Crovalimab
(paroxysmal nocturnal haemoglobinuria)

Addendum to Project A24-94
(dossier assessment)[1]

ADDENDUM

Project: A25-12 Version: 1.0 Status: 14 Feb 2025 DOI: 10.60584/A25-12_en

[1] Translation of the addendum *Crovalimab (paroxysmale nächtliche Hämoglobinurie) – Addendum zum Projekt A24-94 (Dossierbewertung)*. Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher

Institute for Quality and Efficiency in Health Care

Topic

Crovalimab (paroxysmal nocturnal haemoglobinuria) – Addendum to Project A24-94

Commissioning agency

Federal Joint Committee

Commission awarded on

28 January 2025

Internal Project No.

A25-12

https://doi.org/10.60584/A25-12_en

Address of publisher

Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Siegburger Str. 237
50670 Köln
Germany

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

Recommended citation

Institute for Quality and Efficiency in Health Care. Crovalimab (paroxysmal nocturnal haemoglobinuria); Addendum to Project A24-94 (dossier assessment) [online]. 2025 [Accessed: DD.MM.YYYY]. URL: https://doi.org/10.60584/A25-12_en.

Keywords

Crovalimab, Hemoglobinuria – Paroxysmal, Benefit Assessment, NCT04432584, NCT04434092

IQWiG employees involved in the addendum

- Michael Köhler
- Katharina Hirsch
- Katrin Nink
- Sabine Ostlender
- Katharina Wölke

Table of contents

List of tables

Page

List of figures

Page

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
C5	complement component 5
CTCAE	Common Terminology Criteria for Adverse Events
FACIT	Functional Assessment of Chronic Illness Therapy
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MAVE	major adverse vascular event
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed-effects model with repeated measures
PNH	paroxysmal nocturnal haemoglobinuria
pRBC	packed red blood cells
PT	Preferred Term
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class
VAS	visual analogue scale

1 Background

On 28 January 2025, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Project A24-94 (Crovalimab – Benefit assessment according to §35a Social Code Book V) [1].

The commission comprises the assessment of the analysis of the COMMODORE 1 study corrected by the pharmaceutical company (hereinafter referred to as the “company”) in the commenting procedure and following the oral hearing [2,3], taking into account the information provided in the dossier [4].

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

2 Assessment

In its comments, the company resubmitted all analyses of the COMMODORE 1 study already presented in the dossier on research question 2 of the benefit assessment (adult and paediatric patients 12 years of age or older with a weight of ≥ 40 kg with paroxysmal nocturnal haemoglobinuria [PNH] who have been treated with a complement component 5 [C5] inhibitor for ≥ 6 months and are clinically stable) in corrected form [2].

In its comments and in the oral hearing, the company stated that a review of a point of criticism from dossier assessment A24-94 regarding unexplained censorings for the outcome of all-cause mortality found that all analyses of the COMMODORE 1 study prepared for the benefit assessment had been flawed. According to the company, there had been a programming error, as a result of which the programmes on which the analyses were based were not linked to the complete data range. This resulted in the inadvertent use of data sets that had not undergone all data cleaning activities and for which additional data from the comparative phase had been collected [2,3,5]. According to the company, the consequence of this error was that analyses on the data cut-off of 16 November 2022 were erroneously presented for the dossier assessment.

According to the company, the data submitted as part of the comments are the first correct analysis with data as of 31 May 2023. These analyses are relevant for the present assessment [4].

According to the company's explanations in the oral hearing [5], changes occurring at individual points in the patient characteristics compared with the analyses presented with the dossier assessment are due to data cleaning that took place after the data cut-off of 16 November 2022.

The analyses of the COMMODORE 2 study for research question 1 of the benefit assessment (adult and paediatric patients 12 years of age or older with a weight of ≥ 40 kg with PNH with high disease activity, characterized by clinical symptoms of haemolysis) were not affected by this error. Hence, no new data are available for research question 1.

2.1 Assessment of the COMMODORE 1 study on the basis of the corrected analyses

2.1.1 Study characteristics

The description of the COMMODORE 1 study can be found in dossier assessment A24-94 [1].

Study course and data cut-offs

A comprehensive description of the study course and the available data cut-offs of the COMMODORE 1 study can be found in dossier assessment A24-94 [1]. The corrected analysis dated 31 May 2023 was used for the present benefit assessment.

Patient characteristics in COMMODORE 1

Table 1 shows the patient characteristics of the included study.

Table 1: 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]	7.0 [1.6; 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)	56.0 (33.2)
PNH clone size (%) granulocytes	54.9 (28.5)	62.3 (29.5)
PNH clone size (%) monocytes	80.8 (22.1)	87.0 (21.5)
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 screening, n (%)[b]	10 (23)	10 (24)
Number of units of pRBC transfused within 12 months prior to screening, n (%)		
0	33 (77)	32 (76)
> 0 to < 4	4 (9)	2 (5)
≥ 4 to < 14	4 (9)	5 (12)
≥ 14	2 (5)	3 (7)
Number of units of pRBC transfused within 12 months prior to screening, median [min; max]	0 [0; 14]	0 [0; 24]

Table 1: 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**
Treatment discontinuation (randomized treatment phase), n (%)[c, d]	ND	ND
Study discontinuation (total study duration), n (%)[e]	2 (4.5)	2 (4.8)

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 factor: 12 vs. 10 patients with pRBC transfusion are specified for the stratification factor.
c. According to the information in the dossier [4], 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, according to the information in the dossier. Over the entire duration of the study, 2 (4.5%) vs. 7 (16,7%) patients discontinued treatment until the analysis on 31 May 2023.
e. No information is available for the randomized study phase.

F: female; IV: intravenous; 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 largely correspond to the information in the dossier assessment. The patient characteristics in the COMMODORE 1 study were largely comparable between the study arms. A comprehensive description of the patient characteristics can be found in dossier assessment A24-94 [1]. Minor discrepancies from the dossier assessment arise in the case of individual data, for example regarding the time between diagnosis and study start or the clone size. According to the company, this was due to data cleaning (see Chapter 2).

For the analyses of the Day 120 safety update of 31 May 2023, there is still no information 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 versus 2 patients (4.5% versus 4.8%).

Risk of bias across outcomes (study level)

Table 2 shows the risk of bias across outcomes (risk of bias at study level).

Table 2: 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	Yes	Low
RCT: randomized controlled trial							

The risk of bias at study level was rated as low. This assessment differs from dossier assessment A24-94, which rated the risk of bias as high for the outcome of all-cause mortality due to unexplained censorings in the course of the study [1]. The corrected Kaplan-Meier curves for all-cause mortality submitted with the comments no longer show any unexplained censorings (see Appendix A).

Transferability of the study results to the German health care context

The company's information on transferability of the study results is described in dossier assessment A24-94 [1].

2.1.2 Results on added benefit

2.1.2.1 Outcomes included

The detailed description of the outcomes of the COMMODORE 1 study can be found in dossier assessment A24-94 [1].

For the outcomes of fatigue (recorded with Functional Assessment of Chronic Illness Therapy [FACIT]-Fatigue) and health status (recorded with the EQ-5D visual analogue scale [VAS]), dossier assessment A24-94 described that responder analyses on worsening from baseline would be useful for the present research question, where patients are already clinically stable. These analyses could provide information on how many patients do not achieve the treatment goal of keeping the disease stable or achieving an improvement. However, such an operationalization was neither available in the dossier, nor was it presented in the company's comments. The company presented mixed-effects model with repeated measures (MMRM) analyses in its comments (as well as in the dossier), however. These analyses, which include all patient values, show a consistent effect with the responder analyses. It is therefore not be

assumed that an analysis of “worsening” would lead to deviating results (see supplementary presentation in Appendix B).

2.1.2.2 Risk of bias

Table 3 describes the risk of bias for the results of the relevant outcomes.

Table 3: 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	L	L	H[g]	L	H[g, h]	H[g, h]	–[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. Large difference between the treatment groups (> 5 percentage points) regarding the proportion of patients who were not considered in the analysis.
i. No suitable data available; for justification see Section I 3.2.1 of dossier assessment A24-94 [1].
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; L: low; MAVE: major adverse vascular event; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; 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, major adverse vascular events (MAVEs), serious adverse events (SAEs), severe adverse events (AEs), and infections (AEs).

Due to subjective recording of outcomes in the presence of lack of blinding, the risk of bias was assessed 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 an additional large difference between treatment groups (> 5 percentage points) regarding the proportion of patients who were not considered in the analysis.

2.1.2.3 Results

Table 4 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, calculations conducted by the Institute are provided in addition to the data from the company's comments. 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 [6]. Accordingly, as in the dossier assessment, calculations were performed by the Institute.

Common AEs, SAEs and discontinuations due to AEs are listed in Appendix C.

Table 4: 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		Eculizumab		Crovalimab vs. eculizumab
	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])	43	10 (23.3)	37	1 (2.7)	8.60 [1.16; 64.10]; 0.008[c]
Health status (EQ-5D VAS – improvement[f])	43	11 (25.6)	37	7 (18.9)	1.35 [0.58; 3.13]; 0.591[c]
Health-related quality of life	No suitable data[g]				
Side effects					
AEs (supplementary information)	44	35 (79.5)	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 reactionsm	No suitable data[g]				
Infections[m, n] (infections and infestations [SOC, AEs])	44	19 (43.2)	42	17 (40.5)	1.07 [0.65; 1.76]; 0.827[h]

Table 4: 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 [6]); 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 decrease by ≥ 15 points from baseline to Week 25 is considered a clinically relevant improvement (scale range: 0 to 100). g. For justification see Section I 3.2.1 of dossier assessment A24-94 [1]. h. Institute's calculations, p-value unconditional exact test (CSZ method according to [6]). 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; MAVE: major adverse vascular event; n: number of patients with (at least one) event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SOC: System Organ Class; 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 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)

A statistically significant difference between treatment groups in favour of crovalimab was found for the outcome of fatigue (recorded using the FACIT-Fatigue). There is a hint of added benefit of crovalimab in comparison with eculizumab.

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 (for justification see Section I 3.2.1 of dossier assessment A24-94 [1]). 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 an indication 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 each of the outcomes of injection site reactions and infusion related reactions (for justification see Section I 3.2.1 of dossier assessment A24-94 [1]). 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.

2.1.2.4 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.

2.1.3 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 *General Methods* of IQWiG [7].

The approach for deriving an overall conclusion on the added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

2.1.3.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level was estimated from the results presented in Section 2.1.2.3 (see Table 5).

Determination of the outcome category for symptom outcomes

It cannot be inferred from the dossier or the company's comments whether the following symptom outcome is serious/severe or non-serious/non-severe. The classification of this outcome is explained below.

Fatigue (recorded using the FACIT-Fatigue)

The total score of the FACIT-Fatigue questionnaire can range from 0 to 52, with higher scores indicating a better condition or better functioning [8]. A score of 43.5 corresponds to the mean value of the general population [9]. According to the information provided in the company's comments, patients in the COMMODORE 1 study had a mean baseline score of 39.5 and were therefore presumably mostly not in the range of serious symptoms. Therefore, the outcome of fatigue (recorded using the FACIT-Fatigue) was assigned to the outcome category of non-serious/non-severe symptoms/late complications.

Table 5: 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)	23.3 vs. 2.7 RR: 8.60 [1.16; 64.10]; RR: 0.12 [0.02; 0.86][d]; p = 0.008 Probability: “hint”	Outcome category: non-serious/non-severe symptoms/late complications Added benefit, extent: “minor”
Health status (EQ-5D VAS – improvement)	25.6 vs. 18.9 RR: 1.35 [0.58; 3.13]; p = 0.591	Lesser/added benefit not proven

Table 5: 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]
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: "indication"	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)	43.2 vs. 40.5 RR: 1.07 [0.65; 1.76]; p = 0.827	Greater/lesser harm not proven

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 estimate and CI, as not informative; the result of the statistical test is decisive for the derivation of the added benefit. The extent in this non-serious/non-severe outcome was rated as no more than marginal.
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

2.1.3.2 Overall conclusion on added benefit

Table 6 summarizes the results taken into account in the overall conclusion on the extent of added benefit.

Table 6: 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**
Non-serious/non-severe symptoms/late complications ▪ Fatigue: hint of an added benefit – extent: "minor"	Serious/severe side effects ▪ Severe AEs: indication 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	

The COMMODORE 1 study showed a hint of minor added benefit for the outcome of fatigue on the one hand, and an indication of a greater harm of minor extent for the outcome of severe AEs on the other. In summary, an added benefit of crovalimab versus eculizumab is not proven for patients with PNH who have been treated with a C5 inhibitor for ≥ 6 months and are clinically stable. This concurs with the company's assessment.

2.2 Summary

The corrected data subsequently submitted by the company in the commenting procedure change the conclusion on the added benefit of crovalimab from dossier assessment A24-94 regarding research question 2 (clinically stable after at least 6 months of treatment with a C5 inhibitor): An added benefit of crovalimab in comparison with eculizumab is not proven. No new data were presented for research question 1 (high disease activity), so there is no change compared with dossier assessment A24-94.

Table 7 below shows the result of the benefit assessment of crovalimab, taking into account dossier assessment A24-94 and the present addendum.

Table 7: 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]	Added benefit not proven[e, 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; PNH: paroxysmal nocturnal haemoglobinuria

The G-BA decides on the added benefit.

3 References

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Crovalimab (paroxysmale nächtliche Hämoglobinurie); Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung [online]. 2024 [Accessed: 16.12.2024]. URL: https://doi.org/10.60584/A24-94.

2. Roche Pharma. Stellungnahme zum IQWiG-Bericht Nr. 1900: Crovalimab (paroxysmale nächtliche Hämoglobinurie); Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung. [Soon available under: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/1127/#beschluesse in the document "Zusammenfassende Dokumentation"].

3. Roche Pharma. Nachreichung von Unterlagen zur mündlichen Anhörung vom 27.01.2025. [Soon available under: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/1127/#beschluesse in the document "Zusammenfassende Dokumentation"].

4. Roche Pharma. Crovalimab (Piasky); Dossier zur Nutzenbewertung gemäß § 35a SGB V [online]. 2024 [Accessed: 20.01.2025]. URL: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/1127/#dossier.

5. Gemeinsamer Bundesausschuss. Crovalimab: mündliche Anhörung gemäß § 35 a Abs. 2 SGB V - stenografisches Wortprotokoll [online]. 2025 [Accessed: 03.02.2025]. URL: https://www.g-ba.de/downloads/91-1031-1127/2025-01-27_Wortprotokoll_Crovalimab_D-1102.pdf.

6. 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.

7. 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.

8. Cella D, Eton DT, Lai JS et al. Combining anchor and distribution-based methods to derive minimal clinically important differences on the Functional Assessment of Cancer Therapy (FACT) anemia and fatigue scales. J Pain Symptom Manage 2002; 24(6): 547-561. https://doi.org/10.1016/s0885-3924(02)00529-8.

9. Montan I, Lowe 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.

Appendix A Kaplan-Meier curves for the outcome of overall survival in the COMMODORE 1 study (research question 2: clinically stable after at least 6 months of treatment with a C5 inhibitor)

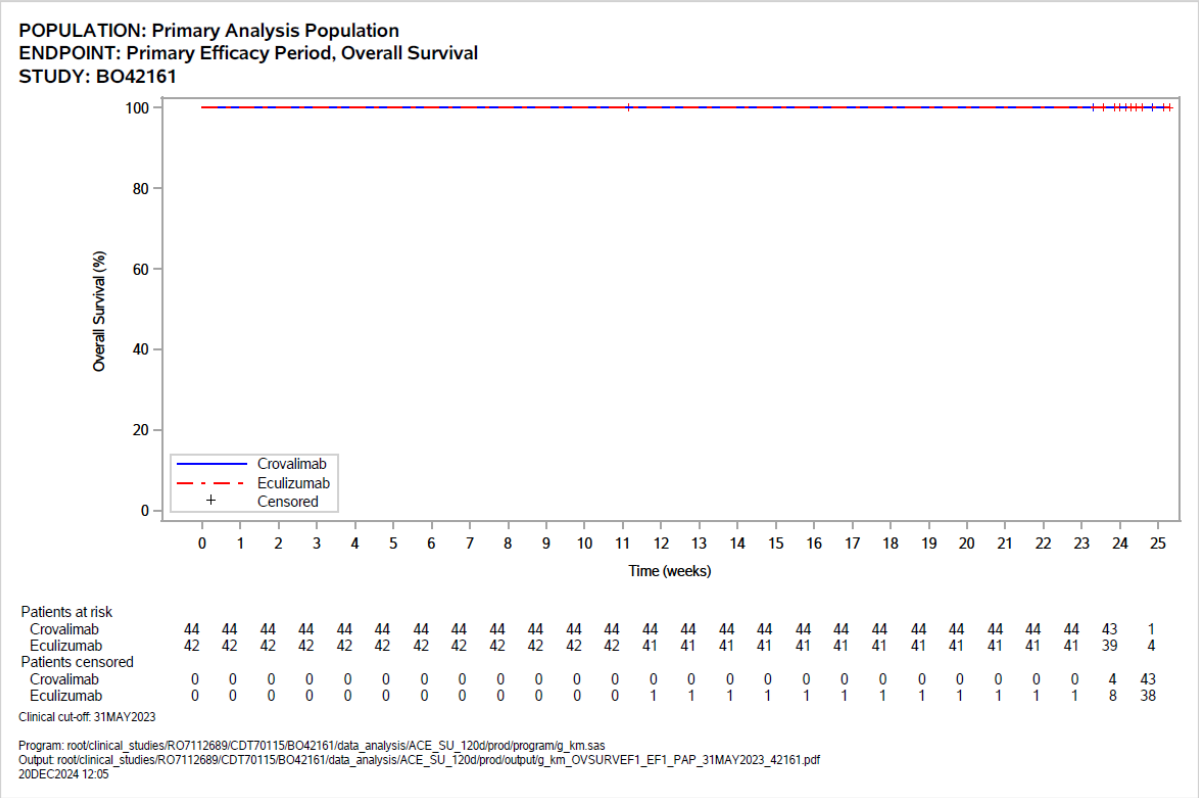

Figure 1: Kaplan-Meier curves for the outcome of all-cause mortality, COMMODORE 1 (research question 2: clinically stable after at least 6 months of treatment with a C5 inhibitor)

Appendix B MMRM analyses for the outcomes of FACIT-Fatigue and EQ-5D VAS in the COMMODORE 1 study (research question 2: clinically stable after at least 6 months of treatment with a C5 inhibitor)

Table 8: Results (morbidity, continuous) – RCT, direct comparison: crovalimab vs. eculizumab (research question 2: clinically stable after at least 6 months of treatment with a C5 inhibitor)

Study Outcome category	Crovalimab			Eculizumab			Crovalimab vs. eculizumab
Outcome	N[a]	Values at baseline mean (SD)	Change at Week 25 mean[b] (SE)	N[a]	Values at baseline mean (SD)	Change at Week 25 mean[b] (SE)	MD [95% CI][b]; p-value[c] SMD [95% CI]
COMMODORE 1							
Morbidity							
Fatigue (FACIT-Fatigue – MMRM)[d]	ND	39.00 (10.30)	1.37 (1.20)	ND	40.14 (8.46)	–2.33 (1.28)	3.70 [0.32; 7.09]; 0.038 Hedges' g: 0.41 [-0.02; 0.84][e]
Health status (EQ-5D VAS – MMRM)[f]	ND	72.75 (21.71)	3.79 (2.67)	ND	72.76 (18.26)	1.79 (2.84)	2.00 [–5.55; 9.55]; 0.609

a. Number of patients taken into account in the effect estimation; baseline values are based on data of 44 and 42 patients.
b. MMRM analysis adjusted for visit, baseline value, and interaction between treatment and visit. It is unclear whether the effect (MD) represents the difference in the changes at a specific point in time (at Week 25) or in the changes averaged over the course of the study.
c. Institute's calculation (t-test).
d. Higher (increasing) values indicate improved symptoms; positive effects (intervention minus comparison) indicate an advantage for the intervention (scale range: 0 to 52 points).
e. Institute's calculation based on MD and CI from the MMRM analysis.
f. Higher (increasing) values indicate improved symptoms; positive effects (intervention minus comparison) indicate an advantage for the intervention (scale range: 0 to 100 points).

CI: confidence interval; FACIT: Functional Assessment of Chronic Illness Therapy-Fatigue; MD: mean difference; MMRM: mixed-effects model with repeated measures; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation; SMD: standardized mean difference; SE: standard error; VAS: visual analogue scale

Appendix C Results on side effects

For the overall rates of AEs, SAEs, and severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3), the following tables present events for System Organ Classes (SOCs) and Preferred Terms (PTs) according to the Medical Dictionary for Regulatory Activities (MedDRA), each on the basis of the following criteria:

- Overall rate of AEs (irrespective of severity grade): events that occurred in at least 10% of patients in one study arm
- Overall rates of severe AEs (e.g. CTCAE grade ≥ 3) and SAEs: events that occurred in at least 5% of patients in one study arm
- In addition, for all events irrespective of severity grade: events that occurred in at least 10 patients and in at least 1% of patients in one study arm

There were no discontinuations due to AEs in the COMMODORE 1 study. There is therefore no table on discontinuations due to AEs.

Table 9: Common AEs[a] – RCT, direct comparison: crovalimab vs. eculizumab (research question 2: clinically stable after at least 6 months of treatment with a C5 inhibitor)

Study	Patients with event n (%)	
SOC[b] **PT[b]**	**Crovalimab** **N = 44**	**Eculizumab** **N = 42**
COMMODORE 1		
Overall AE rate	35 (79.5)	28 (66.7)
Blood and lymphatic system disorders	5 (11.4)	1 (2.4)
Gastrointestinal disorders	9 (20.5)	5 (11.9)
General disorders and administration site conditions	12 (27.3)	6 (14.3)
Pyrexia	7 (15.9)	0 (0)
Hepatobiliary disorders	5 (11.4)	0 (0)
Immune system disorders	8 (18.2)	0 (0)
Type III immune complex mediated reaction	7 (15.9)	0 (0)
Infections and infestations	19 (43.2)	17 (40.5)
COVID-19	6 (13.6)	7 (16.7)
Injury, poisoning and procedural complications	11 (25.0)	4 (9.5)
Infusion related reaction	6 (13.6)	0 (0)
Musculoskeletal and connective tissue disorders	7 (15.9)	5 (11.9)
Nervous system disorders	5 (11.4)	3 (7.1)
Headache	5 (11.4)	1 (2.4)
Skin and subcutaneous tissue disorders	8 (18.2)	1 (2.4)

a. Events that occurred in ≥ 10% of the patients in at least one study arm.
b. MedDRA version 25.1; SOC and PT notation taken without adaptation from Appendix 4-G of the comments.

AE: adverse event; COVID-19: coronavirus disease 2019; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; ND: no data; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class

Table 10: Common SAEs[a] – RCT, direct comparison: crovalimab vs. eculizumab (research question 2: clinically stable after at least 6 months of treatment with a C5 inhibitor)

Study	**Patients with event n (%)**	
SOC[b]	**Crovalimab N = 44**	**Eculizumab N = 42**
COMMODORE 1		
Overall SAE rate	6 (13.6)	1 (2.4)
Infections and infestations	3 (6.8)	1 (2.4)

a. Events that occurred in ≥ 5% of the patients in at least one study arm.
b. MedDRA version 25.1; SOC notation taken without adaptation from Appendix 4-G of the comments.

MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class

Table 11: Common severe AEs (CTCAE ≥ 3) [a] – RCT, direct comparison: crovalimab vs. eculizumab (research question 2: clinically stable after at least 6 months of treatment with a C5 inhibitor)

Study	**Patients with event n (%)**	
SOC[b]	**Crovalimab N = 44**	**Eculizumab N = 42**
COMMODORE 1		
Overall rate of severe AEs (CTCAE grade ≥ 3)	8 (18.2)	1 (2.4)
Blood and lymphatic system disorders	3 (6.8)	0 (0)

a. Events that occurred in ≥ 5% of the patients in at least one study arm.
b. MedDRA version 25.1; SOC notation taken without adaptation from Appendix 4-G of the comments.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; RCT: randomized controlled trial; SOC: System Organ Class