Medicinrådet

Bilag til Medicinrådets anbefaling vedrørende crovalimab til behandling af paroksystisk natlig hæmoglobinuri (PNH)

Vers. 1.0

Bilagsoversigt

1. Forhandlingsnotat fra Amgros vedr. crovalimab
2. Ansøgers endelige ansøgning vedr. crovalimab

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20.01.2025

DBS/KLE

Forhandlingsnotat

Dato for behandling i Medicinrådet	29.01.2024
Leverandør	Roche
Lægemiddel	PiaSky (crovalimab)
Ansøgt indikation	Behandling af voksne og pædiatriske patienter i alderen 12 år eller ældre med en vægt på 40 kg og derover med paroksystisk natlig hæmoglobinuri (PNH)
Nyt lægemiddel / indikationsudvidelse	Nyt lægemiddel

Prisinformation

Amgros har forhandlet følgende pris på PiaSky:

Tabel 1: Forhandlingsresultat

Lægemiddel	Styrke	Pakningsstørrelse	AIP (DKK)	Forhandlet SAIP (DKK)	Rabatprocent ift. AIP
Piasky	340 mg	2 ml (170 mg/ml)	88,635,00	[redacted]	[redacted]

Prisen er betinget af Medicinrådets anbefaling.

Aftaleforhold

Amgros har indgået en aftale med leverandøren, [redacted]. Leverandøren har mulighed for at sætte prisen ned i hele aftaleperioden.

Konkurrencesituationen

Leverandøren har ansøgt om vurdering af PiaSky til 1. og 2. linje behandling af PNH.
Der er flere lægemidler på markedet, som har indikation til PNH: Ultomiris (ravulizumab), Aspaveli (pegcetacoplan) og Soliris (eculizumab), samt dennes biosimilære version Bekemv (eculizumab). Aspaveli er anbefalet af Medicinrådet til 1. og 2. linje behandling. De øvrige lægemidler er aldrig blevet vurderet i Medicinrådet.

Amgros er orienteret om, at Medicinrådet udarbejder en behandlingsvejledning og en omkostningsanalyse for PNH, som vil være til behandling på mødet i [redacted].

[redacted].

Tabel 2 viser lægemiddeludgifter på sammenlignelige lægemidler.

Tabel 2: Sammenligning af lægemiddeludgifter pr. patient

Lægemiddel	Styrke	Paknings-størrelse	Dosering	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. år (SAIP, DKK)
Piasky	340 mg	2 ml (170 mg/ml)	680 mg hver 4. uge SC.	[redacted]	[redacted]
Bekemv (eculizumab)	300 mg	1 stk	900 mg hver 2. uge IV	[redacted]	[redacted]
Ultomiris (ravulizumab)	1.100 mg	1.100 mg/11 ml	3.300 mg hver 8. uge IV	[redacted]	[redacted]
Aspaveli (pegcetacoplan)	1.080 mg	1 stk.	1.080 mg 2 gange om ugen SC.	[redacted]	[redacted]

*Kilde: "Udkast: Medicinrådets anbefaling vedr. crovalimab til behandling af paroksystisk natlig hæmoglobinuri (PNH)". Der anvendes doser for vedligeholdelsesår da der er tale om livslang behandling. Doseringen for PiaSky er beregnet ud fra en gennemsnitlig patientvægt på 68 kg.

Status fra andre lande

Tabel 3: Status fra andre lande

Land	Status	Kommentar	Link
Norge	Under vurdering		Link til status
Sverige	Under vurdering		Link til status
England	Anbefalet	Crovalimab anbefales, inden for dets markedsføringstilladelse, som en mulighed for behandling af paroksystisk natlig hæmoglobinuri hos personer på 12 år og derover, som vejer 40 kg eller mere. Det anbefales til personer, som: • har hæmolyse med kliniske symptomer, der indikerer høj sygdomsaktivitet • er klinisk stabile efter at have fået en komplementkomponent 5-hæmmer i mindst de sidste 6 måneder.	Link til anbefaling

Sammenfatning

[redacted]

Application for the assessment of PiaSky (crovalimab) for Paroxysmal Nocturnal Haemoglobinuria (PNH)

Color scheme for text highlighting	
Color of highlighted text	Definition of highlighted text
	Confidential information
[Other]	[Definition of color-code]

Contact information

Contact information	
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[If a company wishes to use external representation in relation to the application for evaluation of a new medicine / extension of indications, the following power of attorney must be completed and sent to medicinraadet@medicinraadet.dk.]

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Tables and Figures

Abbreviations

AE	Adverse event
ADA	Antidrug antibody
BMF	Bone marrow failure
BTH	Breakthrough haemolysis
C3	Complement protein C3
C5	Complement protein C5
CAC	Complement-amplifying complex
CCOD	Clinical cutoff date
CI	Confidence Interval
CTCAE	Common Terminology Criteria for Adverse Events
DTDC-related T3H reactions	Drug-target-drug complexes type 3 hypersensitivity reactions
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30
EQ-5D-5L	5-dimension 5-level EuroQoL questionnaire
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy – Fatigue
GPI	Glycosylphosphatidylinositol
GHS	Global health status
Hb	Haemoglobin

HRQoL	Health-related quality of life
IgG1	Immunoglobulin G1
IL17	Item Library 17
IPIG	International PNH Interest Group
IV	Intravenous
LDH	Lactate dehydrogenase
MAVE	Major adverse vascular event
MedDRA	Medical Dictionary for Regulatory Activities
MFS	Multidimensional fatigue scale
NCI	National Cancer Institute
NICE	National Institute for Health and Care Excellence
PedsQL	Pediatric Quality of Life Inventory
PGI-S	Patient Global Impression of Severity
PIGA	Phosphatidylinositol glycan anchor biosynthesis class A
PNH	Paroxysmal nocturnal haemoglobinuria
PNH-SQ	Paroxysmal nocturnal haemoglobinuria – Symptom Questionnaire
PPQ	Patient Preference Questionnaire
pRBC	Packed red blood cell
PT	Preferred term
QxW	Every x weeks
QoL	Quality of life
QLQ-AA/PNH-54	Quality-of-Life Tool for Patients with Aplastic Anaemia and/or PNH – 54 items
R	Randomization
RBC	Red blood cell
SAE	Serious adverse event
SC	Subcutaneous
SD	Standard deviation
SE	Standard error
SMART-Ig	Sequential monoclonal antibody recycling technology – immunoglobulin
SmPC	Summary of Product Characteristics
SOC	System Organ Class
TA	Transfusion avoidance
TSQM-9	Treatment Satisfaction Questionnaire for Medication – 9
ULN	Upper limit of normal
VAS	Visual analog scale

1. Regulatory information on the medicine

Overview of the medicine	
Proprietary name	PiaSky
Generic name	Crovalimab
Therapeutic indication as defined by EMA	PiaSky as monotherapy is indicated for the treatment of adult and paediatric patients 12 years of age or older with a weight of 40 kg and above with paroxysmal nocturnal haemoglobinuria (PNH): • In patients with haemolysis with clinical symptom(s) indicative of high disease activity. • In patients who are clinically stable after having been treated with a complement 5 inhibitor for at least the past 6 months.
Marketing authorization holder in Denmark	Roche Pharmaceuticals A/S
ATC code	L04AA25
Combination therapy and/or co-medication	Monotherapy
(Expected) Date of EC approval	August 22, 2024
Has the medicine received a conditional marketing authorization?	No
Accelerated assessment in the European Medicines Agency (EMA)	No
Orphan drug designation (include date)	No
Other therapeutic indications approved by EMA	None
Other indications that have been evaluated by the DMC (yes/no)	None
Dispensing group	BEGR
Packaging – types, sizes/number of units and concentrations	Each vial contains 340 mg of crovalimab in 2 mL (170 mg/mL)

2. Summary table

Summary	
Therapeutic indication relevant for the assessment	Crovalimab as monotherapy is indicated for the treatment of adult and paediatric patients 12 years of age or older with a weight of 40 kg and above with paroxysmal nocturnal haemoglobinuria (PNH) in patients with haemolysis with clinical symptom(s) indicative of high disease activity as well as in patients who are clinically stable after having been treated with a complement 5 inhibitor for at least the past 6 months.
Dosage regiment and administration	The recommended dosing regimen consists of one loading dose administered by intravenous infusion (on Day 1), followed by four additional weekly loading doses administered by subcutaneous injection (on Days 2, 8, 15, and 22). The maintenance dose starts on Day 29 and is then administered every 4 weeks by subcutaneous injection. The doses are based on the patient's body weight.
Choice of comparator	Eculizumab. Ravulizumab is used in the health economic assessment only, as agreed with the DMC
Prognosis with current treatment (comparator)	The prognosis has improved significantly with the advent of C5 inhibitors. Therapy with C5 inhibitors has shown to reduce the thromboembolic risk, thereby impacting on the disease course, morbidity, and long-term survival (1)
Type of evidence for the clinical evaluation	**Pivotal study:** COMMODORE 2: Head-to-head phase 3, randomized study conducted in patients, body weight ≥ 40 kg, diagnosed with PNH and have not been previously treated with a complement protein C5 (C5) inhibitor therapy. Primary objective: To demonstrate that crovalimab has non-inferior efficacy versus eculizumab, based on the co-primary efficacy endpoints of haemolysis control and transfusion avoidance. **Supportive study:** COMMODORE 1: Phase 3, randomized study, evaluating the safety, pharmacokinetics, pharmacodynamics and efficacy of crovalimab compared with eculizumab in patients with PNH currently treated with complement inhibitors.
Most important efficacy endpoints (Difference/gain compared to comparator)	Only efficacy endpoints from COMMODORE 2 are mentioned here. Crovalimab demonstrated non-inferiority to eculizumab for the co-primary efficacy endpoints of haemolysis control from week 5 through week 25, and transfusion avoidance (TA) from baseline through week 25. **Hemolysis control:** The odds ratio (crovalimab vs eculizumab) was 1.02 and the lower limit of the 95% confidence interval (CI) for the odds ratio of 0.57 was greater than the pre-defined non-inferiority margin of 0.2. **TA:** The weighted difference in the proportion of patients with TA (crovalimab versus eculizumab) was −2.8% with a lower limit of the 95% CI of −15.67%, which was higher than the pre-defined non-inferiority margin of −20%. Crovalimab demonstrated non-inferiority to eculizumab for the secondary efficacy endpoints of proportion of patients with breakthrough haemolysis (BTH) and haemoglobin stabilization from baseline through Week 25. **(BTH)**: The weighted difference in proportions of patients with BTH (crovalimab vs eculizumab) was −3.9%, and the

Summary	
	upper limit of the 95% CI for the difference in the proportions was 5.3%, which is lower than the pre-defined non-inferiority margin of 20%. **Stabilized Haemoglobin:** The weighted difference (crovalimab versus eculizumab) was 2.2% and the lower limit of the 95% CI of −11.4% was higher than the pre-defined non-inferiority margin of −20%.
Most important serious adverse events for the intervention and comparator	**COMMODORE 2:** In the primary safety period, SAEs that were considered by the investigator to be related to the study drug were reported in 3.0% vs 1.4%, in the crovalimab arm vs the eculizumab arm, respectively. In the crovalimab arm they were: thrombocytopenia, pyrexia, epistaxis, infusion-related reaction. In the eculizumab arm it was thrombocytopenia. **COMMODORE 1:** There were no SAEs that were considered by the investigator to be related to crovalimab or eculizumab in the primary safety period. The most frequent treatment-related AE by PT in the crovalimab arm was transient immune complex reactions (15.9% vs 0% in the eculizumab arm). Two of these were of Grade 1 or 2 in severity and four events were of Grade 2.
Impact on health-related quality of life	HRQoL is assessed using EQ-5D-5L and EORTC QLQ-C30. There is no difference in HRQoL between crovalimab and eculizumab in both COMMODORE 2 and 1. The economic model is a cost minimization model, so HRQoL is assumed equal and left out of the model.
Type of economic analysis that is submitted	Cost-minimizing
Data sources used to model the clinical effects	COMMODORE 1 and COMMODORE 2
Data sources used to model the health-related quality of life	Not applicable.
Life years gained	Not applicable.
QALYs gained	Not applicable.
Incremental costs	-10.6 mio. DKK
ICER (DKK/QALY)	Not applicable.
Uncertainty associated with the ICER estimate	Weight of the patients has the biggest impact on the incremental costs. QALY unaffected by assumptions in the model.
Number of eligible patients in Denmark	0-1 new eligible patients pr year. Currently 25-30 patients are treated with C5 inhibitors in Denmark.

Summary	
Budget impact (in year 5)	-12.2 mio. DKK

3. The patient population, intervention, choice of comparator(s) and relevant outcomes

3.1 The medical condition

Paroxysmal nocturnal haemoglobinuria (PNH) is a rare, clinically heterogeneous blood disorder characterized by intravascular haemolysis due to uncontrolled activation of the terminal complement pathway (2, 3). It can develop at any age, with the average age of onset in the early 30s and can be fatal if left untreated. Important complications and symptoms of PNH include thrombosis, anaemia and transfusion requirements, fatigue and myelodysplastic syndrome.

3.1.1 The Pathophysiology

PNH develops when hematopoietic cells acquire somatic mutations in the X-linked gene encoding phosphatidylinositol glycan anchor biosynthesis class A (PIGA) (4, 5). Mutations in PIGA result in a deficiency in the glycosylphosphatidylinositol (GPI) protein, which is responsible for anchoring other protein moieties to the surface of erythrocytes, granulocytes, monocytes, platelets and lymphocytes (4, 5). The progeny of affected cells are deficient in all GPI-anchored proteins that are normally expressed on hematopoietic cells, including the complement regulatory proteins CD59 and CD55 (6). These proteins have key roles related to complement cascade within the immune system: CD59 blocks the formation of the membrane attack complex on the cell surface, preventing complement-mediated damage to erythrocytes and platelets ((7, 8); and CD55 controls early complement activation, inhibiting C3 and C5 convertases (9, 10). The absence of these regulatory proteins leads to complement-mediated lysis of the red blood cells and, in turn, intravascular haemolysis, resulting in anaemia and haemoglobinuria and risk of potentially life-threatening thromboembolic events.

3.1.2 The clinical presentation and symptoms

Due to the complement-mediated haemolysis, patients with PNH may present with varying intial symptoms, from fatigue and weakness, haemoglobinuria (dark urine), smooth muscle dystonia (abdominal pain, erectile dysfuntion, and dysphagia) to more severe symptoms including dyspnea (i.e., shortness of breath), thrombosis and renal dysfunction or damage (2, 3); later in the course of this chronic disease, bone marrow

failure (BMF) can also occur. The severity and types of symptoms can vary widely among individuals.

3.1.2.1 Thrombosis

The most common complication of PNH is thrombosis, which can occur at any site, but typically in the intra-abdominal and cerebral veins (11). Patients with PNH are reported to have at least a 62-fold higher risk of a thrombotic event than the general population (12). It is reported that these thrombotic events account for up to 67% of PNH-related deaths (1, 13). Hence, thromboembolism is the most common cause of mortality in patients with PNH (when the cause is known) (11). Like many of the clinical manifestations of PNH, the incidence of thrombosis is variable and a positive correlation exists with PNH clone size (14-17).

3.1.2.2 Anaemia

Chronic anaemia and the need for transfusion are common outcomes for patients with PNH, regardless of treatment with C5 inhibitors (17, 18), and at least 36% of patients can experience continued transfusion dependence requiring one or more transfusions a year (19).

3.1.2.3 Fatigue

Fatigue is highly prevalent and debilitating in PNH, in both C5 inhibitor experienced and naive patients, with a significant impact on patients' wellbeing and daily functioning (16, 20). Compared with the general population, the levels of fatigue that patients with PNH experience are clinically worse and often severe. Studies have reported total FACIT-Fatigue scores approximately 8–14 points lower (indicating clinically worse fatigue) for patients with PNH compared with the general population (20).

3.1.2.4 Haemoglobinuria

As a result of the haemolysis, free Hb is released in the serum and eventually excreted via the urine (haemoglobinuria) leading to dark coloured urine. However, not every 19 patient with PNH has dark urine: haemoglobinuria is cited by almost 50% of patients (13).

3.1.2.5 Renal dysfunction or damage

Free Hb is toxic to the kidneys. Hence, kidney failure is a source of morbidity and mortality in patients with PNH. Renal dysfunction or damage present in up to 65% of PNH patients (21).

3.1.3 Classification of PNH

The International PNH Interest Group (IPIG) has developed a classification scheme of PNH based on the clinical manifestation of the disease including clone size, haemolysis and bone marrow disorder. The three subtypes are: classical PNH, PNH in the context of other primary bone marrow disorders and subclinical PNH (22).

3.1.4 Method of diagnosis

Detection of PNH as early as possible is essential for improving prognosis. However, PNH diagnosis is frequently delayed as a result of the varied clinical symptoms at presentation (23). Diagnosis of PNH can take from close to 2 years to more than 5 years and often requires visits to multiple healthcare providers to reach a correct diagnosis (24). A diagnosis of PNH may be suspected if a patient presents with intravascular haemolysis symptoms (i.e., cytopenia, bone marrow failure, thrombosis, Coombs'-negative haemolysis and haemoglobinuria), with no known cause (25). Diagnosis typically involves a combination of blood tests, including a complete blood count (CBC), flow cytometry to detect deficient proteins on blood cells, and tests for hemolysis.

3.1.5 Patient prognosis

Evidence suggests that if left untreated, the 10-year mortality among patients with PNH is 29% (26). In the 1990s, before the introduction of C5 inhibitors, median survival of patients with PNH was estimated as 10 years (2). Data from the Korean PNH registry suggests that among the patients who died, prevalence of thromboembolism, impaired renal function and PNH-cytopenia was 53.5%, 16.3% and 63%, respectively (27), suggesting that these factors may be associated with poorer prognosis. This is in line with data from the International PNH Registry that suggest that thrombotic events and impaired renal function are major complications of the disease (16).

In the International PNH Registry, mortality was estimated as 5.2% in a sample of 2356 patients with any PNH type, who were followed up for a median of 24 months (28). By subtype, mortality was 5.1% for those with classic PNH (median follow-up, 24 months) and 11.7% for PNH in the context of aplastic anaemia (median follow-up 12 months) (28).

The prognosis for PNH has improved significantly with the advent of complement inhibitors, though the disease still requires careful management. The current therapy with C5 inhibitors has shown to reduce the thromboembolic risk, thereby impacting on the disease course, morbidity, and long-term survival (1).

3.2 Patient population

In a Danish study of the PNH population, it was found that during the study period (1977-2016), 115 patients were registered with PNH. At diagnosis their median age was 48.4 (IQR: 44.5-51.9) years, and the median age of death was 67.3 (IQR: 62.3-72.3) years (29). In a different study conducted in Denmark, median age of death was 71.5 (95% CI: 56.5-79.6) (30). The incidence rates per 100.000 person-years in 2008-1016 were 0.08 for PNH, and the prevalence per 100.000 was in 2015 1.04 (30). In a third registry study from Denmark, the prevalence was found to be increasing from 2006 (13 patients) to 2021 (62 patients) (31).

Table 1 Incidence and prevalence in the past 5 years

Year	[2019]	[2020]	[2021]	[2022]	[2023]
Incidence in Denmark (30, 32)	3-4/year 0,08/ 100.000 individuals	3-4/year 0,08/ 100.000 individuals	3-4/year 0,08/ 100.000 individuals	3-4/year 0,08/ 100.000 individuals	3-4/year 0,08/ 100.000 individuals
Prevalence in Denmark (30)	60 1,04/ 100.000 individuals	61 1,04/ 100.000 individuals	62 1,04/ 100.000 individuals	62 1,04/ 100.000 individuals	62 1,04/ 100.000 individuals
Global prevalence *	5-20/mill.	5-20/mill.	5-20/mill.	5-20/mill.	5-20/mill.

* For small patient groups, also describe the worldwide prevalence. Although epidemiological data are sparse, previous estimates of PNH prevalence range from 5 to 20 patients per one million population (33, 34).

The patient population of interest to this application are PNH patients classified as "classic PNH" which includes patients with heamolysis and thrombosis. For patients with classical PNH, C5 inhibition is recommended as treatment option in Denmark (35, 36). Of the full PNH population, approximately 50% are candidates for complement inhibition. Currently between 25-30 patients are treated with C5 inhibitors (36), and all of these will be candidates for crovalimab. The incidence is 3-4 patients per year (30, 32), and half of these will be candidates for complement inhibition. We estimate that 0-1 patients per year will be candidates for crovalimab treatment due to the new recommendation of pegcetacoplan and patient preferences.

Table 2 Estimated number of patients eligible for treatment

Year	Year 1	Year 2	Year 3	Year 4	Year 5
Number of patients in Denmark who are eligible for treatment in the coming years*. Reference: (35, 36)	25-30	25-30	25-30	25-30	25-30

3.3 Current treatment options

In Denmark the treatment guideline for PNH has been published by the Danish Haematological Society in 2013 (35). Treatment alternatives include blood transfusion, oral iron and folic acid supplementation, bone marrow transplantation, and medicines targeting the complement system.

Current Danish treatment guidelines are based on the treatment algorithm outlined by the PNH Education Study Group (PESG) founded on the three treatment categories: Supportive/immunosuppressive treatments, treatments changing the course of disease, and potential curative treatment. These international treatment guidelines are based on

the publication ‘Diagnosis and management of paroxysmal nocturnal hemoglobinuria’ by Parker et al. 2005 (22), and the update on PNH diagnosis and management (37).

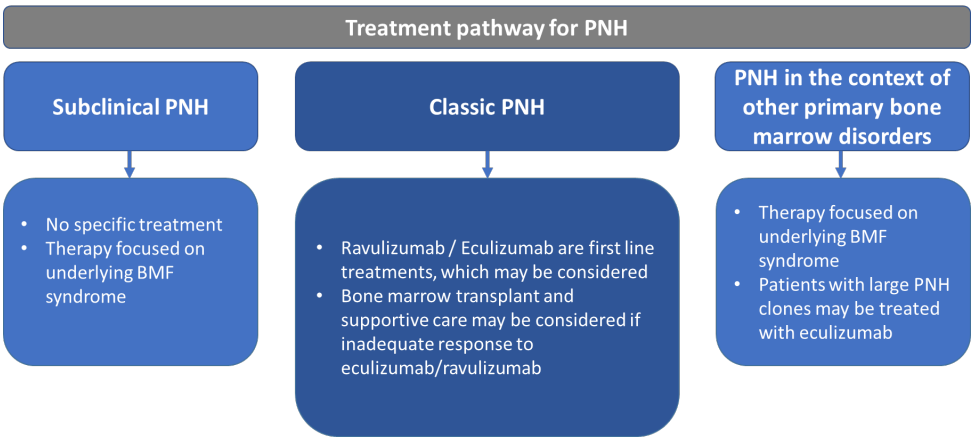


Figure 1 Treatment pathway for PNH.

BMF, bone marrow failure; PNH, paroxysmal nocturnal haemoglobinuria. Source: Based on recommendations described in (38).

Complement inhibitor therapy

To date, EMA have approved two C5 inhibitors for patients with PNH: eculizumab (Soliris)(39) and ravulizumab (Ultomiris) (40), two biosimilars of eculizumab: Bekemv and Epysqli (41, 42), and one C3 inhibitor: pegcetacoplan (Aspaveli) (43). Both eculizumab and ravulizumab are administered IV: eculizumab every 2 weeks and ravulizumab every 8 weeks. Pegcetacoplan is administered SC twice weekly.

In Denmark, C5 inhibitors are standard of care for treatment of PNH. Patients that do not have a satisfactory response on C5 inhibitors can be shifted to pegcetacoplan. In August 2024, pegcetacoplan was also recommended for treating complement inhibitor naïve adults with PNH (32).

Ravulizumab and eculizumab are considered equal (44), but ravulizumab is preferred due to its longer dosing interval and more consistent complement inhibition compared to eculizumab. With the introduction of biosimilar eculizumab in 2023, there has been a significant reduction in the price of eculizumab. This means that the majority of patients are currently treated with biosimilar eculizumab. According to a Danish PNH expert around 8-9 patients in Denmark are treated with ravulizumab (personal communication with Senior Consultant Ulrik Overgaard).

A small percentage of patients find that treatment with eculizumab or ravulizumab is not effective enough in preventing anemia. Currently, there are around 25-30 patients in Denmark receiving treatment with either ravulizumab or eculizumab, of which approximately 8-10 do not have a satisfactory response (36).

3.4 The intervention

PiaSky (crovalimab) is an IgG1 monoclonal antibody of the engineered IgG1 kappa subclass with silenced Fc gamma receptor and C1q binding. Crovalimab specifically binds to C5 of the complement system, with high affinity in a domain of the β-chain, thus inhibiting its cleavage into C5a and C5b and preventing the generation of the terminal complement complex C5b9. Crovalimab inhibits terminal complement-mediated intravascular haemolysis in patients with PNH.

Crovalimab is a humanized antibody developed based on SMART-Ig technology, with pH-dependent antigen binding and enhancement of neonatal Fc receptor binding to improve antibody recycling efficiency, which results in prolonged complement inhibition through reduced C5 accumulation and a prolonged crovalimab functional half-life (typical half-life of 58.7 days (45).

Overview of intervention	
Therapeutic indication relevant for the assessment	PiaSky (crovalimab) as monotherapy is indicated for the treatment of adult and paediatric patients 12 years of age or older with a weight of 40 kg and above with paroxysmal nocturnal haemoglobinuria (PNH): • In patients with haemolysis with clinical symptom(s) indicative of high disease activity. • In patients who are clinically stable after having been treated with a complement 5 inhibitor for at least the past 6 months
Method of administration	PiaSky is administered as an intravenous (IV) infusion (first dose) and as a subcutaneous (SC) injection (subsequent doses).
Dosing	The recommended dosing regimen consists of one loading dose administered by intravenous infusion (on Day 1), followed by four additional weekly loading doses administered by subcutaneous injection (on Days 2, 8, 15, and 22). The maintenance dose starts on Day 29 and is then administered every 4 weeks by SC injection. The doses to be administered are based on the patient's body weight, as shown in below. For patients switching from treatment with another complement inhibitor, the first intravenous loading dose of PiaSky should be administered at the time of the next scheduled complement inhibitor administration. The administration of the additional SC loading doses and maintenance doses of PiaSky will follow as per the schedule shown below. **PiaSky dosing regimen based on body weight**

Overview of intervention			
	Body weight	**≥ 40 kg to < 100 kg**	**≥ 100 kg**
	Loading Dose Day 1 Day 2, 8, 15, 22	1 000 mg (intravenous) 340 mg (subcutaneous)	1 500 mg (intravenous) 340 mg (subcutaneous)
	Maintenance dose Day 29 and Q4W[a] thereafter	680 mg (subcutaneous)	1 020 mg (subcutaneous)
	[a] Q4W=every 4 weeks		
Dosing in the health economic model (including relative dose intensity)	Same as above. Weight assumed like a pooled population from COMMODORE 1 AND 2 (46, 47). 3.43% ≥ 100 Kg 96.57% < 100 Kg		
Should the medicine be administered with other medicines?	No, this medicine is used as monotherapy		
Treatment duration / criteria for end of treatment	Crovalimab is intended for long-term treatment unless the discontinuation of crovalimab is clinically indicated. Owing to its mechanism of action, crovalimab therapy must be administered with caution to patients with active systemic infections. End of treatment can be needed due to immunogenicity leading to loss of exposure and efficacy. Patients may develop anti-drug antibodies (ADAs) that can interfere with crovalimab exposure. Development of ADAs may lead to loss of crovalimab exposure, which may subsequently result in loss of crovalimab efficacy. Loss of efficacy and loss of exposure resulting from ADA development has been observed in patients treated with crovalimab in clinical studies.		
Necessary monitoring, both during administration and during the treatment period	It is recommended that patients are monitored for the first 30 days after switching from eculizumab or ravulizumab to crovalimab for occurrence of the symptoms of transient immune complex reactions.		
Need for diagnostics or other tests (e.g. companion	To reduce the risk of infection, all patients must be vaccinated with a tetravalent meningococcal vaccine at least 2 weeks prior to receiving the first dose of crovalimab. A Controlled Access Program regarding vaccination status will be		

Overview of intervention	
diagnostics). How are these included in the model?	introduced for PiaSky. However monitoring of vaccination status for current PNH patients is already part of clinical practice in Denmark.
Package size(s)	Each vial of 2 mL contains 340 mg of crovalimab. Each mL of solution for injection/infusion contains 170 mg crovalimab.

3.4.1 The intervention in relation to Danish clinical practice

Owing to its advanced recycling mechanism (SMART-Ig), crovalimab has a long half-life (estimated as 58.7 days (45) and high bioavailability (100% in the COMPOSER study (48), enabling it not only to be administered SC, but also at a reduced dosing schedule (every 4 weeks) compared with other complement inhibitors administered SC (49).

The SC administration of crovalimab enables potential administration at home by the patient or a caregiver rather than being administered at the clinic. Crovalimab therefore provides a more convenient and less invasive therapeutic option for patients compared with eculizumab and ravulizumab, which are administered via IV infusion. Moreover, the less frequent dosing schedule and possibility of administration at home, reduces healthcare burden for both the patient and health care professional.

Crovalimab binds to a different C5 binding site than eculizumab and ravulizumab and is therefore effective for patients with the C5 R885H polymorphisms that are not treatable using the current standard of care (50).

With the introduction of crovalimab in Denmark it is expected that crovalimab will replace eculizumab and ravulizumabin the current treatment algorithm, both in newly diagnosed patients and in patients currently treated with a C5 inhibitor. This is based on the non-inferior efficacy compared to eculizumab (COMMODORE 2) (46), and its favourable administration form. Additionally, the phase III study (COMMODORE I) has shown that crovalimab is safe and effective in patients switching from another C5 inhibitor (47).

3.5 Choice of comparator(s)

Based on consultations with clinical experts, it has been confirmed that the majority of patients treated with a C5 inhibitor has been switched to biosimilar eculizumab, however, 8-9 patients remain on ravulizumab (personal communication with Senior Consultant Ulrik Overgaard). It is assumed that all newly diagnosed PNH patients who are candidates for C5 inhibitor treatment, will start treatment with biosimilar eculizumab. Since crovalimab is indicated for the treatment of adult and paediatric PNH patients 12 years or above, with either high disease activity or in patients who are clinically stable after having been treated with a C5 inhibitor for at least the past 6 months, the relevant comparators are therefore eculizumab and ravulizumab. However,

in the clinical studies ALXN1210-PNH-301 and ALXN1210-PNH-302, it was demonstrated that ravulizumab was non-inferior to eculizumab (44, 51), and therefore eculizumab will be the main comparator, and ravulizumab will only be included as a comparator in the health economic model as agreed with the DMC.

Overview of comparator (eculizumab) (39)	
Generic name	Eculizumab
ATC code	L04AA25
Mechanism of action	Eculizumab is a terminal complement inhibitor that specifically binds to the complement protein C5 with high affinity, thereby inhibiting its cleavage to C5a and C5b and preventing the generation of the terminal complement complex C5b-9. Eculizumab preserves the early components of complement activation that are essential for opsonization of microorganisms and clearance of immune complexes (52).
Method of administration	Intravenously
Dosing	The PNH dosing regimen for adult patients (≥18 years of age) consists of a 4-week initial phase followed by a maintenance phase: Initial phase: 600 mg of eculizumab administered via a 25 – 45 minute (35 minutes ± 10 minutes) intravenous infusion every week for the first 4 weeks. Maintenance phase: 900 mg of eculizumab administered via a 25 – 45 minute (35 minutes ± 10 minutes) intravenous infusion for the fifth week, followed by 900 mg of eculizumabs administered via a 25 – 45 minute (35 minutes ± 10 minutes) intravenous infusion every 14 ± 2
Dosing in the health economic model (including relative dose intensity)	Eculizumab was dosed per local prescribing information (as above), included loading doses followed by maintenance dosing with intravenous infusion every 2 weeks.
Should the medicine be administered with other medicines?	No, this medicine is used as monotherapy
Treatment duration/ criteria for end of treatment	Eculizumab is intended for long-term treatment unless the discontinuation of eculizumab is clinically indicated.
Need for diagnostics or other tests (i.e. companion diagnostics)	Treatment with eculizumab increases the risk of severe infection and sepsis, especially of Neisseria meningitidis and other Neisseria species, including disseminated gonorrhoeae. All patients must be monitored for signs of meningococcal infection. The need for patients to be vaccinated against Neisseria meningitidis two weeks prior to receiving eculizumab and to receive antibiotic prophylaxis.
Package size(s)	One vial of 30 ml contains 300 mg of eculizumab (10mg/ml)

3.6 Cost-effectiveness of the comparator(s)

Eculizumab has not previously been assessed by the Danish Medicines Council (DMC) because it was taken into use before the establishment of the DMC in 2017. According to the DMCs guidelines, it is therefore necessary to carry out a comparison against placebo, in this case, best supportive care (blood transfusions etc). However, this comparison falls under what is defined by the DMC as a disproportionately cost-effective comparison. Additionally, eculizumab/biosimilar is considered as an established standard Danish treatment practice over a longer period according to Danish clinical experts. Therefore, also according to the DMC's method's guide, a supplementary analysis against placebo will not be carried out in the current application as it is deemed irrelevant

3.7 Relevant efficacy outcomes

3.7.1 Definition of efficacy outcomes included in the application

The primary efficacy objective for the COMMODORE 2 study was to evaluate the efficacy of crovalimab compared with eculizumab, based on the non-inferiority assessment of the co-primary endpoints listed below. If non-inferiority was established for the co-primary endpoints, then the secondary endpoints, including superiority testing of primary and secondary endpoints, were tested using a pre-specified hierarchical order. Both co-primary efficacy endpoints needed to be met to conclude non-inferiority of crovalimab to eculizumab. For COMMODORE 2, all primary and secondary efficacy outcomes are listed in Table 3. Exploratory outcomes from COMMODORE 2 will not be presented in section 6 and have therefore not been listed in Table 3, but a list of all outcomes can be found in Appendix A.

The primary objective for the COMMODORE 1 study was to evaluate the safety and tolerability of crovalimab compared with eculizumab in C5-inhibitor treated PNH patients. The exploratory efficacy objective of this study was to evaluate the efficacy of crovalimab compared with eculizumab in randomized Arms A and B, and the efficacy of crovalimab in non-randomized Arm C. The exploratory endpoints presented in section 5 are listed in Table 3. All exploratory endpoints are listed in Appendix A.

Table 3 Efficacy outcome measures relevant for the application

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
Transfusion avoidance (TA) [Co-primary endpoint in COMMODORE 2] [Exploratory endpoint in COMMODORE 1]	From baseline through Week 25 (after 24 weeks on treatment)	Proportion of patients who achieve transfusion avoidance Transfusion avoidance is defined as patients who are pRBC transfusion-free and do not require transfusion per protocol-specified guidelines.	pRBC transfusions were recommended when a patient had hemoglobin ≤9 g/dL with clinical signs and symptoms of sufficient severity to warrant transfusion or hemoglobin ≤7 g/dL regardless of clinical signs Note that, as a conservative analysis approach, patients who prematurely withdrew

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
			from study treatment before Week 25 were assumed to have undergone a transfusion.
Haemolysis control [Co-primary endpoint in COMMODORE 2] [Exploratory endpoint in COMMODORE 1]	Q2W from Week 5 through Week 25	Proportion of patients with haemolysis control defined as LDH ≤ 1.5 × ULN	Measured by LDH ≤ 1.5 × ULN from Q2W from Week 5 through Week 25 (as measured at the central laboratory)
Breakthrough Hemolysis (BTH) [Secondary endpoint in COMMODORE 2] [Exploratory endpoint in COMMODORE 1]	From baseline through Week 25	Proportion of patients with BTH. BTH was defined as at least one new or worsening symptom or sign of intravascular hemolysis in the presence of elevated LDH ≥2 ULN after prior reduction of LDH to ≤1.5 x ULN on treatment As a conservative analysis approach, patients withdrawing from study treatment before Week 25 were assumed to have experienced a BTH event in the unobserved period before Week 25.	Intravascular haemolysis was defined by the following: fatigue, haemoglobinuria, abdominal pain, shortness of breath [dyspnea], anaemia [haemoglobin < 10 g/dL], a major adverse vascular event [MAVE[#]] incl. thrombosis, dysphagia, or erectile dysfunction
Stabilization of haemoglobin [Secondary endpoint in COMMODORE 2] [Exploratory endpoint in COMMODORE 1]	From baseline through Week 25	Proportion of patients with stabilized haemoglobin defined as avoidance of a ≥ 2 g/dL decrease in haemoglobin level from baseline, in the absence of transfusion.	Stabilization of haemoglobin was analyzed using the same methodology as for TA. As a conservative analysis approach, patients who withdrew from study treatment before Week 25 were assumed to not have met haemoglobin stabilization criteria
FACIT-Fatigue [Secondary endpoint in COMMODORE 2] [Exploratory endpoint in COMMODORE 1]	From baseline to Week 25	Mean change from baseline in fatigue as assessed by the Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-Fatigue) scale	The FACIT-Fatigue scale is a 13-item patient-reported outcome instrument designed to assess fatigue-related symptoms and impacts on daily functioning, with a total score ranging from 0 to 52.

* Time point for data collection used in analysis (follow up time for time-to-event measures)
[#]A MAVE is defined as any of the following events: thrombophlebitis/deep vein thrombosis; pulmonary embolus; myocardial infarction; transient ischemic attack; unstable angina; renal vein thrombosis; acute

peripheral vascular occlusion; mesenteric/visceral vein thrombosis or infarction; mesenteric/visceral arterial thrombosis or infarction; hepatic/portal vein thrombosis (budd-Chiari syndrome); cerebral arterial occlusion/cerebrovascular accident; cerebral venous occlusion; renal arterial thrombosis; gangrene (non-traumatic, non-diabetic); amputation (non-traumatic, non-diabetic); dermal thrombosis. (46, 47)

Validity of outcomes

All listed efficacy outcome measures are valid and used in the majority of PNH clinical studies as also demonstrated in the DMC assessments of Aspaveli (pegcetacoplan(32, 36). Additionally, a recent systematic review describes the efficacy and safety of current treatments for PNH (53), and key efficacy endpoints across the studies were transfusion avoidance, LDH normalization and stabilized hemoglobin levels similar to what is described in table 3. BTH was a key secondary endpoint in the review.

4. Health economic analysis

4.1 Model structure

A cost minimisation model that was implemented in Microsoft® Excel, with minimal aspects programmed in Visual Basic for Applications. Microsoft® Excel was selected as the most appropriate software for this model as it is freely available and widely understood.

A cost-minimization analysis was conducted between crovalimab and eculizumab with outcomes expressed as incremental costs per patient. The use of this type of economic model is in accordance with Danish Medical Council (54) where the new pharmaceutical has an effect that is equal to the current comparator.

The model considered drug acquisition, administration, blood transfusion, and medical resource use costs. In each two-week cycle, the proportion of patients remaining on treatment (i.e. those who were alive) is determined in order to calculate drug acquisition and administration costs. A scenario analysis is considered in which the proportion of patients remaining on treatment also accounts for spontaneous remission.

In those who remained on treatment, a rate of BTH events is modelled in order to incorporate the costs of single up-dosing for crovalimab and eculizumab, along with the costs of blood transfusions and medical resource use. A proportion of eculizumab patients are assumed to require continuous up-dosing.

For ease of comparison, the model also includes a separate sheet presenting tabulated costs for the first year and the second year onwards. These costs incorporate drug acquisition and administration costs only.

4.2 Model features

Table 4 Features of the economic model

Model features	Description	Justification
Patient population	Adult patients with PNH	Not Available
Perspective	Limited societal perspective	According to DMC guidelines

Model features	Description	Justification
Time horizon	Lifetime (60 years)	To capture all health benefits and costs in line with DMC guidelines. Based on mean age at diagnosis in the Danish population (60 years).
Cycle length	2 weeks	Consistent with length of eculizumab treatment cycle (55)
Half-cycle correction	Yes	
Discount rate	3.5 % 2.5 %	The DMC applies a discount rate of 3.5 % for first 35 years, then 2.5% for until 75 years (56)
Intervention	Crovalimab	
Comparator(s)	Eculizumab	According to national treatment guideline.
Outcomes	BTH-events, Blood transfusions, Spontaneous remission and up-dosing	These are the relevant endpoint in the commodore-studies and for patients

5. Overview of literature

5.1 Literature used for the clinical assessment

This application is primarily based on the pivotal phase III study COMMODORE 2 (BO42162), a randomised eculizumab-controlled study in complement inhibitor-naïve patients. The application is supported by two additional Phase III studies: COMMODORE 1 (BO42161), a supportive eculizumab-controlled study in switch patients and COMMODORE 3 (YO42311), a supportive study in complement inhibitor-naïve patients from China. All three studies have been published, please see Table 5, and since the comparator is relevant to Danish clinical practice, a systematic literature review has not been performed.

Table 5 Relevant literature included in the assessment of efficacy and safety

Reference (Full citation incl. reference number)*	Trial name*	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of*
Röth, A. *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) doi:10.1002/ajh.27412. (46)	COMMODORE 2	NCT04434092 BO42162	Actual study start date: 10/08/2020 Actual primary completion: 16/11/2022 Data cut-off 16/11/2022 Future data cut-offs (estimated study completion) 30/06/2028	Effectiveness of crovalimab vs. eculizumab in patients with PNH naive to complement inhibition
Scheinberg, P. *et al.* Phase 3 randomized COMMODORE 1 trial: Crovalimab versus eculizumab in complement inhibitor-experienced patients with paroxysmal nocturnal hemoglobinuria. *Am. J. Hematol.* (2024) doi:10.1002/ajh.27413. (47)	COMMODORE 1	NCT04432584 BO42161	Actual study start date: 30/09/2020 Estimated primary completion: 16/11/2022 Data cut-off 16/11/2022 Estimated study completion: 01/09/2029	Safety of crovalimab vs. eculizumab in patients with PNH currently treated with complement inhibitors Descriptive comparison of the efficacy of crovalimab vs eculizumab in patients with PNH currently treated with complement inhibitors
Liu, H. *et al.* Efficacy and safety of the C5 inhibitor crovalimab in complement inhibitor-naive patients with PNH (COMMODORE 3): A multicenter, Phase 3, single-arm study. *Am. J. Hematol.* **98**, 1407–1414 (2023). (57)	COMMODORE 3	NCT04654468 YO42311	Actual study start date: 17/03/2021 Estimated primary completion: 10/02/2022 Data cut-off 10/08/22 Estimated study completion: 18/02/2028	Used in the pooled safety analysis only

* If there are several publications connected to a trial, include all publications used.

5.2 Literature used for the assessment of health-related quality of life

Health-related quality of life data was obtained from COMMODORE 2 and 1 (see Table 5) where crovalimab was compared to eculizumab, a comparator relevant to Danish clinical practice, and therefore a literature search was not conducted. Data was obtained from the Clinical Study reports from COMMODORE 2 and 1 (58, 59).X

Table 6 Relevant literature included for (documentation of) health-related quality of life (See section 10)

Reference (Full citation incl. reference number)	Health state/Disutility	Reference to where in the application the data is described/applied
Not applicable		

5.3 Literature used for inputs for the health economic model

Data from COMMODORE 1 and COMMODORE 2 was used for input to the economic model, and therefore a literature search was not conducted. COMMODORE 1 and COMMODORE 2 is a direct comparision between crovalimab and eculizumab. Crovalimab is owned by Roche Pharmaceuticals and we know that there are no other relevant studies conducted comparing eculizumab and crovalimab.

Table 7 Relevant literature used for input to the health economic model

Reference (Full citation incl. reference number)	Input/estimate	Method of identification	Reference to where in the application the data is described/applied
Röth, A. *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) doi:10.1002/ajh.27412. (46)	BTH, blood transfusion, spontaneous remission	Only direction comparison of crovalimab and eculizumab	Section 8
Scheinberg P, Clé DV, Kim JS, Nur E, Yenerel MN, Barcellini W, et al. Phase 3 randomized COMMODORE 1 trial: Crovalimab versus eculizumab in complement inhibitor-experienced patients with paroxysmal nocturnal hemoglobinuria. American journal of hematology. 2024;99(9):1757-67.	BTH, blood transfusion, spontaneous remission	Only direction comparison of crovalimab and eculizumab	Section 8

6. Efficacy

This application is primarily based on the pivotal phase 3 study, COMMODORE 2 which was designed to evaluate the non-inferiority of crovalimab compared with eculizumab in participants with PNH who have not been previously treated with complement inhibitor therapy. As supportive information, data from COMMODORE 1 has been included. COMMODORE 1 was designed to evaluate the safety of crovalimab compared with eculizumab in participants with PNH currently treated with complement inhibitors.

The main efficacy results to be presented in this application, are therefore from COMMODORE 2. Efficacy results from COMMODORE 1 will be presented as well, however, these were exploratory endpoints in COMMODORE 1 and will therefore only serve as supporting descriptive information. Efficacy outcomes from COMMODORE 3 will not be included since COMMODORE 3 is a study conducted only in China.

6.1 Efficacy of crovalimab compared to eculizumab in patients with PNH

6.1.1 Relevant studies

6.1.1.1 COMMODORE 2

COMMODORE 2 is a phase 3, randomized, open-label, active-controlled, multicenter study conducted in patients who have a body weight ≥ 40 kg, have been diagnosed with PNH and have not been previously treated with a complement protein C5 (C5) inhibitor therapy. The primary objective of the study was to demonstrate that in previously untreated patients with PNH, crovalimab has non-inferior efficacy versus eculizumab, based on the co-primary efficacy endpoints of haemolysis control and transfusion avoidance.

Study design and study period

This study was divided into two parts: randomized arms (Arms A and B), consisting of adult patients (≥ 18 years old), and a descriptive analysis arm (Arm C), consisting of pediatric patients (< 18 years old). Patients were randomized 2:1 to either receive crovalimab (Arm A) or eculizumab (Arm B) for 24 weeks. Paediatric patients all received crovalimab for the same treatment duration in the descriptive Arm C (Figure 2a). If eligible, adult and paediatric patients initially allocated to crovalimab could enter the subsequent crovalimab extension period (up to 5 years). Patients who initially received eculizumab had the option to switch to crovalimab treatment after the 24-week treatment period. Patients not eligible or not willing to enter crovalimab extension period entered the 10 week-end safety follow-up (Figure 2b).

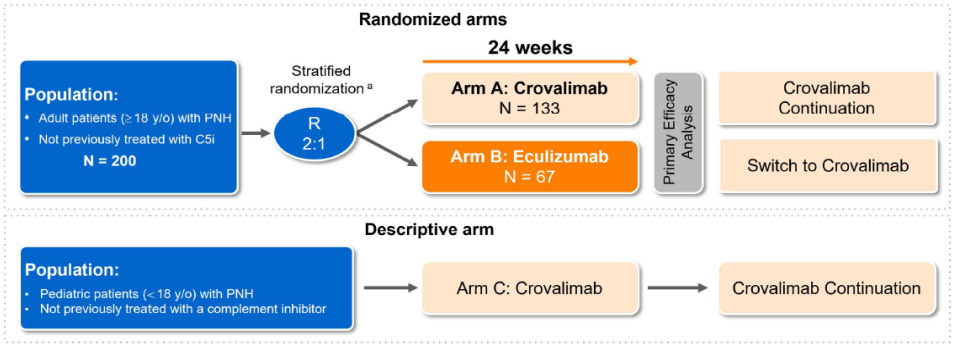
Patients were stratified based on most recent locally measured LDH value (≥2 to ≤4 x upper limit of normal (ULN vs. >4 x ULN) and transfusion history in the prior 6 months (0, >0 to ≤6, and >6 total packed red blood cell (pRBC) units administered)(46).

Intervention

The crovalimab group received a weightbased tiered dosing regimen of crovalimab comprised of a loading series (IV dose on day 1 followed by subcutaneous injection doses on days 2, 8, 15, and 22) and maintenance dosing (subcutaneous injection every 4 weeks starting day 29). Crovalimab self-administration or administration by a caregiver was permitted starting at week 9, after

training and confirmation of proficiency by the healthcare professional. The eculizumab group received eculizumab per local guidelines.

(a)



(b)

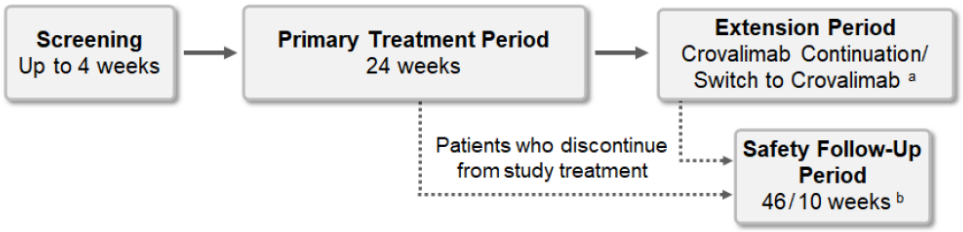


Figure 2. COMMODORE 2 study design and study periods

(**a**) [a]Randomization was stratified based on the most recent LDH value (≥ 2 to ≤ 4 × ULN, and > 4 × ULN) and packed RBC transfusion history (0, > 0 to ≤ 6, and > 6 units) within 6 months prior to randomization. Patients were randomized 2:1 to crovalimab or eculizumab, respectively. Patient number reflects study design, and not actual enrolled patients. C5i, complement protein C5 inhibitor; LDH, lactate dehydrogenase; PNH, paroxysmal nocturnal haemoglobinuria; R, randomization; RBC, red blood cell; ULN, upper limit of normal; y/o, years old (46).

(b) [a]After 24 weeks in the primary treatment period, patients may continue/switch to crovalimab for a maximum of 5 years. [b]Safety follow-up period is 46 weeks for patients who discontinue crovalimab (including a safety follow-up site visit 24 weeks after treatment discontinuation and a safety telephone call 46 weeks [approximately 10.5 months] after treatment discontinuation) and 10 weeks for patients who discontinue eculizumab (46).

Study population

The sample size estimation for the randomized portion of the study (Arms A and B) was based on the noninferiority assessment of the co-primary endpoints of haemolysis control, as assessed by centrally measured LDH, and the proportion of patients who achieve TA during the efficacy period. The final target sample size corresponds to the endpoint that requires the larger number of patients, i.e., TA from baseline to Week 25. Approximately 200 adult patients were to be randomly assigned in a 2:1 ratio to receive either crovalimab (n=133) or eculizumab (n=67), to ensure approximately 180 evaluable patients, assuming a 10% drop-out rate. This sample size was to provide 80% power to demonstrate the non-inferiority of crovalimab to eculizumab with respect to TA, using a non-inferiority margin of -20%, and one-sided Type 1 error rate of 2.5%.

A total of 210 patients were enrolled in COMMODORE 2. All patients weighed ≥40 kg and had documented diagnosis of PNH, confirmed by high sensitivity flow cytometry evaluation with granulocyte and/or monocyte clone size of ≥10%. The main inclusion and exclusion criteria are described in Appendix A. Adult patients (n=204) were randomized to crovalimab (Arm A, n=135)

or to eculizumab (Arm B, n=69). Six paediatric patients entered the paediatric descriptive Arm C. In arm A, one patient did not have a post-baseline LDH assessment; therefore, only 134 patients were analyzed for efficacy.

Most patients received their allocated treatment and completed the primary treatment period of 24 weeks: 95.6% (129 of 135 patients) in Arm A and 98.6% (68 of 69 patients) in Arm B. Most of them continued to receive crovalimab up to the CCOD of 16 November 2022 (94.1% and 95.6%, respectively (46, 60) (Figure 3. Patient disposition in COMMODORE 2 Figure 3).

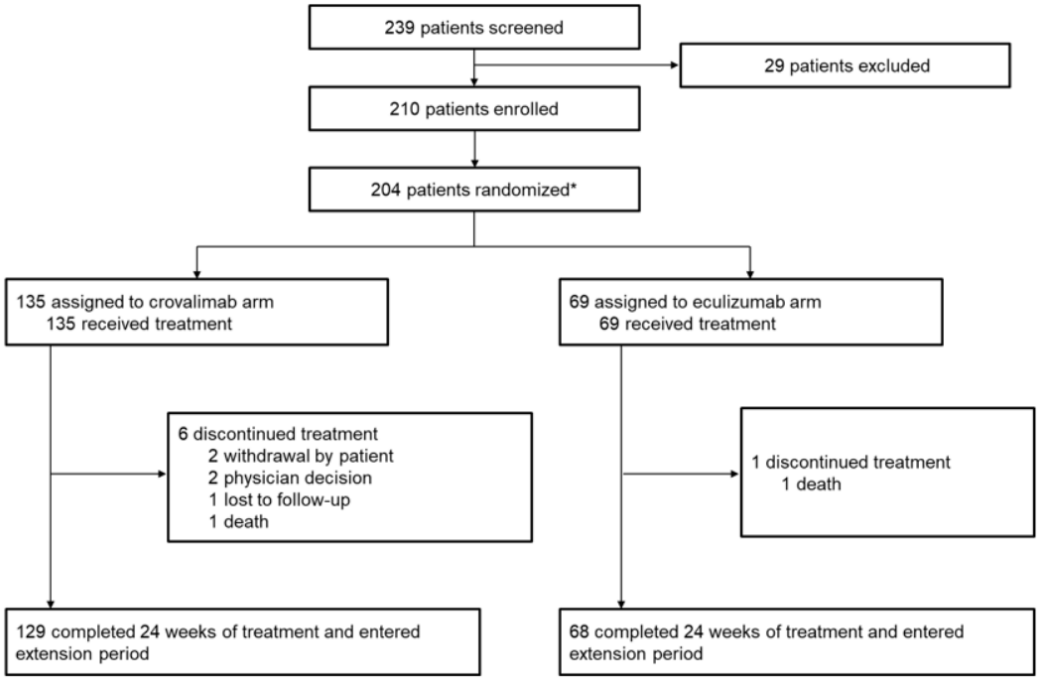


Figure 3. Patient disposition in COMMODORE 2

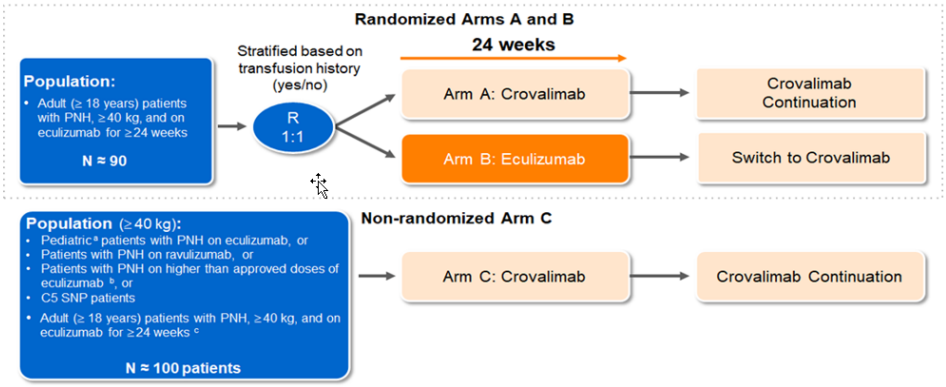
*Six pediatric patients entered the nonrandomized arm and were treated with crovalimab (46)

6.1.1.2 COMMODORE 1

Study design and study periodCOMMODORE 1 is a phase 3, randomized, open-label, active-controlled, multicenter study, designed to evaluate the safety, pharmacokinetics, pharmacodynamics and efficacy of crovalimab compared with eculizumab in patients with PNH currently treated with complement inhibitors. The primary objective for this study was to evaluate the safety and tolerability of crovalimab compared with eculizumab on the basis of various safety endpoints.

COMMODORE 1 consisted of a 4-week screening period and a 24-week primary treatment period, where adult subjects over 40kg were randomized 1:1 to receive crovalimab (Arm A) or eculizumab (Arm B), with randomization stratified by history of packed red blood cell (pRBC) transfusion in the previous 12 months (yes vs. no). The study also included a descriptive arm (Arm C) which is a descriptive cohort which included paediatric patients, patients currently treated with ravulizumab, eculizumab at higher-than-approved doses or with C5 polymorphisms and poorly controlled haemolysis by either of approved anti-C5. Subjects from Arm C all received crovalimab for 24 weeks. Adult and paediatric subjects initially allocated to crovalimab could enter the subsequent crovalimab extension period if eligible. Patients who initially received eculizumab had the option to switch to crovalimab after 24 weeks. Safety follow-up was 46 weeks for 46 weeks for patients who discontinue crovalimab and 10 weeks for other patients (47, 60) (Figure 4a and b).

(a)



(b)

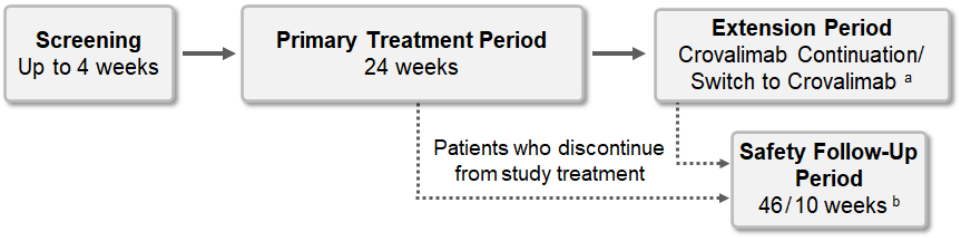


Figure 4 COMMODORE 1 study design and study periods

(a) [a]Patients < 18 years old. [b]Higher-than-approved doses of eculizumab: > 900 mg per dose and/or more frequently than Q2W. [c]This cohort was opened in Arm C (following the stop of randomization into Arms A and B) to patients who had been receiving eculizumab at the approved dose for least 24 weeks and have LDH ≤ 1.5 x ULN at screening. C5, complement protein C5; PNH, paroxysmal nocturnal haemoglobinuria; Q2W, every 2 weeks; R, randomization; SNP, single nucleotide polymorphism (47).

(b) [a]After 24 weeks in the primary treatment period, patients may continue/switch to crovalimab for a maximum of 5 years and then according to Roche Global Policy on Continued Access to Investigational Medicinal Products. [b]Safety follow-up period is 46 weeks for patients who discontinue crovalimab (including a safety follow-up site visit 24 weeks after treatment discontinuation, and a safety telephone call 46 weeks [approximately 10.5 months] after treatment discontinuation) and 10 weeks for patients who discontinue eculizumab (47).

Intervention

Patients randomized to crovalimab received a weight-based tiered dosing regimen of crovalimab, including a loading series (IV dose on Day 1 followed by weekly subcutaneous doses on Days 2, 8, 15, and 22) and maintenance dosing (subcutaneous doses every 4 weeks starting Day 29). Patients randomized to eculizumab continued on the approved maintenance dose of eculizumab (900 mg IV every 2 weeks).

Study population

Sample size

COMMODORE 1 was initially designed to enroll ≈200 patients with PNH into the randomized arms to evaluate the efficacy of crovalimab versus eculizumab and ≈50 patients with PNH in the non-randomized arm. However, given the evolving treatment landscape, with a reduced pool of patients treated with eculizumab over time, randomization was terminated in November 2022. With this change, the initially targeted sample size for the randomized arms could not be reached, providing insufficient statistical power for efficacy analyses. Therefore, all efficacy endpoints became exploratory, and safety became the new primary objective.

Patient disposition

In this study, adult patients (≥18 years old, weighing ≥40 kg) were eligible for inclusion into the randomized arms if they had a documented diagnosis of PNH, confirmed by high-sensitivity flow cytometry, with granulocyte or monocyte GPI-deficient clone size ≥10%. Patients enrolled were receiving approved dosing of eculizumab (900 mg every 2 weeks) for ≥24 weeks prior to the first study drug administration and had lactate dehydrogenase (LDH) levels of ≤1.5 × (ULN) at screening (47).

At the 16 November 2022 CCOD, 146 patients had been screened and 89 patients were randomized in the study. Of these patients, 45 were randomized to crovalimab (Arm A) and 44 were randomized to eculizumab (Arm B). Of the 45 patients randomized to the crovalimab arm, 39 patients (86.7%) completed 24 weeks of treatment and then continued to receive crovalimab treatment in the crovalimab extension period; one 1 patient received no treatment. Of these, 37 patients continued to receive crovalimab treatment up to the CCOD. Of the 45 patients in the crovalimab arm, five 5 patients were still ongoing in the primary treatment period as of the CCOD. Of the 44 patients randomized to the eculizumab arm, 35 patients (79.5%) completed 24 weeks of eculizumab treatment and switched to crovalimab treatment upon entering the crovalimab extension period; two patients received no treatment. Of these, 32 patients continued to receive crovalimab treatment up to the CCOD (16 November 2022). Of the 44 patients in the eculizumab arm, five patients were still ongoing in the primary treatment period as of the CCOD.

At the time of primary analysis, 38 patients were enrolled in the non-randomized Arm C of the study; enrollment is currently ongoing. In Arm C, 21 patients were enrolled into the prior ravulizumab cohort, 10 patients were enrolled into the prior high-dose eculizumab cohort, six patients were enrolled into the C5 polymorphism cohort and one patient was enrolled into the pediatric cohort. All patients in these Arm C cohorts received crovalimab treatment. The single patient in the pediatric cohort was enrolled only approximately 2 weeks prior to the primary analysis CCOD and therefore efficacy data for this patient are limited and not described herein.

Table 8 Overview of study design for studies included in the comparison

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up period
COMMODORE 2 NCT04434092 BO42162	Phase 3, randomized, open-label, active-controlled, multicenter study	After 24 weeks in the primary treatment period, patients may continue/switch to crovalimab for a maximum of 5 years	Patients who have a body weight ≥ 40 kg, have been diagnosed with PNH and have not been previously treated with a C5 inhibitor therapy.	Arm A: Patients who received crovalimab as part of this study did so according to a weight-based tiered dosing approach schedule. An initial IV loading dose was administered on Week 1 Day 1, followed by four weekly SC doses on Week 1 Day 2, then on Weeks 2, 3 and 4. Maintenance dosing began at Week 5 and continued every 4 weeks (Q4W) thereafter, for a total of 24 weeks of primary treatment, followed by the treatment extension period of no more than 5 years. Arm C: Patients received a loading series of crovalimab doses comprising an IV dose on Day 1 Week 1, followed by weekly crovalimab SC doses for 4 weeks, at Week 1 (Day 2) and then at Weeks 2, 3 and 4. Maintenance doses began at	Arm B: Patients randomized to eculizumab received induction doses of 600 mg on Days 1, 8, 15 and 22, followed by maintenance doses of 900 mg on Day 29 and every 2 weeks (Q2W) thereafter. Patients randomized to eculizumab had the opportunity to switch to crovalimab as part of the extension period of the study, once they had completed at least 24 weeks of treatment with eculizumab, if the treating physician determined that this was in their best interest.	<u>The co-primary endpoints were:</u> • Proportion of patients who achieve TA from baseline through Week 25 (after 24 weeks on treatment) • TA is defined as patients who are pRBC transfusion-free and do not require transfusion per protocol-specified guidelines. • Proportion of patients with haemolysis control, measured by LDH ≤ 1.5 × ULN from Week 5 through Week 25 (as measured at the central laboratory) <u>Secondary efficacy endpoints were:</u> • proportion of patients with BTH from baseline through Week 25 • proportion of patients with stabilization of haemoglobin from baseline through Week 25; and • mean change from baseline to Week 25 in fatigue, as assessed by the FACIT-Fatigue scale.

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up period
				Week 5 and were administered Q4W thereafter.		
COMMODORE 1 NCT04432584 BO42161	Phase 3, global, randomized, active-controlled, multicenter study of crovalimab vs eculizumab	After 24 weeks in the primary treatment period, patients may continue/switch to crovalimab for a maximum of 5 years	Patients who have a body weight ≥ 40 kg, have been diagnosed with PNH currently treated with a complement protein C5 (C5) inhibitor therapy.	Arm A: Crovalimab will be administered at a dose of 1000 mg IV (for participants with body weight between 40 and 100kg) or 1500 mg IV (for participants with body weight >=100kg) on Week 1 Day 1. On Week 1 Day 2 and on Weeks 2, 3 and 4, it will be administered at a dose of 340 mg SC. For Week 5 and Q4W thereafter, it will be administered at a dose of 680 mg SC (for participants with body weight between 40 and 100kg) or 1020 mg SC (for participants with body weight >=100kg). Arm C: Crovalimab will be administered at a dose of 1000 mg IV (for participants with body weight between 40 and 100kg) or 1500 mg IV (for participants with body weight >=100kg) on Week 1 Day 1. On	Arm B: Participants will receive 900 mg dose of eculizumab starting on Day 1 and Q2W (every 2 weeks) thereafter for a total of 24 weeks of study treatment. After 24 weeks of study eculizumab treatment, participants will have the option to switch to crovalimab or to discontinue from the study after completion of 10 weeks of safety follow-up.	<u>Exploratory efficacy endpoints presented in section 6:</u> • Proportion of patients who achieve TA from baseline through Week 25 (after 24 weeks on treatment) TA is defined as patients who are pRBC transfusion-free and do not require transfusion per protocol-specified guidelines. • Proportion of patients with haemolysis control, measured by LDH ≤ 1.5 × ULN from Week 5 through Week 25 (as measured at the central laboratory) • Proportion of patients with BTH from baseline through Week 25 • Proportion of patients with stabilization of haemoglobin from baseline through Week 25 • Mean change from baseline to Week 25 in fatigue, as assessed by the FACIT-Fatigue scale. <u>Additional exploratory efficacy endpoints (not presented in section 6)</u> • Percentage change from baseline in LDH levels averaged over Weeks 21, 23 and 25 based on central laboratory LDH measurements. • Proportion of patients with central LDH ≤ 1 × ULN from baseline through Week 25. • Total number of units (based on local equivalent) of pRBCs transfused per patient by Week 25.

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up period
				Week 1 Day 2 and on Weeks 2, 3 and 4, it will be administered at a dose of 340 mg SC. For Week 5 and Q4W thereafter, it will be administered at a dose of 680 mg SC (for participants with body weight between 40 and 100kg) or 1020 mg SC (for participants with body weight >=100kg)		• Proportion of patients who have experienced a MAVE[#] from baseline through Week 25. • Proportion of patients who reach or maintain a haemoglobin level of at least 10 g/dL, without subsequent decrease below 9 g/dL, in the absence of a transfusion.

[#]A MAVE is defined as any of the following events: thrombophlebitis/deep vein thrombosis; pulmonary embolus; myocardial infarction; transient ischemic attack; unstable angina; renal vein thrombosis; acute peripheral vascular occlusion; mesenteric/visceral vein thrombosis or infarction; mesenteric/visceral arterial thrombosis or infarction; hepatic/portal vein thrombosis (budd-Chiari syndrome); cerebral arterial occlusion/cerebrovascular accident; cerebral venous occlusion; renal arterial thrombosis; gangrene (non-traumatic, non-diabetic); amputation (non-traumatic, non-diabetic); dermal thrombosis.

6.1.2 Comparability of studies

Both COMMODORE 2 and COMMODORE 1 are head-to-head studies which provide a direct comparison of crovalimab (the intervention) with eculizumab (the comparator).

6.1.2.1 Comparability of patients across studies

Table 9 Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety

	COMMODORE 2		COMMODORE 1					
	Arm A	Arm B	Arm A	Arm B	Arm C	Arm C	Arm C	Arm C
	Crovalimab N = 135	Eculizumab N = 69	Crovalimab N = 45	Eculizumab N = 44	Crovalimab (< 18 years) n = 1	Crovalimab (Prior Ravulizumab) n = 21	Crovalimab (Prior High-Dose Eculizumab) n = 10	Crovalimab (C5 Polymorphism Cohort) n = 6
Age years **Median (range)**	36.0 (18–76)	38.0 (17–78)	42.0 (21–81)	49.0 (22–85)	16.0 (16–16)	45.0 (27–70)	32.0 (20–58)	58.0 (38–80)
Age <18, n (%)	0	2 (2.9)	0	0	1 (100.0)	0	0	0
Age 18–64, n (%)	122 (90.4)	58 (84.1)	40 (88.9)	37 (84.1)	0	20 (95.2)	10 (100.0)	3 (50.0)
Age ≥ 65, n (%)	13 (9.6)	9 (13.0)	5 (11.1)	7 (15.9)	0	1 (4.8)	0	3 (50.0)
Female	58 (43.0)	34 (49.3)	24 (53.3)	22 (50.0)	0	9 (42.9)	6 (60.0)	4 (66.7)
Male	77 (57.0)	35 (50.7)	21 (46.7)	22 (50.0)	1 (100.0)	12 (57.1)	4 (40.0)	2 (33.3)
Race, n (%)								

	COMMODORE 2		COMMODORE 1					
	Arm A	Arm B	Arm A	Arm B	Arm C	Arm C	Arm C	Arm C
	Crovalimab N = 135	Eculizumab N = 69	Crovalimab N = 45	Eculizumab N = 44	Crovalimab (< 18 years) n = 1	Crovalimab (Prior Ravulizumab) n = 21	Crovalimab (Prior High-Dose Eculizumab) n = 10	Crovalimab (C5 Polymorphism Cohort) n = 6
Asian	86 (63.7)	51 (73.9)	9 (20.0)	7 (15.9)	0	11 (52.4)	0	6 (100.0)
White	45 (33.3)	16 (23.2)	34 (75.6)	32 (72.7)	1 (100.0)	9 (42.9)	6 (60.0)	0
Black or African American	3 (2.2)	1 (1.4)	2 (4.4)	1 (2.3)	0	0	1 (10.0)	0
Unknown	1 (0.7)	1 (1.4)	0	4 (9.1)	0	1 (4.8)	3 (30.0)	0
Ethnicity, n (%)								
Hispanic or Latino	18 (3.3)	6 (8.7)	8 (17.8)	8 (18.2)	0	1 (4.8)	1 (10.0)	0
Not Hispanic or Latino	114 (84.4)	61 (88.4)	36 (80.0)	31 (70.5)	1 (100.0)	20 (95.2)	5 (50.0)	6 (100.0)
Not stated	3 (2.2)	2 (2.9)	1 (2.2)	5 (11.4)	0	0	4 (40.0)	0
Weight at baseline, kg (n)			44	42				

	COMMODORE 2		COMMODORE 1					
	Arm A	Arm B	Arm A	Arm B	Arm C	Arm C	Arm C	Arm C
	Crovalimab N = 135	Eculizumab N = 69	Crovalimab N = 45	Eculizumab N = 44	Crovalimab (< 18 years) n = 1	Crovalimab (Prior Ravulizumab) n = 21	Crovalimab (Prior High-Dose Eculizumab) n = 10	Crovalimab (C5 Polymorphism Cohort) n = 6
Median (range)	66.1 (42.0–140.3)	62.2 (47.0–122.0)	80.0 (45.2–120.0)	75.1 (47.2–126.4)	53.0 (53.0–53.0)	69.5 (46.0–91.0)	66.0 (48.1–82.0)	66.2 (44.0–89.2)
< 40 kg, n (%)	0	0	0	0	0	0	0	0
≥ 40 kg to < 100 kg, n (%)	131 (97.0)	66 (95.7)	41 (93.2)	38 (90.5)	1 (100.0)	21 (100.0)	10 (100.0)	6 (100.0)
≥ 100 kg, n (%)	4 (3.0)	3 (4.3)	3 (6.8)	4 (9.5)	0	0	0	0
PNH History								
Median (range) time from PNH diagnosis to enrollment, years	2.6 (0.0–48.5)	2.9 (0.0–31.0)	6.3 (0.0–26.8)	10.4 (0.8–28.0)	3.8 (3.8–3.8)	9.6 (0.6–50.3)	6.5 (0.8–27.1)	5.8 (0.1–13.0)
History of PNH-relevant conditions prior to enrollment, n (%)								

	COMMODORE 2		COMMODORE 1					
	Arm A	Arm B	Arm A	Arm B	Arm C	Arm C	Arm C	Arm C
	Crovalimab N = 135	Eculizumab N = 69	Crovalimab N = 45	Eculizumab N = 44	Crovalimab (< 18 years) n = 1	Crovalimab (Prior Ravulizumab) n = 21	Crovalimab (Prior High-Dose Eculizumab) n = 10	Crovalimab (C5 Polymorphism Cohort) n = 6
Aplastic anaemia	53 (39.3)	26 (37.7)	15 (33.3)	16 (36.4)	0	9 (42.9)	2 (20.0)	1 (16.7)
Myelodysplastic syndrome	6 (4.4)	6 (8.7)	0	0	0	0	0	0
Renal impairment	11 (8.1)	6 (8.7)	7 (15.6)	8 (18.2)	0	4 (19.0)	1 (10.0)	2 (33.3)
Major adverse vascular events (MAVE)	21 (15.6)	10 (14.5)	10 (22.2)	10 (22.7)	0	2 (9.5)	0	3 (50.0)
History of pRBC transfusion within 12 months prior to screening								
Patients with pRBC transfusion, n (%)	103 (77.4)	50 (73.5)	10 (22.7)	11 (25.0)	0	3 (14.3)	4 (40.0)	3 (50.0)

	COMMODORE 2		COMMODORE 1					
	Arm A	Arm B	Arm A	Arm B	Arm C	Arm C	Arm C	Arm C
	Crovalimab N = 135	Eculizumab N = 69	Crovalimab N = 45	Eculizumab N = 44	Crovalimab (< 18 years) n = 1	Crovalimab (Prior Ravulizumab) n = 21	Crovalimab (Prior High-Dose Eculizumab) n = 10	Crovalimab (C5 Polymorphism Cohort) n = 6
Median (range) number of units of pRBC transfused	3.8 (0.0–43.5)	3.0 (0.0–41.0)	0.0 (0.0–14.0)	0.0 (0.0–24.0)	0.0 (0.0–0.0)	0.0 (0.0–8.0)	0.0 (0.0–8.0)	4.0 (0.0–54.0)
Median (range) haemoglobin value at baseline (g/L)	85.0 (63.0–135.0)	87.0 (58.0–810.0)	112.5 (72.0–153.0)	106.5 (68.0–144.0)	149.0 (149.0–149.0)	108.0 (76.0–151.0)	103.5 (59.6–119.0)	83.0 (78.0–129.0)
Median (range) haptoglobin value at baseline (g/L)	0.05 (0.05–0.05)	0.05 (0.05–0.05)	0.05 (0.05–2.2)	0.05 (0.05–1.1)	0.05 (0.05–0.05)	0.05 (0.05–0.64)	0.05 (0.05–0.74)	0.05 (0.05–0.05)
Median (range) LDH value at baseline (U/L)[a]	1638.0 (458.0–3804.0)	1811.0 (475.5–4761.5)	237.5 (138.0–406.0)	225.5 (155.5–455.5)	NA	NA	NA	NA
Median (range) LDH value at baseline (× ULN)[a]	7.0 (2.0–16.3)	7.7 (2.0–20.3)	1.0 (0.6–1.7)	1.0 (0.7–1.9)	1.5 (1.5–1.5)	1.0 (0.6–1.4)	0.9 (0.7–1.3)	6.1 (1.8–20.7)

	COMMODORE 2		COMMODORE 1					
	Arm A	Arm B	Arm A	Arm B	Arm C	Arm C	Arm C	Arm C
	Crovalimab N = 135	Eculizumab N = 69	Crovalimab N = 45	Eculizumab N = 44	Crovalimab (< 18 years) n = 1	Crovalimab (Prior Ravulizumab) n = 21	Crovalimab (Prior High-Dose Eculizumab) n = 10	Crovalimab (C5 Polymorphism Cohort) n = 6
LDH value at baseline, n (%) [a]								
< 2 × ULN	1 (0.7)	0	20 (45.5)	24 (57.1)	-	-	-	-
-≥ 2 to ≤ 4 × ULN	22 (16.4)	10 (14.5)	21 (47.7)	16 (38.1)	-	-	-	-
> 4 × ULN	111 (82.8)	59 (85.5)	3 (6.8)	2 (4.8)	-	-	-	-
< ULN	-	-	-	-	0	10 (47.6)	5 (50.0)	0
≥ ULN to ≤ 1.5 × ULN	-	-	-	-	0	11 (52.4)	5 (50.0)	0
> 1.5 × ULN	-	-	-	-	1 (100.0)	0	0	6 (100.0)

[a]Baseline LDH is defined as the mean of all central LDH values, collected within 28 days prior to the first on-study drug administration including the predose value from Day 1. In COMMODORE 2, LDH values at baseline according to the above defintion are reported for 134 patients in the crovalimab arm and 69 patients in the eculizumab arm. In COMMODORE 1, values are reported for 44 and 42 patients in the crovalimab and eculizamab arm, respectively. LDH, lactate dehydrogenase; PNH, paroxysmal nocturnal haemoglobinuria; pRBC, packed red blood cell; SD, standard deviation; ULN, upper limit of normal (58, 59).

COMMODORE 2

Baseline demographics and disease characteristics were generally balanced between the crovalimab and eculizumab arms. At baseline, median age was 36 years (range 18–76 years) in the crovalimab arm and 38 years (range 17–78 years) in the eculizumab arm. In both arms the majority of patients were within the age range of 18 to 64 years (crovalimab, 90.4%; eculizumab, 84.1%). Of note, two patients in the eculizumab arm were below 18 years of age (both 17 years) at time of randomization. The proportion of male patients was 57.0% in the crovalimab arm versus 50.7% in the eculizumab arm. The median weight at baseline was 66.1 kg (range 42.0–140.3 kg) and 62.2 kg (range 47.0–122.0 kg) in the crovalimab and eculizumab arms, respectively; the majority of the patients weighed between ≥ 40 to < 100.0 kg at baseline (crovalimab, 97.0%; eculizumab, 95.7%). The median time from PNH diagnosis to enrollment was comparable in both arms (crovalimab arm, 2.56 years [range 0–48.5 years]; eculizumab arm, 2.93 years [range 0.0–31.0 years]). The mean LDH values at baseline were 7.6 × ULN (standard deviation [SD]: 3.38) and 7.8 × ULN (SD: 3.54), respectively. Baseline haemoglobin levels were also balanced between the crovalimab (median, 85.0 g/L; range, 63.0–135.0 g/L) and eculizumab arms (87.0 g/L; range, 58.0–810.g/L). Of note, the maximum baseline haemoglobin value in the eculizumab arm of 810 g/L was a result of erroneous data entry. The history of pRBC transfusions within 12 months prior to screening was comparable in the crovalimab and eculizumab arms (77.4% vs 73.5%, respectively), with a median number of 3.75 (range, 0–43.5) and 3.0 (range, 0–41.0) units of transfused pRBC, respectively.

Patients had a median PNH clone size of 90.8% versus 95.1% for monocytes, 60.3% versus 74.6% for granulocytes, and 60.1% versus 57.5% for erythrocytes in the crovalimab and eculizumab arms, respectively. Patients in the crovalimab and eculizumab arms had comparable history of PNH-relevant conditions prior to enrollment (aplastic anaemia, 39.3% vs 37.7%; myelodysplastic syndrome, 4.4% vs 8.7%; and renal impairment, 8.1% vs 8.7%, respectively). MAVEs prior to baseline were reported in approximately 15% of patients in both arms. A higher proportion of patients enrolled in COMMODORE 2 had a history of aplastic anaemia or myelodysplastic syndrome compared with other clinical trials in patients with PNH (61). Individuals presenting with both PNH and these comorbidities typically have higher transfusion rates than those with only PNH (16, 62, 63). The inclusion of these patients in COMMODORE 2 may have impacted primary endpoints including transfusion avoidance.

The majority of patients in the crovalimab and eculizumab arms had at least one previous medical condition (74.1% vs 81.2%, respectively). The most frequent previous medical conditions were hypertension (crovalimab arm, 22.2% vs eculizumab arm, 14.5%), cholelithiasis (6.7% vs 8.7%) and myelodysplastic syndrome (4.4% vs 8.7%). Most patients in each arm received at least one previous or concomitant treatment (crovalimab, 99.3% vs eculizumab, 98.6%). The most common concomitant medications were ophthalmologics (78.5 vs 87.5%), antibacterials for systemic use (76.3% vs 75.4%) and otologics (62.2% vs 68.1%).

COMMODORE 1

The demographic and baseline characteristics were generally balanced between the randomized treatment arms (Arm A and B). The median age was 42.0 years (range: 21–81) in the crovalimab arm and 49.0 years (range: 22–85) in the eculizumab arm. Most patients were within the age range of 18 to 64 years (crovalimab, 88.9%; and eculizumab, 84.1%). No pediatric patients were enrolled in the randomized arms. Approximately half of the patients were male (46.7% and 50.0%). The majority of patients were White (75.6% and 72.7%), or Asian (20.0% and 15.9%). The median weight at baseline was 80.0 kg (range: 45.2–120.0) and 75.1 kg (range: 47.2–126.4) in the crovalimab and eculizumab arms, respectively; most patients weighed between ≥ 40 kg and < 100 kg (93.2% and 90.5%). The median time from PNH diagnosis to enrollment was shorter in the crovalimab arm (6.3 years [range: 0.0–26.8]) than in the eculizumab arm (10.4 years [range: 0.8–28.0]). The mean LDH value at baseline was 1.1 × ULN (SD: 0.28) and 1.0 × ULN (SD: 0.24) in the crovalimab and eculizumab arms, respectively. The median haemoglobin at baseline was 112.5 g/L (range: 72.0–153.0) and 106.5 g/L (range: 68.0–144.0) in the crovalimab and eculizumab arms, respectively. In the crovalimab and eculizumab arms, 22.7% and 25.0% of patients had a history of pRBC transfusion within 12 months prior to screening. Patients had a median PNH clone size of 88.6% and 96.3% for monocytes (crovalimab range:13.8–100.0%; eculizumab range: 7.6–99.9%), 66.5% and 67.9% for granulocytes (crovalimab range:1.7–92.4%; eculizumab range: 2.16–97.8%), and 44.6% and 46.5% for erythrocytes (crovalimab range: 2.6–100.0%; eculizumab range: 1.3–100.0%) in the crovalimab and eculizumab arms, respectively. No patients reported a history of myelodysplastic syndrome prior to enrollment. Aplastic anaemia was reported in 33.3% and 36.4% and renal impairment was reported in 15.6% and 18.2% of patients in the crovalimab and eculizumab arms, respectively. History of MAVE, as defined in the protocol exclusion criteria, was reported in 22.2% and 22.7% of patients in the crovalimab and eculizumab arms, respectively.

A higher proportion of patients enrolled in COMMODORE 1 had a history of aplastic anaemia compared with other clinical trials in patients with PNH (61). Individuals presenting with both PNH and aplastic anaemia typically have higher transfusion rates than those with only PNH (16, 62). The inclusion of these patients in COMMODORE 1 may have impacted trial endpoints.

The majority of patients in the crovalimab and eculizumab arms had at least one previous medical condition (75.6% vs 72.7%, respectively). The most frequent previous medical conditions were hypertension (crovalimab arm: 16.6% vs eculizumab arm: 27.3%), cholelithiasis (8.9% vs 11.4%) and hypothyroidism (8.9% vs 6.8%). The proportion of patients that received at least one concomitant medication in the crovalimab and eculizumab arm was 93.3% and 86.4%, respectively. The most common concomitant medications were topical products for joint and muscular pain (crovalimab: 64.4%; eculizumab: 72.7%), ophthalmologicals (64.4% vs 61.4%) and antibacterials for systemic use (71.1% vs 50.0%).

6.1.3 Comparability of the study population(s) with Danish patients eligible for treatment

Table 10 Characteristics in the relevant Danish population and in the health economic model

	Value in Danish population (30, 31).(30)	Value used in health economic model (46, 47)
Age at diagnosis (95% CI)	48.4 (31.7;67.0)	41 years (NA; NA) – Like Commodore
Female (95% CI)	50.0 (40.6;59.4)	50 %
Patient weight*	N/A	67.92 kg
Age at death, years (95% CI)	71.5 (56.5;79.6)	As background population
Median survival, years (95% CI)	23.2 (6.8; N/A)	As background population

*According to Danish clinical experts, weight of PNH patients is similar to background

6.1.4 Efficacy – results per [COMMODORE 2 – complement inhibitor naïve patients]

For COMMODORE 2, the primary efficacy analysis was conducted once the last patient randomized into the trial completed 24 weeks of study treatment or discontinued early, whichever happened first. Hypothesis testing was conducted based on the primary analysis population and based on data collected during the primary efficacy period (first 24 weeks of treatment), whereas efficacy summaries over time included all data up to the CCOD (16 November 2022).

The 'primary analysis population' was used for both the co-primary endpoints and the key secondary endpoints. It was defined as follows: all randomized patients in Arms A and B who received at least one dose of the originally assigned treatment and having at least one valid LDH level assessment by the central laboratory after the first IV infusion by planned treatment. In arm A, one patient did not have a post-baseline LDH assessment; therefore, only 134 patients were analyzed for efficacy. For patients enrolled in the descriptive analysis arm, the analysis population for the efficacy analyses was the 'efficacy evaluable population – Arm C', defined as all patients who received at least one dose of treatment with crovalimab and have at least one central LDH level assessment after the first IV infusion. This analysis population was used for exploratory endpoints.

As mentioned in section 3.7.1, if non-inferiority was established for the co-primary endpoints, then the secondary endpoints, including superiority testing of primary and secondary endpoints, were tested using a pre-specified hierarchical order. Both co-primary efficacy endpoints needed to be met to conclude non-inferiority of crovalimab to eculizumab.

6.1.4.1 Primary efficacy endpoints

Crovalimab demonstrated non-inferiority to eculizumab for the co-primary efficacy endpoints of haemolysis control (defined as central LDH ≤ 1.5 × ULN from Week 5 through Week 25), and transfusion avoidance (defined as the proportion of patients with

transfusion avoidance from baseline to Week 25). These results are described in more detail below. All statistical methods are described in Appendix B.

Haemolysis Control

Crovalimab demonstrated non-inferiority compared with eculizumab treatment for haemolysis control as measured by central LDH ≤ 1.5 × ULN from Week 5 through Week 25. The odds ratio for haemolysis control (crovalimab vs eculizumab) was 1.02 and the lower limit of the 95% confidence interval (CI) for the odds ratio of 0.57 was greater than the pre-defined non-inferiority margin of 0.2 (Table 11).

The mean proportion of patients with haemolysis control as measured by central LDH ≤ 1.5 × ULN from Week 5 through Week 25 was 79.3% (95% CI: 72.86, 84.48) for the crovalimab arm and 79.0% (95% CI: 69.66, 85.99) for the eculizumab arm.

Table 11. Mean Proportion of Patients Achieving Haemolysis Control

(Central LDH ≤ 1.5 × ULN) from Week 5 through Week 25 (Primary Analysis Population; as of CCOD: 16 November 2022)

Outcome	**Crovalimab (Arm A) n = 134**	**Eculizumab (Arm B) n = 69**
Mean proportion of patients achieving controlled haemolysis (95% CI)	79.3% (72.86, 84.48)	79.0% (69.66, 85.99)
Odds ratio (95% CI)	1.02 (0.57, 1.82)[a] p = 0.9504[b] *Non-inferiority margin for lower 95% CI limit = 0.2*	

[a]An odds ratio > 1 favors crovalimab.

[b]The pre-defined statistical testing hierarchy was broken before superiority testing could be conducted for the co-primary efficacy endpoint of haemolysis control. Therefore, the p-value reported is descriptive only. CI, confidence interval; CCOD, clinical cutoff date; LDH, lactate dehydrogenase; ULN, upper limit of normal (46, 60).

The proportion of patients achieving haemolysis control increased from 0% in both treatment arms at baseline to 81.0% of patients in the crovalimab arm and 83.8% of patients in the eculizumab arm at Week 5. These proportions remained between 75.2% and 83.8% in the crovalimab arm and between 73.8% and 85.1% in the eculizumab arm through Week 25 (Figure 5). Data available up to CCOD for the crovalimab arm indicated that the proportion of patients with haemolysis control remained stable after Week 25 (46, 60).

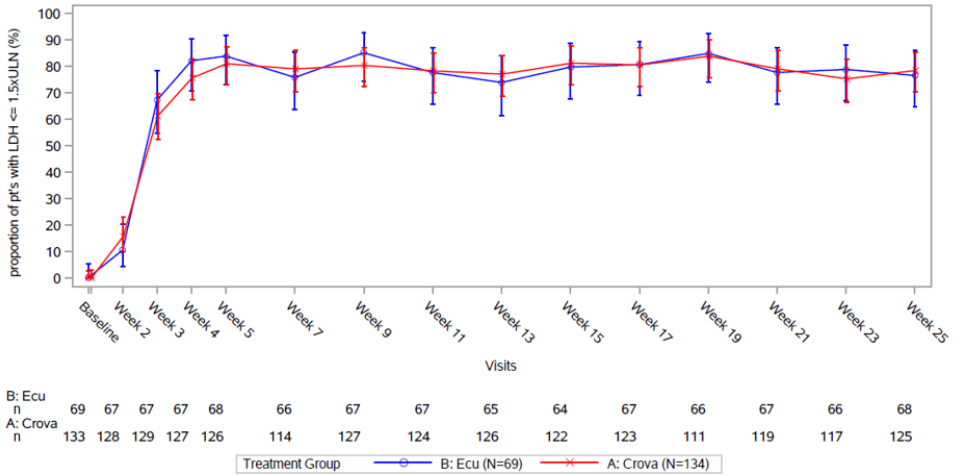


Figure 5. Proportion of Patients (95% CI) with Haemolysis Control (i.e., Central LDH ≤ 1.5 x ULN) through Week 25 by Visit (Primary Analysis Population; as of CCOD: 16 November 2022)

For each group, CIs are displayed only for visits with at least 10 patients. Baseline LDH is defined as the mean of all central LDH values, collected within 28 days prior to the first on-study drug administration including the predose value from Day 1.

CI, confidence interval; CCOD, clinical cutoff date; Crova, crovalimab; Ecu, eculizumab; LDH, lactate dehydrogenase; ULN, upper limit of normal (46).

Maintenance of haemolysis control (central LDH ≤ 1.5 × ULN) was also demonstrated by the eculizumab-treated patients who switched to crovalimab following the 24-week primary treatment period with eculizumab. Out of the 68 eculizumab-treated patients who switched to crovalimab, 50 patients in Arm B (73.5%; 95% CI: 61.43, 83.50) had haemolysis control at time of switch (Switch Baseline). From Switch Baseline to 25 weeks later (Switch Week 25), the proportion of patients with haemolysis control ranged from 77.3% to 89.7% at each visit (Figure 6). Of the 43 patients who switched to crovalimab at least 24 weeks before CCOD, the mean proportion of Arm B switch patients with haemolysis control during the period after switch through Switch Week 25 was 87.6% (95% CI: 79.79, 92.68)(59).

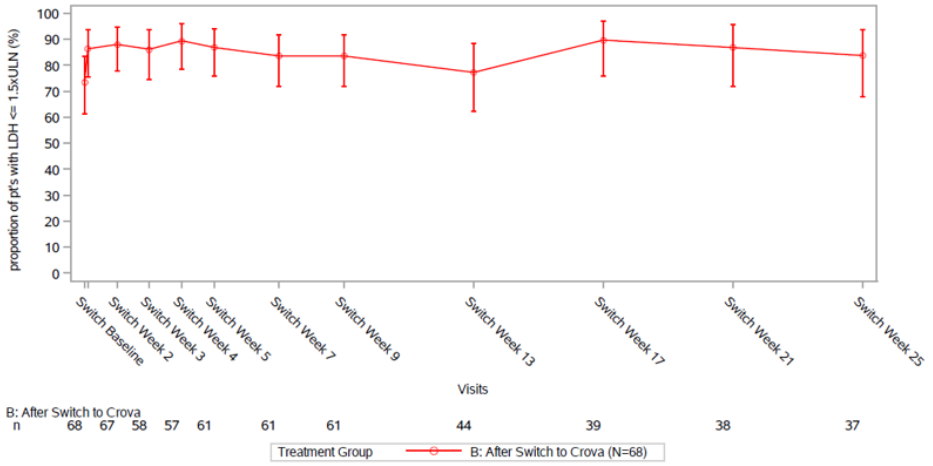


Figure 6. Proportion of Patients (95% CI) Achieving Haemolysis Control (Central LDH ≤ 1.5 x ULN) by Visit (Crovalimab Efficacy Population; Arm B Switch; as of CCOD: 16 November 2022)

For each group, CIs are displayed only for visits with at least 10 patients. Switch Baseline LDH is defined as the mean of all central LDH values, collected within 28 days prior to the first dose of crovalimab including the predose value from Switch Day 1. CI, confidence interval; CCOD, clinical cutoff date; Crova, crovalimab; LDH, lactate dehydrogenase; ULN, upper limit of normal (59).

Sensitivity analyses were conducted to assess the robustness of the results for the haemolysis control co-primary efficacy endpoint using different analysis population definitions (i.e., in the randomized population as well as in the per-protocol population) and evaluating the impact of different statistical models and model assumptions, as well as of missing central LDH values. Overall, the results of the different sensitivity analyses were consistent with the primary analysis of haemolysis control, thereby confirming the robustness of the haemolysis control results.

Transfusion Avoidance (TA)

Crovalimab demonstrated non-inferiority compared with eculizumab for TA from baseline through Week 25. The weighted difference in the proportion of patients with transfusion avoidance (crovalimab vs eculizumab) was −2.8% with a lower limit of the 95% CI of −15.67%, which was higher than the pre-defined non-inferiority margin of −20% (Table 12). Note that, as a conservative analysis approach, patients who prematurely withdrew from study treatment before Week 25 were assumed to have undergone a transfusion.

In the crovalimab arm, 65.7% (95% CI: 56.91, 73.52) of patients were transfusion free from baseline through Week 25 compared with 68.1% (95% CI: 55.67, 78.53) of patients in the eculizumab arm. Statistical superiority of crovalimab compared with eculizumab was not met (p = 0.67)(46, 60).

Table 12. Proportion of Patients Achieving Transfusion Avoidance

From Baseline through Week 25 (Primary Analysis Population; as of CCOD: 16 November 2022)

Outcome	**Crovalimab (Arm A) n = 134**	**Eculizumab (Arm B) n = 69**
Patients with transfusion avoidance[a], n (%)	88 (65.7)	47 (68.1)
95% CI for proportion	(56.91, 73.52)	(55.67, 78.53)
Weighted difference in proportion (95% CI)	−2.8% (−15.67, 11.14) p = 0.6655 *Non-inferiority margin for lower 95% CI limit = −20%*	

[a]One patient in the crovalimab arm discontinued treatment before Week 25 without a transfusion and was conservatively assumed to have had a transfusion. CCOD, clinical cutoff date; CI, confidence interval (46, 60)

Of patients who completed at least 24 weeks of eculizumab treatment then switched to crovalimab (43 Arm B switch patients), 33 (76.7%) patients (95% CI: 61.00, 87.72) achieved TA in the period after switching to crovalimab through Switch Week 25 (59).

Sensitivity analyses were also conducted to assess the robustness of the results for the transfusion avoidance co-primary efficacy endpoint using different analysis population

definitions (i.e., in the randomized population as well as in the per-protocol population). Overall, the results of the sensitivity analyses were consistent with the results from the primary analysis, thereby confirming the robustness of the TA results.

6.1.4.2 Secondary efficacy endpoints:

Crovalimab demonstrated non-inferiority to eculizumab for the secondary efficacy endpoints of proportion of patients with BTH from baseline through Week 25, and proportion of patients who achieved haemoglobin stabilization from baseline to Week 25. After non-inferiority was achieved in the two co-primary and two key secondary endpoints, superiority testing was performed for TA per the pre-defined hierarchical testing sequence and was not met (p =0.67), thus breaking the testing hierarchy. For this reason, FACIT-Fatigue could not be tested for non-inferiority and the results are only descriptive. Similarly, the hemolysis control as well as all secondary endpoints could not be tested for superiority. The results for the secondary endpoints are described in more detail below.

Breakthrough Haemolysis (BTH)

Crovalimab demonstrated non-inferiority compared with eculizumab in terms of BTH. The proportion of patients with a BTH event from baseline through Week 25 was 10.4% (95% CI: 6.04, 17.21) in the crovalimab arm compared with 14.5% (95% CI: 7.54, 25.50) in the eculizumab arm. The weighted difference in proportions of patients with BTH (crovalimab vs eculizumab) was −3.9%, and the upper limit of the 95% CI for the difference in the proportions was 5.3%, which is lower than the pre-defined non-inferiority margin of 20% (Table 13)(46, 60).

Table 13. Proportion of Patients with Breakthrough Haemolysis

From Baseline through Week 25 (Primary Analysis Population; as of CCOD: 16 November 2022)

Outcome	**Crovalimab (Arm A) n = 134**	**Eculizumab (Arm B) n = 69**
Patients with at least one BTH[a], n (%)	14 (10.4)	10 (14.5)
95% CI for proportion	(6.04, 17.21)	(7.54, 25.50)
Weighted difference in proportion (95% CI)	−3.9% (−14.82, 5.26) p = 0.4358[b] *Non-inferiority margin for upper 95% CI limit = 20%*	

Patients who discontinued treatment before Week 25 are considered to have a BTH event.
[a]Four patients in the crovalimab arm and one patient in the eculizumab arm without a BTH event discontinued treatment before Week 25 and were considered to have experienced a BTH event as a conservative analysis approach.
[b]The pre-defined statistical testing hierarchy was broken before superiority testing could be conducted for the secondary efficacy endpoint of BTH. Therefore, the p-value reported is descriptive only. BTH, breakthrough haemolysis; CCOD, clinical cutoff date; CI, confidence interval (46, 60).

Of patients who completed at least 24 weeks of eculizumab treatment and then switched to crovalimab (Arm B Switch patients), a total of 7 of the 43 (16.3%, 95% CI:

7.33, 31.30) were regarded as having had a BTH event from Switch Baseline to Switch Week 25. Of these, three patients who had not had a BTH event and had discontinued crovalimab treatment before Switch Week 25 were considered to have had a BTH event as a conservative analysis approach.

Stabilized Haemoglobin

Crovalimab demonstrated non-inferiority compared with eculizumab in terms of haemoglobin stabilization. The proportion of patients reaching haemoglobin stabilization (avoidance of a ≥ 2 g/dL decrease in haemoglobin level from baseline, in the absence of transfusion) from baseline through Week 25 was 63.4% (95% CI: 54.63, 71.45) in the crovalimab arm compared with 60.9% (95% CI: 48.35, 72.17) in the eculizumab arm. The weighted difference in proportion of patients with haemoglobin stabilization (crovalimab vs eculizumab) was 2.2% and the lower limit of the 95% CI of −11.4% was higher than the pre-defined non-inferiority margin of −20% (Table 14) (46, 60).

Table 14. Proportion of Patients with Stabilized Haemoglobin

From Baseline through Week 25 (Primary Analysis Population; as of CCOD: 16 November 2022)

Outcome	**Crovalimab (Arm A) n = 134**	**Eculizumab (Arm B) n = 69**
Patients with haemoglobin stabilization[a], n (%)	85 (63.4)	42 (60.9)
95% CI for proportion	(48.35, 72.17)	(54.63, 71.45)
Weighted difference in proportion (95% CI)	2.2% (–11.37, 16.31) p = 0.7496[b] *Non-inferiority margin for lower 95% CI limit = –20%*	

Stabilized haemoglobin is defined as avoidance of a ≥ 2 g/dL decrease in haemoglobin level from baseline, in the absence of transfusion.
Patients who discontinued treatment before Week 25 are considered to not have had stabilized haemoglobin.
[a]One patient in the crovalimab arm discontinued treatment before Week 25 with haemoglobin stabilization and was conservatively assumed to have not had a haemoglobin stabilization.
[b]The pre-defined statistical testing hierarchy was broken before superiority testing could be conducted for the secondary efficacy endpoint of stabilized haemoglobin. Therefore, the p-value reported is descriptive only. CCOD, clinical cutoff date; CI, confidence interval. (46, 60).

In Arm B, among patients who completed at least 24 weeks of treatment then switched to crovalimab, 27 of 43 patients (62.8%; 95% CI: 46.72, 76.61) achieved haemoglobin stabilization from Switch Baseline to Switch Week 25. Of these, two patients who were haemoglobin stabilized while on study discontinued treatment before Week 25 and were therefore conservatively assumed as not having stabilized haemoglobin (59).

FACIT-Fatigue: Change from Baseline to Week 25

Due to the break in the statistical testing hierarchy, non-inferiority testing for FACIT-Fatigue was not performed and the results are considered descriptive only. The adjusted

mean change from baseline to Week 25 in FACIT-Fatigue was numerically higher for the crovalimab arm compared with the eculizumab arm.

FACIT-Fatigue was assessed in adult patients only. The total FACIT-Fatigue score is based on the sum of 13 items that assess fatigue, which can range from 0 to 52, with higher scores indicating lower fatigue severity and a positive change from baseline indicating an improvement. Studies that have attempted to identify general population norms on the FACIT-Fatigue score have placed the mean in the range of 43.5–46.6 points (64-66), while a cutoff of 30 or 34 points has been suggested to indicate severe fatigue (66-68).

FACIT-Fatigue data were evaluable in 95.5% of adult patients in the crovalimab arm and 95.7% of adult patients in the eculizumab arm at each visit from baseline through Week 25.

The mean FACIT-Fatigue scores at baseline were below normative values and similar in the crovalimab (36.0 points [95% CI: 34.29, 37.76]) and eculizumab arms (35.1 points [95% CI: 32.28, 37.90]; Table 15; Figure 7). Improvement in fatigue was observed by Week 2, with the mean score increasing to 40.9 points (95% CI: 39.57, 42.28) in the crovalimab arm compared with 38.9 points (95% CI: 36.35, 41.47) in the eculizumab arm. Further improvement in levels of fatigue were reported up to Week 25, with the mean score increasing to 44.3 points (95% CI: 43.15, 45.52) in the crovalimab arm compared with 41.4 points (95% CI: 39.29, 43.47) in the eculizumab arm. By Week 25, fatigue scores for the crovalimab arm were similar to normative population values (64, 66, 67). The adjusted mean change from baseline at Week 25 in FACIT-Fatigue was 7.8 points (95% CI: 6.49, 9.09) in the crovalimab arm compared with 5.2 points (95% CI: 3.42, 6.89) in the eculizumab arm (Table 15), exceeding the threshold (≥ 5 points) for clinically meaningful change for both treatment arms (69).

The reported improvements in the FACIT-Fatigue scores in the crovalimab arm are maintained after Week 25, based on the available data reported up to the CCOD (46, 60).

Table 15. Mean Change from Baseline to Week 25 in FACIT-Fatigue Scores

Primary Analysis Population; as of CCOD: 16 November 2022.

Outcome	**Crovalimab (Arm A) n = 134**	**Eculizumab (Arm B) n = 69**
Baseline, n	134	67
Mean (SE)	36.0 (0.88)	35.1 (1.41)
Week 25, n	128	66
Adjusted mean change from baseline to Week 25 in FACIT-Fatigue, (SE)	7.8 (0.66)	5.2 (0.88)
Difference in adjusted mean change (95% CI)	2.6 (0.68, 4.60) p = 0.0087[a]	

[a]The pre-defined statistical testing hierarchy was broken before superiority testing could be conducted for the secondary efficacy endpoint of FACIT-Fatigue. Therefore, the p-value reported is descriptive only. CCOD, clinical cutoff date; CI, confidence interval; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy – Fatigue; SE, standard error. (46, 60).

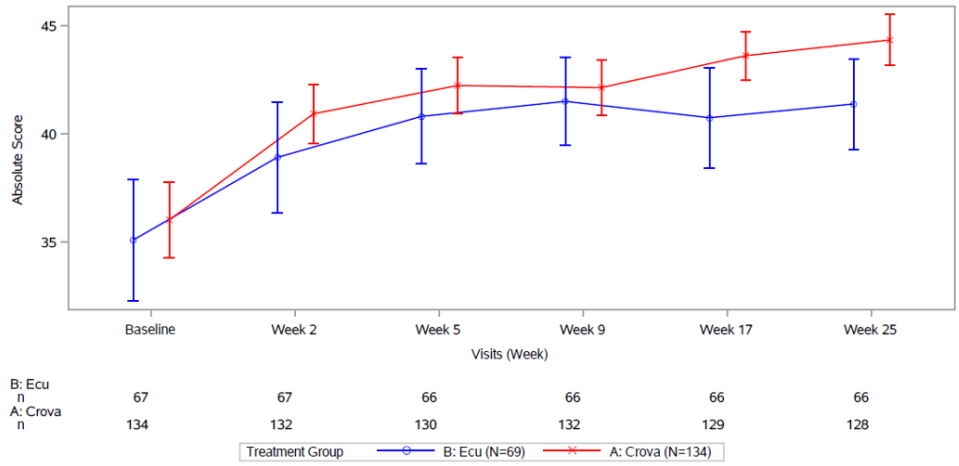


Figure 7. Mean FACIT-Fatigue Scores (95% CI) through to Week 25 by Visit

Primary Analysis Population; as of CCOD: 16 November 2022. For each group, CIs are only displayed for visits with at least 10 patients. CCOD, clinical cutoff date; CI, confidence interval; Crova, crovalimab; Ecu, eculizumab; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy – Fatigue. (46, 60).

For the Arm B switch patients, the mean FACIT-Fatigue scores at Switch Baseline were slightly below normative values in 41 of 43 patients (41.1 points; standard error [SE], 1.19). The adjusted mean change from Switch Baseline to Switch Week 25 in FACIT-Fatigue was 0.18 points (95% CI: −2.72, 3.09) in 36 of 43 patients who completed at least 24 weeks of treatment then switched to crovalimab (Arm B Switch patients).

6.1.5 Efficacy – results per [COMMODORE 1 – complement inhibitor-experienced patients]

There are no primary or secondary efficacy endpoints in COMMODORE 1. The primary objective of the study is safety. The exploratory efficacy objective of this study was to evaluate the efficacy of crovalimab compared with eculizumab in randomized Arms A and B, and the efficacy of crovalimab in non-randomized Arm C. All exploratory efficacy endpoint analyses were descriptive, with no formal statistical testing being conducted.

Efficacy analyses were performed on the ‘efficacy population’, defined as all enrolled patients who received at least one dose of study drug, and have at least one centrally processed LDH level assessment after the first IV infusion.

The ‘24-week efficacy population’ was similar to the efficacy population but restricted to patients recruited at least 24 weeks before CCOD (November 16, 2022).

The efficacy results presented in this section are for the randomized comparison of crovalimab (Arm A) versus eculizumab (Arm B). The efficacy analyses included all randomized patients in Arms A and B who were recruited at least 24 weeks before CCOD, who received at least one dose of the originally assigned treatment and who had at least one valid LDH level assessment by the central laboratory after the first IV infusion. This

corresponded to 39 patients in the crovalimab arm and 37 patients in the eculizumab arm. In addition, results are presented for the 35 eculizumab-treated patients who switched to crovalimab after the 24-week treatment period (Arm B switch patients).

6.1.5.1 Exploratory efficacy endpoints

At the time of the CCOD for the primary analysis, crovalimab and eculizumab showed similar exploratory efficacy results for haemolysis control (defined as central LDH ≤ 1.5 × ULN from baseline through Week 25), TA (from baseline to Week 25) and BTH (from baseline through Week 25). The proportion of patients achieving stabilized haemoglobin was numerically higher for the eculizumab arm than for the crovalimab arm. The adjusted mean change from baseline to Week 25 in FACIT-Fatigue was positive in the crovalimab arm and negative in the eculizumab arm, but overall was comparable between the crovalimab and the eculizumab arms. These results are described in more detail in the sections below.

Haemolysis Control

The mean proportion of patients achieving haemolysis control (central LDH ≤ 1.5 × ULN) during the primary treatment period was 92.9% (95% CI: 86.62, 96.39) for the crovalimab arm vs 93.7% (95% CI: 87.26, 97.04) for the eculizumab arm (Table 16).

Table 16. Mean Proportion of Patients Achieving Haemolysis Control
(Central LDH ≤ 1.5 × ULN) from Baseline through Week 25 (24-Week Efficacy Population; as of CCOD: 16 November 2022)

Outcome	Crovalimab (Arm A) n = 39	Eculizumab (Arm B) n = 37
Mean proportion of patients achieving controlled haemolysis (95% CI)	92.9% (86.62, 96.39)	93.7% (87.26, 97.04)
Odds ratio (95% CI)	0.88 (0.28, 2.77)[a]	

Only patients who were recruited at least 24 weeks before CCOD are included.
[a]An odds ratio > 1 favors crovalimab.
CI, confidence interval; CCOD, clinical cutoff date; LDH, lactate dehydrogenase; ULN, upper limit of normal. (47).

The mean proportion of patients with central LDH ≤ 1.5 × ULN at baseline was 93.2% in the crovalimab arm vs 95.2% in the eculizumab arm, and this stayed generally high, ranging between 76.9–100.0% of patients in the crovalimab arm vs 86.1–97.2% of patients in the eculizumab arm up to Week 25 (Figure 8). Data available up to CCOD for the crovalimab arm indicated that the proportion of patients with haemolysis control remained stable after Week 25 (47).

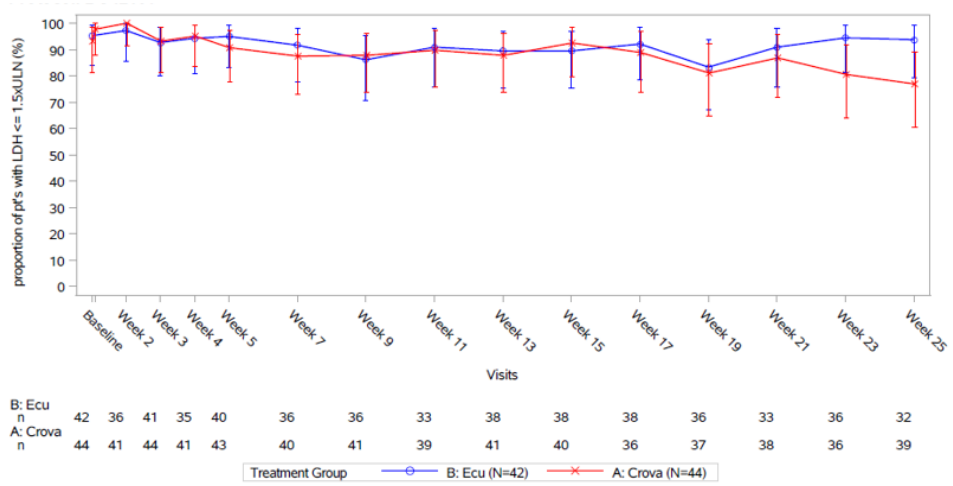


Figure 8. Proportion of Patients (95% CI) with Haemolysis Control
I.e., (Central LDH ≤ 1.5 × ULN) through Week 25 by Visit (24-Week Efficacy Population; as of CCOD: 16 November 2022). For each group, CIs are only displayed for visits with at least 10 patients.
CI, confidence interval; CCOD, clinical cutoff date; Crova, crovalimab; Ecu, eculizumab; LDH, lactate dehydrogenase; ULN, upper limit of normal. (47).

In Arm B, among patients who completed at least 24 weeks of treatment and then switched to crovalimab (Arm B switch patients), the mean proportion of patients achieving haemolysis control (central LDH ≤ 1.5 × ULN) was 95.6% (95% CI:87.32, 98.58).

Out of the 35 Arm B patients who switched to crovalimab, 31 (88.6%; 95% CI: 73.26, 96.80) patients had haemolysis control (central LDH ≤ 1.5 × ULN) at Switch Baseline. The proportion of patients with haemolysis control ranged between 89.7–100.0% across all following visits up to Switch Week 25 (i.e., week number 25 after switching from eculizumab to crovalimab; Figure 9) (47).

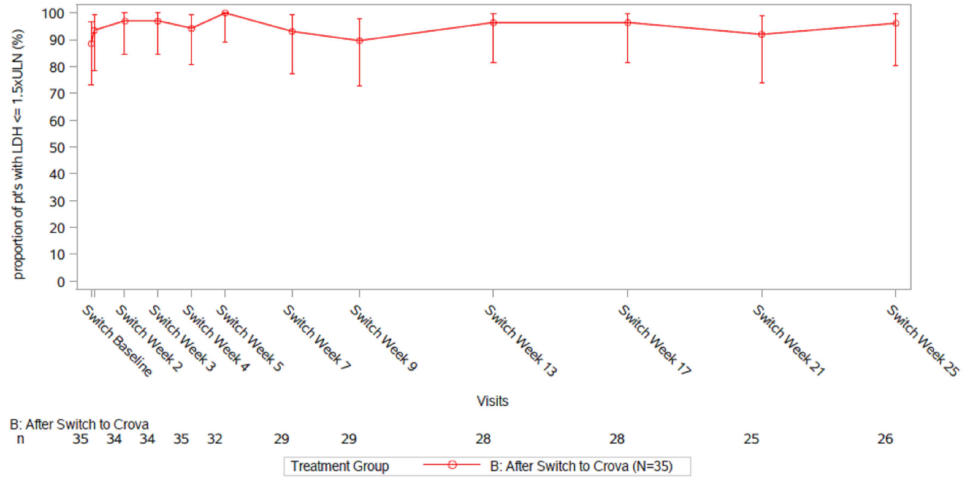


Figure 9. Proportion of Patients (95% CI) Achieving Haemolysis Control
(Central LDH ≤ 1.5 × ULN) by Visit (Crovalimab Efficacy Period, Arm B Switch Patients; as of CCOD: 16 November 2022). For each group, CIs are only displayed for visits with at least 10 patients.
CI, confidence interval; CCOD, clinical cutoff date; Crova, crovalimab; LDH, lactate dehydrogenase; ULN, upper limit of normal. (58).

Transfusion Avoidance (TA)

The proportion of patients who achieved TA from baseline through Week 25 was 79.5% (95% CI: 63.06, 90.13) for the crovalimab arm (Arm A) versus 78.4% (95% CI: 61.34, 89.58) for the eculizumab arm (Arm B; Table 17) (47).

Table 17. Proportion of Patients Achieving Transfusion Avoidance

From Baseline through Week 25 (24-Week Efficacy Population; as of CCOD: 16 November 2022)

	Crovalimab (Arm A) n = 39	**Eculizumab (Arm B) n = 37**
Patients with transfusion avoidance[a], n (%)	31 (79.5)	29 (78.4)
95% CI for proportion	(63.06, 90.13)	(61.34, 89.58)
Weighted difference in proportion (95% CI)	1.8% (−16.67, 19.94)	

Only patients that were recruited at least 24 weeks before CCOD are included.
[a]One patient in the eculizumab arm discontinued treatment before Week 25 without a transfusion and was conservatively assumed to have had a transfusion.
CCOD, clinical cutoff date; CI, confidence interval. (47).

The mean number of pRBC units transfused from baseline to Week 25 in all randomized patients was 0.97 (95% CI: 0.24, 1.70) in the crovalimab arm and 1.89 (95% CI: 0.53, 3.25) in the eculizumab arm.

In Arm B, among patients who completed at least 24 weeks of treatment and then switched to crovalimab, 23 of 28 (82.1%) achieved TA after switching to crovalimab through Switch Week 25. Two patients in the prior ravulizumab cohort and one patient in the high-dose eculizumab cohort did not have a transfusion on study, but as a conservative analysis approach were regarded as having had a transfusion given that they discontinued the study treatment prior to Week 25 (47).

Breakthrough Haemolysis (BTH)

The proportion of patients with BTH from baseline through Week 25 was 10.3% (95% CI: 3.34, 25.16) for the crovalimab arm versus 13.5% (95% CI: 5.08, 29.57) for the eculizumab arm (Table 18) (47).

Table 18. Proportion of Patients with BTH from Baseline through Week 25

(24-Week Efficacy Population; as of CCOD: 16 November 2022)

Outcome	Crovalimab (Arm A) n = 39	Eculizumab (Arm B) n = 37
Patients with at least one BTH[a], n (%)	4 (10.3)	5 (13.5)
95% CI for proportion	(3.34, 25.16)	(5.08, 29.57)
Weighted difference in proportion (95% CI)	−3.5% (−19.20, 11.68)	

Patients who discontinued treatment before Week 25 are considered to have a BTH event. Only patients who were recruited at least 24 weeks before CCOD are included.
[a]Two patients in the eculizumab arm without a BTH event discontinued treatment before Week 25 and were considered to have experienced a BTH event as a conservative analysis approach.
BTH, breakthrough haemolysis; CCOD, clinical cutoff date; CI, confidence interval. (47).

In Arm B, among patients who completed at least 24 weeks of treatment and then switched to crovalimab, a total of 5 of 28 (17.9%) were regarded as having had a BTH event from Switch Baseline to Switch Week 25. Of these, three patients did not have BTH on study but as a conservative analysis approach were regarded to have had a BTH event due to treatment discontinuation before completing 24 weeks of treatment (47).

Stabilized Haemoglobin

The proportion of patients with stabilized haemoglobin from baseline through Week 25 was 59.0% (95% CI: 42.19, 74.02) in the crovalimab arm versus 70.3% (95% CI: 52.83, 83.56) in the eculizumab arm (Table 19) (47).

Table 19. Proportion of Patients with Stabilized Haemoglobin

From Baseline through Week 25 (24-Week Efficacy Population; as of CCOD: 16 November 2022)

Outcome	Crovalimab (Arm A) n = 39	Eculizumab (Arm B) n = 37
Patients with haemoglobin stabilization[a], n (%)	23 (59.0)	26 (70.3)
95% CI for proportion	42.19, 74.02)	(52.83, 83.56)
Weighted difference in proportion (95% CI)	−10.8% (−30.84, 10.39)	

Stabilized haemoglobin is defined as avoidance of a ≥ 2 g/dL decrease in haemoglobin level from baseline, in the absence of transfusion. Patients who discontinued treatment before Week 25 are considered to not have had stabilized haemoglobin. Only patients who were recruited at least 24 weeks before CCOD are included.
[a]One patient in the eculizumab arm discontinued treatment before Week 25 with haemoglobin stabilization and was conservatively assumed to have not had a haemoglobin stabilization.
CCOD, clinical cutoff date; CI, confidence interval. (47).

The proportion of patients who reached or maintained a haemoglobin level of at least 10 g/dL (without subsequent decrease below 9 g/dL, in the absence of transfusion) from baseline through Week 25 was 53.8% (95% CI: 37.38, 69.57) in the crovalimab arm versus 64.9% (95% CI: 47.42, 79.28) in the eculizumab arm.

In Arm B, among patients who completed at least 24 weeks of treatment and then switched to crovalimab, a total of 18 of 28 (64.3%) were regarded to have achieved haemoglobin stabilization from Switch Baseline to Switch Week 25. As a conservative

analysis approach, due to treatment discontinuation before completing 24 weeks of treatment, one patient was regarded to not have had haemoglobin stabilization (58).

FACIT-Fatigue

FACIT-Fatigue was assessed in adult patients only. FACIT-fatigue data were evaluable in 86.4% of adult patients in the crovalimab arm (n = 38) and 76.2% of adult patients in the eculizumab arm (n = 32) at each visit from baseline through Week 25. The adjusted mean change in FACIT-Fatigue scores from baseline to Week 25 was positive (1.1; 95% CI: –1.47, 3.65) for the crovalimab arm and negative (−2.6; 95% CI: −5.35, 0.12) for the eculizumab arm and the adjusted mean difference between the arms was 3.7 (95% CI: 0.05-7.36). The reported improvements in the FACIT-Fatigue scores in the crovalimab arm are maintained after Week 25, based on the available data reported up to CCOD (Table 20) (47, 58).

Table 20: Mean Change from Baseline to Week 25 in FACIT-Fatigue Scores

(24-Week Efficacy Population; as of CCOD: 16 November 2022)

Outcome	**Crovalimab (Arm A) n = 39**	**Eculizumab (Arm B) n = 37**
Baseline, n	39	37
Mean (SE)	39.1 (1.62)	40.1 (1.44)
Week 25, n	38	32
Adjusted mean change from baseline to Week 25 in FACIT-Fatigue[a], (SE)	1.1 (1.29)	−2.6 (1.37)
Difference in adjusted mean change (95% CI)	3.7 (0.05, 7.36)	

Only patients who were recruited at least 24 weeks before CCOD are included.
[a]FACIT-Fatigue was assessed in adult patients. CCOD, clinical cutoff date; CI, confidence interval; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy – Fatigue; SE, standard error. (47).

Summary of exploratory efficacy endpoints

Exploratory efficacy results during the 24-week primary treatment period further indicated maintenance of disease control. Patients who switched from eculizumab to crovalimab showed similar results to those who continued eculizumab for hemolysis control, TA, BTH, and self-reported fatigue. The proportion of patients who achieved hemoglobin stabilization was numerically higher in the eculizumab arm; however, this was only driven by a difference of three patients between the arms. In both arms, most hemoglobin decreases without a concurrent transfusion were singular decreases in the context of a complement activating condition, with or without a reported breakthrough hemoly sis event per protocol. Moreover, this difference across arms was not seen in the transfusion avoidance endpoint. In general, efficacy in the eculizumab arm of this study was consistent with the known treatment effects of eculizumab (44, 51, 61).

7. Comparative analyses of efficacy

This application is primarily based on the pivotal phase 3 study COMMODORE 2 (BO42162), a randomised head-to-head study comparing crovalimab to eculizumab in complement inhibitor-naïve PNH patients. Supportive information is from COMMODORE 1 (BO42161), a phase 3, randomized, head-to-head study, designed to evaluate the safety, pharmacokinetics, pharmacodynamics and efficacy of crovalimab compared with eculizumab in patients with PNH currently treated with complement inhibitors. Therefore only Table 21 and Table 23 with results from the comparative analyses have been completed in this section.

7.1.1 Differences in definitions of outcomes between studies

Not applicable

7.1.2 Method of synthesis

Not applicable

7.1.3 Results from the comparative analysis

Table 21 Results from the comparative analysis of crovalimab vs. eculizumab for PNH patients not previously treated with C5 inhibitors (COMMODORE 2)

Outcome measure	crovalimab (N=134)	eculizumab (N=69)	Result
Mean proportion of patients achieving controlled haemolysis, Week 5 through Week 25	79.3% (95% CI: 72.86, 84.48)	79.0% (95% CI: 69.66, 85.99)	Odds Ratio: 1.02 (95% CI 0.57; 1.82)
Patients with transfusion avoidance, from Baseline through Week 25	88/134, 65.7% (95% CI: 56.91; 73.52)	47/69, 68.1% (95 % CI: 55.67; 78.53)	Weighted difference in proportion −2.8% (95% CI: −15.67, 11.14)
Patients with at least one Breakthrough Haemolysis, from Baseline through Week 25	14/134, 10.4% (95% CI: 6.04; 17.21)	10/69, 14.5% (95% CI: 7.54, 25.50)	Weighted difference in proportion −3.9% (95% CI: −14.82; 5.26)
Patients with Stabilized Haemoglobin, from Baseline through Week 25	85/134, 63.4% (95% CI: 54.63, 71.45)	42/69, 60.9% (95% CI: 48.35; 72.17)	Weighted difference in proportion 2.2% (95% CI: -11.37;16.31)

Table 22 Results from the comparative analysis of crovalimab vs. eculizumab for PNH patients not previously treated with C5 inhibitors (COMMODORE 1)

Outcome measure	crovalimab (N=134)	eculizumab (N=69)	Result
Mean proportion of patients achieving controlled haemolysis, Week 5 through Week 25	92.9% (95% CI 86.62, 96.39)	93.7% (95% CI 87.26, 97.04)	Odds ratio (95% CI) 0.88 (0.28, 2.77)
Patients with transfusion avoidance, from Baseline through Week 25	31/39, 79.5% (95% CI: 63.06, 90.13)	29/37, 78.4% (95 % CI 61.34, 89.58)	Weighted difference in proportion (95% CI) 1.8% (−16.67, 19.94)
Patients with at least one Breakthrough Haemolysis, from Baseline through Week 25	4/39, 10.3% (95% CI: 3.34, 25.16)	5/37, 13.5% (95% CI: 5.08, 29.57)	Weighted difference in proportion (95% CI) −3.5% (−19.20, 11.68)
Patients with Stabilized Haemoglobin, from Baseline through Week 25	23/39, 59.0% (95% CI: 42.19, 74.02)	26/37, 70.3% (95% CI: 52.83, 83.56)	Weighted difference in proportion (95% CI) −10.8% (-30.84, 10.39)
Adjusted mean change from baseline to Week 25 in FACIT-Fatigue, (SE)	1.1 (1.29)	−2.6 (1.37)	Difference in adjusted mean change (95% CI) 3.7 (0.05, 7.36)

All exploratory efficacy endpoint analyses were descriptive, with no formal statistical testing being conducted

7.1.4 Efficacy – results per [outcome measure]

Not applicable

8. Modelling of efficacy in the health economic analysis

8.1 Presentation of efficacy data from the clinical documentation used in the model

The drug under review demonstrates similar clinical effects (i.e., has at least equivalent effectiveness and/or efficacy and be equivalently or less harmful) compared to the most appropriate comparator(s), based on the investigation in two randomized clinical trials, in C5 pre-treated and naïve patients, using eculizumab as comparator, showing non-inferior results across all endpoints.

Overall, crovalimab provides similar efficacy to eculizumab in the treatment of PNH. The drug under review is anticipated to result in equivalent or lesser costs to the health system. The costs considered in this economic analysis are treatment and administration costs. Pooled patients' population was modelled to show the cost difference between the different available treatments for PNH. The reason for using the pooled population rather than COMMODORE 1 and 2 seperately, is that while the COMMODORE programme defined C5-naive and C5-experienced patients into separate groups for the trials, it's important to note that both populations have the same pathophysiology and thus have similar therapeutic needs; similarly, learnings and data from these two patient groups can be extrapolated between studies, in many cases.

PNH is not an inherently progressive disease, given the stability of the PNH clone during treatment. The fundamental pathophysiologic mechanism underlying the disease is the GPI-anchor deficient hematopoietic stem cell clone (13, 70). The loss of GPI-anchored proteins CD55 and CD59 in the peripheral blood elements derived from this clone permits unregulated complement-mediated destruction of RBCs and platelets, resulting in intravascular hemolysis, anemia, and thrombosis. Complement inhibition provides effective control of PNH disease manifestations without changing the underlying hematopoietic stem cell clone, and individuals who are exposed to C5 inhibition continue to have the same underlying disease as treatment-naive patients. This is reflected among patients who are chronically treated with C5 inhibition. Despite good response to treatment, reflected in decreased occurrence of intravascular hemolysis, anemia, and thrombosis; the size of the hematopoietic stem cell PNH clone, measured by the granulocyte clone, does not change over time (71). The stability of the PNH hematopoietic stem cell clone, together with its inherent non-malignant properties, support the argument that patients treated with C5 inhibition have the same underlying disease as treatment-naive patients (37).

Given the lack of a biological difference, patients who are treatment-naive and those who switch treatment are not considered distinct patient populations. Therefore, efficacy of complement inhibition in switch patients is expected to parallel the efficacy results seen in treatment-naive patients once the hemolysis control has been achieved, as published in prior studies in this indication (51, 72). Similarly, the safety profile of crovalimab is expected to be similar in treatment-naive and switch patients, with the exception of the risk of Drug-target-drug complexes type 3 hypersensitivity reactions (DTDC-related T3H reactions), which uniquely characterizes switch patients in the period immediately following the switch.

Clinical data used in the cost-comparison model include:

- BTH
- Blood transfusions
- Spontaneous remission
- Mortality.

8.1.1 Extrapolation of efficacy data

No applicable

8.1.1.1 Extrapolation of efficacy

Table 23 Summary of assumptions associated with extrapolation of efficacy

Method/approach	Description/assumption
Data input	Not applicable
Model	Not applicable
Assumption of proportional hazards between intervention and comparator	Not applicable
Function with best AIC fit	Not applicable
Function with best BIC fit	Not applicable
Function with best visual fit	Not applicable
Function with best fit according to evaluation of smoothed hazard assumptions	Not applicable
Validation of selected extrapolated curves (external evidence)	Not applicable
Function with the best fit according to external evidence	Not applicable
Selected parametric function in base case analysis	Not applicable
Adjustment of background mortality with data from Statistics Denmark	Yes
Adjustment for treatment switching/cross-over	No
Assumptions of waning effect	No
Assumptions of cure point	Yes. The rate of spontaneous remission used in the scenario analysis was taken from NICE TA698 (50) (0.0006 per 2-week cycle), which was calculated using data reported in Hillmen et al (8).

8.1.1.2 Extrapolation of [effect measure 2]

Not applicable

8.1.2 Calculation of transition probabilities

Table 24 Transitions in the health economic model

Health state (from)	Health state (to)	Description of method	Reference
Not applicable			

The following probabilities were included in the model:

BTH
Blood transfusions
Spontaneous remission
Mortality.

BTH

The 2-weekly probability of BTH events (0.85%) was taken from Quist et al (55) and assumed to be equivalent across all considered comparators. The proportion of BTH events in the eculizumab arm which are CAC-related (35.29%) was calculated from Quist et al (55), which reported that across the eculizumab arms in COMMODORE 1 and COMMODORE 2, 6 of the 17 BTH events which occurred were CAC-related BTH events.

Blood transfusions

A constant rate of blood transfusions is applied in all treatment arms, which differs based on whether a BTH event occurs within the model cycle. The rates were derived from the 2-weekly probabilities of blood transfusions in 'BTH' states and 'no BTH' states reported for eculizumab-treated patients in Quist et al (55). The 2-weekly probabilities are presented in Table 25.

Table 25 Blood transfusion data

Event	2-weekly probability
Blood transfusions (no BTH states)	9%
Blood transfusions (BTH states)	30%

Abbreviations: BTH, breakthrough hemolysis.

Spontaneous remission

The rate of spontaneous remission used in the scenario analysis was taken from NICE TA698 (73) (0.0006 per 2-week cycle), which was calculated using data reported in Hillmen et al (2).

Mortality

Background mortality is informed by general population life tables for Danish population based on 'Key figures including general mortality' on the DMC's website (49)

8.2 Presentation of efficacy data from [additional documentation]

Not applicable

8.3 Modelling effects of subsequent treatments

Not applicable

8.4 Other assumptions regarding efficacy in the model

The model has the following assumptions, each with a specific rationale.

- Firstly, it is assumed that 40% of complement-amplifying complex (CAC)-related breakthrough hemolysis (BTH) events in patients receiving eculizumab are treated with a single up-dose of the same drug. This assumption is based on clinical opinion from NICE TA698 (73), which suggested that a single up-dose would suffice to re-establish blockade for patients on C5 inhibitors. This is supported by data from the COMMODORE 2 trial, where 4 out of 10 patients who experienced a BTH event received rescue treatment.
- Similarly, it is assumed that 40% of CAC-related BTH events in patients receiving crovalimab are managed with a single up-dose of crovalimab. The rationale for this assumption comes from the COMMODORE 2 trial, where a single rescue dose of 340 mg of crovalimab was administered to patients experiencing BTH due to an acute event such as illness, trauma, or surgery. In this trial, 4 out of 10 patients with recorded BTH events received rescue treatment.
- Another assumption is that the treatment effect for all therapies remains constant over time. This is based on evidence showing that eculizumab provides a long-term treatment effect, and crovalimab has demonstrated non-inferiority to eculizumab in clinical studies.
- Also, it was assumed that the safety profiles between Crovalimab and eculizumab are similar and therefore adverse event (AE) costs were not considered. The discontinuation rate between all comparator was set equal.
- Monitoring was also assumed to be equal between crovalimab and eculizumab, therefore no differences in monitoring are anticipated between the considered comparators. Similarly for the medical resource use where no differences in medical resource use are anticipated between the considered comparators. Both monitoring and medical resource use were not included in the model.
- The model assumed that the requirement for the meningococcal vaccine and prophylactic antibiotics is the same between the considered comparators and was not included in the model.
- Lastly, the model assumes that the risk of death in all treatment arms is equivalent to that of the general population. This assumption is supported by evidence indicating that the availability of complement inhibitors has aligned

the life expectancy of patients with PNH to that of the general population.

8.5 Overview of modelled average treatment length and time in model health state

Table 26 Estimates in the model

	Modelled average [effect measure] (reference in Excel)	Modelled median [effect measure] (reference in Excel)	Observed median from relevant study
Crovalimab	Not applicable	Not applicable	Not applicable
Eculizumab	Not applicable	Not applicable	Not applicable

Table 27 Overview of modelled average treatment length and time in model health state, undiscounted and not adjusted for half cycle correction (adjust the table according to the model)

Treatment	Treatment length [months]	Health state 1 [months]	Health state 2 [months]
Crovalimab	Not applicable - life time treatment	Not applicable	Not applicable
Eculizumab	Not applicable - life time treatment	Not applicable	Not applicable

The duration of treatment for both crovalimab and eculizumab is until remission (spontaneuous remission is coniserderd in the scenario analysis) or unacceptable toxicity. No stopping rule was applied in the model.

9. Safety

9.1 Safety data from the clinical documentation

In this section safety data from the clinical studies COMMODORE 2 and COMMODORE 1 are presented separately. A pooled analysis of safety from COMMODORE 1, 2 and 3 will be presented at the end of this section in Table 30 followed by There were no SAEs with a frequency of ≥ 5% in the three studies – COMMODORE 1, COMMODORE 2 and COMMODORE 3. Please refer to Appendix E for a list of all SAEs in COMMODORE 1 and 2.

Table 31 reporting serious adverse events with a frequency ≥ 5% across the pooled safety population. Separate safety data from COMMODORE 3 will not be presented due to the patient characteristics of the population, the study was conducted only in China.

The term “primary safety period” is used and defined as follows:

- For Arm A, the Primary Safety Period starts with dose Day 1 and ends on the day of the last assessment prior to Week 25 dose administration or date of withdrawal from study, whichever occurs first.

- For Arm B, the Primary Safety Period starts with dose Day 1 and ends on the last assessment prior to the switch to crovalimab or date of withdrawal from study, whichever occurs first.

9.1.1 COMMODORE 2

The safety evaluable population included all randomized patients (from Arms A (crovalimab arm), B (eculizumab arm) and C (pediatric crovalimab arm)) who received ≥1 dose of study drug. This section, including Table 28, focuses on the randomized arm A and Arm B of the study. The descriptive peadiatric Arm C is described in a subsection after the table.

The median treatment duration during the primary treatment period was similar in the crovalimab and eculizumab arms (20.1 weeks [range: 0.1–23.1 weeks] vs 22.1 weeks [range: 6.1–26.1 weeks]). The treatment duration was calculated as the date of the last study drug administration (Week 21 in the crovalimab arm and Week 23 in the eculizumab arm) minus the date of the first study drug administration (Week 1) plus one day, thus the calculation did not capture exposure up to Week 25. The calculated treatment duration is therefore approximately 2 weeks longer per definition in the eculizumab arm.

After the patients completed the primary treatment period of 24 weeks, there was a possibility for Arm A patients to continue crovalimab treatment and for Arm B patients to switch to crovalimab. In the crovalimab arm (Arm A) up to CCOD (16 November 2022), the median treatment duration was 48.3 weeks (range: 0.1–107.9 weeks), with 57.0% of the patients having had a treatment duration of at least 48 weeks. At the CCOD, median treatment duration with crovalimab for eculizumab (Arm B) switch patients was 24.1 weeks (range: 0.3–76.3), with a median of 11 doses (range: 2–24) administered. Overall, 58.8% of the switch patients (40 of 68) had a treatment duration of at least 24 weeks.

Table 28 Overview of safety events, COMMODORE 2.

Primary safety period. The median treatment duration during the primary treatment period was (20.1 weeks [range: 0.1–23.1 weeks] in the crovalimab arm and 22.1 weeks [range: 6.1–26.1 weeks] in the eculizumab arm

	Intervention Crovalimab (N=135) (46, 59, 60)	Comparator Eculizumab (N=69) (46, 59, 60)	Difference, % (95 % CI)[a]
Number of adverse events, n	[redacted]	[redacted]	[redacted]
Number and proportion of patients with ≥1 adverse events, n (%)	105 (77.8)	55 (79.7)	-1.9 (9.9, -13.7)
Number of serious adverse events*, n	[redacted]	[redacted]	[redacted]
Number and proportion of patients with ≥ 1	14 (10.4)	9 (13.0)	-2.7 (6.8, -12.1)

	Intervention Crovalimab (N=135) (46, 59, 60)	Comparator Eculizumab (N=69) (46, 59, 60)	Difference, % (95 % CI)[a]
serious adverse events*, n (%)			
Number of CTCAE grade ≥ 3 events, n	[redacted]	[redacted]	[redacted]
Number and proportion of patients with ≥ 1 CTCAE grade ≥ 3 events[§], n (%)	24 (17.8)	17 (24.6)	-6.8 (10.8, -14.9)
Number of adverse reactions, n	[redacted]	[redacted]	[redacted]
Number and proportion of patients with ≥ 1 adverse reactions, n (%)	45 (33.3)	24 (34.8)	-1.5 (12.3, -15.2)
Number and proportion of patients who had a dose reduction, n (%)**	1 (0.7)	0	0.7 (-0.7, 2.2)
Number and proportion of patients who discontinue treatment regardless of reason, n (%)	6 (4.4)	1 (1.4)	3 (-1.5, 7.5)
Number and proportion of patients who discontinue treatment due to adverse events, n (%)	1 (0.7)	1 (1.4)	-0.7 (2.5, -3.9)

Only treatment-emergent AEs are displayed.

§ CTCAE v. 5.0 must be used if available.
* A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect (see the ICH's complete definition).
** Number and proportion of patients who had a dose reduction due to an AE
[a] 95% CI for risk differences is calculated using the Wald method

During the primary safety period, the overall safety profile of crovalimab in COMMODORE 2 was consistent with the known safety profile of C5 inhibitors, and no additional safety concerns were identified. The safety results in the randomized safety population during the primary safety period indicated that crovalimab was well tolerated during the primary treatment period in treatment-naive patients with PNH. The safety profile of crovalimab was comparable to that of eculizumab, with key safety parameters

being similar between the two treatment arms. Below relevant safety categories will be described in further details.

All AEs

In the randomized safety population, 77.8% of patients treated with crovalimab and 79.7% of patients treated with eculizumab had at least one AE during the primary treatment period. Infusion-related reaction was the most commonly reported AE by PT in both the crovalimab (15.6%) and eculizumab (13.0%) arms.

The most frequently reported laboratory abnormality AEs reported in the crovalimab and eculizumab arms were: neutrophil count decreased (12.6% and 10.1%), white blood cell count decreased (11.9% and 10.1%), hypokalemia (11.1% and 13.0%) and hypocalcemia (5.9% and 10.1%). Roche's medical review has shown that a large majority of these events can be explained by laboratory abnormalities already present at baseline, relevant medical history, underlying disease and concurrent medications, and generally, the laboratory abnormalities that worsened from baseline were not associated with clinical consequences.

Other AEs reported in ≥10% of patients of either arm of the crovalimab and/or eculizumab arms, respectively, were pyrexia (8.9% and 10.1%) and upper respiratory tract infection (8.1% and 13.0%)[redacted]

AEs related to treatment

During the primary safety period, the proportion of patients with adverse reactions was comparable between the crovalimab arm (33.3%, 45 patients) and the eculizumab arm (34.8%, 24 patients). The most frequent adverse reaction by MedDRA Preferred Term (PT), with an incidence of ≥ 10% of patients in either the crovalimab or eculizumab arms were: infusion-related reaction (15.6%, and 13.0%), white blood cell count decreased (11.9%, and 10.1%), and neutrophil count decreased (11.1%, and 10.1%), respectively (46, 59).

Infusion-related reactions and injection-site reactions

The most frequently reported symptoms of infusion-related reactions in the crovalimab arm were headache (13.3%) and abdominal pain (1.5%). The rest of the symptoms occurred in single patients, including dizziness, paraesthesia, vomiting, nausea, arthralgia, pain in extremity, chills, pyrexia, dry eye, rash and haematoma. Headache (8.7%) was the most frequently reported symptom of infusion-related reactions in the eculizumab arm. The rest of the symptoms occurred in single patients and included abdominal pain, vomiting, nausea, and back pain.

There were 14 events in 7 patients (5.2%) treated with crovalimab of injection-site reactions. All events were Grade 1 or 2 in severity. Of these one patient experienced 8 events of injection site reactions (by PT), all of which were Grade 2 in severity. No additional cases of injection-site reactions were reported in patients in the crovalimab arm who continued on crovalimab after the primary safety period up to CCOD (60).

Grade ≥ 3 AEs

The proportion of patients with Grade 3–5 AEs in the crovalimab arm was 17.8% and 24.6% in the eculizumab arm.

SAEs

The proportion of patients with at least one SAE in the crovalimab arm (10.4%) during the primary safety period was comparable to the eculizumab arm (13.0%). For al list of all SAEs, please refer to Appendix E. SAEs that were considered by the investigator to be related to the study drug were reported in 3.0% vs 1.4%, in the crovalimab arm vs the eculizumab arm, respectively. In the crovalimab arm, four patients experienced SAEs that were considered by the investigator to be related to the study drug, and all had recovered at the time of the CCOD. The SAEs experienced by these patients included: thrombocytopenia, pyrexia, epistaxis and a infusion-related reaction. The single patient in the eculizumab arm with a related SAE, experienced thrombocytopenia.

In the period between the end of the primary safety period and the CCOD, two patients each experienced an SAE of upper respiratory tract infection considered by the investigator as related to the study drug. Both events were reported to have been resolved by CCOD without any dose modification/interruption.

Fatal AEs

Overall, there were three fatal AEs, all unrelated to treatment; two in the crovalimab arm (myocardial infarction before start of treatment and respiratory hemorrhage 127 days after last crovalimab administration as the patient had already discontinued from study treatment due to “physician’s decision”), and one in the eculizumab arm (ischemic stroke; assessed to be due to PNH based on etiologic factors) (46).

AEs leading to withdrawal of treatment

One patient each from the crovalimab (0.7%) and eculizumab (1.4%) arms experienced an AE leading to discontinuation of treatment during the primary safety period. The patient in the crovalimab arm experienced a Grade 4 SAE of thrombocytopenia that led to withdrawal of treatment due to worsening of myelodysplastic syndrome reported at baseline. The AE was assessed to be treatment-related. The patient received no additional treatment for the AE and was reported to have recovered by the CCOD. In the eculizumab arm, the patient experienced a Grade 5 (fatal) SAE of ischemic stroke that led

to withdrawal of treatment. The investigator assessed the SAE as not related to eculizumab (see sub-section Fatal AEs) (46).

AEs leading to dose modification
In the crovalimab arm one patient experienced an AE that led to dose reduction (nausea). In addition two AEs (one event each of feeling cold and peripheral coldness) lead to dose increase (46, 59).

Arm C (descriptive pediatric crovalimab arm)
Arm C included six pediatric patients (< 18 years old) with a body weight ≥ 40 kg who met all the other inclusion and exclusion criteria for the study. No pediatric patients discontinued study treatment up to the CCOD. Due to the small number of patients enrolled in the descriptive pediatric arm, results should be interpreted with caution.

[redacted]

9.1.2 COMMODORE 1

In the COMMODORE 1 study, the safety analyses were performed on the 'safety evaluable population', defined as all enrolled patients who received at least one dose of study drug, with patients grouped according to the treatment received.

This section, including Table 29, focuses on the randomized crovalimab Arm A (n=44 patients) and eculizumab Arm B (n=42 patients). The exploratory Arm C is described in a subsection after the Table 29.

The median treatment duration during the primary safety period was 20.1 weeks (range: 2.1–22.3) in the crovalimab arm (Arm A) and 22.1 weeks (range: 0.1–26.1) in the eculizumab arm (Arm B). The treatment duration was calculated as the date of the last study drug administration (Week 21 in the crovalimab arm and Week 23 in the eculizumab arm) minus the date of the first study drug administration (Week 1) plus one day, thus the calculation did not capture exposure up to Week 25. The calculated treatment duration is therefore approximately 2 weeks longer per definition in the eculizumab arm.

After the primary treatment period, patients had the opportunity to continue in the extension period where all patients received crovalimab. In the crovalimab arm up to the

CCOD, the median treatment duration was 52.0 weeks (range: 2.1–108.4). The majority of patients (54.5%) had a treatment duration of at least 48 weeks. At the CCOD, the median treatment duration with crovalimab for eculizumab (Arm B) switch patients was 32.1 weeks (range: 3.1–84.1 weeks), with a median of 13 doses (range: 5–26 doses) administered. The majority of patients (74.3%) had a treatment duration of at least 24 weeks.

Table 29 Overview of safety events from COMMODORE 1

Primary safety period. Medium treatment duration (range), weeks for crovalimab: 20.1 (2.1–22.3) and eculizumab: 22.1 (0.1–26.1)

	Intervention Crovalimab (N=44) (47, 58)	Comparator Eculizumab (N=42) (47, 58)	Difference, % (95 % CI)[a]
Number of adverse events, n	[redacted]	[redacted]	[redacted]
Number and proportion of patients with ≥1 adverse events, n (%)	34 (77.3)	28 (66.7)	10.6 (-8.3, 29.5)
Number of serious adverse events*, n	8	3	N/A
Number and proportion of patients with ≥ 1 serious adverse events*, n (%)	6 (13.6)	1 (2.4)	11.3 (0.1, 22.4)
Number of CTCAE grade ≥ 3 events, n	[redacted]	[redacted]	[redacted]
Number and proportion of patients with ≥ 1 CTCAE grade ≥ 3 events[§], n (%)	8 (18.2)	1 (2.4)	15.8 (3.5, 28.1)
Number of adverse reactions, n	[redacted]	[redacted]	[redacted]
Number and proportion of patients with ≥ 1 adverse reactions, n (%)	14 (31.8)	0	31.8 (18.1, 45.6)
Number and proportion of patients who had a	[redacted]	[redacted]	[redacted]

	Intervention Crovalimab (N=44) (47, 58)	Comparator Eculizumab (N=42) (47, 58)	Difference, % (95 % CI)[a]
dose reduction, n (%)**			
Number and proportion of patients who discontinue treatment regardless of reason*, n (%)**	[redacted]	[redacted]	[redacted]
Number and proportion of patients who discontinue treatment due to adverse events, n (%)	0	0	N/A

* A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect (see the ICH's complete definition).
** Number and proportion of patients who had a dose reduction due to an AE
*** 5 patients in each arm were still ongoing in the 24 week primary treatment period at clinical cutoff date
§ CTCAE v. 5.0 must be used if available.
[a] 95% CI for risk differences is calculated using the Wald method.

During the primary safety period, the overall safety results indicated that crovalimab was well tolerated in patients with PNH switching from eculizumab. The overall safety profile was consistent with that expected for a C5 inhibitor, except for a newly identified risk of transient immune complex reactions which only occur in patients who switch between crovalimab and another C5 inhibitor. Below relevant safety categories will be described in further details.

All AEs

During the primary safety period, 77.3% of the patients in the crovalimab arm and 66.7% of the patients in the eculizumab arm experienced at least one AE. AEs reported in ≥10% of patients of either arm were pyrexia (15.9% with crovalimab vs. 2.4% with eculizumab), headache (11.4% vs 2.4%), COVID-19 (13.6 vs. 16.7%), infusion-related reactions (13.6% vs 0) and transient immune complex reactions (15.9% vs 0%) (47).

AEs related to treatment

The proportion of patients with adverse reactions in the crovalimab arm (31.8%) was higher compared with the eculizumab arm (0%). The most frequent adverse reaction by PT (≥ 5%) in the crovalimab arm were: transient immune complex reactions (15.9%), infusion-related reactions (13.6%) and injection-related reactions (9%). These are described further below. (47, 58).

Transient immune complex reactions

Transient immune complex reactions (also known as drug-target-drug-complexes) were expected only in the crovalimab arm at the time of switching from eculizumab to crovalimab due to each C5 inhibitor binding to a different epitope on C5. When both antibodies are present in the circulation, transient immune complexes may form. Therefore, patients who switched from eculizumab to crovalimab are at risk of developing transient immune complex reactions. Patients who have never previously been treated with a C5 inhibitor or patients in whom previous C5 inhibitor treatment has cleared from the body are not at risk of transient immune complex reactions.

In the crovalimab arm, 7 (15.9%) patients experienced at least one transient immune complex reaction. All were considered by the investigator as related to study treatment. The majority of events were grade 1 or 2 in severity (two events of Grade 1, four events of Grade 2 and one event of grade 3), all of which were resolved without dose modifications/interruptions. The grade 3 reaction resolved after treatment of the AE. Time to onset of transient immune complex reactions ranged from 9 to 15 days.

The most common manifestations of transient immune complex reactions were rash (5 patients (11%)), and arthralgia and/or myalgia (5 patients (11%)), with no evidence of renal involvement. The one patient with a severe transient immune complex reaction had symptoms of arthralgia, dizziness, abdominal pain, and nausea. Treatments used for mild/moderate reactions were mainly analgesics or nonsteroidal anti-inflammatories for arthralgia, and antihistamines and topical steroids for rash; systemic steroids were also used for the severe reaction (47, 58).

No additional transient immune complex reactions were reported in the crovalimab arm after the primary safety period and up to the CCOD.

Infusion-related reactions and injection-site reactions
Infusion-related reactions (related to a single IV loading dose) also occurred only in the crovalimab arm (6 patients (14%) vs. 0 with eculizumab), likely due to the steady receipt of eculizumab for ≥24 weeks before study enrollment. All infusion-related reactions experienced in the crovalimab arm were Grade 1 or 2 in severity and resolved without dose modification/interruption. The most common symptom of infusion-related reactions was headache (5%). Injection-related reactions were expected to occur only in the crovalimab arm due to the subcutaneous administration which is unique to crovalimab. There were five events in four (9.1%) patients treated with crovalimab. All events were Grade 1 in severity (47, 58).

AEs grade ≥ 3
The proportion of patients with at least one Grade 3–5 AE in the crovalimab arm (18.2%) was higher compared with the eculizumab arm (2.4%). The higher proportion of Grade 3-5 AEs reported in the crovalimab arm was not driven by known risks associated with crovalimab, and most events occurred in single patients across various PTs with no pattern indicative of a safety concern associated with crovalimab. There were no patients in either arm with Grade 5 AEs. In the crovalimab arm, the only reported Grade 3–5 AE by PT with two or more patients was [redacted]. All other Grade 3–5 AEs occurred in single

patients, and include [redacted]pneumonia (SAE), urinary tract infection (SAE), hypersensitivity, transient immune complex reactions, hyperbilirubinaemia (SAE), skin laceration (SAE), [redacted]The majority of reported Grade 3–5 AEs were Grade 3, with only one patient who experiencing a serious Grade 4 neutropenia event which was assessed as not related to study drug and resolved without treatment for the AE. In the eculizumab arm, one patient experienced a serious Grade 3 pneumonia event and a serious Grade 3 pyelonephritis event. Both events resolved with treatment of AEs and no dose modification/interruption. There were no patients in either arm with Grade 5 AEs (47).

SAEs

Six patients (13.6 %) in the crovalimab arm and one patient (2.4 %) in the eculizumab arm experienced an SAE. These are all listed in Appendix E. Importantly, none of the SAEs were considered by the investigator to be related to crovalimab or eculizumab in the primary safety period (47).

9.1.3 Pooled analysis of safety data from COMMODORE 1, COMMODORE 2 and COMMODORE 3

Safety data up to the latest CCOD of the studies COMMODORE 1 (CCOD: 16 Nov 2022), COMMMODORE 2 (CCOD: 16 Nov 2022) and COMMODORE 3 (CCOD: 10 Aug 2022) were pooled and analysed, in order to perform a comprehensive assessment of the safety profile of crovalimab for the treatment of PNH. The data is presented below in Table 30.

Table 30 Overview of safety events - COMMODORE 1, COMMODORE 2 and COMMODORE 3.

Safety Data up to CCOD are pooled from the studies COMMODORE 1, COMMODORE 2 and COMMODORE 3. Median treatment duration weeks (range) was 52.14 (0.1-107.9) for crovalimab naïve patients, 32.29 (0.3-108.4) for crovalimab switch patients, 44.43 (0.1-10.4) for all crovalimab patients and 22.14 (0.1-26.1) for eculizumab patients.

	Intervention Crovalimab naive (N=192) (source)	Intervention Crovalimab switch (N=185) (source)	Intervention Crovalimab combined (N=377) (source)	Comparator Eculizumab (N=111) (source)	Difference, % (95 % CI)[a]
Number of adverse events, n	1063	692	1755	290	N/A
Number and proportion of patients with ≥1 adverse events, n (%)	174 (90.6)	152 (82.2)	326 (86.5)	83 (74.8)	11.7 (2.9, 20.5)
Number of serious adverse events*, n	41	43	84	16	N/A
Number and proportion of patients with ≥ 1	28 (14.6)	29 (15.7)	57 (15.1)	10 (9.0)	6.1 (-0.3, 12.5)

	Intervention Crovalimab naive (N=192) (source)	Intervention Crovalimab switch (N=185) (source)	Intervention Crovalimab combined (N=377) (source)	Comparator Eculizumab (N=111) (source)	Difference, % (95 % CI)[a]
serious adverse events*, n (%)					
Number of CTCAE grade ≥ 3 events, n	120	76		25	N/A
Number and proportion of patients with ≥ 1 CTCAE grade ≥ 3 events§, n (%)	50 (26.0)	46 (24.9)	96 (25.5)	18 (16.2)	9.2 (1.1, 17.4)
Number of adverse reactions, n	423	155		70	N/A
Number and proportion of patients with ≥ 1 adverse reactions, n (%)	93 (48.4)	70 (37.8)	163 (43.2)	24 (21.6)	21.6 (12.5, 30.8)
Number and proportion of patients who had a dose reduction, n (%)**	8 (4.2)	8 (4.3)	16 (4.2)	3 (2.7)	1.5 (-2.1, 5.2)
Number and proportion of patients who discontinue treatment regardless of reason, n (%)	N/A	N/A	N/A	N/A	N/A
Number and proportion of patients who discontinue treatment due to adverse events, n (%)	1 (0.5)	3 (1.6)	4 (1.1)	1 (0.9)	0.2 (-1.9, 2.2)

* A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect (see the ICH's complete definition).
** Number and proportion of patients who had a dose modification/interruption due to an AE
*** 5 patients in each arm were still ongoing in the 24 week primary treatment period at clinical cutoff date
§ CTCAE v. 5.0 must be used if available.
[a] 95% CI for risk differences is calculated using the Wald method. The difference is calculated between the pooled crovalimab cohort and the eculizumab cohort. Source: (60)

As the major differences in the safety profiles across categories and between treatment arms have already been addressed in the COMMODORE 2 and COMMODORE 1 safety subsections, these will not be described further for the pooled population. However due to the general relevance of infections with N. meningitis (including Meningococcal meningitis) in patients with PNH, the infection data across the studies is presented below.

Infections

The proportion of patients who experienced at least one infection was 46.9% in the combined (naïve + switch) crovalimab population and 36.0% in the total eculizumab population. The most frequently reported infections in the combined crovalimab and total eculizumab populations were COVID-19 (16.2% vs 9.9%), upper respiratory tract infection (14.6% vs 9.0%), and urinary tract infection (5.8% vs 6.3%), respectively. The majority were Grade 1−2 events. In the total crovalimab and total eculizumab populations, Grade 3 events were experienced in 4.8% and 3.6% of patients, and one patient in each population had a Grade 4 event (0.3%, pyelonephritis and 0.9%, central nervous system infection), respectively. There were no cases of infection with N. meningitis (including Meningococcal meningitis) (60).

SAEs with a frequency of ≥ 5% across COMMODORE 1 + 2 + 3

There were no SAEs with a frequency of ≥ 5% in the three studies – COMMODORE 1, COMMODORE 2 and COMMODORE 3. Please refer to Appendix E for a list of all SAEs in COMMODORE 1 and 2.

Table 31 Serious adverse events (time point)

Adverse events	Intervention (N=x)		Comparator (N=x)	
	Number of patients with adverse events	Number of adverse events	Number of patients with adverse events	Number of adverse events
Adverse event, n (%)	NA	NA	NA	NA

* A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect (see the ICH's complete definition).

Summary of safety data across the three studies

Overall, the safety profile of crovalimab appears similar to that of eculizumab in patients with PNH, both in treatment naïve patients and in patients already on treatment with eculizumab. While some imbalances between arms were observed in COMMODORE 1, safety parameters were more balanced in COMMODORE 2. The key difference in COMMODORE 2 was that patients in each arm began treatment at the same time, whereas in COMMODORE 1, patients in the eculizumab arm had already stabilized on their treatment.

The most commonly reported AEs with crovalimab were pyrexia, headache, infections, infusion-related reactions, injection-related reactions) and transient immune complex-mediated reactions which occurred only in switch patients. Important to mention is that

the transient immune complex-mediated reactions were resolved without dose modifications/interruptions. Meningococcal infection is an important risk of crovalimab related to its mode of action, however no cases of meningococcal meningitis were reported across the studies (60).

Table 32 Adverse events used in the health economic model

Adverse events	Intervention	Comparator		
	Frequency used in economic model for intervention	Frequency used in economic model for comparator	Source	Justification
Adverse event, n (%)	Not applicable			

9.2 Safety data from external literature applied in the health economic model

Not applicable. AEs are not applied in the health economic model. For AEs appearing in more than 10 %, refer to section 9.1.1 and 9.1.2.

Table 33 Adverse events that appear in more than X % of patients

Adverse events	Intervention (N=x)			Comparator (N=x)			Difference, % (95 % CI)	
	Number of patients with adverse events	Number of adverse events	Frequency used in economic model for intervention	Number of patients with adverse events	Number of adverse events	Frequency used in economic model for comparator	Number of patients with adverse events	Number of adverse events
Adverse event, n	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

10. Documentation of health-related quality of life (HRQoL)

Exploratory efficacy objectives in COMMODORE 1 and 2 included the evaluation of the treatment effect of crovalimab compared to eculizumab based on patient-reported outcome (PRO) instruments (see all PROs included in the study in Appendix A). HRQoL assessed using the EuroQol-5 Dimensions-5 Levels Questionnaire (EQ-5D-5L) and the

European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) will be presented in this application (Table 34).

Table 34 Overview of included HRQoL instruments

Measuring instrument	Source	Utilization
EQ-5D-5L Utility and VAS scores	COMMODORE 2 and 1	Clinical effectiveness Presented in section 10.1
EORTC QLQ-C30 Physical functioning, role functioning and GHS/QoL	COMMODORE 2 and 1	Clinical effectiveness Presented in Appendix F

EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EQ-5D-5L: EuroQol-5 Dimensions-5 Levels Questionnaire; GHS: Global Health Status; QoL: Quality of life

10.1 Presentation of the health-related quality of life [EQ-5D-5L]

10.1.1 Study design and measuring instrument

[redacted]

10.1.2 Data collection

[redacted]

[redacted]

Table 35 Pattern of missing data and completion – COMMODORE 2

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)
		crovalimab		
Baseline *	[redacted]	[redacted]	[redacted]	[redacted]
Week 2	[redacted]	[redacted]	[redacted]	[redacted]
Week 5	[redacted]	[redacted]	[redacted]	[redacted]
Week 9	[redacted]	[redacted]	[redacted]	[redacted]
Week 17	[redacted]	[redacted]	[redacted]	[redacted]
Week 25	[redacted]	[redacted]	[redacted]	[redacted]
		eculizumab		
Baseline*	[redacted]	[redacted]	[redacted]	[redacted]
Week 2	[redacted]	[redacted]	[redacted]	[redacted]
Week 5	[redacted]	[redacted]	[redacted]	[redacted]
Week 9	[redacted]	[redacted]	[redacted]	[redacted]
Week 17	[redacted]	[redacted]	[redacted]	[redacted]
Week 25	[redacted]	[redacted]	[redacted]	[redacted]

*Baseline is the patient's last observation prior to initiation of study drug in the primary treatment period. This questionnaire is only reported by patients >= 18 years.

Table 36 Pattern of missing data and completion – COMMODORE 1

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)
		crovalimab		

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
Baseline *	[redacted]	[redacted]	[redacted]	[redacted]
Week 2	[redacted]	[redacted]	[redacted]	[redacted]
Week 5	[redacted]	[redacted]	[redacted]	[redacted]
Week 9	[redacted]	[redacted]	[redacted]	[redacted]
Week 17	[redacted]	[redacted]	[redacted]	[redacted]
Week 25	[redacted]	[redacted]	[redacted]	[redacted]
		eculizumab		
Baseline*	[redacted]	[redacted]	[redacted]	[redacted]
Week 2	[redacted]	[redacted]	[redacted]	[redacted]
Week 5	[redacted]	[redacted]	[redacted]	[redacted]
Week 9	[redacted]	[redacted]	[redacted]	[redacted]
Week 17	[redacted]	[redacted]	[redacted]	[redacted]
Week 25	[redacted]	[redacted]	[redacted]	[redacted]

*Baseline is the patient's last observation prior to initiation of study drug in the primary treatment period. This questionnaire is only reported by patients >= 18 years.

10.1.3 HRQoL results for COMMODORE 2

[redacted]

[redacted]

Table 37 HRQoL [EQ-5D-5L utility] summary statistics, COMMODORE 2:

Summary of Absolute Scores and Change from Baseline by Visit, EQ-5D-5L utility in COMMODORE 2, Period on Initially Assigned Treatment, Primary Analysis Population. This questionnaire is only reported by patients >= 12 years.

	Intervention Crovalimab naive		Comparator Eculizumab		Intervention vs. comparator
	N	Mean (SE)	N	Mean (SE)	Difference (95% CI) p-value**
Baseline*	[redacted]				
Week 2	[redacted]				
Week 5	[redacted]				
Week 9	[redacted]				
Week 17	[redacted]				
Week 25	[redacted]				

*Baseline is the patient's last observation prior to initiation of study drug in the primary treatment period.

**The analyses were purely descriptive and not powered to detect differences

Figure 10 Plot of Absolute Scores with 95% CI by Visit, EQ-5D-5L Utility, Primary Efficacy Period, Primary Analysis Population, COMMODORE 2 (59)

Table 38 HRQoL [EQ-5D-5L VAS] summary statistics – COMMODORE 2

Summary of Absolute Scores and Change from Baseline by Visit, EQ-5D-5L VAS in COMMODORE 2, Period on Initially Assigned Treatment, Primary Analysis Population. This questionnaire is only reported by patients >= 12 years.

	Intervention Crovalimab naive		**Comparator Eculizumab**		**Intervention vs. comparator**
	N	Mean (SE)	N	Mean (SE)	Difference (95% CI) p-value**
Baseline*					
Week 2					
Week 5					
Week 9					
Week 17					
Week 25					

*Baseline is the patient's last observation prior to initiation of study drug in the primary treatment period.

**The analyses were purely descriptive and not powered to detect differences

Figure 11 Plot of Absolute Scores with 95% CI by Visit, EQ-5D-5L VAS, Primary Efficacy Period, Primary Analysis Population, COMMODORE 2 (59)

10.1.4 HRQoL results for COMMODORE 1

[redacted]

[redacted]

[redacted].

Table 39 HRQoL [EQ-5D-5L utility] summary statistics, COMMODORE 1

Summary of Absolute Scores and Change from Baseline by Visit, EQ-5D-5L utility in COMMODORE 2, Period on Initially Assigned Treatment, Primary Analysis Population. This questionnaire is only reported by patients >= 12 years.

	Intervention Crovalimab naive		Comparator Eculizumab		Intervention vs. comparator
	N	Mean (SE)	N	Mean (SE)	Difference (95% CI) p-value**
Baseline*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 17	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 25	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*Baseline is the patient's last observation prior to initiation of study drug in the primary treatment period.

**The analyses were purely descriptive and not powered to detect differences

Figure 12 Plot of Absolute Scores with 95% CI by Visit, EQ-5D-5L Utility, Primary Efficacy Period, Primary Analysis Population, COMMODORE 1 (58)

Table 40 HRQoL [EQ-5D-5L VAS] summary statistics – COMMODORE 1

Summary of Absolute Scores and Change from Baseline by Visit, EQ-5D-5L VAS in COMMODORE 1, Period on Initially Assigned Treatment, Primary Analysis Population. This questionnaire is only reported by patients >= 12 years.

	Intervention Crovalimab naive		Comparator Eculizumab		Intervention vs. comparator
	N	Mean (SE)	N	Mean (SE)	Difference (95% CI) p-value**
Baseline*	[redacted]				
Week 2	[redacted]				
Week 5	[redacted]				
Week 9	[redacted]				
Week 17	[redacted]				
Week 25	[redacted]				

*Baseline is the patient's last observation prior to initiation of study drug in the primary treatment period.
**The analyses were purely descriptive and not powered to detect differences

Figure 13 Plot of Absolute Scores with 95% CI by Visit, EQ-5D-5L VAS, Primary Efficacy Period, Efficacy Evaluable Population, COMMODORE 1 (4)

10.2 Health state utility values (HSUVs) used in the health economic model

Not applicable

10.2.1 HSUV calculation

Not applicable

10.2.1.1 Mapping

Not applicable

10.2.2 Disutility calculation

Not applicable

10.2.3 HSUV results

Not applicable

Table 41 Overview of health state utility values [and disutilities]

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
Not applicable				

10.3 Health state utility values measured in other trials than the clinical trials forming the basis for relative efficacy

Not applicable

10.3.1 Study design

Not applicable

10.3.2 Data collection

Not applicable

10.3.3 HRQoL Results

Not applicable

10.3.4 HSUV and disutility results

Not applicable

Table 42 Overview of health state utility values [and disutilities]

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
Not applicable				

Table 43 Overview of literature-based health state utility values

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
Not applicable				

11. Resource use and associated costs

Medicine costs for intervention and comparator are presented in the table below.

Table 44 Medicine costs used in the model

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
Crovalimab **Price: 88,635 DKK**	Loading Dose: *Body weight ≥40 kg to <100 kg:* Week 1: Day 1: 1000 mg IV Day 2: 340 mg SC Weeks 2, 3, and 4: 340 mg SC QW *Body weight ≥100 kg:* Week 1: Day 1: 1500 mg IV Day 2: 340 mg SC Weeks 2, 3, and 4: 340 mg SC QW Maintenance dose *Body weight ≥40 kg to <100 kg:* Week 5 and Q4W thereafter: 680 mg SC *Body weight ≥100 kg:* Week 5 and Q4W thereafter: 1020 mg SC	Not appicable	Monthly	No

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
Eculizumab **Price: 33744.58 DKK**	Loading dose: *Adult or paediatric patients with body weight ≥40 kg* Weeks 1–4: 600 mg QW Maintenance dose *Adult or paediatric patients with body weight ≥40 kg* Week 5 and Q2W thereafter: 900 mg	Not appicable	Every 2 weeks	No

Single up-dosing

Cost of up-dosing is presented below.

Frequency	Crovalimab		Eculizumab	
	Dose	Cost (DKK)	Dose	Cost (DKK)
One-off	340.00	88,635.00	300.00	33,744.58

Continuous up-dosing

A constant proportion of 20% of eculizumab patients are assumed to require continuous up-dosing, in line with the assumption made by Quist et al (55).

Eculizumab	
Dose per cycle	Cost per cycle (DKK)
1,200 mg	134,978.32

11.1 Medicine costs – co-administration

Not applicable

11.2 Administration costs

Patients receiving crovalimab treatment are trained in subcutaneous (SC) self administration following the initial dosing phase; a one-off training cost for crovalimab is calculated in the model assuming the the number of hours of training required to train patients in self-administration and the hourly wages of a nurse specialist, in line with TA778 (75)

Eculizumab is administered via intravenous infusion. The infusion costs are the administration costs included in the model for eculizumab and the loading dose of crovalimab, the administration cost was calculated based on the infusion time and time

required from the nurses and pharmacists. It is assumed that a pharmacist will spend 15 minutes preparing the medication.

The duration of administration for eculizumab (for both the loading dose and maintenance dose) were derived from the Summary of Product Characteristics (SmPC)(39), as presented in Table 46. Where a range was given in the SmPC, e.g. a 25–45-minute infusion, the mid-point was used. The cost of nurse time is applied over these durations in the model, with an additional 1-hour observation time included. The wages of the pharmacists and nurses are presented in the Table 45.

Table 45: Wage per hour, hospital staff

Job classification	Cost per working hour	Source
pharmacist specialist	501 DKK	Medicinradet (76)
nurse specialist	462 DKK	Medicinradet (77)

Table 46 Administration costs used in the model

Administration type	Nurse time	Pharmacist time	Frequency	Unit cost [DKK]	DRG code	Reference
Eculizumab Loading Dose IV infusion	35 min infusion and 60 min monitoering	15 min	[every week]	856.8	Not Applicable	Medicinrådet (77), Medicinrådet (76), Eculizumab SPC (39),
Eculizumab maintenance Dose IV infusion	35 min infusion and 60 min monitoering	15 min	[every 2 weeks]	856.8	Not Applicable	Medicinrådet (77), Medicinrådet (76), Eculizumab SPC (39),
Crovalimab IV loading Dose	60 min infusion (90 min for patients > 100 kg) and 60 min monitoring	15 min	Week 1, Day 1	1057.2	Not Applicable	Medicinrådet (77), Medicinrådet (76),Crovalimab SPC (60)
Crovalimab SC loading Dose	60 min monitoring	15 min	Week 1, Day 2 Week 2, 3,4	587.3	Not Applicable	Medicinrdet (77), Medicinrådet (76),Crovalimab SPC (60)

11.3 Disease management costs

Table 47 Disease management costs used in the model

Activity	Frequency	Unit cost [DKK]	DRG code	Reference
General ward hospitalization	Proportion of patients requiring the service per event 23%	4,394.55	17MA01	Quist et al (55)

Activity	Frequency	Unit cost [DKK]	DRG code	Reference
Intensive care unit hospitalisation	Proportion of patients requiring the service per event 1%	4,394.55	17MA01	Quist et al (55)
Dialysis	Proportion of patients requiring the service per event 4%	3034	11PR10	Quist et al (55)
Consultant Visit	Proportion of patients requiring the service per event 100%	1,054.00	Tariff of a doctor as outlined in Medicinrådets unit cost overview(77)	Quist et al (55)
Packed red blood cells administration	Units per transfusion (with BTH state 1.83) No BTH state 1.59	4,218	16PR02	DRG2024

11.4 Costs associated with management of adverse events

Table 48 Cost associated with management of adverse events

DRG code	Unit cost/DRG tariff
Not applicable	

11.5 Subsequent treatment costs

Not applicable

Table 49 Medicine costs of subsequent treatments

Medicine	Strength	Package size	Pharmacy purchase price [DKK]	Relative dose intensity	Average duration of treatment
Not applicable					

11.6 Patient costs

Table 50 Patient costs used in the model

Activity	Time spent [minutes, hours, days]
One time Cost for Loading Dose (transport costs and time spent)	**Time Spent:** Loading Dose for Crovalimab includes: IV time infusion (120 minutes for patients weight less than 100) &

Activity	Time spent [minutes, hours, days]
	(150 minutes for patients weight >100) Plus four SC doses (Monitoring time 60 minutes) Cost = 946 DKK Eculizumab Loading Dose: Four weekly doses with 95 minutes infusion time Cost = 1,191 DKK **Transport Cost:** Crovalimab loading dose: 5 times transportation (1 IV dose + 4 SC) Cost = 700 DKK Eculizumab Loading dose: 4 times transportation Cost = 560 DKK
Maintenance Dose Cost (transport costs and time spent)	**Time Spent:** Crovalimab: not applicable Eculizumab: 2 weekly cycle infusion time for 95 minutes Cost = 298 DKK **Transport Cost:** Crovalimab: not applicable Eculizumab 1 transportation per cycle Cost = 140 DKK

11.7 Other costs (e.g. costs for home care nurses, out-patient rehabilitation and palliative care cost)

Not applicable

12. Results

12.1 Base case overview

Table 51 Base case overview

Feature	Description
Comparator	Eculizumab
Type of model	Cost minimization model
Time horizon	60 years (life time)
Treatment line	Naïve treatment or C5 inhibitor treated population
Measurement and valuation of health effects	Not applicable
Costs included	Drug acquisition Administration cost

Feature	Description
	Blood Transfusion Medical resource use Patient costs
Dosage of medicine	Based on weight
Average time on treatment	Both intervention and comparator have no discontinuation rate or until spontaneous remission
Parametric function for PFS	Not applicable
Parametric function for OS	Not applicable
Inclusion of waste	Not applicable
Average time in model health state Health state 1 Health state 2 Health state 3 Death	Not applicable

12.1.1 Base case results

Table 52 Base case results, discounted estimates

	[Intervention]	[Comparator]	Difference
Medicine costs	53.107.995	62.952.481	-9.844.486
Administration	620.696	1.116.232	-495.536
Costs associated with management of AEs	Not applicable	Not applicable	Not applicable
Monitoring costs	20.860	20.860	0
Subsequent treatment	Not applicable	Not applicable	Not applicable
Patient time and transportation costs	1.638	253.567	-251.929
Total costs	**53.751.189**	**64.343.140**	**-10.591.951**
Life years gained (health state A)	Not applicable	Not applicable	Not applicable
Life years gained (health state B)	Not applicable	Not applicable	Not applicable
Total life years	**Not applicable**	**Not applicable**	**Not applicable**
QALYs (state A)	Not applicable	Not applicable	Not applicable

	[Intervention]	[Comparator]	Difference
QALYs (state B)	Not applicable	Not applicable	Not applicable
QALYs (adverse reactions)	Not applicable	Not applicable	Not applicable
Total QALYs	Not applicable	Not applicable	Not applicable
Incremental costs per life year gained		**Not applicable**	
Incremental cost per QALY gained (ICER)		**Not applicable**	

12.2 Sensitivity analyses

12.2.1 Deterministic sensitivity analyses

Results for the ten most influential parameters identified by univariate sensitivity analysis, based on the comparison between crovalimab and eculizumab, a tornado diagram displaying the impact of the five most influential parameters is presented in Figure 14. The most influential parameters were the proportion of patient's weight, baseline age, discount rate and proportion of patients requiring eculizumab continuous up-dosing.

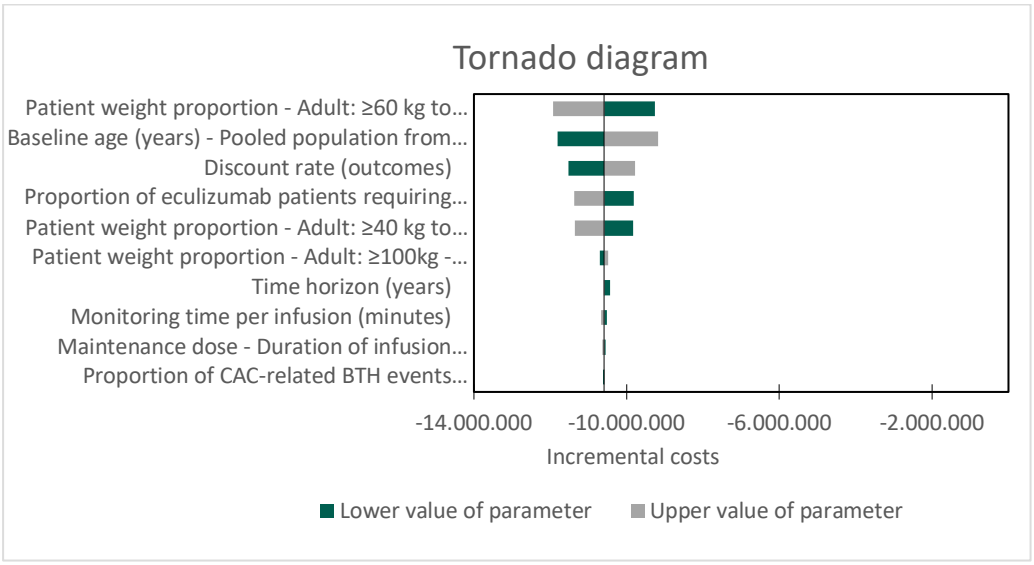


Figure 14 Tornado diagram

Table 53 One-way sensitivity analyses results

	Change	Reason / Rational / Source	Incremental cost (DKK)	% change from base-case incremental costs	Incremental benefit (QALYs)	ICER (DKK / QALY)
Base case			-10,591,951			
Spontaneous remission	Included	The proportion of patients remaining on treatment also accounts for spontaneous remission.	-8,674,433	18%		
Time horizon	20 years	A base-case model time horizon of 60 years was assumed to capture all relevant costs across a lifetime horizon. Time horizon is varied in the scenario analysis to explore the impact on results.	-6,607,776	37%	N/A	N/A
	40 years		-9,816,062	8%		N/A
No discounting	0	The impact of applying no discount rate for cost is explored.	-19,695,956	-85%	N/A	N/A
Baseline age	25 years	This scenarios explore the impact of adjusting the model starting age on costs.	-12,609,781	-19%	N/A	N/A
BTH Event rate	0.001	The impact of varying the 2-weekly BTH event rate in the economic model is explored.	-10,733,607	0%	N/A	N/A
Proportion of patients requiring single up-dosing	20%	A 40% treatment rate for CAC-related BTH events is assumed in the cost-comparison model. This parameter is varied to explore the impact of potential variability in up-dosing treatment rates on overall costs.	-10,667,980	0%	N/A	N/A
Proportion of patients requiring Continuous up dosing	10%	To reflect the potential variability in the proportion of people requiring continuous eculizumab up-dosing.	-8,633,841	18%	N/A	N/A
	24%		-11,375,195	-8%		

	Change	Reason / Rational / Source	Incremental cost (DKK)	% change from base-case incremental costs	Incremental benefit (QALYs)	ICER (DKK / QALY)
Patient weight proportion>100	10%	The impact of changing the proportion patient's weight is explored	-9,591.906	10%	N/A	N/A
Patient weight proportion>60 <100	80%	The impact of changing the proportion patient's weight is explored	-10,591,951	-0%	N/A	N/A

12.2.2 Probabilistic sensitivity analyses

Not applicable

13. Budget impact analysis

As stated earlier, we expect 0-1 new patients a year and 25 current patients on C5-inhibtors. Like the 0-1 new patients a year, we also expect/assume that 0-1 patients a year will stop treatment. Thus, we assume a contant number of potential patients of 25.

Table 54 Number of new patients expected to be treated over the next five-year period if the medicine is introduced (adjusted for market share)

	Year 1	Year 2	Year 3	Year 4	Year 5
			Recommendation		
Crovalimab	25	25	25	25	25
Eculizumab	0	0	0	0	0
			Non-recommendation		
Crovalimab	0	0	0	0	0
Eculizumab	25	25	25	25	25

Budget impact

Table 55 Expected budget impact of recommending the medicine for the indication

	Year 1	Year 2	Year 3	Year 4	Year 5
The medicine under consideration is recommended	70,6 mio. DKK	59,4 mio. DKK	59,4 mio. DKK	59,3 mio. DKK	59,2 mio. DKK

	Year 1	Year 2	Year 3	Year 4	Year 5
The medicine under consideration is NOT recommended	73,1 mio. DKK	71,6 mio. DKK	71,6 mio. DKK	71,5 mio. DKK	71,4 mio. DKK
Budget impact of the recommendation	-2,6 mio. DKK	-12,2 mio. DKK	-12,2 mio. DKK	-12,2 mio. DKK	-12,2 mio. DKK

14. List of experts

Roche has received input and consulted:

Ulrik Overgaard, consultant, teamleader, Clinic for Blood diseases, Copenhagen University Hospital (Rigshospitalet). Phone: +45 35455375

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Appendix A. Main characteristics of studies included

Table 56 Main characteristic of studies included

Trial name: COMMODORE 2 (BO42162)	**NCT number: NCT04434092**
Objective	The primary objective of the study was to demonstrate that in previously untreated (C5 naïve) patients with PNH, crovalimab has non-inferior efficacy versus eculizumab, based on the co-primary efficacy endpoints of haemolysis control (defined as central lactate dehydrogenase [LDH] ≤ 1.5 × ULN) and transfusion avoidance (TA; defined as patients who are packed red blood cell [pRBC] transfusion-free and do not require transfusion per protocol-specified guidelines).
Publications – title, author, journal, year	Röth, A. *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) doi:10.1002/ajh.27412. (46)
Study type and design	COMMODORE 2 is a phase 3, randomized, open-label, active-controlled, multicenter study conducted in patients who have a body weight ≥ 40 kg, have been diagnosed with paroxysmal nocturnal haemoglobinuria (PNH) and have not been previously treated with a complement protein C5 (C5) inhibitor therapy. The primary analysis has been completed (Data cut-off 16/11/2022), but the extension period is ongoing. This study was divided into two parts: - Two randomized arms where patients were randomized 2:1 to receive crovalimab (Arm A) or eculizumab (Arm B). Stratification factors were most recent locally measured LDH value (≥2 to ≤4 x ULN vs. >4 x ULN) and transfusion history in the prior 6 months (0, >0 to ≤6, and >6 total packed red blood cell (pRBC) units administered). One non-randomized arm (Arm C) exploring crovalimab in pediatric patients (< 18 years old).
Sample size (n)	200 patients were planned. 210 patients were enrolled (204 patients in the randomized arms and 6 patients in the nonrandomized arm)
Main inclusion criteria	• Signed Informed Consent Form • Signed Assent Form when appropriate, as determined by patient's age and individual site and country standards • Body weight ≥40 kg at screening

Trial name: COMMODORE 2 (BO42162)	NCT number: NCT04434092

- Willingness and ability to comply with all study visits and procedures
- Documented diagnosis of paroxysmal nocturnal hemoglobinuria (PNH), confirmed by high sensitivity flow cytometry evaluation of white blood cells with granulocyte or monocyte clone size of ≥10%, within 6 months prior to randomization
- Lactate dehydrogenase (LDH) level ≥2× upper limit of normal (ULN) at screening (as per local assessment)
- Presence of one or more of the following PNH-related signs or symptoms within 3 months prior to screening: fatigue, hemoglobinuria, abdominal pain, shortness of breath (dyspnea), anemia (hemoglobin <10 g/dL), history of a major adverse vascular event (including thrombosis), dysphagia, or erectile dysfunction; or history of packed red blood cell (pRBC) transfusion because of PNH
- Vaccination against Neisseria meningitidis <3 years prior to initiation of study treatment; or, if not previously done, vaccination administered no later than 1 week after the first study-drug administration. Vaccination currency should be maintained throughout the study in accordance with most current local guidelines or standard of care as applicable in patients with complement deficiency
- Vaccination against Haemophilus influenzae type B and Streptococcus pneumoniae according to national vaccination recommendations (eg, ACIP guidelines)
- Patients who have been vaccinated (partially or in full) against SARS-CoV-2 with a locally approved vaccine are eligible to be randomized/enrolled in the study, 3 days or longer after inoculation. Patients who have not been vaccinated against SARS-CoV-2 are also eligible to be in the study
- Platelet count ≥30 000/mm3 at screening without transfusion support within 7 days of lab testing
- Absolute neutrophil count >500/µL at screening
    - Short-acting granulocyte colony-stimulating factorsmust not have been administered within 14 days of lab testing
    - Long-acting granulocyte colony-stimulating factors must not have been administered within 28 days of lab testing
- For patients receiving other therapies (eg, immunosuppressants, corticosteroids, iron supplements, anticoagulants, erythrocyte-

Trial name: COMMODORE 2 (BO42162)	NCT number: NCT04434092
	stimulating agents): stable dose for ≥28 days prior to screening and up to the first drug administration • Adequate hepatic function, with alanine aminotransferase ≤3×ULN at the time of screening; no clinical signs or known laboratory/radiographic evidence consistent with cirrhosis • Adequate renal function, defined as serum creatinine ≤2.5×ULN and creatinine clearance by Cockcroft-Gault formula ≥30 mL/min For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception
Main exclusion criteria	• Current or previous treatment with a complement inhibitor • History of allogeneic bone marrow transplantation • History of Neisseria meningitidis infection within 6 months prior to screening and up to first study-drug administration • Known or suspected immune deficiency (eg, history of frequent recurrent infections) • Known or suspected hereditary complement deficiency • Known human immunodeficiency virus infection and with a CD4+ cell count <200 cells/µL within 24 weeks prior to screening ▪ Patients with human immunodeficiency virus infection who have a CD4+ cell count >200 cells/µL and meet all other criteria are eligible • Infection requiring hospitalization or treatment with IV antibiotics within 28 days prior to screening and up to the first drug administration, or oral antibiotics within 14 days prior to screening and up to the first drug administration • Active systemic bacterial, viral, or fungal infection within 14 days before first drug administration • Presence of fever (≥38°C) within 7 days before the first drug administration • Immunized with a live attenuated vaccine within 1 month before first drug administration • History of malignancy within 5 years prior to screening and up to the first drug administration, with the following exceptions: ▪ Patients with any malignancy treated with curative intent and the malignancy has been in remission without treatment for >5 years prior to the first drug administration are eligible

  - Patients with curatively treated basal or squamous cell carcinoma of the skin or in situ carcinoma of the cervix at any time prior to the first drug administration, with no evidence of recurrence, are eligible
  - Patients with low-grade, early-stage prostate cancer (Gleason score 6 or below, Stage 1 or 2) with no requirement for therapy at any time prior to the first drug administration are eligible
- History of myelodysplastic syndrome with Revised International Prognostic Scoring System (IPSS-R) prognostic risk categories of intermediate, high and very high
- History of hypersensitivity, allergic, or anaphylactic reactions to any ingredient contained in crovalimab or eculizumab, including hypersensitivity to human, humanized, or murine monoclonal antibodies or known hypersensitivity to any constituent of the product
- Pregnant or breastfeeding, or intending to become pregnant during the study, within 6 months after the final dose of crovalimab, or 3 months after final dose of eculizumab (or longer if required by the local product label; eg, 5 months after the final dose of eculizumab in the United Kingdom and the European Union according to the summary of product characteristics)
  - Women of childbearing potential must have a negative serum pregnancy test result within 28 days prior to initiation of study drug
- Participation in another interventional treatment study with an investigational agent or use of any experimental therapy within 28 days of screening or within five half-lives of that investigational product, whichever is greater
- Substance abuse within 12 months prior to screening, in the investigator's judgment
- Concurrent disease, treatment, procedure or surgery, or abnormality in clinical laboratory tests that could interfere with the conduct of the study, may pose any additional risk for the patient, or would, in the opinion of the investigator, preclude the patient's safe participation in and completion of the study
- Splenectomy ≤6 months prior to screening
- Positive for hepatitis B surface antigen at screening
- Positive for hepatitis C virus (HCV) antibody at screening

Trial name: COMMODORE 2 (BO42162)	NCT number: NCT04434092
	▪ Patients who are seropositive for HCV but without detectable HCV RNA are eligible History of or ongoing cryoglobulinemia at screening
Intervention	Arm A (n = 135): The crovalimab group received a weightbased tiered dosing regimen of crovalimab comprised of a loading series (IV dose on day 1 [1000 mg for body weight 40 to <100 kg or 1500 mg for weight ≥ 100 kg] followed by subcutaneous injection doses on days 2, 8, 15, and 22 [340 mg]) and maintenance dosing (subcutaneous injection every 4 weeks starting day 29 [680 mg for body weight 40 to <100 kg or 1020 mg for weight ≥ 100 kg]). Crovalimab self-administration or administration by a caregiver was permitted starting at week 9, after training and confirmation of proficiency by the healthcare professional. Arm C (n=6): Patients received a loading series of crovalimab doses comprising an IV dose on Day 1 Week 1, followed by weekly crovalimab SC doses for 4 weeks, at Week 1 (Day 2) and then at Weeks 2, 3 and 4. Maintenance doses began at Week 5 and were administered Q4W thereafter.
Comparator(s)	Arm B (n= 69): Patients randomized to eculizumab received induction doses of 600 mg on Days 1, 8, 15 and 22, followed by maintenance doses of 900 mg on Day 29 and every 2 weeks (Q2W) thereafter. Eculizumab could be administered within ± 2 days of the scheduled dose, except for the doses administered in the first 4 weeks, which had to be administered on the scheduled day. No eculizumab dose modifications were permitted during the study. Dosing followed the local prescribing information or, if enrolled in a country without access to commercial eculizumab, the pharmacy manual. Patients randomized to eculizumab had the opportunity to switch to crovalimab as part of the extension period of the study, once they had completed at least 24 weeks of treatment with eculizumab, if the treating physician determined that this was in their best interest.
Follow-up time	Of the 135 patients randomized to crovalimab, 129 patients (95.6%) completed 24 weeks of treatment in the primary treatment period and continued to receive crovalimab in the crovalimab extension period. In total, 127 patients continued to receive crovalimab treatment up to the 16 November 2022 CCOD (clinical cutoff date). Of the 69 patients randomized to eculizumab, 68 patients (98.6%) completed 24 weeks of treatment in the primary treatment period and

Trial name: COMMODORE 2 (BO42162)	NCT number: NCT04434092
	switched to crovalimab treatment in the crovalimab extension period. Of these 68 patients, 65 continued to receive crovalimab treatment up to the CCOD; the other three patients discontinued study treatment and did not enter the safety follow-up. The median treatment duration during the primary treatment period was similar in the crovalimab and eculizumab arms (20.1 weeks (range: 0.1-23.1 weeks) vs 22.1 weeks (range: 6.1-26.1 weeks). In the crovalimab arm up to CCOD, the median treatment duration was 48.3 weeks (range: 0.1-107.9 weeks) and for Arm B Switch patients the median treatment duration with crovalimab was 24.1 weeks (range: 0.3-76.3 weeks) at CCOD (59).
Is the study used in the health economic model?	Yes
Primary, secondary and exploratory endpoints	**Endpoints included in this application:** *Primary endpoints:* The co-primary endpoints were: • Proportion of patients who achieve transfusion avoidance (TA) from baseline through Week 25 (after 24 weeks on treatment). ▪ TA is defined as patients who are pRBC transfusion-free and do not require transfusion per protocol-specified guidelines. • Proportion of patients with haemolysis control, measured by LDH ≤ 1.5 × ULN from Week 5 through Week 25 (as measured at the central laboratory). *Key secondary endpoints* • Proportion of patients with BTH from baseline through Week 25. • Proportion of patients with stabilization of haemoglobin from baseline through Week 25 • Mean change from baseline to Week 25 in fatigue, as assessed by the Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-Fatigue) scale. *Exploratory endpoints (Patient Reported Outcomes)* • mean change from baseline to Week 25 in physical functioning, role functioning and global health status (GHS)/quality of life (QoL) scales of the European Organization for Research and Treatment

of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30).

- Mean change from baseline to Week 25 in EQ-5D-5L .

Other endpoints (not reported in this application):

Exploratory objectives

- Select disease-related symptoms (abdominal pain, headaches, dyspnea, dysphagia, chest pain and erectile dysfunction) of the EORTC Item Library (for patients aged ≥ 18 years).
- mean change from baseline to Week 25 in Pediatric Quality of Life™ (PedsQL™) multidimensional fatigue scale (MFS) and the Physical Functioning scale of the PedsQL Core (for patients aged 8–17 years).
- mean treatment satisfaction with crovalimab or eculizumab, as assessed by the Treatment Satisfaction Questionnaire for Medication – 9 (TSQM-9) at Week 25 (for patients aged ≥ 18 years).
- proportion of patients with preference for crovalimab or eculizumab at Week 41, for patients randomized to eculizumab who switch to crovalimab after 24 weeks of eculizumab treatment, as assessed through use of the Patient Preference Questionnaire (PPQ) developed by the Sponsor (for patients aged ≥18 years).
- mean change over time in QoL, as assessed by Quality of Life Questionnaire – Aplastic Anaemia/Paroxysmal nocturnal haemoglobinuria (QLQ-AA/PNH), and in overall health status, as assessed by Patient Global Impression of Severity Survey (PGI-S; for patients aged ≥18 years).
- total number of units (based on local equivalent) of pRBCs transfused per patient by Week 25.
- proportion of patients with central LDH (as measured at the central laboratory) ≤ 1 × ULN from Week 5 through Week 25.
- time from baseline to the first time central LDH ≤ 1 × ULN.
- time from baseline to the first time central LDH ≤ 1.5 × ULN.
- percentage change from baseline to Week 25 in central LDH levels.

Trial name: COMMODORE 2 (BO42162)	NCT number: NCT04434092
	• proportion of patients who reach a haemoglobin level of at least 10 g/dL, without subsequent decrease below 9 g/dL, in the absence of a transfusion. • proportion of patients experiencing a MAVE from baseline through Week 25. *Safety Reporting and Analyses* The safety objective for this study was to evaluate the overall safety of crovalimab compared to eculizumab, on the basis of the following endpoints: • incidence and severity of adverse events (AEs), with severity determined according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events, Version 5 (CTCAE v5); • change from baseline in targeted vital signs; • change from baseline in targeted clinical laboratory test results; • incidence and severity of injection-site reactions, infusion-related reactions, hypersensitivity and infections (including meningococcal meningitis); • incidence of AEs leading to study drug discontinuation; and • incidence and severity of clinical manifestations of transient immune complexes formation in patients who switched to crovalimab treatment from eculizumab treatment. In addition, immunogenicity was assessed by summarizing the numbers and proportions of anti-drug antibody (ADA)-positive patients and ADA-negative patients at baseline and after drug administration.
Method of analysis	The primary efficacy objective of the study was to assess the non-inferiority of crovalimab compared with eculizumab with respect to the co-primary endpoints of hemolysis control and transfusion avoidance. The study sample size was calculated with respect to the transfusion avoidance endpoint, as it required more patients for a powered statistical analysis. A sample size of approximately 180 efficacy-evaluable patients would provide 80% power to demonstrate the non-inferiority of crovalimab to eculizumab with respect to transfusion avoidance, using a one-sided Type 1 error rate of 2.5%. Assuming a 10% drop-out rate, a sample size of 200 patients in the randomized arms was selected to ensure approximately 180 efficacy-evaluable patients. Non-inferiority of crovalimab compared with eculizumab would be claimed if both co-primary endpoints were met, defined as: (1) the

Trial name: COMMODORE 2 (BO42162)	NCT number: NCT04434092
	lower bound of the 95% confidence interval (CI) for the difference in proportion of patients with transfusion avoidance between crovalimab and eculizumab being greater than -20%, and (2) the lower bound of the 95% CI for the odds ratio (OR) of crovalimab versus eculizumab for hemolysis control being greater than 0.2. The difference between proportions was computed using Mantel–Haenszel weights and its 95% CIs using the stratified Newcombe method. A generalized estimating equations model was used to estimate adjusted log-odds ratios of LDH ≤1.5 _ ULN of crovalimab versus eculizumab. If non-inferiority of crovalimab versus eculizumab was established for the co-primary endpoints then further non-inferiority and superiority testing of primary and secondary endpoints were to be conducted using the following hierarchical order: (3) BTH (noninferiority), (4) hemoglobin stabilization (non-inferiority), (5) transfusion avoidance (superiority), (6) hemolysis control (superiority), (7) BTH (superiority), (8) hemoglobin stabilization (superiority), (9) FACIT-Fatigue (non-inferiority), and (10) FACIT-Fatigue (superiority). BTH and hemoglobin stabilization were analyzed using statistical methods similar to transfusion avoidance. For these three binary endpoints, patients who discontinued treatment before completing the primary treatment period were conservatively assumed to have experienced the unfavorable outcome. A mean improvement in the FACIT-Fatigue total score of ≥5 points is considered clinically meaningful(78) with an increase from baseline indicating improved fatigue symptoms The primary analysis population used for analysis of all primary and secondary efficacy endpoints included all randomized patients who received ≥1 dose of crovalimab or eculizumab and had ≥1 central LDH level assessment after the first IV infusion.
Subgroup analyses	The robustness of the treatment effect of crovalimab versus eculizumab in terms of the co-primary efficacy endpoints of haemolysis control and transfusion avoidance was investigated in pre-defined subgroups based on key baseline demographic and disease characteristics (age, sex, region, eculizumab available region, race, pRBC units transfused in the 6 months prior to baseline, local LDH level at randomization, body weight and prior diagnosis of aplastic anaemia). It should be noted that in some subgroups, the small sample size and the wide 95% CIs preclude the ability to draw robust conclusions about the consistency of the treatment effect. Acknowledging this limitation, point estimates in the crovalimab arm were generally consistent across subgroups for haemolysis control and for transfusion avoidance, confirming the robustness of the treatment effect of crovalimab across clinically meaningful subgroups.

Trial name: COMMODORE 2 (BO42162)	NCT number: NCT04434092
Other relevant information	A total of 204 adult and 6 paediatric subjects were randomized in numerous sites in 25 countries. Countries with the highest number of sites were Spain (9 sites) and China (7 sites). The highest number of patients were enrolled in China (82 patients, 39%) and Thailand (19 patients, 9%).

Trial name: COMMODORE 1 (BO42161)	NCT number: NCT04432584
Objective	The primary objective for this study was to evaluate the safety and tolerability of crovalimab compared with eculizumab on the basis of various safety endpoints. COMMODORE 1 was initially designed to enroll ≈200 patients with PNH into the randomized arms to evaluate the efficacy, safety, pharmacokinetics, pharmacodynamics and impact on HRQoL of crovalimab versus eculizumab in patients with PNH previously treated with the approved dose of eculizumab (i.e., patients with PNH switching from current C5 inhibitors to crovalimab) as well as ≈50 patients with PNH in the non-randomized arm. However, given the evolving treatment landscape, with a reduced pool of patients treated with eculizumab over time, randomization was terminated in November 2022. With this change, the initially targeted sample size for the randomized arms could not be reached, providing insufficient statistical power for efficacy analyses. Therefore, all efficacy endpoints became exploratory, and safety became the new primary objective. Patients switching from eculizumab were selected as the primary randomized population in the COMMODORE 1 study as eculizumab has been the standard of care for treating patients with PNH for some time and has been used by the vast majority of patients. Patients in the study were randomized and stratified according to their transfusion history (whether they had received a transfusion of pRBCs within 12 months prior to randomization) to ensure the two randomized arms were balanced for transfusion history.
Publications – title, author, journal, year	Scheinberg, P. *et al.* Phase 3 randomized COMMODORE 1 trial: Crovalimab versus eculizumab in complement inhibitor-experienced patients with paroxysmal nocturnal hemoglobinuria. *Am. J. Hematol.* (2024) doi:10.1002/ajh.27413 (47)
Study type and design	COMMODORE 1 (NCT04432584) is an global, randomized, open-label, multicenter, phase 3 trial evaluating crovalimab versus eculizumab in patients with PNH currently treated with complement inhibitors. The primary analysis has been completed (Data cut-off 16/11/2022), but the extension period is ongoing.

Trial name: COMMODORE 1 (BO42161)	NCT number: NCT04432584
	The study consisted of a 4-week screening period and a 24-week primary treatment period, where adult patients (≥ 18 years old) were randomized 1:1 to receive crovalimab or eculizumab, with randomization stratified by history of packed red blood cell (pRBC) transfusion in the previous 12 months (yes vs. no). This was followed by an extension period, during which patients randomized to crovalimab could continue crovalimab treatment, and patients randomized to eculizumab could switch to crovalimab. If a patient discontinued study treatment at any time, they entered a safety follow-up period. Randomization into Arms A and B was stopped in November 2022 per protocol version 6, at which time the enrollment in these arms was projected to be approximately 90 patients. In addition to the randomized arms, a non-randomized arm (Arm C), consisted of pediatric patients (< 18 years old) currently treated with eculizumab, patients (regardless of age) currently treated with ravulizumab, patients (regardless of age) currently treated with eculizumab at higher than the approved dose for PNH (> 900 mg per dose and/or more frequently than Q2W), or patients (regardless of age) with known complement C5 polymorphism whose haemolysis was poorly controlled by eculizumab or ravulizumab. Following the stop of randomization into Arms A and B, an additional cohort of adult patients (≥ 18 years) who had been receiving eculizumab at the approved dose for at least 24 weeks prior to study entry was added to Arm C, to continue study access for this population in a non-randomized setting. None of the patients in this additional cohort were newly enrolled at the time of CCOD (16 November 2022), as randomization had stopped in November 2022 (as stated above).
Sample size (n)	127 patients were enrolled. Of these, 89 patients were enrolled in the randomized arms (45 in the crovalimab arm and 44 in the eculizumab arm) and 38 patients in the nonrandomized arm.
Main inclusion criteria	• Documented treatment with eculizumab according to the approved dosing recommended for paroxysmal nocturnal hemoglobinuria (PNH; 900 mg every 2 weeks) and completion of a minimum of 24 weeks of treatment prior to Day 1 • Lactate dehydrogenase (LDH) levels ≤1.5×the upper limit of normal (ULN) at screening (as per local assessment) ▪ Samples must be obtained on a scheduled eculizumab-dosing day prior to eculizumab administration • Signed Informed Consent Form

- Signed Assent Form when appropriate, as determined by patient's age and individual site and country standards
- Body weight ≥40 kg at screening
- Willingness and ability to comply with all study visits and procedures
- Documented diagnosis of PNH, confirmed by high sensitivity flow cytometry evaluation of white blood cells, with granulocyte or monocyte clone size ≥10%, within 6 months prior to randomization (Arm A and B) or enrollment (Arm C)
- Vaccination against Neisseria meningitidis serotypes A, C, W, and Y <3 years prior to initiation of study treatment. Vaccination against serotype B should be administered in accordance with the most current local guidelines or standard of care (SOC), as applicable in patients with complement deficiency. If not previously administered or no longer current, vaccination must be completed no later than 1 week after the first study drug administration. Vaccination currency with vaccination against serotypes A, C, W, Y, and B should be maintained throughout the study, according to local guidelines or SOC as applicable in patients with complement deficiency. In the absence of clear local guidelines for *Neisseria meningitidis*, the Advisory Committee on Immunization Practices 2020 Guidelines are recommended
    - If vaccination is completed <2 weeks prior to initiation or after the start of study treatment, appropriate antibiotic prophylaxis must be maintained from first study drug administration, continuing for at least 2 weeks after completion of vaccination or according to local SOC as applicable in patients with complement deficiency, whichever is longer. If vaccination is administered during screening, and prophylactic antibiotics are not to be administered, the vaccination must take place at least 2 weeks prior to the first dose of study drug. Patients who refuse vaccination against *Neisseria meningitidis* are not eligible for the study
- Vaccination against *Haemophilus influenzae* type B and *Streptococcus pneumoniae* according to national vaccination recommendations (eg, Advisory Committee on Immunization Practices guidelines). If not previously administered or no longer current, vaccination should be completed no later than 1 week after the first study drug administration. If vaccination is completed <2 weeks prior to initiation or after the start of study

treatment, appropriate antibiotic prophylaxis must be maintained from first study drug administration, continuing for at least 2 weeks after completion of vaccination or according to local SOC, whichever is longer. If vaccination is administered during screening, and prophylactic antibiotics are not to be administered, the vaccination must take place at least 2 weeks prior to enrollment. Patients who refuse vaccination against *Haemophilus influenzae* type B and *Streptococcus pneumoniae* when recommended are not eligible for the study

- Patients who have been vaccinated (partially or in full) against SARS-CoV-2 with a locally approved vaccine are eligible to be randomized/enrolled in the study, 3 days or longer after inoculation. Patients who have not been vaccinated against SARS-CoV-2 are also eligible to be in the study
- Platelet count ≥30000/mm3 at screening without transfusion support within 7 days of lab testing
- Absolute neutrophil count >500/mL at screening
    - Short-acting, granulocyte-colony-stimulating factors (G-CSFs) must not have been administered within 14 days of lab testing
    - Long-acting G-CSFs must not have been administered within 28 days of lab testing
- For patients continuing to receive other therapies concomitantly with crovalimab (eg, immunosuppressants, corticosteroids, iron supplements, anticoagulants, erythrocyte-stimulating agents): stable dose for ≥28 days prior to the first study drug administration
- Adequate hepatic function, including both aspartate transaminase (AST) and alanine transaminase (ALT) ≤3×ULN at the time of screening; no clinical signs or known laboratory/radiographic evidence consistent with cirrhosis
    - AST ≤3×ULN is not applicable for patients with known C5 polymorphism (eg, Arg885) with poorly controlled hemolysis by eculizumab or ravulizumab, per investigator's assessment
- Adequate renal function, defined as serum creatinine ≤2.5×ULN and creatinine clearance by Cockcroft-Gault formula ≥30 mL/min
- For female patients of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception, as defined below:

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	▪ Female patients of childbearing potential must remain abstinent or use contraceptive methods with a failure rate of <1% per year during the treatment period and for 46 weeks (approximately 10.5 months) after the final dose of crovalimab or for 3 months after the final dose of eculizumab (or longer if required by the local product label; eg, 5 months after the final dose of eculizumab in the United Kingdom and the European Union according to the Summary of Product Characteristics [SmPC]). A longer period of abstinence or use of contraceptive methods after discontinuing study treatment may be needed based on exposure to other medicinal products (eg, ravulizumab) according to their respective local labels ▪ A female patient is considered to be of childbearing potential if the patient is postmenarchal, has not reached a postmenopausal state (^{3}12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (ie, removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (eg, Müllerian agenesis). The definition of childbearing potential may be adapted for alignment with local guidelines or regulations ▪ Examples of contraceptive methods with a failure rate of <1% per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices ▪ The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (eg, calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of contraception. If required per local guidelines or regulations, locally recognized adequate methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form In addition, for the randomized arms: Age ≥18 years at the time of signing the Informed Consent Form
Main exclusion criteria	• Major adverse vascular event within 6 months prior to first drug administration (Day 1)

- Pre-enrollment hemoglobin value ≤7 g/dL, or pre-enrollment hemoglobin value >7 g/dL and ≤9 g/dL with concurrent signs and symptoms of anemia, including: angina, syncope, lightheadedness, confusion, severe or worsening shortness of breath, severe or worsening fatigue, stroke, transient ischemic attack, or new or worsening heart failure
    - Hemoglobin must be measured prior to randomization/enrollment, within 5 days before Week 1 Day 1 of study drug administration. If more convenient and if in accordance with local regulations, this hemoglobin measurement may be performed at a hospital or laboratory that is not the study site. At that time, if the patient does not meet the eligibility criteria, the patient must be transfused with packed red blood cells and reassessed with a post-transfusion hemoglobin measurement to confirm eligibility before randomization/enrollment
- History of allogeneic bone marrow transplantation
- History of *Neisseria meningitidis* infection within 6 months prior to screening and up to first study drug administration (Day 1)
- Known or suspected immune deficiency (eg, history of frequent recurrent infections)
- Known or suspected hereditary complement deficiency
- Known human immunodeficiency virus infection and a CD4+ cell count <200 cells/mL within 24 weeks prior to screening
    - Patients with a human immunodeficiency virus infection who have a CD4+ cell count >200 cells/mL and meet all other criteria are eligible
- Infection requiring hospitalization or treatment with IV antibiotics within 28 days prior to screening and up to the first drug administration (Day 1), or oral antibiotics within 14 days prior to screening and up to the first drug administration (Day 1)
- Active systemic bacterial, viral, or fungal infection within 14 days before first drug administration (Day 1)
- Presence of fever (≥38°C or 100.4°F) within 7 days prior to first drug administration (Day 1)
- Immunized with a live attenuated vaccine within 1 month before first drug administration (Day 1)

- History of malignancy within 5 years prior to screening and up to the first drug administration (Day 1), with the following exceptions:
    - Patients with any malignancy appropriately treated with curative intent and the malignancy has been in remission without treatment for >5 years prior to study drug administration (Day 1) are eligible
    - Patients with curatively treated basal or squamous cell carcinoma of the skin or in situ carcinoma of the cervix at any time prior to study drug administration (Day 1) are eligible
    - Patients with low-grade, early-stage prostate cancer (Gleason score 6 or below, Stage 1 or 2) with no requirement for therapy at any time prior to study drug administration (Day 1) are eligible
- History of myelodysplastic syndrome with Revised International Prognostic Scoring System (IPSS-R) prognostic risk categories of intermediate, high, and very high
- History of hypersensitivity, allergic, or anaphylactic reactions to any ingredient contained in crovalimab or eculizumab, including hypersensitivity to human, humanized, or murine monoclonal antibodies or known hypersensitivity to any constituent of the product
- Pregnant or breastfeeding, or intending to become pregnant during the study, within 46weeks (approximately 10.5 months) after the final dose of crovalimab, or 3 months after the final dose of eculizumab (or longer if required by the local product label; eg, 5 months after the final dose of eculizumab in the United Kingdom and the European Union according to the SmPC)
    - Female patients of childbearing potential must have a negative serum pregnancy test result within 28 days prior to initiation of study drug
- Participation in another interventional treatment study with an investigational agent or use of any experimental therapy within 28 days of screening or within 5 half-lives of that investigational product, whichever is greater
    - Patients enrolled in an eculizumab or ravulizumab interventional study are eligible provided they fulfill eligibility (eg, are willing and able to comply with the study

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	assessments) and stop their participation in current trial before randomization/enrollment • Substance abuse within 12 months prior to screening, in the investigator's judgment • Concurrent disease, treatment, procedure, or surgery or abnormality in clinical laboratory tests that could interfere with the conduct of the study, may pose any additional risk for the patient, or would, in the opinion of the investigator, preclude the patient's safe participation in and completion of the study • Splenectomy ≤6 months prior to screening • Positive for hepatitis B surface antigen (HBsAg) at screening • Positive for hepatitis C virus (HCV) antibody at screening ▪ Patients who are seropositive for HCV but without detectable HCV RNA are eligible History of or ongoing cryoglobulinemia at screening
Intervention	45 patients were randomized to crovalimab (Arm A) and 38 patients were included in the descriptive Arm C that consisted of subgroups of patients previously treated with complement inhibitors (based on age, type of inhibitor, dose and polymorphism) The crovalimab group received a weightbased tiered dosing regimen of crovalimab comprised of a loading series (IV dose on day 1 [1000 mg for body weight 40 to <100 kg or 1500 mg for weight ≥ 100 kg] followed by subcutaneous injection doses on days 2, 8, 15, and 22 [340 mg]) and maintenance dosing (subcutaneous injection every 4 weeks starting day 29 [680 mg for body weight 40 to <100 kg or 1020 mg for weight ≥ 100 kg]). Crovalimab self-administration or administration by a caregiver was permitted starting at Week 9 after they were trained and had their proficiency confirmed by a healthcare professional. Patients who did not wish to self-inject or have a caregiver administer crovalimab could continue to have crovalimab administered by the investigator or other study site staff.
Comparator(s)	For patients randomized to eculizumab, dosing followed the local prescribing information. Patients received approved maintenance dose of eculizumab (900 mg) starting on study Day 1 of Week 1, 2 weeks from their last dose of eculizumab, and Q2W thereafter for a total of 24 weeks of study treatment (primary treatment period).

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	44 patients were randomized to eculizumab (Arm B). To obtain additional efficacy and safety data on crovalimab, patients randomized to eculizumab in Arm B had the opportunity to switch to crovalimab once they had completed 24 weeks of treatment with eculizumab
Follow-up time	Of the 45 patients randomized to the crovalimab arm, 39 patients (86.7%) completed 24 weeks of treatment and then continued to receive crovalimab treatment in the crovalimab extension period; one 1 patient received no treatment. Of these, 37 patients continued to receive crovalimab treatment up to the CCOD (16 November 2022). Of the 45 patients in the crovalimab arm, five 5 patients were still ongoing in the primary treatment period as of the CCOD. Of the 44 patients randomized to the eculizumab arm, 35 patients (79.5%) completed 24 weeks of eculizumab treatment and switched to crovalimab treatment upon entering the crovalimab extension period; two patients received no treatment. Of these, 32 patients continued to receive crovalimab treatment up to the CCOD (16 November 2022). Of the 44 patients in the eculizumab arm, five patients were still ongoing in the primary treatment period as of the CCOD. The median treatment duration during the primary safety period was 20.1 weeks (range: 2.1-22.3 weeks) in the crovalimab arm and 22.1 weeks (range: 0.1-26.1 weeks) in the eculizumab arm. In the crovalimab arm up to CCOD, the median treatment duration was 52.0 weeks (range: 2.1-108.4 weeks) and for Arm B Switch patients was the median treatment duration 32.1 weeks (range: 3.1 - 84.1 weeks) at the CCOD (58).
Is the study used in the health economic model?	Yes
Primary, secondary and exploratory endpoints	**Endpoints included in this application:** The primary objective of the study was to evaluate the safety and tolerability of crovalimab compared with eculizumab. Efficacy was an exploratory objective only. All exploratory efficacy endpoint analyses were descriptive, with no formal statistical testing being conducted. *Exploratory endpoints* • Proportion of patients with haemolysis control defined as central LDH ≤ 1.5 × ULN from baseline through week 25 • Proportion of patients who achieve TA from baseline through Week 25 (after 24 weeks on treatment).

  - TA is defined as patients who are pRBC transfusion-free and do not require transfusion per protocol-specified guidelines.
- Proportion of patients with BTH from baseline through Week 25.
  - BTH is defined as at least one new or worsening symptom or sign of intravascular haemolysis (fatigue, haemoglobinuria, abdominal pain, shortness of breath [dyspnea], anaemia [haemoglobin < 10 g/dL], a MAVE [as defined in study protocol, including thrombosis], dysphagia or erectile dysfunction) in the presence of elevated LDH ≥ 2 × ULN after prior reduction of LDH to ≤ 1.5 × ULN on treatment.
- Proportion of patients with stabilization of haemoglobin from baseline through Week 25.
  - Stabilized haemoglobin is defined as avoidance of a ≥ 2 g/dL decrease in haemoglobin level from baseline, in the absence of transfusion.
- mean change from baseline to Week 25 in fatigue, as assessed by FACIT-Fatigue (for adults aged ≥ 18 years).
- mean change from baseline to Week 25 in physical functioning, role functioning and global health status (GHS)/quality of life (QoL) scales of the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30).
- Mean change from baseline to Week 25 in EQ-5D-5L .

Other endpoints (not reported in this application):

Exploratory objectives

- Select disease-related symptoms (abdominal pain, headaches, dyspnea, dysphagia, chest pain and erectile dysfunction) of the EORTC Item Library (for patients aged ≥ 18 years).
- mean change from baseline to Week 25 in PedsQL MFS, and the physical functioning scale of the PedsQL Core (for patients aged 8–17 years);
- proportion of patients with preference for crovalimab after switching from eculizumab or ravulizumab at Week 17 (Arms A and C), as assessed through use of a PPQ developed by the Sponsor (for patients aged ≥ 12 years); and

- mean treatment satisfaction with crovalimab or eculizumab at Week 25, as assessed by the TSQM-9 (for patients aged ≥ 18 years).
- Percentage change from baseline in LDH levels averaged over Weeks 21, 23 and 25 based on central laboratory LDH measurements.
- Proportion of patients with central LDH ≤ 1 × ULN from baseline through Week 25.
- Total number of units (based on local equivalent) of pRBCs transfused per patient by Week 25.
- Proportion of patients who have experienced a MAVE from baseline through Week 25.
- Proportion of patients who reach or maintain a haemoglobin level of at least 10 g/dL, without subsequent decrease below 9 g/dL, in the absence of a transfusion.

Safety Reporting and Analyses

The primary objective for this study was to evaluate the safety and tolerability of crovalimab compared with eculizumab on the basis of the following endpoints:

- incidence and severity of adverse events, with severity determined according to NCI CTCAE v5;
- change from baseline in targeted vital signs;
- change from baseline in targeted clinical laboratory test results;
- incidence and severity of injection-site reactions, infusion-related reactions, hypersensitivity and infections (including meningococcal meningitis);
- incidence of AEs leading to study drug discontinuation;
- incidence and severity of clinical manifestations of transient immune complexes formation in patients who switched to crovalimab treatment from eculizumab or ravulizumab treatment.

In addition, immunogenicity was assessed by summarizing the numbers and proportions of ADA-positive patients and ADA-negative patients at baseline and after drug administration.

Method of analysis	Exploratory efficacy was assessed in the efficacy-evaluable population, which included patients who were randomized ≥24 weeks before the

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	clinical cutoff date, received ≥1 dose of crovalimab or eculizumab, and had ≥1 central LDH level assessment after the first IV infusion. Efficacy data are reported from baseline through Week 25. Weighted differences in proportions of patients with transfusion avoidance, breakthrough hemolysis, and hemoglobin stabilization were computed using Mantel–Haenszel weights, and 95% CIs were estimated using the stratified Newcombe method (79). For these three binary endpoints, patients who discontinued treatment before completing the primary treatment period were conservatively assumed to have experienced the unfavorable outcome. For hemolysis control, a generalized estimating equation model was used to estimate the adjusted log-odds ratio of central LDH ≤1.5 x ULN between the crovalimab and eculizumab arms, taking into account the intra-individual correlation between central LDH values across visits and adjusting for baseline covariates. The 95% CIs for the proportions of patients with transfusion avoidance, breakthrough hemolysis, and hemoglobin stabilization were calculated using Wilson's method with continuity correction. Fatigue was assessed by changes in the FACIT-Fatigue, a 13-item measure that evaluates self-reported fatigue and its impact on daily activities and function, in patients aged ≥18 years old (80). Total FACIT Fatigue scores can range from 0 to 52, with higher scores indicating lower fatigue severity and a positive change from baseline indicating an improvement.26 Mean adjusted change in FACIT-Fatigue score from baseline to Week 25 was estimated using a mixed-effect model for repeated measures. All statistical analyses are descriptive
Subgroup analyses	Not applicable
Other relevant information	Patients were enrolled from 70 sites across 25 countries: • Western Europe: Spain (14 patients, 11.0%), Poland (11 patients, 8.7%), Italy (7 patients, 5.5%), Portugal (6 patients, 4.7%), Belgium (5 patients, 3.9%), Greece (4 patients, 3.1%), Netherlands (4 patients, 3.1%) France (2 patients, 1.6%), Ireland (2 patients, 1.6%), Czech Republic (1 patient, 0.8%), Estonia (1 patient, 0.8%) Germany (1 patient, 0.8%), Hungary (1 patient, 0.8%) and United Kingdom (1 patient, 0.8%); • Asia: Japan (17 patients, 13.4%), Republic of Korea (9 patients, 7.1%), Taiwan (3 patients, 2.4%), Hong Kong (1 patient, 0.8%), Singapore (1 patient, 0.8%); • Latin America: Brazil (15 patients, 11.8%); • Middle East: Turkey (10 patients, 7.9%) and Saudi Arabia (1 patient, 0.8%);

Trial name: COMMODORE 1 (BO42161)	NCT number: NCT04432584
	North America: United States (2 patients, 1.6%), Canada (1 patient, 0.8%).

Appendix B. Efficacy results per study

Results per study

Table 57 Results per study – COMMODORE 2

Results of COMMODORE 2 (NCT04434092)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Co-primary endpoint Mean proportion of patients achieving controlled haemolysis (Central LDH ≤ 1.5 × ULN) from Week 5 through Week 25	**Crovalimab (Arm A)**	134	79.3% (72.86, 84.48)	0.3	-9.66 to 10.23	0.95	Odds ratio: 1.02	(0.57, 1.82)	0.950	Non-inferiority margin for lower 95% CI limit= 0.2 P-value evaluates the superiority test The difference between proportions was computed using Mantel–Haenszel weights and its 95% CIs using the stratified Newcombe method. A generalized estimating equations model was used to estimate adjusted log-odds ratios of LDH ≤1.5 _ ULN of crovalimab versus eculizumab.	(46, 60)
	Eculizumab (Arm B)	69	79.0% (69.66, 85.99)								

Results of COMMODORE 2 (NCT04434092)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Co-primary endpoint Patients with transfusion avoidance from Baseline through Week 25	**Crovalimab (Arm A)**	134	65.7% (56.91, 73.52)	Difference in proportions (%) −2.8%	(−15.67, 11.14)	0.6655				95% CI for proportion is calculated using the Wilson's method with continuity correction. 95% CI for the difference in proportions of patients with Transfusion avoidance is calculated by Stratified Newcombe CI method; non-inferiority is met when the lower limit of the 95% CI is greater than -20%. p-Value evaluates the superiority test. Patients who discontinued treatment before Week 25 are assumed to have had a Transfusion.	(46, 60)
	Eculizumab (Arm B)	69	68.1% (55.67, 78.53)								
Secondary endpoint: Patients with at least one Breakthrough	**Crovalimab (Arm A)**	134	10.4% (6.04, 17.21)	Weighted difference in proportion	(−14.82, 5.26)	0.4358				95% CI for BTH proportion is calculated using the Wilson's method with continuity correction. 95% CI for the difference in proportions is calculated by Stratified Newcombe CI method; non-inferiority	(46, 60)

Results of COMMODORE 2 (NCT04434092)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Haemolysis from Baseline through Week 25	**Eculizumab (Arm B)**	69	14.5% (7.54, 25.50)	(crova-ecu) −3.9%						is met when the upper limit of the 95% CI is less than 20%. p-Value test (Mantel-Haenszel) for superiority. Patients who discontinued treatment before Week 25 are considered to have a BTH event.	
Secondary endpoint: Patients with Stabilized Haemoglobin from Baseline through Week 25	**Crovalimab (Arm A)**	134	63.4% (54.63, 71.45)	Weighted difference in proportion (crova-ecu) 2.2%	(-11.4, 16.3)	0.750				95% CI for Proportion of patients with Stabilized Hemoglobin is calculated using the Wilson's method with continuity correction. 95% CI for the difference in proportions of patients with Stabilized Hemoglobin calculated by Stratified Newcombe CI method; non-inferiority is met when the lower limit of the 95% CI is greater than -20%. p-Value test (Mantel-Haenszel) for superiority. Patients who discontinued treatment before Week 25 are considered to not have had stabilized hemoglobin.	(46, 60)
	Eculizumab (Arm B)	69	60.9% (48.35-72.17)								
Adjusted mean Change from	**Crovalimab (Arm A)**	134	7.79		(0.68, 4.6)	p = 0.0087*				Estimates include patients with an assessment at baseline. Estimates are	(46, 60)

Results of COMMODORE 2 (NCT04434092)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Baseline to Week 25 in FACIT-Fatigue Scores			(6.49, 9.09)	Difference in adjusted mean: 2.64						from analysis based on a mixed-effect model of repeated measures using unstructured covariance matrix.	
	Eculizumab (Arm B)	69	5.15 (3.42, 6.89)								

* The pre-defined statistical testing hierarchy was broken before superiority testing could be conducted for the secondary efficacy endpoint of FACIT-Fatigue. Therefore, the p-value reported is descriptive only

Table 58 Results per study – COMMODORE 1

Results of COMMODORE 1* (NCT04432584)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Mean proportion of patients achieving controlled haemolysis (Central LDH ≤ 1.5 × ULN) from Week 5 through Week 25	**Crovalimab (Arm A)**	39	92.9% (86.62, 96.39)	0.8	-6.38 to 7.98	0.82	Odds ratio 0.88	(0.28, 2.77)		For hemolysis control, a generalized estimating equation model was used to estimate the adjusted log-odds ratio of central LDH ≤1.5 _ ULN between the crovalimab and eculizumab arms, taking into account the intra-individual correlation between central LDH values across visits and adjusting for baseline covariates.	(47)
	Eculizumab (Arm B)	37	93.7% (87.26, 97.04)								
Averaged percentage change in Central LDH	**Crovalimab (Arm A)**	39	16.6% (3.39, 29.82)	12.1	(−7.44, 31.58)	N/A	N/A	N/A	N/A		(47)

Results of COMMODORE 1* (NCT04432584)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
from Baseline to Average of Weeks 21, 23, and 25	**Eculizumab (Arm B)**	37	4.5% (−9.74, 18.81)								
Patients Achieving Transfusion Avoidance from Baseline through Week 25	**Crovalimab (Arm A)**	39	79.5% (63.06, 90.13)	Weighted difference, % 1.8	(-16.7,19.9)	N/A	N/A	N/A	N/A	Weighted differences in proportions of patients with transfusion avoidance were computed using Mantel–Haenszel weights, and 95% CIs were estimated using the stratified Newcombe method.	(47)
	Eculizumab (Arm B)	37	78.4% (61.34, 89.58)								
Patients with at least one breakthrough Haemolysis from Baseline through Week 25	**Crovalimab (Arm A)**	39	10.3% (3.34, 25.16)	Weighted difference, % -3.5	(-19.2, 11.7)	N/A	N/A	N/A	N/A	Weighted differences in proportions of patients with breakthrough hemolysiswere computed using Mantel‑Haenszel weights, and 95% CIs were estimated using the stratified Newcombe method.	(47)
	Eculizumab (Arm B)	37	13.5% (5.08, 29.57)								

Results of COMMODORE 1* (NCT04432584)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Patients with Stabilized Haemoglobin from Baseline through Week 25	**Crovalimab (Arm A)**	39	59.0% (42.19, 74.02)	Weighted difference, % -10.8	(-30.8, 10.4)	N/A	N/A	N/A	N/A	Weighted differences in proportions of patients with transfusion avoidance, breakthrough hemolysis, and hemoglobin stabilization were computed using Mantel‑Haenszel weights, and 95% CIs were estimated using the stratified Newcombe method.	(47)
	Eculizumab (Arm B)	37	70.3% (52.83, 83.56)								
Mean change from baseline to week 25 in FACIT-Fatigue scores	**Crovalimab (Arm A)**		1.1 (-1.5,3.7)	Difference in mean change: 3.7	(0.05, 7.36)	N/A	N/A	N/A	N/A	Mean adjusted change in FACIT-Fatigue score from baseline to Week 25 was estimated using a mixed-effect model for repeated measures	(47)
	Eculizumab (Arm B)		-2.6 (-5.4,0.1)								

* There are no primary or secondary efficacy endpoints in this study. The primary objective of the study is safety. Efficacy was an exploratory objective only. All exploratory efficacy endpoint analyses were descriptive, with no formal statistical testing being conducted.

Appendix C. Comparative analysis of efficacy

Not applicable. Commodore 1 and 2 are head-to-head study which provide a direct comparison of crovalimab and eculizumab regimens. Results are presented in Appendix B.

Table 59 Comparative analysis of studies comparing [intervention] to [comparator] for patients with [indication]

Outcome		Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
	Studies included in the analysis	Difference	CI	P value	Difference	CI	P value		

Appendix D. Extrapolation

This Appendix is not applicable

D.1 Extrapolation of [effect measure 1]

D.1.1 Data input

D.1.2 Model

D.1.3 Proportional hazards

D.1.4 Evaluation of statistical fit (AIC and BIC)

D.1.5 Evaluation of visual fit

D.1.6 Evaluation of hazard functions

D.1.7 Validation and discussion of extrapolated curves

D.1.8 Adjustment of background mortality

D.1.9 Adjustment for treatment switching/cross-over

D.1.10 Waning effect

D.1.11 Cure-point

D.2 Extrapolation of [effect measure 2]

Appendix E. Serious adverse events

E.1 SAEs for COMMODORE 2 and COMMODORE 1

SAEs for COMMODORE 2 (Arm A and Arm B) and COMMODORE 1 (Arm A and Arm B) are presented in the Table 60 and Table 61 below. As COMMODORE 3 was not used for reporting efficacy, as it exclusively included Chinese patients, SAEs for this study have not been presented in this Appendix.

Table 60 COMMODORE 2: Summary of Serious AEs by Preferred Term

(Primary Safety Period, Randomized Safety Population)

Safety Outcome; MedDRA System Organ Class and MedDRA Preferred Term	**Crovalimab (Arm A) n = 135**	**Eculizumab (Arm B) n = 69**
Total number of patients with at least one AE, n (%)	14 (10.4%)	9 (13.0%)
Overall total number of events	[redacted]	[redacted]
Infections and Infestations		
Total number of patients with at least one AE, n (%)	4 (3.0%)	5 (7.2%)
Total number of events	4	5
COVID-19	1 (0.7%)	1 (1.4%)
Pneumonia	2 (1.5%)	0
Central nervous system infection	0	1 (1.4%)
Pyelonephritis	1 (0.7%)	0
Sepsis	0	1 (1.4%)
Tuberculosis	0	1 (1.4%)
Urinary tract infection	0	1 (1.4%)
Blood and lymphatic system disorders		
Total number of patients with at least one AE, n (%)	3 (2.2%)	3 (4.3%)
Total number of events	[redacted]	[redacted]
Aplastic anaemia	2 (1.5%)	1 (1.4%)
Thrombocytopenia	1 (0.7%)	1 (1.4%)
Febrile neutropenia	0	1 (1.4%)
Respiratory, thoracic and mediastinal disorders		
Total number of patients with at least one AE, n (%)	3 (2.2%)	0
Total number of events	3	0
Epistaxis	2 (1.5%)	0
Respiratory tract haemorrhage	1 (0.7%)	0
Cardiac disorders		

Safety Outcome; MedDRA System Organ Class and MedDRA Preferred Term	Crovalimab (Arm A) n = 135	Eculizumab (Arm B) n = 69
Total number of patients with at least one AE, n (%)	1 (0.7%)	1 (1.4%)
Total number of events	1	1
Cardiac failure	0	1 (1.4%)
Myocardial infarction	1 (0.7%)	0
General disorders and administration site conditions		
Total number of patients with at least one AE, n (%)	1 (0.7%)	1 (1.4%)
Total number of events	[redacted]	[redacted]
Pyrexia	1 (0.7%)	1 (1.4%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Total number of patients with at least one AE, n (%)	1 (0.7%)	1 (1.4%)
Total number of events	1	1
Myelodysplastic syndrome	0	1 (1.4%)
Thyroid cancer	1 (0.7%)	0
Gastrointestinal disorders		
Total number of patients with at least one AE, n (%)	1 (0.7%)	0
Total number of events	1	0
Small intestinal haemorrhage	1 (0.7%)	0
Hepatobiliary disorders		
Total number of patients with at least one AE, n (%)	0	1 (1.4%)
Total number of events	0	1
Cholecystitis chronic	0	1 (1.4%)
Injury, poisoning and procedural complications		
Total number of patients with at least one AE, n (%)	1 (0.7%)	0
Total number of events	1	0
Infusion-related reaction	1 (0.7%)	0
Nervous system disorders		
Total number of patients with at least one AE, n (%)	0	1 (1.4%)
Total number of events	0	1
Ischaemic stroke	0	1 (1.4%)
Psychiatric disorders		
Total number of patients with at least one AE, n (%)	1 (0.7%)	0
Total number of events	1	0
Affective disorder	1 (0.7%)	0
Skin and subcutaneous tissue disorders		

Safety Outcome; MedDRA System Organ Class and MedDRA Preferred Term	Crovalimab (Arm A) n = 135	Eculizumab (Arm B) n = 69
Total number of patients with at least one AE, n (%)	1 (0.7%)	0
Total number of events	1	0
Henoch–Schönlein purpura	1 (0.7%)	0
Vascular disorders		
Total number of patients with at least one AE, n (%)	1 (0.7%)	0
Total number of events	1	0
Hypovolaemic shock	1 (0.7%)	0

Investigator text for AEs encoded using MedDRA version 25.1. Only treatment-emergent AEs are displayed. For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of 'Total number of events' rows, multiple occurrences of the same AE in an individual are counted separately. Events are sorted by descending overall total frequency. (46, 59)
AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities.

Table 61 COMMODORE 1: Summary of Serious AEs by Preferred Term

(Primary Safety Period, Randomized Safety Population)

Safety Outcome; MedDRA System Organ Class and MedDRA Preferred Term	Crovalimab (Arm A) n = 44	Eculizumab (Arm B) n = 42
Total number of patients with at least one AE, n (%)	6 (13.6)	1 (2.4%)
Overall total number of events	8	3
Infections and infestations		
Total number of patients with at least one AE, n (%)	3 (6.8%)	1 (2.4%)
Total number of events	3	2
Pneumonia	1 (2.3%)	1 (2.4%)
Nasopharyngitis	1 (2.3%)	0
Pyelonephritis	0	1 (2.4%)
Urinary tract infection	1 (2.3%)	0
Blood and lymphatic system disorders		
Total number of patients with at least one AE, n (%)	1 (2.3%)	0
Total number of events	1	0
Neutropenia	1 (2.3%)	0
General disorders and administration-site conditions		
Total number of patients with at least one AE, n (%)	1 (2.3%)	0
Total number of events	1	0
Pyrexia	1 (2.3%)	0
Hepatobiliary disorders		
Total number of patients with at least one AE, n (%)	1 (2.3%)	0
Total number of events	1	0

Safety Outcome; MedDRA System Organ Class and MedDRA Preferred Term	Crovalimab (Arm A) n = 44	Eculizumab (Arm B) n = 42
Hyperbilirubinaemia	1 (2.3%)	0
Injury, poisoning and procedural complications		
Total number of patients with at least one AE, n (%)	1 (2.3%)	0
Total number of events	1	0
Skin laceration	1 (2.3%)	0
Nervous system disorders		
Total number of patients with at least one AE, n (%)	0	1 (2.4%)
Total number of events	0	1
Transient ischaemic attack	0	1 (2.4%)
Reproductive system and breast disorders		
Total number of patients with at least one AE, n (%)	1 (2.3%)	0
Total number of events	1	0
Cervical dysplasia	1 (2.3%)	0

Investigator text for AEs encoded using MedDRA version 25.1. Only treatment-emergent AEs are displayed. For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately. Events are sorted by descending overall total frequency (58).
AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities.

E.2 A description of the safety profile for the exploratory cohort (Arm C, non-randomized crovalimab treatment arm) in COMMODORE 1

At the time of primary analysis, 38 patients were enrolled in the non-randomized Arm C of the study. 21 patients were enrolled into the prior ravulizumab cohort, 10 patients were enrolled into the prior high-dose eculizumab cohort, six patients were enrolled into the C5 polymorphism cohort and one patient was enrolled into the pediatric cohort. All patients in these Arm C cohorts received crovalimab treatment. The single patient in the pediatric cohort was enrolled approximately 2 weeks prior to the primary analysis CCOD and the data for this patient are therefore limited.

[redacted]The numbers (and %) of patients with at least one AE in each exploratory cohort were: 18 (85.7%) in the prior ravulizumab cohort[redacted]

The proportion of patients with treatment-related AEs were: 47.6% in the prior ravulizumab cohort;

[redacted]

The proportion of patients with at least one Grade 3–5 AE were: 42.9% in the prior ravulizumab cohort [redacted]

The proportion of patients with at least one treatment-related SAE were: 14.3% in the prior ravulizumab [redacted] All patients who experienced a treatment-related SAE were of the type transient immune complex reactions.

In addition, one patient (4.8%) in the prior ravulizumab cohort experienced a Grade 3 SAE of sepsis leading to withdrawal of treatment. No patients in the other exploratory cohorts experienced AEs that led to withdrawal of treatment.

Two patients (9.5%) in the prior ravulizumab cohort experienced AEs that led to dose modification/interruption (nasopharyngitis and infusion-related reaction).

In the non-randomized crovalimab treatment arm (Arm C), 23.8% (five patients) in the prior ravulizumab cohort [redacted] experienced at least one transient immune complex reaction event [redacted] All reported transient immune complex reactions in the Arm C cohorts were considered by the investigator as related to study treatment (58).

Appendix F. Health-related quality of life

F.1 Study design and measuring instrument [EORTC QLQ-C30]

F.1.1 Study design and measuring instrument

[redacted]

[redacted]

F.1.2 Data collection

[redacted]

[redacted]

[redacted]

Table 62 Pattern of missing data and completion – COMMODORE 2

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)
		crovalimab		
Baseline*	[redacted]	[redacted]	[redacted]	[redacted]
Week 2	[redacted]	[redacted]	[redacted]	[redacted]
Week 5	[redacted]	[redacted]	[redacted]	[redacted]
Week 9	[redacted]	[redacted]	[redacted]	[redacted]
Week 17	[redacted]	[redacted]	[redacted]	[redacted]
Week 25	[redacted]	[redacted]	[redacted]	[redacted]
		eculizumab		
Baseline*	[redacted]	[redacted]	[redacted]	[redacted]
Week 2	[redacted]	[redacted]	[redacted]	[redacted]
Week 5	[redacted]	[redacted]	[redacted]	[redacted]

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
Week 9	[redacted]	[redacted]	[redacted]	[redacted]
Week 17	[redacted]	[redacted]	[redacted]	[redacted]
Week 25	[redacted]	[redacted]	[redacted]	[redacted]

*Baseline is the patient's last observation prior to initiation of study drug in the primary treatment period. This questionnaire is only reported by patients >= 18 years.

Table 63 Pattern of missing data and completion COMMODORE 1

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)
		crovalimab		
Baseline*	[redacted]	[redacted]	[redacted]	[redacted]
Week 2	[redacted]	[redacted]	[redacted]	[redacted]
Week 5	[redacted]	[redacted]	[redacted]	[redacted]
Week 9	[redacted]	[redacted]	[redacted]	[redacted]
Week 17	[redacted]	[redacted]	[redacted]	[redacted]
Week 25	[redacted]	[redacted]	[redacted]	[redacted]
		eculizumab		
Baseline*	[redacted]	[redacted]	[redacted]	[redacted]
Week 2	[redacted]	[redacted]	[redacted]	[redacted]
Week 5	[redacted]	[redacted]	[redacted]	[redacted]
Week 9	[redacted]	[redacted]	[redacted]	[redacted]
Week 17	[redacted]	[redacted]	[redacted]	[redacted]

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
Week 25	[redacted]	[redacted]	[redacted]	[redacted]

*Baseline is the patient's last observation prior to initiation of study drug in the primary treatment period. This questionnaire is only reported by patients >= 18 years.

F.1.3 HRQoL results for COMMODORE 2

F.1.3.1 EORTC QLQ-C30 Physical Functioning

[redacted]

Table 64 HRQoL [EORTC QLQ-C30 physical functioning] summary statistics

Summary of Absolute Scores and Change from Baseline by Visit in COMMODORE 2, EORTC QLQ-C30 Physical Functioning, Period on Initially Assigned Treatment, Primary Analysis Population

	Intervention Crovalimab naive		Comparator Eculizumab		Intervention vs. comparator
	N	Mean (SE)	N	Mean (SE)	Difference (95% CI) p-value**
Baseline*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Intervention Crovalimab naive		Comparator Eculizumab		Intervention vs. comparator
Week 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 17	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 25	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

This questionnaire is only reported by patients >= 18 years.
*Baseline is the patient's last observation prior to initiation of study drug in the primary treatment period.
**The analyses were purely descriptive and not powered to detect differences

Table 65 HRQoL [EORTC QLQ-C30 physical functioning] summary statistics

Summary of Absolute Scores and Change from Baseline by Visit in COMMODORE 2, EORTC QLQ-C30 Physical Functioning, Crovalimab Efficacy Period, Crovalimab Switch Efficacy Analysis Population 2 - Arm B

	B: After Switch to Crovalimab		Intervention vs. comparator
	N	Mean (SE)	Difference (95% CI) p-value
Switch baseline*	[redacted]	[redacted]	N/A
Switch Week 2	[redacted]	[redacted]	N/A
Switch Week 5	[redacted]	[redacted]	N/A
Switch Week 9	[redacted]	[redacted]	N/A
Switch Week 17	[redacted]	[redacted]	N/A
Switch Week 25	[redacted]	[redacted]	N/A

*Switch Baseline is the patient's last observation prior to initiation of study drug in the extension period. This questionnaire is only reported by patients >= 18 years.

[redacted]

Figure 15 Absolute EORTC QLQ-C30 Physical Functioning Scores with 95% CIs through Week 25 by Visit (Primary Analysis Population), COMMODORE 2 (59)

F.1.3.2 EORTC QLQ-C30 Role Functioning

[redacted]

Table 66 HRQoL [EORTC QLQ-C30 role functioning] summary statistics

Summary of Absolute Scores and Change from Baseline by Visit in COMMODORE 2, EORTC QLQ-C30 Role Functioning, Period on Initially Assigned Treatment, Primary Analysis Population

	Intervention Crovalimab naive		Comparator Eculizumab		Intervention vs. comparator
	N	Mean (SE)	N	Mean (SE)	Difference (95% CI) p-value**

	Intervention Crovalimab naive		Comparator Eculizumab		Intervention vs. comparator
Baseline*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 17	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 25	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*Baseline is the patient's last observation prior to initiation of study drug in the primary treatment period.
This questionnaire is only reported by patients >= 18 years.
**The analyses were purely descriptive and not powered to detect differences

Table 67 HRQoL [EORTC QLQ-C30 Role Functioning] summary statistics

Summary of Absolute Scores and Change from Baseline by Visit in COMMODORE 2, EORTC QLQ-C30 Role Functioning, Crovalimab Efficacy Period, Crovalimab Switch Efficacy Analysis Population 2 - Arm B

	B: After Switch to Crovalimab		Intervention vs. comparator
	N	Mean (SE)	Difference (95% CI) p-value
Switch baseline*	[redacted]	[redacted]	N/A
Switch Week 2	[redacted]	[redacted]	N/A
Switch Week 5	[redacted]	[redacted]	N/A
Switch Week 9	[redacted]	[redacted]	N/A
Switch Week 17	[redacted]	[redacted]	N/A
Switch Week 25	[redacted]	[redacted]	N/A

*Switch Baseline is the patient's last observation prior to initiation of study drug in the extension period. This questionnaire is only reported by patients >= 18 years.

Figure 16 Absolute EORTC QLQ-C30 Role Functioning Scores with 95% CIs through Week 25 by Visit (Primary Analysis Population), COMMODORE 2 (59)

F.1.3.3 EORTC QLQ-C30 GHS/QoL

Table 68 HRQoL [EORTC QLQ-C30 GHS/QoL] summary statistics

Summary of Absolute Scores and Change from Baseline by Visit in COMMODORE 2, EORTC QLQ-C30 GHS/QoL, Period on Initially Assigned Treatment, Primary Analysis Population

	Intervention Crovalimab naive		Comparator Eculizumab		Intervention vs. comparator
	N	Mean (SE)	N	Mean (SE)	Difference (95% CI) p-value**
Baseline*	[redacted]				
Week 2	[redacted]				
Week 5	[redacted]				
Week 9	[redacted]				
Week 17	[redacted]				
Week 25	[redacted]				

*Baseline is the patient's last observation prior to initiation of study drug in the primary treatment period.
This questionnaire is only reported by patients >= 18 years.
**The analyses were purely descriptive and not powered to detect differences

Table 69 HRQoL [EORTC QLQ-C30 GHS/QoL] summary statistics

Summary of Absolute Scores and Change from Baseline by Visit in COMMODORE 2, EORTC QLQ-C30 GHS/QoL, Crovalimab Efficacy Period, Crovalimab Switch Efficacy Analysis Population 2 - Arm B

	B: After Switch to Crovalimab		Intervention vs. comparator
	N	Mean (SE)	Difference (95% CI) p-value
Switch baseline*	[redacted]		N/A
Switch Week 2	[redacted]		N/A
Switch Week 5	[redacted]		N/A
Switch Week 9	[redacted]		N/A
Switch Week 17	[redacted]		N/A
Switch Week 25	[redacted]		N/A

*Switch Baseline is the patient's last observation prior to initiation of study drug in the extension period. This questionnaire is only reported by patients >= 18 years.

Figure 17 Absolute EORTC QLQ-C30 GHS/QoL Scores with 95% Cis through Week 25 by Visit (Primary Analysis Population), COMMODORE 2 (59)

F.1.4 HRQoL results for COMMODORE 1

F.1.4.1 EORTC QLQ-C30 Physical Functioning

Table 70 HRQoL [EORTC QLQ-C30 physical functioning] summary statistics

Summary of Absolute Scores and Change from Baseline by Visit in COMMODORE 1, EORTC QLQ-C30 Physical Functioning, Period on Initially Assigned Treatment, Primary Analysis Population

	Intervention Crovalimab naive		Comparator Eculizumab		Intervention vs. comparator
	N	Mean (SE)	N	Mean (SE)	Difference (95% CI) p-value**
Baseline*	[redacted]				
Week 2	[redacted]				
Week 5	[redacted]				
Week 9	[redacted]				
Week 17	[redacted]				
Week 25	[redacted]				

*Baseline is the patient's last observation prior to initiation of study drug in the primary treatment period.
This questionnaire is only reported by patients >= 18 years.
**The analyses were purely descriptive and not powered to detect differences

Table 71 HRQoL [EORTC QLQ-C30 physical functioning] summary statistics

Summary of Absolute Scores and Change from Baseline by Visit in COMMODORE 1, EORTC QLQ-C30 Physical Functioning, Crovalimab Efficacy Period, Crova Switch Efficacy Analysis Population 2 - Arm B

	B: After Switch to Crovalimab		Intervention vs. comparator
	N	Mean (SE)	Difference (95% CI) p-value
Switch baseline*	[redacted]		N/A
Switch Week 2	[redacted]		N/A
Switch Week 5	[redacted]		N/A
Switch Week 9	[redacted]		N/A

	B: After Switch to Crovalimab	Intervention vs. comparator
Switch Week 17	[redacted]	N/A
Switch Week 25	[redacted]	N/A

*Switch Baseline is the patient's last observation prior to initiation of study drug in the extension period. This questionnaire is only reported by patients >= 18 years.

[redacted]

Figure 18 Plot of Absolute Scores with 95% CI by Visit, EORTC QLQ-C30 Physical Functioning

Primary Efficacy Period, Efficacy Evaluable Population, COMMODORE 1 (58)

F.1.4.2 EORTC QLQ-C30 Role Functioning

[redacted]

Figure 19 Plot of Absolute Scores with 95% CI by Visit, EORTC QLQ-C30 Role Functioning

Primary Efficacy Period, Efficacy Evaluable Population, COMMODORE 1 (58)

Table 72 HRQoL [COMMODORE 1 - EORTC QLQ-C30 role functioning] summary statistics

Summary of Absolute Scores and Change from Baseline by Visit in COMMODORE 1, EORTC QLQ-C30 Role Functioning, Period on Initially Assigned Treatment, Primary Analysis Population

	Intervention Crovalimab naive		Comparator Eculizumab		Intervention vs. comparator
	N	Mean (SE)	N	Mean (SE)	Difference (95% CI) p-value**
Baseline*	[redacted]				
Week 2	[redacted]				
Week 5	[redacted]				
Week 9	[redacted]				
Week 17	[redacted]				
Week 25	[redacted]				

*Baseline is the patient's last observation prior to initiation of study drug in the primary treatment period.
This questionnaire is only reported by patients >= 18 years.
**The analyses were purely descriptive and not powered to detect differences

Table 73 HRQoL [COMMODORE 1 - EORTC QLQ-C30 Role Functioning] summary statistics

Summary of Absolute Scores and Change from Baseline by Visit in COMMODORE 1, EORTC QLQ-C30 Role Functioning, Crovalimab Efficacy Period, Crova Switch Efficacy Analysis Population 2 - Arm B

	B: After Switch to Crovalimab		Intervention vs. comparator
	N	Mean (SE)	Difference (95% CI) p-value
Switch baseline*	[redacted]	[redacted]	N/A
Switch Week 2	[redacted]	[redacted]	N/A
Switch Week 5	[redacted]	[redacted]	N/A
Switch Week 9	[redacted]	[redacted]	N/A
Switch Week 17	[redacted]	[redacted]	N/A
Switch Week 25	[redacted]	[redacted]	N/A

*Switch Baseline is the patient's last observation prior to initiation of study drug in the extension period. This questionnaire is only reported by patients >= 18 years.

F.1.4.3 Global Health Status/Quality of Life (GHS/QoL)

[redacted]

Table 74 HRQoL [EORTC QLQ-C30 GHS/QoL] summary statistics

Summary of Absolute Scores and Change from Baseline by Visit in COMMODORE 1, EORTC QLQ-C30 GHS/QoL, Period on Initially Assigned Treatment, Primary Analysis Population

	Intervention Crovalimab naive		Comparator Eculizumab		Intervention vs. comparator
	N	Mean (SE)	N	Mean (SE)	Difference (95% CI) p-value**

	Intervention Crovalimab naive	Comparator Eculizumab	Intervention vs. comparator
Baseline*	[redacted]	[redacted]	[redacted]
Week 2	[redacted]	[redacted]	[redacted]
Week 5	[redacted]	[redacted]	[redacted]
Week 9	[redacted]	[redacted]	[redacted]
Week 17	[redacted]	[redacted]	[redacted]
Week 25	[redacted]	[redacted]	[redacted]

*Baseline is the patient's last observation prior to initiation of study drug in the primary treatment period.
This questionnaire is only reported by patients >= 18 years.
**The analyses were purely descriptive and not powered to detect differences.

Table 75 HRQoL [EORTC QLQ-C30 GHS/QoL] summary statistics

Summary of Absolute Scores and Change from Baseline by Visit in COMMODORE 1, EORTC QLQ-C30 GHS/QoL, Crovalimab Efficacy Period, Crova Switch Efficacy Analysis Population 2 - Arm B

	B: After Switch to Crovalimab		Intervention vs. comparator
	N	Mean (SE)	Difference (95% CI) p-value
Switch baseline*	[redacted]	[redacted]	N/A
Switch Week 2	[redacted]	[redacted]	N/A
Switch Week 5	[redacted]	[redacted]	N/A
Switch Week 9	[redacted]	[redacted]	N/A
Switch Week 17	[redacted]	[redacted]	N/A
Switch Week 25	[redacted]	[redacted]	N/A

*Switch Baseline is the patient's last observation prior to initiation of study drug in the extension period. This questionnaire is only reported by patients >= 18 years.

[redacted]

Figure 20 Plot of Absolute Scores with 95% CI by Visit, EORTC QLQ-C30 GHS/QoL, Primary Efficacy Period, Efficacy Evaluable Population, COMMODORE 1 (58)

F.2 HRQoL summary statistics for EQ-5D-5L for Crovalimab Switch Efficacy Analysis Population

F.2.1 COMMODORE 2

Table 76 HRQoL [EQ-5D-5L VAS] summary statistics, COMMODORE 2

Summary of Absolute Scores and Change from Baseline by Visit in COMMODORE 2, EQ-5D-5L VAS, Crovalimab Efficacy Period, Crova Switch Efficacy Analysis Population 2 - Arm B

	B: After Switch to Crovalimab		Intervention vs. comparator
	N	Mean (SE)	Difference (95% CI) p-value
Switch baseline*	[redacted]	[redacted]	N/A
Switch Week 2	[redacted]	[redacted]	N/A
Switch Week 5	[redacted]	[redacted]	N/A
Switch Week 9	[redacted]	[redacted]	N/A
Switch Week 17	[redacted]	[redacted]	N/A
Switch Week 25	[redacted]	[redacted]	N/A

*Switch Baseline is the patient's last observation prior to initiation of study drug in the extension period. This questionnaire is only reported by patients >= 12 years.

Table 77 HRQoL [EQ-5D-5L utility] summary statistics, COMMODORE 2

Summary of Absolute Scores and Change from Baseline by Visit in COMMODORE 2, EQ-5D-5L utility, Crovalimab Efficacy Period, Crova Switch Efficacy Analysis Population 2 - Arm B

	B: After Switch to Crovalimab		Intervention vs. comparator
	N	Mean (SE)	Difference (95% CI) p-value
Switch baseline*	[redacted]	[redacted]	N/A
Switch Week 2	[redacted]	[redacted]	N/A
Switch Week 5	[redacted]	[redacted]	N/A
Switch Week 9	[redacted]	[redacted]	N/A
Switch Week 17	[redacted]	[redacted]	N/A
Switch Week 25	[redacted]	[redacted]	N/A

*Switch Baseline is the patient's last observation prior to initiation of study drug in the extension period. This questionnaire is only reported by patients >= 12 years.

F.2.2 COMMODORE 1

Table 78 HRQoL [EQ-5D-5L VAS] summary statistics, COMMODORE 1

Summary of Absolute Scores and Change from Baseline by Visit in COMMODORE 1, EQ-5D-5L VAS, Crovalimab Efficacy Period, Crova Switch Efficacy Analysis Population 2 - Arm B

	B: After Switch to Crovalimab		Intervention vs. comparator
	N	Mean (SE)	Difference (95% CI) p-value
Switch baseline*	[redacted]	[redacted]	N/A
Switch Week 2	[redacted]	[redacted]	N/A
Switch Week 5	[redacted]	[redacted]	N/A
Switch Week 9	[redacted]	[redacted]	N/A
Switch Week 17	[redacted]	[redacted]	N/A
Switch Week 25	[redacted]	[redacted]	N/A

*Switch Baseline is the patient's last observation prior to initiation of study drug in the extension period. This questionnaire is only reported by patients >= 12 years.

Table 79 HRQoL [EQ-5D-5L utility] summary statistics, COMMODORE 1

Summary of Absolute Scores and Change from Baseline by Visit in COMMODORE 2, EQ-5D-5L utility, Crovalimab Efficacy Period, Crova Switch Efficacy Analysis Population 2 - Arm B

	B: After Switch to Crovalimab		Intervention vs. comparator
	N	Mean (SE)	Difference (95% CI) p-value
Switch baseline*	[redacted]	[redacted]	N/A
Switch Week 2	[redacted]	[redacted]	N/A
Switch Week 5	[redacted]	[redacted]	N/A
Switch Week 9	[redacted]	[redacted]	N/A
Switch Week 17	[redacted]	[redacted]	N/A
Switch Week 25	[redacted]	[redacted]	N/A

*Switch Baseline is the patient's last observation prior to initiation of study drug in the extension period. This questionnaire is only reported by patients >= 12 years.

Appendix G. Probabilistic sensitivity analyses

This Appendix is not applicable

Table 80. Overview of parameters in the PSA

Input parameter	Point estimate	Lower bound	Upper bound	Probability distribution
Not applicable				

Appendix H. Literature searches for the clinical assessment

H.1 Efficacy and safety of the intervention and comparator(s)

This appendix is not applicable

Table 81 Bibliographic databases included in the literature search

Database	Platform/source	Relevant period for the search	Date of search completion

Abbreviations:

Table 82 Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search

Abbreviations:

Table 83 Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search

H.1.1 Search strategies

Table 84 of search strategy table for [name of database]

No.	Query	Results
#1		88244
#2		85778

No.	Query	Results
#3		115048
#4		7011
#5		10053
#6		12332
#7		206348
#8		211070
#9	#7 OR #8	272517
#10	#3 AND #6 AND #9	37

H.1.2 Systematic selection of studies

[Describe the selection process, incl. number of reviewers and how conflicts were resolved. Provide a table with criteria for inclusion or exclusion.]

Table 85 Inclusion and exclusion criteria used for assessment of studies

Clinical effectiveness	Inclusion criteria	Exclusion criteria
Population		
Intervention		
Comparators		
Outcomes		
Study design/publication type		
Language restrictions		

[Insert the PRISMA flow diagram(s) here (see example here) or use the editable diagram at the end of this document.]

Table 86 Overview of study design for studies included in the analyses

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
Study 1						
Study 2						

H.1.3 Excluded fulltext references

H.1.4 Quality assessment

H.1.5 Unpublished data

Appendix I. Literature searches for health-related quality of life

I.1 Health-related quality-of-life search

Health-related quality of life data was obtained from COMMODORE 2 and 1 (see Table 5) where crovalimab was compared to eculizumab, a comparator relevant to Danish clinical practice, and therefore a literature search was not conducted, thus this appendix is not applicable.

Table 87 Bibliographic databases included in the literature search

Database	Platform	Relevant period for the search	Date of search completion

Abbreviations:

Table 88 Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search

Table 89 Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search

I.1.1 Search strategies

Table 90 Search strategy for [name of database]

No.	Query	Results
#1		88244
#2		85778
#3		115048
#4		7011
#5		10053
#6		12332
#7		206348
#8		211070
#9	#7 OR #8	272517
#10	#3 AND #6 AND #9	37

I.1.2 Quality assessment and generalizability of estimates

I.1.3 Unpublished data

Appendix J. Literature searches for input to the health economic model

J.1 External literature for input to the health economic model

Not applicable

J.1.1 Ex. Systematic search for […]

Table 91 Sources included in the search

Database	Platform/source	Relevant period for the search	Date of search completion

Abbreviations:

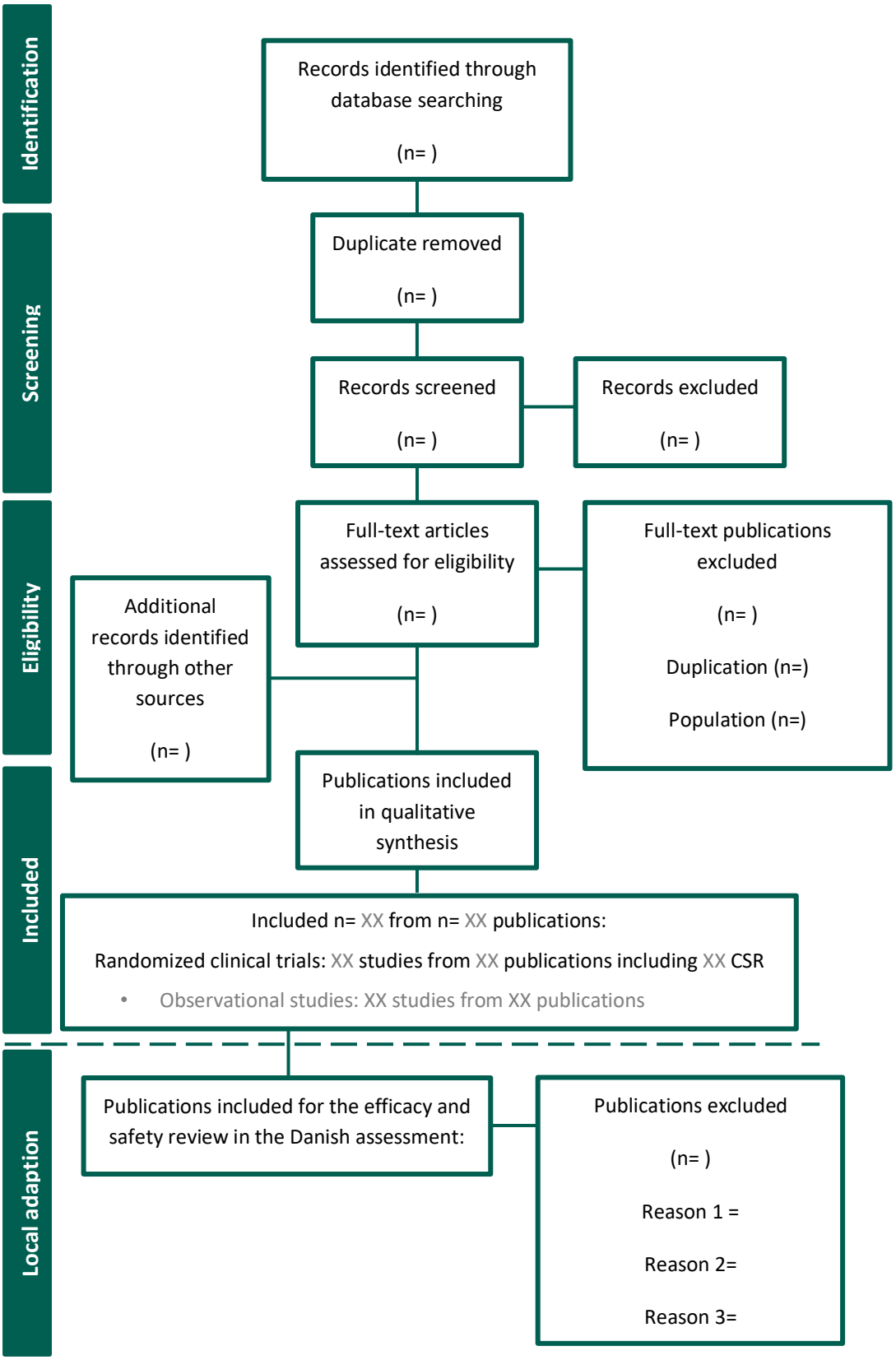
J.1.2 Ex. Targeted literature search for [estimates]

Table 92 Sources included in the targeted literature search

Source name/ database	Location/source	Search strategy	Date of search

Abbreviations:

Example of PRISMA diagram. The diagram is editable and may be used for recording the records flow for the literature searches and for the adaptation of existing SLRs.



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