y	No[g]	No[g]	Y	No[h]

a. The results on all-cause mortality are based on the information on fatal AEs.
b. Defined as the proportion of patients who were pRBC transfusion-free from baseline through Week 25 and did not require transfusion per protocol-specified guidelines.
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 thrombosis, gangrene (non-traumatic, non-diabetic), amputation (non-traumatic, non-diabetic), dermal thrombosis, other.
d. Severe AEs are operationalized as CTCAE grade ≥ 3 events.
e. Operationalized as AEs with the MedDRA PT type III immune complex mediated reaction.
f. Operationalized as AEs of the MedDRA SOC infections and infestations.
g. No suitable data available; for the reasoning, see Section I 3.2.1 of the present benefit assessment.
h. No further specific AEs were identified based on the AEs occurring in the relevant study.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; FACIT-Fatigue: Functional Assessment of Chronic Illness Therapy-Fatigue; Hb: haemoglobin; MAVE: major adverse vascular event; MedDRA: Medical Dictionary for Regulatory Activities; PNH: paroxysmal nocturnal haemoglobinuria; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class; VAS: visual analogue scale; Y: yes

Notes on outcomes

The comments made in Section I 3.2.1 of this benefit assessment on the outcomes of transfusion avoidance, infusion related reactions, injection site reactions, breakthrough haemolysis, health-related quality of life (using EORTC QLQ-C30 functional scales) and PNH-related symptoms (using the EORTC IL40) also apply analogously to the COMMODORE 1 study.

Operationalization of the outcomes of fatigue and health status

For the outcomes of fatigue, recorded using the FACIT-Fatigue, and health status, recorded using the EQ-5D VAS, the company presented responder analyses on the improvement from baseline for both studies. The response criterion of the company was 8 points for the FACIT-Fatigue (scale range 0 to 52 points) and 15 points for the EQ-5D VAS (scale range 0 to 100

points). Both response thresholds correspond to 15% of the respective scale range and are used for the benefit assessment. For patients with high disease activity, who are considered in research question 1 of the present benefit assessment, the operationalization as improvement from baseline is adequate, as the treatment goal here is a reduction in symptoms. However, in the present research question 2 (clinically stable after at least 6 months of treatment with eculizumab), the treatment goal is to keep the patient's disease stable or to achieve an improvement. A patient who achieves this treatment goal therefore shows no worsening. With regard to the treatment goal and the patient population included in the COMMODORE 1 study, responder analyses on worsening from baseline would therefore be useful to obtain information on how many patients do not achieve this goal. Such an operationalization is not available in the company's dossier, however. However, improvement compared with baseline is a relevant operationalization also in this research question and is used for the benefit assessment. The company additionally presented mixed-effects model with repeated measures (MMRM) analyses in Appendix 4-G of Module 4 A of the dossier. These analyses, which include all patient values, show only marginal changes over the course of the study in both study arms and provide no evidence that an analysis of "worsening" would lead to deviating results (see supplementary presentation in I Appendix D of the full dossier assessment).

I 4.2.2 Risk of bias

Table 21 describes the risk of bias for the results of the relevant outcomes.

Table 21: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: crovalimab vs. eculizumab (research question 2: clinically stable after at least 6 months of treatment with a C5 inhibitor)

Study	Study level	Outcomes													
		All-cause mortality[a]	Transfusion avoidance[b]	MAVE[c]	Fatigue (FACIT-Fatigue)	Health status (EQ-5D VAS)	Health-related quality of life	SAEs	Severe AEs[d]	Discontinuation due to AEs	Type III hypersensitivity reactions[e]	Injection site reactions	Infusion related reactions	Infections[f]	Other specific AEs
COMMODORE 1	H	H[g]	H[g, h]	H[g]	H[g, h, i]	H[g, h, i]	–[j]	H[g]	H[g]	H[g, k]	H[g, h]	–[j]	–[j]	H[g]	–

a. The results on all-cause mortality are based on the information on fatal AEs.
b. Defined as the proportion of patients who were pRBC transfusion-free from baseline through Week 25 and did not require transfusion per protocol-specified guidelines.
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 thrombosis, gangrene (non-traumatic, non-diabetic), amputation (non-traumatic, non-diabetic), dermal thrombosis, other.
d. Severe AEs are operationalized as CTCAE grade ≥ 3.
e. Operationalized as AEs with the MedDRA PT type III immune complex mediated reaction.
f. Operationalized as AEs of the MedDRA SOC infections and infestations.
g. High risk of bias across outcomes.
h. Lack of blinding in the presence of subjective recording of outcomes.
i. Large difference between the treatment groups (> 5 percentage points) regarding the proportion of patients who were not considered in the analysis.
j. No suitable data available; for the reasoning, see Section I 3.2.1 of the present benefit assessment.
k. Lack of blinding in the presence of subjective decision on treatment discontinuation.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; FACIT-Fatigue: Functional Assessment of Chronic Illness Therapy-Fatigue; H: high; Hb: haemoglobin; MAVE: major adverse vascular event; MedDRA: Medical Dictionary for Regulatory Activities; PNH: paroxysmal nocturnal haemoglobinuria; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

The risk of bias for the results of all outcomes was rated as low. One reason for this is the high risk of bias across outcomes, which results from a high proportion of censorings that cannot be explained by study discontinuation (see Table 19). For the results of the outcomes of transfusion avoidance, fatigue, health status, discontinuation due to AEs, and type III hypersensitivity reactions (AEs), the subjective recording of outcomes in the presence of lack of blinding also contributes to the high risk of bias. For the patient-reported outcomes of fatigue and health status, there was an additional large difference between treatment groups (> 5 percentage points) regarding the proportion of patients who were not considered in the analysis.

I 4.2.3 Results

Table 22 summarizes the results for the comparison of crovalimab with eculizumab in patients with PNH who are clinically stable after at least 6 months of treatment with a C5 inhibitor. Where necessary, IQWiG calculations are provided to supplement the data from the company's dossier. Despite the small sample size, the company used an asymptotic test (Wald test) for the side effect outcomes, but an exact test (CSZ test) leads to more valid results and is therefore considered more adequate [25]. Thus, the Institute conducted its own calculations.

Common AEs, SAEs and discontinuations due to AEs are listed in I Appendix E of the full dossier assessment.

Table 22: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: crovalimab vs. eculizumab (research question 2: clinically stable after at least 6 months of treatment with a C5 inhibitor) (multipage table)

Study Outcome category	Crovalimab		Eculizumab		Crovalimab vs. eculizumab
Outcome	**N**	**Patients with event n (%)**	**N**	**Patients with event n (%)**	**RR [95% CI]; p-value**
COMMODORE 1					
Mortality					
All-cause mortality[a]	44	0 (0)	42	0 (0)	–
Morbidity					
Transfusion avoidance[b]	44	35 (79.5)	42	34 (81.0)	0.98 [0.80; 1.21]; 0.913[c]
MAVE[d]	44	0 (0)	42	1 (2.4)	0.32 [0.01; 7.61]; 0.363[c]
Fatigue (FACIT-Fatigue – improvement[e])	38	6 (15.8)	32	1 (3.1)	5.05 [0.64; 39.81]; 0.094[c]
Health status (EQ-5D VAS – improvement[f])	38	8 (21.1)	32	5 (15.6)	1.35 [0.49; 3.71]; 0.629[c]
Health-related quality of life	No suitable data[g]				
Side effects					
AEs (supplementary information)	44	34 (77.3)	42	28 (66.7)	–
SAEs	44	6 (13.6)	42	1 (2.4)	5.73 [0.72; 45.59]; 0.066[h]
Severe AEs[i]	44	8 (18.2)	42	1 (2.4)	7.64 [0.998; 58.46]; 0.018[h, j]
Discontinuation due to AEs	44	0 (0)	42	0 (0)	–
Type III hypersensitivity reaction[k] (type III immune complex mediated reaction [PT, AEs])	44	7 (15.9)	42	0 (0)	–[l]; 0.007[h]
Injection site reactions[m]	No suitable data[g]				
Infusion related reactions[m]	No suitable data[g]				
Infections[m, n] (infections and infestations [SOC, AEs])	44	18 (40.9)	42	15 (35.7)	1.15 [0.67; 1.96]; 0.709[h]

Table 22: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: crovalimab vs. eculizumab (research question 2: clinically stable after at least 6 months of treatment with a C5 inhibitor) (multipage table)

Study Outcome category Outcome	Crovalimab N	Crovalimab Patients with event n (%)	Eculizumab N	Eculizumab Patients with event n (%)	Crovalimab vs. eculizumab RR [95% CI]; p-value
a. The results on all-cause mortality are based on the information on fatal AEs. b. Defined as the proportion of patients who were pRBC transfusion-free from baseline through Week 25 and did not require transfusion per protocol-specified guidelines. c. Institute's calculation of RR, CI (asymptotic) and p-value (unconditional exact test, CSZ method according to [25]); the company presented p-values for the effect measure of weighted risk reduction; these are not relevant for the benefit assessment. d. 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, 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. e. A score increase by ≥ 8 points from baseline to Week 25 is considered a clinically relevant improvement (scale range: 0 to 52). f. A score increase by ≥ 15 points from baseline to Week 25 is considered a clinically relevant improvement (scale range: 0 to 100). g. See Section I 3.2.1 of the present dossier assessment for the reasoning. h. Institute's calculations, p-value unconditional exact test (CSZ method according to [25]). i. Operationalized as CTCAE grade ≥ 3. j. Discrepancy between p-value (exact) and CI (asymptotic) due to different calculation methods. k. Predefined as AE of special interest (AESI) according to the study protocol. l. No presentation of effect estimation and CI, as these are not informative. m. Presented in the study as "selected AE". n. Including no cases of meningococcal meningitis. AE: adverse event; CI: confidence interval; CSZ: convexity, symmetry, z-score; CTCAE: Common Terminology Criteria for Adverse Events; FACIT-Fatigue: Functional Assessment of Chronic Illness Therapy-Fatigue; Hb: haemoglobin; LDH: lactate dehydrogenase; MAVE: major adverse vascular event; n: number of patients with (at least one) event; N: number of analysed patients; PNH: paroxysmal nocturnal haemoglobinuria; PT: Preferred Term; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SOC: System Organ Class; ULN: upper limit of normal; VAS: visual analogue scale					

On the basis of the available information, no more than hints, e.g. of an added benefit, can be determined for all outcomes.

Mortality

All-cause mortality

The results on all-cause mortality are based on data on fatal AEs. No events for the outcome of all-cause mortality occurred in the COMMODORE 1 study. There is no hint of an added benefit of crovalimab in comparison with eculizumab; an added benefit is therefore not proven.

Morbidity

Transfusion avoidance

No statistically significant difference between treatment groups was found for the outcome of transfusion avoidance. There is no hint of an added benefit of crovalimab in comparison with eculizumab; an added benefit is therefore not proven.

MAVE

No statistically significant difference between treatment groups was found for the outcome of MAVE. There is no hint of an added benefit of crovalimab in comparison with eculizumab; an added benefit is therefore not proven.

Fatigue (recorded using the FACIT-Fatigue)

No statistically significant difference between treatment groups was found for the outcome of fatigue (recorded using the FACIT-Fatigue). There is no hint of an added benefit of crovalimab in comparison with eculizumab; an added benefit is therefore not proven.

Health status (recorded using the EQ-5D VAS)

No statistically significant difference between treatment groups was found for the outcome of health status (recorded using the EQ-5D VAS). There is no hint of an added benefit of crovalimab in comparison with eculizumab; an added benefit is therefore not proven.

Health-related quality of life

No suitable data are available for the outcome of health-related quality of life (see Section I 3.2.1 for reasons). There is no hint of an added benefit of crovalimab in comparison with eculizumab; an added benefit is therefore not proven.

Side effects

SAEs

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

Severe AEs

A statistically significant difference between treatment groups to the disadvantage of crovalimab was found for the outcome of severe AEs. There is a hint of greater harm from crovalimab in comparison with eculizumab.

Discontinuation due to AEs

No events occurred for the outcome of discontinuation due to AEs in the COMMODORE 1 study. There is no hint of greater or lesser harm from crovalimab in comparison with eculizumab; greater or lesser harm is therefore not proven.

Specific AEs

Type III hypersensitivity reactions (AEs)

A statistically significant difference between treatment groups to the disadvantage of crovalimab was found for the outcome of type III hypersensitivity reaction (AEs). However, the difference is no more than marginal for this outcome in the category of non-serious/non-severe side effects. There is no hint of greater or lesser harm from crovalimab in comparison with eculizumab; greater or lesser harm is therefore not proven.

Injection site reactions and infusion related reactions

No suitable data are available for the outcomes of injection site reactions and infusion related reactions. In each case, there is no hint of greater or lesser harm from crovalimab in comparison with eculizumab; greater or lesser harm is therefore not proven.

Infections (AEs)

No statistically significant difference between treatment groups was found for the outcome of infections (AEs). There is no hint of greater or lesser harm from crovalimab in comparison with eculizumab; greater or lesser harm is therefore not proven.

I 4.2.4 Subgroups and other effect modifiers

The following subgroup characteristics are taken into account in the present benefit assessment:

- sex (male versus female)
- age (< 65 years versus ≥ 65 years)
- history of pRBC transfusion in the previous 12 months before randomization (yes versus no)

The mentioned subgroup characteristics were not prespecified in the COMMODORE 1 study. The characteristic of history of pRBC transfusion in the previous 12 months before randomization was also a stratification factor for randomization.

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

In accordance with the described methods, no relevant effect modification was identified for the outcomes for which suitable data are available.

I 4.3 Probability and extent of added benefit

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

I 4.3.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level is estimated from the results presented in Section I 4.2 (see Table 23).

Table 23: Extent of added benefit at outcome level: crovalimab vs. eculizumab (research question 2: clinically stable after at least 6 months of treatment with a C5 inhibitor) (multipage table)

Outcome category **Outcome**	**Crovalimab vs. eculizumab** **Proportion of events (%)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
All-cause mortality	0 vs. 0 RR: –[c]	Lesser/added benefit not proven
Morbidity		
Transfusion avoidance	79.5 vs. 81.0 RR: 0.98 [0.80; 1.21]; p = 0.913	Lesser/added benefit not proven
MAVE	0 vs. 2.4 RR: 0.32 [0.01; 7.61]; p = 0.363	Lesser/added benefit not proven
Fatigue (FACIT-Fatigue – improvement)	15.8 vs. 3.1 RR: 5.05 [0.64; 39.81]; p = 0.094	Lesser/added benefit not proven
Health status (EQ-5D VAS – improvement)	21.1 vs. 15.6 RR: 1.35 [0.49; 3.71]; p = 0.629	Lesser/added benefit not proven
Health-related quality of life	No suitable data	Lesser/added benefit not proven
Side effects		
SAEs	13.6 vs. 2.4 RR: 5.73 [0.72; 45.59]; p = 0.066	Greater/lesser harm not proven
Severe AEs	18.2 vs. 2.4 RR: 7.64 [0.998; 58.46]; RR: 0.13 [0.02; 1.002][d]; p = 0.018 Probability: “hint”	Outcome category: serious/severe side effects Greater harm[e], extent: “minor”[f]
Discontinuation due to AEs	0 vs. 0 RR: –[c]	Greater/lesser harm not proven
Type III hypersensitivity reactions (AEs)	15.9 vs. 0 RR: –[g] p = 0.007	Greater/lesser harm not proven[h]
Injection site reactions	No suitable data	Greater/lesser harm not proven
Infusion related reactions	No suitable data	Greater/lesser harm not proven
Infections (AEs)	40.9 vs. 35.7 RR: 1.15 [0.67; 1.96]; p = 0.709	Greater/lesser harm not proven

Table 23: Extent of added benefit at outcome level: crovalimab vs. eculizumab (research question 2: clinically stable after at least 6 months of treatment with a C5 inhibitor) (multipage table)

Outcome category **Outcome**	**Crovalimab vs. eculizumab** **Proportion of events (%)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
a. Probability provided if there is a statistically significant and relevant effect. b. Depending on the outcome category, estimations of effect size are made with different limits based on the upper limit of the confidence interval (CI_u). c. An effect estimation (including confidence interval and p-value) was not carried out as no events occurred. d. Institute's calculation; reversed direction of effect to enable the use of limits to derive the extent of added benefit. e. The result of the statistical test is decisive for the derivation of the added benefit. f. Discrepancy between CI and p-value due to different calculation methods; the extent is rated as "minor". g. No presentation of effect estimation and CI, as not informative; the result of the statistical test is decisive for the derivation of the added benefit; the extent for this non-serious/severe outcome is rated as no more than "minor". h. The extent of the effect in this non-serious/non-severe outcome was no more than marginal. AE: adverse event; CI: confidence interval; CI_u: upper limit of the confidence interval; FACIT-Fatigue: Functional Assessment of Chronic Illness Therapy-Fatigue; MAVE: major adverse vascular event; RR: relative risk; SAE: serious adverse event; VAS: visual analogue scale		

I 4.3.2 Overall conclusion on added benefit

Table 24 summarizes the results taken into account in the overall conclusion on the extent of added benefit.

Table 24: Positive and negative effects from the assessment of crovalimab in comparison with eculizumab (research question 2: clinically stable after at least 6 months of treatment with a C5 inhibitor)

Positive effects	**Negative effects**
–	Serious/severe side effects ▪ Severe AEs: hint of greater harm – extent: "minor"
No suitable data are available on the outcome of health-related quality of life, and the specific AEs of injection site reactions and infusion related reactions.	
AE: adverse event	

In the COMMODORE 1 study, a hint of greater harm of minor extent was shown for the outcome of severe AEs. At the same time, there were no positive effects of crovalimab compared with eculizumab. In summary, there is a hint of lesser benefit of crovalimab versus eculizumab for adult patients with PNH who have been treated with a C5 inhibitor for ≥ 6 months and are clinically stable.

No data are available from the COMMODORE 1 study for the assessment of the added benefit of crovalimab compared with eculizumab for the treatment of paediatric patients 12 years of age or older who have been treated with a C5 inhibitor for ≥ 6 months and are clinically stable. An added benefit of crovalimab compared with eculizumab is therefore not proven for paediatric patients 12 years of age or older.

This differs from the company's assessment, which did not provide any separate information on the added benefit for the population of patients who have been treated with a C5 inhibitor for ≥ 6 months and are clinically stable (research question 2 of the present benefit assessment) and did not derive any added benefit across research questions.

I 5 Probability and extent of added benefit – summary

The result of the assessment of the added benefit of crovalimab in comparison with the ACT is summarized in Table 25.

Table 25: Crovalimab – probability and extent of added benefit

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
1	Adult and paediatric patients 12 years of age or older with a weight of ≥ 40 kg with paroxysmal nocturnal haemoglobinuria (PNH) with high disease activity, characterized by clinical symptoms of haemolysis[b, c]	**Eculizumab** or ravulizumab[d]	Added benefit not proven[e]
2	Adult and paediatric patients 12 years of age or older with a weight of ≥ 40 kg with PNH who have been treated with a C5 inhibitor for ≥ 6 months and are clinically stable[b]	**Eculizumab** or ravulizumab[d]	▪ Adults: hint of lesser benefit[f] ▪ Paediatric patients 12 years of age or older: added benefit not proven[f]

a. Presented is the respective ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company according to the inclusion criteria in Module 4 A Section 4.2.2 is printed in **bold**.
b. The presented therapeutic indication is assumed to include only patients requiring therapy who have PNH and clinical symptoms of haemolysis. Patients with concomitant bone marrow failure – including in the context of aplastic anaemia – are disregarded in this assessment. For the present therapeutic indication, allogeneic stem cell transplantation is assumed not to be indicated at the time point of treatment with crovalimab. In addition, when determining the ACT, it is assumed that patients do not have a medical indication to switch treatment to C3 inhibition at the time of treatment with crovalimab.
c. In patients who remain symptomatic despite treatment with a C5 inhibitor, continuing inadequate therapy when optimization options exist does not constitute the ACT. Any dose modifications which may be needed in the treatment with eculizumab or ravulizumab are assumed to be exhaustively covered by way of adjustments to the dosing interval.
d. Supportive measures in accordance with the generally accepted state of medical knowledge are assumed to be conducted both in the intervention arm and in the control arm.
e. Data from randomized trials are only available for patients aged ≥ 18 years. It remains unclear whether the observed effects can be transferred to patients aged 12 to 17 years.
f. No data from randomized trials are available for patients who were pretreated with ravulizumab.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee

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

I 6 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. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Allgemeine Methoden; Version 7.0 [online]. 2023 [Accessed: 02.09.2024]. URL: https://www.iqwig.de/methoden/allgemeine-methoden_version-7-0.pdf.

2. Skipka G, Wieseler B, Kaiser T et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. Biom J 2016; 58(1): 43-58. https://doi.org/10.1002/bimj.201300274.

3. F. Hoffmann-La Roche. A Phase III, Randomized, Open-Label, Active-Controlled, Multicenter Study Evaluating The Efficacy And Safety Of Crovalimab Versus Eculizumab In Patients With Paroxysmal Nocturnal Hemoglobinuria (PNH) Not Previously Treated With Complement Inhibitors; study BO42162; Clinical Study Report [unpublished]. 2023.

4. Hoffmann-La Roche. To evaluate the efficacy of crovalimab compared to eculizumab based on the non-inferiority assessment of the following co-primary endpoints [online]. [Accessed: 23.10.2024]. URL: https://euclinicaltrials.eu/search-for-clinical-trials/?lang=en&EUCT=2023-506498-36-00.

5. Hoffmann-La Roche. A Phase III Study Evaluating the Efficacy and Safety of Crovalimab Versus Eculizumab in Participants With Paroxysmal Nocturnal Hemoglobinuria (PNH) Not Previously Treated With Complement Inhibitors. (COMMODORE 2) [online]. 2024 [Accessed: 23.10.2024]. URL: https://clinicaltrials.gov/study/NCT04434092.

6. F. Hoffman-La Roche. A Phase III, Randomized, Open-Label, Active-Controlled, Multicenter Study Evaluating The Efficacy And Safety Of Crovalimab Versus Eculizumab In Adult And Adolescent Patients With Paroxysmal Nocturnal Hemoglobinuria (Pnh) Not Previously Treated With Complement Inhibitors [online]. [Accessed: 23.10.2024]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2019-004931-21.

7. Röth A, He G, Tong H et al. Phase 3 randomized COMMODORE 2 trial: Crovalimab versus eculizumab in patients with paroxysmal nocturnal hemoglobinuria naive to complement inhibition. Am J Hematol 2024. https://doi.org/10.1002/ajh.27412.

8. Roche. Piasky 340 mg Injektions-/Infusionslösung [online]. 2024 [Accessed: 22.10.2024]. URL: https://www.fachinfo.de.

9. Alexion. Soliris 300mg Konzentrat zur Herstellung einer Infusionslösung [online]. 2023 [Accessed: 22.10.2024]. URL: https://www.fachinfo.de.

10. Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie. Paroxysmale nächtliche Hämoglobinurie (PNH); Leitlinie [online]. 2024 [Accessed: 22.10.2024]. URL: https://www.onkopedia.com/de/onkopedia/guidelines/paroxysmale-naechtliche-haemoglobinurie-pnh/@@guideline/html/index.html.

11. Bundesärztekammer. Querschnitts-Leitlinien zur Therapie mit Blutkomponenten und Plasmaderivaten, Gesamtnovelle 2020 [online]. 2020 [Accessed: 12.11.2024]. URL: https://www.wbbaek.de/fileadmin/user_upload/_old-files/downloads/pdf-Ordner/MuE/Querschnitts-Leitlinien_BAEK_zur_Therapie_mit_Blutkomponenten_und_Plasmaderivaten-Gesamtnovelle_2020.pdf.

12. Brodsky RA, Peffault de Latour R, Rottinghaus ST et al. Characterization of breakthrough hemolysis events observed in the phase 3 randomized studies of ravulizumab versus eculizumab in adults with paroxysmal nocturnal hemoglobinuria. Haematologica 2021; 106(1): 230-237. https://doi.org/10.3324/haematol.2019.236877.

13. Almeida AM, Bedrosian C, Cole A et al. Clinical benefit of eculizumab in patients with no transfusion history in the International Paroxysmal Nocturnal Haemoglobinuria Registry. Intern Med J 2017; 47(9): 1026-1034. https://doi.org/10.1111/imj.13523.

14. Montan I, Löwe B, Cella D et al. General Population Norms for the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue Scale. Value Health 2018; 21(11): 1313-1321. https://doi.org/10.1016/j.jval.2018.03.013.

15. Paul Ehrlich-Institut. Hämovigilanzbericht [online]. 2021. URL: https://www.pei.de/SharedDocs/Downloads/DE/newsroom/pflichtberichte/haemovigilanzberichte/haemovigilanz-bericht-2021.pdf?__blob=publicationFile&v=5.

16. Gilliss BM, Looney MR, Gropper MA. Reducing noninfectious risks of blood transfusion. Anesthesiology 2011; 115(3): 635-649. https://doi.org/10.1097/ALN.0b013e31822a22d9.

17. Müller MM, Geisen C, Zacharowski K et al. Transfusion of Packed Red Cells: Indications, Triggers and Adverse Events. Dtsch Arztebl Int 2015; 112(29-30): 507-517; quiz 518. https://doi.org/10.3238/arztebl.2015.0507.

18. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Isatuximab (multiples Myelom, nach ≥ 1 Vortherapie) – Nutzenbewertung gemäß § 35a SGB V (frühe Nutzenbewertung); Dossierbewertung [online]. 2021 [Accessed: 11.07.2023]. URL: https://www.iqwig.de/download/a21-60_isatuximab_nutzenbewertung-35a-sgb-v_v1-0.pdf.

19. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Ravulizumab (paroxysmale nächtliche Hämoglobinurie) – Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung [online]. 2019 [Accessed: 11.07.2023]. URL: https://www.iqwig.de/download/a19-59_ravulizumab_nutzenbewertung-35a-sgb-v_v1-0.pdf.

20. Weitz I, Meyers G, Lamy T et al. Cross-sectional validation study of patient-reported outcomes in patients with paroxysmal nocturnal haemoglobinuria. Intern Med J 2013; 43(3): 298-307. https://doi.org/10.1111/j.1445-5994.2012.02924.x.

21. Groth M, Singer S, Niedeggen C et al. Development of a disease-specific quality of life questionnaire for patients with aplastic anemia and/or paroxysmal nocturnal hemoglobinuria (QLQ-AA/PNH)-report on phases I and II. Ann Hematol 2017; 96(2): 171-181. https://doi.org/10.1007/s00277-016-2867-8.

22. Fayers PM, Aaronson NK, Bjordal K et al. EORTC QLQ-C30 scoring manual [online]. 2001 [Accessed: 12.11.2024]. URL: https://www.eortc.org/app/uploads/sites/2/2018/02/SCmanual.pdf.

23. EORTC. Questionnaires [online]. 2024 [Accessed: 02.12.2024]. URL: https://qol.eortc.org/questionnaires/.

24. European Organisation for Research and Treatment of Cancer. EORTC quality of life group item library user guidelines [online]. 2022 [Accessed: 12.11.2024]. URL: https://www.eortc.org/app/uploads/sites/2/2022/10/EORTC-Item-Library-User-Guidelines.pdf.

25. Martín Andrés A, Silva Mato A. Choosing the optimal unconditioned test for comparing two independent proportions. Computat Stat Data Anal 1994; 17(5): 555-574. https://doi.org/10.1016/0167-9473(94)90148-1.

26. F. Hoffmann-La Roche. A Phase III, Randomized, Open-Label, Active-Controlled, Multicenter Study Evaluating the Safety, Pharmacokinetics, Pharmacodynamics, and Efficacy of Crovalimab versus Eculizumab in Patients with Paroxysmal Nocturnal Hemoglobinuria (PNH) Currently Treated with Complement Inhibitors; study BO42161; Clinical Study Report [unpublished]. 2023.

27. Hoffmann-La Roche. A Study Evaluating The Safety, Pharmacokinetics, and Efficacy Of Crovalimab Versus Eculizumab In Participants With Paroxysmal Nocturnal Hemoglobinuria (PNH) Currently Treated With Complement Inhibitors (COMMODORE 1) [online]. [Accessed: 23.10.2024]. URL: https://euclinicaltrials.eu/ctis-public/view/2023-506526-37-00?lang=en.

28. Hoffmann-La Roche. A Study Evaluating The Safety, Pharmacokinetics, and Efficacy Of Crovalimab Versus Eculizumab In Participants With Paroxysmal Nocturnal Hemoglobinuria (PNH) Currently Treated With Complement Inhibitors (COMMODORE 1) [online]. 2024 [Accessed: 23.10.2024]. URL: https://clinicaltrials.gov/study/NCT04432584.

29. F. Hoffmann-La Roche. A phase III, randomized, open-label, active-controlled, multicenter study evaluating the safety, pharmacokinetics, pharmacodynamics, and efficacy of crovalimab versus eculizumab in patients with paroxysmal nocturnal hemoglobinuria (PNH) currently treated with complement inhibitors [online]. [Accessed: 23.10.2024]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2020-000597-26.

30. Scheinberg P, Clé DV, Kim JS et al. Phase 3 randomized COMMODORE 1 trial: Crovalimab versus eculizumab in complement inhibitor-experienced patients with paroxysmal nocturnal hemoglobinuria. Am J Hematol 2024. https://doi.org/10.1002/ajh.27413.

31. Food and Drug Administration. Application Number: 761388Orig1s000; Integrated Review [online]. 2024 [Accessed: 25.10.2024]. URL: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2024/761388Orig1s000IntegratedR.pdf.

The full report (German version) is published under https://www.iqwig.de/en/projects/a24-94.html.