NICE National Institute for Health and Care Excellence

Cost Comparison Appraisal

Crovalimab for treating paroxysmal nocturnal haemoglobinuria in people 12 years and over [ID6140]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

COST COMPARISON APPRAISAL

Crovalimab for treating paroxysmal nocturnal haemoglobinuria in people 12 years and over [ID6140]

Contents:

The following documents are made available to stakeholders:

Access the **final scope** and **final stakeholder list** on the NICE website.

1. **Company submission** from Roche
2. **Company summary of information for patients (SIP)** from Roche
3. **Clarification questions and company responses**
4. **NICE medicines optimisation team (MOT) report**
5. **Patient group, professional group and NHS organisation submissions** from:
   a. PNH Support
   b. National PNH Service
6. **External Assessment Report** prepared by Kleijnen Systematic Reviews
7. **External Assessment Report – factual accuracy check**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal: cost-comparison

Crovalimab for treating paroxysmal nocturnal haemoglobinuria [ID6140]

Document B

Company evidence submission

May 2024

File name	Version	Contains confidential information	Date
ID6140_crovalimab for PNH_DocB_RPL_100524_noCON	1.0	No	10 May 2024

Contents

Tables and figures

Abbreviations

AE	adverse event

ADA	antidrug antibody
AED	access evidence dossier
AESI	adverse event of special interest
ASCT	allogeneic stem cell transplantation
BMF	bone marrow failure
BOI	burden of Illness
BTH	breakthrough haemolysis
C3	complement protein C3
C5	complement protein C5
CCOD	clinical cutoff date
CI	confidence interval
CES	carer experience scale
COVID-19	coronavirus disease 2019
CRF	case record form
CSR	clinical study report
DASS-21	Depression, Anxiety and Stress Scale – 21 items
ECG	electrocardiogram
EMA	European Medicines Agency
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
FACT-G	Functional Assessment of Cancer Therapy – General
FAP	full analysis
GEE	generalized estimating equation
GPI	glycosylphosphatidylinositol
GHS	global health status
Hb	haemoglobin

HCP	healthcare professional
HRQoL	health-related quality of life
IgG1	immunoglobulin G1
IL40	Item Library 40
IPIG	International PNH Interest Group
IV	intravenous
LDH	lactate dehydrogenase
MAC	membrane attack complex
MAVE	major adverse vascular event
MFS	multidimensional fatigue scale
MMRM	mixed model for repeated measures
NIM	non-inferiority margin
NORD	National Organization for Rare Disorders
NMPA	National Medical Products Administration
OLE	open-label extension
PAP	primary analysis population
PD	pharmacodynamics
PedsQL	Pediatric Quality of Life Inventory
PedsQL MFS	Pediatric Quality of Life Multidimensional Fatigue Scale
PGI-S	Patient Global Impression of Severity
PICOS	population, interventions, comparators, outcomes and studies
PIGA	phosphatidylinositol glycan anchor biosynthesis class A
Pk	pharmacokinetic
PNH	paroxysmal nocturnal haemoglobinuria
PNH-SQ	Paroxysmal nocturnal haemoglobinuria – Symptom Questionnaire
PPIE(c/p)	patient public involvement and engagement (caregiver/patient)
PPQ	Patient Preference Questionnaire

pRBC	packed red blood cell
PRO	patient reported outcomes
PT	preferred term
PY	patient-years
Q2W	every 2 weeks
Q4W	every 4 weeks
QTcF	QT interval corrected by the Fridericia formula
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
RBC	red blood cell
SAE	serious adverse event
SC	subcutaneous
SD	standard deviation
SE	standard error
SLR	systematic literature review
SMART-Ig	sequential monoclonal antibody recycling technology – immunoglobulin
SMR	standard mortality ratio
SOC	System Organ Class
TA	transfusion avoidance
TSQM-9	Treatment Satisfaction Questionnaire for Medication – 9
ULN	upper limit of normal
VAS	visual analog scale

B.1 Decision problem, description of the technology and clinical care pathway

B.1.1 Decision problem

The submission covers the technology's full marketing authorisation for this indication.

The expected marketing authorisation for crovalimab [redacted] While the expected marketing authorisation is broader than the population covered by the NICE recommendation for ravulizumab, which only includes adults, eculizumab is available through an NHS service specification ([B05/S(HSS)/a]) for adults and children with PNH (1). As such, to avoid potentially disadvantaging people with PNH aged between 12 and 18 years who weigh 40 kg or more, the population addressed in this submission covers the full marketing authorisation for crovalimab.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with paroxysmal nocturnal haemoglobinuria	• [redacted] • [redacted] • [redacted] • [redacted]	The population addressed in the submission is in line with the population covered in the draft SmPC.
Intervention	Crovalimab (PiaSky®)	Crovalimab (PiaSky®)	N/A
Comparator(s)	● Eculizumab ● Ravulizumab ● Pegcetacoplan ● Iptacopan (subject to NICE evaluation) ● Danicopan with a C5 inhibitor (subject to NICE evaluation)	● Eculizumab ● Ravulizumab	Eculizumab and ravulizumab are established C5-inhibitors for the treatment of PNH. Following the cost comparison process, which assesses similarity in health benefits, safety and overall costs to existing treatment options, eculizumab and

			ravulizumab were deemed to be the most appropriate treatments to compare to.
Outcomes	The outcome measures to be considered include: ● overall survival ● intravascular haemolysis ● extravascular haemolysis ● breakthrough haemolysis ● transfusion avoidance ● haemoglobin ● thrombotic events ● adverse effects of treatment ● health-related quality of life.	The outcome measures to be considered include: ● overall survival ● haemolysis control ● transfusion avoidance ● stabilised haemoglobin ● thrombotic events ● adverse effects of treatment ● health-related quality of life.	Probability of death, or overall survival, is captured in the economic model, but assumed to be equivalent across all modelled treatments. Stabilised haemoglobin was considered in the appraisal of ravulizumab for PNH (TA698), and should therefore also be considered.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year.	A cost comparison case will be presented comparing the cost per patient per year of crovalimab versus comparators. Costs will be considered from a National Health Service (NHS) and Personal Social Services perspective.	N/A

	If the technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication, a cost comparison may be carried out. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability and cost of biosimilar and generic		

	products should be taken into account.		
Subgroups to be considered	● People not previously treated with complement inhibitors (treatment naive) ● People currently treated with complement inhibitors	● People not previously treated with complement inhibitors (treatment naive) ● People currently treated with complement inhibitors ● Paediatrics	People with PNH aged 12 and above are covered by the anticipated marketing authorisation for crovalimab. Paediatric data from the pivotal studies is presented in the submission.
Special considerations including issues related to equity or equality	None identified	None identified	N/A

B.1.2 Description of the technology being evaluated

Table 2: Technology being evaluated

UK approved name and brand name	Crovalimab (PiaSky®)
Mechanism of action	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)
Marketing authorisation/ CE mark status	Crovalimab does not have a UK marketing authorisation. Date of application is anticipated for [redacted] via International Recognition Procedure. The expected MHRA approval date is between [redacted]
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	New proposed indication: • [redacted] • [redacted] • [redacted] • [redacted] • [redacted] • [redacted] • [redacted] • [redacted]

Method of administration and dosage	IV infusion (first dose) or SC injection (subsequent doses) For SC administration, a syringe, transfer needle and injection needle are needed. *Loading dose:* **Bodyweight ≥ 40 kg to < 100 kg** Day 1: 1000 mg IV Days 2, 8, 15 and 22: 340 mg SC **Bodyweight ≥ 100 kg** Day 1: 1500 mg IV Days 2, 8, 15 and 22: 340 mg SC *Maintenance dose:* **Bodyweight ≥ 40 kg to < 100 kg** Day 29 and Q4W thereafter: 680 mg SC **Bodyweight ≥ 100 kg** Day 29 and Q4W thereafter: 1020 mg SC *Loading dose:* One loading dose by IV infusion (day 1), followed by four loading doses administered QW subcutaneously (starting on Day 2). *Maintenance dose:* The maintenance dose is started on Day 29 and administered Q4W subcutaneously. Crovalimab is intended for long-term treatment.
Additional tests or investigations	None
List price and average cost of a course of treatment	£9,500 per 340mg vial £5,332,628 (life-time acquisition cost at list price)
Patient access scheme/commercial	[redacted] (PAS price of [redacted] per 340mg vial)

arrangement (if applicable)	

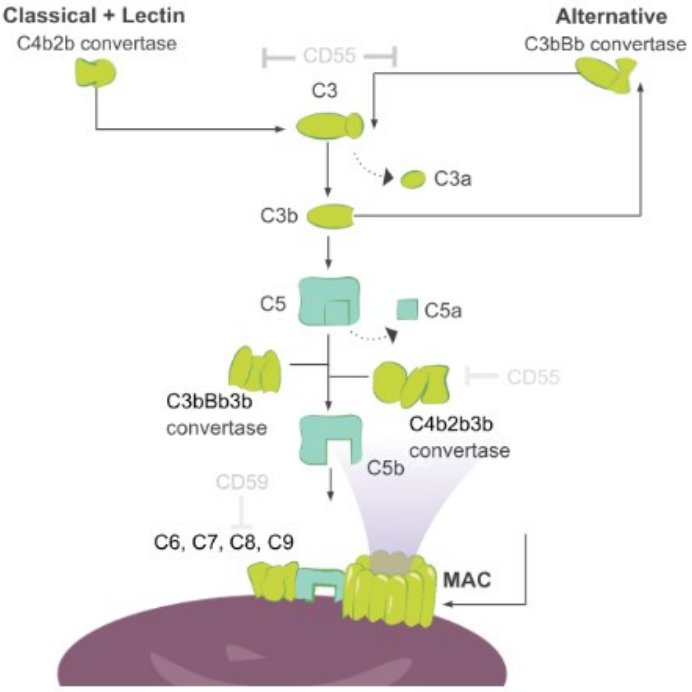
IV, intravenous; QW, once weekly; Q4W, every 4 weeks; SC, subcutaneous.

B.1.3 Health condition and position of the technology in the treatment pathway

B.1.3.1 Disease background

Paroxysmal nocturnal haemoglobinuria (PNH) develops when hematopoietic cells acquire somatic mutations in the X-linked gene encoding phosphatidylinositol glycan anchor biosynthesis class A (PIGA). 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 (2, 3). 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 (4). 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 (5, 6); and CD55 controls early complement activation, inhibiting C3 and C5 convertases (7, 8) (Figure 1).

Figure 1: The complement cascade. Adapted from Brodsky RA (9)



PNH is a progressive haematological disorder, the absence of regulatory proteins leads to uncontrolled complement- mediated lysis and, in turn, intravascular haemolysis (red blood cell destruction), resulting in anaemia and haemoglobinuria and risk of potentially life-threatening thromboembolic events. It may also lead to bone marrow failure (BMF), end organ damage and increased risk of death (9-14). Prior to the availability of complement protein C5 (C5) inhibitors, PNH had been fatal in approximately 35% of patients within 5 years of diagnosis. Thromboembolic events were the leading cause of death in patients with PNH (40–67% of deaths with known cause) and were reported in patients despite prophylactic anticoagulation therapy (15). In the era of C5 inhibitors, mortality has been estimated as 5.2% in the International PNH Registry, over a median follow-up period of 24 months (16).

It is an extremely rare, lifelong condition, the incidence of PNH in the UK has been estimated as 1 in 770,000 each year, with a predicted prevalence of approximately 1 in 62,500 (17). An estimated 1025 people in the UK are diagnosed or living with PNH from April 2022 to April 2023 (18). In England, Wales and Northern Ireland, approximately 300 people are currently on complement inhibitors, with a further 60 or so patients in clinical trials / non-NHS funded complement inhibition. PNH can occur at any age but is most frequently diagnosed between the ages of 30-40 years old (19).

B.1.3.2 Clinical management

The clinical pathway of care for patients with PNH in the United Kingdom (UK) is managed through a PNH National Service that was initiated in April 2009 (18). The PNH National Service has two main centres: one at St James' University Hospital in Leeds, and the second at King's College Hospital in London; and a further eight outreach clinics around the UK (Birmingham, Bristol, Lanarkshire, Liverpool, Manchester, Oxford, Peterborough and Southampton). Referrals to the service are received from around the UK on suspicion of PNH (normally from local haematologists), and on confirmed diagnosis of PNH, patients are managed on a shared care basis between the PNH National Service and referring haematologists.

Allogeneic bone marrow transplantation is the only curative treatment for PNH (4, 9). However, bone marrow transplantation is not usually offered as a first-line (1L) treatment for classic PNH, owing to the risks of transplant-related morbidity and mortality (20, 21).

Historically, corticosteroids have been used to improve haemoglobin (Hb) levels and reduce haemolysis; however, the use of corticosteroids is limited by long-term toxicity and insufficient

efficacy (9). As such, complement inhibitors are more effective treatment options. C5 inhibitors are globally recognized as the standard of care (SOC) for PNH. They aim to reduce the number of thromboembolic events and to reduce the risk of intravascular haemolysis, progression of pulmonary pressures and renal impairment, as well as improving PNH symptoms and patient HRQoL (22). Eculizumab (Soliris; Alexion/AstraZeneca) and ravulizumab (Ultomiris; Alexion/AstraZeneca), two C5 inhibitors with equivalent efficacy and safety, are widely used to treat patients with PNH in countries where they are available. UK clinical experts consulted by Roche noted that ravulizumab has become the preferred choice in many countries due to its less frequent administration schedule (every 8 weeks compared to every 2 weeks for eculizumab). Clinical experts suggested that approximately 5% of people with PNH are treated with eculizumab, with it mainly used in specific circumstances, such as, pregnancy, paediatric patients, and in those who prefer more clinical contact. As such, ravulizumab is considered to represent the most relevant comparator to crovalimab.

Eculizumab, an intravenously (IV) administered humanised anti-C5 antibody, was the first treatment to receive approval for PNH in 2007 in the US and the EU (23, 24). Engineered from eculizumab, ravulizumab is a longer acting, humanised anti-C5 antibody, approved for use in PNH by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) in 2018 and 2019 respectively (25, 26). The safety and efficacy of ravulizumab compared with eculizumab in patients with PNH was assessed in two open-label, randomised, active-controlled Phase III clinical trials (27, 28). Ravulizumab was found to be non-inferior to eculizumab across all efficacy endpoints, including the primary efficacy endpoint of percentage change in LDH levels from baseline to Day 183 (Kulasekararaj et al. 2019; Lee et al. 2019).

Two eculizumab biosimilars, Sb12 (Epysqli®; Samsung Bioepis NL BV) and ABP 959 (Bekemv®; Amgen Technology), were approved by the MHRA in 2024 for the treatment of adults and children with PNH. Both therapies are administered via IV infusion every 2 weeks and were approved based on similarities to eculizumab with equivalent safety and effectiveness (29, 30)).

Complement C3 inhibitors are also an effective treatment option for PNH, aiming to reduce the risk of extravascular haemolysis (31). The C3-targeting proximal complement inhibitor, pegcetacoplan (Aspaveli [Swedish Orphan Biovitrum AB] and Empaveli [Apellis Pharmaceuticals]), has been approved in some countries. It is administered subcutaneously (SC) and is indicated for the treatment of adult patients with PNH in the US, but has a more

restricted label in the EU/UK where it is indicated for the treatment of adults with PNH who are anaemic after treatment with a C5 inhibitor for at least 3 months (32, 33). The efficacy and safety of pegcetacoplan compared with eculizumab in patients with PNH was assessed in a randomised, open-label, active comparator-controlled clinical trial (34). Pegcetacoplan treatment resulted in significantly improved Hb levels compared with eculizumab ($p < 0.0001$). These results were further supported by two uncontrolled studies in patients with PNH (35).

Additional proximal inhibitors, targeting factors B or D are also in development for the treatment of PNH. Iptacopan, a factor B inhibitor, received approval for PNH in December 2023 in the USA (36), and recently received a positive recommendation from the Committee for Medicinal Products for Human Use (CHMP) on the 21st March 2024 (37). Iptacopan is a twice-daily, orally administered treatment that targets the alternative complement pathway. The efficacy of iptacopan is supported by two Phase III studies (38, 39). Danicopan, a factor D inhibitor, developed as an add-on therapy to current C5 inhibitors, received approval for PNH in March 2024 in the USA (40), and received a positive recommendation from the Committee for Medicinal Products for Human Use (CHMP) on the 22nd February 2024 (41). The efficacy of danicopan is supported by findings from the Phase III ALPHA trial (42).

Adult patients with PNH and haemolysis with clinical symptom(s) indicative of high disease activity in the UK are currently treated with ravulizumab or eculizumab. As previously mentioned, the UK preference is to use ravulizumab due to its 8 weekly dosing schedule, and as such 95% of first-line PNH patients currently treated with C5 inhibitors receive ravulizumab (43). The exact criteria used by the PNH National Service (43) to determine treatment eligibility for C5 complement inhibitors are:

- Thrombosis related to PNH
- Complications associated with haemolysis:
    - Renal failure
    - Pulmonary hypertension
- Haemolytic (lactate dehydrogenase [LDH] levels > 1.5 times the upper limit of normal [ULN]) PNH with either of the following:
    - With anaemia (Hb < 9 g/L) or
    - With agreement with Joint Service colleagues at multidisciplinary team (MDT)
- Exceptional cases (not fulfilling the above criteria) with approval across PNH National Service centres and the National Commissioners

PNH patients who are or may soon become pregnant during the course of treatment are preferentially prescribed eculizumab during and for at least 3 months postpartum.
In addition, based on equivalent safety and effectiveness, two eculizumab biosimilars (Epysqli and Bekemv), approved by the MHRA in 2024 for the treatment of adults and children with PNH are currently being integrated into the UK PNH service. UK clinical experts noted that patients currently on eculizumab (solaris) will be offered to switch to one of the 2 biosimialars, or ravulizumab in the coming months. As only small proportion of PNH patients are currently treated with eculizumab (5%), and with biosimilar uptake yet to be established, Epysqli and Bekemv were not considered relevant comparators.

Finally, for those patients established on C5 complement inhibitors for 3 months, but with continued anaemia (Hb < normal range), the option to switch to the C3 inhibitor pegcetacoplan can be considered.

B.1.3.2.1 Proposed care pathway including crovalimab

The proposed indication for crovalimab is as follows:

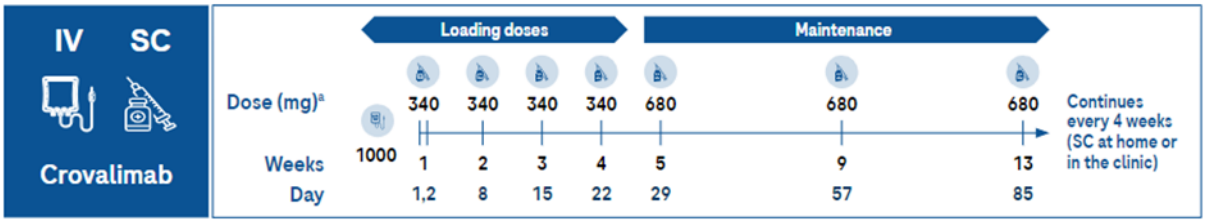
[redacted]

[redacted]Crovalimab is an immunoglobulin G1 (IgG1) monoclonal antibody of the engineered IgG1 kappa subclass with silenced Fc gamma receptor and complement component 1q binding. It binds specifically to human C5 with high affinity in a domain of the β-chain, inhibiting C5 cleavage into C5a and C5b and preventing the generation of the terminal complement complex C5b9 (membrane attack complex [MAC]) (44). Crovalimab has been 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).

For treatment, a loading dose of crovalimab (1000 or 1500 mg [depending on body weight] intravenous [IV]) is administered on Day 1 of the treatment cycle, followed by four loading doses (340 mg subcutaneous [SC]) once per week, starting on day 2. Following this, a

maintenance dose of crovalimab (680 or 1020 mg [depending on body weight] SC) is administered on Day 29 and every 4 weeks thereafter (46).

Figure 2: Crovalimab treatment schedule and dosing (example based on body weight less than 100kg), adapted from (47-49)

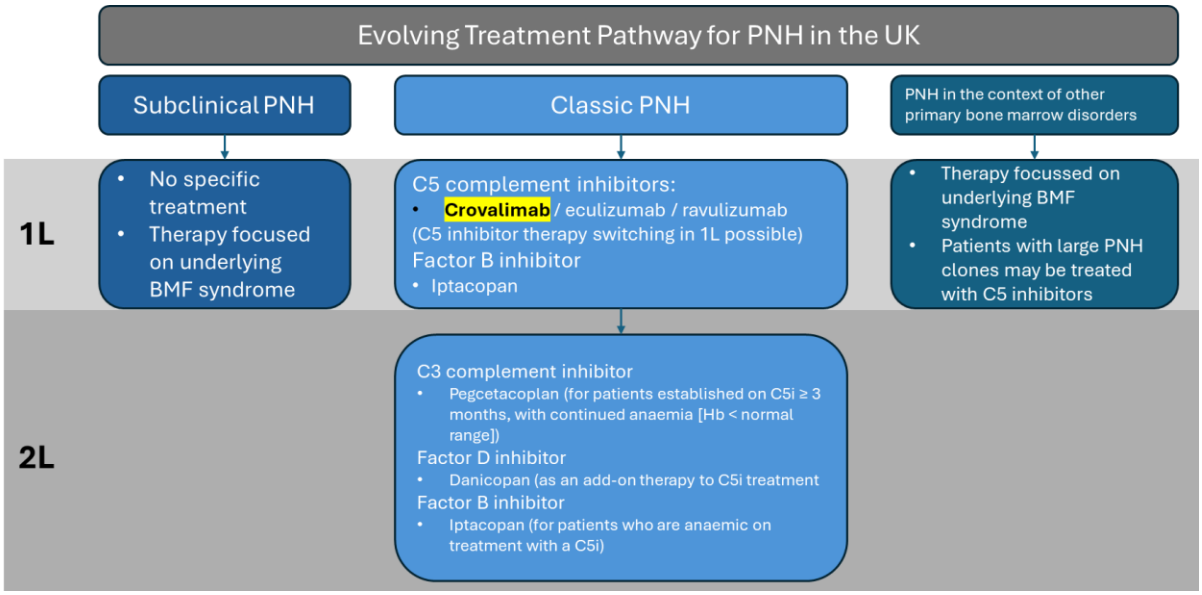


IV, intravenous; SC, subcutaneous; mg, milligrams.

Based on key recommendations by Bektas et al. (50), crovalimab is expected to sit alongside eculizumab and ravulizumab, as a potential 1L treatment option for patients with classic PNH (Figure 3). Crovalimab may also be considered as an alternative C5 inhibitor option for patients currently stable on treatment with eculizumab or ravulizumab. Similarly, as per expert clinician insight, patients on eculizumab have been transitioned to ravulizumab or vice-versa in certain clinical scenarios, and either could be used as an alternative to crovalimab as needed. In addition to crovalimab inclusion, the current care pathway is likely to change in the coming years owing to the evolving PNH landscape. For example, it may be the case that as shown, C3 and factor (B or D) inhibitors are utilised as second-line (2L) therapy or in combination with C5 inhibitors, for patients who fail to fully respond on C5 inhibitors.

Figure 3: Proposed care pathway for PNH: crovalimab's position within the

recommendations adapted from (50)



1L, first-line; 2L, second-line; BMF, bone marrow failure; C3/5, complement protein C3/5; PNH, paroxysmal nocturnal haemoglobinuria; Hb, haemoglobin; C5i, complement protein 5 inhibitor.

B.1.3.3 Unmet medical need

PNH is typically treated by complement inhibition. In a 2022 review published by Partnering4PNH (a member organization providing international guidelines for PNH management), it was noted that C5 inhibitors, eculizumab and ravulizumab, are approved and widely recommended (e.g., the USA, Canada, Japan and various EU countries) (51). However, these C5 inhibitors are associated with various levels of treatment burden, because of the mode of administration and/or the frequency of the dosing schedule. The IV administration of eculizumab and ravulizumab is relatively invasive and also carries risks of infection and vascular complications.

The long half-life and high bioavailability of crovalimab not only enables it to be administered SC rather than IV, but at a dosing schedule of every 4 weeks. Evidence related to PNH and other chronic conditions shows that these two treatment factors – mode of administration and dosing frequency – are valuable to patients and can impact their QoL. In a phase 3 clinical trial comparing SC ravulizumab (discontinued) to IV ravulizumab in patients with PNH, patients reported increased satisfaction with the SC route of administration compared with the IV route

in a treatment administration satisfaction questionnaire (52). Limited evidence exists on the caregiver burden for IV hospital infusion versus SC home treatment for PNH. However, for haemophilia A, a similar chronic disease, in a discrete choice experiment, caregivers significantly preferred treatment administered SC versus IV (53).

B.1.4 Equality considerations

While the potential recommendation of crovalimab is not expected to impact equity of access to C5 inhibitors in England, the availability of subcutaneous crovalimab could reduce the treatment burden for people with PNH (see Section B.1.3.3).

The expected marketing authorisation for crovalimab covers people with PNH aged between 12 and 18 years old. While this is broader population than that covered by recommendation for ravulizumab, age is a protected characteristic under the Equality Act 2010, and given the NHS service specification for eculizumab covers this age group, this population should be considered in this appraisal.

B.2 Key drivers of the cost effectiveness of the comparator(s)

B.2.1 Clinical outcomes and measures

The comparators for crovalimab in this appraisal are the licensed C5 inhibitors, eculizumab and ravulizumab.

Eculizumab has been assessed by NHS England, and is available to people with PNH under the service specification (For Paroxysmal Nocturnal Haemoglobinuria Service (Adults and Adolescents) [B05/S(HSS)/a]) (1).

Ravulizumab has been evaluated by NICE (TA698) (54) and is recommended as an option for treating PNH in adults:

- With haemolysis with clinical symptoms suggesting high disease activity, or
- Whose disease is clinically stable after having eculizumab for at least 6 months.

***Eculizumab (NHS service specification* [B05/S(HSS)/a])**

The pivotal studies for eculizumab considered in B05/S(HSS)/a were TRIUMPH and SHEPHERD.

- The TRIUMPH study (n=87) (55, 56) was a double-blind, randomised, placebo-controlled, multi-centre, Phase III trial. Patients had to be transfusion dependent (defined as requiring at least four transfusions in the last 12 months) and to have a platelet count in excess of 100 x 109 /l. The patients were randomised to receive either placebo or eculizumab intravenously; eculizumab was given at a dose of 600 mg weekly for four weeks, followed one week later by a 900-mg dose and then 900 mg every other week through to week 26. The two primary end points were the stabilisation of haemoglobin levels and the number of units of packed red cells transfused. Biochemical indicators of intravascular haemolysis and the patients' quality of life were also assessed.
- In the SHEPHERD study (n=97) (57, 58) eculizumab treatment was extended in an open-label, non–placebo controlled, 52-week, Phase III trial assessing both the safety and efficacy of eculizumab in a broader population of patients with PNH. Eculizumab was administered in the same dose schedule as in the TRIUMPH and pilot studies for

a total treatment period of 52 weeks. The TRIUMPH study measured reduction in haemolysis, transfusions requirements, haemoglobin level, quality of life and fatigue.

Ravulizumab (TA698)

The pivotal studies for ravulizumab considered in TA698 (54) were ALXN1210-PNH-301 and ALXN1210-PNH302.

- The ALXN1210-PNH-301 (n=246) (NCT02946463) (59) Phase III, open-label study assessed the non-inferiority of ravulizumab to eculizumab in complement inhibitor–naïve adults with PNH. Patients with lactate dehydrogenase (LDH) ≥1.5 times the upper limit of normal and at least 1 PNH symptom were randomised 1:1 to receive ravulizumab or eculizumab for 183 days. Co-primary efficacy end points were proportion of patients remaining transfusion-free and LDH normalization. Secondary end points were percent change from baseline in LDH, change from baseline in Functional Assessment of Chronic Illness Therapy (FACIT)–Fatigue score, proportion of patients with breakthrough haemolysis, stabilised haemoglobin, and change in serum free C5.

- The ALXN1210-PNH-302 (n=195) (NCT03056040) (60) Phase III, open label study assessed non-inferiority of ravulizumab to eculizumab in people with clinically stable PNH during previous eculizumab therapy. Patients on labeled-dose (900 mg every 2 weeks) eculizumab for >6 months were randomly assigned 1:1 to switch to ravulizumab (n=97) or continue eculizumab (n=98). The primary efficacy end point was percentage change in lactate dehydrogenase (LDH) from baseline to day 183. Key secondary end points included proportion of patients with breakthrough haemolysis, change in Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue score, transfusion avoidance, and stabilised haemoglobin.

Table 3: Key clinical drivers of cost-effectiveness (TA698)

Outcome and measurement scale used in NICE evaluation of ravulizumab	Committee's preferred assumptions in NICE evaluation of ravulizumab	Company comments
Treatment frequency	The committee concluded that people would most likely prefer ravulizumab over eculizumab because of the lower treatment	The relative treatment frequency applied in the economic model is based on the summary of

	frequency and associated positive effect on quality of life	product characteristics for each treatment.
Treatment efficacy	The committee noted the point estimates were in favour of ravulizumab but there was no statistically significant difference between ravulizumab and eculizumab for any of the reported clinical outcomes in either trial. It concluded that ravulizumab and eculizumab are similarly effective.	Equivalent efficacy is assumed for crovalimab, eculizumab and ravulizumab.
Safety	The committee acknowledged the European Medicines Agency concluded that the safety profile of ravulizumab appeared to be similar to that of eculizumab. It concluded that adverse events with ravulizumab are likely to be similar to eculizumab.	Equivalent safety is assumed for crovalimab, eculizumab and ravulizumab.
Higher dose eculizumab	In clinical practice in England, people can get higher doses of eculizumab, typically 1,200 mg, after breakthrough haemolysis and an inadequate disease response. The committee concluded that the proportion of people who get a higher eculizumab dose in the model should be similar to that seen in clinical practice in England.	A proportion of people (20%) with PNH receiving eculizumab are assumed to require continuous up-dosing, in-line with UK clinical expert opinion and published literature.

PNH, paroxysmal nocturnal haemoglobinuria

B.2.2 Resource use assumptions

The resource assumptions, which were relevant to the previous appraisal of ravulizumab, were:

- Intervention and comparator costs;
- Health state costs;
- AE costs;
- Medical resource use costs;
- Administration costs.

Given the analyses used is a cost comparison, the only relevant assumption to this submission is the intervention and comparator costs.

B.3 Clinical effectiveness

B.3.1 Identification and selection of relevant studies

See Appendix D for full details of the process and methods used to identify and select the clinical evidence relevant to the technology being evaluated.

B.3.2 List of relevant clinical effectiveness evidence

Evidence supporting the use of crovalimab is derived from four studies from the clinical development programme, COMPOSER, COMMODORE 1, COMMODORE 2 and COMMDORE 3.

A summary of the clinical effectiveness evidence pertinent to the current appraisal is provided below (Table 4). It is based on the pivotal Phase III study COMMODORE 2 and the supportive Phase III study COMMODORE 1. Evidence from the supportive Phase III study COMMODORE 3 is not included since this was conducted entirely in China. Evidence from COMPOSER is not included as this is a Phase I/II Study. Both supportive studies are mentioned when discussing the totality of the data. See Appendix I for details of these studies.

Table 4: Clinical effectiveness evidence

	Pivotal Study	**Supportive Study**
Study	BO42162 (COMMODORE 2) NCT04434092 (61)	BO42161 (COMMODORE 1) NCT04432584 (62)
Study publications	B042162 Primary Clinical Study Report (63)	B042161 Primary Clinical Study Report (64)
Study design	Phase III, global, randomised, active-controlled, multicentre non-inferiority study of crovalimab versus eculizumab	Phase III, global, randomised, active-controlled, multicentre study of crovalimab versus eculizumab
Population	Randomised Arms A and B: Patients with PNH not previously treated with complement inhibitors Descriptive Arm C: Paediatric patients with PNH not previously treated with complement inhibitors	Randomised Arms A and B: Patients with PNH who had been treated with eculizumab Descriptive Arm C: Subgroups of patients previously treated with complement inhibitors (based on age, type of inhibitor, dose and polymorphism)
Intervention(s)	Crovalimab	Crovalimab

Comparator(s)	Eculizumab	Eculizumab
Indicate if study supports application for marketing authorisation (yes/no)	Yes	Yes
Reported outcomes specified in the decision problem	(Co-primary) ● Haemolysis control ● Transfusion avoidance (Secondary) ● Breakthrough haemolysis ● Stabilised haemoglobin ● HRQL ● Incidence and severity of adverse events and selected AEs	(Primary) ● Incidence and severity of adverse events and selected AEs (Exploratory) ● Haemolysis control ● Transfusion avoidance ● Stabilised haemoglobin ● Breakthrough haemolysis ● HRQL
All other reported outcomes	● Incidence and severity of clinical manifestations of transient immune complexes ● PK and PD endpoints ● Immunogenicity ● Other patient-reported outcomes ● Patient preference	● Incidence and severity of clinical manifestations of transient immune complexes ● PK and PD endpoints ● Immunogenicity ● Other patient-reported outcomes ● Patient preference

PNH, paroxysmal nocturnal haemoglobinuria; HRQL, health-related quality of life; AE, adverse event; PK, pharmacokinetic; PD, pharmacodynamic

B.3.3 Summary of methodology of the relevant clinical effectiveness evidence

Unless otherwise stated, information on COMMODORE 2 and COMMODORE 1 studies were sourced from the primary clinical reports (63, 64).

B.3.3.1 Study design

B.3.3.1.1 COMMODORE 2

COMMODORE 2 is an ongoing, global, randomised, open-label, active-controlled, multicentre Phase III clinical study that enrolled patients with a body weight ≥ 40 kg, diagnosed with PNH

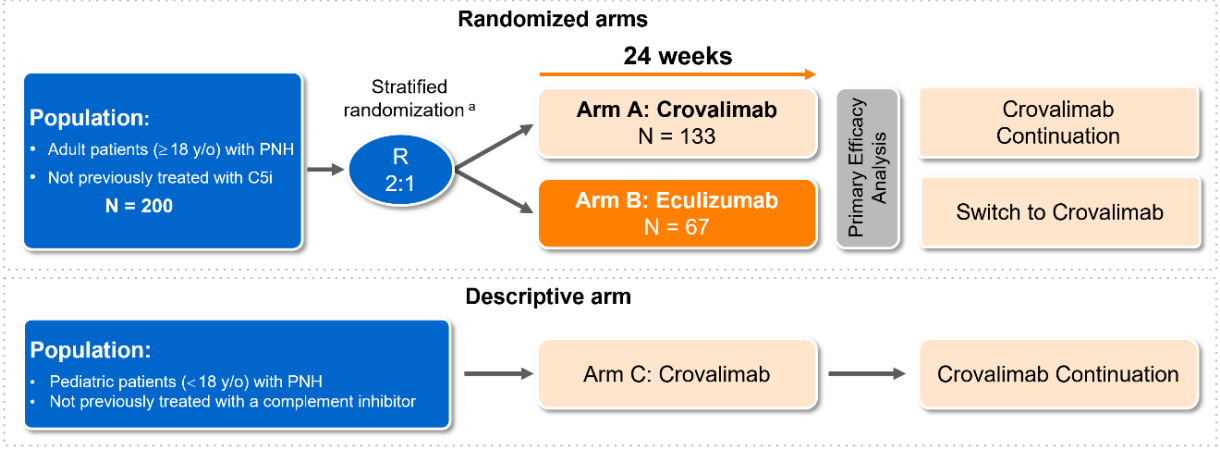
and who have not been previously treated with a complement inhibitor therapy (Figure 4). The study was designed to evaluate the efficacy and safety of crovalimab compared to eculizumab in patients with PNH, who have not been previously treated with a complement inhibitor therapy.

The study was divided into two parts: randomised arms (Arm A and B), consisting of adult patients ($\geq$ 18 years old), and a descriptive, non-randomised arm (Arm C), consisting of paediatric patients ($<$ 18 years old).

A total of approximately 200 patients with PNH were planned to be randomised (in a 2:1 ratio) and treated with crovalimab or eculizumab in Arms A and B for at least 24 weeks (primary treatment period), respectively. Randomisation was stratified based on the most recent LDH value prior to randomisation ($\geq$ 2 to $\leq$ 4 $\times$ upper limit of normal [ULN], and $>$ 4 $\times$ ULN) and pRBC transfusion history (0, $>$ 0 to $\leq$ 6, and $>$ 6 units) within 6 months prior to randomisation. All paediatric patients enrolled in non-randomised Arm C were treated with crovalimab. After having completed at least 24 weeks of crovalimab/eculizumab treatment, patients had the opportunity to continue/switch to crovalimab in the crovalimab extension period (Arm B switch).

The primary efficacy analysis was performed when all randomised patients from Arms A and B had either completed 24 weeks of treatment with crovalimab or eculizumab, or discontinued from the treatment, whichever occurred first. The CCOD for the primary efficacy analysis was 16 November 2022.

Figure 4: COMMODORE 2 overall study design



PNH = paroxysmal nocturnal haemoglobinuria; R = randomisation; ULN = upper limit of normal; y/o = years old.

Note: Prior to protocol version 3, patients of all ages could be enrolled into the randomised arms. In fact, 2 adolescents got randomised to the eculizumab arm. After the creation of Arm C in protocol version 3, all additional paediatric patients were assigned to Arm C.

[a] Randomisation is 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. Patients will be randomised 2:1 to crovalimab or eculizumab, respectively.

B.3.3.1.2 COMMODORE 1

COMMODORE 1 is an ongoing global, randomised, open-label, active-controlled, multicentre Phase III clinical study that enrolled patients with a body weight ≥ 40 kg, diagnosed with PNH and who were currently treated with a complement inhibitor therapy (Figure 5). The study was designed to evaluate the safety, PK, PD, and efficacy of crovalimab compared with eculizumab in patients with PNH switching from eculizumab. It should be noted that the original study design and objectives were amended (See Appendix D.4.4.1).

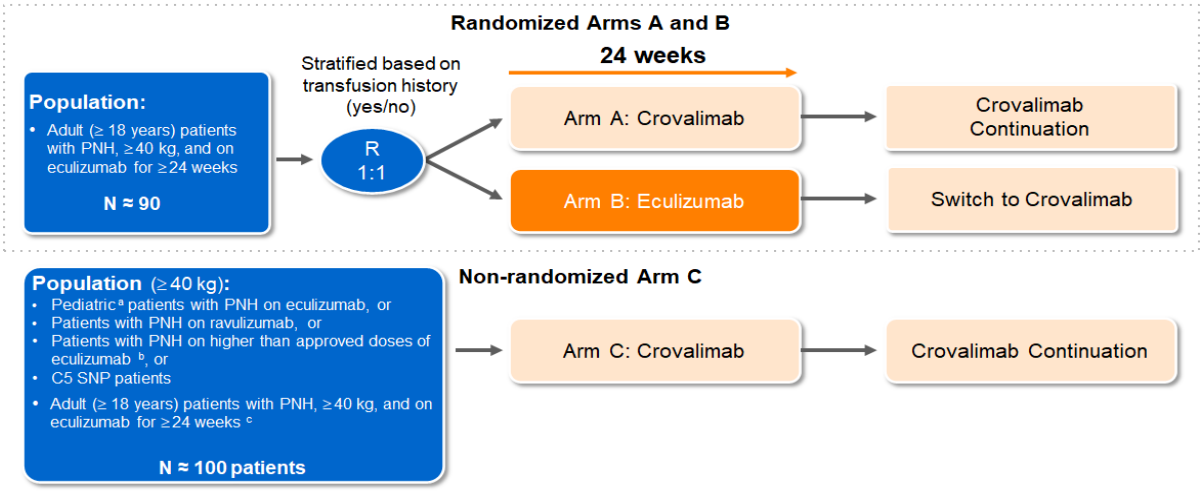
The study was divided into two parts:

- Randomised arms (Arm A and B), consisting of adult patients (≥ 18 years old) who have received eculizumab at the approved dose (900 mg Q2W) for at least a 24-week period to study entry, and have LDH ≤ 1.5 × ULN at screening.
- A non-randomised arm (Arm C), treating patients in the following cohorts of clinical interest with crovalimab:
  - Paediatric patients (< 18 years) currently receiving treatment with eculizumab for at least 12 weeks and who have LDH ≤ 2 × ULN at screening
  - Patients (regardless of age) currently receiving treatment with ravulizumab, defined as at least 16 weeks of ravulizumab and who have LDH ≤ 2 × ULN at screening
  - Patients (regardless of age) currently receiving treatment with eculizumab at higher-than-approved doses for PNH (> 900 mg per dose and/or more frequently than Q2W) for at least 12 weeks and who have LDH ≤ 2 × ULN at screening

- Patients (regardless of age) with known C5 polymorphism and who, per Investigator's assessment, have poorly controlled haemolysis by eculizumab or ravulizumab
- Adult patients (≥ 18 years) with documented treatment with eculizumab at the approved dosing for PNH (900 mg Q2W) and completion of at least 24 weeks of treatment prior to Day 1, with LDH ≤ 1.5 × ULN at screening

Approximately 90 patients with PNH were randomised (in a 1:1 ratio) and treated with crovalimab or eculizumab in Arms A and B for at least 24 weeks. Randomisation was stratified according to a patient's transfusion history (received a transfusion of packed RBCs [pRBCs] within 12 months prior to randomisation, yes vs. no) to ensure a balance of patients with PNH with transfusion history across the two randomised arms of the study. After having completed 24 weeks of crovalimab/eculizumab treatment, all patients had the opportunity to continue/switch to crovalimab in the extension period (Figure 5).

Figure 5: COMMODORE 1 overall study design



PNH = paroxysmal nocturnal haemoglobinuria; Q2W = every 2 weeks; R = randomisation; SNP = single nucleotide polymorphism.

[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 in Arm C was opened (following the stop of randomisation into Arms A and B) to patients who had been receiving eculizumab at the approved dose for least 24 weeks and had an LDH ≤ 1.5 × ULN at screening.

B.3.3.2 Summary of study methodology

	Pivotal Study COMMODORE 2 (63)	Supportive Study COMMODORE 1 (64)
Settings and locations of data collection	COMMODORE 2 was conducted in 25 countries: Argentina, Brazil, Germany, Hong Kong, Japan, Korea, Poland, Portugal, Singapore, Spain, Taiwan, China, Lithuania, Malaysia, Mexico, Philippines, Romania, France, Greece, Netherlands, Sweden, Turkey, Thailand and Ukraine. There were 2 sites in the UK.	COMMODORE 1 was conducted in 25 countries: Brazil, Germany, Hong Kong, Hungary, Italy, Japan, Korea, Poland, Portugal, Singapore, Spain, Taiwan, United States, Belgium, Canada, Czechia, Estonia, France, Greece, Ireland, Netherlands, Saudi Arabia, Sweden and Turkey. There was 1 site in the UK.
Trial design	Randomised, open-label, active-controlled, multicentre study to evaluate the efficacy, safety, PK and PD of crovalimab compared with eculizumab in patients with PNH not previously treated with complement inhibitors Overall N = 210 <u>Randomised arms</u> • Arm A: 135 patients crovalimab • Arm B: 69 patients eculizumab (68 patients switched to crovalimab in extension period)[a] <u>Non-randomised Arm C (crovalimab treatment):</u> • Paediatrics [b]: 6 patients	Randomised, open-label, active-controlled, multicentre study to evaluate the safety, PK, PD, and efficacy of crovalimab compared with eculizumab in patients with PNH currently treated with complement inhibitors Overall N = 127 <u>Randomised arms:</u> ● Arm A: 45 patients crovalimab [c] ● Arm B: 44 patients eculizumab [d] (35 patients switched to crovalimab in extension period) <u>Non-randomised Arm C (crovalimab treatment):</u> • Paediatrics [b]: 1 patient • Prior ravulizumab: 21 patients • Higher-than-approved eculizumab dose:10 patients • Known C5 polymorphism: 6 patients
Trial periods	Screening Period: up to 4 weeks Randomised/Primary treatment period: 24 weeks Extension Period: after completing 24 wks of treatment with crovalimab/eculizamab, patients may continue/switch to crovalimab for a max of 5 yrs Safety follow-up period is 46 weeks for patients who discontinue crovalimab	

Key inclusion criteria	• PNH patients who have not been treated with any complement inhibitor	• Documented treatment with either eculizumab or ravulizumab treatment prior to Day 1
	• Age ≥ 18 years (Arms A and B)[e]; < 18 years (Arm C)	• Age ≥ 18 years (Arms A and B); < 18 years or ≥ 18 years (Arm C)[f]
	• Body weight ≥ 40 kg	
	• Local LDH level ≥ 2 × ULN (All Arms)	• Local LDH level ≤ 1.5 × ULN (Arms A and B) • Local LDH level ≤ 2 × ULN (Arm C, except patients with known C5 polymorphism[g])
	• Documented diagnosis of PNH, confirmed by high sensitivity flow cytometry evaluation of WBCs with granulocyte or monocyte clone size of ≥ 10%, within 6 months prior to randomisation/ enrolment	
	• No transfusion requirement	
	• Presence of one or more of the following PNH-related signs or symptoms within 3 months prior to screening: fatigue, haemoglobinuria, abdominal pain, shortness of breath (dyspnoea), anemia (haemoglobin < 10 g/dL), history of a MAVE (including thrombosis), dysphagia, or erectile dysfunction; or history of pRBC transfusion because of PNH	• Not applicable
	• Platelet count ≥ 30,000/mm^3 at screening without transfusion support within 7 days of lab testing	
	• Vaccination against Neisseria meningitidis serotypes A, C, W and Y < 3 years prior to initiation of study treatment or within 1 week after the first drug administration, 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 prior to initiation of study treatment or within 1 week after the first drug administration	
Key exclusion criteria	• Current or previous treatment with a complement inhibitor	• Not applicable
	• Pre-enrolment haemoglobin value ≤ 7 g/dL, or pre-enrolment haemoglobin value > 7 g/dL and ≤ 9 g/dL with concurrent signs and symptoms of anemia	
	• Not applicable	• MAVE within 6 months prior to first drug administration (Day 1)
	• History of allogeneic bone marrow transplantation	

<table>
<tr><td></td><td colspan="2">

History of Neisseria meningitidis infection within 6 months prior to screening and up to first study drug administration
Known or suspected immune deficiency (e.g., history of frequent recurrent infections)
Known or suspected hereditary complement deficiency
History of myelodysplastic syndrome with IPSS-R prognostic risk categories of intermediate, high and very high

</td></tr>
<tr><td>Trial drugs</td><td colspan="2">

crovalimab was administered according to a weight-based tiered dosing approach schedule as below across both studies.

<table>
<tr><th>Body Weight</th><th>≥ 40 kg to < 100 kg</th><th>≥ 100kg</th></tr>
<tr><td>Loading Dose
Day 1
Day 2, 8, 15, 22</td><td>
1000 mg (IV)
340 mg (SC)</td><td>
1500 mg (IV)
340 mg (SC)</td></tr>
<tr><td>Maintenance Dose
Day 29 and Q4W thereafter</td><td>
680 mg (SC)</td><td>
1020 mg (SC)</td></tr>
<tr><td colspan="3">IV = intravenous; Q4W = every 4 weeks; SC = subcutaneous.</td></tr>
</table>

Eculizumab was administered at label dose; 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 (900 mg every 2 weeks)

</td></tr>
<tr><td>Primary outcome</td><td>The primary efficacy objective for this study was to evaluate the efficacy of crovalimab compared with eculizumab, based on the non-inferiority assessment of the co-primary endpoints (Arms A/B):

Proportion of patients who achieve TA from baseline to Wk 25

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 Wk 5 through Wk 25 (as measured at the central laboratory)
</td><td>There are no primary or secondary efficacy endpoints in this study. 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,
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
</td></tr>
</table>

		switched to crovalimab treatment from eculizumab or ravulizumab treatment. ● Proportion of patients who develop ADAs

Secondary outcomes	**Key secondary endpoints (Arms A/B):**
	• Proportion of patients with BTH from baseline through Wk 25
	  • BTH was defined as at least one new or worsening symptom or sign of intravascular haemolysis (fatigue, haemoglobinuria, abdominal pain, shortness of breath [dyspnoea], anaemia [haemoglobin < 10 g/dL], a major adverse vascular event [MAVE ; as defined in Appendix 4 of the COMMODORE 2 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 stabilised haemoglobin from baseline through Wk 25
	  • Stabilised 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 Wk 25 in fatigue as assessed by FACIT-Fatigue score
		N/A

Other exploratory outcomes used	<u>Patient-reported Outcomes</u>: • Mean change from baseline to Wk 25 in Physical Function, Role Function, and Global Health Status scales of EORTC QLQ-C30 • Mean change from baseline to Wk 25 in PedsQL™ • EORTC IL40 • Patient preference <u>Safety endpoints</u>	Efficacy was an exploratory objective only. All exploratory efficacy endpoint analyses were descriptive, with no formal statistical testing being conducted. The exploratory efficacy objective for this study was to evaluate the efficacy of crovalimab versus eculizumab on the basis of the following endpoints:

	• incidence and severity AEs
	• 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 treatment.
	• Proportion of patients who develop ADAs
	
	<u>Other analyses</u>
	• Time from baseline to the first time LDH $\geq 1.5 \times$ ULN
	• Percent change in LDH levels from baseline to Wk 25
	• Mean normalized LDH levels from baseline to Wk 25
	• Total number of units (based on local equivalent) of pRBCs transfused per patient by Wk 25
	• Proportion of patients experiencing a MAVE from baseline through Wk 25
	• PK and PD
		• Percentage change from baseline in LDH levels averaged over Weeks 21, 23 and 25 based on central laboratory LDH measurements.
		• 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 [dyspnoea], 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 stabilisation of haemoglobin from baseline through Week 25.
		  • Stabilised haemoglobin is defined as avoidance of a ≥ 2 g/dL decrease in haemoglobin level from baseline, in the absence of transfusion.
		• Proportion of patients with central LDH ≤ 1.5 × ULN from baseline through Week 25.
		• 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.

Pre-planned subgroups	• Subgroup analyses were performed for the co-primary efficacy endpoints of haemolysis control and TA. The following subgroups were analysed: • Age: < 18; 18 – 64; and ≥ 65 years • Sex: Male; Female • Region: Europe/Central, South and North America; Japan and Rest of Asia Pacific • Eculizumab availability: Yes; No • Race: Asian; Black or African American; White; and Other • Stratification factor: transfusion history of total pRBC units administered in the 6 months prior to randomisation: 0; > 0 to ≤ 6; and > 6 • Stratification factor: LDH value: 2−≤ 4 × ULN; > 4 × ULN • Aplastic anaemia: Yes; No • Body weight (kg): 40 to < 100; ≥ 100	In COMMODORE 1 subgroup analyses were not planned as efficacy was only exploratory.

a Two paediatric patients (> 12 years old) were randomized to eculizumab in Arm B before a separate descriptive Arm C was opened to allow enrolment of paediatric patients (< 18 years old) weighing >40 kg. b Paediatric patients aged < 18 years and >40 kg body weight. c 1 randomized patient in study BO42161 Arm A did not receive crovalimab treatment.

PNH, paroxysmal nocturnal haemoglobinuria; HRQL, health-related quality of life; AE, adverse event; PK, pharmacokinetic; PD, pharmacodynamic; LDH, lactate dehydrogenase; ULN, upper limit of normal; WBC, white blood cell; RBC, red blood cell; MAVE, major adverse vascular event; IPSS-R = with Revised International Prognostic Scoring System;; ADA, anti-drug antibody; BTH, breakthrough haemolysis; Wk, week; TA, transfusion avoidance

B.3.3.3 Demographics and baseline characteristics

An overview of the baseline demographics and disease characteristics across COMMODORE 2 (randomised arms) and COMMODORE 1 (randomised arms) are presented in Table 5 and Table 6, respectively.

Baseline demographics and disease characteristics were generally comparable across the randomised crovalimab and eculizumab treatment arms in COMMODORE 2 and represent the treatment-naïve patient population that was intended to be enrolled

Switch patients enrolled in the randomised arms of COMMODORE 1 were required to have haemolysis control (LDH $\leq 1.5 \times$ ULN) at screening. Overall, the baseline demographics and disease characteristics were comparable across the randomised crovalimab and eculizumab treatment arms.

The patient demographics in Arm B switch patients from COMMODORE 2 and COMMODORE 1 were expected to remain unchanged compared to baseline and were therefore not reanalysed. The other baseline characteristics were also not reanalysed, given the absence of uniform criteria required to switch to crovalimab in the extension period.

Overall, the enrolled patient population across studies represent the treatment-naïve and switch patient populations that were intended to be enrolled.

UK clinical experts consulted by Roche agreed that the characteristics of the patient populations of COMMODORE 1 and 2 were representative of PNH patients treated in UK clinical practice.

Table 5: Demographic characteristics in COMMODORE 2 and COMMODORE 1

	COMMODORE 2[a]		COMMODORE 1[c]	
	Eculizumab (N = 69)	Crovalimab (N = 135)	Eculizumab (N = 44)	Crovalimab (N = 45)
Age (yr)				
Mean (SD)	41.9 (16.0)	40.5 (15.2)	49.5 (14.8)	44.4 (15.6)
Median	38.0	36.0	49.0	42.0
Min–Max	17–78	18–76	22–85	21–81
Age group (yr)				
< 18	2 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
18–64	58 (84.1%)	122 (90.4%)	37 (84.1%)	40 (88.9%)
≥ 65	9 (13.0%)	13 (9.6%)	7 (15.9%)	5 (11.1%)
Sex				
Male	35 (50.7%)	77 (57.0%)	22 (50.0%)	21 (46.7%)
Female	34 (49.3%)	58 (43.0%)	22 (50.0%)	24 (53.3%)
Race				
Asian	51 (73.9)	86 (63.7%)	7 (15.9%)	9 (20.0%)
White	16 (23.2%)	45 (33.3%)	32 (72.7%)	34 (75.6%)
Black or African American	1 (1.4%)	3 (2.2%)	1 (2.3%)	2 (4.4%)
Unknown	1 (1.4%)	1 (0.7%)	4 (9.1%)	0 (0.0%)
Ethnicity				
Hispanic or Latino	6 (8.7%)	18 (13.3%)	8 (18.2%)	8 (17.8%)
Not Hispanic or Latino	61 (88.4%)	114 (84.4%)	31 (70.5%)	36 (80.0%)
Not stated	2 (2.9%)	3 (2.2%)	5 (11.4%)	1 (2.2%)
Unknown	0 (0.0%)	0 (0.0%)	n/a	n/a
Region				
Rest of Asia Pacific	48 (69.6%)	83 (61.5%)	3 (6.8%)	3 (6.7%)
Europe	12 (17.4%)	36 (26.7%)	29 (65.9%)	30 (66.7%)
Central and South America	2 (2.9%)	12 (8.9%)	7 (15.9%)	7 (15.6%)
Japan	3 (4.3%)	2 (1.5%)	4 (9.1%)	5 (11.1%)
North America	4 (5.8%)	2 (1.5%)	1 (2.3%)	0 (0.0%)
Africa and Middle East	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Weight (kg) at baseline				
Mean (SD)	67.13 (15.26)	68.32 (15.76)	76.54 (18.03)	77.01 (17.47)
Median	62.20	66.10	75.10	80.00
Min–Max	47.0–122.0	42.0–140.3	47.2–126.4	45.2–120.0

[a]Randomised Population; [c]All Patients Population.

Crova = crovalimab; Ecu = eculizumab; n/a = not applicable.

yr, year; SD, standard deviation; kg, kilograms

Percentages presented in this table are based on the number of patients with data available for the parameter for which subgroup data are displayed; the denominator used for calculation of the percentages may be smaller than the overall size of the population indicated by N in the column header.

Table 6: Baseline characteristics in COMMODORE 2 and COMMODORE 1

	COMMODORE 2[a]		COMMODORE 1[c]	
	Eculizumab (N = 69)	Crovalimab (N = 135)	Eculizumab (N = 44)	Crovalimab (N = 45)
Time from PNH diagnosis to enrolment (yr)				
Mean (SD)	4.97 (5.91)	5.22 (7.42)	11.17 (7.05)	8.03 (6.56)
Median	2.93	2.56	10.4 [d]	6.34
Min–Max	0.0–31.0	0.0–48.5	0.8–28.0 [d]	0.0–26.8
History of aplastic anemia				
Yes	26 (37.7%)	53 (39.3%)	16 (36.4%)	15 (33.3%)
No	43 (62.3%)	82 (60.7%)	28 (63.6%)	30 (66.7%)
History of myelodysplastic syndrome				
Yes	6 (8.7%)	6 (4.4%)	0 (0.0%)	0 (0.0%)
No	63 (91.3%)	129 (95.6%)	44 (100.0%)	45 (100.0%)
History of major vascular event				
Yes	10 (14.5%)	21 (15.6%)	10 (22.7%)	10 (22.2%)
No	59 (85.5%)	114 (84.4%)	34 (77.3%)	35 (77.8%)
History of pRBC transfusion*				
Yes	50 (73.5%)	103 (77.4%)	11 (25.0%)	10 (22.7%)
No	18 (26.5%)	30 (22.6%)	33 (75.0%)	34 (77.3%)
No. of units of pRBC transfused*				
Mean (SD)	6.63 (8.70)	6.47 (8.27)	2.32 (5.43)	1.55 (3.72)
Median	3.00	3.75	0.00	0.00
Min–Max	0.0–41.0	0.0–43.5	0.0–24.0	0.0–14.0
PNH clone size (granulocytes): %**				
Mean (SD)	61.7 (29.5)	55.8 (26.7)	61.71 (29.69)	54.87 (28.47)
Median	74.6	60.3	67.94	66.46
Min–Max	1.3–95.2	0.8–96.1	2.16–97.76	47.93–1.66
PNH clone size (monocytes): %**				
Mean (SD)	88.1 (15.8)	84.8 (16.2)	86.62 (21.71)	80.84 (22.12)
Median	95.1	90.8	96.32	88.62
Min–Max	41.5–99.9	42.5–100.0	7.60–99.89	13.83–99.96
PNH clone size (erythrocytes): %**				
Mean (SD)	43.2 (24.9)	29.1 (17.5)	54.71 (32.80)	50.09 (30.92)
Median	44.6	25.1	46.52	44.62
Min–Max	0.1–88.9	3.5–96.0	1.26–100.00	2.62–99.98
Haemoglobin value at baseline (g/L)				

	COMMODORE 2[a]		COMMODORE 1[c]	
	Eculizumab (N = 69)	Crovalimab (N = 135)	Eculizumab (N = 44)	Crovalimab (N = 45)
Mean (SD)	99.69 (87.86)	87.18 (14.06)	107.27 (17.66)	109.74 (19.96)
Median	87.00	85.00	106.50	112.50
Min–Max	58.0–810.0 [e]	63.0–135.0	68.0 - 144.0	72.0 - 153.0
LDH value at baseline (× ULN)* **				
Mean (SD)	7.77 (3.54)	7.57 (3.38)	1.00 (0.24)	1.06 (0.28)
Median	7.74	7.00	0.96	1.01
Min–Max	2.0–20.3	2.0–16.3	0.7–1.9	0.6–1.7

* pRBC transfusions within 12 months prior to screening.

** Within 6 months prior to screening.

***Baseline LDH is defined as the mean of all central LDH values taken during screening and the LDH value at Week 1, Day 1 collected prior to the first dose of crovalimab.

[a] Randomised Population.

[c] All Patients Population.

[d] One patient's initial PNH diagnosis day was reported as the same day as their most recent flow cytometry date, leading to a time from PNH diagnosis to enrolment of 0.04 years, which was rounded down to 0.0 year.

[e] Inclusion criteria for this study required patients to have at least 4 transfusions in the prior 12 months to be eligible.

[e] Of note, the maximum baseline haemoglobin value in the eculizumab arm of 810 g/L was a result of erroneous data entry.

yr, year; SD, standard deviation; RBC, red blood cell; PNH, paroxysmal nocturnal haemoglobinuria; LDH, lactate dehydrogenase

Percentages presented in this table are based on the number of patients with data available for the parameter for which subgroup data are displayed; the denominator used for calculation of the percentages may be smaller than the overall size of the population indicated by N in the column header.

B.3.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

The hypothesis tested in COMMODORE 2 was the non-inferiority of crovalimab compared with eculizumab. The primary objective of COMMODORE 1 is safety and efficacy was an exploratory objective only. All exploratory efficacy endpoint analyses were descriptive, with no formal statistical testing being conducted. Here we describe the statistical analyses for COMMODORE 2.

B.3.4.1 Analysis populations

The primary and secondary efficacy analyses were performed based on the primary analysis population (PAP). To evaluate the non-inferiority of crovalimab compared with eculizumab the

PAP includes all randomised patients receiving at least one dose of the assigned treatment and having at least one centrally processed LDH level assessment after the first IV infusion.

For patients in Arm B switching from eculizumab to crovalimab after completing the primary treatment period, the efficacy analysis population was defined as all patients receiving at least one dose of crovalimab and having at least one centrally processed LDH level assessment after the first crovalimab IV infusion. Additionally, efficacy endpoints assessed over 24-week intervals, such as haemolysis control and TA, were analysed on a subset of the efficacy population (24-week Crovalimab Efficacy Population – Arm B Switch), which included patients who switched to crovalimab at least 24 weeks before CCOD.

For patients in Arm C, the efficacy evaluable population was defined as all patients receiving at least one dose of the crovalimab treatment and having at least one centrally processed LDH level assessment after the first IV infusion. This analysis population was used for exploratory endpoints.

The randomised population (intent-to-treat [ITT]) was defined as all randomised patients, according to the originally assigned treatment, and included only patients in Arms A (crovalimab) and B (eculizumab). The Per Protocol (PP) population comprised all randomised patients in Arms A and B who fulfilled the per protocol criteria. Safety was assessed in the 'crovalimab safety population', defined as all patients who have received at least one dose of crovalimab. This includes patients from Arms A, B and C, with assignment based on actual treatment received.

B.3.4.2 Sample size and non-inferiority margin

The sample size estimation was based on the non-inferiority assessment of the co-primary endpoints. The final target sample size was driven by the sample size considerations for TA as this was the co-primary endpoint that required the larger number of patients as compared to the haemolysis control endpoint. A sample size of 200 adult patients randomly assigned in a 2:1 ratio to receive either crovalimab or eculizumab was selected to ensure having approximately 180 evaluable patients (assuming a 10% drop-out rate). This sample size was estimated to provide 80% power to demonstrate the non-inferiority of crovalimab to eculizumab with respect to TA, using a pre-defined non-inferiority margin (NIM) of − 20%, and a one-sided Type 1 error rate of 2.5%.

The NIM for TA was determined based on the data reported in study ALXN1210-PNH-301 (27), by comparing eculizumab-treated patients with untreated patients from the global PNH Registry

for eculizumab-treated patients. Patients treated with eculizumab showed a benefit over untreated patients with a difference of approximately 40 percentage points (TA proportion of 57.1% and 18.6%, respectively), after adjustment for history of transfusions 12 months prior to enrolment. Hence, a difference in TA proportions of -20 percentage points (the pre-defined NIM) preserves at least 50% of the control treatment effect.

Furthermore, PNH is a clinically heterogeneous disease, not only manifesting with intravascular haemolysis and its downstream complications, but can also be associated with aplastic anaemia, myelodysplastic syndrome, and variable extents of bone marrow failure, which may in particular confound transfusion requirements arising from inadequate erythrocyte production rather than an isolated haemolytic process.

With respect to haemolysis control, 116 patients were required to be randomised in a 2:1 ratio to test the non-inferiority of crovalimab compared with eculizumab, with a pre-defined NIM of 0.2 for the odds ratio (OR), 80% power, and a one-sided Type I error rate of 2.5%. Based on data reported in study ALXN1210-PNH-301 (27) and under the assumption that LDH is log-normally distributed, the expected proportion of patients with LDH $\leq 1.5 \times$ ULN (which is the threshold used for the definition of the co-primary endpoint in study COMMODORE 2) was 86%. The same proportion was assumed for crovalimab. The NIM for the OR was calculated with the aim to preserve at least 50% of the original treatment effect of eculizumab against placebo, resulting in a NIM of 0.2. Assuming a 10% drop-out, the total needed sample size for the haemolysis control co-primary endpoint was estimated to be 128 patients. With at least 180 evaluable patients in the COMMODORE 2 study, the power for this endpoint was estimated to be 94%.

B.3.4.3 Statistical analysis of co-primary efficacy endpoints

Both co-primary efficacy endpoints were required to be met to conclude non-inferiority of crovalimab to eculizumab. The primary efficacy analysis was conducted once the last patient randomised into Arms A (crovalimab) and B (eculizumab) had completed 24 weeks of study treatment or discontinued early, whichever happened first.

The co-primary efficacy endpoint of mean proportion of patients with haemolysis control was defined as LDH $\leq 1.5 \times$ ULN from Week 5 through Week 25 (as measured by the central laboratory). A standard Generalized Estimating Equation (GEE) model was used to estimate the adjusted log odds ratio of LDH $\leq 1.5 \times$ ULN due to treatment, taking into account the intra-

individual correlation between LDH control statuses across visits. An unstructured covariance matrix was primarily planned to be applied in the analysis, with other covariance matrix structures to be applied (in the pre-specified order of: Toeplitz, first-order autoregressive [AR1] or compound symmetry) in the case of non-convergence.

Non-inferiority of haemolysis control between crovalimab and eculizumab was demonstrated when the lower limit of the two-sided 95% confidence interval (CI) for the odds ratio, as estimated by the GEE model, was higher than the pre-defined non-inferiority margin of 0.2.

The second co-primary efficacy endpoint was the proportion of patients who achieved TA from baseline through Week 25 (after 24 weeks of treatment). From baseline to Week 25, patients who withdrew early from the treatment were conservatively assumed to have undergone a transfusion. The difference in the proportion of patients between the two treatment arms was computed as a weighted combination of differences between crovalimab and eculizumab within the stratification indicators of transfusion history and baseline LDH categories using Mantel-Haenszel weights.

Non-inferiority with respect to TA was concluded when the lower limit of the 95% CI for the difference between crovalimab and eculizumab was greater than the pre-defined non-inferiority margin of − 20%.

After non-inferiority was demonstrated in the co-primary efficacy endpoints, the secondary efficacy endpoints were assessed for non-inferiority and superiority according to the hierarchy displayed in Table 7. The strict testing hierarchy ensured the family-wise one-sided Type I error rate was controlled at 2.5%.

Table 7 : Hierarchical order for non-inferiority and superiority testing of primary and secondary efficacy endpoints in Study COMMODORE 2

Test	Endpoint
Non-inferiority	*Proportion of patients with TA from baseline through Week 25
Non-inferiority	*Haemolysis control from Week 5 through Week 25
Non-inferiority	Proportion of patients with BTH from baseline through Week 25
Non-inferiority	Proportion of patients with stabilisation of haemoglobin from baseline through Week 25

Test	Endpoint
Superiority	Proportion of patients with TA from baseline through Week 25
Superiority	Haemolysis control from Week 5 through Week 25
Superiority	Proportion of patients with BTH from baseline through Week 25
Superiority	Proportion of patients with stabilisation of haemoglobin from baseline through Week 25
Non-inferiority Superiority	Mean change from baseline to Week 25 in fatigue as assessed through use of the FACIT-Fatigue scale (for adults aged ≥ 18 years) Mean change from baseline to Week 25 in fatigue as assessed through use of the FACIT-Fatigue scale (for adults aged ≥ 18 years)

BTH = Breakthrough Haemolysis; TA = transfusion avoidance; FACIT Fatigue = Functional Assessment of Chronic Illness Therapy- Fatigue.* Co-primary endpoints.

B.3.4.4 Sensitivity analysis of co-primary efficacy endpoints

Sensitivity analyses were performed to assess the robustness of the primary efficacy results, based on different analysis populations, statistical models and model assumptions, and the impact of missing data.

B.3.4.5 Statistical analysis of secondary efficacy endpoints

Statistical analysis of the secondary efficacy endpoints of BTH and haemoglobin stabilisation used similar methodology as for the analysis of the TA co-primary efficacy endpoint. An overview of these analyses, including the methodology used for the secondary endpoint of FACIT-Fatigue is provided in Appendix D.5. Statistical analyses of the exploratory efficacy endpoints for COMMODORE 1 is also detailed in Appendix D.5.

B.3.5 Critical appraisal of the relevant clinical effectiveness evidence

COMMODORE 2 and COMMODORE 1 were conducted in accordance with the principles of the "Declaration of Helsinki" and Good Clinical Practice. The appropriate Ethics Committees and Institutional Review Boards reviewed and approved the studies.

An overview of the quality assessment for COMMODORE 2 and COMMODORE 1 is presented in Table 8. Please refer to Appendix D.3 for the full quality assessment and Appendix D.4 for critical considerations of studies, COMMODORE 2 and COMMODRE 1.

Table 8: Quality assessment results for COMMODORE 2 and COMMODORE 1

	COMMODORE 2	COMMODORE 1
Was randomisation carried out appropriately?	Yes	Yes
Was the concealment of treatment allocation adequate?	N/A [a]	N/A [a]
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	No [a]	No [a]
Were there any unexpected imbalances in drop-outs between groups?	No [b]	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	No [c]

[a] All studies were Open Label

[b] There were 6/135 discontinuations in the crovalimab arm vs 1/69 in the eculizumab arm. However, this is not viewed as unusual.

[c] Randomisation in this study was stopped early and efficacy only became an exploratory objective and was thus evaluated only on patients who had completed at least 24 Weeks of study treatment at the time of CCOD.

B.3.6 Clinical effectiveness results of the relevant studies

B.3.6.1 Overview of efficacy

Efficacy results are not pooled across studies given the differences in the early treatment phase between treatment-naïve and switch patients, the differences in treatment-naïve patient populations with respect to the recent transfusion history, and the differences in the requirements for baseline LDH for switch patients.

This section provides an overview of key results of the individual studies, COMMODORE 2 and COMMODORE 1.

An in depth comparison and analysis of results by all key endpoints, including efficacy analyses for Arm B switch patients from COMMODORE 2 and COMMODORE 1 are presented in Appendix D1.

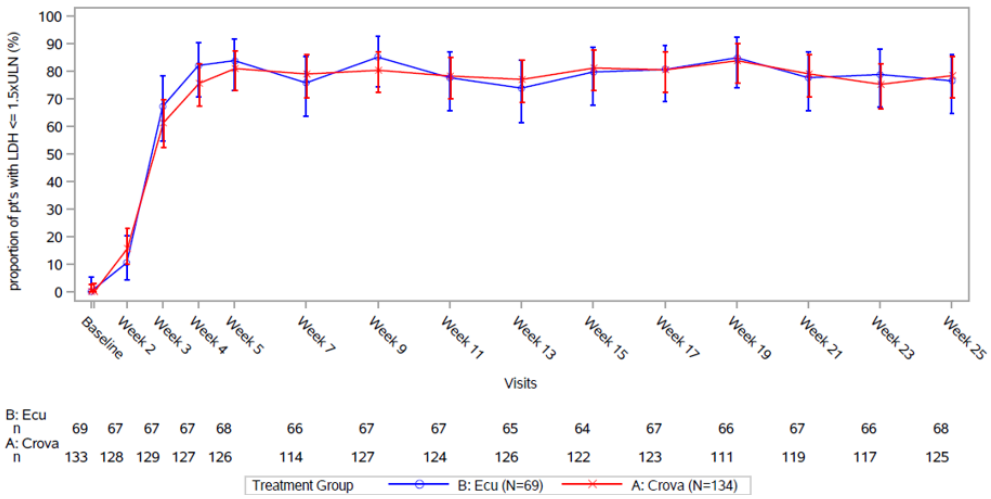
B.3.6.2 Pivotal study COMMODORE 2 efficacy results

In Study COMMODORE 2, crovalimab demonstrated non-inferiority to eculizumab for the co-primary efficacy endpoints of haemolysis control (defined as central LDH $\leq 1.5 \times$ ULN from Week 5 through Week 25), and transfusion avoidance (TA) (defined as the proportion of patients with TA from baseline to Week 25) (Table 9).

- The mean proportion of patients with haemolysis control as measured by central LDH $\leq 1.5 \times$ 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. The odds ratio for haemolysis control (crovalimab versus eculizumab) was 1.02, with a lower limit of the 95% CI of 0.57, which was higher than the pre-defined NIM of 0.2.
- 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. The difference in proportion of patients with TA (crovalimab − eculizumab) was −2.8%, with a lower limit of the 95% CI of −15.67%, which was higher than the pre-defined NIM of −20%.

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 6). Data available up to CCOD (16 November 2022) for the crovalimab arm indicated that the proportion of patients with haemolysis control remained stable after Week 25.

Figure 6: Proportion of patients (95% CI) with haemolysis control (central LDH ≤ 1.5 x ULN)



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.

Sensitivity analyses conducted for the co-primary efficacy endpoints showed consistent results with those from the main analyses, confirming the robustness of the results achieved for the co-primary efficacy endpoints haemolysis control and TA.

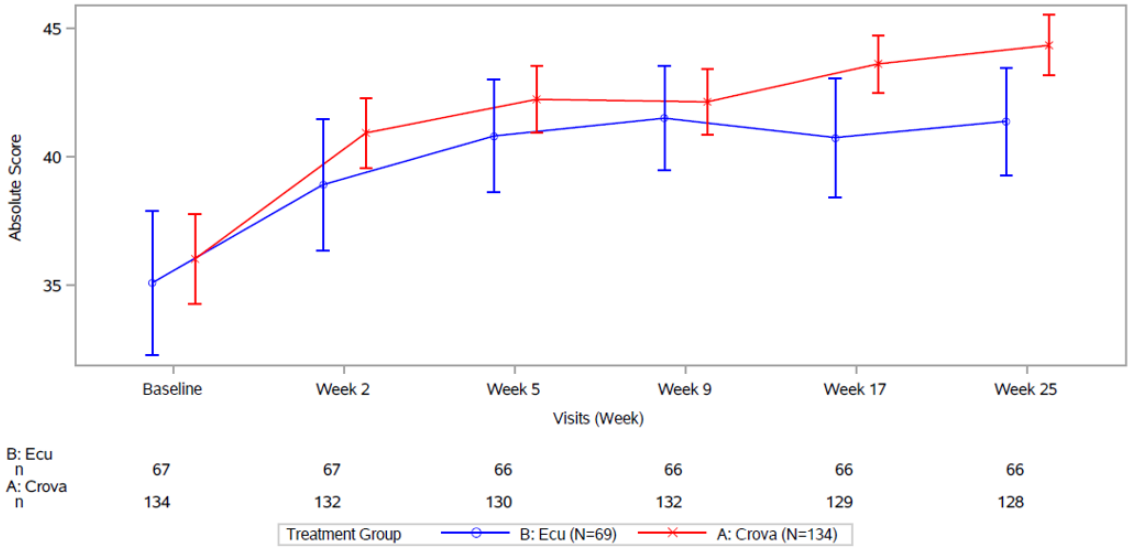
Non-inferiority was also demonstrated for the secondary efficacy endpoints of the proportion of patients with BTH from baseline through Week 25, and the proportion of patients who achieved haemoglobin stabilisation from baseline to Week 25.

- 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: 7.45, 25.50) in the eculizumab arm. The weighted difference in proportions of patients with BTH (crovalimab versus 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 NIM of 20%.
- The proportion of patients reaching haemoglobin stabilisation (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: 54.64, 71.45) in the crovalimab arm compared to

60.9% (95% CI: 48.35, 72.17) in the eculizumab arm. The difference in proportion of patients with haemoglobin stabilisation (crovalimab versus eculizumab) was 2.2%, and the lower limit of the 95% CI of – 11.4% was higher than the pre-defined NIM of – 20%.

Crovalimab also led to a rapid and clinically meaningful improvement (≥ 5 points) of fatigue as measured using the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue instrument from baseline to Week 25. Additionally, the adjusted mean change from baseline to Week 25 in FACIT-Fatigue was numerically higher for the crovalimab arm compared with the eculizumab arm (7.8 points [95% CI: 6.5, 9.1] vs 5.2 points [95% CI: 3.4, 6.9], respectively). (Figure 7 and Table 9). Due to the break in the statistical testing hierarchy non-inferiority testing for FACIT Fatigue was not performed and the results are descriptive.

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.

A graphical representation of the results of the co-primary and secondary efficacy endpoints is shown in Figure 8.

Consistent treatment benefit from crovalimab treatment was also observed in patients who switched from eculizumab to crovalimab in the crovalimab extension period and completed at least 24 weeks of crovalimab treatment (Arm B switch patients). Furthermore, the treatment

benefit of crovalimab observed in paediatric patients was comparable to that of adult patients with PNH in the COMMODORE 2 study (see Section B.3.7).

Table 9: Overview of co-primary and secondary efficacy endpoint results (COMMODORE 2 primary analysis population)

	Eculizumab N = 69	Crovalimab N = 134
Co-Primary Efficacy Endpoints		
Mean Proportion of Patients with Haemolysis Control from Week 5 through Week 25		
Mean Proportion of Patients Achieving Controlled Haemolysis (95% CI)	79.0% (69.66, 85.99)	79.3% (72.86%, 84.48)
Odds Ratio (95% CI)	1.02 (0.57, 1.82)[a]	
	NIM for lower 95% CI limit = 0.2	
Proportion of Patients with Transfusion Avoidance from Baseline through Week 25[b]		
Patients with TA, n (%)	47 (68.1%)	88 (65.7%)
Weighted Difference in Proportion (95% CI)	– 2.8% (– 15.67, 11.14)	
	NIM for lower 95% CI limit = – 20%	
Secondary Efficacy Endpoints		
Proportion of Patients with Breakthrough Haemolysis from Baseline through Week 25[c]		
Patients with at least one BTH, n (%)	10 (14.5%)	14 (10.4%)
Weighted Difference in Proportion (95% CI)	– 3.9% (– 14.82, 5.26)	
	NIM for upper 95% CI limit = 20%	
Proportion of Patients with Stabilised Haemoglobin from Baseline through Week 25[d]		
Patients with Haemoglobin Stabilisation, n (%)	42 (60.9%)	85 (63.4%)
Weighted Difference in Proportion (95% CI)	2.2% (– 11.37, 16.31)	
	NIM for lower 95% CI limit = –20%	
Adjusted Mean Change from Baseline to Week 25 in FACIT-Fatigue[e,f]		
Adjusted Mean Change (SE)	5.2 (0.88)	7.8 (0.66)
Difference in Adjusted Mean (95% CI)	2.6 (0.68, 4.60)	

BTH = breakthrough haemolysis; CI = Confidence Interval; FACIT = Functional Assessment of Chronic Illness Therapy–Fatigue; LDH = lactate dehydrogenase; NIM = non-inferiority margin; TA = transfusion avoidance; ULN = Upper Limit Normal.

[a] An odds ratio > 1 favors crovalimab.

[b] Note, 1 patient in the crovalimab arm discontinued the study prior to Week 25 without a transfusion and was conservatively assumed to have had a transfusion.

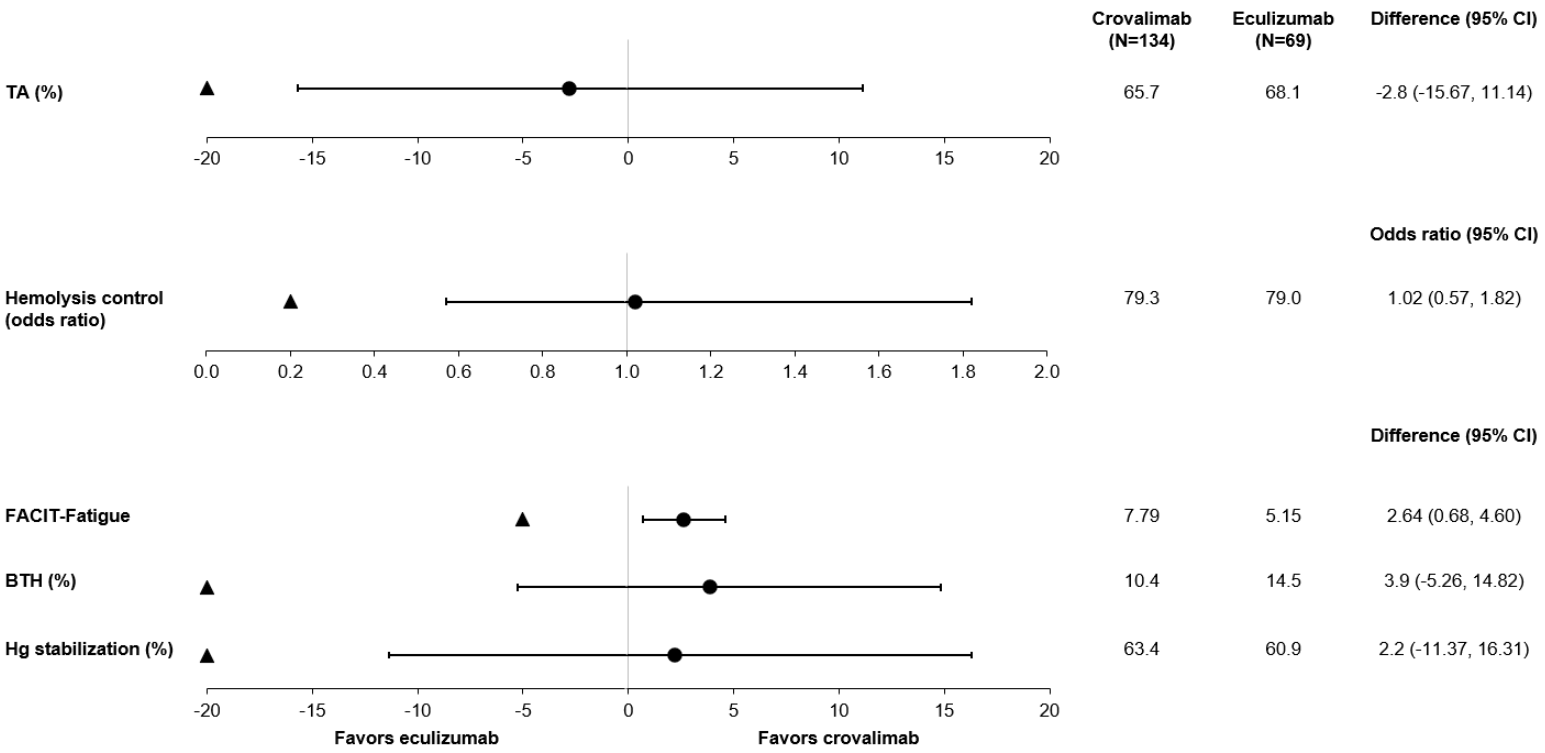
[c] Note, 4 patients in the crovalimab arm and 1 patient in the eculizumab arm discontinued the study prior to Week 25 without a per protocol BTH and were conservatively assumed to have had a BTH.

[d] Note, 1 patient in the crovalimab arm discontinued the study prior to Week 25 with haemoglobin stabilisation and was conservatively assumed to have had a haemoglobin stabilisation.

[e] FACIT-Fatigue was assessed in adult patients only (crovalimab: 134 adult patients and eculizumab: 67 adult patients). The total FACIT-Fatigue score ranges from 0 to 52 with higher scores indicating lower fatigue severity. The threshold for a clinically meaningful improvement is ≥ 5 points (65).

[f] Non-inferiority testing of FACIT-Fatigue was planned to occur only after successful superiority testing of all the other co-primary and secondary efficacy endpoints. Given the outcome of this superiority testing, the comparative results of FACIT-Fatigue are descriptive only.

Figure 8: Graphical representation of co-primary and secondary efficacy endpoint results (COMMODORE 2 primary analysis population)



BTH = breakthrough haemolysis; CI = confidence interval; FACIT-Fatigue = Functional Assessment of Chronic Illness Therapy Fatigue; Hg = haemoglobin; TA = transfusion avoidance.

Note: The black triangles indicate the pre-defined non-inferiority margins. Black dots indicate point estimates, and the lines indicate the respective 95% CIs. The point estimate (95% CI) for the difference in the proportions of patients with BTH, as well as the respective pre-defined non-inferiority margin, is presented in reverse to the presentation in Table 9, as more BTH events are clinically worse, so the presented data favors crovalimab.

B.3.6.3 Supportive study COMMODORE 1 efficacy results

In Study COMMODORE 1, at the time of the clinical cutoff date for the primary analysis, crovalimab and eculizumab showed in a randomised comparison similar exploratory efficacy results for haemolysis control (defined as central LDH $\leq 1.5 \times$ ULN from baseline through Week 25), TA (from baseline through Week 25), and BTH (from baseline through Week 25) (Table 10). The proportion of patients achieving stabilised 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.

Overall, patients who switched from eculizumab to crovalimab (Arm B Switch patients) in the crovalimab extension period maintained disease control, assessed based on exploratory efficacy endpoints including haemolysis control, TA, BTH, haemoglobin stabilisation, and FACIT-Fatigue.

Efficacy results in cohorts of clinical interest

[redacted]

[redacted]

Table 10: Overview of exploratory efficacy results from Study COMMODORE 1 (24-Week efficacy population)

	Eculizumab N=37	Crovalimab N=39
Mean Proportion of Patients with Haemolysis Control from Baseline through Week 25		
Mean Proportion of Patients Achieving Controlled Haemolysis (95% CI)	93.7% (87.26, 97.04)	92.9% (86.62, 96.39)
Odds Ratio (95% CI)	0.88 (0.28, 2.77)	
Proportion of Patients with Transfusion Avoidance from Baseline through Week 25[a]		
Patients with TA, n (%)	29 (78.4%)	31 (79.5%)
Weighted Difference in Proportion, % (95% CI)	1.8 (-16.67, 19.94)	
Proportion of Patients with Breakthrough Haemolysis from Baseline through Week 25[b]		
Patients with at least one BTH, n (%)	5 (13.5%)	4 (10.3%)
Weighted Difference in Proportion, (95% CI)	-3.5 (-19.20, 11.68)	
Proportion of Patients with Stabilised Haemoglobin from Baseline through Week 25[c]		
Patients with Stabilised Haemoglobin, n (%)	26 (70.3%)	23 (59.0%)
Weighted Difference in Proportion (95% CI)	-10.8 (-30.84, 10.39)	
Adjusted Mean Change from Baseline to Week 25 in FACIT Fatigue scores[d]		
Adjusted Mean Change (SE)	-2.6 (1.37)	1.1 (1.29)
Difference in Adjusted Mean (95% CI)	3.71 (0.05, 7.36)	

BTH=breakthrough haemolysis; CI=Confidence Interval; FACIT=Functional Assessment of Chronic Illness Therapy–Fatigue; LDH=lactate dehydrogenase; ULN=Upper Limit Normal; SE=Standard Error; TA=Transfusion Avoidance.

[a] Note, 1 patient in the eculizumab arm discontinued treatment before Week 25 without a transfusion and was conservatively assumed to have had a transfusion.

[b] Note, 2 patients in the eculizumab arm without a BTH event discontinued treatment before Week 25 and were therefore conservatively assumed as having a BTH event.

[c] Note, 1 patient in the eculizumab arm discontinued treatment before Week 25 and was conservatively assumed as not having stabilised haemoglobin.

[d] FACIT-Fatigue scores range from 0–52, with higher scores indicating lower fatigue. FACIT-fatigue questionnaires were collected in adult patients only.

B.3.6.4 Key exploratory efficacy endpoints across COMMODORE 2 and 1

Several exploratory endpoints were evaluated across COMMODORE 2 and COMMDORE 1, this subsection briefly discusses the results for the key exploratory endpoints. (Further details are described in Appendix D.6.6).

Major adverse vascular events (MAVEs)

MAVEs were identified based on protocol-defined events. One patient treated with crovalimab reported a MAVE event (fatal AE of myocardial infarction considered unrelated to study treatment in the randomised crovalimab arm of study COMMODORE 2). Across the randomised studies COMMODORE 2 and COMMODRE 1, two patients treated with eculizumab reported a MAVE (AEs of transient ischemic attack in the eculizumab arms in each study).

Patient-reported outcomes

EORTC QLQ-C30

In addition to patient-reported fatigue using the FACIT-Fatigue further support for the efficacy of crovalimab from the patient perspective was shown by results from the European Organisation for Research and Treatment of Cancer Quality of Life-Core 30 Questionnaire (EORTC QLQ-C30) physical functioning, role functioning, and global health status/quality of life (GHS/QoL) scales (administered in all studies).

Treatment-naive patients in study COMMODORE 2 showed rapid improvement from moderate baseline levels of physical functioning, role functioning and GHS/QoL, with mean values at Week 25 similar to normative population values in both the crovalimab and eculizumab arms (66, 67). While there are no established thresholds for clinically meaningful improvements in EORTC QLQ-C30 scores for PNH patients specifically, the Week 25 improvements from baseline for all examined domains exceeded the thresholds that are generally accepted for cancer patients, which is a 10−point improvement across domains (68). The improvements likewise exceed more recently published domain-specific thresholds from a meta-analysis in cancer patients (69), in which 7 points in physical functioning, 12 points in role functioning, and 8 points in GHS/QoL were considered indicative of clinically meaningful improvement.

In switch patients (randomised arms of study COMMODORE 1), all examined domains remained relatively stable through Week 25. Arm B switch patients (studies COMMODORE

2 and COMMODORE 1) likewise remained relatively stable in all examined domains from switch baseline up to switch Week 25.

EORTC IL40

Relevant PNH symptoms (i.e., dyspnoea, dysphagia, chest pain, headaches, abdominal pain, and erectile dysfunction in males) from the EORTC Item Library were assessed in studies COMMODORE 2 and COMMODRE 1 (adult patients).

From baseline through Week 25, these symptoms improved in treatment-naive patients of study COMMODORE 2 for both treatment arms. The symptoms remained relatively stable from baseline through Week 25 in both treatment arms of study COMMODORE 1 (switch patients) except for erectile dysfunction, which showed a small worsening. All symptoms remained stable from switch baseline through switch Week 25 for Arm B switch patients of studies COMMODORE 2 and COMMODORE 1.

B.3.6.5 Treatment satisfaction and patient preference

Patient treatment satisfaction was assessed using the Treatment Satisfaction Questionnaire for Medication-9 (TSQM-9) in adult patients in all arms of COMMODORE 2 and COMMODORE 1. While the perceived efficacy and overall treatment satisfaction was similar between the randomised arms, patient satisfaction with respect to treatment convenience was higher in the crovalimab arm.

The convenience of crovalimab treatment is also reflected in patients' preference for crovalimab over eculizumab based on the Patient Preference Questionnaire in adult switch patients of Studies COMMODORE 2 (Arm B switch patients) and COMMODORE 1 (randomised crovalimab arm and Arm B switch patients). In both studies, the majority of patients who had at least 17 weeks of treatment with crovalimab treatment preferred it to eculizumab (range across studies and arms: 84.2% – 96.4%). Top reasons for preference for crovalimab included easier treatment administration, fewer hospital visits associated with treatment, shorter duration of treatment administration, and better quality of life.

B.3.7 Subgroup analysis

The robustness of the treatment effect of crovalimab versus eculizumab in terms of the co-primary efficacy endpoints of haemolysis control and TA was also confirmed in subgroup analyses performed in pre-defined subgroups based on key baseline demographic and disease characteristics (see Appendix E for details).

B.3.7.1 Efficacy in paediatric patients

This section provides a summary of efficacy results of paediatric patients enrolled in COMMORODE 1, COMMODRE 2 and also COMMODORE 3 (see Appendix I) which we include here for data completeness given the low patient numbers.

[redacted]

Haemolysis control in paediatric patients

[redacted]

Transfusion avoidance and haemoglobin stabilisation in paediatric patients

[redacted]

Breakthrough haemolysis in paediatric patients

[redacted]

(Appendix D.4.2.2 provides critical discussion on paediatric patients in PNH).

B.3.8 Meta-analysis

As no further Phase III RCTs studying the efficacy and safety of crovalimab for PNH were found, no meta-analysis was conducted.

B.3.9 Indirect and mixed treatment comparisons

See appendix D for full details of the methodology for the indirect comparison or mixed treatment comparison.

The sections below present indirect treatment comparison (ITC) results for the pooled C5-naïve and C5-experienced populations, as well as the subgroup separate C5-naïve and C5-experienced populations. Further details of the subgroups results can be found in the appendix D in section 6.1.3 (C5-naïve) and section 6.3 (C5 experienced). Results are presented by endpoint and using the random effects model as base case as the absence of between study heterogeneity is unlikely. Fixed effects model results are presented in appendix D.

In some instances, the clinical study reports for COMMODORE 1 and 2 conservatively assumed patients to have an event if they discontinued treatment before week 25 as outlined in Table 11. Given that this was not necessarily conducted similarly in studies reporting results for indirect comparators, those events were not included in the NMA.

Table 11: Number of patients who discontinued treatment before week 25 without the event of interest and were conservatively assumed to have the event in the CSR

Endpoint	Eculizumab		Crovalimab	
	COMMODORE 1	COMMODORE 2	COMMODORE 1	COMMODORE 2
Transfusion avoidance	1	0	0	1
Breakthrough haemolysis	2	1	0	4
Haemoglobin stabilisation	1	0	0	1

B.3.9.1 ITC results

B.3.9.1.1 Transfusion avoidance

C5 naive and experienced population pooled

Figure 9: Network for transfusion avoidance based on the % of patients with event -

C5 naive and experienced population pooled

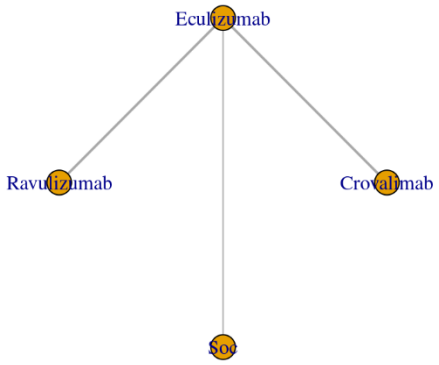


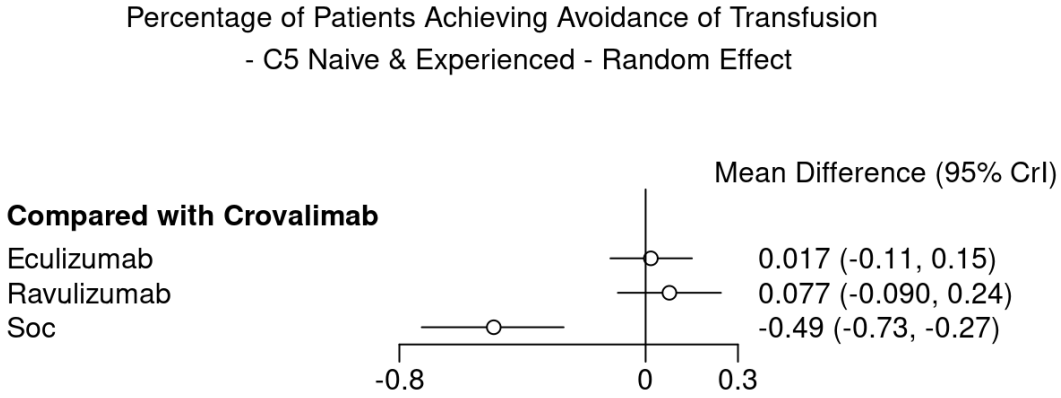
Table 12: Input data – transfusion avoidance - C5 naive and experienced population pooled

Study ID	Population	Treatment	Mean	Standard Error
Study_301	Naive	Ravulizumab	0.736	0.0394388
Study_301	Naive	Eculizumab	0.661	0.0430357
TRIUMPH	Naive	Eculizumab	0.51	0.0784643
TRIUMPH	Naive	Soc	0	0.0249843
COMMODORE_2	Naive	Crovalimab	0.6641791	0.0421422
COMMODORE_2	Naive	Eculizumab	0.681	0.0583163
Study 302	Experienced	Ravulizumab	0.876	0.0334184
Study 302	Experienced	Eculizumab	0.827	0.0382653
COMMODORE_1	Experienced	Crovalimab	0.7948718	0.0690561
COMMODORE_1	Experienced	Eculizumab	0.8108108	0.06927

As presented in Figure 10, the point estimate for the percentage of patients with an event was 7.7 percentage points higher for ravulizumab compared to crovalimab with credible intervals including zero (95% CrI, -0.09, 0.24). The probability of crovalimab being non-inferior to eculizumab and ravulizumab using the 20% threshold applied in COMMODORE 1 and 2 was 99% and 93% respectively. A statistically higher percentage of patients achieved transfusion avoidance on crovalimab compared to standard of care (95% CrI, -0.73, -0.27). The between study heterogeneity estimate (tau) had a median of 0.04 and was close to the prior.

Figure 10: Forest plot - percentage of patients with transfusion avoidance – C5 naïve

and experienced population – random effects

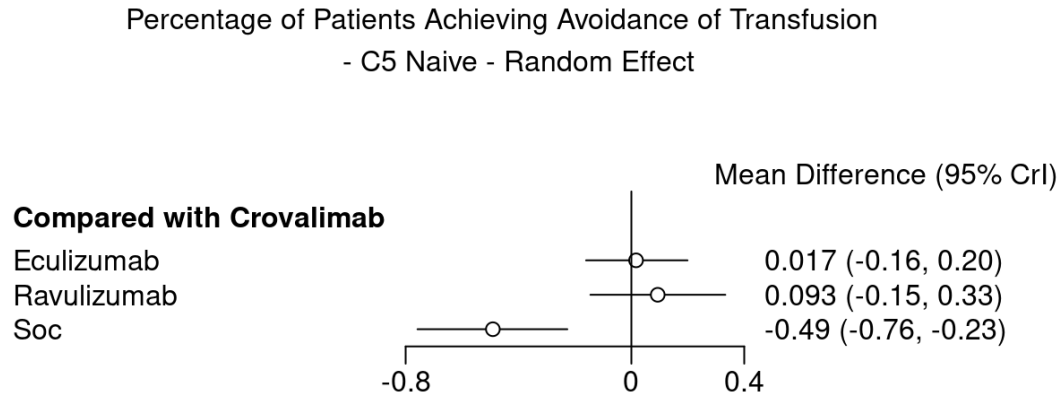


Subgroup results

The random effects model results for C5 naïve (Figure 11) and C5-experienced (Figure 12) populations were consistent with the base case pooled analysis (Figure 10). The probability for crovalimab being non-inferior to ravulizumab was at least 82% (C5 naive analysis, RE model).

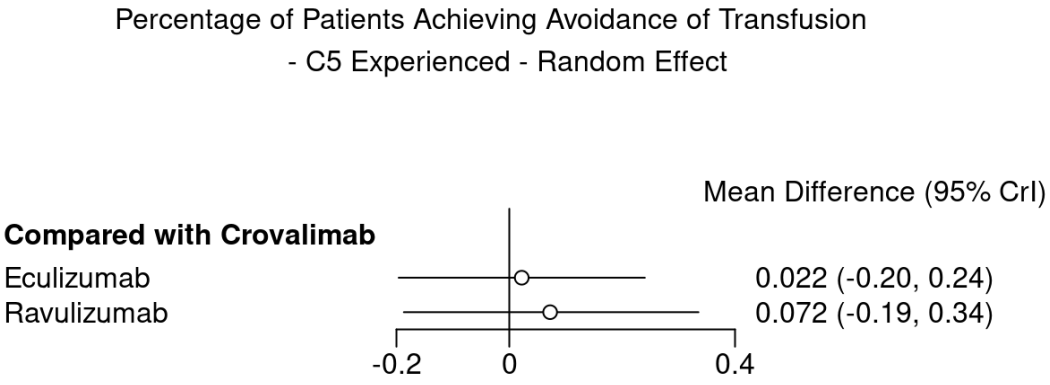
C5 naïve population

Figure 11: Forest plot - percentage of patients with transfusion avoidance – C5 naïve population – random effects



C5 experienced population

Figure 12: Forest plot - percentage of patients with transfusion avoidance – C5 experienced population – random effects



B.3.9.1.2 Breakthrough haemolysis

C5 naive and experienced population pooled

Figure 13: Network for breakthrough haemolysis based on the % of patients with event - C5 naive and experienced population pooled

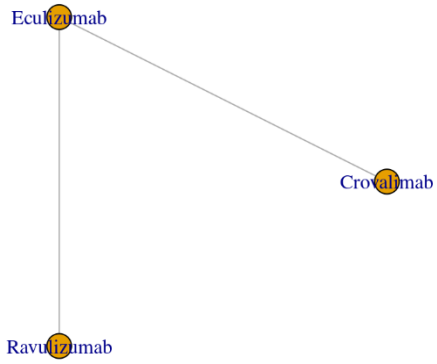


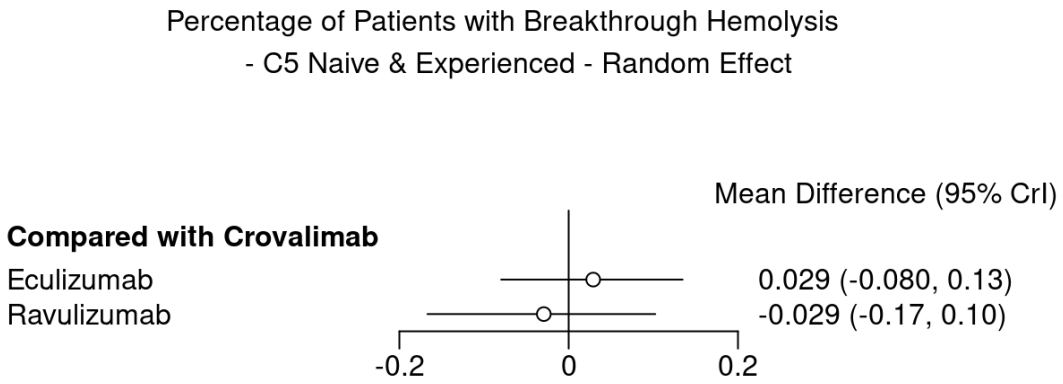
Table 13: Input data – percentage of patients with breakthrough haemolysis - C5 naive and experienced population pooled

Study ID	Population	Treatment	Mean	Standard Error
Study_301	Naive	Ravulizumab	0.04	0.01755
Study_301	Naive	Eculizumab	0.107	0.02814
COMMODORE_2	Naïve	Crovalimab	0.07463	0.02503
COMMODORE_2	Naive	Eculizumab	0.13043	0.04418
Study 302	Experienced	Ravulizumab	0	0.00944
Study 302	Experienced	Eculizumab	0.051	0.025
COMMODORE_1	Experienced	Crovalimab	0.10256	0.05566

COMMODORE_1	Experienced	Eculizumab	0.08108	0.05333

As presented in Figure 14, the point estimate for the percentage of patients with an event was 2.9 percentage points higher for crovalimab compared to ravulizumab with 95% credible intervals including zero (95% CrI, -0.17, 0.10). The probability of crovalimab being non-inferior to eculizumab and ravulizumab using the 20% threshold applied in COMMODORE 1 and 2 was 100% and 99% respectively. The between study heterogeneity estimate (tau) had a median of 0.04 and was close to the prior.

Figure 14: Forest plot - percentage of patients with breakthrough haemolysis – C5 naïve and experienced population – random effects

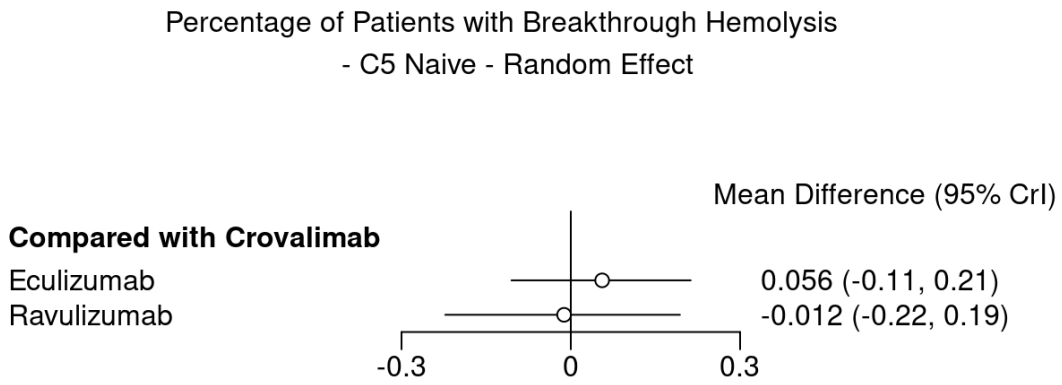


Subgroup results

The random effects model results for C5 naïve (Figure 15) and C5-experienced (Figure 16) populations were consistent with the base case pooled analysis (Figure 14). The probability for crovalimab being non-inferior to ravulizumab was at least 88% (C5 experienced analysis, RE model).

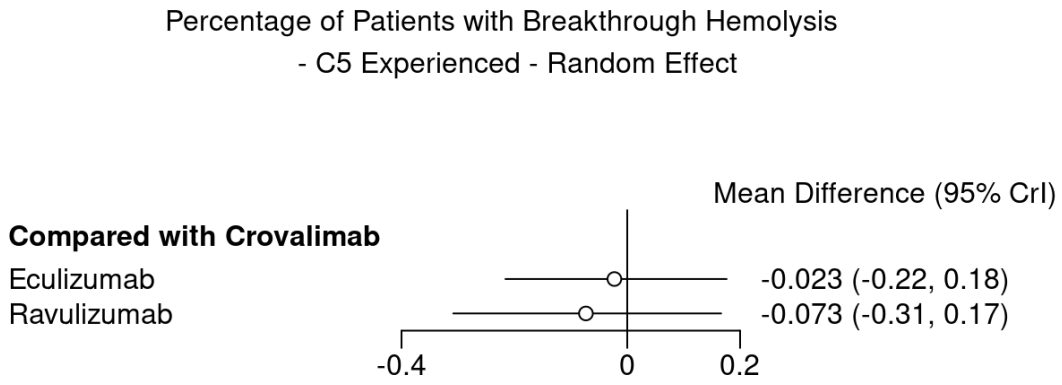
C5 naïve population

Figure 15: Forest plot - percentage of patients with breakthrough haemolysis – C5 naïve population – random effects



C5 experienced population

Figure 16: Forest plot - percentage of patients with breakthrough haemolysis – C5 experienced population – random effects



B.3.9.1.3 Haemoglobin stabilisation

C5 naive and experienced population pooled

Figure 17: Network for haemoglobin stabilisation based on the % of patients with event - C5 naive and experienced population pooled

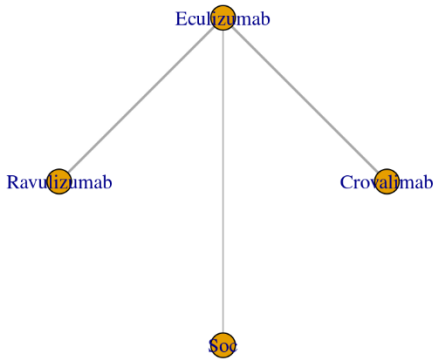


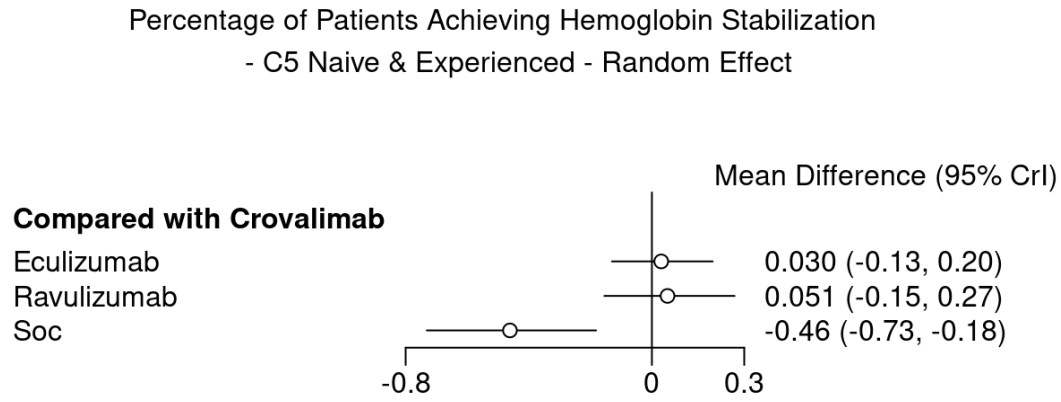
Table 14: Input data – percentage of patients with haemoglobin stabilisation - C5 naive and experienced population pooled

Study ID	Population	Treatment	Mean	Standard Error
Study_301	Naive	Ravulizumab	0.68	0.0417347
Study_301	Naive	Eculizumab	0.645	0.0435204
TRIUMPH	Naive	Eculizumab	0.49	0.0784643
TRIUMPH	Naive	Soc	0	0.0249843
COMMODORE_2	Naive	Crovalimab	0.641791	0.0427374
COMMODORE_2	Naive	Eculizumab	0.609	0.0607653
Study 302	Experienced	Ravulizumab	0.763	0.0451854
Study 302	Experienced	Eculizumab	0.755	0.0453943
COMMODORE_1	Experienced	Crovalimab	0.5897436	0.081199
COMMODORE_1	Experienced	Eculizumab	0.7297297	0.0765695

As presented in Figure 18, the point estimate for the percentage of patients with an event was 5.1 percentage points higher for ravulizumab compared to crovalimab with 95% credible intervals including zero (95% CrI, -0.15, 0.27). A statistically higher percentage of patients achieved haemoglobin stabilisation on crovalimab compared to standard of care (95% CrI, -0.73, -0.18). The probability of crovalimab being non-inferior to eculizumab and ravulizumab using the 20% threshold applied in COMMODORE 1 and 2 was 98% and 92% respectively. The between study heterogeneity estimate (tau) had a median of 0.06 and was close to the prior.

Figure 18: Forest plot - percentage of patients with haemoglobin stabilisation – C5

naïve and experienced population – random effects

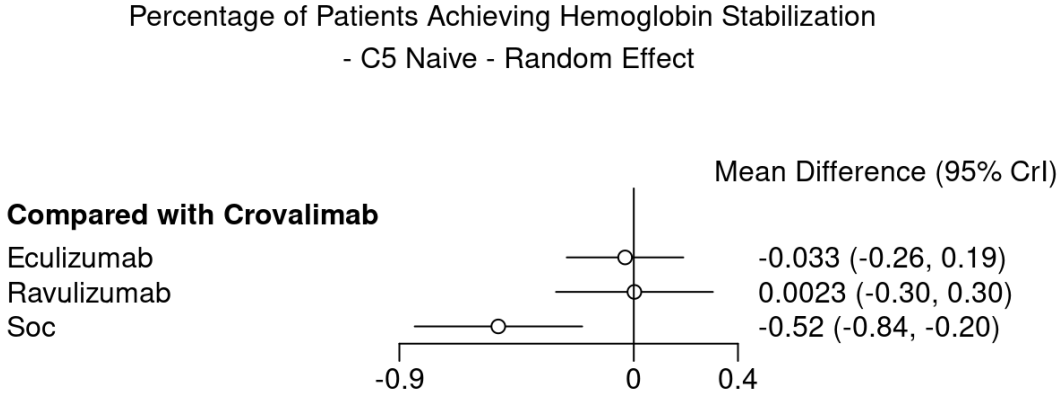


Subgroup results

The random effects model results for C5 naïve (Figure 17) and C5-experienced (Figure 18) populations were consistent with the base case pooled analysis (Figure 16). The probability for crovalimab being non-inferior to ravulizumab was at least 63% (C5 experienced analysis, RE model).

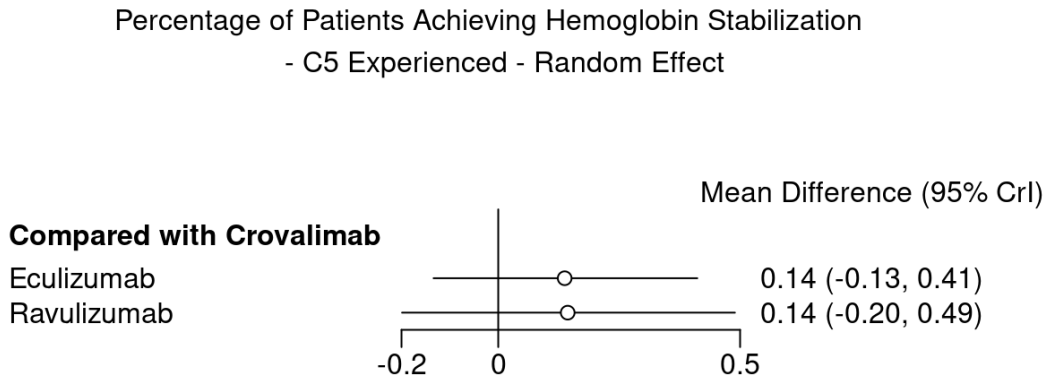
C5 naïve population

Figure 19: Forest plot - percentage of patients with haemoglobin stabilisation – C5 naïve population – random effects



C5 experienced population

Figure 20: Forest plot - percentage of patients with haemoglobin stabilisation – C5 experienced population – random effects



B.3.9.1.4 Number of packed red blood cell transfusions (PRBCT)

C5 naive and experienced population pooled

Figure 21: Network for number of packed red blood cell transfusions - C5 naive and experienced population pooled

Eculizumab_BS = eculizumab biosimilar

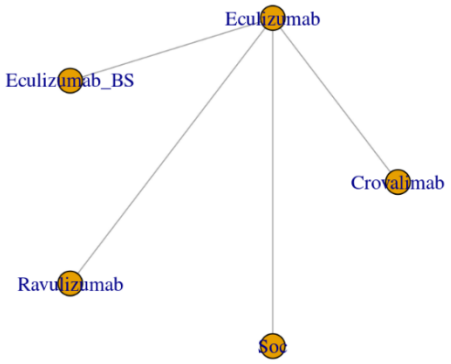


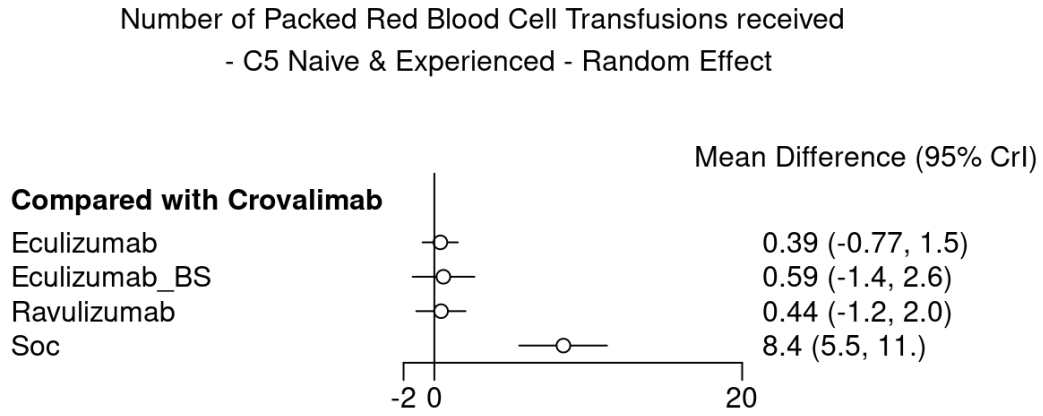
Table 15: Input data – number of packed red blood cell transfusions - C5 naive and

experienced population pooled

Study ID	Population	Treatment	Mean	Standard Error
Study_301	Naive	Ravulizumab	4.8	0.0408
Study_301	Naive	Eculizumab	5.6	0.0487603
TRIUMPH	Naive	Eculizumab	3	0.7
TRIUMPH	Naive	Soc	11	0.8
SB12-3003	Naive	Eculizumab_BS	1.1	0.155
SB12-3003	Naive	Eculizumab	0.9	0.0824
COMMODORE_2	Naive	Crovalimab	2.33	0.0449254
COMMODORE_2	Naive	Eculizumab	2.2	0.07
Study 302	Experienced	Ravulizumab	4.3	0.0490722
Study 302	Experienced	Eculizumab	3.4	0.0307143
COMMODORE_1	Experienced	Crovalimab	0.97	0.0576923
COMMODORE_1	Experienced	Eculizumab	1.89	0.1105405

As presented in Figure 22, the point estimate for the number of PRBCTs was 0.44 higher for ravulizumab compared to crovalimab with 95% credible intervals including zero (95% CrI, -1.2, 2.0). A statistically higher number of transfusions was given for patients on standard of care compared to crovalimab (95% CrI, 5.5, 11.0). The probability of crovalimab being associated with fewer transfusions compared to eculizumab and ravulizumab was 77% and 72% respectively. The between study heterogeneity estimate (tau) had a median of 0.72 and was close to the prior.

Figure 22: Forest plot - number of packed red blood cell transfusions – C5 naïve and experienced population – random effects



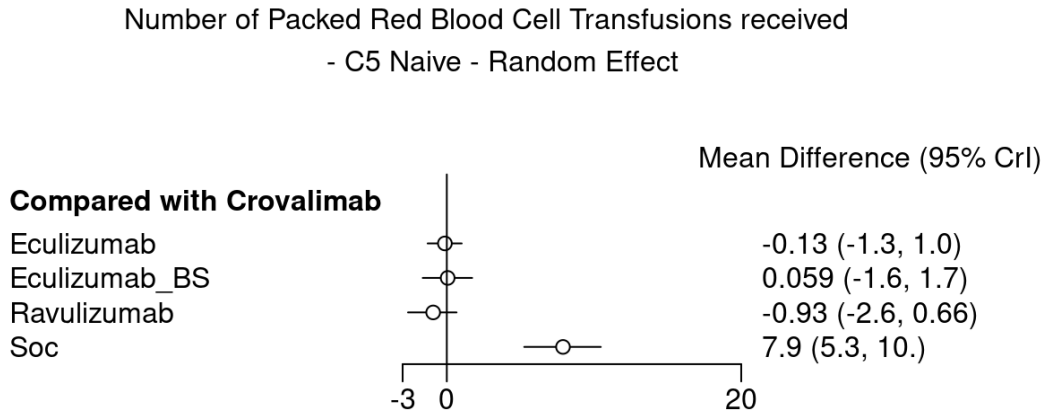
Subgroup results

The random effects model results for C5 naïve (Figure 23) and C5-experienced (Figure 24) populations were consistent with the base case pooled analysis (Figure 22).

C5 naïve population

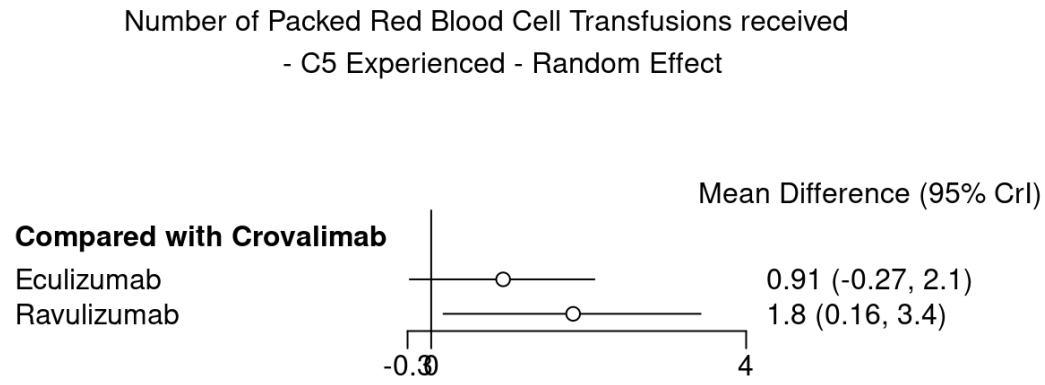
Figure 23: Forest plot - number of packed red blood cell transfusions– C5 naïve

population – random effects



C5 experienced population

Figure 24: Forest plot - number of packed red blood cell transfusions– C5 experienced population – random effects



B.3.9.1.5 FACIT fatigue score

C5 naive and experienced population pooled

Figure 25: Network for FACIT fatigue score change from baseline - C5 naive and experienced population pooled

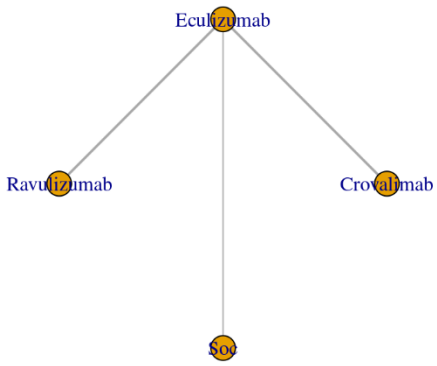
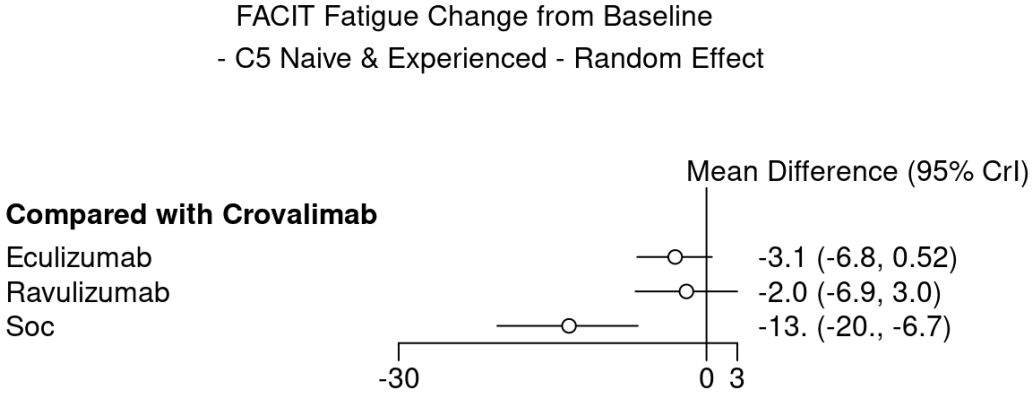


Table 16: Input data – FACIT fatigue score - C5 naive and experienced population pooled

Study ID	Population	Treatment	Mean	Standard Error
Study_301	Naive	Ravulizumab	7.07	0.7780612
Study_301	Naive	Eculizumab	6.4	0.7933673
TRIUMPH	Naive	Eculizumab	6.4	1.2
TRIUMPH	Naive	Soc	-4	1.7
COMMODORE_2	Naive	Crovalimab	7.79	0.877
COMMODORE_2	Naive	Eculizumab	5.15	0.88
Study 302	Experienced	Ravulizumab	2	0.7142857
Study 302	Experienced	Eculizumab	0.54	0.6887755
COMMODORE_1	Experienced	Crovalimab	1.09	1.285
COMMODORE_1	Experienced	Eculizumab	-2.61	1.373

As presented in , the point estimate for the FACIT fatigue score change from baseline was two points smaller for ravulizumab compared to crovalimab with 95% credible intervals including zero (95% CrI, -6.9, 3.0). There was a statistically greater change from baseline for patients on crovalimab compared to standard of care (95% CrI, -10, -6.7). The probability of crovalimab being associated with a greater improvement in the FACIT fatigue score compared to eculizumab and ravulizumab was 95% and 81% respectively. The between study heterogeneity estimate (tau) had a median of 1.73 and was close to the prior.

Figure 26: Forest plot – change in FACIT fatigue score from baseline – C5 naïve and experienced population – random effects

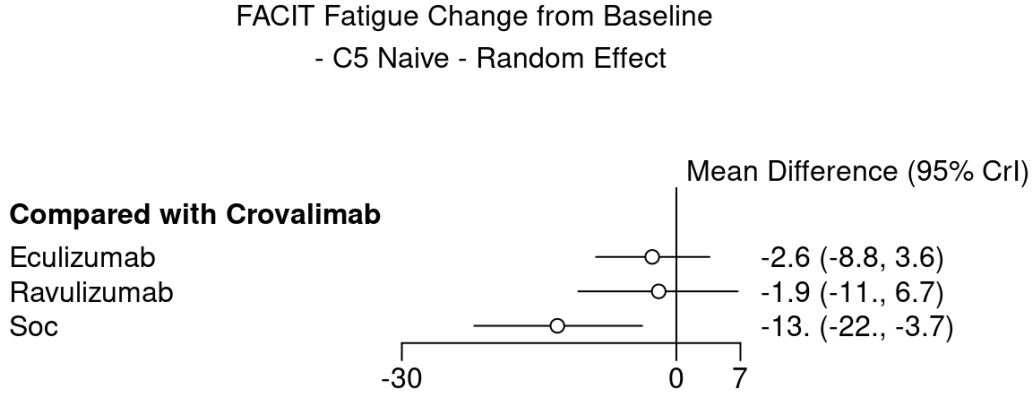


Subgroup results

The random effects model results for C5 naïve (Figure 27) and C5-experienced (Figure 28) populations were consistent with the base case pooled analysis (Figure 26).

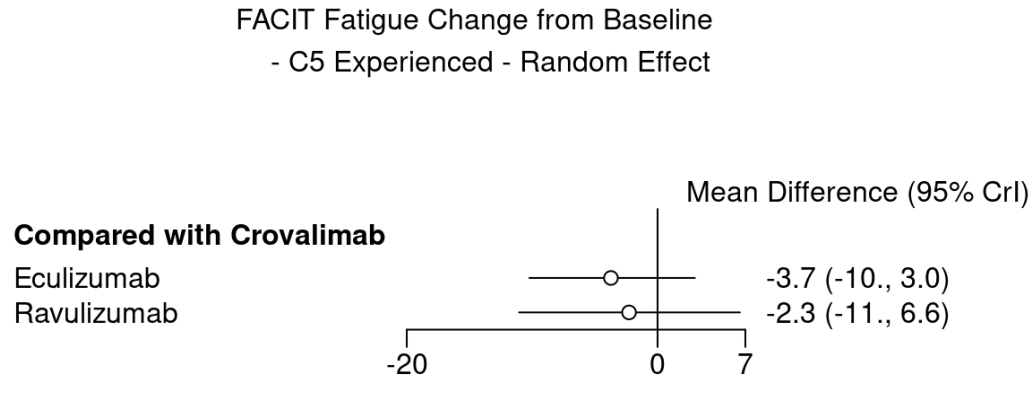
C5 naïve population

Figure 27: Forest plot – FACIT fatigue score change from baseline – C5 naïve population – random effects



C5 experienced population

Figure 28: Forest plot – FACIT fatigue score change from baseline – C5 experienced population – random effects



B.3.9.1.6 Adverse events

C5 naive and experienced population pooled

Figure 29: Network for all adverse events - C5 naive and experienced population pooled

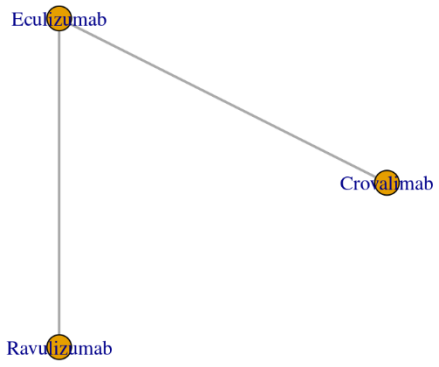


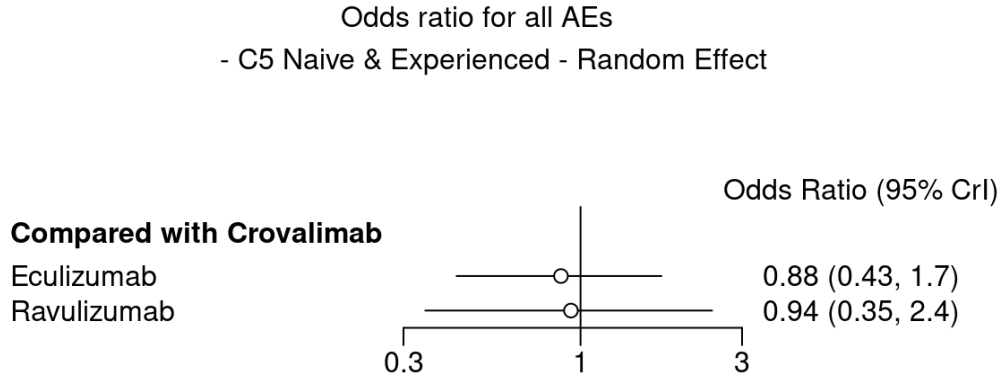
Table 17: Input data – all adverse events - C5 naive and experienced population pooled

Study ID	Population	Treatment	Sample size	Responders
Study_301 Study_301	Naive Naive	Ravulizumab Eculizumab	125 121	110 105
COMMODORE_2	Naive	Crovalimab	135	105
COMMODORE_2	Naive	Eculizumab	69	55
Study 302	Experienced	Ravulizumab	97	85
Study 302	Experienced	Eculizumab	98	86
COMMODORE_1	Experienced	Crovalimab	44	34
COMMODORE_1	Experienced	Eculizumab	42	28

As presented in Figure 30, the point estimate for the all adverse event odds ratio for ravulizumab was 0.94 compared to crovalimab with 95% credible intervals including zero (95% CI, 0.35, 2.4). Odds ratios smaller than one indicate the odds for experiencing the event are lower for the comparator. The between study heterogeneity estimate (tau) had a median of 0.163.

Figure 30: Forest plot – all adverse events – C5 naïve and experienced population –

random effects

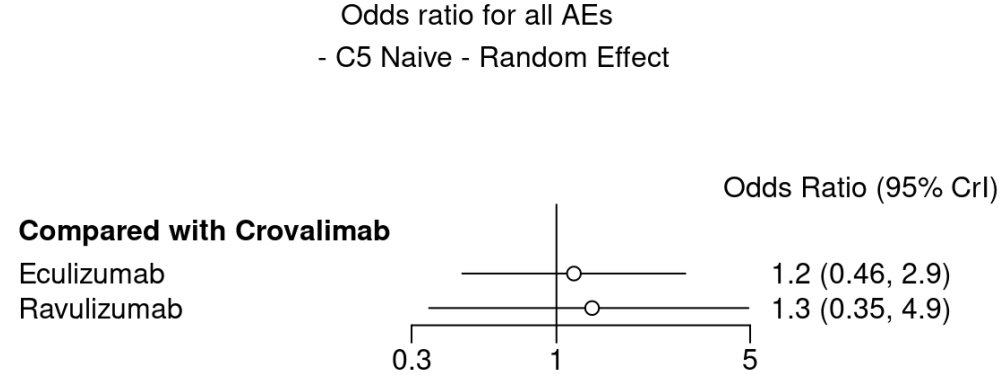


Subgroup results

The random effects model results for C5 naïve (Figure 31) and C5-experienced (Figure 32) populations were consistent with the base case pooled analysis (Figure 30). In the C5 experienced population, some safety parameters had a higher incidence rate in the crovalimab arm compared to the eculizumab arm. However, the events that underlie these imbalances were either reflective of risks unique to the crovalimab arm (Type III hypersensitivity and injection related reaction due to the subcutaneous administration), were less likely to occur in the eculizumab arm as patients start the study stabilised on eculizumab treatment, or relate to a broad set of preferred terms which do not indicate a specific safety concern associated with crovalimab.

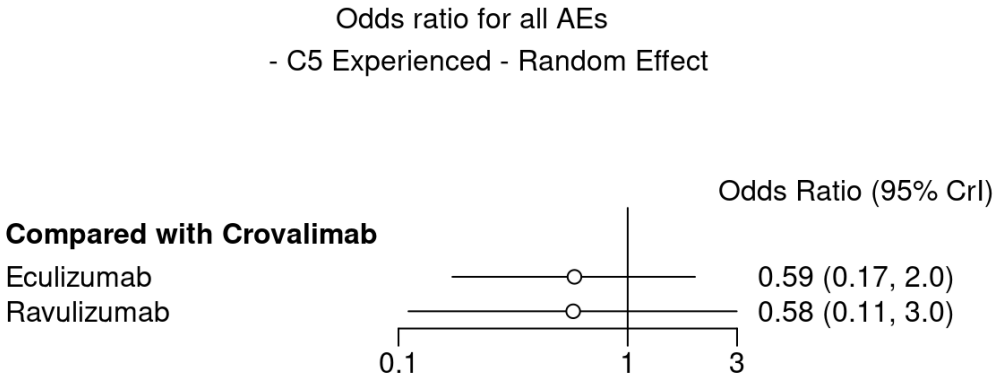
C5 naïve population

Figure 31: Forest plot – all adverse events – C5 naïve population – random effects



C5 experienced population

Figure 32: Forest plot – all adverse events – C5 experienced population – random effects



B.3.9.2 Conclusions of the indirect treatment comparisons

The network meta-analysis shows that there is a high probability that crovalimab is associated with non-inferior efficacy outcomes compared to eculizumab and ravulizumab across key clinical endpoints such as transfusion avoidance, breakthrough haemolysis and haemoglobin stabilisation. The analysis also demonstrates that the safety profile for crovalimab is comparable to eculizumab and ravulizumab, which have well-established safety profiles. Additionally, the results indicate that there is a high probability that crovalimab is associated with better patient reported outcomes compared to other C5-inhibitors measured by the FACIT fatigue score. Non-inferior efficacy and safety compared against other C5 inhibitors, suggests it is reasonable to assume equivalent efficacy and safety between crovalimab, eculizumab and ravulizumab.

B.3.9.3 Uncertainties in the indirect treatment comparisons

The analysis was based on a small set of studies with a small sample size, which is typical in the setting of an ultra-rare disease such as PNH. Therefore, meaningfully informative priors were used to estimate between study heterogeneity in all analyses. It also does not allow forming a network with closed loops. Results should be interpreted accordingly.

Another possible limitation is the pooling of C5 pre-treated and naïve studies in one analysis. However, scenario analyses splitting those two population indicated consistent results.

B.3.10 Adverse reactions

B.3.10.1 Overall safety

In COMMODORE 2 the overall safety profile of crovalimab was consistent with the known safety profile of C5 inhibitors, and no additional safety concerns were identified. The safety results in the randomised 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.

In COMMODORE 1 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 the newly identified risk of transient immune complex reactions, which only occur in patients who switch between crovalimab and another C5 inhibitors (discussed below).

B.3.10.2 Safety in COMMODORE 2

An overview of the safety results in the randomised safety population (crovalimab, 135 patients; eculizumab, 69 patients) during the primary safety period is provided in Table 18.

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].

Adverse events in COMMODORE 2

The proportion of patients with at least one AE was comparable between the crovalimab (77.8%) and the eculizumab (79.7%) arms (Table 18). Infusion-related reaction was the most commonly reported AE by PT in both the crovalimab (15.6%) and eculizumab (13.0%) arms (Table 19).

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%), hypokalaemia (11.1% and 13.0%) and hypocalcaemia (5.9% and 10.1%). The 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 frequently reported AEs in the crovalimab and/or eculizumab arms, respectively, were pyrexia (8.9% and 10.1%) and upper respiratory tract infection (8.1% and 13.0%).

AEs related to treatment in COMMODORE 2

The proportion of patients with treatment-related AEs was comparable between the crovalimab arm (33.3%, 45 patients) and the eculizumab arm (34.8%, 24 patients).

The most frequent treatment-related AEs with an incidence of ≥ 10% of patients in crovalimab and eculizumab arms were: infusion-related reaction (14.8%, and 13.0%), white blood cell count decreased (11.9%, and 10.1%), and neutrophil count decreased (11.1%, and 10.1%).

AEs by severity in COMMODORE 2

The majority of AEs were Grade 1 or 2 in severity in both the crovalimab (60.0%) and eculizumab arms (55.0%). The proportion of patients with Grade 3–5 AEs in the crovalimab arm was 17.8% and 24.6% in the eculizumab arm.

Deaths in COMMODORE 2

During the primary safety period, death was reported in two patients in the crovalimab arm and one patient in the eculizumab arm. The investigator considered none of the deaths to be related to crovalimab.

[redacted]

Serious adverse events in COMMODORE 2

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%). The majority of patients with an SAE experienced a single event. In total, three patients each from the crovalimab and eculizumab arms experienced two or more SAEs. The majority of the SAEs were reported in single patients per arm only, with the exception of pneumonia, aplastic anaemia and epistaxis, which were reported in two patients each in the crovalimab arm.

SAEs considered by the investigator to be related to the study drug were similar across crovalimab and eculizumab arms (3.0% vs 1.4%) This included Grade 4 thrombocytopenia, Grade 3 pyrexia, Grade 2 epistaxis and a Grade 2 infusion-related reaction in four patients in the crovalimab arm. The single patient in the eculizumab arm with a related SAE, experienced a Grade 4 SAE of 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 related to the study drug. Both events were reported to have been resolved by CCOD without any dose modification/interruption.

AEs that led to withdrawal of treatment and dose modification

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 (Grade 4 SAE of thrombocytopenia and Grade 5 [fatal] SAE of ischemic stroke, respectively). The median treatment duration was 20.1 weeks and 22.1 weeks in crovalimab [n = 135] and eculizumab [n = 69] arms, respectively. These patients had different reasons listed for treatment discontinuation: withdrawal due to subject decision and death, respectively. No patients in the crovalimab arm experienced AEs leading to discontinuation of treatment after the primary safety period up to CCOD (16 November 2022).

The proportion of patients who experienced AEs leading to dose modification/interruption during the primary safety period in the crovalimab arm (3.7%) was comparable to the eculizumab arm (4.3%). In the crovalimab arm, five patients experienced, in total, four AEs that led to dose interruption (two events of COVID-19 and one event each of pancytopenia and infusion-related reaction), one AE that led to dose reduction (nausea) and two AEs (one event each of feeling cold and peripheral coldness) that lead to dose increase. All AEs except the infusion-related reaction were reported as not related to the study drug. In the eculizumab arm, three patients experienced in total three AEs that led to dose interruption (sepsis, cholecystitis chronic and COVID-19). All AEs were reported as not related to the study drug.

Adverse events of special interest: Transient immune complex reactions (TICs)

Transient immune complexes only occur in patients switching to/from other C5 inhibitors, which bind different epitopes than crovalimab, and therefore were not relevant or expected in crovalimab-treated patients in Arms A and C or in eculizumab-treated patients in Arm B during the primary treatment period of the study. Accordingly, no AESIs of transient immune complex reactions related to transient immune complexes were reported during the primary safety period in the randomised safety population, which was treatment naive or in patients who continued in the crovalimab arm after the primary safety period up to the 16 November 2022 CCOD.

Selected AEs

In summary, findings related to selected AEs were as follows:

- Injection-site reaction: there were 14 events in seven 7 patients (5.2%) treated with crovalimab. All events were Grade 1 or 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.
- Infusion-related reactions: infusion-related reactions were observed in 9 patients (13.0%) in the eculizumab arm and 21 patients (15.6%) in the crovalimab arm. All events were Grade 1 or 2 in severity. No additional cases of infusion-related reactions were reported in patients in the crovalimab arm who continued on crovalimab after the primary safety period up to CCOD.
- Infections including meningococcal meningitis: in the eculizumab arm, there were 10 events in nine (13.0%) patients, and in the crovalimab arm there were 22 events in 21 (15.6%) patients. There were no cases of infection with *Neisseria meningitidis*, including meningococcal meningitis, in either arm.
- Hypersensitivity other than transient immune complex reactions: in the crovalimab arm, eight (5.9%) patients experienced eight events of hypersensitivity other than transient immune complex reactions. No events were reported in the eculizumab arm.

Table 18 Overview of AEs (Primary Safety Period, Randomised Safety Population)

	COMMODORE 2		COMMODORE 1	
Safety Outcome	**Crovalimab (Arm A) n = 135**	**Eculizumab (Arm B) n = 69**	**Crovalimab (Arm A) n = 44**	**Eculizumab (Arm B) n = 42**
Treatment duration, weeks				
Mean (SD)	19.7 (2.8)	22.0 (2.0)	19.1 (3.7)	20.4 (5.7)
Median (range)	20.1 (0.1–23.1)	22.1 (6.1–26.1)	20.1 (2.1–22.3)	22.1 (0.1–26.1)
Total number of patients with at least one AE, n (%)	105 (77.8)	55 (79.7)	34 (77.3)	28 (66.7)
Total number of AEs, n (%)	421	223	127	67
Total number of deaths, n (%)	2 (1.5)	1 (1.4)	0	0
Total number of patients withdrawn from initial treatment due to AE, n (%)	0	0	0	0
Total number of patients with at least one of the following, n (%)				
Fatal AE	2 (1.5)	1 (1.4)	0	0

	COMMODORE 2		COMMODORE 1	
Safety Outcome	**Crovalimab (Arm A) n = 135**	**Eculizumab (Arm B) n = 69**	**Crovalimab (Arm A) n = 44**	**Eculizumab (Arm B) n = 42**
Treatment duration, weeks				
Mean (SD)	19.7 (2.8)	22.0 (2.0)	19.1 (3.7)	20.4 (5.7)
Median (range)	20.1 (0.1–23.1)	22.1 (6.1–26.1)	20.1 (2.1–22.3)	22.1 (0.1–26.1)
SAE	14 (10.4)	9 (13.0)	6 (13.6)	1 (2.4)
Related SAE	4 (3.0)	1 (1.4)	0	0
Related AE	45 (33.3)	24 (34.8)	14 (31.8)	0
Related AE leading to withdrawal from treatment	1 (0.7)	0	0	0
Related AE leading to dose modification/interruption	1 (0.7)	0	0	0
AE of Grade 3–5	24 (17.8)	17 (24.6)	8 (18.2)	1 (2.4)
AE leading to withdrawal from treatment	1 (0.7)	1 (1.4)	0	0
AE leading to dose modification/interruption	5 (3.7)	3 (4.3)	1 (2.3)	0

Only treatment-emergent AEs are displayed. Multiple occurrences of the same AE in one individual are counted only once except for 'Total number of AEs' row in which multiple occurrences of the same AE are counted separately. AE, adverse event; SAE, serious adverse event.
Source: Study BO42162 Primary CSR, Report 1109893, April 2023. Study BO42161 Primary CSR, Report 1109894, April 2023

Table 19 Summary of Common (≥ 5%) AEs by Preferred Term (Primary Safety Period, Randomised Safety Population)

	COMMODORE 2		COMMODORE 1	
Safety Outcome; MedDRA System Organ Class and MedDRA Preferred Term	**Crovalimab (Arm A) n = 135 n (%)**	**Eculizumab (Arm B) n = 69 n (%)**	**Crovalimab (Arm A) n = 44 n (%)**	**Eculizumab (Arm B) n = 42 n(%)**
Infections and infestations				
Upper respiratory tract infection	11 (8.1%)	9 (13.0%)	3 (6.8%)	1 (2.4%)
COVID-19	11 (8.1%)	4 (5.8%)	6 (13.6%)	7 (16.7%)
Influenza	-	-	2 (4.5%)	3 (7.1%)

	COMMODORE 2		COMMODORE 1	
Safety Outcome; MedDRA System Organ Class and MedDRA Preferred Term	**Crovalimab (Arm A) n = 135 n (%)**	**Eculizumab (Arm B) n = 69 n (%)**	**Crovalimab (Arm A) n = 44 n (%)**	**Eculizumab (Arm B) n = 42 n(%)**
Urinary tract infection	2 (1.5%)	4 (5.8%)	2 (4.5%)	3 (7.1%)
Metabolism and nutrition disorders				
Hypokalaemia	15 (11.1%)	9 (13.0%)	-	-
Hyperuricaemia	11 (8.1%)	6 (8.7%)	-	-
Hypocalcaemia	8 (5.9%)	7 (10.1%)	-	-
Injury, poisoning and procedural complications				
Infusion-related reaction	21 (15.6%)	9 (13.0%)	6 (13.6%)	0
Injection-related reaction	7 (5.2%)	0	3 (6.8%)	0
Gastrointestinal disorders				
Nausea	-	-	3 (6.8%)	2 (4.8%)
Diarrhoea	10 (7.4%)	0	3 (6.8%)	1 (2.4%)
General disorders and administration site conditions				
Pyrexia	12 (8.9%)	7 (10.1%)	7 (15.9%)	1 (2.4%)
Asthenia	-	-	3 (6.8%)	2 (4.8%)
Oedema peripheral	-	-	3 (6.8%)	1 (2.4%)
Investigations				
Neutrophil count decreased	17 (12.6%)	7 (10.1%)	-	-
White blood cell count decreased	16 (11.9%)	7 (10.1%)	-	-
Nervous system disorders				
Headache	11 (8.1%)	3 (4.3%)	5 (11.4%)	1 (2.4%)
Skin and subcutaneous tissue disorders				
Rash	-	-	3 (6.8%)	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. Displayed are MedDRA preferred terms that occurred in ≥ 5% of patients in at least one of the two treatment groups displayed. Events are sorted by descending overall total frequency.
AE, adverse event; COVID-19, coronavirus disease 2019; MedDRA, Medical Dictionary for Regulatory Activities.
Source: Study BO42162 Primary CSR, Report 1109893, April 2023. Study BO42161 Primary CSR, Report 1109894, April 2023

B.3.10.3 Safety in COMMODORE 1

For all results in the safety section, it is relevant to note that 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 stabilised on their treatment. This should be kept in mind when interpreting all safety differences seen in COMMODORE 1.

All AEs in COMMODORE 1

An overview of the safety results in patients treated with crovalimab (n = 44 patients) and with eculizumab (n = 42 patients) during the primary safety period is provided in Table 18. The median treatment duration during the primary safety period was 20.1 weeks (range: 2.1–22.3) in the crovalimab arm and 22.1 weeks (range: 0.1–26.1) in the eculizumab arm.

During the primary safety period, the proportion of patients with at least one AE in the crovalimab arm (77.3%) was higher than in the eculizumab arm (66.7%; Table 18, see previous subsection). This difference was driven by transient immune complex reaction events, injection-related reactions and infusion-related reactions (See below). Transient immune complex reaction events were expected only in the crovalimab arm due to crovalimab and eculizumab binding to different epitopes on C5, and when both are present in the circulation, transient immune complexes may form. Therefore, patients who switched to crovalimab are at risk of developing transient immune complex reactions. Injection-related reactions were also expected to occur only in the crovalimab arm due to SC administration being unique to crovalimab. In addition, infusion-related reactions occurred with lower incidence in the eculizumab arm as patients were stabilised on treatment prior to enrolment.

Additional PTs that occurred more frequently in the crovalimab arm compared with the eculizumab arm included pyrexia and headache. Upon medical review of these AEs, all were Grade 1 or 2 and there was no apparent pattern related to onset or duration.

The AEs by PT occurring in at least 5% of patients in either arm are shown in Table 19. The most frequent AE in the randomised safety population was COVID-19, with 13.6% of patients in the crovalimab arm and 16.7% of patients in the eculizumab arm.

The most frequent AEs by PT for the crovalimab arm were transient immune complex reactions (15.9%) and pyrexia (15.9%), and for the eculizumab arm were COVID-19 (16.7%), influenza (7.1%) and urinary tract infection (7.1%).

The AEs by PT with notable differences (5% or greater) between the arms were (crovalimab and eculizumab):

- Transient immune complex reactions (15.9% and 0 patients);
- pyrexia (15.9% and 2.4%);
- infusion-related reactions (13.6% and 0 patients);

- headache (11.4% and 2.4%);
- injection-related reaction (6.8% and 0 patients);
- arthralgia (6.8% and 0 patients); and
- rash (6.8% and 0 patients).

[redacted]

Adverse events related to treatment

The proportion of patients with treatment-related AEs in the crovalimab arm (31.8%) was higher compared with the eculizumab arm (0%) (Table 18). This difference was driven by PTs of transient immune complex reactions and injection-related reactions, both of which exclusively occurred in the crovalimab arm, and infusion-related reactions, which more likely occur in the crovalimab arm as patients on the eculizumab arm were stabilised on treatment before starting the study.

The most frequent treatment-related AEs by PT (≥ 5%) in the crovalimab arm were: transient immune complex reactions (15.9%), infusion-related reactions (13.6%) and injection-related reactions (6.8%).

[redacted].

AEs by severity

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%). Higher rates Grade 3–4 AEs in the crovalimab compared with the eculizumab arm were driven by risks that were unique to the crovalimab arm (transient immune complex reactions and injection site reactions), risks less likely to occur with participants stabilised on eculizumab (infusion-related reactions), and other

types of AEs that were determined not to indicate a safety concern 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 neutropenia (4.5%, two patients). All other Grade 3–5 AEs occurred in single patients, and include extravascular haemolysis, pneumonia (SAE), urinary tract infection (SAE), hypersensitivity, transient immune complex reactions, hyperbilirubinaemia (SAE), skin laceration (SAE), hypokalaemia and hypertension. The majority of reported Grade 3–5 AEs were Grade 3, with only one patient who experienced a serious Grade 4 neutropenia event that 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.

[redacted].

Deaths

No deaths were reported in either arm during the primary safety period. [redacted].

Serious adverse events

The proportion of patients with at least one SAE in the crovalimab arm (13.6%, six patients) was higher than the eculizumab arm (2.4%, one patient).

In the crovalimab arm, six patients experienced eight SAEs. The most frequent SAE by was infections and infestations (6.8%)

In the crovalimab arm, the majority of SAEs were Grade 2 or 3. Only one patient experienced a Grade 4 neutropenia event, which resolved without treatment for AE and without dose modification/interruption. One patient experienced two SAEs of Grade 3 skin laceration and Grade 3 hyperbilirubinaemia, another patient had two SAEs of Grade 2 pyrexia and Grade 2 cervical dysplasia. All these events resolved with treatment and no dose modification/interruption was performed.

In the eculizumab arm, one patient experienced three SAEs of pneumonia (Grade 3), pyelonephritis (Grade 3) and transient ischemic attack (Grade 2), all of which resolved after treatment of AEs without dose modification/interruption. There were no SAEs that were considered by the investigator to be related to crovalimab or eculizumab in the primary safety period, and no additional treatment-related SAEs were reported up to the CCOD for patients treated with crovalimab.

[redacted].

AEs that led to withdrawal of treatment and dose modification

No patients experienced AEs leading to discontinuation of treatment in the primary safety period and up to the CCOD for patients treated with crovalimab.

[redacted]. No patients in the other exploratory cohorts experienced AEs that led to withdrawal of treatment.

One patient (2.3%) in the crovalimab arm and no patients in the eculizumab arm experienced AEs leading to dose modification/interruption. The patient in the crovalimab arm had an SAE of pneumonia that led to dose interruption.

[redacted].

Adverse events of special interest: transient immune complex reactions (TICs)

As crovalimab binds to a different C5 epitope than eculizumab or ravulizumab, transient immune complexes, composed of the two different monoclonal antibodies bridged by C5, are formed when both treatments are present in the circulation of patients who switch between C5 inhibitor treatments. Therefore, patients who switched from eculizumab (or ravulizumab) to crovalimab (and vice versa) are at risk of developing transient immune complex – associated Type III hypersensitivity (T3H) reactions. Patients who have never previously been treated

with a C5 inhibitor (treatment naive) or patients in whom previous C5 inhibitor treatment has cleared from the body are not at risk of transient immune complex reactions (see Appendix D.4.2.1 for further critique around TICs).

In the crovalimab arm, 7 patients (15.9%) 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 and four events of Grade 2), all of which were resolved without dose modifications/interruptions. One patient experienced a Grade 3 transient immune complex reactions, which resolved after treatment of AE with no dose modification/interruption needed.

The most frequently reported (≥ 10% of patients) symptoms of transient immune complex reactions by SOC were musculoskeletal and connective tissue disorders (11.4%) and skin and subcutaneous tissue disorders (11.4%). None of the transient immune complex reactions had renal manifestations. The majority of symptoms were Grade 1 or 2 in severity. Four Grade 3 symptoms, which were arthralgia, dizziness, abdominal pain upper and nausea, were reported and all occurred in one patient. No additional transient immune complex reactions were reported in the crovalimab arm after the primary safety period up to the CCOD.

[redacted].

Across COMMODORE 1 and COMMODORE 2 (n = 185), the median time to onset for transient immune complex reaction events was 1.6 weeks (range, 0.7–4.4) and the median resolution duration for events was 1.9 weeks (range, 0.4–34.1). Based on time-to-onset for transient immune complex reactions, 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. For mild or moderate transient immune complex reactions, administration of symptomatic treatment (e.g. topical corticosteroids, antihistamines, antipyretics, and/or analgesics) may be considered. For severe reactions, oral or systemic corticosteroid therapy can be initiated and tapered as clinically indicated.

Selected AEs

In summary, findings related to selected AEs were as follows:

- Injection-site reactions: there were five events in four (9.1%) patients treated with crovalimab. All events were Grade 1 in severity.
- Infusion-related reactions: In the crovalimab arm there were six events experienced by six (13.6%) patients. All events were Grade 1 or 2 in severity and resolved without dose modification/interruption. No patients in the eculizumab arm experienced infusion-related reactions.
- Infections including meningococcal meningitis: In the eculizumab arm, there were 21 events in 15 (35.7%) patients, and in the crovalimab arm there were 26 events in 18 (40.9%) patients. In both arms, the majority of infections were Grade 1 or 2 in severity. There were no cases of infection with Neisseria meningitidis, including meningococcal meningitis, in either arm.
- Hypersensitivity other than transient immune complex reactions: In the crovalimab arm, four (9.1%) patients experienced hypersensitivity other than transient immune complex reactions. No events were reported in the eculizumab arm.

Safety in patients switching from ravulizumab treatment

- [redacted]

B.3.10.4 Pooled safety analysis

The pooled safety analysis for a combined study population from COMMODORE 1, COMMODORE 2 and COMMODORE 3 confirms that crovalimab was well tolerated in patients with PNH who were either treatment-naive or switching to crovalimab from eculizumab. Appendix F provides the full analysis; results are reported for the total crovalimab population (n = 377) and the total eculizumab population (n = 111), as well as further grouped by patients' initial complement inhibitor treatment status: crovalimab naive (n = 192) and crovalimab switch (n = 185).

Immunogenicity

The overall safety profile was generally consistent between anti-drug antibody (ADA)-positive and ADA-negative patients. There was no evidence for a clinical impact of ADA status on the safety profile of crovalimab. Details of the pooled immunogenicity data from COMMODORE 1,2 and 3 are presented in Appendix E.

B.3.11 Conclusions about comparable health benefits and safety

Crovalimab, a humanized anti-C5 monoclonal antibody, prevents the uncontrolled activation of the complement cascade and its resulting clinical manifestations. Due to its long half-life, crovalimab can be administered less frequently while maintaining effective steady-state plasma concentrations throughout the dosing interval. Therefore, crovalimab SC dosing and Q4W frequency of administration, with the possibility for self-administration, offers a new treatment option that provides clinical benefit with low treatment burden.

The PNH clinical development program brings experience from 421 patients with PNH treated with crovalimab in the pivotal Phase III study COMMODORE 2, two further Phase III studies, COMMODORE 1 and COMMODORE 3, and the Phase I/II study COMPOSER, together forming the basis for the overall benefit-risk assessment of crovalimab in the broad PNH population including treatment-naive and switch patients, as well as paediatric patients (body weight $\geq$ 40 kg). The patients enrolled across the Phase III studies represent the PNH patient population that was intended to be enrolled.

Crovalimab demonstrated complete, rapid, and sustained terminal complement activity inhibition in patients with PNH, which translated into robust, consistent, clinically meaningful benefit across the relevant efficacy endpoints. The results of the pivotal study COMMODORE 2 are considered clinically relevant and statistically robust as demonstrated by the non-

inferiority of crovalimab compared with eculizumab in the co-primary (haemolysis control and TA) and the secondary endpoints (BTH and haemoglobin stabilisation), and based on additionally clinically meaningful improvement shown in patient-reported fatigue scores. The eculizumab control arm showed efficacy results consistent with historical treatment data, allowing for a meaningful conclusion about the treatment benefit of crovalimab to be drawn. The robustness of these data is further supported by consistent results from sensitivity and subgroup analyses. The results from the pivotal study are furthermore supported by overall consistent confirmatory evidence from–switch patients in studies COMMODORE 2 and COMMODORE 1 (switching from label-dose eculizumab, high-dose eculizumab, or ravulizumab), patients with C5 polymorphisms.

Crovalimab treatment was well tolerated in patients with PNH. In the randomised arms of pivotal study COMMODORE 2, the safety profile of crovalimab was comparable with eculizumab, with key safety parameters being similar between both treatment arms. The safety profile of crovalimab was consistent between the treatment-naive and switch patient populations, with the exception of the TIC - mediated T3H reactions in switch patients. TIC reactions were the only new risk, which was expected in patients who switch between crovalimab and another C5 inhibitor (or vice versa). This is due to crovalimab and eculizumab/ravulizumab binding to different epitopes on C5, and when both 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. The majority of T3H reactions occurred within the first few weeks of treatment start (median onset of 1.6 weeks), were mostly mild or moderate, transient (median duration of 1.9 weeks), and resolved with no change in crovalimab treatment. Immunogenicity did not result in a clinical meaningful impact on PK, PD, efficacy and safety; [redacted].

[redacted].

In the context of PNH disease, which requires lifelong therapy, an SC therapy that can be self-administered without medical supervision minimizes the treatment burden for patients and their caregivers. Self-administration avoids the need to travel to a clinic or infusion center and the resulting interference with work schedules and educational attendance. The feasibility of

self-administration or caregiver administration of crovalimab was shown across the Phase III studies; patients were satisfied with the treatment convenience that SC crovalimab treatment offers, and most patients switching from eculizumab to crovalimab preferred crovalimab over eculizumab, underlying the importance of new treatment options for patients with PNH.

In summary, Roche considers that the efficacy and safety of crovalimab demonstrated in the pivotal Phase III study COMMODORE 2 and in the supportive Study COMMODORE 1 (in addition to COMODORE 3 and COMPOSER) provide robust and consistent evidence to conclude that crovalimab has a positive benefit-risk profile in treatment-naive and in switch patients with PNH.

B.3.12 Ongoing studies

There are no completed or ongoing studies expected to provide additional evidence for the indication being appraised in the next 12 months.

B.4 Cost-comparison analysis

B.4.1 Changes in service provision and management

Crovalimab is anticipated to be used in a homecare setting, in line with currently licensed C5-inhibitor treatments used for PNH, eculizumab and ravulizumab. There are no additional requirements anticipated in terms of service provision or disease management with the inclusion of crovalimab in the treatment pathway

Unlike existing treatment options, administered via IV infusions, after the initial loading phase, crovalimab is self-administered subcutaneously at home, which has the potential to reduce treatment burden to patients and health care professionals.

B.4.2 Cost-comparison analysis inputs and assumptions

B.4.2.1 Features of the cost-comparison analysis

The objective of this analysis was to evaluate the costs associated with crovalimab compared with eculizumab and ravulizumab for the treatment of PNH from a UK (England and Wales) healthcare system perspective. A cost-comparison model was developed to capture the lifetime costs of people with PNH treated with crovalimab, eculizumab or ravulizumab.

Results from the COMMODORE 1 & 2 (61, 62) found comparable proportions of people with haemolysis control and avoidance of blood transfusions when receiving either eculizumab or crovalimab from baseline to week 25. Non-inferiority was also demonstrated across other clinical and safety endpoints.

The results of an indirect treatment comparison also demonstrated that crovalimab was non-inferior to eculizumab and ravulizumab.

As such, a cost comparison whereby treatment efficacy, treatment safety and treatment discontinuation were all set equal was deemed appropriate and the preferred model framework.

An overview of the cost-comparison analysis is presented in Table 20.

Table 20: Summary of the cost-comparison analysis

Feature	Chosen approach
Population	• [redacted]
Intervention	Crovalimab
Comparator(s)	• Eculizumab • Ravulizumab
Outcomes	Mean incremental per-patient costs and total per-patient costs
Perspective	NHS and personal social services (PSS) in England and Wales
Time horizon	Lifetime – 60 Years (assuming maximum age of 100 Years)
Discounting	Costs discounted at 3.5% per annum
Technology acquisition cost	£9,500 (list price) [redacted] – 340mg vial

NHS: National Health Service; PSS: Personal Social Services

B.4.2.2 Model structure

A cost-comparison model was developed in Microsoft Excel ® 2016, considering drug acquisition, administration, blood transfusion, up-dosing 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.

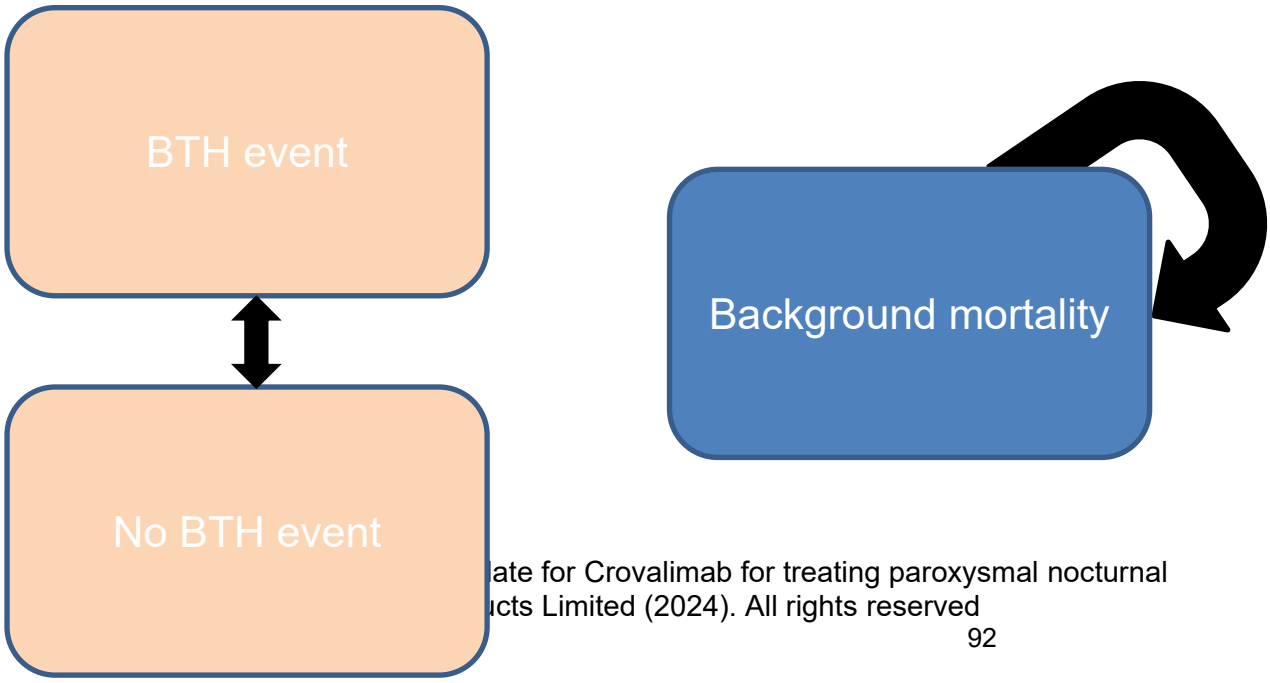
In those who remained on treatment, a rate of breakthrough haemolysis (BTH) events is modelled in order to incorporate the costs of single up-dosing, along with the costs of blood transfusions and medical resource use. Additionally, a proportion of eculizumab patients are assumed to require continuous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

The general modelling approach and inputs were cross referenced with previous technology appraisals and subsequently validated by external health economists and UK clinical experts. If patients discontinue, no switching to other therapies is assumed.

A lifetime time horizon (60 years) was adopted in line with the NICE reference case (70). The time horizon was considered to be sufficiently long to reflect any differences in costs between the technologies being compared. A cycle length of 2-weeks was adopted, reflecting the shortest treatment period (Q2W) which could be applied in the model. In line with the NICE reference case (70) a discount rate of 3.5% was applied to costs and benefits in the model.

To assess the plausibility and robustness of the model predictions, the impact of varying certain assumptions and parameter values were explored in sensitivity and scenario analyses (see Section B.4.4).

Figure 33: Cost-comparison model structure



BTH, breakthrough haemolysis

B.4.2.3 Patient population

The patient population considered in the analysis is patients with PNH, including both those who have and have not previously been treated with complement inhibitors. The model population is reflective of the anticipated marketing authorisation for crovalimab and the populations evaluated in the COMMODORE studies: people aged ≥ 12 years who weigh over 40kg with PNH.

Demographic baseline information (age, weight groups, gender split) is based on pooling COMMODORE 1 and 2 (Table 21).

Table 21: Population data

Characteristic	Value
Baseline age	42.7
Proportion male	53.0%
Mean weight	70 kg

KG, kilogram

B.4.2.4 Clinical data

Clinical data from published sources was used to inform:

- Breakthrough haemolysis (BTH) events
- Blood transfusions
- Mortality.

B.4.2.4.1 Breakthrough haemolysis (BTH)

The 2-weekly probability of BTH events (0.85%) was taken from Quist et al (71) 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 (71), 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.

As crovalimab and ravulizumab both have a long half-life, C5 inhibition-related BTH events linked to incomplete blockade of C5 are assumed to not be possible in these treatment arms. Therefore all the BTH events for people treated with crovalimab or ravulizumab are assumed to be CAC-related.

B.4.2.4.2 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 (71). The 2-weekly probabilities are presented in Table 22.

Table 22: Blood transfusion data

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

Abbreviations: BTH, breakthrough haemolysis.

B.4.2.4.2 Background mortality

Mortality was modelled by applying general population all-cause mortality data obtained from England and Wales National Life Tables published by the Office for National Statistics (2019) based on 2020−2022 mortality data (72). To reflect the patient population in the model, age- and gender-specific mortality rates were combined into a single rate using the proportion of males and mean age set in the model to reflect the patient population in the COMMODORE 1 and 2 studies.

UK clinical experts supported the view that crovalimab was similar in efficacy and safety to eculizumab and ravulizumab. As such, given there was no evidence to suggest that mortality rates would differ across treatments, the annual rate of mortality was assumed to be equivalent for all modelled treatments.

B.4.2.5 Intervention and comparators' acquisition costs

A summary of the acquisition costs for crovalimab, eculizumab and ravulizumab is presented in Table 23 below. The drug acquisition costs for eculizumab and ravulizumab were based on the list price stated in the British National Formulary (73). A confidential patient access scheme (PAS) discount has been agreed with the Department of Health for ravulizumab, whilst any commercial arrangement which exists for eculizumab is not publicly reported. As the size of these discounts are unknown to Roche, the list price for each treatment was used in the base case cost comparison analyses. Scenario analyses exploring the impact of varying the discounts applied to the list price of eculizumab and ravulizumab have been conducted (see section B.4.3).

If recommended, crovalimab will be available with a confidential simple PAS discount price of [redacted] ([redacted] discount to list price £9,500 [340mg vial]). This net price has been used in the base case cost comparison analysis.

Table 23: Acquisition costs of the intervention and comparator technologies

	Crovalimab	Eculizumab	Ravulizumab
Pharmaceutical formulation	340mg vial for subcutaneous injection	300mg solution for IV infusion	300mg solution for IV infusion
(Anticipated) care setting	Hospital (loading) IV Home (maintenance) SC	Hospital (loading) IV) Home (maintenance) IV	Hospital (loading) IV) Home (maintenance) IV
Acquisition cost (excluding VAT) *	£9,500 list [redacted] PAS	**NHS list price (73)** £3,150	**NHS list price (73)** £4,533
Method of administration	Intravenous infusion (loading dose 1) Subcutaneous injection (loading and maintenance)	Intravenous infusion	Intravenous infusion
Doses	**40kg to 100kg** • 1000mg (IV) (day 1) • 340mg (SC) (day 2, week 2, week 3, week 4) • 680mg (SC) (week 5+) **100kg+** • 1500mg (IV) (day 1) • 340mg (SC) (day 2, week 2, week 3, week 4) • 1020mg (SC) (week 5+)	**40kg+** • 600mg (week1, 2, 3, 4) • 900mg (week 5+)	**40kg to 60kg** • 2400mg (week 1, 2) • 3000mg (week 3+) **60kg to 100kg** • 2700mg (week 1, 2) • 3300mg (week 3+) **100kg+** • 3000mg (week 1, 2) • 3600mg (week 3+)
Dosing frequency	Q4W (maintenance)	Q2W (maintenance)	Q8W (maintenance)
Dose adjustments	Single up-dosing for BTH events	Single up-dosing for BTH events Continuous up-dosing for a proportion in-line with expert opinion and literature findings	Single up-dosing for BTH events
Average length of a course of treatment	Lifetime	Lifetime	Lifetime
Average cost of a course of treatment (acquisition costs only)	[redacted]	£5,468,185	£6,635,915

B.4.2.6 Intervention and comparators' healthcare resource use and associated costs

Quist et al (71) was identified as a key publication in the development of the economic model. In this paper, Quist et al assessed the cost-effectiveness of ravulizumab compared to eculizumab from the perspective of the Netherlands, estimating key costs related to PNH related events and treatment up-dosing. Event rates, confirmed as representative to UK clinical practice by experts consulted by Roche, and associated costs, converted to UK currency, have been applied in the economic model.

B.4.2.7 Treatment up-dosing

The proportion of BTH events requiring single up-dosing for crovalimab, eculizumab and ravulizumab patients is 40%, as 4 of the 10 BTH events observed in COMMODORE 2 in the crovalimab arm required single up-dosing.

In clinical practice in England, people can get higher doses of eculizumab, typically 1,200 mg, after breakthrough haemolysis and an inadequate disease response. A constant proportion of 20% of eculizumab patients are assumed to require continuous up-dosing, in line with the UK clinical expert opinion and the assumption made by Quist et al (71).

B.4.2.8 Administration

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 same training requirements as pegcetacoplan outlined in TA778 (74). The training requirements for crovalimab are outlined in Table 24, while the hourly wages for the relevant hospital staff are presented in Table 25.

Table 24: Self-administration training costs

Drug	Nurse specialist time (minutes)	Nurse specialist cost (£/hour)	Training cost	Source
Crovalimab	20	51	£17.00	PSSRU (75) TA778 (74)

Table 25: Wage per hour, hospital staff

Job classification	Cost per working hour	Source
Band 7 pharmacist specialist	£65	PSSRU (75)
Band 6 nurse specialist	£51	PSSRU (75)

Abbreviations: PSSRU, Personal Social Services Research Unit.

Ravulizumab and eculizumab are both administered via intravenous infusion. NHS England is only responsible for the infusion costs associated with the first loading dose and first maintenance dose of eculizumab, and the loading dose and first maintenance dose of ravulizumab. Thereafter, patients receive infusions at home through the homecare infusion service funded by Alexion/AstraZeneca. As such, these NHS-administered infusion costs are the only administration costs included in the model for ravulizumab and eculizumab. In-line with the comparators, homecare costs associated with crovalimab maintenance doses are assumed to be funded by Roche.

The duration of administration for eculizumab and ravulizumab (for both the loading dose and maintenance dose) were derived from the Summary of Product Characteristics (SPC), as presented in Table 26 and Table 27. Where a range was given in the SPC, 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. UK clinical experts consulted by Roche agreed that the approach used to estimate associated healthcare profession time was reasonable.

Table 26: Loading dose infusion durations

Drug	Patient weight	Duration of infusion (minutes)	Nurse specialist time (minutes)	Pharmacist specialist time (minutes)
Crovalimab	< 100	60	120	15
	≥ 100	90	150	15
Eculizumab	All	35	95	15
Ravulizumab	≥ 10 to < 20	45	105	15
	≥ 20 to < 30	35	95	15
	≥ 30 to < 40	31	91	15
	≥ 40 to < 60	45	105	15
	≥ 60 to < 100	35	95	15
	≥ 100	25	85	15

Table 27: Maintenance dose infusion durations

Drug	Patient weight	Duration of infusion (minutes)	Nurse specialist time (minutes)	Pharmacist specialist time (minutes)
Crovalimab	< 100	0	0	0
	≥ 100	0	0	0
Eculizumab	All	35	95	15
Ravulizumab	≥ 10 to < 20	45	105	15
	≥ 20 to < 30	75	135	15
	≥ 30 to < 40	65	125	15
	≥ 40 to < 60	55	115	15
	≥ 60 to < 100	40	100	15
	≥ 100	30	90	15

Subcutaneous loading doses for crovalimab are assumed to be given by a nurse specialist (band 6 - Table 25), and take place in a 20 minute appointment. The cost per dose subcutaneous dose in a clinical setting is estimated to be £17.00.

The unit costs associated with administration for each treatment, informed by the durations, costs and homecare assumptions above, are presented in Table 28.

Table 28: administration costs

Administration type	Crovalimab	Eculizumab	Ravulizumab
IV administration	£119.53	£97.00	£94.88
SC administration, clinical setting	£17.00	-	-
Administration, home setting	£0.00	£0.00	£0.00
SC, training	£16.83		

Intravenous IV, subcutaneous SC

B.4.2.9 Blood transfusions

The costs associated with blood transfusions include the cost of packed red blood cells and red blood cell transfusion administration, as in the NICE appraisal of ravulizumab (76). The mean number of units of red blood cells required per transfusion and rate of blood transfusions are used to calculate the per-cycle transfusion costs in each treatment arm. The mean number of units of red blood cells required differ based on whether a BTH event occurs within the model cycle. Unit costs associated with blood transfusions are shown in Table 29. UK clinical experts agreed the approach taken to cost blood transfusions was appropriate.

Table 29: Blood transfusion unit costs

Resource	Unit cost	Units per transfusion (no BTH states)	Units per transfusion (BTH states)	Source
Red blood cell transfusion administration	£55.11	1	1	Stokes et al, 2018 (inflated from 2014/15 to 2020/21) (77)
Packed red blood cells	£17.15	1.59	1.83	NHS blood and transplant price list; code: BC001 (78)

Abbreviations: NHS, National Health Service.

B.4.2.10 Medical resource use

In line with Quist et al (71), the medical resource use elements considered are comprised of general ward hospitalisations, intensive care unit hospitalisations, dialysis and consultant visits. The proportion of patients requiring general ward hospitalisations, intensive care unit hospitalisations and dialysis per BTH event was derived from Quist et al (71). Follow-up visits with a consultant are costed in the model and applied to patients in all treatment arms, in line with the NICE appraisal for ravulizumab (TA698) (1). It is assumed that the follow-up visits are required twice per year. The medical resource use requirements are presented in Table 30.

Table 30: Medical resource use data

Procedure	Proportion of patients requiring the service per BTH event	Number of units required per event
General ward hospitalisation	23.0%	3
Intensive care unit hospitalisation	1.0%	1
Dialysis	4.0%	1
Consultant visit	100.0%	1

Unit costs for each element of medical resource use were taken from Quist et al (71). Unit costs for medical resource use are presented in Table 31. UK clinical experts agreed with the approach taken to cost medical resource use.

Table 31: Medical resource use costs

Resource	Unit cost	Source
General ward hospitalisation	£591.15	Quist et al (71), converted from €678.99
Intensive care unit hospitalisation	£1,872.72	Quist et al (71), converted from €2,151.00
Dialysis (renal)	£5,184.60	Quist et al (71), converted from €5,955.00
Consultant visit	£122.69	Quist et al (71), converted from €140.92

B.4.2.11 Adverse reaction unit costs and resource use

The relative safety of crovalimab and eculizumab was assessed in COMMODORE 1 and 2 (B.3.10). The safety results found that incidence of AEs was generally comparable across treatment arms (B.3.9-10).

In-line with the safety results from COMMODORE 1 and 2, the results of the indirect treatment comparison, presented in section B.3.8, demonstrated that safety events were similar across crovalimab, eculizumab and ravulizumab. In the C5 experienced population, some safety parameters had a higher incidence rate in the crovalimab arm compared to the eculizumab arm. However, the events that underlie these imbalances were either reflective of risks unique to the crovalimab arm (Type III hypersensitivity and injection related reaction due to the subcutaneous administration), while mild in severity and occurring rarely, were less likely to occur in the eculizumab arm as patients start the study stabilised on eculizumab treatment, or relate to a broad set of preferred terms which do not indicate a specific safety concern associated with crovalimab. This view is in-line with clinical experts consulted by Roche, who agreed that the safety of crovalimab was likely to be similar to that of eculizumab and ravulizumab.

In the model, it is assumed that the safety of crovalimab, eculizumab and ravulizumab is equivalent (see Section B.3.8). As such, cost and resource use related to adverse events have not been included in the base case analysis. The omission of these costs from the base case analysis does not have a significant impact on the overall results.

B.4.2.12 Miscellaneous unit costs and resource use

No further costs or resource use were included within the base case cost-comparison analysis that have not been previously described.

B.4.2.13 Clinical expert validation

Precedents from recent NICE appraisals in PNH were used where available to maintain consistency in where inputs had been previously validated by clinical experts and the NICE appraisal committee.

Clinical data have been incorporated in the economic model from COMMODORE 1 and 2 (63, 64), as well as other published clinical trials (Section B.3.9). The general modelling approach and inputs were crossed referenced with previous technology appraisals, in particular cost comparison appraisals, with key assumptions validated by UK clinical experts. To assess the generalisability of the evidence and plausibility of the model assumptions and predictions, clinical expert validation of the assumptions applied in the base case cost-comparison analysis was sought from a leading UK clinical expert and at a UK advisory board. A summary of the areas of feedback provided by the experts is below:

- Generalisability of the trial population to UK clinical practice (see Section B.3.3.3)
- Single and continuous up-dosing assumptions (see Section B.4.2.7)
- Similarity of crovalimab to eculizumab and ravulizumab in terms of efficacy and safety (see Section B.3.11)
- Healthcare resource use and costs (see Section B.4.2.6-10).

B.4.2.14 Uncertainties in the inputs and assumptions

A summary of the assumptions adopted in the base case cost-comparison analysis is presented in Table 32.

Table 32: Assumptions adopted in the base case cost-comparison analysis

Assumption	Description
Equivalent efficacy across treatments and regimens	The cost-comparison model assumes that the different treatments have equivalent efficacy and safety, regardless of the treatment regimens or injection frequencies. COMMODORE 1 and 2 demonstrate that crovalimab is non-inferior to eculizumab in terms of outcomes and safety (B.3.6). Results from the ITC (Section B.3.9.1) also demonstrated that crovalimab is associated with comparable efficacy and safety versus both eculizumab and ravulizumab.
Mortality	The cohort followed the age- and gender-adjusted mortality probabilities from published by the Office for National Statistics (2019) based on 2020−2022 mortality data (72).

Breakthrough haemolysis	The 2-weely probability of break through haemolysis events occurring are assumed to be consistent across treatments, with 2-week probability of BTH events (0.85%) taken from Quist et al (1). After BTH event occurs, people are assumed to return to the non-BTH health state, with the chance of further BTH events in-line with the 0.85% 2-week probability. The proportion of BTH events in the eculizumab arm which are CAC-related (35.29%) was calculated from Quist et al (1), 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. As C5 inhibition-related BTH events are not possible in the crovalimab and ravulizumab arms, the proportion of BTH events which are CAC-related in these arms is set to 100%.
Single up-dosing	The proportion of BTH events requiring single up-dosing for crovalimab, eculizumab and ravulizumab patients is 40%, as 4 of the 10 BTH events observed in COMMODORE 2 in the crovalimab arm required single up-dosing.
Continuous up-dosing	A constant proportion of 20% of eculizumab patients are assumed to require continuous up-dosing, in line clinical expert opinion and the assumption made by Quist et al (1).
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 (71). The 2-weekly blood transfusion probabilities are 9% (no-BTH state) and 30% (BTH state).
Treatment switching	No treatment switching was assumed in the economic model.
Adverse event probability	The cost minimisation model assumes that the probability of adverse events was the same across all treatments and regimens, so safety is assumed to be equivalent. No adverse events are modelled in the base-case analysis.

BTH: Break through haemolysis; NMA: network meta-analysis; OCT: Optical coherence tomography; T&E: Treat and extend; TA: technology appraisal.

B.4.3 Base-case results

The results of the base case cost-comparison analysis are presented below (Table 33). The results presented to do not account for any discounts from list price for eculizumab and ravulizumab, as these net prices are confidential. Therefore, the base case results presented below assume eculizumab and ravulizumab are provided at list price (73), while crovalimab is provided at its confidential net price (see Section B.1.2).

Table 33: Base case results (crovalimab at net price; eculizumab and ravulizumab at list price)

Cost	Crovalimab	Eculizumab	Ravulizumab
Drug cost	[redacted]	4,100,874	6,627,639
Administration cost	423	498	280
Single up-dosing	14,743	2,030	8,276
Continuous up-dosing	0	1,365,280	0
Blood transfusions	4,309	4,309	4,309
Medical resource use	3,454	3,454	3,454
Mean total cost	[redacted]	**5,476,446**	**6,643,958**
Incremental cost vs Crovalimab		[redacted]	[redacted]

With similar efficacy and comparable safety to eculizumab and ravulizumab, crovalimab represents a cost-effective alternative to currently licensed and NICE recommended C5-inhibitors for PNH. After week 5, the average dose per week is less for crovalimab than ravulizumab, driving the results in this comparison. Differences in costs in the comparison with eculizumab are driven by the 20% of eculizumab treated PNH patients who require continuous up-dosing (1200mg), a proportion deemed reflective of UK clinical practice UK clinical experts. With the majority of PNH patients in England currently receiving ravulizumab, the base-case results show crovalimab represents a [redacted] alternative compared to current standard of care.

Acknowledging ravulizumab is available to the NHS at a confidential discounted price, and the magnitude of discount for eculizumab is also unreported and unknown, the impact of varying the level of discount to list price for eculizumab and ravulizumab was explored in a threshold analysis, presented in Table 34. When adopting the base case cost-comparison assumption, this analysis demonstrates that at the net price, crovalimab remains [redacted] compared with eculizumab and ravulizumab up to a discount levels of [redacted] and [redacted] respectively.

Table 34: Threshold analysis: incremental cost of crovalimab (net price) compared with eculizumab and ravulizumab at varying list price discount levels

Discount	Eculizumab		Ravulizumab	
	Discounted eculizumab price/vial	**Crovalimab incremental cost vs eculizumab**	**Discounted ravulizumab price/vial**	**Crovalimab incremental cost vs ravulizumab**

10%	£2,835	[redacted]	£4,079.70	[redacted]
20%	£2,520	[redacted]	£3,626.40	[redacted]
30%	£2,205	[redacted]	£3,173.10	[redacted]
40%	£1,890	[redacted]	£2,719.80	[redacted]
50%	£1,575	[redacted]	£2,266.50	[redacted]
60%	£1,260	[redacted]	£1,813.20	[redacted]
70%	£945	[redacted]	£1,359.90	[redacted]
80%	£630	[redacted]	£906.60	[redacted]
90%	£315	[redacted]	£453.30	[redacted]

B.4.4 Sensitivity and scenario analyses

B.4.4.1 Deterministic sensitivity analysis

A univariate deterministic sensitivity analysis (DSA) was conducted to assess which parameters have the greatest impact on incremental cost. In the absence of data on the variability around parameter values, each was varied by ±20%. The parameter values used in the deterministic sensitivity analyses are presented in Table 35, respectively. Results of the DSA in the comparison vs eculizumab and ravulizumab are displayed in Figure 34 and Figure 35, respectively, where the parameters that had the greatest impact on incremental costs are presented in the comparisons to eculizumab and ravulizumab Table 35.

The results of the DSA (see Figure 34 and Figure 35) show that drug costs, discount rate, and model starting age have the biggest impact on incremental costs. In the comparison with eculizumab, amending the proportion of people who require continuous up-dosing also had a modest impact on results. Varying the remaining variables had a negligible impact on results. With the exception of reducing the acquisition cost of eculizumab, all results remain consistent with the base case results, concluding that crovalimab is overall [redacted].

Table 35: Parameter values used for DSA

Parameter	Base-case value	Lower value	Higher value	Variation
List price (£) - Eculizumab - 300mg	3,150	2520	3780	± 20%
List price (£) - Ravulizumab - 300mg	4,533	3626.40	5439.60	± 20%

List price (£) - Crovalimab - 340mg	9500	7600	11400	± 20%
Discount rate (costs)	0.035	0.028	0.042	± 20%
Baseline age (years) - Pooled population from COMMODORE 1 and COMMODORE 2	42.70	34.16	51.24	± 20%
Proportion of eculizumab patients requiring continuous up-dosing	0.20	0.16	0.24	± 20%
Proportion male - Pooled population from COMMODORE 1 and COMMODORE 2	0.53	0.42	0.64	± 20%
Time horizon (years)	60	48	72	± 20%
Proportion of CAC-related BTH events requiring single up-dosing	0.40	0.32	0.48	± 20%
2-week probability - All treatments - BTH events	0.0085	0.0068	0.0102	± 20%
Loading dose - Duration of infusion (minutes) - Crovalimab - <100kg	60	48	72	± 20%
Nurse specialist hourly wage (SC administration training)	51	40.80	61.20	± 20%

BTH, breakthrough haemolysis, CAC, compliment amplifying conditions, DSA, deterministic sensitivity analysis; IVT, intravitreal injection, SC, subcutaneous

Figure 34: Tornado diagram - crovalimab vs eculizumab

Figure redacted - CON

Figure 35: Tornado diagram - crovalimab vs ravulizumab

Figure redacted - CON

B.4.4.2 Scenario analysis

The scenario analyses were limited by the availability of relevant data and the number of variables included in the cost minimisation model. Nonetheless, a variety of scenarios were implemented in the economic model to test the robustness of the base-case results to plausible variations in key modelled parameters. Descriptions of each scenario can be seen in Table 36.

Table 36: Scenario descriptions

Variable	Base-case	Scenario	Description
Model starting age	42.70	12 years	The population covered by crovalimab's marketing authorisation includes people aged 12 and above. These scenarios explore the impact of adjusting the model starting age on costs.
		25 years	
		60 years	
Model time horizon	60	40 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.
		80 years	
Discount rate costs	3.5%	1.5%	A 1.5% discount rate is recommended in certain situations, so the impact of applying a lower discount rate for cost is explored.
Home care costs	None	Paid by NHS	Given the uncertainty around homecare costs associated with biosimilar alternatives, a scenario is presented where it is assumed homecare costs are paid by the NHS for those on eculizumab.
Single up-dosing (BTH event treatment proportion)	40%	20%	A 40% treatment rate for CAC-related BTH events is assumed in the cost-comparison model (see section B.4.2.7). This parameter is varied to explore the impact of potential variability in up-dosing treatment rates on overall costs.
		60%	

Continuous eculizumab up-dosing proportion	20%	10%	To reflect the potential variability in the proportion of people requiring continuous eculizumab up-dosing (see section B.4.2.7).
		30%	
BTH event rate (2 weekly)	0.85%	0.1%	The impact of varying the 2-weekly BTH event rate in the economic model is explored.
		2%	
Blood transfusion rate – no BTH state (2 weekly)	9%	5%	The impact of varying the 2-weekly blood transfusion rate (no BTH state) is explored.
		15%	
Blood transfusion rate –BTH state (2 weekly)	30%	15%	The impact of varying the 2-weekly blood transfusion rate (BTH state) is explored.
		45%	

BTH, breakthrough haemolysis, CAC, compliment-amplifying conditions, NHS, national health service

The results of the scenario analysis can be seen in Table 37. Crovalimab is found to be [redacted] at net price compared to list price eculizumab and ravulizumab in all scenarios explored. While the results were moderately sensitive to increasing the model starting age and reducing the rate at which costs are discounted, overall the results support the robustness and conclusions of the base-case analysis.

Table 37: Scenario analyses results (with crovalimab at net prices; eculizumab and ravulizumab at list price)

Parameter	Base-case	Scenario	Incremental cost vs eculizumab	% change from base case incremental cost	Incremental cost vs ravulizumab	% change from base case incremental cost
Base-case	-		[redacted]	N/A	[redacted]	N/A
Model starting age	42.7 years	20 years	[redacted]	[redacted]	[redacted]	[redacted]
		35 years	[redacted]	[redacted]	[redacted]	[redacted]
		60 years	[redacted]	[redacted]	[redacted]	[redacted]
Model time horizon	60	40 years	[redacted]	[redacted]	[redacted]	[redacted]
		80 years	[redacted]	[redacted]	[redacted]	[redacted]
Discount rate	3.5%	1.5%	[redacted]	[redacted]	[redacted]	[redacted]
Homecare costs	Paid by manufacturer	Eculizumab homecare paid by NHS	[redacted]	[redacted]	[redacted]	[redacted]
Single up-dosing (BTH event treatment proportion)	40%	20%	[redacted]	[redacted]	[redacted]	[redacted]
		60%	[redacted]	[redacted]	[redacted]	[redacted]
Continuous eculizumab up-dosing	20%	10%	[redacted]	[redacted]	[redacted]	[redacted]
		30%	[redacted]	[redacted]	[redacted]	[redacted]
BTH event rate (2-weekly)	0.85%	0.1%	[redacted]	[redacted]	[redacted]	[redacted]
		2%	[redacted]	[redacted]	[redacted]	[redacted]
Blood transfusion rate – no BTH state (2 weekly)	9%	5%	[redacted]	[redacted]	[redacted]	[redacted]
		15%	[redacted]	[redacted]	[redacted]	[redacted]
Blood transfusion rate – no BTH state (2 weekly)	30%	10%	[redacted]	[redacted]	[redacted]	[redacted]
		50%	[redacted]	[redacted]	[redacted]	[redacted]

BTH, breakthrough haemolysis, NHS, national health service

B.4.5 Subgroup analysis

The results of clinical subgroup analysis, exploring differences in efficacy and safety in people who are treatment naïve and treatment experienced are described in sections (B.3.6 and B.3.9.1). Further to this, the efficacy and safety of crovalimab in paediatric patients (aged from 12 to 18) and the similarities of these results to the overall COMMODORE 1 and 2 study population are explored in section B.3.7.

The cost comparison analysis focuses on the overall population of people with PNH, in-line with the anticipated wording of the crovalimab marketing authorisation. Given that C5-inhibitor naïve and C5-experienced patients with PNH have the same pathophysiology, with results of COMMODORE 1 and 2 and the ITC confirming comparable efficacy across these subgroups, it was deemed appropriate for the economic analysis to focus on the total population.

B.4.6 Interpretation and conclusions of economic evidence

This economic evaluation focused on comparing the cost of crovalimab with eculizumab and ravulizumab for the treatment of patients with PNH, from a UK health system perspective. The results of the economic evaluation show that crovalimab is likely to be [redacted] for the NHS in comparison to eculizumab and ravulizumab with extensive scenario, subgroup and sensitivity analyses demonstrating consistent results providing further certainty.

The model draws upon clinical data from the COMMODORE 1 and 2 studies, the baseline characteristics of the patients in both trials have been validated by clinical experts and can be considered broadly representative of the corresponding PNH population in the UK.

In-line with the cost comparison appraisal framework, evidence was presented to demonstrate that crovalimab provides similar or greater health benefits to NICE recommended and NHSE approved technologies (eculizumab and ravulizumab). As demonstrated in the results from COMMODORE 1 and 2 and the indirect treatment comparison (see Sections B.3.6 and B.3.9.1) the efficacy of crovalimab is similar to eculizumab and ravulizumab, and safety is comparable. Clinical experts consulted by Roche confirmed that the majority of UK PNH patients treated with C5 inhibitors receive ravulizumab, with eculizumab used in rare and specific circumstances which account for approximately 5% of cases. As such, the results of the indirect treatment comparison demonstrate that crovalimab can be considered similar in efficacy and safety to the treatment primarily used for the treatment of PNH in the NHS, ravulizumab.

A UK NHS perspective was taken with respect to the costs and resource use quantified in the model. All costs were taken from published UK sources or previous NICE technology appraisals in this disease area. This methodology is in accordance with that of the NICE Reference Case (70).

The base case results from the cost comparison show that crovalimab is [redacted] compared to eculizumab and ravulizumab – see Table 33. While current C5 inhibitors used for the treatment in PNH are effective and safe, eculizumab and ravulizumab are associated with various levels of treatment burden, because of the mode of administration and/or the frequency of the dosing schedule. The IV administration of eculizumab and ravulizumab is relatively invasive and also carries risks of infection and vascular complications. Clinical experts consulted by Roche noted that patient preference is at the centre of treatment choices for PNH. Crovalimab subcutaneously self-administrated in a homecare setting, represents a potential new innovative treatment option for patients with PNH. With treatment lasting for life, the convenience and flexibility of self-administration at home may make crovalimab the preferred treatment for some people with PNH. Further to this, whilst homecare costs are currently funded by manufacturers, the long term availability of this paid service is uncertain. As such, a self-administration at home may become a preferred option from an NHS resource use perspective in the future.

The results presented in this submission compare crovalimab at PAS price, to eculizumab and ravulizumab at list price, so should be interpreted with caution. Nevertheless, when varying the prices of eculizumab and ravulizumab, crovalimab remains a cost effective option up to a discount of [redacted] and [redacted] for eculizumab and ravulizumab respectively.

Extensive sensitivity and scenario analyses have been conducted to test the robustness of model results when parameter values were manipulated, alternative approaches implemented, and different data sources utilised. Complete results of these analyses can be found in Section B.4.4.

The key strengths associated with the presented cost-comparison analysis surround its use of the best available evidence to inform the model:

- Clinical effectiveness data taken from a randomised controlled trials (COMMODORE 1 and 2). Crovalimab demonstrated non-inferiority to eculizumab in the co-primary (haemolysis control and TA) and the secondary endpoints (BTH and haemoglobin

stabilisation), and based on additionally clinically meaningful improvement shown in patient-reported fatigue scores.

- The results from the indirect treatment comparison show that crovalimab provides similar or greater health benefits to eculizumab and ravulizumab with comparable safety across all treatments.
- Costs and resource use data taken from well-established UK sources and previous NICE technology appraisals
- Extensive sensitivity and scenario analyses conducted to quantify uncertainty and identify major drivers of cost-effectiveness results

There are no significant limitations associated with the cost-comparison analysis. Uncertainties stemming from the immaturity of trial evidence and the extrapolation of short-term trial evidence are not unique to this analysis and are regularly observed in technology appraisals.

Crovalimab has the potential to offer new and existing PNH patients an alternative and convenient subcutaneous mode of administration, while achieving similar health benefits and safety outcomes to existing intravenous C5-inhibitor treatment options. The results of the cost-comparison demonstrate that crovalimab is a cost-effective treatment option for PNH compared to licensed alternative C5-inhibitors, resulting in savings to the NHS over a lifetime time horizon up to discounts of [redacted] and [redacted] vs eculizumab and ravulizumab respectively. Therefore, crovalimab meets the cost-comparison criteria to be recommended as an option for the treatment of PNH.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Cost comparison appraisal

Crovalimab for treating paroxysmal nocturnal haemoglobinuria [ID6140]

Summary of Information for Patients (SIP)

May 2024

File name	Version	Contains confidential information	Date
ID6140 crovalimab for PNH_SIP_RPL_100524_noCON	1.0	No	10 May 2024

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article

SECTION 1: Submission summary

1a) Name of the medicine (generic and brand name):

Crovalimab (PiaSky®)

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

People 12 years of age or older with a weight of 40 kg and above who have been diagnosed with paroxysmal nocturnal haemoglobinuria (PNH), with excess haemolysis or post-treatment with a complement component 5 (C5) inhibitor.

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

Crovalimab does not currently have a UK marketing authorisation. The expected MHRA approval date is between October 2024 and January 2025.

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

From 2022-2024, Roche provided the following support to a UK-based patient group relevant to Crovalimab/Paroxysmal Nocturnal Haemoglobinuria.

- [2022] A £20,000 sponsorship to **The Aplastic Anaemia Trust** (AAT) to support the conduct of a National Community Survey of people with rare bone marrow failure (incl PNH).

Roche has received the following benefits for providing the sponsorship amount:

- A seat as a silent observer on the Industry Partners Panel
- An invitation to preview the findings ahead of publication;
- Recognition of Roche's support in PR and communications for The National Community Survey

- [2023] A £20,000 sponsorship to **The Aplastic Anaemia Trust** to support their creation of a report and communications campaign following the completion of the aforementioned National Community Survey of people with rare bone marrow failure (incl PNH). The report has been published online: https://www.theaat.org.uk/News/rare-voices-report-is-out-now.

Roche had no editorial control over the content of the report or campaign, however it received the following benefits for providing the sponsorship amount:

- A seat as a silent observer on the Industry Partners panel
- An invitation to preview the final report ahead of publication and see campaign materials and video diaries ahead of release
- Prioritisation of an individual with PNH to feature in a video diary production if they meet the agreed criteria set by the Steering Group
- Recognition of sponsorship in PR materials, the video diaries and the published report

- [2024] A £15,000 sponsorship to **The Aplastic Anaemia Trust** to help people affected by aplastic anaemia, PNH and related conditions to better navigate the healthcare system and receive the vital support they require when they need it. This project commenced in April 2024.

Roche will receive the following benefits for providing the sponsorship:

- Links to the aggregated, anonymised information the AAT publishes publicly online about where their community are and what they have been diagnosed with
- Journey Mapping summary showing the main points of difficulty for different audiences

- Roche will equip The Aplastic Anaemia Trust to provide a diverse range of patient voices for future projects and feedback opportunities benefitting patients, through creation of an “external volunteering opportunities” sign up opportunity at registration
- The AAT will speak to Roche’s staff, online or in person, about the project to communicate the benefits of the work the AAT are doing

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

Crovalimab is a treatment for paroxysmal nocturnal haemoglobinuria (PNH), a rare blood condition that causes red blood cells to be destroyed by a process called haemolysis. PNH can cause symptoms such as dark or black urine, low level of red blood cells (anaemia), and tiredness.

Without treatment, PNH can be life-threatening (estimated 35% fatality within 5 years of diagnosis) (1); however, not all individuals with PNH are affected in the same way. Some patients may have few or mild symptoms, whereas others can experience many different complications, due to having the illness, that impact their overall quality of life.

Medicines that block the activity of a part of the body’s own immune system that attacks the body’s own red blood cells in people with PNH (known as the complement system) have been developed. These medicines (known as complement inhibitors) have greatly improved the lives of people with PNH by reducing the destruction of red blood cells (haemolysis), lowering the need for the transfer of donated blood through a small needle into a vein (blood transfusions), and improving lifespans (estimated mortality with treatment is 5.2%) (2).

An estimated 1025 people in the UK are diagnosed or living with PNH (data from April 2022 to April 2023) (3).

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

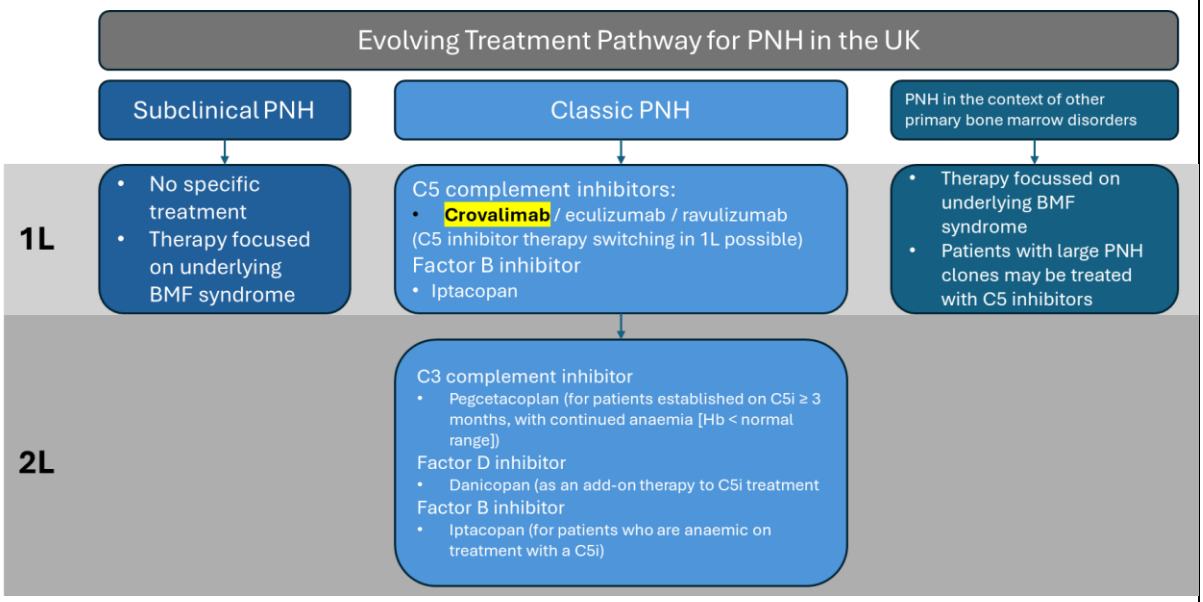
Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?
A diagnosis of PNH may be suspected in individuals who have symptoms of the underlying condition (for example dark red urine, unexplained tiredness). A confirmatory diagnosis is based on clinical evaluation by a specialist healthcare professional, alongside a variety of specific tests. The main confirmatory test for PNH is a type of blood test that can identify the abnormal blood cells produced by patients with PNH. Depending on the numbers of abnormal blood cells present, compared to their normal counterparts, the individual with PNH may or may not require treatment. If no treatment is required up front, then the individual will be monitored to allow continual assessment of the need for treatment. This process would not change with the proposed new treatment.

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed: • What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP. • Please also consider: o if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data. o are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.
The clinical pathway of care for patients with PNH in the United Kingdom (UK) is managed through a PNH National Service that was initiated in April 2009 (3). The PNH National Service has two main centres: one at St James' University Hospital in Leeds, and the second at King's College Hospital in London; and a further eight outreach clinics around the UK (Birmingham, Bristol, Lanarkshire, Liverpool, Manchester, Oxford, Peterborough and Southampton). Referrals to the service are received from around the UK on suspicion of PNH (normally from local haematologists), and on confirmed diagnosis of PNH, patients are managed on a shared care basis between the PNH National Service and referring haematologists. Adult patients with PNH and haemolysis with clinical symptom(s) indicative of high disease activity in the UK are currently treated with the complement inhibitors ravulizumab or eculizumab in the first instance (there are also drugs designed to be similar to eculizumab that have recently been incorporated into the PNH service). Although all of these medicines are equal in terms of activity and safety, the preference is to use ravulizumab due to its less

frequent treatment schedule. However, PNH patients who are or may soon become pregnant during the course of treatment are preferentially treated with eculizumab during and for at least 3 months postpartum. For individuals receiving either of these treatments but not achieving complete control of their symptoms, there is the option to change to an alternative type of complement inhibitor, called pegcetacoplan.

Figure 1: Proposed care pathway for PNH: crovalimab's position within the recommendations adapted from (4)



1L, first-line; 2L, second-line; BMF, bone marrow failure; C3/5, complement protein C3/5; PNH, paroxysmal nocturnal haemoglobinuria; Hb, haemoglobin; C5i, complement protein 5 inhibitor.

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

Disease burden

PNH is associated with considerable disease burden, with patients experiencing a number of clinical symptoms including low red blood cell counts (anaemia), tiredness (fatigue), blood clots (thromboses), kidney disease, abdominal pain and dyspnoea (i.e., shortness of breath) (1, 4). Owing to these symptoms and complications, patients with PNH often experience

impaired health-related quality of life (HRQoL) including the inability to complete normal everyday activities and work (1, 5). In a relevant survey of adults with PNH treated with eculizumab or ravulizumab conducted in France, Germany and the UK from February 1, 2021 through March 31, 2021, 60 (85%) of the 71 surveyed patients with PNH reported impaired daily activity, and almost all patients (98%) in paid employment reported PNH-related work impairment (6).

Treatment-related burden

Initial treatment options for PNH include medicines that work against the body's immune system (complement inhibitors), namely eculizumab, ravulizumab, eculizumab biosimilars (medicines made to be similar to eculizumab), all of which are given by a drip through a vein (intravenously). To control disease progression, patients with PNH require maintenance doses of these intravenous (IV) medicines either every 2 weeks or every 8 weeks, taking up to 3hrs to deliver, depending on the treatment used and the patient's body weight.

Patients treated with these medicines via IV infusion are often required to go to the clinic for regular administration visits. In some countries, for example the UK, IV infusion may be administered at the patient's home by a visiting nurse; however, treatment remains time- and resource-consuming (7).

Frequent, lifelong treatment may feel like a considerable burden to patients and caregivers, especially for patients diagnosed in childhood (though there is little research into how this burden may affect the HRQoL of children). In adults, the dosing regimen of IV eculizumab has been suggested to have a high treatment burden that impacts patient HRQoL (8, 9). In an international study of patients with PNH (n = 95) treated with ravulizumab or eculizumab via IV infusion, 43% of patients agreed that frequency of infusions was the most important factor determining treatment preference between the two treatments (10).

Subcutaneous (SC) maintenance treatment administration can reduce treatment burden by allowing people with PNH more independence and freedom to live their lives. The burden of SC administration is considerably less than that of IV administration, especially when the SC treatment can be self-administered at home. Indeed, in a Phase 3 clinical trial comparing SC ravulizumab (now discontinued) to IV ravulizumab in patients with PNH, patients reported increased satisfaction with the SC route of administration compared with the IV route in a treatment administration satisfaction questionnaire (11).

This was mirrored in patient preference and treatment satisfaction studies of crovalimab, delivered by SC injection, versus either eculizumab or ravulizumab, delivered by IV route. Across two clinical trials, 80-90% of patients preferred crovalimab over eculizumab and 60% preferred crovalimab over ravulizumab. The preference for crovalimab was largely driven by increased convenience due to reduced treatment frequency, and fewer hospital visits along with an easier, and less time-consuming mode of administration (12).

Carer burden

Many patients with PNH may require additional support and care, often living with a caregiver, owing to the substantial disease burden (such as fatigue and other clinical symptoms, and reduced work productivity). A 2021 cross-sectional survey conducted in France, Germany and the UK found that 32.4% of 71 adult patients with PNH surveyed had a caregiver; of these, 82.6% lived with their caregiver (6, 13).

In the COMMODORE BOI study, which includes data from 33 caregivers of patients with PNH in UK, Germany, and France, caregivers of patients receiving IV C5 inhibition treatment reported a mean carer experience scale (CES) score of 68.9 (SD 19.8). This is on a scale of 0–100, with lower scores indicating greater caregiver burden (scores are reduced when a carer experiences impairment in activities outside of caring, reduced support from family and friends, and control over caring, among other factors) (14). As patients with PNH require continued dependence on healthcare resources, including healthcare visits, caregiver burden is likely to be influenced by the number of healthcare visits needed, and the subsequent loss or reduction of work whilst caring for a patient with PNH.

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

Crovalimab is an antibody treatment being considered for PNH. It functions by blocking specific aspects of the immune system (the complement cascade) to prevent it destroying the body's own red blood cells (haemolysis). It does this through preferentially binding a protein in the complement cascade, known as C5. It is also able to recognise a rare form of

the C5 protein and block its function, something that current, similar medicines are unable to do. In addition, to this crovalimab has been designed with an “advanced recycling” mechanism, meaning that it is able to stay, and function within the body longer allowing a reduced dosing schedule (every 4 weeks). Another potential advance of crovalimab is that it is designed to be administered by injection under the skin (subcutaneously), rather than by intravenous infusion like other similar medicines. This means that, after sufficient training, a patient may self-administer crovalimab, or their caregiver may administer crovalimab independently of their healthcare provider.

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 HCP and may have a positive impact on healthcare costs as well as socioeconomic costs.

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines? • Yes / No If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together. If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects. **If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.**
No, crovalimab is not used in combination with other medicines.

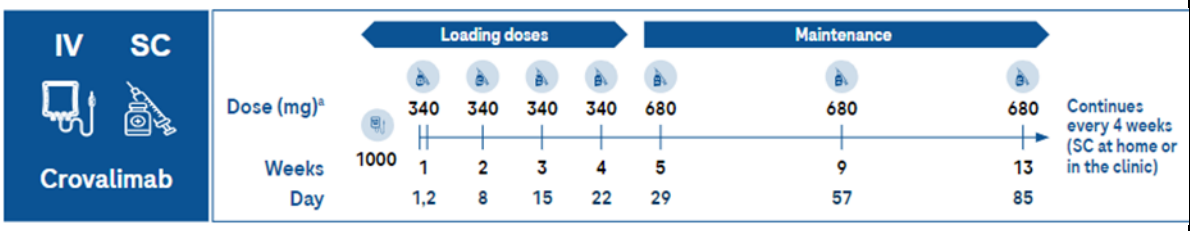
3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for. How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?
Crovalimab is administered via a specific treatment schedule and is dependent on patients’ body weight (BW) for dose. An initial intravenous (IV) loading dose (1000 mg for patients >40kg and <100kg, or 1500 mg for patients >100kg) is given on day 1 of the treatment cycle under the supervision of a physician experienced in the treatment of haematological disorders. Subsequent doses are given by subcutaneous (SC) injection and consist of 4 further loading doses of 340 mg (2 mL low volume injection), received on days 2, 8, 15 and 22 of the cycle, then 4-weekly maintenance doses from day 29 of either 680 mg (>40kg,

<100kg BW; 2 x 2 mL injection) or 1020 mg (>100kg BW; 3 x 2 mL injection). Crovalimab is intended for long-term treatment.

After the initial IV loading dose (usually given in a hospital/clinic setting), the following SC doses (loading and maintenance) can be given at the patient's home, and with appropriate training can be self-administered by the patient, or given by their caregiver, reducing the reliance on a healthcare provider and increasing patient independence and freedom. This is in contrast to the existing, similar treatments that are exclusively delivered via and IV infusion (every 2 or 8 weeks) by a trained healthcare provider, and can take on average 3 hours to administer.

Figure 2: Crovalimab treatment schedule and dosing (example based on body weight less than 100kg), adapted from (15-17)



IV, intravenous; SC, subcutaneous; mg, milligrams.

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

The pivotal Phase 3 study B042162 (COMMODORE 2) (17) and the supportive Phase III study B042161 (COMMODORE 1) (16) provide relevant information for crovalimab in PNH in the UK.

COMMODORE 2 is an ongoing, global, randomised, open-label, active-controlled, multicenter Phase III clinical study that enrolled patients with a body weight over 40 kg, diagnosed with PNH. The study was designed to evaluate the efficacy and safety of crovalimab compared to eculizumab in patients with PNH, who have not been previously treated with a complement inhibitor therapy.

The study was divided into two parts: randomised arms (Arm A and B), consisting of adult patients (over 18 years old), and a descriptive, non-randomised arm (Arm C), consisting of pediatric patients (under 18 years old). A total of approximately 200 patients with PNH were planned to be randomised (in a 2:1 ratio) and treated with crovalimab (Arm A) or eculizumab

(Arm B) for at least 24 weeks (primary treatment period). The primary objective of the study was to demonstrate that in previously untreated patients with PNH, crovalimab is as effective (non-inferior) to eculizumab.

COMMODORE 1 is an ongoing global, randomised, open-label, active-controlled, multicenter Phase III clinical study that enrolled patients with a body weight over 40 kg, diagnosed with PNH and who were currently treated with a complement inhibitor therapy (eculizumab or ravulizumab). The study was designed to evaluate the safety, PK, PD, and efficacy of crovalimab compared primarily with eculizumab in patients with PNH switching from eculizumab.

The study was divided into two parts: randomised arms (Arm A and B), consisting of adult patients (18 years old or over) who have received eculizumab at the approved dose for at least a 24-week period to study entry. A non-randomised arm (Arm C), treating patients in the following cohorts of clinical interest with crovalimab:

- Pediatric patients (under 18 years) currently receiving treatment with eculizumab for at least 12 weeks
- Patients (regardless of age) currently receiving treatment with ravulizumab, (at least 16 weeks)
- Patients (regardless of age) currently receiving treatment with eculizumab at higher-than-approved doses for PNH for at least 12 weeks
- Patients (regardless of age) with known C5 polymorphism and who, per Investigator's assessment, have poorly controlled hemolysis by eculizumab or ravulizumab
- Adult patients (18 years and over) with documented treatment with eculizumab at the approved dosing for PNH and completion of at least 24 weeks of treatment prior to Day 1

Key inclusion criteria (across both studies):

- Body weight greater than 40 kg
- Documented diagnosis of PNH (confirmed by of white blood cells)
- No transfusion requirement
- Platelet count greater or equal to 30,000/mm3 at screening without transfusion support within 7 days
- Vaccination against Neisseria meningitidis serotypes A, C, W and Y, Haemophilus influenzae type B and Streptococcus pneumoniae according to national vaccination

recommendations or standard-of-care as applicable in patients with complement deficiency

Key exclusion criteria (across both studies):

- 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 (e.g., history of frequent recurrent infections)
- Known or suspected hereditary complement deficiency
- History of myelodysplastic syndrome with IPSS-R prognostic risk categories of intermediate, high and very high
- 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

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

In the COMMODORE 2 study, crovalimab was shown to be as effective as eculizumab for the two main study endpoints of haemolysis control (a measure of reduction in red blood cell destruction from Week 5 through Week 25), and transfusion avoidance (TA) (the proportion of patients no longer needing a blood transfusion from baseline to Week 25).
Crovalimab was also shown to be as effective as eculizumab in the other study endpoints measuring the incidence of isolated red blood cell lysis events occurring whilst on either treatment, as well as the stabilisation of the red blood cell component haemoglobin.
Similarly, consistent treatment benefit from crovalimab was seen in patients who switched from eculizumab to crovalimab in the crovalimab extension period and completed at least 24 weeks of crovalimab treatment (i.e., Arm B Switch patients). Furthermore, there is no evidence that crovalimab treatment benefit in paediatric patients is different than that observed in adult patients with PNH in the randomised arms of Study COMMODORE 2.

In the COMMODORE 1 study, crovalimab and eculizumab showed in a randomised comparison similar exploratory efficacy results as reported above. In addition, patients who

switched from eculizumab to crovalimab (Arm B Switch patients) in the crovalimab extension period, maintained disease control.

In the non-randomised Arm C exploratory cohorts that received crovalimab, in both the prior ravulizumab switch (19 patient) and prior high-dose eculizumab switch (9 patient) cohorts, the majority of patients maintained control over PNH-mediated red blood cell destruction from baseline through Week 25. In the C5 polymorphism cohort (6 patients) who, per investigator's assessment, had poorly controlled PNH-mediated red blood cell destruction with eculizumab or ravulizumab, most had a rapid and sustained decrease in red blood cell destruction (measured by the enzyme lactate dehydrogenase levels in a blood test). Suggesting that in this specific population, crovalimab may provide better control than the comparators.

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs).**

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

In the COMMODORE studies patient-reported outcomes were measured by the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30), measuring overall health status and functional and symptom measures. The outcomes of these measures were comparable overall for patients treated with either crovalimab or eculizumab.

Similarly, for patient-reported fatigue (tiredness), measured by the 13-item Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-Fatigue) questionnaire allowing assessment of an individual's level of fatigue during their usual daily activities over the past week, crovalimab performed at least comparably to eculizumab (a numerical benefit in the adjusted FACIT-Fatigue score for crovalimab versus eculizumab was seen in COMMODORE 2).

Patient preference was assessed in patients switching from eculizumab to crovalimab at week 17, with 84% preferring treatment with crovalimab. The remaining patients preferred eculizumab (10.5%) or had no preference (5.3%). The top three reasons for crovalimab

preference were “The way treatment was given was easier”, “Fewer hospital visits associated with treatment” and “Time to administer treatment was shorter”.

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

The overall safety profile of crovalimab was consistent with the known safety profile of C5 inhibitors (eculizumab and ravulizumab), and no additional safety concerns were identified. The safety results in the randomised 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.

The most frequent treatment-related side effects, occurring in over 10% of patients in crovalimab and eculizumab arms were: infusion-related reaction (14.8%, and 13.0%), white blood cell count decreased (11.9%, and 10.1%), and neutrophil count decreased (11.1%, and 10.1%).

For patients switching to crovalimab (or indeed those switching from crovalimab to another C5 inhibitor), there is a risk of developing side effects termed “transient immune complex reactions” (TICs) due to the different binding mechanisms of crovalimab and eculizumab/ravulizumab to the C5 protein in the complement cascade. For those patients switching to crovalimab treatment, 15.9% experienced a TIC reaction of any severity. The majority of TICs were low in severity, all of which were resolved without dose modifications/interruptions. One patient experienced a higher severity of TIC reaction, which resolved after treatment of the side effect with no dose modification/interruption of crovalimab needed.

The most frequently reported symptoms of TIC reactions were musculoskeletal and connective tissue disorders, skin, and subcutaneous tissue disorders.

Across COMMODORE 1 and COMMODORE 2, the average time for a TIC reaction to occur after treatment switch was 1.6 weeks (range, 0.7–4.4) and the average length of time for

resolution was 1.9 weeks (range, 0.4–34.1). Based on this information for these TICs, 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 TICs. It is important also, for patients to be aware of these side effects and remain vigilant for any symptoms that might occur and report them as soon as possible.

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration
-

People with PNH require life-long treatment. Current standard of care treatments, ravulizumab and eculizumab, are both administered intravenously, which can lead to a high treatment burden.

After an initial loading phase, crovalimab can be self-administered at home via subcutaneous injection. This is a new innovation for C5-inhibitor PNH treatments, and could represent a key benefit for people who value the convenience and flexibility associated with self-administered injections.

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

Crovalimab's mode of administration may not be preferred by patients who prefer to have more contact with the health service, as the majority of administrations will be done independently at home.

Transient immune complexes are unique to crovalimab and can form in in patients who have switched to crovalimab treatment from eculizumab or ravulizumab treatment. These mild, transient immune complex reactions manifest primarily as joint pain, fever, dizziness, nausea or skin reactions, and occurred in 16% of people switching from eculizumab to crovalimab in the crovalimab clinical studies.

3j) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

The objective of this analysis was to evaluate the costs associated with crovalimab compared with eculizumab and ravulizumab for the treatment of PNH from a UK (England and Wales) healthcare system perspective. A cost-comparison model was developed to capture the lifetime costs of people with PNH treated with crovalimab, eculizumab or ravulizumab.

Results from the COMMODORE 1 & 2 (18, 19) found comparable proportions of people with haemolysis control and avoidance of blood transfusions when receiving either eculizumab or crovalimab from baseline to Week 25. Similar (non-inferior) results were also demonstrated across other clinical and safety endpoints. The results of an indirect treatment comparison also demonstrated that crovalimab was similar in terms of safety and efficacy compared to ravulizumab, as well as eculizumab.

As such, a cost comparison where treatment efficacy, treatment safety and treatment discontinuation were all set equal was deemed appropriate and the preferred approach to estimate cost differences.

The results of the economic evaluation show that crovalimab has the potential to offer similar health benefits and comparable safety, at similar or lower overall costs to eculizumab and ravulizumab. Crovalimab has the potential to offer new and existing PNH patients an alternative treatment option, with a convenient subcutaneous mode of administration at home, while achieving similar health benefits and safety outcomes to existing intravenous C5-inhibitor treatment options.

3k) Innovation

NICE considers how innovative a new treatment is when making its recommendations. If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)
The long half-life and high bioavailability of crovalimab not only enables it to be administered SC rather than IV, but at a dosing schedule of every 4 weeks. Evidence related to PNH and other chronic conditions shows that these two treatment factors – mode of administration and dosing frequency – are valuable to patients and can impact their quality of life. In a phase 3 clinical trial comparing SC ravulizumab (discontinued) to IV ravulizumab in patients with PNH, patients reported increased satisfaction with the SC route of administration compared with the IV route in a treatment administration satisfaction questionnaire (11). Limited evidence exists on the caregiver burden for IV hospital infusion versus SC home treatment for PNH. However, for haemophilia A, a similar chronic disease, in a discrete choice experiment, caregivers significantly preferred treatment administered SC versus IV (20).

3l) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here
While the potential recommendation of crovalimab is not expected to impact equity of access to C5 inhibitors in England, the availability of subcutaneous crovalimab could reduce the treatment burden for people with PNH. The expected marketing authorisation for crovalimab covers people with PNH aged between 12 and 18 years old. While this is broader population than that covered by recommendation for ravulizumab, age is a protected characteristic under the Equality Act 2010, and given the NHS service specification for eculizumab covers this age group, this population should be considered in this appraisal.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc. Where possible, please provide open access materials or provide copies that patients can access.
• PNH National Service website: https://pnhserviceuk.co.uk/ • The Aplastic Anaemia Trust: https://www.theaat.org.uk/ • PNH Support: https://pnhuk.org/ Further information on NICE and the role of patients**:** • Public Involvement at NICE Public involvement | NICE and the public | NICE Communities | About | NICE • NICE's guides and templates for patient involvement in HTAs Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE • EUPATI guidance on patient involvement in NICE: https://www.eupati.eu/guidance-patient-involvement/ • EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf • National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/ • INAHTA: http://www.inahta.org/ • European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

4b) Glossary of terms

AAT	The Aplastic Anaemia Trust
BMF	bone marrow failure
BOI	burden of Illness
BW	body weight
C3	complement protein C3
C5	complement protein C5
CES	carer experience scale
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30

FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy – Fatigue
HCP	healthcare professional
HRQoL	health-related quality of life
IV	intravenous
MHRA	Medicines and Healthcare products Regulatory Agency
NICE	National Institute for Health and Care Excellence
NHS	National Health Service
PD	pharmacodynamics
PK	pharmacokinetic
PNH	paroxysmal nocturnal haemoglobinuria
PR	public relations
SC	subcutaneous
SD	standard deviation
TA	transfusion avoidance
TIC	transient immune complexes
UK	United Kingdom

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Crovalimab for treating paroxysmal nocturnal haemoglobinuria [ID6140]

Company response to clarification questions

July 2024

File name	Version	Contains confidential information	Date
ID6140 crovalimab EAG clarification letter_RPL_040724_noCON	1.0	Noo	4 July 2024

List of Tables and figures

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Section A: Clarification on effectiveness data

Literature searches

A1 Priority question: No SLR appears to have been conducted to evaluate the cost-effectiveness of crovalimab. Please conduct searches for cost effectiveness data, and provide details of all searches conducted and results found.

As was deemed suitable at the decision problem meeting, a cost comparison submission has been provided by the company. The approach taken to identify the data used in the analysis follows that outlined in relation to cost comparison assessments in the NICE Health Technology Assessment Manual. *"Whenever possible and appropriate, cost data and data sources should be consistent with any corresponding data and sources that were considered appropriate in the published NICE guidance for the comparator(s) for the same population"* [1]. As a full cost-effectiveness analysis was not deemed necessary at the decision problem meeting, an SLR of cost-effectiveness has not been conducted.

A2: Please provide full search strategies (including date ranges and dates searched) for the Cochrane Library (CDSR and CENTRAL) and PubMed as mentioned in D.1.4.

The search strategy for the Cochrane Library (CDSR and CENTRAL) and PubMed (Medline-In-Process) is provided in

Table **1** and **Table 2** below. Searches were run from database inception to 6th December 2022 for the original SLR.

Table 1: Search strategy for CENTRAL and CDSR (using Cochrane)

No.	Query	Results	Facet
1	MeSH descriptor: [Hemoglobinuria, Paroxysmal] explode all trees	55	Disease facet
2	(‘paroxysmal nocturnal haemoglobinuria’ OR ‘nocturnal haemoglobinuria’ OR ‘paroxysmal haemoglobinuria’ OR ‘nocturnal hemoglobinuria’ OR ‘paroxysmal nocturnal haemoglobinuria’ OR ‘marchiafava micheli syndrome’ OR ‘marchiafava syndrome’ OR ‘nocturnal paroxysmal haemoglobinuria’ OR ‘nocturnal paroxysmal hemoglobinuria’ OR ‘pnh’):ti,ab,kw	152	
3	#1 OR #2	152	
4	**#3 in Cochrane Reviews, Trials (CCTR and CDSR) (Conference abstracts and trial records excluded)**	**77**	**Final**

Table 2: Search strategy for MEDLINE In-Process (using PubMed)

No.	Query	Results	Facet
1	"paroxysmal nocturnal hemoglobinuria"[Title/Abstract] OR "nocturnal haemoglobinuria"[Title/Abstract] OR "paroxysmal haemoglobinuria"[Title/Abstract] OR "nocturnal hemoglobinuria"[Title/Abstract] OR "paroxysmal nocturnal haemoglobinuria"[Title/Abstract] OR "marchiafava micheli syndrome"[Title/Abstract] OR "marchiafava syndrome"[Title/Abstract] OR "nocturnal paroxysmal haemoglobinuria"[Title/Abstract] OR "nocturnal paroxysmal hemoglobinuria"[Title/Abstract] OR "pnh"[Title/Abstract]	3,923	Disease facet
2	#1 AND (inprocess[sb]	1	
3	#1 AND (pubstatusaheadofprint)	24	
4	**#2 OR #3**	**25**	**Final**

A3: Section D.1.7.1 states that all searches were updated in March 2024. Please provide full search strategies (including date ranges and dates searched) for all

databases searched and confirm if these numbers are included in the PRISMA flow diagram (Appendix D; Figure 2).

The updated search strategies for Embase/Medline (using Embase.com), the Cochrane Library (CDSR and CENTRAL) and PubMed (Medline-In-Process) are provided in

Table 3, **Table 5** and **Table 4** below. Searches were run from 1st December 2022 to 1st March 2024 for Embase.com and from 2022-2024 for Cochrane and Medline-In-Process. The details of the updated searches were reported separately in Section D.1.7.1 and these numbers were not included in the PRISMA flow diagram.

Table 3: Embase/Medline search strategy (using embase.com)

No.	Query	Results	Facet
1	'paroxysmal nocturnal hemoglobinuria'/exp	7,437	Disease facet
2	'paroxysmal nocturnal hemoglobinuria':ab,ti OR 'nocturnal haemoglobinuria':ab,ti OR 'paroxysmal haemoglobinuria':ab,ti OR 'nocturnal hemoglobinuria':ab,ti OR 'paroxysmal nocturnal haemoglobinuria':ab,ti OR 'marchiafava micheli syndrome':ab,ti OR 'marchiafava syndrome':ab,ti OR 'nocturnal paroxysmal haemoglobinuria':ab,ti OR 'nocturnal paroxysmal hemoglobinuria':ab,ti OR 'pnh':ab,ti	6,773	
3	#1 OR #2	8,822	
4	'clinical trial'/exp OR 'randomization'/de OR 'controlled study'/de OR 'comparative study'/de OR 'single blind procedure'/de OR 'double blind procedure'/de OR 'crossover procedure'/de OR 'placebo'/de OR 'clinical trial' OR 'clinical trials' OR 'controlled clinical trial' OR 'controlled clinical trials' OR 'randomised controlled trial' OR 'randomized controlled trial' OR 'randomised controlled trials' OR 'randomized controlled trials' OR 'randomisation' OR 'randomization' OR randomi OR random NEAR/1 assign OR rct OR 'random allocation' OR 'randomly allocated' OR 'allocated randomly' OR allocated NEAR/2 random OR (single OR double OR triple OR treble) NEAR/1 (blind OR mask) OR placebo OR 'prospective study'/de	12,853,901	Study design facet
5	#3 AND #4	2,724	
6	**#3 AND #4 AND [01-12-2022]/sd NOT [02-03-2024]/sd AND [english]/lim**	**363**	**FINAL**

Table 4: Search strategy for CENTRAL and CDSR (using Cochrane)

No.	Query	Results	Facet
1	MeSH descriptor: [Haemoglobinuria, Paroxysmal] explode all trees	90	Disease facet
2	(‘paroxysmal nocturnal hemoglobinuria’ OR ‘nocturnal haemoglobinuria’ OR ‘paroxysmal haemoglobinuria’ OR ‘nocturnal hemoglobinuria’ OR ‘paroxysmal nocturnal haemoglobinuria’ OR ‘marchiafava micheli syndrome’ OR ‘marchiafava syndrome’ OR ‘nocturnal paroxysmal haemoglobinuria’ OR ‘nocturnal paroxysmal hemoglobinuria’ OR ‘pnh’):ti,ab,kw	404	
3	#1 OR #2	404	
4	**#3 in Cochrane Reviews, Trials (CCTR and CDSR) for 2022-2024 (Conference abstracts and trial records excluded)**	**46**	**Final**

Table 5: Search strategy for MEDLINE In-Process (using PubMed)

No.	Query	Results	Facet
1	"paroxysmal nocturnal hemoglobinuria"[Title/Abstract] OR "nocturnal haemoglobinuria"[Title/Abstract] OR "paroxysmal haemoglobinuria"[Title/Abstract] OR "nocturnal hemoglobinuria"[Title/Abstract] OR "paroxysmal nocturnal haemoglobinuria"[Title/Abstract] OR "marchiafava micheli syndrome"[Title/Abstract] OR "marchiafava syndrome"[Title/Abstract] OR "nocturnal paroxysmal haemoglobinuria"[Title/Abstract] OR "nocturnal paroxysmal hemoglobinuria"[Title/Abstract] OR "pnh"[Title/Abstract]	4,137	Disease facet
2	#1 AND (inprocess[sb])	0	
3	#1 AND (pubstatusaheadofprint)	22	
4	**#2 OR #3**	**22**	**Final**

A4: Please provide details of the search terms used for searches of conference proceedings and clinical trial registries (D.1.4).

We primarily used the search terms for the disease of interest i.e. PNH and its synonyms. These included the following:

- PNH
- ‘Paroxysmal nocturnal hemoglobinuria’
- ‘Nocturnal haemoglobinuria’
- ‘Paroxysmal haemoglobinuria’
- ‘Nocturnal hemoglobinuria’
- ‘Paroxysmal nocturnal haemoglobinuria’
- ‘Marchiafava micheli syndrome’
- ‘Marchiafava syndrome’
- ‘Nocturnal paroxysmal haemoglobinuria’
- ‘Nocturnal paroxysmal hemoglobinuria’

A5: Table 2 in Appendix D reports a single search strategy for both MEDLINE and Embase searches via Embase.com. Please confirm if this is a single search of the Embase database conducted on the understanding that it now contains all records from MEDLINE.

This is correct; a single search was conducted via Embase.com to return both MEDLINE and Embase records. Using Embase.com, de-duplicated search hits from both MEDLINE and Embase databases are retrieved.

A6: Please confirm why American English spellings (such as 'hemoglobinuria' and 'randomized') were not included in the Embase/MEDLINE search strategy (Appendix D, Table 2).

The company would like to confirm that Index/Emtree terms in Embase include American English spellings for 'haemoglobinuria' and 'randomized'. The UK English spellings for all synonyms were also included as part of the title/abstract term search. Please see row 2 and row 4 of the Embase/MEDLINE search strategy (

Table 3 above, response A3) for details.

Decision problem

A7 Priority question: the marketing authorisation includes children from age 12, but the randomised comparison in the trials includes only adults i.e. at least age 18.

a) Please confirm that the decision problem, the proposed license and those expected to receive crovalimab would include children aged at least 12.

The population covered by the final scope was defined as people with PNH. The decision problem addressed in the submission covers the full population covered by the anticipated marketing authorisation, [redacted]

As described in Section B.1.1 of the company submission, while the expected marketing authorisation is broader than the population covered by the NICE recommendation for ravulizumab, which only includes adults, eculizumab is available through an NHS service specification ([B05/S(HSS)/a]) for adults and children with PNH [2] The anticipated marketing authorisation covering paediatric PNH patients is also in line with recent positive CHMP opinion received on the 27th June 2024, and the FDA approval for crovalimab from June 20th 2024.

Crovalimab has the potential to offer people with PNH aged between 12 and 18 an alternative convenient treatment option to eculizumab, which requires more frequent IV administration. As such, based on the available data in this population from the crovalimab Phase III trials (as further described in A7.b) and to avoid potentially disadvantaging people with PNH aged between 12 and 18 years who weigh 40 kg or more, the population addressed in this submission covers the anticipated full marketing authorisation for crovalimab.

b) Please provide comparative clinical evidence for children aged at least 12.

Across the Phase III studies, a total of [redacted], all <18 years old and ≥ 40 kg) were treated with crovalimab up to the primary analysis CCOD (16 November 2022) for studies BO42161 and BO42162, and up to the update analysis CCOD (10 August 2022) for study YO42311:

[redacted]

A discussion of the paediatric data in both treatment-naïve and switch populations is provided in the context of adult population data, although comparisons should be made with caution due to the paediatric group being considerably smaller. The small paediatric sample size is expected given that PNH is an extremely rare disease in adults and is even less frequent in children, with paediatric cases accounting for only 5 to 10% of the reported cases [3-8]. Given these epidemiologic considerations, it is not feasible to conduct a separate study in the PNH paediatric population with a large enough sample size for formal statistical testing to allow drawing of statistically robust conclusions. However, for these young individuals, the potential for a reduced treatment burden offered by crovalimab may be particularly impactful on their quality of life, especially in the context of a chronic disease requiring life-long treatment.

Overall, paediatric patients enrolled in the Phase III studies had similar baseline characteristics, PK, PD, and efficacy, as well as comparable safety profiles as compared with adult patients. This is aligned with the fact that in general, paediatric patients with PNH present a clinical profile and burden of disease similar to that of adult patients. Several retrospective analyses of paediatric series underscored the many similarities in the signs and symptoms of

intravascular haemolysis, serious infections, bone marrow failure and thrombotic events dominating the clinical picture of childhood and adult PNH [8, 9]. Additionally, the International PNH Registry study showed no differences in GPI-deficient granulocyte clone size, the incidence of bone marrow disorders, or the degree of intravascular haemolysis (as measured by LDH levels) between adult and paediatric patients [10].

Demographics and Baseline PNH History of Paediatric Patients

[redacted]

[redacted] generally had similar baseline disease characteristics with regards to clone size, baseline LDH, haemoglobin and transfusion requirements, and PNH sign and symptoms as compared to the overall adult population.

[redacted]

[redacted]

Efficacy in Paediatric Patients

Efficacy data for the endpoints of haemolysis control, transfusion avoidance, breakthrough haemolysis, and haemoglobin stabilisation from the primary treatment period (baseline to Week 25) or first 24 weeks of crovalimab treatment in the extension period (switch baseline to switch Week 25) is presented for the [redacted] Data for the endpoint of FACIT-Fatigue was not collected for paediatrics as the FACIT-Fatigue questionnaire was assessed only in patients ≥ 18 years. Due to the limited sample size, no summary statistics are presented.

In the [redacted] efficacy-evaluable treatment-naïve paediatric patients:

[redacted]

[redacted]

Although the sample size for paediatric patients is low, there is no evidence to suggest that treatment benefit of crovalimab in paediatric treatment-naïve patients is different from that observed in the treatment-naïve adult patients from the randomised arms of Study BO42162 (**Table 6**); Study BO42162 demonstrated the non-inferiority of crovalimab to eculizumab for haemolysis control (Week 5 to Week 25), and transfusion avoidance, breakthrough haemolysis, and haemoglobin stabilisation (baseline to Week 25) in treatment-naïve patients.

Table 6: Overview of efficacy results in study BO42162 (COMMODORE 2) randomised treatment-naïve patients

	Crovalimab Arm A (N=134)[1]	**Eculizumab Arm B (N = 69)**
Mean proportion of patients achieving haemolysis control (central LDH ≤1.5xULN), % (95% CI)	[redacted]	[redacted]
Odds Ratio[2] (95% CI)	[redacted]	
Proportion of patients with Transfusion Avoidance, % (95% CI)	[redacted]	[redacted]
Difference in proportions[3], % (95% CI)	[redacted]	
Proportion of patients with Breakthrough Haemolysis, % (95% CI)	[redacted]	[redacted]
Difference in proportions[3], % (95% CI)	[redacted]	

Proportion of patients with stabilised haemoglobin, % (95% CI)	[redacted]	[redacted]
Difference in proportions[3], % (95% CI)	[redacted]	

CI = confidence interval; LDH = lactate dehydrogenase
[1]One patient randomised to crovalimab did not have post-baseline LDH and was not included in the primary efficacy analysis
[2]Odds ratio calculated as odds for crovalimab divided by odds for eculizumab
[3]Difference calculated as crovalimab minus eculizumab

In the [redacted] efficacy-evaluable switch paediatric patient:

[redacted]

It is of note that as of a more recent CCOD (31 May 2023), [redacted]

Although the sample size for paediatric switch patients is low, there is no evidence to suggest that the treatment benefit of crovalimab is different from that observed in switch adult patients from the randomised arms of Study BO42161 (**Table 7**); Study BO42161 showed that the efficacy (from baseline to Week 25) in patients switching to crovalimab was similar to that of patients continuing eculizumab treatment.

Table 7: Overview of efficacy results in study BO421621 (COMMODORE 1) randomised switch patients

	Crovalimab Arm A (N=39)[1]	**Eculizumab Arm B (N=37)**
Mean proportion of patients achieving haemolysis control (central LDH ≤1.5xULN), % (95% CI)	[redacted]	[redacted]
Odds Ratio[2] (95% CI)	[redacted]	
Proportion of patients with Transfusion Avoidance, % (95% CI)	[redacted]	[redacted]

Difference in proportions[3], % (95% CI)	[redacted]
Proportion of patients with Breakthrough Haemolysis, % (95% CI)	[redacted]
Difference in proportions[3], % (95% CI)	[redacted]
Proportion of patients with stabilised haemoglobin, % (95% CI)	[redacted]
Difference in proportions[3], % (95% CI)	[redacted]

CI = confidence interval; LDH = lactate dehydrogenase
[1]Efficacy analyses included patients who had completed 24 weeks of treatment at the time of the primary analysis CCOD. At the time of primary analysis, five patients in each arm were still in the primary treatment period and therefore excluded in the efficacy analysis.
[2]Odds ratio calculated as odds for crovalimab divided by odds for eculizumab
[3]Difference calculated as crovalimab minus eculizumab

Safety Data in Paediatric Patients

[redacted]

Based on the available safety data in the total crovalimab population, there is no evidence that the safety profile of crovalimab in paediatric patients is different from that observed in adult patients from the total crovalimab population.

Pharmacokinetics/Pharmacodynamics Data in Paediatric Patients

[redacted]

Overall, the pharmacokinetic (PK) and PD profiles were similar between adults and paediatric patients, resulting in a comparable PK/PD relationship between the two groups (Figure 5).

Conclusion

Despite the rarity of PNH in paediatric patients, across the crovalimab Phase III studies, a total of [redacted] paediatric patients have been treated with crovalimab. Consistently with available data on PNH, baseline disease characteristics of the paediatric patients were similar to the ones of the adult patients enrolled across the crovalimab Phase III studies, and based on efficacy, safety, and PK/PD data, there was no evidence to suggest any difference in treatment benefit of crovalimab in paediatric patients compared to adults PNH patients. Furthermore, based on the similarity of the PK/PD/efficacy relationship, the efficacy of crovalimab could be extrapolated from adults to paediatric patients aged ≥12 years and weighing 40 kg and above.

The paediatric evaluation of eculizumab has also shown that C5 inhibitor management strategies of patients with PNH are similar regardless of age and PNH disease classification [11]. Since crovalimab shares the same mechanism of action as eculizumab/ravulizumab, age-dependent management of PNH with crovalimab is not warranted.

Overall, the consistent benefit/risk of crovalimab treatment shown in paediatric and adult patients, and similar pathophysiology of PNH and clinical manifestations of the disease across the age continuum [8, 9, 12], supports the crovalimab treatment benefit in paediatric patients ≥ 40 kg.

Figure 1: Plot of individual profiles of crovalimab concentration-time profiles (across phase III studies up to week 25) in treatment-naïve and treatment-switch PNH patients coloured by age groups

Figure redacted

Figure 2: Plot of individual profiles of free C5 concentration-time profiles (across phase III studies up to week 25) in treatment-naïve and treatment-switch PNH patients coloured by age groups

Figure redacted

Figure 3: Plot of individual profiles of complement activity (CH50)-time profiles (across phase III studies up to week 25) in treatment-naïve and treatment-switch PNH patients coloured by age groups

Figure redacted

Figure 4: Plot of individual profiles of normalized LDH-time profiles (across phase III studies up to week 25) in treatment-naïve and treatment-switch PNH patients coloured by age groups

Figure redacted

Figure 5: Scatterplot of individual observed CH50 versus time-matched crovalimab serum concentrations for the subjects in the crovalimab PD biomarker analysis data set, coloured by age category

Figure redacted

[redacted]. The red curve is a LOESS regression together with the 90% CI as shaded area. The red dashed horizontal line shows the LLOQ. The green dashed horizontal line represents the threshold for complete inhibition of terminal complement activity. The red dashed vertical line shows the crovalimab concentration threshold expected to lead to complete complement C5 inhibition. The first 12 weeks are excluded in switch patients. C5: complement component 5; CH50: terminal complement activity; CI: confidence interval; LIA: liposome immunoassay; LLOQ: lower limit of quantification; LOESS: locally estimated scatterplot smoothing.

c) Please either demonstrate equivalence in clinical evidence for children aged at least 12 for all relevant comparators or conduct a cost effectiveness analysis for children aged at least 12, independent of the one for adults.

The company acknowledges that the marketing authorisation and NICE recommendation of ravulizumab does not cover children aged between 12 and 18. As data in this subgroup is not available for all comparators, it is not possible to demonstrate clinical equivalence to all comparators in this patient group.

C5 inhibition provides effective control of the intravascular haemolysis which is the hallmark of PNH without changing the underlying PIG-A defective hematopoietic stem cell clone which is the pathological basis of the disease [13]. As such, the clinical efficacy of crovalimab in paediatric patients is anticipated to be equivalent to that in adults, where non-inferiority has been demonstrated compared to eculizumab.

While no significant difference is expected in outcomes for paediatrics compared to adults, limited patient numbers and data availability prohibit a full cost-effectiveness analysis from being conducted. The company recognises that these data limitations, and scope of the cost comparison process, present

a potential barrier to recommending crovalimab for use in paediatric patients with PNH. However, as noted in response to question A7.a, crovalimab has the potential to offer paediatric patients with PNH an alternative option to eculizumab, which is associated with an IV treatment burden and administered more frequently than crovalimab. The company therefore asks that the available evidence for paediatric patients is taken into consideration (see A7.b response) to avoid disadvantaging this patient group, who currently have limited treatment options available to them.

A8 Priority question: Some outcomes were omitted from the decision problem.

a) Please explain why overall survival and extravascular haemolysis were not included.

As crovalimab is a C5 inhibitor targeting intravascular haemolysis, all efficacy endpoints included in this study are related to this mechanism. The presence of intravascular haemolysis in the context of PNH can be identified by the highly sensitive biomarker of LDH, in the context of concurrent signs and symptoms of both intravascular haemolysis and anaemia. Further laboratory data which may support the diagnosis of intravascular haemolysis include microscopic analysis of a peripheral blood film. Further to this, the evaluation of intravascular haemolysis related endpoints follows the approach taken in the assessment of other C5 inhibitors. On the other hand, extravascular haemolysis is more poorly defined, both with regards to clinical diagnosis and internationally agreed criteria for the assessment of extravascular haemolysis. Further, the extent of extravascular haemolysis may also be quite heterogeneous and therefore difficult to quantify. As such, the challenge of collecting data on extravascular haemolysis related endpoints is not unique to crovalimab. Therefore, data related to extravascular haemolysis was not systematically collected for this study and no related endpoints were included.

Access to complement inhibition improves the prognosis of PNH considerably, with a survival rate of 96.7% after three years of eculizumab treatment [14]. Therefore, given the study length of 24 weeks, reporting of deaths is only descriptive and should be interpreted accordingly. Further to this, clinical expert opinion suggests that efficacy and safety across all C5 inhibitors considered in

the submission could be considered equivalent, and as such, overall survival is not expected to be different across treatments.

b) Please provide evidence of the treatment effect and/or demonstrate equivalence (crovalimab versus relevant comparators) for each of these two outcomes.

As noted in response to question A8.b, it was not possible to systematically collect extravascular haemolysis data, and the study length means only descriptive data on deaths is available from the COMMODORE studies. Therefore, it is not possible to conduct a meaningful comparative analysis in these outcomes.

A9 Priority question: Biosimilar products are referred to in the NICE scope and the CS states that two have recently been licensed by the MHRA on the basis if their similarity to eculizumab. However, one biosimilar, SB12, was included in the NMA separate to and connected with eculizumab via the SB12-3003 trial.

a) Please confirm that eculizumab biosimilars can be considered as equivalent to eculizumab and that therefore the treatment effect of the biosimilar versus crovalimab, including equivalence, can be assumed to be the same as eculizumab versus crovalimab.

As demonstrated in the SB12-3003 trial, the efficacy and safety of this eculizumab biosimilar (Epysqli), has been shown to be equivalent to that of the eculizumab originator (Soliris). SB12-3003 was included in the NMA network for completeness. Its exclusion is not anticipated to impact the overall results of the NMA, where crovalimab's non-inferiority to eculizumab and ravulizumab was demonstrated in key clinical outcomes; transfusion avoidance, breakthrough haemolysis events, and haemoglobin stabilisation (see section B.3.9.1, document B).

While included in the NMA for completeness, recent uptake data (April 2024 – IQVIA MIDAS [Data on File]) shows that eculizumab biosimilars are yet to be established in UK clinical practice, with only [redacted] sold since their approval, and therefore eculizumab biosimilars do not represent an appropriate comparator for consideration in this appraisal. A UK clinical expert consulted by Roche also noted that overall eculizumab usage is low, with roughly 5 to 7.5% cases of PNH treated with eculizumab, therefore ravulizumab represents the

current standard of care for UK PNH patients, further limiting the relevance of eculizumab biosimilars for consideration.

b) **If eculizumab biosimilars are not to be considered as equivalent to eculizumab the please present a full effectiveness and cost effectiveness analysis of crovalimab versus all comparators including eculizumab biosimilars.**

See response to A9.a, eculizumab biosimilars have demonstrated equivalent efficacy and safety to the eculizumab originator (Soliris). Further to this, eculizumab biosimilars are yet to be established in UK clinical practice, and therefore do not represent an appropriate comparator. As such, a full effectiveness and cost effectiveness analysis comparing crovalimab to eculizumab biosimilars has not been undertaken.

Systematic review

A10: How many reviewers carried out the quality assessment of trials and how did they do this in terms of independence?

Quality assessment of each trial was conducted by two independent reviewers, and discrepancies were resolved by a third reviewer.

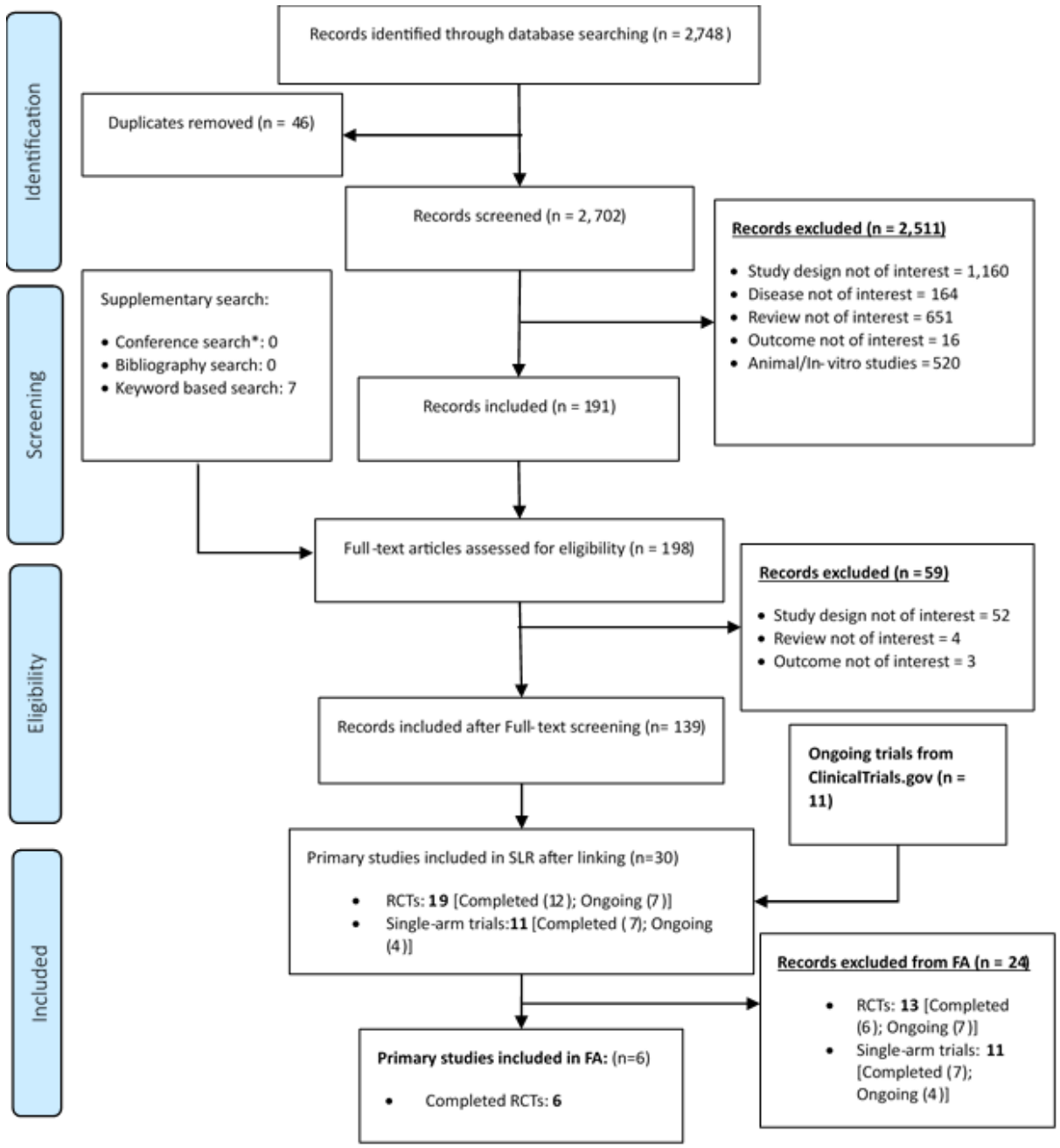
A11 Priority question: Appendix D of the CS (Section D.1.7 and Figure 2) indicates that 25 studies (17 RCTs and 8 single arm studies) were included in the clinical effectiveness SLR. However, figure 2 showed that only 6 RCTs and no single arm studies were included in the feasibility assessment, in subsection D.1.7.1 an update is reported where one more RCT and two more single arm studies are reported, and in the section on feasibility assessment (D.1.8), Table 6 shows 11 RCTs and 6 single trials.

a) **Please provide a complete PRISMA flow chart showing which studies were included and excluded and briefly why they were excluded from the SLR and feasibility assessment.**

The PRISMA flow diagram for the overall SLR (original and March 2024 update) is provided in Figure 6 below. Lists of studies included and excluded from the SLR and feasibility assessment are provided in the Excel file titled “Roche Crovalimab excluded studies SLR_noCON” accompanying this response

(separate worksheets are provided for studies excluded from the SLR and those excluded from the FA).

Figure 6: PRISMA flow diagram of included studies



b) Please provide a complete list of studies excluded at the full paper stage with reasons for exclusion.

A list of the 59 studies excluded at the full paper stage with reasons for exclusion is provided in the first tab of the Excel file titled “Roche Crovalimab excluded studies SLR_noCON” accompanying this response.

Clinical effectiveness evidence

A12 Priority question: How long had patients included in the COMMODORE 1 trial been taking eculizumab before entry to the trial.

As per the key inclusion criteria for Arms A and B in COMMODORE 1, patients must have had documented treatment with eculizumab according to the approved dosing recommended for PNH (900 mg Q2W) and completion of a minimum of 24 weeks of treatment prior to Study Day 1.

Comprehensive historical data on the treatment duration of eculizumab, beyond the 24- weeks prior to study enrolment, are not currently available due to limited insights into potential treatment delays, dose modifications/interruptions. Furthermore, treatment with C5 inhibitors does not change the underlying pathophysiology of PNH. Changes in the underlying PNH clone size are unrelated to treatment with a C5 inhibitor, and therefore the duration of prior eculizumab treatment is not expected to impact treatment outcomes.

A13 Priority question: The test of non-inferiority are stated to be based on a non-inferiority margin (NIM) for transfusion avoidance of a mean of 20%, which was based on point estimates from Study 301 for eculizumab and, the so-called “global PNH registry” for no treatment. However, it is unclear what the estimates and sources are for the haemolysis control NIM odds ratio of 0.2. Also, the NIM

is usually and recommended by the FDA to be based on the difference between the point of no difference and the lowest point on the 95% CI of the treatment effect of the reference treatment, in this case eculizumab, and no treatment/placebo only.[1,2]

a) **Please provide full details of the sources and estimates from these sources for calculation of the NIM for both outcomes.**

See below

b) **Please comment on the appropriateness and implications of the NIM used in the context with the usual method of its calculation in terms of the lowest point on the 95% CI, as recommended by the FDA.**

See below

c) **Please perform an assessment of non-inferiority using the usual method of NIM calculation in terms of the lowest point on the 95% CI, as recommended by the FDA.**

See below.

The company acknowledges the questions and provides the requested information below, separately for the two co-primary endpoints.

Transfusion Avoidance (TA)

a) Full details of the sources and estimates from these sources for calculation of the NIM.

The company would like to clarify that as cited in the Study BO42162 Protocol Version 6 and Statistical Analysis Plan (SAP) Version 3, the information available to the Company from the International Global PNH Registry™ is cited from the ALXN Study 301 Protocol and SAP (NCT02946463). These documents provide only the TA point estimates of eculizumab treated patients (57.1%) and untreated patients (18.6%), resulting in a difference of approximately 40%. Per the Company's review of relevant literature (Soliris Type II Variation Procedure No. EMEA/H/C/000791/II/0066 [cited in ALXN Study 301 SAP] [15, 16], all published manuscripts on the International Global PNH Registry™ as listed in the Published Manuscripts page of the registry site [https://pnhregistry.com/publications]), no additional details, specifically in terms of sample size or standard error, are publicly available to allow for the computation of the 95% confidence interval (CI) for the cited difference.

b) The appropriateness and implications of the NIM.

The NIM was derived using the point estimates from ALXN Study 301 SAP based on operational and feasibility considerations and was considered appropriate in the context of the rarity of PNH. A more conservative NIM being derived using FDA's recommended calculation method would have resulted in an estimated sample size being too large and infeasible given the rarity of PNH.

c) Performing an assessment of non-inferiority using the usual method of NIM calculation in terms of the lowest point on the 95% CI.

Since the 95% CI for the difference cannot be computed as described in a), it is not feasible for the Company to re-derive the NIM using FDA's recommended method of NIM calculation based on the lower bound of the 95% CI for the difference.

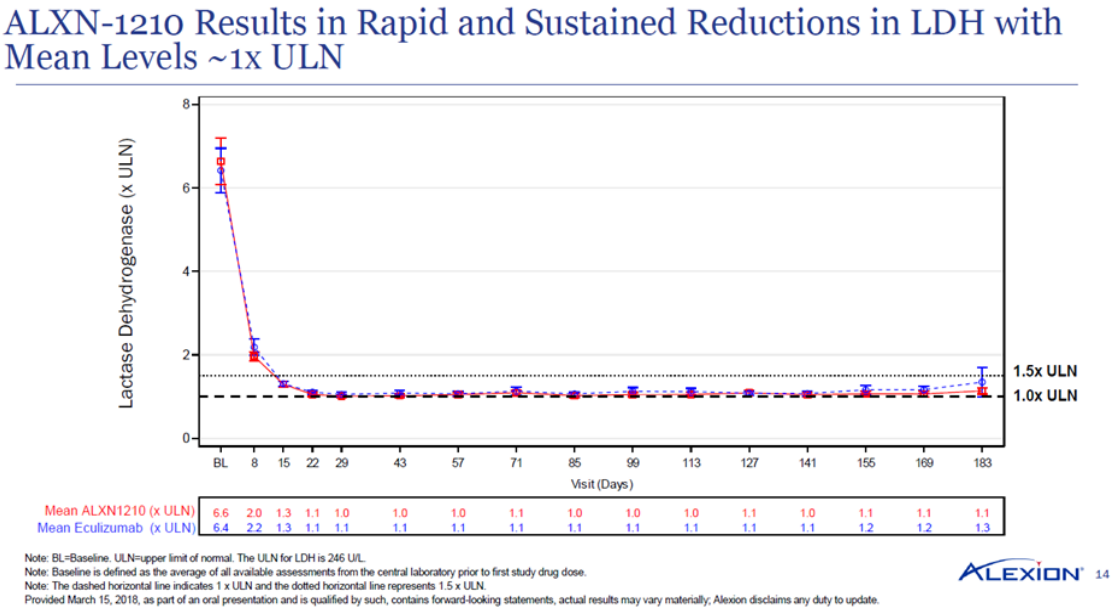
Haemolysis Control (HC)

a) Full details of the sources and estimates from these sources for calculation of the NIM.

Assumption of an 86% Proportion for Eculizumab-treated Patients

The 86% proportion for eculizumab-treated patients achieving HC (LDH ≤ 1.5 × ULN) was estimated using data from the eculizumab arm in the ALXN 301 Study [15], which evaluated the efficacy and safety of ravulizumab compared to eculizumab in patients with PNH who are naïve to complement inhibitor treatment. The graph of means and 95% confidence intervals (CI) in LDH over time was available online from top-line results material provided by Alexion on 15 March 2018 (see Figure 7).

Figure 7: Lactate Dehydrogenase (1 × ULN) Results in ALXN 301 Study



Source: Top-line results material provided by Alexion on 15 March 2018

The Company used the information displayed in this figure for estimation of the proportion of eculizumab-treated patients achieving haemolysis control as detailed in the following steps:

1. Based on Figure 7, numerical values for means and 95% CI (× ULN) at each visit were retrieved (via visual inspection).
2. Standard deviations (SD) at each visit were calculated based on the 95% confidence intervals and the number of eculizumab-treated patients in ALXN 301 study (N = 121) for all visits as follows:

$$SE = \frac{Length\ of\ Error\ bar}{1.96}, SD = SE \times \sqrt{N}$$

From step 1 and step 2, the following data was obtained:

Day	29	43	57	71	85	99	113	127	141	155	169	183
Mean	1.05	1.08	1.06	1.11	1.05	1.12	1.12	1.08	1.07	1.15	1.15	1.34
Error bar	0.05	0.06	0.06	0.1	0.05	0.1	0.09	0.06	0.05	0.1	0.08	0.35
SD	0.28	0.34	0.34	0.56	0.28	0.56	0.51	0.34	0.28	0.56	0.45	1.96

Of note, the Company used N = 121 throughout for simplicity as a conservative calculation approach despite the fact that some visits may have had missing data.

3. Assuming LDH values being log-normally distributed, probabilities of LDH ≤ 1.5 × ULN at each visit were calculated using the means and the standard deviations as follows:

$$Variance\ in\ log(LDH) = log\left[\left(\frac{SD}{Mean}\right)^2 + 1\right]$$

$$Mean\ in\ log(LDH)\ =\ log(Mean) - \frac{Variance\ in\ log(LDH)}{2}$$

$$log(LDH) \sim N(Mean\ in\ log(LDH), Variance\ in\ log(LDH))$$

Based on these parameters, Prob(log(LDH) ≤ log(1.5 × ULN)) was computed as follows:

Day	29	43	57	71	85	99	113	127	141	155	169	183
Prob (LDH ≤ 1.5 x ULN)	0.932	0.891	0.899	0.808	0.932	0.803	0.814	0.891	0.925	0.790	0.814	0.739

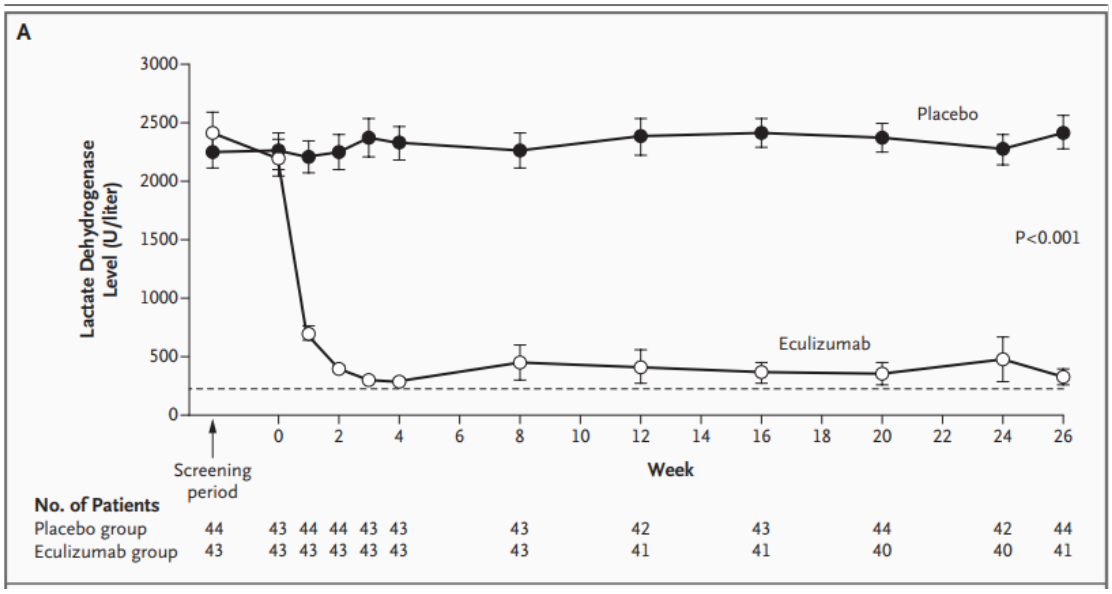
4. The average probability of LDH ≤ 1.5 × ULN from Study Day 29 to Study Day 169 was calculated, resulting in an estimated proportion of 86% for eculizumab-treated patients. As stated in the study BO42162 SAP version 3 (Report 1109893, Appendix 16.1.9, Section 2.3, p. 17), the same proportion was assumed for crovalimab.

The Assumption of a 20% Proportion for Placebo-treated Patients

The assumed 20% proportion in placebo-treated patients was based on the data from the placebo arm in the TRIUMPH study and from information provided in the ALXN 301 study SAP. According to Hillmen and colleagues, all patients had LDH levels at least 5 times above ULN at Week 26 in the placebo group (Figure 8) [17]. In the ALXN 301 study SAP, it was described that the proportion of placebo-treated patients with LDH ≤ 1 × ULN in the TRIUMPH study was 0% at all visits, with upper bounds of the 95% CIs of 10%, with the TRIUMPH study population being restricted to patients with baseline characteristics similar to those expected to enrol in the ALXN 301 study. Based on this and the fact that all patients in the TRIUMPH study had LDH > 5 × ULN,

the upper bound of the 95% CI for the proportion of patients with LDH ≤ 1.5 × ULN also would be estimated as 10%. However, in order to account for the use of different LDH cut-offs for the definition of the haemolysis control endpoint (1.5 × ULN in crovalimab PNH studies compared with 1.0 × ULN in the ALXN 301 study), and given the non-randomized source of the estimated haemolysis control proportions for eculizumab- and placebo-treated patients, the Applicant used a proportion of 20% as a conservative assumption to derive and justify the NIM.

Figure 8: TRIUMPH Study LDH Results



Panel A shows the degree of intravascular haemolysis according to the mean levels of lactate dehydrogenase from baseline (Week 0) to Week 26 in the two study groups. The dashed line indicates the upper limit of the normal range for lactate dehydrogenase (normal range, 103 to 223 U per liter). In the eculizumab group the mean level of lactate dehydrogenase was reduced to just above the upper limit of the normal range at Week 26; of 41 patients in this group who completed the study, 15 had levels within the normal range. In the placebo group, all patients had levels at least five times above the upper limit of normal at Week 26. Source: Figure 1A and its footnote in Hillmen et al. 2006.

b) The appropriateness and implications of the NIM

The choice of the NIM was based on both clinical and statistical considerations, and in the light of the rarity of the disease. From a statistical point of view, as outlined in the BO42162 protocol Version 6 (Report 1109893, Appendix 16.1.1, p.108) and the SAP Version 3 (Report 1109893, Appendix 16.1.9, p.17), the NIM of 0.2 was chosen to preserve at least 50% of the treatment effect of eculizumab compared to placebo. This margin was considered the most clinically acceptable in preserving the eculizumab treatment effect compared to placebo. The robustness of the NIM is further solidified by that fact that haemolysis control is a co-primary endpoint together with TA, both of which were required to meet non-inferiority in order for crovalimab to be claimed non-inferior to eculizumab. Taking all the above aspects into consideration, as well as the expected similarity in safety profile between crovalimab and eculizumab and the convenience of subcutaneous (SC) injection of crovalimab, the selected NIM was interpreted to be clinically acceptable.

c) Performing an assessment of non-inferiority using the usual method of NIM calculation in terms of the lowest point on the 95% CI

Difference between Eculizumab and Placebo

For this calculation, the same assumptions were made on the proportion of patients with LDH ≤ 1.5 × ULN as described in a) (i.e., 86% for eculizumab and 20% for placebo).

In ALXN 301 study, 121 patients were enrolled in the eculizumab arm [15]. For TRIUMPH study, the number of patients used for the NIM derivation was not reported but was estimated based on the 0% proportion of patients with LDH ≤ 1 × ULN, and the corresponding upper bound of the 95% CI of 10%, which were reported in ALXN 301 study SAP. Based on these data, the sample size would be 35 using the Clopper and Pearson exact CI method (i.e., by applying the following formula):

Upper bound = $(x + 1)/[x + 1 + (n - x)/F2(x + 1),2(n - x)(1 - \alpha/2)]$ [18], where x is the number of responders and using a grid search.

From the calculation above, the lower bound of the 95% CI for the Odds Ratio (OR) between eculizumab and placebo was estimated as 9.24 (**Table 8**).

Table 8: Proportions of patients with LDH ≤ 1.5 x ULN and OR between eculizumab and placebo

Results in each arm	OR (95% CI)
eculizumab: 86% (N = 121) [a] vs. Placebo: 20% (N = 35) [b] (Indirect comparison)	24.47 (9.24, 64.82) [c]

[a] Data source: Assumed value from results in ALXN 301 study [15].
[b] Data source: Assumed value from results in TRIUMPH [17] and ALXN 301 Study SAP.
[c] Calculated from the assumed values. 95% CI is calculated by the Wald method.
Note: The OR of 24.6 used in the protocol was derived using the assumed proportions of 86% vs. 20%, while the OR in this table was derived using 104/121 (=85.95%) instead of 86% for eculizumab.

Assessment of non-inferiority using the NIM based on the lower bound of the 95% CI

The rederived NIM based on the lower bound of the 95% CI for the odds ratio (OR) to maintain 50% preserved effect is 0.33 (= $1/9.24^{0.5}$). This rederived NIM is still lower than the estimated lower bound of the 95% CI for the OR of the haemolysis control results [OR 1.02 (95%CI: 0.57, 1.82); see BO42162 CSR Table 17].

Indirect treatment comparison (ITC)

A14 Priority question: Potential prognostic factors were shown in Table 7 of Appendix D.

a) Why was overall survival used as the outcome for assessing prognostic factors, given that it was not an outcome in any of the network meta-analyses (NMAs)?

Overall survival was used to structure the table as the overarching endpoint, however, mediated by age, LDH level, prior transfusions, history of aplastic anaemia and history of major adverse vascular event. These are key trial endpoints and aligned with the stratification factors in COMMODORE 1 and 2. The NICE technology appraisal guidance TA778 also identified Hb level as an additional factor [19]. The feasibility assessment was based on these endpoints.

b) Please justify the NMA feasibility assessment according to factors prognostic or treatment effect modifying for the outcomes included in the NMAs.

As described in section D.1.8 of the submission Appendix, a targeted search identified two observational studies (a multi-centre study (11), n=59, and a registry-based analysis (12), n=2356) and an expert panel review, identified potential prognostic factors or treatment modifiers. These sources indicated that age, PNH subtype, Karnofsky performance score, and thromboembolism/history of thrombosis may be potential prognostic factors or

treatment-effect modifiers for efficacy outcomes (Table 7, Appendix D). In addition, pRBC transfusion history and lactate dehydrogenase (LDH) level were used for stratification in the COMMODORE trials.

Pancytopenia (i.e., bone marrow failure not diagnosed as aplastic anaemia) and thrombocytopenia <30 and infection at diagnosis are also prognostic factors, which were accounted for by excluding these patients from the COMMODORE studies [20, 21].

A15 Priority question: It is reported in Appendix D that there was a qualitative heterogeneity assessment.

a) Please provide the results of this assessment i.e. a comparison of all relevant studies, updated if necessary, by the response to question A11, in terms of all sources of heterogeneity that might affect the estimate of treatment effects in the NMA.

The list of studies considered in the FA is provided in the Excel file titled “Roche Crovalimab excluded studies SLR_noCON” accompanying this response, along with reasons for excluding trials found in the SLR but not in the evidence network. Non-comparative (i.e., single-arm) trials were not considered in the FA, as they are by definition not connected to the evidence network. The SLR identified 19 trials for which data were published or otherwise available, and 7 ongoing RCTs. Of the 19 trials with data published or otherwise available, 13 (described in Table 9) were excluded from the FA.

Table 9: List of studies considered in the FA/NMA

Study identifier	NCT ID	Status	Search	Incl / Excl in FA	Reason of exclusion
CLNP023X2204	NCT03896152	Completed	Initial	Excluded from NMA	The study is not connected to the network.
ECU-PNH-III	NCT04463056	Completed	Initial	Excluded from NMA	Mixed treatment status (treatment-naïve, previously treated); outcomes not reported separately for the two subgroups. The small sample size may also have impaired the randomisation effect for rare events.
PEGASUS	NCT03500549	Completed	Initial	Excluded from NMA	Patients enrolled in this study had no response to earlier anti-C5 treatment (<10.5 g/dL despite receiving a stable dose of eculizumab for 3 months or longer before screening). Non-comparable to COMMODORE 1 trial.
Study-301	NCT02946463	Completed	Initial	Included	
Study-302	NCT03056040	Completed	Initial	Included	
TRIUMPH	NCT00122330	Completed	Initial	Included	
SB12-3003	NCT04058158	Completed	Initial	Included	
ALXN1210-PNH-303	NCT03748823	Completed	Initial	Excluded from NMA	Primary endpoint was evaluated after 10 weeks instead of 24 weeks.
SHEPHERD	NCT00130000	Completed	Initial	Excluded from NMA	Single arm trial
PRINCE	NCT04085601	Completed	Initial	Excluded from NMA	The study is not connected to the network. The only option would be via TRIUMPH, which enrolled patients who were transfusion dependent. Furthermore, TRIUMPH and PRINCE were conducted in different time periods (and geographic locations) adding uncertainty around how comparable the two SOC/Placebo arms are.
APPLY-PNH	NCT04558918	Completed	Initial	Excluded from NMA	Patients included had residual anaemia (Hb <10 g/dl) despite a stable regimen of anti-C5 treatment in the last six months prior to randomisation. Non-comparable to COMMODORE 1 trial.
R3918-PNH-2092	NCT04811716	Completed	Initial	Excluded from NMA	Dose-ranging comparison of pozelimab, in combination with cemdisiran. The study is not connected to the network.

CONSERVE	NCT03829449	Completed	Initial	Excluded from NMA	Single arm trial
ALXN1210-PNH-304	NCT03406507	Completed	Initial	Excluded from NMA	Single arm trial
R3918-PNH-1868	NCT04162470	Completed	Initial	Excluded from NMA	Single arm trial
COMMODORE 3	NCT04654468	Completed	Initial	Excluded from NMA	Single arm trial
COMMODORE 1	NCT04432584	Ongoing	Initial	Included	
COMMODORE 2	NCT04434092	Ongoing	Initial	Included	
ALPHA	NCT04469465	Ongoing	Initial	Excluded from NMA	No results available
ACCESS 2	NCT05131204	Ongoing	Initial	Excluded from NMA	No results available
ACCESS-1	NCT05133531	Ongoing	Initial	Excluded from NMA	No results available
REDEEM-1	NCT05116774	Ongoing	Initial	Excluded from NMA	No results available
CLNP023C12001B	NCT04747613	Ongoing	Initial	Excluded from NMA	Single arm trial
ALXN2040-PNH-303	NCT05389449	Ongoing	Initial	Excluded from NMA	Single arm trial
CLNP023C12303	NCT05630001	Ongoing	Initial	Excluded from NMA	Single arm trial
ABP 959/Eculizumab RP	NR	Complete	Update	Excluded from NMA	Biosimilar study for eculizumab reporting PK results
Study 307	NCT03531255	Ongoing	Update	Excluded from NMA	Single arm trial
APPOINT-PNH	NCT04820530	Complete	Update	Excluded from NMA	Single arm trial
ACCESS-EXT	NCT05744921	Ongoing	Update	Excluded from NMA	Single arm trial
A Study of MY008211A in Adult Patients With Paroxysmal Nocturnal Hemoglobinuria (PNH)	NCT06050226	Ongoing	Update	Excluded from NMA	No results available

Heterogeneity assessment (previously treated PNH)

Treatments

Dosing and treatment schedules for the common comparator arms are shown in **Table 10**. Both COMMODORE 1 and Study-302 administered eculizumab at 900 mg every 2 weeks.

Table 10: Common comparators and dosing schedules for studies in the network.

Study	Comparator arm	Eculizumab
COMMODORE 1	Eculizumab	900 mg IV q2w
Study 302	Eculizumab	900 mg IV q2w

Endpoints

In addition to forming a small network connected by common comparators, key endpoints were similar for the two studies, as summarised in **Table 11**.

Table 11: Endpoints reported across published and ongoing studies compared to COMMODORE 1.

Study identifier	Transfusion avoidance	BTH	Haemo-lysis control	Haemoglobin stabilisation	pRBC transfusion	FACIT-Fatigue score
COMMODO-RE 1	Week 25	Week 25	Week 25	Week 25	Week 25	Week 25
Study 302	Week 26	Week 26	Week 26	Week 26	Week 26	Weeks 0, 4, 26

BTH: breakthrough haemolysis; LDH: lactate dehydrogenase; pRBC: packed red blood cell.

Assessment of the global evidence network indicates that this network of two studies remains connected and potentially informative for up to 6 endpoints: TA, BTH, haemolysis control, Hb stabilisation, pRBC transfusion and FACIT-Fatigue score.

Definitions for the most commonly reported endpoints appeared to be consistent across the published trials, as shown in **Table 11**. In addition, COMMODORE 1 and Study-302 reported outcomes at similar time points (weeks 24-26).

Inclusion / exclusion criteria

Inclusion and exclusion criteria are compared in **Table 12** and **Table 13**, respectively. Study-302 and COMMODORE 1 were consistent in terms of age and diagnostic criteria. As in COMMODORE 1, Study-302 recruited adult patients without age restriction and specified a diagnosis of PNH confirmed by high-sensitivity flow cytometry.

Study-302 included patients previously treated with eculizumab alone for at least 6 months, and employed similar criteria as COMMODORE 1 for minimum patient weight. In COMMODORE 1, eligible patients were required to have LDH levels ≤2x ULN, while in Study-302 LDH levels had to be ≤1.5x ULN.

Table 12: Inclusion criteria for COMMODORE 1 versus other trials.

Trial name	Age	Diagnosis	Prior treatment	Weight	LDH
COMMODORE 1	≥18	Documented PNH, confirmed by high sensitivity flow cytometry	ECU for ≥6 months	≥40 kg	≤2x ULN
Study 302	≥18	Documented PNH, confirmed by high sensitivity flow cytometry	ECU for ≥6 months	≥40 kg	≤1.5x ULN

ECU: eculizumab; HB: haemoglobin; NR: not reported; PNH: paroxysmal nocturnal haemoglobinuria; RAV: ravulizumab.

In terms of exclusion criteria, COMMODORE 1 excluded patients with prior myelodysplastic syndrome, whereas Study-302 excluded patients with other prior disease history such as liver disease. Both trials excluded patients with previous bone marrow transplant and had similar exclusion criteria related to pregnancy/contraception. COMMODORE 1 excluded patients with active hepatitis.

Table 13: Exclusion criteria for COMMODORE 1 versus published trials.

Trial name	Disease history	Prior transplant	Infection	Pregnancy
COMMODORE 1	Myelodysplastic syndrome with IPSS-R intermediate, high or very high risk	Bone marrow	Active hepatitis B/C	Currently or intending
Study 302	Unstable medical conditions (e.g., myocardial ischemia or coexisting chronic anaemia unrelated to PNH) or major cardiac, pulmonary, renal, endocrine, or hepatic disease	Bone marrow	-	Currently pregnant or breastfeeding

NR: not reported; PNH: paroxysmal nocturnal haemoglobinuria; RAV: ravulizumab. Dash (-) indicates criterion not reported.

Overall, inclusion/exclusion criteria including diagnoses, prior treatments, absence of bone marrow transplant history, and absence of serious infections were consistent across both studies.

Baseline characteristics

Differences in baseline characteristics, including prognostic factors/effect modifiers, are shown in

Table 14. Characteristics identified as potential prognostic factors or treatment-

Trial name	Age (yrs)	Sex (male)	Ethnicity (Asian)	LDH (U/L)	Hb (g/dL)	Prior transf-usions	Aplastic anaemia	Dis du (ye
COMMODORE 1	Mn: 44.4 49.5	53% 50%	20% 16%	Mn: 249.2 234.2	Mn: 11.0, 10.7 (Rg: 7.2-15.3, 6.8-14.4)	23%, 25%	33%, 36%	Mc 6.3
Study 302	Mn: 46.6 48.8	49%, 52%	19%, 24%	Mn: 228.0235 .2	Mn: 10.9, 11.1	12%, 13%	35%, 40%	NR

effect modifiers, based on the ad hoc review (Section 3.4), are age, LDH level, prior transfusions, history of aplastic anaemia and history of major adverse vascular event. The NICE technology appraisal guidance TA778 also identified Hb level [22]. The trial populations seem comparable in terms of these characteristics.

Table 14: Baseline characteristics in published trials for previously treated PNH

Trial name	Age (yrs)	Sex (male)	Ethnicity (Asian)	LDH (U/L)	Hb (g/dL)	Prior transf-usions	Aplastic anaemia	Disease duration (years)	Weight (kg)	History of MAVE
COMMODORE 1	Mn: 44.4 49.5	53% 50%	20% 16%	Mn: 249.2 234.2	Mn: 11.0, 10.7 (Rg: 7.2-15.3, 6.8-14.4)	23%, 25%	33%, 36%	Md: 6.3, 10.4	77, 76	23%, 22%
Study 302	Mn: 46.6 48.8	49%, 52%	19%, 24%	Mn: 228.0235 .2	Mn: 10.9, 11.1	12%, 13%	35%, 40%	NR	72, 73	NR

Hb: haemoglobin; LDH: lactate dehydrogenase; Md: median; Mn: mean, NR: not reported; Rg, range; U/L: units per litre; MAVE: major adverse vascular event.

Heterogeneity assessment (treatment-naive)

Treatments

The common comparator arms in the network are compared in **Table 15**. TRIUMPH, Study-301, SB12-3003, and COMMODORE 2 used eculizumab at a consistent dosing schedule. In addition to its eculizumab comparator arm, SB12-3003 investigated a biosimilar of eculizumab as the investigational drug of interest. The dosing schedule for this biosimilar was the same as for the eculizumab comparator.

Table 15: Common comparators and dosing schedules in the network compared to COMMODORE 2.

Study	Comparator arm	Eculizumab
COMMODORE 2	eculizumab	Loading dose of 600mg IV qw for 4 weeks, followed by maintenance dose of 900mg IV q2w
TRIUMPH	eculizumab	Loading dose of 600 mg IV qw for 4 weeks, followed by maintenance dose of 900 mg IV q2w
Study-301	eculizumab	Induction dose of 600mg IV on days 1, 8, 15, and 22 and subsequent maintenance doses 900mg IV on day 29 and q2w thereafter.
SB12-3003	eculizumab	600mg IV qw on weeks 0–3, followed by 900 mg IV q2w on weeks 4–50

ECU: eculizumab; IV: intravenous.

Endpoints

The key endpoints reported across the studies are summarised in **Table 16**. The most commonly reported endpoints were TA (3/4 studies), Hb stabilisation (3/4 studies), RBC transfusion (4/4 studies), and FACIT-Fatigue score (3/4 studies). Definitions for the most commonly reported endpoints (TA, pRBC transfusion, and FACIT-Fatigue) were fairly consistent across the published trials, as shown in **Table 16**, with the exception of Hb stabilisation in TRIUMPH. Therefore, the comparison with the placebo arm in TRIUMPH should be interpreted with caution.

Table 16: Endpoints reported across studies compared to COMMODORE 2

Study identifier	Transfusion avoidance	BTH	Haemolysis control	Haemoglobin stabilisation	pRBC transfusion	FACIT-Fatigue score
COMMOD-ORE 2	week 25	week 25	week 25	week 25	week 25	week 25
TRIUMPH	week 26	-	-	week 26	week 26	weeks 2, 4, 12, 26
Study-301	week 26	week 26	week 26	week 26	week 26	weeks 4, 26
SB12-3003	-	-	-	-	week 26	-

BTH: breakthrough haemolysis; LDH: lactate dehydrogenase; pRBC: packed red blood cell.

Inclusion / exclusion criteria

As shown in

Table 17, inclusion/exclusion criteria across trials were relatively consistent

Trial name	Age	Diagnosis	LDH	Weight	Transplant	Prior treatm
COMMODORE 2	≥18	PNH, confirmed by high sensitivity flow cytometry	≥2 x ULN	≥40 kg	No history of bone marrow transplant	No previous current complement inhibitors
TRIUMPH	✓	✓	✓ ≥1.5	NR	✓	✓
Study-301	✓	✓	✓ ≥1.5	✓	✓	✓
SB12-3003	✓	✓	✓ ≥1.5	NR	✓	✓

with those in COMMODORE 2. Minor differences included LDH levels of ≥2x ULN in COMMODORE 2 (versus ≥1.5x ULN in others). The TRIUMPH study enrolled patients who were transfusion dependent (i.e., at least 4 transfusions in the last 12 months prior to study entry). As noted before, transfusion history is considered a key effect modifier in the NICE technology appraisal guidance TA778; therefore, the comparison with the placebo arm in TRIUMPH should only be interpreted for patients who are transfusion dependent.

Table 17: Inclusion/exclusion criteria for COMMODORE 2 versus published trials

Trial name	Age	Diagnosis	LDH	Weight	Transplant	Prior treatment	Transfusions
COMMODORE 2	≥18	PNH, confirmed by high sensitivity flow cytometry	≥2 x ULN	≥40 kg	No history of bone marrow transplant	No previous or current complement inhibitors	No restriction
TRIUMPH	✓	✓	✓ ≥1.5	NR	✓	✓	Who had received at least four transfusions during the previous 12 months
Study-301	✓	✓	✓ ≥1.5	✓	✓	✓	✓
SB12-3003	✓	✓	✓ ≥1.5	NR	✓	✓	✓

NR: not reported; ULN: upper limit of normal.
Note: ✓ = consistent with COMMODORE 2. LDH = lactate dehydrogenase.

Baseline characteristics

Differences in baseline characteristics are shown in **Table 18**. Characteristics identified as potential prognostic factors or treatment-effect modifiers based on our ad hoc review (Section 3.4) are age, LDH level, prior transfusions, history of aplastic anaemia and history of major adverse vascular event. The NICE technology appraisal guidance TA778 also identified Hb level.

Trials were consistent in terms of patients' age at baseline. LDH levels appeared consistent across trials, except for Study-301 which enrolled patients with lower baseline LDH. Transfusion history was reported either as proportion of patients with prior transfusion, or as mean transfusion events; studies appeared to be consistent except for the SB12-3003 trial, which enrolled a slightly lower proportion of transfused patients compared to Study-301. History of aplastic anaemia was reported in 3 out of 4 published trials, with a slightly higher proportion of patients in COMMODORE 2. Major vascular events were sparsely reported, at similar rates across trials.

For other baseline characteristics, trials were consistent in terms of sex. Ethnic makeup (in terms of proportion of patients with Asian ethnicity) was available in 3 out of 4 published trials. Two trials (TRIUMPH, Study-301) enrolled ~50% patients with Asian ethnicity.

Weight, history of myelodysplastic syndrome, renal impairment, and Hb levels were sparsely reported across trials. In published trials where these parameters were available, the data did not appear to differ substantially from COMMODORE 2.

Overall, the study populations seem reasonably comparable, with the exception of the TRIUMPH study where any interpretation should be made only for transfusion-dependent patients.

Table 18: Baseline characteristics in published trials treatment-naïve PNH versus COMMODORE 2 (current network as at mid-2023)

Study identifier	Age (years)	Sex (male)	Race (Asian)	Weight (kg)	LDH *Mean (SD) Md [Range]*	Transfusion history	Aplastic anaemia	Myelodysplastic syndrome	Renal impairment	Major vascular event	Hb mean (SD) (g/dL)
COMMODORE 2	*Md [range]* 36 [18-76], 38 [17-78]	57%, 51%	74%, 64%	*Md (range)* 66.1 (42.0-140.3), 62.2 (47.0-122.0)	U/L 1770.6 (790.02), 1817.5 (829.09)	With: 77%, 74%	39%, 38%	9%,4%	8%, 9%	16%, 15%	8.7 (1.4), 10.0 (8.8)
TRIUMPH	*Md [range]* 35 [18-78], 41 [20-85]	34%, 47%	NR	NR	NR	NR	14%, 27%	0%, 5%	NR	18%, 21%	NR
Study 301	*Mean (SD)* 44.8 (15.2), 46.2 (16.2)	52%, 57%	47%, 58%	NR	U/L 1578.3 (727.1), 1633.5 (778.8)	With: 83%, 83%	31%, 33%	NR	NR	14%, 21%	9.4 (1.46), 9.6 (1.41)
SB12-3003	*Mean (SD)* 36.3 (13.7), 40.0 (13.4)	44%, 68%	48%, 60%	*Mean (SD):* 64.7 (15.8) 68.4 (14.9)	U/L 2156.0 (1750.6), 2220.2 (2001.6)	With: 56%, 64%	NR	NR	NR	NR	NR

Md: median; LDH: lactate dehydrogenase; NR: not reported; U/L: units per litre; ULN: upper limit of normal; NR: not reported.

b) **Please indicate how any such heterogeneity caused the exclusion of any studies from the network and how it might produce bias where studies subject to such heterogeneity were included.**

As noted in response to A15a, the majority of studies not included in the network were excluded because their inclusion was infeasible because of differences in: study design, endpoints measured, or baseline characteristics. The inclusion of studies where there are known imbalances would have introduced avoidable and unnecessary bias into the NMA results, limiting the interpretability and usability of the findings.

A16 Priority question: the NMA for treatment naïve PNH appears to include a redundant comparator i.e. one unnecessary for estimating the treatment effect of crovalimab vs. those comparators in the decision problem i.e. ravulizumab and eculizumab. This apparently redundant comparator is standard of care without C5 inhibitors. Please reconduct the analysis excluding TRIUMPH, the trial with SoC without C5 inhibitors as comparator.

Please see response to A17 below. The exclusion of TRIUMPH from the network does not alter the overall conclusion of the network meta-analysis, that crovalimab can be considered to have equivalent efficacy and comparable safety to eculizumab and ravulizumab.

A17 Priority question: an identity link was used for all outcomes except adverse events, including proportions and count data. This was justified on the basis of need to calculate the probability of non-inferiority. Please perform all NMAs using a link function better suited to the form of the data e.g. logit for proportions.

Link functions are not necessarily better suited to model proportions. In recent PNH trials including the COMMODORE studies, the endpoints breakthrough haemolysis, transfusion avoidance and haemoglobin stabilisation which are in scope here were analysed comparing mean differences of proportions. This was done in alignment with regulators and informed the trial design. Therefore, the NMA followed this approach to allow interpretation of the results with regards to clinically meaningful differences.

The respective analysis using a logit link and a binomial likelihood in a random effects model are listed below. The analysis also excluded the TRIUMPH study as requested

in A16, even though this is not expected to influence the effect estimates between crovalimab and ravulizumab given the form of the network (star shaped).

The results for all endpoints show wide credible intervals including 1, indicating that with regards to these endpoints crovalimab is associated with a statistically undifferentiated clinical profile.

Figure 9: odds ratio for breakthrough haemolysis - random effects

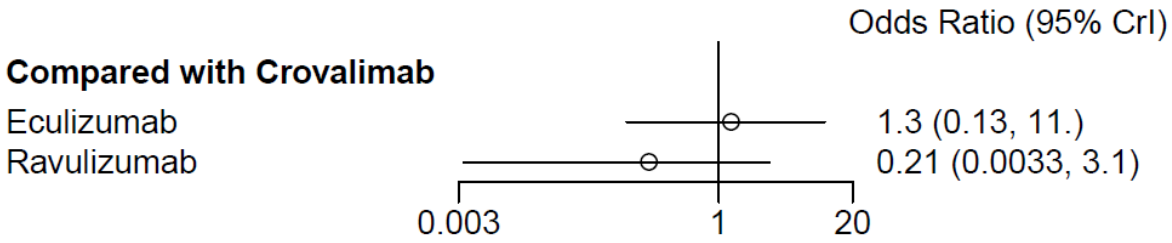


Figure 10: odds ratio for transfusion avoidance - random effects

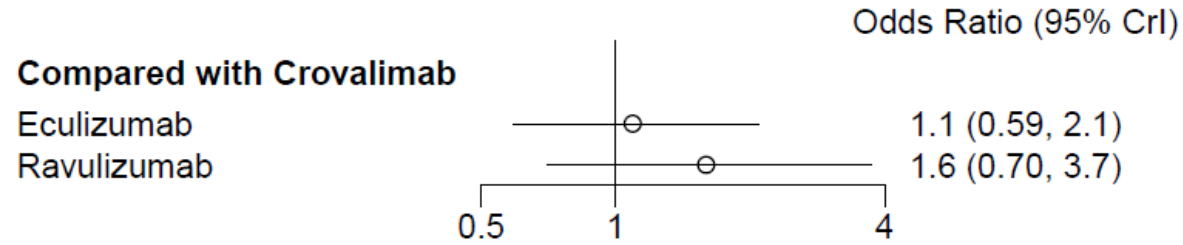
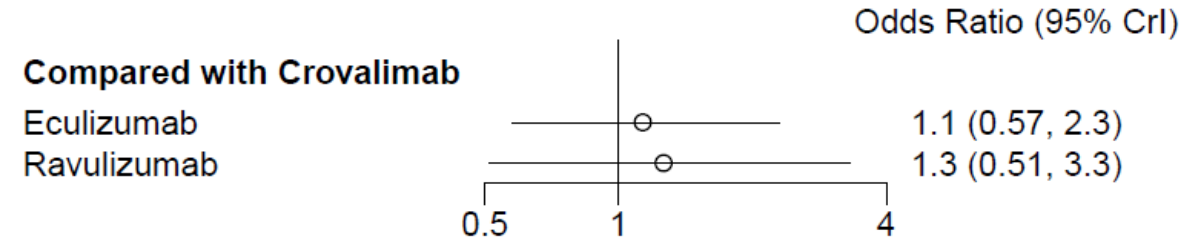


Figure 11: odds ratio for stabilised haemoglobin - random effects



A18 Priority question: Haemolysis control as measured in the COMMODORE trials, specifically as percentage of patients achieving LDH≤ 1.5 ULN, was not an outcome in the NMA.

a) Please explain why this outcome was omitted.

It was not possible to include this outcome in the NMA as the other studies do not use the same threshold, with the ravulizumab trials using a LDH >= 1 threshold.

Clinical feedback obtain by the company was that LDH≤ 1.5 ULN was a more clinically meaningful threshold than LDH = 1. In complement inhibitor-naïve patients with PNH, LDH ≥1.5 × ULN is a significant predictor of thromboembolism, and thromboembolism is a significant predictor of death. Standardised Mortality Ratio (SMR) analysis indicates that LDH ≥1.5 × ULN and anaemia, irrespective of severity, are risk factors for death. In contrast, patients with LDH <1.5 × ULN have a life expectancy similar to that of the general population. These findings suggest that primary treatment goals in PNH should focus on controlling terminal complement activation and intravascular haemolysis (aim for LDH <1.5 × ULN) to prevent thromboembolism and death [23].

As such, LDH≤ 1.5 ULN was used in the crovalimab study, and LDH=1 was not pre-specified in the study, limiting the feasibility of a robust analysis at this threshold. Further to this, the comparison vs eculizumab at the LDH≤ 1.5 ULN threshold is provided within the COMMODORE trials.

b) Please conduct an ITC of haemolysis control using percentage of patients achieving LDH≤ 1.5 ULN or, if not available, another LDH-based measure, with eculizumab and ranibizumab as comparators.

See response to A18.a.

Adverse events

A19 Priority question: A submission from PNH Support has revealed that three patients who switched from ravulizumab to crovalimab suffered severe adverse reactions, at least two of whom had not recovered at the time of the submission, including one who switched over two years ago (April 2022).

a) Please provide in tabular form all treatment related or immune complex related severe adverse event and Grade 3+ adverse event data for patients who have switched from any treatment to crovalimab. This should include all arms of COMMODORE 1 and any other data available to the company.

Data is provided documenting all treatment-related serious adverse events (SAE) and immune complex-related adverse events, and Grade 3+ adverse events, for any patient switching from either eculizumab or ravulizumab to crovalimab (or vice-versa) within the crovalimab clinical trials as requested (see files accompanying this

response: ‘NICE Clarification Q-A19a tabulated data_CON’ and ‘Summary of grade 3-5 AEs by intensity_CON’).

Note, for COMMODORE 3, no patients treated with crovalimab during the study switched to another complement inhibitor, or vice-versa. Therefore, no immune complex-related (Type III hypersensitivity [T3H]) reactions were reported in this study.

To summarise the switch data, in the COMPOSER study, [redacted]

For COMMODORE 1, [redacted]

In the crovalimab arm [redacted]

[redacted]

To summarise all of the above, up to the May 2023 CCOD, [redacted] Thus, the majority of the T3H reactions experienced across the COMMODORE trials were self-limiting, with or without treatment, with no life-threatening or fatal events reported, and resolved without change in crovalimab treatment.

b) Please provide data on the outcome of these patients until the latest follow-up, including on the duration of any of the adverse events.

Patient outcomes for the requested adverse events are provided within the tabulated data (see attached file: NICE Clarification Q-A19a tabulated data). [redacted]

[redacted]

[redacted]

The Company are continuing to assess the data collected from the ravulizumab switch cohort within the descriptive arm (Arm C) of the COMMODORE 1 study. The company will evaluate this data together with clinical investigators from the COMMODORE trials. Updates to clinical efficacy and safety results are planned to be shared at an upcoming meeting (American Society of Hematology Annual Meeting) later in 2024. The company has also committed to support a publication around T3H reaction events, led by clinical experts in the field of PNH, to inform and further educate the clinical community on these adverse events, again to be published later in 2024. In summary, while the evidence shows that T3H reaction events occur relatively rarely and resolve in a timely manner in the majority of cases, the company remains committed to exploring these reactions further and optimising their management in collaboration with the PNH clinical community.

c) Please provide data on the treatment and cost of treatment of these adverse events.

An output summarising all concomitant medications that were administered for the management of the T3H reactions reported in crovalimab switch patients across all PNH Phase III studies was prepared (see accompanying document: 'Summary of concomitant medications used for T3H reactions_CON'). Individual patient data regarding provision of treatment for relevant adverse events can be found within the attached file (NICE Clarification Q-A19a tabulated data). The most frequently used treatments for T3H reactions [redacted]) were paracetamol, prednisolone, methylprednisolone, and prednisone.

Notably, the study protocols of COMMODORE 1 and COMMODORE 2 provided management guidelines for adverse events of T3H. Specifically, treatments recommended included:

Grade 1-2 events:

- For arthralgia, administer analgesics and nonsteroidal anti-inflammatory agents.
- For pruritis and rash, administer antihistamines and topical corticosteroids.

Grade 3 events:

For high fever (e.g., temperature > 38.5°C), more severe arthritis and arthralgias, or more extensive rashes, including extensive vasculitic eruptions, administer oral or IV methylprednisolone 1−2 mg/kg (or equivalent dose of other glucocorticoids). Glucocorticoids can frequently be rapidly tapered, with a total duration of therapy of less than 1 week. However, withdrawal will occasionally result in recurrence of the symptoms, in which case glucocorticoids should be restarted and tapered more slowly.

This guidance is in line with reported output summarising all concomitant medications that were administered for management of T3H reactions.

As described above, where required, the management of grade 3 adverse events was done using inexpensive medicines. Considering this, and the view of UK clinical experts who agreed that crovalimab has a comparable safety profile to the comparators, adverse event costs are expected to be similar across treatments, and have therefore been excluded from the analysis. Given the relative magnitude of acquisition costs compared to other costs related to managing PNH, the exclusion of these costs does not impact the overall results or conclusions of the analysis.

Section B: Clarification on cost-effectiveness data

Model structure

B1 Priority question: On page 90 of the CS, it is mentioned treatment discontinuation was all set equal (for crovalimab, ravulizumab and eculizumab). Also, on page 91 of the CS, it is mentioned that patients cannot switch to another therapy if they discontinue their current treatment. However, treatment discontinuation does not seem to have been included in the cost comparison model. Please clarify whether discontinuation has been considered in the cost comparison model and how. Furthermore, please explain 1) to what extent the assumptions of equal discontinuation across treatments and no switching after

discontinuation are realistic and 2) what would happen to the cost comparison results if patients could switch to another treatment.

PNH is a chronic, lifelong disease, so if patients discontinue treatment symptoms will quickly begin again. As such, a meaningful amount of treatment discontinuation is not expected to occur in this population, nor is it expected to differ across the treatments considered in the analysis.

Clinical expert opinion suggests that the majority of PNH patients are currently treated with ravulizumab, in-line with patient preferences for less frequent administration. Because of this preference, and the risk of discontinuation as noted above, significant treatment switching does not occur. As such, the modelling of switching mirroring what currently occurs in UK clinical practice would have a negligible impact on the overall results and conclusions of the cost comparison analysis.

B2 Priority question: In Table 20 and on page 92 of the CS, it is mentioned that the study population includes children aged 12 years and over. However, it seems that the evidence of crovalimab in children is poor (i.e., the randomised comparison in the trials includes only adults i.e. at least age 18). Please clarify whether it is appropriate to include children in the current cost-comparison analysis, given that this type of analysis is based on the assumption that the clinical effectiveness of the treatments studied is comparable. Please consider the possibility of conducting a cost-effectiveness analysis, rather than a cost comparison, for the children population, if appropriate (see also A7).

Please see response to A7. Due to data limitations, it was not possible to conduct a cost-effectiveness analysis in the subgroup of paediatric patients. All available data relating to the use of crovalimab in paediatric patients is provided in response to A7.b.

The company recognises that data limitations, and scope of the cost comparison process, present a potential barrier to recommending crovalimab for use in paediatric patients with PNH. However, as noted in response to question A7.a, crovalimab has the potential to offer paediatric patients with PNH an alternative option to eculizumab, which is associated with an IV treatment burden and administered more frequently than crovalimab. The company therefore asks that the available evidence for paediatric patients is taken into consideration (see A7 response) to avoid

disadvantaging this patient group, who currently have limited treatment options available to them.

Input parameters

B3 Priority question: Please clarify the choice of preferred source to inform input parameters, since this does not seem to have been done systematically. Please explain why for some parameters trial data, Quist et. al or the NICE appraisal of ravulizumab have been chosen to inform them and the rationale for that. Also, on page 112 of the CS, it is mentioned that "all costs were taken from published UK sources or previous NICE technology appraisals in this disease area". It seems that this is not the case, for example because some cost prices were taken from Dutch sources (see also B8 below). Please clarify this discrepancy.

The company acknowledges that the cost estimates of medical resource use was not sourced from a UK publication. However, in-line with UK clinical expert opinion, treatment efficacy and safety are assumed equivalent for all treatments considered in the economic model. As such, medical resource costs, for which the Quist et al paper was used as a source for unit costs, balance across all treatments in the cost comparison analysis [24]. The inclusion or exclusion of the costs, the unit costs, and source from which they are estimated therefore has no impact on the results.

B4 Priority question: On page 96 of the CS, it is mentioned that the "proportion of BTH events requiring single up-dosing for crovalimab, eculizumab and ravulizumab patients is 40%, as 4 of the 10 BTH events observed in COMMODORE 2 in the crovalimab arm required single up-dosing". Please clarify why this estimate was based on COMMODORE 2 only, and not COMMODORE 1 too. Note also that this estimate is based on 10 events only, meaning that the estimate can be considered very much uncertain. Please clarify why this proportion could have been obtained from other sources such as Quist et al. or NICE TA698. Finally, please explain by how much and for how long the treatments' dose was assumed to increase (for each of the treatments).

As the pivotal Phase III study, COMMODORE 2 was deemed an appropriate source from which to inform the proportion of BTH events requiring single up-dosing. The proportion of 40% requiring single up-dosing was validated as reasonable by UK clinical experts consulted by Roche in the development of the base-case. While this estimate is only based on 10 events, it represents a current estimate of the proportion

of individuals requiring single up-dosing in the population of interest. A similar proportion of people in the supportive Phase III study, COMMODORE 1, (2 of 4) received unscheduled treatments. Taken together, this represents 42.8% (6 of 14) requiring single up-dosing for BTH events.

As demonstrated in the scenario analysis (Table 37, company submission), adjusting this proportion in the economic model has a negligible impact on results. This finding is consistent with the analysis presented in company submission in TA698, where the inclusion of BTH up-dosing has a negligible impact on results (approximately 1% change). The exact proportion of BTH events requiring single up-dosing is not reported in TA698 [19].

Single up-dosing is assumed to take place for 1 cycle (2 weeks) with the one additional dose of treatment, for each respective treatment.

B5 Priority question: Please clarify any discrepancy between the values presented in Table 26 of the CS and the values reported in NICE TA698.

The duration of loading dose administration for eculizumab and ravulizumab were derived from the Summary of Product Characteristics (SPC), as presented in Table 26 of the company submission. Where a range was given in the SPC, 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.

As described in the company submission in TA698 (sections B.2.11 and B.3.5.2) [19] new ravulizumab vial sizes (3mL and 11mL) were not yet available at the time of the appraisal [19]. Now available, and as reflected in the economic analysis, the ravulizumab SPC states loading dose infusion time ranges from 25 to 45 minutes, and is therefore not limited to the 35 minute infusion time which was costed in TA698.

B6 Priority question: Please provide the rationale for the different cost categories included/excluded in the cost comparison model. For example, adverse event costs were not considered in the model based on equal efficacy; however, blood transfusion cost and medical resource use costs were included but these are identical for the three interventions (see Table 33 in the CS). This

choice (excluding adverse events but including blood transfusions and medical resource use) seems inconsistent.

The company acknowledges that the inclusion of medical resource costs in the economic model is inconsistent with the exclusion of adverse events. Adverse costs were excluded on the basis that they are expected to be comparable across treatments and that their inclusion would have negligible impact on costs.

While medical resource use costs were included for completeness, recognising that their inclusion has no impact on results, and to maintain consistency with other costs, these costs have been removed from the updated base-case (see response to B7, **Table 19**).

B7: The unit costs of packed red blood cells are reported as £17.15 in Table 29 of the CS. However, in TA698, these costs are much higher (£128.99). Please clarify this discrepancy. In addition, please explain how to interpret the value shown in model "Cost Inputs" – cell F20 (composition mg for blood transfusions).

Thank you for identifying this error. The original cost of £17.15 was sourced from the NHS blood component variable price list, as opposed to the full cost price list (£158.18). This cost differs from that applied in TA698 but represents a more current estimate of packed red blood cells from the same source used in TA698.

As described above in relation to medical resource use, while blood transfusion costs were included for completeness, these costs are equivalent across treatments, and therefore have been removed from the updated base-case.

As shown in **Table 19** and **Table 20** below, the exclusion of medical resource use costs (see response to B6) and blood transfusion costs has no impact on the comparison of costs.

Table 19: Company updated base-case

Cost	Crovalimab	Eculizumab	Ravulizumab
Drug cost	[redacted]	4,100,874	6,627,639

Administration cost	423	498	280
Single up-dosing	14,743	2,030	8,276
Continuous up-dosing	0	1,365,280	0
Mean total cost	[redacted]	5,468,683	6,636,195
Incremental cost vs Crovalimab		[redacted]	[redacted]

Table 20: Company original base-case

Cost	Crovalimab	Eculizumab	Ravulizumab
Drug cost	[redacted]	4,100,874	6,627,639
Administration cost	423	498	280
Single up-dosing	14,743	2,030	8,276
Continuous up-dosing	0	1,365,280	0
Blood transfusions	4,309	4,309	4,309
Medical resource use	3,454	3,454	3,454
Mean total cost	[redacted]	5,476,446	6,643,958
Incremental cost vs Crovalimab		[redacted]	[redacted]

B8: Table 31 in the CS provides the medical resource use costs included in the model. These unit costs were taken from a Dutch study by Quist et al. (which presented cost prices and tariffs from the Netherlands) and then "converted". Please clarify why and how these costs were converted and not estimated from appropriate UK sources. If possible, please estimate them from appropriate UK sources, as cost prices may vary considerably between jurisdictions.

See response to B6. In-line with UK clinical expert opinion, treatment efficacy and safety are assumed equivalent for all treatments considered in the economic model. As such, the medical resource costs in the economic model are equal for all treatments. The inclusion or exclusion of these costs, the unit costs, and source from which they are estimated therefore has no impact on the results.

As noted in response to question B6, medical resource use has been removed from the updated base-case. As such, no alternative medical resource use estimates are provided.

Model results

B9 Priority question: On page 47 of the CS, under overview of efficacy, it is stated that "Efficacy results are not pooled across studies given the differences in the early treatment phase between treatment-naïve and switch patients, the differences in treatment-naïve patient populations with respect to the recent

transfusion history, and the differences in the requirements for baseline LDH for switch patients". Based on this general statement, please clarify why cost comparison analyses are based on a pooled population only. To align with the previous statement, please include in the model the option to run the analyses for the treatment-naïve population, treatment-experienced population, and pooled population separately. Please provide results separately as well. Regarding the pooled population, please indicate what proportion of patients is treatment naïve and treatment experienced, and if the results for the pooled population should be obtained as a weighted average of those two.

While the COMMODORE programme defined C5-naïve 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 (HSC) clone [25, 26]. 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 haemolysis, anaemia, 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-naïve patients. This is reflected among patients who are chronically treated with C5 inhibition. Despite good response to treatment, reflected in decreased occurrence of intravascular haemolysis, anaemia, and thrombosis; the size of the hematopoietic stem cell PNH clone, measured by the granulocyte clone, does not change over time [27]. 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-naïve patients [13].

[redacted]

[redacted]

[redacted]Given the lack of a biological difference, patients who are treatment-naïve 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-naïve patients once the haemolysis control has been achieved, as published in prior studies in this indication [15, 28]. Similarly, the safety profile of crovalimab is expected to be similar in treatment-naïve and switch patients, with the exception of the risk of DTDC-related T3H reactions, which uniquely characterizes switch patients in the period immediately following the switch (as discussed in response to B11). As such, the provision of separate results in these subgroups or pooling the overall population using a weighted average is not expected to impact the overall results and conclusions of this cost comparison analysis.

Model validation

B10 Priority question: Please provide all details of UK advisory board and any other consultation with clinical experts.

A UK clinical advisory board was conducted on 12th September 2023 to seek expert advice on the proposed approach to the HTA evidence submission strategy for crovalimab. A separate expert engagement session was conducted on 11th April 2024 with one UK clinician to gain expert opinion on key clinical and economic aspects of the HTA evidence submission. The minutes from these sessions are provided in the documents titled “Roche Crovalimab HTA NICE Advisory Board Report 2023 [Data on File]” and “Roche Crovalimab HTA NICE Expert Engagement Board Report 2024 [Data on File]” accompanying this response.

Model implementation

B11 Priority question: Please include in the model transient immune complex reactions as these are expected to have additional costs (and possibly related quality of life decrements) associated to switching to crovalimab. Please include in the model the option to run with and without these costs.

Transient immune complex reactions (TICRs) occurred in [redacted] of crovalimab-treated participants in COMMODORE 1 (Arm A) [29].

- [redacted] [29].
- [redacted] [29].
- Treatments used for Grade 1 and 2 reactions were mainly analgesics or non-steroidal anti-inflammatory drugs for arthralgia, as well as antihistamines and topical steroids for rash. For Grade 3 reactions, additional treatments that were used included oral or IV steroids (e.g. methylprednisolone) (Roche, Data on File, 2023).
    - [redacted] patients received treatment, of which [redacted] patient received steroids (betamethasone & prednisolone). Other treatments were paracetamol ([redacted]), loxoprofen ([redacted]), ketoprofen (two patients), naproxen ([redacted]), cetirizine ([redacted]) and topical fluocinolone ([redacted]).

[redacted]

In summary, as described above and as noted in response to A19c, costs associated with the management of transient immune complex reactions are negligible, with the reactions being resolved on average (median) in under 2 weeks. Considering this, and the view of UK clinical experts who agreed that crovalimab has a comparable safety profile to the comparators, adverse event costs are expected to be similar across treatments, and have therefore been excluded from the analysis. Given the magnitude of acquisition costs in the cost comparison analysis, the inclusion of adverse event costs, which are expected to be similar, is not anticipated to impact the overall conclusions of the analysis.

B12 Priority question: Please provide results of two scenario analyses where eculizumab's costs are replaced by those of its available biosimilars.

The known list price of eculizumab biosimilars (Bekemv and Epysqli) are the same as eculizumab (Soliris). The base-case analysis presented in the document B (section

B.4.3) compares crovalimab at its known net price to the list price of eculizumab (Soliris, Bekemv and Epysqli), thereby capturing the known acquisition costs of the comparators. Acknowledging that the biosimilars may be available to the NHS at a confidential discounted price, a threshold analysis was presented in Table 34 of document B, demonstrating the impact of varying the acquisition cost of eculizumab, and ravulizumab.

Further to the above, while eculizumab biosimilar products are now available, recent treatment usage information highlights that they are yet to be used in clinical practice ([redacted] sold since their approval earlier this year – IQVIA MIDAS [Data on file]). The same treatment uptake data, in-line with UK clinical expert opinion, highlights that eculizumab (Soliris) is rarely used in UK practice, with approximately 7.5% of PNH patients treated with eculizumab. As such, eculizumab biosimilars do not meet the requirement to be considered a comparator in this appraisal.

In summary, Roche does not have the confidential cost information required to conduct the requested analysis, nor is it appropriate to consider a comparison to eculizumab biosimilars in this appraisal.

B13: On page 112 of the CS, it is explained that the administration of eculizumab and ravulizumab is relatively invasive and carries a higher risk of infection and vascular complications compared to crovalimab, which may have a lower level of treatment burden. Please clarify whether the costs associated with infections and vascular complications were included in the cost-comparison analysis, and if not, why they were excluded.

Eculizumab and ravulizumab administered intravenously (IV) are the mainstay of current therapy for PNH in the UK. To control disease progression, patients with PNH require maintenance doses of these IV C5 inhibitors, which can range in frequency from 2 to 8 weeks and involve infusion times ranging from 25 to 75 minutes depending on treatment and patients' weight [30-33]. Thus, patients treated with C5 inhibitors via IV infusion are required to go to the clinic for regular administration visits. In the UK, IV infusion may be administered at the patient's home by a visiting nurse; however, treatment remains time- and resource-consuming [34].

Adverse side effects with IV treatment include increased vascular risk, infection at the site of administration and infusion reactions, which can further impact on patients' HRQoL. While the treatment burden of crovalimab is expected to be less than IV

eculizumab and ravulizumab, overall safety of all treatments considered in the decision problem is expected to be comparable. As such, in the presented cost comparison analysis, where equivalent efficacy and safety is assumed, adverse events are not taken into account. In the case of administration reactions, the exclusion of these costs for all treatments represents a conservative assumption. However, given the magnitude of these costs relative to acquisition costs, the exclusion of these costs is expected to have a negligible impact on the results.

Section C: Textual clarification and additional points

C1: Please provide a definition of CAC-related BTH events since it seems that these have not been defined in the CS. Please explain why it is important to distinguish this type of events.

Breakthrough haemolysis (BTH) is the return of haemolytic disease activity during treatment with a complement C5 inhibitor. BTH events may occur due to suboptimal C5 inhibition (which is known for eculizumab; [14, 35-37], but may also distinctly occur due to the presence of an external complement-activating condition (CAC), such as an infection, trauma, or other inflammatory events [38]. CAC- related BTH events are defined by a triggering event that generally precedes the BTH event, causing excessive complement activation which overloads the inhibitory activity of a C5 inhibitor (despite maintaining adequate PK concentrations); this manifests as an increase in intravascular haemolysis, leading to LDH increase and signs/symptoms of haemolysis [39]. It is important to distinguish between BTH events related to suboptimal C5 inhibition vs a CAC, given that the former is related to the suboptimal dosing regimen of the drug itself, while the latter is unrelated to drug dosing and is rather sporadic, and in most cases a self-limiting event over time. It is of note that both ravulizumab and crovalimab have weight-based dosing regimens that provide complete terminal complement inhibition through the entire dosing interval; ravulizumab has shown to reduce the risk of suboptimal C5 inhibition - related BTH events [40] and crovalimab has not had any BTH events attributed to an inadequate/inappropriate dosing regimen (Section B.4.2.4.1 of CS Document B).

C2: On CS page 94 it is mentioned that "Mortality was modelled by applying general population all-cause mortality data obtained from England and Wales

National Life Tables published by the Office for National Statistics (2019) based on 2020−2022 mortality data". Please clarify what year was used, 2019 or 2020-2022. If the latter was used, please discuss the impact of COVID 19 on excess mortality and why this choice is deemed appropriate.

The Office for National Statistics' life tables using 2020-2022 mortality data was published in 2024; the reference to 2019 was included in error [41]. This data was selected as the most current UK mortality estimates, representing the population of interest for this appraisal. While mortality rates in the 2020-2022 period remain higher than pre-COVID 19, life expectancy has not changed significantly. Applying mortality data from 2019 or earlier would therefore have a negligible impact on results, and would be less generalisable to current UK clinical practice than using those already applied in the economic model.

C3: On CS page 99 it is mentioned that "follow-up visits are required twice per year". Please clarify how these follow-up visits are defined. Are these the same as "consultant visits" in Table 30? If yes, should not the number of units be 2?

The units noted in Table 30 are for each event, meaning the time of one consulted visit is costed twice a year (2 events) in the economic model. As discussed in response to questions B6 and B8, medical resource use has been excluded from the updated company base-case (see **Table 19**).

C4: Please provide the evidence to support the statement "given there was no evidence to suggest that mortality rates would differ across treatments, the annual rate of mortality was assumed to be equivalent for all modelled treatments" (CS page 94).

Access to complement inhibition improves the prognosis of PNH considerably, with a survival rate of 96.7% after three years of eculizumab treatment [14]. With the results of COMMODORE 1 & 2, and the network meta-analysis, demonstrating that crovalimab is associated with non-inferior efficacy outcomes and comparable safety, it is therefore expected that survival across treatments will be equivalent. This view was supported by UK clinical experts who suggested that they did not expect any meaningful differences in treatment outcomes across the different C5 inhibitors.

C5: Please clarify the role of spontaneous remission included in the cost comparison model since this is not mentioned in CS Doc B.

Functionality remains in the economic model to explore the possibility of spontaneous remission. Given the assumption of equal efficacy and safety, it was assumed that the

occurrence of spontaneous remission would also be equivalent across all modelled treatments, with a negligible impact on the comparison of costs.

Given uncertainty around the rate and cause, spontaneous remission was not considered in the company base-case in TA698. Recognising this uncertainty and the limited impact the inclusion of spontaneous remission would have on results, it was not explored in a scenario analysis.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Crovalimab for treating paroxysmal nocturnal haemoglobinuria [ID6140]

NICE medicines optimisation briefing

January 2023

Advice

A full single technology appraisal of crovalimab is unlikely to add value. A fast-track appraisal with a cost comparison comparing crovalimab to other specialist treatments licensed for paroxysmal nocturnal haemoglobinuria (PNH) is likely to be appropriate, assuming that results of the ongoing phase 3 studies continue to suggest the efficacy and safety of crovalimab is similar to eculizumab.

Rationale

Crovalimab, a C5 inhibitor, may show similar clinical efficacy and safety to other C5 inhibitors already recommended in national guidance for PNH at a similar point in the treatment pathway (eculizumab and ravulizumab). This is based on results from 1 fully published single-arm phase 3 trial and preliminary analyses from 2 ongoing phase 3 trials comparing crovalimab and eculizumab (expected to be completed in 2028 and 2029).

Technology appraisal guidance has already recommended ravulizumab as an option for treating PNH in adults with haemolysis and clinical symptoms suggesting high disease activity, or whose disease is clinically stable after having eculizumab for at least 6 months in TA698 (May 2021). Ravulizumab and eculizumab are similar in terms of clinical effectiveness and safety, but ravulizumab is more cost-effective. National guidance on using eculizumab for PNH has been issued by NHS England (NHS standard contract for PNH service, 2013).

Crovalimab is a subcutaneous injection, which some people may prefer over the intravenous treatments, eculizumab and ravulizumab. Preliminary analyses from 1 of

the ongoing trials comparing crovalimab with eculizumab suggest PNH remained stable in people who switched from eculizumab to crovalimab. Mild-to-moderate hypersensitivity reactions were sometimes seen when people changed to crovalimab; however, these were self-limiting.

Technology overview

Crovalimab is a monoclonal antibody that inhibits C5, a complement protein that plays a role in inflammatory processes and the destruction of blood cells. Crovalimab is in development for treating PNH. Phase 3 trials are investigating a weight-based dosing schedule using 1 intravenous (1,000 mg or 1,500 mg) and 4 subcutaneous (340 mg) weekly loading doses, followed by subcutaneous maintenance doses (680 mg or 1,020 mg) every 4 weeks (NIHR Health Technology Briefing: crovalimab, 2022).

Context

Two monoclonal antibodies that inhibit C5 are licensed for treating PNH, eculizumab and ravulizumab. Ravulizumab has been assessed by NICE and is recommended as an option for PNH in adults (TA698). NHS England has issued guidance on eculizumab for treating PNH in adults and young people (NHS standard contract for PNH service, 2013).

NICE has also recommended pegcetacoplan (a C3 inhibitor) as an option for treating PNH in adults who are still anaemic after at least 3 months' treatment with a C5 inhibitor (TA778). Technology appraisals are in development for 2 proximal complement inhibitors, danicopan (a Factor D inhibitor, ID5088) and iptacopan (a Factor B inhibitor, ID6176).

Table 1: Characteristics of crovalimab compared with eculizumab and ravulizumab

	Crovalimab	Eculizumab	Ravulizumab
Mechanism of action	C5 inhibitor	C5 inhibitor	C5 inhibitor
Indication	PNH (Details to be confirmed when marketing authorisation is granted. The published phase 3 trial includes adults and children aged 12 years and over weighing 40 kg or more with haemolysis and frequent transfusions)	PNH in adults and children - evidence of clinical benefit is demonstrated in people with haemolysis with clinical symptom(s) indicative of high disease activity, regardless of transfusion history (eculizumab SPC)	PNH in adults and children (body weight over 10 kg) - with haemolysis with clinical symptom(s) indicative of high disease activity - who are clinically stable after having been treated with eculizumab for at least the past 6 months (ravulizumab SPC)
Dosage and route of administration	Dosages used in phase 3 trials for adults and children aged 12 years and over with a body weight of 40 kg or more Initiation: 1,000 mg or 1,500 mg (based on body weight) by intravenous infusion on day 1 followed by 340 mg by subcutaneous injection every week for 4 weeks beginning on day 2 Maintenance: 680 mg or 1,020 mg (based on body weight)	Licensed dosages for adults and children with a body weight of 40 kg or more Initiation: 600 mg by intravenous infusion every week for 4 weeks Maintenance: 900 mg by intravenous infusion every 2 weeks beginning at week 5 (See the SPC for dosages for children with lower body weights)	Licensed dosages for adults and children with a body weight of 40 kg or more Initiation: a single dose of 2,400 mg to 3,000 mg (based on body weight) by intravenous infusion Maintenance: 3,000 mg to 3,600 mg (based on body weight) by intravenous infusion every 8 weeks, beginning 2 weeks after the loading dose (See the SPC for dosages for children with lower body weights)

	by subcutaneous injection every 4 weeks beginning at week 5 (Dosages to be confirmed when marketing authorisation is granted)		
Resource impact	Subcutaneous treatment: lower service delivery costs than intravenous treatment (potentially delivered by homecare or self-administered at home after training)	Intravenous treatment: invasive, higher service delivery costs than subcutaneous treatment (clinic costs, health professional time) Can be delivered by homecare	Intravenous treatment: invasive, higher service delivery costs than subcutaneous treatment (clinic costs, health professional time) Ravulizumab is given less often than eculizumab, which may save costs (TA698) Can be delivered by homecare

Current practice

NHS England commissions services for adults and young people with PNH from Highly Specialist Centres, including services delivered on an outreach basis as part of a provider network (Prescribed Specialised Services Manual, 2023).

Most treatments for PNH are provided locally (including blood transfusions, anticoagulation and iron supplements) with support from the PNH National Service. However, the complement inhibitors (eculizumab, ravulizumab and pegcetacoplan) are funded, prescribed and administered by the PNH National Service. Not everyone with PNH is eligible for treatment with complement inhibitors. Agreed indications for eculizumab and ravulizumab include thrombosis related to PNH, haemolysis with clinical symptoms, and complications associated with haemolysis.

NICE recommends ravulizumab as an option for treating PNH in adults:

- with haemolysis with clinical symptoms suggesting high disease activity, **or**
- whose disease is clinically stable after having eculizumab for at least 6 months.

The clinical effectiveness and safety of ravulizumab and eculizumab were found to be similar in clinical trials and, in the NICE committee's preferred analysis and all the other cost-effectiveness scenarios presented, ravulizumab was more cost-effective than eculizumab (TA698).

In children, medicines for PNH are commissioned by NHS England under their policy for Commissioning medicines for children in specialised services. This states that medicines approved for adults in a NICE technology appraisal can be made available for children subject to certain conditions.

The PNH National Service has advised that ravulizumab is generally used first-line in adults, young people and children, except in pregnancy when eculizumab is

preferred. Pegcetacoplan is considered for adults who still have anaemia after 3 months' treatment with ravulizumab or eculizumab (a trial is ongoing in children).

From April 2022 to April 2023, 281 people (30% of those within the PNH National Service in England) were prescribed complement inhibitors (eculizumab, ravulizumab or pegcetacoplan) for PNH. A further 58 people (6%) received complement inhibitors by other funding routes; for example, in a clinical trial (may include crovalimab trials; Annual report 2023).

It is expected that in 2025 to 2026 an estimated 386 people with PNH will be eligible for treatment with a C5 inhibitor in England. Of these, it has been estimated that 341 will have ravulizumab and 45 will have eculizumab (Ravulizumab resource impact template, 2021). Crovalimab may also be an option for some of these people if it receives a marketing authorisation.

Factors for decision making

Effectiveness

COMMODORE 3 (Liu et al. 2023) was an open-label, single-arm phase 3 trial undertaken in 5 centres in China. The trial assessed the efficacy and safety of crovalimab in 51 people with PNH who had not previously had a C5 inhibitor. Participants were 12 years or over (median age 31 years), weighed 40 kg or more, had haemolysis and had received at least 4 blood transfusions within the previous 12 months.

Crovalimab was given according to a weight-based dosing schedule for a median duration of 32 weeks. The loading doses comprised 1 intravenous infusion (1,000 mg or 1,500 mg) followed by 4 once-weekly 340 mg subcutaneous injections on day 2 and weeks 2, 3 and 4. Maintenance treatment with subcutaneous injections (680 mg or 1,020 mg) were subsequently given every 4 weeks starting at week 5. From week 9, crovalimab could be self-administered.

The mean proportion of participants who had haemolysis control (co-primary endpoint) between weeks 5 and 25 of crovalimab treatment was 78.7% (95%

confidence interval [CI] 67.8% to 86.6%; the lower CI is above the predefined trial success threshold of 60%). Around half of participants did not need a blood transfusion between baseline and week 25 of crovalimab treatment, which was a statistically significant improvement compared with the proportion not needing a transfusion in the 24 weeks before screening (51% compared with 0% respectively, p<0.0001; co-primary endpoint).

Two global randomised open-label phase 3 clinical trials are ongoing, comparing crovalimab with eculizumab in people with PNH (COMMODORE 2 and COMMODORE 1). These studies have not yet been completed; however, preliminary results have been published in abstract form.

COMMODORE 2 (Roth et al. 2023) includes C5 inhibitor-naïve people with haemolysis (n=204). Participants were randomised 2:1 to crovalimab (dosage as in COMMODORE 3) or eculizumab (loading dose 600 mg intravenously every week for 4 weeks then 900 mg intravenously every 2 weeks). The primary analyses found that, at week 25, crovalimab was non-inferior to eculizumab for the co-primary endpoints, haemolysis control (79.3% compared with 79.0% respectively; odds ratio 1.02, 95% CI 0.57 to 1.82, the lower 95% CI is above the prespecified success threshold of 0.2) and transfusion avoidance (65.7% compared with 68.1% respectively; weighted difference −2.8%, 95% CI −15.7% to 11.1%, the lower 95% CI is above the prespecified success threshold of −20%).

COMMODORE 1 (Scheinberg et al. 2023) includes adults who have been receiving a maintenance dose of eculizumab (900 mg intravenously every 2 weeks) for at least 24 weeks (n=89 at the time of the primary analysis, still recruiting). Participants are being randomised 1:1 to crovalimab (dosage as in COMMODORE 3) or continuing treatment with eculizumab. The primary outcome of this study is safety. Primary analyses of exploratory efficacy endpoints suggest that people who switched from eculizumab to crovalimab maintained disease control. At week 25, similar proportions of people in both groups experienced haemolysis control (about 93%, no statistical analysis reported) and transfusion avoidance (about 79%, no statistical analysis reported).

Safety

In COMMODORE 3 (Liu et al. 2023), 76% of participants (39/51) receiving crovalimab had a treatment-related adverse event but no adverse events caused treatment discontinuation. One serious treatment-related adverse event was reported (bacteraemia). Adverse events occurring in at least 10% of participants were upper respiratory tract infections (47%, 24/51) and weight increase (12%, 6/51).

The COMMODORE 3 trial authors reported that the overall safety data were consistent with the known safety profile of C5 inhibitors. No medication errors leading to dose modification or injection site reactions were recorded during self-administration of crovalimab.

In the primary analysis in COMMODORE 2 (Roth et al. 2023), the proportion of people experiencing adverse events was similar in the crovalimab and eculizumab groups (around 79%). Serious infections occurred in 3% of people receiving crovalimab and 7% of people receiving eculizumab.

The primary analysis in COMMODORE 1 (Scheinberg et al. 2023) found that adverse events occurred in 77% of people in the crovalimab group and 67% of people in the eculizumab group. Serious infections were reported in 7% of people treated with crovalimab and 2% of people treated with eculizumab. In the crovalimab group, 16% of people had self-limiting type 3 hypersensitivity events when they switched from eculizumab. These were mostly mild-to-moderate urticarial rashes, arthralgia and vasculitis.

Patient centred factors

Crovalimab is a subcutaneous injection that can either be given by a healthcare professional in clinics or by self-injection at home. Self-injection requires training. Eculizumab and ravulizumab are intravenous infusions that are given by a healthcare professional. Home infusion may be considered for people who have tolerated infusions well in the clinic. The infusions can take up to 45 minutes for eculizumab and 75 minutes for ravulizumab.

Frequency of maintenance treatment differs between the C5 inhibitors used for PNH. According to the NICE technology appraisal, ravulizumab has benefits on quality of life compared with eculizumab because it is given every 8 weeks rather than every 2 weeks. Crovalimab is administered subcutaneously every 4 weeks and may also offer some benefits in terms of quality of life. Some people may prefer the relative infrequency of 8-weekly administration of ravulizumab, while others may prefer not to attend a clinic to receive treatment and choose to self-inject crovalimab at home or receive eculizumab or ravulizumab infusions by homecare. Dexterity or needle-phobia challenges may also affect choice of treatment.

Health inequalities

PNH is a rare condition, which may affect access to specialist treatment. From April 2022 to April 2023, 926 people in England were within the PNH National Service (Annual report 2023). The PNH National Service has 2 main centres in England (in Leeds and London) as well as several outreach centres. The service aims to review and manage everyone with PNH through a shared care agreement with their local haematology unit. However, complement inhibitors are prescribed and administered by the PNH National Service. This means there may be health inequalities in accessibility for people living in more remote areas of the UK, people who would need to travel long distances or people who may have difficulties travelling because of co-morbidities or disabilities.

Limitations of the evidence

Evidence on the clinical effectiveness and safety of crovalimab is from 1 fully published non-comparative phase 3 trial, and preliminary analyses from 2 ongoing phase 3 comparative trials. The medicine is not yet licensed in the UK, Europe or US.

The fully published trial, COMMODORE 3 is an open-label, single-arm trial and, therefore, has limitations. However, it is difficult to conduct randomised controlled trials in rare diseases because few people may be eligible for inclusion. COMMODORE 3 was undertaken in China where C5 inhibitors are not readily available and people with PNH often have transfusion dependence and haemolysis. The COMMODORE 3 study population may not reflect the UK population with PNH

because C5 inhibitors are available in the UK. It is also possible there may be other differences relating to ethnicity and the healthcare system.

COMMODORE 1 and 2 are randomised controlled trials comparing crovalimab with eculizumab, which is a suitable comparator. These worldwide, multicentre trials include centres in the UK and Europe and are likely to reflect the UK population and healthcare system better than COMMODORE 3. However, COMMODORE 1 (in people treated with eculizumab) is still recruiting, and both COMMODORE 1 and 2 are still ongoing with study completion not expected until 2029 and 2028, respectively.

All 3 COMMODORE trials are open-label, which may cause bias. However, the primary efficacy outcomes of haemolysis control and transfusion dependence are relatively objective.

No trials are currently comparing crovalimab with ravulizumab. Two phase 3 non-inferiority trials have compared the clinical effectiveness and safety ravulizumab and eculizumab in adults with PNH. Ravulizumab was non-inferior to eculizumab for all primary and key secondary endpoints in both trials (SPC). There were no differences in terms of adverse events (TA698).

Eculizumab and ravulizumab are licensed for treating PNH in adults and children (body weight over 10 kg for ravulizumab). All 3 COMMODORE trials excluded people weighing less than 40 kg, and COMMODORE 3 included only 3 young people aged between 12 years and 18 years. Therefore, the safety and efficacy of crovalimab in children and young people is uncertain. It is not yet known if crovalimab will be approved for treating PNH in children.

NICE National Institute for Health and Care Excellence

Cost Comparison Appraisal

Crovalimab for treating paroxysmal nocturnal haemoglobinuria [ID6140]

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

NICE National Institute for Health and Care Excellence

About you

1.Your name	[redacted]
2. Name of organisation	PNH Support
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	PNH Support (www.pnhuk.org) is a Charitable Incorporated Organisation registered with the Charities Commission of England and Wales (no.1161518). The four patient trustees operate within PNH Support's constitution dated 30 April 2015 amended on 16 May 2021. The Constitution is an 'Association' model and has 156 voting members. The objects of PNH Support are as follows: 1) To promote, protect and preserve the physical and mental health of those diagnosed with PNH who reside in England, Wales and Northern Ireland (either permanently or temporarily) through the provision of support, education, advocacy and practical advice; 2) To advance the education of patients with PNH who reside in England, Wales and Northern Ireland, in particular but not exclusively, by the provision of advice and a point of contact for newly diagnosed PNH patients, in England, Wales and Northern Ireland. We moderate a closed Facebook group with 315 members, send email updates to members, hold regional face-to-face and online patient and family meetings and a biennial patient and family conference. PNH Support is funded by donations, honoraria and consultancy fees (for the provision of advice relating to the lived experience of PNH).
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.]	**Roche Products (crovalimab)** 09.11.23 - £750.00 - attending patient advisory board meeting 25.05.23 - £1,125.00 - preparation, attendance and follow up for two day patient advisory board **Novartis (iptacopan)** 30.04.24 - £560.50 - advice provided regarding patient safety programme and discussions re patient engagement activities 14.11.23 - £501.50 - advice provided regarding market research study, patient advisory board content 15.08.23 - £619.50 - providing patient advocate perspective as part of the Novartis Global Oncology Patient Involvement Panel (GOPIP) on awareness raising campaign, preparation for a September 2023 patient advisory board, working together 06.06.23 - £737.50 - providing patient advocate perspective re discussing awareness raising campaign; proposed patient engagement plans 30.06.23 - £236.00 - providing patient advocate perspective re advice on sharing trial results and patient engagement strategy

If so, please state the name of the company, amount, and purpose of funding.	**Alexion Pharmaceuticals (danicopan eculizumab, ravulizumab)** 01.09.23 - £190 - providing a patient advocate perspective on trial design **Alexion AstraZeneca Rare Diseases, Roche (crovalimab)** and **Swedish Orphan Biovitrum (pegcetacoplan)** contributed to funding for a National Community Survey project which surveyed 7 rare disease communities including PNH Support. The report of this survey called 'Rare Voices" can be found here
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	On 23 October 2023, PNH Support made a patient/carer submission for appraisal ID 6176 (iptacopan) which provided responses to questions 6, 7 and 8 in relation to 75 patients and 19 carers and we refer you to the responses provided in that submission. Due to survey fatigue, we chose not to survey the wider PNH patient/carer population again and therefore only requested those patients (and carers) treated with danicopan or crovalimab (as the NICE danicopan appraisal was also imminent) to complete another online survey in December 2023. Our survey in December 2023 (comprising primarily multi-choice questions) of PNH patients and carers across England and Wales who had been treated with danicopan or crovalimab was disseminated via: email to PNH Support members; posts on our closed Facebook group; email by the PNH National Service (Kings College Hospital, London) to patients for which they held email addresses; and email by the PNH National Service (St James's Hospital, Leeds) to patients treated with these drugs. Three respondents were patients treated with crovalimab at the time of the December 2023 survey. No carers of patients treated with crovalimab responded. We did not collect information on whether these patients were treatment naive or had switched from eculizumab or ravulizumab (see question 13). All three patients are living in England. **Ethnicity:** One respondent identified as **"**English / Welsh / Scottish / Northern Irish / British". One identified as "Ukrainian", and one identified as Chinese. **Gender:** Two respondents were female, and one was male. **Age:** The mean age of respondents was 40. More recently in April 2024, we became aware of a patient who had switched from ravulizumab to crovalimab in 2022 but had stopped the trial due to experiencing a serious adverse event, the impact of which is still ongoing (more detail below in question 13). This person's responses had not been collected in the December 2023 survey as they had stopped treatment with crovalimab by then.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Patient respondents to our December 2023 survey were asked to describe what life is like for them to currently live with PNH where they could choose more than one multi-choice answer. 100% (n=3/3) said their PNH is managed well, 67% (n=2/3), chose "I consider myself to have a normal quality of life" and 33% (n=1/3) chose "Living with (or caring for someone with) PNH has a minimal impact on my life"; **In terms of symptoms**, patients were asked if they experienced any PNH symptoms and to select as many as were listed and/or to provide their own. 67% (n=2/3) experience fatigue (e.g. exhaustion, limited energy, heaviness in limbs)". Patients were then asked to rate their fatigue with 1 being not fatigued at all and 10 being severely fatigued, to which 2/3 patients provided ratings, with the mean rating being 5. Other symptoms selected are listed below. • 1/3 experience "Yellow pigmenting in eyes due to jaundice"; • 1/3 experience "Anaemia requiring blood red blood cell transfusions"; • 1/3 experience "Blood clot/s"; • 1/4 experience "Leg pain"; • 1/3 experience "Abdominal pain" • 1/3 experience "Breakthrough haemolysis (return of dark urine/return of my symptoms/anaemia)" ;B • 1/3 experience "Digestive problems e.g. gas, bloating, slow digestion"

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	**Current Treatments – Patients (n=3)** When asked in our December 2023 survey what they thought of the current PNH treatments available on the NHS (where they could choose more than one answer and/or provide their own), 100% (n=3/3) said they were satisfied with currently available treatments and 67% (n= 2/3) said **t**he opportunity to take part in clinical trials is an advantage. One patient who said they were satisfied with the available treatments also chose they would like there to be treatment options with different delivery methods and more treatments which provide a better quality of life. **Current Care - Patients (n=3)** Care provided by the PNH National Service and care provided by the NHS (outside the PNH National Service) was asked about separately. When patients were asked to choose what they thought of the current care available for PNH **from the PNH National Service** from a Likert scale with 5 options, 100% (n=3/3) chose “Very satisfactory”; When patients were asked to choose (from the same scale) what they thought of the current care available from the NHS for PNH **outside the PNH National Service (**e.g. GPs, local haematologists (not part of the PNH National Service), other healthcare professionals), 67% (n=2/3) chose “Very satisfactory” and 33% (n=1/3) chose “Neither satisfactory nor unsatisfactory”
8. Is there an unmet need for patients with this condition?	When patients were asked to choose what they thought their unmet needs were ("unmet need" was described as something that is not addressed by current NHS care or available treatments) and to choose all responses that applied and were relevant to them: 67% (n=2/3) chose “I don't have any unmet needs” and 33% (n=1/3) chose “I prefer not to say”. Our survey for appraisal ID6176 (iptacopan) identified that 61% (n=46/75) of patients and 63% (n=12/19) of carers said they would like more treatment options with different delivery methods. That survey also identified that 45% (n=34/75) of patients and 47% (n=9/19) of carers said they would like there to be more treatment options which provide patients with better quality of li**f**e (less symptoms etc).

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	The three patient respondents treated with crovalimab at the time of the December 2023 survey were asked what they thought the advantages of the treatment were (where they could choose more than one answer and/or provide their own). 100% (n=3/3) chose all of the following reasons: • "The delivery method of this treatment (i.e. injection)". • "It has improved my PNH symptoms". One patient said "*Some indicators are still not back to normal, but the positive effect is obvious"* • "It has a positive impact on my ability to work or undertake education". One patient worked full time, one worked part time (and was a part time student) and one was a full time student. • "It has a positive impact on my mental health" 67% (n= 2/3) chose both: "The frequency of the treatment i.e. every 4 weeks" and "It has a positive impact on my family and social life" 33% (n=1/3) chose "The ability to travel with the medication" When asked "Since you started treatment with crovalimab, are any of the following true for you (choose all that apply)": • 33% (n=1/3) chose both: "I can now work full time" and "I can now provide care for dependants i.e. children, parents etc"; • 33% (n=1/3) chose both: "I can now work part time" and "I can now study part time" • 33% (n=1/3) chose "I can now study full time"

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	The three patient respondents treated with crovalimab at the time of the December 2023 survey were asked what they thought the disadvantages of the treatment were (where they could choose more than one answer and/or provide their own): 67% (n=2/3) chose "There are no disadvantages and 33% (n=1/3) chose "The frequency of the treatment (i.e. once every 4 weeks) is a disadvantage"

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Patients whose veins are damaged by repeated intravenous infusions from other C5 inhibitors and who have an option to be treated with this alternative delivery method for a C5 inhibitor would benefit. Patients who will benefit less from this treatment are those: • who experience clinically significant extravascular haemolysis and associated symptoms (including anaemia requiring blood transfusions) whilst being treated with a C5 inhibitor. • who have issues with dexterity and/or eyesight (with regard to injecting themselves) • with needle phobias (with regard to injecting themselves)

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	We are not aware of any equality issues.

Other issues

13. Are there any other issues that you would like the committee to consider?	We are aware that there are three groups of patients who have been treated with crovalimab in trials: 1) treatment naïve patients; 2) those switched from eculizumab; and 3) those switched from ravulizumab. Over the last month we have become aware of three patients globally who had serious adverse reactions when switched from ravulizumab to crovalimab and at least two of whom we understand are still negatively affected by these injuries today. We are hopeful that these serious adverse events were correctly represented in terms of their severity and duration in the data submitted to the regulators, however as the data for the patients who were switched from ravulizumab to crovalimab has not yet been published, we have not been able to satisfy ourselves that this is the case. We are deeply concerned that patients who may switch from ravulizumab to crovalimab may be at risk of experiencing a serious adverse event which could be life changing and that the nature of this risk should be appropriately understood, represented and disseminated. We are aware of a patient in England who switched from ravulizumab to crovalimab two years ago (April 2022) and then stopped the crovalimab trial after experiencing a serious adverse event. To this day, this patient experiences constant numbness and pain in both hands which are very sensitive to changes in temperature and which numbness makes it difficult to write and otherwise use their hands. The patients also has frequent pain and numbness down one side (arm and leg) and severe cramping in her legs and hands. The patient currently takes Pregabalin and Duloxetine to assist with these symptoms (which have side effects e.g. fatigue and is also under the care of neurologists and a physiotherapist, who are attempting to treat her as she understands she has nerve damage. Her quality of life, her mental health, as well as her family and social life have been significantly negatively impacted by this situation over the last two years. She is also now unable to work as a result of her injuries which has also had financial implications.

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• Should this treatment be approved by NICE, we are concerned that patients who may switch from treatment with ravulizumab to crovalimab may be at risk of experiencing a severe adverse event and consider that this risk should be clearly understood, quantified and shared with both healthcare professionals and patients. • Our survey for appraisal ID6176 (iptacopan) identified that 61% (n=46/75) of PNH patients and 63% (n=12/19) of carers would like more treatment options with different delivery methods. That survey also identified that 45% (n=34/75) of patients and 47% (n=9/19) of carers would like there to be more treatment options which provide patients with better quality of lif**e** (less symptoms etc). • Despite available treatments**,** fatigue is one symptom with which most PNH patients still live: 100% (n=3/3) of patients from our December 2023 survey still experience fatigue with a mean fatigue rating of 5/10 (with 1 being not fatigued at all and 10 being severely fatigued). Our previous survey for appraisal ID 6176 (iptacopan) revealed that 83% (n=62/75) of patients still experience fatigue with a mean fatigue rating of 6/10. • All surveyed patients treated with crovalimab (n=3/3) identified its main advantages to be: the delivery method i.e. injection; the fact it had improved their PNH symptoms; that it had had a positive impact on both their mental health and their ability to work or undertake education. • All surveyed patients treated with crovalimab (n=3/3) are now able to either work full time, work part time (and study part time) or study full time. Employment means patients can contribute more fully to society and can rely less on the State and their families leading to increased independence and quality of life.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal
Crovalimab for treating paroxysmal nocturnal haemoglobinuria [ID6140]
NHS organisation submission

Thank you for agreeing to give us your views on the technology and the way it should be used in the NHS.

The Department of Health and Social Care and the Welsh Government provide a unique perspective on the technology, which is not typically available from the published literature. NICE believes it is important to involve NHS organisations that are responsible for commissioning and delivering care in the NHS in the process of making decisions about how technologies should be used in the NHS.

To help you give your views, we have provided a template. The questions are there as prompts to guide you. You do not have to answer every question. Short, focused answers, giving a Department of Health and Social Care and Welsh Government perspective on the issues you think the committee needs to consider, are what we need.

NICE National Institute for Health and Care Excellence

About you

Your name	[redacted]
Name of your organisation	NHSE commissioned National PNH service (Leeds and London)
Please indicate your position in the organisation	• A specialist in the treatment of people with the condition for which NICE is considering this technology? • A specialist in the clinical evidence base that is to support the technology (e.g. participation in clinical trials for the technology)?
Do you have any links with, or funding from, the tobacco industry? Please declare any direct or indirect links to, and receipt of funding from the tobacco industry	No

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences in opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and	PNH is a rare haemolytic and thrombotic condition. We have approximately 1000 patients within our service, with 406 patients on complement inhibition: 342 Ravulizumab, eculizumab or Pecetacoplan (NHS funded) and approximately 64 within clinical trials. Indications for treatment include haemolytic PNH with anaemia, and a high LDH, PNH related complications such as renal failure, PNH related thrombosis, pregnancy (eculizumab only) and exceptional circumstances. There is no geographical variation across the UK. No difference of opinion between clinicians within the PNH service, as patients needing complement inhibition (currently approved drugs Eculizumab, Eculizumab biosimilars, Ravulizumab and Pegcetacoplan) are discussed in the National Joint MDT.

what are their respective advantages and disadvantages?	Crovalimab is an alternate C5 inhibitor to (Eculizumab and Ravulizumab), which is administered subcutaneously (self-administered) every 4 weekly, after an initial single intravenous infusion (in hospital)on D1 and weekly injections (5 dose-D2,D8, D15, D22 and D29). Current alternatives: Eculizumab, Eculizumab biosimilars and Ravulizumab. Advantages: Independence for patients as this is self-administered every 4 weekly and gives better patient convenience. Avoids the need for cannulation which is the disadvantage for the existing therapies (Eculizumab and Ravulizumab) and life long intravenous infusions. Disadvantages: Although non-inferior in terms of efficacy in complement inhibitor naïve populations, there is risk of transient immune complexes leading to side-effects when patients switch from Eculizumab/Ravulizumab to Crovalimab (in previous treated PNH patients). No data of safety available in pregnancy Other comparator products are currently within clinical trials: Potentially more effective proximal complement inhibitors are in clinical trials and Iptacopan is also undergoing NICE review process. The addition of Danicopan to background of C5 inhibitors (Ecu/Ravu) is also undergoing NICE review.

To what extent and in which population(s) is the technology being used in your local health economy?	New patients with haemolytic PNH (as an alternative to Eculizumab and Ravulizumab) Patients who are adequately stable/controlled on Eculizumab/Ravulizumab and who want to switch to a self-administered injection for convenience and patient preference.
Is there variation in how it is being used in your local health economy?	No
Is it always used within its licensed indications? If not, under what circumstances does this occur?	Not applicable, as not licensed and only used in clinical trials
What is the impact of the current use of the technology on resources?	As Crovalimab would be self-administered, this would reduce the use of health care resources, especially as the current treatments need administration of the medication (eculizumab and ravulizumab) by homecare nurses in the community. The first dose of Crovalimab is intravenous and hence will be administered in hospital like eculizumab/Ravulizumab.
What is the outcome of any evaluations or audits of the use of the technology?	
What is your opinion on the appropriate use of the technology?	The PNH National Service welcomes the option for patients to have an option of self administered treatment for patients, who are currently only able to use 2 weekly or 8 weekly intravenous eculizumab or Ravulizumab respectively. The clinical trial data have shown Crovalimab to be an effective treatment for managing PNH, improving quality of life and have independence in treatment due to self administration. It will expand treatment options available for patients and improve patient choice.

Potential impact on the NHS if NICE recommends the technology

What impact would the guidance have on the delivery of care for patients with this condition?	The PNH service would continue to provide the same service with appointments, advice and emergency out of hours care. The subcutaneous self-administered modality of administration every 4 weekly treatment will reduce homecare nursing requirements significantly
In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional resources (for example, staff, support services, facilities or equipment)?	Specialist care: PNH is an ultrarare condition, all patients should continue to be managed by the National PNH service, who have the expertise and experience in treating patients, advising about medication, and managing complications/infections if they arise. No additional resource will be needed
Can you estimate the likely budget impact? If this is not possible, please comment on what factors should be considered (for example, costs, and epidemiological and clinical assumptions).	It is likely to have no direct impact on budget from a PNH service point of view, however homecare services/nursing provision within homecare would be reduced (this is currently outsourced)
Would implementing this technology have resource implications for other services (for example, the trade-off between using funds to buy more diabetes	No

nurses versus more insulin pumps, or the loss of funds to other programmes)?	
Would there be any need for education and training of NHS staff?	No. The PNH service is familiar with the use of Crovalimab in clinical trial settings. We would need to do additional patient sessions if this drug is approved

Equality

Please let us know if you think that this appraisal: **Could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licenced** **Could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology** **Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.**	No No No
Please tell us what evidence should be obtained to enable the committee to identify and consider such impacts.	Not applicable

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others.

Other issues

Please include here any other issues you would like the appraisal committee to consider when appraising this technology	

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in collaboration with:

Erasmus School of Health Policy & Management

Maastricht University

Crovalimab for treating paroxysmal nocturnal haemoglobinuria [ID6140]

Produced by Kleijnen Systematic Reviews (KSR) Ltd, in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University

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Confidential data are redacted.

Rider on responsibility for report:

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

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Contributions of authors:

Nigel Armstrong acted as project lead and health economist/reviews manager on this assessment, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Isaac Corro Ramos acted as health economic project lead, critiqued the company's economic evaluation, and contributed to the writing of the report. Huiqin Yang and Jiongyu Chen acted as a systematic reviewer, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Marten Poley acted as health economist on this assessment, critiqued the company's economic evaluation and contributed to the writing of the report. Lisa Stirk critiqued the search methods in the submission and contributed to the writing of the report. Robert Wolff critiqued the company's definition of the decision problem, contributed to the writing of the report and supervised the project.

Abbreviations

AE	Adverse event
BS	Biosimilars
BTH	Breakthrough haemolysis
CAC	Compliment amplifying conditions
CCOD	Clinical cutoff date
CDSR	Cochrane Database of Systematic Reviews
CENTRAL	Cochrane Central Register of Controlled Trials
CI	Confidence interval
CrI	Credible interval
CS	Company submission
DP	Decision problem
EAG	External Assessment Group
ESHPM	Erasmus School of Health Policy and Management
EUR	Erasmus University Rotterdam
FACIT	Functional Assessment of Chronic Illness Therapy
FDA	Food and Drug Administration
FE	Fixed effect
Hb	Haemoglobin
ICU	Intensive care unit
iMTA	Institute for Medical Technology Assessment
Incr.	Incremental
IV	Intravenous
KSR	Kleijnen Systematic Reviews Ltd
LDH	Lactate dehydrogenase
MA	Marketing authorisation
MAVE	Major adverse vascular event
Md	Median
Me	Mean
MeSH	Medical subject headings
MHRA	Medicines and Healthcare products Regulatory Agency
N/A	Not applicable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
NIM	Non-inferiority margin
NL	Netherlands
NMA	Network meta-analysis
NR	Not reported
OR	Odds ratio
OS	Overall survival
PAS	Patient Access Scheme
PNH	Paroxysmal nocturnal haemoglobinuria
Q2W	Once every 2 weeks
Q4W	Once every 4 weeks
Q8W	Once every 8 weeks
RBC	Red blood cell
RCT	Randomised controlled trial
RE	Random effects
Rg	Range
RoB	Risk of bias
SAE	Serious adverse events
SAP	Statistical Analysis Plan

SC	Subcutaneous
SD	Standard deviation
SE	Standard error
SLR	Systematic literature review
SoC	Standard of care
STA	Single Technology Appraisal
T3H	Type III hypersensitivity
TA	Transfusion avoidance
TA	Technology Appraisal
TIC	Transient immune complex
UK	United Kingdom
U/L	Units per litre
ULN	Upper limit of normal
URTI	Upper respiratory tract infection
UTI	Urinary tract infection

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1. Summary of the EAG's view of the company's cost-comparison case

The External Assessment Group (EAG) believes that the company has demonstrated that crovalimab is equivalent in efficacy to at least one of the other technologies in the treatment of paroxysmal nocturnal haemoglobinuria (PNH), eculizumab, and therefore a cost-comparison case is appropriate. This is based on two randomised controlled trials (RCTs) of the same design (COMMODORE 1 and COMMODORE 2) that compared crovalimab with eculizumab for a follow-up period of 24 weeks. COMMODORE 1 studied patients with PNH previously treated with eculizumab whilst COMMODORE 2 studied patients not previously treated with complement (C5) inhibitors (C5-naïve).[1] This conclusion should be caveated in that equivalence is less likely for those previously treated (C5-experienced) given the formation of transient immune complexes (TICs), which might lead to the transient enhancement of crovalimab clearance resulting in risk of a transient below-target exposure, as described by the company in Appendix D.[2] Also, the evidence for this population is weaker given the smaller size of the COMMODORE 1 trial and efficacy outcomes being only exploratory. However, a major caveat is that both of these RCTs were in adults (≥18 years of age) only, and therefore it is questionable what can be inferred about the treatment effect of crovalimab versus any comparator in a paediatric population, particularly those included in the proposed indication of [redacted].

The EAG requested the company to provide data relating to paediatric patients. In responding to the EAG's request, the company provided additional data relating to paediatric patients. The results for paediatric patients were similar to those for adult patients. However, the sample sizes were very small and there were no comparative data. Therefore, there were uncertainties regarding equivalence between crovalimab and any comparator for the outcomes considered in children.

It is also important to note that, although safety seems comparable for the C5 inhibitor naïve patients, this appears not to be the case for the previously treated, with a substantial proportion suffering TIC-associated Type III hypersensitivity (T3H) reactions, which might be quite severe and long-lasting.[1, 3]

For COMMODORE 2 (C5-naïve), equivalence was demonstrated in both co-primary outcomes, mean proportion of patients with haemolysis control as measured by central lactate dehydrogenase (LDH) ≤1.5 x upper limit of normal (ULN), and proportion of patients with transfusion avoidance (TA).[1] The odds ratio for haemolysis control (crovalimab versus eculizumab) was 1.02, with a lower limit of the 95% confidence interval (CI) of 0.57, which was higher than the pre-defined non-inferiority margin (NIM) of 0.2, and the difference in proportion of patients with TA (crovalimab - eculizumab) was -2.8%, with a lower limit of the 95% CI of -15.67%, which was higher than the pre-defined NIM of -20%. Equivalence was also demonstrated for the secondary efficacy endpoints of the proportion of patients with breakthrough haemolysis (BTH) and the proportion of patients who achieved haemoglobin stabilisation. The point estimates of all but one of these four outcomes favoured crovalimab and the overlap in all 95% CIs of the point of no difference was substantial for all four outcomes. Also, the adjusted mean change from baseline to Week 25 in Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-Fatigue) was numerically higher for the crovalimab arm compared with the eculizumab arm (7.8 points [95% CI: 6.5, 9.1] versus 5.2 points [95% CI: 3.4, 6.9], respectively).

For COMMODORE 1 (C5-experienced), the efficacy outcomes were described as only exploratory.[1] However, the 95% CIs for haemolysis control, TA, BTH proportion and stabilised haemoglobin proportion showed considerable overlap of the point of no difference. There is more uncertainty in equivalence in that the sample sizes were small and the point estimates for all of the above outcomes except TA were in favour of eculizumab.

The company also claimed equivalence between crovalimab and ravulizumab.[1] For a cost-comparison to be appropriate, equivalence only has to be demonstrated with one treatment that is in use in United Kingdom (UK) clinical practice. However, the economic model does assume this for ravulizumab as well as eculizumab and so its validity might be important to establish. The opinion of the EAG is that the network meta-analysis (NMA) used by the company to demonstrate equivalence does appear to show equivalence for the outcomes considered.

2. Critique of the decision problem in the company's submission

In terms of population, as opposed to the National Institute for Health and Care Excellence (NICE) Final Scope,[4] the company's decision problem (DP) focuses only on patients [redacted][1] [redacted] This is consistent with the proposed marketing authorisation (MA).[1] It is also consistent with the randomised controlled trials (RCTs) comparing crovalimab with eculizumab, COMMODORE 2 and COMMODORE 1 (treated with eculizumab on entry to the trial) respectively.[1] The RCT evidence was only for adults.

EAG comment: The External Assessment Group (EAG) would suggest that a recommendation be made only for adults given the lack of RCT data on a paediatric population.

The intervention in the decision problem and the RCTs is as in the NICE scope.

The comparators in the decision problem and the RCTs are those in the NICE scope i.e., eculizumab and ravulizumab.

The NICE scope mentions the need to consider biosimilars (BS) to the comparators in the economic analysis and the company submission (CS) states that two have recently been licensed by the Medicines and Healthcare products Regulatory Agency (MHRA) on the basis of their similarity to eculizumab.[1, 4] However, one biosimilar, SB12, was included in the network meta-analysis (NMA) separate to and connected with eculizumab via the SB12-3003 trial.[1] The company were therefore asked to confirm that eculizumab BS can be considered as equivalent to eculizumab and that therefore the treatment effect of the BS versus crovalimab, including equivalence, can be assumed to be the same as eculizumab versus crovalimab.[5] Otherwise, if eculizumab BS are not to be considered as equivalent to eculizumab then the company were asked to present a full effectiveness and cost effectiveness analysis of crovalimab versus all comparators including eculizumab BS.

In responding to the EAG's request, the company stated that the efficacy and safety of this eculizumab BS (Epysqli) has been shown to be equivalent to that of the eculizumab originator (Soliris) as demonstrated in the SB12-3003. The exclusion of eculizumab BS was not anticipated to have an impact on the overall results of the NMA, where the non-inferiority of crovalimab to eculizumab and ravulizumab was demonstrated in key clinical outcomes (transfusion avoidance, breakthrough haemolysis events, and haemoglobin stabilisation). The company further stated that the recent uptake data (April 2024, IQVIA MIDAS) showed that, with only [redacted] sold since their approval, eculizumab BS are yet to be established in UK clinical practice, so eculizumab BS does not represent an appropriate comparator. Therefore, the full effectiveness and cost effectiveness analysis comparing crovalimab to eculizumab BS were not performed.[6] The EAG considers that the reason for the exclusion of eculizumab BS was acceptable.

The following outcomes were omitted from the decision problem: overall survival (OS), intravascular haemolysis and extravascular haemolysis were not included.

The EAG requested in the clarification letter that the outcomes omitted from the decision problem be included, to which the company responded that outcomes were related to the mechanism of the intervention and that overall survival was not expected to differ between treatments.[6]

The EAG requested the company to provide evidence of the treatment effect and/or demonstrate equivalence (crovalimab versus relevant comparators) for the outcomes of OS and extravascular haemolysis. In responding to the EAG's request, the company stated that it was not possible to systematically collect extravascular haemolysis data and only descriptive data on deaths was available from the COMMODORE studies. Therefore, it was not possible to perform a comparative analysis in these outcomes.[6] The EAG acknowledged the limitations in the available data.

3. Summary of the EAG's critique of clinical effectiveness evidence submitted

3.1 Systematic literature review methods

3.1.1 Searches

Searches covered a good range of resources including MEDLINE and Embase (via Embase.com), the Cochrane Database of Systematic Reviews (CDSR) and the Cochrane Central Register of Controlled Trials (CENTRAL) (via the Cochrane Library), and MEDLINE in Process (via PubMed). Additional searches were carried out for three named conference proceedings held between 2020-2022 and three trials registries. Bibliographies of recent systematic reviews were also searched. Searches were conducted on 6 December 2022 and updated on 1 July 2024.

The CS, Appendix D and the Company's response to clarification provided sufficient details for the EAG to appraise the literature searches. Searches were transparent and reproducible, and comprehensive strategies were used.[1, 2, 6]

EAG comment: For both the original and update searches, Embase and MEDLINE were searched simultaneously via Embase.com. This approach has limitations when using subject heading terms which could affect recall of results. Embase subject heading terms (Emtree) were used in the search strategy, and although simultaneous searching of Embase.com should automatically identify and search for equivalent MEDLINE medical subject heading (MeSH) terms, it is not clear if this is the case for all potentially useful MeSH terms, particularly in the study design filter. Given the potential limitations of this approach, the EAG considers it preferable to search each database separately, or at least to ensure inclusion of both Emtree and MeSH terms in the search strategy.

The Embase.com December 2022 search does not appear to have searched using both UK and US English spelling variants in the title/abstract searches (Appendix D, Table 2), however as the UK terms appear to be duplicated, and the update searches sent in the response to clarification include both variants, the EAG considers it possible that the spelling may have been auto-corrected in the CS.

The systematic literature review (SLR) may have benefitted from separate adverse (AE) events searches conducted to capture AEs that are long-term, rare or unanticipated and therefore less likely to be retrieved by searches containing an RCT filter as documented in Appendix D.[7] The EAG was also concerned that limiting the Embase.com searches to the English language may have introduced potential language bias. Current best practice states that 'To reduce the risk of introducing bias, searches should not be restricted by language'.[8]

Overall, however, the EAG has no major concerns about the literature searches conducted.

3.1.2 Inclusion screening

The study eligibility criteria for the SLR[2] are broadly aligned with the domains presented in the NICE Final Scope[4] and the company's DP.[1]

Identified studies were assessed for eligibility at both the title and abstract and full-text screening stages by two independent reviewers. Disagreements were resolved by a third reviewer.[2] Data from included studies were extracted into a pre-specified data extraction table in Microsoft® Excel® by two independent reviewers. Disagreements were resolved by a third reviewer. [2] Assessment of risk of bias (RoB) was undertaken by an unspecified number of reviewers. For the RCTs, the reviewers used the seven-criteria checklist provided in Section 2.5 of the NICE Single Technology Appraisal (STA) user guide.[9]

Appendix D of the CS (Section D.1.7 and Figure 2) indicates that 25 studies (17 RCTs and eight single arm studies) were included in the clinical effectiveness SLR.[2] Of these, 11 and five had completed. Figure 2 showed that only six RCTs and no single arm studies were included in the feasibility assessment. However, in subsection D.1.7.1 an update is reported where one more RCT and two more single arm studies are reported. Also, in the section on feasibility assessment (D.1.8), Table 6 shows 11 RCTs and six single trials.

EAG comment: Because the number of trials included was unclearly reported, the company were asked for clarification, to which they responded by reproducing the PRISMA flowchart.[6] This combined with Table 9 in the clarification letter response suggests that 30 studies (19 RCTs and 11 single arm) were assessed for the NMA and that six RCTs were eventually included, after excluding all single arm studies, those not connected to the network or with no results or because of lack of comparability of outcome or population (four trials).

The EAG requested the information on the number of reviewers who carried out the quality assessment of trials and how they did this in terms of independence. The company responded that the quality assessment of each trial was conducted by two independent reviewers, and discrepancies were resolved by a third reviewer.

3.2 Identified randomised controlled trials

Information on the included RCTs was gleaned from Document B[1] and Appendices D to H (inclusive)[2] of the CS and the company's clarification response documents.[6]

3.2.1 Methods

The company identified two RCTs of similar design (COMMODORE 1 and COMMODORE 2) that compared crovalimab with eculizumab for a follow-up period of 24 weeks.[1] COMMODORE 1 studied patients with PNH previously treated with eculizumab (C5-experienced) whilst COMMODORE 2 studied patients not previously treated with complement inhibitors (C5-naïve).[1] They are both phase III and multicentre and were in adults (≥18 years of age) only. However, COMMODORE 2, a non-inferiority trial, was referred to as the pivotal study and COMMODORE 1 as a supportive study. In keeping with this, the former had primary efficacy outcomes, the co-primary haemolysis control and transfusion avoidance, in contrast to the latter, which primary safety outcomes of AEs. However, the fundamental difference was that COMMODORE 2 was in the C5 naïve and COMMODORE 1 in the C5 experienced. Both included the incidence and severity of clinical manifestations of transient immune complexes (TICs), but it was reported in Appendix D, Section D.4.2.1 that these were of particular interest in COMMODORE 1, given that they arise as a result of treatment switching when for a short time two C5 inhibitors, eculizumab and crovalimab, might bind to the C5 protein.[2]

In COMMODORE 2, for the primary outcomes there was a target sample size of 200 to achieve a power of 80% to test for a pre-defined non-inferiority margin (NIM) and a one-sided Type 1 error rate of 2.5% when randomised to crovalimab or eculizumab in the ratio of 2:1.[1] The NIM was a mean difference of -20% for transfusion avoidance (TA) and an odds ratio of 0.2 for haemolysis control. The TA NIM is stated to be based on 50% of the difference between the point estimates of eculizumab and no treatment based, the former, 57.1%, coming from an RCT of eculizumab versus ravulizumab, Study 301[10] and the latter, 18.6%, from what the company refer to as the global PNH Registry.[1]

Both trials also had a non-randomised arm (Arm C), Arm C of COMMODORE 2 consisting of children (<18 years of age).[1] Arm C of COMMODORE 1 consisted partly of children, all patients previously treated with eculizumab, as well as adults previously treated with either ravulizumab or

higher than approved doses of eculizumab: it also was open to those randomised to eculizumab after 24 weeks.

There is also another Phase III study, COMMODORE 3, evidence for which was not included because it was conducted entirely in China.[1]

EAG comment: The EAG questions the calculation of the NIM. The U.S. Food and Drug Administration (FDA) recommends a method based on the difference between the point of no difference and the lowest point on the 95% confidence interval (CI) of the treatment effect of the reference treatment, in this case eculizumab, and no treatment/placebo only.[11] Because the lowest point of the 95% CI is, by definition, lower than the difference between the point estimates, the NIM calculated this way must necessarily be lower and thus any test for non-inferiority must be more stringent. The company were therefore asked to clarify the sources and methods of calculating the NIM, justify the method and recalculate if not using the one recommended by the FDA.[5] The company responded that the EAG were correct that NIM was not calculated using the standard FDA recommended method.[6] Instead, the method used was less conservative, as presumed by the EAG. They stated that the estimated sample size would have been infeasible given the rarity of the condition. The EAG understands this argument, but this does undermine to some degree the use of a NIM to determine equivalence, thus resulting in the need to apply judgment regarding other indicators i.e., 95% credible interval (CrI) overlap of point of no difference, small treatment effect point estimates or point estimates in favour of crovalimab, as the EAG have done.

The EAG considers it reasonable to have excluded COMMODORE 3, given that, as well as having been conducted in China, it was only a single arm study, which limits its value in demonstrating relative efficacy or equivalence. Also, the safety data is of limited value given that it was in the C5 treatment-naïve and, as described below, the main concern regarding safety is in the C5 experienced patients.

For the TA outcomes, the EAG further requested the details of the sources and estimates from these sources for calculation of the NIM. The company provided the following response: *'The company would like to clarify that as cited in the Study BO42162 Protocol Version 6 and Statistical Analysis Plan (SAP) Version 3, the information available to the Company from the International Global PNH Registry™ is cited from the ALXN Study 301 Protocol and SAP (NCT02946463). These documents provide only the TA point estimates of eculizumab treated patients (57.1%) and untreated patients (18.6%), resulting in a difference of approximately 40%. Per the Company's review of relevant literature (Soliris Type II Variation Procedure No. EMEA/H/C/000791/II/0066 [cited in ALXN Study 301 SAP], all published manuscripts on the International Global PNH Registry™ as listed in the Published Manuscripts page of the registry site [https://pnhregistry.com/publications]), no additional details, specifically in terms of sample size or standard error, are publicly available to allow for the computation of the 95% confidence interval (CI) for the cited difference.'* The EAG acknowledged the limitations of the available data.

For the TA outcomes, the EAG also requested the company to perform an assessment of non-inferiority by using the usual method of NIM calculation in terms of the lowest point on the 95% CI. The company responded that since the 95% CI for the difference cannot be computed due to the lack of relevant data, it was not feasible to re-calculate the NIM by using the FDA's recommended method of NIM calculation based on the lower bound of the 95% CI for the difference. The EAG acknowledged the infeasibility of rederiving the NIM by using the FDA's recommended approach given that there was a lack of relevant data.

For the haemolysis control outcomes, the EAG requested full details of the sources and estimates from these sources for calculation of the NIM. The company provided the following response: *'The 86%*

proportion for eculizumab-treated patients achieving HC (LDH ≤ 1.5 × ULN) was estimated using data from the eculizumab arm in the ALXN 301 Study, which evaluated the efficacy and safety of ravulizumab compared to eculizumab in patients with PNH who are naïve to complement inhibitor treatment. The graph of means and 95% CI in LDH over time was available online from top-line results material provided by Alexion on 15 March 2018.'

For the haemolysis control outcomes, the EAG also requested the company to perform an assessment of non-inferiority using the usual method of NIM calculation in terms of the lowest point on the 95% CI. In responding this request, the company performed an assessment of non-inferiority using the usual method of NIM calculation in terms of the lowest point on the 95% CI.

For the calculation of treatment effect size between eculizumab and placebo, the company made the assumptions for the proportion of patients with lactate dehydrogenase (LDH) ≤ 1.5 × upper limit of normal (ULN): 86% for eculizumab and 20% for placebo. From this calculation, the lower bound of the 95% CI for the odds ratio (OR) between eculizumab and placebo was estimated as 9.24 (see Table 3.1).

Table 3.1: Proportions of patients with LDH ≤ 1.5 x ULN and OR between eculizumab and placebo

Results in each arm	OR (95% CI)
Eculizumab: 86% (N=121)[a] vs. placebo: 20% (N=35)[b] (indirect comparison)	24.47 (9.24, 64.82)[c]
Based on Table 8 of the response to the request for clarification[6] [a] Data source: Assumed value from results in ALXN 301 study [b] Data source: Assumed value from results in TRIUMPH and ALXN 301 Study SAP. [c] Calculated from the assumed values. 95% CI is calculated by the Wald method. Note: The OR of 24.6 used in the protocol was derived using the assumed proportions of 86% vs. 20%, while the OR in this table was derived using 104/121 (=85.95%) instead of 86% for eculizumab. CI = confidence interval; LDH = lactate dehydrogenase; OR = odds ratio; ULN = upper limit of normal	

Based on the assessment of non-inferiority by using the NIM based on the lower bound of the 95% CI, the re-calculated NIM based on the lower bound of the 95% CI for the OR to maintain 50% preserved effect is 0.33 (= $1/9.24^{0.5}$). Therefore, this re-calculated NIM was still lower than the estimated lower bound of the 95% CI for the OR of the haemolysis control outcome (OR 1.02, 95% CI: 0.57, 1.82). The EAG considers that the results still demonstrated non-inferiority in this outcome by applying the re-derived NIM based on the lower bound of the 95% CI.

3.2.2 Results

3.2.2.1 Efficacy

For COMMODORE 2, Table 3.2 shows the main outcomes. As stated above, equivalence in the primary outcome of mean proportion of patients with haemolysis control as measured by central LDH ≤1.5 x ULN was demonstrated: from Week 5 through Week 25 this 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. The odds ratio for haemolysis control (crovalimab versus eculizumab) was 1.02, with a lower limit of the 95% CI of 0.57, which was higher than the predefined NIM of 0.2. Equivalence was also demonstrated for proportion transfusion free: 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. The difference in proportion of patients with TA (crovalimab - eculizumab) was -2.8%, with a lower limit of the 95% CI of -15.67%, which was higher than the predefined NIM of -20%. Non-inferiority was also demonstrated for the secondary efficacy endpoints of the proportion of patients with

breakthrough haemolysis (BTH) from baseline through Week 25, and the proportion of patients who achieved haemoglobin stabilisation from baseline to Week 25. Also, the adjusted mean change from baseline to Week 25 in Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-Fatigue) was numerically higher for the crovalimab arm compared with the eculizumab arm (7.8 points [95% CI: 6.5, 9.1] versus 5.2 points [95% CI: 3.4, 6.9], respectively).

Table 3.2: Overview of co-primary and secondary efficacy endpoint results (COMMODORE 2 primary analysis population)

	Eculizumab (N=69)	Crovalimab (N=134)
Co-Primary Efficacy Endpoints		
Mean Proportion of Patients with Haemolysis Control from Week 5 through Week 25		
Mean Proportion of Patients Achieving Controlled Haemolysis (95% CI)	79.0% (69.66, 85.99)	79.3% (72.86, 84.48)
Odds Ratio (95% CI)	1.02 (0.57, 1.82)[a]	
	NIM for lower 95% CI limit = 0.2	
Proportion of Patients with Transfusion Avoidance from Baseline through Week 25[b]		
Patients with TA, n (%)	47 (68.1%)	88 (65.7%)
Weighted Difference in Proportion (95% CI)	– 2.8% (– 15.67, 11.14)	
	NIM for lower 95% CI limit = – 20%	
Secondary Efficacy Endpoints		
Proportion of Patients with Breakthrough Haemolysis from Baseline through Week 25[c]		
Patients with at least one BTH, n (%)	10 (14.5%)	14 (10.4%)
Weighted Difference in Proportion (95% CI)	– 3.9% (– 14.82, 5.26)	
	NIM for upper 95% CI limit = -20%	
Proportion of Patients with Stabilised Haemoglobin from Baseline through Week 25[d]		
Patients with Haemoglobin Stabilisation, n (%)	42 (60.9%)	85 (63.4%)
Weighted Difference in Proportion (95% CI)	2.2% (– 11.37, 16.31)	
	NIM for lower 95% CI limit = –20%	
Adjusted Mean Change from Baseline to Week 25 in FACIT-Fatigue[e,f]		
Adjusted Mean Change (SE)	5.2 (0.88)	7.8 (0.66)
Difference in Adjusted Mean (95% CI)	2.6 (0.68, 4.60)	

Based on Table 9 of the CS[1]

[a] An odds ratio > 1 favours crovalimab.

[b] Note, 1 patient in the crovalimab arm discontinued the study prior to Week 25 without a transfusion and was conservatively assumed to have had a transfusion.

[c] Note, 4 patients in the crovalimab arm and 1 patient in the eculizumab arm discontinued the study prior to Week 25 without a per protocol BTH and were conservatively assumed to have had a BTH.

[d] Note, 1 patient in the crovalimab arm discontinued the study prior to Week 25 with haemoglobin stabilisation and was conservatively assumed to have had a haemoglobin stabilisation.

[e] FACIT-Fatigue was assessed in adult patients only (crovalimab: 134 adult patients and eculizumab: 67 adult patients). The total FACIT-Fatigue score ranges from 0 to 52 with higher scores indicating lower fatigue severity. The threshold for a clinically meaningful improvement is ≥ 5 points.

[f] Non-inferiority testing of FACIT-Fatigue was planned to occur only after successful superiority testing of all the other co-primary and secondary efficacy endpoints. Given the outcome of this superiority testing, the comparative results of FACIT-Fatigue are descriptive only.

BTH = breakthrough haemolysis; CI = confidence interval; CS = company submission; FACIT = Functional Assessment of Chronic Illness Therapy–Fatigue; NIM = non-inferiority margin; SE = standard error; TA = transfusion avoidance

For COMMODORE 1, Table 3.3 shows the main efficacy outcomes, all of which were stated to be exploratory. However, the 95% CIs for haemolysis control, transfusion avoidance, breakthrough haemolysis proportion and stabilised haemoglobin proportion showed considerable overlap of the point of no difference. There is more uncertainty in equivalence in that the sample sizes were small (n=39 and 37 for crovalimab and eculizumab respectively. Also, the point estimates for all outcomes of the above outcomes except transfusion avoidance were in favour of eculizumab. This might be explained by the transient enhancement of crovalimab clearance resulting in risk of a transient below-target exposure, as mentioned above. However, seven out of 39 patients experienced this in the crovalimab arm of COMMODORE 1, although only one was above Grade 2 (Grade 3) and none required a dose modification/interruption.

Table 3.3: Overview of exploratory efficacy results from Study COMMODORE 1 (24-Week efficacy population)

	Eculizumab (N=37)	Crovalimab (N=39)
Mean Proportion of Patients with Haemolysis Control from Baseline through Week 25		
Mean Proportion of Patients Achieving Controlled Haemolysis (95% CI)	93.7% (87.26, 97.04)	92.9% (86.62, 96.39)
Odds Ratio (95% CI)	0.88 (0.28, 2.77)	
Proportion of Patients with Transfusion Avoidance from Baseline through Week 25[a]		
Patients with TA, n (%)	29 (78.4%)	31 (79.5%)
Weighted Difference in Proportion, % (95% CI)	1.8 (-16.67, 19.94)	
Proportion of Patients with Breakthrough Haemolysis from Baseline through Week 25[b]		
Patients with at least one BTH, n (%)	5 (13.5%)	4 (10.3%)
Weighted Difference in Proportion, (95% CI)	-3.5 (-19.20, 11.68)	
Proportion of Patients with Stabilised Haemoglobin from Baseline through Week 25[c]		
Patients with Stabilised Haemoglobin, n (%)	26 (70.3%)	23 (59.0%)
Weighted Difference in Proportion (95% CI)	-10.8 (-30.84, 10.39)	
Adjusted Mean Change from Baseline to Week 25 in FACIT-Fatigue scores[d]		
Adjusted Mean Change (SE)	-2.6 (1.37)	1.1 (1.29)
Difference in Adjusted Mean (95% CI)	3.71 (0.05, 7.36)	

Based on Table 10 of the CS[1]

[a] Note, 1 patient in the eculizumab arm discontinued treatment before Week 25 without a transfusion and was conservatively assumed to have had a transfusion.

[b] Note, 2 patients in the eculizumab arm without a BTH event discontinued treatment before Week 25 and were therefore conservatively assumed as having a BTH event.

[c] Note, 1 patient in the eculizumab arm discontinued treatment before Week 25 and was conservatively assumed as not having stabilised haemoglobin.

[d] FACIT-Fatigue scores range from 0–52, with higher scores indicating lower fatigue. FACIT-fatigue questionnaires were collected in adult patients only.

BTH = breakthrough haemolysis; CI = confidence interval; CS = company submission; FACIT = Functional Assessment of Chronic Illness Therapy–Fatigue; SE = standard error; TA = transfusion avoidance

EAG comment: Both of the RCTs were in adults (≥18 years of age) only and therefore it is questionable what can be inferred about the treatment effect of crovalimab versus any comparator in a paediatric population, particularly those included in the proposed indication of 12 years of age or older.

For COMMODORE 1, the EAG requested to the company to provide the information on the length of time for patients on receiving eculizumab before entry to the trial. The company responded that based on the inclusion criteria in the trial of COMMODORE 1, patients must have had documented treatment with eculizumab according to the approved dosing (900 mg once every two weeks (Q2W)) recommended for PNH and completion of a minimum of 24 weeks of treatment prior to Study Day 1. However, comprehensive historical data on the treatment duration of eculizumab, beyond the 24- weeks prior to study enrolment, are not available. The EAG considers that it was unclear about the data of washout period for the treatment switching from eculizumab to crovalimab.

3.2.2.2 Safety

Tables 3.4 and 3.5 provide summaries of the adverse events experienced in both COMMODORE trials. In COMMODORE 2, the AE rates of the two arms are similar with slightly fewer patients experiencing Grade 3 to 5 AEs and serious adverse events (SAEs), but more treatment related SAEs in the crovalimab arm. However, in COMMODORE 1, a much higher proportion of patients experienced Grade 3 to 5 AEs (18.2 versus 2.4%), SAEs (13.6 versus 2.4%) and treatment related AEs (31.8 versus 0%), although none of the treatment related AEs were reported to be SAEs. Note that the sample size was small in COMMODORE 2, so 2.4% refers to one patient.

Specifically, in COMMODORE 2 upper respiratory tract infections (URTI) and urinary tract infections (UTI) seemed to be less common with crovalimab, whereas infusion or injection related reactions, diarrhoea and headache were more common. This pattern was generally seen in COMMODORE 1 with the exception of URTI. However, in COMMODORE 1 pyrexia and rash were more common with crovalimab (15.9 versus 2.4% and 6.8 versus 0% respectively). The company also reported that arthralgia was more common (6.8 versus 0%). The most common related AE in COMMODORE 1 was TIC reactions (15.9%), followed by infusion and injection related reactions (13.6% and 6.8% respectively).

Transient immune complex reactions were identified as AEs of special interest and an explanation provided, which was that they are composed of the two different monoclonal antibodies bridged by C5, which form when both treatments are present in the circulation of patients who switch between C5 inhibitor treatments. Therefore, patients who switched from eculizumab (or ravulizumab) to crovalimab (and vice versa) are at risk of developing TICs and TIC-associated T3H reactions. They would not develop if there was no switching or if there was a washout period, which was described in the Appendices as "*infeasible*" (p. 61).[2] In COMMODORE 1, all but one of seven (15.9%) of the T3H reactions was Grade 1 or 2, only one being Grade 3, which was reported to have resolved after treatment with no dose modification/interruption. In that one patient, the symptoms were arthralgia, dizziness, abdominal pain upper and nausea. It was reported that the median resolution duration for events was 1.9 weeks (range, 0.4–34.1). The rate observed in prior ravulizumab and prior high-dose eculizumab cohorts of Arm C of COMMODORE 1 were [redacted] and [redacted] of the prior eculizumab cohort experienced a dose interruption. No further details were reported. [redacted] were observed in the paediatric cohort.

EAG comment: The safety profile for crovalimab does seem to be very similar to that of eculizumab in the C5-naïve with most AEs that affect those treated with crovalimab being relatively mild and transient. However, this is not the case with those switching from eculizumab or ravulizumab: a substantial proportion will suffer AEs that, although mostly relatively mild, can last several weeks and up to more than six months. A submission from PNH Support also revealed that three patients who switched from ravulizumab to crovalimab suffered what were described as severe adverse reactions, at least two of whom had not recovered at the time of the submission.[3] The company were therefore requested to tabulate all treatment related or immune complex related, SAE and Grade 3+ AE data for

patients who have switched from any treatment to crovalimab.[5] They were requested to include the outcome of these patients until the latest follow-up, including the duration of any of the AEs and any data on the treatment and cost of treatment of these AEs. The company responded by providing this information as requested.[6]

Addition information from the clarification response[6] included that in Arm C of COMMODORE 1, [redacted] The company reported in answer to question A19a that [redacted], and referred to A19b for more detail. However, only [redacted] were mentioned in the answer to A19b, where it was reported that [redacted] (confirmed in the table provided by the company (ID6140 crovalimab Roche Clarification Q-A19a tabulated data v1.0 04072024 IC CON).[12]

The data from the company response to clarification showed that up to the May 2023, [redacted] The majority of the T3H reactions experienced among patients across the COMMODORE trials were self-limiting and resolved without changes in crovalimab treatment. There were no life-threatening or fatal events reported.[6]

Table 3.4: Overview of AEs (Primary Safety Period, Randomised Safety Population)

	COMMODORE 2		COMMODORE 1	
Safety Outcome	**Crovalimab (Arm A) n=135**	**Eculizumab (Arm B) n=69**	**Crovalimab (Arm A) n=44**	**Eculizumab (Arm B) n=42**
Treatment duration, weeks				
Mean (SD)	19.7 (2.8)	22.0 (2.0)	19.1 (3.7)	20.4 (5.7)
Median (range)	20.1 (0.1–23.1)	22.1 (6.1–26.1)	20.1 (2.1–22.3)	22.1 (0.1–26.1)
Total number of patients with at least one AE, n (%)	105 (77.8)	55 (79.7)	34 (77.3)	28 (66.7)
Total number of AEs, n (%)	421	223	127	67

	COMMODORE 2		COMMODORE 1	
Safety Outcome	**Crovalimab (Arm A) n=135**	**Eculizumab (Arm B) n=69**	**Crovalimab (Arm A) n=44**	**Eculizumab (Arm B) n=42**
Total number of deaths, n (%)	2 (1.5)	1 (1.4)	0	0
Total number of patients withdrawn from initial treatment due to AE, n (%)	0	0	0	0
Total number of patients with at least one of the following, n (%)				
Fatal AE	2 (1.5)	1 (1.4)	0	0
SAE	14 (10.4)	9 (13.0)	6 (13.6)	1 (2.4)
Related SAE	4 (3.0)	1 (1.4)	0	0
Related AE	45 (33.3)	24 (34.8)	14 (31.8)	0
Related AE leading to withdrawal from treatment	1 (0.7)	0	0	0
Related AE leading to dose modification/interruption	1 (0.7)	0	0	0
AE of Grade 3–5	24 (17.8)	17 (24.6)	8 (18.2)	1 (2.4)
AE leading to withdrawal from treatment	1 (0.7)	1 (1.4)	0	0
AE leading to dose modification/interruption	5 (3.7)	3 (4.3)	1 (2.3)	0

Based on Table 18 of the CS[1]
Only treatment-emergent AEs are displayed. Multiple occurrences of the same AE in one individual are counted only once except for 'Total number of AEs' row in which multiple occurrences of the same AE are counted separately.
AE = adverse event; CS = company submission; SAE = serious adverse event; SD = standard deviation

Table 3.5: Summary of Common (≥ 5%) AEs by Preferred Term (Primary Safety Period, Randomised Safety Population)

	COMMODORE 2		COMMODORE 1	
Safety Outcome; MedDRA System Organ Class and MedDRA Preferred Term	**Crovalimab (Arm A) n=135 n (%)**	**Eculizumab (Arm B) n=69 n (%)**	**Crovalimab (Arm A) n=44 n (%)**	**Eculizumab (Arm B) n=42 n (%)**
Infections and infestations				
Upper respiratory tract infection	11 (8.1%)	9 (13.0%)	3 (6.8%)	1 (2.4%)
COVID-19	11 (8.1%)	4 (5.8%)	6 (13.6%)	7 (16.7%)
Influenza	-	-	2 (4.5%)	3 (7.1%)
Urinary tract infection	2 (1.5%)	4 (5.8%)	2 (4.5%)	3 (7.1%)
Metabolism and nutrition disorders				
Hypokalaemia	15 (11.1%)	9 (13.0%)	-	-
Hyperuricaemia	11 (8.1%)	6 (8.7%)	-	-
Hypocalcaemia	8 (5.9%)	7 (10.1%)	-	-

	COMMODORE 2		COMMODORE 1	
Safety Outcome; MedDRA System Organ Class and MedDRA Preferred Term	**Crovalimab (Arm A) n=135 n (%)**	**Eculizumab (Arm B) n=69 n (%)**	**Crovalimab (Arm A) n=44 n (%)**	**Eculizumab (Arm B) n=42 n (%)**
Injury, poisoning and procedural complications				
Infusion-related reaction	21 (15.6%)	9 (13.0%)	6 (13.6%)	0
Injection-related reaction	7 (5.2%)	0	3 (6.8%)	0
Gastrointestinal disorders				
Nausea	-	-	3 (6.8%)	2 (4.8%)
Diarrhoea	10 (7.4%)	0	3 (6.8%)	1 (2.4%)
General disorders and administration site conditions				
Pyrexia	12 (8.9%)	7 (10.1%)	7 (15.9%)	1 (2.4%)
Asthenia	-	-	3 (6.8%)	2 (4.8%)
Oedema peripheral	-	-	3 (6.8%)	1 (2.4%)
Investigations				
Neutrophil count decreased	17 (12.6%)	7 (10.1%)	-	-
White blood cell count decreased	16 (11.9%)	7 (10.1%)	-	-
Nervous system disorders				
Headache	11 (8.1%)	3 (4.3%)	5 (11.4%)	1 (2.4%)
Skin and subcutaneous tissue disorders				
Rash	-	-	3 (6.8%)	0

Based on Table 19 of the CS[1]
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. Displayed are MedDRA preferred terms that occurred in ≥ 5% of patients in at least one of the two treatment groups displayed. Events are sorted by descending overall total frequency.
AE = adverse event; COVID-19 = coronavirus disease 2019; CS = company submission; MedDRA = Medical Dictionary for Regulatory Activities

3.2.2.3 Paediatric patients

[redacted]

Efficacy

[redacted]

[redacted] ***Safety***

It was reported that in Arm C of COMMODORE there were [redacted] **EAG comment:** The EAG asked the company to confirm that the decision problem, the proposed license and those expected to receive crovalimab would include children at least 12 years of age. The company responded that the population covered by the final scope was defined as patients with PNH. The decision problem addressed in the submission covers the full population covered by the anticipated marketing authorisation, [redacted] In responding to the EAG's request, the company provided additional data relating to paediatric patients. The results for paediatric patients appear to be similar to those for adult patients. However, the sample sizes were very low and there was no comparative evidence. Therefore, the applicability of any conclusions regarding equivalence between crovalimab and any comparator in children has not been demonstrated.

3.3 Summary and critique of network meta-analysis

3.3.1 Methods

The company provide a NMA to synthesise clinical effectiveness and safety evidence at week 25 for the C5-naïve populations, C5-experienced populations and combination C5-naïve and C5-experienced populations.[1] Network meta-analyses were conducted for six key outcomes: transfusion avoidance, breakthrough haemolysis, haemoglobin stabilisation, number of packed red blood cell transfusion, FACIT fatigue score and adverse events. It is reported in Appendix D[2] that there was a qualitative heterogeneity assessment, although no results were provided. An identity link was used for all outcomes except adverse events, including proportions and count data. This was justified based on need to calculate the probability of non-inferiority.

EAG comment: The NICE scope outcome of OS was not subjected to NMA, which might be considered a limitation. The company was asked why OS was used as the outcome for assessing prognostic factors, given that it was not an outcome in any of the NMAs (clarification letterA14a). In responding to the EAG's request, the company stated that the outcome of OS was used to structure the table as the overarching endpoint, but this was mediated by age, LDH level, prior transfusions, history of aplastic anaemia and history of major adverse vascular event (MAVE). These were key trial outcomes and aligned with the stratification factors in COMMODORE 1 and 2. The NICE technology appraisal guidance (TA778) also identified Hb level as an additional prognostic factor.[6, 13]

The company was also asked to justify the NMA feasibility assessment according to factors prognostic or treatment effect modifying for the outcomes included in the NMAs (clarification letter A14b). In responding to the EAG's request, the company stated that a targeted search was performed. The search identified two observational studies (a multi-centre study, n=59 and a registry-based analysis, n=2,356) and an expert panel review, which identified potential prognostic factors or treatment modifiers. These sources suggested that age, PNH subtype, Karnofsky performance score, and thromboembolism/history of thrombosis might be potential prognostic factors or treatment-effect modifiers for efficacy outcomes.

In addition, pancytopenia (i.e., bone marrow failure not diagnosed as aplastic anaemia) and thrombocytopenia <30 and infection at diagnosis are also prognostic factors, which were taken into account as these patients were excluded from the COMMODORE trials.[6] The EAG considers that the approach used by the company to identify the potential prognostic factors or treatment effect modifier was acceptable.

The company was asked to provide the results of this assessment and indicate how any such heterogeneity caused the exclusion of any studies from the network and how it might produce bias where studies subject to such heterogeneity were included (clarification letter A15). In responding to the EAG's request, the company provided reasons for excluding trials from the network. The company stated that single-arm trials were not considered in this feasibility assessment, as these trials were not connected to the network. The SR identified 19 trials where data were published or otherwise available, and seven ongoing RCTs. Of the 19 trials with data published or otherwise available, 13 trials were excluded from the feasibility assessment mainly because these studies were not connected to the network or the primary outcome of the study was assessed at 10 weeks instead of 24 weeks. [6]The EAG considers that the reasons for the exclusion of these studies appear to be appropriate.

Furthermore, for the studies that were included in the network for patients with previously treated PNH, the company performed heterogeneity assessment based on dosing and treatment schedules, primary outcomes, inclusion and exclusion criteria.[6] The results of this assessment indicated that inclusion/exclusion criteria including diagnoses, prior treatments, absence of bone marrow transplant history, and absence of serious infections were consistent across both included studies relating to patient with previously treated PNH (COMMODORE 1 and Study-302). The company further made an assessment on the differences in baseline characteristics, including prognostic factors or treatment effect modifiers for studies with patients with previously treated PNH (See Table 3.6). Patients' characteristics, which are identified as potential prognostic factors or treatment-effect modifiers, are age, LDH level, prior transfusions, history of aplastic anaemia, and history of MAVE. The NICE technology appraisal guidance TA778 also identified haemoglobin (Hb) level as a treatment effect modifier.[13] Based on the assessment, the trial populations appear to be generally comparable in terms of these characteristics.[6]

For studies with treatment-naïve patients, the company performed heterogeneity assessment based on dosing and treatment schedules, primary outcomes, inclusion and exclusion criteria.[6] The TRIUMPH, Study-301, SB12-3003, and COMMODORE 2 trials used eculizumab at a consistent dosing schedule. In terms of outcomes, the most commonly reported outcomes were TA, Hb stabilisation, red blood cell (RBC) transfusion, and FACIT-Fatigue score. The definitions for these most commonly reported outcomes (TA, RBC transfusion, and FACIT-Fatigue) were generally consistent across the majority of included trials, with the exception of definition for Hb stabilisation in the trial of TRIUMPH. Given this limitation, the comparison with the placebo arm in the trial of TRIUMPH should be interpreted with caution. Furthermore, inclusion/exclusion criteria across trials were generally consistent to those in the COMMODORE trial. However, the TRIUMPH trial recruited patients who received at least four transfusions in the last 12 months prior to study entry. It should be noted that transfusion history is considered an important effect modifier in the NICE technology appraisal guidance TA778.[6, 13] Therefore, the findings of the TRIUMPH trial (with a comparison with the placebo arm) are only appliable for patients who are transfusion dependent.

Furthermore, for studies with treatment-naïve patients, the company also performed an assessment on the differences in baseline characteristics, including prognostic factors or treatment effect modifiers (see Table 3.7).[6] Patients' characteristics, which are identified as potential prognostic factors or treatment-effect modifiers, are age, LDH level, prior transfusions, history of aplastic anaemia, history of MAVE and Hb level. The baseline LDH levels were generally consistent across the majority of trials;

however, the Study-301 trial recruited patients with lower baseline LDH. In terms of transfusion history, the SB12-3003 trial recruited a slighter lower proportion of transfused patients compared to that of study-301.The baseline data of history of aplastic anaemia were reported in three trials. There was a slightly higher proportion of patients with history of aplastic anaemia in the COMMODORE 2 trial. There were similar rates of major vascular events across trials where reported. In addition, the baseline data of Hb levels were only reported in two trials (COMMODORE 2 and study 301). The Hb levels were generally consistent between the two trials (COMMODORE 2 and study 301).[6] The EAG considers that although there were variations in a number of baseline characteristics in some studies, these were generally consistent across the majority of studies.

For the C5-naïve population, the NMA apparently include a redundant comparator, standard of care (SoC) without C5 inhibitors.[1] The company was asked to reconduct the analysis excluding TRIUMPH, the trial with SoC without C5 inhibitors (clarification letter A16). In responding to the EAG's request, the company reconducted the analysis by excluding the TRIUMPH trial from the network. The company responded that the exclusion of the TRIUMPH trial from the network did not influence the effect estimates between crovalimab and ravulizumab.[6]

The company was asked to perform NMAs using a link function better suited to the form of the data e.g., logit for proportions (clarification letter A17). In responding to the EAG's request, the company stated that in recent trials with patients with PNH including the COMMODORE studies, the outcomes of breakthrough haemolysis, transfusion avoidance and haemoglobin stabilisation were analysed by comparing the mean differences of proportions. This was conducted in alignment with regulators. Therefore, the NMA followed this approach to allow the interpretation of the findings in terms of clinically meaningful differences. The company performed the updated analyses by using a logit link based on a random effect model. The updated results are presented in Table 3.12. The updated analysis also excluded the TRIUMPH trial. The updated analyses by using a logit link and excluding the TRIUMPH trial did not change the overall conclusion of NMA.[6] The EAG considers that the analysis approach used by the company is acceptable.

Haemolysis control as measured in the COMMODORE trials, specifically as percentage of patients achieving LDH ≤ 1.5 ULN, was not an outcome in the NMA. The company was asked to explain why this outcome was omitted, and conduct an indirect treatment comparison of haemolysis control using percentage of patients achieving LDH ≤ 1.5 ULN or, if not available, another LDH-based measure, with eculizumab and ranibizumab as comparators (clarification letter A18).[5] In responding to the EAG's request, the company stated that it was not possible to include this outcome in the NMA because the included studies did not use the same threshold. The threshold of LDH ≤ 1.5 ULN was used in the crovalimab study. However, the threshold of LDH >= 1 ULN was used in the ravulizumab trials. It should be also noted that the threshold of LDH = 1 ULN was not pre-specified in the crovalimab study.[6] The EAG considers that, given the inconsistency in the threshold of LDH used in included studies, it was appropriate not to perform the analysis for this outcome in the NMA.

Table 3.6: Baseline characteristics in included trials for patients with previously treated PNH

Trial name	Age (yrs)	Sex (male)	Ethnicity (Asian)	LDH (U/L)	Hb (g/dL)	Prior transfusions	Aplastic anaemia	Disease duration (years)	Weight (kg)	History of MAVE
COMMODORE 1	Mn: 44.4 49.5	53% 50%	20% 16%	Mn: 249.2 234.2	Mn: 11.0, 10.7 (Rg: 7.2-15.3, 6.8-14.4)	23%, 25%	33%, 36%	Md: 6.3, 10.4	77, 76	23%, 22%
Study 302	Mn: 46.6 48.8	49%, 52%	19%, 24%	Mn: 228.0235.2	Mn: 10.9, 11.1	12%, 13%	35%, 40%	NR	72, 73	NR

Based on Table 14 of clarification response[6]

Hb = haemoglobin; LDH = lactate dehydrogenase; MAVE = major adverse vascular event; Md = median; Mn = mean, NR = not reported; PNH = paroxysmal nocturnal haemoglobinuria; Rg = range; U/L = units per litre

Table 3.7: Baseline characteristics in included trials for patients with treatment-naïve PNH

Study identifier	Age (years)	Sex (male)	Race (Asian)	Weight (kg)	LDH *Mean (SD) Md [Range]*	Transfusion history	Aplastic anaemia	Myelo-dysplastic syndrome	Renal impairment	Major vascular event	Hb mean (SD) (g/dL)
COMMODORE 2	*Md [range]* 36 [18-76], 38 [17-78]	57%, 51%	74%, 64%	*Md (range)* 66.1 (42.0-140.3), 62.2 (47.0-122.0)	U/L 1770.6 (790.02), 1817.5 (829.09)	With: 77%, 74%	39%, 38%	9%,4%	8%, 9%	16%, 15%	8.7 (1.4), 10.0 (8.8)
TRIUMPH	*Md [range]* 35 [18-78], 41 [20-85]	34%, 47%	NR	NR	NR	NR	14%, 27%	0%, 5%	NR	18%, 21%	NR
Study 301	*Mean (SD)* 44.8 (15.2), 46.2 (16.2)	52%, 57%	47%, 58%	NR	U/L 1,578.3 (727.1), 1,633.5 (778.8)	With: 83%, 83%	31%, 33%	NR	NR	14%, 21%	9.4 (1.46), 9.6 (1.41)
SB12-3003	*Mean (SD)* 36.3 (13.7), 40.0 (13.4)	44%, 68%	48%, 60%	*Mean (SD):* 64.7 (15.8) 68.4 (14.9)	U/L 2,156.0 (1,750.6), 2,220.2 (2,001.6)	With: 56%, 64%	NR	NR	NR	NR	NR

Based on Table 18 of response to the request for clarification[6]

Hb = haemoglobin; LDH = lactate dehydrogenase; Md = median; NR = not reported; PNH = paroxysmal nocturnal haemoglobinuria; SD = standard deviation; U/L = units per litre

3.3.2 Results

The NMAs demonstrated varying results in the relative efficacy of crovalimab compared to eculizumab and ravulizumab. Random effects (RE) models were used as a base-case for the results, and fixed effect (FE) model results were also provided.[14] The pooled C5-naïve and C5-experienced FE results are shown in Table 3.8 for comparison with the RE results. The results for all outcomes for C5-naïve, C5-experienced and pooled C5-naïve and C5-experienced using the RE model are shown in Tables 3.9 to 3.11. Note the colour code: pale (as opposed to dark) means 95% CrIs overlap the null effect (point of no difference), orange indicates point estimate in favour of comparator, green indicates point estimate in favour of crovalimab.

- For the C5-naïve population, with the RE model, across all six endpoints, the 95% CrIs for crovalimab included the point of no difference, suggesting no statistically significant difference compared to eculizumab and ravulizumab. The results of the FE model were not consistent with the RE model in two endpoints (not shown). Specifically, ravulizumab was significantly worse than crovalimab in the FE model for number of packed RBC transfusion, and eculizumab significantly worse than crovalimab in the FE model for FACIT-Fatigue score. The probability of crovalimab being non-inferior was at least 82% in transfusion avoidance, but not reported for other endpoints.
- For the C5-experienced population, with the RE model, the 95% CrI not crossing the point of no difference appears to suggest that crovalimab is a little more efficacious than ravulizumab in number of packed RBC transfusions. However, across the other five endpoints, the 95% CrIs crossed the point of no difference, suggesting no statistically significant difference compared to eculizumab and ravulizumab. In the FE model, both eculizumab or ravulizumab were significantly higher than crovalimab in number of packed RBC transfusions. Eculizumab was significantly lower than crovalimab in FE model for FACIT-Fatigue score. The probability of crovalimab being non-inferior was at least 85% and 63% in breakthrough haemolysis and haemoglobin stabilisation respectively, but not reported for other endpoints.
- For pooled C5-naïve and C5-experienced populations, the 95% CrIs for all outcomes crossed the point of no difference, indicating no statistically significant difference in treatment effect between crovalimab and either eculizumab or ravulizumab. Although some of the point estimates appear to suggest that crovalimab is little less efficacious than eculizumab or ravulizumab, results are very uncertain. Across multiple endpoints, crovalimab consistently demonstrated high probabilities of non-inferiority. Specifically, the probabilities of crovalimab being non-inferior to eculizumab and ravulizumab exceeded 90% in transfusion avoidance, breakthrough haemolysis and haemoglobin stabilisation. The results for the six outcomes in the FE model were consistent with the RE model.

EAG comment: Although there is a little variation depending on model (RE versus FE), population (naïve or experienced) and outcome, it appears that there is no clear advantage to any of the three treatments, which would indicate equivalence. It should be noted that as the TRIUMPH trial recruited patients who received at least four transfusions in the last 12 months prior to study entry, the findings of the TRIUMPH trial (with a comparison with the placebo arm) are only appliable to patients who are transfusion dependent. The responses to questions from the clarification letter suggested that the analysis by using the logit link function and excluding the TRIUMPH trial (which recruited patients who were transfusion dependent) from the network did not change the overall findings of the NMA.[6] However, the analyses of NMA were only based on short-term follow-up data at 24 weeks, there was a lack of data regarding the long-term equivalence for the outcomes considered.

Table 3.8: Results of NMAs for pooled C5-naïve and C5-experienced populations in FE model

Outcome	Total number of studies in network	Eculizumab vs. crovalimab	Ravulizumab vs. crovalimab
		Mean difference (95% CrI)[a]	
Transfusion avoidance	5	0.016 (-0.097,0.13)	0.077 (-0.062,0.21)
Breakthrough haemolysis	4	0.033 (-0.050,0.11)	-0.024 (-0.12,0.067)
Haemoglobin stabilisation	5	0.020 (-0.10,0.14)	0.043 (-0.11,0.19)
Number of packed red blood cell transfusions	6	0.19 (0.058,0.33)	0.32 (0.16, 0.48)
FACIT-Fatigue score	5	-3.0 (-5.0, -0.92)	-1.8 (-4.4, 0.69)
		Odds ratios (95% CrI)[b]	
Adverse events	4	0.89 (0.51, 1.6)	0.94 (0.42, 2.1)

Based on various figures in NMA appendix[14]
[a] null effect is zero; [b] null effect is 1
CrI = credible interval; FACIT-Fatigue = Functional Assessment of Chronic Illness Therapy–Fatigue; FE = fixed effect; NMA = network meta-analysis

Table 3.9: Results of NMAs for pooled C5-naïve and C5-experienced populations in RE model

Outcome	Total number of studies in network	Eculizumab vs. crovalimab	Ravulizumab vs. crovalimab
		Mean difference (95% CrI)[a]	
Transfusion avoidance	5	0.017 (-0.11,0.15)	0.077 (-0.090,0.24)
Breakthrough haemolysis	4	0.029 (-0.080,0.13)	-0.029 (-0.17,0.10)
Haemoglobin stabilisation	5	0.030 (-0.13,0.20)	0.051 (-0.15,0.27)
Number of packed red blood cell transfusions	6	0.39 (-0.77,1.5)	0.44 (-1.2, 2.0)
FACIT-Fatigue score	5	-3.1 (-6.8, 0.52)	-2.0 (-6.9, 3.0)
		Odds ratios (95% CrI)[b]	
Adverse events	4	0.88 (0.43, 1.7)	0.94 (0.35, 2.4)

Based on Section B.3.9.1 of Document B[1]. [a] null effect is zero; [b] null effect is 1.
CrI = credible interval; FACIT-Fatigue = Functional Assessment of Chronic Illness Therapy–Fatigue; NMA = network meta-analysis; RE = random effects

Table 3.10: Results of NMAs for C5-naïve populations in RE model

Outcome	Total number of studies in network	Eculizumab vs. crovalimab	Ravulizumab vs. crovalimab
		Mean difference (95% CrI)[a]	
Transfusion avoidance	5	0.017 (-0.16, 0.20)	0.077(-0.090, 0.24)
Breakthrough haemolysis	4	0.056 (-0.11, 0.21)	-0.012(-0.22, 0.19)
Haemoglobin stabilisation	5	-0.033(-0.26, 0.19)	0.0023(-0.30, 0.30)
Number of packed red blood cell transfusions	6	-0.13 (-1.3, 1.0)	-0.93(-2.6, 0.66)
FACIT-Fatigue score	5	-2.6 (-8.8, 3.6)	-1.9(-11, 6.7)
		Odds ratios (95% CrI)[b]	
Adverse events	4	1.2 (0.46, 2.9)	1.3 (0.35, 4.9)

Based on Section B.3.9.1 of Document B[1] [a] null effect is zero; [b] null effect is 1.
CrI = credible interval; FACIT-Fatigue = Functional Assessment of Chronic Illness Therapy–Fatigue; NMA = network meta-analysis; RE = random effects

Table 3.11: Results of NMAs for C5-experienced populations in RE model

Outcome	Total number of studies in network	Eculizumab vs. crovalimab	Ravulizumab vs. crovalimab
		Mean difference (95% CrI)[a]	
Transfusion avoidance	5	0.022 (-0.20, 0.24)	0.072 (-0.19, 0.34)
Breakthrough haemolysis	4	-0.023 (-0.22, 0.18)	-0.073 (-0.31, 0.17)
Haemoglobin stabilisation	5	0.14 (-0.13, 0.41)	0.14 (-0.20, 0.49)
Number of packed red blood cell transfusions	6	0.91 (-0.27, 2.1)	1.8 (0.16, 3.4)
FACIT-Fatigue score	5	-3.7 (-10.0, 3.0)	-2.3(-11., 6.6)
		Odds ratios (95% CrI)[b]	
Adverse events	4	1.2 (0.46, 2.9)	1.3 (0.35, 4.9)

Based on Section B.3.9.1 of Document B[1] [a] null effect is zero; [b] null effect is 1.
CrI = credible interval; FACIT-Fatigue = Functional Assessment of Chronic Illness Therapy–Fatigue; NMA = network meta-analysis; RE = random effects

Table 3.12: Updated results of NMA – RE model

Outcome - Odds ratios (95% CrI)[a]	Total number of studies in network	Eculizumab vs. crovalimab	Ravulizumab vs. crovalimab
Transfusion avoidance	4	1.1 (0.59,2.1)	1.6 (0.70,3.7)
Breakthrough haemolysis	4	1.3 (0.13,11.)	0.21 (0.0033,3.1)
Haemoglobin stabilisation	4	1.1(0.57,2.3)	1.3 (0.51,3.3)

Based on Figure 9, 10 and 11 in clarification response[6]
[a] null effect is 1.
CrI = credible interval; NMA = network meta-analysis; RE = random effects

4. EAG critique of cost comparison evidence submitted

4.1 Decision problem for cost comparison

The patient population defined in the NICE Final Scope is people with PNH.[4] This is different from the population considered by the company in the cost comparison model which is patients with PNH, including both those who have (treatment-experienced) and have not (treatment-naïve) previously been treated with complement inhibitors. The modelled population is considered to be reflective of the anticipated marketing authorisation for crovalimab, and is in line with the populations evaluated in the COMMODORE studies, thus restricted to people aged ≥ 12 years who weigh over 40 kg.[15, 16] The company's analyses comparing crovalimab with eculizumab and ravulizumab were based on pooling COMMODORE 1 and 2 data, therefore, there is no distinction between treatment-naïve and treatment-experienced patients. Furthermore, as mentioned in Section 2 of this report, the RCT evidence was only available for adults.

EAG comment: It is unknown whether the conclusions from the cost comparison analyses could be generalised to patients aged 12-18 years since evidence was provided only for adults. In response to the clarification questions,[6] the company acknowledged that evidence on the efficacy of crovalimab in children is limited. The Phase III studies of crovalimab included only [redacted]. The company concluded that there is no evidence to suggest that the treatment benefit of crovalimab in paediatric patients is different from that observed in adult patients. However, the company also recognised that the data limitations (the small paediatric sample size) may present a potential barrier to recommending crovalimab for use in paediatric patients with PNH. The company requested consideration of the available evidence for paediatric patients to avoid disadvantaging this patient group, as crovalimab has the potential to offer children with PNH an alternative treatment option with a smaller burden of treatment.

Regarding the pooling of treatment-naïve and treatment-experienced patients, the company confirmed that the model did not provide separate results for these subgroups.[6] The company indicated that these subgroups have the same underlying disease pathophysiology and, therefore, are not considered distinct patient populations. The efficacy of treatment with C5 inhibitors is expected to be similar across these groups. This is why, according to the company, the provision of separate results (or pooling the overall population using a weighted average) is not expected to impact the overall results of the cost comparison analysis. However, based on the clinical expert and patient organisation opinion presented in this submission, the EAG considers that these subgroups may have different adverse event profiles and that there is no clear consensus around the impact of these adverse events on patients outcomes.[3, 17] The EAG sees this a source of uncertainty in the cost comparison analyses. A distinction between treatment-naïve and treatment-experienced patients could have been made if the results were presented separately for these two subgroups, which would help resolving the uncertainty associated with this issue.

4.2 Cost effectiveness searches

No cost effectiveness searches were conducted for this submission. In the response to clarification, the company stated that: "*As was deemed suitable at the decision problem meeting, a cost comparison submission has been provided by the company. The approach taken to identify the data used in the analysis follows that outlined in relation to cost comparison assessments in the NICE Health Technology Assessment Manual. Whenever possible and appropriate, cost data and data sources should be consistent with any corresponding data and sources that were considered appropriate in the published NICE guidance for the comparator(s) for the same population*".[18] As a full cost effectiveness

analysis was not deemed necessary at the decision problem meeting, an SLR of cost effectiveness has not been conducted.[6]

4.3 Company cost comparison model

The cost-comparison model developed in Microsoft Excel® 2016 assumed a lifetime time horizon (60 years), with a two-week cycle length, reflecting the shortest treatment period (Q2W) which is applied in the model (eculizumab). A half-cycle correction and a discount rate of 3.5% were also applied. The cost categories distinguished in the model are drug acquisition, administration, blood transfusion, up-dosing and medical resource use costs, and they were estimated from the UK National Health Service (NHS) perspective. In response to the clarification questions,[6] the company omitted from the model blood transfusions and medical resource use costs, since these were identical across treatment arms. This was done to be in line with not including adverse event costs for the same reason. The model structure consists of a simple alive/dead model, where alive patients are assumed to be on treatment; therefore, there is no treatment discontinuation included in the model. While on treatment, patients are assumed to be at (a constant) risk of experiencing BTH events (see CS Figure 33).[1]

EAG comment: The current model structure can be regarded as a simplified version of the model used in TA698,[19] and therefore, a reasonable choice for a cost comparison analysis.

It was not entirely clear though whether treatment discontinuation has been considered in the cost comparison model and, if so, how. In response to clarification question B1,[6] the company explained that treatment discontinuation (and thus switching to another treatment) is unlikely in these patients, as symptoms of this chronic disease will quickly return if treatment is discontinued. This would also explain that treatment discontinuation is not expected to differ across the treatments considered in the cost comparison analysis.

Moreover, as explained above, the EAG is uncertain that treatment switching could lead to additional costs and adverse events (transient immune complexes), which are currently not included in the cost comparison model. Therefore, the impact on the incremental costs (and potentially on health-related quality of life decrements associated to transient immune complexes) between crovalimab and its comparators in treatment-experienced patients might not have been completely captured in the economic analyses. For a further discussion of the exclusion of transient immune complexes in patients switching treatment, please see Section 4.4.8.6 – Adverse events.

4.4 Model parameters

4.4.1 Patient characteristics

Patient characteristics included in the model (age, weight groups and gender split) were sourced from the COMMODORE 1 and 2 trials and based on the pooled population. This resulted in a baseline age of 42.7 years, a mean weight of 70 kg and 53% male patients.

EAG comment: As mentioned above, there is limited evidence for the paediatric population. Also, the company assumed a pooled population of treatment-naïve and treatment-experienced patients. See EAG comment to Section 4.1 of this report for further details.

4.4.2 Breakthrough haemolysis

The company assumed that, while on treatment, patients are at a constant risk of experiencing BTH events. The two-weekly probability of experiencing BTH events was 0.85%, as sourced from Quist et al. 2023.[20] This probability was assumed to be the same for all three treatments.

The company also assumed that 35.29% of the BTH events in the eculizumab arm are compliment amplifying conditions (CAC)-related, as calculated from Quist et al. 2023, which reported that six out of the 17 BTH events observed in the eculizumab arms of COMMODORE 1 and 2 were CAC-related BTH events.[20] The company finally assumed that, since crovalimab and ravulizumab have a long half-life, C5 inhibition-related BTH events which are linked to incomplete blockade of C5 are not possible. Thus, all BTH events for crovalimab and ravulizumab patients are assumed to be CAC-related.

EAG comment: In general, the company has not systematically selected a preferred source to inform input parameters (e.g., for some parameters trial data, Quist et al. 2023 or the NICE appraisal of ravulizumab have been chosen to inform them). In response to clarification question B3,[6] the company acknowledged that cost estimates of medical resource use were not sourced from UK publications. However, given that treatment efficacy and safety were assumed equivalent for all treatments considered in the model, medical resource costs are equal across all treatments in the cost comparison analysis. Therefore, the source from which they are estimated has no impact on the incremental results.

Also, in response to clarification question C1,[6] the company provided a definition of CAC-related BTH events, since this was missing from the main submission, and clarified the distinction between BTH events related to suboptimal C5 inhibition versus CAC events.

4.4.3 Blood transfusions

The company assumed a constant rate of blood transfusions in all treatment arms. This rate differs though depending on whether a BTH event occurs or not. The two-weekly probability of needing a blood transfusion was 9% (no BTH) and 30% (BTH), as sourced from Quist et al. 2023.[20]

EAG comment: The costs of blood transfusions have been removed from the analysis after clarification. This was done to enhance consistency in how blood transfusion costs, medical resource use costs, and adverse events costs (all considered equal between the three treatment arms), were handled in the cost comparison model (note that adverse events costs were already excluded from the analysis in the original CS).

4.4.4 Mortality

The company included mortality in the cost comparison model by using general population all-cause mortality data for 2020-2022,[21] adjusted for the age and sex of the patient population in the COMMODORE 1 and 2 trials.[15, 16]

EAG comment: The company indicated that UK clinical experts supported the assumption that crovalimab was similar in efficacy and safety to both eculizumab and ravulizumab, and that, given that there was no evidence to suggest that mortality rates would differ across treatments, mortality rates were assumed to be equivalent for all treatments. However, the EAG could not find in the CS any evidence suggesting that mortality rates would not differ across treatments. In response to clarification question C4,[6] the company explained that crovalimab is associated with non-inferior efficacy outcomes according to trial data. Therefore, it is expected that survival across treatments will be equivalent. This view was supported by UK clinical experts who suggested that they did not expect any meaningful differences in treatment outcomes across the different C5 inhibitors.

Regarding the potential impact of the COVID-19 pandemic on the survival estimates, the company explained in response to clarification question C2 that 2020-2022 UK mortality data were used (being the most current mortality estimates).[6] The company further indicated that, while mortality rates in the 2020-2022 period remain higher than pre-COVID-19, life expectancy has not changed significantly.

Therefore, applying mortality data from 2019 or earlier would have a negligible impact on results (but would be less generalisable to current UK clinical practice).

4.4.5 Treatment effect

The company assumed the same treatment efficacy (as well as treatment safety and treatment discontinuation) for crovalimab, ravulizumab and eculizumab. Therefore, there are no treatment effect parameters included in the cost comparison model.

EAG comment: Based on the NMA, it is reasonable to assume that all three treatments are equivalent. However, as the NMA only considered outcomes at 24 weeks, there is currently no evidence regarding the long-term equivalence between crovalimab, ravulizumab and eculizumab.

4.4.6 Treatment safety

As mentioned above, the company assumed the same treatment safety (as well as treatment efficacy and treatment discontinuation) for crovalimab, ravulizumab and eculizumab. Therefore, there are no adverse events included in the cost comparison model.

EAG comment: Transient immune complexes seem to be relevant for patients switching from eculizumab or ravulizumab to crovalimab. The EAG considers it uncertain whether completely excluding these adverse events is appropriate. For a detailed discussion we refer to Section 4.4.8.6 – Adverse events.

4.4.7 Treatment discontinuation

The company indicated that patients may discontinue treatment, but that discontinuation rates were all set equal for crovalimab, ravulizumab and eculizumab. Furthermore, the company mentioned that patients cannot switch to another therapy if they discontinue their current treatment. However, treatment discontinuation does not seem to have been included in the cost comparison model.

EAG comment: As explained above, in response to clarification question B1,[6] the company explained that treatment discontinuation is unlikely in these patients (symptoms would quickly return if treatment is discontinued). Because of this, treatment discontinuation is not expected to differ across treatment arms.

4.4.8 Costs

4.4.8.1 Acquisition costs

The acquisition costs for crovalimab, ravulizumab and eculizumab can be found in CS Table 23,[1] Table 4.1 below summarises these costs and presents the information about the anticipated setting (hospital or home), the administration mode (intravenously, IV or subcutaneously, SC), the recommended doses and frequencies. Acquisition costs for eculizumab and ravulizumab were based on their list prices obtained from the British National Formulary.[22] A simple patient access scheme (PAS) discount of [redacted]% to crovalimab list price was used in the base-case cost comparison analysis.

Table 4.1: Summary of acquisition costs

	Crovalimab	Eculizumab	Ravulizumab
Anticipated setting	Hospital (loading) IV Home (maintenance) SC	Hospital (loading) IV Home (maintenance) IV	Hospital (loading) IV Home (maintenance) IV

	Crovalimab	Eculizumab	Ravulizumab
Acquisition costs	[redacted] ([redacted]% PAS) – 340 mg vial (SC injection)	£3,150 – 300 mg solution (IV infusion)	£4,533 – 300 mg solution (IV infusion)
Administration	IV infusion (loading dose 1) SC injection (loading and maintenance)	IV infusion	IV infusion
Doses	**40 kg to 100 kg** 1,000 mg (IV) (day 1) 340 mg (SC) (day 2, week 2, week 3, week 4) 680 mg (SC) (week 5+) **100 kg+** 1,500 mg (IV) (day 1) 340 mg (SC) (day 2, week 2, week 3, week 4) 1,020 mg (SC) (week 5+)	**40 kg+** 600 mg (week 1, 2, 3, 4) 900 mg (week 5+)	**40 kg to 60 kg** 2,400 mg (week 1, 2) 3,000 mg (week 3+) **60 kg to 100 kg** 2,700 mg (week 1, 2) 3,300 mg (week 3+) **100 kg+** 3,000 mg (week 1, 2) 3,600 mg (week 3+)
Frequency	Q4W (maintenance)	Q2W (maintenance)	Q8W (maintenance)

Based on Table 23 in CS.[1]
CS = company submission; IV = intravenous; kg = kilogram; mg = milligram; PAS = Patient Access Scheme; SC = subcutaneous

4.4.8.2 Treatment up-dosing

The company assumed that treatment up-dosing is possible and distinguished between single and continuous up-dosing. The proportion of BTH events requiring single up-dosing was assumed to be the same for crovalimab, eculizumab and ravulizumab patients, and equal to 40%, since four of the 10 BTH events observed in the crovalimab arm of the COMMODORE 2 trial required single up-dosing. The company explained that, after BTH events, and an inadequate disease response, eculizumab patients can receive a higher dose, usually 1,200 mg. It was assumed that 20% of eculizumab patients require continuous up-dosing. This assumption was based on UK clinical expert opinion and Quist et al. 2023.[20]

EAG comment: The EAG considered the estimate for the proportion of patients receiving single up-dosing uncertain since it was only based on 10 BTH events. In response to clarification question B4,[6] the company indicated that the COMMODORE 2 Phase III study was deemed an appropriate source to inform the proportion of BTH events requiring single up-dosing (40%). While acknowledging that this estimate is only based on 10 events, it was also validated by UK clinical experts. Furthermore, the company stated that scenario analyses demonstrated that adjusting this proportion in the cost comparison model had a negligible impact on the results (see CS Table 37).[1] The proportion of patients receiving continuous up-dosing for eculizumab (20%) was in line with the estimate used in TA698.[19] This proportion was also varied in the scenario analyses (CS Table 37).[1]

4.4.8.3 Administration costs

The unit costs associated with administration of each treatment were presented in CS Table 28,[1] and summarised in Table 4.2 below. These calculations were based on the durations of the infusions (Table 26 – for loading dose – and Table 27 – for maintenance dose – in the CS) and the hourly costs of hospital staff (pharmacist specialists and nurse specialists – Table 25 in the CS).[1] Furthermore, it was assumed that, following the initial dosing phase, patients can self-administer subcutaneous crovalimab after they

have been trained to do so (Table 24 in the CS).[1] Home care costs were ignored, as these were assumed to be funded by the pharmaceutical companies.

Table 4.2: Summary of administration costs

Administration type	Crovalimab	Eculizumab	Ravulizumab
IV administration	£119.53	£97.00	£94.88
SC administration, clinical setting	£17.00	-	-
Administration, home setting	£0.00	£0.00	£0.00
SC, training	£16.83		
Based on Table 28 in CS[1] CS = company submission; IV = Intravenous IV; SC = subcutaneous			

4.4.8.4 Blood transfusions costs

Blood transfusion costs were assumed to be equal for crovalimab, ravulizumab and eculizumab. These costs included the cost of packed red blood cells (£17.15) and red blood cell transfusion administration (£55.11 – see CS Table 29).[1] The company referred to TA698 as relevant source for to inform these costs.[19] The average number of units of red blood cells required per transfusion was assumed to be 1.59, if no BTH event occurs within a model cycle, and 1.83 otherwise. The company indicated that UK clinical experts considered the approach taken to cost blood transfusions appropriate.

EAG comment: The price for packed red blood cells in TA698 was £128.99, whereas in the CS, these are reported to be £17.15. In response to clarification question B7,[6] the company explained that this was an error. The original cost of £17.15 was sourced from the NHS blood component variable price list, as opposed to the full cost price list (£158.18). The latter differs from the one applied in TA698 but represents a more recent price. In any case, as previously mentioned, the costs of blood transfusions have been removed from the updated base-case analysis presented after clarification. This was done to enhance consistency in how three cost categories (i.e., blood transfusion costs, medical resource use costs, and adverse events costs), all considered equal between the three treatment arms, were handled (note that adverse events costs were already excluded from the analysis in the original CS).

4.4.8.5 Medical resource use resulting from BTH events

As mentioned on page 99 of the CS,[1] medical resource use following a BTH event included general ward hospitalisations, intensive care unit (ICU) hospitalisations, dialysis, and consultant visits. Based on a study by Quist et al. 2023,[20] the proportion of patients requiring general ward hospitalisations, ICU hospitalisations, dialysis, and consultant visits per BTH was estimated at 23.0%, 1.0%, 4.0%, and 100.0%, respectively. Unit costs prices, which were also taken from the study by Quist, were as follows: £591.15 (general ward hospitalisation), £1,872.72 (ICU hospitalisation), £5,184.60 (dialysis), and £122.69 (consultant visit). From this, it can be calculated that the total costs of medical resource use per BTH event amount to £756.69, which was included in the model. Since the proportion of patients experiencing a BTH event was assumed to be the same between the treatment arms, the costs resulting from BTH events were identical between the groups treated with either crovalimab, eculizumab, or ravulizumab.

EAG comment: As explained above for blood transfusion costs, medical resource use following BTH events have also been removed from the updated base-case analysis after clarification, because they are equivalent across the treatments included in the model.

4.4.8.6 Adverse events

Based on the safety results of crovalimab compared to eculizumab from COMMODORE 1 and 2, the company considered that the incidence of AEs was generally comparable across both treatment

arms (Section 3.2.2.2). Furthermore, the company referred to the results of the indirect treatment comparison, discussed in Section 3.3.2, to assume that safety events were similar across crovalimab, eculizumab and ravulizumab. Therefore, cost and resource use related to adverse events were not included in in the cost comparison model. The company concluded that the omission of these costs did not have a significant impact on the overall results, but no scenario was presented.

EAG comment: Clinical experts consulted by the company agreed that most likely the safety of crovalimab was similar to that of eculizumab and ravulizumab. However, the company mentioned that in the treatment-experienced population, some AEs had a higher incidence in the crovalimab arm than in the eculizumab arm. The company explained that these events were "*either reflective of risks unique to the crovalimab arm (Type III hypersensitivity and injection related reaction due to the subcutaneous administration), while mild in severity and occurring rarely, were less likely to occur in the eculizumab arm as patients start the study stabilised on eculizumab treatment, or relate to a broad set of preferred terms which do not indicate a specific safety concern associated with crovalimab*".[1] Generally, adverse event costs are expected to be similar across crovalimab and the comparators and have therefore been excluded from the analysis.

The EAG considered that transient immune complexes should have been discussed in more detail in the CS. In response to clarification question B11,[6] the company mentioned that these reactions (which occurred in [redacted]% of crovalimab-treated participants in the COMMODORE 1 trial) were resolved [redacted] and that the costs associated with managing these reactions can be considered negligible.

The minutes from the advisory board conducted by the company do not show a complete consensus about transient immune complexes according to the EAG. For example, one of the topline takeaways cited by the company was that clinical experts [redacted].[17] Furthermore, the company indicated that Dr Munir (one of the experts participating in the advisory board) [redacted].[17]

In addition, the Patient Organisation Submission accompanying the CS, explicitly mentioned that "*over the last month we have become aware of three patients globally who had serious adverse reactions when switched from ravulizumab to crovalimab and at least two of whom we understand are still negatively affected by these injuries today. We are hopeful that these serious adverse events were correctly represented in terms of their severity and duration in the data submitted to the regulators, however as the data for the patients who were switched from ravulizumab to crovalimab has not yet been published, we have not been able to satisfy ourselves that this is the case. We are deeply concerned that patients who may switch from ravulizumab to crovalimab may be at risk of experiencing a serious adverse event which could be life changing and that the nature of this risk should be appropriately understood, represented and disseminated. We are aware of a patient in England who switched from ravulizumab to crovalimab two years ago (April 2022) and then stopped the crovalimab trial after experiencing a serious adverse event. To this day, this patient experiences constant numbness and pain in both hands which are very sensitive to changes in temperature and which numbness makes it difficult to write and otherwise use their hands. The patient also has frequent pain and numbness down one side (arm and leg) and severe cramping in her legs and hands. The patient currently takes Pregabalin and Duloxetine to assist with these symptoms (which have side effects e.g. fatigue and is also under the*

care of neurologists and a physiotherapist, who are attempting to treat her as she understands she has nerve damage. Her quality of life, her mental health, as well as her family and social life have been significantly negatively impacted by this situation over the last two years. She is also now unable to work as a result of her injuries which has also had financial implications".[3]

Considering this, and despite the trial data presented in the CS and the company's response to clarification question B11, the EAG is still uncertain whether it is appropriate to exclude TICs from the analyses. And, therefore, the EAG would like this potential issue to be completely clarified during the Appraisal Committee Meeting.

Finally, in response to clarification question B13,[6] the company explained why the costs associated with infections and vascular complications were not included in the cost comparison analysis. These costs may be relevant to consider, as the administration of eculizumab and ravulizumab (administered intravenously) is relatively invasive and carries a higher risk of infection and vascular complications compared to crovalimab. The company indicated that these costs of side effects from intravenous treatment were ignored, because the overall safety of all treatments in the analysis was considered comparable, which is why, in general, the costs of adverse events were ignored. Apart from the fact that the exclusion of these costs probably has a minimal impact on the results, according to the company, it represents a conservative assumption, as the inclusion of these costs would favour crovalimab.

4.5 EAG model check

The EAG conducted a range of checks on the company's cost-comparison model. This included a verification that the cost parameters are in line with the costs described in the CS,[1] (which led to finding an error in the price used for packed red blood cells as mentioned above), and an inspection of the main formulae used in Microsoft® Excel®. The EAG did not find any major issues.

In response to clarification question C5,[6] the company explained that functionality remains in the economic model to explore the possibility of spontaneous remission, and that, given the assumption of equal efficacy and safety, the company assumed that the occurrence of spontaneous remission would also be equivalent across all modelled treatments, with a negligible impact on the comparison of costs. The company further explained that given uncertainty around the rate and cause, spontaneous remission was not considered in the company base-case in TA698. Because of the limited impact on the results, it was not explored in a scenario analysis by the company. However, the impact on the model results may not be "negligible" according to the EAG and, therefore, this scenario was explored by the EAG in Section 4.7 of this report.

4.6 Company's model results

The company base-case results compared the total costs for crovalimab, ravulizumab and eculizumab for the COMMODORE 1 and 2 trials pooled patient population. For crovalimab the PAS price indicated above was used, whilst list prices were used for ravulizumab and eculizumab (see CS Table 33).[1] A threshold analysis, where different discounts (ranging from 10% to 90%) to eculizumab and ravulizumab list prices were assumed, was explored by the company. However, these are not discussed in the EAG report since the results using the appropriate discounted prices for ravulizumab and eculizumab are presented in a confidential appendix presented separately to this report.

The results of the company's base-case analysis, after excluding blood transfusion costs and medical resource use following BTH events after clarification, are reported in the company's response to the clarification letter in Table 19,[6] and summarised in Table 4.3 below. From this table, it appears that the total costs (including drug cost, administration cost, and costs of treatment up-dosing) were lowest in the patients treated with crovalimab. Compared to eculizumab, the costs were lower in the crovalimab

treatment arm due to lower costs of (continuous) treatment up-dosing. Compared to ravulizumab, the cost difference was mainly explained by lower drug costs. Overall, looking at the total costs, it can be concluded that treatment with crovalimab (at PAS price) is cost-saving compared to eculizumab and ravulizumab (at list prices).

Uncertainty around model assumptions was assessed by the company through one-way sensitivity analyses and scenario analyses. For the one-way sensitivity analysis, the company assumed ± 20% variation around the mean value for the following parameters: crovalimab, eculizumab and ravulizumab list prices, costs discount rate, baseline age, proportion of eculizumab patients requiring continuous up-dosing, proportion of males in the population, time horizon, proportion of CAC-related BTH events requiring single up-dosing, 2-week probability of experiencing BTH events, the duration of the loading dose for crovalimab and the nurse specialist hourly wage. The sensitivity analyses results showed that the parameters with the most impact on the incremental costs were the list prices of eculizumab and ravulizumab, the discount rate, and the model starting age. Still, crovalimab remained a [redacted]. Price reductions for eculizumab and ravulizumab based on actual discounted prices (instead of an assumed discounted percentage) are shown in a confidential appendix presented separately to this report.

The scenario analyses explored by the company included changing assumptions around the model starting age, the model time horizon, the costs discount rate, a scenario where it is assumed homecare costs are paid by the NHS for those on eculizumab, the proportion of patients requiring single or continuous up-dosing, the rates of BTH events and blood transfusions. The scenario analysis revealed that crovalimab was [redacted] compared to eculizumab and ravulizumab in all scenarios explored. The results were most sensitive to the model starting age and the discount rate. However, the results of the scenario where the baseline starting age is varied are likely to be invalid since age is expected to be greatly correlated with weight, especially for children. Therefore, the EAG did an exploratory analysis, taking into account the relationship between age and weight (see Section 4.7).

No subgroup analyses were included in the cost comparison model.

Table 4.3: Company base-case (discounted, crovalimab PAS price, eculizumab and ravulizumab list price)

Cost category	Crovalimab (£)	Eculizumab (£)	Ravulizumab (£)
Drug cost	[redacted]	4,100,874	6,627,639
Administration cost	423	498	280
Single up-dosing	14,743	2,030	8,276
Continuous up-dosing	0	1,365,280	0
Mean total cost	[redacted]	**5,468,683**	**6,636,195**
Incremental cost versus crovalimab	N/A	[redacted]	[redacted]

Based on Table 33 in CS, Table 19 in response to clarification letter, and economic model.[1, 6, 23]
CS = company submission; N/A = not applicable; PAS = Patient Access Scheme

4.7 EAG exploratory analysis

The EAG requested the company to include adverse events in the cost comparison model and to present results per treatment-naïve and treatment-experienced subgroups as explained above. Since this functionality was not implemented by the company, the EAG was unable to run these scenarios.

The EAG also wanted to explore a scenario for the children population, by varying both the baseline starting age and weight, since these are expected to be correlated, as mentioned above. However, the

minimum age included in the model is 20 years. Therefore, the EAG was also unable to run scenarios for the children population.

Despite the limitations just described, the model seems robust, and the company's base-case assumptions well-justified in general, with possibly the exception of excluding adverse events. Therefore, the EAG did not define a new base-case.

The EAG undertook though some additional exploratory analyses using the company's model as submitted in response to the clarification letter.[23] The analyses presented in this section reflect the PAS discount price for crovalimab whilst list prices were used for eculizumab and ravulizumab. Results using discounted prices for eculizumab and ravulizumab are shown in a confidential appendix presented separately to this report. The scenario analyses explored by the EAG are the following:

- Varying both model starting age and weight at the same time to account for correlation. Given that the model does not allow to run analyses for younger ages, the EAG explored the scenario where the starting age is 20 years. The EAG used NHS 2021 overweight and obesity tables to provide an estimate of the weight of 20-years old patients.[24] From these tables, it could be seen that the average weight for a 35-44 years person (accounting for 53% males) in the general population was 81 kg. In the cost comparison model, baseline age is 42.7 years and baseline weight is 70 kg. This means approximately 11 kg difference between the model and the general population. For the scenario where the age at baseline is 20 years, the EAG assumed the same difference in kg between the modelled and general population, resulting in a model baseline weight of 58 kg.
- Changing the proportion of patients per body weight category. In the base-case, the company assumed the following distribution of patients per body weight category: ≥100 kg = 5.00%, ≥60 kg to <100 kg = 65.00%, ≥40 kg to <60 kg = 30.00%, as observed in the COMMODORE trials. To account for the potential uncertainty around these estimates, the EAG explored three alternative scenarios. However, in the absence of an alternative estimate that could be deemed as representative of the UK patient population, the EAG considered three "extreme" scenarios where each category is equal to 100%. Thus, these scenarios should be considered exploratory only, but they are likely implausible.
- Including spontaneous remission in the analysis and changing the probability of experiencing it. The bi-weekly probability of spontaneous remission was set at 0.06% in the company's cost comparison model. However, the source for this value it is not mentioned. It is nevertheless one of the values used in TA698.[19] A ± 20% variation around that value (0.04%, and 0.08%) was assumed for the other two scenarios.

The results of these scenarios are presented in Table 4.4. These were most sensitive to changes in body weight category ([redacted]) and including high rates of spontaneous remission ([redacted]). In any case, crovalimab remained a [redacted].

Table 4.4: EAG scenarios (discounted, crovalimab PAS price, eculizumab and ravulizumab list price)

Scenario	Base-case	Scenario	Incr. cost vs. eculizumab (£)	% change base-case	Incr. cost vs. ravulizumab (£)	% change base-case
Base-case	-	-	[redacted]	-	[redacted]	-
Starting age (and weight)	42.7 years 70 kg	20 years 58 kg	[redacted]	[redacted]	[redacted]	[redacted]
Body weight category	≥100 kg = 5.00% ≥60 kg to <100 kg = 65.00% ≥40 kg to <60 kg = 30.00%	≥100 kg = 100% ≥60 kg to <100 kg = 0% ≥40 kg to <60 kg = 0%	[redacted]	[redacted]	[redacted]	[redacted]
		≥100 kg = 0% ≥60 kg to <100 kg = 100% ≥40 kg to <60 kg = 0%	[redacted]	[redacted]	[redacted]	[redacted]
		≥100 kg = 0% ≥60 kg to <100 kg = 0% ≥40 kg to <60 kg = 100%	[redacted]	[redacted]	[redacted]	[redacted]
Spontaneous remission	Excluded	Included (0.06% bi-weekly prob.)	[redacted]	[redacted]	[redacted]	[redacted]
		Included (0.04% bi-weekly prob.)	[redacted]	[redacted]	[redacted]	[redacted]
		Included (0.08% bi-weekly prob.)	[redacted]	[redacted]	[redacted]	[redacted]

Based on Economic model[23]
EAG = Evidence Assessment Group; Incr. = incremental; kg = kilogram; PAS = Patient Access Scheme

5. EAG commentary on the robustness of evidence submitted by the company

The company's evidence appears to be robust enough to confirm comparability of efficacy and safety between crovalimab and eculizumab given relatively high quality RCT data, from COMMODORE 1 (C5-experienced) and COMMODORE 2 (C5-naïve) on most major outcomes (OS was omitted).[1] It also is largely robust enough to confirm equivalence versus ravulizumab, although with more uncertainty given the use of an NMA, which showed some variation in results. However, there is more uncertainty in the C5-experienced population given the smaller size of the COMMODORE 1 trial and the point estimates for all of the outcomes except transfusion avoidance being in favour of eculizumab. Of particular concern is that a substantial proportion of those patients who switched from either eculizumab or ravulizumab suffered from TIC-associated Type III hypersensitivity reactions, which might be quite severe and long-lasting.[1, 3] Regarding the pooling of treatment-naïve and treatment-experienced patients in the cost comparison model, the company confirmed that the model did not provide separate results for these subgroups and indicated that these subgroups have the same underlying disease pathophysiology and, therefore, are not considered distinct patient populations.[6] However, based on the clinical expert and patient organisation opinion presented in this submission, the EAG considers that these subgroups may still have different adverse event profiles and that there is no clear consensus around the impact of these adverse events on patients' outcomes.[3, 17] The EAG sees this a source of uncertainty in the cost comparison analyses. The EAG would like this potential issue to be completely clarified during the Appraisal Committee Meeting.

The EAG would also question the applicability the evidence to the paediatric population given that only adults were included in the RCTs.[1] In responding to the EAG's request, the company provided evidence relating to paediatric population at the clarification response stage. The results for paediatric patients were similar to those for adult patients. However, the sample size of the paediatric population was very small and there were no comparative data. Therefore, the EAG considers that there was uncertainty regarding equivalence between crovalimab and relevant comparators for the outcomes considered in the paediatric population. It should be noted that the Phase III studies of crovalimab included only [redacted][6] and this paediatric population has not been included in the cost comparison model.

Despite the limitations described above, the current model structure can be regarded as a simplified version of the model used in TA698,[19] and therefore, a reasonable choice for a cost comparison analysis. A distinction between treatment-naïve and treatment-experienced patients, and the inclusion of paediatric patients in the cost comparison model, would help resolving the uncertainty associated with the issues previously described.

With the PAS price for crovalimab and list prices for eculizumab and ravulizumab, crovalimab is estimated to be a [redacted]. Results with PAS price reductions for eculizumab and ravulizumab are shown in a confidential appendix presented separately to this report.

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Single Technology Appraisal

Crovalimab for treating paroxysmal nocturnal haemoglobinuria [ID6140]

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Monday 5 August 2024** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as [redacted] should be highlighted in turquoise and all information submitted as '[redacted]' in pink.

Issue 1

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Description of TIC-associated T3H reactions as a "substantial proportion" - pages 7, 17 and 41.	Page 7: "It is also important to note that, although safety seems comparable for the C5 inhibitor naïve patients, this appears not to be the case for the previously treated, with a substantial proportion suffering TIC-associated Type III hypersensitivity (T3H) reactions, which might be quite severe and long-lasting." Replace with: "It is also important to note that although safety seems comparable for the C5 inhibitor-naïve patients, [redacted]% of patients who switched to crovalimab experienced Grade 3 TIC-associated type III hypersensitivity (T3H) reactions; [redacted]% of switch patients experienced a T3H reaction described by their doctor as "serious". In most cases, the adverse events related to these reactions resolve within a number of weeks (median duration [redacted] weeks [range: [redacted] to [redacted] weeks]). Safety information from the crovalimab studies indicate that [redacted]% of switch patients experienced T3H events of any grade that were long-lasting ([redacted])." Page 17: "However, this is not the case with those switching from eculizumab or ravulizumab: a substantial proportion will suffer AEs that, although mostly relatively mild, can last several weeks and up to more than six months." Replace with: "However, there is a difference for patients switching from eculizumab or ravulizumab. In this group, [redacted]% experienced TIC-associated type III hypersensitivity (T3H) reactions of any grade. Although most of these reactions are relatively mild, with [redacted]% of switch	The description used in the report stating a "substantial" or "significant" proportion is subjective, and could be misinterpreted by those reading the document. We propose accuratel	Not a factual inaccuracy.

	patients having T3H events classified as ‘serious’, they can be long-lasting, [redacted] Page 41: “Of particular concern is that a substantial proportion of those patients who switched from either eculizumab or ravulizumab suffered from TIC-associated Type III hypersensitivity reactions, which might be quite severe and long-lasting.” Replace with: “Of note is the proportion ([redacted]%) of those patients who switched from either eculizumab or ravulizumab and experienced TIC-associated type III hypersensitivity reactions of any grade, of which the events in [redacted]% of patients were described by their doctor as “serious” and in [redacted]% of patients lasted [redacted].	y reporting the proportion of individuals who had Grade 3 or higher TIC reactions, in alignment with the severity of adverse events typically considered in NICE appraisals.	

Issue 2

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 9 - inaccurate wording.	Page 9: “Therefore, the full effectiveness and cost effectiveness analysis comparing crovalimab to eculizumab BS were performed.” Proposed amendment “Therefore, the full effectiveness and cost effectiveness analysis comparing crovalimab to eculizumab BS were **not** performed.”	Factual accuracy.	Corrected.

Issue 3

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Lack of full context relating to the infeasibility of a washout period- EAG report - page 17.	Page 17: “They would not develop if there was no switching or if there was a washout period, which was described in the Appendices as “infeasible” (p. 61)”	The description of the infeasibility of a washout period is within page 64 of the CS appendixes. Indeed, a washout period between C5 inhibitors is not	Not a factual inaccuracy. The EAG can find no mention of an explanation for the infeasibility in the Appendices. However, the EAG accepts that this explanation for the infeasibility makes sense, and this will

	Proposed amendment: “They would not develop if there was no switching or if there was a washout period, which was described in the Appendices as “infeasible” (p. 64), due to an unacceptable risk of breakthrough haemolysis and other deleterious symptoms of PNH.”	clinically recommended as this would put patients at risk of breakthrough haemolysis. The risk arises from the incomplete capture of "free" C5, leading to inefficient inhibition of the complement cascade and subsequent complement-mediated destruction of red blood cells (and other blood cell types).	probably makes sense to the committee.

Issue 4

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**EAG response**
A submission from PNH	Page 17: “A submission from	The claim of three patients cannot be substantiated with available clinical data. Roche’s [redacted] had engagements with PNH Support between [redacted] and [redacted] in relation to these concerns. Roche requested further information from PNH Support for these cases to facilitate proper adverse event reporting and to comply with our pharmacovigilance (PV) obligations. However, PNH Support could only provide the requested information for the UK patient highlighted in their submission to NICE. It should be noted that this patient switched from ravulizumab to crovalimab	Not a factual inacura

Support reporting 3 patients with long-lasting TIC reactions - Page 17.	PNH Support also revealed that three patients who switched from ravulizumab to crovalimab suffered what were described as severe adverse	[redacted] Of the patients who switched C5i treatments and experienced Grade 3 T3H-related events across the COMMODORE trials, [redacted] patients had events that were described as “serious” by their doctor, [redacted] of those initially switched from ravulizumab to crovalimab ([redacted]). From our data, the [redacted] ravulizumab switch patients who experienced T3H-related events are detailed in the table below. As evident, there are [redacted] [redacted]	cy. The EAG have presented the data as reported by the company in the clarification letter response.

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

reactions, at least two of whom had not recovered at the time of the submission.[3] The company were therefore requested to tabulate all treat

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

C5i, complement C5 inhibitor; CCCOD, clinical cut-off date; Crova, crovalimab; Rav, ravulizumab;T3H, type 3 hypersensitivity

	ment related or immune complex related, SAE and Grade 3+ AE data for patients who have switched from any treatment to crovalimab.[5]		

	They were requested to include the outcome of these patients until the latest follow-up, including the duration of any of the AEs and any data on the		

	treatment and cost of treatment of these AEs. The company responded by providing this information as requested.” Proposed amendmen		

	t: “A submission from PNH Support also suggested that three patients who switched from ravulizumab to crovalimab suffered what were described as		

	severe adverse reactions, at least two of whom had not recovered at the time of the submission. The company were therefore requested to		

	tabulate all treatment-related or immune complex-related, SAE and Grade 3+ AE data for patients who switched from any treatment to		

	crovalimab. They were requested to include the outcome of these patients up to the latest follow-up, including the duration of any of the AEs and any		

	data on the treatment and cost of treatment of these AEs. The company responded with the requested information, showing that [redacted]% of patie		

	nts who switched from either eculizumab or ravulizumab to crovalimab experienced type III hypersensitivity reactions described by their doctors as		

	“serious”, with reactions in [redacted]% of switch patients lasting [redacted].		

Issue 5

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 26 - incorrect terminology.	Page 26: “For the C5-naïve population, with the RE model, across all six endpoints, the 95% CrIs for crovalimab included the point of no difference, suggesting no statistically significant difference	In the context of Bayesian analysis, there is no “significance”, just no statistical difference.	Not a factual inaccuracy – the concept of significance was invoked in order to aid interpretation, but using the word “suggesting” as opposed to “implying”. The EAG consider that this is only helpful in

	compared to eculizumab and ravulizumab.” Proposed amendment “For the C5-naïve population, with the RE model, across all six endpoints, the 95% CrIs for crovalimab included the point of no difference, suggesting no statistical difference compared to eculizumab and ravulizumab.” Page 26 “However, across the other five endpoints, the 95% CrIs crossed the point of no difference, suggesting no statistically significant difference compared to eculizumab and ravulizumab.” Proposed amendment “However, across the other five endpoints, the 95% CrIs crossed the point of no difference, suggesting no statistical difference compared to eculizumab and ravulizumab.”		supporting the possibility of equivalence.

Issue 6

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 26 - factual accuracy.	Page 26: “The probability of crovalimab being non-inferior was at least 82% in transfusion avoidance, but not reported for other endpoints.” Proposed amendment “The probability of crovalimab being non-inferior was at least 82% in transfusion avoidance, 92% in haemoglobin stabilisation and 88% in breakthrough haemolysis.”	The probability of crovalimab being non-inferior was reported for other endpoints in document B (sections B.3.9.1.2-3).	Not a factual inaccuracy – the 82% referred to the C5-naïve population, but the 92% applies to the mixed and the 88% to the C5-experienced populations respectively.

Issue 7

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 26 - accurately describing the availability of evidence.	Page 26: “However, the analyses of NMA were only based on short-term follow-up data at 24 weeks, there was a lack of data regarding the long-term equivalence for the outcomes considered.”	Accurately describing the availability of data from which to conduct the NMA.	Not a factual inaccuracy.

	Proposed amendment “However, due to limited data availability with the follow-up periods of the studies included in the NMA stopping at 24 weeks, there was a lack of data regarding the long-term equivalence for the outcomes considered.”		

Issue 8

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**EAG response**
Page 26 - typo.	Page 26: “It should be noted that as the TRIUMPH trial recruited patients who received at least four transfusions in the last 12 months prior to study entry, the findings of the TRIUMPH trial (with a comparison with the placebo arm) are only appliable to patients who are transfusion dependent.” Proposed amendment “It should be noted that as the TRIUMPH trial recruited patients who received at least four transfusions in the last 12	Correct language.	The EAG can find no difference between their text and the proposed amendment.

	months prior to study entry, the findings of the TRIUMPH trial (with a comparison with the placebo arm) are only applicable to patients who are transfusion dependent."		

Issue 9

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**EAG response**
Page 18 - the section is inaccurate with regards to what was provided in the clarification response to questions	Page 18: "The company reported in answer to question A19a that four patients had documented unresolve	There appears to be some misunderstanding regarding the response details in A19a and A19b. To clarify, [redacted] were mentioned in the answer to A19b. [redacted]	The EAG could only count five patients as indicated by patient number. Also, for only two patients was it clearly stated that the event was not resolved. To count three instead of two patients, the company might be referring to [redacted]

A19a and A19b.	d T3H reactions as of the May 2023 CCOD, and referred to A19b for more detail. However, only five patients were mentioned in the answer to A19b, where it was reported that the events had not resolved in two of them”		[redacted] Given the continued lack of clarity, the EAG has not made any further changes.

	Proposed amendment: “The company reported in answer to question A19a that [redacted], and referred to A19b for more detail. Six patients were mentioned in the answer to A19b where it was reported		

	that [redacted]"		

Issue 10

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In Table 4.1, page 33/34, the subcutaneous doses of crovalimab for a 100kg + person are given as grams (g).	Correct the unit of mass to milligrams (mg).	Factual accuracy.	Corrected.

Issue 11

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The EAG includes an excerpt from the Patient Organisation (PNH Support) submission on page	Page 36: "In addition, the Patient Organisation Submission accompanying the CS, explicitly mentioned that *"over the last*	According to the clinical trial data submitted to NICE and various regulatory bodies ([redacted]), the claims made in the Patient Organisation submission cannot be verified. Indeed, [redacted], we propose removing the quoted excerpt and rewording it as suggested. The justification of this is based on both an unsubstantiated claim (1), and a factual inaccuracy (2): 1) "over the last month we have become aware of three patients globally who had serious adverse reactions when switched from ravulizumab to crovalimab" [redacted] 2) "We are aware of a patient in England who switched from ravulizumab to crovalimab two years ago (April 2022) and then stopped the crovalimab trial after experiencing a serious adverse event."	Not a factual inaccuracy. The EAG have clearly attributed this quote to the Patient Organisation

36. There are a number of aspects of this submission that we are unable to verify from our clinical data, and also some factual inaccuracies	*month we have become aware of three patients globally who had serious adverse reactions when switched from ravulizumab to crovalimab and at least two of*	• [redacted] • [redacted] • [redacted] Of note, in relation to the concerns of the Patient Organisation around the publication of data, we are continuing to assess the data collected from the ravulizumab switch cohort within the descriptive arm (Arm C) of the COMMODORE 1 study. It is currently being evaluated together with clinical investigators from the COMMODORE trials. Updated results for clinical efficacy and safety are planned to be shared at an upcoming meeting (American Society of Hematology Annual Meeting) later in 2024. We have also committed to support a publication around T3H reaction events, led by clinical experts in the field of PNH, to inform and further educate the clinical community on these adverse events, again to be published later in 2024.	Submission.

within .	*whom we understand are still negatively affected by these injuries today. We are hopeful that these serious adverse events were correctly represented in terms of their severity and*		

	duration in the data submitted to the regulators, however as the data for the patients who were switched from ravulizumab to crovalimab has not yet been published, we have		

	not been able to satisfy ourselves that this is the case. We are deeply concerned that patients who may switch from ravulizumab to crovalimab may be at risk of experiencing a serious		

	adverse event which could be life changing and that the nature of this risk should be appropriately understood, represented and disseminated. We are aware of a patient in England who		

	switched from ravulizumab to crovalimab two years ago (April 2022) and then stopped the crovalimab trial after experiencing a serious adverse event. To this day, this		

	patient experiences constant numbness and pain in both hands which are very sensitive to changes in temperature and which numbness makes it difficult to write and otherwi		

	se use their hands. The patient also has frequent pain and numbness down one side (arm and leg) and severe cramping in her legs and hands. The patient currently		

	takes Pregabalin and Duloxetine to assist with these symptoms (which have side effects e.g. fatigue and is also under the care of neurologists and a physiotherapist, who are attemp		

	ting to treat her as she unders tands she has nerve damag e. Her quality of life, her mental health, as well as her family and social life have been signific antly negativ ely impact ed by		

	this situation over the last two years. She is also now unable to work as a result of her injuries which has also had financial implications." Proposed amendment: "In		

	addition, the Patient Organisation Submission accompanying the CS expressed deep concerns around transient immune complexes, along with their hopes that these events		

	are accurately represented in the data submitted to regulatory authorities.”		

(Please add further lines to the table as necessary)