CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761388Orig1s000

INTEGRATED REVIEW

Integrated Review

Table 1. Application Information

Application type	BLA
Application number(s)	761388
Priority or standard	STANDARD
Submit date(s)	6/19/2023
Received date(s)	6/20/2023
PDUFA goal date	6/20/2024
Division/office	Division of Nonmalignant Hematology (DNH)
Review completion date	Electronic Stamp
Established/proper name	Crovalimab-akkz
(Proposed) proprietary name	PIASKY
Pharmacologic class	Complement inhibitor
Other product name(s)	RO7112689
Applicant	Genentech, Inc.
Dosage form(s)/formulation(s)	INJECTION
Dosing regimen	One loading dose administered by intravenous (IV) infusion, followed by 4 additional loading doses administered by subcutaneous injection. The maintenance dose is then administered every 4 weeks by subcutaneous injection. Dosage is based on weight.
Applicant-proposed indication(s)/ population(s)	The treatment of adult and pediatric patients with paroxysmal nocturnal hemoglobinuria (PNH)
SNOMED CT code for proposed indication disease term(s)[a]	1963002: Paroxysmal nocturnal hemoglobinuria (disorder)
Regulatory action	Approval
Approved dosage (if applicable)	One loading dose administered by intravenous (IV) infusion, followed by 4 additional loading doses administered by subcutaneous injection. The maintenance dose is then administered every 4 weeks by subcutaneous injection. Dosage is based on weight.
Approved indication(s)/ population(s) (if applicable)	The treatment of adult and pediatric patients 13 years and older with paroxysmal nocturnal hemoglobinuria (PNH) and body weight of at least 40 kg.
SNOMED CT code for approved indication disease term(s)[a]	1963002: Paroxysmal nocturnal hemoglobinuria (disorder)

[a.] For internal tracking purposes only.
Abbreviations: BLA, Biologics License Application; DNH, Division of Nonmalignant Hematology; IV, intravenous; PDUFA, Prescription Drug User Fee Act; PNH, paroxysmal nocturnal hemoglobinuria; SNOMED CT, Systematized Nomenclature of Medicine Clinical Terms

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Glossary

ADA	antidrug antibody
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AR	adverse reaction
AR(1)	first order autoregressive
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BLA	biologics license application
BLQ	below the limit of quantification
BP	blood pressure
BTH	breakthrough hemolysis
BW	body weight
CCOD	clinical cutoff date
CDER	Center for Drug Evaluation and Research
CL	clearance
CLCR	creatinine clearance
C_{max}	maximum plasma concentration
C_{trough}	lowest plasma concentration at a steady state
DTDC	drug-target-drug complex
DPACC	Division of Pulmonology, Allergy, and Critical Care
ELISA	enzyme linked immunosorbent assay
E-R	exposure-response
ETASU	elements to assure safe use
FACIT	Functional Assessment of Chronic Illness Therapy
FDA	Food and Drug Administration
GCP	good clinical practice
GEE	generalized estimating equation
GPI	glycosylphosphatidylinositol
HI	hepatic impairment
HV	healthy volunteer
IND	investigational new drug
ISR	incurred sample reproducibility
ITT	intent-to-treat
IV	intravenous
IVH	intravascular hemolysis
K_d	exponential decay constant
LDH	lactate dehydrogenase
LLOQ	lower limit of quantification
MAC	membrane attack complex
MAVE	major adverse vascular event
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities

MMRM	mixed-effect model for repeated measure
NAb	neutralizing antibody
NIM	noninferiority margin
NOAEL	no observed adverse effect level
OLE	open-label extension
OR	odds ratio
OSI	Office of Scientific Investigations
PD	pharmacodynamic
PI	Prescribing Information
PK	pharmacokinetic
PK/PD	pharmacokinetics/pharmacodynamics
PMR	postmarketing requirement
PNH	paroxysmal nocturnal hemoglobinuria
pRBC	packed red blood cell
PT	preferred term
PY	patient-years
QW	once weekly
Q2W	every 2 weeks
Q4W	every 4 weeks
RBC	red blood cell
REMS	risk evaluation and mitigation strategy
RI	renal impairment
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SOC	system organ class
TA	transfusion avoidance
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
ULOQ	upper limit of quantification
UN	unstructured
WBC	white blood cell

I. Executive Summary

1. Summary of Regulatory Action

The Applicant, Genentech, Inc., submitted this BLA for the approval of crovalimab, proposed trade name (PIASKY), a complement C5 inhibitor, for the treatment of adult and pediatric patients with paroxysmal nocturnal hemoglobinuria (PNH). The proposed dosage regimen consists of one loading dose administered by intravenous infusion (on Day 1), followed by four additional weekly loading doses administered by subcutaneous (SC) injection (on Days 2, 8, 15, and 22). The maintenance dose starts on Day 29 and is then administered every 4 weeks by SC injection. Dosage is based on the patient's body weight.

The Applicant submitted results from one adequate and well-controlled study (COMMODORE-2), with confirmatory evidence from pharmacodynamic/mechanistic data, which provide substantial evidence of effectiveness of crovalimab for the indication and supports approval for the treatment of adult and pediatric patients 13 years of age and older with PNH weighing ≥40 kg.

COMMODORE-2 was a multicenter, randomized, open-label, active-controlled trial that compared crovalimab to eculizumab on transfusion avoidance and hemolysis control in patients (body weight ≥ 40 kg) with PNH who were naïve to complement inhibitor therapy, and provided compelling evidence of a therapeutic effect on these endpoints. These findings were supported by confirmatory evidence from pharmacodynamic/mechanistic data from three other clinical studies. Overall, the persuasive results make reliance on a single, adequate, and well-controlled study, with confirmatory evidence from relevant pharmacodynamic/mechanistic data, appropriate to support approval in this rare, serious, and life-threatening disease.

Similar to other complement C5 inhibitors, crovalimab has a serious risk of bacterial meningitis, which requires a risk evaluation and mitigation strategy (REMS) with elements to assure safe use. Crovalimab also has a unique risk of type III hypersensitivity reactions, which occurs in some patients switching from either eculizumab or ravulizumab (approved C5 inhibitors) to crovalimab and in patients switching from crovalimab to either eculizumab or ravulizumab. The type III hypersensitivity reactions are caused by simultaneous circulating levels of eculizumab (or ravulizumab) and crovalimab, which bind to different epitopes on C5, forming drug-target-drug complexes. This risk will be included as a Warning and can be mitigated by waiting long enough between stopping eculizumab (or ravulizumab) and starting crovalimab, or between stopping crovalimab and starting eculizumab (or ravulizumab) so that only one C5 inhibitor is circulating in the body. Therefore, healthcare providers should consider the benefits of the timing of switching C5 inhibitors vs. the risks of Type III hypersensitivity reactions.

The application was reviewed by a multidisciplinary review team. Each discipline recommends approval, and the signatory authority concurs that the application should be approved. The overall benefit-risk profile is favorable as described in the Benefit-Risk Framework (Table 2).

Postmarketing requirements and commitments include a registry and completion of the ongoing PNH trials to further characterize the long-term safety of crovalimab, along with a descriptive pregnancy safety study.

For detailed information supporting the basis for the approval, refer to the detailed section included in this Interdisciplinary Assessment document, the product quality review, and other memoranda, such as the REMS review.

2. Benefit-Risk Assessment

2.1. Benefit-Risk Framework

Table 2. Benefit-Risk Framework

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of condition	• PNH is a rare, serious, and life-threatening chronic disease characterized by uncontrolled complement activation, resulting in hemolytic anemia, which may require blood transfusions. Other manifestations include thromboembolism, bone marrow failure, dysphagia, abdominal pain, pulmonary hypertension, renal impairment, and erectile dysfunction. • The disease is caused by somatic mutations in the *PIG-A* gene in hematopoietic stem cells, leading to the loss of complement inhibitor proteins CD55 and CD59 on red blood cell surfaces. The loss of complement inhibition results in complement-mediated intravascular hemolysis. Extravascular hemolysis also occurs due to complement-mediated destruction of erythrocytes by the reticuloendothelial system (macrophages in the liver and spleen). • Prior to the availability of complement inhibitors, historical studies have shown the median survival for PNH to be between 10 and 15 years from the time of diagnosis.	• PNH is a rare and chronic disease resulting in serious clinical manifestations from dysregulated complement activation, including intravascular and extravascular hemolysis, leading to severe anemia, as well as thrombosis, bone marrow failure, and other systemic manifestations. • PNH requires life-long therapy.
Current treatment options	• Patients with PNH often require support with blood transfusions and/or anticoagulation. • Five drugs have been approved for PNH, all of which are complement inhibitors. Eculizumab, approved in 2007, and ravulizumab, approved in 2018, are C5 inhibitors like crovalimab and target intravascular hemolysis. Pegectacoplan, approved in 2021, is a C3 inhibitor (targeting both intravascular and extravascular hemolysis). Iptacopan, approved in 2023, is a factor B inhibitor (targeting both intravascular and extravascular hemolysis). Danicopan,	• There are two C5 inhibitors, one C3 inhibitor, one factor B inhibitor, and one factor D inhibitor approved for PNH, all of which have shown effect in terms of hemoglobin response, transfusion avoidance, or improvement in markers of hemolysis. Approved drugs for PNH are administered intravenously, by subcutaneous injection, or orally and carry a serious risk of infection, including encapsulated organism infections. • HSCT is curative but has certain eligibility requirements and substantial morbidity and mortality.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	approved in 2023, is a factor D inhibitor (targeting extravascular hemolysis). – Eculizumab is administered as an intravenous infusion, and increases hemoglobin while also reducing the need for red blood cell (RBC) transfusions compared to placebo. – Ravulizumab is administered either subcutaneously or by intravenous infusion and is noninferior with regard to transfusion avoidance and hemolysis (measured by lactate dehydrogenase [LDH]) compared to eculizumab. – Pegcetacoplan is administered by subcutaneous injection and is superior in change from baseline on hemoglobin and noninferior in transfusion avoidance compared to eculizumab. – Iptacopan is administered orally and is superior in increase in hemoglobin and transfusion avoidance compared to eculizumab or ravulizumab (C5 inhibitors). – Danicopan is administered orally in combination with ravulizumab or eculizumab, and is superior to C5 inhibitors alone in increase in hemoglobin, transfusion avoidance, and FACIT-Fatigue. • All five drugs have warnings in the label for serious infections and are available only through a REMS, with elements to assure safe use due to the risk of meningococcal infection or encapsulated organism infections. • HSCT remains the only curative treatment for PNH, but it is associated with high mortality (~30%) and morbidity rates.	

Benefit	• Evidence of benefit is primarily derived from COMMODORE-2, a randomized, open-label, active-controlled, multicenter study in patients with PNH and evidence of hemolysis (LDH ≥2×ULN), naïve to complement inhibitor treatment. A total of 204 subjects were randomized 2:1 to receive either crovalimab (n=135) or eculizumab, which is another C5 inhibitor (n=69) for 24 weeks. • At baseline, the median LDH was 7×ULN (range: 2-16.3) for the crovalimab group and 7.7×ULN (range: 2-20.3) for the eculizumab group. In the previous 12 months prior to study enrollment, 77.4% of subjects in the crovalimab group and 73.5% of subjects in the eculizumab group had at least one blood transfusion. • The mean proportion of subjects with hemolysis control (LDH ≤1.5×ULN) from Week 5 through Week 25 in subjects treated with crovalimab compared to eculizumab was 79.3% vs. 79.0%, respectively, resulting in an odds ratio of 1.02 [95% CI: 0.57, 1.82]. The proportion of subjects who achieved transfusion avoidance from baseline to Week 25 was 65.7% for crovalimab vs. 68.1% for eculizumab, with a difference in proportions of -2.8% [95% CI: -15.7, 11.1]. The difference in proporitions of subjects with breakthrough hemolysis was -3.9% [95% CI: -14.8, 5.3]. The difference in proportions of subjects with stabilized hemoglobin was 2.2% [95% CI: -11.4, 16.30]. The observed changes described above would not occur spontanesously. • Confirmatory evidence of effect is demonstated from three other clinical studies: COMMODORE-3, COMPOSER and COMMODORE-1, which provide compelling PD evidence (LDH decrease or stabilization) and mechanistic support (complement inhibition) to provide substantial evidence of effectivness. • In clinical trials, efficacy was evaluated in 12 pediatric subjects treated with crovalimab between the ages of 13-17 years, with a body weight >40 kg. Nine of the 12 subjects were complement inhibitor naïve. The proportion of subjects with a history of transfusions in the prior 12 months was 58%, and the baseline median LDH was 6.4×ULN (range: 1.1-26.6). Hemolysis control from baseline to Week 25 was	• Substantial evidence of effectiveness of crovalimab for the treatment of patients with PNH was established with one adequate and well-controlled trial, COMMODORE-2, and confirmatory evidence provided from COMMODORE-3, COMPOSER and COMMODORE-1. • Based on COMMODORE-2, the benefits of crovalimab in patients with PNH naïve to C5 inhibitor therapy include hemolysis control, as well as transfusion avoidance, a procedure that carries risks for infection and transfusion-related reactions. Crovalimab demonstrated similar benefits to another FDA-approved C5 inhibitor, eculizumab. It is unclear how the benefits with crovalimab compare to the FDA-approved C3 inhibitor and factor B inhibitor, which target intra- and extravascular hemolysis, as there is no head-to-head comparison. • In patients previously treated with a C5-inhibitor, crovalimab is expected to have similar benefits, based on similar effects in transfusion avoidance and hemolysis control between crovalimab and eculizumab. • Adolescents (ages 13-17 years) also demonstrated similar benefits to those seen in adults treated with crovalimab. • Compared to other FDA-approved C5 inhibitors, crovalimab has the added benefit of less frequent dosing through the subcutaneous route.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	achieved in 7 of the 9 subjects who were treatment-naïve, and and the 3 subjects switching from eculizumab or ravulizumab to crovalimab maintained hemolysis control through 24 weeks of crovalimab treatment . Nine (six subjects who were treatment-naïve and three subjects who switched from eculizumab or ravulizumab) out of the 12 pediatric subjects achieved transfusion avoidance and hemoglobin stabilization, and no subjects had a breakthrough hemolysis event during the 24-week treatment period.	
Risk and risk management	• Crovalimab's safety was evaluated primarily in COMMODORE-2 and COMMODORE-1 (a prematurely discontinued study comparing switching to crovalimab vs. continued eculizumab in patients treated with eculizumab). • In COMMODORE-2, serious adverse events occurred in 6% of subjects, pneumonia and epistaxis each occurred in 2 subjects. In COMMODORE-1, serious adverse events occurred in 7% of subjects. • The most common adverse reactions (>10%) were infusion related reaction, respiratory tract infections, viral infections, and type III hypersensitivity reaction. • Patients who are switching from another C5 inhibitor to crovalimab, or from crovalimab to another C5 inhibitor, are at risk of type III hypersensitivity reactions related to the formation of DTDCs. Signs and symptoms of type III hypersensitivity reactions occurred in clinical trials, including arthralgia, rash, pyrexia, myalgia, headache, fatigue, petechiae, abdominal pain and axonal neuropathy. Some of these reactions were serious and had not fully resolved at the time of last follow-up. • Infusion and injection-related reactions occurred in clinical trials. One subject experienced a serious infusion-related reaction (Grade 2 nausea, vomiting, abdominal pain, headache, and pyrexia resulting in hospitalization). • Similar to other complement inhibitors, serious infections due to encapsulated organisms were reported in clinical trials. Although no meningococcal infections were reported, this	• The safety data submitted were sufficient to characterize the toxicity profile of crovalimab. • The risks of crovalimab are broadly comparable to those of other approved C5 inhibitors. • One exception is that crovalimab can cause a serious risk of type III hypersensitivity reactions in patients switching from or to another C5 inhibitor. Type III hypersensitivity reactions will be listed in the label as a warning. This risk can be mitigated by waiting until the prior C5 inhibitor has cleared from the body before initiating crovalimab, and waiting until crovalimab has cleared from the body before initiating another C5 inhibitor. Therefore, healthcare providers should consider the benefits of the timing of switching C5 inhibitors vs. the risks of Type III hypersensitivity reactions. • Similar to other complement inhibitors, a REMS with ETASU is required. The goal of the REMS is to mitigate the risk of serious meningococcal infections. The REMS will help ensure that: – Patients are up to date with vaccinations against *Neisseria meningitidis* serogroups A, C, W, Y and B according to current ACIP recommendations (or receive prophylactic antibiotics if indicated). – Patients and prescribers are aware of early signs and symptoms of meningococcal nfections and the need for immediate medical evaluation. • The other risks of crovalimab are expected to be tolerability issues and/or are monitorable and actionable.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	remains an expected risk based on crovalimab's mechanism of action.	• Postmarketing requirements will be issued at the time of approval to assess the long-term safety of crovalimab, as it may be administered life-long for this chronic disease.

Source: Generated by the FDA review team.
Abbreviations: ACIP, Advisory Committee or Immunization Practices; BTH, breakthrough hemolysis; C3, complement 3; C5, complement 5; CI, confidence interval; DTDC, drug-target-drug-complexes; ETASU, elements to assure safe use; FACIT, Functional Assessment of Chronic Illness Therapy; FDA, Food and Drug Administration; HSCT, hematopoietic stem cell transplantation; LDH, lactate dehydrogenase; MOA, mechanism of action; n, number of subjects in treatment arm; PIG-A, phosphatidylinositol glycan class A; PNH, paroxysmal nocturnal hemoglobinuria; RBC, red blood cell; REMS, risk evaluation and mitigation strategy; ULN, upper limit of normal

2.2. Conclusions Regarding Benefit-Risk

PNH is a rare, serious, life-threatening, and chronic hematologic disease caused by a somatic mutation in the *PIG-A* gene leading to chronic hemolysis, thrombosis, and other systemic effects. Spontaneous remissions do not occur without treatment. Complement inhibitors (ravulizumab, eculizumab, pegcetacoplan, iptacopan, and danicopan) approved for PNH reduce the need for blood transfusions, stabilize/increase hemoglobin, and/or stabilize/reduce hemolysis.

The benefits of crovalimab (C5 inhibitor) for the treatment of adults with PNH were established on the basis of high rates of hemolysis control (which is expected to improve the signs and symptoms of anemia) and transfusion avoidance (a procedure which carries risk). The trials were not designed to assess other benefits (e.g., thrombosis or mortality). Compared to the other approved C5 inhibitors, crovalimab also has less frequent dosing by the SC route (every 4 weeks for maintenance dosing compared to weekly for ravulizumab) and of SC administration instead of intravenous infusion, which may be preferred by some patients.

Crovalimab carries a risk of type III hypersensitivity reactions in patients switching from or to another C5 inhibitor, otherwise crovalimab's risks appear generally comparable to those of the other approved complement C5 inhibitors. All C5 inhibitors, including crovalimab, have a risk for meningococcal meningitis, for which a REMS is required. This REMS ensures, for example, that patients are vaccinated against meningococcus (or receive temporary prophylactic antibiotics until vaccination is up to date). The long-term safety of crovalimab will be further assessed with a postmarketing requirement and commitments.

Crovalimab's risk of type III hypersensitivity reactions can be adequately mitigated by spacing out the other C5 inhibitor and crovalimab in patients who are switching C5 inhibitors, which will be communicated as a warning in the label and Medication Guide. However, prolonged discontinuation of therapy risks PNH becoming uncontrolled. Therefore, healthcare providers should consider the benefits of the timing of switching C5 inhibitors vs. the risks of Type III hypersensitivity reactions.

The FDA concludes that crovalimab's benefits outweigh its risks for the treatment of PNH when crovalimab is used according to the approved labeling.

II. Interdisciplinary Assessment

3. Introduction

Product Introduction

The Applicant, Genentech, Inc., seeks approval of PIASKY (crovalimab) for the treatment of adult and pediatric patients with paroxysmal nocturnal hemoglobinuria (PNH). Crovalimab injection is a recombinant humanized anti-C5 monoclonal antibody of the IgG1 subtype. Crovalimab binds to the complement protein C5, inhibiting its cleavage to C5a and C5b and prevents the formation of the membrane attack complex (MAC). In patients with PNH, crovalimab inhibits terminal complement-mediated intravascular hemolysis (IVH). Crovalimab binds to a different C5 epitope than currently available C5 inhibitors. Crovalimab is engineered using the Sequential Monoclonal Antibody Recycling Technology Immunoglobulin technology with pH-dependent antigen binding allowing for enhancement of neonatal FcRn binding to improve antigen disposal and antibody recycling efficiency; this further prolongs the half-life of crovalimab so that the maintenance dosages can be administered every 4 months.

Crovalimab is a new biological product that was granted orphan designation in September 2017 for PNH. The drug is supplied in a 340 mg/2 mL solution in a single-use vial. The proposed dosage regimen consists of one loading dose administered by intravenous (IV) infusion (patients weighing ≥40 kg to <100 kg: 1000 mg, patients weighing ≥100 kg: 1500 mg), followed by four additional weekly loading doses of 340 mg administered by subcutaneous (SC) injection. The maintenance dose is then administered every 4 weeks (Q4W) by SC injection (patients weighing ≥40 kg to <100 kg: 680 mg, patients weighing ≥100 kg: 1020 mg).

Analysis of Condition

PNH is a rare, life-threatening hematopoietic stem cell disorder in which uncontrolled complement activation leads to hemolytic anemia, thrombosis, and cytopenias (Brodsky 2014; DeZern and Brodsky 2015). The condition is caused by an acquired mutation of the X-linked gene *PIG-A*, which results in a deficiency in the glycosylphosphatidylinositol anchor, leading to a deficit of glycosylphosphatidylinositol-linked complement regulatory proteins (i.e., cluster of differentiation CD55 and CD59) on the cell surface of erythrocytes. CD55 inhibits proximal complement activation, and deficiency of CD55 leads to increased C3 convertase activity and C3d-associated extravascular hemolysis. CD59 inhibits terminal complement activation, and deficiency of CD59 increases MAC formation and induces IVH. The absence of CD55 and CD59 results in chronic, uncontrolled complement activation that causes hemolysis and other PNH manifestations. The hemolysis can be exacerbated by stress due to surgery, trauma, or other triggers of inflammation.

The prevalence of PNH is estimated to be as high as 15.9 individuals per million worldwide (Roth et al. 2018). The disease may occur more frequently in Southeast Asia, where the occurrence of aplastic anemia is greater, as aplastic anemia is a known risk factor for developing PNH. The median age at diagnosis is during the 30s (Socie et al. 1996; Schrezenmeier et al. 2014), and children can be uncommonly affected. The condition is due to an X-linked

chromosome mutation and affects females at a slightly higher rate than males. Signs and symptoms of PNH include anemia (due to a combination of intravascular and extravascular hemolysis); fatigue; generalized malaise; dyspnea; dark urine due to hemoglobinuria; renal insufficiency from hemosiderin deposition, leading to tubulointerstitial inflammation, along with dysphagia or esophageal spasms; abdominal pain; back pain; and erectile dysfunction, which all occur due to smooth muscle dystonia (Shah and Bhatt 2024). Thrombosis is the most common cause of mortality in patients with PNH. Laboratory characteristics associated with PNH include increased lactate dehydrogenase (LDH), low haptoglobin, and unconjugated bilirubinemia due to IVH.

Analysis of Current Treatment Options

Approved treatment for PNH consists of complement inhibitors (i.e., eculizumab, ravulizumab, pegcetacoplan, iptacopan and danicopan), which have shown benefit in terms of hemoglobin response, other markers of hemolysis, and/or transfusion avoidance (TA). All of these therapies are only available through an elements to assure safe use (ETASU) risk evaluation and mitigation strategy (REMS) because of the risk for serious infections caused by encapsulated bacteria or meningococcal infections.

Eculizumab is a C5 inhibitor administered by IV infusion every 2 weeks (Q2W). Ravulizumab, another C5 inhibitor is administered by IV infusion every 8 weeks or by SC injection once weekly (SC dosing is not approved for pediatric patients). After loading doses, crovalimab is administered SC Q4W, which may be preferred by some patients over the more frequent SC dosing of ravulizumab or the IV route of administration of eculizumab and ravulizumab.

Other treatment options on managing symptoms and complications of PNH include supportive therapies such as blood transfusion, anticoagulation, systemic corticosteroids, iron replacement therapy, and growth factors. Hematopoietic stem cell transplantation is the only cure. However, hematopoietic stem cell transplantation is associated with high mortality; therefore, it is not a therapeutic option for most patients (Bektas et al. 2020).

Substantial Evidence of Effectiveness

Substantial evidence of effectiveness was established based on one adequate and well-controlled clinical study (COMMODORE-2), along with confirmatory pharmacodynamic (PD)/mechanistic data from three other studies (COMMODORE-3, COMPOSER and COMMODORE-1).

COMMODORE-2 is a randomized, open-label, active-controlled (eculizumab), noninferiority, multicenter trial that evaluated the efficacy and safety of crovalimab in patients with PNH not previously treated with complement inhibitors. The co-primary endpoints of TA and hemolysis control and major key secondary endpoints of breakthrough hemolysis (BTH) and stabilized hemoglobin met the Applicant's prespecified noninferiority margins (NIMs). Because there were concerns with the Applicant's chosen NIMs, the statistical review team performed further evaluations using more stringent NIMs, which the efficacy endpoints also met. In addition, the effects of crovalimab on these endpoints are compelling as these changes would not occur spontaneously in the absence of treatment.

Confirmatory PD/mechanistic evidence comes from three other studies: COMMODORE-3, COMPOSER and COMMODORE-1, all of which showed consistent effects of crovalimab on hemolysis control (assessed with LDH), target engagement (free C5) and complete inhibition of

the terminal complement pathway (assessed with CH50). Improvements in PNH red blood cell (RBC) clone size (reflecting an increase in RBCs that have the PNH defect and are susceptible to complement-mediated hemolysis, yet remain intact because of complement inhibition) was observed in complement inhibitor naïve subjects. The findings from these three studies would not occur spontaneously in PNH and provide mechanistic support based on the well understood pathophysiology of PNH and crovalimab's mechanism of action directly targeting a major driver of the disease pathophysiology.

Safety Database

The safety database for crovalimab was adequate for the proposed indication, dosing regimen, and intended patient population. Overall, crovalimab has an acceptable safety profile in both patients who are complement C5 inhibitor treatment-naïve and in patients with complement C5 inhibitor experience. The most significant risk is serious meningococcal infections for which a REMS with ETASU will be required like with the other C5 inhibitors. In addition, patients who switch from another C5 inhibitor to crovalimab, or from crovalimab to another C5 inhibitor, are at risk of developing type III hypersensitivity reactions related to the formation of drug-target-drug-complexes. This risk can be mitigated in switch patients by adequately spacing out the other C5 inhibitor and crovalimab. Other risks include infusion and injection site reactions, regardless of prior experience with complement inhibitors. The most common adverse reactions (ARs) (≥10%) were infusion-related reaction, respiratory tract infection, viral infections, and, in those who switch C5 inhibitors, type III hypersensitivity reactions.

A detailed discussion of these findings is included in the pertinent sections of this review (Sections 7 and 17).

Crovalimab Administration

The Applicant submitted a simulated human factors validation study (HFVS) in this application to support the proposal for crovalimab to be administered by self or a lay caregiver. The Division of Medication Error Prevention Analysis conducted a review and determined that the results do not support administration of crovalimab by adults and pediatric patients or lay caregivers. (b) (4)

The clinical team and DMEPA considered all the available data including data from the clinical trials in reaching the decision to limit to only health care provider administration. Although there were patients who self-administered crovalimab in the clinical trial those patients had a high level of oversight and instruction, which would not be expected to occur consistently in patients who receive the drug in actual practice, making it difficult to reliably conclude from the clinical trial data what will happen in the real-world.

In summary, DMEPA recommended that the label should include the statement, "Administered by Healthcare Professionals Only" as the human factors validation study (HFVS) results do not support administration of the proposed product by adult and pediatric patients with PNH and lay caregivers. For a complete discussion regarding the recommendation for crovalimab to only be administered by healthcare professionals, see the finalized reviews by DMEPA in DARRTS dated March 15, 2024, April 24, 2024, and June 18, 2024.

3.1. Review Issue List

3.1.1. Key Efficacy Review Issues

3.1.1.1. Assessing the Adequacy of Noninferiority Margins for Major Efficacy Endpoints in COMMODORE-2

3.1.1.2. Evidence of Effectiveness in Patients Who Are Treatment Experienced With Another C5 Inhibitor

3.1.1.3. Applicability of Foreign Efficacy Data to the U.S. Population

3.1.1.4. Efficacy in the Pediatric Patient Population

3.1.1.5. Efficacy Effects of Crovalimab IV Rescue Doses in COMMODORE-2

3.1.2. Key Safety Review Issues

3.1.2.1. Meningococcal Infection

3.1.2.2. Type III Hypersensitivity Reaction

3.1.2.3. Applicability of Foreign Safety Results to the U.S. Population

3.1.2.4. Self-Administration or Lay Caregiver Administration of Crovalimab

3.2. Approach to the Clinical Review

The clinical trials that are pertinent to support the benefit-risk assessment of crovalimab are summarized in Table 3. The assessment of benefit was primarily based on COMMODORE-2, a randomized, open-labeled, active control study in patients with PNH. COMMODORE-3, COMPOSER and COMMODORE-1 were reviewed for confirmatory evidence of effectiveness of crovalimab.

In the active-controlled COMMODORE-2 study, the control drug was Soliris (eculizumab). Per the Applicant, Soliris (NDC 25682-001-01/BLA 125166) was sourced via (b) (4) directly from the Marketing Authorization Holder,

Alexion Pharmaceuticals Inc., Boston, Massachusetts, U.S. and manufacturing was performed at (b) (4). The last FDA inspection of the manufacturing facility occurred on (b) (4)

The assessment of risk was based primarily on data from the primary treatment period in COMMODORE-2 and COMMODORE-1, but also included an analysis of the pooled PNH safety set in subjects receiving crovalimab in extension periods of COMMDORE 2 and COMMODORE-1, along with safety data from COMPOSER and COMMODORE-3 studies.

Table 3. Clinical Trials Submitted in Support of Efficacy and/or Safety Determinations[a] for Crovalimab

Trial Identifier (NCT#)	Trial Population	Trial Design	Regimen, Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized[b]	Number of Centers and Countries
COMMODORE-2 (BO42162) NCT04434092 Ongoing	Randomized arms: Adult subjects with PNH not previously treated with complement inhibitors. Descriptive arm C (received crovalimab): Pediatric subjects with PNH not previously treated with complement inhibitors, age <18 years, ≥40 kg	Phase 3, Randomized (2:1), open-label, active-controlled, noninferiority multicenter study. Also contained a non-randomized arm C	Crovalimab: Loading doses[c] as indicated at bottom of this table. From Week 5 onwards: Subjects ≥40 kg to <100 kg: 680 mg SC Q4W. Subjects ≥100 kg: 1020 mg SC Q4W. Eculizumab (approved dose regimen): Induction doses of 600 mg IV on Days 1, 8, 15, and 22 Maintenance doses of 900 mg IV on Day 29 and Q2W thereafter. Duration: Primary Analysis at Week 25. Option given to subjects in crovalimab arm to continue treatment in an open-label extension at the Q4W dose received in main phase.	Co-Primary endpoints: • Transfusion avoidance from baseline through Week 25 • Hemolysis control (LDH ≤1.5×ULN) from Week 5 through Week 25. Secondary: • Breakthrough hemolysis from baseline through Week 25. • Stabilization of hemoglobin from baseline through Week 25 • Mean change from baseline to Week 25 in fatigue, as assessed by the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue.	Planned: 239 Randomized arms: N=204 (crovalimab: 135, eculizumab: 69) Descriptive arm: 6	Centers: 67 Countries: 25
COMMODORE-1 (BO42161) NCT04432584 Ongoing	Subjects with PNH with current or previous treatment with complement inhibitors Randomized arms: Adults treated for at least 24 weeks with eculizumab at the approved dose for PNH.	Phase 3 Randomized (1:1), open-label, active-controlled, multicenter study Also had a non-randomized arm C	Crovalimab: Loading doses[c] as indicated at bottom of this table. From Week 5 onwards: Subjects ≥40 kg to <100 kg: 680 mg SC Q4W Subjects ≥100 kg: 1020 mg SC Q4W Eculizumab: Maintenance doses of 900 mg IV on Day 1 (2 weeks after last prestudy dose) and Q2W thereafter	Primary endpoint: Safety This study had the following exploratory efficacy endpoints: • Percent change from baseline in LDH levels averaged over Weeks 21, 23, and 25. • Transfusion avoidance from baseline through Week 25 (after 24 weeks on treatment).	Planned: 90 Randomized arms: N=89 (crovalimab: 45 [1 did not receive treatment], eculizumab: 44 [2 did not receive treatment]) Descriptive Arm C: 38 (pediatric subjects treated with eculizumab: 1, subjects treated with ravulizumab: 21, subjects treated with higher than approved doses of	Centers: 70 Countries: 25

Trial Identifier (NCT#)	Trial Population	Trial Design	Regimen, Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized[b]	Number of Centers and Countries
	Descriptive Arm C involving cohorts (subjects received crovalimab): • Pediatric subjects currently treated (for ≥12 weeks) with eculizumab. • Subjects (regardless of age) currently treated (for ≥16 weeks) with ravulizumab. • Subjects (regardless of age) currently treated (for ≥12 weeks) with higher than approved doses of eculizumab. • Subjects (regardless of age) with known C5 polymorphism and an inadequate response to eculizumab or ravulizumab.		Duration: Primary Analysis at Week 25. Option given to subjects in crovalimab arm to continue treatment in an open-label extension at the Q4W dose received in main phase.	• Breakthrough hemolysis from baseline through Week 25. • Stabilization of hemoglobin from baseline through Week 25.	eculizumab: 10, subjects with C5 polymorphism: 6)	
COMMODORE-3 (YO42311) NCT04654468 Ongoing	Subjects with PNH (age ≥12 years, weight 40 kg), not previously treated with complement inhibitors	Phase 3 single-arm, multicenter, study	Crovalimab Loading doses[c] as indicated at bottom of this table. From Week 5 onwards: Subjects ≥40 kg to <100 kg: 680 mg SC Q4W Subjects ≥100 kg: 1020 mg SC Q4W Duration: Primary Analysis at Week 25. Option given to subjects to continue treatment in an open-label extension at the Q4W dose received in main phase. Treatment ongoing.	Co-Primary endpoints: • The difference in the proportion of subjects who achieve transfusion avoidance from baseline through Week 25 (after 24 weeks on treatment) and the proportion of subjects with transfusion avoidance within 24 weeks of screening. • Hemolysis control (LDH ≤1.5×ULN) from Week 5 through Week 25. Secondary endpoints:	Planned: 59 Enrolled: 51	Centers: 5 Countries: 1 China)

Trial Identifier (NCT#)	Trial Population	Trial Design	Regimen, Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized[b]	Number of Centers and Countries
				• Breakthrough hemolysis from baseline through Week 25. • Stabilization of hemoglobin from baseline through Week 25. • Mean change from baseline to Week 25 in fatigue, as assessed by the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue (adults aged 18 years)		
COMPOSER (BP39144) NCT03157635 Ongoing	Part 1: Healthy volunteers Part 2: Treatment-naïve subjects with PNH Part 3: Subjects with PNH switched from Eculizumab Part 4: Subjects with PNH Arm A: Treatment-naïve Arm B: Switched treatment from eculizumab	Phase 1/2 FIH study: Part 1 (SAD): Randomized, blinded, adaptive, placebo-controlled, parallel group Part 2 (intrasubject dose-escalation): Open-label, multiple dose, global multicenter, intra-individual dose escalation Part 3 (dose ranging optimization): Open-label, multiple dose, global multicenter Part 4: (Phase 3 dose optimization) Open-label, multiple dose, global multicenter, 2−arm	Part 1: Single crovalimab doses of 75 or 125 mg IV, or 100 mg SC Part 2: 3 ascending IV doses (375 mg [Day 1], 500 mg [Day 8], 1000 mg [Day 22]. Then QW dosing 170 mg SC from Day 36 onward. Duration: 20 weeks, then entry into open-label extension (median overall duration at time of clinical cut off: 2.42 years) Part 3: All subjects given loading dose of 1000 mg IV, then: Arm A: 8 SC doses of 170 mg QW from Day 8, followed by 680 mg Q4W from Day 64 onwards Arm B: 340 mg SC Q2W from Day 8 onwards Arm C: 170 mg SC QW from Day 8 onwards.	Primary endpoint: • Safety/tolerability Secondary endpoint: • PK/PD	Planned: 59 Enrolled: 59 Part 1: 15 subjects (3 cohorts at 5 subjects [3 crovalimab 2 placebo]) Part 2: 10 subjects Part 3: 19 subjects (Arm A: 7, Arm B: 6, Arm C: 6) Part 4: 15 subjects (8 naïve subjects; 7 subjects switched from eculizumab)	Centers: 15 Countries: 7

Trial Identifier (NCT#)	Trial Population	Trial Design	Regimen, Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized[b]	Number of Centers and Countries
		Open-label extension	Duration: 20 weeks, then entry into open-label extension (median overall duration at time of clinical cut-off:1.51 years) Part 4: Loading dose of 1000 mg IV on Day 1, followed by 340 mg SC on Days 2, 8, 15, and 22. From Day 29 onwards: 680 mg SC Q4W. Duration: 20 weeks, then entry into open-label extension (median overall duration at time of clinical cut off: 0.54 years)			

Source: Generated by the FDA review team.
Note: Subjects ≥40 kg to <100 kg: Week 1, Day 1: 1000 mg IV, Week 1, Day 2: 340 mg SC, Weeks 2, 3, and 4: 340 mg SC QW
Note: Subjects ≥100 kg: Week 1, Day 1: 1500 mg IV, Week 1, Day 2: 340 mg SC, Weeks 2, 3, and 4: 340 mg SC QW
[a] Includes all submitted clinical trials, even if not reviewed in-depth, except for Phase 1 and pharmacokinetic studies.
[b] If no randomization, then replace with "Actual Enrolled"
[c] Crovalimab loading doses during Weeks 1 to 4 in COMMODORE-2, COMMODORE-3, and COMMODORE-1:
Abbreviations: C5, complement component 5; FACIT, Functional Assessment of Chronic Illness Therapy; FIH, first-in-human; IV, intravenous; LDH, lactate dehydrogenase; N, number of subjects in treatment arm; PK/PD, pharmacokinetic/ pharmacodynamic; PNH, paroxysmal nocturnal hemoglobinuria; QW, every week; Q2W, every two weeks; Q4W, every four weeks; SAD, Single Ascending Dose; SC, subcutaneous; ULN, upper limit of normal

4. Patient Experience Data

Table 4. Patient Experience Data Submitted or Considered

Data Submitted in the Application		
Check if Submitted	**Type of Data**	**Section Where Discussed, if Applicable**
Clinical Outcome Assessment Data Submitted in the Application		
☒	Patient-reported outcome	Section 6 (Efficacy) includes a discussion of the FACIT-Fatigue endpoint.
☐	Observer-reported outcome	
☐	Clinician-reported outcome	
☐	Performance outcome	
Other Patient Experience Data Submitted in the Application		
☐	Patient-focused drug development meeting summary	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☐	If no patient experience data were submitted by Applicant, indicate here.	
Data Considered in the Assessment (But Not Submitted by Applicant)		
Check if Considered	**Type of Data**	**Section Where Discussed, if Applicable**
☐	Perspectives shared at patient stakeholder meeting	
☐	Patient-focused drug development meeting summary report	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☐	Other: (please specify)	

Source: CSR.
Abbreviations: FACIT, Functional Assessment of Chronic Illness Therapy

5. Pharmacologic Activity, Pharmacokinetics, and Clinical Pharmacology

5.1. Nonclinical Assessment of Potential Effectiveness

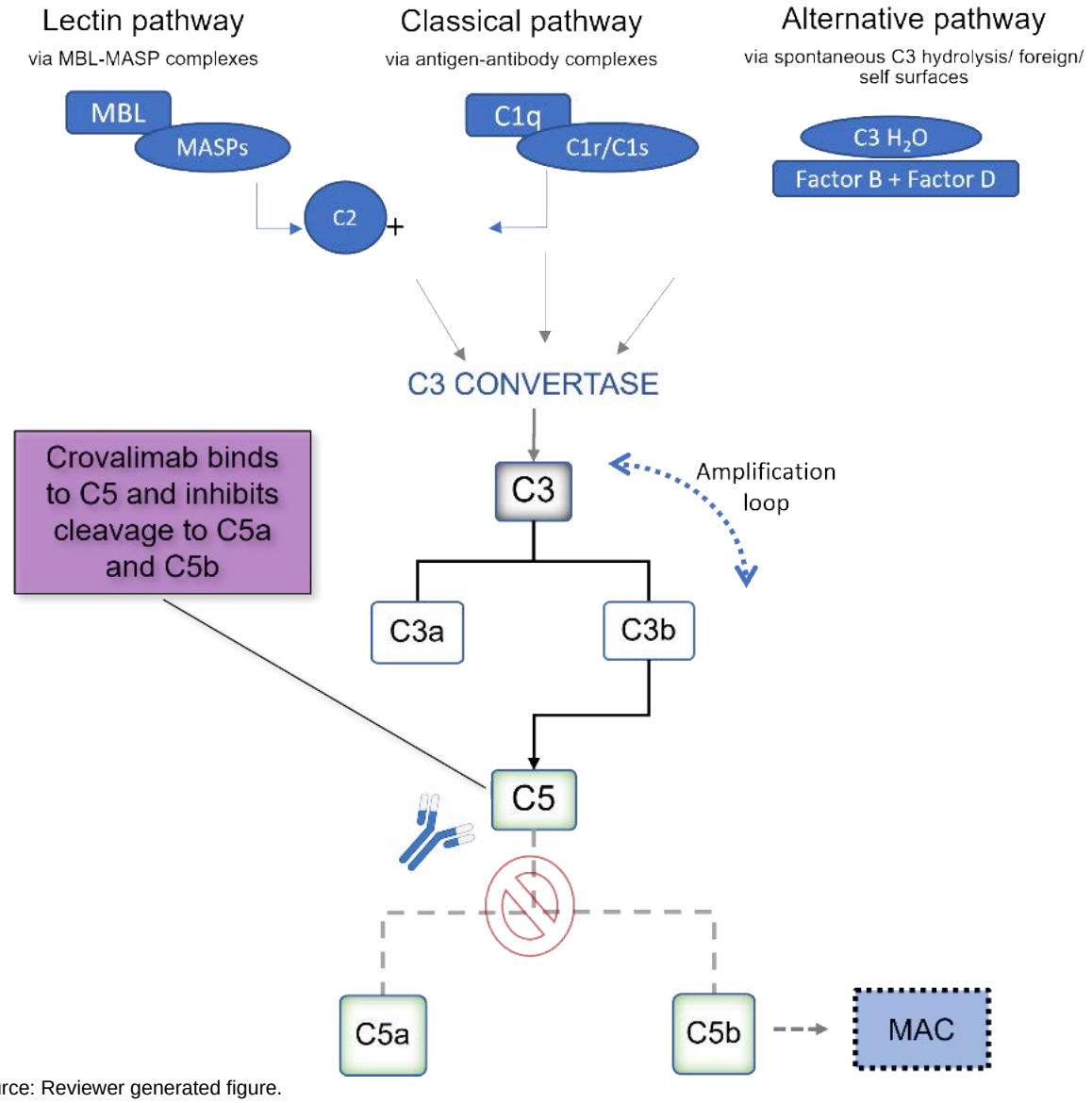
5.1.1. Primary Pharmacology

The complement system is a key component of the innate immune response that, in coordination with antibodies and phagocytic cells, directly lyses non-self-structures, opsonizes pathogens, and promotes inflammation. There are three pathways in the complement system:

- The lectin pathway, which is triggered by mannan-binding lectin, a normal serum constituent that binds some encapsulated bacteria.
- The classical pathway, which is triggered by an antibody or by direct binding of complement component C1q to the pathogen surface.
- The alternative pathway, which is triggered directly on pathogen surfaces.

All three pathways converge at the formation of the C3 convertase (Figure 1), which cleaves and activates protein C3, generating C3a and C3b.

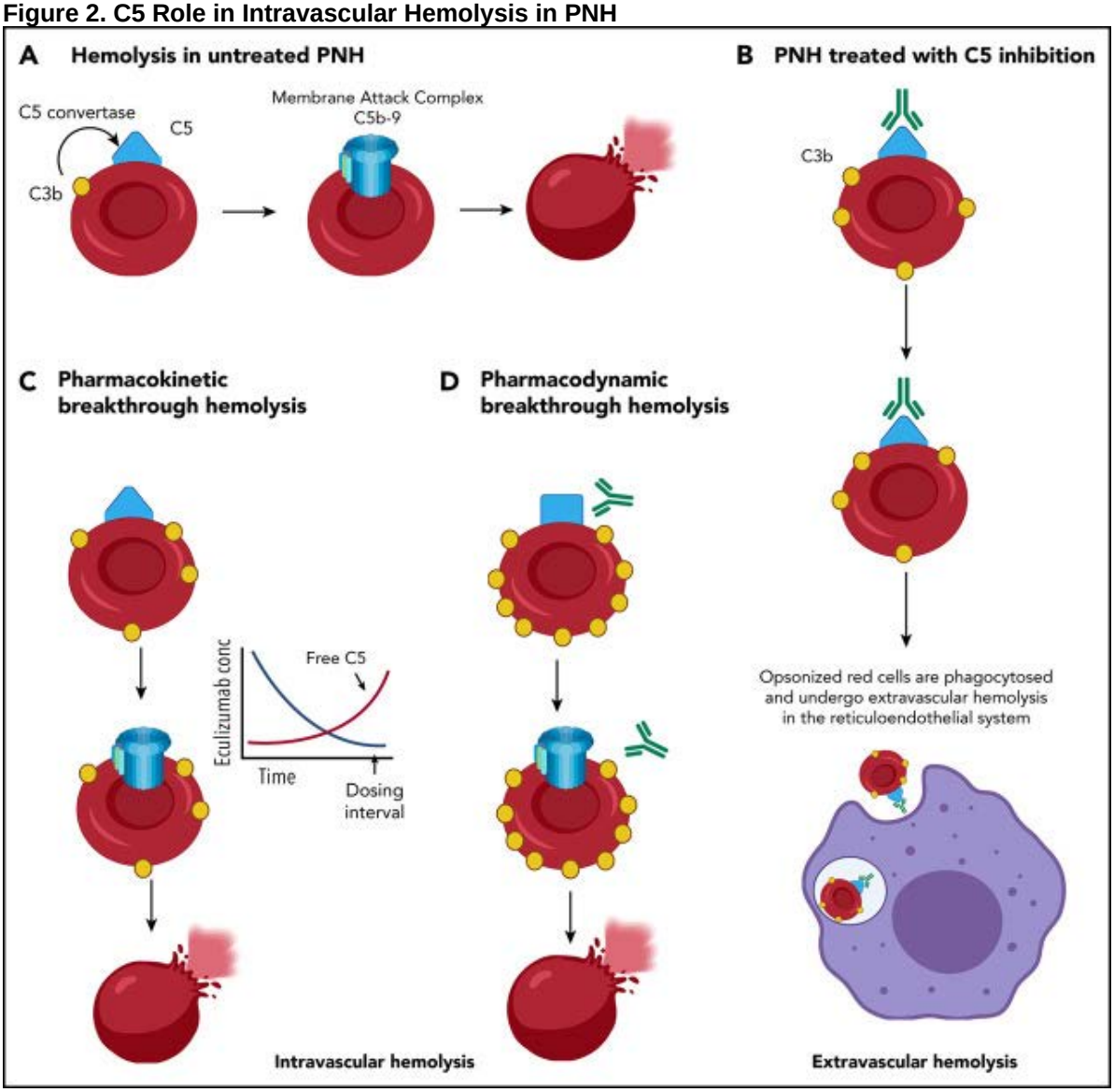
Figure 1. Mechanism of Action of Crovalimab



Source: Reviewer generated figure.
Abbreviations: C2, complement component 2; C3, complement component 3; C4, complement component 4; C5, complement component 5; C5a, complement component 5 subunit a; C5b-9, complement component 5 complex; MAC, membrane attack complex

C3b is responsible for C3-mediated opsonization and can bind additional factors to generate the C5 convertase that cleaves the C5 protein, generating C5a and C5b. C5b initiates the formation of the MAC, which is the terminal cytolytic effector of the complement system. Erythrocyte deficiency of surface anchoring of complement regulators CD55, which regulates formation and stability of C3 and C5 convertases, and CD59, which blocks the formation of MAC, is driven by somatic mutations in the *PIG-A* gene. The uncontrolled cleavage of C5 and lack of regulation of MAC leads to IVH, a hallmark of PNH, resulting in anemia, hemoglobinuria, and the risk of potentially life-threatening thromboembolic events (Figure 2).

Figure 2. C5 Role in Intravascular Hemolysis in PNH



Source: Brodsky RA. How I treat paroxysmal nocturnal hemoglobinuria. Blood. 2021 Mar;137(10):1304-1309. DOI: 10.1182/blood.2019003812. PMID: 33512400; PMCID: PMC7955407 (Brodsky 2021).
Abbreviations: C5, complement component 5; PNH, paroxysmal nocturnal hemoglobinuria

Crovalimab is a humanized, anti-C5, monoclonal antibody that binds to human and cynomolgus monkey C5 protein with comparable affinity (values in the low nanomolar range at pH 7.4), as evaluated using surface plasmon resonance. Binding of crovalimab to C5 is intended to prevent its cleavage into C5a and C5b and, subsequently, the formation of MAC, thereby impeding MAC-mediated RBC lysis as occurs in patients with PNH.

Crovalimab was developed using Sequential Monoclonal Antibody Recycling Technology that combines isoelectric point, pH-dependent affinity, and increased neonatal FcRn binding. Interaction with the FcRn facilitates recycling and prolongs the half-life of crovalimab, which is intended to allow for SC administration of small doses after a single loading dose.

Crovalimab binds a different epitope than other C5 inhibitors (e.g., eculizumab and ravulizumab). Consequently, when crovalimab is present in circulation with either eculizumab or ravulizumab, drug-target-drug complexes (DTDCs) can form with the other anti-C5 mAbs.

5.1.2. In Vitro/Ex Vivo/In Vivo Data Showing Proof of Concept

Crovalimab binds to human and cynomolgus monkey C5 protein with comparable affinity (values of $1.72\pm0.06\times10^{-10}$ and $2.00\pm0.02\times10^{-10}$ mol/L at pH 7.4, respectively), as evaluated from surface plasmon resonance studies. Complement inhibition and downstream effector functions were evaluated in an in vitro and in vivo pharmacokinetics/pharmacodynamics (PK/PD) study and in repeated dose toxicology studies in monkeys. Crovalimab drug substance was found to inhibit antibody-sensitive chicken RBC lysis, induced by human and cynomolgus monkey serum, in a dose-dependent manner (half maximal inhibitory concentration values of 0.834 ± 0.050 and 0.958 ± 0.041 μg/mL, respectively). Crovalimab did not inhibit antibody-sensitized chicken RBC lysis induced by rabbit or rat serum at the maximum concentration tested, demonstrating a lack of activity in these species.

A single-dose PK/PD study in healthy monkeys given a human equivalent loading dose of up to 387.1 mg of crovalimab followed with a single human equivalent dose of up to 77.4 mg resulted in accumulation of total C5 and dose-dependent complete complement inhibition from Days 14 to 35. Crovalimab exposures, after repeated dosing in monkeys, resulted in up to a 90% decrease in total hemolytic activity (CH50) and free-C5 concentrations. Levels were not fully reversable after the recovery period, consistent with the long half-life characteristics of crovalimab. The totality of the in vitro pharmacology, in vitro RBC lysis, and in vivo CH50 activity in nonhuman primates demonstrate that crovalimab binds C5 protein, inhibits C5-dependent RBC lysis, and is expected to reduce uncontrolled C5-dependent complement activation in patients with PNH.

Additionally, crovalimab has no binding activity to the first subcomponent of the classical pathway, C1q protein, as evaluated in an enzyme linked immunosorbent assay. Crovalimab targets the terminal components of the complement system and spares the proximal components, which are mediated by C3 and are mainly responsible for microbial opsonization and immune complex clearance (CL).

5.2. Clinical Pharmacology/Pharmacokinetics

Table 5. Summary of Clinical Pharmacology and Pharmacokinetics

Characteristic	Drug Information
Pharmacologic Activity	
Established pharmacologic class (EPC)	Complement C5 inhibitor
Mechanism of action	Crovalimab is a monoclonal antibody that binds with high affinity to complement protein 5 (C5), inhibiting its cleavage into C5a and C5b, preventing the formation of the terminal complement complex C5b-9. In patients with paroxysmal nocturnal hemoglobinuria (PNH), crovalimab inhibits terminal complement-mediated intravascular hemolysis (IVH).
Active moieties	Crovalimab
QT prolongation	As crovalimab is a monoclonal antibody, it has a low likelihood of direct ion channel interactions and QT prolongation.
General Information	
Bioanalysis	Crovalimab concentrations in serum samples were determined using a validated enzyme linked immunosorbent assay (ELISA) with a lower limit of quantification of 50 ng/mL assay (Refer to Appendix 14.3).
Healthy subjects versus patients	Not compared as the dosing regimens were different between healthy subjects and patients. The population pharmacokinetic (PK) analysis did not include disease status for covariate screening.
Drug exposure at steady state following the therapeutic dosing regimen (or single dose, if more relevant for the drug)	**Table 6. The Exposure of Crovalimab at Steady State** **Body Weight** / **N** / **AUC_{ss} [mcg×days/mL]** / **$C_{max,ss}$ [mcg/mL]** / **$C_{trough,ss}$ [mcg/mL]** **≥40 kg to <100 kg** / 204 / 7788±2250 / 303±86 / 238±72 **≥100 kg** / 6 / 6365±1910 / 246±70 / 195±63 Source: Generated by the FDA review team. Note: Data expressed as mean ± SD. Abbreviations: AUC_{ss}, area under the concentration-time curve at steady state; $C_{max,ss}$, maximum plasma concentration at steady state; $C_{trough,ss}$, plasma concentration reached by drug immediately before administration of the next dose at steady state; N, total number of subjects; SD, standard deviation

Characteristic	Drug Information
Range of effective dose(s) or exposure	For patients with body weight ≥40 kg to <100 kg, the dosing regimen consists of one loading dose (1000 mg) administered by intravenous (IV) infusion (on Day 1), followed by four additional weekly loading doses administered by subcutaneous (SC) injection at 340 mg (on Days 2, 8, 15, and 22). The maintenance dose (680 mg) starts on Day 29 and is then administered every 4 weeks by SC injection. For patients with body weight ≥100 kg, the IV loading dose is 1500 mg on Day 1, followed by four additional weekly loading doses administered by SC injection at 340 mg (on Days 2, 8, 15, and 22). The maintenance dose (1020 mg) starts on Day 29 and is then administered every 4 weeks by SC injection. The proposed dosing regimen is to ensure that the trough concentration of crovalimab is above 100 µg/mL to exert its complete terminal complement activity inhibition as measured by both CH50 and free-C5 levels.
Maximally tolerated dose or exposure	The maximally tolerated dosing regimen consists of one loading dose (1500 mg) administered by IV infusion (on Day 1), followed by four additional weekly loading doses administered by SC injection at 340 mg (on Days 2, 8, 15, and 22). The maintenance dose (1020 mg) starts on Day 29 and is then administered every 4 weeks by SC injection. This dosing regimen was applied in the pivotal trial and is the recommended dosing regimen for patients with body weight ≥100 kg.
Dose proportionality	Crovalimab exhibits dose proportional pharmacokinetics over the range from 75 to 1500 mg when administered as single IV doses and from 680 to 1020 mg when administered as SC injections once every four weeks.
Accumulation	There is no meaningful accumulation of crovalimab with the proposed dosing regimen in patients with PNH. Considering the higher first IV loading dose and more frequent dosing for the following 4 SC loading doses, the exposure in the first 28 days is expected to be larger than the 28-day cycle at steady state.
Time to achieve steady-state	Steady-state serum crovalimab concentrations were achieved approximately 12 weeks following the first dose.
Bridge between to-be-marketed and clinical trial/study formulations	The formulation used in the pivotal trial is the same as the to-be-marketed formulation. No pharmacokinetic bridge is needed.
Absorption	
Bioavailability	The bioavailability is 83% following SC administration.
Food effect (fed/fasted)	Not applicable.
Geometric least square mean and 90% CI	Not applicable.

Characteristic	Drug Information
Distribution	
Volume of distribution	The geometric mean central and peripheral volume of distribution is 3.23 L [90% CI: 3.16, 3.29] and 2.32 L [90% CI: 2.02, 2.67], respectively.
Plasma protein binding	Not applicable.
Drug as substrate of transporters	Not applicable.
Elimination	
Mass balance results	Not applicable.
Clearance	In PNH treatment-naïve patients, the geometric mean clearance is 0.0791 L/day [90% CI: 0.0678, 0.0872]. In patients switching from other C5 inhibitor therapies, crovalimab clearance is enhanced due to the presence of drug-target-drug complexes (DTDCs), which is higher initially and decreases over time.
Half-life	The estimated geometric mean terminal half-life is 53.1 days [90% CI: 47.7, 58.6].
Metabolic pathway(s)	Crovalimab is expected to be catabolized by lysosomal proteolysis into small peptides and amino acids.
Primary excretion pathways (% dose)	Primarily via lysosomal proteolysis.
Intrinsic Factors and Specific Populations	
Body weight	Body weight is negatively associated with steady state PK exposures of crovalimab. The proposed dosing regimen for patients with body weight ≥100 kg is higher by 50% for the first loading dose (Day 1) and maintenance doses (Day 29 onwards).
Age	After inclusion of body weight, population pharmacokinetic analyses in subjects with PNH showed that age (13-85 years of age) did not meaningfully influence the pharmacokinetics of crovalimab.
Renal impairment	No clinically significant differences in the pharmacokinetics of crovalimab were observed based on renal impairment (mild, moderate, and severe).
Hepatic impairment	No clinically significant differences in the pharmacokinetics of crovalimab were observed based on mild hepatic impairment. Crovalimab has not been studied in patients with moderate or severe hepatic impairment.
Drug Interaction Liability (Drug as Perpetrator)	
Inhibition/induction of metabolism	Not applicable.
Inhibition/induction of transporter systems	Not applicable.

Characteristic	Drug Information
Immunogenicity (if Applicable)	
Bioanalysis	Samples were first tested in the screening assay for detection of antidrug antibody (ADA) responses to crovalimab. Samples that screened positive were further analyzed by competitive binding with crovalimab to determine if the detected positive response is specific to crovalimab. The confirmed ADA-positive samples were further characterized for their neutralizing activity. However, there are issues identified with the neutralizing antibody assay. Thus, the results of neutralizing antibodies are not reviewed for this submission. There will be a postmarketing commitment to further optimize and validate an assay for neutralizing antibodies. Refer to Section 14.4 for more details.
Incidence	In the COMMODORE-2 study, 30.0% (42/140) of treatment-naïve subjects who received crovalimab and 34.3% (23/67) of subjects who switched from treatment with another C5 inhibitor to crovalimab (switch subjects) tested positive for anti-crovalimab antibodies following 24 weeks of treatment. Across Studies COMMODORE-1, COMMODORE-2, and COMMODORE-3, the incidence of treatment-emergent ADAs was 31.4% (60/191) and 23.4% (43/184) in treatment-naïve subjects and subjects who switched from treatment with another C5 inhibitor to crovalimab, respectively.
Clinical impact	The total clearance of crovalimab increased by 25% in ADA-positive subjects with medium/high titers (≥104) in comparison to the clearance in subjects without ADA or with low ADA titers (<104). Approximately 3% (11/375) of ADA-positive subjects had a loss of pharmacological activity (based on CH50 or free C5) coinciding with decreased crovalimab exposure, with variable impact on clinical response, including loss of efficacy manifesting as a loss of hemolysis control.

Source: Generated by the FDA review team, following review of the Applicant's submitted data.
Abbreviations: ADA, antidrug antibody; C5, complement compound 5; CH50, 50% Haemolytic Complement Activity of Serum; CI, confidence interval; DTDC, drug target drug complex; ELISA, enzyme linked immunosorbent assay; EPC, established pharmacologic class; IV, intravenous; IVH, intravascular hemolysis; N, total number of subjects; PK, pharmacokinetic; PNH, paroxysmal nocturnal hemoglobinuria; SC, subcutaneous; Tmax, time to peak drug concentration

6. Efficacy (Evaluation of Benefit)

6.1. Assessment of Dose and Potential Effectiveness

Recommended Dosing Regimen

The recommended dosage for crovalimab in adult and adolescent patients with PNH is shown in Table 7. Modification of the maintenance dose is required if the patient's body weight (BW) changes to become consistently greater than or equal to 100 kg or lower than 100 kg and ≥40 kg during the course of therapy.

Table 7. Crovalimab Dosing Regimen Based on Body Weight

	Body Weight	
Dosing Regimen	**40 kg to <100 kg**	**100 kg**
Loading Dose		
Day 1	1,000 mg (IV)	1,500 mg (IV)
Day 2, 8, 15, 22	340 mg (SC)	340 mg (SC)
Maintenance Dose		
Day 29 and Q4W thereafter	680 mg (SC)	1,020 mg (SC)

Source: The proposed drug label for crovalimab.
Abbreviations: IV, intravenous; SC, subcutaneous; Q4W, every 4 weeks

Selection of Dosing Regimen for the Phase 3 Trials

Identifying a Target Crovalimab Trough Concentration

One dose-finding Phase 1/2 study, COMPOSER (BP39144) was conducted to identify the recommended dosage of crovalimab for the pivotal trials. This study included four parts. In Part 1, healthy volunteers (HVs) received a single-ascending dose of crovalimab (75 mg IV, 125 mg IV, or 1000 mg SC) or placebo. In Part 2, treatment-naïve subjects received single-ascending IV doses of crovalimab (375 mg, 500 mg, or 1000 mg), followed by once weekly 170 mg SC injections. The pharmacokinetics (PK), PD, immunogenicity, efficacy, and safety data were assessed. Early evaluation of the PK/PD relationship showed that crovalimab induced a concentration-dependent inhibition of terminal complement activity, assessed using the PD markers CH50 and free C5. The data showed that crovalimab concentrations above approximately 100 μg/mL resulted in complete inhibition of the terminal complement activity as indicated by low CH50 values (close or below the lower limit of quantification [10 U/mL]).

Evaluating the Impact of DTDCs on Crovalimab Exposure

In Part 3, a variety of dosing regimens, including a single IV loading dose of 1000 mg crovalimab, followed by once weekly (170 mg), Q2W (340 mg), or Q4W (680 mg) SC injections, for a total treatment duration of 20 weeks, was evaluated in subjects who switched from eculizumab. The aim of Part 3 was to select the dosing regimen that was able to maintain the target crovalimab concentration (100 μg/mL) for complete inhibition of terminal complement activity, while avoiding the formation of DTDCs. Crovalimab and other C5 inhibitors (eculizumab or ravulizumab) bind different epitopes on C5; such that, complexes comprised of

the antibodies bridged by C5 may form when both are present in the circulation. Such DTDCs were observed in subjects switching from eculizumab or ravulizumab in clinical studies. In subjects switching from eculizumab, mean DTDC profiles over time showed that large DTDCs (Fractions 1 to 4, which corresponds to DTDCs having a molecular weight above 670 kDa, and which, are larger than the biggest Ab1-Ag complex) were cleared within 8 weeks. In subjects switching from eculizumab high-dose (off-label dose), the DTDC profiles (sum of Fractions 1 to 4) over time were similar to the ones switching from eculizumab label-dose. In subjects switching from ravulizumab, Fractions 1 to 4 persisted for a longer duration (approximately 24 weeks) in comparison to subjects switching from eculizumab, which may be explained by the longer half-life of ravulizumab in comparison to eculizumab. Formation of DTDCs may transiently enhance crovalimab CL, resulting in lower drug exposures that may potentially impair the pharmacological effect of crovalimab. DTDCs can also lead to type III hypersensitivity ARs. To address the transient increase in crovalimab CL due to DTDCs, the Applicant introduced a loading dose period, which resulted in a higher concentration of crovalimab and displaced the equilibrium between crovalimab, eculizumab, and C5. Based on the data, to address the impact of DTDCs on crovalimab CL, the Applicant selected a single IV loading dose of 1000 mg crovalimab, followed by a 340 mg SC dose on Days 2, 8, 15, and 22, then 680 mg SC Q4W from Day 29 onwards for further evaluation in Part 4.

Optimizing the Dosing Regimen Based on Body Weight

In Part 4, BW was considered in dosing regimen optimization. BW was identified as a significant covariate for the exposure and dosing of crovalimab. To address the impact of BW on crovalimab exposure, a tiered weight dosing was implemented. Subjects in Arm 4a (treatment-naïve subjects) or Arm 4b (switch subjects from eculizumab) either received 680 mg SC Q4W (BW ≥40 kg to <100 kg) or 1020 mg SC Q4W (BW ≥100 kg) from Day 29 onwards. Data showed that crovalimab concentrations above 100 μg/mL were achieved at the end of the IV infusion and remained stable in both the primary treatment period (from baseline to Week 20) and throughout the open-label extension (OLE) period in both treatment-naïve and switch subjects. The selected dosing regimen also led to rapid, complete, and sustained complement inhibition:

- In treatment-naïve subjects, CH50 levels were reduced from a mean baseline level of approximately 60 U/mL to very low levels close to or below the lower limit of quantification (i.e., <10 U/mL), achieved immediately after the end of infusion and maintained at low levels throughout the treatment period.
- In switch subjects, CH50 levels were maintained at low levels (close to or below the lower limit of quantification) throughout the treatment period.
- Free C5 concentrations were reduced to very low levels (<0.001 g/L) from Week 2 (first post-dose PD sample) of crovalimab treatment and were sustained throughout the treatment period demonstrating complete inhibition of terminal complement activity. Based on these results, the Applicant carried forward the dosing regimen applied in Part 4 with a minor change – the single IV loading doses are 1000 mg and 1500 mg for patients with BW ≥40 kg to <100 kg and ≥100 kg, respectively. No major changes were made in the composition of formulations used between Phase 1/2 and pivotal trials.

Evaluation of the Proposed Dosing Regimen

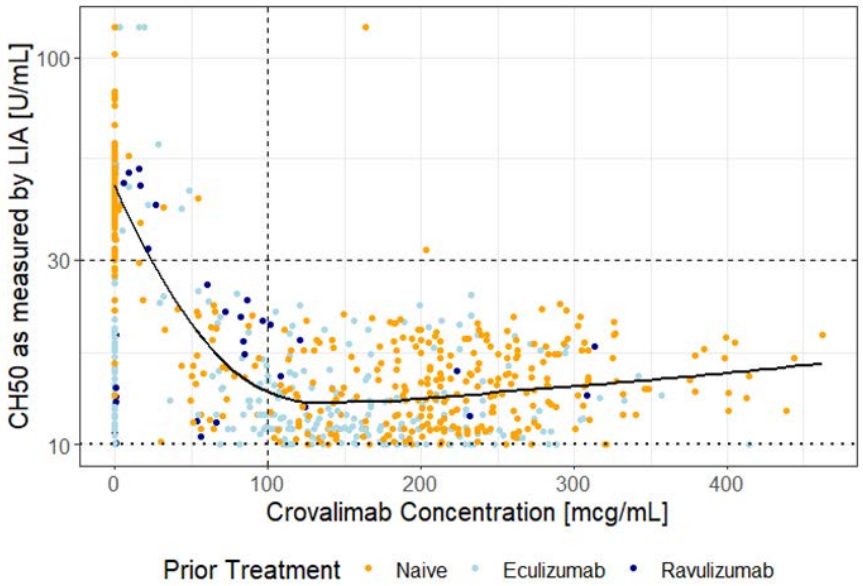
The Applicant's proposed dosage of crovalimab was evaluated in the pivotal Phase 3, randomized, double-blind, active-controlled trial, COMMODORE-2 (BO42162).

The study was divided into two parts: randomized Arms A and B comparing crovalimab (Arm A) to eculizumab (Arm B), and a nonrandomized Arm C, assessing crovalimab in pediatric patients (<18 years old, with BW ≥40 kg). In the randomized crovalimab arm (Arm A), 94.8% (128 out of 135) of subjects had trough crovalimab exposures above 100 μg/mL throughout the treatment duration. Five subjects had partial loss of exposure (defined as at least two consecutive crovalimab concentrations ≥10 and <100 μg/mL), and 2 subjects had complete loss of exposure (defined as <10 μg/mL). In Arm B, 91.2% (62 out of 68) of subjects who switched to crovalimab had an exposure above 100 μg/mL throughout the treatment duration. A total of 6 subjects had partial (n=3) or complete loss of exposure (n=3). In Arm C, serum concentrations of crovalimab were above 100 μg/mL in 6 out of 6 pediatric subjects.

After treatment initiation, CH50 was reduced to low levels of activity, with most observations ranging from 10 to 30 U/mL in all 3 arms from Week 2 of treatment (first postdose PD sample), indicating complete inhibition of the terminal complement activity. Complement activity inhibition was generally sustained throughout the treatment period. Free C5 concentrations in both treatment-naïve (Arm A and Arm C) and Arm B switch subjects with PNH, were decreased from baseline levels (ranging from 0.00 to 1.11 g/L in arm A, from 0.00 to 0.21 g/L in Arm B switch, and from 0.15 to 0.40 g/L in Arm C) to very low levels (<0.0001 g/L) from Week 2 of crovalimab treatment (first post-dose PD sample), providing evidence of complete inhibition of terminal complement activity early in the treatment course. The low levels of free C5 (<0.0001 g/L) were sustained throughout the assessment period in most subjects. Refer to clinical and statistical reviews in Section 6.2 for interpretation of primary efficacy endpoint results.

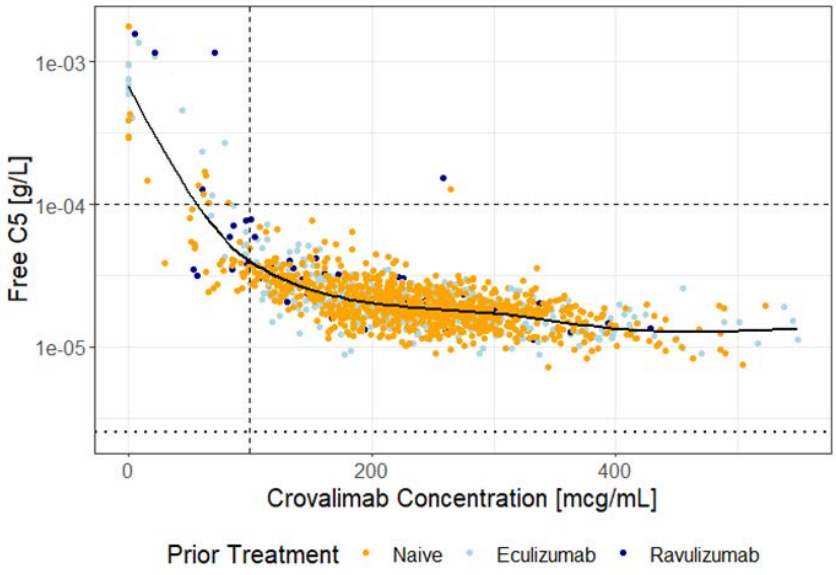
The population PK simulations showed that 92.8% of the treatment-naïve patients and 91.4% of the switch patients were expected to have crovalimab concentrations above the threshold of 100 μg/mL over the entire time course of crovalimab treatment. Observed exposure-response (E-R) analyses suggested saturated responses for terminal complement activity and normalized LDH with plasma crovalimab concentrations above 100 μg/mL, which was consistent in both treatment-naïve and prior-treated subjects with PNH (Figure 3, Figure 4, and Figure 5). Logistic regression was performed to evaluate the correlation between the population PK estimated PK exposure metrics and the safety outcomes, including serious adverse events (SAEs), adverse events of special interest, Grade 3+ adverse events (AEs), and infection. None of the relationships were found to be statistically significant.

Figure 3. Time-Matched CH50 Versus Crovalimab Plasma Concentration at Steady State[a]



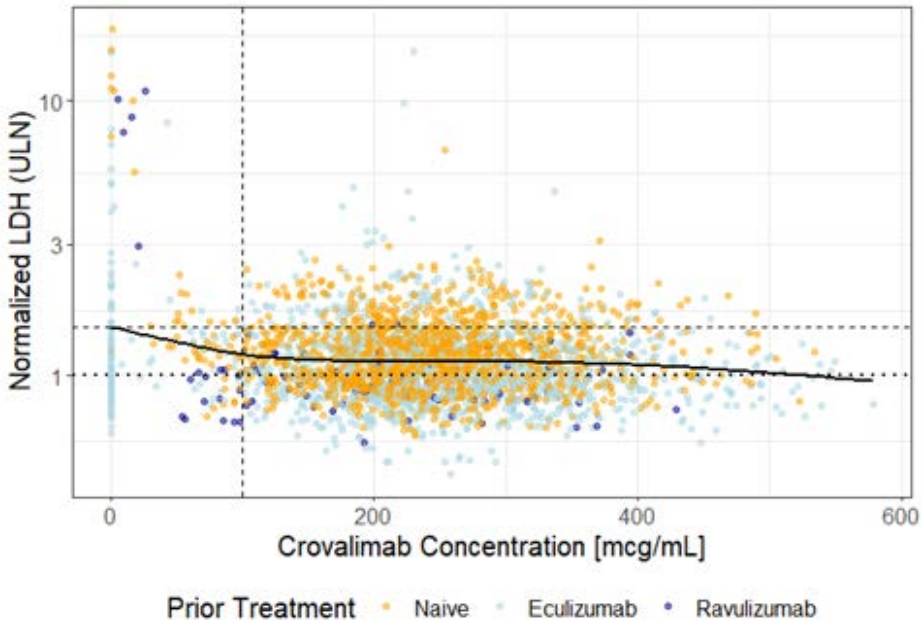
Source: Reviewer analysis.
[a] Data from COMPOSER, COMMODORE-1, COMMODORE-2, and COMMODORE-3
Note: Vertical dashed line: 100 mcg/mL
Note: Horizontal dotted line: 10 U/mL, lower limit of quantification
Note: Horizontal dashed line: 30 U'mL, threshold of complete terminal complements activity inhibition
Note: Solid black line: loess regression
Abbreviations: CH50, 50% Hemolytic Complement Activity of Serum; LIA, liposome immunoassay

Figure 4. Time-Matched Free C5 Versus Crovalimab Plasma Concentration at Steady State in Subjects Included in Phase 3 Trials[a]



Source: Reviewer analysis.
[a] COMMODORE-1, COMMODORE-2, and COMMODORE-3
Note: Vertical dashed line: 100 mcg/mL
Note: Horizontal dotted line: 2.5e-6 g/L, lower limit of quantification
Note: Horizontal dashed line: 1e-4 g/L, threshold of complete terminal completment activity inhibition
Note: Solid black line: loess regression
Abbreviations: C5, complement component 5

Figure 5. Time-matched LDH Versus Crovalimab Plasma Concentration at Steady State[a]



Source: Reviewer analysis.
[a] Data from COMPOSER, COMMODORE-1, COMMODORE-2, and COMMODORE-3
Note: Data for the first 12 weeks excluded
Note: Vertical dashed line: 100 mcg/mL
Note: Horizontal dotted and dashed line: 1X and 1.5X ULN
Note: Solid black line: loess regression
Abbreviations: LDH, lactate dehydrogenase; ULN, upper limit of normal

Appropriateness of 100 kg as Body Weight Cut-Off for Dose Increase

The steady state PK exposures of crovalimab are predicted to be negatively associated with BW, therefore, the Applicant proposed 50% higher first loading dose and maintenance dose (Day 29 onwards) for patients with BW ≥100 kg. The review team assessed the appropriateness of 100 kg as the BW cut-off to receive a higher dosing regimen. In the population PK analysis, a larger fraction (approximately 10%) of patients with BW 90 to 100 kg was estimated to have steady-state trough crovalimab concentration below 100 μg/mL compared to those in other BW groups with the proposed dosing cut off at 100 kg. However, review of the E-R relationship for complement activity and LDH (Figure 3, Figure 4, and Figure 5) showed that crovalimab concentrations between 50 to 100 μg/mL also showed suppression of complement activity and LDH below the threshold, suggesting that a modest decrease in trough crovalimab concentration below 100 μg /mL would not be clinically meaningful. Further, the fractions of patients with steady state trough concentration below 50 μg/mL were comparable between patients with BW 90 to <100 kg (3.96%) and ≥100 kg (3.51%). As a result, a relatively larger fraction of patients in the BW group 80 to 100 kg with steady-state trough concentration <100 μg/mL was not considered clinically relevant. Therefore, the proposed BW cut-off of 100 kg is reasonable to receive a higher crovalimab dose.

6.2. Clinical Studies/Trials Intended to Demonstrate Efficacy

The adequate and well-controlled trial that evaluated the efficacy is COMMODORE-2 (Study BO42162) entitled, "A Phase 3, Randomized, Open-Label, Active-Controlled, Multicenter Study Evaluating the Efficacy and Safety of Crovalimab Versus Eculizumab in Patients with PNH Not Previously Treated with Complement Inhibitors."

Confirmatory evidence of effectiveness included PD and mechanistic data from studies COMMODORE-1, COMMODORE-3, and COMPOSER. See Section 15 and 16, for study design and results.

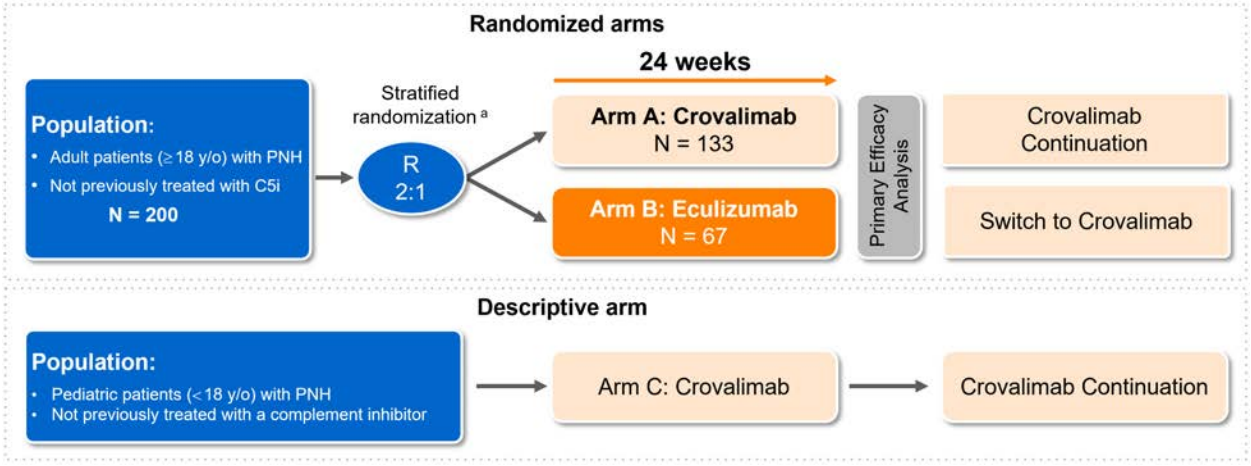
6.2.1. COMMODORE-2 (Study BO42162)

6.2.1.1. Design, COMMODORE-2 (Study BO42162)

COMMODORE-2 is a Phase 3, randomized, open-label, active-controlled, noninferiority, multicenter trial 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 is comprised of two parts: (1) randomized arms (Arms A and B) consisting of adult patients (≥18 years of age) and (2) a descriptive nonrandomized arm (Arm C) consisting of pediatric patients (<18 years old, BW ≥40 kg). For patients in Arms A and B, randomization was stratified by LDH level (≥2 to ≤4×upper limit of normal (ULN) or >4×ULN) and by the number of packed red blood cells (pRBCs) transfused within 6 months prior to randomization (0 units, >0 to ≤6 units or >6 units). Patients in all three arms were allowed to be transfused prior to randomization to reach a hemoglobin level above the specified threshold to be eligible for the study (i.e., hemoglobin >7 g/dL or hemoglobin >9 g/dL if with concurrent signs and symptoms of anemia).

For Arms A and B, a total of approximately 200 adult patients (≥18 years of age) were to be randomized to either crovalimab or eculizumab in a 2:1 ratio. Enrollment of patients without a history of transfusion in the past year was to be capped at 20%.

Figure 6. Study Design, COMMODORE-2



Source: COMMODORE-2 protocol.
Abbreviations: N, total number of subjects; PNH, paroxysmal nocturnal hemoglobinuria

For subjects who were randomized to crovalimab (and subjects in Arm C), an initial IV loading dose was administered on Week 1, Day 1, followed by four weekly crovalimab SC doses on Week 1, Day 2, then on Weeks 2, 3, and 4. Maintenance dosing began at Week 5 and continued Q4W thereafter, for a total of 24 weeks of the primary treatment period, followed by an optional treatment extension period. Crovalimab could be administered within ±2 days of the scheduled dose, except for the Week 1 Day 1 and Week 1 Day 2 doses, which were to be administered on the scheduled day. Crovalimab was administered according to a weight-based tiered dosing schedule (see Table 8). Due to risks of hypersensitivity and infusion-related reactions, the first IV infusion and the first five SC injections of crovalimab were administered in a clinical environment with resuscitation equipment available for immediate use.

Table 8. Weight-Based Tiered Crovalimab Dosing Schedule

Body Weight	Crovalimab Loading Doses (Weeks 1–4)	Crovalimab Maintenance Doses (Week 5 and Q4W thereafter)
≥40 kg to <100 kg	Week 1 Day 1: 1000 mg IV Day 2: 340 mg SC Weeks 2, 3 and 4 340 mg SC QW	680 mg SC
≥100 kg	Week 1 Day 1: 1500 mg IV Day 2: 340 mg SC Weeks 2, 3 and 4 340 mg SC QW	1020 mg SC

Source: COMMODORE-2 protocol.
Note: Dose modification is only required if the subject's body weight changes by 10% or more to exceed or become equal to 100 kg or to fall below 100 kg during the course of therapy.
Abbreviations: IV, intravenous; Q4W, every 4 weeks; QW, every week; SC, subcutaneous

For subjects who were randomized to eculizumab, dosing and management of specific AEs were per the local prescribing information (PI) (or pharmacy manual in countries without access to commercial eculizumab). Eculizumab was to be administered as induction doses of 600 mg on

Days 1, 8, 15, and 22, followed by maintenance doses of 900 mg on Day 29 and Q2W thereafter. This dosing matches the recommended dosage in the U.S. PI. Dose modification of eculizumab was not permitted during the study. After completing 24 weeks of treatment, subjects were allowed to switch to crovalimab during the extension period. The first crovalimab dose was administered at the visit when the next scheduled administration of eculizumab would have occurred (i.e., Week 25 visit). Subjects who switched from eculizumab followed the same crovalimab dosing and schedule as subjects randomized or assigned to crovalimab, starting with an initial IV loading dose, followed by four weekly SC doses on Weeks 1 to 4 and maintenance doses of Q4W starting on Week 5.

Rescue therapy could be administered to subjects receiving crovalimab only. Rescue dosing of one or more additional IV doses of crovalimab could be administered at the discretion of the investigator, if a subject who received crovalimab experienced signs and symptoms of the underlying PNH, such as BTH, which could have been due to an acute event such as acute illness, trauma, or surgery. The recommended dose administered was crovalimab IV 340 mg (regardless of BW) infused over 30 minutes.

A subject could receive pRBC transfusion when meeting either of the following criteria:

- Hemoglobin value ≤9 g/dL, with signs and symptoms of sufficient severity to warrant a transfusion (e.g., angina, syncope, lightheadedness, confusion, severe or worsening shortness of breath, severe or worsening fatigue, stroke, transient ischemic attack, or new or worsening heart failure).
- Hemoglobin value ≤7 g/dL, regardless of presence of clinical signs or symptoms.

Following the 24-week primary treatment period, subjects could continue or switch to crovalimab treatment for a maximum of 5 years during the extension period. Subsequently, subjects were allowed to continue crovalimab treatment according to the Roche Global Policy on Continued Access to Investigational Medicinal Products.

There was an independent Data Monitoring Committee to review the safety data of the study.

Overall, the study design of COMMODORE-2 was reasonable. An open-label design is acceptable given the vastly different dosing regimens of crovalimab and eculizumab (i.e., different dosing frequency and route of administration). The primary treatment period of 24 weeks is sufficient to determine benefit and is consistent with other approved drugs for PNH. The comparator (eculizumab) is an FDA approved drug for PNH. The Applicant used the U.S.-approved Soliris (eculizumab) at all study sites.

6.2.1.1.1. Objectives and Endpoints, COMMODORE-2 (Study BO42162)

The primary efficacy objective was to evaluate the efficacy of crovalimab compared to eculizumab based on the noninferiority assessment of the following co-primary endpoints:

- Proportion of subjects who achieve TA from baseline through Week 25 (after 24 weeks on treatment). TA was defined as subjects who are pRBC transfusion-free and did not require transfusion per protocol-specified guidelines.
- Proportion of subjects with hemolysis control, measured by LDH ≤1.5×ULN from Week 5 through Week 25 (as measured at the central laboratory).

The secondary efficacy objective was to evaluate the efficacy of crovalimab compared to eculizumab based on the noninferiority assessment of the following endpoints:

- Proportion of subjects with BTH from baseline through Week 25. BTH was defined as at least one new or worsening symptom or sign of IVH (fatigue, hemoglobinuria, abdominal pain, shortness of breath [dyspnea], anemia [hemoglobin <10 g/dL], a major adverse vascular event (MAVE) [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 subjects with stabilization of hemoglobin from baseline through Week 25. Stabilized hemoglobin was defined as avoidance of a ≥2 g/dL decrease in hemoglobin level from baseline, in the absence of transfusion.
- Mean change from baseline to Week 25 in fatigue, as assessed by the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue instrument. However, assessments of patient-reported outcomes such as FACIT-Fatigue are difficult to interpret in an open-label study design.

The superiority of the primary and secondary endpoints was to be evaluated provided that noninferiority was demonstrated.

The primary endpoints of hemolysis control and TA are clinically meaningful in a PNH population that is experiencing hemolysis, one of the signs of PNH. These endpoints have been used to establish benefit for other approved drugs to treat PNH (see Section 3). The study was open-label introducing possible bias given the nature of the trial design however several of the endpoints were objective as they were based on laboratory measures (i.e., LDH and hemoglobin stabilization). Bias may have been introduced when determining the need for RBC transfusions. The Applicant addressed this concern by including guidelines for when a subject should receive a transfusion, which included a hemoglobin <7 g/dL or a hemoglobin level of ≤9 g/dL with signs and/or symptoms to warrant a transfusion. In the protocol, the Applicant describes the signs and symptoms that would warrant a transfusion. In clinical practice, patients are often transfused when symptomatic from anemia. The guidelines for transfusions were reasonable and the risk of bias for the transfusion endpoint is likely minimized. However, patient-reported outcome endpoints such as FACIT-Fatigue can potentially be impacted by the subjects' knowledge of treatment assignment and, therefore, this endpoint is difficult to interpret in an open-label trial. The definition of BTH, as described above is acceptable. While there is no standardized definition for BTH, elevated LDH level is the most commonly used biomarker (Brodsky et al. 2021).

6.2.1.2. Eligibility Criteria, COMMODORE-2 (Study BO42162)

The study enrolled patients (BW ≥40 kg) diagnosed with PNH (confirmed by high sensitivity flow cytometry evaluation of white blood cells with granulocyte or monocyte clone size of ≥10%, within 6 months) who have not been previously treated with a complement-inhibitor. In addition, patients had one or more PNH-related signs or symptoms within 3 months prior to screening (fatigue, hemoglobinuria, abdominal pain, dyspnea, hemoglobin ≤10 g/dL, history of a MAVE (including thrombosis), dysphagia, or erectile dysfunction; or history of pRBC transfusion), and LDH level ≥2×ULN. Vaccinations were required against *Neisseria meningitidis* serotypes A, C, W, and Y (within 3 years), *Haemophilus influenzae* type B and *Streptococcus pneumoniae* according to national vaccination recommendations (e.g., Advisory Committee on Immunization Practices guidelines). Patients enrolled to the randomized arms (Arms A and B) and nonrandomized arm (Arm C) had to be ≥18 years and <18 years of age, respectively.

Key exclusion criteria included hemoglobin value ≤7 g/dL, or hemoglobin value >7 g/dL and ≤9 g/dL with concurrent signs and symptoms of anemia (including angina, syncope, lightheadedness, confusion, severe or worsening shortness of breath, severe or worsening fatigue, stroke, transient ischemic attack, or new or worsening heart failure). Patients were excluded for history of allogeneic bone marrow transplantation, known or suspected immune deficiency (e.g., history of frequent recurrent infections) or hereditary complement deficiency, splenectomy within 6 months, or active systemic bacterial, viral, or fungal infection within 14 days.

Other inclusion/exclusion criteria of the study are presented in Section 15.1.

6.2.1.3. Statistical Analysis Plan, COMMODORE-2 (Study BO42162)

Determination of Sample Size

The sample size estimation for the randomized portion of the study (Arms A and B) was based on the noninferiority assessment of the co-primary endpoints of hemolysis control, as assessed by centrally measured LDH, and the proportion of subjects who would achieve TA during the efficacy period. The final target sample size corresponded to the endpoint that required the larger number of subjects, i.e., TA from baseline to Week 25. Approximately 200 adults were randomly assigned in a 2:1 ratio to receive either crovalimab (N=133) or eculizumab (N=67), to ensure approximately 180 evaluable subjects, assuming a 10% dropout rate. This sample size would provide 80% power to demonstrate the noninferiority of crovalimab to eculizumab with respect to TA, using a NIM of -20%, a proportion of subjects with TA of 66.1% for eculizumab-treated subjects (Lee et al. 2019), and one-sided type 1 error rate of 2.5%.

With regards to hemolysis control, 116 subjects were required in a 2:1 ratio to test the noninferiority of crovalimab versus eculizumab, with a NIM of 0.2 in the odds ratio (OR) scale, 80% power, a proportion of subjects achieving hemolysis control (LDH ≤1.5×ULN) of 86% for eculizumab-treated subjects, and one-sided test at 0.025 Type I error rate. The proportion for eculizumab-treated subjects achieving hemolysis control was estimated using published data from the eculizumab arm in ALXN1210-PNH-301 study (Lee et al. 2019). Under the assumption of LDH being log-normally distributed, the expected proportion below 1.5×ULN was 86%. Assuming a 10% dropout, the total needed sample size would be 128 subjects (85 randomized to

crovalimab and 43 to eculizumab). With 180 evaluable subjects expected in the study, the power for this endpoint would be 94%. Hence, the joint power for both TA and LDH would be 75% if they were uncorrelated. If there were no dropouts and all 200 subjects contributed at least one LDH sample then the power for TA would be 84% and for LDH 96%.

Determination of Noninferiority Margins

Transfusion Avoidance

The NIM for TA was determined based on the published data reported in Study ALXN1210-PNH-301 (also referred to as ALXN 301), comparing eculizumab-treated patients with untreated patients from the global PNH Registry for eculizumab-treated patients. In the study, patients treated with eculizumab showed a benefit over untreated patients, with a difference of approximately 40% (TA proportion of 57.1% and 18.6%, respectively), after adjustment for history of transfusions 12 months prior to enrollment. Hence, with a difference in proportions of -20%, the NIM would preserve at least 50% of the control treatment effect. This NIM was also defined based on operational considerations, given the rarity of PNH.

Hemolysis Control

The NIM for hemolysis control in the OR scale was obtained as $1/OR^{0.5}=0.2$, where OR =24.6 assuming 86% of patients receiving eculizumab would reach LDH ≤1.5×ULN compared to an upper bound of the 95% Cl of the proportion among placebo-treated patients of 20%. The assumed 20% proportion in placebo-treated patients was based on the published data from the placebo arm in the TRIUMPH study (Hillmen et al. 2006) and from information provided in the published ALXN 301 Study (Lee et al. 2019).

During the IND stage, the Agency had concerns on the proposed NIMs for both co-primary endpoints because the NIMs for the two co-primary endpoints were derived based on the point estimate of the treatment effect of eculizumab. Additionally, the NIM for TA was based on the global PNH Registry data owned by another company (i.e., Alexion Pharmaceuticals, Inc.), therefore, it is not possible to determine if the PNH population has similar demographics and baseline characteristics as subjects in COMMODORE-2. The Applicant did not provide justification for the NIMs for the key secondary endpoints in the statistical analysis plan (SAP). However, these concerns were addressed during the review of this BLA. For details, see Section 6.3.1.

Analysis Population

- The Randomized Population consisted of all randomized subjects.
- The Primary Analysis Population consisted of all randomized subjects who received at least one dose of the originally assigned treatment and had at least one valid LDH level assessment by the central laboratory after the first IV infusion.
- The Per Protocol Population consisted of all randomized subjects who fulfilled the following criteria.
  - Received only assigned treatment per randomized schedule.
  - Received all planned doses in full within ±3 days of the scheduled day of administration.

  - Met required hemoglobin level at enrollment, and where applicable followed protocol-specified baseline transfusion guidelines.
  - Had met the following inclusion criteria:
    - LDH ≥2×ULN at screening (as per local assessment).
    - Documented diagnosis of PNH, confirmed by high sensitivity flow cytometry evaluation of white blood cells, with granulocyte or monocyte clone size ≥10%, within 6 months prior to randomization.
    - BW ≥40 kg at screening.
  - Had not met the following exclusion criteria:
    - MAVE in the 6 months prior to Study Day 1.
    - Current or previous treatment with a complement inhibitor.
    - Platelet count <30,000/mm^3 (30×10^9/L) at screening.
    - Absolute neutrophil count <500/μL (0.5×10^9/L) at screening.
    - History of bone marrow transplantation.

- The Safety Population consisted of all randomized subjects who received at least one dose of the study drug.

During the IND stage, the Agency recommended that the randomized population (i.e., intent-to-treat (ITT) population) be used for the primary analysis, because the randomized population can fairly distribute subjects to treatment arms and preserve randomization. The Applicant stated that the ITT population in a noninferiority (NI) study might potentially bias results toward the alternative hypothesis due to study quality issues such as protocol violations and early study discontinuations. The Agency did not object to the Applicant's proposed primary analysis population. However, the Agency suggested that ITT along with the per protocol population be used as sensitivity analyses to ensure the robustness of the final efficacy results.

Analysis of the Co-Primary Efficacy Endpoints

Hemolysis Control

A generalized estimating equation (GEE) model was used to estimate the adjusted log-OR of LDH ≤1.5×ULN due to treatment and taking into account the intra-individual correlation between LDH control statuses across visits. The dependent variable was the binary indicator for hemolysis control. Independent covariates were categorical effects of treatment and visit, visit by treatment interaction, continuous baseline LDH, and number of pRBC units administered within the 6 months prior to randomization. The noninferiority hypothesis between crovalimab relative to eculizumab was tested by comparing the lower bound of the 95% Cl for the OR to the NIM of 0.2.

The primary analysis applied an unstructured (UN) correlation matrix. In the event that convergence was not achieved in the primary analysis using the UN covariance matrix structure, different structures [in this order: Toeplitz, first order autoregressive (AR(1)) and compound symmetry] would be applied.

Any data missing due to an intercurrent event were not imputed for the primary analysis; rather, the GEE model used all observed data to provide estimates for the full 24-week period.

The primary analysis was repeated using:

- ITT population
- Per protocol population

The following imputation approaches were performed to assess robustness of the GEE model:

- Markov chain Monte Carlo assuming missing data were missing at random.
- Pattern mixture models or tipping point analyses to assess if missing data were missing not at random and the impact of missing not at random on inferences.

There were concerns on the proposed GEE model for the co-primary endpoint of hemolysis control considering the strong assumption that data can only be missing completely at random. In the SAP, the Applicant stated that the missing completely at random assumption is reasonable for this disease setting because a missing LDH value that depends on unknown information would be unlikely to occur.

The Applicant provided several sensitivity and supplementary analyses to address the Agency's concern and results are shown in Section 6.2.1.4.3.

Transfusion Avoidance

The percentage of subjects with TA was computed for the two randomized arms. As a conservative approach, subjects who prematurely withdrew from study treatment was assumed to have undergone a transfusion. A difference in the percentage of subjects with TA in the two treatment arms was calculated, along with a 95% Cl for the difference using the stratified Newcombe Cl method (Yan and Su 2010).

The difference between the two treatment arms was computed as a weighted combination of the differences between crovalimab and eculizumab arms within the stratification indicators of transfusion history and baseline LDH categories using Mantel-Haenszel weights (Agresti 2013).

Noninferiority with respect to TA would be concluded if the lower limit of the 95% Cl for the difference between crovalimab and eculizumab for TA was greater than the NIM of -20%.

The primary analysis was repeated using:

- ITT population
- Per protocol population

Subgroup Analyses

Comparative subgroup analyses describing the co-primary endpoints were conducted for the primary analysis population. The specified subgroups were:

- Age: <18, ≥18 - <65, ≥65 years
- Sex: Male, Female
- Region: North America, Central and South America, Europe, Africa and Middle East, Japan, Rest of Asia Pacific
- Eculizumab availability: Yes, No

- Race: Asian, Black or African American, White, Other
- [Stratification factor]: transfusion history of total pRBC units administered in the 6 months prior to randomization: 0, >0 to ≤6, and >6
- [Stratification factor]: LDH value (2 to ≤4×ULN, and >4×ULN)
- Aplastic anemia: Yes, No
- BW (kg): 40 to <60, 60 to <100, ≥100

The Agency recommended that the Applicant should include a subgroup analysis based on North America versus Non-North America, and the Applicant agreed.

Analysis of the Secondary Efficacy Endpoints

Breakthrough Hemolysis

The proportion of subjects with BTH from baseline through Week 25 was analyzed using the same methodology as TA. As a conservative approach, subjects withdrawn before Week 25 were deemed to have experienced BTH in the unobserved period. If the upper limit of the 95% Cl for the difference between crovalimab and eculizumab in the proportion of subjects with BTH was less than the NIM of 20%, then crovalimab would be declared noninferior to eculizumab.

Hemoglobin Stabilization

The proportion of subjects with stabilization of hemoglobin from baseline through Week 25 was analyzed using approaches similar to TA. As a conservative approach, subjects who withdrew early were assumed to not have hemoglobin stabilization. If the lower limit of the 95% Cl for the difference between crovalimab and eculizumab in the proportion of subjects with stabilized hemoglobin was greater than the NIM of -20%, then crovalimab would be declared noninferior to eculizumab.

FACIT-Fatigue

The change from baseline to Week 25 in fatigue, as assessed by the FACIT-Fatigue questionnaire was analyzed using a mixed model for repeated measure assuming normally distributed scores, with adjustment for stratification factors, and baseline FACIT-Fatigue score. An UN covariance matrix was used to model the within-subject errors. In the event that the model did not converge with UN covariance matrix, a more parsimonious structure would be considered in the following order until model convergence was achieved: Toeplitz, AR(1) and compound symmetry.

The NIM was a -5-point score, where higher scores indicated less fatigue, and hence the noninferiority hypothesis was tested comparing the lower limit of the 95% Cl for the difference with a NIM of -5 points (Cella et al. 2002). The summary statistics for score was presented by treatment group for baseline and treatment visits. Noninferiority of crovalimab compared to eculizumab would be declared if the null hypothesis of inferiority was rejected.

There were concerns about the interpretability of the FACIT-Fatigue endpoint given the open-label design. In addition, due to the hierarchical testing order and nonsignificant results of the superiority test of TA, the FACIT-Fatigue results were considered descriptive and exploratory.

For all of the above key secondary endpoints, the Applicant did not provide justification for the NIMs in the SAP. The Agency sent information requests to ask for justification during the BLA review. This issue is discussed further in Section 6.3.1.

Multiplicity Adjustment

If noninferiority was established for the co-primary endpoints, then the secondary endpoints, including superiority testing of primary and secondary endpoints, would be tested using the hierarchical order tabulated in Table 9. The family-wise Type I error rate was controlled at the one-sided 2.5% level.

Table 9. Order of Testing Within the Hierarchical Testing for Multiplicity Control, COMMODORE-2

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

Source: The Applicant's statistical analysis plan.
[C] Co-primary endpoints which will be tested together.
Abbreviations: BTH, Breakthrough Hemolysis; TA, transfusion avoidance; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy-Fatigue

Interim Analyses

No efficacy interim analysis was planned.

6.2.1.4. Results of Analyses, COMMODORE-2 (Study BO42162)

6.2.1.4.1. Data Quality and Integrity, COMMODORE-2 (Study BO42162)

Data were provided electronically in standard data format, with a study data tabulation model and analysis data model (Genentech 2023b). Statistical analysis software programs used to create key efficacy and safety outputs for the study were submitted along with the data. The Applicant also provided clear definition files for datasets and detailed analysis programs to assist the review.

6.2.1.4.2. Subject Disposition, Baseline Demographics and Disease Characteristics, COMMODORE-2 (Study BO42162)

Subject Disposition

In COMMODORE-2, a total of 210 subjects were enrolled. Among the 210 subjects, 204 adult subjects were randomized (crovalimab: 135, eculizumab: 69) and six pediatric subjects were enrolled in the nonrandomized arm. All six subjects in the nonrandomized arm received crovalimab treatment.

Randomized Population

All subjects who were randomized and received at least one dose of the study treatment were included in the safety population. The primary efficacy analysis population consisted of subjects who received at least one dose of study treatment and had at least one centrally processed LDH level assessment after the first IV infusion of study drug. One subject randomized to the crovalimab arm died due to myocardial infarction on Day 2 (which was considered not related to the study drug). No postbaseline LDH assessment was conducted for this subject and therefore, this subject was not included in the primary efficacy analysis population. The primary efficacy analysis population was comprised of 203 subjects (crovalimab: 134, eculizumab: 69).

Most of the subjects (96.6%) in the randomized arms completed the 24 weeks of the primary treatment period and continued in the extension period.

Table 10. Analysis Populations and Subject Disposition, COMMODORE-2, Randomized Population

Analysis Population/Subject Disposition	Crovalimab (Naïve) (N=135)	Eculizumab (Naïve) (N=69)	Total (N=204)
Randomized population	135	69	204
Safety population	135	69	204
Primary efficacy analysis population	134[a]	69	203
Per protocol population	112	59	171
Crovalimab switch population (subjects randomized to eculizumab and switched to crovalimab in the extension period)	0	68	68
Completed primary treatment period (of 24 weeks), n (%)	129 (95.6%)	68 (98.6%)	197 (96.6%)
Discontinued treatment before Week 24, n (%)	6 (4.4%)	1 (1.4%)	7 (3.4%)
Reason for treatment discontinuation, n (%)			
Death	1 (0.7%)[a]	1 (1.4%)[d]	2 (1.0%)
Lost to follow-up	1 (0.7%)	0	1 (0.5%)
Physician decision	2 (1.5%)[b]	0	2 (1.0%)
Subject withdrawal	2 (1.5%)[c]	0	2 (1.0%)
Started crovalimab in the extension treatment period (subjects in the eculizumab arm switched to crovalimab)	129 (95.6%)	68 (98.6%)	197 (96.6%)
Discontinued crovalimab on/after Week 24, n (%)	2 (1.5%)	3 (4.3%)	5 (2.5%)
Reason for treatment discontinuation, n (%)			
Subject withdrawal	2 (1.5%)	2 (2.9%)	4 (2.0%)
Adverse event	0	1 (1.4%)[e]	1 (0.5%)
Ongoing treatment in the extension period, n (%)	127 (94.1%)	65 (94.2%)	192 (94.1%)

Source: ADSL.xpt and CSR.
[a] One subject in the crovalimab arm died due to myocardial infarction on Day 2 (which was considered not related to the study drug). No postbaseline LDH assessment was conducted for this subject. This subject was not included in the primary efficacy analysis population.
[b] Two subjects discontinued from study treatment due to physician decision. One subject discontinued on Day 30 due to high fever after resuming crovalimab treatment at Week 4, following a treatment interruption. The other subject discontinued from study treatment on Day 45 due to progressive worsening of baseline aplastic anemia.
[c] One subject withdrew on Day 151 due to worsening thrombocytopenia in the context of worsening baseline myelodysplastic syndrome. The other subject withdrew from study treatment on Day 176 due to pregnancy.
[d] One subject discontinued study treatment before 24 weeks due to a TEAE of fatal ischemic stroke on Day 71.
[e] One subject discontinued from study treatment on Day 262 due to an AE of demyelinating polyneuropathy.
Abbreviations: AE, adverse event; n, number of subjects in subset; N, total number of subjects; TEAE, treatment-emergent adverse event

In the randomized population, the majority of subjects were enrolled from Asia (66.7%) and Europe (23.5%). No subjects were enrolled from the U.S. China enrolled the greatest proportion of subjects (37.7%). Concerns with a lack of U.S. subjects enrolled in the study is discussed in Section 6.3.2 of this review.

Table 11. Subject Enrollment by Country, COMMODORE-2, Randomized Population

Region	Crovalimab (Naïve) (N=135) n (%)	Eculizumab (Naïve) (N=69) n (%)	Total (N=204) n (%)
Asia	85 (63.0%)	51 (73.9%)	136 (66.7%)
China	50 (37.0%)	27 (39.1%)	77 (37.7%)
Thailand	10 (7.4%)	9 (13.0%)	19 (9.3%)
Korea (South)	8 (5.9%)	6 (8.7%)	14 (6.7%)
Malaysia	5 (3.7%)	2 (2.9%)	7 (3.4%)
The Philippines	4 (3.0%)	4 (5.8%)	8 (3.9%)
Taiwan	3 (2.2%)	0	3 (1.5%)
Japan	2 (1.5%)	3 (4.3%)	5 (2.5%)
Singapore	2 (1.5%)	0	2 (1.0%)
Hong Kong	1 (0.7%)	0	1 (0.5%)
Europe	36 (26.7%)	12 (17.4%)	48 (23.5%)
Spain	10 (7.4%)	1 (1.4%)	11 (5.4%)
Germany	5 (3.7%)	3 (4.3%)	8 (3.9%)
Poland	5 (3.7%)	2 (2.9%)	7 (3.4%)
Great Britain	3 (2.2%)	0	3 (1.5%)
Portugal	3 (2.2%)	2 (2.9%)	5 (2.5%)
France	2 (1.5%)	0	2 (1.0%)
Romania	2 (1.5%)	1 (1.4%)	3 (1.5%)
Ukraine	2 (1.5%)	0	2 (1.0%)
Greece	1 (0.7%)	0	1 (0.5%)
Lithuania	1 (0.7%)	0	1 (0.5%)
The Netherlands	1 (0.7%)	0	1 (0.5%)
Sweden	1 (0.7%)	2 (2.9%)	3 (1.5%)
Turkey	0	1 (1.4%)	1 (0.5%)
Central and South America	12 (8.8%)	2 (2.9%)	14 (6.9%)
Brazil	6 (4.4%)	2 (2.9%)	8 (3.9%)
Argentina	6 (4.4%)	0	6 (2.9%)
North America	2 (1.5%)	4 (5.8%)	6 (2.9%)
Mexico	2 (1.5%)	4 (5.8%)	6 (2.9%)

Source: ADSL.xpt.
Abbreviations: N, total number of subjects; n, number of subjects in subset

Nonrandomized Arm

In the nonrandomized arm, none of the pediatric subjects discontinued study treatment up to the clinical cutoff period. It was reported that all six subjects entered the extension treatment period after completing the primary treatment period. In the nonrandomized arm, five subjects (83.3%) were enrolled from China and 1 subject (16.7%) from Spain.

Baseline Demographics and Disease Characteristics

Randomized Population

In the randomized population, the subject demographics were generally similar between the two arms. Approximately half (54.9%) were males, two-thirds (67.2%) Asian and the median age was 36.5 years (range: 17 to 78). All except two subjects were at least 18 years of age. Two subjects were 17 years of age and were randomized to the eculizumab arm prior to the opening of the separate pediatric-specific nonrandomized arm and switched to the crovalimab arm in the extension period after completing the primary treatment period. One of the two subjects was reported to have turned 18 years of age at the time of switching to crovalimab in the extension period, while the other subject was still 17 years old at the time of switching.

Table 12. Baseline Demographics, COMMODORE-2, Randomized Population

Demographic	Crovalimab (Naïve) (N=135)	Eculizumab (Naïve) (N=69)	Total (N=204)
Gender, n (%)			
Male	77 (57.0%)	35 (50.7%)	112 (54.9%)
Female	58 (43.0%)	34 (49.3%)	92 (45.1%)
Age (yr) at first administration of study drug			
Mean (SD)	40.5 (15.2)	41.9 (16.0)	41 (15.5)
Median	36	38	36.5
Range	18-76	17-78	17-78
<18 years, n (%)	0	2 (2.9%)	2 (1.0%)
8 to 64 years, n (%)	122 (90.4%)	58 (84.1%)	180 (88.2%)
≥65 years, n (%)	13 (9.6%)	9 (13.0%)	22 (10.8%)
≥75, n (%)	2 (1.5%)	2 (2.9%)	4 (2.0%)
Race, n (%)			
Asian	86 (63.7%)	51 (73.9%)	137 (67.2%)
White	45 (33.3%)	16 (23.2%)	61 (29.9%)
Black or African American	3 (2.2%)	1 (1.4%)	4 (2.0%)
Unknown	1 (0.7%)	1 (1.4%)	2 (1.0%)
Ethnicity, n (%)			
Hispanic or Latino	18 (13.3%)	6 (8.7%)	24 (11.8%)
Not Hispanic or Latino	114 (84.4%)	61 (88.4%)	175 (85.8%)
Not reported	3 (2.2%)	2 (2.9%)	5 (2.5%)
Weight (kg)			
Median	66	62	65
Range	12-140	47-122	12-140
Weight category (kg)			
<40 kg	0	0	0
≥40 kg to <100 kg	131 (97.0%)	66 (95.7%)	197 (96.6%)
≥100 kg	4 (3.0%)	3 (4.3%)	7 (3.4%)

Source: ADSL.xpt, ADVS.xpt.
Abbreviations: n, number of subjects in subset; N, total number of subjects; SD, standard deviation; yr, year

Baseline disease characteristics were also similar between the two arms. The median hemoglobin was 8.5 g/dL (range: 5.8 to 13.5) and median LDH 1691 U/L (range: 458 to 4762), with most subjects (83.7%) having LDH >4×ULN. Three quarters of subjects (76.1%) had a history of pRBC transfusion in the last 12 months, and the median units of pRBC transfused was 3.5 units (range: 0 to 43.5). Prior history of aplastic anemia and myelodysplastic syndrome (MDS) was

reported in 38.7% and 5.9% of subjects, respectively. Median clone size was higher in the eculizumab arm for monocytes, granulocytes and erythrocytes. In the crovalimab and eculizumab arms, the median PNH clone size was 90.9% and 95.1% for monocytes, 91.4% and 93.6% for granulocytes and 25.3% and 44.6% for erythrocytes, respectively. A larger PNH clone size at baseline is associated with greater disease burden, higher risk of thrombotic events and MAVEs (Dingli et al. 2023). However, a similar proportion of subjects in the two arms (crovalimab: 15.6%, eculizumab: 14.5%) had major vascular events at baseline.

At baseline, most of the subjects (91.2%) were receiving at least one concomitant medication that included systemic corticosteroids (34.8%), antithrombotic agents (25.5%) and immunosuppressive therapies (17.6%).

The majority of subjects were immunized with meningococcal-ACWY (crovalimab: 96.3%; eculizumab: 98.6%) and received *Streptococcus pneumoniae* vaccines (crovalimab: 78.5%, eculizumab: 72.5%). A smaller proportion of subjects received *Haemophilus influenzae* type B vaccination (crovalimab: 34.1%, eculizumab: 20.3%).

Table 13. Baseline Disease Characteristics, COMMODORE-2, Randomized Population

Baseline Disease Characteristic	Crovalimab (Naïve) (N=135)	Eculizumab (Naïve) (N=69)	Total (N=204)
Age (yr) at PNH diagnosis			
Mean (SD)	35.8 (15.5)	37.4 (16.4)	36.4 (15.8)
Median	31.0	32.1	31.5
Range	11.5-74.7	11.2-76.8	11.2-76.8
At least one PNH-related sign/symptom within 3 months, n (%)			
Yes	135 (100%)	69 (100%)	204 (100%)
Hemoglobin (g/dL)			
Median	8.5	8.5	8.5
Range	6.3-13.5	5.8-12.9	5.8-13.5
Haptoglobin (g/L)			
n	85	42	127
Median	0.05	0.05	0.05
Range	0.05-0.05	0.05-0.05	0.05-0.05
LDH (U/L)			
n	134	69	203
Median	1638	1811	1691
Range	458-3804	476-4762	458-4762
LDH (x ULN)			
n	134	69	203
Median	7.0	7.7	7.2
Range	2.0-16.3	2.0-20.3	2.0-20.3
LDH category			
n	134	69	203
<2×ULN	1 (0.7%)	0	1 (0.5%)
≥2 to ≤4×ULN	22 (16.4%)	10 (14.5%)	32 (15.8%)
>4×ULN	111 (82.8%)	59 (85.5%)	170 (83.7%)
History of pRBC transfusion within 12 months, n (%)			
n	133	68	201
Yes	103 (77.4%)	50 (73.5%)	153 (76.1%)

Baseline Disease Characteristic	Crovalimab (Naïve) (N=135)	Eculizumab (Naïve) (N=69)	Total (N=204)
Number of units of pRBC transfused			
n	132	67	199
Median	3.8	3.0	3.5
Range	0-43.5	0-41.0	0-43.5
Number of units of pRBC transfused (category), n (%)			
n	132	67	199
0	30 (22.7%)	18 (26.9%)	24.1%)
>0 to <4	36 (27.3%)	16 (23.9%)	52 (26.1%)
≥4 to <14	47 (35.6%)	22 (32.8%)	69 (34.7%)
≥14	19 (14.4%)	11 (16.4%)	30 (15.1%)
History of aplastic anemia, n (%)			
Yes	53 (39.3%)	26 (37.7%)	79 (38.7%)
History of myelodysplastic syndrome, n (%)			
Yes	6 (4.4%)	6 (8.7%)	12 (5.9%)
History of renal impairment, n (%)			
Yes	11 (8.1%)	6 (8.7%)	17 (8.3%)
History of major vascular events, n (%)			
Yes	21 (15.6%)	10 (14.5%)	31 (15.2%)
Medications, n (%)			
Prior or concomitant medication	134 (99.3%)	68 (98.6%)	202 (99.0%)
At baseline	125 (92.6%)	61 (88.4%)	186 (91.2%)
Systemic corticosteroids	46 (34.1%)	25 (36.2%)	71 (34.8%)
Anticoagulant	35 (25.9%)	17 (24.6%)	52 (25.5%)
Immunosuppressive therapy	23 (17.0%)	13 (18.8%)	36 (17.6%)

Source: ADSL.xpt, ADCM.xpt, ADLB.xpt, ADKLD.xpt.
Abbreviations: LDH, lactic dehydrogenase; N, total number of subjects; n, number of subjects in subset; PNH, paroxysmal nocturnal hemoglobinuria; pRBC, packed red blood cell; SD, standard deviation; ULN, upper limit of normal; yr, year;

Nonrandomized Arm

In the pediatric nonrandomized arm, the median age was 16.5 years (range: 13 to 17), 4 subjects (66.7%) were males, and 5 subjects were Asian (83.3%). The median weight was 67.8 kg (range: 50 to 98.5). The median hemoglobin was 8.1 g/dL (range: 6.6 to 9.6), median normalized LDH was 6.4×ULN (range: 3.5 to 26.6). A total of 4 subjects (66.7%) had a prior history of pRBC transfusion. The median units of pRBC transfused was 1.25 units (range: 0 to 40.5). A total of 3 subjects (50%) had a history of aplastic anemia. All six pediatric subjects were immunized with meningococcal-ACWY and *Streptococcus pneumoniae* vaccines prior to study drug administration. One subject also received meningococcal B and *Haemophilus influenzae* type B vaccines.

6.2.1.4.3. Analysis of the Primary and Secondary Endpoints, COMMODORE-2 (Study BO42162)

Efficacy Results of Primary Endpoints

The primary analysis results of the co-primary endpoints of hemolysis control and TA are shown in Table 14.

Note that for the hemolysis control endpoint, the GEE model used the AR(1) covariance matrix because the UN and Toeplitz covariance matrices, which had a higher priority, did not converge.

Table 14. Analysis Results for the Co-Primary Endpoints, COMMODORE-2, Primary Analysis Population

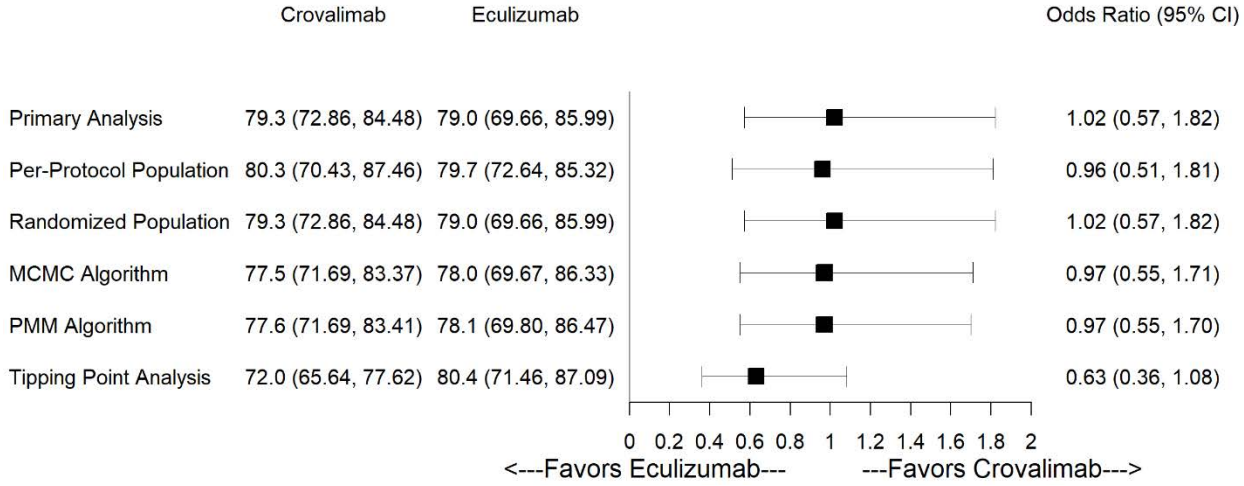
Endpoints	Measures	Crovalimab N=134	Eculizumab N=69
Mean proportion of subjects with hemolysis control from Week 5 through Week 25	Mean Proportion of Subjects Achieving Controlled Hemolysis (95% CI)	79.3% (72.9, 84.5)	79.0% (69.7, 86.0)
	Odds Ratio (95% CI)	1.02 (0.57, 1.82)	
Proportion of subjects with TA from baseline through Week 25[a]	Subjects with TA, n (%)	88 (65.7%)	47 (68.1%)
	Weighted Difference in Proportion (95% CI)	-2.8% (-15.7, 11.1)	

Source: Applicant's Clinical Study Report.
[a] One subject in the crovalimab arm discontinued the study prior to Week 25 without a transfusion and was conservatively assumed to have had a transfusion.
Abbreviations: CI, confidence interval; n, number of subjects in subset; N, total number of subjects; TA, transfusion avoidance

The co-primary endpoints of TA and hemolysis control met the NIMs pre-specified in the study protocol (i.e., -20% for TA and 0.2 for hemolysis control). Because there were concerns with the Applicant's chosen NIMs, the statistical review team performed additional evaluations using more stringent NIMs, which the aforementioned endpoints also met. See Section 6.3.1 for details.

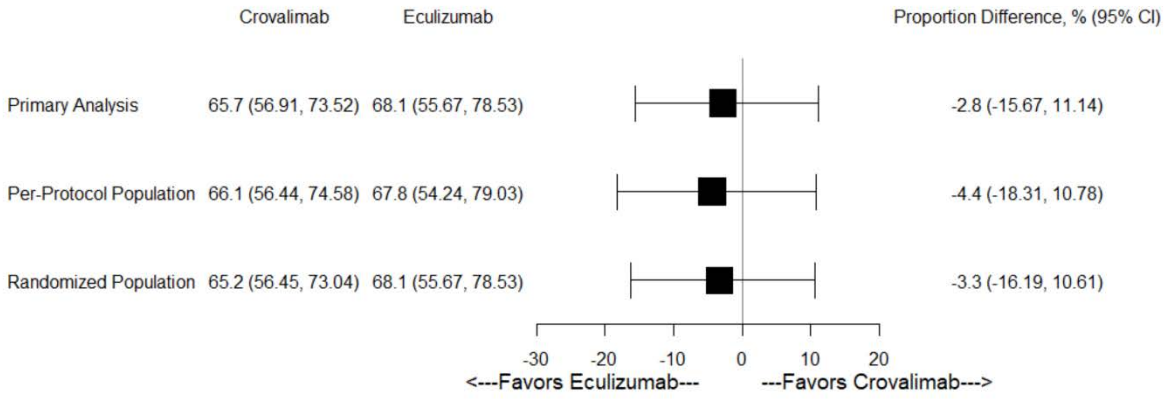
The sensitivity analysis results of the co-primary endpoints of hemolysis control and TA are shown in Figure 7 and Figure 8, respectively.

Figure 7. Results of the Prespecified Sensitivity Analyses for the Hemolysis Control Endpoint, COMMODORE-2



Source: Adapted from the Applicant's Clinical Study Report.
Abbreviations: CI, confidence interval; MCMC, Markov Chain Monte Carlo; PMM, predictive mean matching

Figure 8. Results of the Prespecified Sensitivity Analyses for the TA Endpoint, COMMODORE-2



Source: Adapted from the Applicant's Clinical Study Report.
Abbreviations: CI, confidence interval; TA, transfusion avoidance

Hemolysis Control

The exploratory results of sensitivity analyses are consistent with the primary analysis result for the hemolysis control endpoint.

The primary analysis model of GEE assumed missing data were missing completely at random. To ensure the robustness of the primary analysis results, the Applicant performed multiple imputations with Markov Chain Monte Carlo, pattern mixture models, and tipping point analyses to assess the impact of missing data.

The Applicant was also asked to explore reasons why the UN and Toeplitz covariance matrix did not converge. In the response, the Applicant stated that the main reason for nonconvergence with the UN and Toeplitz covariance matrix structures was due to the large number of correlation parameters that needed to be estimated as compared to other simpler covariance matrix structures such as AR(1). Specifically, for a GEE model with p visit time points (for COMMODORE-2, p=11 visits), p(p +1)/2 (66 in COMMODORE-2) parameters need to be estimated with UN covariance matrix structure, while p (11 in COMMODORE-2) parameters have to be estimated with Toeplitz covariance matrix structure, as compared to AR(1) for which only 2 parameters need to be estimated. In addition, the Applicant stated that the GEE model is generally robust against misspecification of the covariance matrix structure when the robust standard errors are used and that the regression estimates are known to remain consistent and the gain in efficiency when the exact covariance matrix structure is specified is minimal (Liang and Zeger 1986; Ballinger 2004).

To further assess the robustness of the GEE, the FDA recommended that the Applicant conduct the supplementary analysis using the logistic generalized linear mixed model.

The Applicant followed our recommendation. By using the generalized linear mixed model, an estimated OR (crovalimab versus eculizumab) of 0.97 (95% CI: 0.43, 2.16) was obtained. The Applicant noted that the generalized linear mixed model is a conditional model with a subject-

specific interpretation in contrast to the GEE model with a population average interpretation. By using an approximation of the marginal effect provided by the SAS GLIMMIX Procedure, the Applicant obtained an estimated OR of 1.01 (95% CI: 0.56, 1.82), which is similar to the results from the GEE model.

Transfusion Avoidance

The results of the sensitivity analyses are, in general, consistent with those of the primary analysis for the TA endpoint.

For TA, one subject (0.7%) in the crovalimab arm discontinued the study prior to Week 25 without a transfusion and was conservatively assumed to have had a transfusion. Nine subjects (6.7%) in the crovalimab arm and five subjects (7.2%) in the eculizumab arm had at least one missed visit, excluding those subjects who had early discontinuation of study treatment. Of these, five subjects (3.7%) in the crovalimab arm and three subjects (4.3%) in the eculizumab arm did not have a transfusion during the primary treatment period in the first 24 weeks.

Per our request, the Applicant conducted the following sensitivity analyses to assess the impact of missing data.

- Adverse outcome for both arms: Subjects who discontinued study treatment or had at least one missed pRBC transfusion assessment visit before Week 25 were assumed to have undergone a transfusion.
- Worst case scenario for crovalimab (most conservative): Subjects who discontinued study treatment or had at least one missed pRBC transfusion assessment visit in the crovalimab arm before Week 25 were assumed to have undergone a transfusion. Subjects in the eculizumab arm without any evidence of pRBC transfusion were assumed to not have undergone a transfusion, irrespective of discontinuation from study treatment or missed pRBC transfusion assessment visit.

The Applicant's sensitivity analysis results are shown in Table 15.

Table 15. Sensitivity Analyses Results for the Transfusion Avoidance Endpoint to Assess the Impact of Missing Data, COMMODORE-2, Primary Analysis Population

Transfusion Avoidance Endpoint Analysis	Subjects With TA n (%) (95 CI for Proportion)		Weighted Difference in Proportions (95 CI)
	Crovalimab N=134	Eculizumab N=69	
Primary Analysis	88 (65.7%) (56.91, 73.52)	47 (68.1%) (55.67, 78.53)	-2.8 (-15.67, 11.14)
Sensitivity Analysis			
1) Adverse outcome for both arms	83 (61.9%) (53.12, 70.07)	44 (63.8%) (51.25, 74.74)	-2.2% (-15.58, 11.93)
2) Worst case scenario for crovalimab (most conservative)	83 (61.9%) (53.12, 70.07)	47 (68.1%) (55.67, 78.53)	-6.6% (-19.51, 7.49)

Source: Applicant's responses to the Agency's information requests.
Abbreviations: N, total number of subjects; n, number of subjects in subset; CI, confidence interval; TA, transfusion avoidance

The results of Sensitivity Analysis 1 are consistent with those of the primary analysis. For Sensitivity Analysis 2, results are slightly worse, but this worst-case assumption holds only in the extreme and unlikely situations.

In addition, the Applicant highlighted that a need for a transfusion is an ongoing multifactorial assessment and is a clinical event, which may occur at scheduled or unscheduled visits based on the individual subject clinical picture. Therefore, even if a scheduled study visit was missed per protocol, this does not preclude the ongoing assessment of a subject's PNH disease and requirements for transfusions, which would be recorded in the electronic case report form. Therefore, the assumption of a missed transfusion event for every missed scheduled study visit, as such, is in itself considered conservative.

Efficacy Results of Key Secondary Endpoints

The primary analysis results of the key secondary endpoints are shown in Table 16.

Table 16. Analysis Results for the Key Secondary Endpoints, COMMODORE-2, Primary Analysis Population

Endpoints	Measures	Crovalimab N=134	Eculizumab N=69
Proportion of Subjects with BTH from Baseline through Week 25[a]	Subjects with at least one BTH, n (%)	14 (10.4%)	10 (14.5%)
	Weighted Difference in Proportion (95% CI)	-3.9% (-14.82, 5.26)	
Proportion of Subjects with Stabilized Hemoglobin from Baseline through Week 25[b]	Subjects with Hemoglobin Stabilization, n (%)	85 (63.4%)	42 (60.9%)
	Weighted Difference in Proportion (95% CI)	2.2% (-11.37, 16.31)	
Adjusted Mean Change from Baseline to Week 25 in FACIT-Fatigue	Adjusted Mean Change (SE)	7.8 (0.66)	5.2 (0.88)
	Difference in Mean Absolute change (95% CI)	2.6 (0.68, 4.60)	

Source: Applicant's clinical study report.
[a] Four subjects in the crovalimab arm and 1 subject in the eculizumab arm discontinued the study prior to Week 25 and were considered to have experienced a BTH event as a conservative analysis approach.
[b] One subject in the crovalimab arm discontinued the study prior to Week 25 with hemoglobin stabilization and was conservatively assumed to not have had hemoglobin stabilization.
Abbreviations: BTH, breakthrough hemolysis; CI, confidence interval; FACIT, Functional Assessment of Chronic Illness Therapy; n, number of subjects in subset; N, total number of subjects; SE, standard error

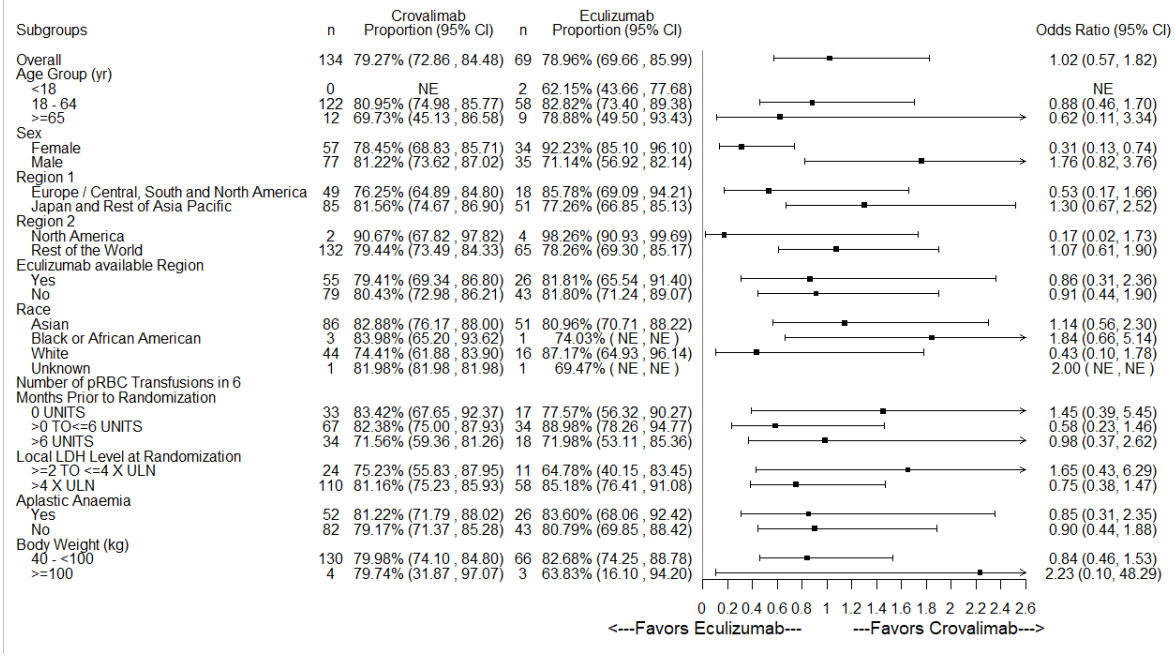
The key secondary endpoints of BTH and stabilized hemoglobin met the NIMs pre-specified in the study protocol (i.e., 20% for BTH and -20% for stabilized hemoglobin). Because there were concerns with the Applicant's chosen NIMs, the statistical review team performed further evaluations using more stringent NIMs, which the aforementioned endpoints also met. See Section 6.3.1 for details.

Regarding the FACIT-Fatigue scores, the Applicant's results can only be considered descriptive due to the hierarchical testing order and non-significant results of the superiority test of TA. In addition, there are concerns with interpretability of the FACIT-Fatigue scores due to the open-label design of the trial. Therefore, results of FACIT-Fatigue scores are not included in the label.

6.2.1.4.4. Subgroup Analysis of the Primary Endpoints, COMMODORE-2 (Study BO42162)

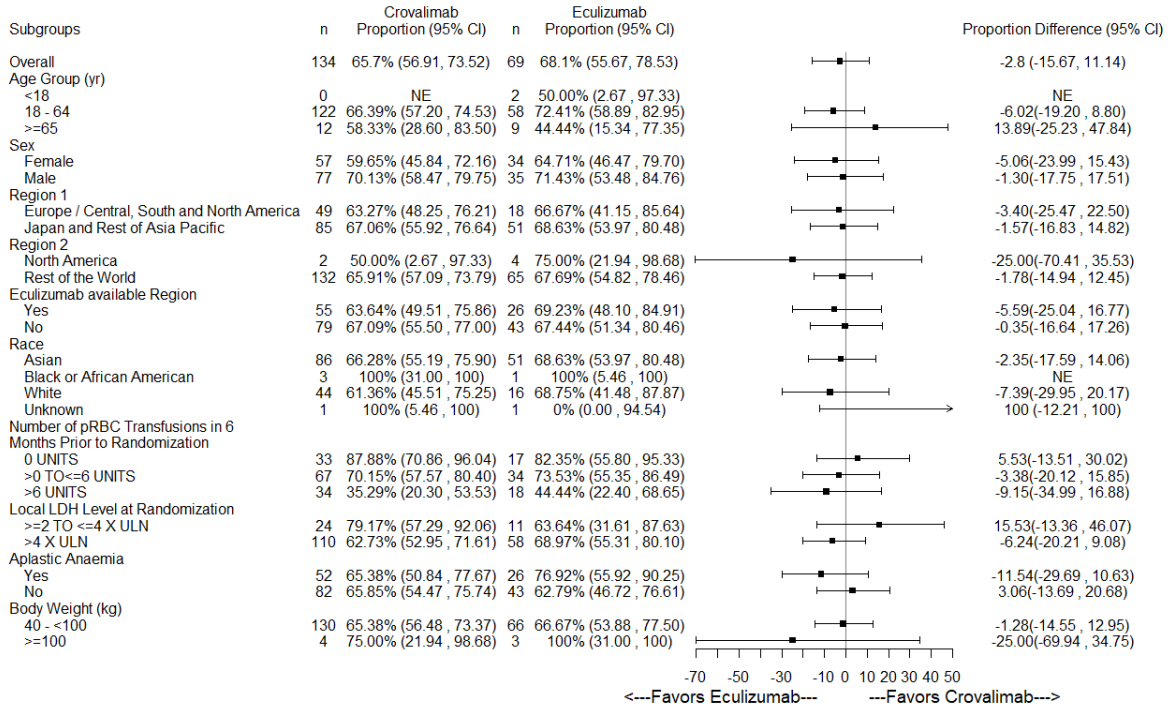
The Applicant conducted subgroup analyses for both co-primary endpoints to assess the potential differences in the treatment effect for various demographic and clinical characteristics groups, as shown in Figure 9 and Figure 10.

Figure 9. Subgroup Analyses for the Hemolysis Control Endpoint, COMMODORE-2, Primary Analysis Population



Source: Adapted from the Applicant's clinical study report and responses to the Agency's information requests.
Abbreviations: CI, confidence interval; LDH, lactate dehydrogenase; NE, not evaluable; pRBC, packed red blood cell; ULN, upper limit of normal; yr, year

Figure 10. Subgroup Analyses for the TA Endpoint, COMMODORE-2 (Primary Analysis Population)



Source: Adapted from the Applicant's clinical study report and responses to the Agency's information requests.
Abbreviations: CI, confidence interval; LDH, lactate dehydrogenase; NE, not evaluable; pRBC, packed red blood cell; TA, transfusion avoidance; ULN, upper limit of normal; yr, year

Considering the small sample size of the subgroups, which resulted in wide CIs, no inferential conclusion can be drawn, and results should be interpreted with caution.

6.2.2. Confirmatory Evidence of Effectiveness

PNH is a rare, serious, life-threatening disease. It is reasonable in this situation to establish effectiveness based on one adequate and well-controlled study plus confirmatory evidence. COMMODORE-2, which is described above, is an adequate and well-controlled study that provides persuasive evidence of crovalimab's effectiveness. The Applicant also conducted additional clinical studies described below, which provide confirmatory evidence of effectiveness for crovalimab based on the observed PD and mechanistic effects that would not be expected to occur spontaneously in this disease.

6.2.2.1. COMMODORE-3 (Study YO42311)

COMMODORE-3 is a Phase 3, single-arm, multicenter study conducted in China, of crovalimab given as a single agent in adolescent and adults subjects with PNH who have not been previously treated with complement inhibitor therapy. Other key inclusion criteria included LDH level >2x ULN and at least 4 blood transfusions in the previous 12 months. During screening, retrospective collection of medical data for the 24 weeks prior to enrollment occurred, included transfusion history, LDH and hemoglobin laboratory data. Subjects received 24 weeks of crovalimab therapy using the same dosing regimen of crovalimab as was used in COMMODORE-2. Subjects were

allowed to continue crovalimab after completing 24 weeks of therapy. The co-primary efficacy endpoints included the mean proportion of subjects with hemolysis control measured by LDH ≤1.5x ULN from Week 5 through Week 25 and the difference in the proportion of subjects who achieved TA from baseline through Week 25 (after 24 weeks of treatment). Both co-primary endpoints were required to achieve a 2-sided significance level of 0.05 to conclude positive study results. Subjects also had PD and biomarker assessments. See further details regarding the study design in Section 15.2 of the review.

A total of 51 subjects were enrolled and treated with crovalimab across five clinical sites in China at the time of the clinical data cutoff date. Due to COVID-19 travel restrictions, approximately half of the subjects were missing the required PD and biomarker assessments for each visit after Week 25.

Results

The co-primary efficacy endpoints of hemolysis control and TA were met at the time of the clinical cutoff date (CCOD). The mean proportion of subjects with hemolysis control (i.e., LDH ≤1.5×ULN) from Week 5 through Week 25 was 78.7% (95% CI: 67.8%, 86.6%), which met the prespecified success criterion of 60% based on the lower limit of the two-sided 95% CI. The 60% success criterion was chosen to preserve about 60% of the treatment effect of eculizumab based on the point estimate of eculizumab's treatment effect in the published eculizumab trials (TRIUMPH and ALXN1210-PNH-301). The hemolysis control result also met a success criterion of 66.9% which is based on the lower bound of the 95% CI of the treatment effect of eculizumab instead of the point estimate. The difference in the proportion of subjects with TA from baseline through Week 25 and the proportion of subjects with TA within 24 weeks prior to screening was 51.0% (95% CI: 34.3%, 65.1%), which was statistically significant ($p<0.0001$) at the prespecified, 2-sided type I error level of 0.05.

For the subjects that had PD and biomarker assessments, complement levels, as measured by free C5 concentrations, were reduced from a mean baseline level of 226.6 mg/L to mean levels of <0.1 mg/L from Week 2 of crovalimab treatment, providing evidence of complete inhibition of free C5. Terminal complement activity (CH50) was reduced from a mean baseline level of 48 U/mL (SD: 11.7 U/mL) to levels near or below the limit of quantification (i.e., <10 U/mL) from Week 2 of treatment with crovalimab, providing evidence of complete inhibition of terminal complement activity. Clone size was also evaluated, and the RBC PNH clone size increased from mean baseline levels of 46.9% (SD: 22.2%) to 69.6% (SD: 24.1%) at Week 25, consistent with decreased hemolysis of glycosylphosphatidylinositol-deficient PNH cells. For complete study results see Section 16.2 in the review.

Conclusion

This single-arm study enrolled patients with PNH who had not received prior complement therapy for PNH and required at least 4 RBC transfusions within 12 months prior to screening and had active hemolysis (mean LDH 9×ULN at baseline). Although the study is single-arm, the observed changes would not be expected to occur spontaneously in this population. These findings included the 51% difference in the proportion of subjects with TA from baseline through Week 25 and within 24 weeks prior to screening and hemolysis control, along with an increase in PNH RBC clone size, and near complete inhibition of complement biomarkers. These findings are also consistent with findings observed in COMMODORE-2.

6.2.2.2. COMPOSER (Study BP39144)

COMPOSER was a first-in-human study that was designed to evaluate the safety and tolerability, PK, and PD of crovalimab in healthy male volunteers (Part 1) and in patients with PNH (Parts 2 Part 3, Part 4, and OLE). Part 1 was a randomized, adaptive, placebo-controlled, parallel group study in HVs. Part 2 was an open-label, non-randomized, multiple-dose, multicenter, intra-individual dose escalation study in patients with PNH who were treatment-naïve. Part 3 was an open-label, nonrandomized, multiple-dose, multicenter study in patients with PNH switched from eculizumab. Part 4 was an open-label, nonrandomized, multicenter, two-arm (Arm A: treatment-naïve, Arm B: patients previously treated with eculizumab) study in patients with PNH. Subjects in Parts 2, 3 and 4 were eligible to enroll in the OLE. In Parts 2, 3, and 4, 44 total patients with PNH enrolled in the study (18 treatment-naïve and 26 subjects who switched from eculizumab to crovalimab) and of these, 43 entered the OLE. Further details regarding the study design are included in Section 15.4 of the review.

Results

Analysis of the PD markers for complement inhibition (CH50 and free C5 concentration), in the 44 subjects who received at least one dose of study drug, demonstrated low CH50 and low free C5 concentrations in the majority of subjects providing evidence of sustained complete terminal complement inhibition by crovalimab. Complement inhibition was generally achieved immediately after the first dose of crovalimab and was maintained.

During the OLE period, exploratory efficacy endpoints of hemolysis control (change in LDH), TA and hemoglobin stabilization were analyzed. No formal efficacy evaluation was prespecified and results were descriptive in nature. The efficacy results evaluated from week 20 to the CCOD of November 1, 2021, are as follows. The median treatment duration of crovalimab during the OLE period (for the 43 subjects who entered the OLE period) was 2.7 years (range: 0.18 to 4.1) The median LDH at baseline was 1.1×ULN (range: 0.7 to 4.8) for subjects who switched from eculizumab to crovalimab and 4.8×ULN (range: 1.9 to 20.4) for subjects who were complement inhibitor treatment naïve. Among the 43 subjects, 17 subjects (40%) had a history of transfusion up to 1 year prior to starting crovalimab treatment, with a median of 5 units of RBC transfused (range: 1 to 48).

In the OLE analysis, mean normalized LDH was generally maintained below 1.5×ULN, with 80% to 100% of subjects at each visit having LDH ≤1.5×ULN. Across the 24-week intervals, the proportion of subjects achieving TA (82.9% to 91.7%) and hemoglobin stabilization (79.5% to 87.5%) remained high. For complete study results see Section 16.4 in the review.

Conclusion

COMPOSER provides further PD evidence as demonstrated by maintaining LDH <1.5 ULN along with mechanistic support from suppression of complement levels. In a disease where spontaneous remission is not expected, these findings are attributable to administration of crovalimab and are consistent with the findings from COMMODORE-3 and COMMODORE-2.

6.2.2.3. COMMODORE-1 (Study BO42161)

COMMODORE-1 was a Phase 3, randomized, open-label, active-controlled, multicenter trial in patients with PNH currently treated with a complement inhibitor therapy. The study was comprised of randomized arms (Arms A [crovalimab] and B[eculizumab]) consisting of adult patients (≥18 years of age) who had been receiving eculizumab at the approved dose for PNH for at least 24 weeks and a nonrandomized arm (Arm C) consisting of cohorts of patients treated with a C5 inhibitor (i.e., eculizumab or ravulizumab). While the study was ongoing, the Applicant stopped randomization into Arms A and B in November 2022. The Applicant determined that enrollment of a sufficient number of patients would not be attainable to support a meaningful powered efficacy analysis, given the evolving treatment landscape (i.e., multiple available therapies for patients with PNH, delays due the COVID-19 pandemic, and a reduced pool of eculizumab-pretreated patients over time). The projected enrollment in the two arms was approximately 90 subjects and the primary analysis of the study was conducted at the same time as the primary analysis of COMMODORE-2. Efficacy in COMMODORE-1 was updated to become an exploratory objective and the results were descriptive, with no formal statistical noninferiority and superiority testing. The exploratory efficacy endpoints included percent change from baseline in LDH levels averaged over Weeks 21, 23, and 25, proportion of subjects who achieved TA from baseline through Week 25, percent change in LDH, BTH and hemoglobin stabilization. Subjects also had PD and biomarker assessments. The exploratory endpoints were analyzed following the methods pre-specified in the revised SAP. Further details regarding the study design are provided in Section 15.3 of the review.

A total of 127 subjects (randomized arms [crovalimab: 45, eculizumab: 44], nonrandomized arm: 38) were enrolled, which is about 64% of the initially targeted enrollment. Enrollment of subjects in the randomized arms had stopped, but the enrollment in the nonrandomized arm is ongoing. The mean LDH value at baseline was 1.1×ULN (SD 0.28) and 1.0×ULN (SD 0.24) in the crovalimab and eculizumab arms, respectively. In the randomized crovalimab arm, free C5 concentrations in switch subjects were high at baseline above the limit of quantification while subjects were still exposed to eculizumab (this is because C5 bound to eculizumab is measured as free C5 in the assay). In both the randomized crovalimab and eculizumab arms, baseline levels of terminal complement activity (CH50 measured by liposome immunoassay) were low (close to or below the limit of quantification [<10 U/mL]) as the subjects were exposed to eculizumab.

Results

In terms of PD markers, the mean proportion of subjects achieving hemolysis control (central LDH <1.5×ULN) during the primary treatment period was 92.9% (95% CI: 86.6, 96.4) for the crovalimab arm versus 93.7% (95% CI: 87.3, 97) for the eculizumab arm. The mean percentage change in central LDH from baseline to the average over Weeks 21, 23 and 25 was 16.6% (95% CI: 3.30, 29.82) for the crovalimab arm versus 4.5% (95% CI: -9.74, 18.81) for the eculizumab arm.

After crovalimab treatment initiation in the Arm B Switch subjects, PD markers of complement inhibition of free C5 and CH50 were also evaluated. Serum free C5 rapidly decreased to very low levels (mean levels <0.0001 g/L) from Switch Week 2 of crovalimab treatment, thus providing evidence of maintenance of complete inhibition of terminal complement activity. The low levels of free C5 (<0.0001 g/L) were sustained throughout the assessment period (up to

Switch Week 25) in most subjects. After crovalimab treatment initiation, mean CH50 were maintained at low levels (close to or below the limit of quantification [<10 U/mL]) thus providing evidence of sustained inhibition of terminal complement activity throughout the crovalimab treatment period.

Conclusion

The interpretation of the efficacy endpoint of TA is limited due to study enrollment stopping prematurely. However, the study provides confirmatory evidence based on the mechanistic PD data (CH50 and free C5 levels) and the PD marker of LDH. In a disease where spontaneous remission is unlikely to happen, the sustained control of hemolysis and complement markers are attributable to the administration of crovalimab, are consistent with the findings from COMMODORE-3, COMPOSER and COMMODORE-1, and all together provide confirmatory evidence of effectiveness of crovalimab.

6.3. Key Efficacy Review Issues

6.3.1. Assessing the Adequacy of Noninferiority Margins for Major Efficacy Endpoints in COMMODORE-2

Issue

The Agency had concerns with the Applicant's prespecified NIMs for the major efficacy endpoints in COMMODORE-2.

Background

During the IND stage, the Agency recommended the Applicant provide justification of the NIMs for all major efficacy endpoints. In the final SAP, the Applicant provided justification for the NIMs for the two co-primary endpoints, but not for the key secondary endpoints.

During the BLA review, the Agency questioned the Applicant's justification for the co-primary endpoint NIMs, which were derived from the point estimate of the treatment effect of eculizumab. In addition, the NIM for TA was based on the global PNH Registry data owned by another company (i.e., Alexion Pharmaceuticals, Inc.) and therefore the information of the lower bound of the 95% CI of the treatment effect of eculizumab could not be obtained for calculating a more conservative NIM.

Assessment

Transfusion Avoidance

During the BLA review, the Agency questioned the prespecified NIM of -20% for the co-primary endpoint of TA because it was based on the reported point estimate of the treatment effect of eculizumab and was based on registry data. A more stringent NIM was derived by the statistical review team using the TRIUMPH trial, a published randomized placebo-controlled study of eculizumab in patients with PNH (Hillmen et al. 2006).

In the TRIUMPH trial, the difference between the TA response proportions of two treatment groups is 51.2% (95% CI: 36.1%, 66.3%). Based on the lower bound of the 95% CI of the treatment effect, the NIM corresponding to the preservation of at least 50% of the treatment effect of eculizumab is -18%, with 50% being a commonly chosen value for the preserved effect according to the FDA Guidance for Industry on Non-Inferiority Clinical Trials. In COMMODORE-2, The proportion of subjects who achieved TA from baseline to Week 25 is 65.7% (95% CI: 56.9%, 73.5%) for crovalimab versus 68.1% (95% CI: 55.7%, 78.5%) for eculizumab, with a difference in proportions of -2.8% (95% CI: -15.7%, 11.1%). Therefore, the lower bound of the 95% CI is not lower than the more stringent NIM of -18%.

The TRIUMPH study required all subjects enrolled to have a blood transfusion in the prior 12 months, compared to the current study (COMMODORE-2), which did not have a requirement for a transfusion for enrollment, and capped subjects without a history of transfusion in the past year prior to randomization to be around 20%. Therefore, the statistical review team conducted an additional noninferiority analysis on a subgroup of subjects in COMMODORE-2 who received a recent transfusion prior to enrollment, so that the populations from the TRIUMPH study and COMMODORE-2 are more comparable. Among 203 (134 of crovalimab and 69 of eculizumab) subjects in the primary analysis set, there are 152 (102 of crovalimab and 50 of eculizumab) subjects who received at least one transfusion within 12 months prior to screening. The lower bound obtained on this subset with transfusion history is -17.6%, which still meets the more stringent NIM of -18%.

Hemolysis Control

During the BLA review, the Agency questioned the prespecified NIM of 0.2 for the co-primary endpoint of hemolysis control because it was based on the point estimate of the treatment effect of eculizumab in the OR scale, as described in Section 6.2.1.4. As suggested by the Agency, the Applicant rederived a NIM of 0.33, which was based on the lower bound of the 95% CI of the treatment effect of eculizumab in the OR scale (i.e., 9.24) and corresponded to the preservation of at least 50% treatment effect of eculizumab.

In COMMODORE-2, the mean proportion of subjects with hemolysis control from Week 5 through Week 25 in subjects treated with crovalimab compared to eculizumab was 79.3% (95% CI: 72.9%, 84.5%) versus 79.0% (95% CI: 69.7%, 86.0%), respectively, resulting in an OR of 1.02 (95% CI: 0.57, 1.82). The lower bound of 0.57 is greater than the more stringent NIM of 0.33.

Breakthrough Hemolysis

The Applicant provided the following justification for the NIM for BTH during the BLA review.

- The NIM was derived based on data from the TRIUMPH study (Hillmen et al., 2006). However, given that in the TRIUMPH study BTH was not analyzed and, therefore, not all relevant data for the assessment of BTH was collected, only the objective LDH portion of the definition of BTH could be utilized in deriving the NIM for this endpoint (in COMMODORE-2, BTH was defined as at least one new or worsening symptom or sign of IVH in the presence of elevated LDH ≥2×ULN after prior reduction of LDH to ≤1.5×ULN on treatment). As stated in the ALXN 301 study SAP (FDA 2017), the TRIUMPH study showed a benefit of eculizumab over placebo in the LDH portion of the definition of BTH with a difference of -81.4%, with a

95% CI of (-69.8%, -92.96%). Using the lower bound of -69.8% as a conservative estimate of the eculizumab benefit and calculating the NIM to preserve 50% of the eculizumab effect, this results in a NIM of approximately 35%. Similar to the ALXN 301 study (FDA 2017), the Applicant has chosen a more conservative NIM of 20%.

The Agency questioned the Applicant's justification for the NIM for BTH because it was calculated based on the point estimate of the eculizumab's treatment effect. However, a NIM of 10% was accepted for the BTH endpoint when approving ravulizumab (another C5 inhibitor). In COMMODORE 2, the weighted difference in proportion (95% CI) for BTH comparing crovalimab to eculizumab was -3.9% (-14.83%, 5.26%). The upper bound of 5.26% in this BTH primary analysis result was lower than the more stringent NIM of 10%.

Stabilized Hemoglobin

The Applicant provided the following justification for the NIM for stabilized hemoglobin during the BLA review.

- The NIM was derived based on data from the TRIUMPH study (Hillmen et al. 2006), which showed a benefit of eculizumab over placebo with a difference of 39.5% in the proportion of subjects with stabilized hemoglobin, defined as avoidance of a ≥2 g/dL decrease in hemoglobin level from baseline in the absence of transfusion through Day 183 (as stated in ALX 301 study SAP (FDA 2017)). Calculating the NIM to preserve 50% of the eculizumab effect, results in a NIM of approximately -20%. While a more conservative NIM could be constructed using the lower bound of the 95% CI for the difference, the resulting sample size would be prohibitive in light of the rarity of PNH and the paucity of eculizumab-naïve patients.

The Agency questioned the Applicant's justification for the NIM for stabilized hemoglobin and recommended that the Applicant recalculate the NIM based on the lower bound of eculizumab's treatment effect (as reported in Hillmen et al.) or explore possible values of the NIM if the information on the lower bound is unavailable. The Applicant acknowledged the Agency's recommendation and rederived a more stringent NIM of -12.8% based on the following reasons. In the TRIUMPH study, TA was achieved in 0% of subjects in the placebo group (0 of 44) (Hillmen et al. 2006). As the definition for hemoglobin stabilization requires "the absence of transfusion through treatment period", the proportion of subjects who achieved hemoglobin stabilization in the placebo group would also be 0% (0 of 44). Given the difference between eculizumab and placebo of 39.5% provided in the ALXN-301 Study SAP (FDA 2017), the proportion of subjects who achieved hemoglobin stabilization in the eculizumab group was derived as 39.5% (17 of 43). From these results, the lower bound of the 95% CI was derived as 25.6% using the exact CI through the Agresti-Min method (Agresti and Min 2001). Accordingly, the rederived NIM (based on the lower bound of the 95% CI of 25.6%) to maintain 50% of eculizumab effect was -12.8%. This more stringent NIM is lower than the lower bound (i.e., -11.4%) of the 95% CI for the difference in the hemoglobin stabilization primary analysis result.

Change in FACIT-Fatigue

The Applicant provided the following justification for the NIM for FACIT-Fatigue during the BLA review.

- The NIM was derived based on data from the TRIUMPH study (Hillmen et al. 2006) which showed a benefit of eculizumab over placebo with a difference in FACIT-Fatigue change from baseline to Week 26 of 10.4. Calculating the NIM to preserve 50% of the eculizumab effect, results in a NIM of -5. While a more conservative NIM could be constructed using the lower bound of the 95% CI for the difference, the resulting sample size would be prohibitive in light of the rarity of PNH and the paucity of eculizumab-naïve patients.

The Agency did not evaluate the appropriateness of the proposed NIM for FACIT-Fatigue because these results were considered descriptive only due to the hierarchical testing order and nonsignificant results of the superiority test of TA. In addition, the results are difficult to interpret given the open-label design of COMMODORE-2.

Conclusion

The co-primary endpoints of TA and hemolysis control and major key secondary endpoints of BTH and stabilized hemoglobin met the NIMs pre-specified in the study protocol. Since the Agency had concerns with the Applicant's chosen NIMs, the statistical review team performed further evaluations using more stringent NIMs, which the aforementioned endpoints also met. Given the study power was based on the Applicant's chosen NIMs, the review team does not have further concerns regarding the efficacy of the study drug based on the NI analyses. In addition, the effects of crovalimab on these endpoints are compelling as these changes would not occur spontaneously in the absence of treatment (Hill et al. 2017).

6.3.2. Evidence of Effectiveness in Patients Who Are Treatment Experienced With Another C5 Inhibitor

Issue

The Applicant proposed a broad indication: treatment of adult and pediatric patients with PNH. This indication includes patients who are C5 inhibitor-naïve and patients who switched from another C5 inhibitor to crovalimab.

Background

The Phase 3 trial for this application, COMMODORE-2, enrolled 135 subjects with treatment-naïve PNH who received crovalimab. Data to support the treatment of patients with crovalimab previously treated with a C5 inhibitor includes descriptive data from Arm B from COMMODORE-2, descriptive data from COMPOSER, E-R analyses and the well understood pathophysiology of the disease.

The review team analyzed the data and the Applicant's justification to determine whether the efficacy data, along with the E-R relationship supports the effectiveness of crovalimab for patients who are treatment naïve and for patients switching to crovalimab from another C5 inhibitor.

Assessment

The efficacy of crovalimab was similar in the C5 inhibitor-naïve population and those who switched to crovalimab from another C5 inhibitor therapy.

- In COMMODORE-2, the exploratory switch data from Arm B included 68 subjects previously treated with eculizumab of whom 43 subjects switched to crovalimab for at least 24 weeks before data cut-off in the OLE. Of the 43 subjects that switched to crovalimab at least 24 weeks before data cutoff, the mean proportion of subjects with hemolysis control (LDH <1.5X ULN) after switch through Week 25 was 87.6% (95% CI: 79.8, 96.7). In terms of TA, 33/43 (76.7%), (95% CI: 61, 87.7) achieved TA in the period after switching to crovalimab through switch Week 25. In addition, 62.8% (95% CI: 46.7, 76.6) of subjects in the 24-week crovalimab efficacy population achieved hemoglobin stabilization from switch baseline to week 25. Overall, these findings are consistent with the efficacy results in the complement inhibitor naïve population. In addition, hemolysis control, TA and hemoglobin stabilization would not be expected to occur spontaneously. See Section 16.1 for detailed results.
- In COMPOSER, 25 subjects with PNH who were previously treated with eculizumab were enrolled across Part 3 (19 subjects) and Part 4 (7 subjects) of the study. The mean normalized LDH remained below 1.5×ULN from Week 1 Day 1 through the 20-week treatment period. Maintenance of disease control was also observed for TA rates and hemoglobin stabilization rates in the switch subjects. Complement inhibition as measured by CH50 values were also maintained in all seven subjects in Part 4 and in general for the 19 subjects in Part 3.
- The descriptive efficacy results from randomized switch subjects in COMMODORE-1 also provide additional data (See Section 6.2.2.2) and were consistent with the data in switch subjects in COMPOSER and in Arm B switch subjects in COMMODORE-2.
- E-R analyses: Crovalimab is known to have a direct effect on terminal complement activity endpoints of CH50 and free C5. A time-matched analysis for all available data except the first 12 weeks of treatment for switch subjects was performed. No relevant differences were observed between treatment-naïve and switch subjects for CH50 levels (Figure 60). No relevant differences were observed between treatment naïve and switch subjects in terms of free C5 concentration (Figure 64). The observed E-R relationships for PD are comparable for treatment naïve subjects and prior-treated subjects switching from either eculizumab or ravulizumab.
- The pathophysiology of PNH involves uncontrolled complement activation, resulting in intravascular and extravascular hemolysis. The underlying disease pathophysiology is unchanged in C5-experienced patients. Therefore, there is no expected difference in response to crovalimab between C5 inhibitor naïve and experienced patients. The efficacy results from the randomized arms of COMMODORE-2 are consistent with the efficacy results from C5 experienced subjects enrolled in PNH studies COMPOSER and the exploratory switch arm B in COMMODORE-2.

Conclusion

The Agency concluded that there was sufficient data and understanding of the pathophysiology of the disease of PNH to support the indication, which includes treatment naïve patients and patients switching from a previous C5 inhibitor therapy.

6.3.3. Applicability of Foreign Efficacy Data to the U.S. Population

Issue

In the active-controlled portion of COMMODORE-2, no subjects from the U.S. clinical sites were enrolled in the randomized arms.

Background

The randomized population consisted of subjects mostly enrolled from Asia (66.7%) and Europe (23.5%) in COMMODORE-2 as shown in Table 11. The review team assessed whether the efficacy results in COMMODORE-2 could be applied to the U.S. patient population.

Assessment

Subgroup analyses by race and region for the co-primary endpoints of hemolysis control and TA for COMMODORE-2 were conducted. Subgroup analyses by race and region for the co-primary endpoints in COMMODORE-2 showed overlapping confidence intervals among these subgroups. See Figure 9 and Figure 10.

Based on the disease pathology (i.e., mutation in *PIG-A* gene) and mechanism of action of crovalimab, it is not expected that there would be a difference in the treatment effect across races or geographic regions. The PK of crovalimab also showed no difference between Asian and non-Asian patients. See Section 8.1.

Conclusion

Based on the data provided in this submission and the known disease pathology, there is no basis to conclude that the efficacy of crovalimab in patients with PNH would be different between race or region, and the FDA concludes that the efficacy results of the pivotal, COMMODORE-2 is applicable to the U.S. patient population.

6.3.4. Efficacy in the Pediatric Patient Population

Issue

The proposed crovalimab indication for treatment of patients with PNH includes pediatric patients, however, only a small number of pediatric patients (crovalimab naïve: 9 subjects, crovalimab switch: 1 subject) were evaluated for efficacy.

Background

At the original CCOD on November 16, 2022, a total of 11 pediatric subjects with PNH (and ≥40 kg) received crovalimab (crovalimab naïve: 9 subjects, crovalimab switch: 2 subjects) across the Phase 3 trials (COMMODORE-1 [crovalimab switch: 1 subject in the nonrandomized arm],

COMMODORE-2 [crovalimab naïve: 6 subjects in the nonrandomized arm, crovalimab switch: 1 subject during the extension period], COMMODORE-3 [crovalimab naïve: 3 subjects]). The pediatric subject in the nonrandomized arm in COMMODORE-1 (crovalimab switch) was enrolled approximately 2 weeks prior to the cutoff date of the primary analysis and did not have sufficient follow-up time to be assessed for efficacy and was, therefore, excluded from the efficacy analysis.

In the 10 pediatric subjects, the baseline age ranged from 13 to 17 years, six subjects were females and nine were Asians. The baseline disease characteristics were generally similar to those in the adult patient population. In the 9 pediatric subjects who were crovalimab naïve, the median baseline hemoglobin level was 7.6 g/dL (range: 6.6 to 9.6 g/dL), the median LDH was 7.3×ULN (range: 3.5 to 26.6×ULN), 7 patients had a history of pRBC transfusion within the 12 months prior to enrollment with a median of 20 units of pRBC transfused (range: 1.0 to 40.5 units), and five subjects had a history of aplastic anemia. Overall, the pediatric subjects enrolled had severe disease. In COMMODORE-2, one pediatric subject received eculizumab during the primary treatment period and switched to crovalimab during the extension period. This subject did not receive transfusion 12 months prior to randomization but had a history of aplastic anemia. At switch baseline, the subject had a hemoglobin level of 10.7 g/dL and LDH of 1.34×ULN.

A request for information was sent to the Applicant to provide efficacy updates on the pediatric subject who was enrolled in the nonrandomized arm in COMMODORE-1 (crovalimab switch) approximately 2 weeks prior to the cutoff date of the primary analysis and did not have sufficient follow-up time to be assessed for efficacy. On May 8, 2024, the Applicant provided an update on efficacy on this pediatric subject [(b) (6)] who switched from standard dose eculizumab. In addition, efficacy data were provided on one additional pediatric subject [(b) (6)] who switched from ravulizumab and was enrolled in the nonrandomized arm in COMMODORE-1 after the primary analysis cutoff date and had received crovalimab up to Week 25.

Subject [(b) (6)] was a 16-year-old white male enrolled in Türkiye. At baseline, normalized LDH was 1.1×ULN and hemoglobin 14.9 g/dL. No pRBC transfusions were given within 12 months prior to enrollment. This subject did not have a medical history of aplastic anemia or MDS, renal impairment (RI) or a MAVE.

Subject [(b) (6)] was a 13-year-old White male enrolled from a clinical site in the U.S. Baseline normalized LDH was 1.3×ULN and hemoglobin 11.3 g/dL. No pRBC transfusions were given within 12 months prior to enrollment. This subject did not have a history of aplastic anemia or MDS, RI or MAVE.

The review team conducted subgroup analysis for the efficacy endpoints in pediatric subjects to assess if the results were consistent with those of the adult patient population.

Assessment

Efficacy Endpoints

Transfusion Avoidance

In the 9 complement-inhibitor naïve pediatric subjects, 6 subjects (COMMODORE-2: 4 subjects, COMMODORE-3: two subjects) (66.7%) achieved TA from baseline through Week 25.

In the 3 pediatric subjects who switched from eculizumab/ravulizumab to crovalimab, TA was maintained from switch baseline to Week 25 in all 3 subjects.

Hemolysis Control

In the 9 complement-inhibitor naïve pediatric subjects, a total of 7 (77.8%) subjects (COMMODORE-2: 5 subjects, COMMODORE-3: 2 subjects) reached LDH ≤1.5×ULN by Week 4 that was sustained during the first 24 weeks of treatment.

In the 3 pediatric subjects who switched from eculizumab/ravulizumab to crovalimab, all 3 subjects maintained LDH ≤1.5×ULN from switch baseline to Week 25.

Breakthrough Hemolysis

No BTH events were reported from baseline to Week 25 in the 12 pediatric subjects.

Hemoglobin Stabilization

In the complement-inhibitor naïve pediatric subjects, 6 of the 9 subjects (66.7%) (COMMODORE-2: 4 subjects, COMMODORE-3: 2 subjects) achieved hemoglobin stabilization from baseline through Week 25.

In the 3 pediatric subjects who switched from eculizumab/ravulizumab to crovalimab, all 3 patients achieved hemoglobin stabilization from switch baseline to Week 25.

Table 17. Efficacy Results in Pediatric Subjects With PNH, COMMODORE-2 and COMMODORE-3

Efficacy Results	Crovalimab (Naïve) (N=9) n (%)	Crovalimab (Switch) (N=3) n (%)
Subjects with transfusion avoidance	6 (66.7%)	3 (100%)
Subjects achieving hemolysis control	7 (77.8%)	3 (100%)
Subjects with breakthrough hemolysis	0	0
Subjects with hemoglobin stabilization	6 (66.7%)	3 (100%)

Source: ADKLDH.xpt and ADEF.xpt.
Abbreviations: N, total number of subjects; n, number of subjects in subset; PNH, paroxysmal nocturnal hemoglobinuria

The Clinical Pharmacology discipline conducted E-R analysis (i.e., for free C5 and LDH) and found that the overall E-R relationship using the proposed crovalimab dose regimen in pediatric patients 13 to 17 years of age was consistent with the adult population to support extrapolation of efficacy to adolescent patients with PNH. See Section 8.1.

Conclusion

The efficacy results of crovalimab in pediatric subjects were consistent with those of the adult patients. The efficacy results were supported by the E-R relationship, which showed consistent results between pediatric subjects 13 to 17 years of age and the adult patient population. The review team recommends that the indication for treatment of patients with PNH include pediatric patients 13 years and older, as the youngest subject enrolled in clinical trials was 13 years old.

6.3.5. Efficacy Effects of Crovalimab IV Rescue Doses in COMMODORE-2

Issue

In COMMODORE-2, administration of additional IV rescue doses was permitted for patients in the crovalimab arm and not in the eculizumab arm.

Background

In COMMODORE-2, subjects who experienced signs and symptoms of underlying PNH, such as BTH, were permitted to receive additional IV rescue doses. However, additional rescue doses were only allowed for subjects in the crovalimab arm and not for subjects in the eculizumab arm. Since there is an imbalance between the two arms in the administration of rescue doses, the review team assessed if the additional rescue doses administered in the crovalimab arm affected the overall efficacy results.

Assessment

COMMODORE-2

In COMMODORE-2, unscheduled IV doses of crovalimab were administered as rescue therapy to a total of four subjects during the primary treatment period (two subjects received one additional IV dose and the other two subjects received two additional IV doses). It was reported that two of the four subjects received one rescue dose each in the context of a BTH event with a concurrent complement activating condition (e.g., infection or any event leading to inflammation such as surgery) while maintaining complete C5 inhibition, one subject received two rescue doses in the context of antidrug antibody (ADA) positivity with loss of PK/PD and the fourth subject received two rescue doses unrelated to either BTH and/or a complement activating condition or ADA leading to loss of PK/PD. The subject who had ADA had neutralizing antibodies with complete loss of exposure and pharmacological activity and no improvement in efficacy following the administrations of the two IV rescue doses.

None of the four subjects who received rescue doses of crovalimab achieved the TA co-primary efficacy endpoint. Regarding the hemolysis control co-primary efficacy endpoint, it is difficult to assess whether the (single or two) rescue doses or resolution of the complement activating trigger caused the decrease in the LDH levels. However, at the time of the IV rescue doses, all (except the 1 subject who was ADA positive) had crovalimab exposure above 100 mcg/mL and complete terminal complement activity inhibition (as measured by CH50 and free C5). Therefore, it is not likely that the single or two rescue doses reduced the LDH levels.

With regard to the key secondary endpoints, none of the four subjects achieved the hemoglobin stabilization endpoint and a total of three subjects had a BTH event during the primary treatment period. The subject who received two rescue doses (unrelated to either BTH and/or a complement activating condition or ADA leading to loss of PK/PD) had complete terminal complement activity inhibition at the time of the IV rescue administration and did not achieve the TA or the hemoglobin stabilization endpoint. However, this subject did not have a BTH event during the primary treatment period.

Sensitivity analyses for the co-primary endpoints for COMMODORE-2 were conducted excluding the subjects who received additional IV crovalimab rescue doses. The results are shown below.

Mean Proportion of Subjects with Hemolysis Control from Week 5 through Week 25:

- Original OR (95% CI): 1.02 (0.57, 1.82)
- Sensitivity analysis OR (95% CI): 1.06 (0.59, 1.90)

Proportion of Subjects with TA from Baseline through Week 25:

- Original weighted difference in proportion (95% CI): -2.8% (-15.67, 11.14)
- Sensitivity analysis weighted difference in proportion (95% CI): -1.0% (-13.89,12.94)

Conclusion

Only 4 subjects received rescue crovalimab doses in the randomized period of COMMODORE-2. The sensitivity analyses of the co-primary and major efficacy endpoints excluding subjects who received rescue crovalimab doses in COMMODORE-2 were consistent with the primary efficacy results. It does not appear that the administration of crovalimab rescue doses affected the overall efficacy results. Rescue doses of crovalimab did not appear to result in hemoglobin stabilization during the BTH event.

7. Safety (Risk and Risk Management)

7.1. Potential Risks or Safety Concerns Based on Nonclinical Data

Crovalimab was evaluated in good laboratory practice-compliant acute and chronic (6-month) toxicology studies in cynomolgus monkeys, which is the only pharmacologically-relevant species. An enhanced pre- and postnatal development study in monkeys as well as a carcinogenicity risk assessment were conducted. Doses used in chronic toxicology studies produced terminal complement inhibition of up to ~90%.

Two potential safety concerns were identified from the chronic toxicology study, which are discussed below followed by their relevance to clinical safety.

- Findings at the infusion and injection sites such as fibrosis (IV), hemorrhage (IV), mononuclear cell infiltrates (IV and SC), retention of crovalimab, and/or pigmentation

(IV and SC) occurred across all doses in crovalimab-treated animals, consistent with injection- and infusion-related reactions observed in clinical trials.

- Secondary findings of immunogenicity to crovalimab, including ADAs, biomarkers of systemic inflammation, and arteritis/periarteritis in several tissues (See Section 5.1 for detailed findings) defined the no observed adverse effect level in the chronic toxicology study in monkeys. Immunogenic responses to humanized antibodies in monkeys are generally not considered predictive of human immunogenic risk. Exposures up to 18× the maximum recommended human dose were evaluated.

Infection Risk

The complement system is a well-established, innate immune defense modulator against pathogens and, given crovalimab's mechanism of action and experience with the drug class (see Section 5.1), treatment with crovalimab is anticipated to increase the risk of infections. Available nonclinical data for crovalimab do not suggest a different infection-risk profile than other approved therapies of the same drug class. The risk of infections related to crovalimab was monitored in clinical trials and will be appropriately addressed in relevant sections of product labeling.

C5-Eculizumab-Crovalimab Complex Formation

Because crovalimab binds a different C5 epitope than eculizumab, formation of DTDCs can result in crovalimab and eculizumab circulating simultaneously. Formation of DTDCs poses a risk for hypersensitivity and immunogenicity reactions in patients with PNH who switch between crovalimab and eculizumab. Such complexes would also be expected with other therapeutic C5 antibodies that bind a different epitope than crovalimab.

In vitro analysis of eculizumab, recombinant human C5 (rhC5), and crovalimab in plasma or saline solution showed that crovalimab binds to an eculizumab-hC5 complex to form DTDCs with the largest DTDCs formed in the presence of nearly equimolar amounts of eculizumab, rhC5, and crovalimab. Consistent with crovalimab's pH-dependent characteristics, crovalimab dissociates from DTDCs at pH 6.0, whereas the DTDCs were formed at pH 7.4. DTDC formation was not studied in animal models based on limitations in cross-species reactivity to both products and the limitations of animal-to-human extrapolation of immune responses.

Carcinogenicity

The risk of carcinogenicity for crovalimab is considered low based on a weight-of-evidence risk assessment that considered the mechanism of action, review of the literature (including an assessment of previous theorical considerations regarding the potential for tumor progression after complement inhibition), information on class effects, and the lack of preneoplastic lesions in monkeys administered crovalimab for up to 26 weeks. Crovalimab is not active in rats and likely mice; therefore, rodent studies are not feasible.

7.2. Potential Risks or Safety Concerns Based on Drug Class or Other Drug-Specific Factors

Crovalimab is a humanized anticomplement component 5 (C5) monoclonal antibody. Other approved antihuman C5 antibodies include Soliris (eculizumab) and Ultomiris (ravulizumab-cwvz). Both eculizumab and ravulizumab-cwvz are indicated for the treatment of patients with PNH and both drugs have REMS with ETASU due to the risk of serious meningococcal infections. Other safety concerns listed in the Warnings and Precautions section of the PI of these drugs include other infections, monitoring for disease manifestations of PNH after treatment discontinuation, and prevention and management of thromboembolic events and infusion-related reactions. In patients with PNH, the most frequently reported ARs of eculizumab (≥10%) are headache, nasopharyngitis, back pain, and nausea, and for ravulizumab-cwvz, the most common ARs (≥10%) are upper respiratory tract infection, headache, injection site reactions, and diarrhea.

7.3. Potential Risks or Safety Concerns Identified Through Postmarket Experience

Crovalimab is not approved in the U.S. or any foreign market for any indication.

7.4. FDA Approach to the Safety Review

7.4.1. Sources of Data for Clinical Safety Assessment

The BLA contained the following four clinical studies of crovalimab in patients with PNH:

- COMMODORE-2 (Study BO42162) entitled, “A Phase 3, Randomized, Open-Label, Active-Controlled, Multicenter Study Evaluating the Efficacy and Safety of Crovalimab Versus Eculizumab in Patients with PNH Not Previously Treated with Complement Inhibitors.” For a summary of the study design, see Section 6.2.1.
- COMMODORE-1 (Study BO42161) entitled, “A Phase 3, Randomized, Open-Label, Active-Controlled, Multicenter Study Evaluating the Safety, PK, PD, and Efficacy of Crovalimab Versus Eculizumab in Patients with PNH Currently Treated with Complement Inhibitors.” For a summary of the study design, see Section 15.3.1.
- COMMODORE-3 (Study YO42311) entitled, “A Phase 3, Multicenter, Single Arm Study Evaluating the Efficacy, Safety, PK, and PD of Crovalimab in Patients with PNH Not Previously Treated with Complement Inhibition.” For a summary of study design, see Section 16.1.
- COMPOSER (Study BP39144) entitled, “An Adaptive Phase 1/2 Study to Assess Safety, Efficacy, PK and PD of RO7112689 in HVs and Patients with PNH.” For a summary of study design, see Section 16.2.

The safety evaluation of crovalimab is primarily based on the analyses of the randomized, controlled, primary treatment period of the two active-controlled, Phase 3 studies in patients with

PNH (COMMODORE-1 and COMMODORE-2). Safety data from COMMODORE-3 and COMPOSER were also reviewed.

7.4.2. Safety Analysis Plan and Definitions

The Applicant's translations of verbatim terms to Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (PT) for the events reported in the above four clinical studies were reviewed and found to be acceptable. Treatment-emergent adverse events (TEAEs) were defined as events that occurred on or after the first dose of study drug. AEs were to be recorded during the study and until 46 weeks (approximately 10.5 months) after the last dose of crovalimab and 10 weeks after the last dose of eculizumab. The terminal half-life of crovalimab is estimated to be 53.1 days (90% CI: 47.7, 58.6). Per the eculizumab PI, the half-life of eculizumab is approximately 11.25 to 17.25 days. Therefore, a safety follow-up of 46 weeks and 10 weeks for crovalimab and eculizumab, respectively, is acceptable to maintain follow-up for 5.5 half-lives.

AEs were graded according to the National Cancer Institute Common Technology Criteria for Adverse Events, Version 5.0 coding system. AEs were analyzed by MedDRA PT (version 25.1) and by pooling similar AEs (referred to as the Food and Drug Administration MedDRA query). The Food and Drug Administration MedDRA query analysis is similar to a customized MedDRA query.

For subjects who received the control (eculizumab) during the primary treatment period and switched to crovalimab in the extension period in COMMODORE-1 and COMMODORE-2, safety data occurring during the eculizumab-treated period or during the safety follow-up period were attributed to eculizumab. In subjects who switched to crovalimab, safety data occurring on or after the first dose of crovalimab were attributed to crovalimab.

7.4.3. Reviewer Approach to Safety Evaluation

Clinical trial data were independently analyzed using JMP software. No major data quality or integrity issues were identified that would preclude performing a safety review for this BLA. There were no major issues identified with respect to recording, coding, and categorizing AEs.

The safety review included the following:

- Electronic submissions of the clinical study reports and other relevant portions of the BLA were reviewed.
- Safety data were audited or reproduced.
- Pooled safety analyses were conducted when appropriate.
- Assessment of the Applicant's responses to FDA information requests.
- Review of the relevant published literature.
- Review of the 120-day safety update.

Pooling of Data Within and Across Trials

For more information on pooled results from the safety database, see Section 17.1. Crovalimab was administered using the proposed dosing regimen in COMMODORE-1, COMMODORE-2, and COMMODORE-3. Safety data up to the CCOD (which includes the primary treatment and extension treatment periods) from subjects in COMMODORE-1, COMMODORE-2, and COMMODORE-3 were pooled by crovalimab-naïve (i.e., subjects who previously did not receive a complement inhibitor therapy and received crovalimab), crovalimab-switch (i.e., subjects who were previously treated with a complement inhibitor and switched to crovalimab) and eculizumab groups for a total pooled safety set. The pooled set included 385 subjects (crovalimab: 274, eculizumab: 111). Among the 111 subjects who received eculizumab during the primary period, a total of 103 subjects (COMMODORE-2: 68 subjects, COMMODORE-1: 35 subjects) switched to crovalimab during the extension period.

Table 18. Pooled Analysis of COMMODORE-1, COMMODORE-2, and COMMODORE-3, Safety Population

Studies	Crovalimab (Naïve) (N=192)	Crovalimab (Switch) (N=185)	Eculizumab Total (N=111)
COMMODORE-2	141[d]		69[b]
		68[a]	
COMMODORE-1		82[e]	42[c]
		35[a]	
COMMODORE-3	51		

Source: SCS.
Note: COMMODORE-2 enrolled subjects starting (b) (6) and COMMODORE-1 starting (b) (6). The clinical cutoff date for both COMMODORE-1 and COMMODORE-2 was November 16, 2022. In COMMODORE-3, the date of first subject enrollment was (b) (6), and clinical cutoff date was August 10, 2022.
Note: Crovalimab (naïve): Subjects with PNH previously not treated with complement inhibitors who received crovalimab.
Note: Crovalimab (switch): Subjects with PNH previously treated with complement inhibitors before switching to crovalimab.
[a] Subjects who were randomized to eculizumab and switched to crovalimab once they had completed the primary treatment period (i.e., at least 24 weeks of treatment with eculizumab) in COMMODORE-1 and COMMODORE-2.
[b] Eculizumab (naïve): Subjects with PNH from COMMODORE-2 who were previously not treated with a complement inhibitor and received eculizumab during the primary treatment period of 24 weeks.
[c] Eculizumab (experienced): Subjects with PNH from COMMODORE-1 previously treated with eculizumab and continued receiving eculizumab during the primary treatment period of 24 weeks.
[d] Includes 135 subjects randomized to the crovalimab investigational arm and 6 subjects enrolled in the descriptive arm.
[e] Includes 44 subjects randomized to the crovalimab investigational arm and 38 subjects enrolled in the descriptive arm.
Abbreviations: N, total number of subjects; PNH, paroxysmal nocturnal hemoglobinuria

7.5. Adequacy of the Clinical Safety Database

The safety database is adequate for a comprehensive safety assessment of crovalimab for the proposed indication, patient population, dosage regimen, and duration. The BLA included safety information from a total of 444 subjects (PNH: 429, healthy subjects: 15) across the four clinical trials.

Although the safety database is small for a chronically administered drug, considering PNH is a rare disease and the safety analyses include two active-controlled trials (COMMODORE-1 and COMMODORE-2), the size and nature of the clinical database is acceptable. Similar to other approved complement inhibitors for PNH, the review team is recommending a postmarketing requirement (PMR) to further assess the long-term safety of crovalimab.

COMMODORE-1 and COMMODORE-2

Randomized Arms

Primary Treatment Period

Exposure during the primary treatment period is shown in Table 19 below. The median duration of exposure to crovalimab during the primary treatment period in COMMODORE-1 and COMMODORE-2 was similar (COMMODORE-2: 20.1 weeks [range: 0.1 to 23.1], COMMODORE-1: 20.1 weeks [range: 2.1 to 22.3]). The median duration of exposure to eculizumab was also similar in the two trials (COMMODORE-2: 22.1 weeks [range: 6.1 to 26.1], COMMODORE-1: 22.1 weeks [range: 0.1 to 26.1]). The difference of duration of exposure between the two arms in the studies was due to the difference in the treatment regimen (i.e., the maintenance dose of crovalimab is given Q4W versus eculizumab is given Q2W).

Table 19. Duration of Treatment, Primary Treatment Period, COMMODORE-1 and COMMODORE-2, Safety Population

	COMMODORE-2		COMMODORE-1	
Variable	Crovalimab (Naïve) (N=135)	Eculizumab (Naïve) (N=69)	Crovalimab (Switch) (N=44)	Eculizumab (Experienced) (N=42)
Duration of treatment (weeks)				
Mean (SD)	19.7 (2.8)	22.0 (2.0)	19.1 (3.7)	20.4 (5.7)
Median (Q1, Q3)	20.1 (20.0, 20.3)	22.1 (22.1, 22.3)	20.1 (20.1, 20.3)	22.1 (22.1, 22.1)
Range	0.1- 23.1	6.1-26.1	2.1-22.3	0.1- 26.1
Total exposure (person years)	51	29	16	16
Subjects treated by duration, n (%)				
<12 weeks	3 (2.2%)	1 (1.4%)	2 (4.5%)	4 (9.5%)
12 to <24 weeks	132 (97.8%)	67 (97.1%)	42 (95.5%)	35 (83.3%)
24 to <36 weeks	0	1 (1.4%)	0	3 (7.1%)

Source: ADEX.xpt and ADSL.xpt.
Note: The treatment duration was calculated as the date of the last study drug administration (Week 21 in the crovalimab arm and Week 23 in the eculizumab arm) minus the date of the first study drug administration (Week 1) plus 1 day, thus the calculation did not capture exposure up to Week 25.
Abbreviations: N, total number of subjects; n, number of subjects in subset; Q1, Quarter 1; Q3, Quarter 3; SD, standard deviation

As shown in Table 20 below, in the crovalimab arm, the median IV and SC dose intensity during the primary treatment period was 100% in the two studies (COMMODORE-2 [IV range: 95.0 to 175.0, SC range: 82.1 to 116.7], COMMODORE-1 [IV range: 99.7 to 137.5, SC range: 100 to 100]).

In subjects who received crovalimab, additional rescue IV doses of 340 mg were allowed if a subject had signs and symptoms of PNH; unscheduled IV doses of crovalimab were administered as rescue therapy to 4 subjects in COMMODORE-2 (2 subjects received 1 additional IV dose and the other 2 subjects received 2 additional IV doses). In COMMODORE-1, a total of 2 subjects received 1 additional unscheduled IV dose of crovalimab on Days 16 and 156, respectively. No clinically significant TEAEs (such as infusion reactions) were reported with the rescue doses.

Eculizumab was administered as IV infusion only. The median IV dose intensity of eculizumab was 100% (range: 100 to 100) in both trials. No rescue doses of eculizumab were administered in the two trials.

Table 20. Summary of Exposure, Primary Treatment Period, COMMODORE-1 and COMMODORE-2, Safety Population

	COMMODORE-2		COMMODORE-1	
Variable	**Crovalimab (Naïve) (N=135)**	**Eculizumab (Naïve) (N=69)**	**Crovalimab (Switch) (N=44)**	**Eculizumab (Experienced) (N=42)**
Total IV dose intensity (%)				
Median	100.0	100.0	100.0	100.0
Range	95.0 -175.0	100-100	99.7-137.5	100.0-100.0
Total SC dose intensity (%)				
Median	100.0	NE	100.0	NE
Range	82.1-116.7	NE-NE	100.0-100.0	NE-NE
Number of unscheduled IV doses, n (%)				
0 doses	131 (97.0%)	69 (100%)	42 (95.5%)	42 (100%)
1 dose	2 (1.5%)	0	2 (4.5%)	0
2 doses	2 (1.5%)	0	0	0

Source: ADEX.xpt and CSR.
Note: IV dose intensity is a percentage based on actual intravenous dose / total planned intravenous dose.
Note: SC dose intensity is a percentage based on actual subcutaneous dose / total planned subcutaneous dose.
Abbreviations: IV, intravenous; n, number of subjects in subset; N, total number of subjects; NE, not evaluable ; SC subcutaneous

Primary Treatment Period and Extension Period

In COMMODORE-1 and COMMODORE-2, the median treatment duration from randomization up to the CCOD (which includes both the primary treatment period and extension period) in the crovalimab-naïve arm was 48.3 weeks (range: 0.1 to 107.9) and 52.0 weeks (range: 2.1 to 108.4) in the crovalimab-switch arm (Table 21). In total, 57.1% and 54.5% of subjects had a treatment duration of ≥48 weeks in the crovalimab-naïve and crovalimab-switch arms, respectively. During the primary treatment and extension periods, additional unscheduled IV doses of crovalimab were administered to eight subjects in COMMODORE-2 (one additional dose to five subjects, two additional doses to two subjects, and three additional doses to one subject) and to four subjects in COMMODORE-1 (one additional dose to three subjects and two additional doses to one subject).

Table 21. Summary of Exposure up to the Clinical Cutoff Date, Crovalimab Arm, COMMODORE-1 and COMMODORE-2, Safety Population

	COMMODORE-2	COMMODORE-1
Variable	**Crovalimab (Naïve) (N=135)**	**Crovalimab (Switch) (N=44)**
Duration of treatment (weeks)		
Mean (SD)	49.2 (18.9)	51.9 (27.2)
Median (Q1, Q3)	48.3 (32.4, 60.3)	52.0 (32.2, 69.1)
Range	0.1-107.9	2.1-108.4

Variable	COMMODORE-2 Crovalimab (Naïve) (N=135)	COMMODORE-1 Crovalimab (Switch) (N=44)
Subjects treated by duration, n (%)		
<12 weeks	3 (2.2%)	2 (4.5%)
12 to <24 weeks	3 (2.2%)	4 (9.1%)
24 to <36 weeks	31 (23.0%)	6 (13.6%)
34 to <48 weeks	21 (15.6%)	8 (18.2%)
48 to <72 weeks	61 (45.2%)	14 (31.8%)
≥72 weeks	16 (11.9%)	10 (22.7%)
Total IV dose intensity (%)		
Median	100.0	100.0
Range	95.0-202.0	99.7-175.0
Total SC dose intensity (%)		
Median	100.0	100.0
Range	93.4-108.3	98.1-100.0
Number of unscheduled IV doses, n (%)		
0 doses	127 (94.1%)	40 (90.9%)
1 dose	5 (3.7%)	3 (6.8%)
2 doses	2 (1.5%)	1 (2.3%)
3 doses	1 (0.7%)	0

Source: ADEX.xpt and CSR.
Abbreviations: IV, intravenous; N, total number of subjects; n, number of subjects in subset; Q1, Quarter 1; Q3, Quarter 3; SC subcutaneous; SD, standard deviation

Nonrandomized Arms

In COMMODORE-2, the treatment duration in the 6 pediatric subjects ranged from 21 to 57 weeks. All six subjects completed the primary treatment period and treatment was ongoing in the crovalimab extension period as of the CCOD. No pediatric subjects received additional unscheduled IV doses.

In COMMODORE-1, the median treatment duration across the 4 cohorts was 36.2 weeks (range: 0.3 to 100.1) and 31.6% of subjects received crovalimab for at least 48 weeks. A total of four subjects (prior-ravulizumab cohort: three subjects, prior-high-dose eculizumab cohort: one subject) received additional IV doses of crovalimab. The summary of crovalimab exposure of the four cohorts in the nonrandomized arm in COMMODORE-1 up to the CCOD is shown in Table 22 below.

Table 22. Summary of Crovalimab Exposure up to the Clinical Cutoff Date, Nonrandomized Arm, COMMODORE-1, Safety Population

Variable	Crovalimab <18 Years (N=1)	Crovalimab Prior Ravulizumab (N=21)	Crovalimab Prior-High-Dose Eculizumab (N=10)	Crovalimab C5 SNP (N=6)
Duration of treatment (weeks)				
Mean (SD)	2.1 (NE)	36.0 (24.1)	38.5 (19.5)	56.2 (28.8)
Median (Q1, Q3)	2.1 (2.1, 2.1)	36.1 (20.0, 40.1)	38.1 (28.0, 56.0)	50.2 (32.4, 76.1)
Range	2.1-2.1	2.3-80.1	0.3-64.1	28.1-100.1
Subjects treated by duration, n (%)				
<12 weeks	1 (100%)	4 (19.0%)	1 (10.0%)	0
12 to <24 weeks	0	2 (9.5%)	1 (10.0%)	0
24 to <36 weeks	0	4 (19.0%)	2 (20.0%)	2 (33.3%)
34 to <48 weeks	0	6 (28.0%)	2 (20.0%)	1 (16.7%)
48 to <72 weeks	0	1 (4.8%)	4 (40.0%)	1 (16.7%)
≥72 weeks	0	4 (19.0%)	0	2 (33.3%)
Total IV dose intensity (%)				
Median	100.0	100.0	100.0	100.0
Range	100.0-100.0	100.0-134.0	100.0-137.5	100.0-100.0
Total SC dose intensity (%)				
Median	100.0	100.0	100.0	100.0
Range	100.0-100.0	85.7-102.4	100.0-100.0	100.0-100.0
Number of unscheduled IV doses, n (%)				
0 doses	1 (100%)	18 (85.7%)	9 (10.0%)	6 (100%)
1 dose	0	3 (14.3%)	1 (10.0%)	0

Source: CSR
Abbreviations: IV, intravenous; n, number of subjects in subset; N, total number of subjects; Q1, Quarter 1; Q3, Quarter 3; SC subcutaneous; SD, standard deviation

7.6. Safety Results

7.6.1. Safety Results, COMMODORE-1 and COMMODORE-2

Overall Summary

The overall safety profile of crovalimab at the proposed dose regimen for the treatment of adult and pediatric patients 13 years and older with PNH and BW ≥40 kg appears acceptable. Overall, crovalimab was well tolerated with a safety profile generally consistent with other approved complement inhibitors, with the exception of type III hypersensitivity reactions. The safety analysis showed crovalimab to have an acceptable safety profile in both subjects who were complement inhibitor naïve and in subjects previously treated with a C5 inhibitor. No new safety concerns were identified in the COMMODORE-1 and COMMODORE-2 extension periods or nonrandomized arms, although additional long-term safety data are needed given the small database and limited longer exposure times. To assess the long-term safety of crovalimab, a PMR for a registry in adult and pediatric patients 13 years and older with PNH and up to 5 years of safety follow-up will be issued. Postmarketing commitments to complete COMMODORE-1, COMMODORE-2, and COMPOSER will be requested from the Applicant. No additional safety concerns emerged from an analysis of the larger pooled population (see Section 17). No new safety concerns were identified in the 120-day safety update. A brief overview of the key safety findings from COMMODORE-1 and COMMODORE-2 is provided below.

Deaths

In the crovalimab-naïve arm of COMMODORE-2, a total of two subjects experienced a TEAE (myocardial infarction and respiratory tract hemorrhage) that had a fatal outcome, although neither event was due to crovalimab.

In COMMODORE-1, no deaths or TEAEs that led to discontinuation of the study drug were reported during the primary treatment period. One subject who received crovalimab during the primary treatment period and continued crovalimab during the extension period died due to colorectal cancer. The event of colorectal cancer was not related to crovalimab.

Serious Adverse Reactions

Serious ARs occurred in 6% of subjects receiving crovalimab in COMMODORE-2, including pneumonia and epistaxis, which occurred in two subjects each.

In COMMODORE-1, serious ARs were reported in three subjects (7%) receiving crovalimab. Serious ARs included pneumonia, nasopharyngitis, and urinary tract infection, which occurred in one subject each.

AEs Leading to Drug Discontinuation

In COMMODORE-2, one subject developed Grade 4 thrombocytopenia that led to study drug discontinuation during the primary treatment period. During the extension period of

COMMODORE-2, 1 subject who received eculizumab and switched to crovalimab after the 24-week randomized period experienced a Grade 3 distal axonal demyelinating polyneuropathy that led to discontinuation of crovalimab.

In COMMODORE-1, 1 subject who received eculizumab during the primary 24-week randomized treatment period and switched to crovalimab experienced a Grade 3 type III immune complex-mediated reaction that led to crovalimab discontinuation.

Common Adverse Reactions

In COMMODORE-2, in subjects who were complement inhibitor treatment naïve, the most frequently reported ARs (≥10%) in the crovalimab-naïve arm were infusion-related reactions, respiratory tract infections and viral infections.

In COMMODORE-1, in subjects who were previously treated with eculizumab and switched to crovalimab, the safety profile of the crovalimab-switch group was generally comparable to subjects who were complement treatment naïve (crovalimab naïve) except for the occurrence of type III hypersensitivity reactions due to the formation of DTDCs. The most commonly reported ARs (≥10%) in the crovalimab switch arm were viral infections, respiratory tract infections, type III hypersensitivity reactions, infusion-related reactions, peripheral edema, and headache.

7.6.1.1. Overview of Treatment-Emergent Adverse Events Summary, COMMODORE-1 and COMMODORE-2

Randomized Arms

Primary Treatment Period

Table 23 summarizes the safety results of the primary treatment period in COMMODORE-1 and COMMODORE-2. In COMMODORE-2, in subjects who were complement inhibitor treatment naïve, the safety results were similar between the crovalimab-naïve and eculizumab-naïve arms during the primary treatment period. In COMMODORE-1, in subjects who received eculizumab prior to study enrollment, the incidence of serious TEAEs (13.6% versus 2.4%), any TEAEs (77.3% versus 66.7%), and Grade 3 or 4 TEAEs (18.2% versus 2.4%) were all higher in the crovalimab-switch arm compared to the eculizumab-experienced arm, mostly due to type III hypersensitivity reactions in the switch subjects. In a cross-study comparison, the overall safety results of subjects in the crovalimab-naïve, eculizumab-naïve, and crovalimab-switch arms were similar.

In both studies, most of the TEAEs were Grade 1 or 2 in severity (COMMODORE-2 [crovalimab-naïve: 61.5%, eculizumab-naïve: 56.5%], COMMODORE-1 [crovalimab-switch:59.1%, eculizumab: 64.3%]).

Table 23. Overview of TEAEs, Primary Treatment Period, COMMODORE-1 and COMMODORE-2, Safety Population

	COMMODORE-2		COMMODORE-1	
Adverse Event	**Crovalimab (Naïve) (N=135) n (%)**	**Eculizumab (Naïve) (N=69) n (%)**	**Crovalimab (Switch) (N=44) n (%)**	**Eculizumab (Experienced) (N=42) n (%)**
Deaths	2 (1.5%)	1 (1.4%)	0	0
Serious TEAEs	14 (10.4%)	9 (13.0%)	6 (13.6%)	1 (2.4%)
Any TEAEs	105 (77.8%)	55 (79.7%)	34 (77.3%)	28 (66.7%)
Grade 3[a]	16 (11.9%)	13 (18.8%)	7 (15.9%)	1 (2.4%)
Grade 4[a]	6 (4.4%)	3 (4.3%)	1 (2.3%)	0
TEAE leading to discontinuation of study drug	1 (0.7%)	1 (1.4%)	0	0
TEAE leading to dose modification of study drug	5 (3.7%)	3 (4.3%)	1 (2.3%)	0

Source: ADAE.xpt.
[a] Based on maximum grade.
Abbreviations: N, total number of subjects; n, number of subjects in subset; TEAE, treatment-emergent adverse event

Extension Period

Table 24 summarizes the safety results of the crovalimab-naïve and crovalimab-switch groups during the extension period in COMMODORE-1 and COMMODORE-2. In the pooled analysis of COMMODORE-1 and COMMODORE-2, the overall safety of the crovalimab-naïve and crovalimab-switch groups appears broadly similar. Also see Table 133, describing the pooled safety results of COMMODORE-1, COMMODORE-2, and COMMODORE-3 per 100 patient-years, which accounts for the differences in follow-up between the crovalimab and eculizumab arms.

Table 24. Overview of TEAEs up to the Clinical Cutoff Date, Extension Period, COMMODORE-1 and COMMODORE-2, Safety Population

	COMMODORE-2		COMMODORE-1		Crovalimab (Switch) Pooled (N=142)
Adverse Event	Crovalimab (Naïve)[b] (N=129)	Crovalimab (Switch)[c] (N=68)	Crovalimab (Switch)[b] (N=39)	Crovalimab (Switch)[c] (N=35)	
Deaths	0	0	1 (2.6%)	0	1 (0.7%)
Serious TEAEs	9 (7.0%)	6 (8.8%)	7 (18.0%)	4 (11.4%)	17 (12.0%)
Any TEAEs	75 (58.1%)	50 (73.5%)	19 (48.7%)	30 (85.7%)	99 (69.7%)
Grade 3[a]	14 (10.9%)	10 (14.7%)	3 (7.7%)	8 (22.9%)	23 (16.2%)
Grade 4[a]	0	3 (4.4%)	1 (2.6%)	1 (2.9%)	5 (3.5%)
TEAE leading to discontinuation of study drug	0	1 (1.5%)	0	1 (2.9%)	2 (1.4%)
TEAE leading to dose modification of study drug	2 (1.6%)	3 (4.4%)	0	0	3 (2.1%)

Source: ADAE.xpt.
[a] Based on maximum grade.
[b] Continued crovalimab treatment from the primary treatment period.
[c] Switched from eculizumab to crovalimab in the extension period.
Abbreviations: N, total number of subjects; TEAE, treatment-emergent adverse event

Nonrandomized Arms

The overall safety results of the cohorts in the descriptive arms of COMMODORE-1 and COMMODORE-2 are summarized in Table 25. The analysis of the safety results in these cohorts is based on small sample sizes and should be interpreted with caution.

In the pediatric cohort of COMMODORE-2, the incidence of TEAEs was 83.2% (5 subjects). No serious TEAEs or Grade 3 or 4 TEAEs were reported in the pediatric cohorts in COMMODORE-1 and COMMODORE-2.

Table 25. Overview of TEAEs up to the Clinical Cutoff Date, Nonrandomized Arm, COMMODORE-1 and COMMODORE-2, Safety Population

	COMMODORE-2	COMMODORE-1			
Adverse Event	**Crovalimab (<18 years) (N=6) n (%)**	**Crovalimab (<18 years) (N=1) n (%)**	**Crovalimab (Prior Ravulizumab) (N=21) n (%)**	**Crovalimab (Prior-High-Dose Eculizumab) (N=10) n (%)**	**Crovalimab (C5 SNP) (N=6) n (%)**
Deaths	0	0	0	0	0
Serious TEAEs	0	0	7 (33.3%)	2 (20.0%)	0
Any TEAEs	5 (83.2%)	0	18 (85.7%)	10 (100.0%)	5 (83.3%)
Grade 3[a]	0	0	9 (42.9%)	3 (30.0%)	2 (33.3%)
Grade 4[a]	0	0	0	0	0
TEAE leading to discontinuation of study drug	0	0	1 (4.8%)	0	0
TEAE leading to dose modification of study drug	0	0	2 (9.5%)	1 (10.0%)	1 (16.7%)

Source: ADAE.xpt.
[a] Based on maximum grade.
Abbreviations: N, total number of subjects; n, number of subjects in subset; TEAE, treatment-emergent adverse event

7.6.1.2. Deaths, COMMODORE-1 and COMMODORE-2

Randomized Arms

During the primary treatment period, a total of three deaths (crovalimab-naïve: two [1.5%], eculizumab-naïve: one [1.4%]) occurred in COMMODORE-2, and no deaths occurred in COMMODORE-1.

In COMMODORE-2, two subjects in the crovalimab-naïve arm died; one had a myocardial infarction and the other had respiratory tract hemorrhage. One subject in the eculizumab arm died due to ischemic stroke. The subject who died due to respiratory tract hemorrhage in the crovalimab-naïve arm had discontinued from the study drug on Day 30 due to the physician's decision and was in the safety follow-up period when the AE occurred on Day 151. This subject also had multiple infections (including pneumonia and COVID-19) and a lung neoplasm that likely contributed to the event of respiratory tract hemorrhage. The other subject in the crovalimab-naïve arm died on Day 2 due to myocardial infarction after receiving the first dose of crovalimab. creatine kinase, CK-MB, and troponin I levels were reported to be elevated in the sample taken prior to the first dose of crovalimab, indicating that the subject experienced ischemia and myocardial damage before the first dose of crovalimab.

After the primary treatment period, one additional death occurred in a 51-year-old female who received crovalimab during the primary and extension treatment periods. This subject died of colorectal cancer on Day 211 in COMMODORE-1. No other risk factors for colorectal cancer were reported for this subject. Long-term carcinogenicity studies and genotoxicity studies have not been conducted with crovalimab, but the risk of carcinogenicity for crovalimab is considered low based on a weight-of-evidence risk assessment. No additional deaths were reported in COMMODORE-2 after the primary treatment period up to the CCOD.

The narratives for subjects who received crovalimab and had a fatal outcome are provided in Section 17.3.

Table 26. Deaths up to the Clinical Cutoff Date, COMMODORE-1 and COMMODORE-2, Safety Population

Treatment Group Cause of Death	Age/Sex	Study Day of Death	Day of Death Relative to Last Dose	Study Period
COMMODORE-2				
Crovalimab (naïve)				
Myocardial infarction	66F	2	1	Primary period
Respiratory tract hemorrhage	68M	151	127	Primary period
Eculizumab (naïve)				
Ischemic stroke	47M	71	28	Primary period
COMMODORE-1				
Crovalimab (experienced)				
Colorectal cancer	51F	211	6	Extension period

Source: ADAE.xpt.
Abbreviations: F, female; M, male

Nonrandomized Arms

In the nonrandomized arms in COMMODORE-1 and COMMODORE-2, no deaths were reported.

7.6.1.3. Serious Treatment-Emergent Adverse Events, COMMODORE-1 and COMMODORE-2

Randomized Arms

Primary Treatment Period

In COMMODORE-2, the incidence of serious TEAEs in subjects who were complement inhibitor naïve was similar between the two arms (crovalimab-naïve: 10.4%, eculizumab-naïve: 13.0%) during the primary treatment period. Serious TEAEs reported in more than one subject in the crovalimab arm included pneumonia and epistaxis (two subjects each). A summary of subjects with reported serious TEAEs in the crovalimab arm in COMMODORE-2 are presented below:

- A total of four subjects developed a serious TEAE in the infections and infestations system organ class (SOC) (pneumonia: two subjects [(b) (6)], pyelonephritis: one subject [(b) (6)], COVID-19: one subject [(b) (6)]). Known ARs of complement C5 inhibitors include infections.
- A total of two subjects ((b) (6)) had serious aplastic anemia and one subject ((b) (6)) had serious thrombocytopenia. Both subjects with serious aplastic anemia had a history of aplastic anemia, and the subject with serious thrombocytopenia had a history of MDS. Therefore, these events are likely due to the underlying disease.
- A total of three subjects reported serious bleeding events (epistaxis: two subjects [(b) (6)], respiratory tract hemorrhage: one subject [(b) (6)], small intestinal hemorrhage: one subject [(b) (6)]). The cause of the serious small intestinal hemorrhage (in the subject who also had a fatal respiratory tract hemorrhage, described in Section 7.6.1.2) was likely related to the underlying lung neoplasm. In the two subjects with serious epistaxis, the events cannot be excluded as a possible effect of crovalimab.
- One subject [(b) (6)], described in Section 7.6.1.2, had a myocardial infarction that had a fatal outcome that was not related to crovalimab.
- One subject [(b) (6)] experienced serious pyrexia that was considered a systemic injection reaction. The injection reaction was due to crovalimab..
- One subject [(b) (6)] experienced a serious infusion reaction due to crovalimab. This subject was hospitalized for infusion-related reaction (Grade 2 nausea, vomiting, abdominal pain, headache, and pyrexia). The infusion was held after receiving 950 mg of crovalimab (planned crovalimab IV loading dose was 1000 mg). The subject was given rehydration treatment. The SC administration of crovalimab was started on Day 2 and the subject continued crovalimab SC treatment. On Day 5, the symptoms of infusion-related reaction resolved, and the subject was discharged from the hospital.
- One subject [(b) (6)] had thyroid cancer. It was reported that the thyroid nodules were diagnosed approximately 7.5 years prior to study enrollment for which no prior treatment was administered. Therefore, this serious TEAE is not likely due to crovalimab.

- One subject [(b) (6)] had serious affective disorder, which was considered related to self-withdrawal of schizophrenia treatment before screening. Medical history in this subject included schizophrenia.
- One subject [(b) (6)] experienced serious Henoch-Schonlein purpura. This subject had influenza several days before the onset of Henoch-Schonlein purpura which likely contributed to the event.
- One subject [(b) (6)] experienced serious hypovolemic shock. This subject had urinary tract infection and episodes of diarrhea. The urinary tract infection resolved after treatment with antibiotics. All clinical symptoms improved, including the event of hypovolemic shock that resolved.

In summary, when considering causality, eight subjects (5.9%) had serious ARs due to crovalimab, which included events of infection, epistaxis, hypovolemic shock and infusion reaction.

Table 27. Serious TEAEs, Primary Treatment Period, Crovalimab Arm, COMMODORE-2, Safety Population

System Organ Class Preferred Term	Crovalimab (Naïve) (N=135) n (%)	Eculizumab (Naïve) (N=69) n (%)
All	14 (10.4%)	9 (13.0%)
Infections and Infestations	4 (3.0%)	5 (7.2%)
Pneumonia	2 (1.5%)	0
COVID-19	1 (0.7%)	1 (1.4%)
Pyelonephritis	1 (0.7%)	0
Blood and lymphatic system disorders	3 (2.2%)	3 (4.3%)
Aplastic anemia	2 (1.5%)	1 (1.4%)
Thrombocytopenia	1 (0.7%)	1 (1.4%)
Respiratory, thoracic and mediastinal disorders	3 (2.2%)	0
Epistaxis	2 (1.5%)	0
Respiratory tract hemorrhage	1 (0.7%)	0
Cardiac disorders	1 (0.7%)	1 (1.4%)
Myocardial infarction	1 (0.7%)	0
General disorders and administration site conditions	1 (0.7%)	1 (1.4%)
Pyrexia	1 (0.7%)	1 (1.4%)
Gastrointestinal disorders	1 (0.7%)	0
Small intestinal hemorrhage	1 (0.7%)	0
Injury, poisoning and procedural complications	1 (0.7%)	0
Infusion related reaction	1 (0.7%)	0
Neoplasms benign, malignant and unspecified	1 (0.7%)	1 (1.4%)
Thyroid cancer	1 (0.7%)	0
Psychiatric disorders	1 (0.7%)	0
Affective disorder	1 (0.7%)	0
Skin and subcutaneous tissue disorders	1 (0.7%)	0
Henoch-Schonlein purpura	1 (0.7%)	0

System Organ Class Preferred Term	Crovalimab (Naïve) (N=135) n (%)	Eculizumab (Naïve) (N=69) n (%)
Vascular disorders	1 (0.7%)	0
Hypovolemic shock	1 (0.7%)	0

Source: ADAE.xpt.
Note: Incidences are based on the number of subjects, not the number of events. Although a subject may have had 2 or more clinical AEs, the subject is counted only once in a category. The same subject may appear in different categories.
Abbreviations: AE, adverse event; COVID-19, coronavirus disease of 2019; N, total number of subjects; n, number of subjects in subset; TEAE, treatment-emergent adverse event

In COMMODORE-1, in subjects who had previously been treated with eculizumab, the overall incidence of serious TEAEs was higher in the crovalimab-switch arm (13.6%) compared with the eculizumab-experienced arm (2.4%) during the primary treatment period. A summary of subjects with reported serious TEAEs in the crovalimab arm in COMMODORE-1 is presented below.

- A total of three subjects had serious infection (pneumonia: one subject [(b) (6)], nasopharyngitis: one subject [(b) (6)], urinary tract infection: one subject [(b) (6)]). ARs of complement C5 inhibitors include infections.
- One subject had neutropenia [(b) (6)]. At baseline, the neutrophil count was reported to be 0.002×10^9/L. On Day 126, the subject had Grade 4 neutropenia (absolute neutrophil count 0.282×10^9/L; normal range: 3.15 to 6.2×10^9/L). It was reported that the subject was asymptomatic, and neutropenia was probably a post COVID-19 infection complication. No treatment was administered. The neutrophil count increased to 1.57×10^9/L (within normal range) on Day 154. Considering the low baseline absolute neutrophil count that improved while continuing crovalimab, this event of serious neutropenia is most likely not related to the study treatment.
- One subject [(b) (6)] had serious pyrexia that required hospitalization. The cause of pyrexia was due to underlying disease.
- One subject [(b) (6)] had hyperbilirubinemia, which was reported as related to concomitant medication (sitagliptin/metformin given for diabetes mellitus) and returned to baseline without change in the study treatment.
- One subject [(b) (6)] reported serious skin laceration. It was reported that the subject accidentally hurt his right elbow on wood while working.
- One subject [(b) (6)] developed cervical dysplasia. On Day 85, the subject was diagnosed with Grade 2 cervical dysplasia and cervical conical resection was performed. The event was considered resolved.

In summary, after considering causality, a total of three subjects (6.8%) experienced serious ARs related to crovalimab, this included infectious events.

Table 28. Serious TEAEs, Primary Treatment Period, Crovalimab Arm, COMMODORE-1, Safety Population

System Organ Class Preferred Term	Crovalimab (Switch) (N=44) n (%)	Eculizumab (Experienced) (N=42) n (%)
All	6 (13.6%)	1 (2.4%)
Infections and infestations	3 (6.8%)	1 (2.4%)
Pneumonia	1 (2.3%)	1 (2.4%)
Nasopharyngitis	1 (2.3%)	0
Urinary tract infection	1 (2.3%)	0
Blood and lymphatic system disorder	1 (2.3%)	0
Neutropenia	1 (2.3%)	0
General disorders and administration site conditions	1 (2.3%)	0
Pyrexia	1 (2.3%)	0
Hepatobiliary disorders	1 (2.3%)	0
Hyperbilirubinemia	1 (2.3%)	0
Injury, poisoning and procedural complications	1 (2.3%)	0
Skin laceration	1 (2.3%)	0
Reproductive system and breast disorders	1 (2.3%)	0
Cervical dysplasia	1 (2.3%)	0

Source: ADAE.xpt.
Note: Incidences are based on the number of subjects, not the number of events. Although a subject may have had 2 or more clinical AEs, the subject is counted only once in a category. The same subject may appear in different categories.
Abbreviations: AE, adverse event; n, number of subjects in subset; N, total number of subjects; TEAE, treatment-emergent adverse event

Extension Period

During the extension period in COMMODORE-2, nine subjects (7.0%) who continued crovalimab treatment and six subjects (8.8%) who switched from eculizumab to crovalimab experienced a serious TEAE.

During the extension period of COMMODORE-1, a total of 11 subjects (14.9%) experienced a serious TEAE (7 out of 39 subjects [18.0%] who received crovalimab during the primary treatment period and 4 out of 35 subjects [11.4%] who switched to crovalimab in the extension period).

The most common SAEs were related to infections. Serious TEAEs that occurred in more than one subject in the crovalimab-naïve or switch groups during the extension period were respiratory tract infection, pneumonia, COVID-19 and BTH. BTH is considered related to the underlying disease.

Type III hypersensitivity and demyelinating polyneuropathy SAEs were each reported in one crovalimab-switch subject. These risks are discussed in Section 7.7.2.

Table 29. Serious TEAEs up to the Clinical Cutoff Date, Extension Period, COMMODORE-1 and COMMODORE-2, Safety Population

	COMMODORE-2		COMMODORE-1	Crovalimab (Switch) Pooled (N=142) n (%)
System Organ Class Preferred Term	Crovalimab (Naïve) (N=129) n (%)	Crovalimab (Switch) (N=68) n (%)	Crovalimab (Switch) (N=74) n (%)	
All	9 (7.0%)	6 (8.8%)	11 (14.9%)	17 (12.0%)
Infections and Infestations	6 (4.7%)	2 (2.9%)	5 (6.8%)	7 (4.9%)
Respiratory tract infection[a]	2 (1.6%)	0	1 (1.4%)	1 (0.7%)
Pneumonia	2 (1.6%)	0	2 (2.7%)	2 (1.4%)
Dengue fever	1 (0.8%)	0	0	0
Infection	1 (0.8%)	0	0	0
Influenza	1 (0.8%)	0	0	0
Gastroenteritis	0	1 (1.5%)	0	1 (0.7%)
Septic shock	0	1 (1.5%)	0	1 (0.7%)
COVID-19	0	0	2 (2.7%)	2 (1.4%)
Pyelonephritis	0	0	1 (1.4%)	1 (0.7%)
Systemic bacterial infection	0	0	1 (1.4%)	1 (0.7%)
Urinary tract infection	0	0	1 (1.4%)	1 (0.7%)
Blood and lymphatic system disorders	1 (0.8%)	1 (1.5%)	2 (2.7%)	3 (2.1%)
Anemia	0	1 (1.5%)	0	1 (0.7%)
Breakthrough hemolysis	1 (0.8%)	0	2 (2.7%)	2 (1.4%)
Febrile neutropenia	0	0	1 (1.4%)	1 (0.7%)
Respiratory, thoracic and mediastinal disorders	1 (0.8%)	0	0	0
Epistaxis	1 (0.8%)	0	0	0
Cardiac disorders	1 (0.8%)	0	0	0
Coronary artery disease	1 (0.8%)	0	0	0
Renal and urinary disorders	0	1 (1.5%)	0	1 (0.7%)
Paroxysmal nocturnal hemoglobinuria	0	1 (1.5%)	0	1 (0.7%)
Neoplasms benign, malignant and unspecified	0	2 (2.9%)	1 (1.4%)	3 (2.1%)
Mantle cell lymphoma	0	1 (1.5%)	0	1 (0.7%)
Myelodysplastic syndrome	0	1 (1.5%)	0	1 (0.7%)
Colorectal cancer	0	0	1 (1.4%)	1 (0.7%)
Gastrointestinal disorders	0	0	2 (2.7%)	2 (1.4%)
Obstructive pancreatitis	0	0	1 (1.4%)	1 (0.7%)
Ileus	0	0	1 (1.4%)	1 (0.7%)
Immune system disorders	0	0	1 (1.4%)	1 (0.7%)
Type III immune complex mediated reaction	0	0	1 (1.4%)	1 (0.7%)

System Organ Class Preferred Term	COMMODORE-2 Crovalimab (Naïve) (N=129) n (%)	COMMODORE-2 Crovalimab (Switch) (N=68) n (%)	COMMODORE-1 Crovalimab (Switch) (N=74) n (%)	Crovalimab (Switch) Pooled (N=142) n (%)
Injury, poisoning and procedural complications	1 (0.8%)	0	1 (1.4%)	1 (0.7%)
Limb traumatic amputation	1 (0.8%)	0	0	0
Skin laceration	0	0	1 (1.4%)	1 (0.7%)
Open globe injury	0	0	1 (1.4%)	1 (0.7%)
General disorders and administration site conditions	0	0	1 (1.4%)	1 (0.7%)
Pyrexia	0	0	1 (1.4%)	1 (0.7%)
Nervous system disorder	1 (0.8%)	1 (1.5%)	0	1 (0.7%)
Demyelinating polyneuropathy	0	1 (1.5%)	0	1 (0.7%)
Seizure	1 (0.8%)	0	0	0
Hepatobiliary disorder	0	1 (1.5%)	1 (1.4%)	2 (1.4%)
Cholelithiasis	0	1 (1.5%)	0	1 (0.7%)
Hyperbilirubinemia	0	0	1 (1.4%)	1 (0.7%)
Reproductive system and breast disorders	0	0	1 (1.4%)	1 (0.7%)
Cervical dysplasia	0	0	1 (1.4%)	1 (0.7%)

Source: ADAE.xpt.
Note: Incidences are based on the number of subjects, not the number of events. Although a subject may have had 2 or more clinical AEs, the subject is counted only once in a category. The same subject may appear in different categories.
[a] Includes respiratory infection and upper respiratory infection.
Abbreviations: AE, adverse event; COVID-19, coronavirus disease of 2019; N, total number of subjects; n, number of subjects in subset; TEAE, treatment-emergent adverse event

Nonrandomized Arms

In COMMODORE-2, no serious TEAEs were reported in the pediatric cohort up to the CCOD.

In COMMODORE-1, a total of 9 subjects (23.7%) experienced serious TEAEs in the nonrandomized arm (prior-ravulizumab cohort: 7 subjects [33.3%], prior-high-dose eculizumab cohort: 2 subjects [20.0%]) up to the CCOD. In the prior-high-dose eculizumab cohort, serious autoimmune hemolytic anemia in the setting of COVID-19 and a type III immune complex-mediated reaction was reported in one subject each. Serious TEAEs reported in the prior-ravulizumab cohort were type III immune complex-mediated reaction (n=3); (extravascular) hemolysis (n=2); and axonal neuropathy, calculus urinary, cholangitis, infection, sepsis, and viral infection, each in one subject. No subjects in the pediatric or C5 polymorphism cohorts reported a serious TEAE. type III hypersensitivity reaction and axonal neuropathy are discussed further in Section 7.7.2 of the review.

7.6.1.4. Adverse Events Leading to Treatment Discontinuation, COMMODORE-1 and COMMODORE-2

Randomized Arms

In COMMODORE-2, 1 subject in the crovalimab-naïve arm experienced Grade 4 thrombocytopenia during the primary treatment period on Day 139 that led to discontinuation of the study treatment due to worsening MDS that was reported at baseline. It has been reported that the subject received no treatment for the TEAE and recovered. Patients with PNH are at increased risk for bone marrow failure and MDS; therefore, this event is likely not related to crovalimab (Sun and Babushok 2020).

Table 30. Summary of TEAEs Leading to Treatment Discontinuation, Primary Treatment Period, COMMODORE-2, Safety Population

System Organ Class Preferred Term	Crovalimab (Naïve) (N=135) n (%)	Eculizumab (Naïve) (N=69) n (%)
All	1 (0.7%)	1 (1.4%)
Blood and lymphatic system disorders	1 (0.7%)	0
Thrombocytopenia	1 (0.7%)	0
Nervous system disorders	0	1 (1.4%)
Ischemic stroke	0	1 (1.4%)

Source: ADAE.xpt.
Abbreviations: n, number of subjects in subset; N, total number of subjects; TEAE, treatment-emergent adverse event

After the primary treatment period, no additional subjects in the crovalimab-naïve arm experienced a TEAE leading to treatment discontinuation. In subjects who received eculizumab and switched to crovalimab after the 24-week randomized period, one subject (USUBJID (b) (6)) experienced a Grade 3 distal axonal demyelinating polyneuropathy that led to discontinuation of crovalimab. The narrative for this subject is presented in Section 17.3, and the risk of axonal neuropathy is discussed further in Section 7.7.2 of this review.

In COMMODORE-1, no subjects had a TEAE leading to discontinuation of the study drug during the primary treatment period. Among subjects who received eculizumab during the

primary 24-week randomized treatment period and switched to crovalimab, one subject (USUBJID [redacted] (b) (6)) experienced a Grade 3 type III immune complex-mediated reaction that led to treatment discontinuation. The narrative for this subject is presented in Section 17.4, and the AR is discussed further in Section 7.7.2.

Nonrandomized Arms

In COMMODORE-2, no subjects in the pediatric cohort experienced a TEAE leading to discontinuation of the study drug. In COMMODORE-1, one subject (USUBJID [redacted] (b) (6)) in the prior-ravulizumab cohort experienced a Grade 3 sepsis event that led to withdrawal of crovalimab. The narrative for this subject is presented in Section 17.3.

7.6.1.5. Adverse Events Leading to Treatment Modification, COMMODORE-1 and COMMODORE-2

Randomized Arms

Primary Treatment Period

During the primary treatment period, similar proportions of subjects in the two treatment arms had a dose modification due to TEAEs in COMMODORE-2 (crovalimab: 3.7%, eculizumab: 4.3%) and COMMODORE-1 (crovalimab: 2.3%, eculizumab: 0). The TEAEs were reported as resolved in both studies except for two subjects in COMMODORE-2 (one subject who experienced pancytopenia in the crovalimab-naïve arm and one subject who had chronic cholecystitis in the eculizumab-naïve arm). Overall, dose modifications were rare and usually were due to infections leading to dose interruption.

Table 31. Summary of TEAEs Leading to Treatment Modification of the Study Drug, Primary Treatment Period, COMMODORE-1 and COMMODORE-2, Safety Population

	COMMODORE-2		COMMODORE-1	
System Organ Class Preferred Term	Crovalimab (Naïve) (N=135) n (%)	Eculizumab (Naïve) (N=69) n (%)	Crovalimab (Switch) (N=44) n (%)	Eculizumab (Experienced) (N=42) n (%)
All	5 (3.7%)	3 (4.3%)	1 (2.3%)	0
Dose interrupted	3 (2.2%)	3 (4.3%)	1 (2.3%)	0
Reason for dose interruption				
COVID-19	2 (1.5%)	1 (1.4%)	0	0
Cholecystitis chronic	0	1 (1.4%)	0	0
Infusion related reaction	1 (0.7%)	0	0	0
Sepsis	0	1 (1.4%)	0	0
Pancytopenia	1 (0.7%)	0	0	0
Pneumonia	0	0	1 (2.3%)	0
Dose reduced	1 (0.7%)	0	0	0
Reason for dose reduction				
Nausea	1 (0.7%)	0	0	0

System Organ Class Preferred Term	COMMODORE-2 Crovalimab (Naïve) (N=135) n (%)	COMMODORE-2 Eculizumab (Naïve) (N=69) n (%)	COMMODORE-1 Crovalimab (Switch) (N=44) n (%)	COMMODORE-1 Eculizumab (Experienced) (N=42) n (%)
Dose increased	1 (0.7%)	0	0	0
Reason for dose increase				
Feeling cold	1 (0.7%)	0	0	0
Peripheral coldness	1 (0.7%)	0	0	0

Source: ADAE.xpt.
Note: Incidences are based on the number of subjects, not the number of events. Although a subject may have had two or more clinical AEs, the subject is counted only once in a category. The same subject may appear in different categories.
Abbreviations: AE, adverse event; COVID-19, coronavirus disease of 2019; N, total number of subjects; n, number of subjects in subset; TEAE, treatment-emergent adverse event

Extension Period

During the extension period of COMMODORE-2, there were a total of five subjects (crovalimab-naïve: two subjects [1.6%, due to COVID-19], crovalimab-switch: three subjects [4.4%, due to a type III immune complex-mediated reaction, abdominal pain, and mantle cell lymphoma, respectively]) who had treatment modification (all treatment interruption) due to TEAEs. All TEAEs resolved, except the subject who had mantle cell lymphoma. In COMMODORE-1, there were no additional subjects who experienced a TEAE that led to treatment modification.

Nonrandomized Arms

In COMMODORE-2, no subjects in the pediatric cohort had a dose modification due to a TEAE. In COMMODORE-1, a total of four subjects had dose modification (dose interruption: three subjects due to an infusion reaction [prior-ravulizumab cohort], COVID-19 [C5 SNP cohort] and type III hypersensitivity reaction [prior high eculizumab dose cohort], dose increase: one subject due to nasopharyngitis [prior-ravulizumab cohort]). All TEAEs resolved.

7.6.1.6. Significant Adverse Events, COMMODORE-1 and COMMODORE-2

Randomized Arms

Primary Treatment Period

In COMMODORE-2, Grade 3 or higher TEAEs occurred in 17.8% of subjects in the crovalimab-naïve arm and 24.6% in the eculizumab-naïve arm during the primary 24-week treatment period. The incidence of Grade 4 TEAEs was similar between the two arms (crovalimab-naïve: six subjects [4.4%], eculizumab-naïve: three subjects [4.3%]). Grade 4 TEAEs that occurred in the crovalimab-naïve arm were aplastic anemia (n=2), neutropenia (n=2), thrombocytopenia (n=2) and pyelonephritis (n=1). Patients with PNH are at increased risk of aplastic anemia, therefore, it is more likely that the aplastic anemia events, including cytopenias were related to the underlying disease. However, the event of pyelonephritis was likely related to crovalimab.

Table 32. Grade 3 or Higher TEAEs, Primary Treatment Period, Crovalimab Arm, COMMODORE-2, Safety Population

System Organ Class Preferred Term	Crovalimab (Naïve) (N=135) n (%)	Eculizumab (Naïve) (N=69) n (%)
All	24 (17.8%)	17 (24.6%)
Grade 3[b]	16 (11.9%)	13 (18.8%)
Grade 4[b]	6 (4.4%)	3 (4.3%)
Grade 5[b]	2 (1.5%)	1 (1.4%)
Blood and lymphatic system disorders	14 (10.4%)	10 (14.5%)
Neutropenia[a]	9 (6.7%)	8 (11.6%)
Leukopenia[a]	3 (2.2%)	1 (1.4%)
Aplastic anemia	2 (1.5%)	1 (1.4%)
Thrombocytopenia[a]	2 (1.5%)	1 (1.4%)
Anemia[a]	3 (2.2%)	1 (1.4%)
Pancytopenia	1 (0.7%)	0
Infections and infestations	4 (3.0%)	4 (5.8%)
Pneumonia	2 (1.5%)	0
COVID-19	1 (0.7%)	0
Pyelonephritis	1 (0.7%)	0
Hepatobiliary disorders	2 (1.5%)	3 (4.3%)
Hepatic injury[a]	1 (0.7%)	2 (2.9%)
Respiratory, thoracic and mediastinal disorders	2 (1.5%)	0
Epistaxis	1 (0.7%)	0
Respiratory tract hemorrhage	1 (0.7%)	0
Vascular disorders	2 (1.5%)	0
Hypertension	1 (0.7%)	0
Hypovolemic shock	1 (0.7%)	0
Cardiac disorders	1 (0.7%)	1 (1.4%)
Myocardial infarction	1 (0.7%)	0
Neoplasms benign, malignant and unspecified	1 (0.7%)	1 (1.4%)
Thyroid cancer	1 (0.7%)	0
Gastrointestinal disorders	1 (0.7%)	0
Small intestinal hemorrhage	1 (0.7%)	0
General disorders and administration site conditions	1 (0.7%)	0
Pyrexia	1 (0.7%)	0
Psychiatric disorders	1 (0.7%)	0
Affective disorder	1 (0.7%)	0
Skin and subcutaneous tissue disorders	1 (0.7%)	0
Henoch-Schonlein purpura	1 (0.7%)	0

Source: ADAE.xpt.
Note: Incidences are based on the number of subjects, not the number of events. Although a subject may have had 2 or more clinical AEs, the subject is counted only once in a category. The same subject may appear in different categories.
[a] Grouped terms: Neutropenia includes neutropenia, neutrophil count decreased and febrile neutropenia. Leukopenia includes white blood cell count decreased. Thrombocytopenia includes platelet count decreased. Anemia includes anemia and aplastic anemia. Hepatic injury includes hepatic function abnormal, hypertransaminasemia and alanine aminotransferase increased.
[b] Based on maximum grade.
Abbreviations: AE, adverse event; COVID-19, coronavirus disease of 2019; n, number of subjects in subset; N, total number of subjects; TEAE, treatment-emergent adverse event

In COMMODORE-1, in subjects who had previously received treatment with eculizumab the incidence of ≥ Grade 3 TEAEs was higher in the crovalimab switch arm (18.2%) compared with the eculizumab-experienced arm (2.4%) during the primary treatment period, which was most likely because subjects in the eculizumab arm had been on stable treatment with eculizumab prior to study enrollment, reflecting subjects who had been tolerating eculizumab. In the

crovalimab-switch arm, ≥Grade 3 TEAE that occurred in two or more subjects were neutropenia (Grade 3 and 4 neutropenia was reported in one subject, respectively). There was one subject in the crovalimab-switch arm who had a Grade 3 type III immune complex-mediated reaction. This AR is discussed in further detail in Section 7.7.2.

Table 33. Grade 3 or Higher TEAEs, Primary Treatment Period, Crovalimab Arm, COMMODORE-1, Safety Population

System Organ Class Preferred Term	Crovalimab (Switch) (N=44) n (%)	Eculizumab (Experienced) (N=42) n (%)
All	8 (18.2%)	1 (2.4%)
Grade 3[a]	7 (15.9%)	1 (2.4%)
Grade 4[a]	1 (2.3%)	0
Blood and lymphatic system disorders	3 (6.8%)	0
Neutropenia	2 (4.5%)	0
Extravascular hemolysis	1 (2.3%)	0
Infections and infestations	2 (4.5%)	1 (2.4%)
Pneumonia	1 (2.3%)	1 (2.4%)
Urinary tract infection	1 (2.3%)	0
Immune system disorders	2 (4.5%)	0
Hypersensitivity	1 (2.3%)	0
Type III immune complex mediated reaction	1 (2.3%)	0
Hepatobiliary disorders	1 (2.3%)	0
Hyperbilirubinemia	1 (2.3%)	0
Injury, poisoning and procedural complications	1 (2.3%)	0
Skin laceration	1 (2.3%)	0
Metabolism and nutrition disorders	1 (2.3%)	0
Hypokalemia	1 (2.3%)	0
Vascular disorders	1 (2.3%)	0
Hypertension	1 (2.3%)	0

Source: ADAE.xpt.
Note: Incidences are based on the number of subjects, not the number of events. Although a subject may have had 2 or more clinical AEs, the subject is counted only once in a category. The same subject may appear in different categories.
[a] Based on maximum grade.
Abbreviations: AE, adverse event; n, number of subjects; N, total number of subjects; n, number of subjects in subset; TEAE, treatment-emergent adverse event

Extension Period

Table 34 summarizes ≥Grade 3 TEAEs that occurred during the extension period in COMMODORE-1 and COMMODORE-2.

In COMMODORE-2, among the 68 subjects who received eculizumab during the primary treatment period and switched to crovalimab, the incidence of ≥ Grade 3 TEAEs was 19.1% during the extension period. A total of three subjects (4.4%) reported Grade 4 TEAEs that were most likely due to the underlying disease (i.e., neutropenia, anemia, aplastic anemia, and MDS, one case each).

In COMMODORE-1, the overall incidence of ≥ Grade 3 TEAEs was 18.9% in the crovalimab-switch population during the extension period. There was one Grade 5 TEAE of colorectal cancer as described in Section 7.6.1.2. Grade 4 TEAEs were reported in a total of two subjects (neutropenia and obstructive pancreatitis, one subject each). Among the 35 subjects who received eculizumab during the primary treatment period and switched to crovalimab, the

incidence of ≥ Grade 3 TEAEs during the extension period was 25.7% (9 subjects), and among the 39 subjects who received crovalimab during the primary treatment period and continued crovalimab during the extension period, the incidence of ≥ Grade 3 TEAEs was lower at 12.8% (5 subjects).

Table 34. Grade 3 or Higher TEAEs up to the Clinical Cutoff Date, Extension Period, COMMODORE-1 and COMMODORE-2, Safety Population

	COMMODORE-2		COMMODORE-1	Crovalimab (Switch) Pooled (N=142) n (%)
System Organ Class Preferred Term	Crovalimab (Naïve) (N=129) n (%)	Crovalimab (Switch) (N=68) n (%)	Crovalimab (Switch) (N=74) n (%)	
All	14 (10.9%)	13 (19.1%)	14 (18.9%)	29 (20.4%)
Grade 3[b]	14 (10.9%)	10 (14.7%)	11 (14.9%)	23 (16.2%)
Grade 4[b]	0	3 (4.4%)	2 (2.7%)	5 (3.5%)
Grade 5[b]	0	0	1 (1.4%)	1 (0.7%)
Infections and Infestations	4 (3.1%)	2 (2.9%)	4 (5.4%)	6 (4.2%)
Respiratory infection[a]	2 (1.6%)	1 (1.5%)	1 (1.4%)	2 (1.4%)
Pneumonia	1 (0.8%)	0	0	0
Dengue fever	1 (0.8%)	0	0	0
Urinary tract infection	1 (0.8%)	0	0	0
Septic shock	0	1 (1.5%)	0	1 (0.7%)
COVID-19	0	0	1 (1.4%)	1 (0.7%)
Pyelonephritis	0	0	1 (1.4%)	1 (0.7%)
Urinary tract infection	0	0	1 (1.4%)	1 (0.7%)
Blood and lymphatic system disorders	7 (5.4%)	5 (7.4%)	4 (5.4%)	9 (6.3%)
Neutropenia[a]	1 (0.8%)	2 (2.9%)	2 (2.7%)	4 (2.8%)
Anemia[a]	2 (1.6%)	2 (.9%)	0	2 (1.4%)
Thrombocytopenia	0	1 (1.5%)	1 (1.4%)	2 (1.4%)
Leukopenia	1 (0.8%)	1 (1.5%)	0	1 (0.7%)
Hemolysis[a]	3 (2.3%)	0	2 (2.7%)	2 (1.4%)
Febrile neutropenia			1 (1.4%)	1 (0.7%)
Respiratory, thoracic and mediastinal disorders	1 (0.8%)	0	0	0
Epistaxis	1 (0.8%)	0	0	0
Cardiac disorders	1 (0.8%)	0	0	0
Coronary artery disease	1 (0.8%)	0	0	0
Neoplasms benign, malignant and unspecified	0	2 (2.9%)	1 (1.4%)	3 (2.1%)
Mantle cell lymphoma	0	1 (1.5%)	0	1 (0.7%)
Myelodysplastic syndrome	0	1 (1.5%)	0	1 (0.7%)
Colorectal cancer			1 (1.4%)	1 (0.7%)
General disorders and administration site conditions	1 (0.8%)	0	1 (1.4%)	1 (0.7%)
Asthenia	1 (0.8%)	0	1 (1.4%)	1 (0.7%)
Gastrointestinal disorders	0	1 (1.5%)		1 (0.7%)
Ascites	0	1 (1.5%)		1 (0.7%)
Obstructive pancreatitis	0	0	1 (1.4%)	1 (0.7%)
Ileus	0	0	1 (1.4%)	1 (0.7%)
Immune system disorders	0	4 (5.9%)	3 (4.1%)	7 (4.9%)
Type III immune complex mediated reaction	0	4 (5.9%)	3 (4.1%)	7 (4.9%)
Nervous system disorder	0	1 (1.5%)	0	1 (0.7%)
Demyelinating polyneuropathy	0	1 (1.5%)	0	1 (0.7%)

System Organ Class Preferred Term	COMMODORE-2 Crovalimab (Naïve) (N=129) n (%)	COMMODORE-2 Crovalimab (Switch) (N=68) n (%)	COMMODORE-1 Crovalimab (Switch) (N=74) n (%)	Crovalimab (Switch) Pooled (N=142) n (%)
Hepatobiliary disorder	2 (1.6%)	3 (4.4%)	3 (4.1%)	6 (4.2%)
Hepatic injury[a]	2 (1.6%)	3 (4.4%)	2 (2.7%)	5 (3.5%)
Cholangitis	0	0	1 (1.4%)	1 (0.7%)
Renal and urinary disorders	0	0	1 (1.4%)	1 (0.7%)
Acute kidney injury	0	0	1 (1.4%)	1 (0.7%)
Metabolism and nutrition disorders	0	0	1 (1.4%)	1 (0.7%)
Diabetes mellitus	0	0	1 (1.4%)	1 (0.7%)
Injury, poisoning and procedural complications	0	0	2 (2.7%)	2 (1.4%)
Contusion	0	0	1 (1.4%)	1 (0.7%)
Open globe injury	0	0	1 (1.4%)	1 (0.7%)

Source: ADAE.xpt.
Note: Incidences are based on the number of subjects, not the number of events. Although a subject may have had 2 or more clinical AEs, the subject is counted only once in a category. The same subject may appear in different categories.
[a] Grouped terms: Respiratory tract infection includes respiratory tract infection and upper respiratory tract infection. Anemia includes anemia, aplastic anemia and autoimmune hemolytic anemia. Neutropenia includes neutropenia and febrile neutropenia. Hemolysis includes hemolysis and breakthrough hemolysis. Hepatic injury includes alanine aminotransferase increased, hyperbilirubinemia and hepatotoxicity.
[b] Based on maximum grade.
Abbreviations: COVID-19, coronavirus disease of 2019; n, number of subjects in subset; N, total number of subjects; TEAE, treatment-emergent adverse event

Nonrandomized Arms

In COMMODORE-2, no pediatric subjects had ≥ Grade 3 TEAEs up to the CCOD.

In COMMODORE-1, a total of 14 subjects (36.8%) in the nonrandomized arm developed Grade 3 TEAEs up to the CCOD. No Grade 4 TEAEs were reported. The incidence of Grade 3 TEAEs in this small cohort was the highest in the prior-ravulizumab cohort (42.9%, 9 subjects) followed by the C5 polymorphism cohort (33.3%, 2 subjects) and prior-high-dose eculizumab (30.0%, 3 subjects). Grade 3 type III immune complex-mediated reactions were reported in a total of 5 subjects (prior-ravulizumab cohort: 3 subjects [14.3%], prior-high-dose eculizumab: 2 subjects [20.0%]). In addition, a total of two subjects (9.5%) in the prior-ravulizumab cohort experienced Grade 3 hemolysis.

Table 35. Grade 3 or Higher TEAEs up to the Clinical Cutoff Date, Nonrandomized Arm, COMMODORE-1, Safety Population

System Organ Class Preferred Term	Crovalimab (<18 years) (N=1) n (%)	Crovalimab (Prior Ravulizumab) (N=21) n (%)	Crovalimab (Prior-High-Dose Eculizumab) (N=10) n (%)	Crovalimab (C5 SNP) (N=6) n (%)
All	0	9 (42.9%)	3 (30.0%)	2 (33.3%)
Grade 3[b]	0	9 (42.9%)	3 (30.0%)	2 (33.3%)
Immune system disorders	0	3 (14.3%)	2 (20.0%)	0
Type III immune complex mediated reaction	0	3 (14.3%)	2 (20.0%)	0
Blood and lymphatic system disorders	0	3 (14.3%)	1 (10.0%)	0
Hemolysis[a]	0	2 (9.5%)	0	0
Autoimmune hemolytic anemia	0	0	1 (10.0%)	0
Neutropenia[a]		1 (4.8%)	0	0

System Organ Class Preferred Term	Crovalimab (<18 years) (N=1) n (%)	Crovalimab (Prior Ravulizumab) (N=21) n (%)	Crovalimab (Prior-High-Dose Eculizumab) (N=10) n (%)	Crovalimab (C5 SNP) (N=6) n (%)
Infections and infestations	0	2 (9.5%)	0	0
Sepsis	0	1 (4.8%)	0	0
Viral infection	0	1 (4.8%)	0	0
Cardiac disorders	0	1 (4.8%)	0	0
Cardiac failure	0	1 (4.8%)	0	0
General disorders and administration site conditions	0	1 (4.8%)	0	0
Systemic inflammatory response syndrome	0	1 (4.8%)	0	0
Hepatobiliary disorders	0	1 (4.8%)	0	1 (16.7%)
Hepatic injury[a]	0	0	0	1 (16.7%)
Cholangitis[a]	0	1 (4.8%)	0	0
Injury, poisoning and procedural complications	0	1 (4.8%)	0	0
Injection related reaction	0	1 (4.8%)	0	0
Nervous system disorders	0	1 (4.8%)	0	0
Axonal neuropathy	0	1 (4.8%)	0	0
Renal and urinary disorders	0	1 (4.8%)	0	0
Calculus urinary	0	1 (4.8%)	0	0
Vascular disorders	0	0	0	1 (16.7%)
Hypertension	0	0	0	1 (16.7%)

Source: ADAE.xpt.
Note: Incidences are based on the number of subjects, not the number of events. Although a subject may have had 2 or more clinical AEs, the subject is counted only once in a category. The same subject may appear in different categories.
[a] Grouped terms: Hemolysis includes hemolysis and extravascular hemolysis. Neutropenia includes neutrophil count decreased. Hepatic injury includes alanine aminotransferase increased and aspartate aminotransferase increased. Cholangitis includes cholangitis and cholangitis acute.
[b] Based on maximum grade.
Abbreviations: AE, adverse event; C5, complement component 5; N, total number of subjects; n, number of subjects in subset; SNP, single nucleotide polymorphism; TEAE, treatment-emergent adverse event

7.6.1.7. Treatment-Emergent Adverse Events, COMMODORE-1 and COMMODORE-2

Randomized Arms

Primary Treatment Period

In COMMODORE-2, the overall incidences of TEAEs were similar between the two treatment arms (crovalimab-naïve: 77.8%, eculizumab-naïve: 79.7%) during the primary treatment period. The most frequently reported ARs (≥10%) in the crovalimab-naïve arm were infusion-related reactions, respiratory tract infections, and viral infections. The TEAEs that occurred at a ≥5% higher incidence in the crovalimab-naïve arm compared with the eculizumab-naïve arm were injection related reactions (5.9%) and diarrhea (7.4%).

For TEAEs that occurred in ≥5% of subjects, the clinical team determined cytopenias (leukopenia, neutropenia, and thrombocytopenia) were likely related to the underlying disease given PNH is a bone marrow failure syndrome. Hemorrhage was not an AR as this was a group term that included events unrelated to crovalimab (i.e., Henoch-Schonlein purpura, respiratory

tract hemorrhage, and gastrointestinal hemorrhage). Hepatic injury was not considered related to crovalimab; this is discussed further in Section 7.6.1.10. Pyrexia occurred in the context of infections, injection and infusion reactions and therefore is captured by those other ARs. Based on the mechanism of action, crovalimab is not likely to cause hypokalemia and hypocalcemia. The ARs that occurred in ≥2% of subjects in the crovalimab naïve arm are listed in Table 37, and were considered related to crovalimab.

Table 36. TEAEs That Occurred in ≥2% of Subjects, Primary Treatment Period, Crovalimab Arm, COMMODORE-2, Safety Population

System Organ Class FMQ (Narrow)/Preferred Term	Crovalimab (Naïve) (N=135) n (%)	Eculizumab (Naïve) (N=69) n (%)
All	105 (77.8%)	55 (79.7%)
Blood and lymphatic system disorders		
Leukopenia[a]	66 (48.9%)	33 (47.8%)
Neutropenia[a]	58 (43.0%)	38 (55.1%)
Thrombocytopenia[a]	24 (17.8%)	8 (12.0%)
Aplastic anemia	3 (2.2.%)	1 (1.4%)
Hemolysis[a]	3 (2.2%)	0
Metabolism and nutrition disorders		
Hypokalemia	15 (11.1%)	9 (13.0%)
Hyperuricemia	11 (8.1%)	6 (8.7%)
Hypocalcemia	8 (5.9%)	7 (10.1%)
Infections and infestations		
Respiratory tract infection[a]	17 (12.6%)	14 (20.3%)
Viral infection[a]	15 (11.1%)	5 (7.2%)
COVID-19	11 (8.1%)	4 (5.8%)
Influenza	4 (3.0%)	0
Injury, poisoning and procedural complications		
Infusion related reaction	21 (15.6%)	9 (13.0%)
Injection related reaction[a]	8 (5.9%)	0
General disorders and administration site conditions		
Pyrexia	12 (8.9%)	7 (10.1%)
Fatigue[a]	4 (3.0%)	1 (1.4%)
Peripheral edema[a]	4 (3.0%)	0
Nervous system disorders		
Headache[a]	11 (8.1%)	4 (5.8%)
Vascular disorders		
Hemorrhage[a]	11 (8.1%)	4 (5.8%)
Gastrointestinal disorders		
Diarrhea[a]	10 (7.4%)	1 (1.4%)
Nausea	6 (4.4%)	2 (2.9%)
Abdominal pain[a]	5 (3.7%)	1 (1.4%)
Dyspepsia[a]	4 (3.0%)	0
Vomiting	3 (2.2%)	1 (1.4%)
Odynophagia	3 (2.2%)	0
Musculoskeletal and connective tissue disorders		
Myalgia	4 (3.0%)	0
Arthralgia	3 (2.2%)	3 (4.3%)

System Organ Class FMQ (Narrow)/Preferred Term	Crovalimab (Naïve) (N=135) n (%)	Eculizumab (Naïve) (N=69) n (%)
Respiratory, thoracic and mediastinal disorders		
Rhinorrhea	3 (2.2%)	3 (4.3%)
Cough	3 (2.2%)	2 (2.9%)
Dyspnea	3 (2.2%)	0
Renal and urinary disorders		
Renal and urinary tract infection	3 (2.2%)	4 (5.8%)
Skin and subcutaneous tissue disorders		
Ecchymosis	3 (2.2%)	1 (1.4%)
Hepatobiliary disorders		
Hepatic injury[a]	3 (2.2%)	3 (4.3%)

Source: ADAE.xpt.
Note: Incidences are based on the number of subjects, not the number of events. Although a subject may have had 2 or more clinical AEs, the subject is counted only once in a category. The same subject may appear in different categories.
[a] Grouped terms: Abdominal pain includes abdominal pain and abdominal pain upper. Diarrhea includes diarrhea and diarrhea infectious. Dyspepsia includes dyspepsia and abdominal pain upper. Fatigue includes fatigue, asthenia and malaise. Headache includes headache and migraine. Hepatic injury includes alanine aminotransferase increased, hypertransaminasemia and hepatic function abnormal. Hemolysis includes hemolysis and extravascular hemolysis. Hemorrhage includes petechiae, contusion, application site hemorrhage, ecchymosis, epistaxis, Henoch-Schonlein purpura, eye hemorrhage, small intestinal hemorrhage, respiratory tract hemorrhage, and rectal hemorrhage. Leukopenia includes ≥ Grade 2 leukocyte count low. Respiratory tract infection includes nasopharyngitis, pharyngitis, rhinitis, rhinitis allergic, pneumonia and upper respiratory tract infection. Neutropenia includes ≥ Grade 2 neutrophil count low. Peripheral edema includes edema peripheral and peripheral swelling. Renal and urinary tract infection includes urinary tract infection and nephrolithiasis. Thrombocytopenia includes ≥ Grade 2 platelet count low. Viral infection includes viral infection, COVID-19, influenza, herpes virus infection and oral herpes.
Abbreviations: AE, adverse event; COVID-19, coronavirus disease of 2019; FMQ, Food and Drug Administration Medical Query; N, total number of subjects; n, number of subjects in subset; TEAE, treatment-emergent adverse event

In COMMODORE-1, in subjects who previously received treatment with eculizumab, the overall incidence of TEAEs was higher in the crovalimab-switch arm (77.3%) compared with the eculizumab-experienced arm (66.7%) during the primary treatment period, which was driven by type III hypersensitivity reactions and injection-related reactions (see Sections 7.6.1.8.4 and 7.6.1.8.1). The most frequently reported ARs (≥10%) in the crovalimab-switch arm were viral infections, respiratory tract infections, type III hypersensitivity reactions, infusion-related reactions, peripheral edema, and headache.

For TEAEs that occurred in ≥5% of subjects, the clinical team determined cytopenias (leukopenia, neutropenia, and thrombocytopenia) were related to the underlying disease, pyrexia occurred due to infections and infusion/injection reactions, all other TEAEs which occurred in ≥5% of subjects were considered related to crovalimab.

Table 37. TEAEs That Occurred in >1% of Subjects, Primary Treatment Period, Crovalimab Arm, COMMODORE-1, Safety Population

System Organ Class FMQ (narrow)/ Preferred Term	Crovalimab (Switch) (N=44) n (%)	Eculizumab (Experienced) (N=42) n (%)
All	34 (77.3%)	28 (66.7%)
Infections and infestations		
Viral infection[a]	10 (22.7%)	9 (21.4%)
Respiratory tract infection[a]	8 (18.2%)	2 (4.8%)
COVID-19	6 (13.6%)	7 (16.7%)
Urinary tract infection	2 (4.5%)	3 (7.1%)
Influenza	2 (4.5%)	3 (7.1%)
Pneumonia	2 (4.5%)	1 (2.4%)
Blood and lymphatic system disorders		
Neutropenia[a]	17 (38.6%)	12 (28.6%)
Leukopenia[a]	16 (36.4%)	11 (26.2%)
Thrombocytopenia[a]	5 (11.4%)	6 (14.3%)
General disorders and administration site conditions		
Pyrexia[a]	8 (18.2%)	1 (2.4%)
Peripheral edema[a]	5 (11.4%)	1 (2.4%)
Fatigue[a]	4 (9.1%)	5 (11.9%)
Immune system disorders		
Type III immune complex mediated reaction	7 (15.9%)	0
Immunization reaction	2 (4.5%)	1 (2.4%)
Injury, poisoning and procedural complications		
Infusion related reaction	6 (13.6%)	0
Injection related reaction	4 (9.1%)	0
Nervous system disorders		
Headache	5 (11.4%)	1 (2.4%)
Skin and subcutaneous tissue disorders		
Rash[a]	4 (9.1%)	0
Pruritus	2 (4.5%)	0
Gastrointestinal disorders		
Diarrhea	3 (6.8%)	1 (2.4%)
Nausea	3 (6.8%)	2 (4.8%)
Musculoskeletal and connective tissue disorders		
Arthralgia	3 (6.8%)	0
Hepatobiliary disorders		
Cholelithiasis	2 (4.5%)	0
Cardiac disorders		
Systemic hypertension[a]	2 (4.5%)	0

Source: ADAE.xpt.
Note: Incidences are based on the number of subjects, not the number of events. Although a subject may have had 2 or more clinical AEs, the subject is counted only once in a category. The same subject may appear in different categories.
[a] Grouped terms: Fatigue includes fatigue, malaise and asthenia. Injection related reaction includes injection related reaction and injection-site reaction. Leukopenia includes ≥ Grade 2 leukocyte count low. Nasopharyngitis includes nasopharyngitis and upper respiratory tract infection. Neutropenia includes ≥ Grade 2 neutrophil count low. Rash in rash and skin exfoliation. Peripheral edema includes edema peripheral and peripheral swelling. Pyrexia includes pyrexia and febrile nonhemolytic transfusion reaction. Respiratory tract infection includes respiratory tract infection, nasopharyngitis, pneumonia and upper respiratory tract infection. Systemic hypertension includes hypertension. Thrombocytopenia includes ≥ Grade 2 platelet count low. Viral infection includes viral infection, COVID-19, influenza and respiratory syncytial virus infection.
Abbreviations: AE, adverse event; COVID-19, coronavirus disease of 2019; FMQ, Food and Drug Administration Medical Query; N, total number of subjects; n, number of subjects in subset; TEAE, treatment-emergent adverse event

Extension Period

The most frequently reported TEAEs (≥5%) in the crovalimab-naïve group in COMMODORE-2 were infections, viral infections, COVID-19, respiratory tract infections, neutropenia, and leukopenia. The most common pooled TEAEs (≥5%) in the crovalimab-switch group in COMMODORE-1 and COMMODORE-2 were viral infections, COVID-19, type III immune complex-mediated reactions, respiratory tract infections, headache, injection-related reactions, pyrexia, and leukopenia. No new safety signals were identified in the safety extension period.

Table 38. TEAEs That Occurred in >2% of Subjects up to the Clinical Cutoff Date, Extension Period, COMMODORE-1 and COMMODORE-2, Safety Population

System Organ Class FMQ/Preferred Term	COMMODORE-2 Crovalimab (Naïve) (N=129) n (%)	COMMODORE-2 Crovalimab (Switch) (N=68) n (%)	COMMODORE-1 Crovalimab (Switch) (N=74) n (%)	Crovalimab (Switch) Pooled (N=142) n (%)
All	75 (58.1%)	50 (73.5%)	49 (66.2%)	99 (69.7%)
Infections and infestations				
Viral infection[a]	20 (15.5%)	6 (8.8%)	17 (23.0%)	23 (16.2%)
COVID-19	19 (14.7%)	6 (8.8%)	13 (17.6%)	19 (13.4%)
Respiratory tract infection[a]	16 (12.4%)	7 (10.3%)	9 (12.2%)	16 (11.3%)
Nasopharyngitis	4 (3.1%)	1 (1.5%)	4 (5.4%)	5 (3.5%)
Urinary tract infection[a]	4 (3.1%)	2 (2.9%)	2 (2.7%)	4 (2.8%)
Gastroenteritis	0	2 (2.9%)	1 (1.4%)	3 (2.1%)
Injury, poisoning and procedural complications				
Injection related reaction[a]	1 (0.8%)	4 (5.9%)	5 (6.8%)	9 (6.3%)
Infusion related reaction	1 (0.8%)	2 (2.9%)	4 (5.4%)	6 (4.2%)
Gastrointestinal disorders				
Abdominal pain[a]	3 (2.3%)	4 (5.9%)	2 (2.7%)	6 (4.2%)
Dyspepsia	3 (2.3%)	2 (2.9%)	1 (1.4%)	3 (2.1%)
Diarrhea	1 (0.8%)	2 (2.9%)	2 (2.7%)	4 (2.8%)
Odynophagia	1 (0.8%)	0	2 (2.7%)	2 (1.4%)
Immune system disorders				
Type III immune complex mediated reaction	0	11 (16.2%)	8 (10.8%)	19 (13.4%)
General disorders and administration site conditions				
Pyrexia[a]	5 (3.9%)	5 (7.4%)	4 (5.4%)	9 (6.3%)
Fatigue[a]	4 (3.1%)	2 (2.9%)	5 (6.8%)	7 (4.9%)
Peripheral edema	1 (0.8%)	1 (1.5%)	3 (4.1%)	4 (2.8%)
Nervous system disorders				
Headache[a]	5 (3.9%)	5 (7.4%)	7 (9.5%)	12 (8.5%)
Dizziness[a]	1 (0.8%)	4 (5.9%)	1 (1.4%)	5 (3.5%)
Blood and lymphatic system disorders				
Neutropenia[a]	7 (5.4%)	5 (7.4%)	1 (1.4%)	6 (4.2%)
Leukopenia[a]	7 (5.4%)	8 (11.8%)	1 (1.4%)	9 (6.3%)
Hemolysis[a]	4 (3.1%)	0	2 (2.7%)	2 (1.4%)
Anemia[a]	3 (2.3%)	2 (2.9%)	0	2 (1.4%)
Thrombocytopenia[a]	1 (0.8%)	3 (4.4%)	2 (2.7%)	5 (3.5%)

System Organ Class FMQ/Preferred Term	COMMODORE-2 Crovalimab (Naïve) (N=129) n (%)	COMMODORE-2 Crovalimab (Switch) (N=68) n (%)	COMMODORE-1 Crovalimab (Switch) (N=74) n (%)	Crovalimab (Switch) Pooled (N=142) n (%)
Respiratory, thoracic, and mediastinal disorders				
Cough	4 (3.1%)	0	1 (1.4%)	1 (0.7%)
Dyspnea	2 (1.6%)	1 (1.5%)	1 (1.4%)	2 (1.4%)
Metabolism and nutrition disorders				
Hypokalemia	5 (3.9%)	3 (4.4%)	0	3 (2.1%)
Hypocalcemia	0	3 (4.4%)	0	3 (2.1%)
Hypomagnesemia	2 (1.6%)	1 (1.5%)	0	1 (0.7%)
Hyperuricemia	1 (0.8%)	3 (4.4.%)	0	3 (2.1%)
Cardiac disorders				
Arrhythmia[a]	2 (1.6%)	1 (1.5%)	0	1 (0.7%)
Musculoskeletal and connective tissue disorders				
Back pain	3 (2.3%)	0	5 (6.8%)	5 (3.5%)
Arthralgia	2 (1.6%)	1 (1.5%)	4 (5.4%)	5 (3.5%)
Arthritis[a]	1 (0.8%)	2 (2.9%)	2 (2.7%)	4 (2.8%)
Myalgia	1 (0.8%)	1 (1.5%)	1 (1.4%)	2 (1.4%)
Hepatobiliary disorders				
Hepatic injury[a]	3 (2.3%)	4 (5.9%)	3 (4.1%)	7 (4.9%)
Vascular disorder				
Hemorrhage[a]	3 (2.3%)	0	6 (8.1%)	6 (4.2%)
Neoplasms benign, malignant, and unspecified				
Malignancy[a]	2 (1.6%)	2 (2.9%)	2 (2.7%)	4 (2.8%)
Skin and subcutaneous tissue disorders				
Pruritus	1 (0.8%)	1 (1.5%)	1 (1.4%)	2 (1.4%)

Source: ADAE.xpt.
Note: Incidences are based on the number of subjects, not the number of events. Although a subject may have had 2 or more clinical AEs, the subject is counted only once in a category. The same subject may appear in different categories.
[a] Grouped terms: Abdominal pain includes abdominal pain and abdominal pain upper. Anemia includes anemia, aplastic anemia, autoimmune hemolytic anemia and iron deficiency anemia. Arrhythmia includes sinus arrhythmia, tachycardia and ventricular extrasystoles. Arthritis includes arthritis, osteoarthritis, periarthritis and rheumatoid arthritis. Dizziness includes dizziness and vertigo. Headache includes headache and migraine. Hemolysis includes hemolysis and breakthrough hemolysis. Hemorrhage includes contusion, intermenstrual bleeding and epistaxis. Hepatic injury includes ALT increased, AST increased, hepatotoxicity, liver injury and liver function test abnormal. Fatigue includes asthenia and fatigue. Injection related reaction includes injection related reaction and injection-site reaction. Leukopenia includes white blood cell count decreased. Malignancy includes colorectal cancer, mantle cell lymphoma and prostate cancer. Neutropenia includes febrile neutropenia, neutropenia and neutrophil count decreased. Pyrexia includes pyrexia, febrile neutropenia and febrile nonhemolytic transfusion reaction. Respiratory tract infection includes bronchitis, influenza, nasopharyngitis, pharyngitis, pharyngotonsillitis, pneumonia, respiratory tract infection bacterial and upper respiratory tract infection. Thrombocytopenia includes thrombocytopenia and white blood cell count decreased. Urinary tract infection includes cystitis, pyelonephritis and urinary tract infection. Viral infection includes COVID-19, dengue fever, gastrointestinal viral infection, herpes virus infection, herpes zoster, influenza, oral herpes and viral infection.
Abbreviations: AE, adverse event; COVID-19, coronavirus disease of 2019; FMQ, Food and Drug Administration Medical Query; N, total number of subjects; n, number of subjects in subset; TEAE, treatment-emergent adverse event

Nonrandomized Arms

In COMMODORE-2, a total of 5 of the 6 pediatric subjects (83.3%) developed TEAEs. The only TEAE that was reported in more than 1 subject was hyperuricemia (33.3%, 2 subjects). Other TEAEs that were reported in one subject each were aphthous ulcer, contusion, fatigue, headache, hypocalcemia, hypokalemia, hypomagnesemia, pyrexia, and urinary tract infection. All TEAEs were Grade 1 or 2 in severity and considered nonserious.

In COMMODORE-1, a total of 33 subjects (86.8%) experienced TEAEs in the nonrandomized arm and the incidence was broadly similar between the cohorts (prior-ravulizumab cohort: 85.7%, prior-high-dose eculizumab cohort: 100%, C5 SNP cohort: 83.3%). In the prior-ravulizumab cohort, the most frequently reported TEAEs (≥20%) were infections, pyrexia, type III immune complex-mediated reactions, viral infections, and myalgia. In the prior-high-dose eculizumab cohort, the most frequent TEAEs (≥20%) were infections, viral infections, COVID-19, urinary tract infections, type III immune complex-mediated reactions, fatigue, and headache. In the C5 polymorphism cohort, TEAEs that occurred in more than one subject were infections and respiratory infections.

No new safety concerns were identified in the nonrandomized arms.

7.6.1.8. Adverse Events of Special Interest

Based on nonclinical studies and prior clinical experience with crovalimab, adverse events of special interest included injection site reactions, infusion-related reactions, infections including meningococcal meningitis, type III hypersensitivity reactions, hypersensitivity reactions (excluding type III hypersensitivity reactions), and MAVEs.

Table 39 summarizes TEAEs of special interest that occurred during the primary treatment period in COMMODORE-1 and COMMODORE-2.

Table 39. Summary of Adverse Events of Special Interest, Primary Treatment Period, COMMODORE-1 and COMMODORE-2, Safety Population

	COMMODORE-2		COMMODORE-1	
Adverse Event of Special Interest	**Crovalimab (Naïve) (N=135) n (%)**	**Eculizumab (Naïve) (N=69) n (%)**	**Crovalimab (Switch) (N=44) n (%)**	**Eculizumab (Experienced) (N=42) n (%)**
Injection related reactions	8 (5.9%)	0	4 (9.1%)	0
Infusion related reactions	21 (15.6%)	9 (13.0%)	6 (13.6%)	0
Infections	32 (23.7%)	25 (36.2%)	18 (40.9%)	15 (35.7%)
Meningococcal meningitis	0	0	0	0
Type III hypersensitivity reactions	0	0	7 (15.9%)	0
Hypersensitivity reactions other than type III hypersensitivity reactions	8 (5.9%)	0	4 (9.1%)	0
MAVE	1 (0.7%)	1 (1.4%)	0	1 (2.4%)

Source: ADAE.xpt.
Note: Incidences are based on the number of subjects, not the number of events. Although a subject may have had 2 or more clinical AEs, the subject is counted only once in a category. The same subject may appear in different categories.
Abbreviations: AE, adverse event; MAVE, major adverse vascular events; N, total number of subjects; n, number of subjects in subset

summarizes the TEAEs of special interest that occurred in the pooled analysis of COMMODORE-1, COMMODORE-2, and COMMODORE-3. Further details of this pooled analysis are discussed in the subsections below.

Table 40. Summary of Adverse Events of Special Interest, Pooled Analysis of COMMODORE-1, COMMODORE-2, and COMMODORE-3, Safety Population

Adverse Event of Special Interest	Crovalimab (Naïve) (N=192) n (%)	Crovalimab (Switch) (N=185) n (%)	Crovalimab Total (N=377) n (%)	Eculizumab Total (N=111) n (%)
Injection site reactions	8 (4.2%)	18 (9.7%)	26 (6.9%)	0
Infusion related reactions	23 (12.0%)	17 (9.2%)	40 (10.6%)	9 (8.1%)
Infections	98 (51.0%)	79 (42.7%)	177 (46.9%)	40 (36.0%)
Meningococcal meningitis	0	0	0	0
Type III hypersensitivity reactions	0	33 (17.8%)	33 (8.8%)	0
Hypersensitivity reactions other than type III hypersensitivity reactions	11 (5.7%)	20 (10.8%)	31 (8.2%)	0
MAVE	1 (0.5%)	0	1 (0.3%)	2 (1.8%)

Source: ADAE.xpt.
Note: The median duration of exposure differs between the treatment groups (eculizumab: 22.1 weeks [range: 0.1 to 26.1], crovalimab naïve: 52.1 weeks [range: 0.1 to 107.9], crovalimab switch: 32.3 weeks [range: 0.3 to 108.4], crovalimab total: 44.4 weeks [range: 0.1 to 108.4]).
Note: Incidences are based on the number of subjects, not the number of events. Although a subject may have had 2 or more clinical AEs, the subject is counted only once in a category. The same subject may appear in different categories.
Abbreviations: AE, adverse event; MAVE, major adverse vascular events; N, total number of subjects; n, number of subjects in subset

7.6.1.8.1. Injection Reactions

Injection reactions occurred only in subjects who received crovalimab due to SC administration of crovalimab. Eculizumab is administered by IV infusion only. Therefore, injection reaction was not reported in subjects who received eculizumab. Per study protocol, AEs that occurred during or within 24 hours after crovalimab administration and were considered related to the crovalimab injection were captured as injection reactions.

Overall, 26 subjects (6.9%) who received crovalimab experienced injection-related reactions or injection site reactions. The incidence of these reactions was higher in the crovalimab switch population (9.7%) compared to the complement-naïve population (4.2%). None of the events were considered serious. One subject in the crovalimab switch population (from the prior-ravulizumab cohort in COMMODORE-1) had a Grade 3 injection-related reaction that resolved with no dose modification or interruption. Associated symptoms reported in this subject were erythema, rash, and urticaria. Another subject experienced a Grade 3 injection site rash that also resolved without dose modification. The remaining events were Grade 1 or 2 in severity.

The median time to onset of the first injection reaction was 8.5 days (range: 2 to 365) after the first dose of crovalimab, and the median duration of the first injection reaction was 2 days (range: 1 to 46) in the 26 subjects who had injection reactions. For all injection reactions experienced in the 26 subjects, the median time to onset was 16 days (range: 2 to 365) after the first dose of crovalimab, and the median duration was 2 days (range: 1 to 105). The median time to onset of all injection reactions experienced in the crovalimab-switch population was 16 days (range: 2 to 365) after the first dose of crovalimab and 15.5 days (range: 2 to 197) after the first dose of crovalimab in the crovalimab-naïve population. The median duration of all injection

reactions in the crovalimab-switch population was 3 days (range: 1 to 105) and 2 days (range: 1 to 2) in the crovalimab-naïve population.

A total of eight subjects (2.1%) who were all in the crovalimab-switch group had Grade 1 or 2 events which were not resolved at the CCOD.

Most subjects (69%) experienced injection reaction once and 7 subjects (27%, all crovalimab-switch) experienced injection reactions 2 to 4 times while in the study. In addition, there was one subject who was crovalimab-naïve and experienced an injection reaction nine times while in the study.

Injection-related reactions will be listed in the crovalimab label as a Warning and Precaution.

Table 41. Summary of Injection Reactions, Pooled Analysis of COMMODORE-1, COMMODORE-2, and COMMODORE-3, Safety Population

Preferred Term	Crovalimab (Naïve) (N=192) n (%)	Crovalimab (Switch) (N=185) n (%)	Crovalimab Total (N=377) n (%)
All	8 (4.2%)	18 (9.7%)	26 (6.9%)
Injection related reaction	7 (3.6%)	17 (9.2%)	24 (6.4%)
Injection site reaction	1 (0.5%)	1 (0.5%)	2 (0.5%)
Symptoms of injection reaction that occurred in >1 subject			
Headache	3 (1.6%)	6 (3.2%)	9 (2.4%)
Injection site erythema	2 (1.0%)	2 (1.1%)	4 (1.1%)
Injection site pruritus	1 (0.5%)	1 (0.5%)	2 (0.5%)
Injection site pain	1 (0.5%)	1 (0.5%)	2 (0.5%)
Injection site swelling	1 (0.5%)	1 (0.5%)	2 (0.5%)
Erythema	0	2 (1.1%)	2 (0.5%)
Pruritus	0	2 (1.1%)	2 (0.5%)
Myalgia	0	2 (1.1%)	2 (0.5%)
Malaise	0	2 (1.1%)	2 (0.5%)

Source: ADAE.xpt.
Note: The median duration of exposure differs between the treatment groups (crovalimab naïve: 52.1 weeks [range: 0.1 to 107.9], crovalimab switch: 32.3 weeks [range: 0.3 to 108.4], crovalimab total: 44.4 weeks [range: 0.1 to 108.4]).
Note: Incidences are based on the number of subjects, not the number of events. Although a subject may have had 2 or more clinical AEs, the subject is counted only once in a category. The same subject may appear in different categories.
Abbreviations: AE, adverse event; N, total number of subjects; n, number of subjects in subset

7.6.1.8.2. Infusion-Related Reactions

Crovalimab was administered by IV infusion once (on Day 1) and then by SC injection for the remainder of the study. Eculizumab was administered only by IV infusion throughout the study. The incidence of infusion-related reactions was 10.6% in the total crovalimab group and 8.1% in the total eculizumab group in the pooled population (includes studies COMMODORE-1, COMMODORE-2, and COMMODORE-3). This pooled analysis includes subjects from COMMODORE-1 who have prior experience with eculizumab, therefore it is expected that these subjects would have a lower rate of infusion reactions, as they are already tolerating the drug. In subjects who received crovalimab, the most frequently reported symptom of infusion related reaction (>2%) was headache (7.2%). One subject ([redacted](b) (6)) who received crovalimab in COMMODORE-2 experienced a serious Grade 2 infusion-related reaction that resulted in hospitalization for symptoms of nausea, vomiting, abdominal pain, headache, and pyrexia. The

symptoms resolved after interruption of crovalimab (see Section 7.6.1.3 for the subject narrative). All events were Grade 1 or 2 in severity. Subjects who experienced infusion-related symptoms were treated with acetaminophen, ibuprofen, diphenhydramine, and/or H2-receptor antagonists, or equivalent medications per local standard practice.

Infusion-related reactions will be listed in the crovalimab label as a Warning and Precaution.

Table 42. Summary of Infusion Related Reactions, Pooled Analysis of COMMODORE-1, COMMODORE-2, and COMMODORE-3, Safety Population

Preferred Term	Crovalimab (Naïve) (N=192) n (%)	Crovalimab (Switch) (N=185) n (%)	Crovalimab Total (N=377) n (%)	Eculizumab Total (N=111) n (%)
All	23 (12.0%)	17 (9.2%)	40 (10.6%)	9 (8.1%)
Symptoms of infusion related reaction that occurred in >1 subject in the crovalimab group				
Headache	18 (9.4%)	9 (4.9%)	27 (7.2%)	6 (5.4%)
Rash (pruritic)	2 (1.0%)	4 (2.2%)	6 (1.6%)	0
Dizziness	1 (0.5%)	2 (1.1%)	3 (0.8%)	0
Pyrexia	2 (1.0%)	0	2 (0.5%)	0
Nausea	1 (0.5%)	1 (0.5%)	2 (0.5%)	0
Abdominal pain	2 (1.0%)	0	2 (0.5%)	1 (0.9%)

Source: ADAE.xpt.
Note: The median duration of exposure differs between the treatment groups (eculizumab: 22.1 weeks [range: 0.1 to 26.1], crovalimab naïve: 52.1 weeks [range: 0.1 to 107.9], crovalimab switch: 32.3 weeks [range: 0.3 to 108.4], crovalimab total: 44.4 weeks [range: 0.1 to 108.4]).
Note: Incidences are based on the number of subjects, not the number of events. Although a subject may have had 2 or more clinical AEs, the subject is counted only once in a category. The same subject may appear in different categories.
Abbreviations: AE, adverse event; N, total number of subjects; n, number of subjects in subset;

7.6.1.8.3. Infections Including Meningococcal Meningitis

In the pooled analyses of COMMODORE-1, COMMODORE-2, and COMMODORE-3, the overall incidence of infection was 46.9% in the total crovalimab group and 36% in the total eculizumab group. Because of different exposure durations, the team also assessed the rates by 100 patient-years, which showed that the number of reported infections was lower in the total crovalimab group (88.7, 95% CI: 73.8, 105.7) compared to the total eculizumab group (120.6, 95% CI: 92.0, 155.2). The median time to first onset of infection was longer in the total crovalimab group (15.1 weeks, range: 0.1 to 98.0) compared with the total eculizumab group (7.2 weeks, range: 0.1 to 23.6). In both groups, most infections were Grade 1 or 2 in severity. There were no cases of infection that had a fatal outcome in either group. Grade 4 events were reported in one subject in each group (crovalimab: pyelonephritis, eculizumab: central nervous system infection). One subject in the crovalimab-switch population had a Grade 3 infection (sepsis) that led to withdrawal from treatment.

In subjects who received crovalimab, the most frequently reported infections (≥5%) were COVID-19, upper respiratory tract infection, and urinary tract infection. In the crovalimab-naïve and switch subgroups, the median onset of first infection was longer in the crovalimab-naïve population (22.5 weeks, range: 0.3 to 98.0 weeks) compared to the crovalimab-switch population (10.3 weeks, range: 0.1 to 59.7 weeks), which could have been because subjects who switched to crovalimab were already exposed to a C5 inhibitor. Increased susceptibility to infections is a known risk associated with C5 inhibitors.

No cases of meningitis due to *Neisseria meningitidis* were reported across the entire crovalimab PNH development program. However, one case of grade 3 Meningococcal meningitis (*Neisseria meningitidis* serotype X), was reported on Day 430 in Study BO42354, a study evaluating the efficacy, safety, PK, and PD of crovalimab in pediatric patients with atypical hemolytic uremic syndrome. The subject was vaccinated against serotype ACWY. The event resolved after 4 days, with no change to crovalimab treatment.

Infections will be listed in the crovalimab label as a Warning and Precaution, along with a boxed warning with a REMS for serious meningococcal infections consistent with class labeling for other C5 inhibitors.

Table 43. Summary of Infections, Pooled Analysis of Studies COMMODORE-1, COMMODORE-2, and COMMODORE-3, Safety Population

Infection	Crovalimab (Naïve) (N=192)	Crovalimab (Switch) (N=185)	Crovalimab Total (N=377)	Eculizumab Total (N=111)
All, n (%)	98 (51.0%)	79 (42.7%)	177 (46.9%)	40 (36.0%)
TEAE with a fatal outcome	0	0	0	0
Serious TEAE	11 (5.7%)	12 (6.5%)	23 (6.1%)	6 (5.4%)
Grade 3 or 4	10 (5.2%)	9 (4.9%)	19 (5.0%)	5 (4.5%)
TEAE leading to study drug withdrawal	0	1 (0.5%)	1 (0.3%)	0
TEAE leading to dose modification/interruption	4 (2.1%)	3 (1.6%)	7 (1.9%)	2 (1.8%)
Time to onset of first TEAE (weeks)				
Mean (SD)	24.3 (18.0)	13.3 (13.3)	19.3 (16.9)	9.5 (6.4)
Median	22.5	10.3	15.1	7.2
Range	0.3-98.0	0.1-59.7	0.1-98.0	0.1-23.6
Infections that occurred in >5 subjects in the crovalimab group by preferred term, n (%)				
COVID-19	29 (15.1%)	32 (17.3%)	61 (16.2%)	11 (9.9%)
Upper respiratory tract infection	45 (23.4%)	10 (5.4%)	55 (14.6%)	10 (9.0%)
Urinary tract infection	13 (6.8%)	9 (4.9%)	22 (5.8%)	7 (6.3%)
Nasopharyngitis	7 (3.6%)	10 (5.4%)	17 (4.5%)	2 (1.8%)
Influenza	5 (2.6%)	4 (2.2%)	9 (2.4%)	3 (2.7%)
Pneumonia	5 (2.6%)	2 (1.1%)	7 (1.9%)	3 (2.7%)
Pharyngitis	4 (2.1%)	2 (1.1%)	6 (1.6%)	1 (0.9%)
Bronchitis	2 (1.0%)	4 (2.2%)	6 (1.6%)	0

Source: ADAE.xpt and SCS.
Note: The median duration of exposure differs between the treatment groups (eculizumab: 22.1 weeks [range: 0.1 to 26.1], crovalimab naïve: 52.1 weeks [range: 0.1 to 107.9], crovalimab switch: 32.3 weeks [range: 0.3 to 108.4], crovalimab total: 44.4 weeks [range: 0.1 to 108.4]).
Note: Incidences are based on the number of subjects, not the number of events. Although a subject may have had 2 or more clinical AEs, the subject is counted only once in a category. The same subject may appear in different categories.
Abbreviations: AE, adverse event; COVID-19, coronavirus disease of 2019; N, total number of subjects; n, number of subjects in subset; SD, standard deviation; TEAE, treatment-emergent adverse event

7.6.1.8.4. Type III Hypersensitivity Reactions

In subjects switching from eculizumab or ravulizumab (i.e., a C5 inhibitor that binds a different epitope than crovalimab) to crovalimab, type III hypersensitivity reactions occurred due to the transient formation of DTDCs comprised of eculizumab or ravulizumab, crovalimab, and C5. DTDCs also occurred in subjects switching from crovalimab to either eculizumab or ravulizumab, upon discontinuation from or completion of crovalimab. Type III hypersensitivity

reactions were not expected to occur after the CL period of DTDCs. Type III hypersensitivity reactions will be included in the label as a warning. The Division of Pulmonology, Allergy, and Critical Care (DPACC) provided a consult review regarding the type III hypersensitivity reactions. DPACC's conclusion was consistent with the results described below and recommendations provided in Section 7.7.2 of this review.

The following characteristics were considered by the Applicant when defining type III hypersensitivity reactions associated with DTDC formation (Usman and Annamaraju 2024):

- Typical onset is delayed by a week or more after dose administration, and the reaction may persist for days to over a week.
- Reactions may involve the skin, joints, and/or kidneys.
- Typical signs and symptoms may include purpura; petechial or urticarial rashes affecting the lower extremities bilaterally; arthralgia; enlarged and/or tender lymph nodes/spleen.
- Histopathological finding of small vessel vasculitis and laboratory evidence of glomerulonephritis.
- Type III hypersensitivity reactions are not expected to occur after the CL period of DTDCs.

Type III hypersensitivity reactions were reported in a total of 33 subjects (17.8%) who previously received a complement inhibitor and switched to crovalimab at the time of the primary CCOD for the BLA, which includes the primary treatment period and extension period. An additional 6 subjects were reported to have type III hypersensitivity reactions in the 120-day safety update. Therefore, in the entire development program, 39 subjects (19.4%) reported type III hypersensitivity reactions. As expected, type III hypersensitivity reactions were not reported during the primary treatment period in complement inhibitor-naïve subjects who received crovalimab or eculizumab (in COMMODORE-2 and COMMODORE-3) or subjects who continued treatment with eculizumab from prior to entry of COMMODORE-1. At the primary CCOD, serious events were reported in 5 out of 33 subjects (15.2%). Most events were Grade 1 (27.3%) or 2 (33.3%) in severity. A total of 13 out of 33 subjects (39.4%) had Grade 3 events including 1 subject who developed Grade 3 axonal neuropathy. No Grade 4 or 5 events were reported (see Table 44 below).

In the entire crovalimab development program (including the 120-day safety update), a total of 8 out of 39 subjects (20.5%) experienced a serious type III hypersensitivity reaction. More than half of the events were Grade 1 (25.6%) or 2 (33.3%) in severity and Grade 3 events were reported in 16 subjects (41%), this included one subject that developed grade 3 axonal neuropathy. No Grade 4 or 5 events were reported. See Table 150 in Section 17.5.

Table 44. Summary of Type III Hypersensitivity Reactions, COMMODORE-1 and COMMODORE-2, Safety Population at time of BLA Submission

	Crovalimab Switch (N=185)			Crovalimab Total (N=377)
System Organ Class Preferred Term	Any Grade n (%)	Grade 2 n (%)	Grade 3 n (%)	Any Grade n (%)
All	33 (17.8%)	11 (5.9%)	13 (7.0%)	33 (8.8%)
Immune system disorders	33 (17.8%)	11 (5.9%)	13 (7.0%)	33 (8.8%)
Type III immune complex mediated reaction	33 (17.8%)	11 (5.9%)	13 (7.0%)	33 (8.8%)
Nervous system disorders	1 (0.5%)	0	1 (0.5%)	1 (0.3%)
Axonal neuropathy	1 (0.5%)	0	1 (0.5%)	1 (0.3%)

Source: ADAE.xpt and SCS
Abbreviations: N, total number of subjects; n, number of subjects in subset

In the initial BLA, the most frequently reported symptoms (>2%) of type III hypersensitivity were arthralgia, rash, pyrexia, myalgia, headache, purpura, and fatigue. Grade 3 symptoms occurred in 6.5% of the crovalimab switch population. Grade 3 symptoms reported in more than one subject were arthralgia, pyrexia, headache, rash, myalgia, purpura, fatigue, and abdominal pain. One subject with a type III hypersensitivity reaction had a TEAE (i.e., chromaturia) under the Renal and Urinary Disorder SOC. There was no clinically significant trend in renal function, although the sample size is small. In the 120-day safety update, the most frequently reported symptoms including Grade 3 events were also consistent with those reported in the initial BLA. In the entire BLA (including the 120-day safety update), symptoms of type III hypersensitivity reactions that occurred in more than 2 subjects were arthralgia, rash, pyrexia, myalgia, headache, fatigue, petechiae and abdominal pain. See Table 151 in Section 17.5.

Table 45. Summary of Symptoms of Type III Hypersensitivity Reactions that Occurred in >1 Subject (Any Grade) or in at Least 1 Subject (≥Grade 3 TEAE), COMMODORE-1 and COMMODORE-2, Safety Population at time of BLA Submission

	Crovalimab Switch (N=185)	
System Organ Class Preferred Term	Any Grade n (%)	Grade 3 n (%)
All	33 (17.8%)	12 (6.5%)
Musculoskeletal and connective tissue disorders	21 (11.4%)	9 (4.9%)
Arthralgia[a]	18 (9.7%)	8 (4.3%)
Myalgia	6 (3.2%)	2 (1.1%)
Pain in extremity	2 (1.1%)	0
Skin and subcutaneous tissue disorders	20 (10.8%)	4 (2.2%)
Rash[a]	15 (8.1%)	2 (1.1%)
Purpura[a]	4 (2.2%)	2 (1.1%)
Erythema	2 (1.1%)	0
General disorders and administration site conditions	10 (5.4%)	3 (1.6%)
Pyrexia	7 (3.8%)	3 (1.6%)
Fatigue[a]	4 (2.2%)	2 (1.1%)
Edema[a]	2 (1.1%)	0
Nervous system disorders	8 (4.3%)	5 (2.7%)
Headache	5 (2.7%)	3 (1.6%)
Axonal neuropathy	1 (0.5%)	1 (0.5%)
Dizziness	1 (0.5%)	1 (0.5%)

System Organ Class Preferred Term	Crovalimab Switch (N=185) Any Grade n (%)	 Grade 3 n (%)
Gastrointestinal disorders	4 (2.2%)	2 (1.1%)
Abdominal pain	3 (1.6%)	2 (1.1%)
Nausea	2 (1.1%)	1 (0.5%)
Vascular disorders	2 (1.1%)	1 (0.5%)
Vasculitis	2 (1.1%)	1 (0.5%)
Renal and urinary disorders	1 (0.5%)	1 (0.5%)
Chromaturia	1 (0.5%)	1 (0.5%)

Source: ADAE.xpt and SCS.
[a] Grouped terms: Arthralgia includes arthralgia, joint stiffness and joint swelling. Rash includes rash, rash erythematous, rash macular, rash maculo-papular and rash popular. Purpura includes Henoch-Schonlein purpura and petechiae. Fatigue includes asthenia and fatigue. Edema includes peripheral edema.
Abbreviations: N, total number of subjects; n, number of subjects in subset

In the initial BLA, the median time to onset of a type III hypersensitivity reaction (after switching from eculizumab: 1.6 weeks [range: 0.7 to 4.4], after switching from ravulizumab: 2.0 weeks [range: 1.3 to 4.3]) and the median duration (prior-eculizumab group: 1.9 weeks [range: 0.4 to 34.1], prior-ravulizumab group: 1.7 weeks [range: 1.0 to 11.9]) were similar between subjects who switched from eculizumab and ravulizumab; however, the sample size in the prior-ravulizumab group is small (N=21). In the 120-day safety update, consistent results were observed. See Table 152 and Table 153.

Two subjects experienced a relatively longer duration of type III hypersensitivity events (≥12 weeks). One subject ([redacted] (b) (6)) experienced Grade 2 rash, neck pain, and pain in the extremity that started on Day 15. The rash subsided after 15 days; however, the neck pain and pain in the extremity did not resolve for 239 days. The symptoms resolved with no modification of crovalimab therapy. The other subject ([redacted] (b) (6)) had Grade 1 pyrexia, Grade 2 arthralgia, and Grade 2 rash starting on Day 13. Pyrexia and rash subsided after 10 days, however, arthralgia persisted for 89 days with no change in crovalimab therapy.

Table 46. Time to Onset of First Type III Hypersensitivity Reaction, COMMODORE-1 and COMMODORE-2, Safety Population at time of BLA Submission

Time to First Onset of Type III Hypersensitivity Reaction	Crovalimab Switch Prior Eculizumab (N=164)	 Prior Ravulizumab (N=21)	 Total (N=185)
Total number of subjects, n (%)	28 (17.1%)	5 (23.8%)	33 (17.8%)
Time to onset to first AE (weeks)			
Mean (SD)	1.9 (0.92)	2.3 (1.21)	1.9 (0.96)
Median	1.6	2.0	1.6
Range	0.7-4.4	1.3-4.3	0.7-4.4
Time to onset of first AE (category), n (%)			
<1 week	3 (10.7%)	0	3 (9.1%)
1 to <2 weeks	14 (50.0%)	2 (40.0%)	16 (48.5%)
2 to <4 weeks	10 (35.7%)	2 (40.0%)	12 (36.4%)
4 to <6 weeks	1 (3.6%)	1 (20.0%)	2 (6.1%)
≥6 weeks	0	0	0

Source: SCS, confirmed by ADAE.xpt.
Abbreviations: AE, adverse event; N, total number of subjects; n, number of subjects in subset; SD, standard deviation

Table 47. Duration of Type III Hypersensitivity Reaction, COMMODORE-1 and COMMODORE-2, Safety Population at time of BLA Submission

	Crovalimab Switch		
Duration of Type III Hypersensitivity Reaction	Prior Eculizumab (N=164)	Prior Ravulizumab (N=21)	Total (N=185)
Total number of events	29	7	36
Total number of resolved events[a]	26	5	31
Duration (weeks)[a]			
Mean (SD)	4.1 (6.82)	4.1 (4.50)	4.1 (6.44)
Median	1.9	1.7	1.9
Range	0.4-34.1	1.0-11.9	0.4-34.1
Duration (category)[a], n (%)			
<1 week	4 (15.4%)	0	4 (12.9%)
1 to <2 weeks	10 (38.5%)	3 (60.0%)	13 (41.9%)
2 to <4 weeks	6 (23.1%)	0	6 (19.4%)
4 to <8 weeks	3 (11.5%)	1 (20.0%)	4 (12.9%)
8 to <12 weeks	1 (3.8%)	1 (20.0%)	2 (6.5%)
≥12 weeks	2 (7.7%)	0	2 (6.5%)

Source: SCS
[a] Resolved events refer to events with outcome "Recovered/Resolved" or "Resolving/Recovering."
Abbreviations: N, total number of subjects; n, number of subjects in subset; SD, standard deviation

Correlation of the Time Interval Between the Different C5 Inhibitor Treatment and Severity of Type III Hypersensitivity

In COMMODORE-1 and COMMODORE-2, subjects switching from eculizumab/ravulizumab to crovalimab were required to receive their first dose of crovalimab on the day of the next scheduled dosing day of the previous C5 inhibitor to minimize IVH and complications associated with PNH. Generally, eculizumab is administered Q2W and ravulizumab every 8 weeks.

The pooled safety data from COMMODORE-1 and COMMODORE-2 were utilized to assess the relation of the time interval between the last dose of the C5 inhibitor and the first dose of crovalimab with the occurrence of type III hypersensitivity reactions.

The following was reported by the Applicant:

- There was no difference in the time interval of the last dose of C5 inhibitor and the first dose of crovalimab and the development of a type III hypersensitivity reaction (see Table 154 in the Appendix).
- In subjects who experienced a type III hypersensitivity reaction event, there was no correlation of the time between the last dose of prior treatment and first crovalimab dose with the severity of the type III hypersensitivity reaction (see Table 155 in the Appendix).
- Based on the CCOD of May 31, 2023 (the primary CCOD of COMMODORE-1 and COMMODORE-2 was November 16, 2022), a total of 201 subjects had switched from eculizumab or ravulizumab to crovalimab in COMMODORE-1 and COMMODORE-2, and 39 (19.4%) subjects had a type III hypersensitivity reaction. Out of 42 total type III hypersensitivity reactions, 37 (88%) resolved, including 1 (2.4%) which resolved with crovalimab discontinuation, 2 (4.8%) which resolved with crovalimab interruption and 34 (81%) which resolved without discontinuation, interruption, or dose change in crovalimab therapy. Four subjects (10%) had not fully recovered from symptoms of type III

hypersensitivity reactions at the time of their last follow up visit .The subject narratives are presented below. For full narratives, see Section 17.4.

- Subject (b) (6) received seven doses of ravulizumab prior to study enrollment. On Day 9 after receiving the first crovalimab SC dose, the subject developed Grade 3 rash on both legs and arms, which was ascribed to a serious, systemic Grade 3 type III immune complex-mediated reaction and was admitted to the hospital. The events were reported as unresolved despite receiving treatment with corticosteroids and antihistamines.
- Subject (b) (6) switched to crovalimab after completing the primary treatment period with eculizumab in COMMODORE-2. On Day 199, the subject developed Grade 3 arthralgia, which was ascribed to a non-serious Grade 3 type III immune complex-mediated reaction. The subject developed severe pain leading to decreased quality of life. He received treatment with methylprednisolone. The event of type III immune complex mediated reaction remained unresolved at the time of study discontinuation.
- Subject (b) (6) was randomized to the eculizumab arm in COMMODORE-2. After completing the primary treatment with eculizumab on Day 183 and switching to crovalimab on Day 197, the subject developed the first hypersensitivity reaction on Day 207 (following the most recent administration of SC crovalimab on Day 204). The first episode of Grade 2 type III hypersensitivity reaction lasted for 24 days. The subject had the last dose of crovalimab on Study Day 218 and switched to treatment with ravulizumab on Day 244 (i.e., 26 days after the last crovalimab dose). On Day 245, the subject experienced an event of a type III hypersensitivity reaction (Grade 2 myalgia, erythema, joint swelling, arthralgia, and Grade 1 dysesthesia). The events were ongoing at the time the subject completed the safety follow-up on Day 386. Treatment for both events included betamethasone butyrate propionate/prednisolone and paracetamol.

In addition, there was one subject (USUBJID (b) (6)) who had type III hypersensitivity reaction that was resolving/recovering.

- Subject ((b) (6)), who was enrolled in the prior-ravulizumab cohort in COMMODORE-1, developed the first episode of Grade 2 type III hypersensitivity reaction starting on Day 14 and lasting for 12 days. The first event resolved after treatment with codeine, paracetamol, buclizine hydrochloride, and prednisolone. The subject discontinued crovalimab on Study Day 29 and switched to treatment with ravulizumab on Day 42 (i.e., 13 days after the last crovalimab dose). On Day 52, the subject experienced the second event of a type III hypersensitivity reaction (Grade 3 myalgia, axonal neuropathy, Grade 2 muscular weakness and arthralgia). The event was resolving at the time the subject completed the safety follow-up on Day 364 after treatment with methylprednisolone and amitriptyline at the time of the CCOD.

Due to the limited number of subjects with a time interval between the last dose of the C5 inhibitor and the first dose of crovalimab being outside of the expected dosing intervals of eculizumab or ravulizumab and experiencing a type III hypersensitivity reaction, a conclusion cannot be made whether changes to the time interval influences the occurrence, severity, or reversibility of type III hypersensitivity reactions. However, the FDA expects, based on the pathophysiology of the type III hypersensitivity reactions, that a prolonged time interval would mitigate the risk (e.g., after 5.5 half-lives since the last dose of the prior C5 inhibitor have passed

before crovalimab is initiated). However, such a prolonged wait risks uncontrolled PNH. Therefore, prescribers will be advised to consider the benefits of the timing of the switch against the risks of Type III hypersensitivity reactions.

Type III Hypersensitivity Reactions in Subjects Who Switched From Crovalimab to a C5 Inhibitor

In COMMODORE-1 and COMMODORE-2, a total of 8 subjects switched from crovalimab to a C5 inhibitor after discontinuing crovalimab (as of the CCOD of May 31, 2023).

Table 48. Treatment History for Subjects Who Switched From Crovalimab to a C5 Inhibitor After Discontinuing Crovalimab

Treatment History / Number of Patients	Study BO42162 N=4	Study BO42161 N=4	Crova Total N=8
Crova ⇒ Ecu	2	0	2
Ecu ⇒ Crova ⇒ Ecu	1	2	3
Ecu ⇒ Crova ⇒ Ravu	1*	0	1
Ravu ⇒ Crova ⇒ Ravu	0	2*	2

Source: Applicant's response.
Note: BO42161 = COMMODORE-1, BO42162 = COMMODORE-2.
*One subject in each study experienced a type III hypersensitivity reaction after having switched from crovalimab to another C5 inhibitor.
Abbreviations: C5, complement component 5; Crova, Crovalimab; Ecu, Eculizumab; N, total number of subjects; Ravu, Ravulizumab

Six of the eight subjects switched two times (i.e., at study entry from another C5 inhibitor to crovalimab, as well as at study discontinuation from crovalimab to another C5 inhibitor). Of the 8 subjects who switched from crovalimab to another C5 inhibitor, 2 subjects (25%) each experienced 2 events of type III hypersensitivity reactions. Brief subject narratives are described above, as both subjects did not have resolved type III hypersensitivity reactions at the time to the clinical data cut off. The full narratives for the two subjects are presented in Section 17.3.

Type III Hypersensitivity Reaction by Race and Region

In the pooled analysis of COMMODORE-1 and COMMODORE-2, the overall incidence of a type III hypersensitivity reaction was similar by race (White: 16.9%, Asian: 17.9%) and region (Europe: 17.1%, Asia: 18.3%). The incidences of Grade 3 events were slightly higher in Whites (7.9%) and Europe (9.8%) compared with Asians (4.8%) and Asia (4.9%), respectively, although results should be interpreted with caution given the small sample sizes.

Table 49. Summary of Type III Hypersensitivity Reactions by Race, Pooled Analysis of COMMODORE-1 and COMMODORE-2, Safety Population

Crovalimab Switch (N=185)							
White (N=89) n (%)		Asian (N=84) n (%)		Black/African American (N=4) n (%)		Unknown (N=8) n (%)	
All grade	Grade 3	All grade	Grade 3	All grade	Grade 3	All grade	Grade 3
15 (16.9%)	7 (7.9%)	15 (17.9%)	4 (4.8%)	2 (50.0%)	1 (25.0%)	1 (12.5%)	1 (12.5%)

Source: ADAE.xpt.
Abbreviations: N, total number of subjects; n, number of subjects in subset

Table 50. Summary of Type III Hypersensitivity Reactions by Region, Pooled Analysis of COMMODORE-1 and COMMODORE-2, Safety Population

Crovalimab Switch (N=185)							
Europe (N=82) n (%)		Asia (N=82) n (%)		North America (N=7) n (%)		Central/South America (N=14) n (%)	
All grade	Grade 3	All grade	Grade 3	All grade	Grade 3	All grade	Grade 3
14 (17.1%)	8 (9.8%)	15 (18.3%)	4 (4.9%)	0	0	4 (28.6%)	1 (7.1%)

Source: ADAE.xpt.
Abbreviations: N, total number of subjects; n, number of subjects in subset

7.6.1.8.5. Hypersensitivity Reactions Other Than Type III Hypersensitivity Reactions

In the assessment of hypersensitivity reactions other than type III hypersensitivity reactions, “injection related reactions” (defined as AEs that occurred during or within 24 hours after crovalimab injection) were included in the grouped PT search strategy. Hypersensitivity reactions were identified using the MedDRA lowest level term of “allergic reaction.”

Overall, 8.2% of subjects in the pooled crovalimab group and no subjects in the pooled eculizumab group reported hypersensitivity reactions (this analysis did not include type III hypersensitivity reactions) up to the CCOD (see Table 51). The majority of the hypersensitivity reactions (excluding the type III hypersensitivity reactions) were due to injection-related reactions (6.4%). Most of the cases were Grade 1 or 2. A total of two subjects (0.5%) reported Grade 3 events, which were injection related reaction (COMMODORE-1, prior-ravulizumab cohort) and hypersensitivity (COMMODORE-1, crovalimab-switch arm). Both Grade 3 events resolved with no dose modification or interruption. No events of anaphylaxis were reported.

A total of two subjects in the crovalimab-switch population reported type IV hypersensitivity reaction which were Grade 1 and 2 delayed vaccine hypersensitivity reactions, respectively. Type IV hypersensitivity reactions involve the cellular immune system that results in a T-cell response and inflammation.

As noted previously, infusion and injection site reactions will be listed as a Warning and Precaution in the label.

Table 51. Summary of Hypersensitivity Other Than Type III Hypersensitivity Reactions, Pooled Analysis of COMMODORE-1, COMMODORE-2, and COMMODORE-3, Safety Population

Preferred Term	Crovalimab (Naïve) (N=192) n (%)	Crovalimab (Switch) (N=185) n (%)	Crovalimab Total (N=377) n (%)	Eculizumab Total (N=111) n (%)
All	11 (5.7%)	20 (10.8%)	31 (8.2%)	0
Injection related reaction	7 (3.6%)	17 (9.2%)	24 (6.4%)	0
Hypersensitivity reaction	4 (2.1%)	1 (0.5%)	5 (1.3%)	0
Type IV hypersensitivity reaction	0	2 (1.1%)	2 (0.5%)	0

Source: CSR and ADAE.xpt.
Note: The median duration of exposure differs between the treatment groups (eculizumab: 22.1 weeks [range: 0.1 to 26.1], crovalimab naïve: 52.1 weeks [range: 0.1 to 107.9], crovalimab switch: 32.3 weeks [range: 0.3 to 108.4], crovalimab total: 44.4 weeks [range: 0.1 to 108.4]).
Note: Incidences are based on the number of subjects, not the number of events. Although a subject may have had 2 or more clinical AEs, the subject is counted only once in a category. The same subject may appear in different categories.
Abbreviations: AE, adverse event; N, total number of subjects; n, number of subjects in subset

7.6.1.8.6. Major Adverse Vascular Events

Per protocol, a MAVE was defined as any of the following PT events: thrombophlebitis/deep vein thrombosis, pulmonary embolus, myocardial infarction, transient ischemic attack, unstable angina, renal vein thrombosis, acute peripheral vascular occlusion, mesenteric/visceral vein thrombosis or infarction, mesenteric/visceral arterial thrombosis or infarction, hepatic/portal vein thrombosis (Budd-Chiari syndrome), cerebral arterial occlusion/cerebrovascular accident, cerebral venous occlusion, renal arterial thrombosis, gangrene (nontraumatic, nondiabetic), amputation (nontraumatic, nondiabetic), dermal thrombosis, and other events.

In the Phase 3 crovalimab PNH studies, a total of three subjects (crovalimab: one subject, eculizumab: two subjects) developed a MAVE.

In COMMODORE-2, one subject each in the crovalimab-naïve and eculizumab-naïve arms had a MAVE during the primary treatment period. Both subjects had a prior history of MAVE. The subject (USUBJID (b) (6)) in the crovalimab-naïve arm experienced myocardial infarction on Day 1 and died on Day 2. It was reported that the cardiac enzyme levels were elevated prior to the first dose of crovalimab in this subject. See Sections 7.6.1.2 and 17.3 for the subject narrative on this case. The subject in the eculizumab-naïve arm had a transient ischemic attack on Day 49 that occurred 6 days after the last dose of the study drug. This subject died on Day 71.

In COMMODORE-1, one subject in the eculizumab-experienced arm had a MAVE (transient ischemic attack) during the primary treatment period.

No other cases of MAVE were reported in the extension period of COMMODORE-1 and COMMODORE-2, or in COMMODORE-3.

The number of events of MAVE are too small to make a conclusion if crovalimab decreases the risk of MAVE.

7.6.1.9. Laboratory Findings, COMMODORE-1 and COMMODORE-2

Randomized Arms

PNH is a rare bone marrow failure disorder that presents with hemolytic anemia, thrombosis, and peripheral blood cytopenias (Brodsky 2014). With hemolytic anemia, jaundice and hepatosplenomegaly are often seen mimicking liver diseases, causing elevated serum aspartate aminotransferase (AST) and bilirubin levels (Murakami and Shimizu 2013). In COMMODORE-1 and COMMODORE-2, increases in liver enzymes and bilirubin were reported in both crovalimab and eculizumab arms. The tables below summarize the incidences of newly occurring or worsening laboratory abnormalities that occurred during the primary treatment period in COMMODORE-1 and COMMODORE-2. This section presents a frequency-based analysis of the objective laboratory assessments. Laboratory data are summarized according to National Cancer Institute-Common Terminology Criteria for Adverse Events grading of the adlb.xpt dataset. Assessment of AE reporting based on laboratory assessments is included in the analysis of AEs in the sections above. Overall, no clinically relevant laboratory findings were identified. No additional clinically relevant laboratory findings were identified in the extension period.

In COMMODORE-2, in subjects who were complement inhibitor treatment naïve, the shifts in laboratory abnormalities in the crovalimab-naïve arm were generally similar to the eculizumab-naïve arm. Most laboratory abnormalities were Grade 1 or 2 in severity. The only laboratory abnormality that was ≥5% higher in the crovalimab-naïve arm compared with the eculizumab-naïve arm was lymphocytes low (crovalimab: 48.9%, eculizumab: 42.0%). However, low lymphocytes are common in PNH due to the underlying bone marrow failure. In addition, the lymphocyte change was a minimal change from baseline in COMMODORE-1 and COMMODORE-2.

Table 52. Newly Occurring or Worsening Laboratory Abnormalities Postbaseline, Primary Treatment Period, COMMODORE-2, Safety Population

	Crovalimab (Naïve) (N=135) n (%)			Eculizumab (Naïve) (N=69) n (%)		
Laboratory Parameter	**Any Grade**	**≥Grade 2**	**Grade 3/4**	**Any Grade**	**≥Grade 2**	**Grade 3/4**
Hematology tests						
Leukocytes low	90 (66.7%)	66 (48.9%)	19 (14.1%)	49 (71.0%)	33 (47.8%)	7 (10.1%)
Lymphocytes low	66 (48.9%)	53 (39.3%)	17 (12.6%)	29 (42.0%)	19 (27.5%)	4 (5.8%)
Lymphocytes high	4 (3.0%)	4 (3.0%)	3 (2.2%)	3 (4.3%)	3 (4.3%)	1 (1.4%)
Neutrophils low	70 (51.9%)	58 (43.0%)	35 (25.9%)	44 (63.8%)	38 (55.1%)	18 (26.1%)
Platelet low	41 (30.4%)	24 (17.8%)	12 (8.9%)	27 (39.1%)	8 (12.0%)	4 (5.8%)

	Crovalimab (Naïve) (N=135) n (%)			Eculizumab (Naïve) (N=69) n (%)		
Laboratory Parameter	**Any Grade**	**≥Grade 2**	**Grade 3/4**	**Any Grade**	**≥Grade 2**	**Grade 3/4**
Chemistry tests						
Albumin low	11 (8.1%)	4 (3.0%)	2 (1.5%)	7 (10.1%)	2 (4.8%)	1 (1.4%)
ALP high	48 (35.6%)	2 (1.5%)	1 (0.7%)	26 (37.7%)	1 (1.4%)	0
ALT high	37 (24.4%)	5 (3.7%)	0	28 (40.6%)	4 (5.8%)	2 (4.8%)
AST high	4 (3.0%)	0	0	10 (14.5%)	4 (5.8%)	0
Bilirubin high	104 (77.0%)	56 (41.5%)	6 (4.4%)	58 (84.1%)	31 (44.9%)	4 (5.8%)
Calcium low	25 (18.5%)	1 (0.7%)	0	19 (27.5%)	2 (4.8%)	1 (1.4%)
Calcium high	11 (8.1%)	0	0	3 (4.3%)	0	0
Creatinine high	17 (12.6%)	11 (8.1%)	0	6 (8.7%)	4 (5.8%)	0
Glucose low	13 (9.6%)	3 (2.2%)	2 (1.5%)	15 (21.7%)	1 (1.4%)	1 (1.4%)
Potassium low	37 (27.4%)	37 (27.4%)	4 (3.0%)	31 (44.9%)	31 (44.9%)	4 (5.8%)
Potassium high	4 (3.0%)	0	0	4 (5.8%)	1 (1.4%)	0
Sodium low	21 (15.6%)	1 (0.7%)	0	10 (14.5%)	0	0
Sodium high	6 (4.4%)	1 (0.7%)	1 (0.7%)	4 (5.8%)	0	0
Coagulation tests						
INR high	34 (25.2%)	5 (3.7%)	4 (3.0%)	22 (31.9%)	1 (1.4%)	0
aPTT high	12 (8.9%)	3 (2.2%)	0	7 (10.1%)	1 (1.4%)	0

Source: ADLB.xpt, adapted from Applicant's submission
Abbreviations: ALP, alkaline phosphatase; ALT, alanine transaminase; aPTT, partial thromboplastin time; AST, aspartate transferase; INR, international normalized ratio; N, total number of subjects; n, number of subjects in subset

In COMMODORE-1, the incidence of newly occurring or worsening laboratory abnormalities during the primary treatment period in subjects who were previously treated with eculizumab were generally similar or greater in the crovalimab-switch arm compared with the eculizumab-experienced arm. This trend was also observed with TEAEs (see Table 37, Table 29, and Table 28), which is most likely due to subjects in the eculizumab arm being relatively stable on eculizumab prior to study entry and continuing treatment with eculizumab during the study.

Table 53. Newly Occurring or Worsening Laboratory Abnormalities Postbaseline, Primary Treatment Period, COMMODORE-1, Safety Population

	Crovalimab (Switch) (N=44) n (%)			Eculizumab (Experienced) (N=42) n (%)		
Laboratory Parameter	**Any Grade**	**≥Grade 2**	**Grade 3/4**	**Any Grade**	**≥Grade 2**	**Grade 3/4**
Hematology tests						
Leukocytes low	22 (50.0%)	16 (36.4%)	8 (18.2%)	15 (34.7%)	11 (26.2%)	5 (11.9%)
Lymphocytes low	29 (65.9%)	18 (40.1%)	8 (18.2%)	19 (45.2%)	14 (33.3%)	4 (9.5%)
Lymphocytes high	1 (2.3%)	1 (2.3%)	1 (2.3%)	2 (4.8%)	2 (4.8%)	1 (2.4%)
Neutrophils low	19 (43.2%)	17 (38.6%)	9 (20.5%)	14 (33.3%)	12 (28.6%)	6 (14.3%)
Platelet low	17 (38.6%)	5 (11.4%)	1 (2.3%)	14 (33.3%)	6 (14.3%)	3 (7.1%)

	Crovalimab (Switch) (N=44) n (%)			Eculizumab (Experienced) (N=42) n (%)		
Laboratory Parameter	**Any Grade**	**≥Grade 2**	**Grade 3/4**	**Any Grade**	**≥Grade 2**	**Grade 3/4**
Chemistry tests						
Albumin low	5 (11.4%)	2 (4.5%)	1 (2.3%)	2 (4.8%)	2 (4.8%)	2 (4.8%)
ALP high	7 (15.9%)	1 (2.3%)	0	5 (11.9%)	0	0
ALT high	12 (27.3%)	1 (2.3%)	1 (2.3%)	11 (26.2%)	0	0
AST high	19 (43.2%)	0	0	11 (26.2%)	2 (4.8%)	0
Bilirubin high	31 (70.5%)	11 (25.0%)	0	31 (73.8%)	8 (19.0%)	1 (2.4%)
Calcium low	6 (13.6%)	1 (2.3%)	0	4 (9.5%)	0	0
Calcium high	7 (15.9%)	2 (4.5%)	2 (4.5%)	0	0	0
Creatinine high	7 (15.9%)	2 (4.5%)	0	5 (11.9%)	3 (7.1%)	1 (2.4%)
Glucose low	4 (9.1%)	2 (4.5%)	1 (2.3%)	4 (9.5%)	0	0
Potassium low	10 (22.7%)	10 (22.7%)	1 (2.3%)	6 (14.3%)	6 (14.3%)	0
Potassium high	6 (13.6%)	1 (2.3%)	0	4 (9.5%)	3 (7.1%)	2 (4.8%)
Sodium low	3 (6.8%)	0	0	10 (23.8%)	1 (2.4%)	1 (2.4%)
Sodium high	1 (2.3%)	0	0	2 (4.8%)	1 (2.4%)	0
Coagulation tests						
INR high	12 (27.3%)	2 (4.5%)	1 (2.3%)	12 (28.6%)	1 (2.4%)	1 (2.4%)
aPTT high	1 (2.3%)	1 (2.3%)	0	2 (4.8%)	0	0

Source: ADLB.xpt, adapted from Applicant's submission, Nonrandomized Arms.
Abbreviations: ALP, alkaline phosphatase; ALT, alanine transaminase; aPTT, partial thromboplastin time; AST, aspartate transferase; INR, international normalized ratio; N, total number of subjects; n, number of subjects in subset

In COMMODORE-2, most subjects in the pediatric cohort who reported a shift in laboratory value from baseline were Grade 1 or 2 in severity. Shifts to Grade 3 or 4 from baseline were seen for lymphocytes high (2/6 subjects) and neutrophils low (2/6 subjects).

In COMMODORE-1, no laboratory abnormalities in the pediatric cohort (N=1) were reported. The laboratory abnormalities observed in the prior-ravulizumab, prior-high-dose eculizumab and C5 SNP cohorts were broadly consistent with those reported in the crovalimab-switch arm in COMMODORE-1.

Table 54. Newly Occurring or Worsening Laboratory Abnormalities Postbaseline, Nonrandomized Arms, COMMODORE-1 and COMMODORE-2, Safety Population

	COMMODORE-2		COMMODORE-1					
	Crovalimab (Pediatric Subjects, Naïve) (N=6) n (%)		Crovalimab (Prior Ravulizumab) (N=21) n (%)		Crovalimab (Prior-High-Dose Eculizumab) (N=10) n (%)		Crovalimab (C5 SNP) (N=6) n (%)	
Laboratory Parameter	**Any Grade**	**Grade 3/4**	**Any Grade**	**Grade 3/4**	**Any Grade**	**Grade 3/4**	**Any Grade**	**Grade 3/4**
Hematology tests								
Leukocytes low	1 (16.7%)	0	9 (42.9%)	1 (4.8%)	5 (50.0%)	0	5 (83.3%)	1 (16.7%)
Lymphocytes low	2 (33.3%)	0	14 (66.7%)	7 (33.3%)	6 (60.0%)	2 (20.0.%)	5 (83.3%)	2 (33.3%)
Lymphocytes high	2 (33.3%)	2 (33.3%)	1 (4.8%)	0	1 (10.0%)	1 (10.0%)	0	0
Neutrophils low	4 (83.3%)	2 (33.3%)	9 (42.9%)	1 (4.8%)	2 (20.0.%)	1 (10.0%)	3 (50.0%)	2 (33.3%)
Platelet low	0	0	6 (28.6%)	0	3 (30.0%)	1 (10.0%)	3 (50.0%)	1 (16.7%)
Chemistry tests								
Albumin low	1 (16.7%)	0	3 (14.3%)	0	1 (10.0%)	0	2 (33.3%)	0
ALP high	3 (50.0%)	0	9 (42.9%)	0	1 (10.0%)	0	1 (16.7%)	0
ALT high	2 (33.3%)	0	12 (57.1%)	1 (4.8%)	2 (20.0.%)	0	4 (66.7%)	1 (16.7%)
AST high	0	0	12 (57.1%)	1 (4.8%)	1 (10.0%)	0	1 (16.7%)	1 (16.7%)
Bilirubin high	5 (83.3%)	0	15 (71.4%)	1 (4.8%)	7 (70.0.%)	0	3 (50.0%)	0
Calcium low	1 (16.7%)	0	4 (19.0%)	1 (4.8%)	1 (10.0%)	0	1 (16.7%)	0
Calcium high	0	0	2 (9.5%)	1 (4.8%)	1 (10.0%)	0	2 (33.3%)	0
Creatinine high	0	0	3 (14.3%)	1 (4.8%)	2 (20.0.%)	0	1 (16.7%)	0
Glucose low	2 (33.3%)	0	1 (4.8%)	0	3 (30.0%)	0	0	0
Potassium low	1 (16.7%)	0	6 (28.6%)	1 (4.8%)	2 (20.0.%)	0	2 (33.3%)	0
Potassium high	0	0	1 (4.8%)	0	2 (20.0.%)	0	2 (33.3%)	0
Sodium low	2 (33.3%)	0	3 (14.3%)	0	2 (20.0.%)	1 (10.0%)	1 (16.7%)	1 (16.7%)
Sodium high	0	0	0	0	1 (10.0%)	0	0	0
Coagulation tests								
INR high	3 (50.0.%)	0	11 (52.4%)	0	1 (10.0%)	0	3 (50.0%)	0
aPTT high	0	0	1 (4.8%)	0	0	0	1 (16.7%)	0

Source: ADLB.xpt, adapted from Applicant's submission.
Abbreviations: ALP, alkaline phosphatase; ALT, alanine transaminase; aPTT, partial thromboplastin time; AST, aspartate transferase; C5, complement component 5; INR, international normalized ratio; N, total number of subjects; n, number of subjects in subset; SNP, single nucleotide polymorphism

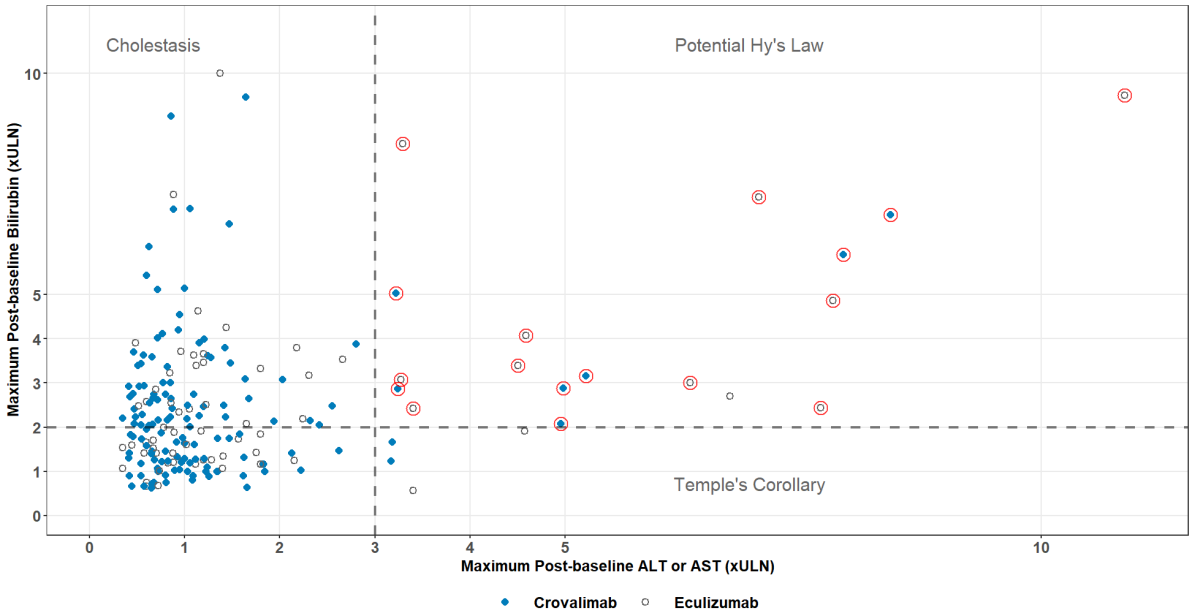
7.6.1.10. Assessment of Drug-Induced Liver Injury, COMMODORE-1, COMMODORE-2, and COMMODORE-3

COMMODORE-1 and COMMODORE-2

Primary Treatment Period

In COMMODORE-2, a total of 7 subjects (5.2%) in the crovalimab arm compared to 10 subjects, (13.0%) in the eculizumab arm met potential Hy's law criteria (Figure 11 and Table 55). For incidence of elevated liver enzymes, refer to Table 56.

Figure 11. Hepatocellular Drug-Induced Liver Injury Screening Plot, Primary Treatment Period, COMMODORE-2, Safety Population



Source: adlb.xpt; Software: R.
Each data point represents a subject plotted by their maximum ALT or AST versus their maximum total bilirubin values in the post-baseline period. A potential Hy's Law case (red circle) was defined as having any postbaseline total bilirubin equal to or exceeding 2X ULN within 30 days after a postbaseline ALT or AST equal to or exceeding 3X ULN, and ALP less than 2X ULN (note ALP values are not circled). All subjects with at least one postbaseline ALT or AST and bilirubin are plotted. The within 30 days analysis window rule does not apply to cholestatic DILI and temple's corollary cases. In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.
Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DILI, drug-induced liver injury; TB, total bilirubin; ULN, upper limit of normal

Table 55. Subjects in Each Quadrant for Potential Hepatocellular DILI Screening Plot, Primary Treatment Period, COMMODORE-2, Safety Population

Quadrant	Crovalimab N=135 n/N_w (%)	Eculizumab N=69 n/N_w (%)
Potential Hy's Law (right upper)	7/133 (5.3)	10/68 (14.7)
Cholestasis (left upper)	66/134 (49.3)	26/69 (37.7)
Temple's corollary (right lower)	2/134 (1.5)	2/69 (2.9)
Total	75/134 (56)	38/69 (55.1)

Source: adlb.xpt; Software: R.
Note: A potential Hy's Law case was defined as having any postbaseline total bilirubin equal to or exceeding 2X ULN within 30 days after a postbaseline ALT or AST equal to or exceeding 3X ULN, and ALP less than 2X ULN. The within 30 days analysis window rule does not apply to cholestatic DILI and temple's corollary cases.
Note: In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.
Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DILI, drug-induced liver injury; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data; ULN, upper limit of normal

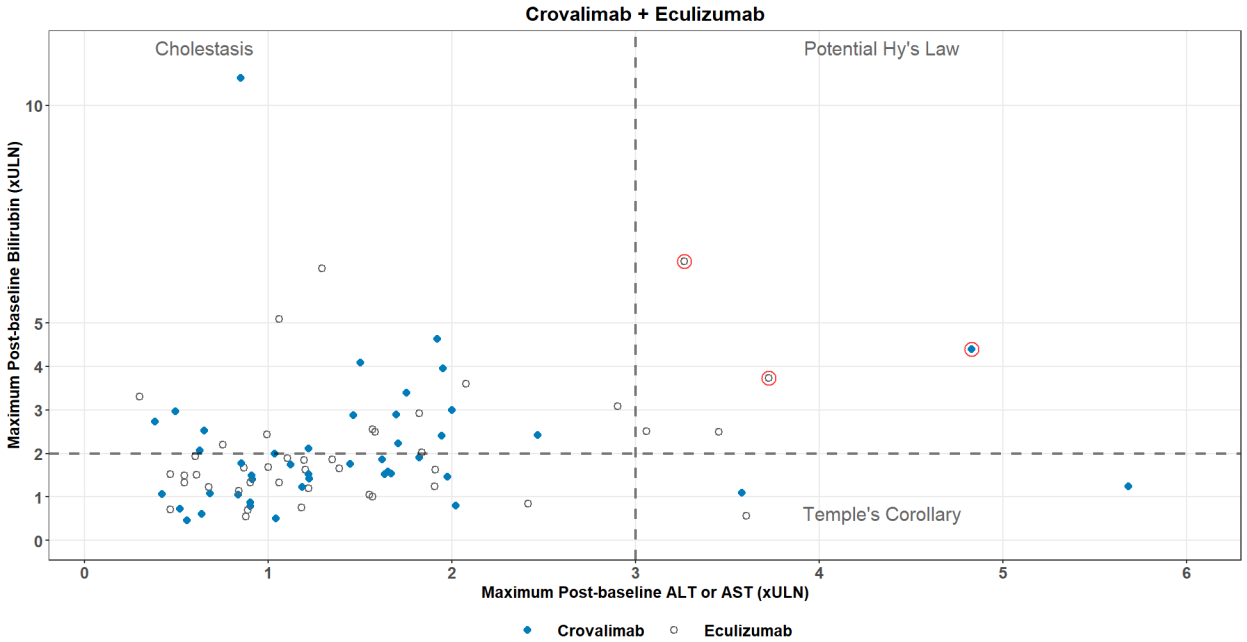
Table 56. Subjects With One or More Liver Biochemistry Analyte Values Exceeding Specified Levels, Primary Treatment Period, COMMODORE-2, Safety Population

Laboratory Parameter	Crovalimab N=135 n/N_w (%)	Eculizumab N=69 n/N_w (%)	Crovalimab vs. Eculizumab Risk Difference (%) (95% CI)
Alkaline phosphatase, high (U/L)			
Level 1 (>1.5X ULN)	13/133 (9.8)	11/68 (16.2)	-6.4 (-17.8, 2.9)
Level 2 (>2X ULN)	4/133 (3.0)	2/68 (2.9)	0.1 (-7.4, 5.1)
Level 3 (>3X ULN)	2/133 (1.5)	1/68 (1.5)	0.0 (-6.5, 4.1)
Alanine aminotransferase, high (U/L)			
Level 1 (>3X ULN)	8/134 (6.0)	6/69 (8.7)	-2.7 (-12.3, 4.4)
Level 2 (>5X ULN)	2/134 (1.5)	4/69 (5.8)	-4.3 (-12.6, 0.6)
Level 3 (>10X ULN)	0/134 (0)	0/69 (0)	0 (-5.3, 2.8)
Aspartate aminotransferase, high (U/L)			
Level 1 (>3X ULN)	5/134 (3.7)	11/69 (15.9)	-12.2 (-23.0, -4.2)[a]
Level 2 (>5X ULN)	2/134 (1.5)	5/69 (7.2)	-5.8 (-14.5, -0.4)[a]
Level 3 (>10X ULN)	0/134 (0)	1/69 (1.4)	-1.4 (-7.8, 1.4)
Bilirubin, total, high (mg/dL)			
Level 1 (>1.5X ULN)	87/134 (64.9)	48/69 (69.6)	-4.6 (-17.6, 9.3)
Level 2 (>2X ULN)	73/134 (54.5)	36/69 (52.2)	2.3 (-12.0, 16.7)
Level 3 (>3X ULN)	33/134 (24.6)	23/69 (33.3)	-8.7 (-22.3, 4.1)

Source: adlb.xpt; Software: R.
Note: Threshold levels 1, 2, and 3 as defined by the Standard Safety Tables & Figures Integrated Guide (FDA 2022).
Note: Duration is the 24-week randomized period.
Note: Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Note: In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.
[a] indicates that 95% confidence interval excludes zero.
Abbreviations: CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data; ULN, upper limit of normal

In COMMODORE-1, one subject (2.3%) in the crovalimab arm and two subjects (4.8%) in the eculizumab arm met the criteria for a potential Hy's law case (see Figure 12 and Table 57). For incidence of elevated liver enzymes, refer to Table 58.

Figure 12. Hepatocellular Drug-Induced Liver Injury Screening Plot, Primary Treatment Period, COMMODORE-1, Safety Population



Source: adlb.xpt; Software: R.
Note: Each data point represents a subject plotted by their maximum ALT or AST versus their maximum total bilirubin values in the postbaseline period. A potential Hy's Law case (red circle) was defined as having any postbaseline total bilirubin equal to or exceeding 2X ULN within 30 days after a postbaseline ALT or AST equal to or exceeding 3X ULN, and ALP less than 2X ULN (note ALP values are not circled). All subjects with at least one postbaseline ALT or AST and bilirubin are plotted. The within 30 days analysis window rule does not apply to cholestatic DILI and temple's corollary cases. In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.
Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DILI, drug-induced liver injury; TB, total bilirubin; ULN, upper limit of normal

Table 57. Subjects in Each Quadrant for Potential Hepatocellular DILI Screening Plot, Primary Treatment Period, COMMODORE-1, Safety Population

Quadrant	Crovalimab N=44 n/N_w (%)	Eculizumab N=42 n/N_w (%)
Potential Hy's Law (right upper)	1/42 (2.4)	2/41 (4.9)
Cholestasis (left upper)	16/43 (37.2)	7/41 (17.1)
Temple's corollary (right lower)	2/43 (4.7)	1/41 (2.4)
Total	19/43 (44.2)	10/41 (24.4)

Source: adlb.xpt; Software: R.
Note: A potential Hy's Law case was defined as having any postbaseline total bilirubin equal to or exceeding 2X ULN within 30 days after a postbaseline ALT or AST equal to or exceeding 3X ULN, and ALP less than 2X ULN. The within 30 days analysis window rule does not apply to cholestatic DILI and temple's corollary cases.
Note: In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.
Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DILI, drug-induced liver injury; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data; ULN, upper limit of normal

Table 58. Subjects With One or More Liver Biochemistry Analyte Values Exceeding Specified Levels, Primary Treatment Period, COMMODORE-1, Safety Population

Laboratory Parameter	Crovalimab N=44 n/N_w (%)	Eculizumab N=42 n/N_w (%)	Crovalimab vs. Eculizumab Risk Difference (%) (95% CI)
Alkaline phosphatase, high (U/L)			
Level 1 (>1.5X ULN)	3/43 (7.0)	1/42 (2.4)	4.6 (-6.3, 16.7)
Level 2 (>2X ULN)	1/43 (2.3)	1/42 (2.4)	-0.1 (-10.4, 10.0)
Level 3 (>3X ULN)	1/43 (2.3)	0/42 (0)	2.3 (-6.2, 12.1)
Alanine aminotransferase, high (U/L)			
Level 1 (>3X ULN)	2/44 (4.5)	2/42 (4.8)	-0.2 (-12.0, 11.1)
Level 2 (>5X ULN)	1/44 (2.3)	0/42 (0)	2.3 (-6.3, 11.9)
Level 3 (>10X ULN)	0/44 (0)	0/42 (0)	0.0 (-8.5, 8.1)
Aspartate aminotransferase, high (U/L)			
Level 1 (>3X ULN)	1/44 (2.3)	3/41 (7.3)	-5.0 (-17.6, 5.5)
Level 2 (>5X ULN)	0/44 (0)	0/41 (0)	0.0 (-8.7, 8.1)
Level 3 (>10X ULN)	0/44 (0)	0/41 (0)	0.0 (-8.7, 8.1)
Bilirubin, total, high (mg/dL)			
Level 1 (>1.5X ULN)	24/43 (55.8)	23/41 (56.1)	-0.3 (-21.2, 20.7)
Level 2 (>2X ULN)	16/43 (37.2)	11/41 (26.8)	10.4 (-9.8, 29.7)
Level 3 (>3X ULN)	5/43 (11.6)	6/41 (14.6)	-3.0 (-18.7, 12.3)

Source: adlb.xpt; Software: R.
Note: Threshold levels 1, 2, and 3 as defined by the Standard Safety Tables & Figures Integrated Guide (FDA 2022).
Note: Duration is 24-week randomized period.
Note: Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Note: In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.
Abbreviations: CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data; ULN, upper limit of normal

All subjects who received crovalimab and met the Hy's law criteria during the primary treatment period in COMMODORE-1 and COMMODORE-2 had elevated bilirubin values at baseline (Grade ≥2 bilirubin [>1.5 to 3.0×ULN]) that remained elevated during the study (graphical representation of liver enzymes for each of the subjects that met potential Hy's law is shown in Section 17.1.1.1). Elevations in total bilirubin and AST are common in patients with PNH, which is associated with IVH. Other possible reasons in these subjects included ADA leading to IVH, complement activating conditions (including COVID-19) and/or BTH events that may transiently increase hemolysis, ongoing low-level IVH (elevation of LDH ≥1.5xULN despite complete complement inhibition) with or without decreasing hemoglobin or potential extravascular hemolysis, past medical history related to a hepatic disorder or abnormalities prior to enrollment which were ongoing on study, and concomitant medications known to cause elevations in liver enzymes. In the majority of cases, liver enzyme elevations were transient despite continuation of crovalimab therapy. No subject discontinued or interrupted therapy due to hepatotoxicity. These events were not assessed as potential drug-induced liver injury. The liver biochemistry analyses of these subjects are presented in Section 17.1.1.7.

Extension Period

During the extension period, a total of three additional subjects met the Hy's law criteria in COMMODORE-2 (crovalimab-naïve: two subjects and crovalimab-switch: one subject) and no additional subjects met the Hy's law criteria in COMMODORE-1. These events were also not assessed as potential drug-induced liver injury due to increased baseline bilirubin that stayed

mostly elevated throughout the study, which was related to the underlying hemolytic disease. The liver biochemistry analyses of the three subjects are presented in Section 17.1.1.1.

Hepatotoxicity TEAEs

In COMMODORE-1 and COMMODORE-2, a total of two subjects (USUJIDs: (b) (6)) who received crovalimab were reported with TEAEs of "liver injury" and "hepatotoxicity", respectively.

USUBJID (b) (6) was a 32-year-old Asian male who was randomized to the crovalimab naïve arm in COMMODORE-2 and developed Grade 1 liver injury on Day 297 (AST 47 U/L [normal range: 15-40 U/L], alanine aminotransferase (ALT) 130 U/L [normal range: 9-50 U/L] and normal bilirubin level) that resolved on Day 413 without treatment modification of the study treatment. Prior to the event, the subject received treatment with celecoxib which may cause liver injury although the timing of the celecoxib (on Day 223, Days 229 to 234 and Days 244 to 248) in relation to the liver test abnormalities does not make celecoxib a likely explanation for the findings..

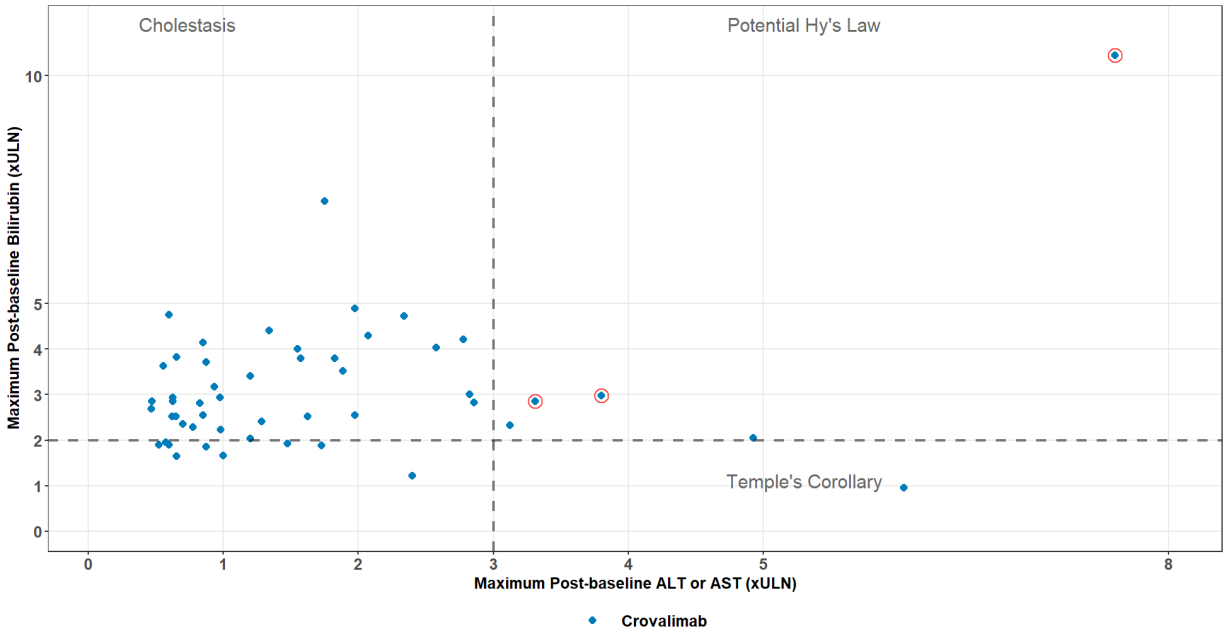
USUBJID (b) (6) was a 28-year-old White male who was randomized to the crovalimab-switch arm and experienced Grade 3 hepatotoxicity on Day 442. The event of hepatotoxicity resolved 5 days later, on Day 447, without treatment modification of the study drug. Prior to this event, the subject developed Grade 3 febrile neutropenia on Day 438. Treatment for febrile neutropenia included paracetamol, prophylactic micafungin, and posaconazole, all of which can cause hepatotoxicity.

It is not likely that the study drug caused hepatic injury in these cases.

COMMODORE-3

In the single-arm COMMODORE-3 conducted in China, a total of 3 subjects (5.9%) met Hy's Law criteria up to the CCOD (Figure 13).

Figure 13. Hepatocellular Drug-Induced Liver Injury Screening Plot, Primary Treatment Period, COMMODORE-3, Safety Population



Source: adlb.xpt; Software: R.
Each data point represents a subject plotted by their maximum ALT or AST versus their maximum total bilirubin values in the postbaseline period. A potential Hy's Law case (red circle) was defined as having any postbaseline total bilirubin equal to or exceeding 2X ULN within 30 days after a postbaseline ALT or AST equal to or exceeding 3X ULN, and ALP less than 2X ULN (note ALP values are not circled). All subjects with at least one postbaseline ALT or AST and bilirubin are plotted.
Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal

The liver biochemistry analyses of the three subjects are presented in Section 17.1.1.7. Similar to cases that met the Hy's Law criteria in COMMODORE-1 and COMMODORE-2, all cases had elevated bilirubin at baseline, which remained elevated throughout the study. Liver enzyme elevations were transient and were also not assessed as potential drug-induced liver injury. The liver enzyme elevations resolved in the three subjects without changes to crovalimab treatment.

There was one subject (USUBJID: [redacted] (b) (6)), a 28-year-old Asian male who received crovalimab in COMMODORE-3 and developed Grade 1 hepatic insufficiency on Study Day 307. Baseline total bilirubin was 60.1µmol/L (normal range: 5 to 21), AST 133 U/L (normal range: 15 to 40), ALT 25 U/L (normal range: 9 to 50), alkaline phosphatase 82 U/L (normal range: 45 to 125). The total bilirubin stayed elevated throughout the study. The ALT levels were in the normal range during the study, except on Day 307 (Week 43) when the ALT level increased to 67 U/L (Grade 1 hepatic insufficiency), followed by a decrease to 19 U/L at Week 49 while continuing crovalimab. Given the transient nature of the liver enzyme increase and improvement while on crovalimab, it is unlikely that the event of hepatic insufficiency is related to crovalimab.

7.6.1.11. Vital Signs, COMMODORE-1 and COMMODORE-2

Randomized Arms

The tables below summarize postbaseline vital sign results during the primary treatment period in COMMODORE-1 and COMMODORE-2. Generally, there were no significant differences in

the incidences of postbaseline systolic blood pressure (BP) ≥140 mm Hg, diastolic BP ≥90 and heart rate ≥100 beats/min (or <60 beats/min) between the crovalimab and eculizumab arms. Individual subjects had various vital sign abnormalities. There was no significant changes in mean systolic and diastolic BP.

Table 59. Vital Signs Abnormalities Postbaseline, Primary Treatment Period, COMMODORE-2, Safety Population

	Crovalimab (Naïve) (N=135) n (%)		Eculizumab (Naïve) (N=69) n (%)	
Vital Sign	Baseline	Maximum Postbaseline	Baseline	Maximum Postbaseline
Blood pressure (mm Hg)				
Systolic BP <120	43 (31.9%)	17 (12.6%)	28 (40.6%)	9 (13.0%)
Systolic BP ≥120 and <140	75 (55.6%)	86 (63.7%)	30 (43.5%)	46 (66.7%)
Systolic BP ≥140 and <160	14 (10.4%)	26 (19.3%)	8 (11.6%)	10 (14.5%)
Systolic BP ≥160	3 (2.2%)	5 (3.7%)	3 (4.3%)	4 (5.8%)
Missing	0	1 (0.7%)	0	0
Diastolic BP <80	91 (67.4%)	42 (31.1%)	54 (78.3%)	27 (39.1%)
Diastolic BP ≥80 and <90	35 (25.9%)	69 (51.1%)	11 (15.9%)	35 (50.7%)
Diastolic BP ≥90	9 (6.7%)	23 (17.0%)	4 (5.8%)	7 (10.1%)
Missing	0	1 (0.7%)	0	0
Heart rate (beats/min)				
Heart rate ≥100	9 (6.7%)	43 (31.9%)	2 (2.9%)	14 (20.3%)
Heart rate <60	3 (2.2.%)	1 (0.7%)	2 (2.9%)	0

Source: ADVS.xpt.
Abbreviations: BP, blood pressure; min, minute; N, total number of subjects; n, number of subjects in subset

Table 60. Vital Signs Laboratory Abnormalities Postbaseline, Primary Treatment Period, COMMODORE-1, Safety Population

	Crovalimab (Switch) (N=44) n (%)		Eculizumab (Experienced) (N=42) n (%)	
Vital Sign	Baseline	Maximum Postbaseline	Baseline	Maximum Postbaseline
Blood pressure (mm Hg)				
Systolic BP <120	18 (40.9%)	2 (4.5%)	20 (47.6%)	1 (2.4%)
Systolic BP ≥120 and <140	21 (47.7%)	26 (59.1%)	17 (40.5%)	24 (57.1%)
Systolic BP ≥140 and <160	4 (9.1%)	12 (27.3%)	5 (11.9%)	14 (33.3%)
Systolic BP ≥160	1 (2.3%)	4 (9.1%)	0	3 (7.1%)
Diastolic BP <80	34 (77.3%)	13 (29.5%)	28 (66.7%)	12 (28.6%)
Diastolic BP ≥80 and <90	9 (20.5%)	22 (50.0%)	11 (26.2%)	19 (45.2%)
Diastolic BP ≥90	1 (2.3%)	9 (20.5%)	3 (7.1%)	11 (24.2%)
Heart rate (beats/min)				
Heart rate ≥100	2 (4.5%)	7 (15.9%)	1 (2.4%)	6 (14.3%)
Heart rate <60	0	0	3 (7.1%)	0

Source: ADVS.xpt.
Abbreviations: BP, blood pressure; min, minute; N, total number of subjects; n, number of subjects in subset

Nonrandomized Arms

In COMMODORE-2, no significant changes in vital signs were observed in the pediatric nonrandomized arm. Baseline and postbaseline maximum systolic BP values of the six pediatric subjects were <140 mm Hg except for one subject who had postbaseline maximum value of 144

mm Hg. Baseline and postbaseline diastolic BP values of the six pediatric subjects were all <80 mm Hg. A total of two subjects had a postbaseline heart rate of ≥100 beats/min who had baseline heart rate of 90 and 97 beats/min, respectively.

In COMMODORE-1, postbaseline vital sign results in the prior-ravulizumab, prior-high-dose eculizumab and C5 SNP cohorts were generally consistent with the those observed in the crovalimab arms in COMMODORE-1 and COMMODORE-2. No vital sign abnormality was observed in the pediatric cohort.

Table 61. Vital Signs Abnormalities Postbaseline up to the Clinical Cutoff Date, Nonrandomized Arm, COMMODORE-1, Safety Population

	Crovalimab (Prior Ravulizumab) (N=21) n (%)		Crovalimab (Prior-High-Dose Eculizumab) (N=10) n (%)		Crovalimab (C5 SNP) (N=6) n (%)	
Vital Sign	**Baseline**	**Maximum Postbaseline**	**Baseline**	**Maximum Postbaseline**	**Baseline**	**Maximum Postbaseline**
Blood pressure (mm Hg)						
SBP <120	9 (42.9%)	3 (14.3%)	7 (70.0%)	1 (10.0%)	1 (16.7%)	1 (16.7%)
SBP ≥120 and <140	10 (47.6%)	12 (57.1%)	3 (30.0%)	6 (60.0%)	4 (66.7%)	1 (16.7%)
SBP ≥140 and <160	2 (9.5%)	5 (23.8%)	0	3 (30.0%)	1 (16.7%)	2 (33.3%)
SBP ≥160	0	1 (4.8%)	0	0	0	2 (33.3%)
DBP <80	16 (76.2%)	6 (28.6%)	8 (80.0%)	4 (40.0%)	5 (83.3%)	3 (50.0.%)
DBP ≥80 and <90	5 (23.8%)	10 (47.6%)	2 (20.0%)	4 (40.0%)	1 (16.7%)	3 (50.0.%)
DBP ≥90	0	5 (23.8%)	0	2 (20.0%)	0	0
Heart rate (beats/min)						
Heart rate ≥100	1 (4.8%)	6 (28.6%)	0	6 (60.0%)	0	2 (33.3%)
Heart rate <60	1 (4.8%)	0	1 (10.0%)	0	0	0

Source: ADVS.xpt
Abbreviations: C5, complement component 5; DBP, diastolic blood pressure; min, minute; N, total number of subjects; n, number of subjects in subset; SBP, systolic blood pressure; SNP, single nucleotide polymorphism

The Applicant provided cases of hypertension TEAEs that occurred in COMMODORE-1 and COMMODORE-2 (using the November 16, 2022, CCOD). A total of six subjects were reported with hypertension TEAEs, as shown in Table 62 below.

In five cases (COMMODORE-1 nonrandomized arm: four cases, COMMODORE-2 crovalimab arm: one case), the event occurred while on crovalimab treatment. The sixth case occurred in a subject ([redacted]) while randomized to the eculizumab arm.

Table 62. Overview of Reported TEAEs of Hypertension up to the Clinical Cutoff Date, COMMODORE-1 and COMMODORE-2, Safety Population

Study	Arm	Patient ID	Most extreme grade	Outcome	Hypertension at baseline	Concomitant medication for hypertension	Action taken with crovalimab due to AE
BO42161	C	[redacted]	Grade 1	Resolved	yes	yes[a]	Dose not changed
BO42161	C		Grade 3	Not resolved	yes	yes[c]	Dose not changed
BO42161	C		Grade 2	Resolving	no	yes[d]	Dose not changed
BO42161	C		Grade 3	Resolving	no	yes[d]	Dose not changed
BO42162	A		Grade 3	Not resolved	no	yes[d]	Not applicable[e]
BO42162	B		Grade 2	Resolving	no	yes[d]	Dose not changed

Source: Response to information request.
Note: BO42161 = COMMODORE-1, BO42162 = COMMODORE-2.
[a] Ongoing antihypertensives at baseline with no change during the study or as a result of the AE.
[b] Event inactivated after the CCOD in October 2023.
[c] Ongoing antihypertensives at baseline with additional medications added after the start of the event.
[d] Medication started after first study drug administration.
[e] The event occurred after the last dose of study drug was administered; therefore, the action take with crovalimab is not applicable.
[f] Event onset during eculizumab primary treatment period, ongoing at the time of switch to crovalimab.
Abbreviations: AE, adverse event; CCOD, clinical cutoff date; ID, identification

Of the six subjects, two ([redacted]) had a medical history of hypertension at baseline and both were receiving antihypertensive medications. Subject [redacted] had no change in the antihypertensives during the study. Subject [redacted] was receiving losartan 50 mg daily at baseline. On Study Day 168, the subject initiated hydrochlorothiazide 25 mg daily, and on Day 169, the dose of losartan was increased (100 mg daily) and on Day 217, the subject started treatment with amlodipine 5 mg twice daily.

In one subject ([redacted]), the TEAE onset was on Day 40 which was 16 days after crovalimab discontinuation. The subject was in the safety follow-up at the time of the onset of the TEAE. From Day 41 to 147, various antihypertensives were given. On Day 148, furosemide

(20 mg once daily) was started and treatment with furosemide was ongoing at the time of final contact.

In the remaining two subjects, the hypertension TEAE started after baseline, and treatment with antihypertensives was initiated during the study as follows:

- (b) (6): The onset of the TEAE was on Day 57, and treatment with amlodipine (5 mg once daily) was started on the same day and was ongoing at the final contact.
- (b) (6): The TEAE onset was on Day 114, and treatment with amlodipine (5 mg once daily) was started on the same day and was ongoing at the final contact.

In summary, in a total of four subjects, the dose of antihypertensive was either increased or there was a change in the antihypertensive medication (n=2 subjects) or treatment with antihypertensives was initiated (n=2 subjects) while on crovalimab treatment. Given the small number of hypertension TEAEs reported in COMMODORE-1 and COMMODORE-2, along with no change in the mean systolic or diastolic BP compared to baseline, there is insufficient evidence to suggest that crovalimab increases the risk for developing hypertension.

Subgroups, COMMODORE-1 and COMMODORE-2

An overview of TEAEs by demographic subgroup is summarized in Table 63 and Table 64. Results should be interpreted with caution given the small sample sizes.

For subgroup analyses of type III hypersensitivity reaction by race and region, see Section 7.6.1.8.4.

Table 63. Overview of Treatment-Emergent Adverse Events by Demographic Subgroup, COMMODORE-2, Safety Population

Characteristic	Crovalimab N=135 n/N_s (%)	Eculizumab N=69 n/N_s (%)	Crovalimab vs. Eculizumab Risk Difference (%) (95% CI)
Sex			
Female	49/58 (84.5)	25/34 (73.5)	11.0 (-5.7, 29.6)
Male	56/77 (72.7)	30/35 (85.7)	-13.0 (-27.1, 4.4)
Age group, years			
<65	97/122 (79.5)	49/60 (81.7)	-2.2 (-13.6, 11.1)
≥65	8/13 (61.5)	6/9 (66.7)	-5.1 (-42.1, 35.4)
Age group ≥75, years			
≥75	½ (50.0)	½ (50.0)	-0.0 (-74.9, 74.9)
Race			
Asian	65/86 (75.6)	41/51 (80.4)	-4.8 (-18.4, 10.4)
Black or African American	3/3 (100)	1/1 (100)	0 (-63.1, 83.7)
White	36/45 (80.0)	12/16 (75.0)	5.0 (-16.0, 31.9)
Unknown	1/1 (100)	1/1 (100)	0 (-88.5, 88.5)
Ethnicity			
Hispanic or Latino	15/18 (83.3)	4/6 (66.7)	16.7 (-17.9, 57.4)
Not Hispanic or Latino	87/114 (76.3)	49/61 (80.3)	-4.0 (-16.0, 9.6)
Not reported	3/3 (100)	2/2 (100)	0 (-61.5, 70.6)

Source: adae.xpt; Software: R.
Note: Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Abbreviations: CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects with adverse event; N_s, total number of subjects for each specific subgroup and were assigned to that specific arm

Table 64. Overview of Treatment-Emergent Adverse Events by Demographic Subgroup, COMMODORE-1, Safety Population

Characteristic	Crovalimab N=44 n/N_s (%)	Eculizumab N=42 n/N_s (%)	Crovalimab vs Eculizumab Risk Difference (%) (95% CI)
Sex, n (%)			
Female	19/24 (79.2)	12/21 (57.1)	22.0 (-5.4, 47.2)
Male	15/20 (75.0)	16/21 (76.2)	-1.2 (-28.0, 25.4)
Age group, years, n (%)			
<65	30/39 (76.9)	25/35 (71.4)	5.5 (-14.5, 25.7)
≥65	4/5 (80.0)	3/7 (42.9)	37.1 (-21.3, 74.8)
Age group ≥75, years, n (%)			
≥75	3/3 (100)	1/3 (33.3)	66.7 (-16.8, 94.6)
Race, n (%)			
Asian	8/9 (88.9)	6/7 (85.7)	3.2 (-34.4, 44.4)
Black or African American	2/2 (100)	1/1 (100)	0.0 (-74.2, 85.2)
Unknown	0/0 (NA)	3/4 (75.0)	NA
White	24/33 (72.7)	18/30 (60.0)	12.7 (-10.7, 35.2)
Ethnicity, n (%)			
Hispanic or Latino	7/7 (100)	8/8 (100)	0.0 (-37.0, 34.0)
Not Hispanic or Latino	26/36 (72.2)	16/29 (55.2)	17.0 (-6.4, 39.4)
Not Reported	1/1 (100)	4/5 (80.0)	20.0 (-70.0, 65.6)

Source: adae.xpt; Software: R.
Note: Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Abbreviations: CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects with adverse event; N_s, total number of subjects for each specific subgroup and were assigned to that specific arm

7.6.1.12. Immunogenicity, Pooled Analyses, COMMODORE-1, COMMODORE-2, and COMMODORE-3

In the pooled database from COMMODORE-1, COMMODORE-2, and COMMODORE-3, the incidence of treatment-emergent ADAs was 27.5% in the 375 ADA-evaluable crovalimab subject population that consisted of all subjects with at least one ADA assessment conducted during the primary and extension periods (crovalimab-naïve population: 31.4% [60 subjects out of 191], crovalimab-switch population: 23.4% [43 subjects out of 184]). The median time to development of postbaseline ADAs was 12.4 weeks (range: 1.1 to 48.1 weeks) in the treatment-naïve subjects and 13.4 weeks (range: 2.1 to 36.3 weeks) in subjects who were previously treated with another C5 inhibitor. A total of two subjects who were treatment naïve had neutralizing ADAs that resulted in complete loss of exposure and PD activity. One of the subjects experienced uncontrolled hemolysis and discontinued the study. Neutralizing ADAs were not reported in the crovalimab-switch population.

In the total crovalimab population, the incidence of any TEAE was similar between the ADA-positive (89.3%) and ADA-negative subjects (85.7%). The incidences of serious and Grade 3 to 5 TEAEs were slightly higher in the ADA-positive subjects (serious TEAE: 18.4%, Grade 3 to 5: 35.9%) compared with the ADA-negative subjects (serious TEAE: 13.6%, Grade 3 to 5: 21.3%).

The difference in the Grade 3 to 5 and serious TEAEs by ADA status was driven by the difference in the crovalimab-switch population (Grade 3-5 TEAEs [ADA-positive: 44.2%, ADA-negative: 19.1%], serious TEAEs [ADA-positive: 20.9%, ADA-negative: 14.2%]). In the crovalimab-switch population, the incidence of Grade 3 to 5 TEAEs in the Immune System

Disorders SOC was slightly higher in the ADA-positive subjects compared with ADA-negative subjects (ADA-positive: 11.6% [5 subjects], ADA-negative: 6.4% [9 subjects]). However, in the crovalimab-switch population, the only reported TEAE in the Immune System Disorders SOC was type III hypersensitivity reactions, which was due to the formation of DTDCs rather than anti-crovalimab ADAs. The median time to onset of the type III hypersensitivity reactions was 1.6 weeks (range: 0.7 to 4.4); therefore, in the majority of cases, the onset of the type III hypersensitivity reaction precedes ADA-onset in subjects with ADA. However, there was one subject ((b) (6)) who had positive ADA 22 days and Grade 3 type III hypersensitivity reaction 31 days after switching to crovalimab from eculizumab (see subject narrative in Section 7.6.1.8.4). This subject had a Grade 3 type III hypersensitivity reaction that remained unresolved. In addition, there were two subjects ((b) (6) in COMMODORE-1 who experienced serious, Grade 3 type III hypersensitivity reactions that resolved. These 2 subjects developed a type III hypersensitivity reaction after 10 days and an ADA-positive result after 12 and 16 weeks, respectively, from the crovalimab-switch baseline (see Section 17.4 for subject narratives).

Table 65. Summary of TEAE by Crovalimab ADA Status, Pooled Analysis of COMMODORE-1, COMMODORE-2, AND COMMODORE-3, ADA-Evaluable Population

	Crovalimab (Naïve) (N=191)		Crovalimab (Switch) (N=184)		Crovalimab Total (N=375)	
TEAE by ADA Status	ADA Negative (N=131) n (%)	ADA Positive (N=60) n (%)	ADA Negative (N=141) n (%)	ADA Positive (N=43) n (%)	ADA Negative (N=272) n (%)	ADA Positive (N=103) n (%)
Deaths	1 (0.8%)	1 (1.7%)	1 (0.7%)	0	2 (0.7%)	1 (1.0%)
Serious TEAEs	17 (13.0%)	10 (16.7%)	20 (14.2%)	9 (20.9%)	37 (13.6%)	19 (18.4%)
Any TEAEs	118 (90.1%)	55 (91.7%)	115 (81.6%)	37 (86.0%)	233 (85.7%)	92 (89.3%)
Grade 3-5	31 (23.7%)	18 (30.0%)	27 (19.1%)	19 (44.2%)	58 (21.3%)	37 (35.9%)
TEAE leading to discontinuation of study drug	1 (0.8%)	0	2 (1.4%)	1 (2.3%)	3 (1.1%)	1 (1.0%)
TEAE leading to dose modification/ interruption of study drug	5 (3.8%)	3 (5.0%)	5 (3.5%)	3 (7.0%)	10 (3.7%)	6 (5.8%)
Type III hypersensitivity reactions	0	0	23 (16.3%)	10 (23.3%)	23 (8.5%)	10 (9.7%)

Source: Integrated Summary of Immunogenicity and ADAB.xpt and ADAE.xpt.
Abbreviations: ADA, antidrug antibody; N, total number of subjects; n, number of subjects in subset; TEAE, treatment-emergent adverse event

ADA Titer Levels and the Incidence and Severity of TEAEs

Across all Grades, the incidences of TEAEs were similar between subjects with low ADA titer level and subjects who were ADA negative. At any Grade, the incidence of TEAEs was similar in subjects who were ADA negative (85.7%) and subjects with low ADA titer (87.8%) and medium ADA titer (88.2%) compared to subjects with high ADA titer (100%). The numbers of subjects in the medium (n=17) and high (n=12) titer groups were small and, therefore, the results should be interpreted with caution.

Compared to subjects who were ADA negative, subjects with medium ADA titer had higher incidence of Grade 1 events (35.3% versus 21.7%) and Grade 3 events (29.4% versus 16.9%). A

total of 3 subjects (17.6%) in the medium ADA titer group had Grade 4 events related to PNH (aplastic anemia [n =2] and MDS [n =1]).

In subjects with high ADA titer, the incidence of Grade 1 (8.3%) and Grade 2 events (16.7%) was lower compared to subjects with negative ADA (Grade 1: 21.7%, Grade 2: 42.6%), however, the incidence of Grade 3 and 4 events was higher compared to subjects with ADA negative (Grade 3: 66.7% [n =8] versus 16.9%; Grade 4: 8.3% [n =1] versus 3.7%). Of the 9 subjects who had Grade 3 or 4 events in the high ADA group, no subjects reported Grade 3 or 4 events associated with immunogenicity (e.g., infusion-related reactions, injection-related reactions or hypersensitivity other than type III hypersensitivity) or Grade 3 TEAEs that occurred before the onset of ADA. However, a total of 2 subjects ((b) (6)) had Grade 3 TEAEs that occurred both before and after developing ADA positivity:

- Subject (b) (6) had an onset of Grade 3 white blood cell count decrease and Grade 3 neutrophil count decrease prior to the onset of ADA positivity. Following ADA onset, this subject had an event of breast disorder, mastopathy, which was reported on Day 381 (11 months after first ADA positive results and 5.5 months after the instance of a high ADA titer). Considering the pathogenesis of the mastopathy AE, the event is unlikely to be related to the presence of ADAs.
- Subject (b) (6) had onset of Grade 3 cholangitis on Day 11, which was prior to the onset of ADAs, and a second event of Grade 3 cholangitis on Day 519 (more than 15 months after becoming ADA positive and more than a year after the instance of a high ADA titer). Considering that this subject had a medical history of cholangitis prior to enrolling in the study, cholangitis is not related to the presence of ADAs.

In addition, there were 5 subjects ((b) (6)) who had Grade 3 TEAEs that occurred after the ADA onset:

- Subject (b) (6) had ADA leading to loss of PK and PD and sustained IVH. In addition, Grade 3 hypertension was reported on Day 114, approximately 2 months after becoming ADA positive. It was reported that the increase in systolic (≥140 mmHg) and diastolic (≥80 mmHg) BP was not sustained in this subject. The hypertension event is unlikely to be related to the presence of ADAs. This subject received 14 units of pRBC transfusions and LDH was mostly greater than 1.5×ULN during the study.
- Subject (b) (6) had ADA leading to loss of PK and PD, and sustained IVH. This subject developed Grade 3 worsening of aplastic anemia on Day 344 and ALT increase on Day 356, over 6 months after becoming ADA positive. This subject had a history of aplastic anemia prior to enrollment. The increase in ALT can occur due to loss of efficacy/sustained IVH which was shown by LDH >1.5×ULN on Days 253, 281, 336 and 365 and administration of pRBC transfusions that occurred intermittently from Day 197 to 519.
- Subject (b) (6) had transient Grade 4 lymphocyte count decreased, which was two days in duration, approximately one month after becoming ADA positive. This transient abnormality is unlikely to be related to the presence of ADAs. This subject received 6 units of pRBC transfusions during the study.

- Subjects [redacted] (b) (6) had Grade 3 increased unconjugated blood bilirubin events, around the time of ADA positivity or 140 days after becoming ADA positive, respectively. Elevations in unconjugated bilirubin arise in the context of PNH disease due to hemolysis/loss of efficacy. However, both subjects did not receive any transfusions during the study.

Table 66. Summary of TEAEs by Crovalimab ADA Titer Levels, Pooled Analysis of COMMODORE-1, COMMODORE-2 and COMMODORE-3, ADA Evaluable Population

	ADA Titer Category[b] Crovalimab Total (N=375)			
TEAE by ADA Titer Level[a]	Negative (N=272) n (%)	Low (N=74) n (%)	Medium (N=17) n (%)	High (N=12) n (%)
Any Grade	233 (85.7%)	65 (87.8%)	15 (88.2%)	12 (100%)
Grade 1	59 (21.7%)	14 (18.9%)	6 (35.3%)	1 (8.3%)
Grade 2	116 (42.6%)	31 (41.9%)	1 (5.9%)	2 (16.7%)
Grade 3	46 (16.9%)	16 (21.6%)	5 (29.4%)	8 (66.7%)
Grade 4	10 (3.7%)	3 (4.1%)	3 (17.6%)	1 (8.3%)
Grade 5	2 (0.7%)	1 (1.4%)	0	0

Source: Applicant's response to information request.
[a] Based on most extreme intensity.
[b] Based on a graphical assessment of ADA titers vs. observed concentrations: low (<10^4), medium (≥10^4 - <10^5), and high (≥10^5) ADA titers.
Abbreviations: ADA, antidrug antibody; N, total number of subjects; n, number of subjects in subset; TEAE, treatment-emergent adverse event

No TEAEs of anaphylaxis or cytokine release syndrome were reported in ADA-positive or ADA-negative subjects. The incidence of hypersensitivity reactions other than type III hypersensitivity reactions was similar between the ADA-positive (9.7%) and the ADA-negative (7.7%) subjects. There was no conclusive evidence to suggest that ADA status had a clinical impact on the safety profile of crovalimab.

For immunogenicity leading to loss of exposure and efficacy please refer to Section 14.4.

7.7. Key Safety Review Issues

7.7.1. Meningococcal Infection

Issue

Risk of meningococcal infection associated with complement component 5 (C5) inhibition of the terminal complement pathway.

Background

Crovalimab is a recombinant humanized IgG1-based monoclonal antibody that specifically binds C5 of the terminal complement system. An important risk associated with terminal complement inhibition is increased susceptibility to infections caused by *Neisseria meningitidis*, which has been well characterized with the previously approved C5 inhibitors (i.e., eculizumab and

ravulizumab). Based on the class effect, patients treated with crovalimab are also expected to have an increased risk for meningococcal infections.

The Applicant proposed a boxed warning for serious meningococcal infections in the PI. The Applicant also submitted a REMS to mitigate the risk of meningococcal infections with the use of crovalimab. The proposed REMS includes ETASU that consists of prescriber certification, pharmacy certification, an implementation system, and a REMS assessment timetable. The FDA assessed the events of meningococcal infections associated with the use of crovalimab and the adequacy of the proposed REMS.

Assessment

No cases of infection with *Neisseria meningitidis* occurred in the crovalimab PNH development program up to the CCOD. However, one case of Grade 3 meningococcal meningitis (*Neisseria meningitidis* serotype X) was reported in Study BO42354, a study evaluating the efficacy, safety, PK, and PD of crovalimab in pediatric patients with atypical hemolytic uremic syndrome. The subject was vaccinated against serotype ACWY. The event resolved after 4 days, with no change to crovalimab treatment. In addition, a case of Grade 4 purulent meningoencephalitis was reported separately (in the IND safety report) in a subject who received crovalimab in the single-arm COMMODORE-3 study, conducted in China. Past vaccines included meningococcal vaccine A/C/Y/W-135. The event resolved after interrupting crovalimab and treatment with antibiotics. Patients exposed to C5 inhibitors (including crovalimab) are at increased risk for an invasive disease caused by *N. meningitidis*, even if they develop antibodies following vaccination.

The adequacy of the proposed REMS was reviewed by the Division of Risk Management.

Conclusion

Crovalimab is expected to increase the risk of serious and life-threatening infections caused by *Neisseria meningitidis* based on its mechanism of action. Serious infections, including those caused by *Neisseria meningitidis*, have occurred in the crovalimab development program. Serious infections from *Neisseria meningitidis* will be described in a boxed warning in the U.S. PI. In addition, the FDA is requiring an ETASU REMS to mitigate the risk of *Neisseria meningitidis*, consistent with the approach used with other C5 inhibitors. The REMS for crovalimab requires patients to be vaccinated against *Neisseria meningitidis* serogroups A, C, W, Y, and B prior to starting therapy according to the current Advisory Committee on Immunization Practices recommendations. The risk of other serious infections, including encapsulated organisms, will be included as a Warning and Precaution. It is recommended to vaccinate adult and pediatric patients against *Streptococcus pneumoniae* and pediatric patients against *Haemophilus influenzae* type B infections, in accordance with Advisory Committee on Immunization Practices recommendations.

In addition, the long-term risk of serious infections is also a concern. Therefore, a PMR will be issued at the time of approval for the Applicant to establish or participate in a registry for up to 5 years of follow-up and to submit reports summarizing meningococcal infections and other infections with encapsulated bacteria. See Section 24 for the PMR language.

7.7.2. Type III Hypersensitivity Reaction

Issue

The risk of type III hypersensitivity reaction due to the formation of DTDCs when crovalimab and another C5 inhibitor (e.g., ravulizumab, eculizumab) binds to a different epitope when both are present in the circulation.

Background

Crovalimab is C5 inhibitor that binds to a different C5 epitope than the previously approved C5 inhibitors (i.e., eculizumab and ravulizumab). When both crovalimab and eculizumab (or ravulizumab) are present in the circulation, DTDCs comprised of the two antibodies bridged by C5 are formed. Therefore, patients who previously received a different C5 inhibitor and switch to crovalimab (or vice versa) are at risk for type III hypersensitivity reactions due to the transient formation of DTDCs made of eculizumab or ravulizumab, crovalimab, and C5. Based on the terminal half-life of eculizumab and ravulizumab, the team expects eculizumab to remain in the circulation for approximately 12 weeks after the last dose and the team expects ravulizumab to remain in the circulation for approximately 37 weeks after the last dose.

Assessment

In clinical trials, type III hypersensitivity reactions were reported in 19.4% of subjects who switched from another C5 inhibitor to crovalimab and 25% of subjects who switched from crovalimab to another C5 inhibitor. Four subjects (10%) had not fully recovered from symptoms of type III hypersensitivity reactions at the time of their last follow up visit. Among subjects who experienced type III hypersensitivity reactions, 8 (21%) had serious events.

Signs and symptoms of type III hypersensitivity reactions observed in clinical trials included arthralgia and other musculoskeletal and connective tissue disorders, rash and other skin and SC disorders, headache, axonal neuropathy and other nervous system disorders, pyrexia, asthenia/fatigue, gastrointestinal distress, and vasculitis. Type III hypersensitivity reactions can also manifest as renal abnormalities, although renal dysfunction associated with type III hypersensitivity reactions was not reported in this development program.

Based on the time-to-onset of type III hypersensitivity reactions observed in clinical trials, it is recommended that patients are monitored for the first 30 days after switching from eculizumab or ravulizumab to crovalimab for the occurrence of symptoms of type III hypersensitivity reactions. For details see Sections 7.6.1.8.4 and 17.4.

DPACC was consulted for their expertise in hypersensitivity reactions. The consult team agreed with the Applicant’s conclusion that DTDCs lead to type III hypersensitivity reactions. In addition, the time from switch to onset and type of AEs are both consistent with type III hypersensitivity reactions. Whether switching products multiple times leads to more serious reactions is not clear; however, if patients were to develop ADAs, the risk of more severe reactions could increase with multiple switches. DPACC commented that they did not expect the rate or severity of type III hypersensitivity reactions to differ based on region, race/ethnicity, gender, or any genetic factors. See finalized consult review in DARRTS dated November 1, 2023.

Axonal Neuropathy

A total of two cases of serious axonal neuropathy were reported in COMMODORE-1 and COMMODORE-2. Both occurred in the crovalimab-switch population (i.e., in subjects who switched from a different C5 inhibitor).

The first case (USUBJID (b) (6)) occurred in a subject who was enrolled in the prior-ravulizumab cohort in COMMODORE-1 and received crovalimab. This subject experienced two episodes of type III hypersensitivity reactions. The first episode was of Grade 2 severity, started 14 days after switching to crovalimab, and resolved after 12 days with corticosteroids, antihistamine, and pain medication treatment. This subject experienced Grade 3 sepsis on Day 40 that led to withdrawal of crovalimab. The event of sepsis resolved after receiving treatment with ciprofloxaxin. After receiving the last dose of crovalimab on Day 29 and switching to ravulizumab on Day 42, the subject developed a second type III hypersensitivity reaction (Grade 3) on Day 52, which included symptoms of myalgia, axonal neuropathy, muscular weakness, and arthralgia. The conclusion from the electromyogram/nerve conduction study suggested that this was likely to be a vasculitic mononeuritis multiplex, although there is no reported biopsy confirmation of vasculitis. The axonal neuropathy event was categorized as a systemic type III hypersensitivity reaction. It was reported that the subject had some slow improvement in the symptoms, but functionally, the subject was unable to button her shirt, comb her hair, and shower on her own.

The second case (USUBJID (b) (6)) occurred in a subject randomized to the eculizumab arm in COMMODORE-2 and switched to crovalimab treatment on Day 169 (Week 25, Day 1). The subject had received the last dose of eculizumab on Day 157 (Week 23). The subject discontinued crovalimab treatment due to Grade 3 distal axonal demyelinating polyneuropathy. On Day 246, the subject presented with symptoms of weakness and decreased sensibility in the distal extremities. The subject was also diagnosed with Grade 2 upper respiratory tract infection (*Moraxella catarrhalis*). On Study Day 259, electroneurography was performed, which showed severe Grade 3 distal axonal demyelinating polyneuropathy. It was reported that serial c-reactive protein levels showed a decreasing trend (133 to 150 to 23 to 6 mg/L), following treatment with prednisolone on the assumption of small cell vasculitis as the cause of the polyneuropathy. The event of demyelinating polyneuropathy was unresolved at the time of the CCOD.

While the above two cases had confounders, a Type III hypersensitivity reaction as a cause of or contributor to the axonal neuropathy could not be excluded.

The above two cases were also reviewed by the Division of Neurology. In the first case (USUBJID (b) (6)), besides crovalimab, the differential diagnosis includes a peripheral neuropathy from ciprofloxacin, as ciprofloxacin carries a boxed warning for peripheral neuropathy and has serious ARs of vasculitis and hypersensitivity reactions. The differential also includes critical illness polyneuropathy and myopathy from sepsis. In the second case (USUBJID (b) (6)), the differential diagnosis includes a demyelinating polyneuropathy related to crovalimab, and Guillain-Barré Syndrome related to a *Moraxella catarrhalis* respiratory tract infection. Mannion et al. report that respiratory tract *Moraxella catarrhalis* can promote pathogenicity of myelin-reactive Th17 cells in a rodent model and may contribute to the pathophysiology of central nervous system autoimmunity (Mannion et al. 2023), although it is uncertain how relevant this central demyelination model is to peripheral demyelination. Guillain-

Barré Syndrome has been associated with other influenza-like illnesses, and also with administration of Menactra®, Meningococcal (Groups A, C, Y and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine. This subject also had vitamin B12 and folate deficiency. Vitamin B12 deficiency neurological syndrome can lead to neuropathy which is mainly axonal with some demyelinating features (Kalita et al. 2014). However, the rapidity of onset and severity of this subject's symptoms is not consistent with neuropathy due to chronic vitamin B12 deficiency. The consult review concludes that there are insufficient clinical data to reach a strong conclusion of causality between crovalimab use and the development of axonal or demyelinating neuropathy; however, this risk should be described in labeling. In addition, enhanced pharmacovigilance was recommended because the underlying etiology of the observed cases of neuropathy is unclear due to the limited information available.

Conclusion

Type III hypersensitivity reactions, including axonal neuropathy, occurred in subjects who previously received a C5 inhibitor and switched to crovalimab or switched from crovalimab to another C5 inhibitor. For mild or moderate type III hypersensitivity reactions, patients should receive symptomatic treatment (e.g., topical corticosteroids, antihistamines, antipyretics, and/or analgesics). For severe reactions, patients should initiate and taper oral or systemic corticosteroid therapy as clinically indicated. Type III hypersensitivity reactions will be included in the label as a warning. Initiating crovalimab sooner than 5.5 half-lives from the last dose of a C5 inhibitor eculizumab or ravulizumab and initiating eculizumab or ravulizumab a C5 inhibitor sooner than 5.5 half-lives from the last dose of crovalimab increases the risk of type III hypersensitivity reactions. Healthcare providers should consider the benefits of the timing of switching C5 inhibitors vs. the risks of Type III hypersensitivity reactions. To further understand the long-term risk of type III hypersensitivity reactions, a PMR will be issued at the time of approval to establish a registry to characterize the long-term safety of crovalimab in adult and pediatric patients 13 years and older with PNH and up to 5 years of follow-up, and to submit reports summarizing type III hypersensitivity reactions and axonal neuropathy, along with enhanced pharmacovigilance. See Section 24 for the PMR language.

7.7.3. Applicability of Foreign Safety Results to the U.S. Population

Issue

In the two active-controlled studies COMMODORE-1 and COMMODORE-2, there were no subjects from the U.S. clinical sites among the randomized population.

Background

The randomized population consisted of subjects mostly from Asia (66.7%) and Europe (23.5%) in COMMODORE-2 and from Europe (66.3%) and Asia (16.9%) in COMMODORE-1. In COMMODORE-2, the safety population in both arms consisted of the same number of subjects as the randomized population (crovalimab: 135 subjects, eculizumab: 69 subjects) and in COMMODORE-1, the number of subjects in both arms in the safety population was similar to those of the randomized population (safety population [crovalimab: 44 subjects, eculizumab: 42 subjects], randomized population [crovalimab: 45 subjects, eculizumab: 44 subjects]).

Applicability of foreign safety data to the U.S. population was reviewed. The FDA also conducted subgroup safety analyses by race and region.

Assessment

During the primary treatment period in COMMODORE-1 and COMMODORE-2, the safety results of Asians and Whites were generally similar in subjects who received crovalimab. The numbers of subjects who were in the Black/African American (COMMODORE-2: four subjects, COMMODORE-1: three subjects) and in the unknown (COMMODORE-2: two subjects, COMMODORE-1: four subjects) categories in the two studies were too small to conduct a meaningful analysis for these groups. Across COMMODORE-1 and COMMODORE-2, a total of two subjects from the U.S. clinical sites were enrolled in the nonrandomized arm in COMMODORE-1. No serious TEAEs were reported in the two subjects. For details see Section 7.6.1.11.

Pooled subgroup safety analyses by race and region were also conducted from the Phase 3 crovalimab studies, COMMODORE-1, COMMODORE-2, and COMMODORE-3 to evaluate if the results were consistent. Most of the subjects in the Phase 3 studies were Asian (59.9%) or White (35.5%) and were enrolled from Asia (59.2%) or Europe (31.6%). The safety results of crovalimab (both the naïve and switch populations) were generally similar between subjects who were Asian and White and between subjects enrolled from Asia and Europe. In the crovalimab-naïve group, the incidence of Grade 3 or 4 TEAEs was higher in Asians (28.9%) compared with Whites (17.8%). The differences were mostly due to higher incidences of Grade 3 or 4 TEAEs in Asians in the Blood and Lymphatic System Disorders SOC (neutropenia, thrombocytopenia, leukopenia) and liver injury. For details, see Section 17.1.1.6.

Conclusion

The safety results of crovalimab (both the naïve and switch populations) appear generally consistent by race and region, although there is limited representation of races/ethnicities beyond Whites and Asians and limited representation of regions beyond Asian and Europe. Nonetheless, in the context of this rare disease and based on the pathophysiology of the disease and the mechanism of action of crovalimab as a C5 inhibitor, the FDA does not expect – and there is no evidence to suggest – that the safety profile of crovalimab would be different across ethnicity, race, or region.

7.7.4. Self-Administration or Lay Caregiver Administration of Crovalimab

Issue

The Division of Medication Error Prevention Analysis (DMEPA) conducted a review of the human factor validation study (HFVS) and determined that the results do not support administration of crovalimab by adults and pediatric patients or lay caregivers.

Background

The Applicant submitted a simulated human factors validation study (HFVS) in this application to support the proposal for crovalimab to be administered by self or a lay caregiver. DMEPA

conducted a review and determined that the results do not support administration of the crovalimab by adults and pediatric patients or lay caregivers.

The clinical team and DMEPA also considered all the available data including data from the clinical trials in reaching the decision to limit to only health care provider administration. The patients who participated in the clinical study have a high level of oversight and instruction, and the FDA does not expect patients to consistently have this high level of oversight in actual practice, making it difficult to reliably conclude from the clinical trial data what will happen in the real-world.

Lastly, the FDA considered the context in which crovalimab is being approved. While PNH is a rare, serious and life-threatening disease, there are several other therapies, including another C5 inhibitor that can be administered SC once weekly, such that there is not a high unmet need to apply flexibility for crovalimab self or caregiver administration in the face of the concerns raised in the failed HF study.

Conclusion

The FDA concludes that crovalimab should be limited to administration by healthcare providers only and that the label include the statement, “Administered by Healthcare Professionals Only” as the human factors validation study (HFVS) results do not support administration of the proposed product by adult and pediatric patients with PNH and lay caregivers. For a complete discussion regarding the recommendation for crovalimab to only be administered by healthcare

professionals, see the finalized reviews by DMEPA in DARRTS dated March 15, 2024, April 24, 2024, and June 18, 2024.

8. Therapeutic Individualization

8.1. Intrinsic Factors

Renal Impairment

No dedicated studies were conducted to explore the PK of crovalimab in patients with RI. PopPK analysis was applied to investigate the impact of RI on the PK of crovalimab, using creatinine clearance (CLCR) to represent renal function. The observed ranges were 25.8 to 340 mL/min for CLCR. A trend for decreasing PK exposures with increases in baseline CLCR was noted. However, substantial overlap was observed among the subjects with normal renal function (n=163), mild RI (n=29), moderate RI (n=16), and severe RI (n=2). As noted, the sample size of subjects with severe RI was small. In general, RI is not expected to impact the exposure to monoclonal antibodies significantly. CLCR was not recognized as a significant covariate for the CL of crovalimab. Also, there is no clinically meaningful correlation between the PK exposures and safety outcomes, including SAEs, adverse events of special interest, Grade 3+ AEs, and infection. The trend associated with RI (including severe RI) and PK is not considered clinically relevant. No dose adjustment is therefore warranted for patients with mild, moderate, or severe RI.

Hepatic Impairment

No dedicated studies were conducted to explore the PK of crovalimab in patients with hepatic impairment (HI). AST and ALT were not identified as a significant covariate for crovalimab exposures. No clear trend was observed between the crovalimab exposures and baseline AST (range: 14 to 363 IU/L) and ALT (range: 3 to 108 IU/L) based on the population PK analysis. The dataset from multiple studies includes 46 subjects with ALT >3×ULN, and 1 subject with ALT >5×ULN. No statistically significant influence of transaminase abnormalities was found on crovalimab CL based on the PopPK analysis. No dose adjustment is warranted in patients with mild HI. A dose recommendation for patients with moderate or severe HI was not provided in the label due to the lack of data.

Other Intrinsic Factors

The population PK simulation, based on the proposed dosing regimen, indicated substantial overlap for the individual PK exposure metrics at steady state, stratified by sex (female [n =95] and male [n =115]) and race (Caucasian [n =55], Black and African American [n =3], Asian [n =149], and other or unknown [n =3]) in subjects with PNH (studied BW range: 42 to 140 kg). Crovalimab exposures were negatively associated with BW; therefore, a 50% higher first loading dose and maintenance dose (from Day 29) was proposed for patients with BW ≥100 kg. The population PK simulation showed substantial overlap in steady-state PK metrics following the updated dosing regimen between subjects with BW <100 kg (n=204) and ≥100 kg (n=6). Age was estimated to be a significant covariate for the absorption rate constant based on population PK analysis. However, the simulation showed substantial overlap for the individual PK exposure

metrics at steady state, stratified by age (range: 13 to 76, pediatrics [<18y, n=9], adults [18 to >65y, n=184], and the elderly [≥65y, n=17]). In addition, similar E-R relationships were observed for terminal-complement activity and LDH among age groups (13 to 17 years of age: n=12, 18 to 64 years of age: n=328, 65 years of age and above: n=37). No dose adjustment is required for adolescents and elderly patients. Refer to Section 14.5 for more information.

8.2. Extrinsic Factors

Crovalimab is not expected to show PK interactions with other drugs interfering with the metabolizing CYP450 enzymes because CYP450 enzymes are not involved in the CL pathways of crovalimab. Crovalimab is not expected to alter CYP450 expression because it does not modulate interferon/cytokine levels. Crovalimab is not expected to interact with transporters.

8.3. Plans for Pediatric Drug Development

Crovalimab received orphan-drug designation for the treatment of PNH on September 7, 2017; therefore, crovalimab is exempt from the requirements of the Pediatric Research Equity Act for the proposed indication.

However, the Applicant enrolled pediatric patients with PNH, aged 13 years and older, in COMMODORE-1, COMMODORE-2, and COMMODORE-3. See Sections 6.3.4 and 17.1.1.6. The FDA recommends that crovalimab be indicated for the treatment of adult and pediatric patients 13 years and older with PNH and BW ≥40 kg.

8.4. Pregnancy, Lactation, and Females/Males of Reproductive Potential

Animal Data

- To assess developmental and reproductive toxicity after crovalimab administration, an enhanced pre- and postnatal development study in cynomolgus monkeys was conducted. Pregnant monkeys were administered a loading dose of 100 mg/kg IV on gestational day 20, followed by weekly SC injections of either 10 (low dose) or 100 mg/kg (high dose [HD]) up to parturition. Infants were followed for 6 months postdelivery and untreated with drug to assess viability, growth, and development.
- Pharmacologically active levels of crovalimab were observed in the infants of mothers receiving the high dose (~13-times maximum recommended human dose by area under the concentration-time curve), which resulted in a ~50% transient reduction in complement activity from 70 to 110 days after birth.
- There were no adverse effects of crovalimab on pregnancy parameters or on the viability, growth, and development of infants following treatment of the mother during the gestation

period. The immune response to antigenic challenge at postnatal days 133 to 154 was not altered in infants at any dose, as assessed in a T cell-dependent antibody response assay.

- Testicular findings of focal tubule atrophy with reduced numbers of spermatogenic cells were observed in individual monkeys after crovalimab IV treatment which generally increased in severity with increasing dose. Findings trended towards resolution at the end of the recovery period and are not considered toxicologically meaningful, as findings were also observed in control mice and the IV is not the intended clinical route of administration.

Additional detailed information is available in Section 13.

Table 67. Nonclinical Data Supporting Labeling on Fertility, Pregnancy, and Lactation

Labeling Section	Nonclinical data
8.1 Pregnancy	(b) (4)
8.2 Lactation	There are no data on the presence of crovalimab in either human or animal milk, the effects on the breastfed child, or on milk production. (b) (4)
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility	Long-term carcinogenicity studies and genotoxicity studies have not been conducted with crovalimab. (b) (4)

Source: PI labeling and FDA reviewer.
Abbreviations: AUC, area under the concentration-time curve; $AUC_{0\text{-}28d}$, area under the concentration-time curve for 0-28 days; Cmax, maximum observed plasma concentration; FDA, Food and Drug Administration; GD, gestational Day; IgG, Immunoglobulin G; IV, intravenous; MRHD, maximum recommended human dose; PI, prescribing information

9. Product Quality

Approval With a Postmarketing Commitment

The Office of Pharmaceutical Quality, CDER, recommends approval of BLA 761388 for PIASKY (crovalimab-akkz) manufactured by Roche Diagnostics GmbH and Genentech, Inc. The data submitted in this application are adequate to support the conclusion that the

manufacture of PIASKY (crovalimab-akkz) is well-controlled and leads to a product that is pure and potent. It is recommended that this product be approved for human use under conditions specified in the package insert. The chemistry, manufacturing, and controls postmarketing commitment listed below should be included in the action letter.

- Develop and validate a competitive ligand binding neutralizing antibody (NAb) assay with adequate sensitivity and drug tolerance to test inhibition of crovalimab. This NAb assay will be used to test available confirmed anti-drug antibody positive samples from banked and ongoing clinical studies. Provide a final validation report detailing the performance of the NAb assay.

9.1. Device or Combination Product Considerations

Not applicable.

10. Human Subjects Protections/Clinical Site and Other Good Clinical Practice Inspections/Financial Disclosure Review

Compliance With Good Clinical Practices

COMMODORE-1, COMMODORE-2, COMMODORE-3, and COMPOSER were reviewed and approved by the Independent Ethics Committees or Institutional Review Boards and conducted in accordance with good clinical practice and the Declaration of Helsinki. Written informed consent was obtained from each subject prior to performance of study-specific procedures.

Financial Disclosure

The Applicant provided FDA Financial Certification Form 3454 signed by Eric Olson, the Vice President of U.S. Product Development Regulatory for Genentech, dated May 17, 2023. The Applicant certified to the following statement:

> *"As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators…whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f)."*

COMMODORE-1 and COMMODORE-2 were co-sponsored by Genentech, Inc /F. Hoffmann-La Roche and co-developed with Chugai Pharmaceutical Co., Ltd. COMMODORE-3 is a China-

only study sponsored by Genentech. and COMPOSER was initially co-sponsored by Genentech/Roche; however, in 2022, Chugai became a co-development partner.

The submission contained a list of clinical investigators that participated in COMMODORE-2 (297 principal/sub-investigators), COMMODORE-1 (385 principal/sub-investigators), COMPOSER (101 principal/sub-investigators), and COMMODORE-3 (30 principal/sub-investigators). All investigators reported no disclosable interests except 10 investigators (1 principal and 9 sub-investigators) (10%) in COMPOSER for whom the financial disclosure was not able to be obtained. The Applicant states that they acted with due diligence to obtain the financial disclosure information and provided documentation of attempts to obtain the missing financial disclosure form for the 10 investigators. COMPOSER was a first-in-human supportive Phase 1/2 trial in HVs and in patients with PNH. Therefore, the FDA does not expect this missing financial disclosure information to raise concerns regarding our conclusions of the overall safety and efficacy profile of crovalimab.

In the above four trials, none of the investigators were full- or part-time sponsor employees. Review of the financial disclosures did not raise any concerns about the validity or reliability of the data. See Section 25.

Data Quality and Integrity

The quality and integrity of the submitted data were adequate to support the efficacy and safety of crovalimab for the proposed indication.

Office of Scientific Investigations

The results of the clinical site inspections support the conclusion that the trials were conducted adequately, and that the data generated support the proposed indication. See Section 22.

Protocol Deviations

COMMODORE-2

Overall, 59% of subjects in COMMODORE-2 had at least one major protocol violation up to Week 24 (primary treatment period).

Randomized Arms

For the randomized arms, the incidence of major protocol deviations was higher in the crovalimab arm (62%) compared with the eculizumab arm (52%) mostly due to differences in procedural deviations (crovalimab: 55%, eculizumab: 41%).

During the primary treatment period, major protocol deviations related to COVID-19 were reported in 29 subjects (21%) and 5 subjects (7%) in the crovalimab and eculizumab arms, respectively. It was reported that subjects in the crovalimab arm could continue crovalimab treatment via home-based self-administration but may have not been able to complete the study-site based assessments. In contrast, eculizumab-treated subjects were still required to visit sites for infusion and were, therefore, more likely to complete the required on-site study assessments. Six subjects were enrolled at sites in Ukraine before the outbreak of the conflict in Ukraine in February 2022. All six subjects were randomized to the crovalimab arm. Ten procedural protocol deviations were reported in five of these subjects, which were related to missed or delayed visits

or laboratory assessments due to disruption from the conflict. Subjects were provided with supplies of crovalimab for self-administration.

A total of five subjects (crovalimab: four, eculizumab: one) did not receive the protocol prespecified vaccination criteria at study entry. All subjects subsequently received the appropriate vaccination and/or antibiotic prophylaxis, except for one subject in the crovalimab arm who did not receive the *N. meningitis* serogroups ACWY vaccination or prophylactic antibiotics. One subject in the crovalimab arm had an exclusion criteria deviation, which was classified as 'other', despite the deviation relating to insufficient pneumococcal vaccination-related deviation. No meningococcal, pneumococcal or haemophilus infections were reported in any of these subjects.

Descriptive Arm (Baseline to End of Week 24)

In the pediatric subjects enrolled in the descriptive arm, major protocol deviations occurred in 5 subjects (83%), which were deviations related to procedural assessments (83%) and study drug administration (50%).

Table 68. COMMODORE-2: Major Protocol Deviations, Primary Treatment Period

Deviations	Crovalimab (N=135) n (%)	Eculizumab (N=69) n (%)	Descriptive (Crovalimab) Arm (N=6) n (%)	Total (N=210) n (%)
All subjects with major deviations	84 (62.2%)	36 (52.2%)	5 (83.3%)	124 (59.0%)
Total number of major deviations	182	59	9	250
Inclusion criteria	12 (8.9%)	5 (7.2%)	0	17 (8.1%)
LDH criteria (≥2×ULN) not met	1 (0.7%)	0	0	1 (0.5%)
Vaccination criteria not met	5 (3.7%)	1 (1.4%)	0	6 (2.9%)
Adequate hepatic or renal function criteria not met	1 (0.7%)	0	0	1 (0.5%)
Failure to use contraception with failure rate <1%/year	2 (1.5%)	2 (2.9%)	0	4 (1.9%)
Other Inclusion criteria	4 (3.0%)	2 (2.9%)	0	6 (2.9%)
Exclusion Criteria	4 (3.0%)	2 (2.9%)	0	6 (2.9%)
Failure to meet Hb enrollment requirements or failure to measure Hb within 5 days pre-randomization	3 (2.2%)	1 (1.4%)	0	4 (1.9%)
History of malignancy within 5 years	1 (0.7%)	0	0	1 (0.5%)
Other exclusion criteria	1 (0.7%)	1 (1.4%)	0	2 (1.0%)
Medication	17 (12.6%)	9 (13.0%)	3 (50.0%)	29 (13.8%)
Missed/out of window/received incorrect dose or use of protocol-prohibited therapy	17 (12.6%)	9 (13.0%)	3 (50.0%)	29 (13.8%)
Procedural	74 (54.8%)	28 (40.6%)	5 (83.3%)	105 (50.0%)
Visit/assessment out of window or not Performed/procedure not performed	74 (54.8%)	28 (40.6%)	5 (83.3%)	105 (50.0%)

Source: ADDV.xpt and CSR.
Note: Based on number of subjects. A subject can appear in more than one category.
Abbreviations: Hb, hemoglobin; LDH, lactate dehydrogenase; N, total number of subjects; n, number of subjects in subset; ULN, upper limit of normal

COMMODORE-1

In COMMODORE-1, 64% of subjects had at least one major protocol deviation up to Week 24 (primary treatment period).

Randomized Arms

In the randomized arms, the incidence of major protocol deviations was similar in the two arms (crovalimab arm: 62%, eculizumab: 66%). The most frequently reported major protocol deviations in both arms were procedural deviations (crovalimab: 62%, eculizumab: 52%).

A total of six subjects (crovalimab: 4, eculizumab: 2) did not meet the vaccination criteria. No meningococcal infections were reported in these subjects.

Non-Randomized Arm

In the non-randomized arm, major protocol deviations were reported in 24 subjects (63%). Most (53%) of the deviations were procedural. A total of 5 subjects (13%) did not meet the vaccination criteria. No meningococcal infections were reported in these subjects.

Table 69. COMMODORE-1: Major Protocol Deviations, Primary Treatment Period

Deviations	Crovalimab (N=45) n (%)	Eculizumab (N=44) n (%)	Nonrandomized (Crovalimab) Arm (N=38) n (%)
All subjects with major deviations	28 (62.2%)	29 (65.9%)	24 (63.2%)
Total number of major deviations	70	59	65
Inclusion criteria	7 (15.6%)	8 (18.2%)	6 (15.8%)
LDH criteria not met	2 (4.4%)	2 (4.5%)	0
Vaccination criteria not met	4 (8.9%)	2 (4.5%)	5 (13.2%)
Granulocyte of monocyte clone size ≥10% criteria not met	0	1 (2.3%)	1 (2.6%)
Eculizumab treatment in 24 weeks pre W1D1 out of approved dosing indication for PNH	1 (2.2%)	0	0
Failure to use contraception with failure rate <1%/year	1 (2.2%)	1 (2.3%)	1 (2.6%)
Other Inclusion criteria	0	3 (6.8%)	1 (2.6%)
Exclusion Criteria	0	3 (6.8%)	2 (5.3%)
Failure to meet Hb enrollment requirements or failure to measure Hb within 5 days pre-randomization	0	2 (4.5%)	0
Positive for HBsAg, HCV or cryoglobulinemia	0	1 (2.3%)	0
Other exclusion criteria	0	1 (2.3%)	1 (2.6%)
Subject on other study treatment	0	0	1 (2.6%)
Medication	0	4 (9.1%)	6 (15.8%)
Missed/out of window/received incorrect study medication or continuation of study drug in conflict with protocol	0	4 (9.1%)	6 (15.8%)
Procedural	28 (62.2%)	23 (52.3%)	20 (52.6%)
Visit/assessment out of window or not performed/procedure not performed	28 (62.2%)	23 (52.3%)	20 (52.6%)

Source: ADDV.xpt and CSR
Note: Based on number of subjects. A subject can appear in more than one category.
Abbreviations: Hb, hemoglobin; HBsAg, surface antigen of the hepatitis B virus; HCV, hepatitis C virus; LDH, lactate dehydrogenase; N, total number of subjects; n, number of subjects in subset; PNH, paroxysmal nocturnal hemoglobinuria; W1D1, week 1 day 1

These observed protocol deviations in the two trials are not expected to impact the interpretability of safety and efficacy. The majority of the deviations were related to a visit or procedure occurring out of window. Since assessments for response occurred over a duration of

time, or at multiple time points, it is unlikely that this impacted study results. Furthermore, patients with PNH are closely monitored, therefore it is highly likely that any safety concerns would be missed.

11. Advisory Committee Summary

An advisory committee meeting was not convened to discuss this application. There are several other complement inhibitors approved for PNH, including two C5 inhibitors, and no issues were identified that would have benefitted from a public discussion with external experts.

III. Additional Analyses and Information

12. Summary of Regulatory History

A Type B pre-investigational new drug meeting request was submitted on November 11, 2016 (pre-investigational new drug 131343). Written Responses were issued on January 5, 2017, which discussed the Applicant's plans (b) (4) . The Agency did not agree with the Applicant's proposal and recommended that the Applicant conduct randomized, controlled trials and consider available therapies.

A Type C meeting request was submitted on November 17, 2017, to discuss initiation of an enhanced pre-and postnatal development study in cynomolgus monkeys. In Written Responses, dated January 10, 2018, the Agency stated that the protocol for an enhanced pre- and postnatal development study appears reasonable and will likely result in a study that is sufficient to support a marketing application.

Crovalimab received Orphan-Drug Designation for the treatment of PNH on September 5, 2017.

A Model Informed Drug Development meeting request was submitted on March 14, 2019, and subsequently granted, to obtain feedback from the Agency on the modeling approach to support crovalimab dose selection in a patient population treated with eculizumab and switching to crovalimab. The purpose of the meeting was to discuss modeling approaches used to inform the dose selection and regimen for crovalimab in a Phase 3 study for PNH and the simulation strategy for dose selection based on the population pharmacokinetics (PK) and drug-target-drug complex (DTDC) models.

An End-of-Phase 2 meeting was held on July 17, 2019, to discuss the design of the proposed pivotal studies in patients with PNH, including the primary and key secondary endpoints and high-level statistical analysis plans.

A Type C meeting was submitted on August 2, 2019, to gain agreement from the Agency on the design of the proposed pivotal studies in patients with PNH, including the primary and secondary endpoints and high-level statistical analysis plans. Preliminary comments were provided on October 11, 2019. The Agency stated that they did not agree with the Applicant's proposed clinical development plan and continued to recommend two randomized, controlled trials to

support the proposed indication. The Applicant cancelled the teleconference with the Agency scheduled for October 17, 2019.

A new IND was submitted on March 2, 2020, for the development of crovalimab for the treatment of PNH. Previously, the drug was developed under a pre-investigational new drug. The Agency issued a Study May Proceed letter on April 1, 2020.

The Applicant submitted a request for a Type C meeting on April 22, 2022. The purpose of the meeting was to discuss the content and format of the planned BLA for crovalimab. Preliminary comments were provided to the Applicant on June 30, 2022. The Agency scheduled a teleconference meeting with the Applicant for July 6, 2022. The meeting was cancelled at the Applicant's request on July 5, 2022. The Applicant stated the reason for the cancellation was that the preliminary comments sufficiently addressed the submitted questions.

A Type B pre-BLA meeting was held on April 20, 2023, to discuss the outcome and key conclusions of the Phase 3 COMMODORE-2 study, along with the COMMODORE-3, COMMODORE-1, and COMPOSER studies; to discuss the acceptability of the available clinical data to support a BLA submission; and to seek agreement on the draft risk evaluation and mitigation strategy proposal. The Agency stated in the preliminary comments that the data provided in the meeting package appears sufficient to support a BLA submission. The Agency stated that based on the information available at the time of the meeting request, a risk evaluation and mitigation strategy will be necessary to ensure that the benefits of the drug outweigh the risks of meningococcal infection.

A BLA for crovalimab was submitted on June 20, 2023, for the treatment of adult and pediatric patients with PNH.

The proposed proprietary name, PIASKY, was found conditionally acceptable on September 11, 2023.

13. Pharmacology Toxicology

13.1. Summary Review of Studies Submitted With the Investigational New Drug Application

Crovalimab is engineered as a sequential, monoclonal antibody recycling technology antibody, combining isoelectric point, neonatal FcRn, and pH-dependent affinity binding. These modifications result in an increased functional half-life that is intended to prolong complement inhibition. Crovalimab is administered subcutaneously (SC) after a single, loading intravenous (IV) dose. Additionally, crovalimab binds a different epitope than other C5 inhibitors (e.g., eculizumab and ravulizumab) which results in binding to C5 even if complexed with other anti-C5 mAbs. Ex vivo studies have shown crovalimab blocks hemolysis in patients who have a single, missense C5 heterozygous mutation that leads to an arginine at position 885 (Arg885His).

13.1.1. Crovalimab Pharmacology

Crovalimab binds to human C5 and cynomolgus monkey C5 with comparable affinity in a concentration- and pH-dependent manner. Crovalimab binds to mouse C5 and rat C5 less strongly than to human C5 or cynomolgus monkey C5 by approximately two orders of magnitude (Study No. 1072909, not described in detail in the review). Crovalimab inhibits antibody-sensitized chicken red blood cell (RBC) lysis in a dose-dependent manner in both human and cynomolgus monkey serum. Crovalimab did not inhibit antibody-sensitized chicken RBC lysis induced by rabbit or rat serum at the maximum concentration tested. A pharmacology study in an animal model of PNH was not conducted; however, the Applicant assessed complement inhibition in a pharmacokinetics/pharmacodynamics study and in repeat-dose toxicology studies in monkeys as well as in patients with PNH.

13.2. Individual Reviews of Studies Submitted With the New Drug Application

Table 70. Primary Pharmacology Studies

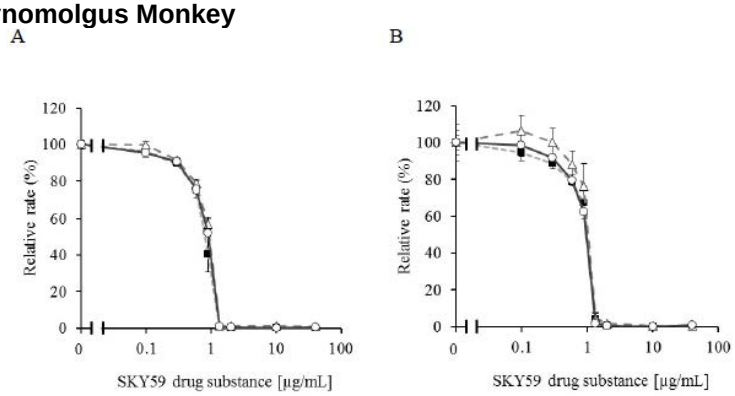
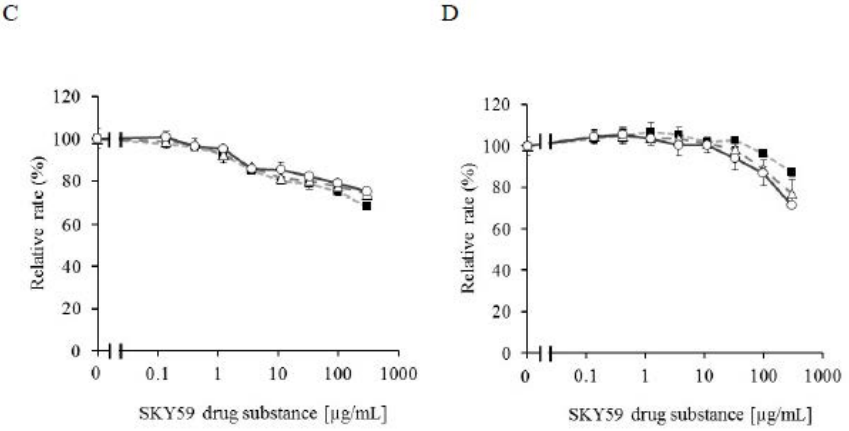
<table>
<tr><th>Study No./ Study Title</th><th>Findings</th></tr>
<tr><td>Study No.: NC1072619

Study Title: Analysis of the Affinity of SKY59 (Crovalimab) Drug Substance to Antigen (Complement Component C5) by Surface Plasmon Resonance

The kinetics and pH-dependent binding of crovalimab to hC5 and cyC5 were measured using surface plasmon resonance studies. measurements were taken in triplicate.</td><td>Binding of crovalimab to C5 is dependent on pH. The association and dissociation phase of crovalimab from hC5 or cyC5 at pH 7.4 and pH 6.0, was observed and was more rapid at pH 6.0 than those at pH 7.4. At pH 7.4, crovalimab binds to hC5 and cyC5 with similar affinity.

Table 71. Summary of K_a, K_d and K_D Values of Crovalimab to Human C5 and Cynomolgus Monkey C5
<table>
<tr><th></th><th>Measurement</th><th>k_a ($\times 10^5$ L/mol·s)</th><th>k_d ($\times 10^{-4}$ 1/s)</th><th>K_D ($\times 10^{-10}$ mol/L)</th></tr>
<tr><td rowspan="3">hC5</td><td>1</td><td>7.72</td><td>1.28</td><td>1.66</td></tr>
<tr><td>2</td><td>7.50</td><td>1.29</td><td>1.72</td></tr>
<tr><td>3</td><td>7.55</td><td>1.34</td><td>1.78</td></tr>
<tr><td rowspan="3">cyC5</td><td>1</td><td>7.37</td><td>1.47</td><td>1.99</td></tr>
<tr><td>2</td><td>7.28</td><td>1.47</td><td>2.02</td></tr>
<tr><td>3</td><td>7.18</td><td>1.43</td><td>1.99</td></tr>
</table>
Source: Applicant submission
Abbreviations: C5, complement component 5; K_a, association rate constant; K_d, dissociation rate constant; K_D, dissociation constant</td></tr>
<tr><td>Study No.: NC1072621

Study Title: The Inhibitory Activity of SKY59 (Crovalimab) Drug Substance Against Hemolysis Induced by Complement Activity in the Serum of Various Species, (Including Amendment 1)</td><td>Crovalimab inhibited, to a similar extent, the lysis of antibody-sensitized chicken RBC induced by complement activity in human (IC_{50}=0.834±0.050 µg/mL) and cynomolgus (IC_{50}=0.958±0.041 µg/mL) serum.</td></tr>
</table>

Study No./ Study Title	Findings
The inhibitory activity of crovalimab against antibody-sensitized chicken RBC lysis (chicken RBC mixed with anti-chicken RBC antibody e.g., antibody sensitized) was measured at 415 nm optical density, the absorbance of hemoglobin.	**Figure 14. Effect of Crovalimab on Antibody-Sensitized Chicken RBC Lysis Induced by Complement Activity in the Serum of Human and Cynomolgus Monkey**  Source: Applicant's submission Note: A, human serum; B, cynomolgus money serum. Note: Points represent the average relative rate (%) of hemolytic activity from triplicate results at each SKY59 (crovalimab) drug substance concentration in each measurement; Exp. 1 (filled square); Exp. 2 (open triangle); Exp. 3 (open circle). Data represent mean ± SD (n=3). Note: SKY59, crovalimab. Abbreviations: RBC, red blood cell Crovalimab, at the maximum concentration tested of 301 µg/mL, inhibited the lysis of antibody-sensitized chicken RBC, induced by complement activity in rabbit or rat serum at less than 50% the relative rate of hemolytic activity. **Figure 15. Effect of SKY59 (Crovalimab) on Antibody-Sensitized Chicken RBC Lysis, Induced by Complement Activity in the Serum of Human and Cynomolgus Monkey**  Source: Applicant submission Note: C, Rabbit serum; D, Rat serum. Note: Points represent the average relative rate (%) of hemolytic activity from triplicate results at each SKY59 (crovalimab) drug substance concentration in each measurement; Exp. 1 (filled square); Exp. 2 (open triangle); Exp. 3 (open circle). Data represent mean ± SD (n=3). Note: SKY59, crovalimab. Abbreviations: Exp, Experiment; RBC, red blood cell; SD, standard deviation

Source: Reviewer-generated table.
Abbreviations: C5, complement component 5; cyC5, cynomolgus monkey C5; hC5, human C5; IC50, half-maximal inhibitory concentration; RBC, red blood cell

13.2.1. Secondary Pharmacology

Crovalimab, engineered with mutations in the Fc region to silence Fc gamma receptors (FcγRs) and complement component 1q (C1q) binding, has pH-dependent binding to FcRn to improve antibody recycling efficiency and half-life, which was confirmed in secondary pharmacology assays. Crovalimab has negligible binding affinity to human and monkey FcγRs when compared to the positive-control antibody, trastuzumab (native human IgG1 constant Fc region), which suggests crovalimab is unlikely to cause immune cell or complement activation (i.e., immune effector function). The affinity of crovalimab to both human and cynomolgus monkey FcRn was 10-fold greater than that of trastuzumab, which suggests recycling of IgG as a plausible mechanism for the prolonged in vivo crovalimab exposure. The binding activity to human C1q was low to none when compared to the positive control, rituximab (human IgG1 mAb), which suggests crovalimab is unlikely to induce complement-dependent cytotoxicity.

Table 72. Secondary Pharmacology Studies

Study No./ Study Title	Findings
Study No.: NC 1072620 Study Title: Evaluation of Binding Activity of SKY59 (Crovalimab) Drug Substance to Fc Receptors by Surface Plasmon Resonance (Including Amendment 1) The interaction of crovalimab with human Fcγ receptors (hFcγRs), cynomolgus Fcγ receptors (cyFcγRs), human neonatal Fc receptor (hFcRn), and cynomolgus neonatal Fc receptor (cyFcRn) was evaluated using surface plasmon resonance studies. Trastuzumab, which has a native human IgG1 constant region, was used as a positive reference control.	Binding activity of crovalimab to hFcRn and cyFcRn was comparable in both species and around 10 times stronger than that of trastuzumab. The binding activity of crovalimab to hFcγRs and cyFcγRs was weaker (lower binding per 1 resonance unit) than that of trastuzumab. **Table 73. Average K_D Values of Crovalimab and Trastuzumab for hFcRn and cyFcRn** SKY59 / trastuzumab hFcRn / cyFcRn / hFcRn / cyFcRn Average K_D (mol/L): 1.70×10^{-7} / 1.78×10^{-7} / 1.73×10^{-6} / 1.98×10^{-6} SD (mol/L): 0.08×10^{-7} / 0.03×10^{-7} / 0.05×10^{-6} / 0.67×10^{-6} Source: Applicant submission Note: SKY59, crovalimab; n=3 Abbreviations: K_D, dissociation constant; hFcRn, human neonatal FC receptor; cγFcRn, cynomolgus monkey neonatal Fc receptor; SD, standard deviation

Study No./ Study Title	Findings
	Table 74. Binding of hFcγRs Per 1 Resonance Unit of Crovalimab and Trastuzumab

		hFcγRIa	hFcγRIIa (H)	hFcγRIIa (R)	hFcγRIIb
SKY59	Average (RU)	-1.36×10^{-3}	-1.16×10^{-3}	-1.06×10^{-3}	-1.15×10^{-3}
	SD (RU)	0.09×10^{-3}	0.18×10^{-3}	0.15×10^{-3}	0.14×10^{-3}
trastuzumab	Average (RU)	1.86×10^{-1}	6.46×10^{-2}	4.00×10^{-2}	7.35×10^{-3}
	SD (RU)	0.00×10^{-1}	0.07×10^{-2}	0.07×10^{-2}	0.12×10^{-3}

		hFcγRIIIa (F)	hFcγRIIIa (V)	hFcγRIIIb NA1	hFcγRIIIb NA2
SKY59	Average (RU)	-2.11×10^{-3}	-1.22×10^{-3}	-8.64×10^{-4}	-6.65×10^{-4}
	SD (RU)	0.07×10^{-3}	0.04×10^{-3}	0.27×10^{-4}	0.80×10^{-4}
trastuzumab	Average (RU)	2.68×10^{-2}	8.12×10^{-2}	7.32×10^{-3}	1.07×10^{-2}
	SD (RU)	0.16×10^{-2}	0.09×10^{-2}	0.26×10^{-3}	0.02×10^{-2}

Source: Applicant submission
Note: SKY59, crovalimab; n=3
Abbreviations: hFcγRIa, human Fc gamma receptor Ia; hFcγRIIa (H), human Fc gamma receptor IIa _167His; hFcγRIIa (R), human Fc gamma receptor IIa_167Arg; hFcγRIIb, human Fc gamma receptor IIb; hFcγRIIIa (F), human Fc gamma receptor IIIa_176Phe; hFcγRIIIa (V), human Fc gamma receptor IIIa_176Val; hFcγRIIIb NA1, human Fc gamma receptor IIIb_neutrophil antigen 1; hFcγRIIIb NA2, human Fc gamma receptor IIIb_neutrophil antigen 2.; RU, resonance unit; SD, standard deviation

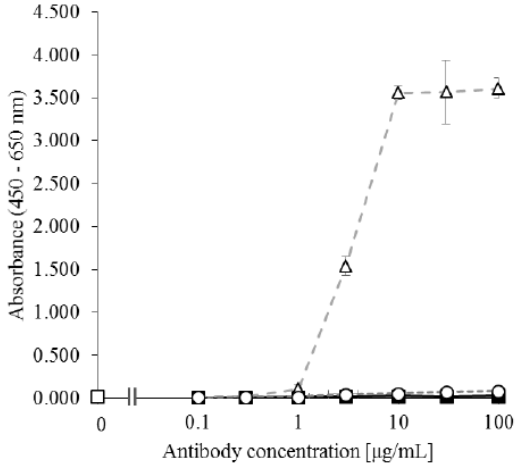
Table 75. Binding of cyFcγRs Per 1 RU of Crovalimab and Trastuzumab

		cyFcγRIa	cyFcγRIIa1	cyFcγRIIa2	cyFcγRIIa3
SKY59	Average (RU)	-2.76×10^{-3}	-4.35×10^{-4}	-5.32×10^{-4}	-2.98×10^{-4}
	SD (RU)	0.05×10^{-3}	0.43×10^{-4}	0.73×10^{-4}	0.23×10^{-4}
trastuzumab	Average (RU)	2.53×10^{-1}	2.01×10^{-2}	1.60×10^{-2}	4.37×10^{-3}
	SD (RU)	0.03×10^{-1}	0.05×10^{-2}	0.05×10^{-2}	0.12×10^{-3}

		cyFcγRIIb	cyFcγRIIIa (S)	cyFcγRIIIa (R)
SKY59	Average (RU)	-4.86×10^{-4}	-9.71×10^{-4}	-1.06×10^{-3}
	SD (RU)	0.70×10^{-4}	1.47×10^{-4}	0.03×10^{-3}
trastuzumab	Average (RU)	2.79×10^{-2}	1.17×10^{-1}	1.02×10^{-1}
	SD (RU)	0.04×10^{-2}	0.01×10^{-1}	0.01×10^{-1}

Source: Applicant submission.
Note: SKY59, crovalimab; n=3
Abbreviations: cyFcγRIa, cynomolgus Fc gamma receptor Ia; cyFcγRIIa1, cynomolgus Fc gamma receptor IIa_1; cyFcγRIIa2, cynomolgus Fc gamma receptor IIa_2; cyFcγRIIa3, cynomolgus Fc gamma receptor IIa_3; cyFcγRIIb, cynomolgus Fc gamma receptor IIb; cyFcγRIIIa (S), Cynomolgus Fc gamma receptor IIIa_42Ser; cyFcγRIIIa (R), cynomolgus Fc gamma receptor IIIa_42Arg

Study No.: NC 1085568 Study Title: Assessment of Binding Activity of RO7112689 (Crovalimab) to Complement Component C1q Binding activity of crovalimab, positive-control	Crovalimab had low-to-no binding activity to C1q protein, which was comparable to that of natalizumab. Rituximab had dose-dependent binding to C1q. Results from the second plate confirmed that the amount of immobilized crovalimab, rituximab, and natalizumab was comparable.

Study No./ Study Title	Findings
rituximab (a human IgG1 antibody), and negative-control natalizumab (a human IgG4 antibody) to human complement component C1q (C1q protein) was evaluated using an enzyme-linked immunosorbent assay (ELISA). Antibodies were plate-bound, and a C1q antibody was used to measure the amount of C1q protein that bound. On a second plate, the immobilized amount of each antibody was also measured using an anti-IgG antibody.	**Figure 16. Binding Activity of Crovalimab, Rituximab, and Natalizumab to Human C1q Protein**  Source: Applicant submission Note The amount of C1q protein bound was expressed as the absorbance (450-650 nm) calculated by the plate reader. The results are plotted as mean and SD (n=4). Points represent the average of measured values for RO7112689 (crovalimab) (filled square), rituximab (open triangle), and natalizumab (open circle). Abbreviations: C1q, complement component 1q subunit

Source: Reviewer-generated table.
Abbreviations: cyFcRn, cynomolgus monkey neonatal Fc receptor; C1q, complement component 1q; ELISA, enzyme-linked immunosorbent assay; IgG, immunoglobulin G; hFcRn, human neonatal FC receptor

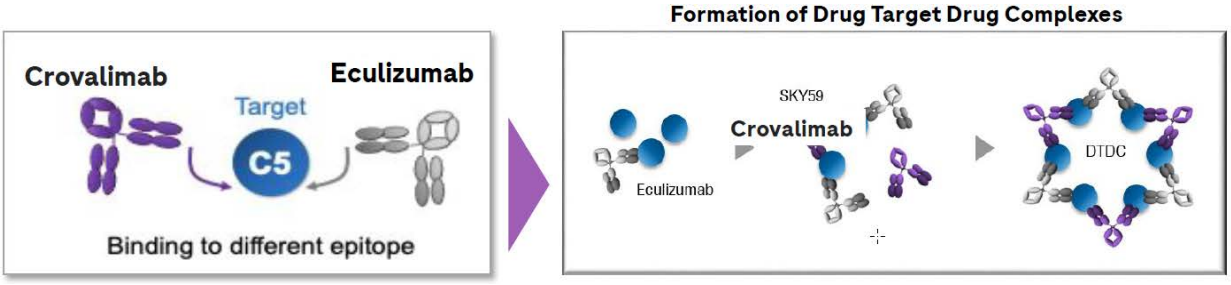
13.2.2. Safety Pharmacology

No stand-alone safety pharmacology studies were conducted but safety pharmacology assessments (cardiovascular, respiratory, and neurobehavioral) were incorporated into the good laboratory practice repeat-dose toxicology studies. No crovalimab-related effects on central nervous system, respiratory function, or cardiovascular parameters were identified in monkeys up to the maximum doses tested of 160 mg/kg IV and 100 mg/kg SC.

13.2.3. Pharmacodynamic Drug Interactions

The ability of crovalimab to bind eculizumab-recombinant human C5 (rhC5) complex in plasma or phosphate-buffered saline at pH 7.4 and pH 6.0 was investigated using size exclusion chromatography (Study No.: 1078065). Crovalimab binds to eculizumab-bound rhC5 to form DTDCs at pH 7.4 and dissociates from these complexes at pH 6.0, according to the pH-dependent characteristic of crovalimab, suggesting that DTDC formation does not impair the recycling properties of crovalimab. Importantly, DTDCs represent a complex drug-target structure (Figure 17) that can present an immunogenicity risk for antidrug antibodies (ADAs) and hypersensitivity reactions in humans.

Figure 17. Formation of Drug-Target-Drug Complexes (DTDCs) Between Crovalimab, C5, and Eculizumab



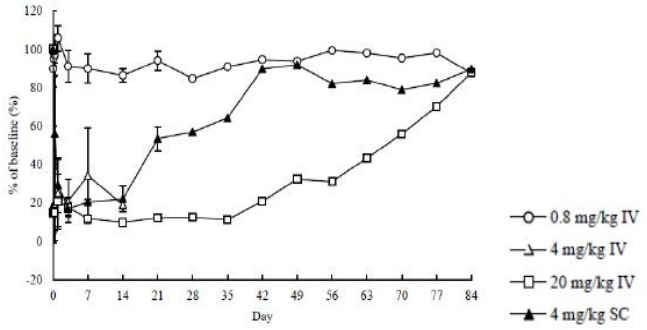
Source: Applicant's submission.
Note: SKY59, crovalimab
Abbreviations: C5, complement component 5; DTDC, drug-target-drug complex

13.2.4. ADME/PK

Consistent with recommendations in the International Council for Harmonisation guidance for industry *S6(R1) Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals* (May 2012), no dedicated tissue distribution, metabolism, or excretion studies were conducted with crovalimab. The metabolism of crovalimab is expected to be similar to that of other IgG monoclonal antibodies. Crovalimab exposure after SC or IV administration to cynomolgus monkeys increased in a dose-dependent manner with low total clearance (CL) resulting in a mean half-life ($t_{1/2}$) of 12 to 20 days. The mean bioavailability of crovalimab was approximately 69% with a time to maximum concentration of 1 to 3 days. ADAs were observed after single IV doses to cynomolgus monkeys as early as Day 7, and crovalimab concentrations was decreased in most ADA-positive animals. Complement activity was inhibited nearly 100% from 14 to 35 days after single IV administration of 4 mg/kg or 20 mg/kg. Activity was restored after crovalimab was completely cleared from plasma, approximately 35 to 84 days after single administration. There was limited inhibition (37% of baseline) of complement activity at 0.8 mg/kg IV. Toxicokinetic/PD parameters after repeated SC and/or IV dose administration were also assessed as part of the good laboratory practice-compliant toxicology studies and in an enhanced pre- and postnatal development study in monkeys.

Table 76. Pharmacokinetic Data

Study/ Study No.	Major Findings
Study No: NC 1068293 Study Title: Evaluation of Pharmacokinetics and Pharmacodynamics Following Single Dose Intravenous or Subcutaneous Administration of SKY59 (Crovalimab) Drug Substance in Cynomolgus Monkeys Blood Sample Collection Times: Day -14, -7, 0, 1, 3 and every 14 days from D7 to D84	Crovalimab concentration in serum increased in a dose-dependent manner. After single IV dose, mean terminal half-life of crovalimab was 12-20 days. Following SC administration, the mean bioavailability of crovalimab was approximately 69% and the time to maximum plasma concentration (T_{max}) was 1-3 days. Complement activity was inhibited at 4 and 20 mg/kg until crovalimab was cleared from plasma. ADAs were detected in 10 out of 16 animals as early as Day 7 and affected either free C5 concentration or complement activity readouts soon after ADAs were detected. These samples were excluded from the PK analysis.

Study/ Study No.	Major Findings
PK/PD parameters, as well as C5 concentration, free C5 concentration, and complement activity (using hemolytic activity), were assessed after single IV (0.8, 4 or 20 mg/mL) or SC (4 mg/kg) administration of SKY59 (crovalimab) to cynomolgus monkeys.	**Table 77. Summary of Mean PK Values After IV or SC Single Administration of Crovalimab** Parameter | IV 0.8 mg/kg | IV 4 mg/kg | IV 20 mg/kg | SC 4 mg/kg T_{max} (d) | -- | -- | -- | 2 T ½ (d) | 19.87 | NC | 11.98 | 15.02 C_{max} (µg/mL) | -- | -- | -- | 41.9 AUC_{0-t} (µg*d/mL) | 288 | NC | 6890 | 979 Source: Applicant submission Note: Dashes = not measured. Abbreviations: ADA, antidrug antibody; AUC, area under the concentration time curve; C_{max}, maximum concentration; IV, intravenous; NC, not calculated due to ADAs; PK, pharmacokinetics; SC, subcutaneous; T_{max}, peak time; $T_{1/2}$, half-life; **Figure 18. Complement Activity in Male Monkeys Following a Single Dose of Crovalimab**  Source: Applicant submission Note: Complement activity was assessed using an RBC lytic assay. The predosing value was set as 100%. Data represent mean ± SD (n=4) where applicable. Values from ADA-positive animals with crovalimab exposure clearly affected were excluded. Abbreviations: ADA, antidrug antibody; IV, intravenous; RBC, red blood cell; SC, subcutaneous; SD, standard deviation

Source: Reviewer generated table.
Abbreviations: ADA, antidrug antibody; C5, complement component 5; IV, intravenous; PD, pharmacodynamic; PK, pharmacokinetic; SC, subcutaneous; t_{max}, time to maximum observed plasma concentration

13.2.5. Toxicology

13.2.5.1. General Toxicology

Repeat-dose general toxicology good laboratory practice-compliant studies of 4 weeks (IV; not submitted to the BLA) or 5 months (SC) with 17-week recovery (IV) and 6-month recovery (SC) durations were conducted in cynomolgus monkeys.

There were no adverse toxicological findings in the 4-week/5-month repeat-dose study up to the highest doses tested (160 mg/kg/week IV and 40 mg/kg/week SC) aside from slight arteritis/periarteritis observed with IV administration, related to immune complex formation of crovalimab. The majority of monkeys (7 of the 8) that presented arteritis/periarteritis findings were positive for ADAs, and immunohistochemistry confirmed the presence of immune

complexes in tissues and plasma in Studies 1072910 and 107753, along with perivascular mononuclear cell infiltrates observed with SC administration. When animals with ADAs were excluded from analysis, exposure to crovalimab showed accumulation with repeated dosing. Crovalimab was pharmacologically active in this study as shown by the accumulation in total C5 plasma concentrations and decreased complement activities (CH50) in all treatment groups.

The extent and severity of organs affected by arteritis/periarteritis increased with increasing dose and did not necessarily correspond with the presence or the number of granular deposits in affected tissues, suggesting some crovalimab effect (e.g., immune-mediated reaction to crovalimab).

A 6-Month Intermittent Subcutaneous or Intravenous Administration Toxicity Study of SKY59 (Crovalimab) in Mature Cynomolgus Monkeys Followed by a 6-Month Recovery Period (Study 1082669)

Key Study Findings

- Microscopic findings of perivascular infiltrate of mononuclear cells, associated with hemorrhage and/or pigmentation, occurred at the injection site in high-dose (HD) animals after IV dosing and at all SC dosing groups.
- Dose-related mild arteritis/periarteritis was observed in several organs in the high SC and IV dose groups at terminal and recovery euthanasia. These findings might be related to deposition of ADA immune complexes or drug-target immune complexes.
- A single crovalimab-related case of membranoproliferative glomerulonephritis, associated with slight degeneration/regeneration of the tubule, hyaline and RBC casts, interstitial infiltrate of neutrophils, interstitial fibrosis, urinalysis changes, and high serum creatinine, occurred in one male in the HD IV group.
- Crovalimab produced pharmacodynamically relevant decreases (>90%) of total hemolytic component (CH50) and increases in total C5 concentrations in all crovalimab-treated animals with a trend for recovery in a few individual animals.
- C5 accumulation was observed in all crovalimab-treated groups with no sex difference and gradually decreased in low dose and medium dose SC groups during the recovery period. No clear decrease was noted in the HD SC or HD IV groups after a 6-month recovery period.
- The no observed adverse effect level (NOAEL) for crovalimab in cynomolgus monkeys after 6 months of SC intermittent dosing is defined at the low dose of 10 mg/kg/week based on the occurrence of arteritis/periarteritis in multiple organs at higher doses tested and single incidences of crovalimab-related microscopic findings. The NOAEL for crovalimab in cynomolgus monkeys is associated with a maximum plasma concentration (C_{max}) of 996 µg/mL and area under the concentration-time curve (AUC) from 0 to 7 days of 5750 µg·d/mL that corresponds to 3.3- and 2.6-times the exposure observed in patients with PNH at the maximum recommended human dose for male and female animals, respectively. Formation and deposition of ADA immune complexes that caused the arteritis/periarteritis in multiple organs occurred in animals in response to a foreign protein and are not likely to represent a risk in patients with PNH.

Table 78. Methods of Intermittent Administration Toxicity Study in Monkeys

Study Features and Methods	Details
GLP Compliance:	Yes
Dose and frequency of dosing:	0, 10, 40 or 100 mg/kg SC once weekly (QW) or 0 or 160 mg/kg IV every 2 weeks (Q2W). Intravenous administration of 100 mg/kg was conducted as the first dosing for subcutaneous groups to reduce the possibility of ADA production. Control animals were dosed IV Q2W and SC weekly from the 2nd to the 27th dosing.
Route of administration:	Subcutaneous and/or intravenous
Formulation/vehicle:	50 mmol/L histidine-aspartate buffer containing 150 mmol/L arginine aspartate and 0.5 mg/mL poloxamer 188, pH 6.0.
Species/strain:	Cynomolgus monkeys
Number/sex/group:	5/sex/ group (main group) selecting 2/sex/groups for recovery group.
Age:	4 to 8 years old
Satellite groups/unique design:	No
Deviation from study protocol affecting interpretation of results:	None of the deviations were considered to have impacted the overall integrity of the study or the interpretation of the study results.

Source: Reviewer generated table.
Abbreviations: ADA, antidrug antibody; GLP, good laboratory practice; IV, intravenous; pH, potential of hydrogen; Q2W, every two weeks; QW, every week; SC, subcutaneous

Table 79. Study 1082669, Observations and Results

Parameters	Major Findings
Mortality	There were no unscheduled mortalities.
Clinical signs, body weights, ophthalmoscopy, ECG, blood pressure, bone marrow examinations, immunophenotyping in peripheral blood.	No crovalimab-related changes occurred in any group. A few instances of significantly different changes compared to the control were observed, but those were considered not biologically significant based on the single incidence and lack of a dose response.
Hematology	A statistically significant increase in absolute lymphocytes counts (up to 64% relative to controls) was observed in males at 10 mg/kg and 100 mg/kg (SC), slightly affecting overall white blood cells (WBC) and basophils counts. The percentage of large unstained cells (%LUC) was increased in males at ≥10 mg/kg (SC). The increase in lymphocytes, WBC, basophils counts, and %LUC may represent a heightened response to protect from infection and/or inflammation, which corresponds with the natural consequence of crovalimab inhibiting the terminal complement pathway. The increase in these parameters was considered nonadverse based on the lack of a dose response and the transient nature. Females did not develop crovalimab-related hematological changes. High fibrinogen levels in 1 male and 1 female at 10 mg/kg (Day 56) and in 1 male at 40 mg/kg (SC) (Day 90 and 126), accompanied with high WBC and neutrophil counts. These animals also had clinical chemistry changes consistent with a crovalimab-related inflammatory response. The male at 10 mg/kg (SC) had microscopic findings of pyogranulomatous inflammation in the femoral bone marrow of the left leg, which corresponded to macroscopic white masses. The male at 40 mg/kg (SC) had perivascular infiltrate of mononuclear cells, hemorrhage, and

<table>
<tr><th>Parameters</th><th>Major Findings</th></tr>
<tr><td></td><td>retention of the test article at the injection site. No changes in fibrinogen levels were observed in recovery animals.

<u>Discussion</u>
There was a consistent, although variable, systemic inflammatory response in crovalimab-dosed animals with no clear dose relationship (also see Clinical chemistry findings). Based on histological findings as well as ADA generation, it is possible that these findings are crovalimab-related.</td></tr>
<tr><td>Complement Inhibition Assessment</td><td>There were decreases of >90% in total complement (CH50) levels in all crovalimab-dosed animals on Days 56, 90, 126, and 182 of dosing. CH50 levels showed a trend to increase but did not fully recover by the end of the recovery period.

Table 80. Summary of Mean CH50 (U/Ml) Values After IV or SC Administration of Crovalimab to Male Monkeys During Dosing Period
<table>
<tr><th></th><th colspan="4">Dosing Day</th></tr>
<tr><th>Dosing Group (mg/kg)</th><th>Pre</th><th>56</th><th>60</th><th>126</th><th>182</th></tr>
<tr><td>Control IV and SC</td><td>37.24</td><td>34.88</td><td>36.16</td><td>38.78</td><td>45.14</td></tr>
<tr><td>SC 10</td><td>41.26</td><td>4.66</td><td>3.68</td><td>3.76</td><td>8.76</td></tr>
<tr><td>SC 40</td><td>49.62</td><td>3.36</td><td>2.90</td><td>3.38</td><td>6.78</td></tr>
<tr><td>SC 100</td><td>44.48</td><td>4.34</td><td>3.46</td><td>4.02</td><td>9.76</td></tr>
<tr><td>IV 160</td><td>49.60</td><td>4.66</td><td>4.24</td><td>3.94</td><td>8.74</td></tr>
</table>
Source: Reviewer generated table from data on study report
Abbreviations: CH50, total complement activity; Pre, predosing; IV, intravenous; SC, subcutaneous

Table 81. Summary of Mean CH50 (U/Ml) Values After IV or SC Administration of Crovalimab to Female Monkeys During Dosing Period
<table>
<tr><th></th><th colspan="4">Dosing Day</th></tr>
<tr><th>Dosing Group (mg/kg)</th><th>Pre</th><th>56</th><th>60</th><th>126</th><th>182</th></tr>
<tr><td>Control IV and SC</td><td>38.92</td><td>34.72</td><td>39.70</td><td>39.48</td><td>38.74</td></tr>
<tr><td>SC 10</td><td>41.16</td><td>3.20</td><td>3.04</td><td>4.60</td><td>4.32</td></tr>
<tr><td>SC 40</td><td>38.30</td><td>2.90</td><td>2.74</td><td>3.92</td><td>3.32</td></tr>
<tr><td>SC 100</td><td>37.12</td><td>2.82</td><td>3.24</td><td>3.98</td><td>3.50</td></tr>
<tr><td>IV 160</td><td>39.42</td><td>3.66</td><td>4.08</td><td>4.44</td><td>4.18</td></tr>
</table>
Source: Reviewer generated table from data on study report
Abbreviations: CH50, total complement activity; IV, intravenous; Pre, predosing; SC, subcutaneous</td></tr>
<tr><td>Clinical chemistry</td><td>A statistically significant increase in percentage (%) of γ-globulin occurred in male monkeys at doses ≥10 mg/kg (SC) and in males and females at 160 mg/kg (IV). A 100 mg/kg male (No. 33) presented arteritis/periarteritis in the heart, kidney, pancreas, and spleen, and a 160 mg/kg IV male (No. 43) presented arteritis/ periarteritis in the epididymis and urinary bladder. These findings might be related to higher circulating IgG levels in these animals, since increases were more notable in IV-dosed monkeys and not found in controls.

Some monkeys showed evidence of an inflammatory response related to the increase α/β-globulin ratio and low albumin in 2 males at both 40 mg/kg and 100 mg/kg dose groups towards the end of the dosing period. A statistically significant high level of creatinine was noted in males at 160 mg/kg (IV) on Day 90 of dosing; however, this change was</td></tr>
</table>

Parameters	Major Findings
	transient and slight in severity. Individually, high creatinine on Day 126 of dosing, and low albumin ratio and A/G ratio on Days 56, 90, and 126 of dosing were noted in 1 male with membranoproliferative glomerulonephritis (No. 43). Discussion Most, but not all, clinical chemistry changes corresponded with histopathology findings of arteritis/periarteritis or mononuclear cell infiltrates at ≥40 mg/kg (SC) and/or 160 mg/kg (IV). Changes in clinical chemistry were considered nonadverse based on the low incidence and transient nature.
Urinalysis	Positive occult blood (grade 4/4) and erythrocytes (grade 2/3) occurred in a single male (No. 43) in the 160 mg/kg (IV) group. This male also had several microscopic findings in the kidney, including bilateral slight glomerulonephritis and presented ADAs. These findings were not present in monkeys assigned to recovery. Positive occult blood (grade 3/4) was noted in one male (No. 41) in the 160-mg/kg (IV) group on Day 179 of recovery. A statistically significant dose-response increase in mean glucose in males at ≥40 mg/kg (SC) and 160 mg/kg (IV) were observed in most animals. Mean glucose levels in monkeys assigned to recovery were similar to control. Urinalysis changes were considered nonadverse based on the low incidence and transient nature of the change.
Gross pathology	White masses in the proximal and distal portion of the femur were observed in a 10 mg/kg (SC) male, which corresponded with microscopic findings of pyogranulomatous inflammation in the femoral bone marrow of the left leg and very slight inflammation in the synovium and/or periosteum in the knee and heel, with slight fibrin deposition in the synovium. No other macroscopic observations were noted in other groups or at the end of recovery.

Parameters	Major Findings
Organ weights	Male Monkeys A crovalimab-related decrease in mean relative testes, epididymitis, seminal vesicle, and prostate weights occurred mostly at 160 mg/kg IV (35-times exposure at the MRHD). Decreased weight in these organs also occurred at 40 and 100 mg/kg SC, but at lower magnitude, and changes were not dose-related with high animal variability. Individual animals in these groups showed histopathological findings of very slight-to-moderate testis atrophy and/or arteritis/periarteritis in the epididymis. Organ weight was similar to controls at the end of recovery. Female Monkeys Dose-related increases occurred in mean values for adrenal and submandibular gland weight compared to control, although the increase did not reach statistical significance. Values were comparable to controls at the end of recovery. Mean organ weight for ovary and thymus weight showed high animal variability and/or were affected by individual animals that presented with ovarian cysts (10 mg/kg) and abnormally high relative thymus weights in each of the 10 and 40 mg/kg group.

Source: Reviewer generated table.
Abbreviations: %LUC, percent large unstained cells; ADA, antidrug antibody; A/G, albumin/globulin; CH50, total complement activity; ECG, electrocardiogram; IgG, immunoglobulin G; IV, intravenous; SC, subcutaneous; MRHD, maximum recommended human dose; WBC, white blood cell

Table 82. Percentage (%) Change of Mean Relative Organ Weights (by BW) From Control in Male Monkeys at the End of the Dosing Period

	Dose Group (mg/kg)			
Organ	10	40	100	160
Testis total	18.3	-11.2	-6.0	-16.53
Epididymis total	10.1	4.9	-10.7	-23.2
Seminal vesicle	27.6	-16.5	-12.2	-21.1
Prostate	-5.5	-27.5	-17.6	-17.6

Source: Reviewer generated table
Abbreviations: BW, body weight

Table 83. Percentage (%) Change of Mean Relative Organ Weights (by BW) From Control in Female Monkeys at the End of the Dosing Period

	Dose Group (mg/kg)			
Organ	10	40	100	160
Adrenal total	16.9	28.3	32.0	51.0
Ovary total	221.4[a]	21.1	22.2	-10.5
Thymus	-18.2	41.4	69.4[b]	42.4 [b, d]
Submandibular gland total	26.4	39.7	48.8	94.8[c, d]
Oviduct total	-10.8	10.8	0	-17.2

Source: Reviewer generated table
[a] % change (-7.5%) was calculated excluding female No. 18 (1/3) who presented with an ovarian cyst and had 9X higher relative organ weight.
[b] Only the 160 mg/kg IV group for thymus weight was significant from control. For the 10 and 40 mg/kg, only one animal in each group presented with abnormally high relative thymus weights compared to control. Only animal No. 30 (40 mg/kg) presented with a thymus cyst graded very slight. No associated findings in animal No. 38 (100 mg/kg).
[c] Only the 160 mg/kg was significant.
[d] $p<0.05$
Abbreviations: BW, body weight; IV, intravenous

Table 84. Study 1082669, Additional Observations and Results 1

Parameters	Major Findings
Histopathology Adequate battery: Yes	Arteritis/Periarteritis Findings End of Dosing Severity of very slight or slight arteritis/periarteritis in various organs (epididymis, urinary bladder, heart, pancreas, spleen, kidneys or vagina) was observed in one 100 mg/kg male (No. 33), as well as one male (No. 43) and one female (No. 48) at 160 mg/kg (IV). **Table 85. Incidence of Arteritis/Periarteritis at the End of 26-Week Dosing With Crovalimab in Cynomolgus Monkeys**

Findings in males	Dose level (mg/kg)				
	0	10	40	100	160
Epididymis					E2*
Urinary bladder					C1*
Heart				C1*	
Pancreas				A1*	
Spleen				A1*	
Kidney (left)				A2*	
Kidney (right)				C3*	

Findings in females	Dose level (mg/kg)				
	0	10	40	100	160
Heart	A1*				
Uterine cervix	D1*				
Vagina					B1

Source: Applicant submission.
Note: Findings in individual animals. Animals evaluated =3/group.
Note: A, mononuclear cell infiltrate, periarterial/arterial wall; B, mixed cell infiltrate, periarterial/arterial wall; C, mononuclear cell infiltrate, periarterial/arterial wall + eosinophilic particles in the arterial wall; D, mixed cell infiltrate, periarterial/arterial wall + eosinophilic particles in the arterial wall; E, mononuclear cell infiltrate, periarterial/arterial wall + periarterial eosinophilic material; *, findings in same animal.
Note: Scores of the distribution based on number of affected arteries: 1, 1-2 arteries; 2, 3-5 arteries; 3, >5 arteries.

Arteritis/Periarteritis Findings End of Recovery

Findings of arteritis/periarteritis were not present at the end of the recovery period in males, except for a single incidence in a 40 mg/kg male and a control male (epididymis and kidney). In females, arteritis/periarterites was observed in various organs (cecum, spleen, stomach, uterus/cervix, vagina, and oviduct with an ovarian cyst) of a 40 mg/kg female and in the uterus/cervix (with presence of an ovarian cyst) in a 160 mg/kg IV female.

Other Findings

Mononuclear cell infiltrates were observed in the kidneys of most crovalimab-dosed monkeys and a single case of slight membranoproliferative glomerulonephritis was also observed in one male (No. 43) in the 160 mg/kg IV group. Findings were not observed in recovery animals.

Very slight-to-slight infiltrate of mononuclear cells, fibrosis, granule-laden macrophage infiltrate, and pigmentation was observed in the SC injection site at all dosed groups for SC dosing. Retention of crovalimab was observed at the 100 mg/kg SC dose. Slight hemorrhage was observed at the injection site in IV dosed animals. Findings were not present in recovery animals dosed IV and were present with lessened severity in individual animals dosed SC.

Focal left adrenal hypertrophy was observed in males at the 40 and 100 mg/kg SC dosing and in one female after IV dosing. Very slight mononuclear cell infiltrates were observed in the brain (cerebrum, midbrain, and/ or medulla oblongata) at the 100 mg/kg SC dose and after IV dosing in individual female monkeys. Findings were not observed in recovery animals.

Lung inflammation (including one incidence of thrombus in one male at 100 mg/kg SC) was observed in all treated monkeys with increased incidence in female animals at the same dose level. Lung inflammation was also observed in one male animal at 10 mg/kg and one male

Parameters	Major Findings
	animal at 160 mg/kg IV after the recovery period. One of two female animals in each of the 100 mg/kg and 160 mg/kg IV dose group showed lung inflammation after the recovery period. Very slight-to-moderate testis atrophy (right and/or left testis), including reduced numbers of spermatogenic cells, was observed in males, which generally increased in incidence and severity with increasing dose. These findings also occurred in the control group at lower incidence. Findings showed a trend towards resolving in recovery animals and no longer showed a dose relationship. One male that did not have arteritis/periarteritis presented with low sperm counts after IV dosing.

Source: Reviewer generated table.
Abbreviations: IV, intravenous; SC, subcutaneous

Table 86. Crovalimab-Related Histopathological Findings in Monkeys After Repeated Dose Administration for 6 Months

Crovalimab-related findings Main Study Animals			Number of animals affected									
			Males					Females				
Dose group (mg/kg)			SC/IV 0	SC 10	SC 40	SC 100	IV 160	SC/IV 0	SC 10	SC 40	SC 100	IV 160
Organ	Finding	Severity										
Adrenal (left)	Focal cortex hypertrophy	Very slight	-	-	1	2	1	-	-	-	-	1
Brain Cerebrum (diencephalon)	Choroid plexus mononuclear cell infiltrate	Very slight	-	-	-	-	-	-	-	-	2	-
Midbrain	Perivascular mononuclear cell infiltrate	Very slight	-	-	-	-	1	-	-	-	1	1
Medulla oblongata	Mononuclear cell infiltrate	Very slight	-	-	-	-	-	-	-	-	1	1
Heart	Mononuclear infiltrate	Very slight	1	-	2	1+	2	-	-	-	1	1
Injection site (cephalic vein and adjacent)	Hemorrhage	Slight	-	-	-	-	2	-	-	-	-	1
Injection site (back, subcutaneous, subcutis)	Fibrosis	Very slight	-	-	1	1	-	-	-	-	1	-
	Granule-laden macrophage infiltrate	Very slight	-	-	2	2	-	-	-	-	-	-
	Mononuclear cell infiltrate	Very slight	-	-	2	2	-	-	2	2	2	-
	Pigmentation	Very slight	-	-	-	1	-	-	-	-	1	-
Kidney	Interstititum mononuclear cell infiltrate	Very slight	-	3	2	2	1s	3	2	2	2	2
Lung (including bronchus, left)	Pleura chronic inflammation	Very slight	-	2	1	1	3	3	2	2	-	3
Lung (including bronchus, right)	Alveolar macrophage aggregation	Very slight	1	2	-	1	1	1	-	-	2	1
	Pleura chronic inflammation	Very slight	1	2	2	-	3	1	3	3	3	2
Testis (left)	Focal tubular atrophy	Very slight	1	-	1	1	1					
		Slight	-	-	-	-	1					
		Moderate	-	1	-	-	1					
	Mononuclear cell infiltrate	Very slight	-	1	1	-	1					
Testis (right)	Focal tubular atrophy	Very slight	1	1	1	-	-					
		Slight	1	-	1	-	2					
		Moderate	-	-	-	2	1					
	Mononuclear cell infiltrate	Very slight	-	-	2	1	2					

Source: Reviewer generated table from study report
Note: Number of animals examined 3/group.
+, same animal presented with nongraded arteritis/ periarteritis, mononuclear cell/ foamy cell infiltrate, slight infiltrate and cell debris in the arterial wall, endothelium hypertrophy, intimal thickening in 1 to 2 arteries. Similar findings in pancreas, spleen, urinary bladder.
S, same animal presented with additional pathology findings with very slight to slight severity: RBC cast, tubule degeneration/ regeneration, interstitium fibrosis, membranoproliferative glomerulonephritis, interstitium neutrophil infiltrate.
Abbreviations: IV, intravenous; RBC, red blood cell; SC, subcutaneous

Table 87. Study 1082669, Additional Observations and Results 2

Parameters	Major Findings
Toxicokinetics	Systemic exposure (C_{max} and AUC) of crovalimab after repeated administration increased except at the 10 mg/kg dose level, where exposure remained steady after repeat dosing. Exposure to crovalimab at the 26th dosing increased in a dose-dependent manner at all doses. Exposure (AUC) in female animals was only slightly decreased at all timepoints measured when compared to male animals. Time to peak drug concentration (T_{max}) generally decreased with repeated administration in the 40 and 100 mg/kg SC treated groups. After IV administration (160 mg/kg), exposure to crovalimab increased with repeated administration and resulted in a systemic exposure (AUC_{0-14d}) of 69000 µg·d/mL after 26 weeks of dosing. After the recovery period, exposure to crovalimab decreased more rapidly after SC dosing with a $T_{1/2}$ from 30.93 to 53.20 days compared to a $T_{1/2}$ from 37.62 to 77.32 days after IV dosing. <u>Discussion</u> Control monkey No. 1 (male recovery), No. 3 (male dosing), and No.4 (male dosing) had detectable levels of crovalimab after the 18th, 24th, and 18th dosing, respectively. While the Applicant argues these animals were not erroneously dosed, Animal 1 had arteritis/periarteritis in the kidney consistent with findings of one male animal at 100 mg/kg SC.

Source: Reviewer generated table.
Abbreviations: AUC, area under the concentration-time curve; AUC_{0-14d}, area under the concentration-time curve from 0-14 days; C_{max}, maximum observed plasma concentration; IV, intravenous; SC, subcutaneous; $T_{1/2}$, half-life; T_{max}, time to maximum observed plasma concentration

Table 88. Mean Toxicokinetic Parameters After SC Repeated Administration of Crovalimab to Cynomolgus Monkeys[a]

		C_0 (µg/mL)	C_{max} (µg/mL)				AUC_{all} (µg*d/mL)				
		Dose	Dose				Dose				
Dose level (mg/kg)	Sex	1st	2nd	9th	18th	26th	1st	2nd	9th	18th	26th
10	M	2270	1030	877	995	1070	10600	6370	5390	6060	6610
	F	1820	967	834	874	786	8470	6070	4580	5200	5180
40	M	2130	1230	1900	2580	2500	9730	7900	11900	16000	16400
	F	1570	1050	1950	2290	2370	7880	6660	11700	14400	14700
100	M	2390	1600	4550	5700	5430	10800	9780	29800	36800	36100
	F	1830	1680	4160	4050	4960	8480	10500	25400	26200	31600

Source: Reviewer generated table
Note: 'Mean AUC_{all}' indicates mean exposure over the 1-week dosing interval, or AUC_{0-7d}. This mean value is multiplied by 4 to estimate exposure over a 28d period for comparison to clinical exposure of 7830 µg*d/ml AUC_{0-28d} at the MRHD.
[a] Data from ADA-positive animals is excluded.
Abbreviations: SC, subcutaneous; C_0, initial concentration, C_{max}, maximum concentration; AUC_{all}, area under the curve from time to last observation

Table 89. Summary of T_{max} and $T_{1/2}$ Parameters After SC Repeated Administration of Crovalimab to Monkeys[a]

		Dose				
		T_{max} (d)				$T_{1/2}$ (d)
Dose (mg/kg)	Sex	2nd	9th	18th	26th	Recovery
10	M	1.50	1.11	0.50	1.50	NC
	F	0.47	0.20	0.33	3.44	41.26
40	M	3.40	2.40	1.33	1.60	NC
	F	2.20	1.92	1.75	1.10	30.93
100	M	4.00	3.33	1.10	2.33	53.20
	F	3.80	0.53	1.47	0.80	38.46

Source: Reviewer generated table
[a] Data from ADA-positive animals is excluded.
Abbreviations: F, female; M, male; NC, not calculated; SC, subcutaneous; $T_{1/2}$, half-life; T_{max}, peak time

Table 90. Study 1082669, Additional Observations and Results 3

Parameters	Major Findings
Plasma C5 concentration	Sex-independent accumulation of C5 up to 4-fold from baseline levels was observed after crovalimab administration. Total C5 concentrations gradually decreased in the 10 and 40 mg/kg (SC) groups during the recovery period but remained steady in the 100 mg/kg (SC) and the 160 mg/kg (IV) groups.
Other Assessments: Menstrual cycle, semen analysis, general behavior and neurobehavioral function, cytokine analysis in serum, ADA	There were no crovalimab-related changes in menstrual cycle, general behavior, or neurobehavioral function. Low sperm counts were noted in an individual male dosed IV that did not have arteritis/periarteritis, which did not resolve by the end of the recovery period. This male also presented with moderate focal tubular atrophy in the testis. There were no clear crovalimab-related changes in serum cytokines during the dosing period. Increases in IL-6 were observed in all groups, including controls. ADAs were detected in 1/10 animals in each of the dosed groups during the dosing period. During the recovery period, ADAs were detected in 3/4 animals in the 10 and 40 mg/kg SC groups and in 0/4 animals in the 100 mg/kg (SC) and 160 mg/kg (IV) groups. Only 1 of the animals with arteritis/periarteritis had ADAs, and only 1 of the animals with inflammatory findings had ADAs in this study. Study 1095668 detected ADA using a different method (Immune complex (IC) method instead of the electrochemiluminescence (ECL) method) and confirmed ADA in most animals. Of note, ADAs in Animal No. 43 (M 160 mg/kg IV) and No. 26 (F 40 mg/kg SC) had the most extensive arteritis/periarteritis, and a 10 mg/kg SC female (Animal No. 16), with hematology and clinical chemistry findings consistent with inflammatory response, could not be determined as positive or negative due to a positive ADA response before dosing.

Source: Reviewer generated table.
Abbreviations: ADA, antidrug antibody; C5, complement component 5; ECL, electrochemiluminescence; IV, intravenous; No., number; SC, subcutaneous

13.2.5.2. Carcinogenicity Studies

Carcinogenicity studies have not been performed with crovalimab. Crovalimab is a monoclonal antibody and is not expected to be genotoxic, as it does not cross the nuclear or mitochondrial membranes or interact directly with DNA or other chromosomal materials. C5 deficiency or dysfunction in humans is not associated with increased carcinogenic risk in humans. Based on the mechanism of action, review of the literature, drug class, and the lack of drug-related preneoplastic lesions in monkeys administered crovalimab for up to 26 weeks, the risk of carcinogenicity of crovalimab is low. Crovalimab is not active in rodents; therefore, carcinogenicity studies are not feasible.

13.2.5.3. Reproductive Toxicology

Enhanced Subcutaneous Study for Effects on Pre- and Postnatal Development in Cynomolgus Monkeys With One Intravenous Loading Dose (Study RO7112689)

Key Study Findings

- A slight increase in incidence of early abortions was observed at 100 mg/kg (2 maternal abortions versus one in each of the control and 10 mg/kg groups). However, crovalimab did not affect other pregnancy outcomes, gestational length, or number of live birth infants.
- Increased growth parameters (head circumference, crown-rump length, and tail length) of up to 20% were observed in infants from crovalimab-treated groups. These changes were consistent with the increases in body weight (BW) observed in these animals. These changes were considered nonadverse due to lack of consequence in related parameters. No crovalimab-related skeletal development effects were observed.
- All crovalimab treated monkeys and their infants were exposed to crovalimab. Maternal exposure to crovalimab increased in a less-than-dose-proportional manner from 10 to 100 mg/kg/dose. Accumulation of crovalimab was observed in the 100 mg/kg/dose group on gestational day 139.
- Infants from crovalimab-treated monkeys were born with circulating levels of crovalimab. Infants from the 100 mg/kg/dose crovalimab group presented up to a 50% reduction in C5 complement activity when compared to control at postnatal day 42. C5 activity returned to baseline levels by postnatal day 70 and postnatal day 119 in male and female infants, respectively. Maternal exposures at the 10 mg/kg dose, which were not associated with a decrease in CH50 in infants, are ~2times C_{max} and AUC of the maximum recommended human dose.
- The NOAEL of crovalimab for both maternal and developmental toxicity in cynomolgus monkeys is defined at 100 mg/kg based on lack of adverse findings. The NOAEL is associated with a systemic maternal exposure C_{max} of 4,310 μg/mL and a mean AUC for all of 26,400 (μg·day)/mL on gestational day 139 and corresponds to 14-times C_{max} and 13-times AUC for the exposure observed in patients with PNH at the maximum recommended human dose.

Table 91. Methods of Pre- and Postnatal Development Study in Monkeys

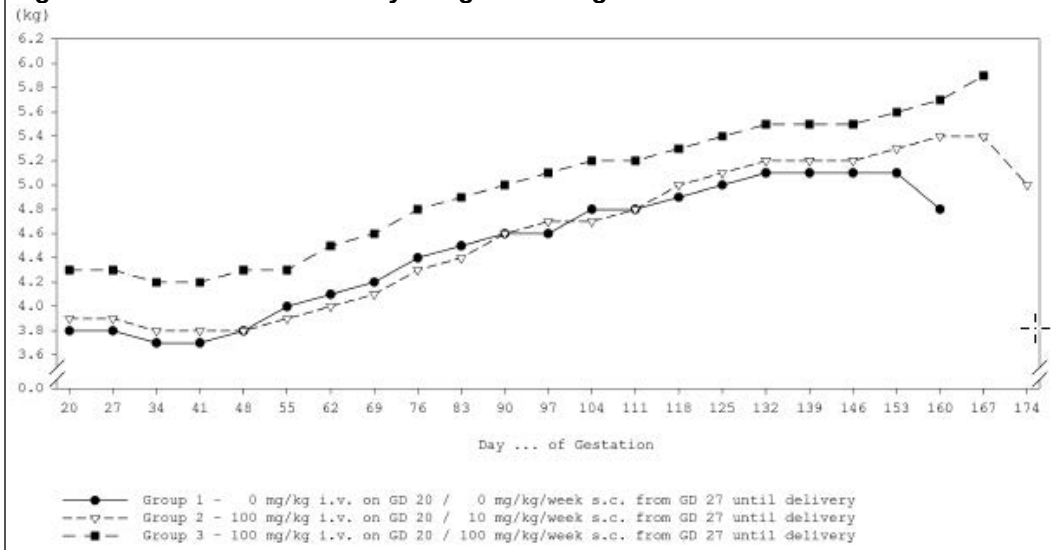
Parameter	Method Details
GLP Compliance	Yes
Dose and frequency of dosing:	IV loading dose of 100 mg/kg on GD 20 followed by 10 or 100 mg/kg SC once weekly from GD 27 until delivery (~GD 160).
Route of administration:	SC
Formulation/vehicle:	Crovalimab (RO7112689)/ 30mM histidine/aspartic acid, 100mM arginine-HCl, 0.05% (w/v), (b) (4) and 0.5 mg/mL Poloxamer 188, pH 5.8
Species/strain:	Cynomolgus monkeys
Number/sex/group:	16 females per group
Satellite groups:	None
Study design:	Maternal animals Assessments included clinical observations, body weights, clinical pathology (on GD 20, 34, 48, 111, and 146; on LD 28, 42, 56, 70, 119, 147 and 181), and pregnancy monitoring (when appropriate on GD 20, 30, 44, 58, 72, 86, 100, 114, 128, 142, and 156 (±1 day) and then every third or fourth day until delivery). Pregnancy outcomes were reported. Terminal evaluations included unscheduled sacrifice due to abortion, stillbirth or infant loss, macroscopic and microscopic examinations, organ weights, and histology analysis. Infants Neonatal evaluations were conducted for external abnormalities and body weights on PND 1, 7, 14, 21, and 28; weekly thereafter; and on the day before necropsy (PND 180±1). Clinical observations for infants were completed twice daily. Morphological measurements were performed on PND 1, 21, 56, 84, and 168. Neurobehavioral test battery was given on PND 1 and 7, and grip strength was tested on PND 28. Skeletal development was examined on PND 35±2 using X-ray on fasted, anesthetized infants to detect abnormalities and to see the developmental stage of bones. Terminal evaluations for infants included necropsy, organ weights, macroscopic and microscopic examinations. Infants were vaccinated on PND 133 and 154. Blood samples were collected on PND 133 (prior to first immunization); PND 140, 147, and 154 (prior to second immunization); and PND 161, 168, and 175 for T-Cell-Dependent Antibody Response Analysis (TDAR). Blood samples were analyzed on PND 21 (hematology and immunophenotyping), 35 (clinical chemistry), and 178 (all parameters). A CH50 analysis was assessed on PND 42, 56, 70, 119, 154, and on the day of necropsy. ADAs for maternal animals was analyzed on predose, GD 27, 90, and 139; LD 28, 42, 56, 70, and 119; and for infants on PND 28, 42, 56, 70, and 119.
Deviation from study protocol affecting interpretation of results:	Protocol deviations neither affected the overall interpretation of study findings nor compromised the integrity of the study.

Source: Reviewer generated table.
Abbreviations: ADA, antidrug antibody; CH50, total complement activity; GD, gestational day; GLP, Good Laboratory Practices; LD, lactation day; PND, postnatal day; SC, subcutaneous; TDAR, T-Cell-Dependent Antibody Response Analysis

Table 92. Study RO7112689, Observations and Results

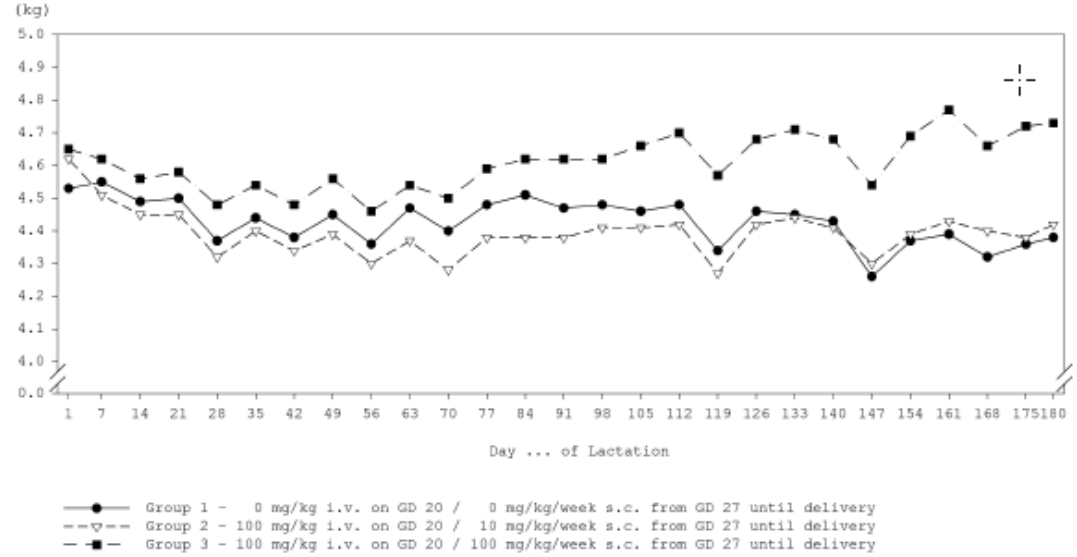
Parameter	Major Findings
Maternal unscheduled necropsy	There were increases in the incidence of abortions before early termination of maternal animals at 100 mg/kg (2 maternal abortions compared to 1 maternal abortion in each of the control and 10 mg/kg groups). The description of individual cases in all groups is as follows: One control female (P0003) was euthanized on Day 103 of the social phase after an abortion on GD 33. Macroscopic examinations of all organs were unremarkable. One female at 10 mg/kg (P0102) was euthanized after a cesarean section on GD 159 because of intrauterine death detected by ultrasound. Macroscopic observations included abnormal surface with a rough mucosa of the uterus and abnormal rough surface and edema of the placenta. Microscopic observations included moderate hypertrophy of the myometrium; moderate hyperplasia of the endometrium in the uterus; and rough surface, edema, moderate acute inflammation, moderate necrosis, and minimal mineralization in the syncytial villi in the placenta. One female at 100 mg/kg (P0211) was euthanized on Day 38 of the social phase after abortion on GD 33 to avoid social stress. Macroscopic examination of spleen, kidney, heart, stomach, liver, and lung were unremarkable. No microscopic evaluation was performed. Clinical signs of slight swelling in the lower abdomen were observed at GD 20 and 27. One female at 100 mg/kg (P0214) was sacrificed on Day 11 of the social phase after abortion on GD 93. Macroscopic observations included bilateral pale discoloration of the kidneys, a marked brown nodule in the anus, and pale discoloration and grey purulent contents of the endometrium in the uterus. Microscopic evaluation was conducted in the uterus only and revealed moderate hypertrophy in the myometrium, which is a pregnancy-associated change. Body weight loss was observed at GD 90, although body weight change was only slightly decreased. The animal was treated with supplemental food at GD 92-93.
Maternal clinical signs	Crovalimab-related increased incidence of soft/liquid feces occurred at 100 mg/kg during the gestation period (several observations in 6 maternal animals in the 100 mg/kg group vs. reduced number of observations in two females in each control and 10 mg/kg group). These changes are considered nonadverse because of lack of other related findings. No crovalimab-related clinical signs occurred during lactation.
Maternal body weights	The initial mean body weight on GD 20 for the control and 10 mg/kg groups was lower than the mean body weight for the 100 mg/kg group. The body weight gain during gestation was comparable for crovalimab-treated groups (Figure 19), but lower body weight gain was observed for the control group, see Table 93.

Figure 19. Mean Maternal Body Weights During Gestation



Source: Applicant submission.
Abbreviations: i.v., intravenously; GD, gestation day; s.c., subcutaneously

All groups had comparable body weight on LD 1, and it fluctuated (Figure 20) during the lactation period with no net gain observed on LD 180, see Table 93.

Parameter	Major Findings
	Figure 20. Mean Maternal Body Weights During Lactation  Source: Applicant's submission. Abbreviations: i.v., intravenously; s.c., subcutaneously **Table 93. Changes in Body Weight in Female Cynomolgus Monkeys During Dosing Period With Crovalimab for 4 Weeks** **Crovalimab (mg/kg)** / **Body Weight (kg) GD 20** / **Body Weight (kg) GD 160[a]** / **Gestation BW Gain (kg)** / **Body Weight (kg) LD 1** / **Body Weight (kg) LD 180** / **Lactation BW Gain (kg)** 0 / 3.76 / 4.57 / 0.81 / 4.53 / 4.38 / -0.15 10 / 3.92 / 5.39 / 1.47 / 4.62 / 4.42 / -0.2 100 / 4.35 / 5.73 / 1.38 / 4.65 / 4.73 / -0.1 Source: Reviewer generated table. [a] GD 160 was chosen as the end of the gestation period because all females in the control group were excluded from body weight measurement thereafter. Only 3 maternal animals remained compared to 8 maternal animals in each treatment group. Abbreviations: BW, body weight; GD, gestation day; LD, lactation day
Maternal clinical pathology	No crovalimab-related changes in hematology and clinical chemistry occurred during gestation and lactation in maternal females.

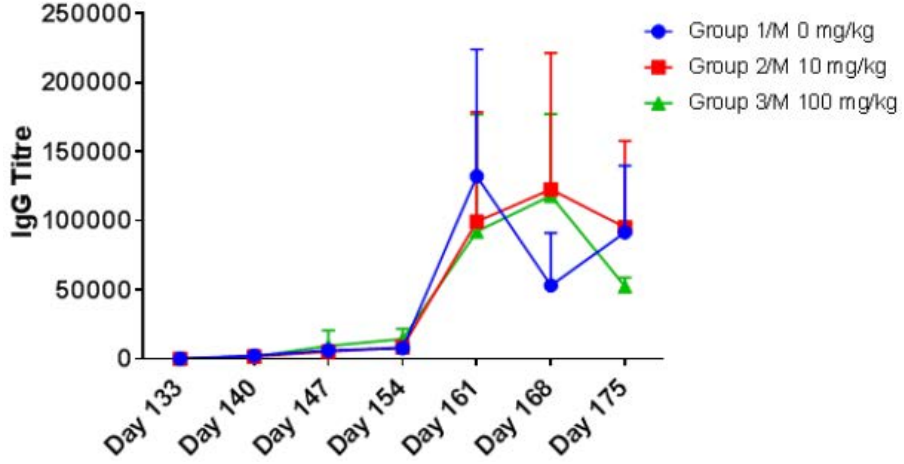
<table>
<tr><th>Parameter</th><th>Major Findings</th></tr>
<tr><td>Pregnancy outcome</td><td>Crovalimab did not affect pregnancy outcome, gestational length, or number of live birth infants at the 10 or 100 mg/kg/dose.

Table 94. Pregnancy Outcomes After Crovalimab Administration
<table>
<tr><th></th><th colspan="3">Dose (mg/kg)</th></tr>
<tr><th>Pregnancy Outcome
Number of Pregnant Females Per Group =16</th><th>0</th><th>10</th><th>100</th></tr>
<tr><td>Number of females with abortion</td><td>2</td><td>3</td><td>3</td></tr>
<tr><td>Number of females with unscheduled cesarean section, uterine death</td><td>-</td><td>1</td><td>-</td></tr>
<tr><td>Percentage prenatal loss</td><td>12.5</td><td>25.0</td><td>18.8</td></tr>
<tr><td>Number of females with unscheduled cesarian section, breech delivery, infant alive</td><td>-</td><td>-</td><td>1</td></tr>
<tr><td>Number of stillbirths</td><td>1</td><td>-</td><td>1</td></tr>
<tr><td>Number of early delivery</td><td>4</td><td>-</td><td>-</td></tr>
<tr><td>Number of infants found dead/ died</td><td>1</td><td>1</td><td>1</td></tr>
<tr><td>Number of infants life born</td><td>13</td><td>12</td><td>12</td></tr>
<tr><td>Mean duration of gestation</td><td>154</td><td>163</td><td>162</td></tr>
</table>
Source: Reviewer generated table.</td></tr>
<tr><td>Maternal necropsy evaluations</td><td>No crovalimab-related findings were observed (spleen, kidney, heart, stomach, liver, and lung). No organ weights or microscopic evaluations were performed.</td></tr>
<tr><td>Infant mortality</td><td>No crovalimab-related infant death occurred in the study. The incidence of infant death was 2, 2, and 2 in the control, 10 mg/kg and 100 mg/kg crovalimab groups, respectively, and all occurred from birth to PND 4. Infant mortality is within expected outcomes for Cynomolgus monkeys (Grossmann et al. 2020).</td></tr>
<tr><td>Infant clinical observations and veterinary treatments</td><td>No crovalimab-related clinical observations were observed, or veterinary care was needed.</td></tr>
<tr><td>Hand-raised infants</td><td>One female infant in the 10 mg/kg and 1 female/1 male infants in the 100 mg/kg groups were hand-raised. Maternal rejection occurred in all three cases and all infants developed properly until the scheduled euthanasia. These outcomes are known to occur spontaneously in cynomolgus monkeys and were considered incidental.</td></tr>
<tr><td>Infant body weight</td><td>Crovalimab-related slight increases in body weight were observed towards the end of the maturation phase in male infants and from Day 14 in female infants. The differences were only statistically significant for female infants on Day 14 and 21 in both crovalimab LD and HD groups. The Applicant deemed these findings crovalimab-related but nonadverse because there were no negative effects, and the FDA agrees with this assessment based on the absence of other related observations/consequences.</td></tr>
<tr><td>Infant external examinations</td><td>There were no crovalimab-related observations.</td></tr>
</table>

Parameter	Major Findings
Infant morphological measurements	Increased growth parameters (head circumference, crown-rump length and tail length) of up to 20% were observed, consistent with body weight increases observed in the crovalimab-treated groups.
Infant neurobehavioral assessment	No crovalimab-related changes in neurobehavioral parameters were observed.
Infant grip strength	No crovalimab-related changes in grip strength were observed.
Infant skeletal development	There were no crovalimab-related skeletal development effects. There was luxation of the 2nd or 3rd metacarpophalangeal joint of the left foot in one infant in each of the treated groups. The Applicant deemed these spontaneous injuries and not related to crovalimab administration.
Infant clinical pathology	No crovalimab-related changes in hematology, coagulation, or clinical chemistry parameters were observed in infants during the maturation phase.
Infant Immunotoxicology	Immunophenotyping Dose-independent increases of up to 2-fold in absolute and/or relative mean B-cell counts (CD20+) were observed at PND 21 in female infants, which returned to levels comparable to control by PND 178. Control values were low on PND 21 but increased on PND 178 to similar values observed for the crovalimab groups on PND 21. The variability, and inconsistency between male/female infants, along with the variability reported in the literature, are the bases for considering this finding unlikely to be related to crovalimab. T-cell Dependent Antibody Response (TDAR/ KLH) Assessments Humoral immune response after an antigen challenge (KLH) was evaluated for infants on PND 133 and 154 to determine primary and secondary immune responses. TDAR assessments were conducted when C5 and CH50 concentrations were back to baseline, approximately on PND 119. The primary immune response consisted of similar IgM levels in male and female groups after the first antigen challenge, with the highest level observed on PND 140 (i.e., 7 days after the antigenic challenge). The response switched to only IgG after the second challenge with the maximum peak approximately 3 weeks after the first challenge, mean IgG levels higher in infants born from crovalimab-treated females, and high interanimal variability. The Applicant referenced literature (Lebrec et al. 2011) reporting a high interanimal variation in kinetics and peak titers, which were the basis for considering differences from control values as incidental and not related to crovalimab.

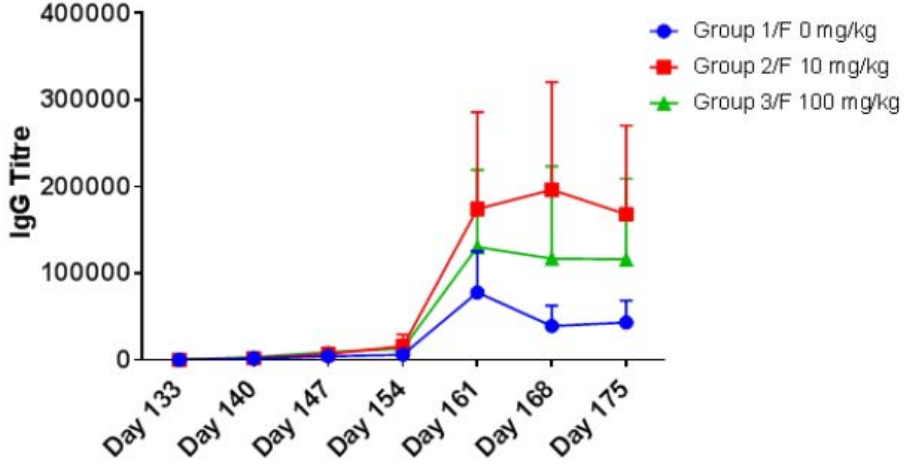
Parameter	Major Findings

Figure 21. Secondary Immune Response in Infants: IgG Titers in Males



Source: Applicant submission
Abbreviations: IgG, immunoglobulin G; M, male

Figure 22. Secondary Immune Response in Infants: IgG Titers in Females



Source: Applicant submission
Abbreviations: F, female; IgG, immunoglobulin G

Parameter	Major Findings
Infant Necropsy Evaluations	Organ Weights No crovalimab-related changes in organ weights were observed in male infants. In female infants, increased kidney (20%) and thymus (-20%) weights were observed in the HD, which did not reach statistical significance. These changes are of note based on the microscopic observations of increased incidence of mononuclear cell infiltrates in the kidney at all doses and the increased B-cell counts identified by immunophenotyping in female infants (see the Immunophenotyping section for detailed observations). However, these changes are considered nonadverse based on the high variability. Macroscopic and Microscopic Observations A higher incidence of mononuclear cell infiltrates in the kidney (HD) and liver (HD in males and MD/HD in females) was observed in infants from crovalimab treated animals. SC Injection Site Unremarkable
Maternal C5 and CH50 determination	C5 Determination C5 levels in maternal animals increased in a time-dependent manner after the IV loading dose of 100 mg/kg, reaching maximum concentration 168 hours after dosing on GD 27. C5 levels remained elevated compared to control values throughout the gestation period and into the lactation period. Levels returned to near predose levels at LD 119 for the 10 mg/kg and LD 181 for the 100 mg/kg (4 to 6 months after the end of dosing).

Table 95. C5 Concentrations in Cynomolgus Monkey Plasma During Gestation

		Plasma Concentration of C5 (µg/mL)					
Gestation Day	Time Point	Group 1 (0 mg/kg)		Group 2 (10 mg/kg)		Group 3 (100 mg/kg)	
		Mean	SD	Mean	SD	Mean	SD
20	0h	104	19	100	21	101	15
	5min	98.6	18.3	106	23	107	17
	2h	97.8	17.8	111	24	115	19
	8h	96.8	17.3	124	29	126	23
	24h	100	16	151	42	152	30
	72h	101	20	183	44	189	24
	168h	105	20	218	55	230	35
27	2h	109	26	217	50	227	39
	8h	109	27	226	46	233	37
	24h	104	24	214	55	233	39
	72h	112	28	241	48	243	32
	168h	113	22	242	59	244	42
90	0h	91.4	23.8	221	70	220	66
	2h	85.6	21.2	207	63	201	58
	8h	86.7	22.0	209	67	209	72
	24h	87.3	21.9	211	56	203	60
	72h	87.3	20.7	219	69	227	68
	168h	91.0	25.0	207	69	224	58
139	0h	91.9	27.2	191	78	251	71
	2h	88.4	24.8	188	72	234	65
	8h	91.0	25.9	184	75	238	63
	24h	90.8	23.2	174	63	230	69
	72h	95.6	23.2	195	72	236	64
	168h	99.0	30.7	193	69	244	72

Source: Applicant submission.
Abbreviations: C5, complement component 5; h, hours; min, minutes; SD, standard deviation

Table 96. C5 Concentrations in Cynomolgus Monkey Plasma During Lactation

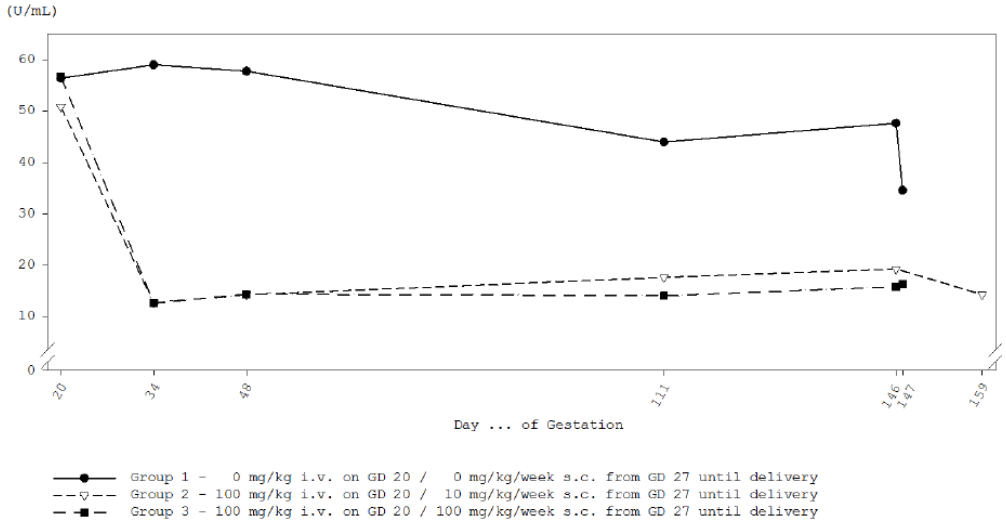
Lactation Day	Plasma Concentration of C5 (µg/mL)					
	Group 1 (0 mg/kg)		Group 2 (10 mg/kg)		Group 3 (100 mg/kg)	
	Mean	SD	Mean	SD	Mean	SD
1	106	32	204	73	255	78
28	101	33	174	29	194	84
42	105	31	165	30	195	81
56	101	28	143	27	163	61
70	90.8	21.5	130	31	165	67
119	100	21	109	21	147	57
154	97.2	18.0	94.5	14.6	122	35
181±1	95.8	21.3	102	17	107	29

Source: Applicant submission.
Abbreviations: C5, complement component 5; SD, standard deviation

CH 50 Levels

Decreases in total hemolytic complement concentrations (CH50) in crovalimab-treated females started on GD 34 and remained low, -60 and -67%, compared to control females during gestation (GD 146), see Figure 23.

Figure 23. Mean Complement (CH50) Levels in Maternal Animals During the Gestation Phase



Source: Applicant submission.
Abbreviations: CH50, 50% Hemolytic Complement Activity of Serum; GD, gestation day; i.v., intravenously; s.c., subcutaneously

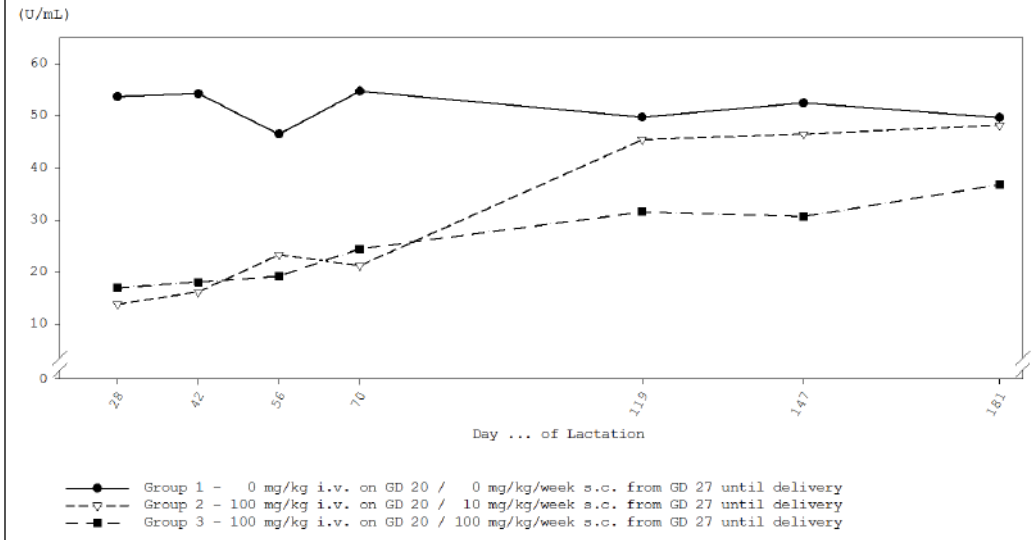
Parameter	Major Findings
	CH50 levels in crovalimab-treated lactating females remained lower, -74% and -68%, at the LD and HD compared to control, but CH50 levels presented a trend for increase starting on LD 28, corresponding with decreasing levels of C5. CH50 concentration changes were dose- and duration-independent and returned to near baseline levels steadily by LD 119 in 10 mg/kg females, while decreases persisted until the end of the study in 100 mg/kg females with a trend of increasing levels. **Figure 24. Mean Complement (CH50) Levels in Maternal Animals During the Lactation Phase**  Source: Applicant submission. Abbreviations: CH50, 50% Hemolytic Complement Activity of Serum; GD, gestation day; i.v., intravenous; s.c., subcutaneous
Infant C5 and CH50 determination	<u>C5 Determination</u> Crovalimab-related increases in C5 concentrations occurred only in infants from maternal animals receiving 100 mg/kg and levels were comparable to control infants by PND 119.

Table 97. C5 Concentrations in Cynomolgus Monkey Plasma in Infants

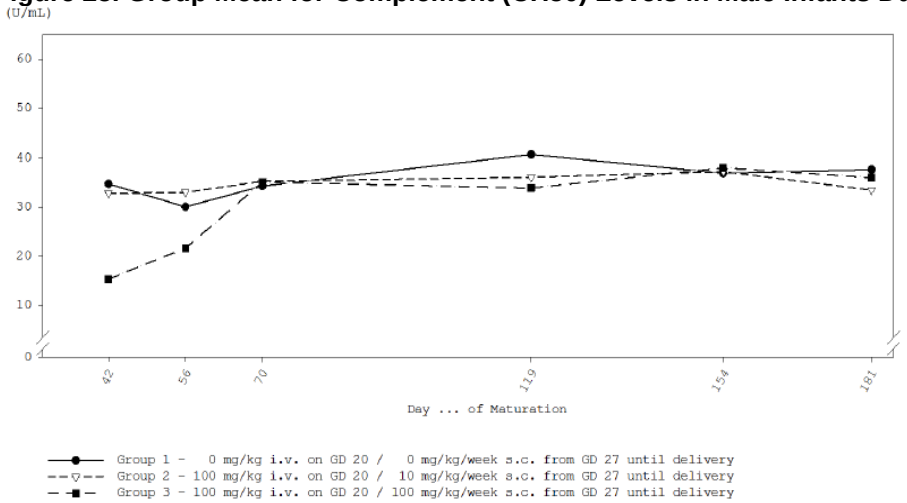
Post Natal Day	Plasma Concentration of C5 (µg/mL) - Infants					
	Group 1 (0 mg/kg)		Group 2 (10 mg/kg)		Group 3 (100 mg/kg)	
	Mean	SD	Mean	SD	Mean	SD
28	65.5	20.2	68.0	16.0	109	32
42	60.9	22.1	68.1	17.0	92.4	30.9
56	57.3	16.6	57.8	12.4	78.5	27.3
70	57.3	7.9	56.5	13.2	73.7	25.4
119	55.5	8.4	58.9	12.2	57.9	11.0
154	54.1	8.8	57.7	16.8	52.9	6.7
181±1	55.8	12.6	59.6	13.6	63.4	12.4

Source: Applicant submission.
Abbreviations: C5, complement component 5; SD, standard deviation

CH50 Determination

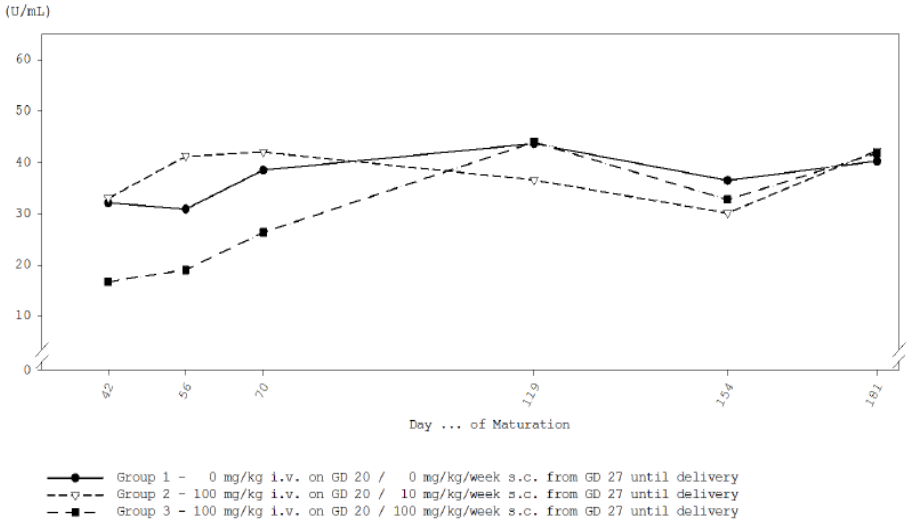
There were crovalimab-related decreases in CH50 concentrations of up to 50% compared to control (at PND 42) in infants born from females administered 100 mg/kg, which returned to comparable control values on PND 70 in males or near control levels on PND 119 in females, See Figure 25 and Figure 26.

Figure 25. Group Mean for Complement (CH50) Levels in Male Infants During the Maturation Phase



Source: Applicant submission
Abbreviations: CH50, 50% Hemolytic Complement Activity of Serum; GD, gestation day; i.v., intravenous; s.c., subcutaneous

Figure 26. Group Mean for Complement (CH50) Levels in Female Infants During the Maturation Phase



Source: Applicant submission
Abbreviations: CH50, 50% Hemolytic Complement Activity of Serum; GD, gestation day; i.v., intravenous; s.c., subcutaneous

Parameter	Major Findings
Toxicokinetics	After the IV loading dose, exposure to crovalimab in maternal animals was comparable in both crovalimab treated groups. After subsequent SC administration, exposure to crovalimab increased in a less-than-dose-proportional manner through the study period, although exposure by GD 90 and GD 139 reached dose-proportionality. Crovalimab accumulation was observed at 100 mg/kg from GD 27 to GD 139. Average terminal half-life of crovalimab was 21.1 and 19.8 days for the 10 mg/kg and 100 mg/kg group, respectively. ADAs were detected in both control and crovalimab-dosed maternal animals during the gestation and lactation period at similar ratios using the electrochemiluminescence (ECL) method. Crovalimab was detected in only one animal from the control group, which was inadvertently dosed with crovalimab. This animal was excluded from toxicokinetic evaluations. **Table 98. Summary of Toxicokinetic Parameters in Maternal Monkeys After Administration of Crovalimab**

Treatment Duration	Species/ Test System	Animals/ Group	Occasions and Dose (mg/kg)	Mean C_{max} (µg/mL)	Mean AUC_{all} (µg·day)/mL
GD 20 until delivery (approximately GD 160)	Pregnant Cynomolgus Monkey	16 F	GD20	RO7112689	
			100 (Group 2)	2400	9950
			100 (Group 3)	2550	10700
			GD27		
			10 (Group 2)	1210	7160
			100 (Group 3)	1910	11000
			GD90		
			10 (Group 2)	614	3800
			100 (Group 3)	3470	21500
			GD139		
			10 (Group 2)	613	3580
			100 (Group 3)	4310	26400

Source: Applicant submission
Note: 'Mean AUC_{all}' indicates mean exposure over the 1-week dosing interval, or AUC0-7d. This mean value is multiplied by 4 to estimate exposure over a 28d period for comparison to clinical exposure of 7830 µg*d/ml AUC0-28d at the MRHD.
Note: RO7112689 (crovalimab) was detected in most infants from maternal animals treated at 10 and 100 mg/kg. Time to maximum plasma concentration (T_{max}) was reached at PND 28 in both groups and crovalimab was detected throughout PND 181 in all animals at the 100 mg/kg groups. Average terminal half-life in plasma in the 10 mg/kg dose group was 24.5 and 24.7 days and in the 100 mg/kg dose group 23.7 and 23.9 days for male and female infants, respectively Based on C_{max} and AUC_{last}, crovalimab exposure increased from
Note: 10 to 100 mg/kg in a slightly more than dose proportional manner and there were no gender differences.
Note: ADA was also detected in infants from both control and dosed groups.
Abbreviations: ADA, antidrug antibody; AUC_{all}, all area under the concentration-time curve; AUC_{last}, area under the concentration-time curve from time 0 to last measurable concentration; C_{max}, maximum observed plasma concentration; F, female; GD, gestation day; MRHD, maximum recommended human dose; PND, postnatal day; T_{max}, time to maximum observed plasma concentration

Parameter	Major Findings

Table 99. Summary of Toxicokinetic Parameters in Infants From Maternal Monkeys Treated With Crovalimab

Treatment Duration	Species/ Test System	Animals/ Group	Occasions and Dose (mg/kg)	Mean C_{max} (µg/mL) (M/F)	Mean $AUCl_{ast}$ (µg·day)/mL (M/F)
			PNDs	RO7112689	
GD 20 until delivery (approximately GD 160)	Infant Cynomolgus Monkey	6 M + 5 F	10 (Group 2)	5.15/6.40	235/279
		5 M + 6 F	100 (Group 3)	118/89.4	4540/4140

Source: Applicant submission
Abbreviations: AUC_{last}, area under the concentration-time curve from time 0 to last measurable concentration; C_{max}, maximum observed plasma concentration; F, Females; GD, Gestation Day; M, Males; PND, postnatal day

Discussion

In this study, ADAs were detected with the same ECL method used in the 6-month toxicology study. Samples from the 6-month toxicity study were later reanalyzed using an immunohistochemistry (ICH) method and showed a positive ADA response in animals, which did not show positive response in the ECL method. Using the ICH method, it was concluded most animals showed ADA-positive responses at each dosing group. The onset of ADA-positive responses occurred on Day 36 for most of the animals in the chronic toxicology study. Of note, the ICH methods detected ADA-positive responses even in samples with high crovalimab concentration. Thus, ADA positivity may be underrepresented in this study.

Source: Reviewer generated table.
Abbreviations: ADA, antidrug antibody; C5, complement component 5; CH50, complement inhibition; CD, cluster of differentiation; ECL, electrochemiluminescence; FDA, Food and Drug Administration; GD, gestation day; HD, high dose; ICH, immunohistochemistry; IgG, immunoglobulin G; KLH, keyhole limpet hemocyanin; MD/HD, mid dose/ high dose ; PND, postnatal day; TDAR, T-Cell-Dependent antibody response

14. Clinical Pharmacology

14.1. In Vitro Studies

Not applicable.

14.2. In Vivo Studies

Study COMPOSER (BP39144)

"An Adaptive Phase 1/2 Study to Assess Safety, Efficacy, PK and Pharmacodynamics (PD) of Crovalimab in healthy volunteers (HVs) and Patients with PNH."

Primary Objective

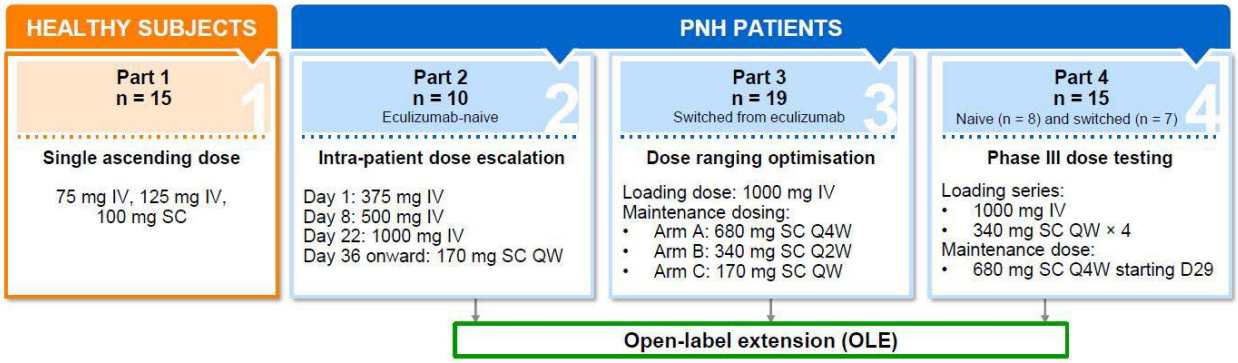
To assess the long-term safety and immunogenicity of crovalimab over an extended treatment period up to 5 years.

COMPOSER was the Applicant's dose-finding study to support dose selection for the pivotal trials.

Study Design

This is a first-in-human Phase 1/2 study consisting of four sequential parts and an open-label extension (OLE) designed to evaluate the safety, tolerability, PK, PD, and efficacy of crovalimab in HVs (Part 1) and in patients with PNH who are either treatment-naïve or who switched from eculizumab to crovalimab (Parts 2, 3, 4, and OLE). A total of 15 HVs (5 in each cohort) and 44 subjects with PNH (10 subjects in Part 2, 19 subjects in Part 3, and 15 subjects in Part 4) were enrolled. The study design is depicted in Figure 27.

Figure 27. Overall Study Design (Study COMPOSER)



Source: Figure 1, page 20, COMPOSER CSR.
Note: Part 4 enrolled treatment-naïve subjects (Arm A, n=8 subjects) and subjects who switched from eculizumab (Arm B, n=7 subjects).
Abbreviations: IV, intravenous; n, number of subjects; OLE, open-label extension; PNH, paroxysmal nocturnal hemoglobinuria; Q2W, biweekly; Q4W, every 4 weeks; QW, weekly; SC, subcutaneous

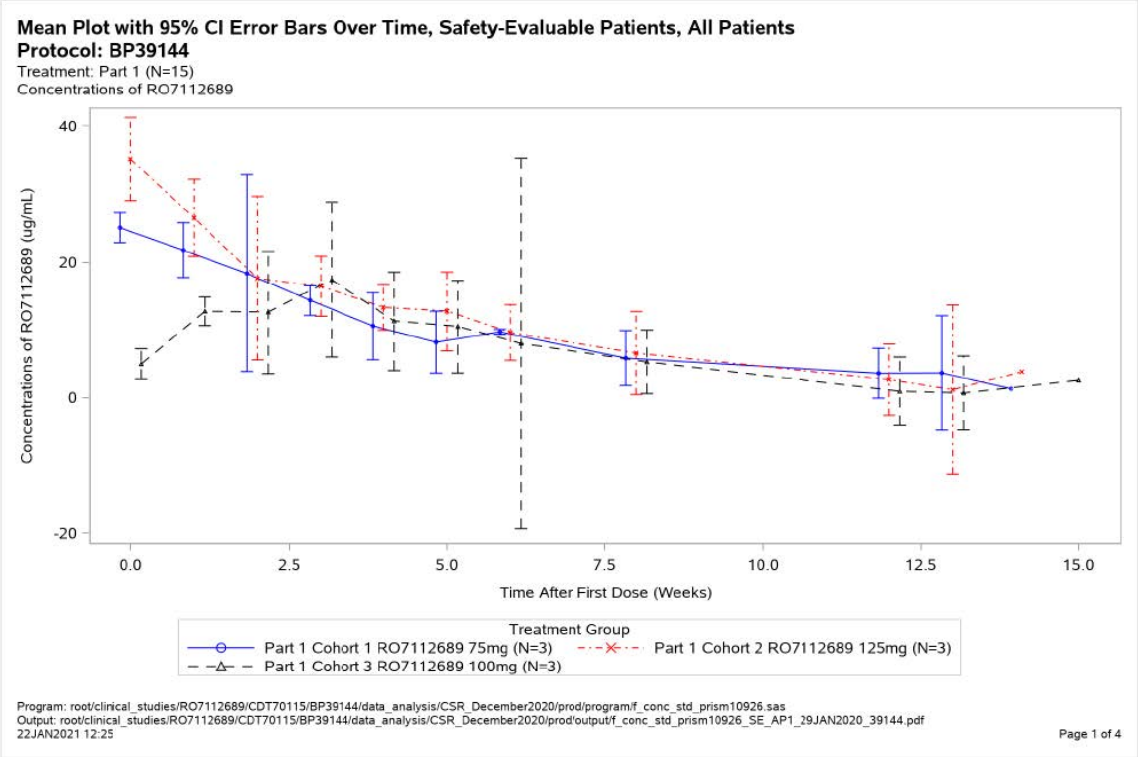
The efficacy of crovalimab was evaluated in Parts 2, 3, and 4. Dose-escalation via IV administration in Parts 1 and 2 was pharmacology-driven, with the main objective to characterize the pharmacokinetics/pharmacodynamics relationship in HVs and subjects with PNH. In Part 3, the aim was to establish the optimal SC dosing regimen with the lowest treatment burden for switch subjects with PNH. In Part 4, the aim was to establish a safe and efficacious dosing regimen in treatment-naïve and in switch subjects with PNH that completely inhibits complement activity with low treatment burden. Subjects enrolling in the OLE from Parts 2, 3, and 4 of the study, initially stayed on the previously assigned crovalimab treatment schedule. With the implementation of the tiered-weight dosing, all subjects in the OLE who were not currently receiving every 4 weeks (Q4W) dosing of crovalimab were required to switch to the Q4W dosing regimen. Subjects either received 680 mg SC Q4W (BW ≥40 kg to <100 kg) or 1020 mg SC Q4W (BW ≥100 kg). Duration of study treatment will be up to 5 years from entry into OLE. Intensive serum samples were collected for measurement of crovalimab, total C5, free C5, CH50, DTDC, as well as ADAs. The potential neutralizing effect of ADAs was not assessed in this study as no validated assay was available at that time.

Results

Pharmacokinetics

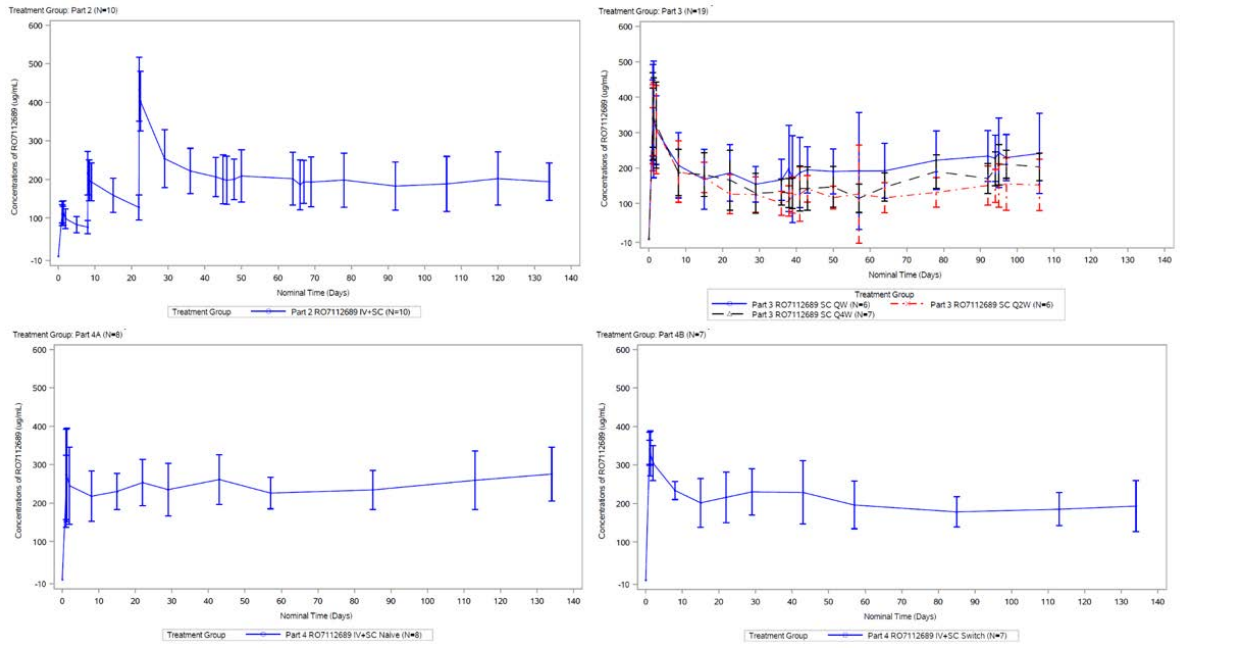
The plasma-concentration-versus-time profile of crovalimab in HVs and subjects with PNH are shown in Figure 28 and Figure 29, respectively. The PK results are shown in Table 100. The Applicant proposed a dosing regimen for the Phase 3 trials, which includes a loading dose and a series of maintenance doses, based on the data obtained in Parts 1 to 3. With the proposed dosing regimen, crovalimab concentrations above 100 μg/mL were achieved at the end of the IV infusion. In addition, trough crovalimab concentrations remained stable in the primary treatment period, which is critical for crovalimab to exert pharmacological effects.

Figure 28. Mean Crovalimab Serum Concentrations and 95% CI (Linear Scale) Over Time for Study COMPOSER, Healthy Volunteers



Source: Figure 1, page 30, Summary of Clinical Pharmacology Studies.
Abbreviations: CI, confidence interval; N, total number of subjects

Figure 29. Mean Crovalimab Serum Concentrations and 95% CI (Linear Scale) Over Time for Study COMPOSER, Parts 2, 3, 4a and 4b, Baseline to Week 20



Source: Figure 2, page 31, Summary of Clinical Pharmacology Studies.
Abbreviations: CI, confidence interval; IV, intravenous; N, total number of subjects; Q2W, every two weeks; Q4W, every four weeks; QW, every week; SC, subcutaneous

Table 100. Summary Statistics of Secondary PK Parameters Derived From the Population PK Model for Study COMPOSER (BP39144)

Cohort / Parameter	N	Mean	SD	Median	Minimum	Maximum
BP39144 Part 1, 75 mg IV						
C_{max} (μg/mL)	3	26.6	3.49	27.6	22.7	29.5
BP39144 Part 1, 125 mg IV						
C_{max} (μg/mL)	3	38.0	12.8	31.3	30.0	52.8
BP39144 Part 1, 100 mg SC						
C_{max} (μg/mL)	3	15.6	3.26	15.0	12.6	19.1
t_{max} (days)	3	9.62	2.31	10.5	7.00	11.4
BP39144 Part 2						
C_{max} (μg/mL)	10	402	115	402	205	580
$C_{max,ss}$ (μg/mL)	10	174	69.5	165	61.9	295
$t_{max,ss}$ (days)	10	5.05	0.919	4.75	3.95	7.00
$AUC_{\tau,ss}$ (μg/mL • days)	10	1210	483	1140	430	2040
$C_{trough,ss}$ (μg/mL)	10	173	69.3	165	61.5	293
$C_{av,ss}$ (μg/mL)	10	172	69.0	163	61.4	292
BP39144 Part 3, QW						
C_{max} (μg/mL)	6	353	110	311	237	490
$C_{max,ss}$ (μg/mL)	6	254	64.3	228	186	347
$t_{max,ss}$ (days)	6	3.79	0.657	3.70	3.10	4.95
$AUC_{\tau,ss}$ (μg/mL • days)	6	1760	447	1580	1290	2410
$C_{trough,ss}$ (μg/mL)	6	251	62.9	224	185	342
$C_{av,ss}$ (μg/mL)	6	252	63.8	226	185	344
BP39144 Part 3, Q2W						
C_{max} (μg/mL)	6	321	94.5	343	156	420
$C_{max,ss}$ (μg/mL)	6	169	46.6	164	101	228
$t_{max,ss}$ (days)	6	6.31	0.854	6.23	5.46	7.82
$AUC_{\tau,ss}$ (μg/mL • days)	6	2310	643	2230	1390	3130
$C_{trough,ss}$ (μg/mL)	6	159	45.4	152	96.8	215
$C_{av,ss}$ (μg/mL)	6	165	45.9	159	99.1	223
BP39144 Part 3, Q4W						
C_{max} (μg/mL)	7	360	93.1	327	270	492
$C_{max,ss}$ (μg/mL)	7	203	76.1	214	80.7	290
$t_{max,ss}$ (days)	7	9.03	1.34	8.51	7.55	11.6
$AUC_{\tau,ss}$ (μg/mL • days)	7	5200	1880	5620	2180	7240
$C_{trough,ss}$ (μg/mL)	7	160	54.7	180	71.9	214
$C_{av,ss}$ (μg/mL)	7	186	67.0	201	77.7	259

Cohort / Parameter	N	Mean	SD	Median	Minimum	Maximum
BP39144 Part 4A						
C_{max} (μg/mL)	8	314	88.4	275	236	459
$C_{max,ss}$ (μg/mL)	8	294	78.7	268	207	402
$t_{max,ss}$ (days)	8	9.02	0.496	9.00	8.26	9.79
$AUC_{\tau,ss}$ (μg/mL • days)	8	7700	1970	7090	5440	10300
$C_{trough,ss}$ (μg/mL)	8	244	56.9	231	175	319
$C_{av,ss}$ (μg/mL)	8	275	70.3	253	194	369
BP39144 Part 4B						
C_{max} (μg/mL)	7	341	48.4	311	293	417
$C_{max,ss}$ (μg/mL)	7	242	66.7	226	197	390
$t_{max,ss}$ (days)	7	8.63	1.10	8.59	7.00	10.6
$AUC_{\tau,ss}$ (μg/mL • days)	7	6130	1780	5840	4530	10000
$C_{trough,ss}$ (μg/mL)	7	185	60.2	177	116	310
$C_{av,ss}$ (μg/mL)	7	219	63.6	208	162	357

Source: Table 3, page 33, Summary of Clinical Pharmacology Studies.
Note: t_{max} as time after first dose and $T_{max,ss}$ as time after most recent dose.
Abbreviations: $AUC_{\tau,ss}$, area under the concentration-time curve for a dosing interval at steady state; $C_{av,ss}$, average concentration at steady state; C_{max}, maximum concentration; $C_{max,ss}$, maximum concentration during a dosing interval at steady state; $C_{trough,ss}$, trough concentration at steady state; IV, intravenous; N, total number of subjects; Q2W, every 2 weeks; Q4W, every 4 weeks; QW, every week; PK, pharmacokinetic; SC, subcutaneous; SD, standard deviation; T_{max}, time to maximum concentration; $t_{max,ss}$, time after most recent dose to reach the maximum concentration at steady state

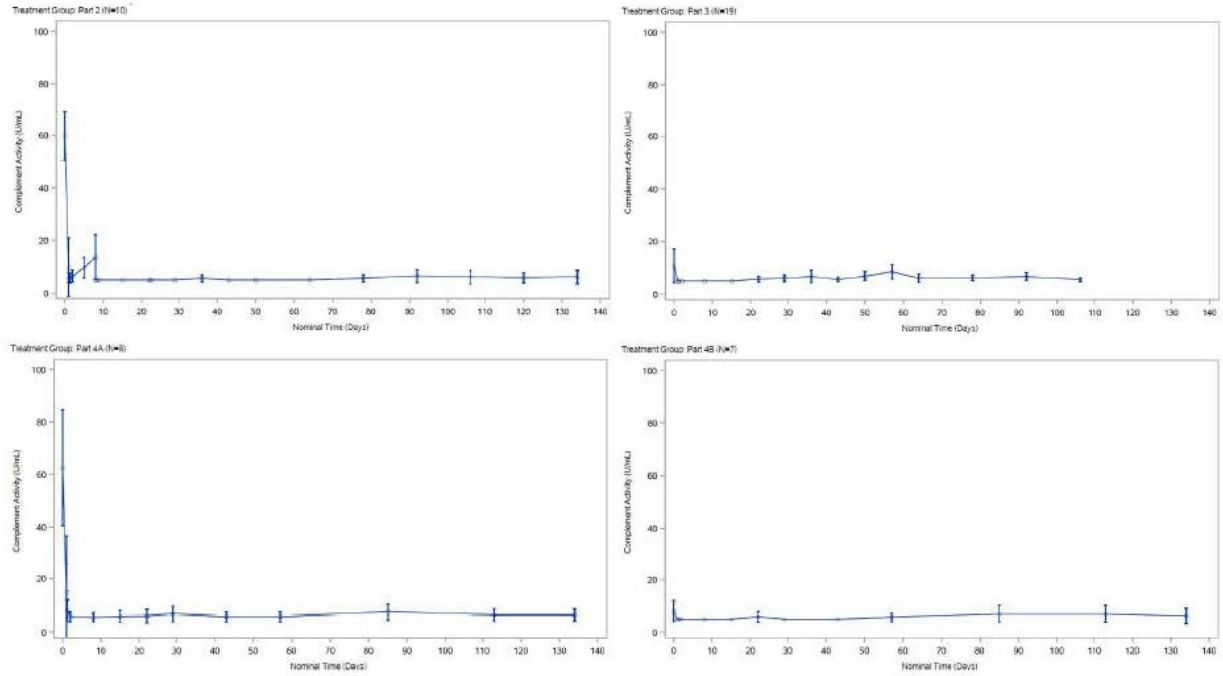
Pharmacodynamics

The objective of treatment with C5 inhibitors is to achieve a complete inhibition of the terminal complement activity. Different dose levels were tested to identify the relevant exposure to achieve this objective. Mean CH50 values from baseline to Week 20 in Parts 2, 3, 4a (treatment naïve), and 4b (switch from eculizumab) are displayed in Figure 30. In Part 2, complement inhibition was achieved immediately after the end of infusion in 9 out of 10 subjects following the initial dose of 375 mg IV. Thereafter, all subjects achieved complement inhibition following the second dose of 500 mg IV, and this complement inhibition was generally maintained throughout the remainder of the observed dosing interval when using a dosing regimen of 170 mg once weekly (QW) by the SC route. In Part 3, complement inhibition was achieved immediately after the end of infusion in all 19 subjects following the initial dose of 1000 mg IV. During the maintenance period, 3 different dosing regimens were investigated with the same total dose per month: 680 mg divided into either QW, every 2 weeks (Q2W), or Q4W SC Doses. Complement inhibition was generally maintained throughout the observation period in all 3 cohorts. Results from Part 4 were to confirm the dose recommendation for Phase 3 pivotal studies. In Part 4: Arm A, complement inhibition was achieved immediately after the end of infusion in 7 out of 8 subjects following the initial dose of 1000 mg crovalimab IV, and by Day 2 (predose) in the one remaining subject who had the highest complement activity (102 U/mL) at baseline. Complement inhibition in Arm A was maintained in all eight subjects throughout the observation period. In Part 4: Arm B, complement inhibition was maintained in all seven subjects throughout the observation period.

CH50 values were supported by free C5 concentration levels (which reflect the extent of binding/nonbinding of C5 to crovalimab), confirming that crovalimab achieved concentration-

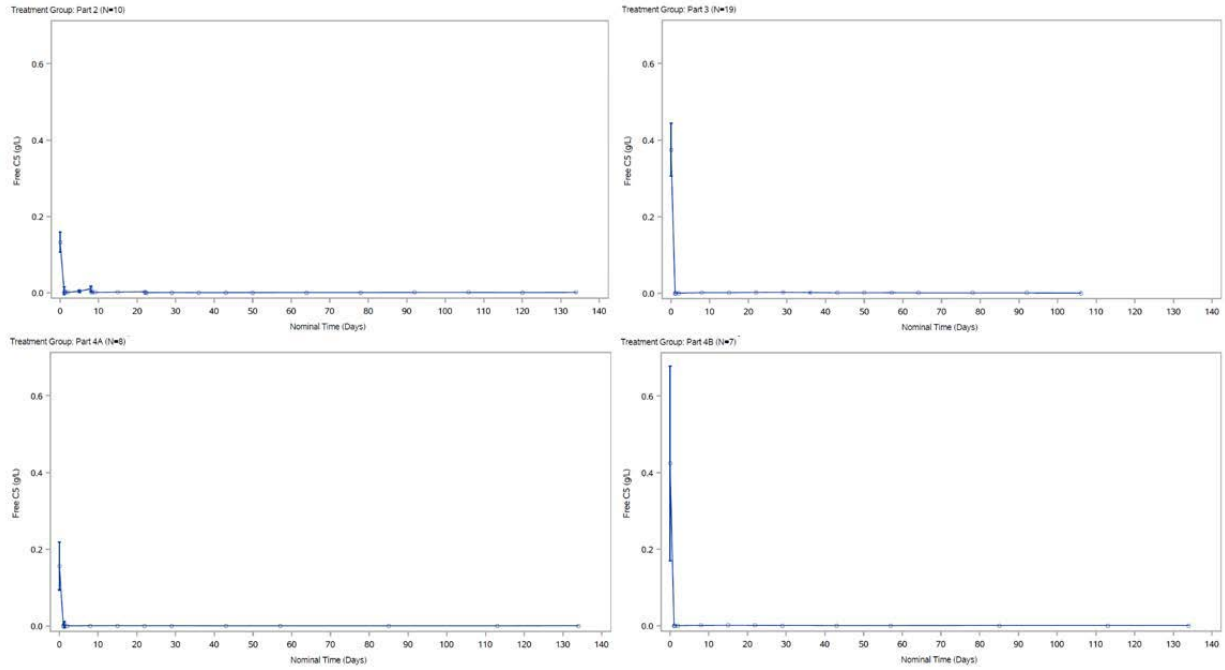
related inhibition of terminal complement activity. Mean free C5 concentrations, in Parts 2, 3, 4a, and 4b, from baseline to Week 20 are displayed in Figure 31. In treatment-naïve subjects with PNH (in Part 2 and 4a), mean (SD) free C5 concentration levels at baseline were 0.133 g/L (0.0367 g/L) and 0.163 g/L (0.081 g/L), respectively. After the initial IV dose, mean free C5 concentrations dropped to low levels (<0.001 g/L) and remained low (~0.001 g/L) throughout the assessment period. In subjects switching from eculizumab (in Part 3 and 4b), due to the nature of the free C5 assay, the presented free C5 levels reflect the binding/nonbinding to crovalimab but not to eculizumab. Therefore, at baseline prior to treatment with crovalimab, high levels of crovalimab-unbound free C5 are seen in both treatment-naïve and switch subjects, despite the switch subjects having terminal complement inhibition as shown by CH50. In Part 3 and 4b, mean (SD) free C5 concentration levels at baseline were 0.375 g/L (0.143 g/L) and 0.424 g/L (0.160 g/L), respectively. After the initial IV dose, mean free C5 concentrations dropped to low levels (~0.001 g/L) in comparison to baseline. Mean free C5 concentrations remained low (~0.001 g/L) throughout the assessment period.

Figure 30. Mean CH50 (Measured by LIA) and 95% CI (Linear Scale) Over Time for Study COMPOSER, Parts 2, 3, 4a, and 4b, Baseline to Week 20



Source: Figure 4, page 37, Summary of Clinical Pharmacology Studies.
Note: Part 2: subjects received single-ascending IV doses on Day 1: 375 mg, Day 8: 500 mg, and Day 22: 1000 mg; then they received 170 mg QW by the SC route. Part 3: subjects received IV loading dose of crovalimab of 1000 mg followed by 3 different SC dosing regimens, Arm A: 680 mg crovalimab SC Q4W, Arm B: 340 mg crovalimab SC Q2W, Arm C: 170 mg crovalimab SC QW. Part 4: subjects received 1000 mg IV followed by 340 mg SC weekly; then subjects received maintenance dose of 680 mg SC Q4W. LIA concentrations below the LLOQ of <10 U/mL were set to 5 U/mL for purposes of analysis.
Abbreviations: CI, confidence interval; IV, intravenous; LIA, liposome immunoassay; LLOQ, lower limit of quantification; N, total number of subjects; Q2W, every 2 weeks; Q4W, every 4 weeks; QW, every week; SC, subcutaneous.

Figure 31. Mean Free C5 Concentrations and 95% CI (Linear Scale) Over Time for Study COMPOSER, Parts 2 and 4a, Baseline to Week 20



Source: Figure 6, page 40, Summary of Clinical Pharmacology Studies.
Note: 0.039E-3 g/L is the LLOQ for Free C5.
Abbreviations: C5, complement component 5; CI, confidence interval; LLOQ, lower limit of quantification; N, total number of subjects

Immunogenicity

In treatment-naïve subjects (Part 2 and Part 4a), all subjects had a negative ADA status at baseline; treatment-emergent ADAs were detected in 10 out of 18 treatment-naïve subjects (55.6%). All treatment-emergent ADAs were treatment-induced ADAs, with two subjects having transient ADAs and 8 subjects having persistent ADAs. In the treatment-switch subjects (Part 3 and Part 4b), at baseline, ADAs were detected in 14 out of 26 subjects (53.8%). In switch subjects, drug-target complexes (circulating C5-eculizumab-C5 or C5-ravulizumab-C5) interfered with the ADA assay, causing false positive readouts at baseline, which led to the high ADA prevalence in switch subjects. Treatment-emergent ADAs were detected in 8 out of 26 subjects (30.8%); 4 out of those 8 subjects had treatment-induced ADAs and the other 4 had treatment-enhanced ADAs. All treatment-induced ADAs in the switch population were persistent in nature which was defined by the Applicant as (i) treatment induced ADA detected at two or more sampling time points during the treatment (including follow-up), where the first and last ADA-positive samples (irrespective of any negative samples in between) were separated by a period of 16 weeks or longer, or (ii) treatment-induced ADA detected only in the last sampling time point of the treatment study period.

14.3. Bioanalytical Method Validation and Performance

The Applicant used an enzyme linked immunosorbent assay (ELISA) procedure to determine serum crovalimab concentrations. The assay is based on the immobilization of a rabbit

monoclonal antibody specific for the Fc portion of crovalimab onto microtiter plates to capture crovalimab present in the samples. Crovalimab is detected by successive addition of recombinant human C5 (hC5), followed by a mouse anti-hC5 monoclonal antibody, and finally by a goat antimouse IgG polyclonal antibody conjugated to horseradish peroxidase, which reacts with its chromogenic substrate (2,2'-azino-bis[3-ethylbenzothiazoline-6-sulfonic acid], ABTS).

Human serum samples were diluted 50-fold with assay buffer. Further dilutions were made using sample dilution buffer containing 2% matrix. Rabbit anti-RS C5 inh MAb, crovalimab Fc mAb was coated on a 96-well immunoplate and then blocked using a nonspecific protein. Quantified RS C5 inh MAb, crovalimab used to prepare standards and quality controls was then added to designated sample wells. Study samples were also added to designated sample wells. Recombinant human C5 was then added. The assay was visualized by the subsequent additions of mouse antihuman C5 mAb, peroxidase-conjugated AffiniPure goat antimouse IgG, Fcγ subclass 1 specific, and a chromogenic substrate (ABTS), and the product of this reaction was detected with a spectrophotometer. The absorbance (A405-A490 value) was proportional to the amount of crovalimab present in the sample.

This assay was first established at Chugai Pharmaceutical Co. Ltd., (b) (4) It was then transferred and validated (b) (4) . The ELISA methods were validated in compliance with the standards set forth in the FDA guidance for industry *Bioanalytical Method Validation* (May 2018). A summary of the validation parameters is presented in Table 101.

Table 101. Summary Review of Crovalimab Serum Assays

Parameter	Crovalimab
Bioanalytical method validation reports	1092728, 1105832, and 1100943
Validation assay range (ng/mL)	50.0 to 3200
QCs (ng/mL)	50, 150, 500, 2560, and 3200
Interday precision (% CV)	1.8 to17.3
Interday accuracy (% bias)	-7.4 to 11.4
Intraday precision (% CV)	0.6 to 22.9
Intraday accuracy (% bias)	-15.3 to 19.7
Reference standard	CROVALIMAB-000-002 (1092728 and 1100943) and PZ1908P039(1105832)
Specificity	All the unspiked individuals generated a response below the LLOQ of 50.0 ng/mL. At least 3 out of 5 individuals at 50.0 ng/mL were within acceptable %bias at each concentration.
Freeze/thaw stability	4 freeze (-20/-80°C)-thaw (room temperature) cycles
Total error (absolute bias + interassay precision)	Intra-assay total error: -20.9% to 28.6% Interassay total error: 7.3% to 19.7%
Selectivity in hemolyzed (5%) and hyperlipidaemic (2%) matrix	Up to 5% hemolysed and 2% intralipid matrix has no impact on the LLOQ of the assay (50.0 ng/mL). Up to 5% hemolyzed and 2% intralipid matrix has no impact on the assay as the unspiked samples generated a response below the LLOQ of 50.0 ng/mL.

Parameter	Crovalimab
Dilution Linearity	Maximum validated dilution factor: 1 in 8000.
Prozone	The absence of a hook effect was demonstrated up to a concentration of 20000 ng/mL.
Interference by Recombinant Human C5	160 ng/mL of human C5 did not interfere with the quantification of crovalimab at 50.0 ng/mL and 3200 ng/mL. Up to 80.0 ng/mL of human C5 did not interfere with the quantification of crovalimab at 50.0 ng/mL and 2560 ng/mL. Up to 160 ng/mL human C5 had no impact on the assay as the unspiked samples generated a response below the LLOQ of 50.0 ng/mL.
Interference of Antibodies Anti-C5 (11F6 and 12F3)	Increasing concentrations of both antibodies 11F6 and 12F3 (100, 200 and 400 µg/mL) interfered with the quantification of crovalimab at 50.0 ng/mL and 3200 ng/mL with the exception of the 50.0 ng/mL at 400 µg/mL of 12F3. Up to 500 µg/mL complement C5 (11F6 and 12F3) had no impact on the assay as the unspiked samples generated a response below the LLOQ of 50.0 ng/mL.
Interference of Mouse Anti-C5	Increasing concentrations of mouse anti-C5 (1.00 to 400 µg/mL) interfered with the quantification of crovalimab at 3200 ng/mL; at 50.0 ng/mL crovalimab quantification was acceptable up to 10.0 µg/mL mouse anti-C5. Up to 400 µg/mL mouse anti-C5 had no impact on the assay as the unspiked samples generated a response below the LLOQ of 50.0 ng/mL.
Interference of Eculizumab	Up to 400 µg/mL eculizumab had no impact on the assay as the unspiked samples generated a response below the LLOQ of 50.0 ng/mL. In presence of 10.0 µg/mL eculizumab, concentrations of 50.0 ng/mL and 3200 ng/mL crovalimab could be recovered. It is noted that up 400 µg/mL eculizumab concentrations of 50.0 ng/mL and 3200 ng/mL could be tolerated but also had conflicting result (some intermediate concentrations did not meet the criteria).
Freeze/Thaw Stability	At least 4 cycles at nominal -20°C. At least 12 cycles at nominal -80°C.
Refrigerated Stability	At least 25 hours 58 minutes at 2-8°C in human serum.
Stock stability	171 days at -80°C
Bench-top stability	At least 48 hours at room temperature in human serum
Processed stability	At least 18 hours at room temperature in formulation solution
Long-term storage stability	At least 250 days at nominal -20°C in human serum At least 191 days at nominal -80°C in human serum

Source: Validation reports 1092728, 1105832, and 1100943.
Note: Target specifications: Accuracy (expressed as %Bias): Bias: ±20%. Bias: ±25% at LLOQ and ULOQ. Precision (expressed as %CV): CV ≤20%; CV ≤25% at LLOQ and ULOQ. Total error (absolute bias + interassay precision): should not exceed 30%; 40% for LLOQ and ULOQ.
Abbreviations: %CV, coefficient of variation; C5, complement component 5; LLOQ, lower limit of quantitation; QC, quality control; ULOQ, upper limit of quantitation

The Applicant used an ELISA assay to determine serum eculizumab concentrations. Sample analysis was performed with a gyrolab immunofluorescence assay using CROVALIMAB-000-Bi as the capture reagent and mouse antihuman IgG4 Fc-Alexa Fluor 647 as the detection reagent. The gyrolab immunofluorescence assay was conducted at a constant serum concentration of 10%. This assay was established by the Applicant, and then the method was transferred to (b) (4)). The ELISA methods were validated in compliance with the standards set forth in the FDA guidance for industry *Bioanalytical Method Validation* (May 2018). A summary of the validation parameters are presented in Table 102.

Table 102. Summary Review of Eculizumab Serum Assays

Parameter	Eculizumab
Bioanalytical method validation reports	1109894 and 1120438
Validation assay range (ng/mL)	3725 to 62500
QCs (ng/mL)	3,725, 11175, 23640, 50000, and 62500
Interday precision (% CV)	5.5 to 27.4
Interday accuracy (% bias)	-1.1 to 16.5
Intraday precision (% CV)	5.5 to 18.0
Intraday accuracy (% bias)	-1.1 to 10.5
Reference standard	00134
Specificity	No interfering peaks were observed in blank serum samples.
Freeze/thaw stability	6 freeze (-20/-80°C)-thaw (room temperature) cycles
Total error (absolute bias + interassay precision)	6.6 to 28.5%
Interference	When C5 Protein concentration up to 72.0 µg/mL, no interference was observed.
Dilution Linearity	Maximum validated dilution factor: 1 in 61.75
Prozone	The absence of a hook effect was demonstrated up to a concentration of 490000 ng/mL.
Refrigerated Stability	At least 70 hours 08 minutes at 2-8°C in human serum.
Stock stability	171 days at -80°C
Bench-top stability	At least 24 hours at room temperature in human serum
Processed stability	At least 24 hours at room temperature
Long-term storage stability	Not reported

Source: Validation reports 1109894 and 1120438.
Target specifications: Accuracy (expressed as %Bias): Bias: ±20%. Bias: ±25% at LLOQ and ULOQ. Precision (expressed as %CV): CV ≤20%; CV ≤25% at LLOQ and ULOQ. Total error (absolute bias + interassay precision): should not exceed 30%; 40% for LLOQ and ULOQ.
Abbreviations: %CV, coefficient of variation; C5, complement component 5; LLOQ, lower limit of quantitation; QC, quality control; ULOQ, upper limit of quantitation

The Applicant used an ELISA assay to determine serum ravulizumab concentrations. Sample analysis was performed with a gyrolab immunofluorescence assay using CROVALIMAB-000-Bi as the capture reagent and mouse antihuman IgG4 Fc-Alexa Fluor 647 as the detection reagent. The gyrolab immunofluorescence assay was conducted at a constant serum concentration of 10%. This assay was established by the Applicant then the method was transferred to (b) (4) The ELISA methods were validated in compliance with the standards set forth in the FDA guidance for industry *Bioanalytical Method Validation* (May 2018). A summary of the validation parameters are presented in Table 103.

Table 103. Summary Review of Ravulizumab Serum Assays

Parameter	Ravulizumab
Bioanalytical method validation reports	1111115
Validation assay range (ng/mL)	3725 to 62500
QCs (ng/mL)	10000, 20000, and 48000
Interday precision (% CV)	≤8.7
Interday accuracy (% bias)	1.0 to 5.9
Interday total error (%)	≤9.9
Intraday precision (% CV)	≤16.6
Intraday accuracy (% bias)	-6.8 to 12.9

Parameter	Ravulizumab
Intraday total error (%)	≤26.2
Reference standard	2535207
Specificity	No interfering peaks were observed in blank serum samples.
Freeze/thaw stability	6 freeze (-20/-80°C)-thaw (room temperature) cycles
Total error (absolute bias + interassay precision)	6.6 to 28.5%
Interference	There was no significant response observed in the matrix blank
Dilution Linearity	Maximum validated dilution factor: 1 in 100
Prozone	The absence of a hook effect was demonstrated up to a concentration of 500000 ng/mL.
Stock stability	171 days at -80°C
Bench-top stability	20 hours at room temperature in human serum
Freeze/Thaw stability	5 cycles at -20°C and -70°C
Processed stability	24.5 hours at 2-8°C and 25 hours at ambient temperature
Long-term storage stability	76 days at -20°C and -70°C

Source: Validation report 1111115.
Note: Target specifications: Accuracy (expressed as %Bias): Bias: ±20%. Bias: ±25% at LLOQ and ULOQ. Precision (expressed as %CV): CV ≤20%; CV ≤25% at LLOQ and ULOQ. Total error (absolute bias + interassay precision): should not exceed 30%; 40% for LLOQ and ULOQ.
Abbreviations: %CV, coefficient of variation; C5, complement component 5; LLOQ, lower limit of quantitation; QC, quality control; ULOQ, upper limit of quantitation

Bioanalytical Performance for Crovalimab

Study COMPOSER (Validation Report 1092728)

Part 1

A total of 247 samples were received at (b) (4) between November 21, 2016, and April 27, 2017, and valid results were obtained for 149 samples crovalimab. The remaining 98 samples were placebos and did not require analysis. Part 1 of the study was conducted in 12 valid assay runs (including 2 incurred sample reproducibility (ISR) runs). In total, 7 runs were rejected. Runs 03, 07, 08, 10, 11, 12, and 13 were rejected as the quality control samples did not meet acceptance criteria. For failed runs, the Applicant repeated the runs with newly prepared calibrators and QCs, as recommended by the FDA guidance for industry *Bioanalytical Method Validation* (May 2018). The runs were repeated successfully with the observed accuracy (expressed as %Bias) and precision (expressed as %CV) as -10 to -5.1 and 8.8 to 15.3, respectively (the required variability is within ±20% of nominal concentrations; except ±25% at lower limit of quantification (LLOQ) and upper limit of quantification (ULOQ)). A total of 21 of the study samples were selected for ISR. ISR was considered acceptable if two-thirds of the ISR samples show a variability of less than 30% of the mean, based on the recommendation from the FDA guidance for industry *Bioanalytical Method Validation* (May 2018). In the present study, 19 out 21(90.5%) ISR samples had variability less than 30% of the mean, which met the requirement. All 149 study samples received were analyzed, and had final analytical results generated within a period of 74 days from sample collection. Hence, the analysis of each individual sample was completed within the validated period of long-term frozen storage stability of 191 days at <-50°C. Sample analysis was conducted with a maximum number of 9 freeze and thaw cycles for an individual sample. The maximum number of freeze and thaw cycles validated was 12. Sample analysis was conducted within the bench top stability of 14.71 hours. This is within the validated stability parameters of 48 hours at <-50°C.

Parts 2, 3, and 4

A total of 939 samples were received at [redacted] between June 28, 2017, to February 12, 2020. This consisted of 308 samples for Part 2, 420 samples for Part 3, and 210 samples for Part 4. Valid results were obtained for 938 samples. Failed runs 101 and 109 consisted of long-term stability assessments. For failed runs, the Applicant repeated the runs with newly prepared calibrators and QCs, as recommended by the FDA guidance for industry *Bioanalytical Method Validation* (May 2018). The runs were repeated successfully with the observed accuracy (expressed as %Bias) and precision (expressed as %CV) as -3.3 to 6.6 and 9.7 to 14.5, respectively (the required variability is within ±20% of nominal concentrations; except ±25% at LLOQ and ULOQ). A total of 104 of the study samples from Part 2 to Part 4 have been selected for ISR (36 samples from Part 2, 49 samples from Part 3, and 19 samples from Part 4). In the present study, 87 out of 104 (83.7%) ISR samples met the acceptance criteria (the determined variability is less than 30% of the mean, based on the recommendation from the FDA guidance for industry *Bioanalytical Method Validation* (May 2018)). A total of 936 samples were analyzed within a period of 176 days from sample collection. Hence, the analysis of these individual samples was completed within the validated period of long-term frozen storage stability of 191 days at <-50°C. Sample analysis was conducted with a maximum number of 8 freeze and thaw cycles for an individual sample. The maximum number of freeze and thaw cycles validated was 12. Sample analysis was conducted within the bench top stability of 29.57 hours. This is within the validated stability parameters of 48 hours at <-50°C.

Study COMMODORE-2 (Validation Reports 1105832 and 1100943)

The concentrations of crovalimab were determined in a total of 1713 human serum samples obtained from clinical study COMMODORE-2. The entire run was conducted in 86 valid assay runs. A total of 10 runs were rejected. Runs 40, 43, 50, 77, 83, 87, and 90 were rejected, because the quality control samples did not meet the acceptance criteria. Runs 63 to 64 were rejected due to a deviation. For failed runs, the Applicant repeated the runs with newly prepared calibrators and QCs, as recommended by the FDA guidance for industry *Bioanalytical Method Validation* (May 2018). The runs were repeated successfully with the observed accuracy (expressed as %Bias) and precision (expressed as %CV) as -0.5 to 0.5 and 0.9 to 2.8, respectively (the required variability is within ±20% of nominal concentrations; except ±25% at LLOQ and ULOQ). A total of 132 (7.7%) of 1713 study samples were selected for ISR, of which 106 (80.3%) samples had variability less than 30% for crovalimab, which met the requirement as at least two-thirds of the ISR samples show a variability of less than 30% of the mean, based on the recommendation from the FDA guidance for industry *Bioanalytical Method Validation* (May 2018). All samples requiring analysis were analyzed, and final analytical results were generated within 518 days after collection. Analysis of individual samples were completed within the validated period of ambient temperature stability and long-term frozen storage stability at -70°C. Analysis of each individual sample was completed within the validated number of 5 freeze and thaw cycles.

Study COMMODORE-3 (Validation Report 1105832)

A total of 672 human serum samples obtained from Study COMMODORE-3 were measured. A total of 26 analytical runs were performed including sample analysis, re-assay, ISR testing, and qualification runs. All analytical runs met the acceptance criteria except SB08. For SB08, the Applicant repeated the run with newly prepared calibrators and QCs, as recommended by the

FDA guidance for industry *Bioanalytical Method Validation* (May 2018). The runs were repeated successfully with the observed accuracy (expressed as %Bias) and precision (expressed as %CV) meeting the acceptance criteria (the required variability is within ±20% of nominal concentrations; except ±25% at LLOQ and ULOQ). The interassay precision of the back-calculated concentrations from reported analytical runs was less than or equal to 2.9% for the useable range of the curve (50.0 ng/mL to 3200 ng/mL). The interassay %Bias of the back-calculated concentrations within this range varied between -0.9 and 1.3. ISR was performed on 70 samples. There were 3 samples that exhibited poor reproducibility and were classified as failures. Overall, 95.7% met the required criteria (ISR was considered acceptable if two-thirds of the ISR samples show a variability of less than 30% of the mean, based on the recommendation from the FDA guidance for industry *Bioanalytical Method Validation* (May 2018)), indicating that the method generated reproducible results and was fit for purpose. All samples were analyzed within the above established storage stability duration, as well as the established benchtop and freezer thaw stability.

Study COMMODORE-1 (Validation Report 1100943)

The concentrations of crovalimab were determined in a total of 1651 human serum samples, obtained from clinical study COMMODORE-1. Sample analysis was performed with a gyrolab immunofluorescence assay using CROVALIMAB-000-Bi as the capture reagent and mAb < C5>M-lgG-Alexa647 as the detection reagent. The gyrolab immunofluorescence assay was conducted at a constant serum concentration of 10%. The entire run was conducted in 78 valid assay runs. Six runs were rejected and repeated. The 6 runs were rejected because the quality control samples did not meet the acceptance criteria. For failed runs, the Applicant repeated the runs with newly prepared calibrators and QCs, as recommended by the FDA guidance for industry *Bioanalytical Method Validation* (May 2018). The runs were repeated successfully with the observed accuracy (expressed as %Bias) and precision (expressed as %CV) as 1.3 to 3.6 and 5.9 to 10.1, respectively (the required variability is within ±20% of nominal concentrations; except ±25% at LLOQ and ULOQ). A total of 135 (8.2%) of 1651 study samples were selected for ISR, of which 107 (79.3%) had variability less than 30% of the mean for crovalimab, which met the ISR recommendation from the FDA guidance for industry *Bioanalytical Method Validation* (May 2018) as at least two-thirds of the ISR samples show a variability of less than 30%. All samples requiring analysis were analyzed, and final analytical results generated within 734 days after collection. Analysis of individual samples were completed within the validated period of ambient temperature stability and long-term frozen storage stability at -70°C. Analysis of each individual sample was completed within the validated number of 5 freeze and thaw cycles.

Bioanalytical Performance for Eculizumab

Study COMMODORE-1 (Validation Report 1120438)

The concentrations of eculizumab were determined in a total of 456 human serum samples, obtained from clinical study COMMODORE-1. The assay was performed at (b) (4) The entire run was conducted in 28 valid assay runs. Two runs were rejected. For failed runs, the Applicant repeated the runs with newly prepared calibrators and QCs, as recommended by the FDA guidance for industry *Bioanalytical Method Validation* (May 2018). The runs were repeated successfully with the observed accuracy (expressed as

%Bias) and precision (expressed as %CV) meeting the acceptance criteria (the required variability is within ±20% of nominal concentrations; except ±25% at LLOQ and ULOQ). The calibration range was between 3725 to 62500 ng/mL. The LLOQ is 3725 ng/mL. The observed accuracy (expressed as %Bias) and precision (expressed as %CV) are -0.8 to 0.7 and 1.1 to 2.5, respectively. A total of 47 (10.3%) of 456 study samples were selected for ISR, and all of these ISR samples had variability less than 30% for eculizumab, which met the ISR recommendation from the FDA guidance for industry *Bioanalytical Method Validation* (May 2018) as at least two-thirds of the ISR samples show a variability of less than 30% of the mean. All samples requiring analysis were analyzed, and final analytical results generated within 518 days after collection. Study samples were analyzed within the proven room temperature storage stability of 24 hours. Analysis of individual samples was completed within the validated period of long-term frozen storage stability at -70°C. Analysis of each individual sample was completed within the validated number of 5 freeze and thaw cycles.

Study COMMODORE-2 (Validation Report 1105837)

The concentrations of eculizumab were determined in a total of 425 human serum samples, obtained from clinical study COMMODORE-2. The assay was performed at (b) (4) The entire run was conducted in 21 valid assay runs. Two runs were rejected and repeated. Run 20a was rejected due to an observed signal in the blank sample, while Run 3b was rejected because the QC samples did not meet the acceptance criteria. For failed runs, the Applicant repeated the runs with newly prepared calibrators and QCs, as recommended by the FDA guidance for industry *Bioanalytical Method Validation* (May 2018). The runs were repeated successfully with the observed accuracy (expressed as %Bias) and precision (expressed as %CV) meeting the acceptance criteria (the required variability is within ±20% of nominal concentrations; except ±25% at LLOQ and ULOQ). The calibration range was between 3725 to 62500 ng/mL. The LLOQ is 3725 ng/mL. A total of 53 (12.5%) of 425 study samples were selected for ISR, and 46 (86.8%) of these ISR samples had variability less than 30% for eculizumab, which met the ISR recommendation from the FDA guidance for industry *Bioanalytical Method Validation* (May 2018) as at least two-thirds of the ISR samples show a variability of less than 30% of the mean. All samples requiring analysis were analyzed, and final analytical results generated within 619 days after collection. Study samples were analyzed within the proven room temperature storage stability of 24 hours. Analysis of individual samples was completed within the validated period of long-term frozen storage stability at -70°C. Analysis of each individual sample was completed within the validated number of 5 freeze and thaw cycles.

Bioanalytical Performance for Ravulizumab

Study COMMODORE-1 (Validation Report 1111115)

The concentrations of ravulizumab were determined in a total of 20 human serum samples obtained from clinical study COMMODORE-1. Sample analysis was performed with a gyrolab immunofluorescence assay using CROVALIMAB-000-Bi as the capture reagent and mAb < C5>M-lgG-Alexa647 as the detection reagent. The gyrolab immunofluorescence assay was conducted at a constant serum concentration of 10%. The entire run was conducted in 8 valid assay runs. One run was rejected, and the repeated run, 7b, was rejected due to an observed signal in the blank sample. For failed runs, the Applicant repeated the runs with newly prepared

calibrators and QCs, as recommended by the FDA guidance for industry *Bioanalytical Method Validation* (May 2018). The runs were repeated successfully with the observed accuracy (expressed as %Bias) and precision (expressed as %CV) meeting the acceptance criteria (the required variability is within ±20% of nominal concentrations; except ±25% at LLOQ and ULOQ). The calibration range was between 3,725 to 62,500 ng/mL. The LLOQ is 3,725 ng/mL. Three (15.8%) of 19 study samples were selected for ISR, and all 3 ISR samples had variability less than 30% for ravulizumab, which met the ISR recommendation from the FDA guidance for industry *Bioanalytical Method Validation* (May 2018), as at least two-thirds of the ISR samples show a variability of less than 30% of the mean. All samples requiring analysis were analyzed, and final analytical results generated within 327 days after collection. Analysis of individual samples was completed within the validated period of long-term frozen storage stability at -70°C. Study samples were analyzed within the proven room temperature storage stability of 20 hours. Analysis of each individual sample was completed within the validated number of 5 freeze and thaw cycles.

Pharmacodynamic Analysis

Study COMMODORE-2

The concentrations of free C5 were determined in a total of 1692 human serum samples, obtained from clinical study COMMODORE-2 at (b) (4) Sample analysis was performed with a gyrolab immunofluorescence assay using CROVALIMAB-000-Bi as the capture reagent and mAb < C5>M-lgG-Alexa647 as the detection reagent. The gyrolab immunofluorescence assay was conducted at a constant serum concentration of 100%. The calibration range was between 2.5 to 3000 ng/mL. The LLOQ is 2.5 ng/mL. Study samples were analyzed within the validated frozen storage stability of 575 days, with the exception of one sample (634 days). Study samples were analyzed within the proven room temperature storage stability of 30.5 hours in a total of 57 analytical runs. Study samples were analyzed within the number of 5 validated free and thaw cycles. A total of 55 out of 57 runs met the acceptance criteria. Two runs were rejected. For failed runs, the Applicant repeated the runs with newly prepared calibrators and QCs, as recommended by the FDA guidance for industry *Bioanalytical Method Validation* (May 2018). The runs were repeated successfully with the observed accuracy (expressed as %Bias) and precision (expressed as %CV) meeting the acceptance criteria (the required variability is within ±20% of nominal concentrations; except ±25% at LLOQ and ULOQ). Of the total 1692 human serum samples, 225 (13.3%) were re-assayed.

The concentrations of free C5 were determined in a total of 908 human serum samples, obtained from clinical study COMMODORE-2 at (b) (4) . Sample analysis was performed with a gyrolab immunofluorescence assay. The gyrolab immunofluorescence assay was conducted at a constant serum concentration of 100%. The calibration range was between 2.5 to 3000 ng/mL. The LLOQ is 2.5 ng/mL. Study samples were analyzed within the validated frozen storage stability of 664 days, within the proven room temperature storage stability of 25 hours, and within the number of 6 validated freeze and thaw cycles. A total of 34 out of 55 runs met the acceptance criteria, 21 runs were rejected. For failed runs, the Applicant repeated the runs with newly prepared calibrators and QCs, as recommended by the FDA guidance for industry *Bioanalytical Method Validation* (May 2018). The runs were repeated successfully with the observed accuracy (expressed as %Bias) and

precision (expressed as %CV) meeting the acceptance criteria (the required variability is within ±20% of nominal concentrations; except ±25% at LLOQ and ULOQ). Of the total 908 human serum samples, 166 (18.3%) were re-assayed.

The concentrations of total C5 were determined in a total of 1112 human serum samples, obtained from clinical study COMMODORE-2 at (b) (4) Sample analysis was performed with a quantitative ELISA using rabbit anti-hC5 mAb as the capture reagent and mouse anti-SKY59 mAb along with peroxidase-conjugated AffiniPure goat antimouse IgG, Fcγ subclass 1 specific as detection reagents. The calibration range was between 3.25 to 208 µg/mL. The LLOQ is 3.25 µg/mL. Study samples were analyzed within the validated frozen storage stability of 498 days, within the proven room temperature storage stability of 24 hours, and within the number of 6 validated freeze and thaw cycles. A total of 34 out of 45 runs met the acceptance criteria, 11 runs were rejected. For failed runs, the Applicant repeated the runs with newly prepared calibrators and QCs, as recommended by the FDA guidance for industry *Bioanalytical Method Validation* (May 2018). The runs were repeated successfully with the observed accuracy (expressed as %Bias) and precision (expressed as %CV) meeting the acceptance criteria (the required variability is within ±20% of nominal concentrations; except ±25% at LLOQ and ULOQ). Of the total 1112 human serum samples, 6 (0.5%) were re-assayed.

The concentrations of DTDCs were determined in a total of 3120 samples (390 human serum samples×8 fractions) obtained from clinical study COMMODORE-2 at (b) (4) Sample analysis was performed with a quantitative ELISA. The calibration range was between 0.0625 to 10000 ng/mL. The CV% and RE% for the QC samples met the acceptance criteria (accuracy: ±20%, the accuracy for at least two-thirds of the QC samples, including at least half at each concentration level should meet the above criteria). No issues were identified with reinjected data or reanalysis values.

Study COMMODORE-1

The concentrations of free C5 were determined in a total of 1640 human serum samples, obtained from clinical study COMMODORE-1 at (b) (4) Sample analysis was performed with a gyrolab immunofluorescence assay using CROVALIMAB-000-Bi as the capture reagent and mAb < C5>M-lgG-Alexa647 as the detection reagent. The gyrolab immunofluorescence assay was conducted at a constant serum concentration of 100%. The calibration range was between 2.5 to 3000 ng/mL. The LLOQ is 2.5 ng/mL. Study samples were analyzed within the validated frozen storage stability of 575 days. Study samples were analyzed within the proven room temperature storage stability of 30.5 hours in a total of 69 analytical runs. Study samples were analyzed within the number of 5 validated free/thaw cycles. A total of 57 out of 69 runs met the acceptance criteria, 12 runs were rejected. For failed runs, the Applicant repeated the runs with newly prepared calibrators and QCs, as recommended by the FDA guidance for industry *Bioanalytical Method Validation* (May 2018). The runs were repeated successfully with the observed accuracy (expressed as %Bias) and precision (expressed as %CV) meeting the acceptance criteria (the required variability is within ±20% of nominal concentrations; except ±25% at LLOQ and ULOQ). Of the total 1680 human serum samples, 219 (13.0%) were re-assayed.

The concentrations of total C5 were determined in a total of 1804 human serum samples, obtained from clinical study COMMODORE-1 at (b) (4)

(b) (4). Sample analysis was performed with a quantitative ELISA using rabbit anti-hC5 mAb as the capture reagent and mouse anti-SKY59 mAb along with peroxidase-conjugated AffiniPure goat antimouse IgG, Fcγ subclass 1 specific as detection reagents. The ELISA assay was conducted at a constant serum concentration of 0.154%. The calibration range was between 6.5 to 208 µg/mL. The LLOQ is 7.8 µg/mL. Study samples were analyzed within the validated frozen storage stability of 698 days, within the proven room temperature storage stability of 24 hours, and within the number of 5 validated freeze and thaw cycles. A total of 58 out of 70 runs met the acceptance criteria, 12 runs were rejected. For failed runs, the Applicant repeated the runs with newly prepared calibrators and QCs, as recommended by the FDA guidance for industry *Bioanalytical Method Validation* (May 2018). The runs were repeated successfully with the observed accuracy (expressed as %Bias) and precision (expressed as %CV) meeting the acceptance criteria (the required variability is within ±20% of nominal concentrations; except ±25% at LLOQ and ULOQ). Of the total 1804 human serum samples, 28 (1.6%) were re-assayed.

The concentrations of DTDCs were determined in a total of 10672 samples (1334 human serum samples×8 fractions), obtained from clinical study COMMODORE-1 at (b) (4) Sample analysis was performed with a quantitative ELISA. The calibration range was between 0.0625 to 10,000 ng/mL. The CV% and RE% for the QC samples met the acceptance criteria (accuracy: ±20%, the accuracy for at least two-thirds of the QC samples, including at least half at each concentration level should meet the above criteria). No issues were identified with reinjected data or reanalysis values.

Study COMPOSER

The concentrations of free C5 were determined in a total of 1078 human serum samples, obtained from clinical study COMPOSER at (b) (4) Sample analysis was performed using a qualified electrochemiluminescence method. Crovalimab is coated on the bottom of the MULTI-ARRAY 96-well plate. Nonspecific binding sites were then blocked. Quantified Recombinant Human C5 was used to prepare standards and QCs were then added to designated sample wells. Study samples were also added to designated wells. Sulfo-tagged anti-C5 antibody was added to the plate after washing. Read buffer containing tripropylamine was added, and the sTag anti-C5 antibody produced a chemiluminescent signal when an electrical voltage was applied. The concentration of free human C5 in samples was then back-calculated from a calibration curve. The calibration range was between 0.195 to 800 ng/mL. All but 4 study samples were analyzed within the validated frozen storage stability of 247 and 422 days. All study samples were analyzed within the proven room temperature storage stability of 31.6 hours in a total of 110 analytical runs. Study samples were analyzed within the number of 20 validated freeze and thaw cycles. A total of 56 out of 110 runs met the acceptance criteria, 54 runs were rejected. For failed runs, the Applicant repeated the runs with newly prepared calibrators and QCs, as recommended by the FDA guidance for industry *Bioanalytical Method Validation* (May 2018). The runs were repeated successfully with the observed accuracy (expressed as %Bias) and precision (expressed as %CV) meeting the acceptance criteria (the required variability is within ±20% of nominal concentrations; except ±25% at LLOQ and ULOQ). Of the total 1680 human serum samples, 111 (6.6%) were re-assayed.

The concentrations of total hC5 were determined in a total of 1074 human serum samples, obtained from clinical study COMPOSER at (b) (4) Sample analysis was performed with a quantitative ELISA using rabbit anti-hC5 mAb as the capture reagent and mouse anti-SKY59 mAb along with peroxidase-conjugated AffiniPure goat antimouse IgG, Fcγ subclass 1 specific as detection reagents. The ELISA assay was conducted at a constant serum concentration of 0.154%. The calibration range was between 7.8 to 208 µg/mL. The LLOQ is 7.8 µg/mL. All but one study samples were analyzed within the validated frozen storage stability of 367 days. Study samples were analyzed within the proven room temperature storage stability of 32 hours, and within the number of 20 validated freeze and thaw cycles. A total of 107 out of 158 runs met the acceptance criteria, 51 runs were rejected. For failed runs, the Applicant repeated the runs with newly prepared calibrators and QCs, as recommended by the FDA guidance for industry *Bioanalytical Method Validation* (May 2018). The runs were repeated successfully with the observed accuracy (expressed as %Bias) and precision (expressed as %CV) meeting the acceptance criteria (the required variability is within ±20% of nominal concentrations; except ±25% at LLOQ and ULOQ). Of the total 1074 human serum samples, 167 (15.5%) were re-assayed.

Study COMMODORE-3

The concentrations of free C5 were determined in a total of 576 human serum samples, obtained from clinical study COMMODORE-3 at (b) (4) . Sample analysis was performed with a gyrolab immunofluorescence assay using CROVALIMAB-000-Bi as the capture reagent and mAb < C5>M-lgG-Alexa647 as the detection reagent. The gyrolab immunofluorescence assay was conducted at a constant serum concentration of 100%. The calibration range was between 2.5 to 3000 ng/mL. The LLOQ is 2.5 ng/mL. Study samples were analyzed within the validated frozen storage stability of 664 days, within the proven room temperature storage stability of 25 hours in a total of 46 analytical runs, and within the number of 6 validated freeze and thaw cycles. A total of 37 out of 46 runs met the acceptance criteria, 9 runs were rejected. For failed runs, the Applicant repeated the runs with newly prepared calibrators and QCs, as recommended by the FDA guidance for industry *Bioanalytical Method Validation* (May 2018). The runs were repeated successfully with the observed accuracy (expressed as %Bias) and precision (expressed as %CV) meeting the acceptance criteria (the required variability is within ±20% of nominal concentrations; except ±25% at LLOQ and ULOQ). Of the total 576 human serum samples, 133 (23.1%) were re-assayed.

The concentrations of total C5 were determined in a total of 576 human serum samples, obtained from clinical study COMMODORE-3 at (b) (4) . Sample analysis was performed with a quantitative ELISA using rabbit anti-hC5 mAb as the capture reagent and mouse anti-SKY59 mAb along with peroxidase-conjugated AffiniPure goat antimouse IgG, Fcγ subclass 1 specific as detection reagents. The ELISA assay was conducted at a constant serum concentration of 0.154%. The calibration range was between 3.25 to 208 µg/mL. The LLOQ is 3.25 µg/mL. Study samples were analyzed within the validated frozen storage stability of 498 days, within the proven room temperature storage stability of 24 hours, and within the number of 6 validated freeze and thaw cycles. A total of 23 out of 31 runs met the acceptance criteria, 8 runs were rejected. For failed runs, the Applicant repeated the runs with newly prepared calibrators and QCs, as recommended by the FDA guidance for industry *Bioanalytical Method Validation* (May 2018). The runs were repeated

successfully with the observed accuracy (expressed as %Bias) and precision (expressed as %CV) meeting the acceptance criteria (the required variability is within ±20% of nominal concentrations; except ±25% at LLOQ and ULOQ). Of the total 576 human serum samples, 14 (1.6%) were re-assayed.

14.4. Immunogenicity Assessment—Impact of PK/PD, Efficacy, and Safety

Summary of Clinical Studies

Immunogenicity of crovalimab was evaluated in one Phase 1/2 study, COMPOSER; one Phase 3 pivotal study, COMMODORE-2; and two Phase 3 supportive studies, COMMODORE-1 and COMMODORE-3. The information proposed for the label is derived from the Phase 3 studies, COMMODORE-1, COMMODORE-2, and COMMODORE-3 since these studies were conducted in the intended population with the recommended dosing regimen. The submitted clinical study results included subjects with data reported up to 24 weeks of treatment. Table 104 contains:

1. The information for COMMODORE-1, COMMODORE-2, and COMMODORE-3 assessing immunogenicity up to 24 weeks.
2. A high-level summary of study results for PK (trough concentration). Overall study design in terms of treatment duration, sampling time, and size was adequate to assess the ADA impact on PK.

Table 104. Summary of Clinical Study Information and Immunogenicity Incidence

Clinical Study Information	Clinical Study Information			
	COMMODORE-2		COMMODORE-1	COMMODORE-3
Dose regime	Loading dose: 100/1500 mg IV D1W1 followed by 340 mg SC on W2, W3, W4 Maintenance dose: 680/1020 mg SC Q4W for total of 24 weeks			
Treatment duration	24 weeks		24 weeks	24 weeks
Status	Ongoing		Ongoing	Ongoing
Arm	Naïve subjects crovalimab arm	Naïve subjects who received crovalimab after on eculizumab for 24 weeks	Crovalimab or eculizumab switch subjects	Naïve subjects crovalimab
Number of subjects received crovalimab	140	67	117	51
Applicant reported ADA incidence	42/140 (30%)	23/67 (34.3%)	20/117 (17%)	18/51 (35.3%)
Applicant reported NAb incidence	2/42 (4.7%)	0%	Not assessed	Not assessed
FDA calculated ADA incidence	42/140 (30%)	23/67 (34.3%)	20/117 (17%)	18/51 (35.3%)
FDA calculated NAb incidence (among ADA+)	2/42 (4.7%)	2/23 (8.7%)	Not assessed	Not assessed

Clinical Study Information	Clinical Study Information			
	COMMODORE-2		COMMODORE-1	COMMODORE-3
Crovalimab Mean Trough Concentration (Range) (µg/mL)				
FDA's analysis	241 (0.025- 834)	245 (0.025-1830)	226 (0.025-677)	219 (0-489)
FDA analysis Mean (standard deviation)	241 (108.66)	245 (131.15)	226 (112.95)	219 (93.41)

Source: Reviewer analysis of the CSR: Integrated Summary of Immunogenicity.
Abbreviations: ADA, antidrug antibody; CSR, Clinical Study Report; D1W1, Day 1 Week 1; FDA, Food and Drug Administration; IV, intravenous; NAb, neutralizing antibody; Q4W, every four weeks; SC, subcutaneous; W2, Week 2; W3, Week 3; W4, Week 4

Highlights of Key Characteristics of Immunogenicity Assays Relevant to This Review

Table 105 shows several assay characteristics that are relevant for the analysis. Refer to the Office of Product Quality Assessment's review for additional details of the ADA and neutralizing antibody (NAb) assay.

From the clinical pharmacology perspective there is a possibility that some ADAs in COMMODORE-2 and COMMODORE-3 may not have been detected due to drug interference in samples with lowest plasma concentration at a steady state (C_{trough}) values higher than 100 µg/mL (the drug tolerance for the method described in Validation Report 1105833); which was observed in up to 89.7% of samples in COMMODORE-2 and 90% of samples in COMMODORE-3. Similarly, the method described in Validation Report 1100912 has a drug tolerance of 500 µg/mL, and the highest crovalimab concentration observed in study COMMODORE-1 was 667 µg/mL, suggesting that the estimated ADA incidence may also be impacted by the drug interference issue. Taken together, the ADA incidence may have been underestimated.

Table 105. Summary of Key ADA Assay Characteristics Related to Immunogenicity Assessment

Study	COMMODORE-1 and COMMODORE-2	COMMODORE-2 and COMMODORE-3
Validation report number	1100912	1105833
Sample analysis site	[redacted] (b) (4)	
Assay sensitivity	≥8 ng/mL	38.5 ng/mL
Drug tolerance	100 ng of PC was detected in the presence of 500 µg/mL of crovalimab	100 ng of PC was detected in the presence of 100 µg/mL of crovalimab

Source: Reviewer analysis.
Abbreviations: ADA, antidrug antibody; PC, positive control; USA, United States of America

Methods for Evaluating the Effect of Immunogenicity on PK of Crovalimab

To evaluate the impact of immunogenicity on PK, the observed crovalimab concentrations were compared in two groups (ADA+ and ADA-) for subjects with time-matched PK and ADA data using the Immunogenicity Specimen (IS) tool developed in-house. At each timepoint, crovalimab geometric mean concentrations were tabulated for ADA+ and ADA- groups. For the statistical comparisons of concentration data between ADA+ and ADA- groups, the geometric mean ratio of ADA+/ADA- and the corresponding 90% CI are presented in Table 106. The impact of ADA titer on PK of crovalimab was investigated with a PopPK modeling approach (refer to Section 14.5 Pharmacometrics Assessment for details).

Effect of Immunogenicity on PK of Crovalimab – Results

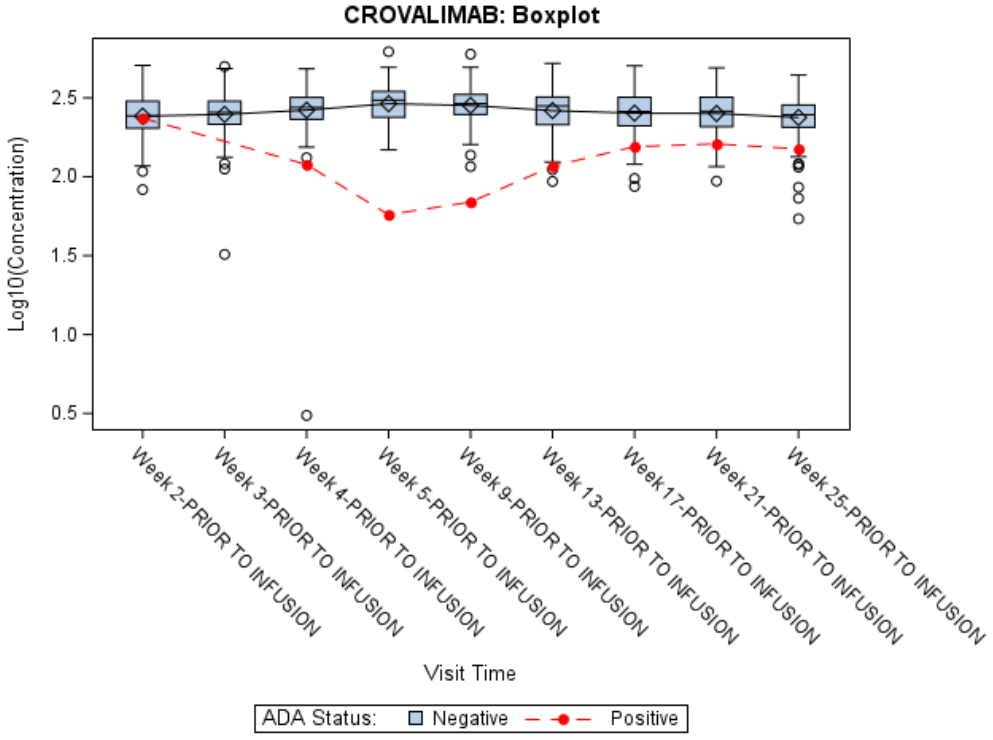
Here, the results of the IS analysis in Studies COMMODORE-1, COMMODORE-2, and COMMODORE-3 are presented (shown in Figure 32, Figure 33, and Figure 34). Table 106, Table 107, and Table 108 summarizes the crovalimab geometric mean concentrations in ADA+ and ADA- subjects during the treatment period. Crovalimab concentrations were lower in ADA-positive subjects in COMMODORE-1, COMMODORE-2, and COMMODORE-3. The geometric mean ratios (ADA+/ADA-) from Week 2 to Week 25 were between 0.09 to 0.52; 0.24 to 0.97; and 0.61 to 0.95 in COMMODORE-1, COMMODORE-2, and COMMODORE-3, respectively.

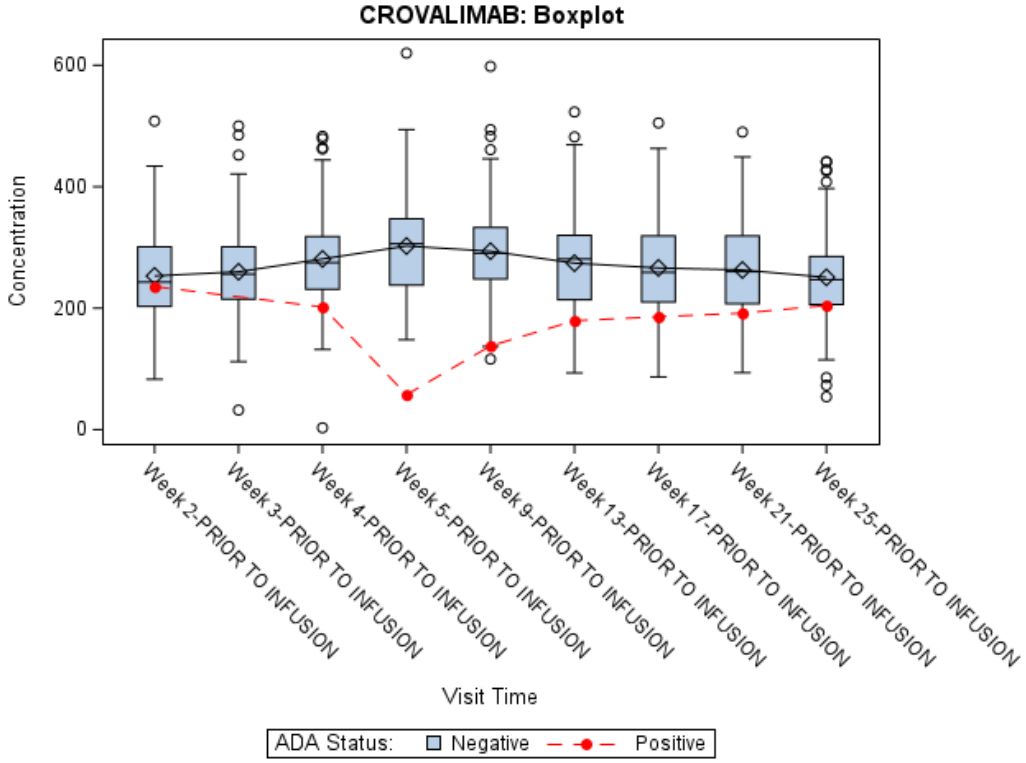
Table 106. Summary of Geometric Mean Concentration by ADA Status at Each Visit in COMMODORE-2

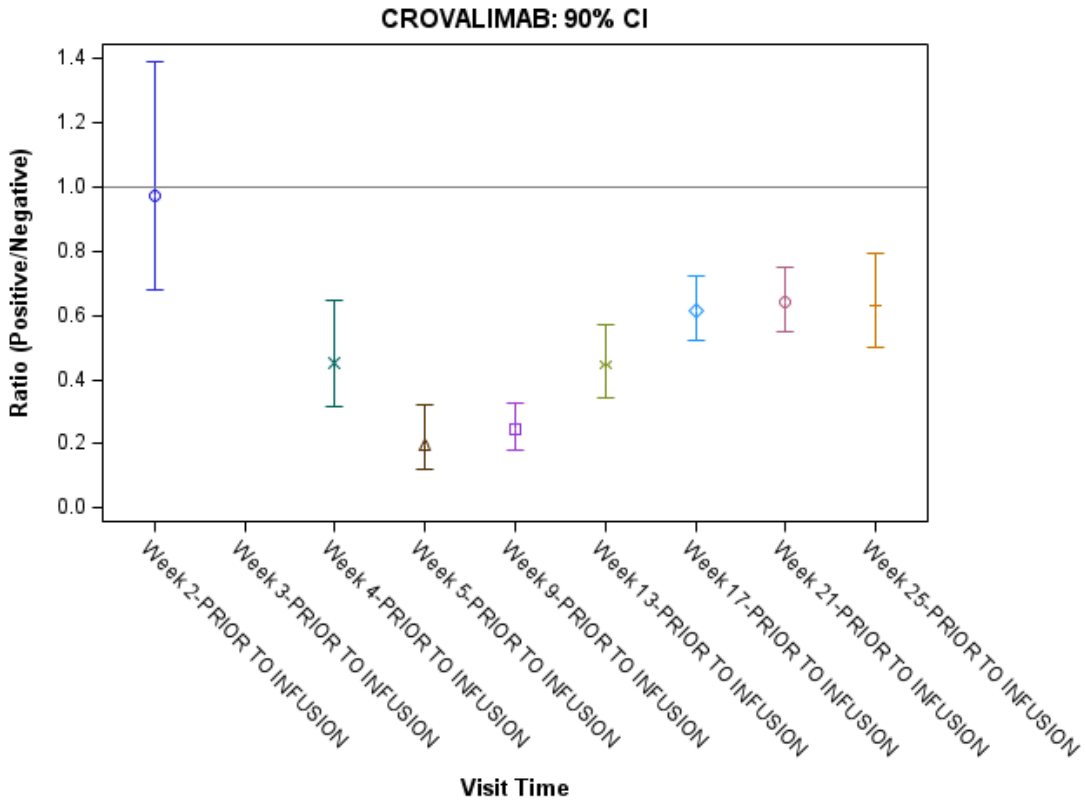
Arm	Treatment Duration (Week)	Total N	Crovalimab Geometric Mean Concentration (µg/mL) ADA+ Group	N	ADA- Group	N	GMR (90%CI) ADA+/ADA-
Crovalimab	2	132	235.50	2	242.23	130	0.97 (0.68,1.39)
	4	134	119.38	5	264.26	129	0.45 (0.31,0.65)
	9	130	69.16	8	282.89	122	0.24 (0.18,0.33)
	13	132	116.60	17	262.39	115	0.44 (0.34,0.57)
	17	130	155.26	25	252.95	105	0.61(0.52,0.72)
	21	127	150.03	27	251.72	100	0.64 (0.55, 0.75)
	25	124	150.03	19	237.62	105	0.63 (0.50, 0.79)

Source: Reviewer analysis.
Abbreviations: ADA, antidrug antibody; CI, confidence interval; GMR, geometric mean ratio; N, number of subjects

Figure 32. Box Plot Analysis of Crovalimab Concentration in Logarithmic (Upper Panel) and Linear Scale (Middle Panel) From ADA-Positive and ADA Negative Samples During the Treatment Period in COMMODORE-2. Bottom Panel: 90% Confidence Interval of the GMR of Drug Concentration at Each Visit







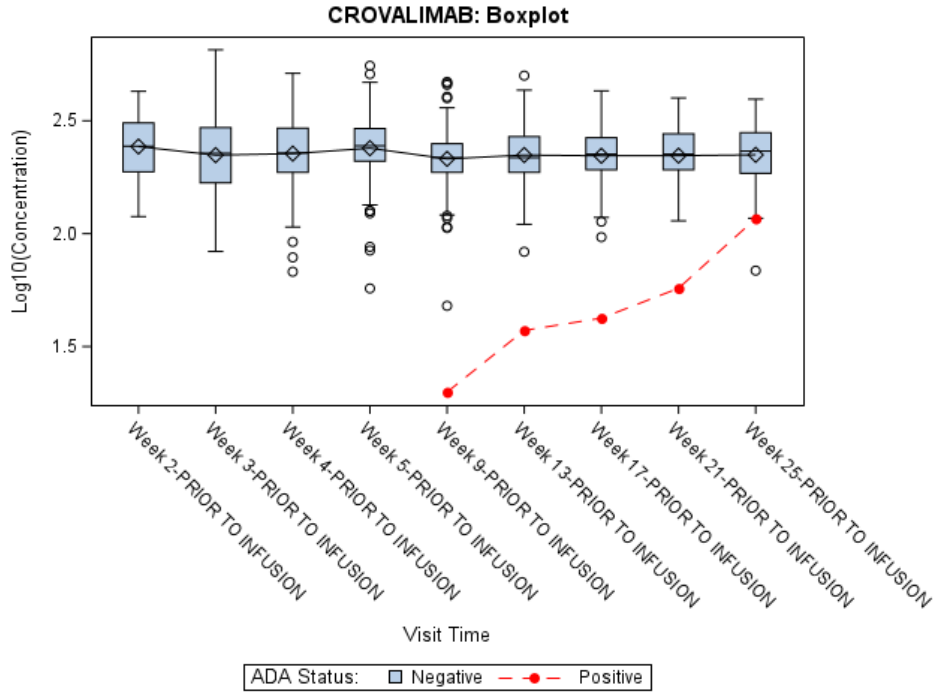
Source: Reviewer analysis.
Abbreviations: ADA, antidrug antibody; CI, confidence interval; GMR, geometric mean ratio

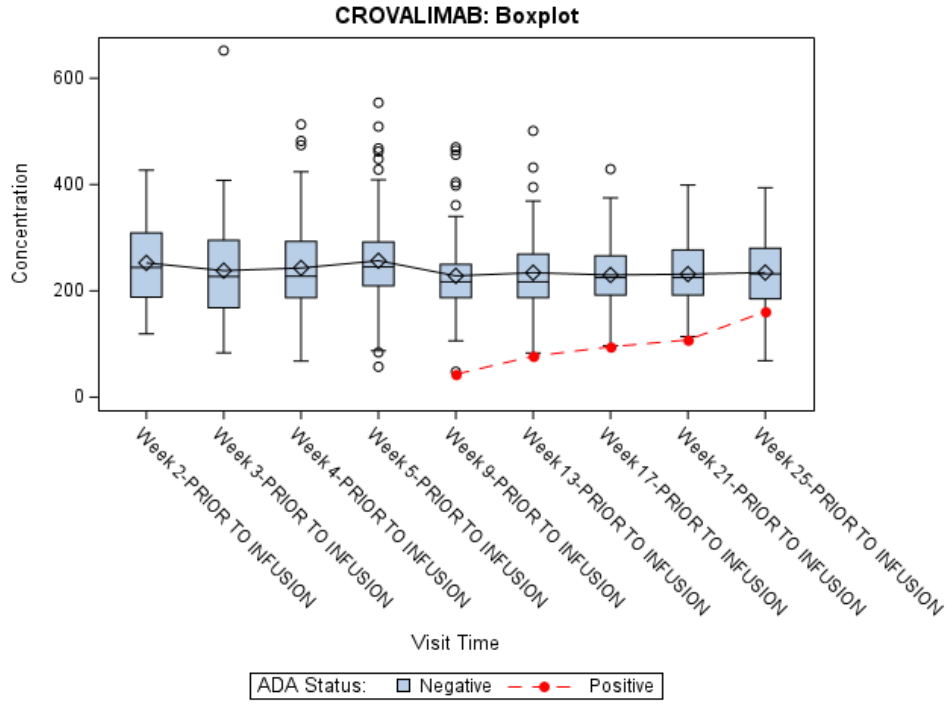
Table 107. Summary of Geometric Mean Concentration by ADA Status at Each Visit in COMMODORE-1

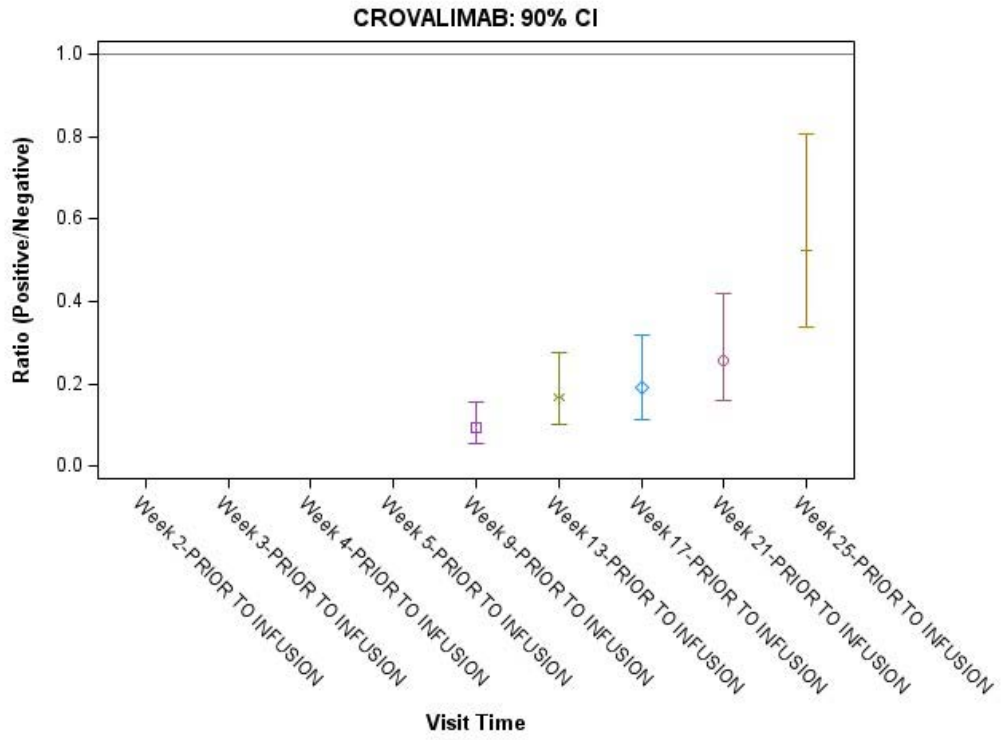
Arm	Treatment Duration (Week)	Total N	Crovalimab Geometric Mean Concentration (µg/mL) ADA+ Group	N	ADA- Group	N	GMR (90%CI) ADA+/ADA-
Crovalimab	9	75	19.87	2	214.35	73	0.09 (0.06, 0.16)
	13	73	37.27	8	222.88	65	0.17 (0.10, 0.27)
	17	69	42.24	10	221.19	59	0.19 (0.11, 0.32)
	21	67	57.27	12	221.53	55	0.26 (0.16, 0.42)
	25	55	116.62	2	223.41	53	0.52 (0.34, 0.81)

Source: Reviewer analysis
Abbreviations: CI, confidence interval; GMR, geometric mean ratio; N, total number of subjects

Figure 33. Box Plot Analysis of Crovalimab Concentration in Logarithmic (Upper Panel) and Linear Scale (Middle Panel) From ADA Positive and ADA Negative Samples During the Treatment Period in COMMODORE-1. Bottom Panel: 90% Confidence Interval of the GMR of Drug Concentration at Each Visit







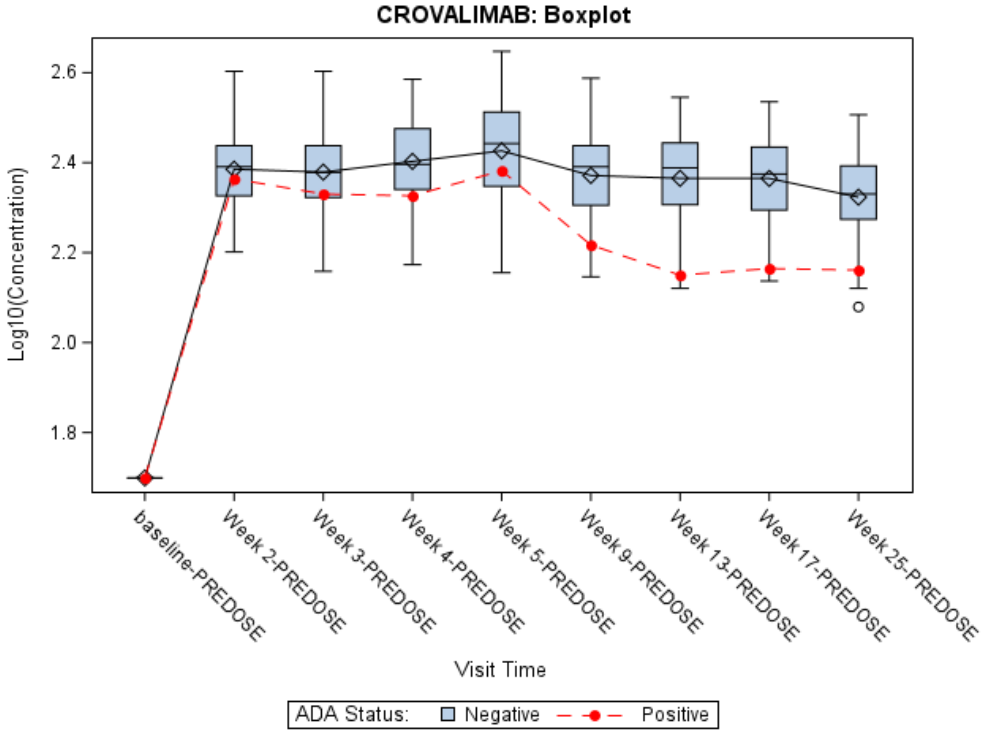
Source: Reviewer analysis
Abbreviations: ADA, antidrug antibody; CI, confidence interval; GMR, geometric mean ratio

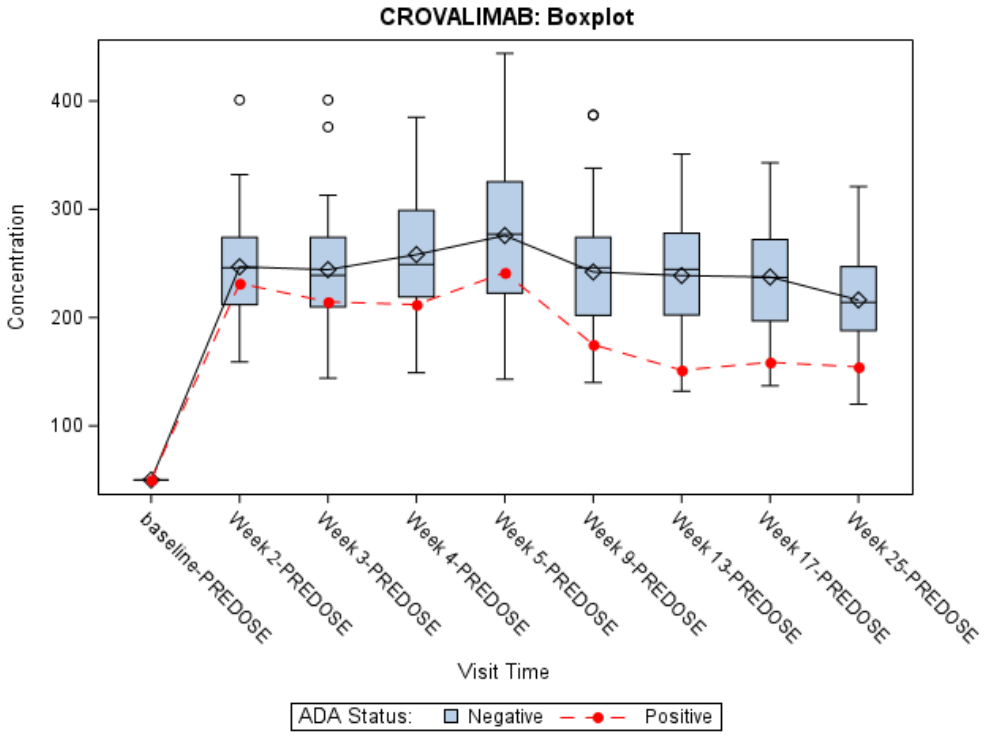
Table 108. Summary of Geometric Mean Concentration by ADA Status at Each Visit in COMMODORE-3

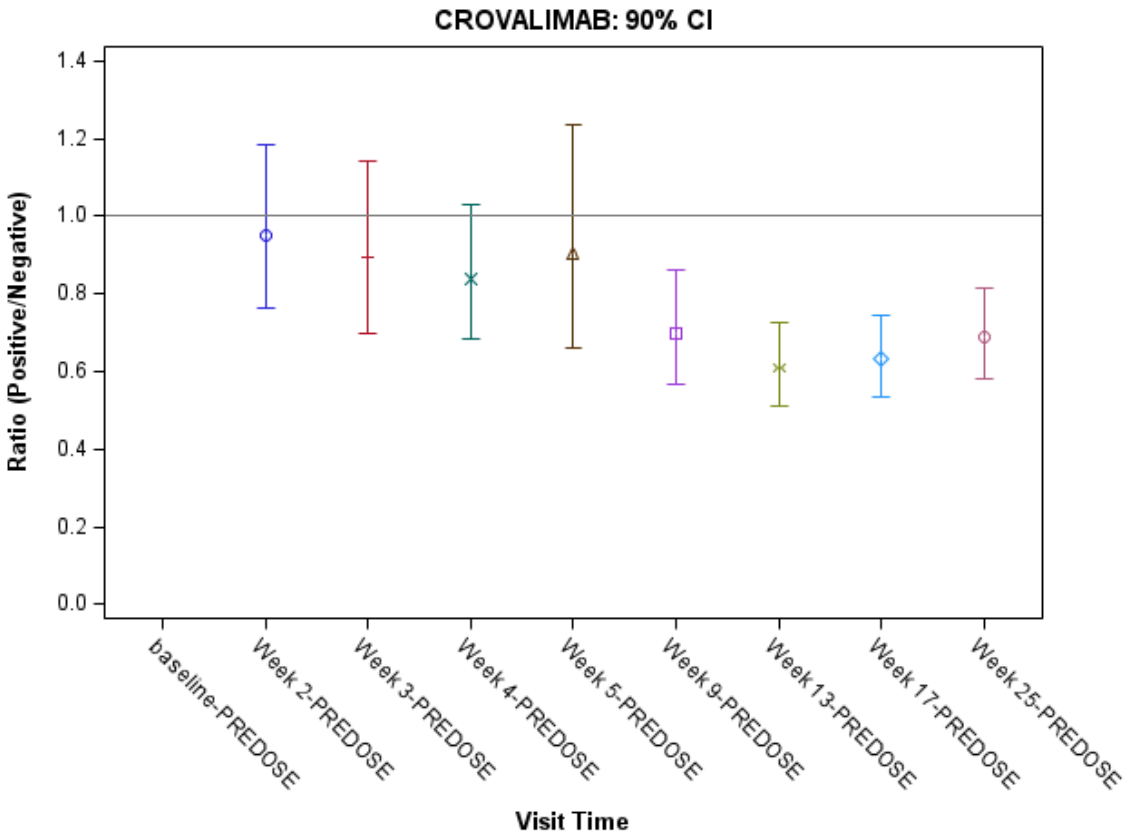
Arm	Treatment Duration (Week)	Total N	Crovalimab Geometric Mean Concentration (µg/mL) ADA+ Group	N	ADA- Group	N	GMR (90%CI) ADA+/ADA-
Crovalimab	2	51	231.11	2	242.88	49	0.95 (0.76,1.18)
	3	51	213.84	2	239.29	49	0.89 (0.70,1.14)
	4	49	211.97	3	252.83	46	0.84 (0.68,1.0)
	5	50	241.10	2	266.83	48	0.90 (0.66, 1.24)
	9	47	164.76	5	235.20	42	0.70 (0.57, 0.86)
	13	47	141.22	11	231.82	36	0.61 (051, 0.72)
	17	44	146.10	16	231.68	28	0.63 (0.53, 0.75
	25	39	144.89	13	210.50	26	0.69 (0.58, 0.82)

Source: Reviewer analysis
Abbreviations: ADA, antidrug antibody; CI, confidence interval; GMR, geometric mean ratio; N, total number of subjects

Figure 34. Box Plot Analysis of Crovalimab Concentration in Logarithmic (Upper Panel) and Linear Scale (Middle Panel) From ADA Positive and ADA Negative Samples During the Treatment Period in COMMODORE-3. Bottom Panel: 90% Confidence Interval of the GMR of Drug Concentration at Each Visit





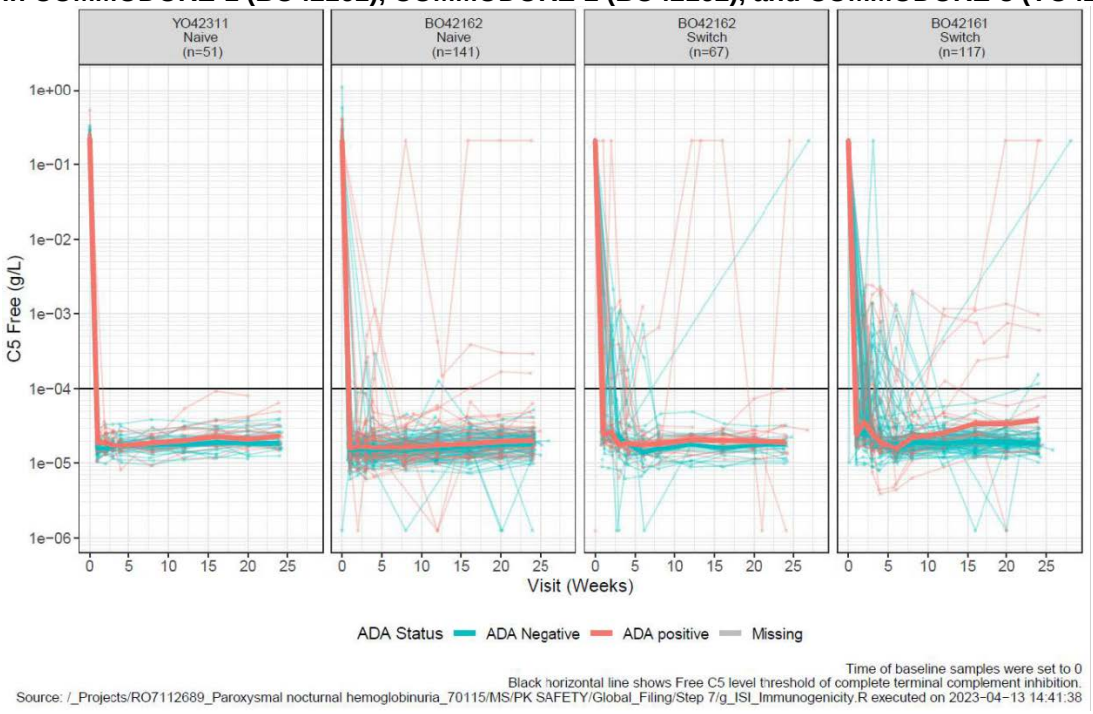


Source: Reviewer analysis
Abbreviations: ADA, antidrug antibody; CI, confidence interval; GMR, geometric mean ratio

The Impact of ADA on the PD of Crovalimab

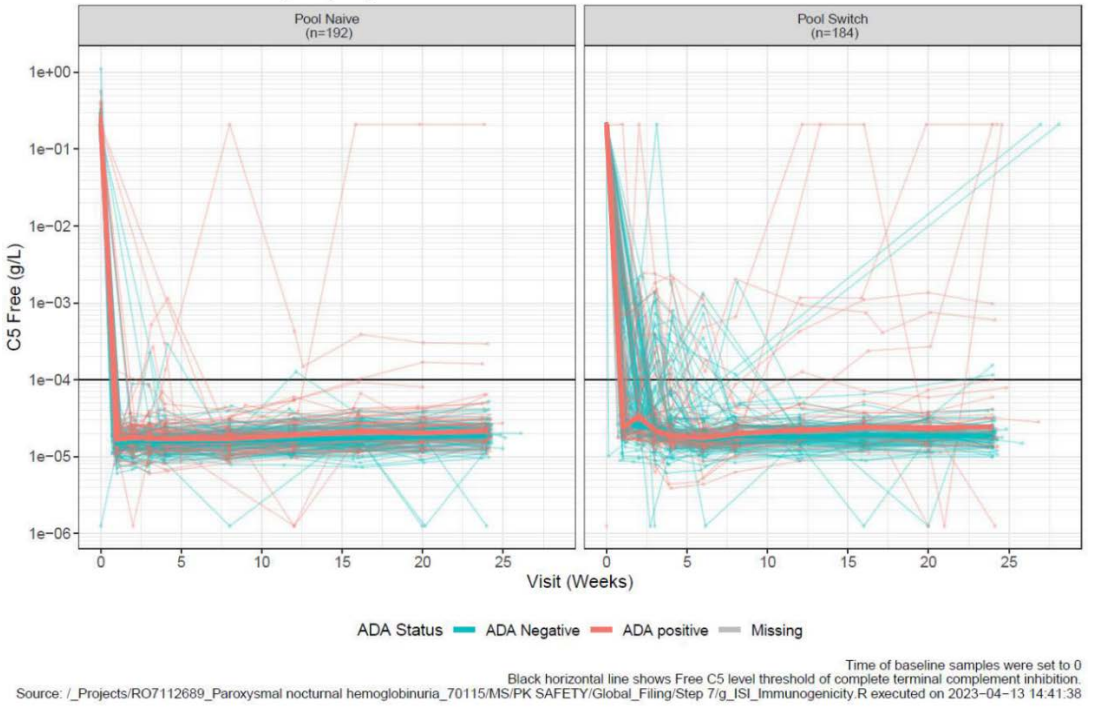
The impact of ADA on the terminal complement activity PD markers, free C5, and CH50 are shown in Figure 35, Figure 36, Figure 37, and Figure 38. It appears that terminal complement inhibition was reduced in some subjects with ADAs. As shown in Table 109, 11 (out of a total of 375, 2.9%) ADA-positive subjects had a loss of exposure and pharmacological activity. Of these 11 subjects, 3 subjects (0.8%) had a partial loss of exposure (crovalimab concentration ≥10 and <100 µg/mL; 1 was a treatment-naïve subject and 2 were switch subjects) and 8 subjects (2.1%) had a complete loss of exposure (crovalimab concentration <10 µg/mL; 2 were treatment-naïve subjects and 6 were switch subjects) across the 3 studies.

Figure 35. Plot of Individual Subject Profiles of Free C5 Over Time (up to Week 25) by ADA Status in COMMODORE-1 (BO42161), COMMODORE-2 (BO42162), and COMMODORE-3 (YO42311)



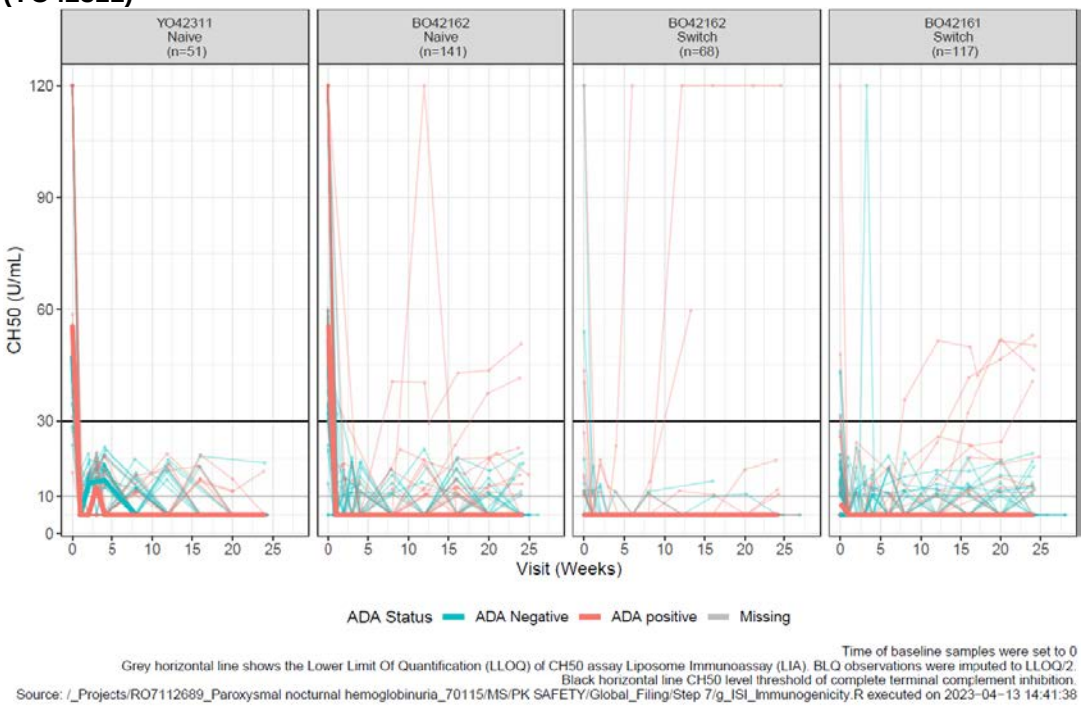
Source: Figure 12, page 45, Integrated Summary of Immunogenicity.
Abbreviations: ADA, antidrug antibody; C5, complement component 5

Figure 36. Plot of Individual Subject Profiles of Free C5 Over Time (up to Week 25) by ADA Status (Treatment-Naïve Versus Switch Subjects)



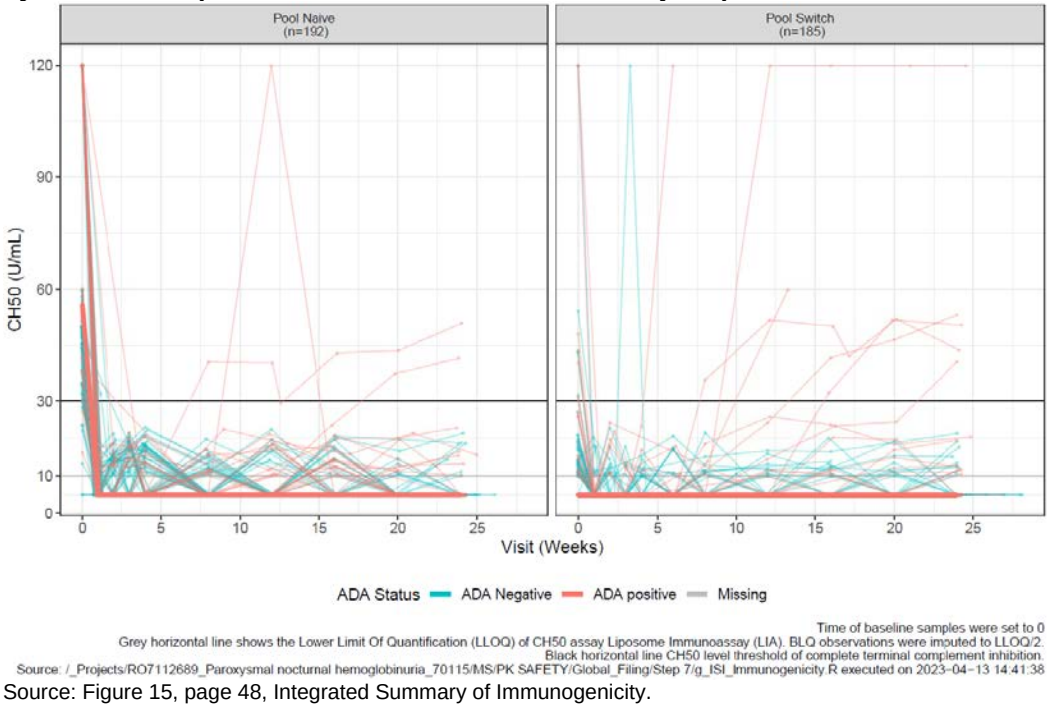
Source: Figure 13, page 46, Integrated Summary of Immunogenicity.
Abbreviations: ADA, antidrug antibody; C5, complement component 5

Figure 37. Plots of Individual Subject Profiles of CH50 Measured by LIA Over Time (up to Week 25) by ADA Status in COMMODORE-1 (BO42161), COMMODORE-2 (BO42162), and COMMODORE-3 (YO42311)



Source: Figure 14, page 47, Integrated Summary of Immunogenicity.
Abbreviations: ADA, antidrug antibody; CH50, terminal complement activity; LIA, liposome immunoassay

Figure 38. Plots of Individual Subject Profiles of CH50 Measured by LIA Over Time (up to Week 25) by ADA Status (Treatment-Naïve Versus Switch Subjects)



Source: Figure 15, page 48, Integrated Summary of Immunogenicity.
Abbreviations: ADA, antidrug antibody; CH50, terminal complement activity; LIA, liposome immunoassay

Table 109. Summary of Proportion of Subjects With Loss of Crovalimab Exposure and Pharmacological Activity in COMMODORE-1 (BO42161), COMMODORE-2 (BO42162), and COMMODORE-3 (YO42311)

Study/Cohort	ADA Status	Number and Proportion of Patients with Loss of Exposure and Pharmacological Activity
BO42162 Crova [Naive] (N = 140)	ADA Negative (N = 98)	0
	ADA Positive (N = 42)	3 (7.1%)
	Total (N = 140)	3 (2.1%)
BO42162 Crova [Switch] (N = 67)	ADA Negative (N = 44)	0
	ADA Positive (N = 23)	4 (17.4%)
	Total (N = 67)	4 (6.0%)
BO42161 Crova [Switch] (N = 117)	ADA Negative (N = 97)	0
	ADA Positive (N = 20)	4 (20.0%)
	Total (N = 117)	4 (3.4%)
YO42311 Crova [Naive] (N = 51)	ADA Negative (N = 33)	0
	ADA Positive (N = 18)	0
	Total (N = 51)	0
Crova [Naive] Total (N = 191)	ADA Negative (N=131)	0
	ADA Positive (N = 60)	3 (5.0%)
	Total (N = 191)	3 (1.6%)
Crova [Switch] Total (N = 184)	ADA Negative (N = 141)	0
	ADA Positive (N = 43)	8 (18.6%)
	Total (N = 184)	8 (4.3%)
Crova Total (N = 375)	ADA Negative (N = 272)	0
	ADA Positive (N = 103)	11 (10.7%)
	Total (N = 375)	11 (2.9%)

Source: Table 9, page 49, Integrated Summary of immunogenicity.
Note: Loss of exposure and pharmacological activity is defined as subjects whose on-treatment crovalimab PK concentration decreases below 100 µg/mL in combination with Free C5 increasing above 0.0001 g/L and LIA increasing above 30 U/mL. The target concentration (100 µg/mL) for complete inhibition of the terminal complement activity is extensively discussed in Sections 6 and 14.5. The Applicant conducted a retrospective review of the data among Phase 3 trials. Based on the analysis, all PNH subjects with loss of exposure (crovalimab concentration below 100 µg/mL for at least two consecutive timepoints) and increase in LDH (>2×ULN) had elevated CH50 measurements >30 U/mL and elevated free C5 measurements >0.0001 g/L. The immunogenicity population consists of all subjects with at least one ADA assessment. Subjects with treatment-emergent ADAs are considered ADA positive. Subjects with no treatment-emergent ADAs are considered ADA negative. All ADA assessments up to CCOD are included to determine ADA status.
Abbreviations: ADA, antidrug antibody; C5, complement component 5; CCOD, clinical cutoff date; Crova, Crovalimab; LIA, liposome immunoassay; N, total number of subjects; PK, pharmacokinetic

The Impact of ADA on the Clinical Outcome of Crovalimab

In COMMODORE-1, COMMODORE-2, and COMMODORE-3, 11 crovalimab-treated subjects had loss of PD based on crovalimab exposure and pharmacological activity (see Table 109). The FDA assessed whether these 11 subjects had loss of clinical response based on the presence of

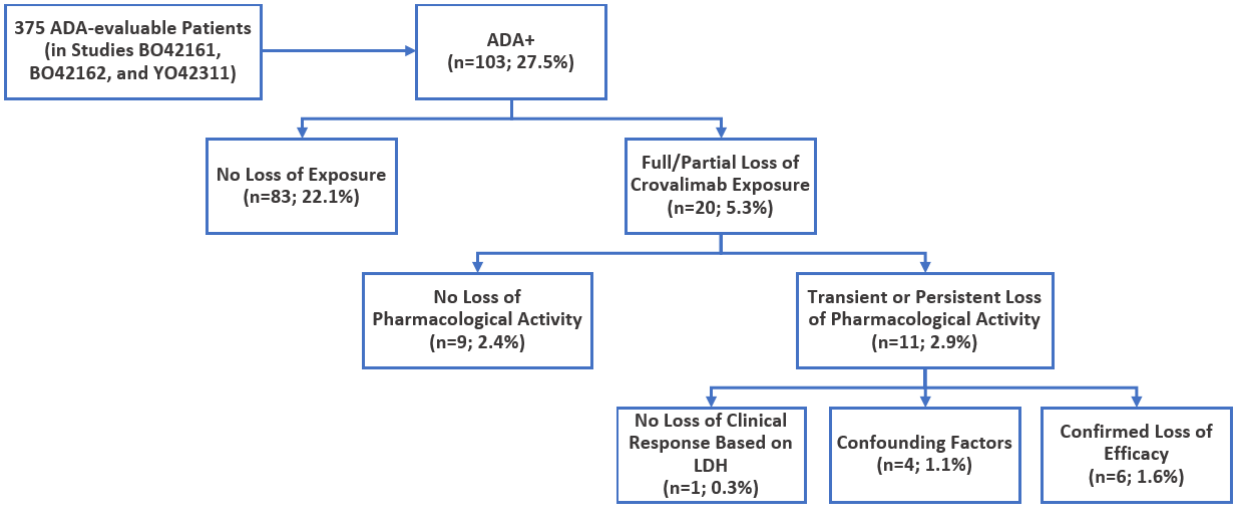
lactate dehydrogenase (LDH) ≥2×upper limit of normal (ULN) on 3 consecutive occasions over at least 4 weeks (sustained intravascular hemolysis (IVH)).

Of these subjects:

- Six subjects had loss of clinical response as defined above.
  - Five subjects had complete loss of crovalimab exposure and pharmacological activity.
  - One subject had partial loss of crovalimab exposure and pharmacological activity and following a dose escalation regained hemolysis control (LDH ≤1.5×ULN) which was maintained up to the clinical cutoff date (CCOD).
- One subject with a complete loss of crovalimab exposure and pharmacological activity did not have loss of clinical response based on LDH and continued to maintain LDH ≤1.5×ULN through the treatment duration up to the CCOD.
- Four subjects had confounding factors that prevented an assessment of the impact on clinical response.
  - Three subjects had insufficient longitudinal data to make an adequate assessment of the impact on clinical response (two subjects due to discontinuation, and one subject due to missing data related to COVID-19 restriction [for this one subject, when central LDH assessments were resumed, LDH was ≤1.5×ULN, and this was sustained until the CCOD]).
  - One subject with a transient increase in LDH ≥2×ULN at two visits had a possible alternative clinical explanation for the increase in LDH, which was concurrent with a diagnosis of mantle cell lymphoma and receipt of chemotherapy, both of which are independently known to cause an increase in LDH.

The overall impact of immunogenicity leading to loss of exposure, loss of pharmacological activity, and efficacy is shown in Figure 39.

Figure 39. Summary of ADA Impact on PK, PD, and Efficacy in COMMODORE-1 (BO42161), COMMODORE-2 (BO42162), and COMMODORE-3 (YO42311)



Source: Figure 18, Page 53, Integrated Summary of Immunogenicity.
Note: ADA + refers to treatment-emergent ADA.
Abbreviations: ADA, antidrug antibody; LDH, lactate dehydrogenase; n, number of subjects; PD, pharmacodynamic; PK, pharmacokinetic.

The immunogenicity assessment schedule in COMMODORE-1, COMMODORE-2, and COMMODORE-3 is acceptable, as ADA samples include both predose samples and postdose samples taken at 1 to 25 weeks after the first exposure of crovalimab. Based on the review by the Office of Biotechnology Products, the ADA assay is valid. However, there are issues identified with the NAb assay. Specifically, no validation reports were submitted for samples quantified at Roche regulated large molecule bioanalytical laboratory. For samples quantified at (b) (4) , drug tolerance at high positive control (30000 ng/mL) is ≤10.0 µg/mL crovalimab, which is below C_{trough}. Due to these issues, the results of neutralizing antibodies are not reviewed for this submission. There was no evidence of a clinical impact of ADA status on the safety profile of crovalimab.

14.5. Pharmacometrics Assessment

Population PK Analysis

A total of 6115 crovalimab concentrations measured from 9 HVs and 421 subjects with PNH from COMMODORE-1, COMMODORE-2, COMMODORE-3, and COMPOSER were used for the development of the population PK model for crovalimab. Of the 421 PNH subjects, 210 were subjects with treatment-naïve PNH and 211 were subjects who switched from another C5 inhibitor therapy. Counts of observation records and subjects in the crovalimab PK analysis data set are presented in Table 110. Subject characteristics are summarized in Table 111, Table 112, Table 113, Table 114, Table 115, and Table 116. ADA negative status was defined as follows: patients were ADA negative if they were ADA negative at baseline and all postbaseline samples were negative, or if they were ADA positive at baseline but did not have any postbaseline samples with a titer that was at least 4-fold greater than the titer of the baseline sample (treatment unaffected).

Table 110. Crovalimab PK Analysis Data Set: Number of Subjects With Observations and Number of Observations, Presented by Population and Study Cohort

Population / Cohort	nID[a]	nObs[b]	nObs/nID[c]
HV			
BP39144 Part 1, 75 mg IV	3	50	16.7
BP39144 Part 1, 125 mg IV	3	51	17.0
BP39144 Part 1, 100 mg SC	3	39	13.0
All	9	140	15.6
PNH naive			
BP39144 Part 2	10	414	41.4
BP39144 Part 4A	8	142	17.8
YO42311	51	701	13.7
BO42162 Arm A	135	1 766	13.1
BO42162 Arm C	6	71	11.8
All	210	3 094	14.7
PNH switch			
BP39144 Part 3, QW	6	176	29.3
BP39144 Part 3, Q2W	6	165	27.5
BP39144 Part 3, Q4W	7	218	31.1
BP39144 Part 4B	7	130	18.6
BO42162 Arm B	68	684	10.1
BO42161 Arm A	44	635	14.4
BO42161 Arm B	35	396	11.3
BO42161 Arm C	38	477	12.6
All	211	2 881	13.7
All			
All	430	6 115	14.2

Source: Population PK Study Report, poppk-1119748, Table 3.
Note: BO42161 = COMMODORE-1, BO42162 = COMMODORE-2, YO42311 = COMMODORE-3, BP39144 = COMPOSER
[a] Number of subjects
[b] Number of observations
[c] Average number of observations per subject
Abbreviations: HV, healthy volunteers; IV, intravenous; nID, number of participant; nObs, number of observations; PNH, paroxysmal nocturnal hemoglobinuria; Q2W, every two weeks; Q4W, every four weeks; QW, every week; SC, subcutaneous

Table 111. Baseline Characteristics of the Healthy Subjects in the Crovalimab PK Analysis Data Set by Study Cohort: Continuous Covariates

	BP39144 Part 1, 75 mg IV N=3	BP39144 Part 1, 125 mg IV N=3	BP39144 Part 1, 100 mg SC N=3	Overall N=9
Age (years)				
Mean (SD)	39.3 (13.9)	39.3 (11.4)	34.0 (11.4)	37.6 (10.9)
Median (min, max)	43.0 (24.0, 51.0)	36.0 (30.0, 52.0)	29.0 (26.0, 47.0)	36.0 (24.0, 52.0)
Body weight (kg)				
Mean (SD)	67.7 (12.3)	72.7 (9.40)	77.8 (8.67)	72.7 (9.90)
Median (min, max)	65.4 (56.7, 81.0)	72.8 (63.2, 82.0)	73.3 (72.3, 87.8)	72.8 (56.7, 87.8)
CH50 (U/mL)				
Mean (SD)	51.0 (2.65)	48.3 (7.09)	56.3 (2.31)	51.9 (5.30)
Median (min, max)	52.0 (48.0, 53.0)	47.0 (42.0, 56.0)	55.0 (55.0, 59.0)	53.0 (42.0, 59.0)
Normalized LDH (x ULN)				
Mean (SD)	0.651 (0.0500)	0.688 (0.105)	0.648 (0.0382)	0.662 (0.0643)
Median (min, max)	0.628 (0.616, 0.708)	0.644 (0.612, 0.808)	0.652 (0.608, 0.684)	0.644 (0.608, 0.808)
C5 free, BP39144 (g/L)				
Mean (SD)	0.0867 (0.0109)	0.0876 (0.0178)	0.101 (0.0224)	0.0919 (0.0169)
Median (min, max)	0.0929 (0.0741, 0.0932)	0.0791 (0.0756, 0.108)	0.0923 (0.0850, 0.127)	0.0923 (0.0741, 0.127)
C5 free, Phase III (g/L)				
Mean (SD)	-	-	-	-
Median (min, max)	-	-	-	-
Missing (N (%))	3 (100%)	3 (100%)	3 (100%)	9 (100%)
C5 total (g/L)				
Mean (SD)	0.0787 (0.0271)	0.0877 (0.0236)	0.0882 (0.00710)	0.0849 (0.0189)
Median (min, max)	0.0631 (0.0629, 0.110)	0.0959 (0.0611, 0.106)	0.0885 (0.0810, 0.0952)	0.0885 (0.0611, 0.110)
CLCR (mL/min)				
Mean (SD)	103 (1.77)	121 (4.44)	131 (15.7)	118 (15.0)
Median (min, max)	104 (101, 104)	120 (117, 126)	129 (117, 148)	117 (101, 148)
AST (IU/L)				
Mean (SD)	19.3 (7.51)	17.7 (2.08)	22.0 (5.29)	19.7 (5.07)
Median (min, max)	19.0 (12.0, 27.0)	17.0 (16.0, 20.0)	20.0 (18.0, 28.0)	19.0 (12.0, 28.0)

Source: Population PK Study Report, poppk-1119748, Table 4.
Note: BP39144 = COMPOSER
Abbreviations: AST, aspartate transaminase; C5, complement component 5; CH50, 50% hemolytic complement; CLCR, creatinine clearance; IU/L, international units per liter; IV, intravenous; LDH, lactate dehydrogenase; N, number of subjects; PK, pharmacokinetic; SC, subcutaneous; SD, standard deviation; ULN, upper limit of normal

Table 112. Baseline Characteristics of the Treatment-Naïve PNH Subjects in the Crovalimab PK Analysis Data Set by Study Cohort: Continuous Covariates

	BP39144 Part 2 N=10	BP39144 Part 4A N=8	YO42311 N=51	BO42162 Arm A N=135	BO42162 Arm C N=6	Overall N=210
Age (years)						
Mean (SD)	53.9 (11.8)	56.6 (10.6)	33.0 (9.43)	40.5 (15.2)	16.0 (1.55)	39.2 (15.1)
Median (min, max)	52.5 (35.0, 74.0)	55.5 (42.0, 73.0)	31.0 (15.0, 58.0)	36.0 (18.0, 76.0)	16.5 (13.0, 17.0)	35.5 (13.0, 76.0)
Body weight (kg)						
Mean (SD)	75.1 (15.8)	76.6 (16.0)	63.8 (11.3)	68.3 (15.8)	69.7 (17.8)	67.9 (15.0)
Median (min, max)	66.8 (58.9, 98.0)	80.1 (56.7, 100)	60.0 (48.9, 100)	66.1 (42.0, 140)	67.8 (50.0, 98.5)	65.2 (42.0, 140)
CH50 (U/mL)						
Mean (SD)	59.7 (13.0)	61.4 (22.4)	64.5 (35.6)	70.4 (37.0)	69.2 (40.2)	68.1 (35.4)
Median (min, max)	56.5 (42.0, 82.0)	55.7 (32.0, 102)	48.5 (16.3, 120)	53.4 (5.00, 120)	51.8 (30.2, 120)	53.4 (5.00, 120)
Normalized LDH (x ULN)						
Mean (SD)	5.51 (2.90)	6.99 (5.86)	9.30 (2.83)	7.34 (3.27)	9.95 (9.92)	7.79 (3.70)
Median (min, max)	4.82 (1.91, 12.1)	5.15 (2.32, 20.4)	9.28 (3.97, 18.0)	6.89 (2.08, 17.4)	6.46 (3.23, 29.8)	7.21 (1.91, 29.8)
C5 free, BP39144 (g/L)						
Mean (SD)	0.133 (0.0367)	0.177 (0.0851)	-	-	-	0.152 (0.0649)
Median (min, max)	0.121 (0.0943, 0.206)	0.145 (0.109, 0.320)	-	-	-	0.132 (0.0943, 0.320)
Missing (N (%))	0 (0%)	0 (0%)	51 (100%)	135 (100%)	6 (100%)	192 (91%)
C5 free, Phase III (g/L)						
Mean (SD)	-	-	0.227 (0.0619)	0.223 (0.0945)	0.243 (0.0868)	0.224 (0.0865)
Median (min, max)	-	-	0.226 (0.138, 0.533)	0.210 (0.0000013, 1.11)	0.224 (0.151, 0.402)	0.210 (0.0000013, 1.11)
Missing (N (%))	10 (100%)	8 (100%)	0 (0%)	0 (0%)	0 (0%)	18 (8.6%)
C5 total (g/L)						
Mean (SD)	0.134 (0.0384)	0.127 (0.0783)	0.125 (0.0268)	0.152 (0.0435)	0.188 (0.0667)	0.145 (0.0443)
Median (min, max)	0.147 (0.0682, 0.183)	0.118 (0.0487, 0.299)	0.123 (0.0819, 0.200)	0.145 (0.0776, 0.336)	0.178 (0.110, 0.268)	0.140 (0.0487, 0.336)
CLCR (mL/min)						
Mean (SD)	102 (34.0)	89.7 (30.5)	155 (50.6)	118 (46.6)	180 (24.8)	127 (50.0)
Median (min, max)	92.5 (62.3, 180)	91.5 (41.9, 127)	145 (39.3, 254)	113 (25.8, 273)	170 (157, 223)	121 (25.8, 273)

Source: Population PK Study Report, poppk-1119748, Table 5
Note: BO42162 = COMMODORE-2, YO42311 = COMMODORE-3, BP39144 = COMPOSER
Abbreviations: C5, complement component 5; CH50, 50% hemolytic complement; CLCR, creatinine clearance; IU/L, international units per liter; IV, intravenous; LDH, lactate dehydrogenase; N, number of subjects; PK, pharmacokinetic; SC, subcutaneous; SD, standard deviation; ULN, upper limit of normal

Table 113. Baseline Characteristics of the Switch PNH Subjects in the Crovalimab PK Analysis Data Set by Study Part/Cohort: Continuous Covariates

	BP39144 Part 3 N=19	BP39144 Part 4B N=7	BO42162 Arm B N=68	BO42161 Arm A N=44	BO42161 Arm B N=35	BO42161 Arm C N=38	Overall N=211
Age (years)							
Mean (SD)	49.5 (11.0)	44.0 (11.0)	41.8 (16.2)	44.7 (15.6)	50.2 (14.8)	44.1 (15.2)	45.0 (15.3)
Median (min, max)	46.0 (33.0, 69.0)	44.0 (29.0, 57.0)	37.5 (17.0, 78.0)	42.5 (21.0, 81.0)	49.0 (26.0, 85.0)	42.5 (16.0, 80.0)	44.0 (16.0, 85.0)
Body weight (kg)							
Mean (SD)	80.1 (26.0)	81.6 (19.2)	68.0 (14.8)	77.0 (17.5)	77.1 (19.2)	67.9 (13.9)	72.9 (17.9)
Median (min, max)	78.2 (40.6, 132)	79.8 (60.4, 114)	65.2 (47.0, 122)	80.0 (45.2, 120)	71.8 (47.4, 126)	68.5 (44.0, 91.0)	71.0 (40.6, 132)
CH50 (U/mL)							
Mean (SD)	10.8 (13.2)	8.14 (4.34)	11.8 (21.0)	9.66 (6.27)	8.00 (5.90)	15.6 (21.1)	11.2 (16.0)
Median (min, max)	5.00 (5.00, 55.0)	5.00 (5.00, 16.0)	5.00 (5.00, 120)	5.00 (5.00, 31.2)	5.00 (5.00, 31.6)	5.00 (5.00, 120)	5.00 (5.00, 120)
Normalized LDH (x ULN)							
Mean (SD)	1.56 (1.11)	1.09 (0.195)	1.86 (3.23)	1.05 (0.276)	1.00 (0.324)	1.96 (3.10)	1.52 (2.31)
Median (min, max)	1.17 (0.850, 4.81)	1.13 (0.688, 1.31)	1.08 (0.701, 23.0)	1.01 (0.577, 1.79)	0.944 (0.620, 2.19)	1.11 (0.624, 18.0)	1.04 (0.577, 23.0)
C5 free, BP39144 (g/L)							
Mean (SD)	0.375 (0.143)	0.379 (0.126)	-	-	-	-	0.376 (0.136)
Median (min, max)	0.377 (0.00129, 0.585)	0.320 (0.268, 0.568)	-	-	-	-	0.364 (0.00129, 0.585)
Missing (N (%))	0 (0%)	0 (0%)	68 (100%)	44 (100%)	35 (100%)	38 (100%)	185 (88%)
C5 free, Phase III (g/L)							
Mean (SD)	-	-	0.206 (0.0262)	0.210 (0)	0.210 (0)	0.210 (0)	0.208 (0.0159)
Median (min, max)	-	-	0.210 (0.0000013, 0.210)	0.210 (0.210, 0.210)	0.210 (0.210, 0.210)	0.210 (0.210, 0.210)	0.210 (0.0000013, 0.210)
Missing (N (%))	19 (100%)	7 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	26 (12%)
C5 total (g/L)							
Mean (SD)	0.320 (0.0741)	0.297 (0.0923)	0.334 (0.0940)	0.301 (0.0663)	0.283 (0.0607)	0.297 (0.109)	0.309 (0.0866)
Median (min, max)	0.301 (0.144, 0.473)	0.296 (0.112, 0.396)	0.320 (0.164, 0.600)	0.302 (0.192, 0.467)	0.283 (0.0826, 0.407)	0.274 (0.0895, 0.570)	0.300 (0.0826, 0.600)
CLCR (mL/min)							
Mean (SD)	118 (50.6)	126 (34.8)	122 (50.4)	127 (54.1)	125 (52.6)	120 (39.3)	123 (48.9)
Median (min, max)	108 (33.6, 225)	130 (83.0, 169)	119 (33.0, 340)	126 (38.9, 298)	126 (27.8, 245)	126 (29.2, 190)	125 (27.8, 340)
AST (IU/L)							
Mean (SD)	30.5 (14.5)	22.3 (7.26)	34.6 (40.4)	38.1 (93.7)	24.6 (8.96)	33.1 (32.9)	32.6 (50.6)

Source: Population PK Study Report, poppk-1119748, Table 6.
Note: BO42161 = COMMODORE-1, BO42162 = COMMODORE-2, BP39144 = COMPOSER
Abbreviations: AST, aspartate transaminase; C5, complement component 5; CH50, 50% hemolytic complement; CLCR, creatinine clearance; IU/L, international units per liter; IV, intravenous; LDH, lactate dehydrogenase; N, number of subjects; PK, pharmacokinetic; SC, subcutaneous; SD, standard deviation; ULN, upper limit of normal

Table 114. Baseline Characteristics of the Healthy Subjects in the Crovalimab PK Analysis Data Set by Study Part: Categorical Covariates

	BP39144 Part 1, 75 mg IV N=3	BP39144 Part 1, 125 mg IV N=3	BP39144 Part 1, 100 mg SC N=3	Overall N=9
Sex				
Male	3 (100%)	3 (100%)	3 (100%)	9 (100%)
Age categories				
18 - 64 years	3 (100%)	3 (100%)	3 (100%)	9 (100%)
Race				
Caucasian	3 (100%)	3 (100%)	2 (67%)	8 (89%)
Asian	0 (0%)	0 (0%)	1 (33%)	1 (11%)
Ethnicity				
non-Asian	3 (100%)	3 (100%)	2 (67%)	8 (89%)
Asian	0 (0%)	0 (0%)	1 (33%)	1 (11%)
Body weight categories				
50 kg < WT ≤ 60 kg	1 (33%)	0 (0%)	0 (0%)	1 (11%)
60 kg < WT ≤ 70 kg	1 (33%)	1 (33%)	0 (0%)	2 (22%)
70 kg < WT ≤ 80 kg	0 (0%)	1 (33%)	2 (67%)	3 (33%)
80 kg < WT ≤ 90 kg	1 (33%)	1 (33%)	1 (33%)	3 (33%)

Source: Population PK Study Report, poppk-1119748, Table 7.
Note: BP39144 = COMPOSER
Abbreviations: IV, intravenous; N, total number of subjects; PK, pharmacokinetic; WT, weight

Table 115. Baseline Characteristics of the Treatment-Naïve PNH Subjects in the Crovalimab PK Analysis Data Set by Study Part: Categorical Covariates

	BP39144 Part 2 N=10	BP39144 Part 4A N=8	YO42311 N=51	BO42162 Arm A N=135	BO42162 Arm C N=6	Overall N=210
Sex						
Male	6 (60%)	6 (75%)	22 (43%)	77 (57%)	4 (67%)	115 (55%)
Female	4 (40%)	2 (25%)	29 (57%)	58 (43%)	2 (33%)	95 (45%)
Age categories						
12 - 17 years	0 (0%)	0 (0%)	3 (5.9%)	0 (0%)	6 (100%)	9 (4.3%)
18 - 64 years	8 (80%)	6 (75%)	48 (94%)	122 (90%)	0 (0%)	184 (88%)
$\geq$ 65 years	2 (20%)	2 (25%)	0 (0%)	13 (9.6%)	0 (0%)	17 (8.1%)
Race						
Caucasian	7 (70%)	3 (38%)	0 (0%)	45 (33%)	0 (0%)	55 (26%)
Black	0 (0%)	0 (0%)	0 (0%)	3 (2.2%)	0 (0%)	3 (1.4%)
Asian	3 (30%)	4 (50%)	51 (100%)	86 (64%)	5 (83%)	149 (71%)
Other or Unknown	0 (0%)	1 (12%)	0 (0%)	1 (0.74%)	1 (17%)	3 (1.4%)
Ethnicity						
non-Asian	7 (70%)	4 (50%)	0 (0%)	49 (36%)	1 (17%)	61 (29%)
Asian	3 (30%)	4 (50%)	51 (100%)	86 (64%)	5 (83%)	149 (71%)
Body weight categories						
40 kg $<$ WT $\leq$ 50 kg	0 (0%)	0 (0%)	3 (5.9%)	10 (7.4%)	1 (17%)	14 (6.7%)
50 kg $<$ WT $\leq$ 60 kg	2 (20%)	2 (25%)	23 (45%)	38 (28%)	1 (17%)	66 (31%)
60 kg $<$ WT $\leq$ 70 kg	4 (40%)	1 (12%)	15 (29%)	27 (20%)	2 (33%)	49 (23%)
70 kg $<$ WT $\leq$ 80 kg	0 (0%)	1 (12%)	5 (9.8%)	35 (26%)	1 (17%)	42 (20%)
80 kg $<$ WT $\leq$ 90 kg	1 (10%)	3 (38%)	3 (5.9%)	15 (11%)	0 (0%)	22 (10%)
90 kg $<$ WT $\leq$ 100 kg	3 (30%)	1 (12%)	2 (3.9%)	6 (4.4%)	1 (17%)	13 (6.2%)
100 kg $<$ WT $\leq$ 110 kg	0 (0%)	0 (0%)	0 (0%)	2 (1.5%)	0 (0%)	2 (0.95%)
110 kg $<$ WT $\leq$ 120 kg	0 (0%)	0 (0%)	0 (0%)	1 (0.74%)	0 (0%)	1 (0.48%)
WT $>$ 120 kg	0 (0%)	0 (0%)	0 (0%)	1 (0.74%)	0 (0%)	1 (0.48%)

Source: Population PK Study Report, poppk-1119748, Table 8.
Note: BO42162 = COMMODORE-2, YO42311 = COMMODORE-3, BP39144 = COMPOSER
Abbreviations: N, total number of subjects; PK, pharmacokinetic; PNH, paroxysmal nocturnal hemoglobinuria; WT, weight

Table 116. Baseline Characteristics of the Switch PNH Subjects in the Crovalimab PK Analysis Data Set by Study Cohort: Categorical Covariates

	BP39144 Part 3 N=19	BP39144 Part 4B N=7	BO42162 Arm B N=68	BO42161 Arm A N=44	BO42161 Arm B N=35	BO42161 Arm C N=38	Overall N=211
Sex							
Male	13 (68%)	6 (86%)	34 (50%)	20 (45%)	17 (49%)	19 (50%)	109 (52%)
Female	6 (32%)	1 (14%)	34 (50%)	24 (55%)	18 (51%)	19 (50%)	102 (48%)
Age categories							
12 - 17 years	0 (0%)	0 (0%)	2 (2.9%)	0 (0%)	0 (0%)	1 (2.6%)	3 (1.4%)
18 - 64 years	16 (84%)	7 (100%)	57 (84%)	39 (89%)	29 (83%)	33 (87%)	181 (86%)
≥ 65 years	3 (16%)	0 (0%)	9 (13%)	5 (11%)	6 (17%)	4 (11%)	27 (13%)
Race							
Caucasian	9 (47%)	3 (43%)	15 (22%)	33 (75%)	25 (71%)	16 (42%)	101 (48%)
Black	0 (0%)	0 (0%)	1 (1.5%)	2 (4.5%)	0 (0%)	1 (2.6%)	4 (1.9%)
Asian	7 (37%)	2 (29%)	51 (75%)	9 (20%)	7 (20%)	17 (45%)	93 (44%)
Other or Unknown	3 (16%)	2 (29%)	1 (1.5%)	0 (0%)	3 (8.6%)	4 (11%)	13 (6.2%)
Ethnicity							
non-Asian	12 (63%)	5 (71%)	17 (25%)	35 (80%)	28 (80%)	21 (55%)	118 (56%)
Asian	7 (37%)	2 (29%)	51 (75%)	9 (20%)	7 (20%)	17 (45%)	93 (44%)
Body weight categories							
40 kg < WT ≤ 50 kg	2 (11%)	0 (0%)	3 (4.4%)	5 (11%)	1 (2.9%)	6 (16%)	17 (8.1%)
50 kg < WT ≤ 60 kg	3 (16%)	0 (0%)	23 (34%)	5 (11%)	6 (17%)	4 (11%)	41 (19%)
60 kg < WT ≤ 70 kg	3 (16%)	2 (29%)	18 (26%)	4 (9.1%)	9 (26%)	11 (29%)	47 (22%)
70 kg < WT ≤ 80 kg	2 (11%)	2 (29%)	14 (21%)	11 (25%)	5 (14%)	7 (18%)	41 (19%)
80 kg < WT ≤ 90 kg	2 (11%)	1 (14%)	5 (7.4%)	11 (25%)	5 (14%)	9 (24%)	33 (16%)
90 kg < WT ≤ 100 kg	3 (16%)	1 (14%)	2 (2.9%)	6 (14%)	5 (14%)	1 (2.6%)	18 (8.5%)
100 kg < WT ≤ 110 kg	1 (5.3%)	0 (0%)	1 (1.5%)	0 (0%)	2 (5.7%)	0 (0%)	4 (1.9%)
110 kg < WT ≤ 120 kg	1 (5.3%)	1 (14%)	1 (1.5%)	2 (4.5%)	1 (2.9%)	0 (0%)	6 (2.8%)
WT > 120 kg	2 (11%)	0 (0%)	1 (1.5%)	0 (0%)	1 (2.9%)	0 (0%)	4 (1.9%)

Source: Population PK Study Report, poppk-1119748, Table 9.
Note: BO42161 = COMMODORE-1, BO42162 = COMMODORE-2, BP39144 = COMPOSER
Abbreviations: N, total number of subjects; PK, pharmacokinetic; PNH, paroxysmal nocturnal hemoglobinuria; WT, weight

Crovalimab PK was well described by a linear two-compartment model with first-order elimination and first-order absorption to describe the SC administration. The typical values of central volume of distribution and central CL were 3.23 L and 0.0791 L/day in a subject with a BW of 75 kg, respectively. A transient CL increase had been observed in the subjects switching from eculizumab or ravulizumab, which is due to the formation of DTDCs. To account for the DTDC-induced CL, an additional time-dependent CLs was added for the switch subjects, the decline of which was controlled by an exponential decay constant (K_d). Covariates evaluated during model development are summarized in Table 117. The final model included the covariate effects of weight on CL and volumes, and of age on the first-order absorption rate constant. The effects of time-varying ADA on CL were evaluated, with separate effects for the three ADA titer groups (Low titer: $<10^4$, medium titer: $\geq 10^4$ and $<10^5$, high titer: $\geq 10^5$). The effect of low ADA titer on CL was not different from that in subjects without ADA. Medium titer and high titer showed similar impact of ADA on CL. As a result, a time-varying effect of medium/high titers of ADA on CL was also included. The parameter estimates of the final model is shown in Table 118. Goodness-of-fit plots showed a relatively adequate fit across the different study populations, and no obvious bias was identified, except minor bias found in the log scale plots of observations versus population and individual predictions (Figure 40, Figure 41, Figure 42, Figure 43, and

Figure 44). Prediction-corrected visual predictive checks showed a relatively good predictive capability of the final population PK model (Figure 45 and Figure 46).

Table 117. Covariate-Parameter Relationships Evaluated in the Crovalimab PK Model Development

Parameter	Type	Covariate[a]
k_a	Structural	age
	Exploratory	race/ethnicity
V_2	Structural	WT[b]
	Exploratory	sex, race/ethnicity, total C5
V_3	Structural	WT[b]
	Exploratory	race/ethnicity, total C5
Overall CL	Structural	WT[c], ADA
	Exploratory	sex, race/ethnicity, total C5, ALB, CLCR[d], AST, ALT
CL_s and K_d	Structural	switch status
	Exploratory	-
Q	Structural	WT[c]
	Exploratory	race/ethnicity, total C5

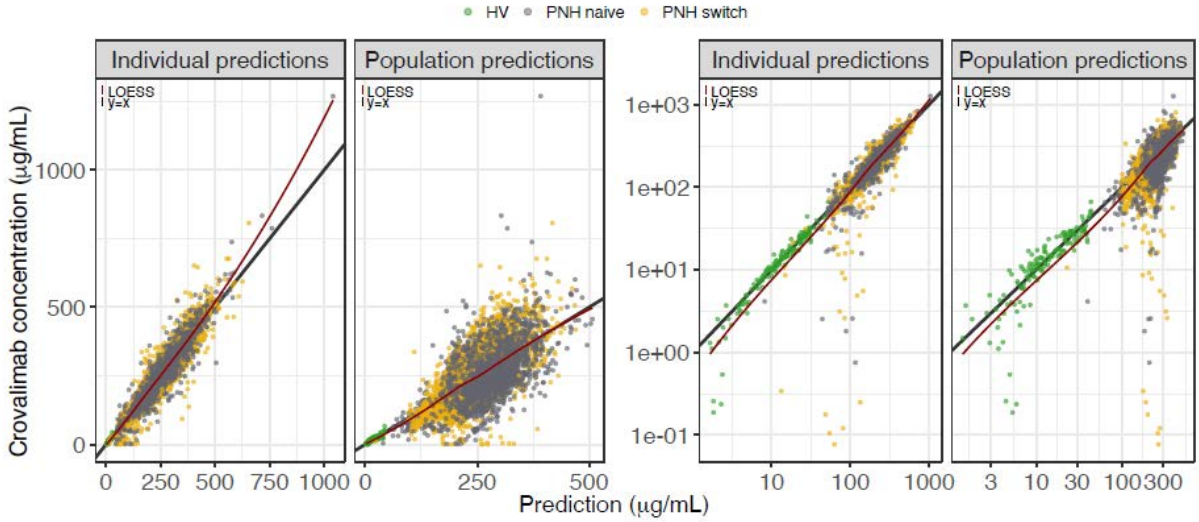
Source: Population PK Study Report, poppk-1119748, Table 14.
[a] Exploratory covariates were only considered for parameters that were associated with IIV.
[b] Initially included allometrically with a fixed exponent of 1.
[c] Included allometrically with a fixed exponent of 0.75.
[d] Calculated using the Cockcroft-Gault formula.
Abbreviations: ADA, antidrug antibody; ALB, albumin; ALT, alanine transaminase; AST, aspartate transaminase; C5, complement component 5; CL, central clearance; CL_s, time-dependent clearance; CLCR, creatinine clearance; k_a, absorption rate constant; K_d, exponential decay constant for CL_s; Q, inter-compartmental clearance; V_2, volume of distribution for central compartment; V_3, volume of distribution for peripheral compartment; WT, weight

Table 118. Parameter Estimates of the Final Crovalimab PK Model

	Final model				
Run	59				
OFV	51794.6				
Condition number	370.5				
	Unit	**Value**	**RSE (%)**	**SHR (%)**	**CI 90%**
Structural parameters					
CL	(L/day)	0.0791	6.70		0.0678 - 0.0872
CL_s	(L/day)	0.0341	17.6		0.0229 - 0.0422
K_d	(1/day)	0.0144	20.6		0.00865 - 0.0195
V_2	(L)	3.23	1.30		3.16 - 3.29
Q	(L/day)	0.168	12.4		0.138 - 0.221
V_3	(L)	2.32	7.17		2.02 - 2.67
k_a	(1/day)	0.126	13.0		0.105 - 0.176
F	(-)	0.830	7.72		0.696 - 0.920
Covariate relations					
WT on CL and Q	(-)	0.750	(FIX)		
WT on V_2 and V_3	(-)	0.684	8.07		0.599 - 0.781
ADA on CL	(-)	0.247	33.5		0.0999 - 0.443
Age on k_a	(-)	-0.459	26.5		-0.788 - -0.281
Interindividual variability					
IIV CL	(CV)	0.206	8.05	29.7	0.183 - 0.284
IIV V_2	(CV)	0.224	5.07	7.52	0.205 - 0.243
IIV k_a	(CV)	0.383	28.0	51.0	0.186 - 0.758
IIV F	(CV)	1.16	26.0	33.4	0.494 - 1.70
IIV V_3	(CV)	0.706	8.70	19.2	0.596 - 0.791
IIV Q	(CV)	0.584	16.6	34.7	0.339 - 0.765
Residual error					
Proportional RUV	(CV)	0.113	3.92	10.1	0.105 - 0.122
Additive RUV rich sampling	(SD)	1.01	23.4		0.259 - 1.41
Additive RUV sparse sampling	(SD)	14.4	10.9		11.7 - 17.0
IIV additive RUV	(CV)	0.787	11.4	43.5	0.640 - 0.950

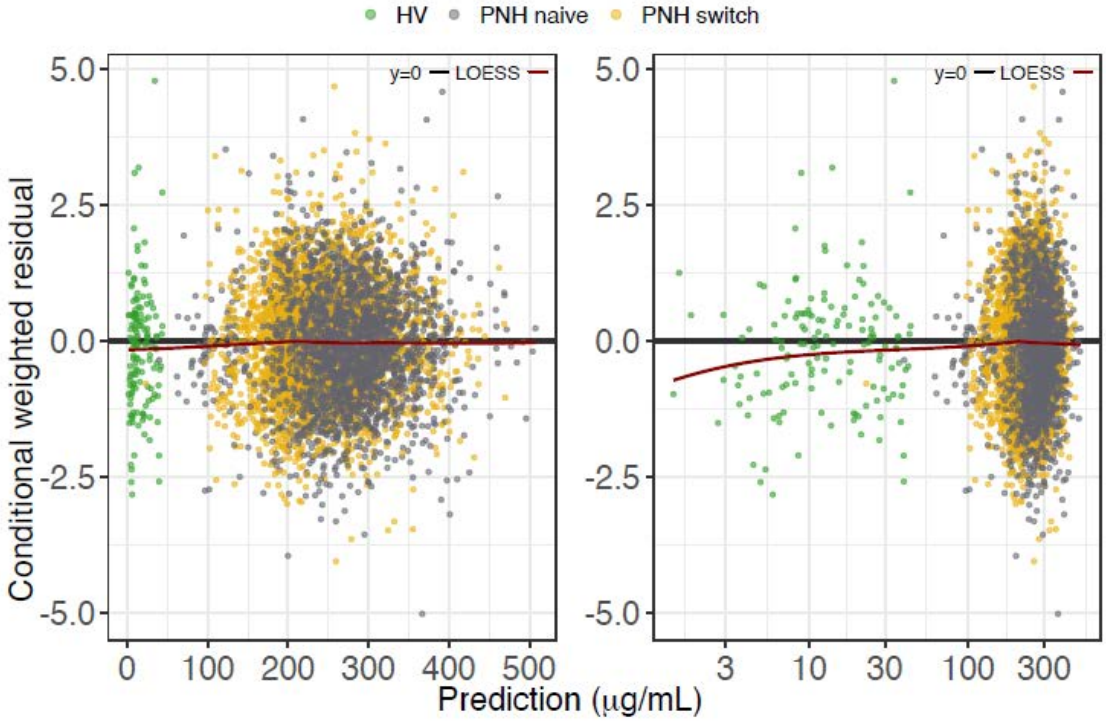
Source: Population PK Study Report, poppk-1119748, Table 14.
Note: The RSE for IIV and RUV parameters are reported on the approximate SD scale. ε-shrinkage reported in row of proportional RUV. CI computed from a non-parametric bootstrap with 500 samples.
Abbreviations: ADA, antidrug antibody; ALB, albumin; ALT, alanine transaminase; AST, aspartate transaminase; C5, complement component 5; CL, central clearance; CLCR, creatinine clearance; CLs, time-dependent clearance; CV, coefficient of variation; F, bioavailability; ka, absorption rate constant; Kd, exponential decay constant for CLs; OFV, objective function value; Q, inter-compartmental clearance; RSE, relative standard error; RUV, residual unexplained variability; SD, standard deviation; SHR, shrinkage; V_2, volume of distribution for central compartment; V_3, volume of distribution for peripheral compartment; WT, weight

Figure 40. Observed Versus Predicted Concentrations for the Final Crovalimab PK Model, Colored by Study Population



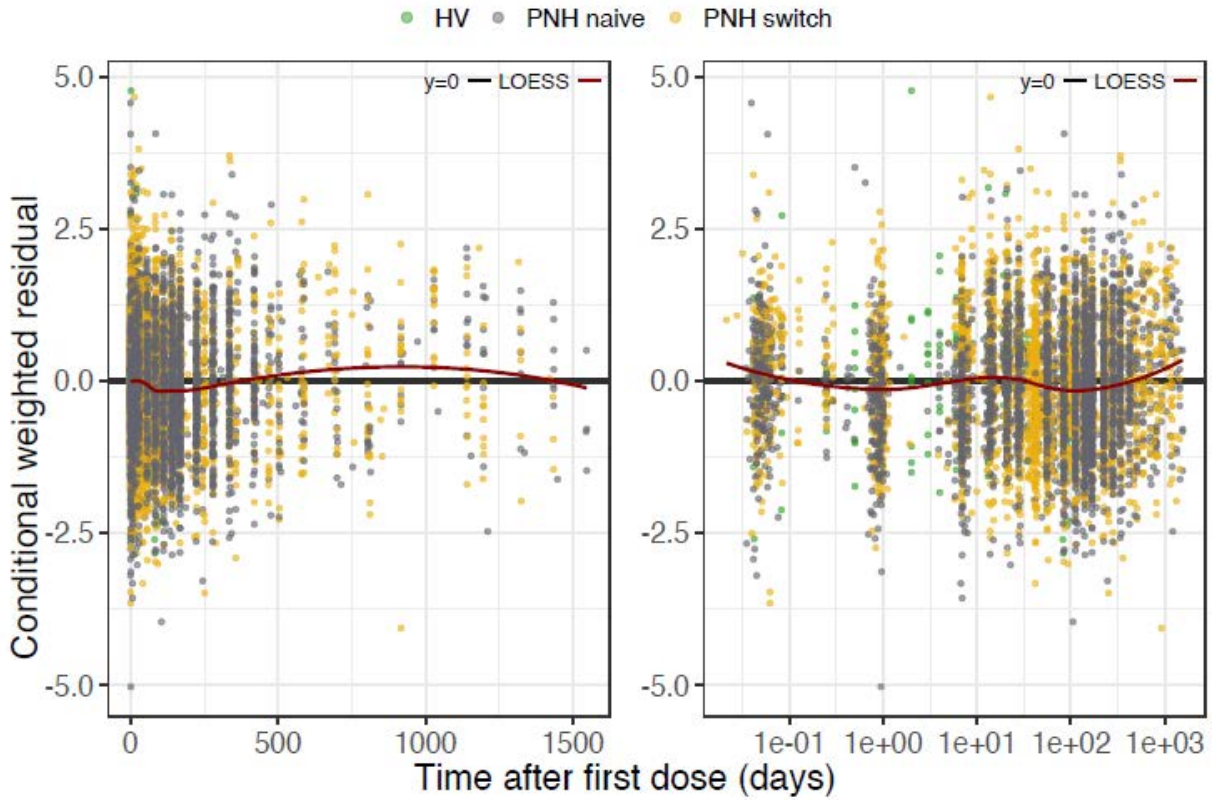
Source: Population PK Study Report, poppk-1119748, Figure A3-2.
Abbreviations: HV, healthy volunteer; PK, pharmacokinetic; PNH, paroxysmal nocturnal hemoglobinuria

Figure 41. CWRES Versus PRED for the Final Crovalimab PK Model, Colored by Study Population



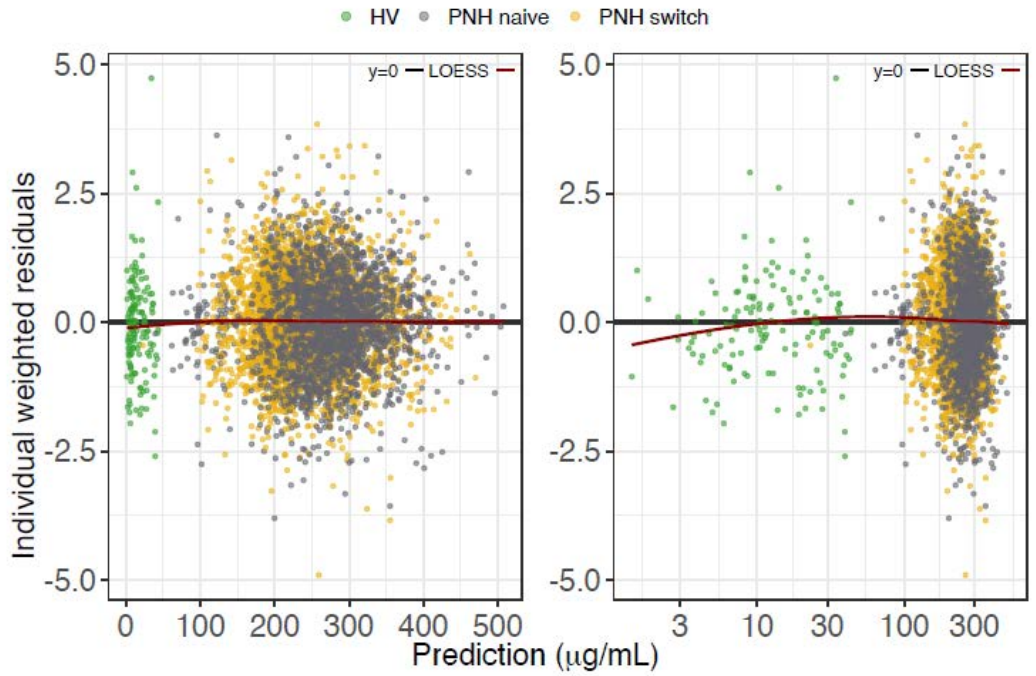
Source: Population PK Study Report, poppk-1119748, Figure A3-4.
Abbreviations: CWRES, conditional weighted residuals; HV, healthy volunteer; LOESS, locally estimated scatterplot smoothing; PK, pharmacokinetic; PNH, paroxysmal nocturnal hemoglobinuria; PRED, prediction

Figure 42. CWRES Versus Time Since First Dose for the Final Crovalimab PK Model, Colored by Study Population



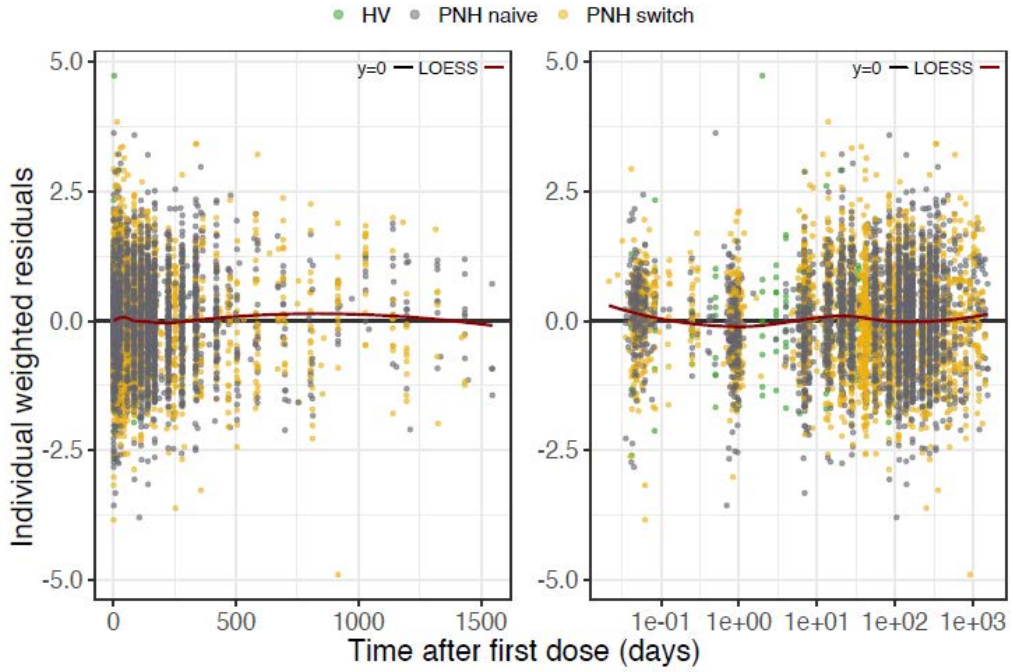
Source: Population PK Study Report, poppk-1119748, Figure A3-6.
Abbreviations: CWRES, conditional weighted residuals; HV, healthy volunteer; LOESS, locally estimated scatterplot smoothing; PK, pharmacokinetic; PNH, paroxysmal nocturnal hemoglobinuria

Figure 43. IWRES Versus PRED for the Final Crovalimab PK Model, Colored by Study Population



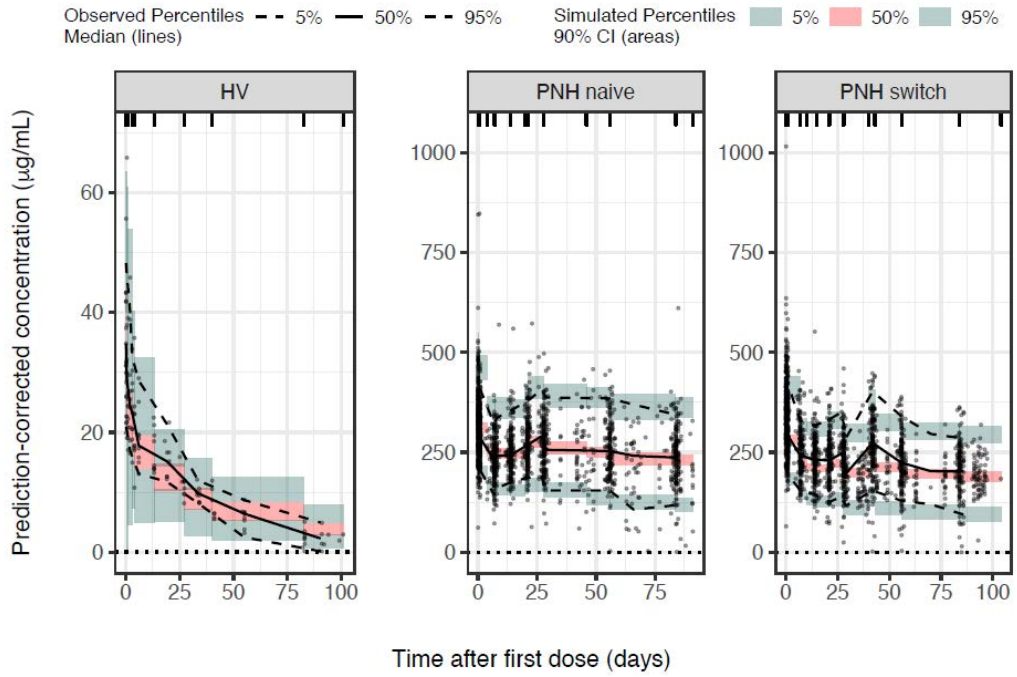
Source: Population PK Study Report, poppk-1119748, Figure A3-8.
Abbreviations: HV, healthy volunteer; IWRES, individual weighted residuals; LOESS, locally estimated scatterplot smoothing; PK, pharmacokinetic; PNH, paroxysmal nocturnal hemoglobinuria

Figure 44. IWRES Versus Time Since First Dose for the Final Crovalimab PK Model, Colored by Study Population



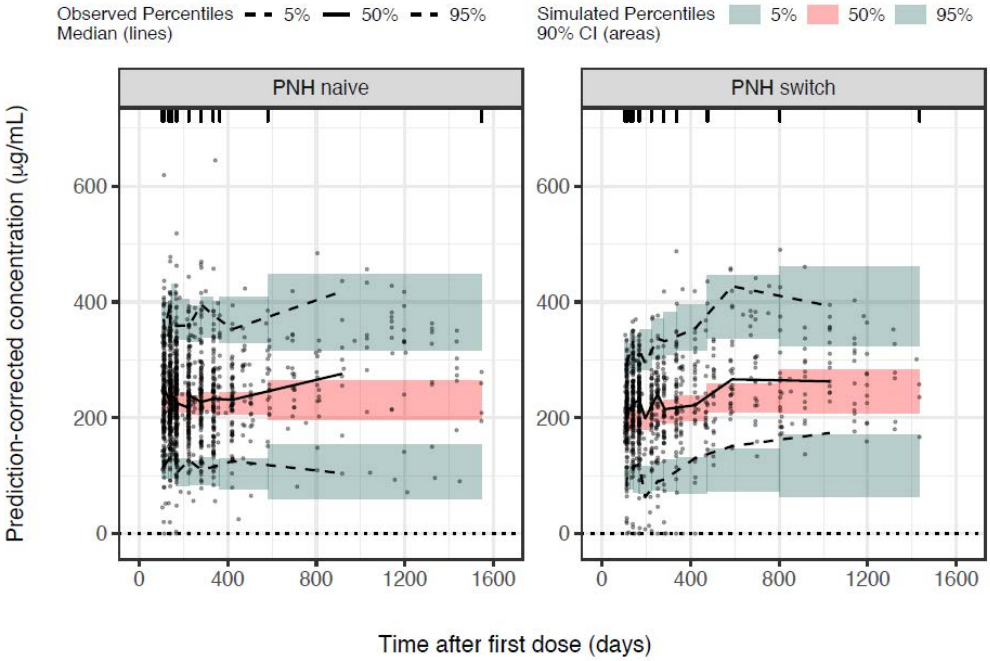
Source: Population PK Study Report, poppk-1119748, Figure A3-10.
Abbreviations: IWRES, individual weighted residuals; HV, healthy volunteer; LOESS, locally estimated scatterplot smoothing; PK, pharmacokinetic; PNH, paroxysmal nocturnal hemoglobinuria

Figure 45. Prediction-Corrected Visual Predictive Check of Crovalimab PK Concentrations Versus Time After First Dose up to Week 14, Stratified by HVs, PNH Naïve, and PNH Switch Subjects



Source: Population PK Study Report, poppk-1119748, Figure 22.
Note: The dashed horizontal line represents the LLOQ. The rugs on the x-scale represent the binning.
Abbreviations: CI, confidence interval; HV, healthy volunteer; PK, pharmacokinetic; PNH, paroxysmal nocturnal hemoglobinuria

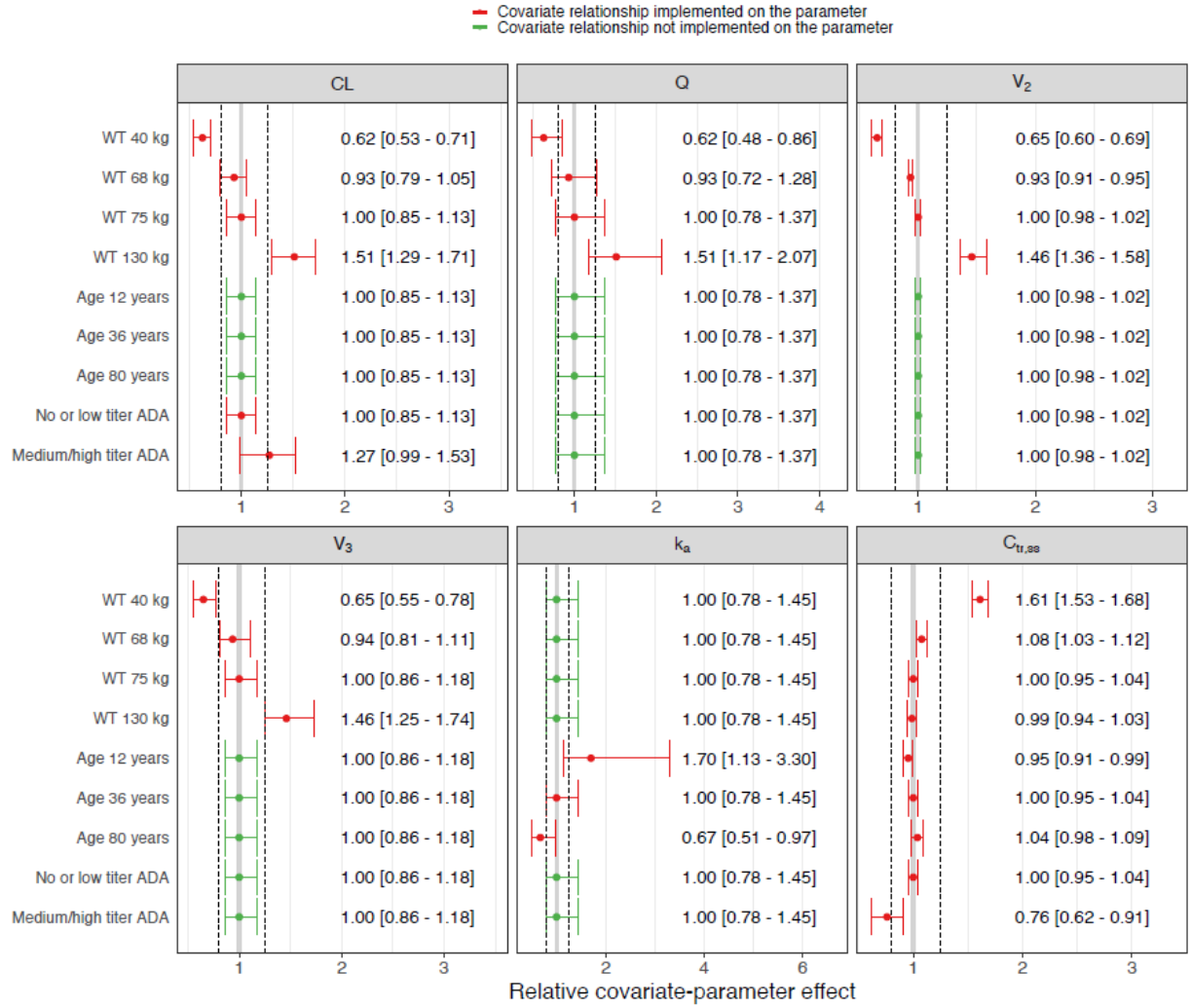
Figure 46. Prediction-Corrected Visual Predictive Check of Crovalimab PK Concentrations Versus Time After First Dose Post Week 14, Stratified by HVs, PNH Naïve, and PNH Switch Subjects



Source: Population PK Study Report, poppk-1119748, Figure 23.
Note: The dashed horizontal line represents the LLOQ. The rugs on the x-scale represent the binning.
Abbreviations: CI, confidence interval; HV, healthy volunteer; PK, pharmacokinetic; PNH, paroxysmal nocturnal hemoglobinuria

The impact of covariates on typical PK parameters (CL, volume of distribution for central compartment, volume of distribution for peripheral compartment, absorption rate constant, inter-compartmental clearance, and C_{trough}) in the final model is summarized in forest plots (Figure 47). The forest plots visualize the effect of extreme values of weight (40 and 130 kg), age (12 and 80 years), and ADA (medium/high titers) compared to the reference subject (75 kg, 36 years, with no ADA or low ADA titers). The reference weight of 75 kg and age of 36 years were taken from the legacy model. To evaluate the impact of a typical weight of the current analysis population, the forest plots also show the impact of the median weight (68 kg).

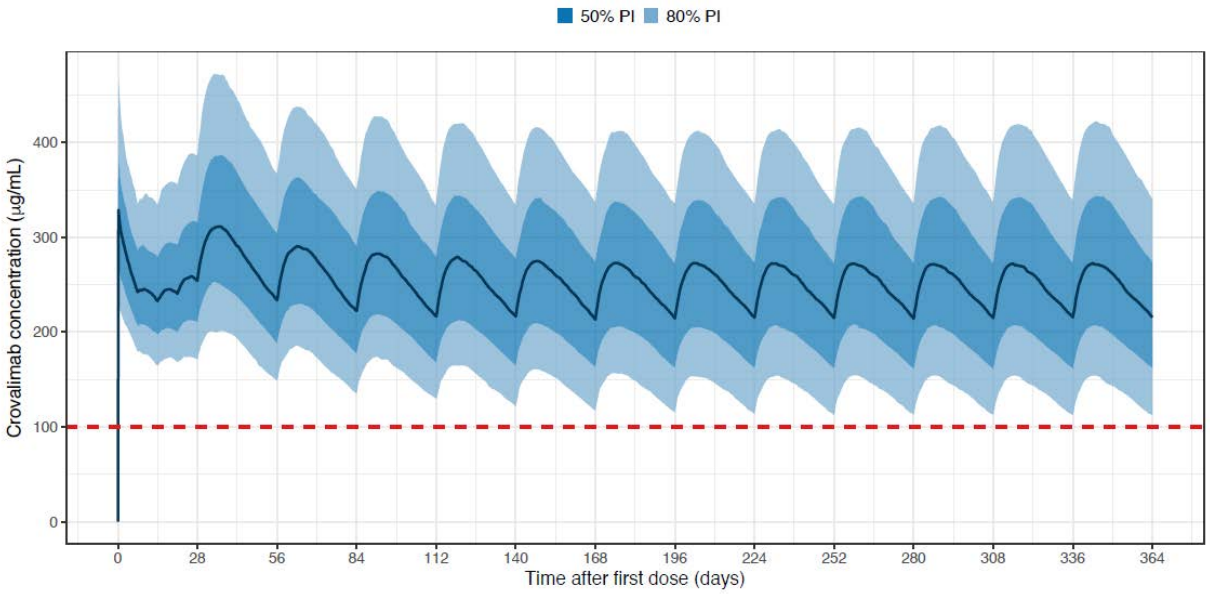
Figure 47. Forest Plots Illustrating the Effects of Covariates on Crovalimab PK Parameters CL, Q, V_2, V_3, k_a, and $C_{trough,ss}$, Conditioned on a Reference Subject, Based on the Final Crovalimab PK Model



Source: Population PK Study Report, poppk-1119748, Figure 25.
Note: Closed dots and error bars, together with their specific values, represent the median of the predicted relative change from the reference subject and its associated 95% CIs; these values are calculated based on a nonparametric bootstrap with 500 samples. The parameter values for a reference subject (WT: 75 kg, age: 36 years, no or low titer ADA) are shown by the solid vertical lines; the dashed vertical lines indicate the 80% to 125% margins relative to the reference subject.
Abbreviations: ADA, antidrug antibody; CL, central clearance; $C_{trough,ss}$, trough concentration at steady state; K_a, absorption rate constant; PK, pharmacokinetic; Q, inter-compartmental clearance; V_2, volume of distribution for central compartment; V_3, volume of distribution for peripheral compartment

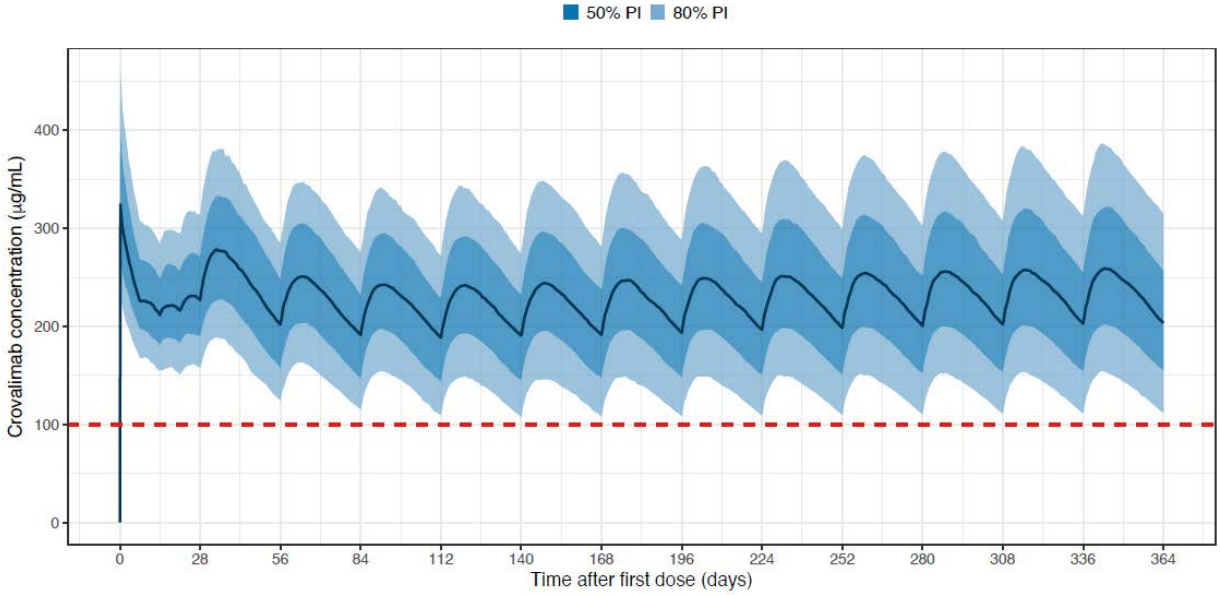
Simulations were performed for a population with a geometric mean (SD) BW of 70.9 (1.3) kg, and a geometric mean (SD) age of 42.1 (1.4) years, based on the PNH subjects in the analysis data set; 8.14% of the subjects, corresponding to the observed percentage of subjects with medium/high ADA titers, were randomly assigned medium/high ADA titers, starting from 12 weeks (approximately median time of onset of ADA development). The final crovalimab PK model was used to predict the concentration-time profiles for a typical treatment-naïve population and switch population of patients with PNH treated with the proposed dosing regimen (Figure 48 and Figure 49). The simulations showed that 92.8% of the treatment-naïve patients and 91.4% of the switch patients are expected to have crovalimab concentrations above the threshold of 100 µg/mL (which was observed to be associated with maximum complement activity inhibition) over the entire time course of crovalimab treatment. The influence of weight was evaluated by simulating steady-state trough concentration profiles for a 36-year-old patient with PNH-stratified BW groups. The simulation result suggested the percentage of patients with steady-state trough crovalimab concentration below 100 mcg/mL was lowest for the weight group of 40-60 kg. This percentage increased with higher BWs and was highest (~10%) for the BW group of 90 to 100 kg (Figure 50).

Figure 48. Simulated Concentration-Time Profiles for Representative Population of Treatment-Naïve Patients With PNH Treated as in Phase 3 Clinical Trials



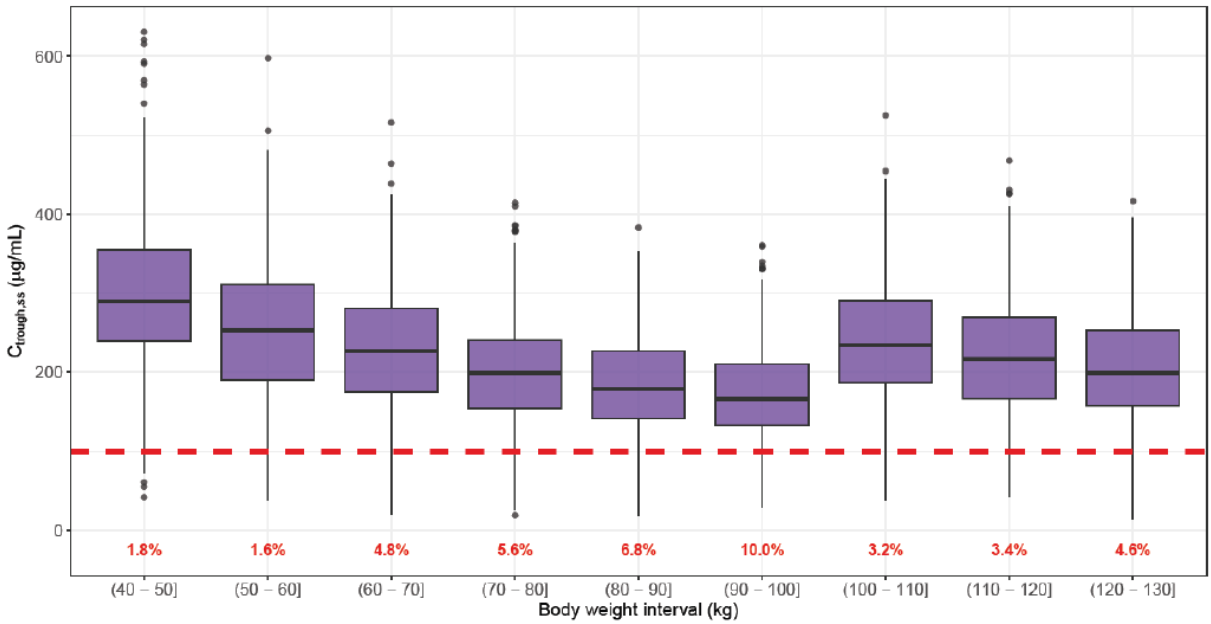
Source: Population PK Study Report, poppk-1119748, Figure 31.
The red dashed horizontal line represents the threshold of 100 mcg/mL. The solid curve represents the median of the simulated population, the shaded areas represent the different PI colored by PI level. WT and age were sampled from independent lognormal distributions with mean and SD from all subjects with PNH in the crovalimab PK analysis data set.
Abbreviations: PI, prediction interval; PNH, paroxysmal nocturnal hemoglobinuria; PK, pharmacokinetic; SD, standard deviation; WT, weight

Figure 49. Simulated Concentration-Time Profiles for Representative Population of Switch Patients With PNH Treated as in Phase 3 Clinical Trials



Source: Population PK Study Report, poppk-1119748, Figure 32.
Note: The red dashed horizontal line represents the threshold of 100 mcg/mL. The solid curve represents the median of the simulated population, the shaded areas represent the different PI colored by PI level. WT and age were sampled from independent lognormal distributions with mean and SD from all subjects with PNH in the crovalimab PK analysis data set.
Abbreviations: PI, prediction interval; PK, pharmacokinetic; PNH, paroxysmal nocturnal hemoglobinuria; SD, standard deviation; WT, weight

Figure 50. Distribution of Simulated $C_{trough,ss}$ Across Body Weight for a PNH Patient Population With the 100 Kg BW Cut off Dosing Regimen

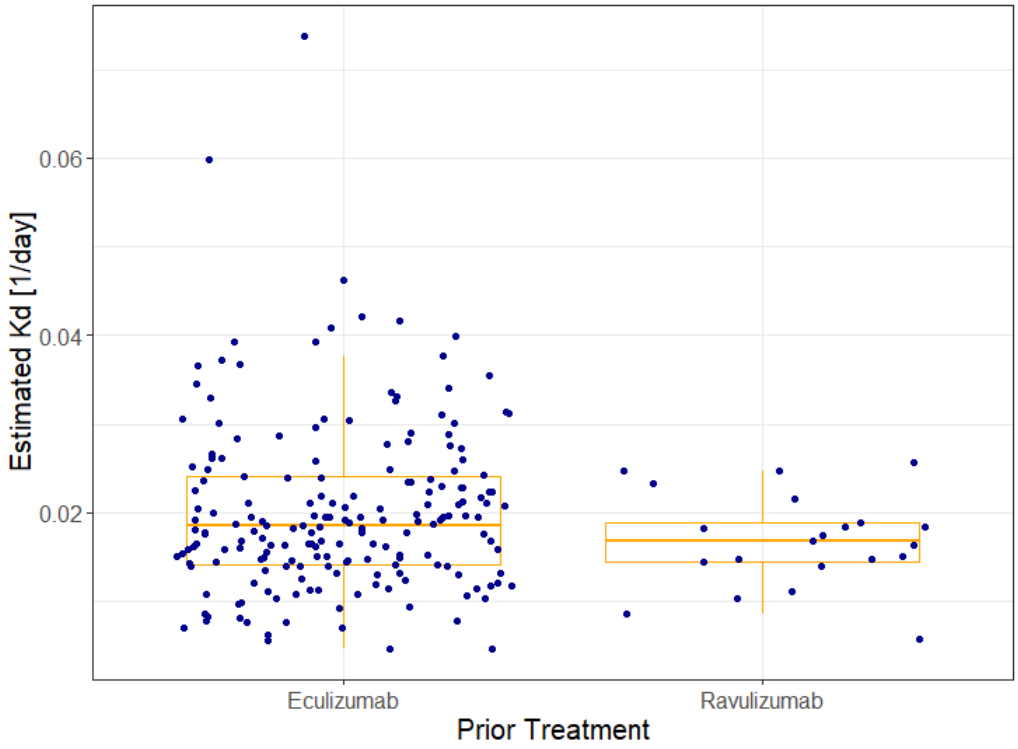


Source: Response to FDA information request received on November 21, 2023, Figure 2.
Note: The horizontal line in a box indicates the median value; the box edges represent the 25th and 75th percentiles; and the whiskers extend to the furthest data point that is no greater than 1.5 times the inter-quartile range. Data beyond the end of the whiskers are plotted as black points. The red numbers represent the percentage of patients with steady-state trough concentration below 100 mcg/mL. The red dashed horizontal line represents a crovalimab concentration threshold of 100 µg/mL.
Abbreviations: BW, body weight; $C_{trough,ss}$, trough concentration at steady state; FDA, Food and Drug Administration

The FDA reproduced the Applicant's final population PK model, which was further applied to evaluate the proposed dosing regimen and for reporting PK parameters and effect of other intrinsic factors on crovalimab PK in the label.

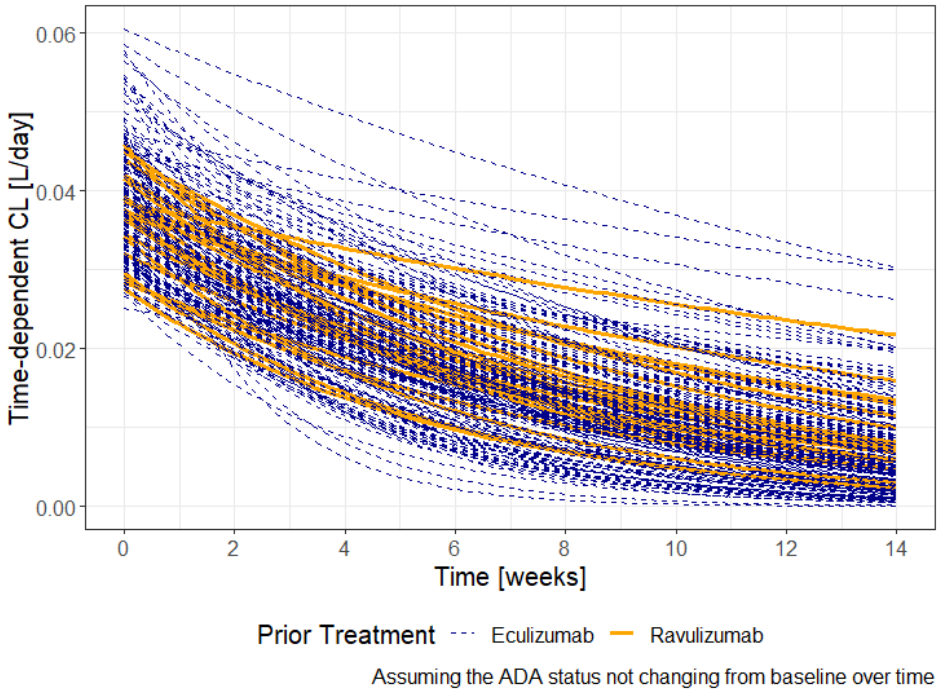
The data from clinical trials showed that DTDCs with eculizumab were cleared within approximately 8 weeks, whereas the DTDC persisted up to Week 21 in subjects switching from ravulizumab. However, the population PK model did not suggest a different decay constant for DTDC-induced time-dependent CL between the subjects switching from eculizumab and ravulizumab. The estimate of interindividual variability of K_d was fixed to 0 in the final model. The FDA performed additional model fitting with estimate of interindividual variability for K_d. The model-predicted individual K_d (Figure 51), as well as the DTDC-induced time-dependent CL over time (Figure 52), showed substantial overlap between the patients with PNH switched from eculizumab and ravulizumab, suggesting no clinically meaningful difference between eculizumab and ravulizumab regarding the switching effect on crovalimab PK in the prior-treated patients with PNH.

Figure 51. Model Estimated Individual K_d for Patients With PNH Switching From Eculizumab and Ravulizumab



Source: Reviewer analysis.
Note: The horizontal line in a box indicates the median value; the box edges represent the 25th and 75th percentiles; and the whiskers extend to the furthest data point that is no greater than 1.5 times the inter-quartile range. Blue dots represent model-estimated Kd.
Abbreviations: Kd, exponential decay constant for time-dependent clearance induced by drug-target-drug complex; PNH, paroxysmal nocturnal hemoglobinuria

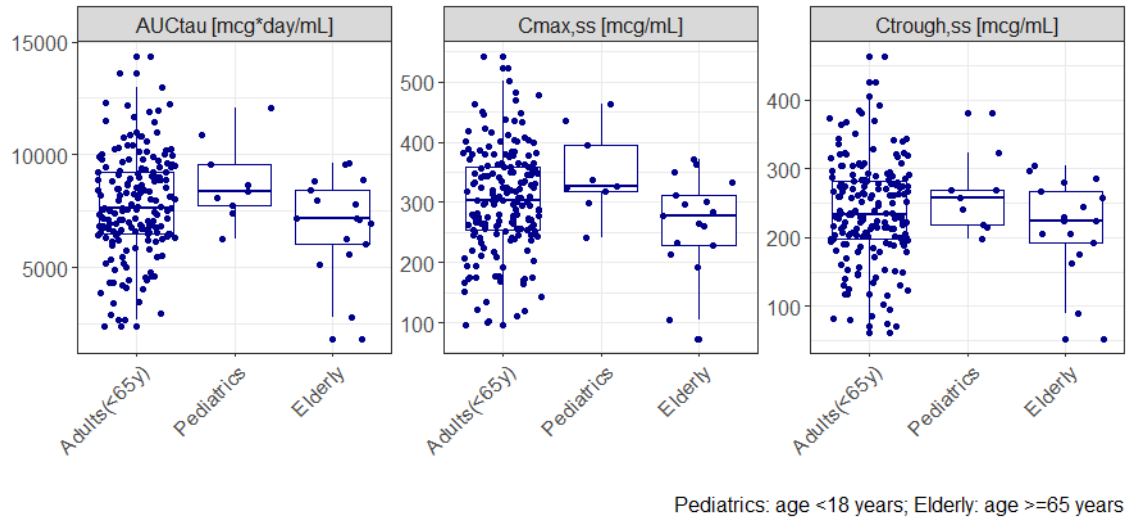
Figure 52. Model Estimated Individual DTDC-Induced Time-Dependent CL for Patients With PNH Switching From Eculizumab and Ravulizumab



Source: Reviewer analysis.
Abbreviations: ADA, antidrug antibody; CL, clearance; DTDC, drug-target-drug complex; PNH, paroxysmal nocturnal hemoglobinuria

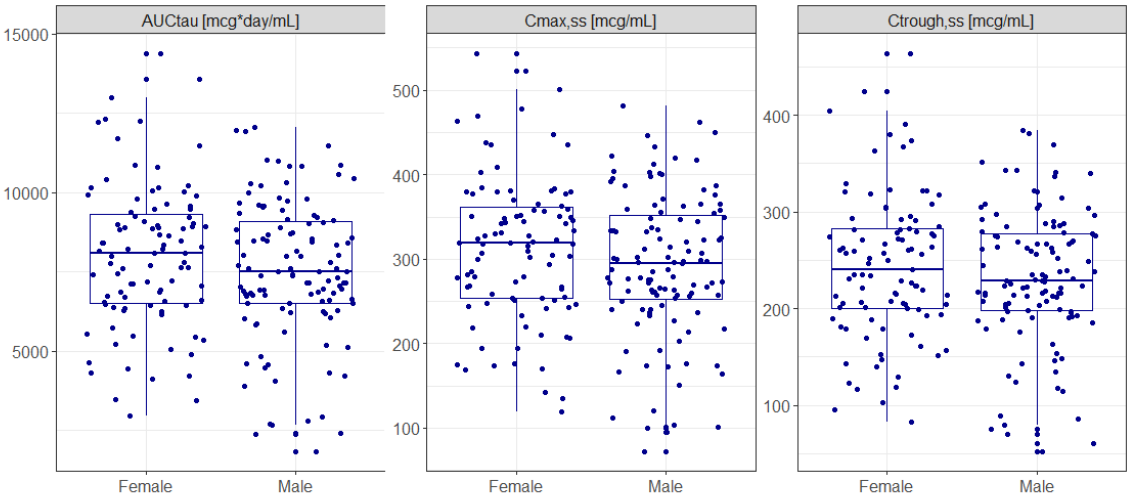
To evaluate the effect of covariates (age, sex, renal impairment (RI), and hepatic impairment on crovalimab PK described in the proposed label, the FDA performed population PK simulations using subjects with PNH (n=210) included in the model development. The individual PK parameters were estimated by the final population PK model. The simulation results showed substantial overlap for the individual PK exposure metrics at steady state, stratified by age (range: 13 to 76, pediatrics [<18y, n=9], adults [18 to >65y, n=184], and elderly [≥65y, n=17], Figure 53), sex (female [n =95] and male [n =115], Figure 54), and race (Caucasian [n =55], Black and African American [n =3], Asian [n =149], and other or unknown [n =3], Figure 55). There is a trend of decreased crovalimab PK exposures with an increase in baseline creatinine CL (Figure 56). However, substantial overlap in PK exposures was observed among the subjects with normal renal function (n=163), mild RI (n=29), moderate RI (n=16), and severe RI (n=2) (Figure 57). As noted, the sample size of subjects with severe RI was small. In general, RI is not expected to impact the exposure to therapeutic proteins significantly. Creatinine CL was not recognized as a significant covariate for the CL of crovalimab. Also, there is no clinically meaningful correlation between the PK exposure and safety outcomes. As a result, the trend associated with RI and PK was not considered clinically relevant (including severe RI). No clear trend was observed between the PK exposures and the hepatic transaminases, baseline aspartate aminotransferase (range: 14 to 363 IU/L, Figure 58), and alanine aminotransferase (range: 3 to 108 IU/L, Figure 59), suggesting no clinically meaningful impact of these transaminase abnormalities on crovalimab. In summary, no clinically meaningful influence of age, sex, race, RI (mild, moderate, and severe), and transaminase abnormalities on crovalimab was observed based on population PK analysis, and no dose adjustment is needed for these intrinsic factors.

Figure 53. Individual PK Exposure Metrics at Steady State Stratified by Age



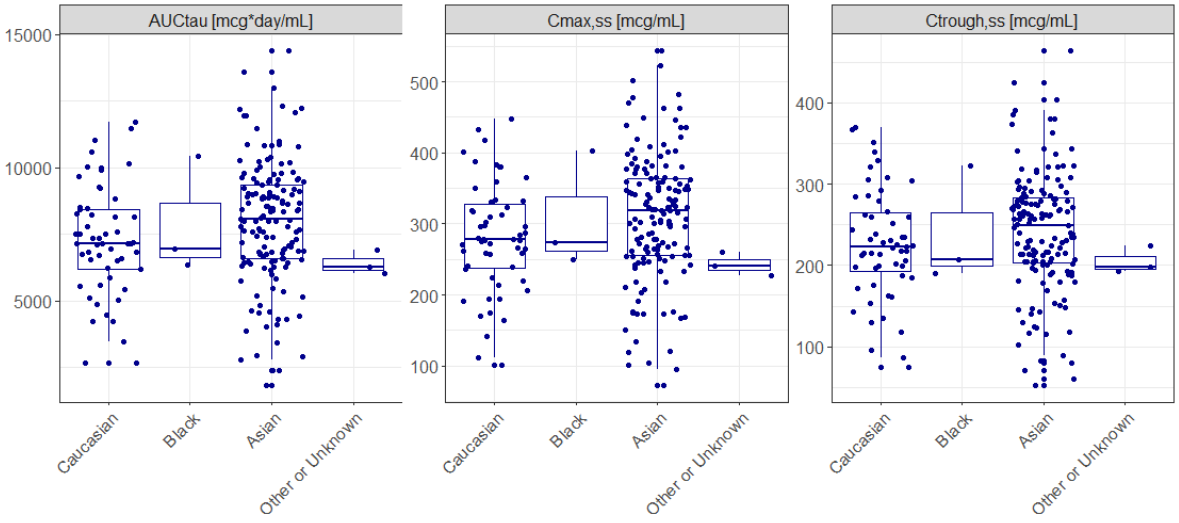
Source: Reviewer analysis.
Note: The horizontal line in a box indicates the median value; the box edges represent the 25th and 75th percentiles; and the whiskers extend to the furthest data point that is no greater than 1.5 times the inter-quartile range. Blue dots represent individual value for corresponding parameter.
Note: Pediatrics: age <18 years; Elderly: age ≥65 years
Abbreviations: AUC_{tau}, area under the concentration-time curve for a dosing interval at steady state; $C_{max,ss}$, maximum concentration at steady state; $C_{trough,ss}$, trough concentration at steady state; PK, pharmacokinetic

Figure 54. Individual PK Exposure Metrics at Steady State Stratified by Sex



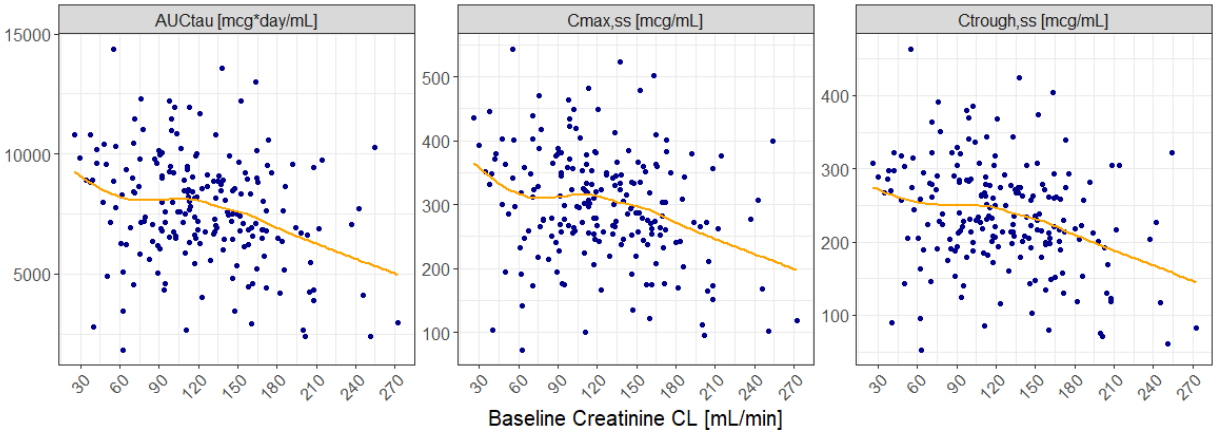
Source: Reviewer analysis.
Note: The horizontal line in a box indicates the median value; the box edges represent the 25th and 75th percentiles; and the whiskers extend to the furthest data point that is no greater than 1.5 times the inter-quartile range. Blue dots represent individual value for corresponding parameter.
Abbreviations: AUC_{tau}, area under the concentration-time curve for a dosing interval at steady state; $C_{max,ss}$, maximum concentration at steady state; $C_{trough,ss}$, trough concentration at steady state; PK, pharmacokinetic

Figure 55. Individual PK Exposure Metrics at Steady State Stratified by Race



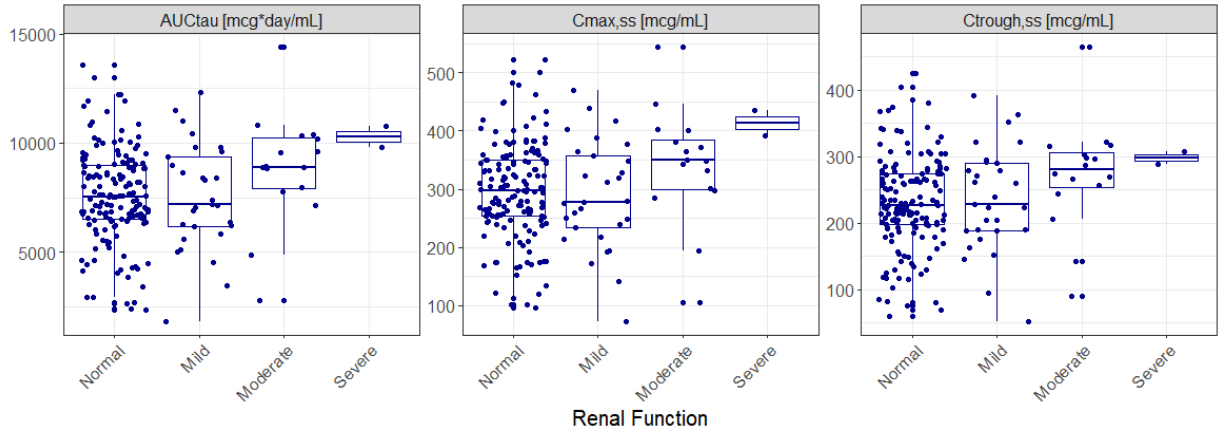
Source: Reviewer analysis.
Note: The horizontal line in a box indicates the median value; the box edges represent the 25th and 75th percentiles; and the whiskers extend to the furthest data point that is no greater than 1.5 times the inter-quartile range. Blue dots represent individual value for corresponding parameter.
Abbreviations: AUC_{tau}, area under the concentration-time curve for a dosing interval at steady state; $C_{max,ss}$, maximum concentration at steady state; $C_{trough,ss}$, trough concentration at steady state; PK, pharmacokinetic

Figure 56. PK Exposure Metrics at Steady State Versus Baseline Creatinine CL



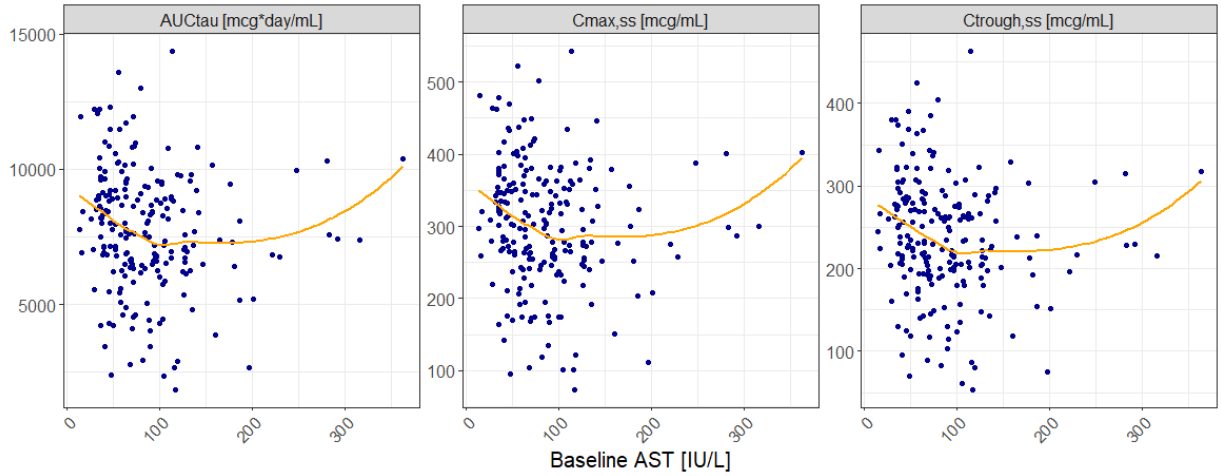
Source: Reviewer analysis.
Note: The horizontal line in a box indicates the median value; the box edges represent the 25th and 75th percentiles; and the whiskers extend to the furthest data point that is no greater than 1.5 times the inter-quartile range. Blue dots represent individual value for corresponding parameter. Orange lines represent loess regression.
Note: Creatinine CL calculated using Cockcroft-Gault formula. Pediatrics data is excluded.
Abbreviations: AUC_{tau}, area under the concentration -time curve for a dosing interval at steady state; $C_{max,ss}$, maximum concentration at steady state; $C_{trough,ss}$, trough concentration at steady state; PK, pharmacokinetic

Figure 57. Individual PK Exposure Metrics at Steady State Stratified by Renal Function



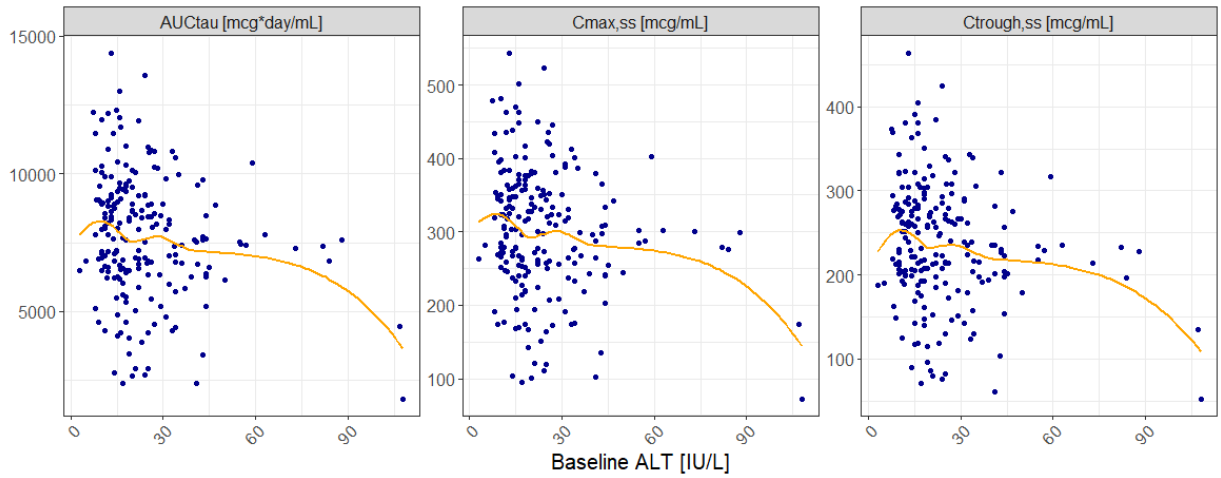
Source: Reviewer analysis.
Note: The horizontal line in a box indicates the median value; the box edges represent the 25th and 75th percentiles; and the whiskers extend to the furthest data point that is no greater than 1.5 times the inter-quartile range. Blue dots represent individual value for corresponding parameter.
Note: Creatinine CL calculated using Cockcroft-Gault formula. Pediatrics data is excluded.
Abbreviations: AUC_{tau}, area under the concentration-time curve for a dosing interval at steady state; $C_{max,ss}$, maximum concentration at steady state; $C_{trough,ss}$, trough concentration at steady state; PK, pharmacokinetic

Figure 58. PK Exposure Metrics at Steady State Versus Baseline AST



Source: Reviewer analysis.
Note: The horizontal line in a box indicates the median value; the box edges represent the 25th and 75th percentiles; and the whiskers extend to the furthest data point that is no greater than 1.5 times the inter-quartile range. Blue dots represent individual value for corresponding parameter. Orange lines represent loess regression.
Abbreviations: AST, aspartate aminotransferase; AUC_{tau}, area under the concentration-time curve for a dosing interval at steady state; $C_{max,ss}$, maximum concentration at steady state; $C_{trough,ss}$, trough concentration at steady state; PK, pharmacokinetic

Figure 59. PK Exposure Metrics at Steady State Versus Baseline ALT



Source: Reviewer analysis.
Note: The horizontal line in a box indicates the median value; the box edges represent the 25th and 75th percentiles; and the whiskers extend to the furthest data point that is no greater than 1.5 times the inter-quartile range. Blue dots represent individual value for corresponding parameter. Orange lines represent loess regression.
Abbreviations: ALT, alanine transaminase; AUC_{tau}, area under the concentration-time curve for a dosing interval at steady state; $C_{max,ss}$, maximum concentration at steady state; $C_{trough,ss}$, trough concentration at steady state; PK, pharmacokinetic

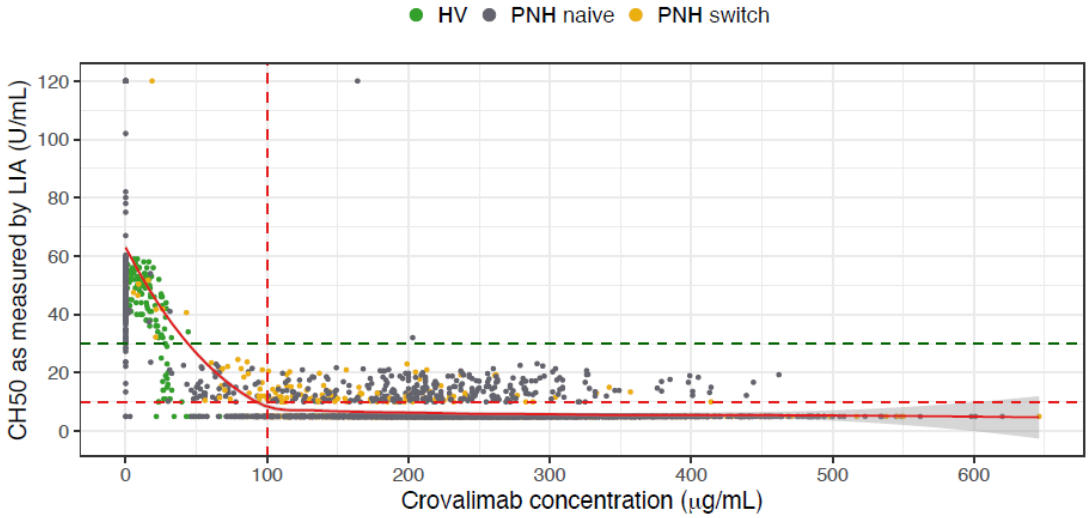
Exposure-Response Analyses

Terminal Complement Activity Endpoints: CH50 and Free C5

Crovalimab has a direct effect on terminal complement activity endpoints, CH50 and free C5. The time-matched analyses included all available data except in switch subjects, where the first 12 weeks of treatment were excluded in the CH50 and free C5 concentration-effect analyses. For CH50, there were a total of 5487 observations (HVs: n=141, PNH naïve: n=2767, and PNH switch: 2579) from 428 subjects (HVs: n=9, PNH naïve: n=209, and PNH switch: 210) included in the analysis. A total of 4471 out of 5487 (81.5%) CH50 observations were below the limit of quantification (BLQ), and 72 (1.31%) observations were above the limit of quantification. For free C5, there were a total of 5108 observations (HVs: n=141, PNH naïve: n=2671, and PNH switch: 2296) from 428 subjects (HVs: n=9, PNH naïve: n=209, and PNH switch: 210) included in the analysis; 25 out of 5108 (0.49%) observations were BLQ, 252 (4.9%) of the baseline observations were above the limit of quantification, and 24 (0.47%) of the observations were postbaseline above the limit of quantification. In total, 97.1% of the CH50 observations and 97.8% of the free C5 observations had a matching PK measurement at the same time.

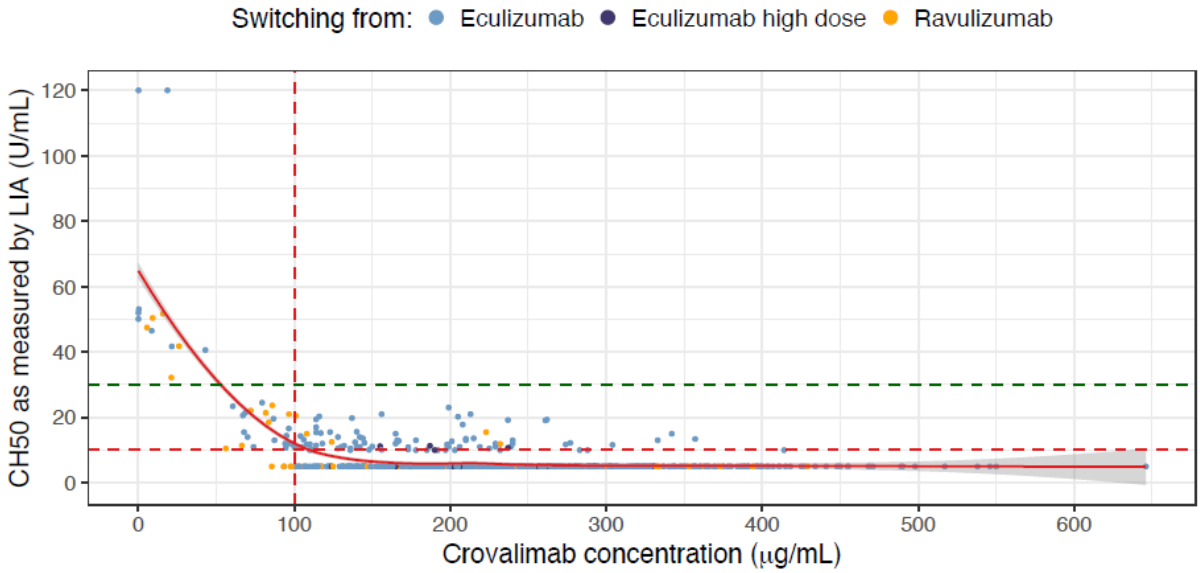
Figure 60, Figure 61, and Figure 62 show time-matched (matched by nominal time) crovalimab concentrations and CH50, colored by study population, switch population, and age category, respectively. A concentration-dependent relationship was observed, with effects close to the maximum at crovalimab concentrations ≥100 µg/mL. For crovalimab concentrations <100 µg/mL, 33.7% of the CH50 samples were below 30 U/mL (complete terminal complement activity), while for crovalimab concentrations ≥100 µg/mL, 99.9% of the CH50 samples were below 30 U/mL. In addition, the locally estimated scatterplot smoothing regression line was below the LLOQ (10 U/mL, observations imputed to 5 U/mL) at concentrations ≥100 µg/mL. No relevant difference was observed between treatment-naïve and switch subjects (Figure 60), between subpopulations (Figure 61), or between age categories (Figure 62).

Figure 60. Scatterplot of Individual Observed CH50 Versus Time-Matched Crovalimab Serum Concentrations Colored by Study Population



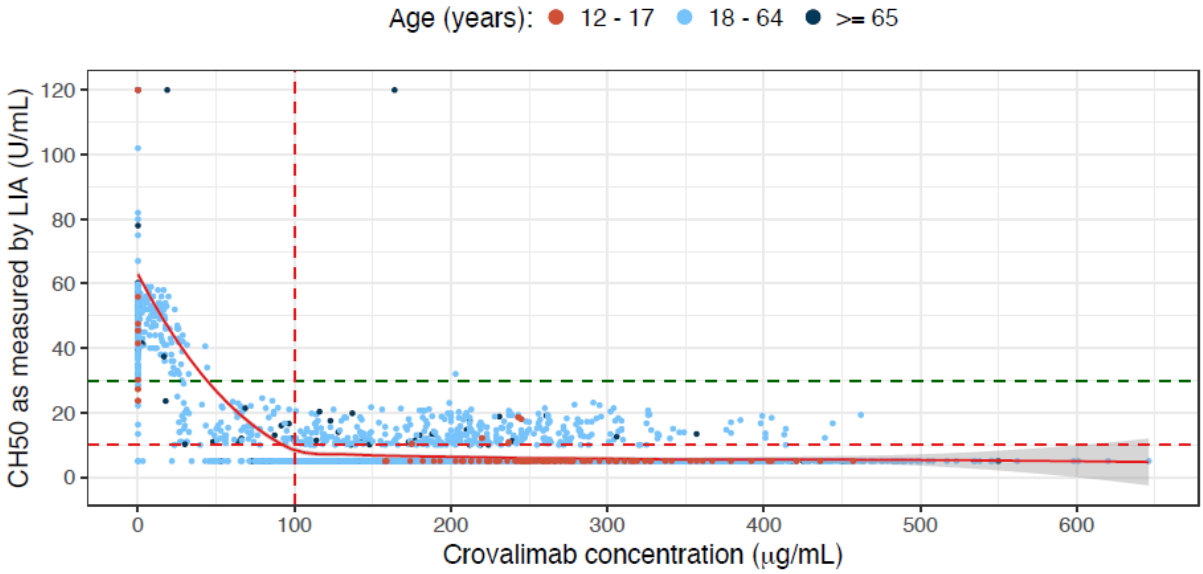
Source: PKPD Study Report, poppk-1119749, Figure 14.
Note: The red curve is a LOESS regression together with the 90% CI as shaded area. The red dashed horizontal line shows the LLOQ. The green dashed horizontal line represents the threshold for complete inhibition of terminal complement activity. The 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 subjects.
Abbreviations: C5, complement component 5; CH50, terminal complement activity; CI, confidence interval; HV, healthy volunteer; LIA, liposome immunoassay; LLOQ, lower limit of quantification; LOESS, locally estimated scatterplot smoothing; PNH, paroxysmal nocturnal hemoglobinuria

Figure 61. Scatterplot of Individual Observed CH50 Versus Time-Matched Crovalimab Serum Concentrations Colored by Switch Population



Source: PKPD Study Report, poppk-1119749, Figure 15.
Note: 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 subjects.
Abbreviations: C5, complement component 5; CH50, terminal complement activity; CI, confidence interval; LIA, liposome immunoassay; LLOQ, lower limit of quantification; LOESS, locally estimated scatterplot smoothing

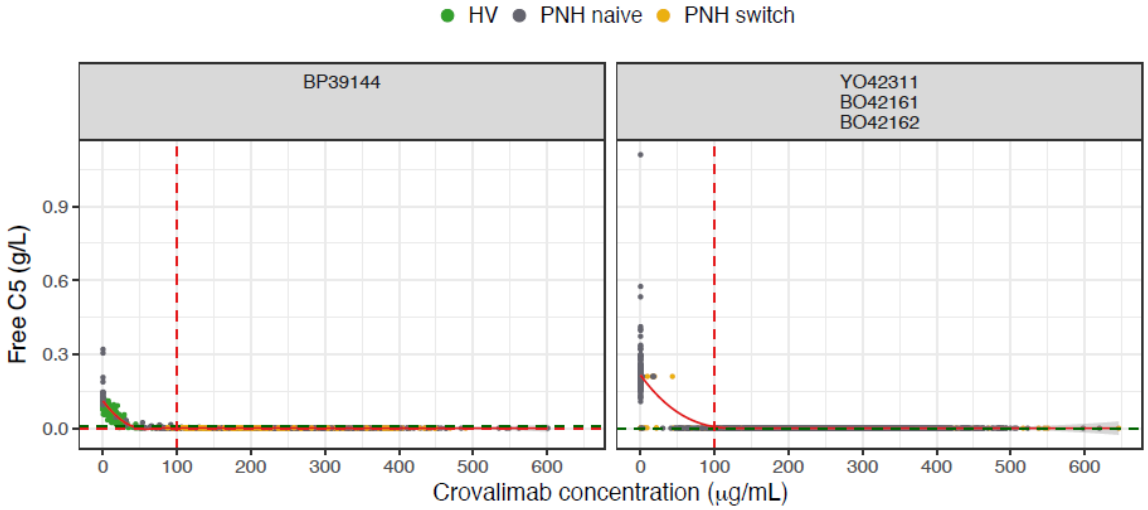
Figure 62. Scatterplot of Individual Observed CH50 Versus Time-Matched Crovalimab Serum Concentrations Colored by Age Category



Source: PKPD Study Report, poppk-1119749, Figure 16.
Note: One subject who was 17 years old at randomization had turned 18 years old at the time of crovalimab initiation and is therefore included in the group 18 to 64 years. 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 subjects.
Abbreviations: C5, complement component 5; CH50, terminal complement activity; CI, confidence interval; LIA, liposome immunoassay; LLOQ, lower limit of quantification; LOESS, locally estimated scatterplot smoothing

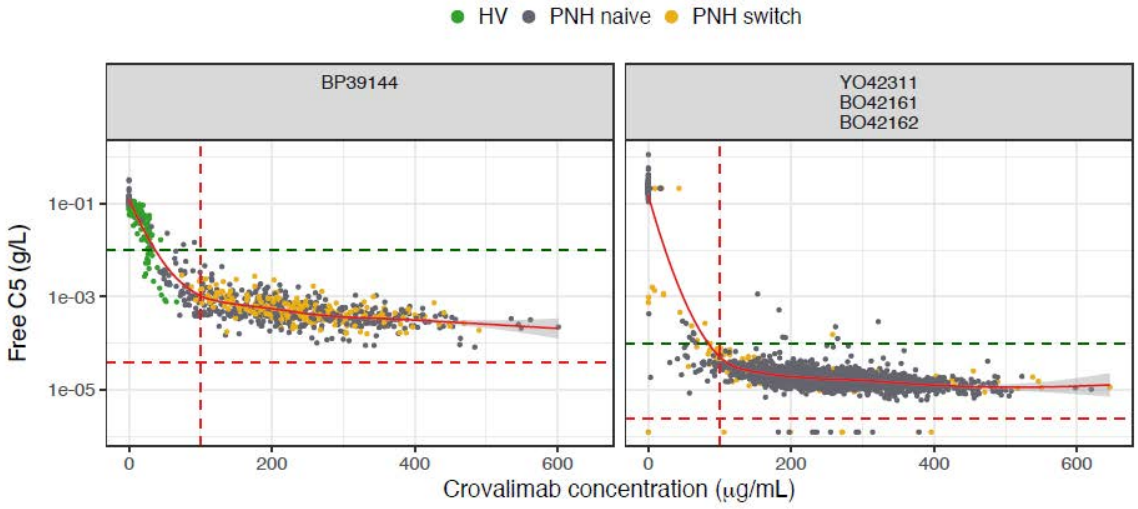
Due to different assays for free C5 in COMPOSER and in the Phase 3 studies, data from the two assays are displayed in different panels (Figure 63). Figure 64, Figure 65, and Figure 66 show time-matched (matched by nominal time) crovalimab concentrations and free C5 concentrations colored by study population, switch population, and age category, respectively. A concentration-dependent relation was observed. Based on the Phase 3 assay, at crovalimab concentrations ≥100 µg/mL, free C5 concentrations were reduced to low levels (<0.0001 g/L), evidencing complete inhibition of terminal activity. For crovalimab concentrations <100 µg/mL, 17.8% of the Phase 3, free C5 concentrations were below 0.0001 g/L, while for crovalimab concentrations ≥100 µg/mL, 99.7% of the Phase 3, free C5 concentrations were below 0.0001 g/L. Higher crovalimab concentrations did not result in a further clinically relevant decrease of free C5 concentrations, thus suggesting that maximum pharmacological effects were achieved. Despite a nonsuccessful cross validation between the two assays, results are consistent across studies. No relevant difference was observed between treatment-naïve and switch subjects (Figure 64). No relevant differences in free C5 concentrations were observed between previous treatments for switch subjects (Figure 65), or between age categories (Figure 66).

Figure 63. Scatterplot of Individual Observed Free C5 Versus Time-Matched Crovalimab Serum Concentrations Stratified by Study and Colored by Study Population



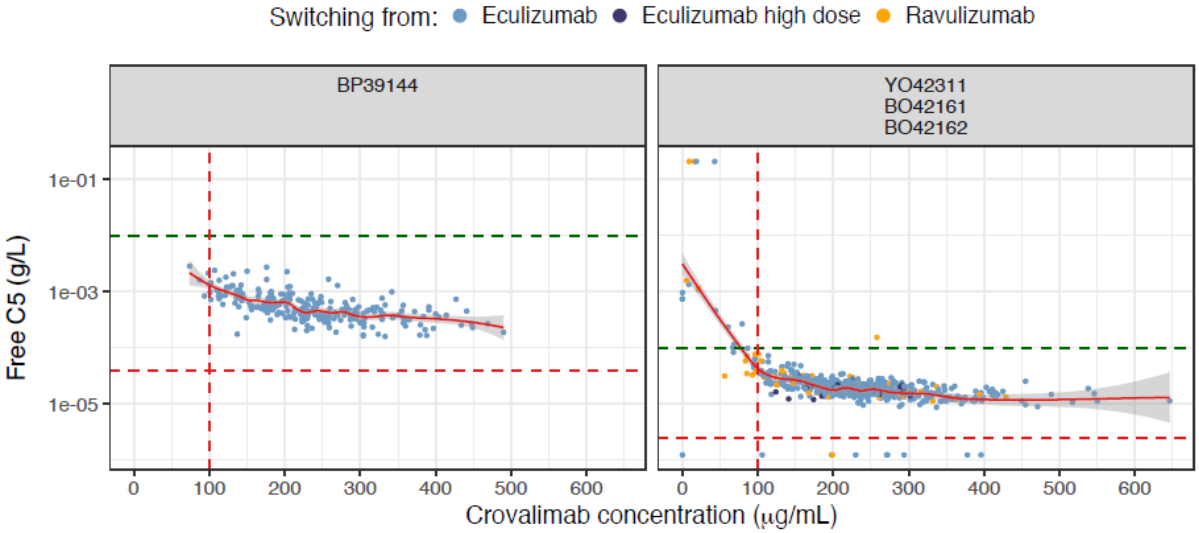
Source: PKPD Study Report, poppk-1119749, Figure 19.
Note: Different free C5 assays were used in COMPOSER and the Phase 3 studies, therefore C5 is displayed in different panels for the different assays. The red curve is a LOESS regression together with the 90% CI as shaded area. The red dashed horizontal 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 a complete complement C5 inhibition. The first 12 weeks are excluded for switch subjects.
Note: BP39144 = COMPOSER, BO42161 = COMMODORE-1, BO42162 = COMMODORE-2, YO42311 = COMMODORE-3
Abbreviations: C5, complement component 5; CI, confidence interval; HV, healthy volunteer; LLOQ, lower limit of quantification; LOESS, locally estimated scatterplot smoothing

Figure 64. Scatterplot of Individual Observed Free C5 Versus Time-Matched Crovalimab Serum Concentrations Stratified by Study and Colored by Study Population



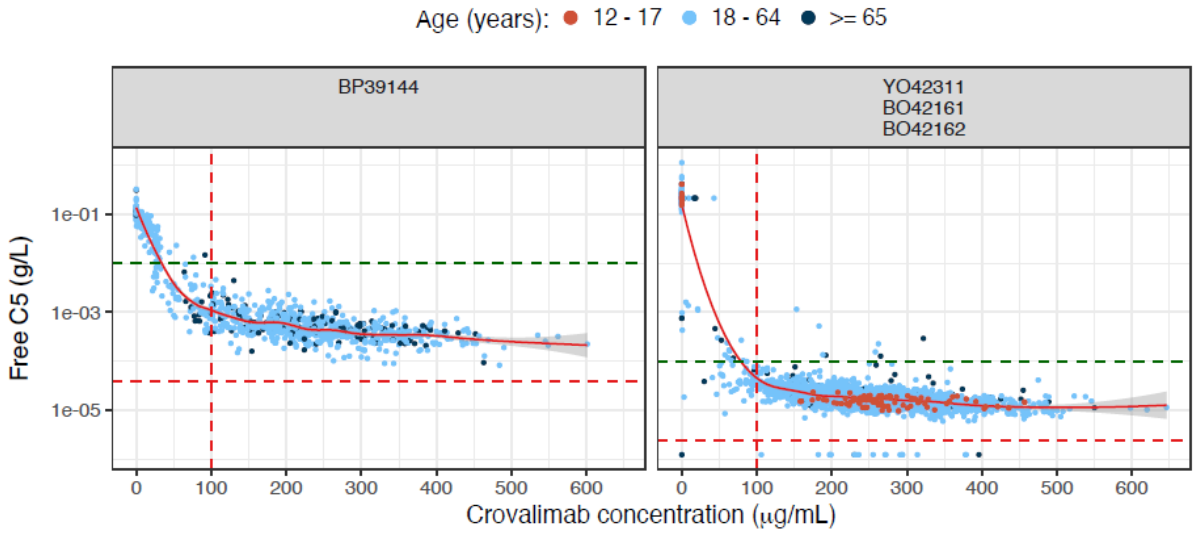
Source: PKPD Study Report, poppk-1119749, Figure 20.
Note: Different free C5 assays were used in COMPOSER and the Phase 3 studies, therefore C5 is displayed in different panels for the different assays. The red curve is a LOESS regression together with the 90% CI as shaded area. The red dashed horizontal 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 a complete complement C5 inhibition. The first 12 weeks are excluded for switch subjects.
Note: BP39144 = COMPOSER, BO42161 = COMMODORE-1, BO42162 = COMMODORE-2, YO42311 = COMMODORE-3
Abbreviations: C5: complement component 5; CI: confidence interval; HV, healthy volunteer; LLOQ: lower limit of quantification; LOESS: locally estimated scatterplot smoothing; PNH, paroxysmal nocturnal hemoglobinuria

Figure 65. Scatterplot of Individual Observed Free C5 Versus Time-Matched Crovalimab Serum Concentrations the Switch Subjects Stratified by Study and Colored by Switch Population



Source: PKPD Study Report, poppk-1119749, Figure 21.
Different free C5 assays were used in COMPOSER and the Phase 3 studies, therefore C5 is displayed in different panels for the different assays. 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 a complete complement C5 inhibition. The first 12 weeks are excluded for switch subjects.
Abbreviations: C5: complement component 5; CI: confidence interval; LLOQ: lower limit of quantification; LOESS: locally estimated scatterplot smoothing

Figure 66. Scatterplot of Individual Observed Free C5 Versus Time-Matched Crovalimab Serum Concentrations Stratified by Study and Colored by Age Group



Source: PKPD Study Report, poppk-1119749, Figure 22.
Note: Different free C5 assays were used in COMPOSER and the Phase 3 studies, therefore C5 is displayed in different panels for the different assays. 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 a complete complement C5 inhibition. The first 12 weeks are excluded for switch subjects.
Abbreviations: C5, complement component 5; CI, confidence interval; LLOQ, lower limit of quantification; LOESS, locally estimated scatterplot smoothing

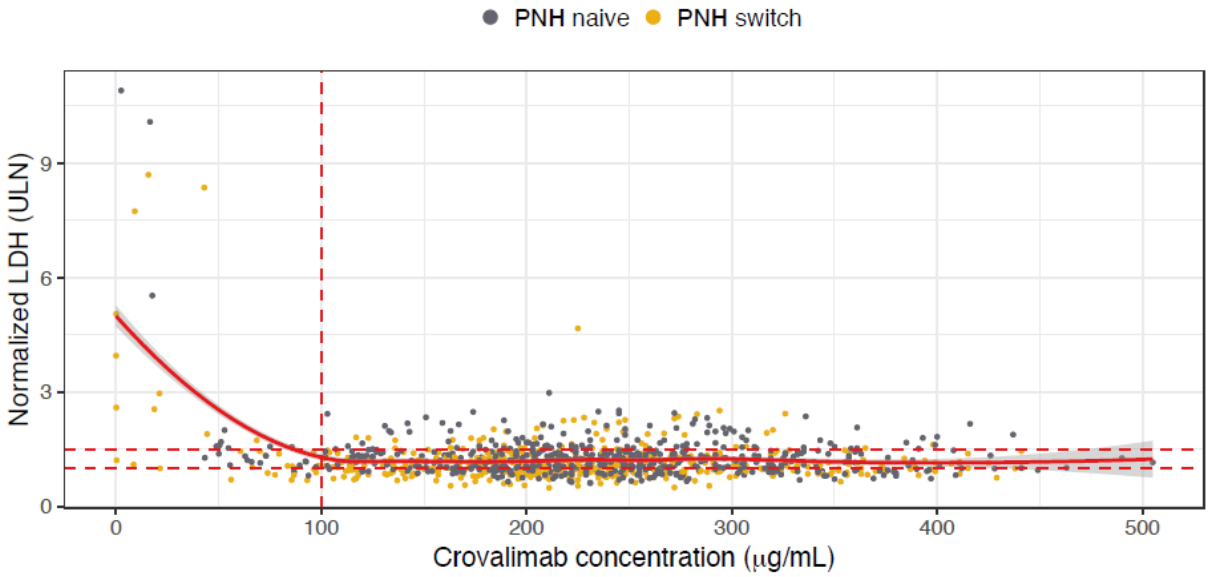
Efficacy Endpoint: LDH

A total of 7278 LDH observations (PNH naïve: n=3799, and PNH switch: 3479) from 420 subjects with PNH (PNH naïve: n=209, and PNH switch: 211) were included in this analysis. Clinical response as measured by LDH takes time for development; thus, time-matched LDH versus crovalimab concentrations were assessed only at steady state, where also stable median LDH levels were expected. This steady state period was defined as follows:

- Observations of the continuous variable collected during last 10 weeks of the primary treatment period for subjects receiving crovalimab before the primary efficacy analysis (i.e., COMPOSER [all subject arms]; COMMODORE-1, COMMODORE-2, and COMMODORE-3 [Arm A and C]), provided that it is more than 12 weeks after the switch in switch subjects.
- Observations of the continuous variable collected during the last 10 weeks of the extension period (up to 24 weeks) for subjects switching to crovalimab after the primary efficacy analysis (i.e., Arm B of COMMODORE-1 and COMMODORE-2), provided that it is more than 12 weeks after the switch.

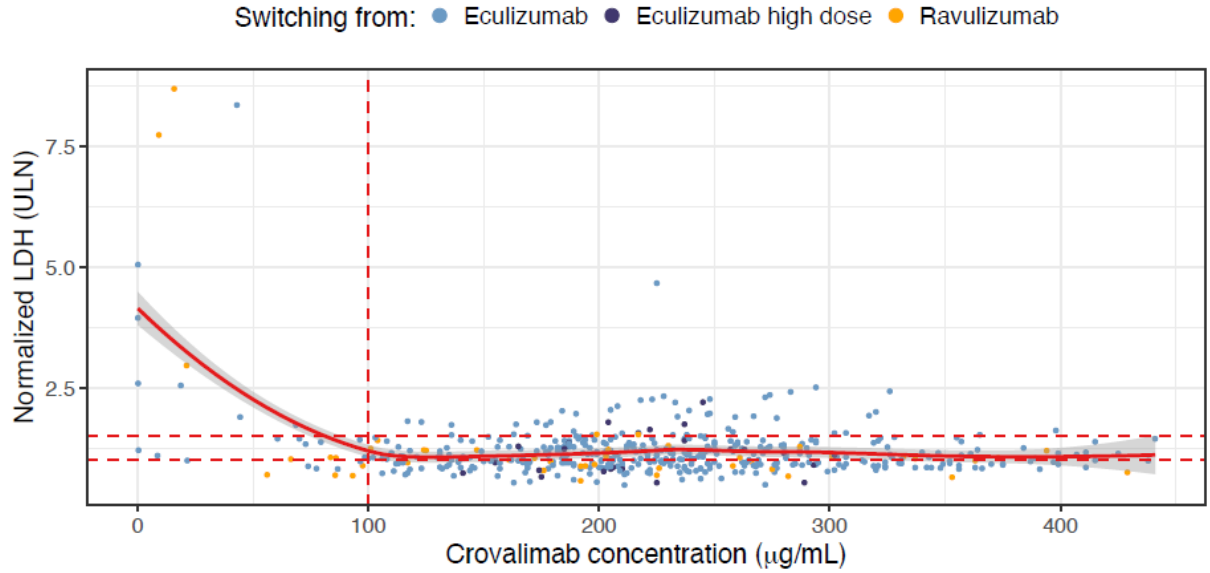
Figure 67, Figure 68, and Figure 69 show time-matched (matched by nominal time) crovalimab concentrations and LDH concentrations (as multiples of ULN) at steady state, colored by study population, switch population, and age category, respectively. At steady state (last 10 weeks of primary treatment period or crovalimab extension period), no relevant exposure-efficacy relationship was found for normalized LDH suggesting that no further reduction in LDH is expected for $C_{trough} \geq 100$ µg/mL. No relevant difference was observed between treatment-naïve and switch subjects (Figure 67), between previous treatments for switch subjects (Figure 68), or between age categories (Figure 69).

Figure 67. Scatterplot of Individual Observed Normalized LDH Versus Time-Matched Crovalimab Serum Concentrations Colored by Study Population



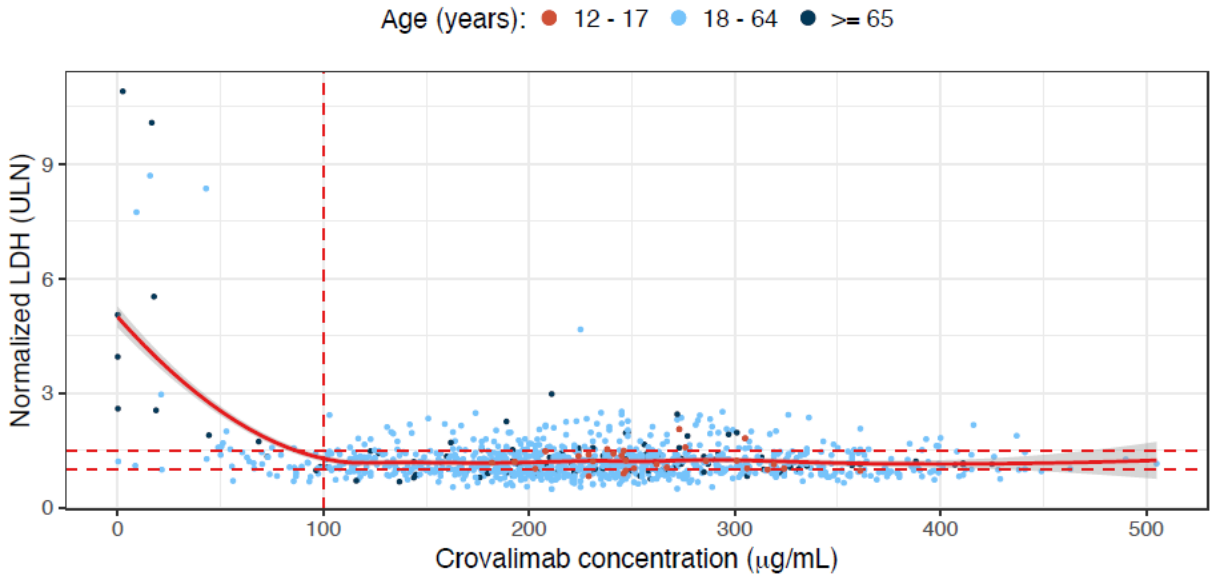
Source: PKPD Study Report, poppk-1119749, Figure 32.
Note: The red curve is a LOESS regression together with the 90% CI as shaded area. The red dashed horizontal lines show the ULN and 1.5×ULN. The red dashed vertical line shows the crovalimab concentration threshold expected to lead to a complete complement C5 inhibition.
Abbreviations: C5, complement component 5; CI, confidence interval; LDH, lactate dehydrogenase; LOESS, locally estimated scatterplot smoothing; PNH, paroxysmal nocturnal hemoglobinuria; ULN, upper limit of normal

Figure 68. Scatterplot of Individual Observed Normalized LDH Versus Time-Matched Crovalimab Serum Concentrations for the Switch Subjects Stratified by Switch Population



Source: PKPD Study Report, poppk-1119749, Figure 33.
Note: The red curve is a LOESS regression together with the 90% CI as shaded area. The red dashed horizontal lines show the ULN and 1.5×ULN. The red dashed vertical line shows the crovalimab concentration threshold expected to lead to a complete complement C5 inhibition.
Abbreviations: C5, complement component 5; CI, confidence interval; LDH, lactate dehydrogenase; LOESS, locally estimated scatterplot smoothing; ULN, upper limit of normal

Figure 69. Scatterplot of Individual Observed Normalized LDH Versus Time-Matched Crovalimab Serum Concentrations Colored by Age Category



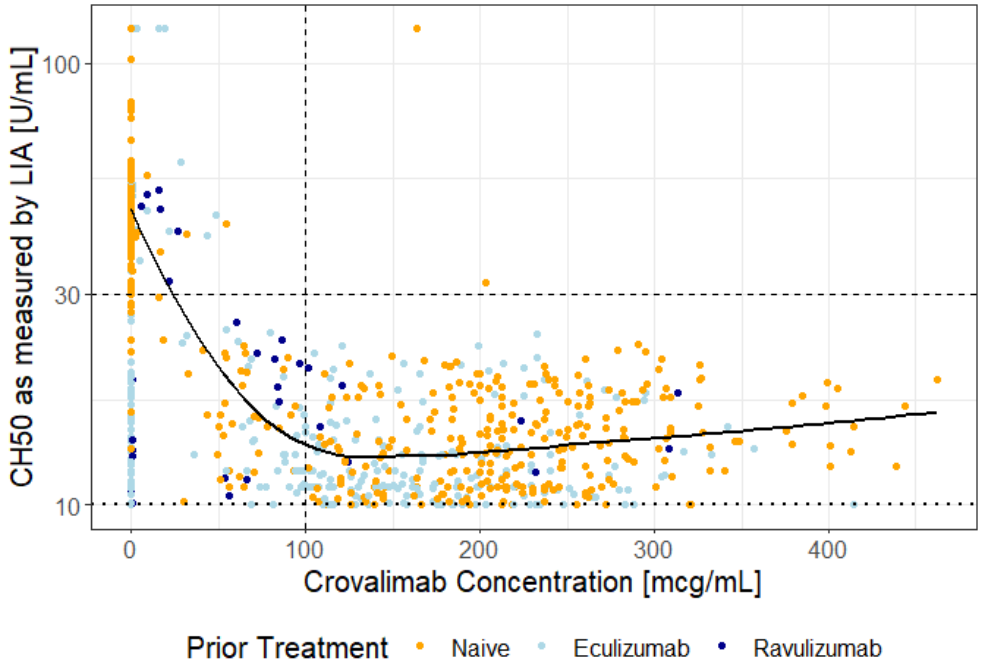
Source: PKPD Study Report, poppk-1119749, Figure 34.
Note: The red curve is a LOESS regression together with the 90% CI as shaded area. The red dashed horizontal lines show the ULN and 1.5×ULN. The red dashed vertical line shows the crovalimab concentration threshold expected to lead to a complete complement C5 inhibition.
Abbreviations: C5, complement component 5; CI, confidence interval; LDH, lactate dehydrogenase; LOESS, locally estimated scatterplot smoothing; ULN, upper limit of normal

Safety Outcomes

Categorical endpoints included the proportions of subjects with any adverse events of special interest (AESI) and any infections. The correlations between the population PK model estimated crovalimab PK exposures (AUC during the dosing interval, AUC from 0 to 24 hours on the last day of exposure, AUC curve for 28 days from 0 to 24 hours on the last day of exposure, C_{max}, and C_{max} at a steady state) and safety outcomes were evaluated by logistic regression. Overall, 2.38%, 2.14%, and 50.6% of the subjects experienced serious adverse events related to crovalimab, any AESI, and infections, respectively. No clinically relevant exposure-safety relationship was observed.

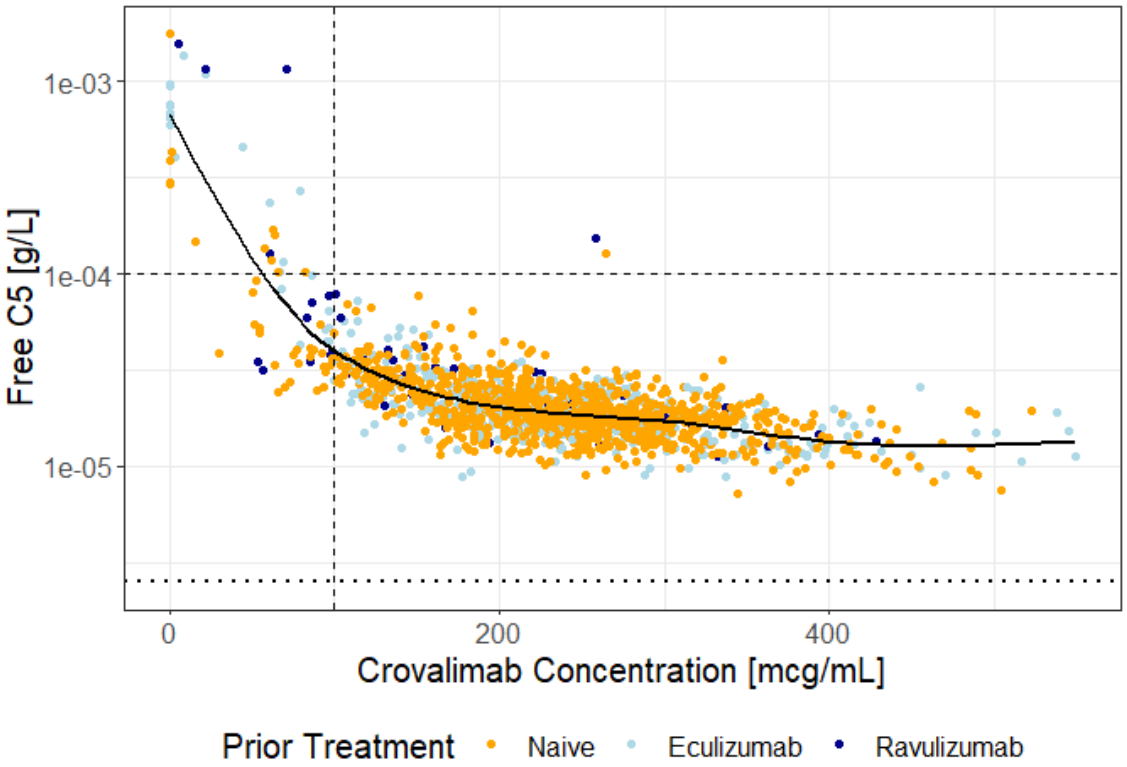
The Applicant's ER analyses for terminal complement activity, efficacy, and safety (any AESI and any infections) appear to be acceptable. The FDA's visual exploration of the observed ER for CH50 (Figure 70), free C5 at steady state (Phase 3 data only, Figure 71), and LDH at steady state (Figure 72) was consistent with the Applicant's analyses. The observed ER relationships for PD and efficacy are comparable for treatment-naïve subjects and prior-treated subjects switching from either eculizumab or ravulizumab.

Figure 70. Time-Matched CH50 Versus Crovalimab Plasma Concentration



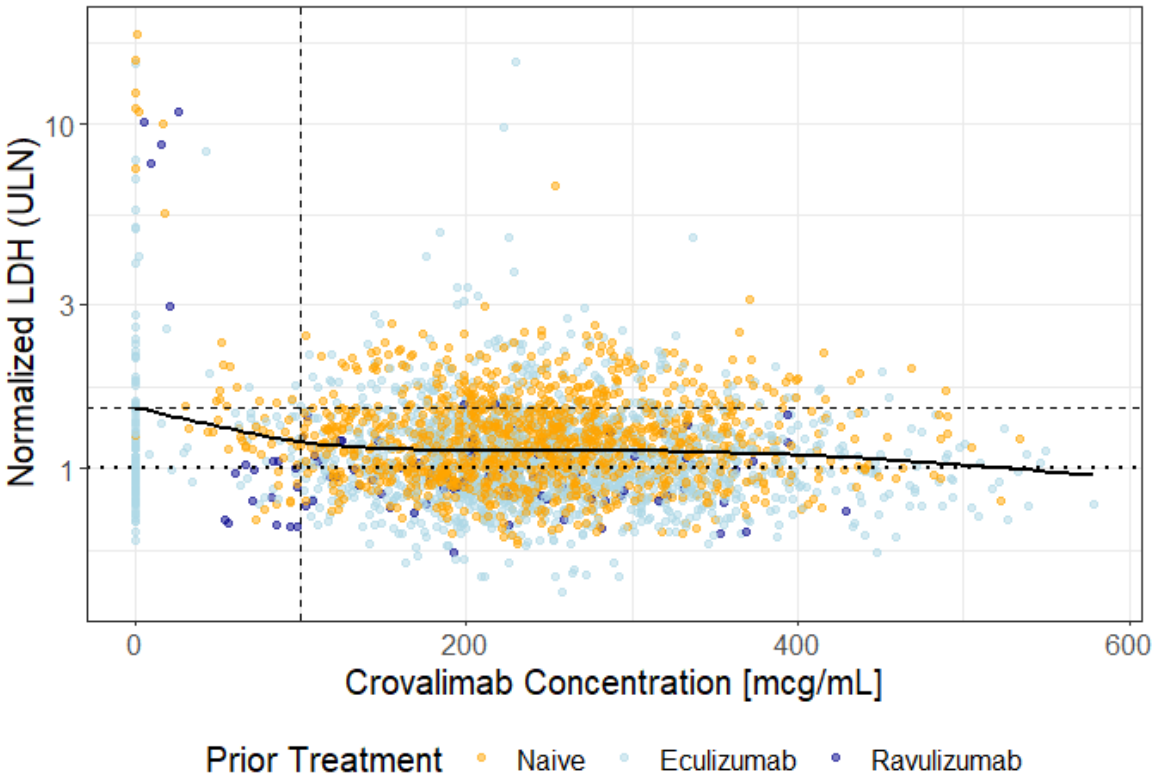
Source: Reviewer analysis
Data from clinical trial COMPOSER, COMMODORE-1, COMMODORE-2, and COMMODORE-3
Note: Vertical dashed line: 100 mcg/mL
Note: Horizontal dotted line: 10 U/mL, lower limit of quantification
Note: Horizontal dashed line: 30 U/mL, threshold of complete terminal completment activity inhibition
Note: Solid black line: loess regression
Abbreviations: CH50, terminal complement activity; LIA, liposome immunoassay; loess, locally estimated scatterplot smoothing

Figure 71. Time-Matched Free C5 Versus Crovalimab Plasma Concentration at Steady State in Subjects Included in Phase 3 Trials



Source: Reviewer analysis
Data from clinical trial COMMODORE-1, COMMODORE-2, and COMMODORE-3
Note: Vertical dashed line: 100 mcg/mL
Note: Horizontal dotted line: 2.5e-6 g/L, lower limit of quantification
Note: Horizontal dashed line: 1e-4 g/L, threshold of complete terminal completment activity inhibition
Note: Solid black line: loess regression
Abbreviations: CH50, terminal complement activity; LIA, liposome immunoassay; loess, locally estimated scatterplot smoothing

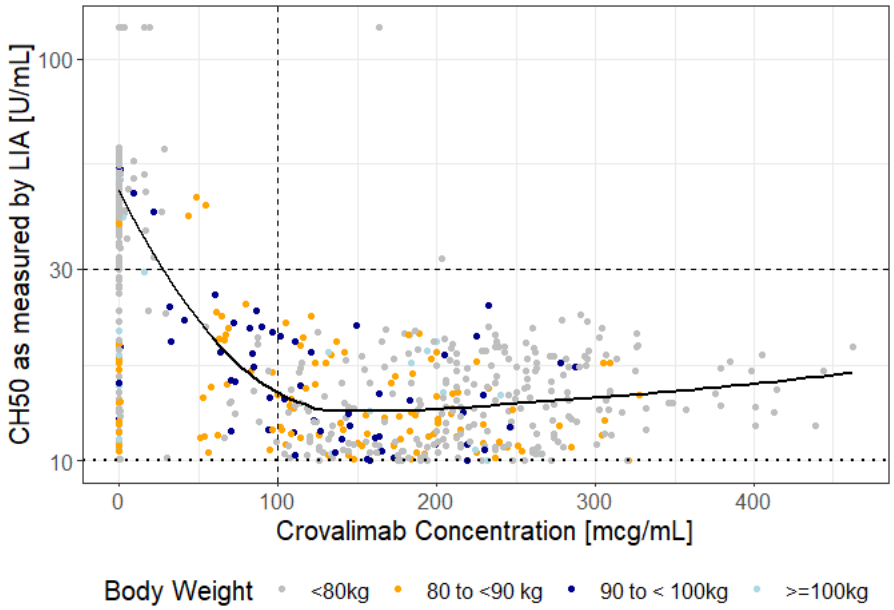
Figure 72. Time-Matched LDH Versus Crovalimab Plasma Concentration at Steady State in Subjects Included in Clinical Trials



Source: Reviewer analysis
Data from clinical trial COMPOSER, COMMODORE-1, COMMODORE-2, and COMMODORE-3
Note: Data for the first 12 weeks excluded
Note: Vertical dashed line: 100 mcg/mL
Note: Horizontal dotted and dashed line: 1X and 1.5X ULN
Note: Solid black line: loess regression
Abbreviations: CH50, terminal complement activity; LDH, lactate dehydrogenase; loess, locally estimated scatterplot smoothing; ULN, upper limit of normal

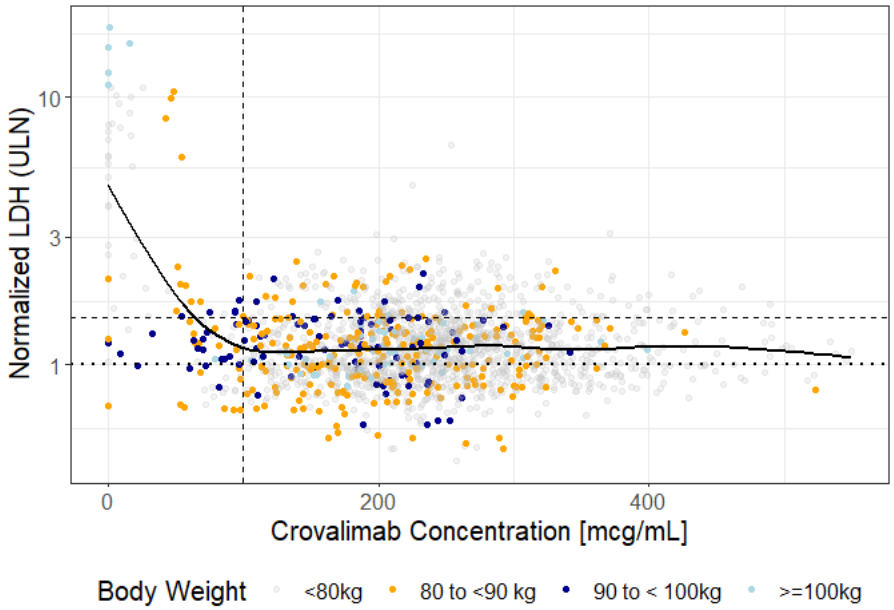
The PK exposures were negatively associated with BW at the same dose level, thereby the Applicant proposed a 50% higher first loading dose and maintenance dose for patients with BW ≥100 kg. In the population PK analysis, a larger fraction (~10%) of patients with BW 90 to 100 kg was estimated to have a steady state trough concentration below 100 µg/mL compared to those in other BW groups with the proposed dosing cut off at 100 kg (refer to population PK analysis section for details). The observed PD response was assessed to evaluate the appropriateness of 100 kg as the cut off to increase the dose. Although a less-than-maximum reduction in CH50 and LDH response was predicted, significant reduction compared to that of the placebo treatment was still observed (e.g., for a steady trough crovalimab concentration above 50 µg/mL) (Figure 70 to Figure 72). The fractions of subjects with a steady trough crovalimab concentration below 50 µg/mL were comparable between subjects with BW 90 to <100 kg (3.96%) and ≥100 kg (3.51%). In addition, ER for terminal complement activity (Figure 73) and LDH (Figure 74) were comparable among the BW groups (<80 kg: n=255, 80 to <90 kg: n=50; 90 to <100 kg: n=20; ≥100 kg: n=13). As a result, a relatively larger fraction of subjects (BW 90 to 100 kg) with steady-state trough concentration <100 µg/mL was not considered as clinically relevant.

Figure 73. Time-Matched CH50 Versus Crovalimab Plasma Concentration in Subjects Included in Clinical Trials, Stratified by Body Weight



Source: Reviewer analysis
Note: Data from clinical trial COMPOSER, COMMODORE-1, COMMODORE-2, and COMMODORE-3
Note: Vertical dashed line: 100 mcg/mL
Note: Horizontal dotted line: 10 U/mL, lower limit of quantification
Note: Horizontal dashed line: 30 U/mL, threshold of complete terminal completment activity inhibition
Note: Solid black line: loess regression
Abbreviations: CH50, terminal complement activity; LIA, liposome immunoassay; loess, locally estimated scatterplot smoothing

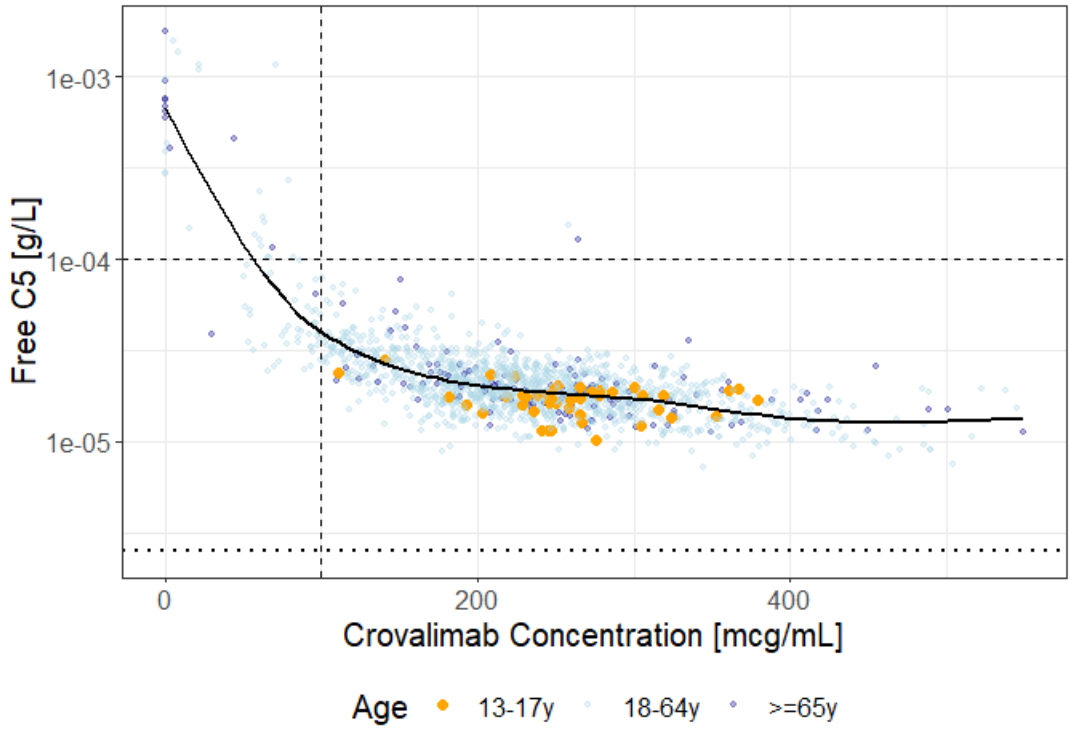
Figure 74. Time-Matched LDH Versus Crovalimab Plasma Concentration at Steady State in Subjects Included in Clinical Trials, Stratified by Body Weight



Source: Reviewer analysis
Note: Data from clinical trial COMPOSER, COMMODORE-1, COMMODORE-2, and COMMODORE-3
Note: Data for the first 12 weeks excluded
Note: Vertical dashed line: 100 mcg/mL
Note: Horizontal dotted and dashed line: 1X and 1.5X ULN
Note: Solid black line: loess regression
Abbreviations: LDH, lactate dehydrogenase; ULN, upper limit of normal; loess, locally estimated scatterplot smoothing

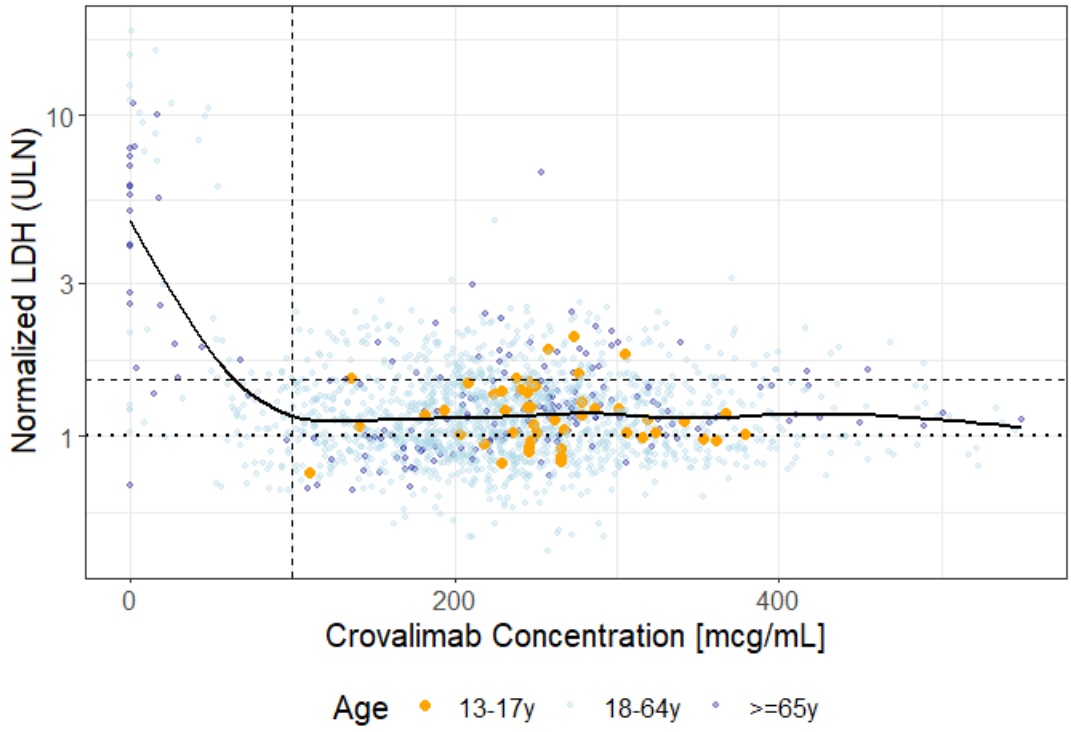
The FDA's ER analyses for terminal complement activity (Figure 75) and LDH (Figure 76) stratified by age groups (13 to 17 years of age: n=12, 18 to 64 years of age: n=328, 65 years of age and above: n=37) were consistent with the Applicant's analysis, suggesting no clinically meaningful impact of age on ER for terminal complement activity inhibition and LDH. Considering the overlapped PK exposures at steady state among these three age groups, no dose adjustment is required for age.

Figure 75. Time-Matched Free C5 Versus Crovalimab Plasma Concentration at Steady State in Subjects Included in Phase 3 Trials, Stratified by Age Groups



Source: Reviewer analysis
Note: Data from clinical trial COMMODORE-1, COMMODORE-2, and COMMODORE-3
Note: Vertical dashed line: 100 mcg/mL
Note: Horizontal dotted line: 2.5e-6 g/L, lower limit of quantification
Note: Horizontal dashed line: 1e-4 g/L, threshold of complete terminal completment activity inhibition
Note: Solid black line: loess regression
Abbreviations: C5, complement component 5; loess, locally estimated scatterplot smoothing

Figure 76. Time-Matched LDH Versus Crovalimab Plasma Concentration at Steady State in Subjects Included in Clinical Trials, Stratified by Age Groups



Source: Reviewer analysis
Note: Data from clinical trial COMPOSER, COMMODORE-1, COMMODORE-2, and COMMODORE-3
Note: Data for the first 12 weeks excluded
Note: Vertical dashed line: 100 mcg/mL
Note: Horizontal dotted and dashed line: 1X and 1.5X ULN
Note: Black solid line: loess regression
Abbreviations: LDH, lactate dehydrogenase; ULN, upper limit of normal

In summary, the proposed dosing regimen and relevant label statements are acceptable.

14.6. Pharmacogenetics

Not applicable.

15. Study/Trial Design

15.1. COMMODORE-2 (Study BO42162)

Protocol Amendments

The clinical trial landmarks and amendments for COMMODORE-2 are summarized in Table 119.

Table 119. Key Landmarks and Key Protocol Amendments, COMMODORE-2

Date	Landmarks
March 13, 2020	Original protocol
May 8, 2020	Version 2: • Clarified the methods and mode of administration of crovalimab (vials) • Capped country-specific enrollment at (b) (4)% of total study population • Removed (b) (4) as inclusion criterion, given confounding by intravascular hemolysis
October 8, 2020	First subject enrolled.
November 20, 2020	Version 3: • Introduction of a separate descriptive Arm C for enrollment of pediatric subjects of all ages weighing ≥40 kg. Prior to this amendment, the study enrolled patients ≥12 years and a minimum weight of 40 kg. • Clarified that SC injections should be given by a caregiver for subjects <12 years of age. • Added language regarding maintaining currency of N. meningitidis vaccination. • Clarified the estimand section regarding handling of intercurrent events. • Added benefit-risk assessment related to the impact of the COVID-19 pandemic on the study conduct and risk to subjects.
July 16, 2021	Version 4: • The (b) (4)% cap on recruitment in any country was removed to allow enrollment flexibility in a rare condition while maintaining generalizability of the study results. • Inclusion criteria and vaccination guidance clarified for vaccination against SARS-CoV-2. • Added exclusion criteria for patients with myelodysplastic syndrome with intermediate-to-very-high Revised International Scoring System scores.
January 24, 2022	Version 5: • Included guidance for dose escalation in subjects treated with crovalimab who experience sustained intravascular hemolysis. • Prohibited therapy has been expanded from “ravulizumab” to “other complement inhibitors” to account for recent marketing authorization of non-C5 inhibitor therapies. • Clarification was provided that if transfusions are given to allow patients to meet the protocol-specific hemoglobin eligibility criterion, the patient’s post-transfusion hemoglobin value had to be confirmed prior to randomization/enrollment. • Pre-enrollment hemoglobin ≤7 g/dL or >7 and ≤9 g/dL with signs or symptoms of anemia was added in the exclusion criteria. • Vaccination requirements for *S. pneumoniae* and *H. influenzae* (where required by local guidelines) clarified to be performed within 1 week of first study drug administration. • Intravenous rescue dose updated from 375 mg to 340 mg. • Prohibited therapy was updated to include any complement inhibitor. • “Treatment discontinuation from crovalimab without switching to another complement inhibitor” as well as “immunogenicity” were added as new risks associated with crovalimab therapy and corresponding guidance was provided. • The list of intercurrent events (ICEs) in the estimand section was expanded to include dose modifications due to experiencing two or more qualifying intravascular hemolysis events or sustained intravascular hemolysis. The analysis strategy for the list of ICEs was updated.

Date	Landmarks
September 30, 2022	Version 6: • Addressed the impact of the longer-than-originally-expected half-life of crovalimab that had emerged from ongoing analyses of data across the development program. This led to updates of sections about the duration of the safety follow-up period (from 24 to 46 weeks), duration of contraception or intention to become pregnant for female subjects (from 24 to 46 weeks), and duration of reporting for pregnancies (from 24 to 46 weeks). • Clarified that transfusions could be given to allow patients to meet the protocol-specific hemoglobin eligibility criterion prior to randomization/enrollment.
November 16, 2022	Clinical data cutoff date
Study ongoing	Last subject last visit

Source: COMMODORE-2 CSR
Abbreviations: AST, aspartate transaminase; C5, complement component 5; COVID-19, coronavirus disease of 2019; ICE, intercurrent event; SC, subcutaneous; ULN, upper limit of normal

Eligibility Criteria

The abbreviated eligibility criteria are provided in Section 6.2.1.2. Key inclusion and exclusion criteria are provided below.

Key Inclusion Criteria

- BW ≥40 kg.
- To qualify for the randomized arms: age ≥18 years.
- To qualify for the descriptive arm: age <18 years.
- Documented diagnosis of PNH, confirmed by high sensitivity flow cytometry and evaluation of white blood cells (WBCs) with granulocyte or monocyte clone size of ≥10% within 6 months.
- LDH level ≥2×ULN (as per local assessment).
- Presence of one or more of the following PNH-related signs or symptoms within 3 months prior to screening: fatigue, hemoglobinuria, abdominal pain, shortness of breath (dyspnea), anemia (hemoglobin <10 g/dL), history of a major adverse vascular event (MAVE) (including thrombosis), dysphagia, erectile dysfunction, or history of packed red blood cell (pRBC) transfusion because of PNH.
- Vaccination against *Neisseria meningitidis* serotypes A, C, W, and Y <3 years prior to initiation of study treatment. Vaccination against serotype B should be administered in accordance with the most current local guidelines or standard-of-care, as applicable in patients with complement deficiency. If not previously administered or no longer current, vaccination must be completed no later than 1 week after the first study drug administration. Vaccination currency, with vaccination against serotypes A, C, W, Y and B, should be maintained throughout the study, according to local guidelines or standard-of-care, as applicable in patients with complement deficiency. In the absence of clear local guidelines for *Neisseria meningitidis*, the Advisory Committee on Immunization Practices 2020 Guidelines are recommended. If vaccination is completed <2 weeks prior to initiation or after the start of study treatment, appropriate antibiotic prophylaxis must be maintained from first

study drug administration, continuing for at least 2 weeks after completion of vaccination or according to local standard-of-care, as applicable in patients with complement deficiency, whichever is longer. If vaccination is administered during screening, and prophylactic antibiotics are not to be administered, the vaccination must take place at least 2 weeks prior to the first dose of study drug. Patients who refuse vaccination against *Neisseria meningitidis* are not eligible for the study.

- Vaccination against *Haemophilus influenzae* type B and *Streptococcus pneumoniae* according to national vaccination recommendations (e.g., Advisory Committee on Immunization Practices guidelines). If not previously administered or no longer current, vaccination should be completed no later than 1 week after the first study drug administration. If vaccination is completed <2 weeks prior to initiation or after the start of study treatment, appropriate antibiotic prophylaxis must be maintained from first study drug administration, continuing for at least 2 weeks after completion of vaccination or according to local standard-of-care, whichever is longer. If vaccination is administered during screening, and prophylactic antibiotics are not to be administered, the vaccination must take place at least 2 weeks prior to enrollment. Patients who refuse vaccination against *Haemophilus influenzae* type B and *Streptococcus pneumoniae* when recommended are not eligible for the study.
- Patients who have been vaccinated (partially or in full) against SARS-CoV-2 with a locally approved vaccine are eligible to be randomized/enrolled in the study 3 days or longer after inoculation. Patients who have not been vaccinated against SARS-CoV-2 are also eligible to be in the study.
- Platelet count ≥30,000/mm^3 without transfusion support within 7 days of laboratory testing.
- Absolute neutrophil count ≥500/mcL.
- Short-acting granulocyte colony-stimulating factors must not have been administered within 14 days of lab testing.
- Long-acting granulocyte colony-stimulating factors must not have been administered within 28 days of lab testing.
- For patients receiving other therapies (e.g., immunosuppressants, corticosteroids, iron supplements, anticoagulants, erythrocyte-stimulating agents): stable dose for ≥28 days prior to the first study drug administration.
- Adequate hepatic function, with alanine aminotransferase/aspartate aminotransferase ≤3×ULN; no clinical signs or known laboratory/radiographic evidence consistent with cirrhosis.
- Adequate renal function, defined as serum creatinine ≤2.5×ULN and creatinine CL by Cockcroft-Gault formula ≥30 mL/min.
- For female patients of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception.

Key Exclusion Criteria

- Pre-enrollment hemoglobin value ≤7 g/dL, or pre-enrollment hemoglobin value >7 g/dL and ≤9 g/dL with concurrent signs and symptoms of anemia, including angina, syncope, lightheadedness, confusion, severe or worsening shortness of breath, severe or worsening fatigue, stroke, transient ischemic attack, or new or worsening heart failure.
- Hemoglobin must be measured prior to randomization/enrollment and 5 days prior to first administration of the study drug (Study Day 1). At that time, if the patient does not meet the eligibility criteria, the patient may be transfused with pRBCs to meet the hemoglobin eligibility threshold.
- Current or previous treatment with a complement inhibitor.
- History of allogeneic bone marrow transplantation.
- History of *Neisseria meningitidis* infection within 6 months prior to screening and up to first study drug administration.
- Known or suspected immune deficiency (e.g., history of frequent recurrent infections).
- Known or suspected hereditary complement deficiency.
- Known HIV infection and with a CD4+ cell count <200 cells/mcL within 24 weeks. Patients with HIV infection who have a CD4+ cell count >200 cells/mcL and meet all other criteria are eligible.
- Infection requiring hospitalization or treatment with IV antibiotics within 28 days, or oral antibiotics within 14 days prior to screening and up to the first drug administration.
- Active systemic bacterial, viral, or fungal infection within 14 days.
- Presence of fever (≥38^{o}C) within 7 days.
- Immunized with a live attenuated vaccine within 1 month.
- History of malignancy within 5 years, with the following exceptions:
  - Patients with any malignancy treated with curative intent and the malignancy has been in remission without treatment for >5 years prior to the first drug administration are eligible.
  - Patients with curatively treated basal or squamous cell carcinoma of the skin or in situ carcinoma of the cervix at any time prior to the first drug administration, with no evidence of recurrence, are eligible.
  - Patients with low-grade, early-stage prostate cancer (Gleason score 6 or below, stage 1 or 2) with no requirement for therapy at any time prior to the first drug administration are eligible.
- History of myelodysplastic syndrome (MDS) with Revised International Prognostic Scoring System prognostic risk categories of intermediate, high, and very high.
- History of hypersensitivity, allergic, or anaphylactic reactions to any ingredient contained in crovalimab or eculizumab, including hypersensitivity to human, humanized, or murine monoclonal antibodies or known hypersensitivity to any constituent of the product.

- Pregnant or breastfeeding, or intending to become pregnant during the study, within 46 weeks (approximately 10.5 months) after the final dose of crovalimab, or 3 months after final dose of eculizumab. Female patients of childbearing potential must have a negative serum pregnancy test result within 28 days prior to initiation of study drug.
- Participation in another interventional treatment study with an investigational agent or use of any experimental therapy within 28 days of screening or within 5 half-lives of that investigational product, whichever is greater.
- Substance abuse within 12 months, in the investigator's judgment.
- Concurrent disease, treatment, procedure or surgery, or abnormality in clinical laboratory tests that could interfere with the conduct of the study, may pose any additional risk for the patient, or would preclude safe participation in the study.
- Splenectomy ≤6 months prior to screening.
- Positive for hepatitis B surface antigen.
- Positive for hepatitis C virus antibody. Patients who are seropositive for hepatitis C virus but without detectable hepatitis C virus RNA are eligible.
- History of or ongoing cryoglobulinemia.

Crovalimab Administration

For the IV infusion on Week 1, Day 1, crovalimab solution was to be diluted in 0.9% (weight/volume) sodium chloride solution prior to administration. For those subjects receiving an initial IV loading dose of 1000 mg, the infusion was to be delivered over 60 (±10) minutes. For those subjects receiving an initial IV loading dose of 1500 mg, the infusion was to be delivered over 90 (±10) minutes. Subjects were to be observed by a health care professional during the IV infusion and for 60 minutes following the completion of IV infusion. The first five SC doses of undiluted drug (on Days 2, 8, 15 and 22) were to be administered in a monitored setting, such as an infusion center, clinic, or hospital. For the first three SC doses (Days 2, 8 and 15), subjects were to be observed by a health care professional for 60 minutes following the drug administration.

Switching to a Different Complement Inhibitor

Subjects who discontinued treatment with crovalimab and switched to a different C5 inhibitor that binds to a different epitope were required to remain in the safety follow-up because of the potential risk of developing a DTDC-mediated type III hypersensitivity reaction, especially within the first few weeks of switching from one C5 inhibitor to another. Typical onset of type III hypersensitivity reactions associated with DTDC formation is delayed by a week or more after dose administration (and the reaction may persist for days to over a week) and may include the skin, joints, and/or kidneys. Typical signs and symptoms may include purpura, petechial or urticarial rashes affecting the lower extremities bilaterally, arthralgia, and enlarged and/or tender lymph nodes/spleen. Hematology and chemistry laboratory tests, physical examination, vital signs, and urinalysis were to be conducted after the first administration, then QW for the first 5 weeks (Weeks 1 to 5), and then at Week 7 and Week 9 after switching from crovalimab to a

standard of care C5 inhibitor. Guidelines for management of type III hypersensitivity reactions were provided (see Table 120).

Subjects who received eculizumab and switched to crovalimab after completing 24 weeks of treatment with eculizumab were also to be monitored, especially within the first few weeks of switching to crovalimab, because of the potential risk of developing a DTDC-mediated type III hypersensitivity reaction. Subjects were to be followed-up by telephone call on Week 1, Day 4 and Week 2, Day 12 (in between visits) of crovalimab treatment for any adverse events (AEs). Subjects were to be closely monitored for signs or symptoms of type III hypersensitivity, especially skin abnormalities, including physical examinations. When a type III hypersensitivity reaction was observed, unscheduled biomarker, PD, ADA, exploratory safety (DTDC), PK samples, and biopsies of skin were to be taken, if considered clinically indicated. Chemistry and hematology tests, urinalysis, vital signs, and limited physical exams were to be conducted after the first administration of crovalimab, then QW for the first 5 weeks (Weeks 1 to 5 of crovalimab administration), then Q2W through Week 9 (Weeks 7 and 9 of crovalimab administration), and then Q4W through Week 25 of crovalimab administration.

Subjects who discontinued treatment with crovalimab or eculizumab without switching to another complement inhibitor were to be monitored for signs and symptoms of serious IVH (e.g., elevated LDH, sudden decrease in hemoglobin, or re-appearance of hemolysis symptoms) for at least 20 weeks (if discontinuing crovalimab) or for at least 8 weeks (if discontinuing eculizumab).

Crovalimab Treatment Modification Plan

Dose modification was only required if the subject's BW changed by ≥10% to exceed or become equal to 100 kg or to fall below 100 kg during the course of therapy.

Dose modification was also considered for the following cases:

- Subjects with two or more qualifying IVH events that occurred within 24 weeks without an identifiable trigger (such as an infectious trigger). Qualifying IVH events were consistent with the definition of breakthrough hemolysis (BTH) (i.e., at least one new or worsening symptom or sign of IVH in the presence of elevated LDH ≥2×ULN after prior reduction of LDH to ≤1.5×ULN on treatment as defined in Section 6.2.1.2) that occur within 1 week before the next maintenance dose.
- Subjects with sustained IVH also occurring without an identifiable trigger. Sustained IVH was defined as LDH ≥2×ULN measured at 3 consecutive assessments and persisting for at least 4 weeks, where each LDH ≥2×ULN measurement was accompanied by at least one sign or symptom of IVH, during the maintenance phase of crovalimab treatment (Week 5 or thereafter).

Subjects for whom a dose modification was appropriate, based on the above criteria, were to have their maintenance dosing regimen increased for the remaining duration of crovalimab treatment as follows:

- Subjects with BW ≥40 kg to <100 kg would increase their maintenance dose from 680 mg Q4W to 1020 mg Q4W.
- Subjects with BW ≥100 kg would increase their maintenance dose from 1020 mg Q4W to 1360 mg Q4W.

Subjects whose maintenance dose was increased due to experiencing two or more qualifying IVH events or sustained IVH were to have additional laboratory assessments performed as follows:

- The subject's LDH, PK, PD, and ADA were to be assessed centrally before the first administration of the increased maintenance dose and four weeks after the first administration of the increased maintenance dose.
- CBC and LDH were to be assessed locally before the first administration of the increased dose, at four weeks after the first administration of the increased maintenance dose, and as clinically indicated thereafter to monitor clinical response.

For subjects with persistent, sustained IVH after 4 weeks of treatment with the increased dose, the risks and benefits of continuing crovalimab treatment were to be evaluated.

Table 120. Crovalimab: Guidelines for Management of Subjects Who Experience Adverse Events

Event	Action to Be Taken
Anaphylaxis	• If an anaphylactic reaction occurs, stop administration and permanently discontinue crovalimab. • Follow anaphylaxis treatment guidelines in Appendix 3.
Infusion-related reaction (IRR)	
IRR: Grade 1, 2, or 3	• The crovalimab infusion should be temporarily held until resolution of symptoms to Grade 1 or better. • Provide full supportive care according to institutional practice. • Monitor patient until complete resolution. • Crovalimab may be continued at the investigator's discretion.
IRR: Grade 4	• The crovalimab infusion should be stopped and not re-initiated. Provide full supportive care according to institutional practice. • Monitor patient until complete resolution. • Discontinue crovalimab.
Injection-Site Reactions	
Injection-site reaction Grade 1 or 2	• Provide full supportive care according to institutional practice. • Monitor patient until complete resolution. • Crovalimab may be continued at the investigator's discretion.
Injection-site reaction Grade 3 [a] or 4	• Provide full supportive care according to institutional practice. • Monitor patient until complete resolution. • Crovalimab may be continued at the investigator's discretion and in discussion with Medical Monitor for Grade 3 ISR. • Discontinue crovalimab if Grade 4 ISR occurs.

Type III Hypersensitivity Reactions (Serum Sickness [b])	
General Guideline	• Upon clinical presentation of a suspected Type III hypersensitivity reaction (initial manifestation of vasculitis, purpura, pruritus, arthralgia, etc.), treat according to severity [a].
Grade 1 or 2 signs and symptoms	• For arthralgia, administer analgesics and nonsteroidal anti-inflammatory agents. • For pruritis and rash, administer antihistamines and topical corticosteroids. • Monitor kidney function and perform urinalysis (Section 4.5.8). • Continue crovalimab.
Grade 3 signs and symptoms	• For high fever (e.g., temperature >38.5°C [>101.3°F]), 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 glucocorticoid). • 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. • Monitor kidney function and perform urinalysis (Section 4.5.8) • Continue crovalimab.
Grade 4 signs and symptoms	• Treat as Grade 3 reaction above • May be continued at the investigator's discretion and in discussion with the Medical Monitor.
Infections	
Meningococcal meningitis	• Treat according to standard of care. • Discuss continuation of crovalimab with Medical Monitor.
Any other infection	• Treat according to standard-of-care on a case-by-case basis, depending on signs and symptoms. • Discuss continuation of crovalimab with Medical Monitor for Grade 3 infections that persist for >7 days. • Discuss continuation of crovalimab with Medical Monitor for any Grade 4 infection.
Other Treatment-related Toxicities Not Described Above	
Grade 1, 2, or 3	• Treat according to local practice. • Crovalimab may be continued at the investigator's discretion.
Grade 4	• Treat according to local practice. • Discontinue crovalimab.
Hy's Law	• Treat according to local practice. • Discontinue crovalimab.

Source: COMMODORE-2 protocol.
[a] Grade 3 injection-site reactions defined as ulceration or necrosis; severe tissue damage; operative intervention indicated. Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae.
[b] Serum Sickness and Serum Sickness-Like Reactions (Wener 2022).
Abbreviations: IRR, infusion related reaction; ISR, injection-site reaction; IV, intravenous

Training for Self-Administration of Crovalimab

In COMMODORE-2, the first five SC doses (Day 2 of Week 1, and Weeks 2, 3, 4, and 5) had to be administered in a monitored setting, such as an infusion center, clinic, or hospital. Over the course of the first five SC doses, subjects and/or subject caregiver(s) were to be trained in SC

administration of crovalimab by a health care provider. (b) (4)

The BLA submission contained a human factors validation study report. The Division of Medication Error Prevention and Analysis reviewed the study report. The Division of Medication Error Prevention and Analysis' overall assessment was that the human factors validation study results do not support administration of the proposed product by adult and pediatric patients or lay caregivers. (b) (4) See the review by the Division of Medication Error Prevention and Analysis in DARRTS.

Permitted Therapy

Use of oral contraceptives (with a failure rate of <1% per year), immunosuppressant therapy, corticosteroids, iron supplements and folic acid were permitted during the study. In general, supportive therapies as clinically indicated, per local standard practice, were advised. Subjects who experience infusion-associated symptoms could be treated with acetaminophen, ibuprofen, diphenhydramine, and/or H2-receptor antagonists, or equivalent medications per local standard practice. Serious infusion-associated events (manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress) were to be managed with supportive therapies as clinically indicated.

Immunizations

As vaccination may further activate complement, subjects with PNH were to be monitored closely for disease symptoms (such as hemolysis after receiving vaccination). Vaccinations (other than against *Neisseria meningitidis* serotypes A, C, W, and Y: or *Haemophilus influenzae* type B and *Streptococcus pneumoniae*) were not to be administered on the same day as a crovalimab administration but, ideally, at a time point between Day +3 after a maintenance dose and Day -3 before the next maintenance dose administration. Vaccinations against SARS-CoV-2 (including locally approved vaccines) were permissible during the course of the study. The administration of the vaccine against SARS-CoV-2 ideally was to follow the schedule recommended above for other vaccines.

15.2. COMMODORE-3 (Study YO42311)

Study Design

COMMODORE-3 is a Phase 3, multicenter, single-arm study conducted in China designed to evaluate the efficacy, safety, PK, and PD of crovalimab in patients ≥12 years of age with PNH and a BW ≥40 kg, who have not been previously treated with a complement-inhibitor therapy. Other inclusion criteria include LDH level ≥2×ULN, at least four transfusions during the prior 12 months, presence of 1 or more of PNH-related signs or symptoms within 3 months, and vaccination against *Neisseria meningitidis*, *Haemophilus influenzae* type B, and *Streptococcus pneumonia* in accordance with the most current local guidelines or standard-of-care.

The co-primary efficacy endpoints are:

- Mean proportion of subjects with hemolysis control measured by LDH ≤1.5x ULN from Week 5 through Week 25 and analyzed by a standard generalized estimating equation model.
- The difference in the proportion of subjects who achieve transfusion avoidance (TA) from baseline through Week 25 (after 24 weeks of treatment) and analyzed by a paired McNemar test with continuity correction.

Both co-primary endpoints were required to achieve a 2-sided significance level of 0.05 to conclude positive study results.

Secondary efficacy endpoints include:

- BTH from baseline through Week 25
- Hemoglobin stabilization from baseline through Week 25

During screening, retrospective collection of medical data for the 24 weeks prior to enrollment occurred. This study was to enroll approximately 50 subjects with PNH to be treated with the proposed crovalimab dose regimen as shown in Table 8 in Section 6.2.1.1 for at least 24 weeks. No interim efficacy analyses were planned for this study. The primary efficacy analysis was to take place once all subjects either completed 24 weeks of treatment with crovalimab or discontinued from the treatment, whichever occurs first. Subjects were required to have received at least one dose of crovalimab treatment and have at least one central LDH level assessment after the first IV infusion to be included in the primary efficacy analysis. After completing 24 weeks of treatment with crovalimab (i.e., Week 25 visit), subjects were allowed to continue crovalimab Q4W until they switch to an extension study (if available), to a commercial product, or receive crovalimab as per the Roche Global Policy on Continued Access to Investigational Medicinal Products.

15.3. COMMODORE-1 (Study BO42161)

15.3.1. Design, COMMODORE-1 (Study BO42161)

COMMODORE-1 is a Phase 3, randomized, open-label, active-controlled, multicenter trial to evaluate the safety, PK, PD, and efficacy of crovalimab compared with eculizumab in patients with PNH currently treated with a complement inhibitor therapy. The study is comprised of randomized arms (Arms A and B), consisting of adult subjects (≥18 years of age) who have been receiving eculizumab at the approved dose for PNH for at least 24 weeks, and a nonrandomized arm (Arm C), consisting of cohorts of subjects treated with a C5 inhibitor (i.e., eculizumab or ravulizumab).

While the study was ongoing, the Applicant stopped randomization into Arms A and B in November 2022. The Applicant determined that enrollment of a sufficient number of subjects would not be attainable to support an adequately-powered efficacy analysis, given the evolving treatment landscape (i.e., multiple available therapies for patients with PNH), delays due the COVID-19 pandemic, and a reduced pool of eculizumab pretreated patients over time. The projected enrollment in the two arms was approximately 90 subjects, and the primary analysis of the study was conducted at the same time as the primary analysis of COMMODORE-2. Efficacy

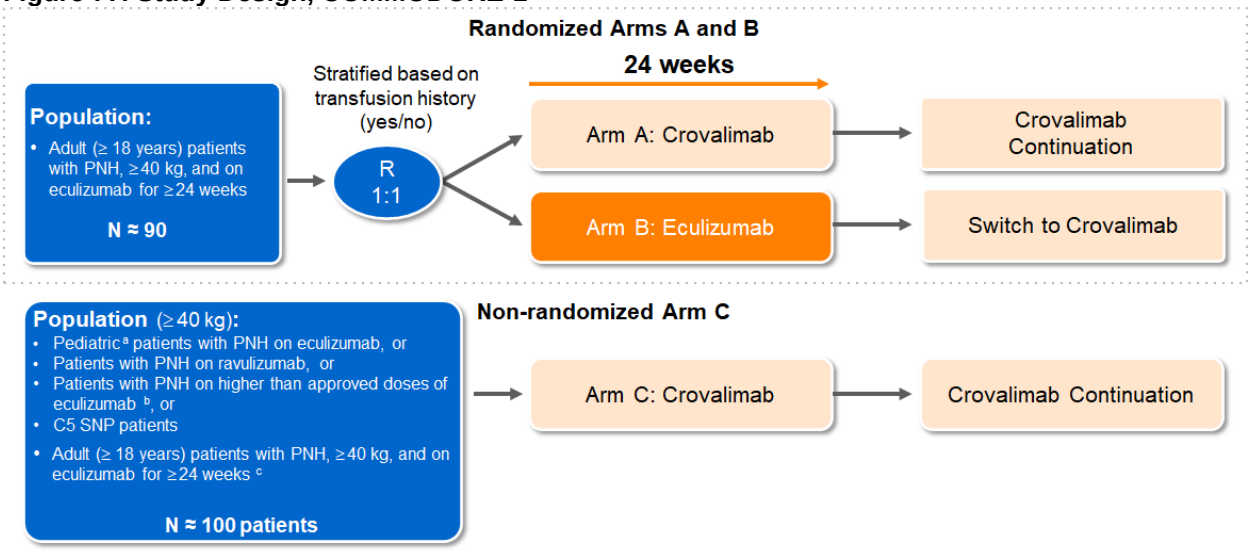
in COMMODORE-1 was updated to become an exploratory objective, and the results were descriptive, with no formal statistical noninferiority and superiority testing. Considering the shift of the efficacy objectives to exploratory, safety became the only primary objective. Enrollment into the nonrandomized Arm C was continued to target approximately 100 subjects in order to maintain the overall safety database for crovalimab-treated subjects.

The nonrandomized arm (Arm C) consists of the following five cohorts:

- Pediatric patients (<18 years of age) currently treated with eculizumab.
- Patients currently treated with ravulizumab.
- Patients currently treated with eculizumab at higher than the approved dose for PNH (>900 mg per dose and/or more frequently than Q2W).
- Patients with a known C5 polymorphism whose hemolysis was poorly controlled by eculizumab or ravulizumab.
- Following the stop of randomization into Arms A and B, Arm C was additionally opened to adult patients (≥18 years) who have been receiving eculizumab at the approved dose for at least 24 weeks prior to study entry.

In the randomized arms, subjects were randomized in a 1:1 ratio to receive crovalimab (Arm A) or eculizumab (Arm B). Randomization was stratified according to their transfusion history (received a transfusion of pRBCs within 12 months prior to randomization, yes versus no). Day 1 of study treatment was scheduled 2 weeks from the subject's last dose of eculizumab.

Figure 77. Study Design, COMMODORE-1



Source: COMMODORE-1 protocol.
[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 will be opened in Arm C (following the stop of randomization into Arms A and B) to patients who have been receiving eculizumab at the approved dose for at least 24 weeks and have LDH ≤1.5×ULN at screening.
Abbreviations: C5 complement component 5; LDH, lactate dehydrogenase; N, total number of subjects; PNH, paroxysmal nocturnal hemoglobinuria; Q2W, every 2 weeks; R, randomization; SNP, single nucleotide polymorphism; ULN, upper limit of normal

Subjects in the crovalimab arms (Arms A and C) received crovalimab consistent with the crovalimab dose regimen in COMMODORE-2 for a total of 24 weeks of study treatment (primary treatment period). After 24 weeks of crovalimab treatment, subjects who derived benefit could continue to receive crovalimab for a maximum of 5 years in the extension period, in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Products. For subjects enrolled in the nonrandomized arm (Arm C), Day 1 of study treatment was to be scheduled at the time of the subject's next scheduled dose of C5 inhibitor. The safety follow-up period was 46 weeks for subjects who discontinued crovalimab, including a safety follow-up site visit 24 weeks after treatment discontinuation, and a safety telephone call 46 weeks (approximately 10.5 months) after treatment discontinuation.

Subjects randomized to the eculizumab arm (Arm B) were to receive the approved maintenance dose of eculizumab (900 mg) starting on Day 1 (2 weeks from the subject's last dose of eculizumab) and Q2W thereafter for a total of 24 weeks of study treatment (primary treatment period). After 24 weeks of eculizumab treatment, subjects had the option to:

- Switch to crovalimab in the extension period: The first crovalimab dose was to be administered at the visit when the next scheduled administration of eculizumab would have occurred (i.e., Week 25 visit). Subjects who switched from eculizumab were to follow the same crovalimab dose and schedule as subjects randomized to receive crovalimab.
- Discontinue from the study after completion of 10 weeks of safety follow-up.

If necessary, patients were allowed to be transfused prior to enrollment to reach a hemoglobin level above the specified transfusion threshold for eligibility (see Section 15.2). Administration of rescue therapy and safety guidelines when switching to a different complement inhibitor were consistent with that in COMMODORE-2. No dose modification of eculizumab was permitted during the study.

There was an independent data monitoring committee to ensure subject safety and clinical trial integrity.

15.3.1.1. Objectives and Endpoints, COMMODORE-1 (Study BO42161)

The primary objective is to evaluate the safety and tolerability of crovalimab compared with eculizumab on the safety endpoints (i.e., incidence of AEs, change from baseline in targeted vital signs/clinical laboratory test results, incidence and severity of injection site reactions, infusion-related reactions, hypersensitivity, infections [including meningococcal meningitis], incidence of AEs leading to study drug discontinuation, incidence and severity of clinical manifestations of DTDC formation in subjects who switched to crovalimab treatment from eculizumab or ravulizumab treatment).

The exploratory efficacy endpoints included the following:

- Percent change from baseline in LDH levels averaged over Weeks 21, 23, and 25 based on central laboratory LDH measurements.
- Proportion of subjects who achieve TA from baseline through Week 25 (after 24 weeks on treatment). The definition of TA is consistent with that in COMMODORE-2.

- Proportion of subjects with BTH from baseline through Week 25. The definition of BTH is consistent with that in COMMODORE-2.
- Proportion of subjects with stabilization of hemoglobin from baseline through Week 25. The definition of stabilized hemoglobin is consistent with that in COMMODORE-2.
- Proportion of subjects with a central LDH ≤1.5×ULN from baseline through Week 25.

15.3.1.2. Eligibility Criteria, COMMODORE-1 (Study BO42161)

COMMODORE-1 enrolled patients diagnosed with PNH (confirmed by high sensitivity flow cytometry evaluation of WBCs, with granulocyte or monocyte clone size ≥10% within 6 months prior to randomization [Arm A and B] or enrollment [Arm C]) who have been previously treated with a complement inhibitor therapy and BW ≥40 kg. Vaccinations were required against *Neisseria meningitidis* serotypes A, C, W, and Y (within 3 years), *Haemophilus influenzae* type B and *Streptococcus pneumoniae* according to national vaccination recommendations (e.g., Advisory Committee on Immunization Practices guidelines). The key exclusion criteria were consistent with those of COMMODORE-2. In addition, patients with a MAVE within 6 months prior to first drug administration (Day 1) were excluded from COMMODORE-1.

The randomized arms (Arms A and B) enrolled adult patients (≥18 years of age) who had been receiving treatment with eculizumab at an approved dose (900 mg Q2W) for at least 24 weeks prior to study entry, and whose IVH was adequately controlled on that dose (LDH ≤1.5×ULN).

The nonrandomized arm (Arm C) enrolled patients who met one of the following criteria:

- Pediatrics (<18 years) currently receiving treatment with eculizumab for at least 12 weeks and have an LDH ≤2×ULN.
- Currently receiving treatment with ravulizumab for at least 16 weeks (regardless of age) and have an LDH ≤2×ULN.
- 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 (regardless of age) and have an LDH ≤2×ULN.
- Possess a known C5 polymorphism and have poorly controlled hemolysis by eculizumab or ravulizumab (regardless of age).
- Adults (≥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 an LDH ≤1.5×ULN (this cohort was included following the termination of randomization into Arms A and B).

15.3.1.3. Statistical Analysis Plan, COMMODORE-1 (Study BO42161)

Determination of Sample Size

The study was initially designed to randomize approximately 200 subjects, with 172 subjects deemed necessary for adequate study power, factoring in a 15% dropout rate for Arms A and B

based on efficacy considerations. However, due to enrollment challenges, the originally targeted sample size for a sufficiently-powered formal statistical testing of efficacy data could not be achieved. It was estimated that at the time of the primary analysis for the study, approximately 90 subjects would be randomly assigned to Arms A and B in a 1:1 ratio to receive either crovalimab (N=45) or eculizumab (N=45).

Enrollment into Arm C continued without interruption, with an expected total of approximately 100 subjects at the end of the study.

Overall, the study was expected to enroll approximately 190 subjects.

Analysis Population

- The randomized population consisted of all randomized subjects in Arms A and B.
- The efficacy-evaluable population for the randomized arms consisted of all randomized subjects who received at least one dose of the originally assigned treatment and had at least one valid LDH level assessment by the central laboratory after the first IV infusion.
- The safety population included all enrolled subjects who received at least one dose of study drug.

Analysis of the Exploratory Efficacy Endpoints

Percent Change From Baseline in LDH Levels

The percent change in LDH levels from baseline averaged over Weeks 21, 23, and 25 between the crovalimab arm (Arm A) and the eculizumab arm (Arm B) was analyzed using the mixed-effect model for repeated measures (MMRM) with fixed, categorical effects of treatment, visit, and visit-by-treatment-arm interaction, as well as the continuous, fixed covariate of baseline LDH, baseline-LDH-by-visit interaction, and the stratification factor of transfusion history. An unstructured covariance matrix was used to model the within-subject errors. In the event that the model did not converge with the unstructured covariance matrix, a more parsimonious structure would be considered in the following order until model convergence was achieved: Toeplitz, first order autoregressive, and compound symmetry. The point estimate for the difference between crovalimab and eculizumab, along with a two-sided 95% CI, was presented.

The model included data from all subjects in the efficacy-evaluable population. All LDH measurements (up to Week 25) were used in the statistical model. Unscheduled central LDH measurements were mapped to the nearest scheduled assessment using windowing. Missing data were assumed as data missing at random as part of the MMRM model.

Hemolysis Control

A generalized estimating equation model was used to estimate the adjusted log-odds ratio of LDH $\leq 1.5 \times$ULN due to treatment, while taking into account the intraindividual correlation between LDH control statuses across visits. The dependent variable was the binary indicator for hemolysis control. The generalized estimating equation model was adjusted for baseline covariates and correlation matrix structure in a similar manner to the MMRM.

Transfusion Avoidance

The percentage of subjects with TA was computed for the two randomized arms. Note that, as a conservative approach, subjects who prematurely withdrew from study treatment were assumed to have undergone a transfusion. A difference in the percentage of subjects with TA in the two treatment arms was calculated, along with a 95% CI for the difference using the stratified Newcombe CI method (Yan and Su 2010). The difference between the two treatment arms was computed as a weighted combination of the differences between the crovalimab and eculizumab arms within the stratification indicator of transfusion history using Mantel-Haenszel weights (Agresti 2013). Total number of units (based on local equivalent) of pRBCs transfused per subject by Week 25 was presented with 95% CI per treatment arm.

TA analysis included only subjects who had completed the 24 weeks of treatment, or discontinued from the study but had their first dose of the relevant study treatment at least 24 weeks prior to the CCOD. Subjects who discontinued treatment before Week 25 and had their first dose of relevant study treatment at least 24 weeks before the CCOD, were conservatively assumed to have had a transfusion.

Breakthrough Hemolysis

The proportion of subjects with BTH from baseline through Week 25 was analyzed using the same approach as TA. As a conservative approach, subjects withdrawing early were assumed to have experienced BTH in the unobserved period.

Hemoglobin Stabilization

The proportion of subjects with stabilization of hemoglobin from baseline through Week 25 was analyzed using approaches similar to TA. As a conservative approach, subjects withdrawing early were assumed to not have hemoglobin stabilization.

Functional Assessment of Chronic Illness Therapy-Fatigue

Functional Assessment of Chronic Illness Therapy-Fatigue scores were analyzed as the change from baseline to Week 25 using the MMRM approach.

Multiplicity Adjustment

The study was updated to exploratory only and hence no multiplicity adjustment was planned.

Interim Analyses

No efficacy interim analysis was planned.

Protocol Amendments

The clinical trial landmarks and amendments for COMMODORE-1 are summarized in Table 121.

Table 121. Key Landmarks and Key Protocol Amendments, COMMODORE-1

Date	Landmarks
March 16, 2020	Original protocol
May 8, 2020	Version 2
September 29, 2020	First subject enrolled
November 20, 2020	Version 3: • Added language regarding maintaining currency of *N. meningitidis* vaccination. • The lower age limit for pediatric patients in Arm C was removed to allow children <12 years who weigh ≥40 kg in the study. Language was added that SC administrations in these subjects should be performed by the caregiver(s). • Clarified the estimand section regarding handling of intercurrent events. • The inclusion criterion of AST ≤3×ULN in Arm C patients with known C5 polymorphism was updated since increased AST can reflect intravascular hemolysis.
July 16, 2021	Version 4: • Updated the primary endpoint (defined as the percent change in LDH levels from baseline averaged over Weeks 21, 23, and 25). • Updated the criteria for platelet count at screening, and granulocyte colony-stimulating factor treatment was also updated to minimize the enrollment of patients with bone marrow failure, who would not benefit from C5 inhibition. • Added exclusion criteria for patients with myelodysplastic syndrome with intermediate to very high Revised International Scoring System scores.
January 22, 2022	Version 5: • Same changes as in COMMODORE-2 were made in COMMODORE-1. In addition, the following revisions were made in COMMODORE-1: – Clarified that the renal function of Arm B subjects switching to crovalimab after completing the eculizumab treatment was to be monitored for the first 10 weeks of crovalimab treatment. – The primary reason for the amendment was to reflect the Applicant's decision to stop randomization into Arms A and B in November 2022. This led to updates to the projected sample size and repositioning of the study objectives, endpoints, and related statistical analysis plan. Given the evolving treatment landscape and a reduced pool of patients treated with eculizumab over time, it has been assessed that there was a low probability in the foreseeable future of reaching complete enrollment into randomized Arms A and B or enrolling a sufficient number of subjects to be able to conduct powered efficacy analyses as originally designed. – At the time of stopping randomization into Arms A and B, enrollment was projected to be approximately 90 subjects in the randomized arms. – Considering the shift of all the efficacy objectives to exploratory and the removal of the associated estimand description in the protocol, the safety objective became the only primary objective of the study, with no change to the safety endpoints that have been previously included. – The primary analysis of COMMODORE-1 was to be conducted at the same time as the primary analysis of COMMODORE-2. – Following the stop of randomization into Arms A and B, Arm C was additionally opened to adult patients (≥18 years) who have been receiving eculizumab at the approved dose for at least 24 weeks prior to study entry, in order to continue study access for this population in a nonrandomized setting.

Date	Landmarks
	– Arm C continues to enroll subjects, with an increased sample size of approximately 100 subjects, which is aligned with the goal of maintaining the safety database for crovalimab-treated subjects.
November 16, 2022	Clinical data cutoff date
Study ongoing	Last subject last visit

Source: COMMODORE-1 CSR
Abbreviations: AST, aspartate transaminase; C5, complement component 5; LDH, lactate dehydrogenase; SC, subcutaneous; ULN, upper limit of normal

15.4. COMPOSER (Study BP39144)

Study Design

COMPOSER is a first-in-human study that consists of four sequential parts and an OLE designed to evaluate the safety, tolerability, PK, and PD of crovalimab in healthy male volunteers (Part 1) and in patients with PNH (Parts 2, 3, 4 and the OLE). Part 1 was a randomized, adaptive, placebo-controlled, parallel group study in HVs who received single IV or SC doses of crovalimab or placebo. This part was observer-blinded (the investigators and all individuals in direct contact with subjects at the investigative site will be blinded, except the pharmacist handling the study drug). Part 2 was an open-label, multiple-dose, multicenter, intraindividual dose escalation study in patients with PNH who were treatment-naïve. Part 3 was an open-label, multiple-dose, multicenter study in patients with PNH who switched from eculizumab. Part 4 is an open-label, multicenter, two-arm (Arm A: treatment-naïve, Arm B: patients previously treated with eculizumab) nonrandomized study in patients with PNH.

Open-Label Extension

Subjects who complete 20 weeks of treatment and derive benefit have the option to enter the OLE period. Subjects transitioning from Parts 2, 3, or 4 are to initially remain on the same SC dose regimen as they were previously receiving and transition to crovalimab dosing that is consistent with the proposed crovalimab dose regimen. IV rescue doses of crovalimab are allowed, consistent with COMMODORE-1 and COMMODORE-2.

The primary objective is to evaluate safety, tolerability, and PD effects of crovalimab on complement activity in patients with PNH. Secondary objectives include characterization of pharmacokinetics/pharmacodynamics, evaluation of immunogenicity and assessment of efficacy as measured by change in LDH, free-hemoglobin and stabilized hemoglobin levels.

16. Efficacy

16.1. COMMODORE-2 (Study BO42162)

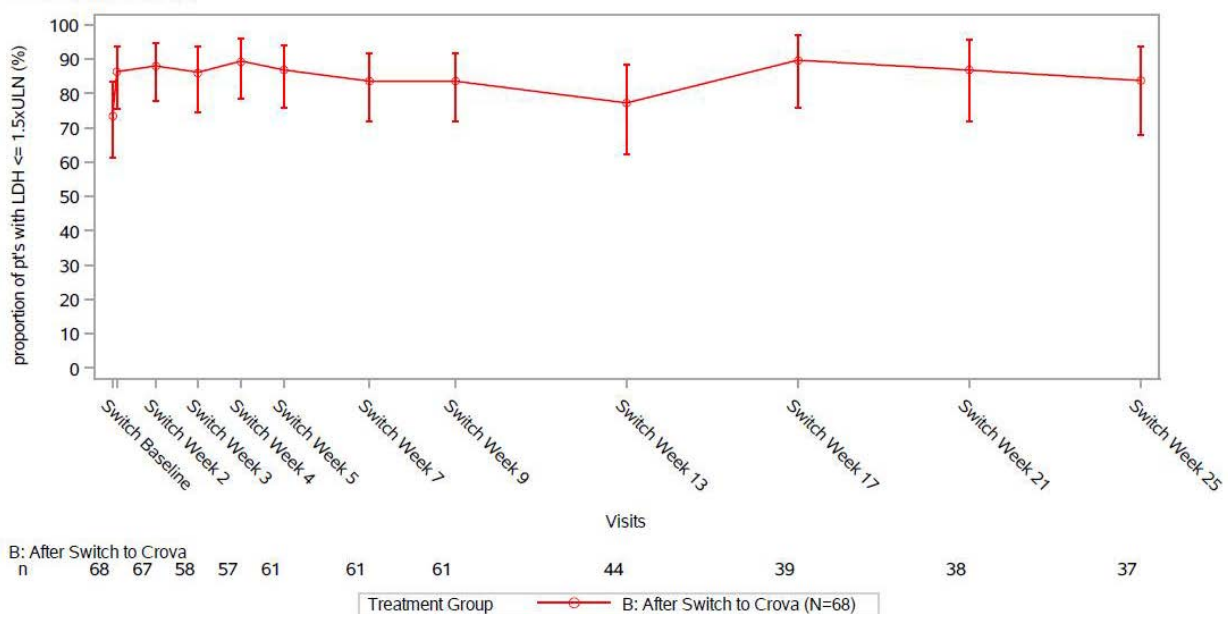
Long-Term Extension Period Exploratory Results for Switch Subjects

Of the 69 subjects randomized to eculizumab, 68 subjects (98.6%) completed 24 weeks of treatment in the primary treatment period and switched to crovalimab treatment in the

crovalimab extension period. In total, 43 subjects switched to crovalimab at least 24 weeks before the CCOD.

Of the 43 subjects that switched to crovalimab at least 24 weeks before the CCOD, the mean proportion of Arm B switch subjects with hemolysis control during the period after switch through switch Week 25 was 87.6% (95% CI: 79.79, 92.68) (see Figure 78).

Figure 78. Proportion of Subjects Achieving Hemolysis Control (Central LDH ≤1.5×ULN) with 95% CI by Visit, Arm B Switch, COMMODORE-2, Crovalimab Efficacy Population



Source: Applicant's CSR
Abbreviations: LDH, lactate dehydrogenase; N, total number of subjects; ULN, upper limit of normal

Eight out of 43 (18.6%) Arm B switch subjects in the 24-Week crovalimab efficacy population had at least one transfusion from switch baseline up to switch Week 25. The mean number of units of pRBCs transfused among these 43 subjects was 1.9 units from switch baseline through switch Week 25.

A total of 7 out of the 43 (16.3%, 95% CI: 7.33, 31.30) Arm B switch subjects in the 24-Week crovalimab efficacy population, were regarded as having had a BTH event from switch baseline to switch Week 25.

A total of 27 of 43 (62.8%, 95% CI: 46.72, 76.61) Arm B switch subjects in the 24-Week crovalimab efficacy population, achieved hemoglobin stabilization from switch baseline to switch Week 25.

16.2. COMMODORE-3 (Study YO42311)

Study Results

In COMMODORE-3, a total of 51 subjects were enrolled and treated with crovalimab across five clinical sites in China at the clinical data cutoff date of August 10, 2022. The first subject

enrollment occurred on March 17, 2021. Of the 51 subjects, 1 subject (2.0%) discontinued the study at Week 22 (prior to the primary analysis) due to a treatment-emergent adverse event (TEAE) of subdural hematoma that had a fatal outcome (see Section 17.1.1.2). The remaining 50 subjects continued into the extension period. At the time of the CCOD, the median treatment duration was 56.1 weeks (range: 20.1 to 72.3).

The median age of the crovalimab-treated subjects was 31 years (range: 15 to 58) with 3 subjects (5.9%) less than 18 years (ages 15, 17, and 17 years) at study enrollment. Approximately half (56.9%) of the subjects were female, and the median weight was 60.0 kg (range: 48.9 to 96.0). All subjects had PNH-related signs or symptoms, and the median LDH value at baseline was 9.3×ULN, with 98.0% of subjects having an LDH >4×ULN. Subjects had a median PNH clone size of 97.4% for monocytes, 95.0% for granulocytes, and 45.9% for erythrocytes. Prior history of aplastic anemia, MDS, and MAVE were reported in 19 subjects (37.3%), 1 subject (2.0%) and 5 subjects (9.8%), respectively.

Efficacy Results

The co-primary efficacy endpoints of hemolysis control and TA were met at the time of the CCOD. The mean proportion of subjects with hemolysis control (i.e., LDH ≤1.5×ULN) from Week 5 through Week 25 was 78.7% (95% CI: 67.8%, 86.6%), which met the prespecified success criterion of 60% (based on the point estimate of the 95% CI of the treatment effect of eculizumab) and a success criterion of 66.9% (based on the lower bound of the 95% CI of the treatment effect of eculizumab) for the lower limit of the two-sided 95% CI. The difference in the proportion of subjects with TA from baseline through Week 25 and within 24 weeks prior to screening was 51.0% (95% CI: 34.3%, 65.1%), which was statistically significant ($p<0.0001$) at the prespecified, 2-sided type I error level of 0.05.

Pharmacodynamic/Biomarker Results

Due to COVID-19 travel restrictions, approximately half of subjects were missing the required PD and biomarker assessments for each visit after Week 25. For the subjects that had PD and biomarker assessments, complement levels, as measured by free C5 concentrations, were reduced from a mean baseline level of 226.6 mg/L to mean levels of <0.1 mg/L from Week 2 of crovalimab treatment, providing evidence of complete inhibition of free C5. The low levels of free C5 were sustained up to Week 49. Terminal complement activity (CH50) was reduced from a mean baseline level of 48 U/mL (SD: 11.7 U/mL) to levels near or BLQ (i.e., <10 U/mL) from Week 2 of treatment with crovalimab, providing evidence of complete inhibition of terminal complement activity.

Clone size was also evaluated, and the RBC PNH clone size (Type II glycosylphosphatidylinositol (GPI)-dim and TYPE III GPI-negative erythrocytes) increased from mean baseline levels of 46.9% (SD: 22.2%) to 69.6% (SD: 24.1%) at Week 25, consistent with decreased hemolysis of GPI-deficient PNH cells.

16.3. COMMODORE-1 (Study BO42161)

16.3.1. Data Quality and Integrity, COMMODORE-1 (Study BO42161)

Data were provided electronically in standard data format, with a study data tabulation model and analysis data model (Genentech 2023a). Statistical analysis software programs used to create key efficacy and safety outputs for the study were submitted along with the data. The Applicant also provided clear definition files for datasets and detailed analysis programs to assist the review.

16.3.2. Subject Disposition, Baseline Demographics and Disease Characteristics, COMMODORE-1 (Study BO42161)

Subject Disposition

In COMMODORE-1, a total of 127 subjects (randomized arms [crovalimab: 45, eculizumab: 44], nonrandomized arm: 38) were enrolled. Enrollment of subjects in the randomized arms had stopped, but the enrollment in the nonrandomized arm is ongoing.

Randomized Population

In the randomized population, a total of three subjects (crovalimab: one, eculizumab: two) were not treated. The safety and efficacy populations were comprised of a total of 86 subjects (crovalimab: 44, eculizumab: 42). The 24-week efficacy population was comprised of a total of 76 subjects (crovalimab: 39, eculizumab: 37). A total of 74 subjects (84.1%) completed the primary 24-week treatment period and received crovalimab in the extension period.

Table 122. Analysis Populations and Subject Disposition, COMMODORE-1, Randomized Population

Analysis Population/Subject Disposition	Crovalimab (Switch) (N=45) n (%)	Eculizumab (Experienced) (N=44) n (%)	Total (N=89) n (%)
Randomized population	45	44	89
Never been treated[a]	1	2	3
Safety population	44	42	86
Efficacy analysis population	44	42	86
24-week efficacy population[d]	39	37	76
Crovalimab switch population (subjects randomized to eculizumab and switched to crovalimab in the extension period)	0	35	35
Crovalimab switch 24-week efficacy population[e]	0	28	28
Ongoing treatment in the primary 24-week period	5	5	10
Completed primary treatment period (of 24 weeks)	39 (86.7%)	35 (79.5%)	74 (83.1%)
Discontinued treatment before Week 24	0	2 (4.5%)	2 (2.2%)
Reason for treatment discontinuation			
Protocol deviation	0	1 (2.3%)	1 (1.1%)

Analysis Population/Subject Disposition	Crovalimab (Switch) (N=45) n (%)	Eculizumab (Experienced) (N=44) n (%)	Total (N=89) n (%)
Other	0	1 (2.3%)	1 (1.1%)
Started crovalimab in the extension period (subjects in the eculizumab switched to crovalimab)	39 (86.7%)	35 (79.5%)	74 (83.1%)
Discontinued crovalimab on/after Week 24	2 (4.4%)	3 (6.8%)	5 (5.6%)
Reason for treatment discontinuation			
Death[b]	1 (2.2%)	0	1 (1.1%)
Subject withdrawal	1 (2.2%)	1 (2.3%)	2 (2.2%)
Physician decision	0	1 (2.3%)	1 (1.1%)
Adverse event	0	1 (2.3%)[c]	1 (1.1%)
Ongoing treatment in the extension period	37 (82.2%)	32 (72.7%)	69 (77.5%)
Completed 24 weeks of treatment	24 (52.3%)	26 (59.1%)	50 (56.2%)

Source: ADSL.xpt and CSR.
* One subject each in the crovalimab and eculizumab arms withdrew from the study. One additional subject in the eculizumab arm was never treated due to physician decision.
[b] Death due to colorectal cancer.
[c] Discontinued due to type III hypersensitivity reaction.
[d] Includes all subjects of the efficacy population who were enrolled at least 24 weeks before clinical cutoff date.
[e] Includes all subjects in the eculizumab arm who switched to crovalimab at least 24 weeks before clinical cutoff date.
Abbreviations: N, total number of subjects; n, number of subjects in subset

In the randomized population, most of the subjects were enrolled from Europe (66.3%) and Asia (16.9%). Brazil (14 subjects) and Spain (13 subjects) were the countries that enrolled the highest number of subjects. No subjects were enrolled from the U.S. (see Section 6.3.3 for further discussion).

Table 123. Subject Enrollment by Country, COMMODORE-1, Randomized Population

Region	Crovalimab (Switch) (N=45) n (%)	Eculizumab (Experienced) (N=44) n (%)	Total (N=89) n (%)
Europe	30 (66.7%)	29 (65.9%)	59 (66.3%)
Spain	6 (13.3%)	7 (15.9%)	13 (14.6%)
Poland	6 (13.3%)	2 (4.5%)	8 (9.0%)
Turkey	5 (11.1%)	2 (4.5%)	7 (7.9%)
Italy	3 (6.6%)	4 (9.1%)	7 (7.9%)
Portugal	3 (6.6%)	2 (4.5%)	5 (5.6%)
Belgium	1 (2.2%)	4 (9.1%)	5 (5.6%)
Greece	2 (4.4%)	2 (4.5%)	4 (4.5%)
Czech Republic	1 (2.2%)	1 (2.3%)	2 (2.2%)
Ireland	1 (2.2%)	1 (2.3%)	2 (2.2%)
The Netherlands	1 (2.2%)	1 (2.3%)	2 (2.2%)
France	0	1 (2.3%)	1 (1.1%)
Estonia	0	1 (2.3%)	1 (1.1%)
Sweden	1 (2.2%)	0	1 (1.1%)
Hungary	0	1 (2.3%)	1 (1.1%)
Asia	8 (17.8%)	7 (15.9%)	15 (16.9%)
Japan	5 (11.1%)	4 (9.1%)	9 (10.1%)
Taiwan	2 (4.4%)	1 (2.3%)	3 (3.4%)
Korea (South)	0	2 (4.5%)	2 (2.2%)
Hong Kong	1 (2.2%)	0	1 (1.1%)

Region	Crovalimab (Switch) (N=45) n (%)	Eculizumab (Experienced) (N=44) n (%)	Total (N=89) n (%)
Central and South America	7 (15.6%)	7 (15.9%)	14 (15.7%)
Brazil	7 (15.6%)	7 (15.9%)	14 (15.7%)
North America	0	1 (2.3%)	1 (1.1%)
Canada	0	1 (2.3%)	1 (1.1%)

Source: ADSL.xpt
Abbreviations: N, total number of subjects; n, number of subjects in subset

Nonrandomized Crovalimab Arm

A total of 38 subjects (prior-ravulizumab cohort: 21, prior-high-dose eculizumab cohort: 10, C5 polymorphism cohort: 6, pediatric cohort: 1) were enrolled. The cohort enrolling adults with prior eculizumab treatment at the approved dose, had not recruited any subjects at the time of primary analysis. All subjects in the nonrandomized arm received treatment with crovalimab. The safety population consisted of 38 subjects. The single subject in the pediatric cohort was enrolled approximately two weeks prior to the time of the primary analysis CCOD and, therefore, was not included in the efficacy analysis. The 24-week efficacy population consisted of 34 subjects (prior-ravulizumab cohort: 19, prior-high-dose eculizumab cohort: 9, C5 polymorphism cohort: 6, pediatric cohort: 0).

A total of four subjects (prior-ravulizumab cohort: three [sepsis AE: one, subject withdrawal: two], prior-high-dose eculizumab cohort: one [withdrawal by subject]) discontinued study treatment during the primary treatment period before Week 24. In the C5 polymorphism cohort, it was reported that one subject discontinued the study treatment on or after 24 weeks of treatment due to lack of efficacy. In the nonrandomized arm, most subjects were enrolled from Europe (18 subjects, 47.4%) and Asia (16 subjects, 42.1%). A total of two subjects were enrolled from the U.S. in the nonrandomized arm.

Baseline Demographics and Disease Characteristics

Randomized Population

In the randomized population, baseline demographics were similar between the two arms. The median age was 47 years (range: 21 to 85), approximately half (48.3%) were males and most (74.2%) were White. No pediatric subjects were enrolled in the randomized arms.

Table 124. Baseline Demographics, COMMODORE-1, Randomized Population

Demographic	Crovalimab (Switch) (N=45)	Eculizumab (Experienced) (N=44)	Total (N=89)
Gender, n (%)			
Male	21 (46.7%)	22 (50.0%)	43 (48.3%)
Female	24 (53.3%)	22 (50.0%)	46 (51.7%)

Demographic	Crovalimab (Switch) (N=45)	Eculizumab (Experienced) (N=44)	Total (N=89)
Age (yr) at first administration of study drug			
Mean (SD)	44.4 (15.6)	49.5 (14.8)	46.9 (15.4)
Median	42	49	47
Range	21-81	22-85	21-85
<18 years	0	0	0
18 to 64 years	40 (88.9%)	37 (84.1%)	77 (86.5%)
≥65 years	5 (11.1%)	7 (15.9%)	12 (12.5%)
Race, n (%)			
Asian	9 (20.0%)	7 (15.9%)	16 (18.0%)
White	34 (75.6%)	32 (72.7%)	66 (74.2%)
Black or African American	2 (4.4%)	1 (2.3%)	3 (3.4%)
Unknown	0	4 (9.1%)	4 (4.5%)
Ethnicity, n (%)			
Hispanic or Latino	8 (17.8%)	8 (18.2%)	16 (18.0%)
Not Hispanic or Latino	36 (80.0%)	31 (70.5%)	67 (75.3%)
Not reported	1 (2.2%)	5 (11.4%)	6 (6.7%)
Weight (kg)			
n	44	42	86
Median	80	75	78.5
Range	45-120	47-126	45-126
Weight category (kg), n (%)			
n	44	42	86
<40 kg	0	0	0
≥40 kg to <100 kg	41 (93.2%)	38 (90.5%)	79 (91.9%)
≥100 kg	3 (6.8%)	4 (9.5%)	7 (8.1%)

Source: ADSL.xpt, ADVS.xpt.
Abbreviations: N, total number of subjects; n, number of subjects in subset; SD, standard deviation; yr, year

The baseline disease characteristics were also generally similar in the two arms. The median LDH was 1×ULN (range: 0.6 to 1.9), the median hemoglobin was 10.9 g/dL (range: 6.8 to 15.3), and 23.9% of subjects had a history of pRBC transfusion within the past 12 months. A history of aplastic anemia and MAVE was reported in 34.8% and 22.5% of subjects, respectively.

Median PNH clone size was higher in the eculizumab arm compared to the crovalimab arm (monocytes [crovalimab: 88.6%, eculizumab: 96.4%], granulocytes [crovalimab: 88.1%, eculizumab: 95.7%], erythrocytes [crovalimab: 44.6%, eculizumab: 54.2%]).

Most of subjects were immunized with meningococcal-ACWY vaccine (crovalimab: 91.1% and eculizumab: 95.5%).

Table 125. Baseline Disease Characteristics, COMMODORE-1, Randomized Population

Baseline Disease Characteristic	Crovalimab (Switch) (N=45) n (%)	Eculizumab (Experienced) (N=44) n (%)	Total (N=89) n (%)
Age (yr) at PNH diagnosis			
Mean (SD)	36.2 (15.4)	39.1 (14.8)	37.7 (15.1)
Median	31.5	37.5	34.3
Range	17.2-79.3	20.0-83.7	17.2-83.7

Baseline Disease Characteristic	Crovalimab (Switch) (N=45) n (%)	Eculizumab (Experienced) (N=44) n (%)	Total (N=89) n (%)
Years on eculizumab before study treatment			
Mean (SD)	4.65 (3.7)	5.91 (3.5)	5.27 (3.6)
Median	2.99	6.17	4.57
Range	0.04-14.71	0.76-13.86	0.04-13.86
At least one of PNH-related signs/symptoms within 3 months			
Yes	45 (100%)	44 (100%)	89 (100%)
Hemoglobin (g/dL)			
n	44	42	86
Median	11.25	10.65	10.85
Range	7.2-15.3	6.8-14.4	6.8-15.3
Haptoglobin (g/L)			
n	43	42	85
Median	0.05	0.05	0.05
Range	0.05-2.18	0.05-1.09	0.05-2.18
LDH (U/L)			
n	44	42	86
Median	237.5	225.5	229.8
Range	138.0-406.0	155.5-455.5	138.0-455.5
LDH (xULN)			
n	44	42	86
Median	1.01	0.96	0.98
Range	0.6-1.7	0.7-1.9	0.6-1.9
LDH category			
n	44	42	86
<ULN	20 (45.5%)	24 (57.1%)	44 (51.2%)
≥ to ≤1.5×ULN	21 (47.7%)	16 (38.1%)	37 (43.0%)
>1.5×ULN	3 (6.8%)	2 (4.8%)	5 (5.8%)
History of pRBC transfusion within 12 months			
n	44	44	88
Yes	10 (22.7%)	11 (25.0%)	21 (23.9%)
Number of units of pRBC transfused			
n	44	44	88
Mean	1.6 (3.7)	2.3 (5.4)	1.9 (4.6)
Median	0	0	0
Range	0-14	0-24	0-24
Number of units of pRBC transfused (category)			
n	44	44	88
0	34 (77.3%)	33 (75.0%)	(76.1%)
>0 to <4	4 (9.1%)	3 (6.8%)	7 (8.0%)
≥4 to <14	4 (9.1%)	5 (11.4%)	9 (10.2%)
≥14	2 (4.5%)	3 (6.8%)	5 (5.7%)
History of aplastic anemia			
Yes	15 (33.3%)	16 (36.4%)	31 (34.8%)
History of myelodysplastic syndrome			
Yes	0	0	0
History of renal impairment			
Yes	7 (15.6%)	8 (18.2%)	15 (16.9%)

Baseline Disease Characteristic	Crovalimab (Switch) (N=45) n (%)	Eculizumab (Experienced) (N=44) n (%)	Total (N=89) n (%)
History of major vascular events			
Yes	10 (22.2%)	10 (22.7%)	20 (22.5%)

Source: ADSL.xpt, ADCM.xpt, ADLB.xpt, ADKLD.xpt.
Abbreviations: LDH, lactate dehydrogenase; N, total number of subjects; n, number of subjects in subset; PNH, paroxysmal nocturnal hemoglobinuria; pRBC, packed red blood cell; SD, standard deviation; ULN, upper limit of normal

Nonrandomized Arm

In the nonrandomized arm, the overall median age was 43 years (range: 16 to 80), half (50%) were males, and most subjects were Asian (44.7%) or White (42.1%). In the C5 polymorphism cohort, all six subjects were Asian and the median age (58 years, range: 38 to 80 years) was greater than in the other cohorts. The baseline demographics information in each cohort of the nonrandomized arm is shown in Table 126.

Table 126. Baseline Demographics, COMMODORE-1, Nonrandomized Arm

Demographic	Crovalimab <18 years (N=1) n (%)	Crovalimab Prior Ravulizumab (N=21) n (%)	Crovalimab Prior-High-Dose Eculizumab (N=10) n (%)	Crovalimab C5 SNP (N=6) n (%)	Total (N=38) n (%)
Gender					
Male	1 (100%)	12 (57.1%)	4 (40.0%)	2 (33.3%)	19 (50.0%)
Female	0	9 (42.9%)	6 (60.0%)	4 (66.7%)	19 (50.0%)
Age (yr)					
Median	16	45	32	58	43
Range	16-16	27-70	20-58	38-80	16-80
<18 years	1 (100%)	0	0	0	1 (2.6%)
18 to 64 years	0	20 (95.2%)	10 (100%)	3 (50.0%)	33 (86.8%)
≥65 years	0	1 (4.8%)	0	3 (50.0%)	4 (10.5%)
Race					
Asian	0	11 (52.4%)	0	6 (100%)	17 (44.7%)
White	1 (100%)	9 (42.9%)	6 (60.0%)	0	16 (42.1%)
Black or African American	0	0	1 (10.0%)	0	1 (2.6%)
Unknown	0	1 (4.8%)	3 (30.0%)	0	4 (10.5%)
Ethnicity					
Hispanic or Latino	0	1 (4.8%)	1 (10.0%)	0	2 (5.3%)
Not Hispanic or Latino	1 (100%)	20 (95.2%)	5 (50.0%)	6 (100%)	32 (84.2%)
Not reported	0	0	4 (40.0%)	0	4 (10.5%)
Weight (kg)					
Median	53	70	66	66	69
Range	53-53	46-91	48-82	44-89	44-91
Weight category (kg)					
<40 kg	0	0	0	0	0
≥40 kg to <100 kg	1 (100%)	21 (100%)	10 (100%)	6 (100%)	38 (100%)
≥100 kg	0	0	0	0	0

Source: ADSL.xpt, ADVS.xpt.
Abbreviation: C5, complement component 5; N, total number of subjects; n, number of subjects in subset; yr, year

In the nonrandomized arm, the median hemoglobin was 10.4 g/dL (range: 6.0 to 15.1), the median LDH was 1.1×ULN (range: 0.6 to 20.7) and 26% of subjects had a prior history of pRBC transfusion. Subjects in the C5 polymorphism cohort generally had more severely affected disease compared to subjects in the other cohorts (median Hb: 8.3 g/dL [range: 7.8 to 12.9], median LDH: 6.1×ULN [range: 1.8 to 20.7], median units of pRBC transfusion: 4 units [range: 0 to 54], 50% of subjects had a history of MAVE]. The baseline disease characteristics information in each cohort of the nonrandomized arm is shown in Table 127.

Table 127. Baseline Disease Characteristics, COMMODORE-1, Nonrandomized Arm

Baseline Disease Characteristic	Crovalimab <18 years (N=1)	Crovalimab Prior Ravulizumab (N=21)	Crovalimab Prior-High-Dose Eculizumab (N=10)	Crovalimab C5 SNP (N=6)	Total (N=38)
Age (yr) at PNH diagnosis					
Mean (SD)	13.0 (NE)	34.3 (12.1)	24.7 (9.1)	53.3 (19.5)	34.2 (15.8)
Median	13.0	33.3	23.4	52.3	32.4
Range	13.0-13.0	11.4-61.4	15.0-42.2	25.9-80.1	11.4-80.1
At least one of PNH-related signs/ symptoms within 3 months, n (%)					
Yes	1 (100%)	21 (100%)	10 (100%)	6 (100%)	38 (100%)
Hemoglobin (g/dL)					
Median	14.9	10.8	10.4	8.3	10.4
Range	14.9-14.9	7.6-15.1	6.0-11.9	7.8-12.9	6.0-15.1
LDH (xULN)					
Median	1.53	1.0	0.9	6.1	1.1
Range	1.5-1.5	0.6-1.4	0.7-1.3	1.8-20.7	0.6-20.7
LDH category, n (%)					
<ULN	0	10 (47.6%)	5 (50.0%)	0	15 (39.5%)
≥ to ≤1.5×ULN	0	11 (52.4%)	5 (50.0%)	0	16 (42.1%)
>1.5×ULN	1 (100%)	0	0	6 (100%)	7 (18.4%)
History of pRBC transfusion within 12 months, n (%)					
Yes	0	3 (14.3%)	4 (40.0%)	3 (50.0%)	10 (26.3%)
Number of units of pRBC transfused					
Mean	0 (NE)	0.57 (1.8)	1.8 (3.1%)	14 (21.4)	3 (9.5)
Median	0	0	0	4	0
Range	0-0	0-8.0	0-8.0	0-54	0-54
Number of units of pRBC transfused (category), n (%)					
0	1 (100%)	18 (85.7%)	6 (60.0%)	3 (50.0%)	73.7%)
to <4	0	2 (9.5%)	2 (20.0%)	0	4 (10.5%)
≥4 to <14	0	1 (4.8%)	2 (20.0%)	1 (16.7%)	4 (10.5%)
≥14	0	0	0	2 (33.3%)	2 (5.3%)
History of aplastic anemia, n (%)					
Yes	0	9 (42.9%)	2 (20.0%)	1 (16.7%)	12 (31.6%)

Baseline Disease Characteristic	Crovalimab <18 years (N=1)	Crovalimab Prior Ravulizumab (N=21)	Crovalimab Prior-High-Dose Eculizumab (N=10)	Crovalimab C5 SNP (N=6)	Total (N=38)
History of myelodysplastic syndrome, n (%)					
Yes	0	0	0	0	0
History of renal impairment, n (%)					
Yes	0	4 (19.0%)	1 (10.0%)	2 (33.3%)	7 (18.4%)
History of major vascular events, n (%)					
Yes	0	2 (9.5%)	0	3 (50.0%)	5 (13.2%)

Source: ADSL.xpt, ADCM.xpt, ADLB.xpt, ADKLD.xpt.
Abbreviations: C5, complement component 5; LDH, lactate dehydrogenase; N, total number of subjects; n, number of subjects in subset; PNH, paroxysmal nocturnal hemoglobinuria; pRBC, packed red blood cell; SD standard deviation; SNP, single nucleotide polymorphism; ULN, upper limit of normal; yr, year

16.3.3. Analysis of the Exploratory Efficacy Endpoints, COMMODORE-1 (Study BO42161)

An overview of the exploratory efficacy results is provided in Table 128. The efficacy results presented in Table 128 were based on the 24-week efficacy population, which included all randomized subjects in Arms A and B that were recruited at least 24 weeks before the CCOD, who received at least one dose of the originally assigned treatment and who had at least one valid LDH level assessment by the central laboratory after the first IV infusion. This corresponded to 39 subjects in the crovalimab arm and 37 subjects in the eculizumab arm.

Table 128. Exploratory Efficacy Analysis Results, COMMODORE-1, 24-Week Efficacy Population

Endpoints	Measures	Crovalimab N=39	Eculizumab N=37
Percent change in LDH from baseline[a]	Averaged Percent Change (95% CI)	15.29 (2.37, 28.21)	3.48 (-10.46, 17.42)
	Difference in Averaged Percent Change (95% CI)	11.82 (-7.25, 30.88)	
Mean proportion of subjects with hemolysis control (Central LDH ≤1.5×ULN) from Baseline through Week 25	Mean Proportion of Subjects Achieving Controlled Hemolysis (95% CI)	92.9% (86.62, 96.39)	93.7% (87.26, 97.04)
	Odds Ratio (95% CI)	0.88 (0.28, 2.77)	
Proportion of subjects with TA from baseline through Week 25	Subjects with TA, n (%)	31 (79.5%)	29 (78.4%)
	Weighted Difference in Proportion, % (95% CI)	1.8 (-16.67, 19.94)	
Proportion of subjects with BTH from baseline through Week 25	Subjects with at least one BTH, n (%)	4 (10.3%)	5 (13.5%)
	Weighted Difference in Proportion, % (95% CI)	-3.5 (-19.20, 11.68)	
Proportion of subjects with stabilized hemoglobin from baseline through Week 25	Subjects with Stabilized Hemoglobin, n (%)	23 (59.0%)	26 (70.3%)
	Weighted Difference in Proportion (95% CI)	-10.8 (-30.84, 10.39)	
Adjusted mean change from baseline to Week 25 in FACIT Fatigue scores	Adjusted Mean Change (SE)	1.09 (1.29)	-2.61 (1.37)
	Difference in Mean Absolute Change scores (95% CI)	3.71 (0.05, 7.36)	

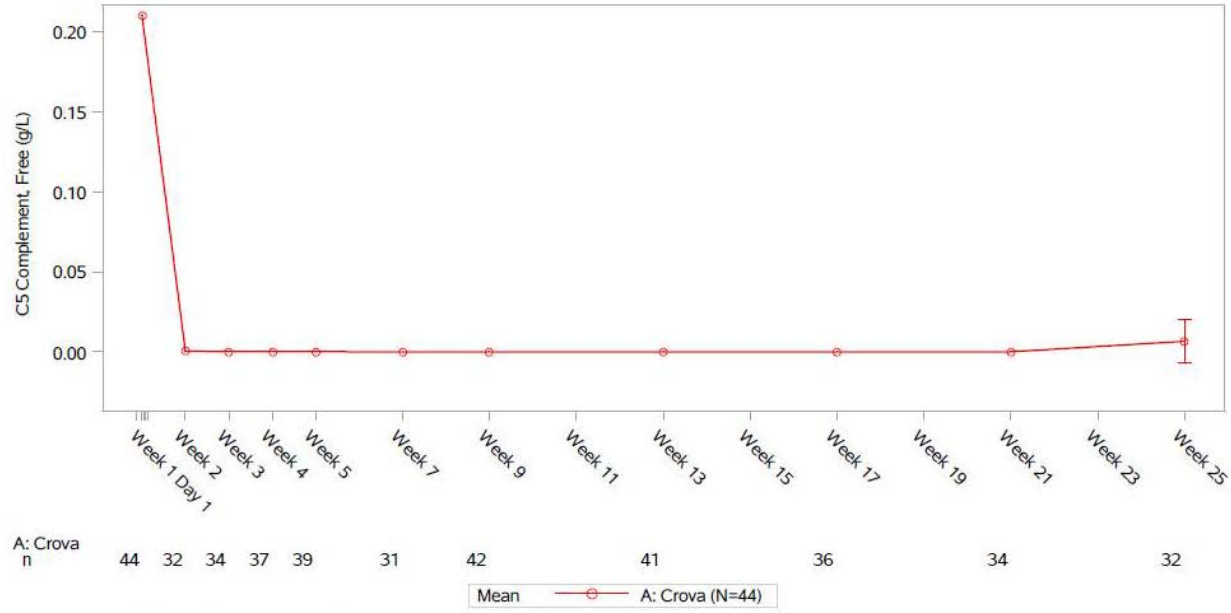
Source: The Applicant's clinical study report and the updated analyses.
[a] The result is based on corrected analysis submitted by the Applicant, instead of the clinical study report.
Abbreviations: BTH, breakthrough hemolysis; CI, confidence interval; FACIT, Functional Assessment of Chronic Illness Therapy; LDH, lactate dehydrogenase; N, total number of subjects; n, number of subjects in subset; SE, standard error; TA, transfusion avoidance; ULN, upper limit of normal

16.3.4. Analysis of Exploratory Biomarker Endpoints, COMMODORE-1 (Study BO42161)

Free C5 Concentration

After crovalimab treatment initiation in the switch PNH subjects, serum free C5 rapidly decreased to very low levels (mean levels <0.0001 g/L) at Week 2 of crovalimab treatment, thus providing evidence of complete inhibition of free C5. The low levels of free C5 (<0.0001 g/L) were sustained throughout the assessment period (up to Week 25) in most subjects (Figure 79).

Figure 79. Mean Free C5 Concentration by Visit, COMMODORE-1

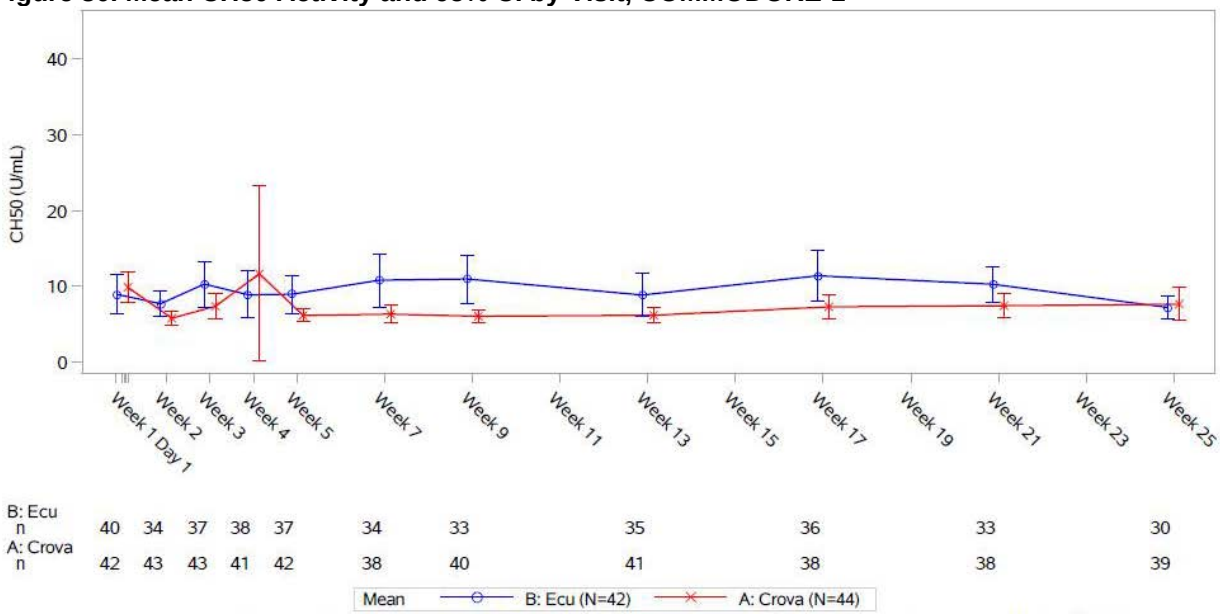


Source: Applicant's CSR.
Abbreviations: C5, complement 5; Crova, crovalimab; N, total number of subjects

Complement Activity (Liposome Immunoassay)

In both the randomized crovalimab and eculizumab arms, baseline levels of terminal complement activity (CH50 measured by liposome immunoassay) were low (close to or BLQ [<10 U/mL]) as the subjects were exposed to eculizumab. After crovalimab treatment initiation (Arm A) or eculizumab treatment continuation (Arm B), mean CH50 was maintained at low levels of activity (close to or BLQ [<10 U/mL]) in both arms. The terminal complement inhibition was generally sustained throughout the primary treatment period up to Week 25 (Figure 80).

Figure 80. Mean CH50 Activity and 95% CI by Visit, COMMODORE-1

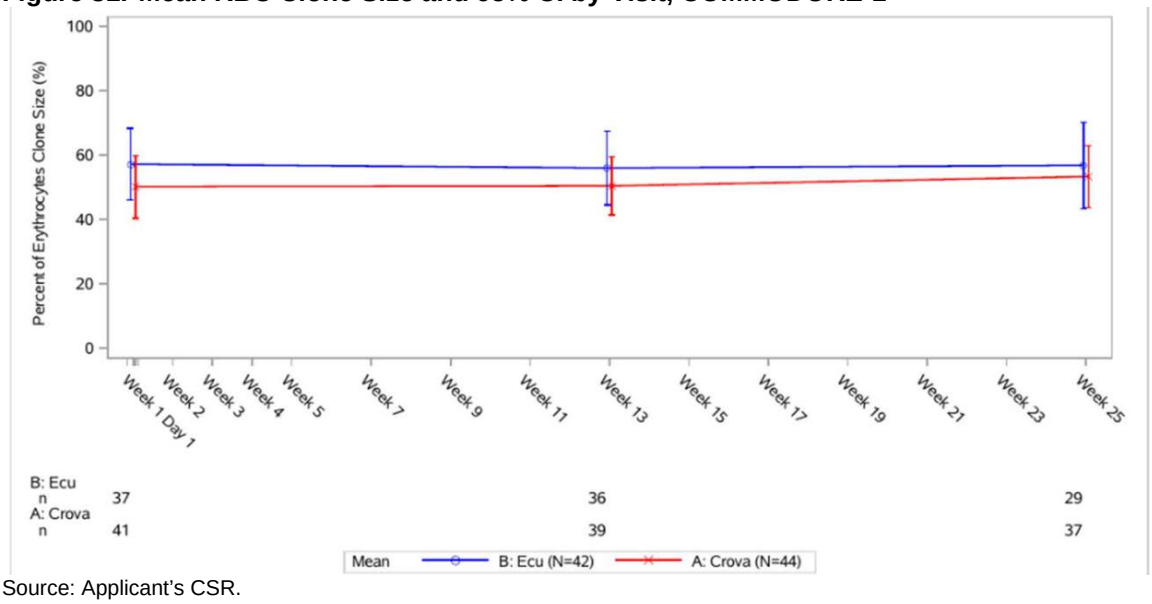


Source: Applicant's CSR.
Abbreviations: CH50, total complement activity; CI, confidence interval; Crova, crovalimab; Ecu, eculizumab; N, total number of subjects; n, number of subjects in subset

PNH Clone Size

The mean PNH clone size (% of cells that lack a GPI anchor) was stable in both erythrocytes and WBCs (granulocytes and monocytes) for both the crovalimab and eculizumab treatment arms from baseline through Week 25 (Figure 81).

Figure 81. Mean RBC Clone Size and 95% CI by Visit, COMMODORE-1



Source: Applicant's CSR.
Note: COMPOSER (Study BP39144)
Abbreviations: CI, confidence interval; Crova, crovalimab; Ecu, eculizumab; N, total number of subjects; n, number of subjects in subset; RBC, red blood cell

16.4. COMPOSER (Study BP39144)

Study Results

The COMPOSER study is being conducted in Japan, Germany, Hungary, Korea, France, Italy, and the Netherlands. The first subject was enrolled on November 14, 2016. The CCOD was November 1, 2021. A total of 59 subjects (HVs: 15 subjects, subjects with PNH: 44 subjects [treatment-naïve: 18 subjects, subjects who switched from eculizumab: 26 subjects]) were enrolled in the study.

In Part 1, a total of 15 subjects were enrolled in three cohorts. In each cohort, 5 healthy adult male volunteers were randomized (3:2) to receive a single IV (Cohorts 1 [75 mg] and 2 [125 mg]) or SC (Cohort 3 [100 mg]) dose of crovalimab or placebo. Most of the subjects were White (80.0%) and the age by cohort ranged from 29 to 43 years (range: 21 to 52).

In Part 2, a total of 10 adult subjects with PNH who were treatment-naïve were enrolled. Subjects received 3, single, ascending IV doses of crovalimab: 375 mg on Day 1, 500 mg on Day 8, and 1000 mg on Day 22. The first SC dose of crovalimab 170 mg administration was initiated on Day 36, followed by weekly 170 mg SC injections for a total of 20 weeks. The majority of subjects enrolled in Part 2 were male (60.0%) and White (70.0%). The median age was 52.5 years (range: 35 to 74 years) and median weight was 66.9 kg (range: 58.9 to 98.0 kg). There were 3 out of 10 subjects with a history of RBC transfusion up to 1 year prior to starting study treatment, with a median of 2 units of transfused RBC (range: 2 to 6). The median treatment duration was 1520 days (range: 1226 to 1618).

In Part 3, a total of 19 adult subjects with PNH who were previously treated with eculizumab were randomly assigned to three different treatment schedules (Arm A: 7 subjects, Arm B: 6 subjects, Arm C: 6 subjects) with an ongoing assessment of safety, tolerability, PK, and PD data. All subjects received a loading dose of 1000 mg crovalimab IV 2 weeks after the last dose of eculizumab. Starting on Day 8, two subjects in Arm A initially received crovalimab 680 mg SC Q4W. After observing possible DTDC-related AEs, the dosing regimen was modified to 170 mg SC weekly for the first 8 doses. At dose 9 (Day 64), subjects started maintenance regimen of 680 mg SC Q4W. Subjects in Arm B received crovalimab 340 mg SC biweekly, and subjects in Arm C received crovalimab 170 mg SC every week. Most of the subjects enrolled in Part 3 were male (68.4%) and White (47.4%) or Asian (36.8%). The median age was 46 years (range: 33 to 69 years). The median weight was 78.2 kg (range: 40.6 to 131.5 kg). Eight of 19 subjects had a history of RBC transfusion up to 1 year prior to randomization, with a median of 5 units of transfused RBC (range: 1 to 21). The median treatment duration was 1197 days (range: 134 to 1435).

In Part 4, a total of 15 adult subjects (Arm A: 8 treatment-naïve, Arm B: 7 subjects previously treated with eculizumab) were enrolled. Subjects received a loading series comprised of 1000 mg crovalimab IV on Day 1, followed by 340 mg SC on Days 2, 8, 15, and 22. From Day 29 onwards, all subjects received 680 mg SC Q4W. The median treatment duration of crovalimab in Part 4 was 2.23 years (range: 0.92 to 2.46). In the treatment-naïve Arm A, most subjects were male (75.0%) and Asian (50.0%) or White (37.5%). The median age was 55.5 years (range: 42 to 73). The median weight was 80.1 kg (range: 56.7 to 100 kg). There were 4 out of 8 subjects with a history of RBC transfusion up to 1 year prior to starting study treatment, with a median of 7 units of transfused RBC (range: 2 to 198). The median treatment duration of Arm A was 827

days (range: 337 to 871). In Arm B, most subjects were male (82.7%) and White (42.9%) or Asian (28.6%). The median age was 44 years (range: 29 to 57 years). The median weight was 79.8 kg (range: 60.4 to 114 kg). There were two out of seven subjects with a history of RBC transfusion up to 1 year prior to randomization, with a median of 3 units of transfused RBC (range: 1 to 5). The median treatment duration of Arm B was 813 days (range: 785 to 897).

Open-Label Extension Period

Among the 44 subjects with PNH, a total of 43 subjects (treatment-naïve: 18 subjects, subjects who switched from eculizumab: 25 subjects) entered the OLE period. Subjects enrolling in the OLE from Parts 2, 3, and 4 initially stayed on the previously assigned treatment schedule. With the implementation of the tiered-weight dosing, introduced during a protocol amendment, all subjects in the OLE who were not currently receiving Q4W dosing were required to switch to the Q4W dosing regimen. Subjects either received 680 mg SC Q4W (BW ≥40 kg to <100 kg) or 1020 mg SC Q4W (BW ≥100 kg).

As of the CCOD (November 1, 2021), a total of 38 subjects were reported to be receiving treatment with crovalimab in the OLE (17 subjects who are treatment-naïve and 21 subjects who switched from eculizumab). The median treatment duration of crovalimab in the 44 subjects with PNH to the CCOD was 3.03 years (range: 0.4 to 4.4).

Efficacy Results

For the OLE period of COMPOSER, only exploratory efficacy endpoints of hemolysis control (change in LDH), TA, stabilized hemoglobin, and BTH were analyzed. Because no formal efficacy evaluation was prespecified for the study, results were descriptive in nature and should be interpreted with caution. During the OLE period, key efficacy results (i.e., evaluated from Week 20 to the CCOD) were as follows:

- Mean normalized LDH was generally maintained below 1.5×ULN and 80% to 100% of subjects at each visit had LDH ≤1.5×ULN.
- Across the 24-week intervals, the proportion of subjects achieving TA (82.9% to 91.7%) and hemoglobin stabilization (79.5% to 87.5%) remained stable.

Across the 24-week intervals, 0.0% to 4.9% of subjects reported a BTH event.

17. Clinical Safety

17.1. Pooled Safety Database and Results, COMMODORE-1, COMMODORE-2, and COMMODORE-3

In the pooled analysis of COMMODORE-1, COMMODORE-2, and COMMODORE-3, the median duration of exposure of the total crovalimab group (44.4 weeks, range: 0.1 to 108.4) was approximately twice as long as the eculizumab group (22.1 weeks, range: 0.1 to 26.1) at the time of the CCOD. There was a difference in exposure between the treatment arms because eculizumab was administered only during the primary treatment period in COMMODORE-1 and

COMMODORE-2, compared with crovalimab that was also administered during the extension period in addition to the primary treatment period in COMMODORE-1, COMMODORE-2, and COMMODORE-3.

In the total crovalimab group, 48.8% of subjects received crovalimab for at least 48 weeks. The median treatment duration of the crovalimab-naïve group (52.1 weeks, range: 0.1 to 107.9) was longer compared to the crovalimab-switch group (32.3 weeks, range: 0.3 to 108.4). The difference was mostly due to the longer period of crovalimab exposure in the single-arm COMMODORE-3 study. This study was conducted in China and enrolled 51 subjects with PNH who were ≥12 years of age and complement inhibitor treatment naïve. The median total IV dose intensity in the eculizumab and crovalimab groups was 100%, and the median total SC dose intensity in the crovalimab group was also 100%. Dose intensity is a percentage based on actual dose administered divided by total planned dose. A total of 18 subjects (4.8%) had received additional rescue IV doses of crovalimab (1 additional dose: 14 subjects, 2 additional doses: 3 subjects, 3 additional doses: 1 subject). An information request was sent to the Applicant to inquire if there was a guideline for the time interval needed between administration of rescue crovalimab doses. Per the Applicant, there were no guidelines regarding the intervals between the rescue doses. Of the 4 subjects who received greater than 1 rescue dose in the study, the time interval between doses ranged from 16 to 177 days. Per the Applicant, based on an integrative analysis of all available clinical data, no evidence for an increased risk of TEAE occurrence (serious adverse events, AESIs, AEs of grade 3 or higher, and infections) at higher crovalimab exposure was identified.

Table 129. Summary of Exposure, Pooled Analysis of COMMODORE-1, COMMODORE-2, and COMMODORE-3, Safety Population, up to the Clinical Cutoff Date

Exposure	Crovalimab (Naïve) (N=192)	Crovalimab (Switch) (N=185)	Crovalimab Total (N=377)	Eculizumab Total (N=111)
Duration of treatment (weeks)				
Mean (SD)	50.9 (17.0)	36.6 (24.3)	43.9 (22.0)	21.4 (3.9)
Median (Q1, Q3)	52.1 (40.0, 60.3)	32.3 (20.1, 52.1)	44.4 (28.4, 56.3)	22.1 (22.1, 22.3)
Range	0.1-107.9	0.3-108.4	0.1-108.4	0.1-26.1
Subjects treated by duration, n (%)				
<12 weeks	3 (1.6%)	31 (16.8%)	34 (9.0%)	5 (4.5%)
12 to <24 weeks	5 (2.6%)	21 (11.4%)	26 (6.9%)	102 (91.9%)
24 to <48 weeks	56 (29.2%)	77 (41.6%)	133 (35.3%)	4 (3.6%)
48 to <72 weeks	109 (56.8%)	36 (19.5%)	145 (38.5%)	0
72 to <96 weeks	16 (8.3%)	15 (8.1%)	31 (8.2%)	0
≥96 weeks	3 (1.6%)	5 (2.7%)	8 (2.1%)	0
Total IV dose intensity (%)				
Median	100.0	100.0	100.0	100.0
Range	95.0-202.0	99.7-175.0	95.0-202.0	100.0-100.0
Total SC dose intensity (%)				
Median	100.0	100.0	100.0	NE
Range	93.4-108.3	85.7-102.4	85.7-108.3	NE-NE

Exposure	Crovalimab (Naïve) (N=192)	Crovalimab (Switch) (N=185)	Crovalimab Total (N=377)	Eculizumab Total (N=111)
Number of unscheduled IV doses				
0 doses	184 (95.8%)	175 (94.6%)	359 (95.2%)	111 (100%)
1 dose	5 (2.6%)	9 (4.9%)	14 (3.7%)	0
2 doses	2 (1.0%)	1 (0.5%)	3 (0.8%)	0
3 doses	1 (0.5%)	0	1 (0.3%)	0

Source: SCS.
Abbreviations: IV, intravenous; N, total number of subjects; n, number of subjects in subset; NE; not evaluable; Q1, Quarter 1; Q3, Quarter 3; SC subcutaneous; SCS, summary of clinical safety; SD, standard deviation

Subject Demographics of the Pooled Population

The baseline subject demographics were generally similar between the total crovalimab and total eculizumab groups. In the total crovalimab and total eculizumab groups, the median age was 38 years (range: 13 to 85) and 44 years (range: 17 to 85), approximately half (51.2% and 50.5%) were males, and most were Asian (59.9% and 52.3%) or White (35.5% and 41.4%), respectively.

The baseline demographics between the crovalimab-naïve and crovalimab-switch groups were largely balanced. The median age at baseline was lower in the crovalimab-naïve group (34 years, range: 13 to 76) compared with the crovalimab-switch group (43 years, range: 16 to 85), which was driven by the higher proportion of pediatric subjects <18 years enrolled in the crovalimab-naïve group (4.7%) compared with the crovalimab-switch group (1.1%) and lower proportion of subjects who were ≥65 years of age in the crovalimab-naïve group (6.8%) compared with in the crovalimab-switch group (14.1%). A higher proportion of subjects were Asian in the crovalimab-naïve group (74.0%) compared with the crovalimab-switch group (45.4%) which was driven by COMMODORE-3, which was conducted in China and only enrolled Chinese subjects, as well as COMMODORE-2, in which 37.7% of subjects were Chinese.

Table 130. Summary of Demographics, Pooled Analysis of COMMODORE-1, COMMODORE-2, and COMMODORE-3, Safety Population

Demographic	Crovalimab (Naïve) (N=192)	Crovalimab (Switch) (N=185)	Crovalimab Total (N=377)	Eculizumab Total (N=111)
Gender				
Male	103 (53.6%)	90 (48.6%)	193 (51.2%)	56 (50.5%)
Female	89 (46.4%)	95 (51.4%)	184 (48.8%)	55 (49.5%)
Age				
Median	34	43	38	44
Range	13-76	16-85	13-85	17-85
Age group (years)				
<18 years	9 (4.7%)	2 (1.1%)	11 (2.9%)	2 (1.8%)
18 to 64 years	170 (88.5%)	157 (84.9%)	327 (86.7%)	93 (83.8%)
≥65 years	13 (6.8%)	26 (14.1%)	39 (10.3%)	16 (14.4%)
Race, n (%)				
Asian	142 (74.0%)	84 (45.4%)	226 (59.9%)	58 (52.3%)
White	45 (23.4%)	89 (48.1%)	134 (35.5%)	46 (41.4%)
Black or African American	3 (1.6%)	4 (2.2%)	7 (1.9%)	2 (1.8%)
Unknown	2 (1.0%)	8 (4.3%)	10 (2.7%)	5 (4.5%)

Demographic	Crovalimab (Naïve) (N=192)	Crovalimab (Switch) (N=185)	Crovalimab Total (N=377)	Eculizumab Total (N=111)
Ethnicity, n (%)				
Hispanic or Latino	19 (9.9%)	20 (10.8%)	39 (10.3%)	14 (12.6%)
Not Hispanic or Latino	170 (88.5%)	153 (82.7%)	323 (85.7%)	90 (81.1%)
Not reported	3 (1.6%)	12 (6.5%)	15 (4.0%)	7 (6.3%)
Region, n (%)				
Europe	37 (19.3%)	82 (44.3%)	119 (31.6%)	39 (35.1%)
Asia	141 (73.4%)	82 (44.3%)	223 (59.2%)	58 (52.3%)
North America	2 (1.0%)	7 (3.8%)	9 (2.4%)	5 (4.5%)
Central/South America or Africa and Middle East	12 (6.3%)	14 (7.6%)	26 (6.9%)	9 (8.1%)
Weight (kg)				
Median	65	70	68	66
Range	42-140	44-126	42-140	47-126

Source: ADSL.xpt.
Abbreviations: N, total number of subjects; n, number of subjects in subset

The baseline disease characteristics were also largely similar between the total crovalimab and total eculizumab groups. The median LDH was 3.4×ULN (range: 0.6 to 26.6) and 5.0×ULN (range: 0.7 to 20.3), 63.4% and 54.5% of subjects received pRBC transfusion within the 12 months, and a history of aplastic anemia was reported in 37.7% and 36.9% of subjects in the total crovalimab and total eculizumab groups, respectively.

As expected, subjects in the crovalimab-switch group had a more stabilized disease compared with the crovalimab-naïve group. In the crovalimab-switch and crovalimab-naïve groups, the median LDH was 1.0×ULN (range: 0.6 to 25.5) and 7.6×ULN (range: 2.0 to 26.6), 42.9% and 83.2% of subjects received pRBC transfusion within the 12 months, respectively. However, history of RI was higher in the crovalimab-switch group (13.5%) compared with the crovalimab-naïve group (6.8%), most likely due to longer disease duration; therefore, it is more likely that the subjects in the crovalimab-switch group had experienced a PNH-related complication (i.e., deteriorating renal function).

Table 131. Summary of Baseline Disease Characteristics, Pooled Analysis of COMMODORE-1, COMMODORE-2, and COMMODORE-3, Safety Population

Baseline Disease Characteristic	Crovalimab (Naïve) (N=192)	Crovalimab (Switch) (N=185)	Crovalimab Total (N=377)	Eculizumab Total (N=111)
LDH (x ULN)				
Median	7.6	1.0	3.4	5.0
Range	2.0-26.6	0.6-25.5	0.6-26.6	0.7-20.3
LDH category, n (%)				
≤ ULN	0	80 (43.2%)	80 (21.2%)	24 (21.6%)
> ULN to ≤2×ULN	1 (0.5%)	90 (48.6%)	91 (24.1%)	18 (16.2%)
>2 to 4×ULN	24 (12.5%)	7 (3.8%)	31 (8.2%)	10 (9.0%)
>4×ULN	167 (87.0%)	8 (4.3%)	175 (46.4%)	59 (53.2%)
History of pRBC transfusion within 12 months, n (%)				
Yes	158 (83.2%)	79 (42.9%)	237 (63.4%)	60 (54.5%)

Baseline Disease Characteristic	Crovalimab (Naïve) (N=192)	Crovalimab (Switch) (N=185)	Crovalimab Total (N=377)	Eculizumab Total (N=111)
Number of units of pRBC transfused				
Mean	10.5 (11.3)	3.9 (7.7)	7.3 (10.2)	5 (7.9)
Median	8	0	2.5	1.0
Range	0-50.0	0-54	0-54	0-41.0
Number of units of pRBC transfused (category)				
n	189	183	372	109
0	32 (16.9%)	105 (57.4%)	(36.8%)	50 (45.9%)
0 to <4	38 (20.1%)	26 (14.2%)	64 (17.2%)	18 (16.5%)
≥4 to <14	59 (31.2%)	34 (18.6%)	93 (25.0%)	27 (24.8%)
≥14	60 (31.7%)	18 (9.8%)	78 (21.0%)	14 (12.8%)
History of aplastic anemia, n (%)				
Yes	75 (39.1%)	67 (36.2%)	142 (37.7%)	41 (36.9%)
History of myelodysplastic syndrome, n (%)				
Yes	7 (3.6%)	6 (3.2%)	13 (3.4%)	6 (5.4%)
History of renal impairment, n (%)				
Yes	13 (6.8%)	25 (13.5%)	38 (10.1%)	13 (11.7%)
History of major vascular events, n (%)				
Yes	26 (13.5%)	31 (16.8%)	57 (15.1%)	19 (17.1%)

Source: SCS.
Abbreviations: LDH, lactate dehydrogenase; N, total number of subjects; n, number of subjects in subset; pRBC, packed red blood cell; SCS, summary of clinical safety ; ULN, upper limit of normal

17.1.1. Safety Results, Pooled Analyses, COMMODORE-1, COMMODORE-2, and COMMODORE-3

17.1.1.1. Overview of Treatment-Emergent Adverse Events Summary, Pooled Analyses, COMMODORE-1, COMMODORE-2, and COMMODORE-3

The pooled safety results of the Phase 3 crovalimab PNH clinical studies, COMMODORE-1, COMMODORE-2, and COMMODORE-3, up to the CCOD, are summarized in Table 132 and per 100 patient-years (PYs) in Table 133, to adjust for differences in exposure between the treatment groups. COMMODORE-3 is an ongoing single arm study conducted in China in patients with PNH ≥12 years of age who were complement inhibitor treatment naïve (see Section 16.1).

The safety results of the crovalimab (naïve and switch) and eculizumab groups were generally consistent with the safety results reported from the controlled Phase 3 studies, COMMODORE-1 and COMMODORE-2. The overall safety results per 100 PYs between the total eculizumab group (serious TEAEs: 32.2, any TEAEs: 582.7) and the total crovalimab group (serious TEAEs: 25.0, any TEAEs: 522.4) were broadly similar. The overall safety results per 100 PYs between the crovalimab-naïve group (serious TEAEs: 20.9, any TEAEs: 542.0) and the crovalimab-switch group (serious TEAEs: 30.8, any TEAEs: 494.8) were also comparable.

Table 132. Summary of Safety, Pooled Analysis of COMMODORE-1, COMMODORE-2, and COMMODORE-3, Safety Population, up to the Clinical Cutoff Date

	Crovalimab (Naïve)		Crovalimab (Switch)		Crovalimab Total		Eculizumab Total	
Safety Results	**# of AEs**	**(N=192) n (%)**	**# of AEs**	**(N=185) n (%)**	**# of AEs**	**(N=377) n (%)**	**# of AEs**	**(N=111) n (%)**
Deaths	3	3 (1.6%)	1	1 (0.5%)	4	4 (1.1%)	1	1 (0.9%)
Serious TEAEs	41	28 (14.6%)	43	29 (15.7%)	84	57 (15.1%)	16	10 (9.0%)
Any TEAEs	1063	174 (90.6%)	692	152 (82.2%)	1755	326 (86.5%)	290	83 (74.8%)
Grade 1[a]	535	41 (21.4%)	345	39 (21.1%)	880	80 (21.2%)	180	33 (29.7%)
Grade 2[a]	408	83 (43.2%)	271	67 (36.2%)	679	150 (39.8%)	85	32 (28.8%)
Grade 3[a]	98	36 (18.8%)	67	39 (21.1%)	165	75 (19.9%)	19	14 (12.6%)
Grade 4[a]	19	11 (5.7%)	8	6 (3.2%)	27	17 (4.5%)	5	3 (2.7%)
TEAE leading to discontinuation of study drug	1	1 (0.5%)	3	3 (1.6%)	4	4 (1.1%)	1	1 (0.9%)
TEAE leading to dose modification/interruption of study drug	10	8 (4.2%)	8	8 (4.3%)	18	16 (4.2%)	3	3 (2.7%)

Source: ADAE.xpt.
Note: COMMODORE-2 enrolled subjects starting October 8, 2020, and COMMODORE-1 starting September 29, 2020. The clinical cutoff date for both COMMODORE-1 and COMMODORE-2 was November 16, 2022. In COMMODORE-3, the date of first subject enrollment was March 17, 2021, and clinical cutoff date was August 10, 2022.
Note: The median duration of exposure differs between the treatment groups (eculizumab total: 22.1 weeks [range: 0.1 to 26.1], crovalimab-naïve: 52.1 weeks [range: 0.1 to 107.9], crovalimab-switch: 32.3 weeks [range: 0.3 to 108.4], crovalimab total: 44.4 weeks [range: 0.1 to 108.4]).
[a] Based on the highest grade per subject.
Abbreviations: AE, adverse event; N, total number of subjects; n, number of subjects in subset; TEAE, treatment-emergent adverse event

Table 133. Summary of Safety Per 100 Patient-Years, Pooled Analysis of COMMODORE-1, COMMODORE-2, and COMMODORE-3, Safety Population, up to the Clinical Cutoff Date

Safety Results	Crovalimab (Naïve) (N=192) PY =196.13 AEs Per 100 PY (95% CI)	Crovalimab (Switch) (N=185) PY =139.85 AEs Per 100 PY (95% CI)	Crovalimab Total (N=377) PY =335.98 AEs Per 100 PY (95% CI)	Eculizumab Total (N=111) PY =49.77 AEs Per 100 PY (95% CI)
Deaths	1.53 (0.32, 4.47)	0.72 (0.02, 3.98)	1.19 (0.32, 3.05)	2.01 (0.05, 11.20)
Serious TEAEs	20.90 (15.00. 28.36)	30.75 (22.25, 41.41)	25.00 (19.94, 30.95)	32.15 (18.38, 52.21)
Any TEAEs	542.00 (509.90, 575.59)	494.80 (458.61, 533.08)	522.35 (498.20, 547.37)	582.73 (517.58, 653.80)
≥ Grade 3	61.19 (50.73, 73.16)	54.34 (42.82, 68.02)	58.34 (50.46, 67.10)	50.24 (32.51, 74.16)
TEAE leading to discontinuation of study drug	0.51 (0.01, 2.84)	2.15 (0.44, 6.27)	1.19 (0.32, 3.05)	2.01 (0.05, 11.20)
TEAE leading to dose modification/interruption of study drug	5.10 (2.45, 9.38)	5.72 (2.47, 11.27)	5.36 (3.18, 8.47)	6.03 (1.24, 17.62)

Source: Per the Applicant.
Abbreviations: AE, adverse event; CI, confidence interval; N, total number of subjects; n, number of subjects in subset; TEAE, treatment-emergent adverse event; PY, patient years

17.1.1.2. Deaths, Pooled Analyses, COMMODORE-1, COMMODORE-2, and COMMODORE-3

In COMMODORE-3, 1 subject died due to subdural hematoma 15 days after the last dose of crovalimab on Day 156. It was reported that the subject fell on the hospital room floor and lost consciousness. A CT scan established the diagnosis of subdural hematoma with cerebral hernia. Emergency treatment was administered; however, potentially life-saving brain surgery was denied by the family. In the afternoon of the same day, the subject died with a diagnosis of Grade 5 subdural hematoma.

For deaths that occurred in COMMODORE-1 and COMMODORE-2, see Section 7.6.1.2.

17.1.1.3. Serious Treatment-Emergent Adverse Events, Pooled Analyses, COMMODORE-1, COMMODORE-2, and COMMODORE-3

In the pooled analysis of COMMODORE-1, COMMODORE-2, and COMMODORE-3, 15.1% of subjects in the total crovalimab group and 9.0% of subjects in the total eculizumab group had at least 1 serious TEAE. The number of serious TEAEs per 100 PYs was 25.0 and 32.2 in the total crovalimab and total eculizumab groups, respectively.

The incidence of serious TEAEs was similar in the crovalimab-naïve (14.6%) and crovalimab-switch (15.7%) groups. The number per 100 PYs was 20.9 in the crovalimab-naïve group and 30.8 in the crovalimab-switch group.

The most frequently reported serious TEAEs (≥1%) in the total crovalimab group were respiratory tract infections, viral infections, pneumonia, hemolysis, type III immune complex-mediated reactions, and anemia. In the crovalimab-switch group, a total of five subjects (USUBJIDs: (b) (6)) experienced a serious type III immune complex-mediated reaction and two subjects (USUBJIDs (b) (6)) experienced serious neuropathy. The subject narratives of these cases are presented in Section 17.3.

Table 134. Serious TEAEs That Occurred in >1 Subject in the Crovalimab Total Group, Pooled Analysis of COMMODORE-1, COMMODORE-2, and COMMODORE-3, Safety Population, up to the Clinical Cutoff Date

System Organ Class FMQ	Crovalimab (Naïve) (N=192) (PY =196.13) n (%) # of AEs (Per 100 PYs)	Crovalimab (Switch) (N=185) (PY =139.85) n (%) # of AEs (Per 100 PYs)	Crovalimab Total (N=377) (PY =335.98) n (%) # of AEs (Per 100 PYs)	Eculizumab Total (N=111) (PY =49.77) n (%) # of AEs (Per 100 PYs)
All	28 (14.6%) 41 (20.9)	29 (15.7%) 43 (30.8)	57 (15.1%) 84 (25.0)	10 (9.0%) 16 (32.2)
Infections and infestations				
Respiratory tract infection[a]	7 (3.6%) 7 (3.6)	2 (1.1%) 3 (2.2)	9 (2.4%) 10 (3.0)	2 (1.8%) 2 (4.0)
Viral infections[a]	2 (1.0%) 3 (1.5)	3 (1.6%) 3 (2.2)	5 (1.3%) 6 (1.8)	1 (0.9%) 1 (2.0)
Pneumonia	4 (2.1%) 4 (2.0)	1 (0.5%) 1 (0.7)	5 (1.3%) 5 (1.5)	1 (0.9%) 1 (2.0)
COVID-19	1 (0.5%) 1 (0.5)	2 (1.1%) 1 (0.7)	3 (0.8%) 1 (0.3)	1 (0.9%) 1 (2.0)
Urinary tract infection	0 0	2 (1.1%) 2 (1.4)	2 (0.5%) 2 (0.6)	1 (0.9%) 1 (2.0)
Blood and lymphatic system disorders				
Hemolysis[a]	1 (0.5%) 1 (0.5)	4 (2.2%) 4 (2.9)	5 (1.3%) 5 (1.5)	0
Anemia[a]	2 (1.0%) 4 (2.0)	2 (1.1%) 2 (1.4)	4 (1.1%) 6 (1.8)	1 (0.9%) 1 (2.0)
Neutropenia[a]	0	2 (1.1%) 2 (1.4)	2 (0.5%) 2 (0.6)	1 (0.9%) 1 (2.0)
Thrombocytopenia[a]	3 (1.6%) 3 (1.5)	0	3 (0.8%) 3 (0.9)	1 (0.9%) 1 (2.0)
Breakthrough hemolysis	1 (0.5%) 1 (0.5)	2 (1.1.%) 2 (1.4)	3 (0.8%) 3 (0.9)	0
Aplastic anemia	2 (1.0%) 4 (2.0)	0	2 (0.5%) 4 (1.2)	1 (0.9%) 1 (2.0)
Immune system disorders				
Type III immune complex-mediated reaction	0	5 (2.7%) 5 (3.6)	5 (1.3%) 5 (1.5)	0
Respiratory, thoracic and mediastinal disorders				
Epistaxis	2 (1.0%) 3 (1.5)	0	2 (0.5%) 3 (0.9)	0

System Organ Class FMQ	Crovalimab (Naïve) (N=192) (PY =196.13) n (%) # of AEs (Per 100 PYs)	Crovalimab (Switch) (N=185) (PY =139.85) n (%) # of AEs (Per 100 PYs)	Crovalimab Total (N=377) (PY =335.98) n (%) # of AEs (Per 100 PYs)	Eculizumab Total (N=111) (PY =49.77) n (%) # of AEs (Per 100 PYs)
General disorders and administration site conditions				
Pyrexia	1 (0.5%) 2 (1.0)	1 (0.5%) 1 (0.7)	2 (0.5%) 3 (0.9)	1 (0.9%) 1 (2.0)
Nervous system disorders				
Neuropathy[a]	0	2 (1.1.%) 2 (1.4)	2 (0.5%) 2 (0.6)	0

Source: ADAE.xpt.
Note: The median duration of exposure differs between the treatment groups (eculizumab total: 22.1 weeks [range: 0.1 to 26.1], crovalimab-naïve: 52.1 weeks [range: 0.1 to 107.9], crovalimab-switch: 32.3 weeks [range: 0.3 to 108.4], crovalimab total: 44.4 weeks [range: 0.1 to 108.4]).
[a] Grouped terms: Anemia includes anemia, aplastic anemia, and autoimmune hemolytic anemia. Hemolysis includes hemolysis, breakthrough hemolysis, and extravascular hemolysis. Respiratory tract infection includes upper respiratory tract infection, influenza, nasopharyngitis, pneumonia, respiratory tract infection, and tuberculosis. Neutropenia includes neutropenia and febrile neutropenia. Thrombocytopenia includes thrombocytopenia and platelet count decreased. Neuropathy includes axonal neuropathy and demyelinating polyneuropathy.
Abbreviations: AE, adverse event; COVID-19, coronavirus disease of 2019; FMQ, Food and Drug Administration Medical Query; N, total number of subjects; n, number of subjects in subset; PY, patient years; TEAE, treatment-emergent adverse event

17.1.1.4. Adverse Events and FDA Medical Queries Leading to Treatment Discontinuation, Pooled Analyses, COMMODORE-1, COMMODORE-2, and COMMODORE-3

In the pooled Phase 3 PNH studies, a total of four subjects (1.1%) in the total crovalimab group (crovalimab-naïve [due to thrombocytopenia], crovalimab-switch [due to demyelinating polyneuropathy, a type III immune complex mediated reaction, and sepsis]) and one subject (0.9%) in the total eculizumab group experienced TEAEs that led to study drug discontinuation up to the CCOD.

Table 135. TEAEs Leading to Treatment Discontinuation, Pooled Analysis of COMMODORE-1, COMMODORE-2, and COMMODORE-3, Safety Population, up to the Clinical Cutoff Date

System Organ Class Preferred Term	Crovalimab (Naïve) (N=192) n (%)	Crovalimab (Switch) (N=185) n (%)	Crovalimab Total (N=377) n (%)	Eculizumab Total (N=111) n (%)
All	1 (0.5%)	3 (1.6%)	4 (1.1%)	1 (0.9%)
Nervous system disorders				
Demyelinating polyneuropathy	0	1 (0.5%)	1 (0.3%)	0
Ischemic stroke	0	0	0	1 (0.9%)
Blood and lymphatic system disorders				
Thrombocytopenia	1 (0.5%)	0	1 (0.3%)	0
Immune system disorders				
Type III immune complex-mediated reaction	0	1 (0.5%)	1 (0.3%)	0
Infections and infestations				
Sepsis	0	1 (0.5%)	1 (0.3%)	0

Source: ADAE.xpt.
Note: The median duration of exposure differs between the treatment groups (eculizumab total: 22.1 weeks [range: 0.1 to 26.1], crovalimab-naïve: 52.1 weeks [range: 0.1 to 107.9], crovalimab-switch: 32.3 weeks [range: 0.3 to 108.4], crovalimab total: 44.4 weeks [range: 0.1 to 108.4]).
Abbreviations: N, total number of subjects; n, number of subjects in subset; TEAE, treatment-emergent adverse event

17.1.1.5. Treatment-Emergent Adverse Events, Pooled Analyses, COMMODORE-1, COMMODORE-2, and COMMODORE-3

Up to the CCOD, the incidence of TEAEs was 86.5% in the total crovalimab group and 74.8% in the total eculizumab group. The number of TEAEs per 100 PYs was 522.4 in the total crovalimab group and 582.7 in the total eculizumab group.

The most frequently reported TEAEs (≥10%) in the total crovalimab group based on Food and Drug Administration Medical Dictionary for Regulatory Activities queries were respiratory tract infections, viral infections, COVID-19, neutropenia, pyrexia, leukopenia, infusion-related reactions, hepatic injury, and headache.

The overall incidence of TEAEs was 90.6% in the crovalimab-naïve group and 82.2% in the crovalimab-switch group. The number of TEAEs per 100 PYs was 542.0 in the crovalimab-naïve group and 494.8 in the crovalimab-switch group.

In subjects who received crovalimab, TEAEs based on Food and Drug Administration Medical Dictionary for Regulatory Activities queries that occurred in a higher proportion of subjects

(≥5%) in the crovalimab-naïve group compared to the crovalimab-switch group included respiratory tract infections, neutropenia, leukopenia, hepatic injury, weight gain, hypokalemia, hyperuricemia, and increased alpha hydroxybutyrate dehydrogenase levels. Increased alpha hydroxybutyrate dehydrogenase were all Grade 1 and reported from COMMODORE-3 that was conducted in China in patients who were complement inhibitor treatment naïve. Some of the subjects with increased alpha hydroxybutyrate dehydrogenase levels had subsequent increases in bilirubin that resolved. TEAEs that occurred in a higher proportion of subjects (≥5%) in the crovalimab-switch group compared to the crovalimab-naïve group were type III immune complex-mediated reactions and injection site reactions. While hepatic injury was reported in 10.6% of subjects, this was primarily driven by elevations in bilirubin, which is not unexpected in a population with hemolytic disease.

Table 136. TEAEs That Occurred in >2% of Subjects in the Crovalimab Total Group, Pooled Analysis of COMMODORE-1, COMMODORE-2, and COMMODORE-3, Safety Population, up to the Clinical Cutoff Date

System Organ Class FMQ (narrow)	Crovalimab (Naïve) (N=192) (PY =196.13) n (%) # of AEs (Per 100 PYs)	Crovalimab (Switch) (N=185) (PY =139.85) n (%) # of AEs (Per 100 PYs)	Crovalimab Total (N=377) (PY =335.98) n (%) # of AEs (Per 100 PYs)	Eculizumab Total (N=111) (PY =49.77) n (%) # of AEs (Per 100 PYs)
All	174 (90.6%)	152 (82.2%)	326 (86.5%)	83 (74.8%)
	1063 (542.0)	692 (494.8)	1755 (522.4)	290 (582.7)
Infections and infestations				
Respiratory tract infection[a]	59 (30.7%)	29 (15.7%)	88 (23.3%)	17 (15.3%)
	75 (39.2)	40 (28.6)	115 (34.2)	22 (44.2)
Viral infections[a]	35 (18.2%)	40 (21.6%)	75 (19.9%)	14 (12.6%)
	39 (19.9)	43 (30.7)	82 (24.4)	16 (32.1)
Nasopharyngitis[a]	54 (28.1%)	21 (11.4%)	73 (19.4%)	13 (11.7%)
	64 (32.6)	29 (20.7)	93 (27.7)	16 (32.1)
COVID-19[a]	29 (15.1%)	32 (17.3%)	61 (16.2%)	11 (9.9%)
	30 (15.3)	33 (23.6)	63 (18.8)	11 (22.1)
Urinary tract infection	13 (6.8%)	9 (4.9%)	22 (5.8%)	7 (6.3%)
	18 (9.2)	9 (6.4)	27 (8.0)	7 (14.1)
Hepatobiliary disorders				
Hepatic injury[a]	33 (17.2%)	7 (3.8%)	40 (10.6%)	4 (3.6%)
	66 (33.7)	9 (6.4)	75 (21.1)	6 (12.1)
Blood and lymphatic system disorders				
Neutropenia[a]	42 (21.9%)	8 (4.3%)	50 (13.3%)	10 (9.0%)
	95 (48.4)	12 (8.6)	107 (31.8)	14 (28.1)
Leukopenia[a]	33 (17.2%)	8 (4.3%)	41 (10.9%)	7 (6.3%)
	87 (44.4)	14 (10.0)	101 (30.1)	16 (32.2)
Thrombocytopenia[a]	10 (5.2%)	6 (3.2%)	16 (4.2%)	2 (1.8%)
	19 (9.7)	12 (8.6)	31 (9.2)	2 (4.0)
Hemolysis[a]	6 (3.1%)	7 (3.8%)	13 (3.4%)	1 (0.9%)
	8 (4.1)	7 (5.0)	15 (4.5)	1 (2.0)
Anemia[a]	8 (4.2%)	3 (1.6%)	11 (2.9%)	1 (0.9%)
	12 (6.1)	5 (3.6)	17 (5.1)	1 (2.0)
Lymphopenia	9 (4.7%)	0	9 (2.4%)	0
	22 (11.2)		22 (6.6)	

System Organ Class FMQ (narrow)	Crovalimab (Naïve) (N=192) (PY =196.13) n (%) # of AEs (Per 100 PYs)	Crovalimab (Switch) (N=185) (PY =139.85) n (%) # of AEs (Per 100 PYs)	Crovalimab Total (N=377) (PY =335.98) n (%) # of AEs (Per 100 PYs)	Eculizumab Total (N=111) (PY =49.77) n (%) # of AEs (Per 100 PYs)
General disorders and administration site conditions				
Pyrexia[a]	22 (11.5%)	23 (12.4%)	45 (11.9%)	8 (7.2%)
	30 (15.3)	30 (21.5)	60 (17.9)	10 (20.1)
Fatigue[a]	9 (4.7%)	14 (7.6%)	23 (6.1%)	6 (5.4%)
	10 (5.1)	18 (12.9)	28 (8.3)	6 (12.1)
Peripheral edema[a]	6 (3.1%)	11 (5.9%)	17 (4.5%)	1 (0.9%)
	6 (3.1)	13 (9.3)	19 (5.7)	1 (2.0)
Weight gain[a]	10 (5.2%)	0	10 (2.7%)	0
	10 (5.1)		10 (3.0)	
Injury, poisoning and procedural complications				
Infusion related reaction	23 (12.0%)	17 (9.2%)	40 (10.6%)	9 (8.1%)
	24 (12.2)	17 (12.2)	41 (12.2)	10 (20.1)
Injection site reaction[a]	8 (4.2%)	18 (9.7%)	26 (6.9%)	0
	16 (8.2)	30 (21.5)	46 (13.7)	
Nervous system disorders				
Headache[a]	16 (8.3%)	22 (11.9%)	38 (10.1%)	5 (4.5%)
	20 (10.2)	30 (21.5)	50 (14.9)	8 (16.1)
Dizziness[a]	3 (1.6%)	8 (4.3%)	11 (2.9%)	3 (2.7%)
	4 (2.0)	13 (9.3)	17 (5.1)	6 (12.1)
Immune system disorders				
Type III immune complex mediated reaction	0	33 (17.8%)	33 (8.8%)	0
		35 (25.0)	35 (10.4)	
Vascular disorders				
Hemorrhage[a]	20 (10.4%)	11 (5.9%)	31 (8.2%)	5 (4.5%)
	26 (13.3)	15 (10.7)	41 (12.2)	7 (14.1)
Metabolism and nutrition disorders				
Hypokalemia	18 (9.4%)	5 (2.7%)	23 (6.1%)	9 (8.1%)
	40 (20.4)	7 (5.0)	47 (14.0)	20 (40.2)
Hyperuricemia	18 (9.4%)	4 (2.2%)	22 (5.8%)	6 (5.4%)
	29 (14.8)	7 (5.0)	36 (10.7)	12 (24.1)
Hypocalcemia	9 (4.7%)	3 (1.6%)	12 (3.2%)	7 (6.3%)
	13 (6.6)	3 (2.2)	16 (4.8)	13 (26.1)

System Organ Class FMQ (narrow)	Crovalimab (Naïve) (N=192) (PY =196.13) n (%) # of AEs (Per 100 PYs)	Crovalimab (Switch) (N=185) (PY =139.85) n (%) # of AEs (Per 100 PYs)	Crovalimab Total (N=377) (PY =335.98) n (%) # of AEs (Per 100 PYs)	Eculizumab Total (N=111) (PY =49.77) n (%) # of AEs (Per 100 PYs)
Gastrointestinal disorders				
Diarrhea[a]	12 (6.3%)	9 (4.9%)	21 (5.6%)	2 (1.8%)
	13 (6.6)	11 (7.9)	24 (7.1)	2 (4.0)
Abdominal pain[a]	8 (4.2%)	12 (6.5%)	20 (5.3%)	2 (1.8%)
	13 (6.6)	13 (9.3)	26 (7.7)	2 (4.0)
Nausea	7 (3.6%)	9 (4.9%)	16 (4.2%)	4 (3.6%)
	8 (4.1)	10 (7.2)	18 (5.4)	5 (10.1)
Dyspepsia[a]	6 (3.1%)	5 (2.7%)	11 (2.9%)	0
	9 (4.6)	5 (3.6)	14 (4.2)	
Vomiting	4 (2.1%)	4 (2.2%)	8 (2.1%)	2 (1.8%)
	4 (2.0)	5 (3.6)	9 (2.7)	2 (4.0)
Musculoskeletal and connective tissue disorders				
Arthralgia	6 (3.1%)	12 (6.5%)	18 (4.8%)	3 (2.7%)
	6 (3.1)	13 (9.3)	19 (5.7)	3 (6.0)
Back pain[a]	5 (2.6%)	9 (4.9%)	14 (3.7%)	3 (2.7%)
	5 (2.6)	9 (6.4)	14 (4.2)	3 (6.0)
Myalgia	5 (2.6%)	7 (3.8%)	12 (3.2%)	2 (1.8%)
	5 (2.6)	7 (5.0)	12 (3.6)	2 (4.0)
Skin and subcutaneous tissue disorders				
Rash[a]	8 (4.2%)	8 (4.3%)	16 (4.2%)	2 (1.8%)
	9 (4.6)	9 (6.4)	18 (5.4)	3 (6.0)
Pruritus[a]	3 (1.6%)	6 (3.2%)	9 (2.4%)	1 (0.9%)
	3 (1.5)	7 (5.0)	10 (3.0)	1 (2.0)
Respiratory, thoracic, and mediastinal disorders				
Cough	8 (4.2%)	3 (1.6%)	11 (2.9%)	3 (2.7%)
	9 (4.6)	3 (2.2)	12 (3.6)	3 (6.0)
Investigations				
Alpha hydroxybutyrate dehydrogenase increased	11 (5.7%)	0	11 (2.9%)	0
	11 (5.6)		11 (3.3)	

Source: ADAE.xpt.
Note: The median duration of exposure differs between the treatment groups (eculizumab total: 22.1 weeks [range: 0.1 to 26.1], crovalimab-naïve: 52.1 weeks [range: 0.1 to 107.9], crovalimab-switch: 32.3 weeks [range: 0.3 to 108.4], crovalimab total: 44.4 weeks [range: 0.1 to 108.4]).
[a] Grouped terms
Abbreviations: AE, adverse event; COVID-19, coronavirus disease of 2019; FMQ, Food and Drug Administration Medical Query; N, total number of subjects; n, number of subjects in subset; PY, patient years; TEAE, treatment-emergent adverse event

17.1.1.6. Subgroup Analyses, Pooled Analyses, COMMODORE-1, COMMODORE-2, and COMMODORE-3

Subgroup safety analyses by age, race, region, and sex were conducted using the pooled data of COMMODORE-1, COMMODORE-2, and COMMODORE-3 to evaluate if the results were consistent across the subgroups. The results should be interpreted with caution due to small sample sizes.

Age

In the crovalimab Phase 3 studies, a total of 11 subjects (2.9%) were <18 years of age, 327 subjects (86.7%) were 18 to 64 years of age, and 39 subjects (10.3%) were ≥65 years of age. The safety results of crovalimab-naïve and switch groups by age are summarized in Table 137. The safety profile of crovalimab-naïve and switch groups was broadly similar between the 18-to-64-year and ≥65-year age groups. In the crovalimab-naïve group, however, the incidence of TEAEs was higher in the 18-to-64-year age group compared with the ≥65-year age group (91.8% versus 76.9%). In the crovalimab switch group, subjects who were ≥65 years of age had higher incidences of serious TEAEs (30.8%) and Grade 3/4 TEAEs (46.2%) compared with subjects who were 18 to 64 years of age (serious TEAEs: 13.4%, Grade 3/4 TEAEs: 21.7%).

Pediatric Subjects

At the primary CCOD of November 16, 2022, a total of 11 pediatric subjects (crovalimab-naïve: 9 subjects, crovalimab-switch: 2 subjects) received crovalimab across the crovalimab Phase 3 trials (COMMODORE-1 [crovalimab-switch: 1 subject in the nonrandomized arm], COMMODORE-2 [crovalimab-naïve: 6 subjects in the nonrandomized arm, crovalimab-switch: 1 subject during the extension period], COMMODORE-3 [crovalimab-naïve: 3 subjects]). In the 11 pediatric subjects, the baseline age ranged from 13 to 17 years and weight ranged from 49 to 99 kg. A total of six subjects were females, nine subjects were Asian, one subject was White, and one had an unknown race. Treatment-emergent AEs were reported in a total of 9 pediatric subjects (81.8%). Most TEAEs were Grade 1 or 2 in severity. Grade 3 TEAEs occurred in a total of two pediatric crovalimab-naïve subjects in COMMODORE-3 (one subject had a Grade 3 blood bilirubin increase and another subject had a Grade 3 neutrophil count decrease). All Grade 3 events resolved without dose modification of the study treatment. No pediatric subjects experienced Grade 4 or 5 TEAEs or TEAEs that were considered serious.

No cases of meningococcal infections were reported across all crovalimab PNH studies. However, there was one case of meningococcal meningitis reported in Study BO42354, a study evaluating the efficacy, safety, PK, and PD of crovalimab in pediatric patients with atypical hemolytic uremic syndrome. The pediatric subject experienced meningococcal meningitis on Day 430 (Grade 3). The pathogen was identified as *Neisseria meningitidis* serotype X (the subject was vaccinated against serotype ACWY). The event subsequently resolved after 4 days, with no change to crovalimab treatment.

Table 137. Adverse Events of Crovalimab by Baseline Age, Pooled Analyses, COMMODORE-1, COMMODORE-2, and COMMODORE-3, up to the Clinical Cutoff Date (Safety Population)

	Crovalimab (Naïve) (N=192)			Crovalimab (Switch) (N=185)		
Adverse Event	**<18 yrs (n=9) n (%)**	**18-64 yrs (n=170) n (%)**	**≥65 yrs (n=13) n (%)**	**<18 yrs (n=2) n (%)**	**18-64 yrs (n=157) n (%)**	**≥65 yrs (n=26) n (%)**
Deaths	0	1 (0.6%)	2 (15.4%)	0	1 (0.6%)	0
Serious TEAEs	0	25 (14.7%)	3 (23.1%)	0	21 (13.4%)	8 (30.8%)
Any TEAEs	8 (88.9%)	156 (91.8%)	10 (76.9%)	1 (50.0%)	127 (80.9%)	24 (92.3%)
Grade 3/4	2 (22.2%)	44 (25.9%)	3 (23.1%)	0	34 (21.7%)	12 (46.2%)
TEAEs leading to withdrawal	0	1 (0.6%)	0	0	1 (0.6%)	2 (7.7%)
TEAEs leading to dose modification/ interruption	0	7 (4.1%)	1 (7.7%)	0	6 (3.2%)	2 (7.7%)

Source: ADAE.xpt.
Abbreviations: N, total number of subjects; n, number of subjects in subset; TEAE, treatment-emergent adverse event

On May 9, 2024, the Applicant provided additional safety information on 1 pediatric subject (BO42161-20126) who was enrolled in the nonrandomized arm in COMMODORE-1 approximately 2 weeks prior to the cutoff date of the primary analysis and 1 subject (BO42161-20130) who switched from ravulizumab and was enrolled in the nonrandomized arm in COMMODORE-1 after the primary analysis cutoff date and had received crovalimab up to Week 25.

One subject (BO42161-20126) experienced one TEAE (Grade 1 viral upper respiratory tract infection) that was resolved after 6 days without dose modification of crovalimab.

One subject (BO42161-20130) had four TEAEs:

- Grade 1 injection-related reaction, which resolved after 8 days and included symptoms of Grade 1 pruritus and pain at the injections site
- Grade 1 skin ulcer that resolved after 4 days
- Grade 1 fatigue that resolved after 71 days
- Grade 2 upper respiratory tract infection that resolved after 6 days

There were no crovalimab dose modifications in this subject due to the TEAEs.

Based on the small sample size, the safety profile of crovalimab in pediatric subjects appears comparable to that of the adult patient population.

Race and Region

Most of the subjects in the Phase 3 crovalimab studies were Asian (59.9%) or White (35.5%) and were enrolled from Asia (59.2%) or Europe (31.6%). The safety results of crovalimab (naïve and switch) were generally similar between subjects who were Asian and White and between subjects enrolled from Asia and Europe. In the crovalimab-naïve group, the incidence of Grade 3 or 4 TEAEs was higher in Asians (28.9%) compared with Whites (17.8%). The differences were mostly due to higher incidences of Grade 3 or 4 TEAEs in Asians in the blood and lymphatic system disorders system organ class (SOC) (neutropenia, thrombocytopenia, leukopenia) and liver injury.

Regarding subjects who were in the Black/African American and unknown categories, the sample sizes were too small for interpretation.

Table 138. Adverse Events of Crovalimab by Race, Pooled Analyses, COMMODORE-1, COMMODORE-2, and COMMODORE-3, up to the Clinical Cutoff Date (Safety Population)

	Crovalimab (Naïve) (N=192)				Crovalimab (Switch) (N=185)			
Adverse Event	Asian (n=142) n (%)	Black/AA (n=3) n (%)	White (n=45) n (%)	Unknown (n=2) n (%)	Asian (n=84) n (%)	Black/AA (n=4) n (%)	White (n=89) n (%)	Unknown (n=8) n (%)
Deaths	2 (1.4%)	0	1 (2.2%)	0	0	0	1 (1.1%)	0
Serious TEAEs	22 (15.5%)	0	6 (13.3%)	0	15 (17.9%)	1 (25.0%)	13 (14.6%)	0
Any TEAEs	128 (90.1%)	3 (100%)	41 (91.1%)	2 (100%)	68 (81.0%)	4 (100%)	73 (82.0%)	7 (87.5%)
Grade 3/4	41 (28.9%)	0	8 (17.8%)	0	22 (26.2%)	2 (50.0%)	21 (23.6%)	1 (12.5%)
TEAEs leading to withdrawal	1 (0.7%)	0	0	0	0	0	3 (3.4%)	0
TEAEs leading to dose modification/ interruption	4 (2.8%)	0	4 (8.9%)	0	4 (4.8%)	0	3 (3.4%)	1 (12.5%)

Source: ADAE.xpt.
Abbreviations: AA, African American; N, total number of subjects; n, number of subjects in subset; TEAE, treatment-emergent adverse event

Table 139. Adverse Events of Crovalimab by Region, Pooled Analyses, COMMODORE-1, COMMODORE-2, and COMMODORE-3, up to the Clinical Cutoff Date (Safety Population)

	Crovalimab (Naïve) (N=192)				Crovalimab (Switch) (N=185)			
Adverse Event	Europe (n=37) n (%)	Asia (n=141) n (%)	North America (n=2) n (%)	CSA/ AME (n=12) n (%)	Europe (n=82) n (%)	Asia (n=82) n (%)	North America (n=7) n (%)	CSA/ AME (n=14) n (%)
Deaths	1 (2.7%)	2 (1.4%)	0	0	1 (1.2%)	0	0	0
Serious TEAEs	5 (13.5%)	22 (15.6%)	1 (50.0%)	0	12 (14.6%)	14 (17.1%)	1 (14.3%)	2 (14.3%)
Any TEAEs	35 (94.6%)	127 (90.1%)	2 (100%)	10 (83.3%)	67 (81.7%)	66 (80.5%)	6 (85.7%)	13 (92.9%)
Grade 3/4	7 (18.9%)	41 (29.1%)	1 (50.0%)	0	19 (23.2%)	22 (26.8%)	1 (14.3%)	4 (28.6%)
TEAEs leading to withdrawal	0	1 (0.7%)	0	0	3 (3.7%)	0	0	0
TEAEs leading to dose modification/ interruption	4 (10.8%)	4 (2.8%)	0	0	4 (4.9%)	4 (4.9%)	0	0

Source: ADAE.xpt.
Abbreviations: AME, Africa Middle East; CSA, Central South America; N, total number of subjects; n, number of subjects in subset; TEAE, treatment-emergent adverse event

Sex

In the crovalimab Phase 3 studies, approximately half (51.2%) of the subjects were males. The safety profile of crovalimab (naïve and switch) was comparable between males and females. In the crovalimab-naïve group, the incidence of Grade 3 or 4 TEAEs was higher in females (33.7%) compared with males (18.4%). The differences were mostly due to higher incidences of Grade 3 or 4 TEAEs in females in the blood and lymphatic system disorders SOC (neutropenia and leukopenia).

Table 140. Adverse Events of Crovalimab by Sex, Pooled Analyses, COMMODORE-1, COMMODORE 2, and COMMODORE-3, up to the Clinical Cutoff Date (Safety Population)

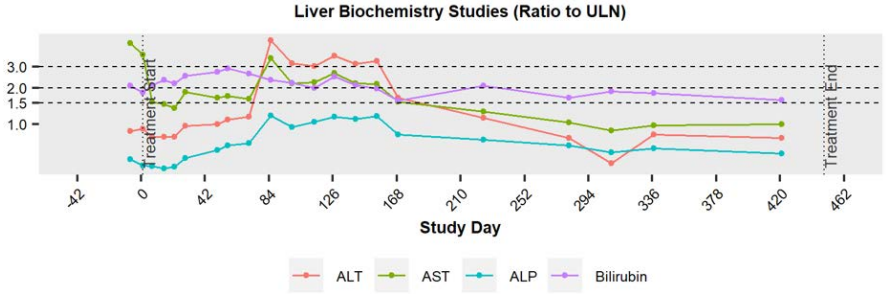
	Crovalimab (Naïve) (N=192)		Crovalimab (Switch) (N=185)	
Adverse Event	**Male (n=103) n (%)**	**Female (n=89) n (%)**	**Male (n=90) n (%)**	**Female (n=95) n (%)**
Deaths	2 (1.9%)	1 (1.1%)	0	1 (1.1%)
Serious TEAEs	15 (14.6%)	13 (14.6%)	14 (15.6%)	15 (15.8%)
Any TEAEs	89 (86.4%)	85 (95.5%)	71 (78.9%)	81 (85.3%)
Grade 3/4	19 (18.4%)	30 (33.7%)	22 (24.4%)	24 (24.3%)
TEAEs leading to withdrawal	1 (1.0%)	0	0	3 (3.2%)
TEAEs leading to dose modification/ interruption	6 (5.8%)	2 (2.2%)	4 (4.4%)	4 (4.2%)

Source: ADAE.xpt.
Abbreviations: N, total number of subjects; n, number of subjects in subset; TEAE, treatment-emergent adverse event

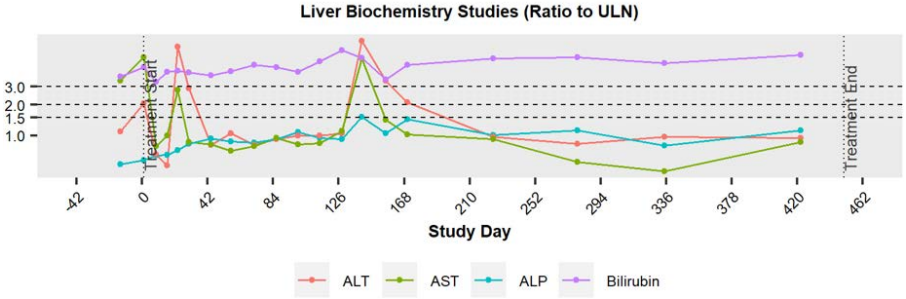
17.1.1.7. Additional Assessment of Drug-Induced Liver Injury, COMMODORE-1, COMMODORE-2, and COMMODORE-3

Figure 82. Graphical Subject Profile, Potential Hy's Law Cases, Primary Treatment Period, COMMODORE-1 and COMMODORE-2

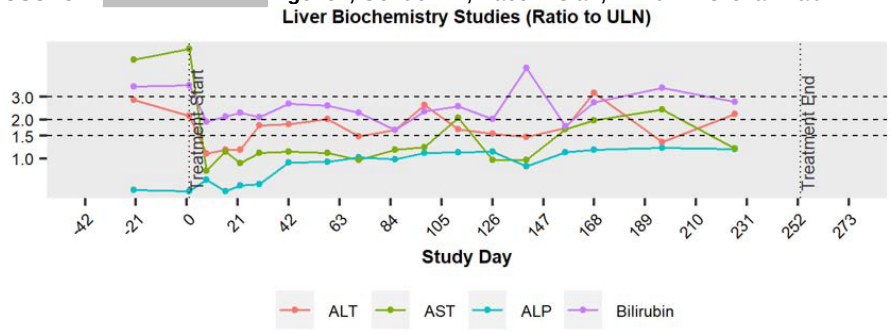
USUBJID (b) (6) **Age: 46, Gender: F, Race: Asian, TRT01A: Crovalimab**



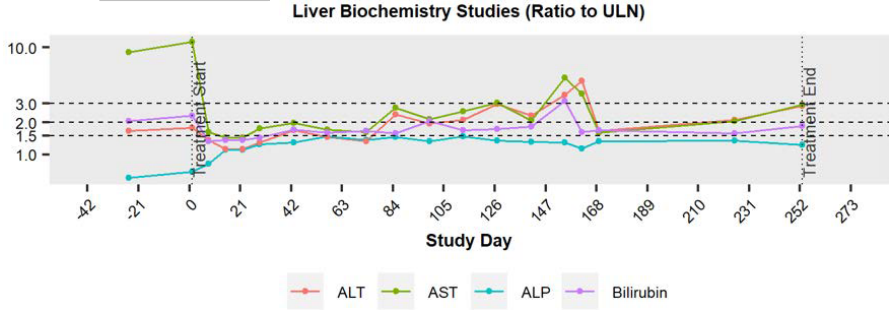
USUBJID (b) (6) **, Age: 32, Gender: M, Race: White, TRT01A: Crovalimab**



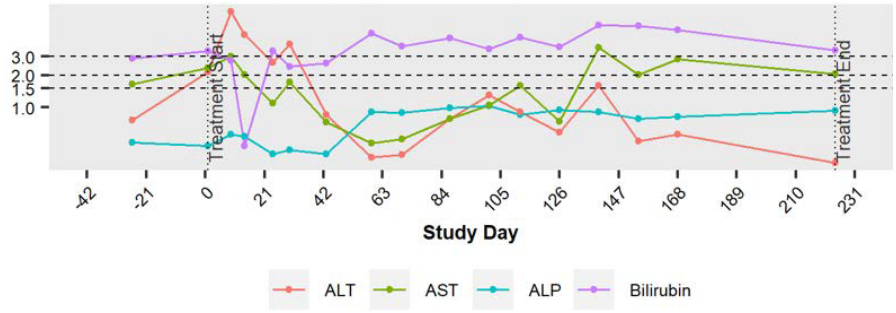
USUBJID (b) (6) **Age: 32, Gender: M, Race: Asian, TRT01A: Crovalimab**



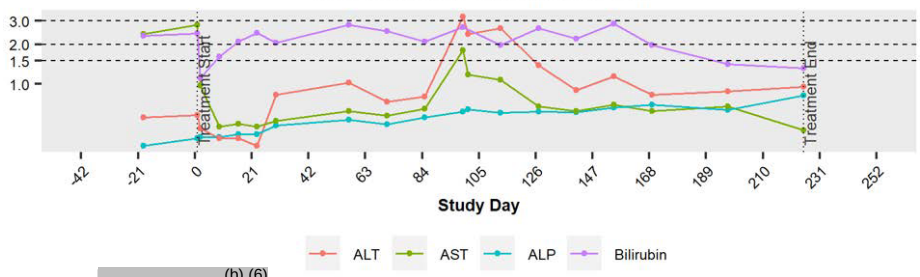
USUBJID (b) (6) **Age: 59, Gender: F, Race: Asian, TRT01A: crovalimab**



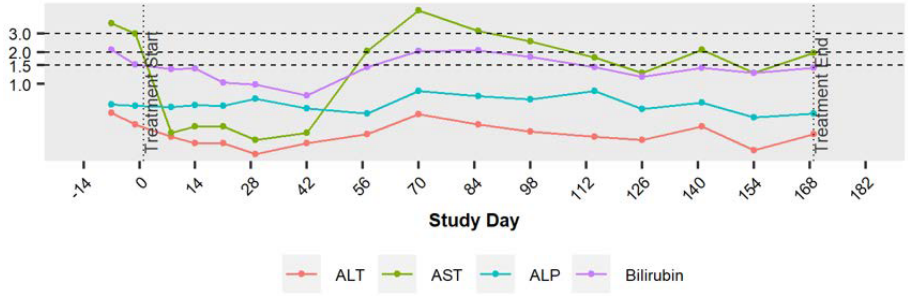
USUBJID (b) (6) **Age: 68, Gender: M, Race: Asian, TRT01A: Crovalimab**



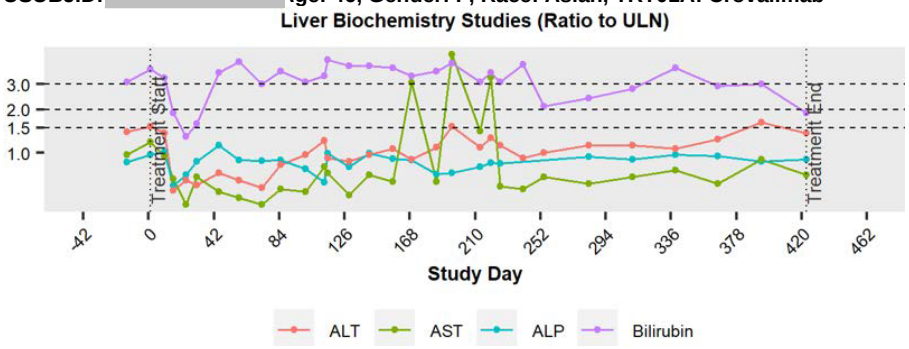
USUBJID (b) (6) **Age: 31, Gender: M, Race: Black or AA, TRT01A: Crovalimab**



USUBJID (b) (6) **Age: 34, Gender: M, Race: Asian, TRT01A: crovalimab**



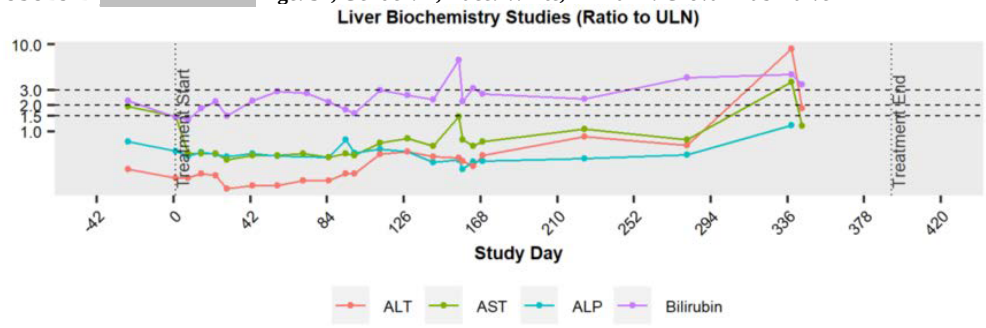
USUBJID: (b) (6) **Age: 46, Gender: F, Race: Asian, TRT01A: Crovalimab**



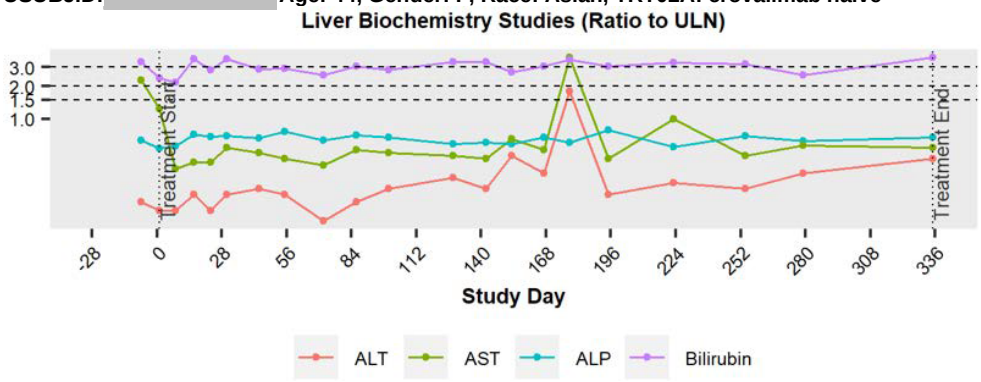
Source: adlb.xpt.
Abbreviations: ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transferase; F, female; M, male; ULN, upper limit of normal

Figure 83. Graphical Subject Profile Graphs, Potential Hy's Law Cases, Extension Period, COMMODORE-2

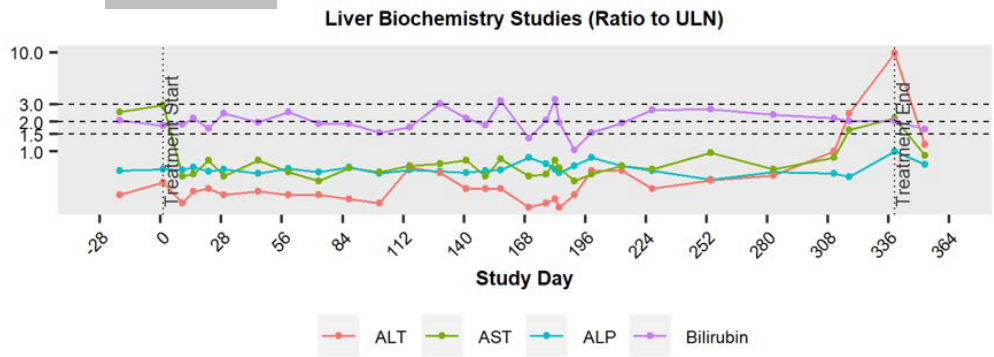
USUBJID (b) (6) **Age: 32, Gender: F, Race: White, TRT02A: Crovalimab Naïve**



USUBJID: (b) (6) **Age: 44, Gender: F, Race: Asian, TRT02A: crovalimab naïve**



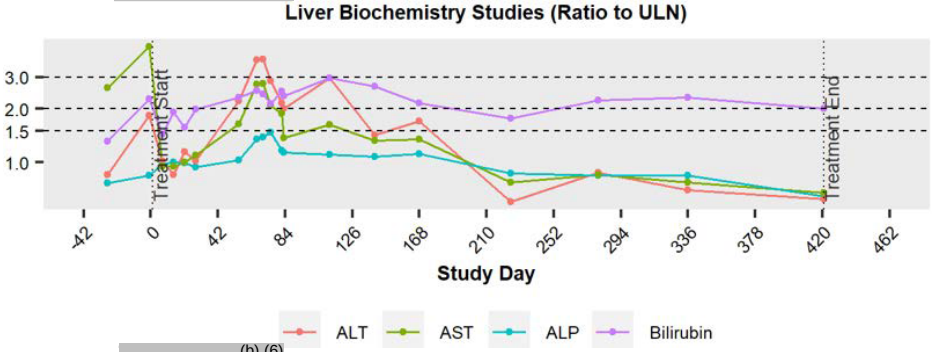
USUBJID: (b) (6) **Age: 31, Gender: F, Race: Asian, TRT02A: Crovalimab Switch**



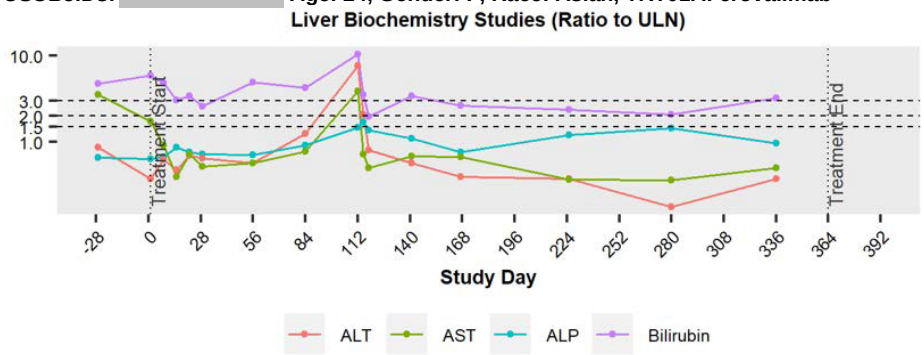
Source: adlb.xpt.
Abbreviations: ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transferase; F, female; M, male; ULN, upper limit of normal

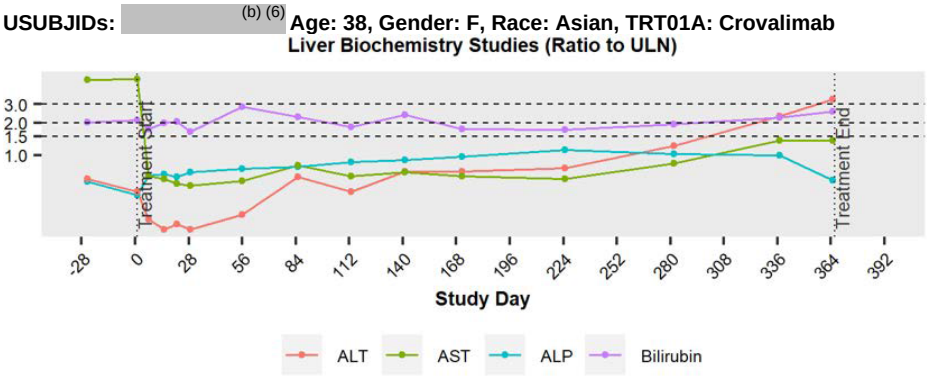
Figure 84. Graphical Subject Profile, Potential Hy's Law Cases, COMMODORE-3

USUBJIDs (b) (6) **Age: 37, Gender: M, Race: Asian, TRT01A: Crovalimab**



USUBJIDs: (b) (6) **Age: 24, Gender: F, Race: Asian, TRT01A: crovalimab**





Source: adlb.xpt.
Note: The hepatic tests improved with no change in crovalimab treatment on Day 386.
Abbreviations: ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transferase; F, female; M, male; ULN, upper limit of normal

17.2. COMPOSER (Study BP39144)

COMPOSER is an adaptive Phase 1/2 study to evaluate the safety, efficacy, PK, and PD of crovalimab in HVs and patients with PNH. The trial design is presented in Section 16.2.

Part 4

The evaluation of safety was conducted for Part 4 of the study since Part 4 administered crovalimab at the proposed dose regimen. The crovalimab proposed dose regimen was administered in 15 adult subjects with PNH (Arm A: 8 treatment-naïve, Arm B: 7 subjects previously treated with eculizumab). The median treatment duration of crovalimab in Part 4 was 2.23 years (range: 0.92 to 2.46). Table 141 summarizes the overall safety results of Part 4. Severity of TEAEs was classified as mild, moderate, or severe.

No deaths or TEAEs leading to discontinuation or treatment modification of the study drug occurred in the study. Serious TEAEs occurred in a total of 3 subjects (20.0%) (crovalimab-naïve: 2 subjects [myocardial infarction and BTH], crovalimab-switch: 1 subject [erysipelas]). TEAEs occurred in 93.3% of subjects and most of the TEAEs were mild (20.0%) or moderate (66.7%) in severity. One subject in the crovalimab-naïve group had severe BTH. Overall, the most frequently reported TEAs (≥20%) were headache, arthralgia, asthenia/fatigue, backpain, gastroenteritis, nasopharyngitis and peripheral edema, consistent with those reported in COMMODORE-2 and COMMODORE-1.

One subject in the crovalimab-naïve group experienced type III hypersensitivity reaction (mild rash erythematous) at time of switch from crovalimab to eculizumab, after discontinuing from the study due to a lack of efficacy. The event of type III hypersensitivity reaction resolved.

No cases of meningococcal meningitis or hypersensitivity (other than type III hypersensitivity reactions) were reported in subjects with PNH during the study.

Overall, the safety profile of crovalimab was generally consistent with the results of the Phase 3 studies.

Table 141. Overview of TEAEs, COMPOSER, Safety Population

Adverse Event	Crovalimab (Naïve) (N=8) n (%)	Crovalimab (Switch) (N=7) n (%)	Crovalimab (Total) (N=15) n (%)
Deaths	0	0	0
Serious TEAEs	2 (25.0%)	1 (14.3%)	3 (20.0%)
Any TEAEs	7 (87.5%)	7 (100%)	14 (93.3%)
Mild	3 (37.5%)	0	3 (20.0%)
Moderate	3 (37.5%)	7 (100%)	10 (66.7%)
Severe	1 (12.5%)	0	1 (6.7%)
TEAE leading to discontinuation of study drug	0	0	0
TEAE leading to dose modification of study drug	0	0	0

Source: ADAE.xpt.
Note: Based on maximum severity.
Abbreviations: N, total number of subjects; n, number of subjects in subset; TEAE, treatment-emergent adverse event

17.3. Additional Safety Explorations

Electrocardiograms and QT

No QTc prolongation was observed in the concentration-QTc analysis. Based on the concentration-QT analysis from COMPOSER and the Phase 3 studies, COMMODORE-1, COMMODORE-2, and COMMODORE-3 in treatment-naïve and switch subjects with PNH, a statistically significant decrease (p=0.0097) in ΔQTcF was found with increasing crovalimab concentrations. However, the effect was very small (ΔQTcF of 5.42 ms at a crovalimab concentration of 600 mcg/mL) in relation to the overall variability, and not in the direction of clinical concern (i.e., lower ΔQTcF at higher exposure). For details, refer to the Cardiac Safety Studies Review, dated April 9, 2024.

Human Carcinogenicity and Tumor Development

In the Phase 3 PNH crovalimab clinical studies, a total of 10 subjects (2.7%, crovalimab-naïve: 7 subjects, crovalimab-switch: 3 subjects) developed TEAEs in the “neoplasms benign, malignant and unspecified (incl cysts and polyps)” Medical Dictionary for Regulatory Activities SOC while receiving crovalimab. The TEAEs were colorectal cancer, desmoid tumor, lipoma, lung neoplasm, mantle cell lymphoma, melanocytic naevus, neoplasm, prostate cancer, skin neoplasm bleeding, and thyroid cancer, in one subject each. Time to onset ranged from 86 to 367 days from the start of crovalimab treatment. The outcome was fatal for the subject who had colorectal cancer (see Section 7.6.1.3) The TEAEs did not recover/resolve in 3 subjects and did recover/resolve in 6 subjects. Carcinogenesis and mutagenesis studies have not been performed with crovalimab to establish the genotoxic potential of crovalimab. However, as noted in Section 7.1, the risk of carcinogenicity for crovalimab is considered low based on a weight-of-evidence risk assessment.

Pediatrics and Assessment of Effects on Growth

A total of 12 pediatric subjects (crovalimab-naïve: 9 subjects, crovalimab-switch: 3 subjects) with PNH (13 to 17 years of age and BW ≥40 kg) received crovalimab in the Phase 3 clinical trials. There was no evidence to suggest that the safety and efficacy of crovalimab would be different between pediatric and adult patients with PNH weighing ≥40 kg. See Sections 6.3.4 and

17.1.1.6. The assessments of crovalimab effects on growth in pediatric patients have not been evaluated.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

No events of overdose were reported in subjects who received crovalimab in the PNH clinical studies. No dedicated studies on the potential for crovalimab to cause dependence were performed. Based on the pharmacological properties and the TEAE profile of crovalimab, there is no evidence to suggest that there are risks of abuse with crovalimab.

Similar to other C5 inhibitors (eculizumab and ravulizumab), monitoring PNH manifestations after discontinuation of crovalimab will be listed as a Warning and Precaution in the label. It is recommended to monitor patients after discontinuation of the C5 treatment to detect hemolysis. Patients with PNH who discontinue crovalimab should be closely monitored for signs and symptoms of serious IVH, identified by elevated LDH levels, along with a sudden decrease in hemoglobin or re-appearance of symptoms such as fatigue, hemoglobinuria, abdominal pain, dyspnea, MAVEs (including thrombosis), dysphagia, or erectile dysfunction. If signs and symptoms of hemolysis occur after discontinuation of crovalimab, restarting treatment with crovalimab should be considered, if appropriate, or initiating another treatment for PNH.

Patients who discontinue crovalimab and soon thereafter, start treatment with other C5 inhibitors (i.e., eculizumab or ravulizumab) that bind different epitopes of C5, are at risk of DTDC-associated type III hypersensitivity reactions. See Section 7.6.1.8.4.

17.4. Subject Narratives

Deaths

USUBJID (b) (6)

This subject was a 66-year-old White female who participated in COMMODORE-2, randomized to the crovalimab arm, and died due to myocardial infarction. Relevant medical history included aplastic anemia and thrombophlebitis/DVT. Concurrent conditions included hypertension. Concomitant medications included candesartan, apixaban, and nebivolol. Laboratory work-up (in the sample drawn right before crovalimab IV infusion) showed a creatine kinase level of 668 U/L (normal range: 34 to 145 U/L), a CK-MB level of 53 U/L, and a troponin I level of 7304 ng/L (normal range not provided for both). Prior to the event of myocardial infarction, the most recent dose of IV crovalimab was administered on Study Day 1 (Week 1, Day 1). On Study Day 1, 2 to 3 hours after the end of crovalimab IV infusion, the subject became unresponsive and was admitted to the cardiac catheterization laboratory. After intervention and stabilization of hemodynamics with continuous norepinephrine and epinephrine infusion, she was transferred to the intensive care unit. The subject had progressive hemodynamic instability that was not under control. The subject was taken to the cardiac catheterization laboratory, and an Impella heart pump was implanted as a last resort. The Impella was implanted successfully, but no hemodynamic effect was seen. The subject had progressive hypotension and ultimately electromechanical uncoupling occurred despite the continued administration of maximal catecholaminergic support, and the subject collapsed. On Study Day 2 at 01:36, the subject died

due to myocardial infarction. No autopsy was performed. The subject had received one dose of IV crovalimab during the study.

USUBJID (b) (6)

This subject was a 68-year-old Asian male who participated in COMMODORE-2, randomized to the crovalimab arm, and died due to respiratory tract hemorrhage. The subject experienced pyrexia and pneumonia on Day 8. On Day 24, pneumonia resolved after receiving treatment. On Day 25, within 24 hours after study treatment administration, appetite of the subject decreased. The subject was noted with Grade 3 pyrexia (body temperature up to 40°C). Pyrexia was considered a systemic injection reaction. The subject received treatment with colchicine, electrolytes (unspecified/glucose), prednisolone, celecoxib, and dexchlorpheniramine maleate. On Study Day 30, his general condition fully recovered and remained stable following discontinuation of antibiotics. On Study Day 30, the subject was discontinued from study treatment due to concerning high fever, which raised again after resuming study treatment on Day 24, and the subject did not resume crovalimab. The subject received a single dose of IV crovalimab and 3 doses of SC crovalimab prior to discontinuation. On Study Day 31, the event of pyrexia was considered as resolved, and he was discharged from the hospital. On Study Day 32, the subject experienced mild chills, and he was again noted with breakthrough Grade 2 pyrexia (initial Grade 1). Subsequently, he was hospitalized. It was reported that pyrexia was classified as of unknown origin. On Study Day 38, the subject experienced bloody stool. CT scan showed active gastrointestinal bleeding with extravasation, and he was diagnosed with Grade 3 small intestinal hemorrhage (initial Grade 2) of unknown cause. It was reported that fever was intermittent, for which he received treatment. On Day 113, PET-CT scan showed a lesion at the right upper lung with hypermetabolism at bone marrow and spleen and was diagnosed with Grade 1 lung neoplasm (nonserious, unrelated). On Study Day 130, he was considered stable enough to be discharged from the hospital. On Study Day 140, he was diagnosed with Grade 1 COVID-19 (nonserious, unrelated), for which no treatment was administered. On Study Day 151, the subject died due to respiratory tract damage (further details not reported). An autopsy was not performed.

USUBJID (b) (6)

This subject was a 51-year-old White female who participated in COMMODORE-1, randomized to the crovalimab arm, and died due to colorectal cancer. Past treatment for PNH included eculizumab administered for approximately 14 years. Prior to the event of colorectal cancer, the most recent dose of SC crovalimab (680 mg) was administered on Day 195 (Week 29). On Study Day 198, the subject presented to the hospital with complaints of not able to eat or drink for several days. On Study Day 202, she was hospitalized. Biopsy from a tumor-like structure of the colon showed aggressive adenocarcinoma. A diagnosis of life-threatening colorectal cancer (initial intensity Grade 2) was made. On Day 211, she died due to colorectal carcinoma. It is unknown if an autopsy was performed.

TEAEs Leading to Study Drug Discontinuation

USUBJID (b) (6)

This subject was a 79-year-old White female who was randomized to the eculizumab arm in COMMODORE-2 and switched to crovalimab treatment on Day 169 (Week 25, Day 1). The

subject completed treatment with eculizumab with the last dose administered on Study Day 157 (Week 23). The subject discontinued crovalimab treatment due to Grade 3 distal axonal demyelinating polyneuropathy. On Day 246, the subject presented with symptoms of weakness and decreased sensibility in distal extremities. It was reported that the subject had no focal subjective symptoms. Subsequently, she was hospitalized. On admission, she had fever and was further diagnosed with Grade 2 upper respiratory tract infection. An MRI of the brain and spine showed no findings of relevance for the symptoms, and a lumbar puncture also did not show any abnormal findings. On Study Day 259, an electroneurography was performed, which showed severe Grade 3 distal axonal demyelinating polyneuropathy. On Study Day 261, electromyography was performed, which showed no signs of myositis or myopathy. It was reported that serial CRP levels showed a decreasing trend (133 to 150 to 23 to 6 mg/L) following treatment with prednisolone on the assumption of small cell vasculitis as the cause of the polyneuropathy. It was reported that symptoms worsened during the first week but were stable later. Repeated neurological examinations showed decreased sensation in both legs below the knees and in the arms distal to the elbow. The weakness was in both legs (distally) with total bilateral peroneus paresis and weakness of both hands without paresis. It was reported that due to weakness in both legs, she was unable to stand or walk without support, but cognitive function remained unchanged. The event of demyelinating polyneuropathy was unresolved at the time of the CCOD. Due to the event of demyelinating polyneuropathy, crovalimab was permanently discontinued on Study Day 262.

USUBJID (b) (6)

This subject was a 61-year-old White female who received crovalimab while enrolled in the prior-ravulizumab cohort in COMMODORE-1. The subject discontinued crovalimab treatment on Day 40 due to sepsis. Prior treatment for PNH included eculizumab for about 20 years and ravulizumab for about 4 years. Relevant medical history included aplastic anemia. On Day 14 (following the most recent administration of crovalimab on Day 8), the subject developed Grade 2 chills and arthralgia, which were ascribed to a Grade 2 serious type III immune complex-mediated reaction, considered to be associated with crovalimab. It was reported that she experienced arthralgia all over the body including elbows, knees, wrists, ankles, and shoulders and was feeling shivery with rigors. The subject was treated with codeine, paracetamol, buclizine hydrochloride, and prednisolone. On Day 25, the event of type III immune complex-mediated reaction was considered resolved. The total duration of the type III immune complex-mediated reaction event was 12 days. There was no change in the study treatment with SC crovalimab due to the event of type III immune complex-mediated reaction. This subject experienced a Grade 3 sepsis that led to withdrawal of crovalimab. Prior to the event of sepsis, the most recent dose of SC crovalimab (680 mg) was administered on Day 29 (Week 5). On Day 40, a diagnosis of Grade 3 sepsis was made, for which the causal pathogen was unknown. Due to the event of sepsis, crovalimab was permanently discontinued on Study Day 40, and PNH treatment was switched to ravulizumab on Day 42. The event of sepsis resolved after receiving treatment with antibiotics (ciprofloxaxin) on Day 45. On Day 52 (following discontinuation of crovalimab and starting treatment with ravulizumab on Day 42), the subject developed Grade 3 myalgia, axonal neuropathy, Grade 2 muscular weakness, and arthralgia, which were ascribed to a serious Grade 3 type III immune complex-mediated reaction (second episode), considered to be associated with crovalimab. The axonal neuropathy event was categorized as a systemic type III hypersensitivity reaction. On Day 55, she was hospitalized due to ongoing intolerable body pain,

allodynia, and reduced sensation in both hands. Clinical features were suggestive of sensory-motor peripheral neuropathy. She received treatment including methylprednisolone. On the same day, she started treatment with amitriptyline for axonal neuropathy. It was reported that she had some slow improvement in the symptoms, but functionally, she had inability to button her shirt, comb her hair, and shower on her own. On Day 71, her prednisolone dose was reduced (20 mg PO once daily), further reduced (10 mg PO once daily) on Day 79, and stopped on Day 86. On Day 105, amitriptyline was stopped, and she started treatment with pregabalin. The events of axonal neuropathy and type III immune complex-mediated reaction were resolving at the time of the CCOD. The duration of the follow-up for the Grade 3 axonal neuropathy was 313 days.

USUBJID (b) (6)

This subject was a 75-year-old White female who participated in COMMODORE-1 and developed a serious Grade 3 type III immune complex-mediated reaction after switching to crovalimab treatment on Day 169 (Week 25, Day 1), following completion of eculizumab during the primary period. Prior to the event of type III immune complex-mediated reaction, the most recent dose of SC crovalimab (340 mg) was administered on Day 190 (Week 28). On Day 194, the subject developed Grade 3 vasculitis, which was ascribed to a Grade 3 type III immune complex-mediated reaction considered to be associated with both crovalimab (SC) and eculizumab. It was reported that the subject experienced itchy erythema. She started treatment with topical methylprednisolone and oral prednisone (30 mg PO once daily). On Day 204, resolution of erythema, secondary to leukocytoclastic vasculitis, was noted. No clinical evidence for hemolysis was found. The same day, the event of type III immune complex-mediated reaction was considered resolved, and the prednisone dose was reduced to 20 mg and stopped on Day 207. The total duration of the type III immune complex-mediated reaction event was 11 days. Due to the type III immune complex-mediated reaction event, study treatment with SC crovalimab was permanently discontinued on Study Day 204. The subject received 12 doses of eculizumab, 1 dose of IV crovalimab, and 4 doses of SC crovalimab prior to discontinuation.

USUBJID (b) (6)

This subject was a 20-year-old Asian male who was randomized to the crovalimab arm in COMMODORE-2 and discontinued study treatment due to Grade 3 thrombocytopenia (25×10^9/L). Concurrent conditions included MDS. The platelet count at baseline was 86×10^9/L (Grade 1). Prior to the event of thrombocytopenia, the most recent dose of SC crovalimab (680 mg) was administered on Day 114. On Study Day 139, the subject presented with hematuria and gum bleeding and was diagnosed with worsening of thrombocytopenia to platelet count of 0×10^9/L (Grade 4). He was transfused with 1 pint of packed cells and concentrated platelets daily. On Study Day 147, the event of Grade 4 thrombocytopenia was considered as resolved, and he was discharged from the hospital. Due to the event of thrombocytopenia, study treatment with SC crovalimab was permanently discontinued on Study Day 141, with the last dose given on Study Day 114. On Study Day 282, the subject withdrew consent from the study. At the time of study discontinuation, Grade 3 thrombocytopenia remained unresolved.

Type III Hypersensitivity Reactions (Serious Cases)

For narratives for USUBJIDs (b) (6), see the TEAEs Leading to Study Drug Discontinuation subsection above.

USUBJID (b) (6)

This subject was a 22-year-old African American male who was randomized to the crovalimab arm in COMMODORE-1 and experienced a serious Grade 3 type III immune complex-mediated reaction. Prior PNH treatment included eculizumab therapy for 5 years. Prior to the type III immune complex-mediated reaction event, the most recent dose of SC crovalimab (340 mg) was administered on Day 8. On Day 10, the subject developed Grade 3 headache, pyrexia, upper abdominal pain, chromaturia, joint stiffness, and swollen fingers, which were ascribed to a serious Grade 3 type III immune complex-mediated reaction and was hospitalized. On Study Day 18, the event of type III immune complex-mediated reaction resolved after treatment with steroids, antipyretics, and analgesics, and the subject was discharged from the hospital. The total duration of the type III immune complex-mediated reaction event was 9 days. There was no change in the study treatment with SC crovalimab due to the type III immune complex-mediated reaction.

USUBJID (b) (6)

This subject was a 48-year-old White female who was randomized to the crovalimab arm in COMMODORE-1 and experienced a serious Grade 3 type III immune complex-mediated reaction. Prior PNH treatment included ravulizumab treatment for more than 1 year. Prior to the type III immune complex-mediated reaction event, the most recent dose of SC Crovalimab (340 mg) was administered on Day 8. On Day 9, within 24 hours following SC crovalimab administration, the subject developed Grade 2 myalgia, as well as Grade 1 peripheral pyrexia and edema, which were ascribed to a serious Grade 3 type III immune complex-mediated reaction. The type III immune complex-mediated reaction event resolved on Day 15 after treatment with antihistamine and paracetamol. The total duration of the type III immune complex-mediated reaction event was 7 days. There was no change in the study treatment with SC crovalimab due to the type III immune complex-mediated reaction.

USUBJID (b) (6)

This subject was a 45-year-old Asian male who was randomized to the crovalimab arm in COMMODORE-1 and experienced a serious type III immune complex-mediated reaction. Prior PNH treatment included ravulizumab for approximately 6 years. On Day 10 (following the most recent administration of crovalimab on Day 9), the subject developed Grade 3 pyrexia, rash, arthralgia, and asthenia which were ascribed to a serious, Grade 3 type III immune complex-mediated reaction and was hospitalized. The subject received methylprednisolone (IV), hydroxyzine, tramadol, paracetamol, levocetirizine, and prednisolone (PO) for type III immune complex-mediated reaction. On Study Day 16, his condition improved after receiving systemic corticosteroids and he was discharged from the hospital. On Study Day 21, the events of type III immune complex mediated reaction was considered resolved. The total duration of the type III immune complex-mediated reaction event was 12 days. There was no change in the study treatment with SC crovalimab due to the type III immune complex-mediated reaction.

In the 120-day safety update, 3 additional subjects had serious type III hypersensitivity reaction.

USUBJID (b) (6)

This subject was a 72-year-old White male randomized to the crovalimab arm in COMMODORE-1. The subject received 24 doses of eculizumab prior to study enrollment. Prior

to the type III immune complex-mediated reaction event, the most recent dose of SC crovalimab (340 mg) was administered on Day 8 (Week 2). On Day 10, the subject developed Grade 3 petechiae, which was ascribed to a systemic Grade 3 type III immune complex-mediated reaction that led to hospitalization. It was reported that the subject was admitted with severe dyspnea and fatigue, requiring assisted ventilation. On Day 11, the subject was diagnosed with a Grade 1 viral respiratory tract infection. The subject was treated with methylprednisolone, dexchlorpheniramine for the hypersensitivity reaction, furosemide, ribavirin for the viral respiratory tract infection, azithromycin, cefepime, and ceftriaxone. On Day 15, the viral respiratory tract infection resolved, and on Day 18, the type III immune complex-mediated reaction resolved. The total duration of the type III immune complex-mediated reaction event was 9 days.

USUBJID (b) (6)

This subject was a 34-year-old White male randomized to the crovalimab arm in COMMODORE-1. The subject received seven doses of ravulizumab prior to study enrollment. Prior to the event of infection and type III immune complex-mediated reaction, the most recent dose of SC crovalimab (340 mg) was administered on Day 2 (Week 1, Day 2). On Day 9, the subject was noted with Grade 1 exanthema on both lower legs and pyrexia. The subject was diagnosed with a Grade 3 infection of unknown origin and was treated with antibiotics. Later that day, the subject received SC crovalimab (340 mg). Approximately 2 hours later, exanthema spread to both thighs (Grade 3 rash), which was ascribed to a serious, systemic, Grade 3 type III immune complex-mediated reaction. On the same day, the subject was admitted to the hospital for fever, exanthema, and infection of unknown origin. He was treated with prednisolone, dimetindene maleate, and apixaban. On Day 10, exanthema further spread to the arms. In addition, BTH was confirmed, and the subject was given a rescue dose of IV crovalimab (340 mg). The events were reported as unresolved and further clinical course of the events occurred following the CCOD. No further follow up was provided.

USUBJID (b) (6)

This subject was a 45-year-old White male, randomized to the crovalimab arm in COMMODORE-1, and had a serious type III immune complex-mediated reaction. Previous treatment for PNH included eculizumab for approximately 8 years and four doses of ravulizumab prior to trial enrollment. Prior to the event of type III immune complex-mediated reaction, the most recent dose of SC crovalimab (340 mg) was administered on Study Day 15 (Week 3). On Day 20, the subject developed multiple, serious Grade 3 non-blanchable palpable purpura, bilaterally over the lower extremities and non-serious Grade 2 pyrexia, which were ascribed to a systemic Grade 3 type III immune complex-mediated reaction that led to hospitalization. The subject received treatment with prednisolone. On Day 24, the type III immune complex-mediated reaction event was resolved, and the subject was discharged from the hospital. The total duration of the type III immune complex-mediated reaction event was 5 days.

Subjects Who Experienced Two Events of Type III Hypersensitivity Reactions

For narratives for USUBJID (b) (6), see the TEAEs Leading to Study Drug Discontinuation subsection above.

USUBJID (b) (6)

This subject was a 64-year-old Asian male who participated in COMMODORE-2 and experienced two events of type III immune complex-mediated reactions. The subject was randomized to the eculizumab arm. On Day 183, the subject completed the study treatment with eculizumab, and on Day 197 (Week 25, Day 1), the subject switched to crovalimab therapy. On Day 207 (following most recent administration of SC crovalimab on Day 204), the subject developed Grade 1 rash and Grade 2 edema and myalgia, which were ascribed to a Grade 2 type III immune complex-mediated reaction, considered to be associated with both crovalimab (IV and SC) and eculizumab. He received treatment with betamethasone butyrate propionate and paracetamol. On Day 230, the type III immune complex-mediated reaction event was considered resolved. The total duration of the type III immune complex-mediated reaction event was 24 days. Due to the type III immune complex-mediated reaction event, study treatment with SC crovalimab was interrupted. On Day 230, the subject withdrew consent from the study treatment. The last dose of SC crovalimab (340 mg) was administered on Day 218 (Week 28). The subject entered the safety follow-up period. The subject had received 16 doses of eculizumab, 1 dose of IV crovalimab, and 4 doses of SC crovalimab during the study. On Day 245, the subject developed Grade 2 myalgia, erythema, joint swelling, arthralgia, and Grade 1 dysesthesia, which were ascribed to a Grade 2 type III immune complex-mediated reaction. He received treatment with paracetamol and prednisolone (tapered dose). It was reported that the type III immune complex-mediated reaction was due to starting ravulizumab following crovalimab withdrawal. The second type III immune complex-mediated reaction event remained unresolved at the time of the last report. The duration of the follow-up for the Grade 2 type III immune complex-mediated reaction was 142 days.

Subjects With Unresolved Type III Hypersensitivity Reactions

For narratives for USUBJID (b) (6), see Type III Hypersensitivity Reactions (Serious Cases) and for USUBJID (b) (6) see Subjects Who Experienced Two Events of Type III Hypersensitivity Reactions.

USUBJID (b) (6)

This subject was a 73-year-old Asian male who was randomized to the eculizumab arm in COMMODORE-2. After completing eculizumab treatment on Day 155 (Week 23), the subject started crovalimab on Day 169 (Week 25 Day 1). Prior to the type III immune complex-mediated reaction event, the most recent dose of SC crovalimab (680 mg) was administered on Day 197 (Week 29). On Study Day 199, the subject developed Grade 3 arthralgia, which was ascribed to a non-serious, Grade 3 type III immune complex-mediated reaction. It was reported that he experienced severe pain, leading to limited self-management in daily life. He received treatment with methylprednisolone. The event of type III immune complex-mediated reaction, with arthralgia, remained unresolved at the time of study discontinuation. On Day 218, the subject withdrew consent from the study, with the last dose of SC crovalimab administered on Day 197 (Week 29).

17.5. 120-Day Safety Update

This section summarizes the safety analysis reported in the 120-day safety update.

The Applicant submitted the 120-day safety update on September 26, 2023. The submission contained cumulative safety data from the two ongoing, controlled, Phase 3 studies, COMMODORE-1 and COMMODORE-2, up to the CCOD of May 31, 2023, and from the Phase 3 single-arm study, COMMODORE-3, up to the CCOD of August 10, 2022, providing approximately 6 months of additional safety data from COMMODORE-1 and COMMODORE-2 beyond the data provided in the initial BLA submission. In addition, the 120-day safety update provided safety data from a total of 11 subjects in the nonrandomized arm (Arm C; previously treated with eculizumab at the approved dose for ≥24 weeks cohort: 4 subjects, previously treated with ravulizumab cohort: 5 subjects, previously treated with higher than approved doses of eculizumab cohort: 2 subjects) of COMMODORE-1, who were enrolled after November 16, 2022, the CCOD of the initial BLA submission for COMMODORE-1. The 120-day safety update also contained safety data from 5 subjects in the eculizumab arm in COMMODORE-1 that contributed to the eculizumab safety assessment at the time of the primary analysis in the initial BLA submission, then switched to crovalimab after reaching the Week 25 visit, providing additional safety data for crovalimab in subjects who switched from eculizumab. No datasets or case report forms were included in the 120-day safety update. Updated safety data from COMMODORE-3 and COMPOSER were also not included.

The 120-day safety update provided safety data from a total of 393 subjects who received crovalimab and 111 subjects who received eculizumab.

Table 142. Pooled Analysis of COMMODORE-1, COMMODORE-2, and COMMODORE-3, Safety Population, 120-Day Safety Update

	Crovalimab N=393		Eculizumab Total (N=111)
Studies	Naïve (N=192)	Switch (N=201)	
COMMODORE-2	141[d]		69[b]
		68[a]	
COMMODORE-1		93[e]	42[c]
		40[a]	
COMMODORE-3	51		

Source: 120-day safety update.
Note: The 120-day safety update includes the 192 subjects who were crovalimab-naïve and completed the primary treatment period at the clinical cutoff date for the original BLA.
Note: Crovalimab (naïve): Subjects with PNH previously not treated with complement inhibitors who received crovalimab.
Note: Crovalimab (switch): Subjects with PNH previously treated with complement inhibitors before switching to crovalimab.
[a] Subjects who were randomized to eculizumab and switched to crovalimab once they had completed the primary treatment period (i.e., at least 24 weeks of treatment with eculizumab) in COMMODORE-1 and COMMODORE-2.
[b] Eculizumab (naïve): Subjects with PNH from COMMODORE-2 who were previously not treated with a complement inhibitor and received eculizumab during the primary treatment period of 24 weeks.
[c] Eculizumab (experienced): Subjects with PNH from COMMODORE-1 previously treated with eculizumab and continued receiving eculizumab during the primary treatment period of 24 weeks.
[d] Includes 135 subjects randomized to the crovalimab investigational arm and 6 subjects enrolled in the descriptive arm.
[e] Includes 44 subjects randomized to the crovalimab investigational arm and 49 subjects enrolled in the descriptive arm.
Abbreviations: N, total number of subjects; PNH, paroxysmal nocturnal hemoglobinuria

Extent of Exposure

In the 120-day safety update, the median treatment duration of the total crovalimab population was 64.0 weeks (range: 0.1 to 136.4), compared with a median treatment duration of 44.4 weeks (range: 28.4 to 56.3) in the initial BLA submission.

Table 143. Summary of Exposure, Pooled Analysis of COMMODORE-1, COMMODORE-2, and COMMODORE-3, Safety Population, 120-Day Safety Update

Duration of Treatment (Weeks)	Crovalimab (Naïve) (N=192)	Crovalimab (Switch) (N=201)	Crovalimab Total (N=393)	Eculizumab Total (N=111)
Median	68.1	56.3	64.0	22.1
Range	0.1-136.1	0.3-136.4	0.1-136.4	0.1-26.1

Source: 120-day safety update.
Abbreviations: N, total number of subjects

Overall Safety Findings

Table 144 summarizes the overall safety results provided in the 120-day safety update. At the CCOD for the 120-day safety update, a total of 8 subjects (2.0%) experienced a TEAE that had a fatal outcome. A higher proportion of subjects had experienced serious TEAEs (22.6% versus 15.1%) and any TEAEs (93.1% versus 86.5%) compared with what was reported in the initial BLA submission. There were no additional subjects in the 120-day safety update who experienced a TEAE that led to discontinuation or treatment modification of the study drug.

Table 144. Summary of Safety, Pooled Analysis of COMMODORE-1, COMMODORE-2, and COMMODORE-3, Safety Population, 120-Day Safety Update

	Initial BLA				120-Day Safety Update			
Adverse Event	Crova (Naïve) (N=192) n (%)	Crova (Switch) (N=185) n (%)	Crova Total (N=377) n (%)	Ecu Total (N=111) n (%)	Crova (Naïve) (N=192) n (%)	Crova (Switch) (N=201) n (%)	Crova Total (N=393) n (%)	Ecu Total (N=111) n (%)
Deaths	3 (1.6%)	1 (0.5%)	4 (1.1%)	1 (0.9%)	6 (3.1%)	2 (1.0%)	8 (2.0%)	1 (0.9%)
Serious TEAEs	28 (14.6%)	29 (15.7%)	57 (15.1%)	10 (9.0%)	43 (22.4%)	46 (22.9%)	89 (22.6%)	10 (9.0%)
Any TEAEs	174 (90.6%)	152 (82.2%)	326 (86.5%)	83 (74.8%)	184 (95.8%)	182 (90.5%)	366 (93.1%)	83 (74.8%)
≥ Grade 3	50 (26.0%)	46 (24.9%)	96 (25.5%)	18 (16.2%)	71 (37.0%)	68 (33.8%)	139 (35.4%)	18 (16.2%)
TEAE leading to discontinuation of study drug	1 (0.5%)	3 (1.6%)	4 (1.1%)	1 (0.9%)	1 (0.5%)	3 (1.5%)	4 (1.0%)	1 (0.9%)
TEAE leading to dose modification/ interruption of study drug	8 (4.2%)	8 (4.3%)	16 (4.2%)	3 (2.7%)	8 (4.2%)	8 (4.0%)	16 (4.1%)	3 (2.7%)

Source: 120-day safety update.
Abbreviations: BLA, biologics licensing application; Crova, Crovalimab; Ecu, Eculizumab; N, total number of subjects; n, number of subjects in subset; TEAE, treatment-emergent adverse event

To account for approximately three times longer treatment duration in the total crovalimab population (median of 64.0 weeks, range: 0.1 to 136.4) compared with the total eculizumab population (median of 22.1 weeks, range: 0.1 to 26.1), the Applicant provided safety analyses adjusted for exposure. The safety results per 100 PYs are provided in Table 145. The overall safety results of the total crovalimab population were broadly comparable to the total eculizumab population.

Table 145. Summary of AEs Per 100 Patient-Years, Pooled Analysis of COMMODORE-1, COMMODORE-2, and COMMODORE-3, Safety Population, 120-Day Safety Update

Adverse Event	Crova (Naïve) (N=192) (PY =266.78) AEs Per 100PY (95% CI)	Crova (Switch) (N=201) (PY =237.10) AEs Per 100PY (95% CI)	Crova Total (N=393) (PY =503.88) AEs Per 100PY (95% CI)	Ecu Total (N=111) (PY =51.08) AEs Per 100PY (95% CI)
Deaths	2.25 (0.83, 4.90)	0.84 (0.10, 3.05)	1.59 (0.69, 3.13)	1.96 (0.05, 10.91)
Serious TEAEs	25.11 (19.46, 31.89)	31.21 (24.51, 39.18)	27.98 (23.55, 33.00)	31.32 (17.90, 50.86)
Any TEAEs	497.03 (470.64, 524.52)	429.78 (403.79, 457.00)	465.39 (446.74, 484.61)	563.79 (500.55, 632.81)
≥ Grade 3	65.97 (56.58, 76.47)	48.50 (40.04, 58.22)	57.75 (51.31, 64.78)	48.94 (31.67, 75.25)
TEAE leading to discontinuation of study drug	0.37 (0.01. 2.09)	1.27 (0.26, 3.70)	0.79 (0.22, 2.03)	1.96 (0.05, 10.91)
TEAE leading to dose modification/ interruption of study drug	3.75 (1.80, 6.89)	3.37 (1.46, 6.65)	3.57 (2.12, 5.65)	5.87 (1.21, 17.16)

Source: 120-day safety update.
Abbreviations: AE, adverse event; CI, confidence interval; N, total number of subjects; n, number of subjects in subset; PY, patient years; TEAE, treatment-emergent adverse event

Deaths

In the 120-day safety update, a total of four additional deaths were reported in the total crovalimab population. Of the four deaths, three deaths occurred in the crovalimab-naïve population in COMMODORE-2 due to COVID-19, COVID-19 pneumonia, and death due to unknown cause (subject died in his sleep and had no symptoms in the days preceding death, with normal hematologic laboratory data; an autopsy was not performed) and one death in a subject in COMMODORE-2 who was treated with eculizumab during the primary treatment period, switched to crovalimab, and died during the extension period due to pneumonia aspiration. After the CCOD of the 120-day safety update (May 31, 2023), one additional death was reported in the crovalimab-switch population in COMMODORE-2. The subject had a subdural hematoma that had a fatal outcome on June 9, 2023. This subject was a 33-year-old Asian female with a history of MDS. At baseline, the subject had Grade 2 thrombocytopenia and Grade 1 neutropenia. It was reported that MDS worsened on Day 99 (with thrombocytopenia worsening to Grade 3) and on Day 210 (with thrombocytopenia worsening to Grade 4 and neutropenia to Grade 2). The event of worsening MDS and thrombocytopenia was not resolved at the time of death. It was also reported that this subject had a urinary tract infection 3 months before death, which may have further contributed to ongoing platelet consumption and bleeding events (e.g., epistaxis and heavy menstrual bleeding) before the fatal event. On Day 648, the subject was admitted to the emergency department and a review of the brain CT scan showed several acute subdural hematomas. On Day 657, the subject died after experiencing progression of acute subdural hematomas, with a brain CT scan showing multiple, new intraparenchymal lobar hemorrhages. It is likely that the subdural hematoma, and subsequent subarachnoid and cerebral bleeding, were caused by thrombocytopenia due to underlying MDS (i.e., deteriorating marrow function).

Serious TEAEs

In the 120-day safety update, the most frequently reported serious TEAEs by preferred term in the total crovalimab group (≥1%) were COVID-19, type III immune complex-mediated reaction, pneumonia, BTH, urinary tract infection, and pyrexia and were generally consistent with the serious TEAEs reported in the initial BLA.

Table 146. Serious TEAEs That Occurred in >1 Subject in the Total Crovalimab Group, Pooled Analysis of COMMODORE-1, COMMODORE-2, and COMMODORE-3, Safety Population, 120-Day Safety Update

System Organ Class Preferred Term	Crovalimab (Naïve) (N=192) n (%)	Crovalimab (Switch) (N=201) (n %)	Crovalimab Total (N=393) n (%)	Eculizumab Total (N=111) n (%)
All	43 (22.4%)	46 (22.9%)	89 (22.6%)	10 (9.0%)
Infections and infestations				
COVID-19	7 (3.6%)	6 (3.0%)	13 (3.3%)	1 (0.9%)
Pneumonia	5 (2.6%)	1 (0.5%)	6 (1.5%)	1 (0.9%)
Urinary tract infection	1 (0.5%)	3 (1.5%)	4 (1.0%)	1 (0.9%)
Sepsis	0	2 (1.0%)	2 (0.5%)	1 (0.9%)
Influenza	1 (0.5%)	1 (0.5%)	2 (0.5%)	0
Upper respiratory tract infection	2 (1.0%)	0	2 (0.5%)	0
Immune system disorders				
Type III immune complex mediated reaction	0	8 (4.0%)	8 (2.0%)	0

System Organ Class Preferred Term	Crovalimab (Naïve) (N=192) n (%)	Crovalimab (Switch) (N=201) (n %)	Crovalimab Total (N=393) n (%)	Eculizumab Total (N=111) n (%)
Blood and lymphatic system disorders				
Breakthrough hemolysis	2 (1.0%)	3 (1.5%)	5 (1.3%)	0
Thrombocytopenia	2 (1.0%)	1 (0.5%)	3 (0.8%)	1 (0.9%)
Aplastic anemia	2 (1.0%)	0	2 (0.5%)	1 (0.9%)
Febrile neutropenia	1 (0.5%)	1 (0.5%)	2 (0.5%)	1 (0.9%)
Anemia	1 (0.5%)	1 (0.5%)	2 (0.5%)	0
Hemolysis	1 (0.5%)	1 (0.5%)	2 (0.5%)	0
Hepatobiliary disorders				
Cholecystitis acute	0	3 (1.5%)	3 (0.8%)	0
General disorders and administration site conditions				
Pyrexia	2 (1.0%)	2 (1.0%)	4 (1.0%)	1 (0.9%)
Investigations				
Platelet count decreased	2 (1.0%)	0	2 (0.5%)	0

Source: 120-day safety update.
Abbreviations: COVID-19, coronavirus disease of 2019; N, total number of subjects; n, number of subjects in subset; TEAE, treatment-emergent adverse event

The Applicant summarized the TEAEs that occurred in at least 5% of subjects in the total crovalimab group by SOC (Table 147). The most commonly reported TEAEs by preferred term (≥10%) in the crovalimab total group were COVID-19, upper respiratory tract infection, pyrexia, neutrophil count decreased, headache, WBC count decreased, and infusion-related reaction, consistent with those reported in the initial BLA. Per the Applicant, the majority of the COVID-19 cases were reported from Asia which is likely due to the COVID-19 surge during the winter of 2022 and 2023.

Table 147. TEAEs That Occurred in ≥5% of Subjects in the Total Crovalimab Group by SOC, Pooled Analysis of COMMODORE-1, COMMODORE-2, and COMMODORE-3, Safety Population, 120-Day Safety Update

System Organ Class Preferred Term	Crovalimab (Naïve) (N=192) n (%)	Crovalimab (Switch) (N=201) n (%)	Crovalimab Total (N=393) n (%)	Eculizumab Total (N=111) n (%)
All	184 (95.8%)	182 (90.5%)	366 (93.1%)	83 (74.8%)
Infections and infestations				
COVID-19	68 (35.4%)	63 (31.3%)	131 (33.3%)	11 (9.9%)
Upper respiratory tract infection	50 (26.0%)	23 (11.4%)	73 (18.6%)	11 (9.9%)
Urinary tract infection	20 (10.4%)	14 (7.0%)	34 (8.7%)	7 (6.3%)
Nasopharyngitis	9 (4.7%)	11 (5.5%)	20 (5.1%)	2 (1.8%)
Gastrointestinal disorders				
Diarrhea	13 (6.8%)	13 (6.5%)	26 (6.6%)	1 (0.9%)
Nausea	8 (4.2%)	12 (6.0%)	20 (5.1%)	4 (3.6%)
General disorders and administration site conditions				
Pyrexia	28 (14.6%)	25 (12.4%)	53 (13.5%)	7 (6.3%)
Fatigue	8 (4.2%)	14 (7.0%)	22 (5.6%)	2 (1.8%)
Investigations				
Neutrophil count decreased	37 (19.3%)	7 (3.5%)	44 (11.2%)	7 (6.3%)
White blood cell count decreased	33 (17.1%)	8 (4.0%)	41 (10.4%)	7 (6.3%)
ALT increased	18 (9.4%)	6 (3.0%)	24 (6.1%)	3 (2.7%)

System Organ Class Preferred Term	Crovalimab (Naïve) (N=192) n (%)	Crovalimab (Switch) (N=201) n (%)	Crovalimab Total (N=393) n (%)	Eculizumab Total (N=111) n (%)
Injury, poisoning and procedural complications				
Infusion related reaction	22 (11.5%)	18 (9.0%)	40 (10.2%)	9 (8.1%)
Injection related reaction	8 (4.2%)	23 (11.4%)	31 (7.9%)	0
Metabolism and nutrition disorders				
Hyperuricemia	19 (9.9%)	7 (3.5%)	26 (6.6%)	6 (5.4%)
Hypokalemia	19 (9.9%)	6 (3.0%)	25 (6.4%)	9 (8.1%)
Musculoskeletal and connective tissue disorders				
Arthralgia	8 (4.2%)	15 (7.5%)	23 (5.9%)	3 (2.7%)
Nervous system disorders				
Headache	17 (8.9%)	26 (12.9%)	43 (10.9%)	4 (3.6%)
Immune system disorders				
Type III immune complex mediated reaction	0	38 (18.9%)	38 (9.7%)	0

Source: 120-day safety update.
Abbreviations: COVID-19, coronavirus disease of 2019; N, total number of subjects; n, number of subjects in subset; SOC, system organ class; TEAE, treatment-emergent adverse event

The analyses in the table above do not account for the longer duration of follow-up for the crovalimab population compared to the eculizumab population. Below, TEAEs per 100 patient-years to better account for these differences in follow-up are presented. With this analysis, most TEAEs did not occur at a notably higher incidence rate with crovalimab compared to eculizumab except for COVID-19, injection-related reaction and type III hypersensitivity reactions.

Table 148. Summary of TEAEs that Occurred in ≥5% of Subjects in the Total Crovalimab Group by SOC, Per 100 Patient-Years, Pooled Analysis of COMMODORE-1, COMMODORE-2 and COMMODORE-3, Safety Population, 120-Day Safety Update

System Organ Class Preferred Term	Crova (naïve) (N=192) (PY =266.78) AEs per 100 PY (95% CI)	Crova (switch) (N=201) (PY =237.10) AEs per 100 PY (95% CI)	Crova Total (N=393) (PY =503.88) AEs per 100 PY (95% CI)	Ecu Total (N=111) (PY =51.08) AEs per 100 PY (95% CI)
All	497.03 (470.64, 524.52)	429.78 (403.79, 457.00)	465.39 (446.74, 484.61)	563.79 (500.55, 632.81)
Infections and infestations				
All infections	88.46 (77.53, 100.50)	94.90 (82.90, 108.14)	91.49 (83.33, 100.24)	123.33 (94.77, 157.79)
COVID-19	25.86 (20.12, 32.73)	26.99 (20.79, 34.47)	26.40 (22.10, 31.28)	21.53 (10.75, 38.53)
Upper respiratory tract infection	23.99 (18.47, 30.63)	11.81 (7.85, 17.07)	18.26 (14.72, 22.39)	27.41 (14.98, 45.98)
Urinary tract infection	10.12 (6.67, 14.72)	7.17 (4.18, 11.48)	8.73 (6.34, 11.72)	13.70 (5.51, 28.23)
Nasopharyngitis	3.37 (1.54, 6.40)	8.86 (5.48, 13.54)	5.95 (4.02, 8.50)	5.87 (1.21, 17.16)

System Organ Class Preferred Term	Crova (naïve) (N=192) (PY =266.78) AEs per 100 PY (95% CI)	Crova (switch) (N=201) (PY =237.10) AEs per 100 PY (95% CI)	Crova Total (N=393) (PY =503.88) AEs per 100 PY (95% CI)	Ecu Total (N=111) (PY =51.08) AEs per 100 PY (95% CI)
Gastrointestinal disorders				
Diarrhea	5.25	6.75	5.95	1.96
	(2.87, 8.80)	(3.86, 10.96)	(4.02, 8.50)	(0.05, 10.91)
Nausea	3.37	5.48	4.37	9.79
	(1.54, 6.40)	(2.92, 9.38)	(2.74, 6.61)	(3.18, 22.84)
General disorders and administration site conditions				
Pyrexia	13.87	13.07	13.50	15.66
	(9.76, 19.12)	(8.88, 18.56)	(10.48, 17.11)	(6.76, 30.86)
Fatigue	3.75	6.33	4.96	3.92
	(1.80, 6.89)	(3.54, 10.43)	(3.21, 7.32)	(0.47, 14.14)
Investigations				
Neutrophil count decreased	35.61	3.80	20.64	21.53
	(28.81, 43.53)	(1.74, 7.21)	(16.96, 25.01)	(10.75, 38.53)
White blood cell count decreased	36.73	6.33	22.43	31.32
	(29.82, 44.77)	(3.54, 10.43)	(18.48, 26.96)	(17.90, 50.86)
ALT increased	9.37	2.53	6.15	5.87
	(6.06, 13.83)	(0.93, 5.51)	(4.18, 8.73)	(1.21, 17.16)
Injury, poisoning and procedural complications				
Infusion related reaction	8.62	7.59	8.14	19.58
	(5.47, 12.94)	(4.50, 12.00)	(5.84, 11.04)	(9.39, 36.00)
Injection related reaction	3.00	14.76	8.53	0.00
	(1.29, 5.91)	(10.28, 20.53)	(6.18, 11.49)	(NE, NE)
Metabolism and nutrition disorders				
Hyperuricemia	12.74	4.64	8.93	23.49
	(8.83, 17.81)	(2.32, 8.30)	(6.51, 11.95)	(12.14, 41.03)
Hypokalemia	17.62	4.22	11.31	39.15
	(12.94, 23.43)	(2.02, 7.76)	(8.57, 14.66)	(23.92, 60.47)
Musculoskeletal and connective tissue disorders				
Arthralgia	3.00	8.01	5.36	5.87
	(1.29, 5.91)	(4.82, 12.51)	(3.53, 7.80)	(1.21, 17.16)
Nervous system disorders				
Headache	8.25	16.03	11.91	9.79
	(5.17, 12.49)	(11.34, 22.00)	(9.09, 15.33)	(3.18, 22.84)
Immune system disorders				
Type III immune complex mediated reaction	0.00	16.87	7.94	0.00
	(NE, NE)	(12.05, 22.97)	(5.67, 10.81)	(NE, NE)

Source: 120-day safety update.
Abbreviations: AE, adverse event; CI, confidence interval; COVID-19, coronavirus disease of 2019; N, total number of subjects; n, number of subjects in subset; NE not evaluable; PY, patient year

Adverse Events of Special Interest

The table below summarizes AEs of special interest reported in the Phase 3 studies in the 120-day safety update. The incidences and characteristics of the events were generally similar to those reported in the initial BLA, except the incidence of infections in the total crovalimab

population increased from 46.9%, reported in the initial BLA submission, to 64.6%. Per the Applicant, the increase is due to the longer exposure time in the total crovalimab population, and the increase in the incidence of reported COVID-19 cases.

Table 149. Summary of Adverse Events of Special Interest, Pooled Analysis of COMMODORE-1, COMMODORE-2, and COMMODORE-3, Safety Population, 120-Day Safety Update

Adverse Event	Crovalimab (Naïve) (N=192) n (%)	Crovalimab (Switch) (N=201) n (%)	Crovalimab Total (N=393) n (%)	Eculizumab Total (N=111) n (%)
Injection site reactions	9 (4.7%)	24 (11.9%)	33 (8.4%)	0
Infusion related reactions	23 (12.0%)	18 (9.0%)	41 (10.4%)	9 (8.1%)
Infections	135 (70.3%)	119 (59.2%)	254 (64.6%)	42 (37.8%)
Meningococcal meningitis	0	0	0	0
Type III hypersensitivity reactions	0	39 (19.4%)	39 (9.9%)	0
Hypersensitivity reactions other than type III hypersensitivity reactions	12 (6.3%)	27 (13.4%)	39 (9.9%)	0

Source: 120-day safety update
Abbreviations: N, total number of subjects; n, number of subjects in subset

Type III Hypersensitivity Reaction

The overall incidence of type III hypersensitivity reaction in the crovalimab switch population in the 120-day safety report (19.4%) was similar to that reported in the initial BLA (17.8%). A total of 23 subjects (11.4%) had Grade 1 or 2 events and 16 subjects (8.0%) had Grade 3 events.

The most frequently reported symptoms (≥5%) were arthralgia and rash, consistent with those reported in the initial BLA. Grade 3 symptoms were consistent with those reported in the primary BLA submission (i.e., arthralgia, myalgia, axonal neuropathy, fatigue/asthenia, headache, pyrexia, rash, [palpable] purpura, petechiae, abdominal pain and vasculitis). One subject (0.5%) each also reported Grade 3 axonal neuropathy and Grade 2 injection related reaction. No type III hypersensitivity reactions with renal manifestations were reported.

In patients who switched to crovalimab from prior eculizumab treatment, the incidence of the type III hypersensitivity reaction was 17.1% (n=30) (Grade 1 or 2: 63.3%, Grade 3: 36.7%) consistent with that reported in the initial BLA. The incidence of type III hypersensitivity reaction in patients who switched from prior ravulizumab treatment, however, increased from 23.8% (n=5) to 34.6% (n=9) in the 120-day safety report. Of the 9 patients who switched from ravulizumab, a total of 4 patients (44.4%) had a Grade 1 or 2 event and 5 patients (55.6%) had a Grade 3 event. No Grade 4 or 5 events of type III hypersensitivity reaction were reported.

Table 150. Summary of Type III Hypersensitivity Reactions, COMMODORE-1 and COMMODORE-2, Safety Population, 120-Day Safety Update

	Crovalimab Switch (N=201)			Crovalimab Total (N=393)
System Organ Class Preferred Term	Any Grade n (%)	Grade 2 n (%)	Grade 3 n (%)	Any Grade n (%)
All	39 (19.4%)	13 (6.5%)	16 (8.0%)	39 (9.9%)
Immune system disorders	38 (18.9%)	12 (6.0%)	16 (8.0%)	38 (9.7%)
Type III immune complex mediated reaction	38 (18.9%)	12 (6.0%)	16 (8.0%)	38 (9.7%)

System Organ Class Preferred Term	Crovalimab Switch (N=201) Any Grade n (%)	 Grade 2 n (%)	 Grade 3 n (%)	Crovalimab Total (N=393) Any Grade n (%)
Injury, poisoning and procedural complications	1 (0.5%)	1 (0.5%)	0	1 (0.3%)
Injection related reaction	1 (0.5%)	1 (0.5%)	0	1 (0.3%)
Nervous system disorders	1 (0.5%)	0	1 (0.5%)	1 (0.3%)
Axonal neuropathy	1 (0.5%)	0	1 (0.5%)	1 (0.3%)

Source: 120-day safety update.
Abbreviations: N, total number of subjects; n, number of subjects in subset

Table 151. Summary of Symptoms of Type III Hypersensitivity Reactions that Occurred in >1 Subject (Any Grade), COMMODORE-1 and COMMODORE-2, Safety Population, 120-Day Safety Update

System Organ Class Preferred Term	Crovalimab Switch Any Grade (N=201) n (%)
All	38 (18.9%)
Skin and subcutaneous tissue disorders	26 (12.9%)
Rash	13 (6.5%)
Petechiae	3 (1.5%)
Erythema	2 (1.0%)
Rash maculo-papular	2 (1.0%)
Musculoskeletal and connective tissue disorders	21 (10.4%)
Arthralgia	17 (8.5%)
Myalgia	6 (3.0%)
Pain in extremity	2 (1.0%)
General disorders and administration site conditions	11 (5.5%)
Pyrexia	8 (4.0%)
Fatigue	2 (1.0%)
Asthenia	2 (1.0%)
Nervous system disorders	8 (4.0%)
Headache	5 (2.5%)
Gastrointestinal disorders	4 (2.0%)
Abdominal pain	3 (1.5%)
Nausea	2 (1.0%)

Source: 120-day safety update
Abbreviations: N, total number of subjects; n, number of subjects in subset

The median time to onset of the first type III hypersensitivity reaction was 1.6 weeks (range: 0.7 to 4.4 weeks), and the median duration was 1.7 weeks (range: 0.4 to 34.1 weeks), consistent with those reported in the initial BLA.

Out of the 42 type III hypersensitivity reaction events reported in the 39 subjects, 37 events (88.1%) resolved, including 1 (2.4%) that resolved with crovalimab discontinuation, 2 (4.8%) that resolved with crovalimab interruption, and 34 (81.0%) that resolved without discontinuation, interruption, or dose change in crovalimab therapy.

Table 152. Time to Onset of First Type III Hypersensitivity Reaction, COMMODORE-1 and COMMODORE-2, Safety Population, 120-Day Safety Update

	Crovalimab Switch (N=201)		
Time to Onset of First Type III Hypersensitivity Reaction	**Prior Eculizumab (N=175) n (%)**	**Prior Ravulizumab (N=26) n (%)**	**Total (N=201) n (%)**
Total number of subjects	30 (17.1%)	9 (34.6%)	39 (19.4%)
Time to onset to first AE (weeks)			
Mean (SD)	1.8 (0.90)	2.2 (0.95)	1.9 (0.91)
Median	1.5	2.0	1.6
Range	0.7-4.4	1.3-4.3	0.7-4.4
Time to onset of first AE (category), n (%)			
<1 week	3 (10.0%)	0	3 (7.7%)
1 to <2 weeks	16 (53.3%)	4 (44.4%)	20 (51.3%)
2 to <4 weeks	10 (33.3%)	4 (44.4%)	14 (35.9%)
4 to <6 weeks	1 (3.3%)	1 (11.1%)	2 (5.1%)
≥6 weeks	0	0	0

Source: 120-day safety update.
Abbreviations: N, total number of subjects; n, number of subjects in subset

Table 153. Duration of Type III Hypersensitivity Reaction, COMMODORE-1 and COMMODORE-2, Safety Population, 120-Day Safety Update

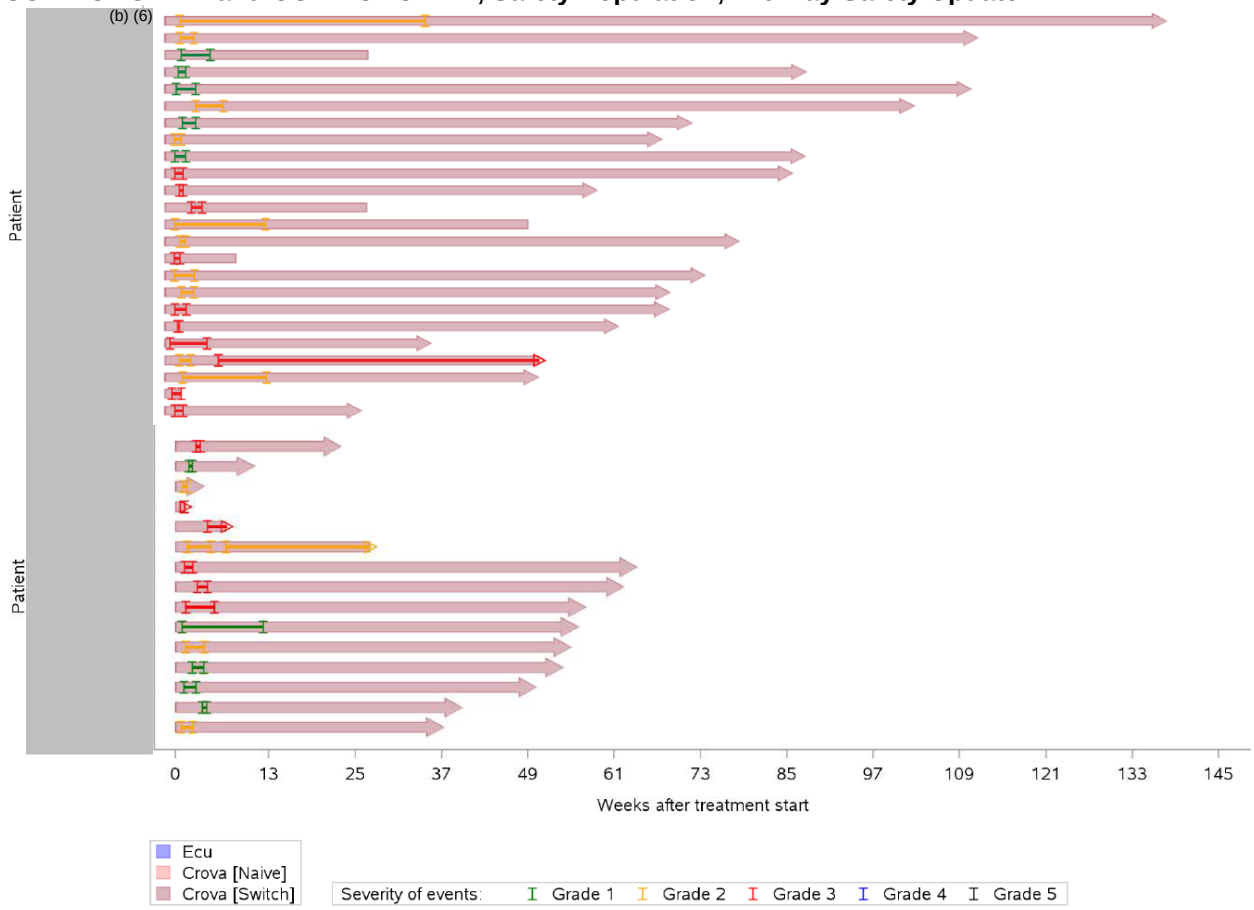
	Crovalimab Switch (N=201)		
Duration of Type III Hypersensitivity Reaction	**Prior Eculizumab (N=175)**	**Prior Ravulizumab (N=26)**	**Total (N=201)**
Total number of events	31	11	42
Total number of resolved events[a]	29	8	37
Duration (weeks)			
Mean (SD)	3.8 (6.50)	2.9 (3.76)	3.6 (5.98)
Median	1.7	1.7	1.7
Range	0.4-34.1	0.6-11.9	0.4-34.1
Duration (category), n (%)			
<1 week	5 (17.2%)	2 (25.0%)	7 (18.9%)
1 to <2 weeks	12 (41.4%)	4 (50.0%)	16 (43.2%)
2 to <4 weeks	6 (20.7%)	0	6 (16.2%)
4 to <8 weeks	3 (10.3%)	1 (12.5%)	4 (10.8%)
8 to <12 weeks	1 (3.4%)	1 (12.5%)	2 (5.4%)
≥12 weeks	2 (6.9%)	0	2 (5.4%)

Source: 120-day safety update.
[a] Resolved events refer to events with outcome "Recovered/Resolved" or "Recovered/Resolved with Sequelae".
Abbreviations: N, total number of subjects; n, number of subjects in subset

The Applicant provided a swimlane plot for the type III hypersensitivity reactions reported in the crovalimab switch population. A total of three subjects were reported with unresolved type III hypersensitivity reactions up to CCOD in the 120-day safety update report.

Two subjects (USUBJIDs: (b) (6)) had two episodes of type III hypersensitivity reactions and the duration of the second episode was relatively longer compared to the first episode of type III hypersensitivity reaction experienced in these subjects.

Figure 85. Swimlane Plot for Type III Hypersensitivity Reactions, Pooled Analysis of COMMODORE-1 and COMMODORE-2, Safety Population, 120-Day Safety Update



Lanes display treatment exposure up to clinical cutoff date, or end of study date, or start of second study treatment (Crova after 25 weeks of Ecu), whichever occured first. An arrow indicates treatment exposure is still ongoing at clinical cutoff date.
I-beam symbols connected by a horizontal line show the start and end of an event. Events that were still ongoing at clinical cutoff date are shown up to this date and marked with an arrow.
CCODs: BO42161/BO42162: 31MAY2023, YO42311: 10AUG2022
Data Extract Dates: BO42161/BO42162: 21JUL2023, YO42311: 26OCT2022

Source: 120-day safety update.
Abbreviations: CCOD, clinical cutoff date; Crova, Crovalimab; Ecu, Eculizumab

Clinical Experience in Subjects Who Switched From Crovalimab to a C3 Inhibitor

To assess the safety in patients who switch from crovalimab to a C3 inhibitor (i.e., pegcetacoplan), an information request was sent to the Applicant to provide the clinical outcome in subjects who received crovalimab and switched to treatment with a C3 inhibitor. Per the Applicant, as of the CCOD of May 31, 2023, a total of two subjects in COMMODORE-1 (USUBJIDs: (b) (6) switched to pegcetacoplan in the safety follow-up period after discontinuing crovalimab treatment. Both subjects were originally randomized to eculizumab and switched to crovalimab in the extension period. Subjects (b) (6) received the last dose of crovalimab treatment on Study Day 560 and 563 and started pegcetacoplan on Study Day 587 and 568, respectively. No AEs were reported for either of the subjects in the safety follow-up period.

Subgroup Analyses

Age

Based on the 120-day safety update, of the 393 subjects treated with crovalimab in COMMODORE-1, 2, and 3, a total of 12 subjects (3.1%) were younger than 18 years of age, 338 subjects (86%) were 18 to 64 years of age, and 43 subjects (10.9%) were 65 years of age and older. The incidences of fatal SAEs were higher in subjects ≥65 years of age (9.3%) compared to subjects aged 18 to 64 years (1.2%). The incidences of serious adverse reactions were also higher in subjects who were 65 years and older (crovalimab-naïve: 7.7%, crovalimab-switch: 6.7%) compared to subjects who were 18 to 64 years of age (crovalimab-naïve: 3.5%, crovalimab-switch: 3.6%). The safety profile of crovalimab by age was consistent with the results reported in the initial BLA. It is unclear whether the higher incidence of SAEs in the ≥65 age group is due to the study drug or simply reflects background AEs in an older population.

Race

In the total crovalimab population, the majority of subjects were Asian (58%) and White (36.9%). The incidences of TEAEs were similar between different races (Asian: 93.0%, White: 93.1%, Black/African American: 100%). The safety profile of crovalimab was generally similar across different races, and consistent with those reported in the initial BLA.

Sex

In the total crovalimab population, approximately half (48.3%) were female. The proportion of subjects who experienced at least one TEAE (male: 91.1%, female: 95.3%) was comparable between males and females and consistent with those reported in the initial BLA.

17.6. Additional Analyses for Type III Hypersensitivity Reactions

Fifteen subjects had a time interval between the last dose of the C5 inhibitor and the first dose of crovalimab being outside of the expected dosing intervals of eculizumab (14±2 days) or ravulizumab (56±2 days), and three of them experienced a type III hypersensitivity reaction.

- Specifically, all three subjects with a type III hypersensitivity reaction switched from ravulizumab and had a time interval of 49, 51, and 114 days between the last dose of ravulizumab and the first dose of crovalimab.
- Severity of these type III hypersensitivity reaction events ranged between Grade 1 to 3 (Grade 1 event occurred in a subject with time interval of 49 days, Grade 2 event in a subject with time interval of 51 days and Grade 3 event in a subject with time interval of 114 days). Signs and symptoms of type III hypersensitivity reactions in these subjects were consistent with what was observed in the total switch population and all events were resolved as of the CCOD of May 31, 2023.

The number of subjects with a time interval between the last dose of the C5 inhibitor and the first dose of crovalimab being outside of the expected dosing intervals of eculizumab or ravulizumab and experiencing a type III hypersensitivity reaction is limited. Therefore, it is not possible to reach a conclusion on whether this influences occurrence, severity, or reversibility of type III hypersensitivity reactions. With limited data, no correlation was observed between the time from the last dose of prior C5 inhibitor treatment and the first crovalimab dose, and the onset, severity, or reversibility of type III hypersensitivity reactions.

Table 154. Summary of Time Between Last Dose of Prior Treatment (Eculizumab or Ravulizumab) and First Crovalimab Dose by Presence/Absence of a Type III Hypersensitivity Reaction, Switch Cohort, Pooled Analysis of COMMODORE-1 and COMMODORE-2, Safety Population

	Crova [Switch] (N=201)			
	Prior Eculizumab (N=174)		Prior Ravulizumab (N=27)	
	No Type III Hypersensitivity (N=144)	Type III Hypersensitivity (N=30)	No Type III Hypersensitivity (N=18)	Type III Hypersensitivity (N=9)
Time between last dose of prior treatment and first Crovalimab dose (days)				
n	104	21	17	9
Mean (SD)	14.04 (1.84)	13.48 (0.75)	67.06 (40.67)	61.22 (19.98)
Median	14.00	14.00	56.00	56.00
25%-ile	13.50	13.00	56.00	56.00
75%-ile	14.00	14.00	57.00	56.00
Min - Max	7.0 - 26.0	12.0 - 15.0	49.0 - 223.0	49.0 - 114.0
Time between last dose of prior treatment and first Crovalimab dose (category)				
n	104	21	17	9
Ecu: <12 days, Ravu: <54 days	1 (1.0%)	0	2 (11.8%)	2 (22.2%)
Ecu: 14+/-2 days, Ravu: 56+/-2 days	97 (93.3%)	21 (100%)	12 (70.6%)	6 (66.7%)
Ecu: >16 days, Ravu: >58 days	6 (5.8%)	0	3 (17.6%)	1 (11.1%)

Source: Applicant response.
Abbreviations: AE, adverse event; Crova, Crovalimab; Ecu, Eculizumab; Max, maximum; Min, minimum; N, total number of subjects; n, number of subjects in subset; Ravu, Ravulizumab; SD, standard deviation

Table 155. Summary of Time Between Last Dose of Prior Treatment (Eculizumab or Ravulizumab) and First Crovalimab Dose by Presence/Absence of a Type III Hypersensitivity Reaction by AE Grade, Pooled Analysis of COMMODORE-1 and COMMODORE-2, Safety Population

	Crova [Switch] (N=201)							
	Prior Eculizumab (N=174)				Prior Ravulizumab (N=27)			
	No Type III Hypersensitivity (N=144)	Type III Hypersensitivity (N=30)			No Type III Hypersensitivity (N=18)	Type III Hypersensitivity (N=9)		
	(N=144)	Grade 1 AE (N=9)	Grade 2 AE (N=10)	Grade 3 AE (N=11)	(N=18)	Grade 1 AE (N=1)	Grade 2 AE (N=4)	Grade 3 AE (N=4)
Time between last dose of prior treatment and first Crovalimab dose (days)								
n	104	7	6	8	17	1	4	4
Mean (SD)	14.04 (1.84)	13.29 (0.49)	13.67 (0.52)	13.50 (1.07)	67.06 (40.67)	49.00 (NE)	54.75 (2.50)	70.75 (28.84)
Median	14.00	13.00	14.00	14.00	56.00	49.00	56.00	56.50
25%-ile	13.50	13.00	13.00	12.50	56.00	49.00	53.50	56.00
75%-ile	14.00	14.00	14.00	14.00	57.00	49.00	56.00	85.50
Min - Max	7.0 - 26.0	13.0 - 14.0	13.0 - 14.0	12.0 - 15.0	49.0 - 223.0	49.0 - 49.0	51.0 - 56.0	56.0 - 114.0
Time between last dose of prior treatment and first Crovalimab dose (category)								
n	104	7	6	8	17	1	4	4
Ecu: <12 days, Ravu: <54 days	1 (1.0%)	0	0	0	2 (11.8%)	1 (100%)	1 (25.0%)	0
Ecu: 14+/-2 days, Ravu: 56+/-2 days	97 (93.3%)	7 (100%)	6 (100%)	8 (100%)	12 (70.6%)	0	3 (75.0%)	3 (75.0%)
Ecu: >16 days, Ravu: >58 days	6 (5.8%)	0	0	0	3 (17.6%)	0	0	1 (25.0%)

Source: Applicant response.
Abbreviations: AE, adverse event; Crova, Crovalimab; Ecu, Eculizumab; Max, maximum; Min, minimum; N, total number of subjects; n, number of subjects in subset; Ravu, Ravulizumab; SD, standard deviation

18. Clinical Virology

Not applicable.

19. Clinical Microbiology

Not applicable.

20. Mechanism of Action/Drug Resistance

Refer to Section 5 of the review for a description of the mechanism of action of Crovalimab. There are no concerns for drug resistance with this class of medications for the proposed indication.

21. Other Drug Development Considerations

None.

22. Data Integrity–Related Consults (Office of Scientific Investigations, Other Inspections)

COMMODORE-2 is the main trial to support the efficacy and safety of crovalimab for the proposed indication. COMMODORE-1 was also chosen for Office of Scientific Investigations (OSI) inspection.

In COMMODORE-2, there were no U.S. subjects among the randomized population. The sites that enrolled the greatest number of randomized subjects (≥10 subjects) were five sites in China (site IDs: 336361, 336339, 336364, 336340 and 336362). OSI requested and reviewed the study monitoring reports of these sites, as travel to China was restricted. In addition, the Applicant was inspected to assess if there was proper monitoring/oversight, if the clinical investigation was conducted in accordance with the study protocol, and if there was proper reporting of AEs.

For COMMODORE-1, one site (ID: 334968) in Portugal (shown in Table 156 below) was chosen for OSI inspection, as no U.S. subjects were enrolled in the randomized arms and enrollment of subjects at this site was relatively higher compared to other clinical sites with low site-specific protocol violation counts.

Table 156. Requested OSI Clinical Site Audit for COMMODORE-1

Protocol ID	Site ID	Number of Enrolled Subjects	Name of the Principal Investigator	Location
BO42161	334968	6	Cristina Goncalves	Centro Hospitalar Do Porto Hospital De Santo António; Largo Prof. Abel Salazar, Porto, 4099-001 Portugal

Source: Completed by the FDA review team from information provided by the Applicant.
Abbreviations: ID, identification; OSI, Office of Scientific Investigations

On August 18, 2023, the Applicant notified the FDA of an observed case of serious noncompliance in good clinical practice (GCP) for COMMODORE-1 and COMMODORE-2 that occurred at the study site of Dr. Cristina Goncalves, Centro Hospitalar do Porto, Hospital de Santo António Largo Prof. Abel Salazar, Porto, 4099-001, Portugal (Site # 334968 and Site # 335055, respectively). The report concerned inadequate principal investigator oversight due to the principal investigator's sick leave from (b) (6) wherein no proper back-up principal investigator was assigned. The principal investigator's absence resulted in nondelegated site staff performing study procedures. The Applicant made the decision to end the principal investigator's (Dr. Cristina Goncalves) participation in COMMODORE-1 and COMMODORE-2 and conducted an assessment to understand the potential impact on the data from this site.

Corrective and preventative actions implemented by the Applicant included the following:

- Placed the site on temporary enrollment hold for the COMMODORE-1 and COMMODORE-2 studies.
- After returning, the principal investigator (Dr. Cristina Goncalves) reviewed subject study visits that occurred during the principal investigator's absence to assess if any AE/serious

adverse event/AESI had occurred and been properly addressed by the attending physician per protocol. The principal investigator documented the review of visits that occurred during her absence in the progress notes with signature and date.

- The principal investigator was replaced by the hospital with a GCP-trained investigator: Dr. Patricia Seabra.
- The monitor trained the new principal investigator on the protocol, reminded the principal investigator about obligations for principal investigator oversight per International Council for Harmonisation GCP, and documented the training in the site training log.

No critical findings were reported during the investigation with regard to the serious GCP noncompliance. The Applicant reported that for all investigational findings, appropriate corrective and preventative actions were undertaken, and measures of effectiveness have been satisfied.

OSI's overall assessment of findings and general recommendations for these sites were as follows:

> *"Based on the inspection results, the studies appear to have been conducted adequately and the study data derived from the clinical investigator site are considered reliable. The sponsor's oversight and monitoring appear adequate, and the clinical data submitted to the Agency for assessment appear acceptable in support of the proposed indication."*

Therefore, the overall compliance with GCP is acceptable. Refer to the finalized OSI review in DARRTS, dated November 15, 2023.

23. Labeling: Key Changes and Considerations

This Prescribing Information (PI) review includes a high-level summary of the rationale for major changes to the near-finalized PI as compared to the Applicant's draft PI (Table 157). The PI was reviewed to ensure that the PI meets regulatory/statutory requirements, is consistent (if appropriate) with labeling guidance, conveys clinically meaningful and scientifically accurate information needed for the safe and effective use of the drug, and provides clear and concise information for the healthcare practitioner.

Table 157. Key Labeling Changes and Considerations

Full PI Sections[a]	Rationale for Major Changes to Finalized PI[b] Compared to Applicant's Draft PI
BOXED WARNING	Revised text from "(b) (4)" to "PIASKY increases the risk of …infections" to avoid minimizing the risk. Revised the mitigating strategies to be consistent with others in the class and the REMS language.
1 INDICATIONS AND USAGE	Added the pediatric age "13 years and older" and "body weight of at least 40 kg" to be clear on the indicated population.
2 DOSAGE AND ADMINISTRATION	2.1 Revised to be consistent with other complement inhibitor (CI) labeling. 2.2 Relocated text regarding switching from another CI to 2.3 for prominence given the risk of Type III hypersensitivity associated with this switching. 2.3 New subsection to describe switching to PIASKY from another CI. Relocated text on dose-modifications to 2.2. Removed all text regarding training of patients/caregivers to administer as this product will only be administered by HCPs due to complicated preparation procedure and results of human factors study.
4 CONTRAINDICATIONS	Clarified that PIASKY is contraindicated 'for initiation in patients with unresolved serious Neisseria meningitidis infection'. Deleted (b) (4) to be consistent with other CI labeling.
5 WARNINGS AND PRECAUTIONS	5.1 Revised to be consistent with other CI labeling. 5.2 Revised to be consistent with the language in the REMS. 5.3 Relocated Warning on Type III Hypersensitivity Reactions… to the highest subsection possible due to its seriousness and the available mitigating strategies to avoid it. 5.6 Deleted (b) (4) as this is not a safety issue; it affects efficacy.
6 ADVERSE REACTIONS	Revised to reflect our usual approach to this section: Described trials used to support safety with cross-reference to 14 for details. Provided most common ARs, exposure, demographic baseline characteristics, and most common serious ARs. Removed (b) (4) leaving list of Adverse Reactions in Table 4. Used FMQs to group AR terms. Added a description of Axonal Neuropathy to Section 6.1.
7 DRUG INTERACTIONS	Revised to describe the formation of DTDCs, which can result in Type III hypersensitivity reactions.
8 USE IN SPECIFIC POPULATIONS (e.g., Pregnancy, Lactation, Females and Males of Reproductive Potential, Pediatric Use, Geriatric Use, Renal Impairment, Hepatic Impairment)	8.1 Revised to be consistent with the FDA draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products — Content and Format* (July 2020). 8.2 Revised to be consistent with the PLLR Labeling Guidance (July 2020).

Full PI Sections[a]	Rationale for Major Changes to Finalized PI[b] Compared to Applicant's Draft PI
	8.4 Revised to be consistent with the FDA draft guidance for industry *Pediatric Information Incorporated Into Human Prescription Drug and Biological Products Labeling Good Review Practice* (March 2019). 8.5 Revised to be consistent with the FDA guidance for industry *Geriatric Information in Human Prescription Drug and Biological Product Labeling* (September 2020).
9 DRUG ABUSE AND DEPENDENCE	Omitted this section as PIASKY does not have risks associated with Abuse and Dependence.
10 OVERDOSAGE	Omitted this section as no clinically useful overdosage information was available to describe.
12 CLINICAL PHARMACOLOGY	12.1 Minimal edits for readability. 12.2 Removed (b) (4). 12.3 Revised first paragraph to provide an overview and summary of the PK characteristics of PIASKY. Other revisions were made to be consistent with the FDA guidance for industry *Clinical Pharmacology Labeling for Human Prescription Drug and Biological Products — Content and Format* (December 2016), and the data submitted with the application.
13 NONCLINICAL TOXICOLOGY	Revised for brevity and to describe the dosing in the reproductive studies.
14 CLINICAL STUDIES	Revised to base section on results of COMMODORE 2 (removed (b) (4) Revised trial description to add the NCT number for COMMODORE 2, provide relevant eligibility criteria, and describe the pediatric patients enrolled in a separate cohort. Added race, ethnicity and baseline hemoglobin categories in table 6. Removed description of FACIT-fatigue results per the FDA guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims* (December 2009); PRO data were not reliable in this open-label trials. Removed reference to "primary" and "secondary" endpoints per the FDA guidance for industry *Clinical Studies Section of Labeling for Human Prescription Drug and Biological Products — Content and Format* (January 2006), "the terms primary endpoint and secondary endpoint are used so variably that they are rarely helpful. The appropriate inquiry is whether there is a well-documented, statistically and clinically meaningful effect on a prospectively defined endpoint, not whether the endpoint was identified as primary or secondary."
17 PATIENT COUNSELING INFORMATION	Revised to reflect changes to the prior sections of USPI.

Full PI Sections[a]	Rationale for Major Changes to Finalized PI[b] Compared to Applicant's Draft PI
Product Quality Sections (i.e., DOSAGE FORMS AND STRENGTHS, DESCRIPTION, HOW SUPPLIED/STORAGE AND HANDLING)	3 Removed "(b) (4)" as it is a vague term and changed "single-use" to "single-dose" to correct the package term. 11 Added established pharmacologic class, added correct package type, added route of administration, added pH adjuster to list of inactive ingredients in the vial.

Source: Generated by the FDA review team.
[a] Product quality sections (Sections 3, 11, and 16) are pooled under the last row in this table; Section 15 (REFERENCES) is not included in this table.
[b] For the purposes of this document, the finalized PI is the PI that will be approved or is close to being approved.
Abbreviations: BLA, Biologics Licensing Application; NDA, New Drug Application; PI, Prescribing Information

23.1. Approved Labeling Types

Upon approval of this application, the following labeling documents will be FDA-approved:

- U.S. PI
- Medication Guide

24. Postmarketing Requirements and Commitments

24.1. Postmarketing Requirements (PMRs)

PMR 4647-1

Establish a registry to characterize the long-term safety of PIASKY (crovalimab-akkz) in adult and pediatric patients 13 years and older with paroxysmal nocturnal hemoglobinuria (PNH) with up to 5 years of follow-up. Yearly safety follow-up data should include a summary of major safety findings including meningococcal infections and other infections with encapsulated bacteria, infusion and injection site related reactions, and hypersensitivity reactions including type III hypersensitivity reactions, and axonal peripheral neuropathy, including multifocal mononeuropathy.

Draft Protocol Submission:	12/2024
Final Protocol Submission:	04/2025
Interim Report #1:	10/2026
Interim Report #2:	10/2027
Interim Report #3:	10/2028
Interim Report #4:	10/2029
Interim Report #5:	10/2030

Interim Report #6:	10/2031
Trial Completion:	06/2032
Final Report Submission:	12/2032

PMR 4647-2

Conduct a worldwide descriptive study that collects prospective and retrospective data in women exposed to PIASKY (crovalimab-akkz) during pregnancy to assess the risk of pregnancy and maternal complications, and adverse effects on the developing fetus, neonate, and infant. Assess infant outcomes through at least the first year of life. The registry should also collect adverse event data for lactating women and infants exposed to crovalimab through breastfeeding to assess for any potential risks to the infant from breastfeeding. The minimum number of patients will be specified in the protocol.

Draft Protocol Submission:	12/2024
Final Protocol Submission:	04/2025
Interim Report:	10/2028
Trial Completion:	06/2032
Final Report Submission:	12/2032

24.2. Postmarketing Commitments (PMCs)

PMC 4647-3

Complete COMMODORE-1 (Study BO42161), "A Phase 3, Randomized, Open-Label, Active-Controlled, Multicenter Study Evaluating the Safety, PK, PD, and Efficacy of Crovalimab Versus Eculizumab in Patients with PNH Currently Treated with Complement Inhibitors."

Trial Completion:	08/2027
Final Report Submission:	02/2028

PMC 4647-4

Complete COMMODORE-2 (Study BO42162), "A Phase 3, Randomized, Open-Label, Active-Controlled, Multicenter Study Evaluating the Efficacy and Safety of Crovalimab Versus Eculizumab in Patients with PNH Not Previously Treated with Complement Inhibitors."

Trial Completion:	08/2027
Final Report Submission:	02/2028

PMC 4647-5

Complete COMPOSER (Study BP39144), "An Adaptive Phase 1/2 Study to Assess Safety, Efficacy, PK and PD of RO7112689 [Crovalimab] in HVs and Patients with PNH."

Trial Completion:	12/2026
Final Report Submission:	06/2027

PMC 4647-6

Develop and validate a competitive ligand binding neutralizing antibody (NAb) assay with adequate sensitivity and drug tolerance to test inhibition of crovalimab. This NAb assay will be used to test available confirmed anti-drug antibody positive samples from banked and ongoing clinical studies. Provide a final validation report detailing the performance of the NAb assay.

Final Validation Report Submission: 06/2026

25. Financial Disclosure

Table 158. Covered Clinical Studies: COMMODORE-1 (BO42161), COMMODORE-2 (BO42162), COMMDORE 3 (YO42311), COMPOSER (BP39144)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 813		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c), and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: Enter text here. Significant payments of other sorts: Enter text here. Proprietary interest in the product tested held by investigator: Enter text here. Significant equity interest held by investigator: Enter text here. Sponsor of covered study: Enter text here.		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Source: Completed by the FDA review team from information provided by the Applicant.
Abbreviations: CFR, Code of Federal Regulations; FDA, Food and Drug Administration

26. References

26.1. Literature

Agresti, A, 2013, Categorical Data Analysis, (3rd Edition), Probability and StatisticsEditors: Balding, D. J., N. A. Cressie, G. M. Fitzmaurice et al., John Wiley & Sons, Inc., 978-0-470-46363-5, https://mybiostats.wordpress.com/wp-content/uploads/2015/03/3rd-ed-alan_agresti_categorical_data_analysis.pdf.

Agresti, A and Y Min, 2001, On Small-Sample Confidence Intervals for Parameters in Discrete Distributions, Biometrics, 57(3):963-971, https://www.ncbi.nlm.nih.gov/pubmed/11550951.

Ballinger, GA, 2004, Using Generalized Estimating Equations for Longitudinal Data Analysis, Organizational Research Methods, 7(2):127-150, https://www.webofscience.com/wos/woscc/full-record/WOS:000220465500001?SID=USW2EC0E66NPM858TuFo1Wu9Y1Xq3.

Bektas, M, C Copley-Merriman, S Khan, SP Sarda, and JM Shammo, 2020, Paroxysmal Nocturnal Hemoglobinuria: Current Treatments and Unmet Needs, J Manag Care Spec Pharm, 26(12-b Suppl):S14-S20, https://www.ncbi.nlm.nih.gov/pubmed/33356783.

Brodsky, RA, 2014, Paroxysmal Nocturnal Hemoglobinuria, Blood, 124(18):2804-2811, https://www.ncbi.nlm.nih.gov/pubmed/25237200.

Brodsky, RA, 2021, How I Treat Paroxysmal Nocturnal Hemoglobinuria, Blood, 137(10):1304-1309, https://www.ncbi.nlm.nih.gov/pubmed/33512400.

Brodsky, RA, R Peffault de Latour, ST Rottinghaus, A Roth, AM Risitano, IC Weitz, P Hillmen, JP Maciejewski, J Szer, JW Lee, AG Kulasekararaj, L Volles, AI Damokosh, S Ortiz, L Shafner, P Liu, A Hill, and H Schrezenmeier, 2021, Characterization of Breakthrough Hemolysis Events Observed in the Phase 3 Randomized Studies of Ravulizumab Versus Eculizumab in Adults With Paroxysmal Nocturnal Hemoglobinuria, Haematologica, 106(1):230-237, https://www.ncbi.nlm.nih.gov/pubmed/31949012.

Cella, D, DT Eton, JS Lai, AH Peterman, and DE Merkel, 2002, Combining Anchor and Distribution-Based Methods to Derive Minimal Clinically Important Differences on the Functional Assessment of Cancer Therapy (FACT) Anemia and Fatigue Scales, J Pain Symptom Manage, 24(6):547-561, https://www.ncbi.nlm.nih.gov/pubmed/12551804.

DeZern, AE and RA Brodsky, 2015, Paroxysmal Nocturnal Hemoglobinuria: A Complement-Mediated Hemolytic Anemia, Hematol Oncol Clin North Am, 29(3):479-494, https://www.ncbi.nlm.nih.gov/pubmed/26043387.

Dingli, D, JP Maciejewski, L Larratt, RS Go, B Hochsmann, K Zu, P Gustovic, and AD Kulagin, 2023, Relationship of Paroxysmal Nocturnal Hemoglobinuria (PNH) Granulocyte Clone Size to Disease Burden and Risk of Major Vascular Events in Untreated Patients: Results From the International PNH Registry, Ann Hematol, 102(7):1637-1644, https://www.ncbi.nlm.nih.gov/pubmed/37199789.

Grossmann, H, GF Weinbauer, A Baker, A Fuchs, and CM Luetjens, 2020, Enhanced Normograms and Pregnancy Outcome Analysis in Nonhuman Primate Developmental Toxicity Studies, Reprod Toxicol, 95:29-36, https://www.ncbi.nlm.nih.gov/pubmed/32413491.

Hill, A, AE DeZern, T Kinoshita, and RA Brodsky, 2017, Paroxysmal Nocturnal Haemoglobinuria, Nat Rev Dis Primers, 3:17028, https://www.ncbi.nlm.nih.gov/pubmed/28516949.

Hillmen, P, NS Young, J Schubert, RA Brodsky, G Socie, P Muus, A Roth, J Szer, MO Elebute, R Nakamura, P Browne, AM Risitano, A Hill, H Schrezenmeier, CL Fu, J Maciejewski, SA Rollins, CF Mojcik, RP Rother, and L Luzzatto, 2006, The Complement Inhibitor Eculizumab in Paroxysmal Nocturnal Hemoglobinuria, N Engl J Med, 355(12):1233-1243, https://www.ncbi.nlm.nih.gov/pubmed/16990386.

Kalita, J, S Chandra, SK Bhoi, R Agarwal, UK Misra, SK Shankar, and A Mahadevan, 2014, Clinical Nerve Conduction and Nerve Biopsy Study in Vitamin B12 Deficiency Neurological Syndrome With a Short-Term Follow-Up, Nutr Neurosci, 17(4):156-163, https://www.ncbi.nlm.nih.gov/pubmed/24256995.

Lebrec, H, L Cowan, M Lagrou, C Krejsa, MB Neradilek, NL Polissar, L Black, and J Bussiere, 2011, An Interlaboratory Retrospective Analysis of Immunotoxicological Endpoints in Nonhuman Primates: T-Cell-Dependent Antibody Responses, J Immunotoxicol, 8(3):238-250, https://www.ncbi.nlm.nih.gov/pubmed/21692639.

Lee, JW, F Sicre de Fontbrune, L Wong Lee Lee, V Pessoa, S Gualandro, W Fureder, V Ptushkin, ST Rottinghaus, L Volles, L Shafner, R Aguzzi, R Pradhan, H Schrezenmeier, and A Hill, 2019, Ravulizumab (ALXN1210) Versus Eculizumab in Adult Patients With PNH Naïve to Complement Inhibitors: the 301 Study, Blood, 133(6):530-539, https://www.ncbi.nlm.nih.gov/pubmed/30510080.

Liang, KY and SL Zeger, 1986, Longitudinal Data-Analysis Using Generalized Linear-Models, Biometrika, 73(1):13-22, https://www.webofscience.com/wos/woscc/full-record/WOS:A1986A734100002?SID=USW2EC0E66NPM858TuFo1Wu9Y1Xq3.

Mannion, JM, BM Segal, RM McLoughlin, and SJ Lalor, 2023, Respiratory Tract *Moraxella Catarrhalis* and *Klebsiella Pneumoniae* Can Promote Pathogenicity of Myelin-Reactive Th17 Cells, Mucosal Immunol, 16(4):399-407, https://www.ncbi.nlm.nih.gov/pubmed/37088262.

Murakami, J and Y Shimizu, 2013, Hepatic Manifestations in Hematological Disorders, Int J Hepatol, 2013:484903, https://www.ncbi.nlm.nih.gov/pubmed/23606974.

Roth, A, J Maciejewski, JI Nishimura, D Jain, and JI Weitz, 2018, Screening and Diagnostic Clinical Algorithm for Paroxysmal Nocturnal Hemoglobinuria: Expert Consensus, Eur J Haematol, 101(1):3-11, https://www.ncbi.nlm.nih.gov/pubmed/29532535.

Schrezenmeier, H, P Muus, G Socie, J Szer, A Urbano-Ispizua, JP Maciejewski, RA Brodsky, M Bessler, Y Kanakura, W Rosse, G Khursigara, C Bedrosian, and P Hillmen, 2014, Baseline Characteristics and Disease Burden in Patients in the International Paroxysmal Nocturnal Hemoglobinuria Registry, Haematologica, 99(5):922-929, https://www.ncbi.nlm.nih.gov/pubmed/24488565.

Shah, N and H Bhatt, 2024, Paroxysmal Nocturnal Hemoglobinuria: StatPearls, https://www.ncbi.nlm.nih.gov/pubmed/32965963.

Socie, G, JY Mary, A de Gramont, B Rio, M Leporrier, C Rose, P Heudier, H Rochant, JY Cahn, and E Gluckman, 1996, Paroxysmal Nocturnal Haemoglobinuria: Long-Term Follow-Up and Prognostic Factors. French Society of Haematology, Lancet, 348(9027):573-577, https://www.ncbi.nlm.nih.gov/pubmed/8774569.

Sun, L and DV Babushok, 2020, Secondary Myelodysplastic Syndrome and Leukemia in Acquired Aplastic Anemia and Paroxysmal Nocturnal Hemoglobinuria, Blood, 136(1):36-49, https://www.ncbi.nlm.nih.gov/pubmed/32430502.

Usman, N and P Annamaraju, 2024, StatPearls: Type III Hypersensitivity Reaction. https://www.ncbi.nlm.nih.gov/pubmed/32644548.

Wener, MH, 2022, Serum Sickness and Serum Sickness-Like Reactions, (Version 26.0, updated May 27, 2022), UpToDateEditors: Adkinson, N. F. and A. M. Feldweg, Wolters Kluwer, https://www.uptodate.com/contents/serum-sickness-and-serum-sickness-like-reactions.

Yan, X and XG Su, 2010, Stratified Wilson and Newcombe Confidence Intervals for Multiple Binomial Proportions, Statistics in Biopharmaceutical Research, 2(3):329-335, https://www.webofscience.com/wos/woscc/full-record/WOS:000292680500004?SID=USW2EC0A80rhgaZqtP1z0gGrH7zRA.

26.2. Guidance for Industry

FDA Guidance for Industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims* (December 2009), Food and Drug Administration (FDA), https://www.fda.gov/media/77832/download.

FDA Guidance for Industry *Clinical Pharmacology Labeling for Human Prescription Drug and Biological Products — Content and Format* (December 2016), Food and Drug Administration (FDA), https://www.fda.gov/media/74346/download.

FDA Guidance for Industry *Clinical Studies Section of Labeling for Human Prescription Drug and Biological Products — Content and Format* (January 2006), Food and Drug Administration (FDA), https://www.fda.gov/media/72140/download.

FDA Draft Guidance for Industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products — Content and Format* (July 2020), Food and Drug Administration (FDA), https://www.fda.gov/media/90160/download.

FDA Guidance for Industry *Pediatric Information Incorporated Into Human Prescription Drug and Biological Products Labeling Good Review Practice* (March 2019), Food and Drug Administration (FDA), https://www.fda.gov/media/84949/download.

ICH Guidance for Industry *S6(R1) Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals* (May 2012), International Council for Harmonisation (ICH), https://www.fda.gov/media/72028/download; https://www.fda.gov/media/78034/download.

FDA Guidance for Industry *Bioanalytical Method Validation* (May 2018), Food and Drug Administration (FDA), https://www.fda.gov/media/70858/download.

FDA Draft Guidance for Industry *Geriatric Information in Human Prescription Drug and Biological Product Labeling Guidance for Industry* (September 2020), Food and Drug Administration (FDA), https://www.fda.gov/media/142162/download.

26.3. Other

FDA, 2017, Drugs@FDA: ULTOMIRIS (BLA 761108) Multidisciplinary Review. Food and Drug Administration (FDA): Office of New Drugs (OND), Division of Nonmalignant Hematology (DNH), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/761108Orig1s000MultidisciplineR.pdf.

FDA Standard Safety Tables and Figures: Integrated Guide (August 2022), Food and Drug Administration (FDA)'s Office of New Drugs (OND): Center for Drug Evaluation and Research (CDER), Biomedical Informatics and Regulatory Review Science (BIRRS) Team, https://downloads.regulations.gov/FDA-2022-N-1961-0046/attachment_1.pdf.

26.4. Submission Datasets

Genentech, 2023a, BLA 761388 PIASKY (crovalimab-akkz) Submission: COMMODORE-1 Datasets Provided to the FDA for the BLA 761388 Submission. \\CDSESUB1\evsprod\BLA761388\0001\m5\datasets\bo42161.

Genentech, 2023b, BLA 761388 PIASKY (crovalimab-akkz) Submission: COMMODORE-2 Datasets Provided to the FDA for the BLA 761388 Submission. \\CDSESUB1\evsprod\BLA761388\0001\m5\datasets\bo42162.

27. Review Team

Table 159. Reviewers of Integrated Assessment

Role	Name(s)
Regulatory project manager	Rolanda K. Bailey
Nonclinical reviewer	Marieli Gonzalez-Cotto, PhD
Nonclinical team leader	Pedro DelValle, MS, PhD, ATS
OCP reviewer(s)	Li Wang, PhD Ye Yuan, PhD
OCP team leader(s)	Sudharshan Hariharan PhD Jiang Liu, PhD
Clinical reviewer	Hyon-Zu Lee, PharmD
Clinical team leader	Carrie Diamond, MD
Biometrics reviewer	Huan Wang, PhD
Biometrics team leader	Yeh-Fong Chen, PhD
Cross-disciplinary team leader	Carrie Diamond, MD
Division director (pharm/tox)	Todd Boucier, PhD
Division director (OCP)	Shirley Seo, PhD
Division director (OB)	Yuan Li Shen, Dr. PH
Division director (clinical)	Ann T. Farrell, MD
Office director (or designated signatory authority)	Hylton V. Joffe, MD, MMSc

Abbreviations: MD, Medical Doctor; MMSc, Master of Medical Science; OCP, Office of Clinical Pharmacology; OB, Office of Biostatistics

Table 160. Additional Reviewers of Application

Office or Discipline	Name(s)
OPQ	OPMA DS/DP: Reyes Candau-Chacon, PhD Facilities: Michael Shanks Secondary: Virginia Carroll, PhD
Microbiology	Reyes Candau-Chacon, PhD
OPDP	Melissa Khashei, PharmD LCDR Jina Kwak, PharmD
OSI	Anthony Orencia
OSE	Cmdr Carol Corbie, RN, BSN, MS
OSE/DEPI	Sarah Kang, PharmD, MS, BCPS Steve Bird, PharmD
OSE/DMEPA	Sue Black, PharmD Nicole Iverson, PharmD Hina Mehta, PharmD Lolita Sterrett, PharmD Millie Shah, PharmD
OSE/DRM	Carla Darling, PharmD, BCPS Jacqueline Sheppard, PharmD
Other: OBP	RBPM: Kelly Ballard, MS ATL: Ian McWilliams, PhD OBP Primary: Cao, Yanyan, PhD DS: Zhen Ren, PhD DP: Yanyan Cao, PhD IA: Rachel Lokanga, PhD Label Reviewer: Diana Pei, PharmD
Other: DMPP	Laurie Buonaccorsi, PharmD Barbara Fuller, RN, BSN, MSN
Other: Associate Director of Labeling	Virginia Kwitkowski, MS, ACNP-BC
Other: Safety	Rosanna Setse, MD, MPH, PhD, Deputy Director for Safety Caden Brennen, MS

Abbreviations: DEPI, Division of Epidemiology; DMEPA, Division of Medication Error Prevention and Analysis; DRISK, Division of Risk Management; OPDP, Office of Prescription Drug Promotion; OPQ, Office of Pharmaceutical Quality; OSE, Office of Surveillance and Epidemiology; OSI, Office of Scientific Investigations

27.1. Reviewer Signatures

Table 27-161 Signatures of Reviewers

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharm-tox/Non-clinical Discipline Secondary Reviewer	Pedro Delvalle OCHEN DPTCHEN	Sections: 5.1, 5.2, 7.1, 8.4, 13	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	Enter comment

Signature: **Pedro Delvalle**

Digitally signed by Pedro Delvalle xxx
Date: 6/20/2024 3:00 PM EDT
GUID: 202462019025

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharm-tox/Non-clinical Discipline Primary Reviewer	Marieli Gonzalez-Cotto OCHEN DPTCHEN	Sections: 5.1, 5.2, 7.1, 8.4, 13	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	Enter comment

Signature: **Marieli Gonzalez-Cotto**

Digitally signed by Marieli Gonzalez-xxx
Date: 6/20/2024 3:00 PM EDT
GUID: 202462019054

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Regulatory Project Manager Discipline Secondary Reviewer	Sejal Kiani ORO DROCHEN	Sections: 12	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	Enter comment

Signature: **Sejal Kiani**

Digitally signed by Sejal Kiani xxx
Date: 6/20/2024 3:01 PM EDT
GUID: 202462019150

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Associate Director for Labeling Discipline Primary Reviewer	Virginia Kwitkowski OCHEN DNH	Sections: 23	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	Enter comment

Signature: **Virginia Kwitkowski**

Digitally signed by Virginia Kwitkows xxx
Date: 6/20/2024 3:02 PM EDT
GUID: 202462019248

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Biostatistics Discipline Primary Reviewer	Huan Wang OB DBIX	Sections: 6, 15-16, 23-26	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	Enter comment

Signature: **Huan Wang**

Digitally signed by Huan Wang
xxx
Date: 6/20/2024 3:03 PM EDT
GUID: 20246201937

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Associate Director for Labeling Discipline Secondary Reviewer	Virginia Kwitkowski OCHEN DNH	Sections: 23	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	Enter comment

Signature: **Virginia Kwitkowski**

Digitally signed by Virginia Kwitkows
xxx
Date: 6/20/2024 3:03 PM EDT
GUID: 202462019326

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Secondary Reviewer	Sudharshan Hariharan OCP DCEP	Sections: 5.2, 6.1, 8.1, 8.2, 14	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	Enter comment

Signature: **Sudharshan Hariharan**

Digitally signed by Sudharshan Hari
xxx
Date: 6/20/2024 3:04 PM EDT
GUID: 20246201949

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Tertiary Reviewer	Jayabharathi Vaidyanathan OCP DCEP	Sections: 5.2, 6.1, 8.1, 8.2, 14	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	Enter comment

Signature: **Jayabharathi Vaidyanathan**

Digitally signed by Jayabharathi Vai
xxx
Date: 6/20/2024 3:04 PM EDT
GUID: 202462019424

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Discipline Secondary Reviewer	Carrie Diamond OCHEN DNH	Sections: 1-4, 6, 7, 8-12, 15-16, 17-19, 20-21, 23-26, 22	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	Enter comment

Signature: Carrie Diamond

Digitally signed by Carrie Diamond xxx
Date: 6/20/2024 3:04 PM EDT
GUID: 202462019433

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Biostatistics Discipline Secondary Reviewer	Yeh Fong Chen OB DBIX	Sections: 6, 15-16, 23-26	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	Enter comment

Signature: Yeh Fong Chen

Digitally signed by Yeh Fong Chen xxx
Date: 6/20/2024 3:04 PM EDT
GUID: 202462019434

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Discipline Primary Reviewer	Hyon-Zu Lee OCHEN DNH	Sections: 1-4, 6, 7, 8-12, 15-16, 17-19, 20-21, 23-26, 22	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	Enter comment

Signature: **Hyon-Zu Lee**

Digitally signed by Hyon-Zu Lee xxx
Date: 6/20/2024 3:06 PM EDT
GUID: 202462019610

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
CMC (OPQ/OBP) Discipline Secondary Reviewer	Ian McWilliams OPQA III DPQA XV	Sections: 9. Product Quality; 24.2. PMCs	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	Enter comment

Signature: **Ian McWilliams**

Digitally signed by Ian McWilliams xxx
Date: 6/20/2024 3:12 PM EDT
GUID: 2024620191247

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Biostatistics Discipline Secondary Reviewer	Yuan Shen OB DBIX	Sections: 6, 15-16, 23-26	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	Enter comment

Signature: **Yuan Shen**

Digitally signed by Yuan Shen xxx
Date: 6/20/2024 3:14 PM EDT
GUID: 2024620191413

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Primary Reviewer	Li Wang OCP DCEP	Sections: 5, 6, 8, and 14	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	Enter comment

Signature: **Li Wang**

Digitally signed by Li Wang xxx
Date: 6/20/2024 3:24 PM EDT
GUID: 2024620192448

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Regulatory Project Manager Discipline Primary Reviewer	Rolanda Bailey ORO DROCHEN	Sections: 12	Based on my assessment of the application: ☐ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☒ Not applicable.	Enter comment

Signature: Rolanda Bailey

Digitally signed by Rolanda Bailey xxx
Date: 6/20/2024 3:27 PM EDT
GUID: 202462019271

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharm-tox/Non-clinical Discipline Tertiary Reviewer	Todd Bourcier OCHEN DPTCHEN	Sections: 5.1, 5.2, 7.1, 8.4, 13	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	Enter comment

Signature: Todd Bourcier

Digitally signed by Todd Bourcier xxx
Date: 6/20/2024 4:16 PM EDT
GUID: 202462020641

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

CARRIE E DIAMOND
06/20/2024 04:24:59 PM

TANYA M WROBLEWSKI
06/20/2024 05:00:51 PM

HYLTON V JOFFE
06/20/2024 05:19:16 PM