27 June 2024
EMA/332145/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Piasky

International non-proprietary name: crovalimab

Procedure No. EMEA/H/C/006061/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Table of contents

List of abbreviations

AC	acceptance criterion
ACIP	Advisory Committee on Immunization Practices
ADA	anti-drug antibody
AE	adverse event
AESI	adverse events of special interest
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ANCOVA	analysis of covariance
AQL	anion-exchange chromatography
AEX	acceptance quality limit
AR	assessment report
or	
AR	acceptable range
ATC	anatomical therapeutic chemical
AUC	area under the concentration−time curve
AUC0-14d	area under the concentration−time curve from 0 to 14 days
AUC0-28d	area under the concentration−time curve from 0 to 28 days
AUC0-7d	area under the concentration−time curve from 0 to 7 days
BMTx	bone marrow transplantation
BTH	breakthrough haemolysis
C1q	complement component C1q
C3	complement component 3
C3d	degraded complement component 3
C4	complement component 4
C5	complement component C5
CCOD	clinical cutoff date
CDC	complement-dependent cytotoxicity
CDM	chemically defined medium
CDR	complementarity determining region
CE(SDS)-CZE-TDMS	top down mass spectrometry
CE-SDS	capillary electrophoresis sodium dodecyl sulfate
CFU	colony-forming unit
CH50	50% haemolytic complement activity
CHMP	Committee for Medicinal Products for Human Use
CHO	Chinese hamster ovary
CI	confidence interval
CIP	clean-in-place

CL	total clearance of the drug
Cmax	maximum plasma concentration observed
COVID-19	coronavirus disease 2019
CPP	critical process parameter
CQA	critical quality attribute
cQC MHM	Commercial Quality Control, Roche Diagnostics GmbH, Mannheim, Germany
cQC PZ	Commercial Quality Control, Roche Diagnostics GmbH, Penzberg, Germany
CRF	case report from
CRS	cytokine release syndrome
CSR	clinical study report
CTCAE	common terminology criteria for adverse events
CTD	common technical document
cy	cynomolgus monkey
CYP	cytochrome P450
CYP	cytochrome P450
DDI	drug-drug interaction
DF	diafiltration
DMC	Data Monitoring Committee
DP	drug product
DRF	dose range-finding
DS	drug substance
dsAET	drug substance analytical evaluation threshold
DTDC	drug-target-drug complex
ECG	electrocardiogram
eCRF	electronic case report form
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life-Core 30 Questionnaire
ePPND	enhanced pre- and postnatal development
EQ-5L-5D	EuroQoL 5-Dimension Questionnaire, 5-level
ESI-MS	electrospray ionisation mass spectrometry
EVA	ethylene vinyl acetate
EVH	extravascular haemolysis
FACIT	functional assessment of chronic illness therapy
Fc	fragment crystallisable
FcRn	neonatal Fc receptor
FcyR	Fc gamma receptors
FDA	U.S. Food and Drug Administration

GCP	good clinical practice
G-CSF	granulocyte colony-stimulating factors
GD	gestation day
GEE	generalised estimating equation
GHS	global health status
GLP	good laboratory practice
GPI	glycosylphosphatidylinositol
GPI-AP	glycosylphosphatidylinositol-anchored protein
h	human
Hb	haemoglobin
HBsAg	Hepatitis B surface antigen
HC	heavy chain
HCCF	harvested cell culture fluid
HCP	health care provider
or	
HCP	host cell protein
HCV	hepatitis C virus
HSCT	haematopoietic stem cell transplantation
HD	high dose
HIC	hydrophobic interaction chromatography
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HRQoL	health-related quality of life
HVAC	heating, ventilation, and air conditioning
IB	investigator’s brochure
ICE	intercurrent event
ICF	informed consent form
ICH	International Council for Harmonisation
ICIEF	imaged capillary isoelectric focusing
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IE-HPLC	ion-exchange high-performance liquid chromatography
IgG1	immunoglobulin G1
IHC	immunohistochemistry
IMP	investigational medicinal product
IPC	in-process control
IPIG	International PNH Interest Group
IPSS-R	revised International Prognostic Scoring System
IRB	Institutional Review Board

IRR	infusion-related reaction
ITT	intent-to-treat
IV	intravenous
IVH	Intravascular haemolysis
IxRS	interactive voice or Web response system
KD	equilibrium dissociation constant
LASA	linear analog scale assessment
LC	light chain
LCL	lower 90% confidence limit of difference of means
LC-MS	liquid chromatography mass spectrometry
LC-MS/MS	liquid chromatography tandem mass spectrometry
LC-UV	liquid chromatography ultraviolet
LDH	lactate dehydrogenase
LIA	liposome immunoassay
LIVCA	limit of in vitro cell age
LL	lower limit
LLN	lower limit of normal
LLOQ	lower limit of quantification
LMW	low molecular weight
LOESS	locally estimated scatterplot smoothing
LS	least-square
LysC	endoproteinase LysC
m	mouse
MA	Marketing authorisation
MAA	Marketing authorisation application
MAC	membrane attack complex
MAR	missing at random
MAVE	major adverse vascular event
MCAR	missing completely at random
MCB	master cell bank
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MES	2-(N-morpholino)ethane sulfonic acid
MFS	Multidimensional Fatigue Scale
MMAEX	multimodal anion-exchange chromatography
MNAR	missing not at random
MO	major objection
MOA	mechanism of action
MS	mass spectrometry

MS/MS	tandem mass spectrometry
NA	not applicable
NAD+	nicotinamide adenine dinucleotide
NADH	nicotinamide adenine dinucleotide (reduced)
NANA	N-acetylneuraminic acid
NCI	National Cancer Institute
NEM	N-ethylmaleimide
NGHC	non-glycosylated heavy chain
NGNA	N-glycolylneuraminic acid
NIM	non-inferiority margin
NOAEL	no observed adverse effect level
NR-CE-SDS	non-reduced capillary electrophoresis sodium dodecyl sulfate
OC	other concern
OLE	open-label extension
OR	odds ratio
PAP	primary analysis population
PD	pharmacodynamics
PedsQL	Paediatric Quality of Life
PF	physical functioning
PGIS	Patient Global Impression of Severity Survey
PHCCF	preharvest cell culture fluid
pI	isoelectric point
PI	product information
or	
PI	principal investigator
PIG-A	phosphatidylinositol glycan anchor biosynthesis class A
PIP	paediatric investigation plan
PK	pharmacokinetics
PK/PD	pharmacokinetic-pharmacodynamic
PL	package leaflet
PL	production line
PMM	pattern mixture mode
PNH	paroxysmal nocturnal haemoglobinuria
PP	per protocol
PPQ	process performance qualification
PQS	pharma quality system
pRBC	packed red blood cell
PRO	patient-reported outcome
PSB	primary seed bank

PT	preferred term
Q2W	every 2 weeks
Q4W	every 4 weeks
QLQ AA/PNH	Quality of Life Questionnaire – Aplastic Anaemia/Paroxysmal Nocturnal Haemoglobinuria
QLQ-C30	Quality of Life-Core 30
QoL	quality of life
QOW	every other week
QW	weekly
r	rat
RBC	red blood cell
R-CE-SDS	reduced capillary electrophoresis sodium dodecyl sulfate
rel.%	relative percent
REM	Roche essential media
RF	Roche feed
RFU	relative fluorescence unit
RMP	risk management plan
RS	reference standard
RTE	Roche trace elements
RU	resonance unit
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SC	subcutaneous
SD	standard deviation
SDM	scale-down model
SDS	sodium dodecyl sulfate
SE	standard error
SEC	size exclusion chromatography
SIP	sterilisation-in-place
SMART	sequential monoclonal antibody recycling technology
SmPC	summary of product characteristics
SNP	single nucleotide polymorphism
SoC	standard of care
SOC	system organ class
SPR	surface plasmon resonance
t1/2	half-life
TA	transfusion avoidance
TAMC	total aerobic microbial count

TK	toxicokinetic
TMDD	target-mediated drug disposition
TSQM-9	Treatment Satisfaction Questionnaire for Medication-9
TTH	tabletop haemolysis
UFDF	ultrafiltration and diafiltration
ULN	upper limit of normal
VAS	visual analog scale
VCD	viable cell density
VdF	volume of distribution
VF	virus filtration, small-virus retentive filtration
VHF	Virosart HF
VMax	Virosart Max
vs.	versus
Vss	volume of distribution at steady state
vWF	von Willebrand factor
WCB	working cell bank
WFI	water for injection
WHO	World Health Organization
WOCBP	woman of childbearing

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Roche Registration GmbH submitted on 19 June 2023 an application for marketing authorisation to the European Medicines Agency (EMA) for Piasky, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The applicant applied for the following indication: "Piasky is indicated for the treatment of adult and paediatric patients with paroxysmal nocturnal haemoglobinuria (PNH) (see section 5.1)."

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

1.3. Information on paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0056/2023 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0056/2023 was not yet completed.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

1.5. Applicant's request for consideration

1.5.1. New active Substance status

The applicant requested the active substance crovalimab contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

1.6. Scientific advice

The applicant received the following scientific advice on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
14 May 2019	EMEA/H/SA/4184/1/2019/III	Fernando de Andrés Trelles and Brigitte Schwarzer-Daum

The scientific advice pertained to the following quality, non-clinical, and clinical aspects:

- the approach to determine the potency of drug substance and drug product at release and during stability for Phase III and commercial material;
- the proposed non-clinical safety studies for a marketing authorisation application;
- the clinical pharmacology plan, in particular in elderly patients, in patients with impaired renal or hepatic functions, the drug-drug interaction and QT studies;
- the clinical pharmacology plan to support the proposed dose and dosing regimen for the planned pivotal Phase III studies in patients with PNH;
- the clinical development programme in paediatric patients with PNH, including the pharmacokinetic analyses based on adult and adolescent patients to determine the dose for children <12 years of age;
- the safety monitoring plan;
- the measures to support self-administration of crovalimab by patients and/or caregivers at home.

1.7. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Alexandre Moreau Co-Rapporteur: Margareta Bego

The application was received by the EMA on	19 June 2023
The procedure started on	13 July 2023
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	4 October 2023
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	16 October 2023
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	16 October 2023
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	9 November 2023
The applicant submitted the responses to the CHMP consolidated List of Questions on	20 February 2024
The following GCP inspection was requested by the CHMP and their outcome taken into consideration as part of the Safety/Efficacy assessment of the product:	
☐ A GCP inspection was performed at one investigator site in Thailand (20-24/11/23), one investigator site in the Philippines (23-27/10/23) and the sponsor in Switzerland (4-8/12/23). The outcome of the inspection carried out was issued on	5 March 2024
The CHMP Rapporteurs circulated the updated CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	18 April 2024
The CHMP agreed on a list of outstanding issues be sent to the	25 April 2024

applicant on	
The applicant submitted the responses to the CHMP List of Outstanding Issues on	27 May 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	12 June 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	21 June 2024
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Piasky on	27 June 2024
The CHMP adopted a report on similarity of Piasky with Aspaveli, Voydeya and Fabhalta on	27 June 2024
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product (see Appendix on NAS)	27 June 2024

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Paroxysmal nocturnal haemoglobinuria (PNH) is a rare, acquired, chronic, life-threatening blood disorder associated with anaemia due to haemolysis. It is most frequently caused by a somatic mutation in the PIGA gene of haematopoietic stem cells. Its onset is often insidious. Although there have been reports of spontaneous remission, the course of the disease is generally chronically progressive.

Haemolysis can result in a range of debilitating consequences such as severe fatigue, chest pain, and transfusion dependence, all of which contribute to a reduced quality of life. If left untreated, PNH can cause severe and potentially fatal complications for patients. Thrombotic events are the main cause of severe complications and death in PNH. PNH requires life-long treatment. Therapy is aimed at controlling complement-mediated haemolysis and thus counteracting anaemia.

2.1.2. Epidemiology

PNH may equally affect males and females, although there may be a slight female preponderance (NORD 2021). PNH has no clear predilection for race or ethnicity (Shah and Bhatt 2021).

PNH has an annual incidence as high as 0.6 per 100,000 persons (Farooq 2020). However, this number may be higher as the disease remains undiagnosed in individuals with limited symptomatology or where the diagnosis is obscured in those with comorbid conditions (Cançado 2021).

PNH prevalence is estimated to be 1−2 per 100,000 persons in the general population (Cançado 2021). It is estimated that overall, in the US, Europe, and Japan, there are about 10,000 patients with this disease (Mandala 2013; Ninomiya and Okura 2022).

Although patients can develop PNH at any age, the typical age of presentation is 30-40 years. Children can be affected by PNH as well, but it is uncommon with PNH predominantly affecting adolescents (Curran 2011; Shah and Bhatt 2021). According to a 2017 analysis of 4,948 patients enrolled in the International PNH Registry, the median age at diagnosis was 36 years (inter-quartile range: 24 – 53 years) (Schrezenmeier *et al.* 2020). Additionally, only 4.2% of patients in this registry were younger than 18 years of age, with a median age of 14 years (min: 1 year; max: 17 years) at enrolment of the paediatric patients (Urbano-Ispizua 2011).

2.1.3. Biologic feature, aetiology and pathogenesis

The natural history of patients with PNH is highly variable. The disease can arise *de novo* or evolve from acquired aplastic anaemia (AA). No universally accepted classification scheme is available, but the International PNH Interest Group (IPIG) classified into 3 categories:

- Classical PNH in which patients have clinical manifestations of haemolysis or thrombosis,
- PNH in the context of the primary bone marrow disorders such as aplastic anaemia or myelodysplastic syndromes,
- Subclinical PNH in which patients have low proportions of PNH clones but no clinical or laboratory evidence of haemolysis or thrombosis.

Patients with haemolytic PNH tend to have near-physiological platelet and neutrophil counts, lactate dehydrogenase (LDH) levels more than 2 times the upper physiological limit (indicative of intravascular

[IVH]), a normocellular bone marrow, an increased reticulocyte count, and a relatively large (usually >50%) population of PNH granulocytes. Patients with aplastic anaemia PNH (acquired AA with a low-to-moderate proportion of a PNH clone) are severely pancytopenic. They tend to have hypocellular bone marrow, relatively low absolute reticulocyte counts (ARCs), and low percentages of PNH granulocytes (De Latour 2008; Socié 2016; Hill 2017; Schrezenmeier 2020).

PNH is acquired through genetic mutations in the Phosphatidylinositol N-acetylglucosaminyl-transferase subunit A gene, which encodes a glycoprotein required for anchoring certain cell surface membrane proteins. Patients with PNH have blood cells that are deficient in glycosyl phosphatidylinositol-anchored proteins, including CD55 and CD59 that are complement regulators, which results in haemolysis due to unregulated complement activation against the blood cells (Brodsky 2014; Hill 2017).

The physiopathology of PNH involves uncontrolled complement activation, resulting in intravascular haemolysis (IVH) and extravascular haemolysis (EVH). It is uncontrolled complement activation that leads to IVH mediated by the C5-dependent membrane attack complex and EVH mediated by accumulation of C3 fragments on RBC surface.

2.1.4. Clinical presentation, diagnosis

Patients with PNH suffer from severe morbidities, including major adverse vascular events (MAVEs) such as thromboembolism, chronic kidney disease, pulmonary hypertension, fatigue, dysphagia, abdominal pain, dyspnoea, chest pain, and erectile dysfunction. Patients with PNH have variable degrees of haemolysis depending on the degree of bone marrow failure, clone size, and degree of complement activation, all of which may vary over time in an individual patient. Retrospective analyses have reported that, despite the best supportive care, the 10-year survival rate in patients with PNH ranged from 50% for patients diagnosed in the mid-20th century to over 70% recently (Schrezenmeier 2014). Thromboembolism is the leading cause of mortality in patients with PNH, accounting for up to 67% of deaths with known causes (Schrezenmeier 2020).

Limited evidence is available for comorbid conditions in PNH patients. A study in the UK on 774 PNH patients reported AA (44%), MDS (24%), cytopenia (7%), acute leukaemia (4%), myeloproliferative neoplasms (2%), and thrombosis with cytopenia (2%) as important co-morbidities and their prevalence (Fattizzo 2021).

2.1.5. Management

The treatment options available to PNH patients differ significantly by country or geographical region. The main therapeutic classes are complement inhibitors targeting C5 such as eculizumab and ravulizumab. Recently, new medicines have been authorised such as Aspaveli (pegcetacoplan) (a C3 inhibitor) targeting the proximal complement, Fabhalta (Iptacopan), a proximal complement inhibitor that specifically binds to FB to inhibit the activation of the AP and amplification loop and Voydeya (Danicopan), an oral small molecule reversible inhibitor of complement factor D (FD) that selectively blocks the complement alternative pathway (AP). Allogeneic haematopoietic stem cell transplantation (HSCT) is a curative option that is available in certain countries but presents significant risks. In countries where the above medical interventions are not currently available, management of patients is mainly through supportive care (Cançado 2021).

Treatment for PNH is symptomatic and supportive where other treatment options are either not available or not recommended depending upon the individual's age, general health, presence of associated disorders, severity of PNH, and degree of underlying bone marrow failure. The following supportive care may be required or recommended: glucocorticoids to ameliorate haemolysis, transfusions and iron supplements as supportive treatment for anaemia, and/or anticoagulants to

prevent thrombotic episodes (Cançado 2021). In addition, immunosuppressive therapy, androgens or haematopoietic growth factors may be administered to patients with PNH and various degrees of bone marrow impairment (Du 2022). These supportive care approaches do not modify the disease pathophysiology and present significant risks associated with chronic use. Long-term use of glucocorticoids is associated with infectious complications and multi-system adverse effects that are dose- and duration-dependent; other immunosuppressive treatments are also associated with infectious complications. In addition, compared to C5 inhibitor treatment, supportive treatment is not expected to improve mortality in patients with PNH (Hill 2017).

2.2. About the product

Piasky (crovalimab) is a recombinant humanised IgG1-based monoclonal antibody that specifically binds with high affinity to component 5 (C5) of the complement system, inhibiting its cleavage into C5a and C5b and thus preventing the formation of the membrane attack complex. Crovalimab causes terminal complement activity inhibition aimed to inhibit terminal complement-mediated intravascular haemolysis.

Crovalimab dosing regimen is based on body weight.

For patients switching from treatment with another complement inhibitor, the first intravenous loading dose of crovalimab should be administered at the time of the next scheduled complement inhibitor administration.

Solution for IV infusion and SC injection are the two pharmaceutical forms for crovalimab. Each vial of 2 mL contains 340 mg of crovalimab at a concentration of 170 mg/mL.

2.3. Type of Application and aspects on development

This application is based on a pivotal Phase III study:
- COMMODORE 2 (BO42162), a randomised eculizumab-controlled study in complement inhibitor-naïve patients;

It is also supported by a single Phase I/II study
- COMPOSER: to assess safety, efficacy, PK and PD of crovalimab in healthy volunteers and patients with PNH

and two additional Phase III studies:
- COMMODORE 1 (BO42161), a supportive eculizumab-controlled study in switch patients;
- COMMODORE 3 (YO42311), a supportive study in complement inhibitor-naïve patients from China.

The applicant sought general scientific advice from the EMA on the development programme and registration strategy for crovalimab in PNH (EMEA/H/SA/4184/1/2019/III). The proposed dosing strategy was overall supported but overexposure in certain subgroups could not be ruled out. Regarding the development programme itself, CHMP highly recommended use of eculizumab as a comparator for studies COMMODORE 1 and 2. The non-inferiority design for both studies was considered acceptable, with valid subgroup analyses and handling of ICEs. Inclusion of paediatric subjects was also discussed but was subject to further discussion with PDCO at the time of the meeting. Also, better characterisation of drug-to-drug complexes (DTDCs) was required, based on emerging safety data from the Phase I/II COMPOSER study.

PEI (Germany) and AEMPS (Spain) also provided scientific advice on the proposed filing strategy on 28 June 2022 and 27 September 2022, respectively.

Concerns about inclusion of paediatric patients in the indication were raised by both health authorities. In addition, one national agency pointed out the limited comparative data in switch patients due to premature stop of recruitment in the randomised arms of study COMMODORE 1 for feasibility reasons. This study is nevertheless expected to provide data on formation of DTDCs and associated risk of type III hypersensitivity.

A pre-submission meeting with the EMA was held on 18 April 2023. The adequacy of the study population with the claimed indication was questioned. Indeed, the number of paediatric patients appears to be limited and no patients weighing less than 40 kg were included across studies. Also, the evolving treatment landscape for PNH should be taken into consideration. Other concerns were raised about DTDCs, the potential efficacy impact of anti-drug antibodies (ADAs), the chosen non-inferiority margins and the handling of intercurrent events (ICEs).

2.4. Quality aspects

2.4.1. Introduction

Crovalimab is a novel, humanised anti-C5 monoclonal antibody (mAb) that binds to complement protein C5 with high affinity, thereby inhibiting its cleavage to C5a and C5b, and preventing the generation of the terminal complement complex, C5b-9 (membrane attack complex [MAC]). Crovalimab inhibits terminal complement-mediated intravascular haemolysis in patients with paroxysmal nocturnal haemoglobinuria (PNH).

Crovalimab finished product (FP) is provided as a sterile solution for infusion/injection. The FP is composed of 170 mg/mL crovalimab in L-histidine/L-aspartic acid buffer, L-arginine hydrochloride, poloxamer 188, pH 5.8 and water for injections.

Crovalimab FP is available in a single-use glass vial.

2.4.2. Active Substance

2.4.2.1. General Information

Crovalimab is a humanised monoclonal antibody based on a human IgG1 framework. The recombinant antibody is produced in CHO cells and consists of two heavy chains and two light chains.

Structure and general properties are sufficiently described, including primary structure details. More detail is provided in the characterisation section below.

Crovalimab has been designed based on Sequential Monoclonal Antibody Recycling Technology (SMART-Ig) using antibody engineering techniques to improve functional properties.

In addition, mutations were introduced in the Fc-portion to eliminate effector functions by abrogating the binding to Fc gamma receptors (FcγR).

These characteristics result in a linear PK, prolonged functional half-life (t1/2), and prolonged terminal complement activity inhibition through reduced free target (C5) accumulation.

The general information provided on crovalimab structural properties is considered to be acceptable.

2.4.2.2. Manufacture, characterisation and process controls

Manufacturers:

Name, address and responsibility for the proposed commercial manufacturers of the active substance (AS) have been provided. Manufacture of AS crovalimab antibody are conducted at Roche Diagnostics GmbH, Nonnenwald 2, 82377, Penzberg, Germany.

No GMP inspections were deemed necessary within the scope of this MAA evaluation procedure. Discrepancies arising between the application form and GMP documentation have been clarified.

For US sites, the applicant provided statements of last inspection dates and excerpts from web site - FDA drug establishment current registration site, with expiration dates stated – 31.12.2023. For these sites, valid GMP is confirmed in the FDA Drug Establishment Current Registration site.

All sites involved in manufacturing and control of the active substance operate in compliance with EU GMP.

Description of manufacturing process and process controls

One batch of AS is defined as the material generated from the harvest of a single production culture, followed by protein recovery and purification.

Cell culture and harvest process

Crovalimab is manufactured using an upstream process resembling a standard process for monoclonal antibody manufacturing. The production bioreactor content is harvested by centrifugation and filtration to remove cells and cell debris and filtered prior to further purification.

Purification

Crovalimab is purified and final conditioned using a combination of chromatography and filtration steps and additional steps for removal and inactivation of potential viral contaminants prior to filling into the container closure system.

Control of Materials:

No raw materials of human/animal origin used during crovalimab manufacturing. The source, history, and generation of the cell substrate are sufficiently described. Overall, the generation and characterisation of the MCB, WCB and cells at an in vitro age comply with the requirements set in the ICH guidelines

Controls of critical steps and intermediates

The AS manufacturing process is developed with defined operational procedures, CPPs, and IPC limits to ensure control of critical steps. The IPC limits employed to control product quality during AS manufacture are described. Depending on criticality, IPCs are tested against defined action limits or acceptance criteria.

Process Validation (PV) and/or Evaluation

The validation approach and data obtained are considered as acceptable. A combination of development data, prior knowledge, clinical manufacturing experience and PV studies are used to establish Process Parameter Acceptable Ranges and to assess PP criticality. A risk ranking and filtering (RRF) assessment is completed for each unit operation to assess the criticality of all PPs based on prior knowledge and product-specific development data. Scale down models (SDMs) are used in the PV studies and the run orders are randomised to avoid systematic biases. In addition, design of experiments (DOE) studies are orthogonal. Each process output (CQA and key performance indicator (KPI)) is measured on each run of the study design. The evaluation of the PV study is performed for each process output separately.

For the assessments of PP ARs, the CQA data from PV studies are compared to the in-process pool limit (IPPL) for each CQA.

Overall, the active substance manufacturing process has been adequately validated.

Manufacturing process development:

During development, different versions of the AS manufacturing process are used.

- Comparability:

The whole comparability strategy and studies are seen compliant with ICH Q5E. A comparability exercise between process versions was performed to assess the impact of the manufacturing process changes on product quality.

Overall, the results of the comparability exercise demonstrated that the manufacturing process changes did not have an adverse impact on the quality, safety, or efficacy of crovalimab.

Characterisation

Elucidation of structure and other characteristics:

A comprehensive characterisation of the AS from both the structural and the biological points of view has been presented in the current dossier.

Additionally, the applicant provided data on description of the methods employed for characterisation together with the data on their qualification.

CQA Assessment:

CQAs and their acceptable ranges form the basis for the control strategy. Each CQA is controlled at the appropriate stage in the manufacturing process. The identities of the crovalimab CQAs and the rationales used to identify them are provided. All methods used for the characterisation studies are qualified as fit for purpose which is endorsed considering the importance of characterisation and structure-activity relationship studies for the CQA definition, for AS/FP specification and for the conclusion on comparability exercise. The provided assessment/data are considered as acceptable.

Impurities:

Information regarding the process-related impurities is provided with the validations of the corresponding methods.

A risk-based approach related to leachables from AS process and the removal of raw materials has been provided.

Overall, the active substance manufacturing process has been adequately characterised.

2.4.2.3. Specification

Specifications:

The active substance specifications include control of identity, purity and impurities, potency, microbiological and other general tests. The specification covers the aspects of quality, identity, heterogeneity, purities, strength, biological activity, and safety.

Overall, the active substance specification is considered acceptable.

Analytical procedures:

- Compendial methods

The compendial methods Appearance, pH, Bioburden and Bacterial endotoxins are performed in accordance with the methods described in the relevant pharmacopoeia.

- Non-compendial methods

In general, the non-compendial analytical procedures are described in sufficient details. Information on the reference standards is included where relevant. System suitability criteria are specified and found adequate to confirm that the methods are in control during routine testing. The applicant provided validation overviews as well as validation reports for the non-compendial methods.

- Batch analyses

Information on the use of the different batches are provided. All batch analysis results meet the specifications that are valid at the time of testing and release for each batch. In addition, all available release data from the AS batches produced during the PPQ and 2022 campaigns meet the proposed commercial release specification acceptance criteria.

- Justification of AS specification:

Refer to justification of FP specification.

Reference standards of materials

Refer to the FP reference standards.

Container Closure System

The AS is stored in drug substance storage container. The specification of the container closure system is provided. The container passed testing according to USP. The material of construction is compliant with the compendial regulations and industry standards and the Ph. Eur.

No leachables of toxicological concern are detected.

2.4.2.4. Stability

A post approval stability commitment has been made.

The proposed shelf life of 36 months at – 40°C is considered acceptable.

2.4.3. Finished Medicinal Product

2.4.3.1. Description of the product and pharmaceutical development

Description of the product

The finished product is provided as a sterile clear to strongly opalescent, almost colourless to brownish yellow, solution for infusion/injection.

The finished product is formulated as 170 mg/mL crovalimab at pH 5.8, which is the same composition as the active substance. Excipients used in the formulation are histidine, aspartic acid, arginine hydrochloride and poloxamer 188. All comply with the requirements and specifications of the relevant Ph. Eur. monographs.

The manufacturing fill parameters were adequately selected to withdraw and administer the nominal volume as declared on the label. The container closure system consists of a Type I glass vial with a fluoro resin-laminated butyl rubber stopper and crimped with an aluminium seal fitted with a plastic flip-off cap.

Pharmaceutical development

A total of four crovalimab formulations were used during development. Changes in formulation during development were sufficient. The rationale used to select the excipients has been sufficiently described in the dossier.

Two finished product manufacturing sites have been established, and the applicant explicitly stated that the differences between the sites are site-specific technical adaptations that were needed due to equipment differences, with no impact on the quality of the final product.

Comparability exercises were performed on finished product batches produced using different manufacturing process versions employed during development, at different manufacturing sites. The comparability showed that there is no significant difference in product quality. Based on the comparison of relevant quality attributes, each set of pre- and post-change finished product batches was determined as suitable for its intended use. The comparability exercises included a quantitative and qualitative comparability assessment of quality attributes, as well as a comparison of accelerated and stress stability data.

Compatibility of the container closure system with the dosage form was adequately assessed with respect to physicochemical testing (i.e. extractables and leachables), stability testing, and container closure integrity testing.

Crovalimab finished product contains no preservative. The microbiological quality complies with European requirements for sterile products and is ensured by a combination of various measures - sterile product-contact components, sterile in-line filtration, environmental and media monitoring - and is confirmed by microbiological IPC testing as well as sterility release testing.

Crovalimab is used diluted for intravenous (IV) infusion and undiluted for subcutaneous (SC) injection. For IV infusion, crovalimab solution is intended to be diluted in 0.9% sodium chloride immediately prior to use. For SC injection, the solution from the vial is intended to be transferred to the injection syringe immediately prior to use. To address potential hold times after the preparation of the infusion bag or syringe and prior to administration, compatibility studies were conducted to confirm the stability of the finished product under recommended in-use conditions. Physicochemical stability of the diluted infusion or syringe were demonstrated for the durations and conditions as listed in the product information. From a microbiological point of view, the prepared infusion bag or syringe should be used immediately.

2.4.3.2. Manufacture of the product and process controls

The finished product manufacture, release and stability testing sites are specified in the dossier. Roche Pharma AG, Germany will be responsible for batch certification in Europe. Valid GMP certificates are available for the finished product sites.

All sites involved in manufacturing and control of the finished product operate in compliance with EU GMP.

Description of manufacturing steps with process flow diagram for each site is presented. The main manufacturing steps include AS thawing, pooling and mixing, bioburden reduction filtration, sterile filtration and filling, capping and crimping, final vial inspection, labelling and secondary packaging and

storage/transportation. Process and hold times and acceptable ranges for the CPPs/non-CPPs for different manufacturing steps that were confirmed during the PPQ are summarised for each manufacturing. One bioburden reduction refiltration is permitted in exceptional cases, such as a technical issue on the filling machine. The impact of refiltration was evaluated at manufacturing scale.

IPCs with action limits/acceptance criteria for manufacture of FP are provided for each manufacturing site. Setting up the IPC ranges as action limits and acceptance criteria depending on criticality is appropriately justified, and the procedures for deviations from the established ranges are described. The proposed ranges have been confirmed during the PPQ. Bioburden analytical method of IPC samples is sufficiently described and considered suitable for the intended purpose.

Process design studies, which were performed using either small-scale models or manufacturing-scale equipment, evaluated the potential impact of process parameters on relevant critical quality attributes. Representativeness of small-scale models is appropriately justified in the dossier. The selection of CPPs and non-CPPs was appropriately justified. The summaries of manufacturing-scale process leachable studies are provided. The results demonstrate that the levels of organic leachables from the FP process are below levels of toxicological significance, therefore process equipment is safe with regards to organic leachables. The list of tested product-contact materials is provided, as requested.

The PPQ activities included validation of all manufacturing steps, process and hold times, media fills and shipping qualification. A total of three consecutive crovalimab FP PPQ runs were performed at each proposed commercial sites and at the proposed commercial range of batch sizes. A bracketing approach was used to cover the minimum and maximum batch sizes, which is acceptable. Data from the PPQ batches showed that all CQAs met their acceptance criteria, all IPCs met their acceptance criteria or action limits, respectively, all CPPs and non-CPPs were maintained within their acceptable ranges and process performance was consistent between the PPQ batches. The manufacturing process is considered validated, within the commercial range of batch sizes, and the provided data are generally acceptable.

The proposed process and hold times have been successfully demonstrated. For the media fill, representative existing qualification data have been presented, which is acceptable. All acceptance criteria were met, demonstrated the acceptability of finished product aseptic processing. Media fill time supports the total the maximum sterile filtration and filling time.

Several studies have been performed to ensure that shipment of crovalimab finished product via qualified passive and active thermal shipping systems is adequate from a thermal and mechanical perspective. The results indicate that the finished product is adequately protected during shipping and that mechanical stress conditions have no impact on product quality. The information provided is acceptable.

2.4.3.3. Product specification

Specifications

The finished product specifications include control of identity, purity and impurities, potency, microbiological and other general tests.

The crovalimab finished product specifications were established using 'state of the art' methods. Overall, the proposed specifications are considered appropriately justified and sufficient to deliver product with consistent quality.

Acceptance criteria setting is based on a combination of several factors: clinical experience, stability and process effects, product-specific knowledge, prior knowledge, current compendia or regulatory guidelines, and formulation development studies.

Characterisation of impurities

Regarding the potential presence of nitrosamine impurities in crovalimab finished product, the applicant states that none of the components carry a risk of introducing possible nitrosamine impurities into the final finished product, either during manufacturing or during storage, and thus, testing of nitrosamines is not required. A summary of the nitrosamine risk assessment has been provided.

The assessment for elemental impurities was conducted according to ICH Q3D and showed that there are no concerns related to elemental impurities in the drug product produced at the site of commercial manufacture.

Analytical procedures and reference standards

The methods for finished product were validated as per ICH Q2 R1 requirements. The applicant established appropriately characterised in-house primary and working reference standards, prepared from lot representative of production. Working reference standards used in the testing of production lots was calibrated against the primary reference material. Documentation of the qualification, storage conditions and stability programme of primary and working reference standards was provided. Protocol for qualification of future primary and working reference materials was also described.

Batch analysis

Analytical results of finished product batches including process validation and clinical trials batches are provided. All batches were manufactured at the intended commercial sites -using the commercial formulation. All results comply with the defined acceptance criteria.

Container closure

The primary container closure system of finished product is described in sufficient detail. Drawings with critical dimensions and specifications are provided, as well as reference to compendial requirements, where applicable.

The product-contacting materials are said to be suitable for packaging sterile liquid products. Details regarding sterilisation method for the CCS, its validation and sterilisation sites, were provided as requested.

The extractables and leachables studies have been provided.

The applicant provided a brief description of the secondary packaging.

2.4.3.4. Stability of the product

A 3-year shelf-life is claimed for the finished product, when stored at 2-8°C and protected from light.

This claim is based on data generated from a combination of process validation and representative clinical batches. Stability studies were carried out in accordance with current ICH guidelines. The containers used in the stability studies were the same as those proposed for routine storage.

The applicant confirmed that in all stability studies (at all conditions, including photostability, temperature cycling studies, with all batches), the methods are appropriately described.

Additional stability studies (i.e., photostability and temperature excursion and patient conveniences studies) were conducted. Results showed that the product is light sensitive and thus should be stored protected from light. Data generated from temperature cycling confirm stability of finished product under conditions that might occur during manufacturing, shipping, and handling. Statement in product information that "Once removed from the refrigerator, the unopened vial can be kept at room temperature (up to 30°C) in its outer carton for no longer than 7 days" is considered suitably demonstrated.

In–use stability has been satisfactorily addressed via both physicochemical and microbiological studies.

In conclusion, the proposed shelf life of 3 years and storage conditions (2-8^{0}C, unopened vial) can be granted. Once removed from the refrigerator, the unopened vial can be kept at room temperature (up to 30 °C) in its outer carton for no longer than 7 days. All of the above considerations are correctly reflected in the product information.

2.4.3.5. Adventitious agents

Three model viruses were used for the viral clearance studies: X-MuLV, MMV and SV-40. The applicant claimed the presence of 4 steps involved in viral removal/inactivation: affinity chromatography, low pH treatment, MMAEX and small virus retentive filtration. The overall viral safety of crovalimab is considered satisfactory.

Questions regarding bioburden testing for non-viral adventitious agents and other concerns raised regarding viral clearance studies data and safety margin calculation have been satisfactorily addressed.

The data provided give sufficient assurance regarding non-viral adventitious agents (risk of contamination with animal TSE) and viral adventitious agents aspects.

2.4.4. Discussion and conclusions on chemical, pharmaceutical and biological aspects

Module 3 is considered to be a good quality dossier. Information on development, manufacture and control of the active substance and finished product have been presented in a satisfactory manner. The outstanding issues have been satisfactorily answered by the applicant. From a quality point of view, marketing authorisation can be granted.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The overall quality of Piasky is considered acceptable when used in accordance with the conditions defined in the SmPC. The different aspects of the chemical, pharmaceutical and biological documentation comply with existing guidelines.

No further recommendations for future quality development have been made.

In conclusion, based on the review of the quality data provided, it is considered that the marketing authorisation application for Piasky is approvable from the quality point of view.

2.5. Non-clinical aspects

2.5.1. Introduction

The non-clinical toxicology programme of crovalimab characterised general toxicity and toxicokinetics following IV and SC administrations up to 26 weeks in a single pharmacologically relevant species (*cynomolgus* monkeys), as recommended in ICH S6(R1) guideline. One DRF study was first performed (non-GLP compliant) with crovalimab administration by IV and SC routes for 2 weeks. Then, one pivotal with 2 different administration schemes (IV up to 4 weeks with 17-week recovery and SC up to 5 months with no recovery) was performed as same as the long-term term study in which both administration routes were used (26-week GLP study SC QW and IV Q2W with 26-week recovery). Since the *cynomolgus* monkey was the only demonstrated pharmacologically relevant species, an enhanced pre- and postnatal development (ePPND) study was conducted in line with ICH S6(R1) guideline. An assessment of the reproductive organs was also included in the repeat-dose toxicity studies to address any potential effect on fertility. Tissue cross reactivity, cytokine release, serum compatibility, and haemolytic potential of crovalimab were assessed *in vitro*.

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

In vitro studies

Crovalimab binds human C5 (hC5) and cynomolgus monkey C5 (cyC5) to the same extent (1.72 and 2.00 ×10-10 mol/L, respectively) and its binding is pH dependent. No binding to rat C5 (rC5) and a weak binding to mouse C5 (mC5) were detected. Inhibition of crovalimab against RBC lysis induced by complement activity was studied in the serum of various species. In human and *cynomolgus* monkey serum, crovalimab dose-dependently inhibited antibody-sensitised chicken RBC lysis with IC_{50} values of 0.834 and 0.958 µg/mL, respectively. However, RBC lysis induced in rabbit or rat serum was inhibited to less than 50% at the maximum tested concentration of 301 µg/mL. These *in vitro* results confirmed that rat, mice and rabbit were not pharmacologically relevant species and therefore were excluded to be selected as species in the toxicity studies. Dog species as relevant pharmacologically animal model was not assessed. The *in vitro* PD studies confirmed that *cynomolgus* monkey is pharmacologically relevant species as binding of hC5 and cyC5 and inhibitory activity results in human and c*ynomolgus* monkey sera were similar.

Submitted literature reference (Fukuzawa and al. Scientific Reports 2017) indicated crovalimab binds to a different C5 epitope than eculizumab and consequently ravulizumab.

Finally, *in vitro* PD programme demonstrated that the affinity of crovalimab to hFcRn or cyFcRn (same extent: KD 1.70 and 1.78 x10-7 mol/L) was approximately 10-fold greater than that of trastuzumab which has a native human IgG1 Fc region. It is agreed that this may contribute to a prolonged plasma exposure of crovalimab through enhancing the FcRn-mediated recycling following endocytotic uptake. It is acknowledged that this mechanism of enhancing the FcRn-mediated recycling following endocytotic uptake was also mentioned as responsible for the longer effect of ravulizumab compared to eculizumab. No comparison between affinity of crovalimab to hFcRn and affinity of ravulizumab to hFcRn have been investigated.

In vivo studies

In vivo pharmacodynamic activity with measurements of total C5, free C5 and CH50 concentrations and RBC lysis assay was assessed in animal safety programme. The results of PD measurements are

presented with no distinction between results from ADA-negative and ADA-positive animals. Therefore, no information on the extent of ADA impact on the PD effect has been provided. However, it could be concluded from the 26-week presented PD results that inhibition of terminal complement activity was observed in all treatment groups despite the emergence of ADA and reduction of crovalimab exposure in some ADA-positive animals. Almost all animal in the pivotal 26-week study were ADA-positive, only few of them presented a PK impact but the PD is conserved during the entire treatment period and only a trend towards recovery is observed at the end of recovery period of 26-weeks. Total C5 tended to accumulate after the administration of crovalimab (4-fold maximum) and free C5 concentrations decreased in dose-dependent manner rapidly after crovalimab injection.

2.5.2.2. Secondary pharmacodynamic studies

The affinity of crovalimab to hFcγRs and cyFcγRs was little or none. Crovalimab had markedly weaker binding activity to C1q compared with rituximab. Crovalimab is unlikely to induce effector functions. Crovalimab is therefore unlikely to activate immune cells or complement.

2.5.2.3. Safety pharmacology programme

No dedicated safety pharmacology studies were performed. No effects on general behaviour and neurobehavioral function, respiration and the cardiovascular system were seen after the first dose or following repeated dosing in the repeated-dose pivotal studies.

2.5.2.4. Pharmacodynamic drug interactions

The drug-target-drug complex (DTDC) formation between crovalimab with another anti-C5 antibody (eculizumab surrogate antibody) was studied. The recycling properties of crovalimab were not impaired by the DTDC formation. No DTDC data have been presented with ravulizumab.

2.5.3. Pharmacokinetics

The pharmacokinetics of crovalimab were studied in *cynomolgus* monkeys, a pharmacologically relevant species. Pharmacokinetic assessments were based on quantification of total target binding-competent crovalimab in plasma and detection of anti-drug antibodies (ADAs). Crovalimab was administered to *cynomolgus* monkeys as single intravenous (IV) administrations over the dose range of 0.8 to 20 mg/kg, and as single subcutaneous (SC) administration at 4 mg/kg. Crovalimab pharmacokinetics after repeated IV and SC dosing were assessed as part of three repeat-dose toxicology studies at doses up to 160 mg/kg IV and 100 mg/kg SC. The toxicokinetics of crovalimab was also assessed in an enhanced pre- and postnatal development (ePPND) study in c*ynomolgus* monkeys, receiving a loading dose of 100 mg/kg as IV bolus on gestation day 20 (GD20), similar to the recommended clinical dosing regimen and to reduce ADA formation, followed by repeated weekly (QW) SC doses of 10 or 100 mg/kg until delivery.

Absorption

The measured bioavailability after single SC administration of 4 mg/kg in *cynomolgus* monkeys was approximately 69%. A slow absorption was measured with Tmax around 1-3 days (up to 7 days). The steady state was reached around week 9-week 11 of dosing which is consistent with the dosing frequency and the elimination half-life.

Crovalimab pharmacokinetics were independent of dose over the dose range of 0.8 to 160 mg/kg. Both AUC and Cmax exposure increased in a dose-proportional manner in the 25-fold dose range from 0.8 to 20 mg/kg. No sex differences were observed through the performed PK programme.

Crovalimab was immunogenic and induced ADA production in *cynomolgus* monkeys in almost all treated monkeys. In some ADA-positive monkeys, an increased systemic CL was observed with a decreased exposure; however, the PD activity is maintained during the whole treatment period and partially recovered in the treatment free period. Therefore, ADA are not considered limiting the toxicological assessment in the presented toxicity studies. Immunogenicity observed in *cynomolgus* monkeys is not considered predictive of the potential immunogenicity of crovalimab in humans.

Distribution, metabolism and excretion

Traditional distribution studies were not conducted for crovalimab, which is an antibody with a molecular weight of 145 kDa. Due to its molecular size, crovalimab is expected to be primarily confined to the vascular space, which is typical for IgG-based mAbs.

CL was in the low range for an IgG (2.66-2.86 mL/kg/d) and independent of the dose. Vss exceeded the plasma volume (69.5-71.8 mL/kg), indicating some distribution into tissues. Crovalimab was transferred via the placenta in pregnant monkeys. Crovalimab was eliminated with a mean $t_{1/2}$ up to 53 days after SC administration once a week in 26-week monkey study. Crovalimab presented a long half-life which is consistent with the recycling properties of crovalimab by binding to the FcRn.

Pharmacokinetic drug interactions

No pharmacokinetic drug interaction studies were conducted.

2.5.4. Toxicology

Several batches were used in the non-clinical programme. The batches used for pivotal repeated-dose toxicity studies (4-week/5-month and 26-week studies) as well as GLP TCR study, GLP haemolysis and blood compatibility and non-GLP cytokine release assay were obtained from manufacturing process v.01 and ePPND was performed with crovalimab from manufacturing process v.02. These manufacturing processes v.01 and 0.2 were also used in clinical studies and were determined to be comparable to the commercial batches manufactured (manufacturing process v1.0). However, the two following batches 5D22SKY and L09LO15-SG115 were not found in the quality dossier, as these two batches were used for non-pivotal studies (2-week DRF and non-GLP TCR studies). Formulations used in cynomolgus monkey was not compared to the one administered in humans.

2.5.4.1. Single dose toxicity

No dedicated single-dose toxicity studies were performed. No relevant findings were observed after the first dose in the repeated-dose studies.

2.5.4.2. Repeat dose toxicity

A dose-range finding study was conducted in *cynomolgus* monkeys (non-GLP study). Crovalimab was administered by IV and SC routes up to 100 mg/kg IV every two weeks (total 2 doses) and up to 40 mg/kg/week SC (total 3 doses). Crovalimab was well tolerated and the exposures were up to 8-fold the median exposure in human measured in the pivotal study (IV) and exposure after SC administration (highest dose) was in the clinical range. Pharmacological activity was confirmed despite all animals presenting an ADA response which impacted the crovalimab exposure in some ADA-positive animals.

The first pivotal study (GLP-compliant) was then performed. Crovalimab was administered IV at dose levels of 10, 40, and 160 mg/kg to *cynomolgus* monkeys QW for 4 weeks (17-week recovery, total of 5 doses), and was administered to an additional group SC at a dose level of 40 mg/kg QW for 5 months

(without recovery period, total of 22 doses). Exposures were respectively 15-fold (IV) and 7-fold (SC) higher than in humans at the maximum recommended dose. Detection of ADA by immune complex assay revealed a positive response in 23 out of 26 animals treated by IV route at D29 and in 4 out of 6 treated by SC route at D22. Most of the ADA positive animals showed no clearly decreased exposure. Pharmacological activity was demonstrated as shown by decreased complement activity during the whole treatment period in both groups returning fully or partially to control levels in some animals by the end of the recovery. After SC injection, very slight local inflammation was observed. After IV injection, arteritis/periarteritis in several tissues in 8 animals were observed. There were no apparent differences in the incidence or severity in the arteritis/periarteritis observed at the end of recovery period compared with those at the end of the dosing period. The immunohistochemistry analysis revealed that the presence of the granular deposits in these observed arteries (except 1 tissue in 2 animals) is consistent with processes of immune complex formation, deposition, pathogenicity, and clearance in these animals.

The second pivotal study is a long-term study in cynomolgus monkeys (GLP-compliant study). Crovalimab was administered SC at dose levels of 10, 40, and 100 mg/kg QW for 26 weeks after a single IV injection of 100 mg/kg on Day 1 of the study and was administered to an additional group IV at a dose level of 160 mg/kg. A recovery of 26 weeks was added in both groups. Exposures (AUC) observed were respectively 18-fold (SC) and 17-fold (IV) higher than in humans at the maximum recommended dose. ADA were detected in 21 out of 30 animals in the SC groups (D36) and in 8 out of 10 animals in the IV group (D15). Crovalimab concentrations decreased in some animals probably due to ADA, but complement activity was inhibited in all the animals during the whole treatment period and returning fully or partially to control levels by the end of the recovery period. Total of 6 animals presented arteritis/periarteritis in one or several tissues in SC 100 mg/kg/week and IV 160 mg/kg/QOW, all animals were tested ADA-positive. In 1 male in the 160 mg/kg (IV) group, in addition, a slight membranoproliferative glomerulonephritis accompanied by tubule-interstitial changes, urinalysis changes, and high serum creatinine were also observed at the end of the dosing period. These changes were considered to be due to immune complex deposition; however, no IC analysis was performed with the tissues presented arteritis/periarteritis as it was performed after the first pivotal study. Reversible local effects perivascular mononuclear cell infiltrate in the subcutis at the injection site was observed in all SC groups.

The adverse effects observed through the repeated-dose toxicity programme appear to be coherent/consistent. Sufficient exposures were achieved in animals and pharmacological activity were maintained during the whole treatment period despite the presence of ADA in most of the tested animals. Arteritis/periarteritis in several tissues were observed in non-pivotal and in pivotal repeated-dose studies and one animal presented a glomerulonephritis at the highest dose tested in the toxicity programme. The immunohistochemistry analysis performed with tissues collected from the first pivotal study confirms that these changes could be due to immune complex deposition. The applicant justified to exclude this effect as not relevant to the human situation to determine the NOAEL.

Local injection site reactions were observed after repeated SC administration. These reversible changes included infiltration of inflammatory cells in the subcutis throughout the dosing period and might be caused by administration of a foreign protein.

2.5.4.3. Genotoxicity

No genotoxicity studies were conducted as crovalimab is a biotechnology-derived pharmaceutical.

2.5.4.4. Carcinogenicity

Similarly, no carcinogenicity studies were conducted as crovalimab is a biotechnology-derived pharmaceutical.

2.5.4.5. Reproductive and developmental toxicity

An enhanced pre- and postnatal development (ePPND) study was conducted in cynomolgus monkeys administered an IV loading dose of 100 mg/kg on GD20, followed by once weekly SC injections of either 10 or 100 mg/kg up to parturition. A control group was treated similarly with the vehicle. The dams and infants were then observed untreated for 6 months. There was no treatment-related effect on pregnancy outcome. Pharmacological activity was demonstrated by decreased complement activity in maternal animals during the whole treatment period in both groups returning fully (low dose) or partially (high dose) to control levels by the end of the lactation period; a reversible decrease in complement activity was also noted in infant animals of the high dose group. No adverse treatment-related effect on postnatal infant development was observed, including skeletal development and immunological development (immunophenotyping, TDAR). Exposure of infant animals to crovalimab was confirmed during the post-natal period and resulted most likely from *in utero* exposure involving FcRn. The NOAEL for pre- and postnatal development was 100 mg/kg/dose in this study, corresponding to exposure levels (AUC) 5- to 14-fold higher than in humans at the maximum recommended dose.

In the 26-week repeat-dose toxicity study conducted in sexually mature *cynomolgus* monkeys, there was no treatment-related effect indicative of a potential treatment-related effect on fertility based on results of semen analysis, evaluation of menstrual cycles, and weight and histopathology of reproductive organs. A tissue cross reactivity study revealed no binding of crovalimab to testis tissues in *cynomolgus* monkeys, which further suggests that crovalimab is unlikely to have a direct effect on the seminiferous epithelium. There are published data that focal atrophy of the seminiferous tubules in the testes can be seen in mature non-human primates, characterised by features including segmental dilation of the seminiferous tubule with thinning of the germinal epithelium, sperm stasis, and/or a decreased number of germ (Creasy, 2012; Pereira Bacares et al., 2017).

Paediatric development from 2 years of age in the PNH indication is supported notably by the completed ePPND study showing no adverse treatment-related effect on postnatal infant development (incl. immune function).

2.5.4.6. Toxicokinetic data

See repeated-dose toxicity section below.

2.5.4.7. Local tolerance

No dedicated local tolerance studies were conducted.

2.5.4.8. Other toxicity studies

A GLP tissue cross-reactivity study was performed to evaluate potential binding of crovalimab to a panel of 36 human and monkey tissues at concentrations of 1 and 10 µg/mL. The tissue cross-reactivity data confirms the expected binding pattern. Compared to the human tissue panel, there was less staining in the cynomolgus monkey tissue panel. This was interpreted to represent differences in the dying process.

Crovalimab up to 17.2 mg/mL is considered compatible with human serum and blood. Very slight reddish colour change without accompanying increase in haemoglobin concentration at 172 mg/mL but this finding was not considered as haemolysis.

The risk for cytokine mediated IRR/CRS of crovalimab was determined as comparable to other low-risk compounds.

2.5.5. Ecotoxicity/environmental risk assessment

In accordance with the guideline CHMP/SWP/4447/00 (1), crovalimab as a protein is exempted from an environmental risk assessment since proteins are unlikely to result in a significant risk to the environment. Therefore, crovalimab is not expected to pose a risk to the environment.

2.5.6. Discussion on non-clinical aspects

Pharmacology

The rationale for the development of Piasky is understood and acknowledged from a non-clinical point of view. The main points which differ from already approved treatments for PNH are: different binding epitope on C5 – could be better for patients with C5 Arg885His single nucleotide polymorphisms (SNPs), final formulation which enables self-medication (low volume, high concentration), and a long half-life which is consistent with the FcRn-mediated recycling properties of crovalimab. The Fukuzawa paper is accepted as evidence of the new recycling model of Antibody binding to target. Even though there are no studies presented in which the new "recycling" method of the antibody is demonstrated, the Fukuzawa paper is considered sufficient.

Pharmacodynamics studies demonstrated that *cynomolgus* monkey is pharmacologically relevant species (crovalimab binds hC5 and cyC5 to the same extent) and that rat, mice and rabbit were not pharmacologically relevant species and therefore were not selected as species in the toxicity studies. Dog species as relevant pharmacologically animal model was not assessed, and justification of these data lacking could have been appreciated. The higher affinity of crovalimab to hFcRn or cyFcRn may contribute to a prolonged plasma exposure of crovalimab through enhancing the FcRn-mediated recycling following endocytotic uptake. A comparison between affinity of crovalimab to hFcRn and affinity of ravulizumab to hFcRn would have been appreciated.

No dedicated *in vivo* pharmacology studies were conducted. Complement inhibition and target engagement (free and total C5 concentrations) were assessed in a single-dose PK/PD study and in the repeat-dose toxicity studies in *cynomolgus* monkeys. Pharmacological activity was confirmed to be maintained through the whole treatment duration and partly or fully reversed at the end of the recovery period consistently with the long elimination half-life, even if emergence of ADA was observed in almost all treated monkeys.

Crovalimab is unlikely to induce effector functions. DTDC formation is expected for any C5 inhibitors binding to a different epitope than crovalimab. It is expected that crovalimab would bind to hC5-eculizumab to form DTDCs larger than 8 Ab and 8 hC5 molecules in plasma and its pH-dependent dissociation characteristic would be exerted at pH 6.0. The applicant didn't discuss in the nonclinical part the safety impact of DTDC formation in humans. The impact of DTDC formation on the safety profile of crovalimab is discussed in clinical safety section. An adequate warning regarding DTDC formation is included in sections 4.2, 4.4, 4.5 and 4.8 of the SmPC.

The applicant did not investigate if DTDCs are formed with different C5 inhibitors and did not confirm this issue *in vivo.* This would have provided information on the safety signals which could arise from

DTDC formation. Since the issue of forming DTDC is controlled and supervised from a clinical point of view, no concern is raised in the nonclinical part of the assessment.

The pharmacology package is adequate, and the mechanism of action is adequately presented in the SmPC section.

Pharmacokinetics

The methods of analysis are considered appropriate.

Traditional distribution, metabolism and excretion studies were not conducted for crovalimab. The pharmacokinetics of crovalimab were studied only in *cynomolgus* monkeys, as it is the only demonstrated pharmacologically relevant species. Pharmacokinetic assessments were based on quantification of total target binding-competent crovalimab in plasma and detection of anti-drug antibodies. One single-dose PK/PD study was performed in addition to the TK parameters measured in repeated-dose toxicity studies. The SC bioavailability was measured at approximately 69%. Crovalimab pharmacokinetics were independent of dose over the dose range. Both AUC and Cmax exposure increased in a dose-proportional manner. No sex differences were observed. Crovalimab was immunogenic and induced ADA production in *cynomolgus* monkeys in almost all treated animals but the pharmacologic activity is preserved during the whole treatment period and partly or fully recovered during the recovery period, consistently with the long half-life. Immunogenicity observed in *cynomolgus* monkeys is not considered predictive of the potential immunogenicity of crovalimab in humans. The PK parameters measured were consistent with the IgG-based mAbs profile.

Toxicology

To support the proposed treatment of adult and paediatric patients with PNH, crovalimab was studied in non-clinical toxicology studies that meet requirements as defined in ICH guideline S6(R1). PD data supported the use of monkey as the only pharmacologically relevant species. Toxicity potential was studied up to 26 weeks with addition of 26 weeks recovery considering the long elimination half-life of the product. Sufficient exposures were achieved in animals and pharmacological activity was confirmed to be maintained through the whole treatment duration even if emergence of ADA was observed in almost all treated monkeys. Pharmacological activity was partly or fully reversed at the end of the recovery period consistently with the long elimination half-life.

Arteritis/periarteritis in several tissues were observed in animals at almost all tested doses. This non-dose-dependent finding was detected in animals during dosing period, as well as after the cessation of dosing, with no apparent differences in the incidence or severity. It was mainly represented by inflammatory cell infiltration within and surrounding the vessel wall, while the vascular wall remained intact. No abnormal changes were observed in clinical signs or other parameters associated with inflammation. In addition, glomerulonephritis was also observed in one animal with arteritis. This animal presented with slight degeneration/regeneration of the tubule, hyaline and RBC casts, interstitial infiltrate of neutrophils and interstitial fibrosis associated with positive occult blood (grade 4), erythrocytes (grade 2) in urinary sediments and high creatinine in blood chemistry, which is considered secondary to glomerulonephritis. An immunohistochemistry study was conducted to provide further information regarding the formation of immune complexes, since the occurrence of arteritis/periarteritis is supposed to be related to immunogenicity. The presence of granular deposits containing crovalimab (human IgG), ADA (monkey IgG or IgM), and/or C3 correlates with immune complex formation and deposition. Indeed, deposits were detected in arteries of all selected tissues from 3 out of 5 animals with histopathologically confirmed arteritis/periarteritis. Although observed deposits were not present in arteries of examined tissues from other 2 animals with arteritis, increased staining of crovalimab, ADA, and/or C3 in mononuclear cells associated with arteritis was noted in these tissues. Taking into account that blood vessel walls and renal glomeruli are two of the most

common sites for immune complex deposition, sometimes evident as granular deposits, arteritis and/or glomerulonephritis noted in crovalimab studies are consistent with the characteristic of immune complex-mediated injury reported for other biotherapeutics ([Bugelski and Treacy 2004], [Rojas et al. 2005], [Ponce et al. 2009], [Shmagel and Chereshnev 2009], [Brinks et al. 2011], [Heyen et al. 2014], [Leach et al. 2014], [Rojko et al. 2014], [Frazier et al. 2015]). Therefore, these changes could be considered as not relevant to the clinical situation and excluded for the determination of the NOAEL as proposed by the applicant.

Local injection site reactions were observed after repeated SC administration. These reversible changes included infiltration of inflammatory cells in the subcutis throughout the dosing period and are caused by administration of a foreign protein.

Besides observed arteritis/glomerulonephritis and local injection site reactions, focal atrophy of the tubules in the testes was noted in males across all dose groups, including the control group following histopathological examination in the 6-months repeat-dose toxicity study. This change, which consisted of focal luminal dilation, decreased number of spermatogenic cells, sperm stasis, and Sertoli cell vacuolation, was unilateral after SC administration, but bilateral after IV administration in mature male *cynomolgus* monkeys. At the end of the recovery period, very slight or slight focal atrophy remained in both tested and control animals. The applicant stated that no crovalimab-related changes were noted in semen analysis, weights of testes and epididymis, and microscopically in the male accessory reproductive organs or endocrine organs. Furthermore, published data have described focal atrophy of the testicular tubules in mature NHPs and based on similar morphology of the testicular changes between affected animals in this study and reported data, the applicant considered the finding in the testes not to be related to crovalimab ([Vidal et al. 2022], [Pereira Bacares et al. 2017]). However, statistically significant low absolute testis (right) weight and low absolute epididymis (total) weight were measured at the end of the dosing period in animals from two different dose groups. In addition, 4 out of 6 animals from these groups developed bilateral focal atrophy in the testes. Although an incidence of this change was similar between SC dosed animals and control animals, slightly higher incidence and bilateral occurrence were noted in IV dosed animals at the end of the dosing period. Dose-dependent increase in exposure was measured across SC dose groups, as well as similar exposures between IV dosed animals and animals dosed with the highest SC dose. Considering that TK data revealed no clear correlation between histopathological finding and systemic exposure, and no binding of crovalimab to testicular tissues from *cynomolgus* monkeys was detected in TCR study, the observed focal atrophy in the testes is unlikely to be associated with crovalimab treatment.

Genotoxicity

In accordance with ICH S6 (R1), genotoxicity studies are not applicable or needed for biotechnology-derived pharmaceuticals. It is not expected that large peptides/proteins, such as crovalimab, would interact directly with DNA or other chromosomal material.

Carcinogenicity

Furthermore, standard carcinogenicity bioassays are generally applicable for biotechnology-derived pharmaceuticals. However, crovalimab inhibits terminal complement activity and due to its immunosuppressive potential, the applicant provided a full carcinogenicity assessment. Crovalimab is not expected to have direct interactions with DNA, and consequently does not promote carcinogenicity or malignant transformation of cells and tissues via mechanisms involving direct DNA damage. Based on assessment of the presented data and published articles, it is concluded that crovalimab has no carcinogenic potential/risk for patients. Therefore, submitted carcinogenicity assessment is considered sufficient and no dedicated carcinogenicity testing is warranted.

Reproductive and developmental toxicity

An enhanced pre- and postnatal development (ePPND) study revealed no treatment-related effect on pregnancy outcomes or development of infants. No finding indicative of a potential treatment-related effect on fertility was observed in the long-term toxicity study.

Immunogenicity

ADA responses were evaluated from control animals in the ePPND study, but not in repeated dose toxicity studies, due to different standard procedures for ADA assessment in the control animals. Unexpectedly high ADA-positive response was detected from the control group in the ePPND study, which was considered unrelated to crovalimab. Indeed, undetectable crovalimab concentrations were noted in this group during the study and no correlation in ADA-positive signals was observed between maternal animals and infants, suggesting that ADA-positive responses in these animals were not caused by specific anti-crovalimab antibodies. Although ADA assessment was not performed in the control group from the 6-month repeated dose toxicity study, ADA-positive signals were detected in three control animals during the acclimation period and two of them developed arteritis/periarteritis during the study. Considering that the control animals were not exposed to crovalimab (with the exception of one animal with arteritis that had very low levels at single time-point), it could be concluded that observed arteritis/periarteritis in these two animals was not crovalimab-related. However, the correlation between ADA formation and occurrence of arteritis was demonstrated; thus, supporting the conclusion about immune complex-mediated origin of this histopathological finding.

Exposure multiples for interspecies comparison were estimated at NOAEL from the 6-month repeat-dose toxicity study and ePPND study, which is the most reliable approach for evaluating possible safety risk in humans. Considering that there was no significant evidence of toxicity, the highest dose in each study was considered as NOAEL. When compared to exposure estimates in patients with PNH, exposure in animals was over 10-fold higher in both toxicity studies at NOAEL, indicating adequate dose-range selection and low toxicity potential of crovalimab.

Tissue cross-reactivity study, blood compatibility study and *in vitro* cytokine release assay revealed no particular effect at the intended clinical concentration.

The results of comparability exercise confirmed that batches used in toxicology studies are comparable to those used in pivotal clinical studies or planned for commercial use. In line with recommendation from ICH S6(R1), purification processes are preferable to remove impurities from the test material. As a result, toxicological qualification of impurities was not conducted.

Environmental risk assessment

The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, crovalimab is not expected to pose a risk to the environment.

Assessment of paediatric data on non-clinical aspects

Paediatric development from 2 years of age in the PNH indication is supported notably by the completed ePPND study showing no adverse treatment-related effect on postnatal infant development (incl. immune function).

2.5.7. Conclusion on the non-clinical aspects

The non-clinical data reveal no special hazard for humans based on repeat dose toxicity studies (including safety pharmacology endpoints), toxicity to reproduction and development and

immunogenicity. From a non-clinical perspective, the submitted data are considered appropriate to support marketing authorisation of Piasky for PNH.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the applicant

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Tabular overview of clinical studies

Study and Phase	Patients	Summary of Study	Region / Patient Number	Status
Pivotal Study				
BO42162 (COMMODORE-2) Phase III Section 1.4.2.1	All ages, ≥ 40kg body weight, naive to C5 inhibitor treatment ("treatment-naive")	Randomized, open-label, active-controlled, multicenter study to evaluate the efficacy, safety, PK and PD of crovalimab compared with eculizumab in patients with PNH not previously treated with complement inhibitors	Global Overall N = 210 Randomized arms Arm A: 135 patients crovalimab Arm B: 69 patients eculizumab (68 patients switched to crovalimab in extension period)[a] Non-randomized Arm C (crovalimab treatment): Pediatrics [b]: 6 patients	Primary analysis complete (1109893) CCOD: 16 Nov 2022 Crovalimab extension period ongoing
Supportive Studies				
YO42311 (COMMODORE-3) Phase III Section 1.4.2.2	Adults and adolescents, ≥ 40kg body weight, naive to C5 inhibitor treatment ("treatment-naive")	A multicenter, single-arm study evaluating the efficacy, safety, PK, and PD of crovalimab in patients with PNH not previously treated with complement inhibitors	China mainland only Overall N = 51 (crovalimab treatment)	Primary analysis complete (1109892) CCOD: 10 Feb 2022 Update analysis complete (1117575) CCOD: 10 Aug 2022 Crovalimab extension period ongoing
BO42161 (COMMODORE-1) Phase III Section 1.4.2.3	All ages, ≥ 40kg body weight, switch from other C5 inhibitors ("switch")	Randomized, open-label, active-controlled, multicenter study to evaluate the safety, PK, PD, and efficacy of crovalimab compared with eculizumab in patients with PNH currently treated with complement inhibitors	Global Overall N = 127 Randomized arms: Arm A: 45 patients crovalimab [c] Arm B: 44 patients eculizumab [d] (35 patients switched to crovalimab in extension period) Non-randomized Arm C (crovalimab treatment): Pediatrics [b]: 1 patient Prior ravulizumab: 21 patients Higher-than-approved eculizumab dose:10 patients Known C5 polymorphism: 6 patients	Primary analysis complete (1109894) CCOD: 16 Nov 2022 Primary treatment period and crovalimab extension period ongoing for all arms Enrollment into Arm C ongoing

Study and Phase	Patients	Summary of Study	Region / Patient Number	Status
Supportive Studies (continued)				
BP39144 (COMPOSER) Phase I/II 2.7.3 SCE, Section 1.2.1.4	Adults, ≥ 40kg body weight, naive to C5 inhibitor treatment ("treatment-naive") or switching from other C5 inhibitors ("switch")	An adaptive study to assess safety, efficacy, PK and PD in healthy volunteers and patients with PNH	Global Overall N = 59 15 healthy volunteers, 18 treatment-naive and 26 switch patients with PNH treated with crovalimab	Primary analysis complete (1101056) (CCOD: 29 Jan 2020) Updated analysis complete (1112075) (CCOD: 1 Nov 2021) OLE period ongoing

C5 = complement component 5; CCOD = clinical cutoff date; OLE = open-label extension; PD = pharmacodynamics; PK = pharmacokinetics; PNH = paroxysmal nocturnal hemoglobinuria.

[a] Two pediatric patients (> 12 years old) were randomized to eculizumab in Arm B before a separate descriptive Arm C was opened to allow enrollment of pediatric patients (< 18 years old) weighing ≥ 40 kg.

[b] Pediatric patients aged < 18 years and ≥ 40 kg body weight.

[c] 1 randomized patient in study BO42161 Arm A did not receive crovalimab treatment.

[d] 2 randomized patients in study BO42161 Arm B did not receive eculizumab treatment.

2.6.2. Clinical pharmacology

Crovalimab is a novel humanised anti-complement component 5 (C5) monoclonal antibody of the immunoglobulin G1 (IgG1) subtype. It binds specifically and with high affinity to C5 and blocks its cleavage into subunits C5a and C5b, thus preventing the formation of the membrane attack complex (MAC), membrane disruption, and consequently cell lysis. Crovalimab is engineered with pH-dependent antigen binding and enhancement of neonatal Fc receptor (FcRn) binding to improve antigen disposal and antibody recycling efficiency. This results in prolonged functional half-life and reduced total target accumulation.

In the current submission, the applicant seeks marketing approval for crovalimab, as monotherapy, for the adult and paediatric patients with paroxysmal nocturnal haemoglobinuria (PNH), including those not previously treated (treatment naïve-patients) and being treated (switch patients) by a complement inhibitor.

The proposed recommended dosing regimen consists of one loading dose administered by intravenous (IV) 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. The doses to be administered are based on the patient's body weight.

Table 1: Crovalimab dosing regimen based on body weight

Body Weight	≥ 40 kg to < 100 kg	≥ 100kg
Loading Dose		
Day 1	1000 mg (IV)	1500 mg (IV)
Day 2, 8, 15, 22	340 mg (SC)	340 mg (SC)
Maintenance Dose		
Day 29 and Q4W thereafter	680 mg (SC)	1020 mg (SC)

IV = intravenous; Q4W = every 4 weeks; SC = subcutaneous.

The drug product for registration is a solution for injection to be administered subcutaneously or by intravenous route. It is proposed under a single concentration: 170 mg/mL; each vial contains 340 mg of crovalimab in 2 mL.

An overview of studies contributing to clinical PK, PD and immunogenicity data is presented in **Table 2.**

Table 2: Summary of clinical pharmacology studies

Study Number	Study Design	Population	No. of Patients Evaluable for PK	No. of Patients Evaluable for PD	No. of Patients Evaluable for Immunogenicity	Dose, Route, and Regimen	Clinical Cutoff Date / Study Status
BP39144 (COMPOSER) (supportive study)	Part 1: Randomized, investigator/subject blinded, adaptive, placebo-controlled, parallel group	Adult (18–75 years), healthy volunteers	9[a]	9[a]	0[b]	Single-ascending dose of crovalimab (75 mg IV, 125 mg IV, or 100 mg SC) or placebo.	Primary analysis CCOD (completion of Parts 1–4): 29 Jan 2020 Primary treatment period completed
	Part 2: multiple-dose, global multicenter, intra-patient dose-escalation study	Adult (18–75 years), treatment-naïve patients with PNH	10	10	10	Single-ascending IV doses of crovalimab (375 mg; 500 mg; 1000 mg), followed by QW 170 mg SC injections for a total treatment duration of 20 weeks.	
	Part 3: multiple-dose, global multicenter study	Adult (18–75 years) patients with PNH, who switch from eculizumab	19	19	19	Single IV loading dose of 1000 mg crovalimab, followed by QW (170 mg), Q2W (340 mg), or Q4W (680 mg) SC injections for a total treatment duration of 20 weeks.	
	Part 4: multiple-dose, global multicenter, two-arm study	Adult (18–75 years) patients with PNH Arm A: treatment-naïve patients Arm B: patients who switch from eculizumab	 8 7	 8 7	 8 7	Single IV loading dose of 1000 mg crovalimab, followed by 340 mg SC dose on Days 2, 8, 15, and 22, then 680 mg SC Q4W from Day 29 onwards, for a total treatment duration of 20 weeks.	
	OLE: open-label extension	Patients who completed Parts 2, 3, and 4, who derived benefit from crovalimab treatment and enrolled into the OLE period	43[c]	43[c]	43[c]	Patients initially stayed on previously assigned treatment schedule. With the implementation of Protocol Version 6, all patients in the OLE who were not currently receiving Q4W dosing were required to switch to the Q4W dosing regimen. Patients either received 680 mg SC Q4W (body weight ≥ 40 kg to < 100 kg) or 1020 mg SC Q4W (body weight ≥ 100 kg).	Update analysis CCOD: 1 Nov 2021 OLE period ongoing

Study Number	Study Design	Population	No. of Patients Evaluable for PK	No. of Patients Evaluable for PD	No. of Patients Evaluable for Immunogenicity	Dose, Route, and Regimen	Clinical Cutoff Date / Study Status
BO42162 (COMMODORE 2) (pivotal study)	Phase III, global, randomized, active-controlled, multicenter study of crovalimab versus eculizumab in patients with PNH not previously treated with complement inhibitors	Randomized arms (A: crovalimab and B: eculizumab): patients with PNH not previously treated with complement inhibitors, ≥ 18 years of age, ≥ 40 kg body weight	Arm A: 135[d] Arm B: 68[de]	Arm A: 134[d] Arm B: 69[d]	Arm A: 134[d] Arm B: 67[de]	Crovalimab: Body weight ≥ 40 to < 100 kg: Loading doses: Week 1, Day 1, 1000 mg IV; Day 2, 340 mg SC. Weeks 2, 3, & 4, 340 mg SC QW. Maintenance dosing: Week 5 and Q4W thereafter, 680 mg SC. Body weight ≥ 100 kg: Loading doses: Week 1, Day 1, 1500 mg IV; Day 2, 340 mg SC. Weeks 2, 3, & 4, 340 mg SC QW. Maintenance dosing: Week 5 and Q4W thereafter, 1020 mg SC. Eculizumab: 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. The duration of the primary treatment period was 24 weeks. After 24 weeks of crovalimab treatment, patients in Arms A and C who derived benefit from the drug could continue to receive crovalimab in the extension period. After at least 24 weeks of eculizumab treatment, patients in Arm B had the option to switch to crovalimab in the extension period.	Primary analysis CCOD: 16 Nov 2022 Primary treatment period completed for randomized arms Crovalimab extension period ongoing
		Descriptive arm (C: crovalimab): pediatric patients with PNH not previously treated with complement inhibitors (< 18 years of age, ≥ 40 kg)	6	6	6		

Study Number	Study Design	Population	No. of Patients Evaluable for PK	No. of Patients Evaluable for PD	No. of Patients Evaluable for Immunogenicity	Dose, Route, and Regimen	Clinical Cutoff Date / Study Status
BO42161 (COMMODORE 1) (supportive study)	Phase III, global, randomized, active-controlled, multicenter study of crovalimab versus eculizumab in patients with PNH currently treated with complement inhibitors	Randomized arms (A: crovalimab and B: eculizumab): patients with PNH currently treated with eculizumab, ≥ 18 years of age, ≥ 40 kg body weight. Non-randomized arm (C: crovalimab):[g] patients with PNH, consisting of:	Arm A: 44 Arm B: 35[e]	Arm A: 44 Arm B: 42	Arm A: 44 Arm B: 35[e]	Crovalimab: Body weight ≥ 40 to < 100 kg: Loading doses: Week 1, Day 1, 1000 mg IV; Day 2, 340 mg SC. Weeks 2, 3, & 4, 340 mg SC QW. Maintenance dosing: Week 5 and Q4W thereafter, 680 mg SC. Body weight ≥ 100 kg: Loading doses: Week 1, Day 1, 1500 mg IV; Day 2, 340 mg SC. Weeks 2, 3, & 4, 340 mg SC QW. Maintenance dosing: Week 5 and Q4W thereafter, 1020 mg SC. Eculizumab: patients continued on approved maintenance IV dose starting on Week 1, Day 1, and continued Q2W thereafter. The duration of the primary treatment period was 24 weeks. After 24 weeks of crovalimab treatment, patients in Arms A and C who derived benefit from the drug could continue to receive crovalimab in the extension period. After at least 24 weeks of study eculizumab treatment, patients in Arm B had the option to switch to crovalimab in the extension period.	Primary analysis CCOD: 16 Nov 2022 Primary treatment period and crovalimab extension period ongoing for all Arms
		(1) pediatric patients currently treated with eculizumab (< 18 years, ≥ 40 kg body weight)	1	1	1		
		(2) patients currently treated with ravulizumab	21	21	21		
		(3) patients currently treated with eculizumab at higher-than-approved dose	10	10	10		
		(4) patients with known C5 polymorphism	6	6	6		

Study Number	Study Design	Population	No. of Patients Evaluable for PK	No. of Patients Evaluable for PD	No. of Patients Evaluable for Immunogenicity	Dose, Route, and Regimen	Clinical Cutoff Date / Study Status
YO42311 (COMMODORE 3) (supportive study)	Phase III, China-only, multicenter, single arm study of crovalimab in patients with PNH not previously treated with complement inhibitors	Adult and adolescent patients with PNH not previously treated with complement inhibitors (≥ 12 years of age, ≥ 40 kg body weight)	51	51	51	Crovalimab: Body weight ≥ 40 to < 100 kg: Loading doses: Week 1, Day 1, 1000 mg IV; Day 2, 340 mg SC. Weeks 2, 3, & 4, 340 mg SC QW. Maintenance dosing: Week 5 and Q4W thereafter, 680 mg SC. Body weight ≥ 100 kg: Loading doses: Week 1, Day 1, 1500 mg IV; Day 2, 340 mg SC. Weeks 2, 3, & 4, 340 mg SC QW. Maintenance dosing: Week 5 and Q4W thereafter, 1020 mg SC. The duration of the primary treatment period was 24 weeks. Patients could then continue crovalimab treatment at the same dose received during the initial 24 weeks.	Primary analysis CCOD: 10 Feb 2022 Primary treatment period completed
	Crovalimab continuation period	Patients who completed the primary treatment period, who derived benefit from crovalimab treatment and enrolled into the crovalimab extension period	50[f]	50[f]	50[f]	Patients stayed on previously assigned treatment schedule. Patients either received 680 mg SC Q4W (body weight ≥ 40 kg to < 100 kg) or 1020 mg SC Q4W (body weight ≥ 100 kg).	Update analysis CCOD: 10 Aug 2022 Crovalimab continuation period ongoing

2.6.2.1. Pharmacokinetics

Methods

Several bioanalytical methods were developed to quantify crovalimab, crovalimab antidrug antibody (ADA), neutralising antibody (NAb), DTDC complex and potential biomarkers as CH50, total and free C5 in human serum samples collected in studies BP39144, YO42311, BO42161 and BO42162.

Absorption

Following SC administration of crovalimab, the typical value of the absorption rate constant (Ka) was estimated to be 0.126 day^{-1} (CV%: 38.3%).

Across Phase 3 trials using the recommended dosing schema, based on the Pop-PK model, the median Tmax,ss at steady state is expected to occur at 8.27 days (range: 5.29−11.5 days) post SC administration. In the pivotal Phase 3 study BO42162, the steady state means Cmax,ss, Ctrough,ss and AUCtau,ss were 303 µg/mL, 241 µg/mL, and 7810 µg/mL.days, respectively in treatment-naïve patients; and were 295 µg/mL, 229 µg/mL, and 7510 µg/mL.days, respectively in switch patients with PNH.

Bioavailability

Based on the Pop-PK analysis, SC bioavailability was estimated at 83% (CV%: 116%)

Distribution

No estimation of Vd/F is provided based on NCA.

Based on the Pop-PK analysis, the estimated typical central volume (V2) and peripheral volume of distribution (V3) were 3.23 L and 2.32 L, respectively, indicating a total Vd between 5 -6 L (equivalent to the plasma volume). The typical V2 and V3 increased with BW with an allometric exponent of 0.68.

Overall, distribution of crovalimab appears primarily confined in the vascular system, which is consistent with reported Vd for other mAbs.

Elimination

Elimination pathways and metabolism of crovalimab were not specifically studied. In the same manner as endogenous IgG, crovalimab is expected to be catabolised by lysosomal proteolysis (degraded into small peptides and amino acids), and then eliminated via large-capacity nonspecific IgG elimination pathway or re-used by the body.

No estimation of CL/F and elimination half-life t1/2 based on NCA was performed.

Based on the Pop-PK analysis, the PKs of crovalimab was described by a two-compartment model with first order elimination. No specific target-mediated drug disposition (TMDD) pathway was identified. The typical clearance (CL) was estimated to be 0.0791 L/day (90% CI: 0.0678−0.0872 L/day) in a patient with body weight of 75 kg. CL was scaled by BW (fixed exponents of 0.75) and increased with increasing WT.

The typical elimination half-life (t1/2) was estimated to be 53.1 days (90% CI: 47.7−58.6 days). This t1/2 is longer compared to other humanised IgG antibodies but appears consistent with the FcRn recycling properties of crovalimab.

Dose proportionality and time dependency

No formal investigation / calculation for dose proportionality was provided.

Results from the Pop-PK analysis support dose proportionality and the linear PK of crovalimab did not suggest target-mediated drug disposition across the dose range investigated.

Following the SmPC recommended loading + maintenance dosage regimens, the steady state appears to be achieved by week 9 to 13; i.e. after the 2nd to the 3rd SC maintenance dose, without an observable time trend (**Figure 1** to **Figure 6**).

The systemic exposure to crovalimab at steady state is characterised based only on Ctrough levels. Across all studies, the observed Ctrough,ss remains above the threshold of 100 µg/mL in more than 90% of patients and were comparable between treatment-naïve and switch patients.

Inter-individual variability

Based on Pop-PK model estimates, inter-individual variability (CV%) was moderate in CL, V2 and ka (estimated to be 20.6%, 22.4 and 38.3%, respectively), while very high inter-individual variability was estimated for bioavailability F (CV = 116%).

Pharmacokinetic in target population

Pivotal PK information on crovalimab in patients was mainly performed through population PK modelling. Dense PK sampling was performed during the phase 1/2 study BP39144 (particularly in Parts 1 and 2, HVs were administered IV or SC doses in Part 1, and treatment-naïve patients were administered IV then SC doses in Part 2) and in subset of patients (n = 17) at steady state between week 21 and week 25 of phase 3 study YO42311 in Chinese treatment-naïve patients with PNH; whereas only sparse PK sampling (mainly pre-dose samples) was performed in the pivotal (BO42162) and supportive phase 3 studies in PNH patients.

Observed crovalimab concentrations profiles in the pivotal study BO42162 from baseline to Week 25 are displayed in linear scales for Arms A, C (treatment-naïve patients) and B (switch patients) in **Figure 1**, **Figure 2** and **Figure 3**, respectively.

The key secondary PK parameters derived from the Pop-PK analysis are summarised in **Table 3.**

Observed crovalimab concentrations profiles in study BO42161 (switch patients) from baseline to Week 25 are displayed in linear scales for Arms A, B, and C in **Figure 4**, **Figure 5** and **Figure 6**, respectively.

Table 4 presents the key secondary PK parameters derived from the Pop-PK analysis.

Observed crovalimab concentrations profiles in study YO42311 (n= 51 Chinese treatment-naive patients) from baseline to Week 49 are displayed in linear scales in **Figure 7**.

Table 5 and **Table 6** present the key PK parameters derived from NCA in a subset of patients at steady state and from the Pop-PK analysis, respectively.

Figure 1. Study BO42162, Arm A. mean Crovalimab serum concentrations and 95% CI (Linear Scale) by visit (PK-Evaluable Population)

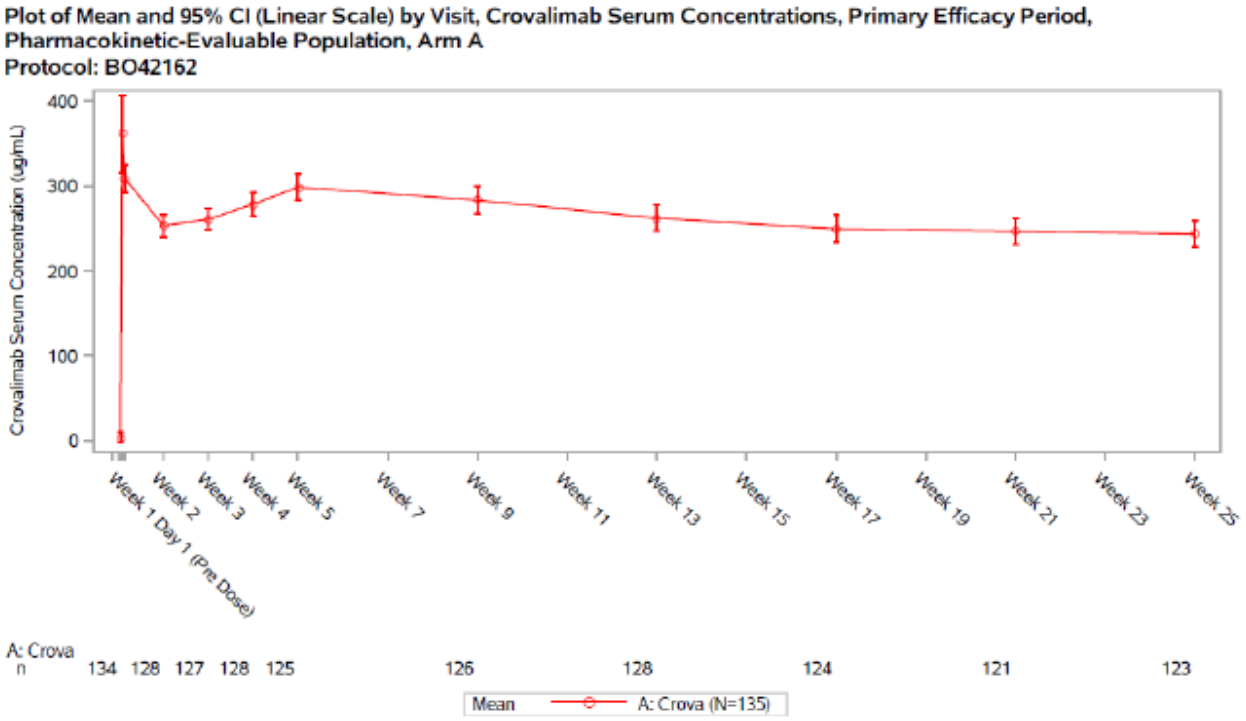


Figure 2: Study BO42162, Arm C. Individual Patient Profiles (Linear Scale) by Visit, Crovalimab Serum Concentrations.

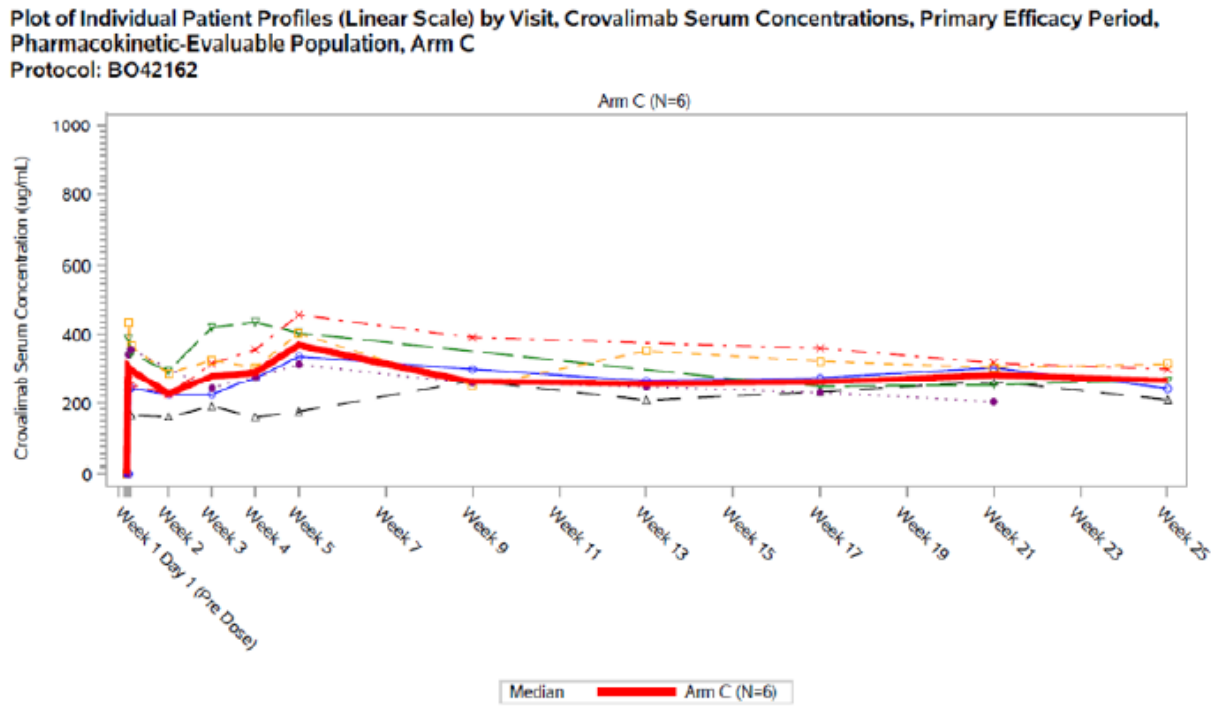


Figure 3: Study BO42162, Arm B. Mean Crovalimab serum concentrations and 95% CI (Linear Scale) by Visit (Switch Patients)

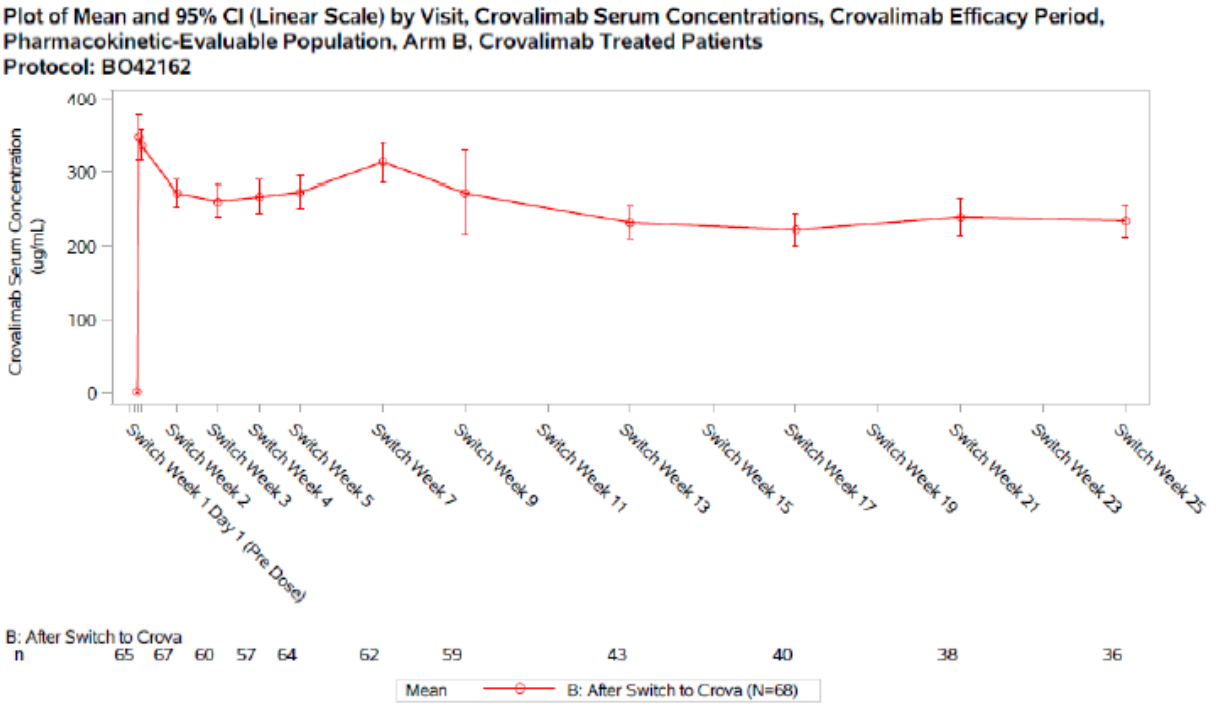


Table 3: Study BO42162. Summary statistics of secondary PK Parameters derived from the Population PK Model

Arm / Parameter	N	Mean	SD	Median	Minimum	Maximum
BO42162 Arm A						
C_{max} (µg/mL)	135	388	110	379	181	1050
$C_{max,ss}$ (µg/mL)	131	303	86.7	303	62.2	545
$t_{max,ss}$ (days)	131	8.14	0.857	8.20	5.29	11.2
$AUC_{\tau,ss}$ (µg/mL • days)	131	7810	2260	7830	1560	14400
$C_{trough,ss}$ (µg/mL)	131	241	72.7	239	44.0	465
$C_{av,ss}$ (µg/mL)	131	279	80.9	279	55.7	515
BO42162 Arm B post switch						
C_{max} (µg/mL)	68	387	80.7	373	218	608
$C_{max,ss}$ (µg/mL)	46	295	87.2	304	82.5	501
$t_{max,ss}$ (days)	46	8.11	0.780	8.09	7.00	9.66
$AUC_{\tau,ss}$ (µg/mL • days)	46	7510	2220	7770	2030	12700
$C_{trough,ss}$ (µg/mL)	46	229	68.7	238	56.9	381
$C_{av,ss}$ (µg/mL)	46	268	79.5	278	72.6	455
BO42162 Arm C						
C_{max} (µg/mL)	6	401	61.9	402	310	475
$C_{max,ss}$ (µg/mL)	6	357	55.1	353	293	439
$t_{max,ss}$ (days)	6	7.31	0.949	7.27	5.76	8.36
$AUC_{\tau,ss}$ (µg/mL • days)	6	8980	1380	8720	7220	11000
$C_{trough,ss}$ (µg/mL)	6	272	47.1	260	210	330
$C_{av,ss}$ (µg/mL)	6	321	49.2	312	258	391

Figure 4: Study BO42161, Arm A. Mean Crovalimab Serum Concentrations and 95% CI (Linear Scale) in switch patients with PNH by Visit

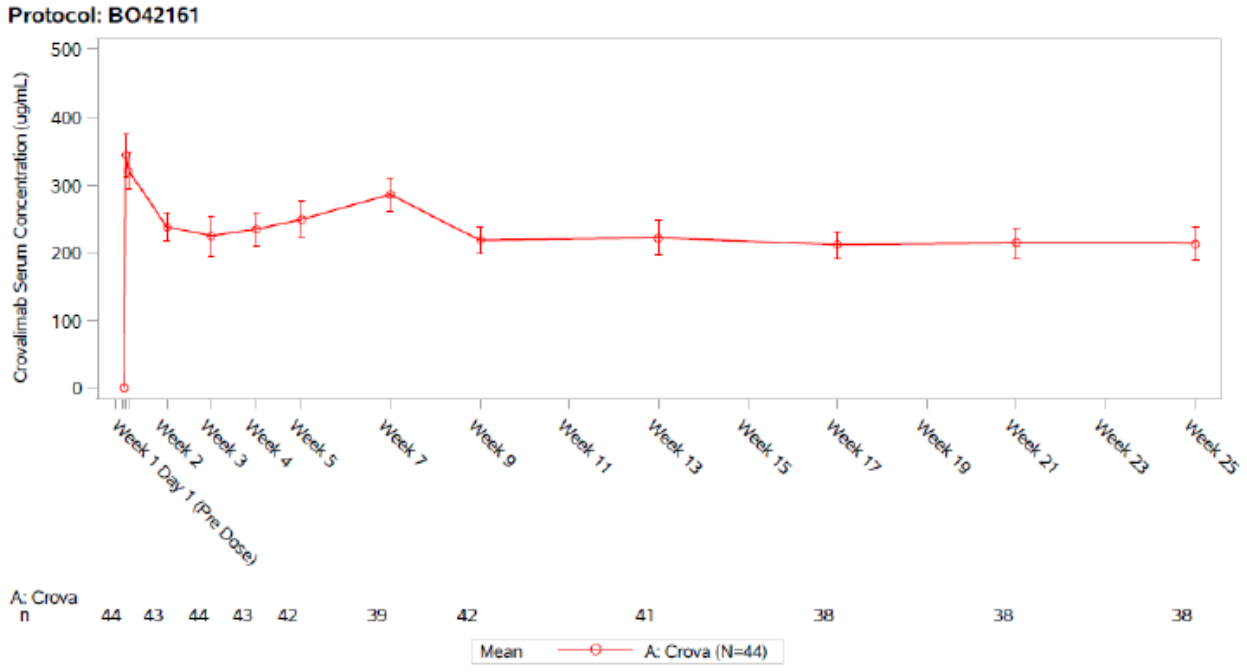


Figure 5: Study BO42161, Arm B (post-switch patients). Mean Crovalimab Serum Concentrations and 95% CI (Linear Scale) in switch patients with PNH by Visit (PK-Evaluable Population)

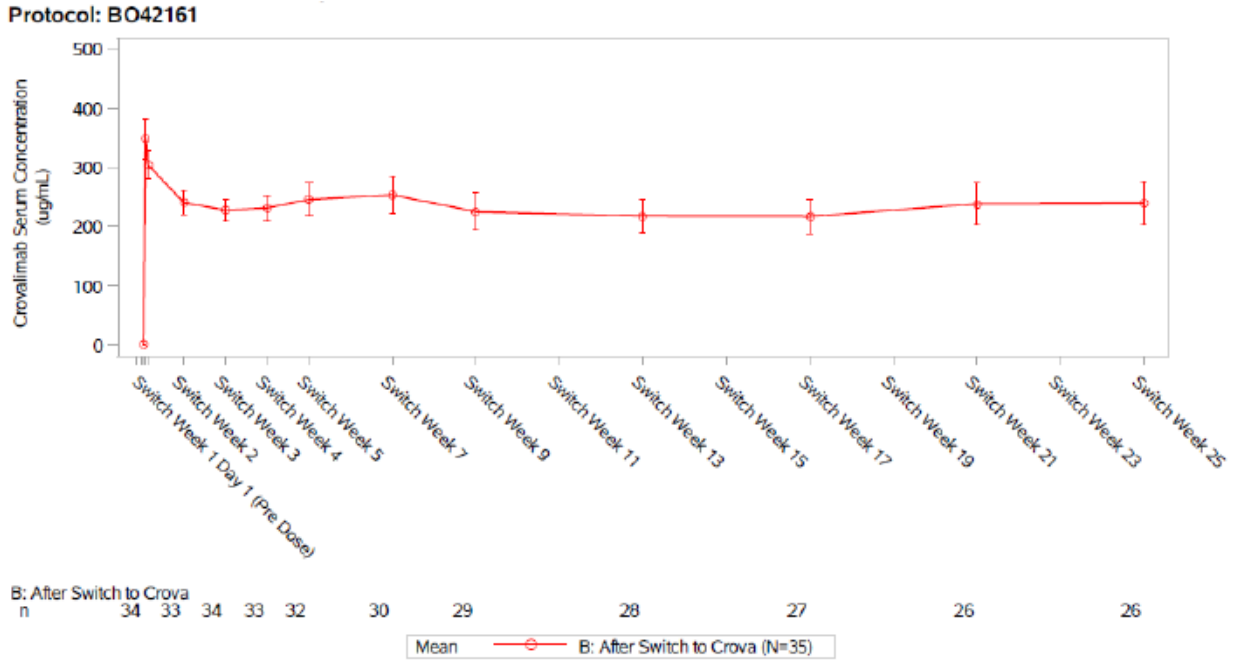


Figure 6: Study BO42162, Arm C. Individual Patient Profiles (Linear Scale) by Visit, Crovalimab Serum Concentrations.

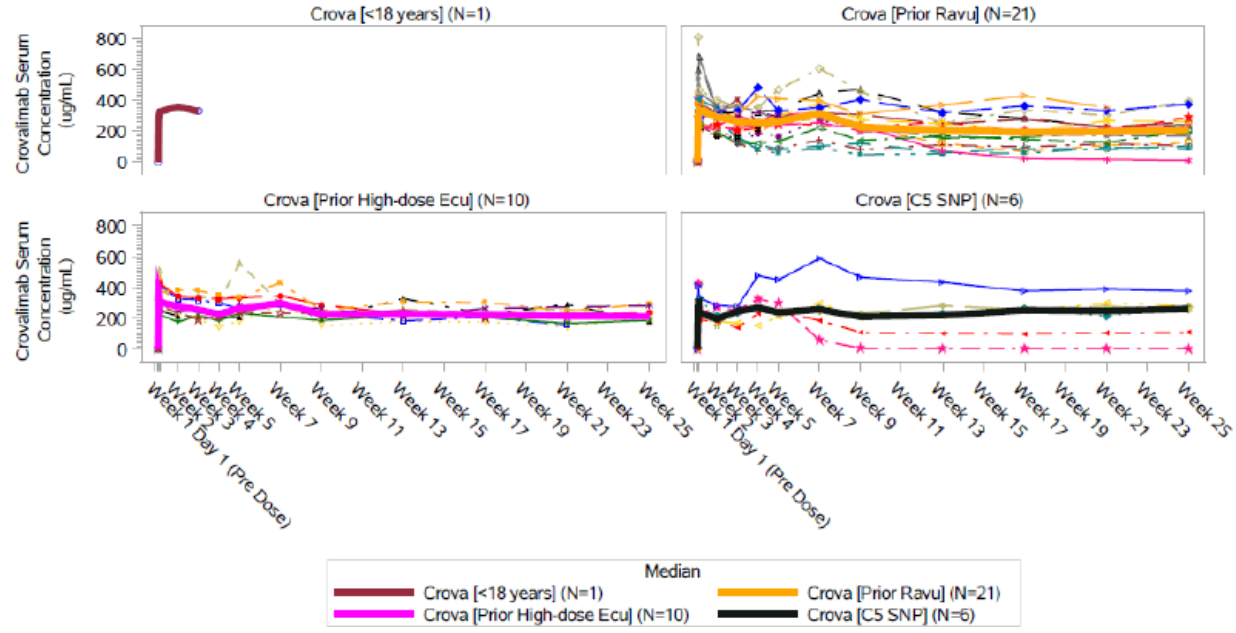


Table 4. Study BO42161. Summary statistics of secondary PK Parameters derived from the population PK model.

Arm / Parameter	N	Mean	SD	Median	Minimum	Maximum
BO42161 Arm A						
C_{max} (µg/mL)	44	359	92.8	346	190	590
$C_{max,ss}$ (µg/mL)	40	269	80.0	275	84.9	418
$t_{max,ss}$ (days)	40	8.63	0.877	8.68	7.00	11.5
$AUC_{\tau,ss}$ (µg/mL • days)	40	6910	2060	7130	2080	10700
$C_{trough,ss}$ (µg/mL)	40	213	65.5	218	58.2	345
$C_{av,ss}$ (µg/mL)	40	247	73.4	254	74.2	384
BO42161 Arm B post switch						
C_{max} (µg/mL)	35	353	63.8	365	226	501
$C_{max,ss}$ (µg/mL)	28	281	88.9	269	20.7	441
$t_{max,ss}$ (days)	28	8.74	0.842	8.74	7.00	10.7
$AUC_{\tau,ss}$ (µg/mL • days)	28	7280	2310	6970	498	11500
$C_{trough,ss}$ (µg/mL)	28	227	73.2	222	13.2	360
$C_{av,ss}$ (µg/mL)	28	260	82.6	249	17.8	411
BO42161 Arm C						
C_{max} (µg/mL)	38	377	104	348	242	657
$C_{max,ss}$ (µg/mL)	32	275	109	281	66.5	492
$t_{max,ss}$ (days)	32	8.42	0.790	8.47	6.54	9.87
$AUC_{\tau,ss}$ (µg/mL • days)	32	7030	2790	7450	1700	12900
$C_{trough,ss}$ (µg/mL)	32	214	87.7	216	50.6	412
$C_{av,ss}$ (µg/mL)	32	251	99.8	266	60.9	462

Figure 7: Mean Crovalimab Concentrations and 95% CI (linear scale from baseline to week 49 (PK Evaluable Population)

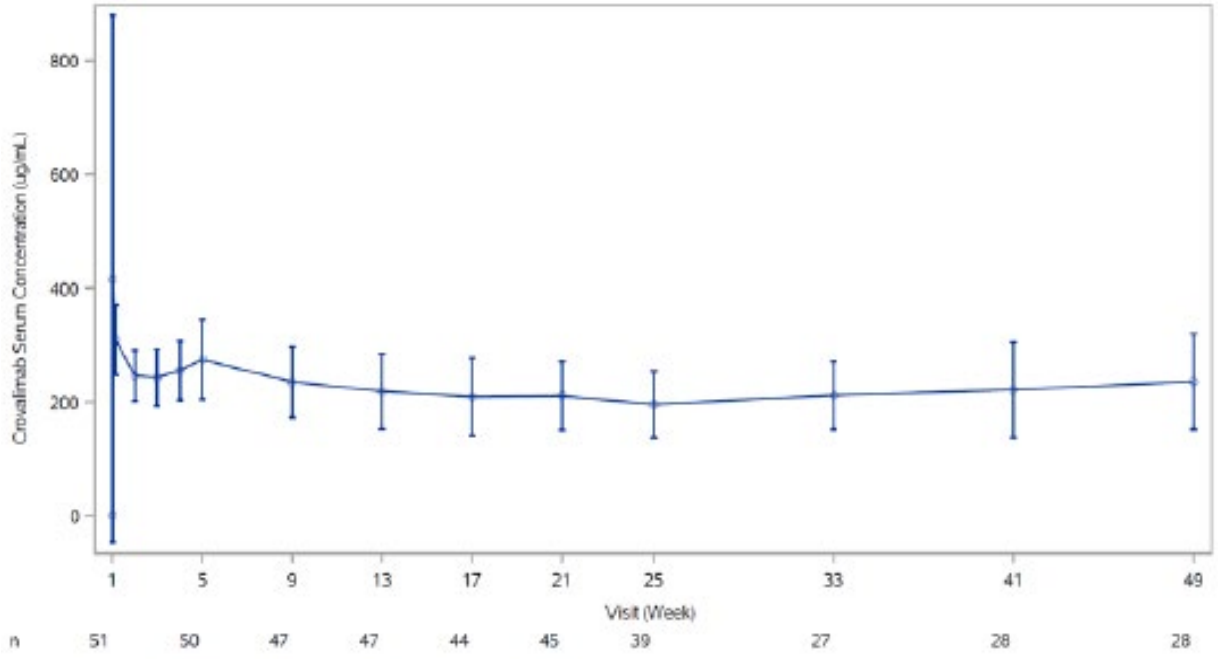


Table 5: Crovalimab PK Parameters from Week 21 to Week 25 (NCA PK Population)

	PK Parameter			
	Tmax (days)	Cmax (ug/mL)	AUCtau (day*ug/mL)	Ctrough (ug/mL)
n	17	17	17	17
Mean	4.65	267	6390	179
95% Lower CL for Mean	3.6	228	5440	152
95% Upper CL for Mean	5.7	306	7340	207
SD	2.03	76.0	1840	53.3
CV % Mean	43.7	28.4	28.8	29.7
Geometric Mean	4.25	257	6140	172
CV % Geometric Mean	45.0	29.8	29.9	30.0
Median	3.00	270	6390	182
Interquartile Range	NE	116	2480	84.0
Minimum	3.00	161	3870	113
Maximum	7.00	412	9750	292

Parameters were derived using profiles from Weeks 21 to 25.

Table 6: Summary Statistics of Secondary PK Parameters Derived from the Population PK Model for Study YO42311

Study / Parameter	N	Mean	SD	Median	Minimum	Maximum
YO42311						
C_{max} (µg/mL)	51	355	63.8	353	228	507
$C_{max,ss}$ (µg/mL)	51	279	79.5	280	81.5	449
$t_{max,ss}$ (days)	51	7.78	0.811	7.76	5.71	9.13
$AUC_{\tau,ss}$ (µg/mL • days)	51	7070	2070	7120	2040	11300
$C_{trough,ss}$ (µg/mL)	51	214	66.4	213	55.2	340
$C_{av,ss}$ (µg/mL)	51	253	73.9	254	72.9	405

Population PK analysis

A population PK model was developed to investigate the PKs of crovalimab following IV and SC dosing. crovalimab serum concentration data collected from phase 1/2 study BP39144 (HVs and patients with PNH), pivotal phase 3 study BO42162 (treatment-naïve patients), and two supportive phase 3 studies YO42311 (Asian treatment-naïve patients) and BO42161 (switch patients) were pooled and analysed using a non-linear mixed effects model. The CCOD were 01 Nov 2021 for Study BP39144, 10 Aug 2022 for Study YO42311, and 16 Nov 2022 for studies BO42162 and BO42161.

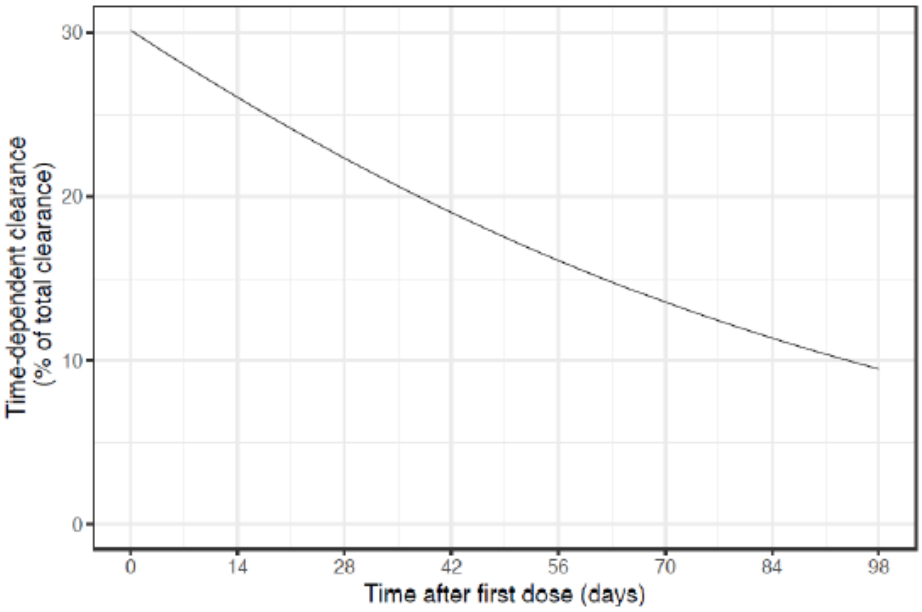
Across studies, the investigated age range was 13−85 years, and the investigated body weight (BW) range was 40.6−140 kg. A wide range of doses, from 75 mg to 1500 mg, was investigated following IV or SC administration. For note, the recommended dosing regimen using a BW-tiered dosing approach was assessed in all phase 3 studies. The final PK dataset consists of 9 HVs, 210 treatment-naïve, and 211 patients switching from other treatments, with a total of 6115 crovalimab concentrations.
The observed concentration-time data Crovalimab PK were adequately described by a 2-compartment mammillary model with first order elimination and a first-order absorption. The model was parameterised in terms of a linear time-independent clearance (CL), an additional time-varying clearance (CLs) only for switch patients, which decreases exponentially with time (with Kd being the exponential decay constant), volume of distribution of the central compartment (V2), inter-compartmental clearance (Q), volume of distribution of the peripheral compartment (V3), first-order absorption rate constant (Ka), and SC bioavailability (F). Standard allometric scaling of BW were applied and included a priori in the structural model, with exponents fixed to 0.75 on clearances and

estimated to 0.684 for volumes. For note, the additional CLs was added for switch patients to describe the transient increase in clearance due to the formation of drug-target-drug complexes (DTDCs).

Selection of covariates (considered only on parameters that were associated with an IIV term) was performed using the stepwise SCM forward step with the statistical selection criterion $p < 0.01$. The identified significant covariate-parameter relationships were baseline AST on CL and baseline total C5 and sex on V2. However the clinical relevance of these covariates was investigated based on Ctrough,ss using Forest plots and were not retained in the final model.

After the covariate selection procedure, in addition to BW effects on clearances and volumes, the covariate effects retained in the final model were the effect of medium/high titres of ADA ($\geq 10^4$) on CL and the effect of age on ka. The equations for the final covariate relationships are given in **Figure 8**.

Figure 8: Visualisation of contribution of time-dependent clearance in switch patients to the overall clearance after the first crovalimab dose.



The contribution of time-dependent CLs in switch patients to the overall clearance (sum of linear and time-dependent clearance), up to 14 weeks after the first crovalimab dose is shown in **Figure 8**. Basic Goodness-of-fit plots are presented in observed versus predicted concentrations for the final crovalimab PK model, coloured by study population. Data are presented on linear scale (left) and linear-log scale (right) (**Figure 9)**.

VPC graphs are presented for time after first dose up to week 14 (**Figure 10**) and post week 14 stratified by PNH naïve and PNH switch patients (**Figure 11**).

Figure 9: Equations for the final covariate model

$$\text{CL (L/day)} = 0.0791\ \text{(L/day)} \cdot \left(\frac{\text{WT}}{75\ \text{(kg)}}\right)^{0.75} \quad \text{if no or low titer ADA}$$

$$\text{CL (L/day)} = 0.0791\ \text{(L/day)} \cdot \left(\frac{\text{WT}}{75\ \text{(kg)}}\right)^{0.75} \cdot (1 + 0.247352) \quad \text{if medium or high titer ADA}$$

$$\text{CL}_s\ \text{(L/day)} = 0.0341\ \text{(L/day)} \cdot \left(\frac{\text{WT}}{75\ \text{(kg)}}\right)^{0.75}$$

$$\text{V}_2\ \text{(L)} = 3.23\ \text{(L)} \cdot \left(\frac{\text{WT}}{75\ \text{(kg)}}\right)^{0.683824}$$

$$\text{k}_a\ \text{(1/days)} = 0.126\ \text{(1/days)} \cdot \left(\frac{\text{age}}{36\ \text{(years)}}\right)^{-0.459}$$

$$\text{V}_3\ \text{(L)} = 2.32\ \text{(L)} \cdot \left(\frac{\text{WT}}{75\ \text{(kg)}}\right)^{0.683824}$$

$$\text{Q (L/day)} = 0.168\ \text{(L/day)} \cdot \left(\frac{\text{WT}}{75\ \text{(kg)}}\right)^{0.75}$$

Figure 10: Visualisation of contribution of time-dependent clearance in switch patients to the overall clearance after the first crovalimab dose.

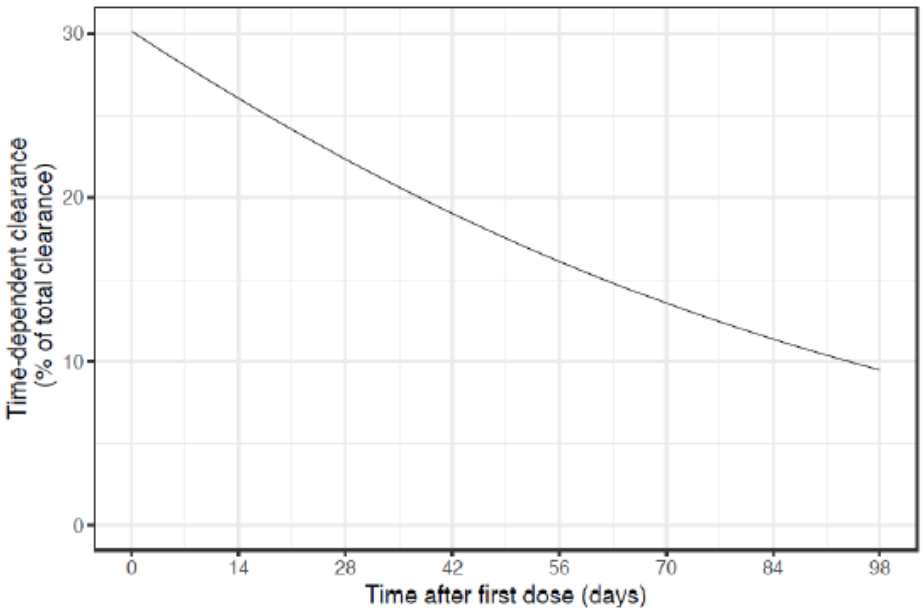


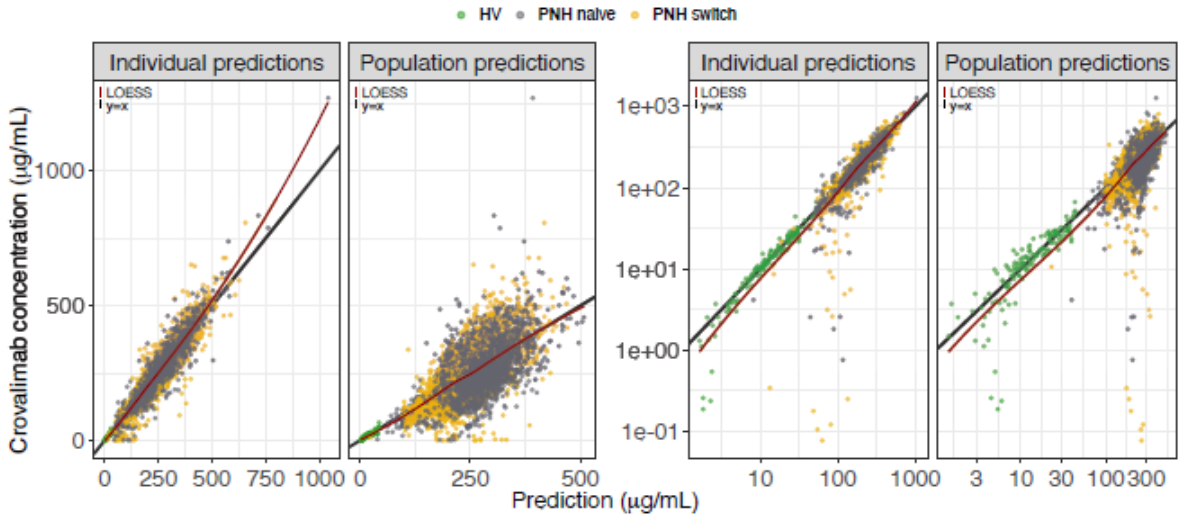
Table 7: Parameter estimates for the final crovalimab population PK model

	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

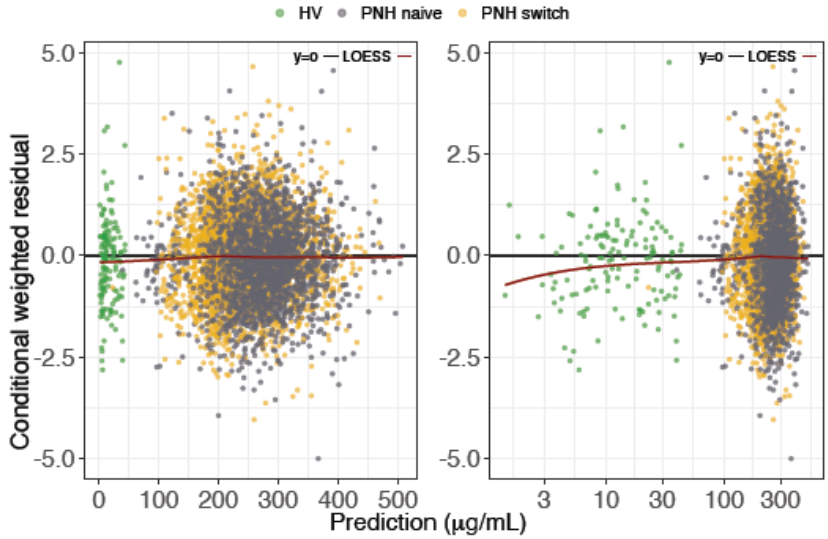
The RSE for IIV and RUV parameters are reported on the approximate SD scale. ε-shrinkage reported in row of proportional RUV. CI computed from a non-parametric bootstrap with 500 samples.

Observed versus predicted concentrations for the final crovalimab PK model, coloured by study population. Data are presented on linear scale (left) and linear-log scale (right).

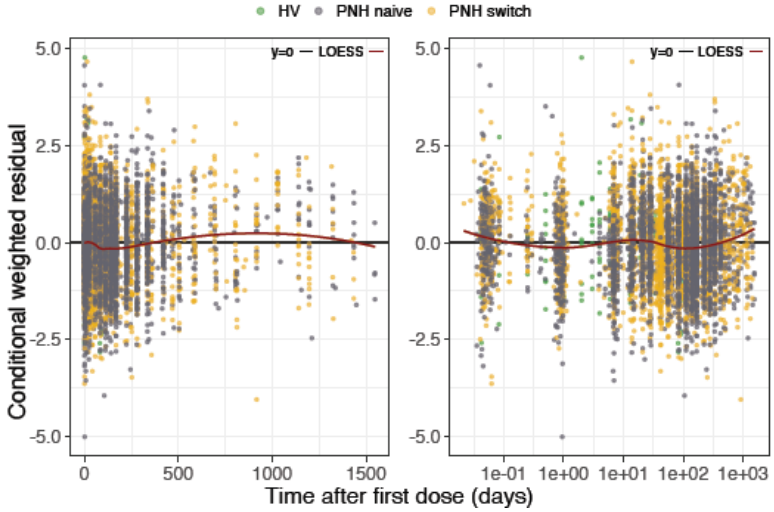
Figure 11: Basic Goodness-of-fit Plots for final Pop-PK model



Conditional weighted residual (CWRES) versus Prediction (PRED) for the final crovalimab PK model, coloured by study population.



CWRES versus time since first dose for the final crovalimab PK model, coloured by study population. Data are presented on linear scale (left) and linear-log scale (right).



QQ plot of CWRES for the final crovalimab PK model, coloured by study population.

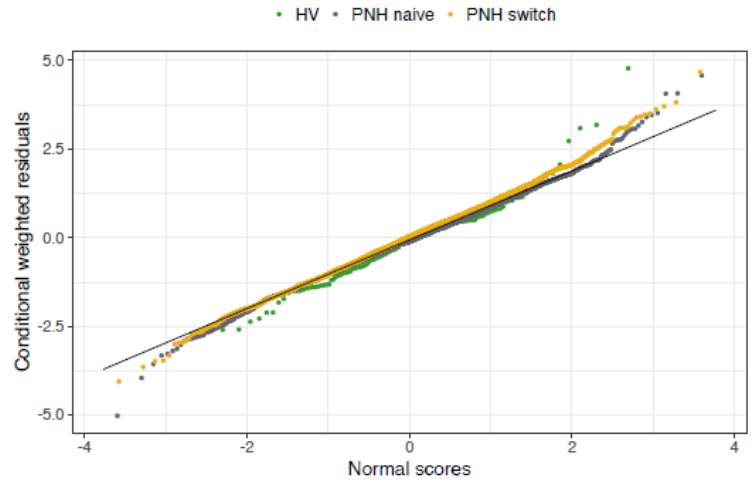
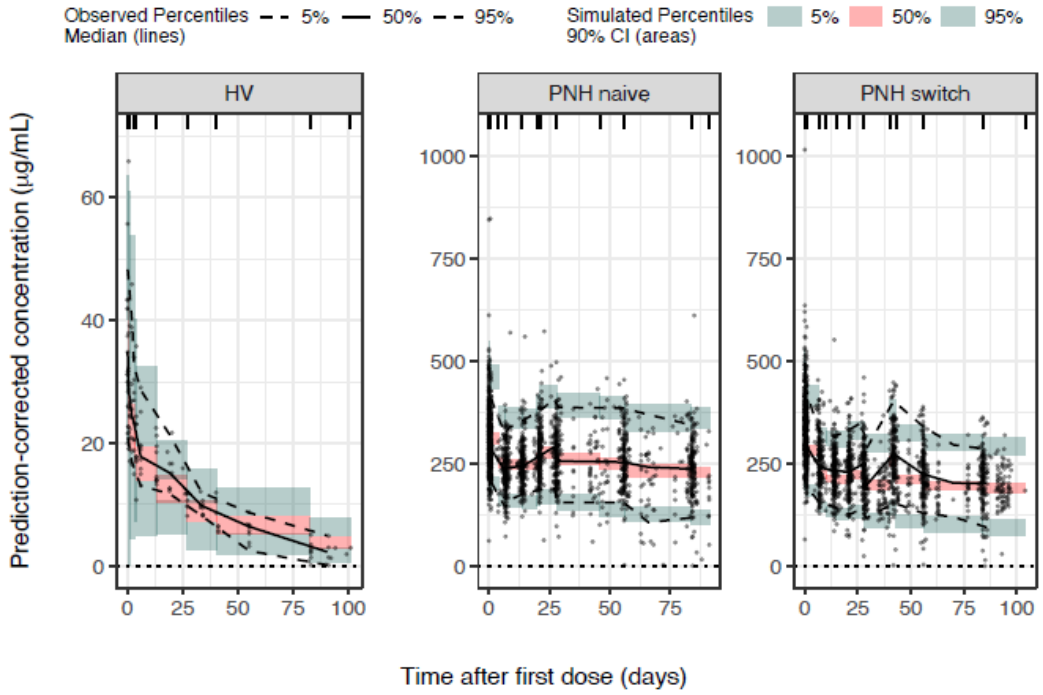
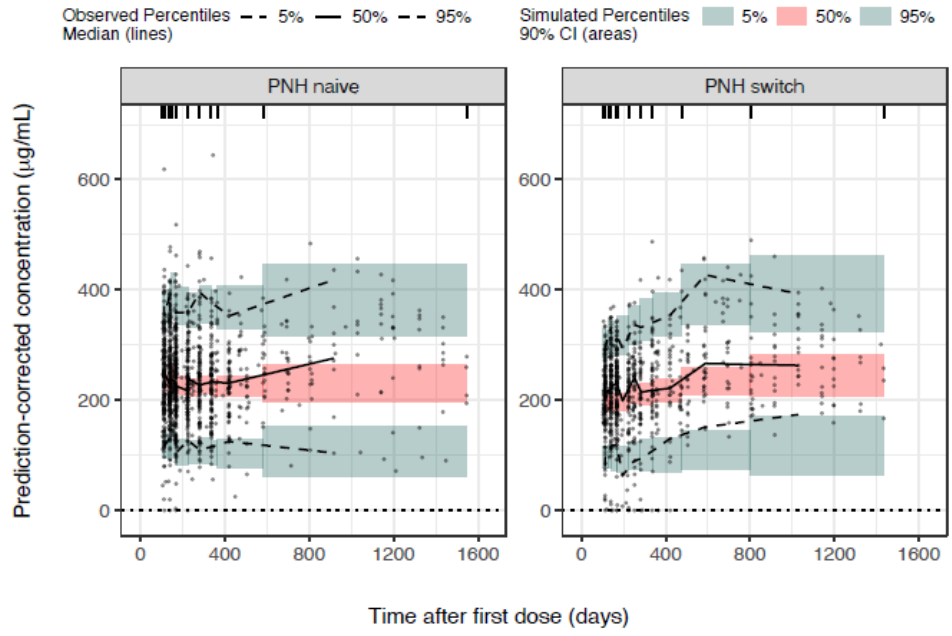


Figure 12: Prediction-corrected VPC of crovalimab PK concentrations versus time after first dose (up to week 14) using the final crovalimab PK model stratified by HVs, PNH naïve and PNH switch patients.



The panels represent the first-time interval starting with the first crovalimab administration and up to a scheduled time of 14 weeks. HVs had no observations scheduled after 14 weeks. The dashed horizontal line represents the LLOQ. The rugs on the x-scale represent the binning.

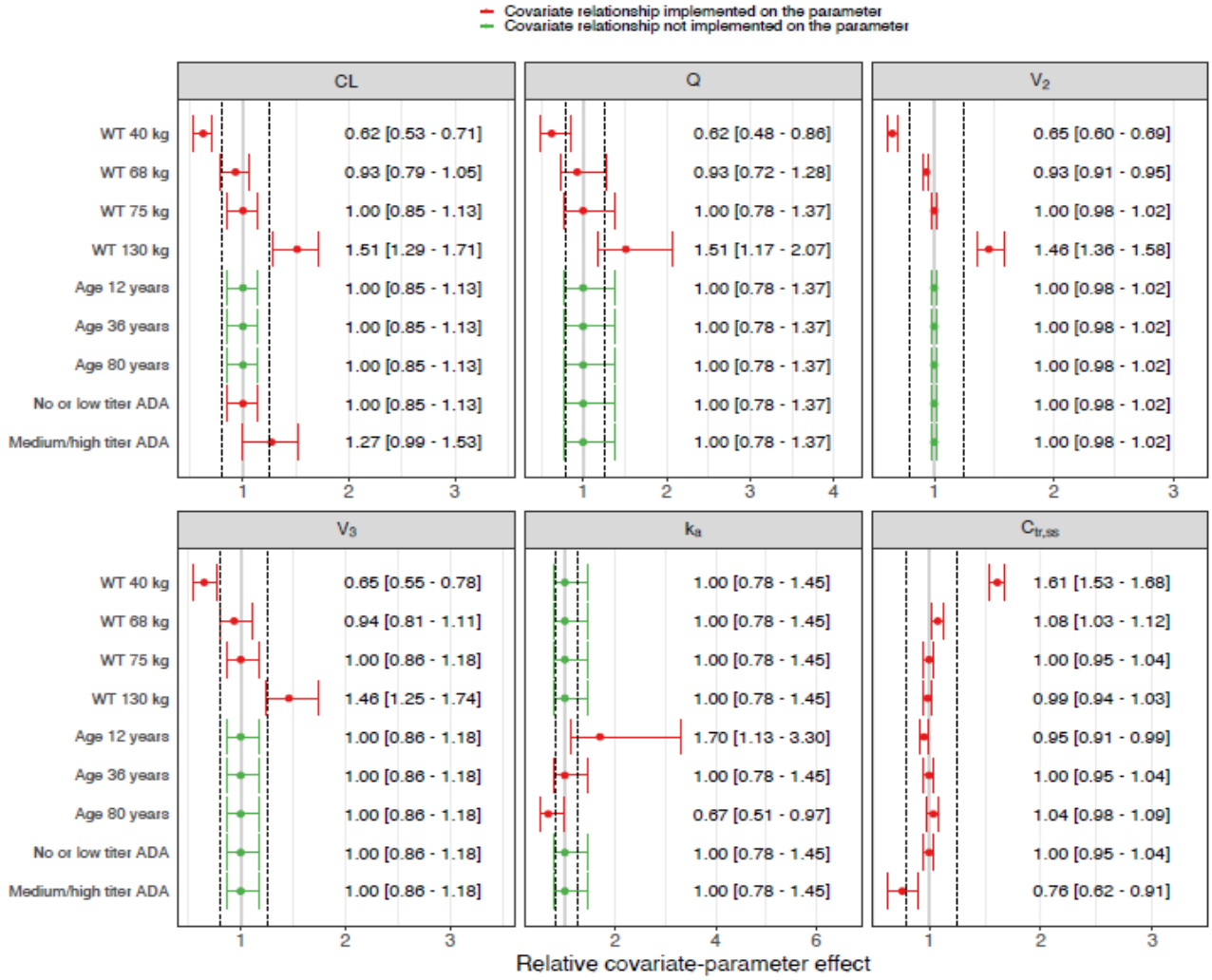
Figure 13: Prediction-corrected VPC of crovalimab PK concentrations versus time after first dose (post week 14) using the final crovalimab PK model stratified by PNH naïve and PNH switch patients.



The impact of covariates on typical PK parameters (CL, V2, V3, ka, Q, and $C_{trough,ss}$) in the final model is summarised in forest plots (**Figure 14**). The forest plots visualise the effect of extreme values of WT

(40 and 130 kg), age (12 and 80 years), and ADA (medium/high titres) compared to the reference subject (75 kg, 36 years, with no ADA or low ADA titres). The reference WT of 75 kg and age of 36 years were taken from the legacy model. To evaluate the impact of a typical WT of the current analysis population the forest plots also show the impact of the median WT (68 kg).

Figure 14: Forest plots illustrating the effects of covariates on crovalimab PK parameters CL, Q, V2, V3, ka, and Ctrough,ss, conditioned on a reference subject, based on the final crovalimab PK model



Special Populations

Renal impairment

The effect of renal impairment as defined using creatinine clearance (CLCR) calculated by the Cockroft-Gault formula (normal [n=326, 75.8%], mild [n=62, 14.4%], moderate [n=38, 8.8%], and severe [n=4, 0.93%]) was evaluated in Pop-PK analysis and was not identified as a significant covariate on crovalimab systemic exposure.

Hepatic impairment

The effect of hepatic impairment as defined using baseline alanine aminotransferase (ALT) levels (normal [n=375, 88.8%], mild [n=46, 11%], moderate [n=0], and severe [n=1]) was evaluated in the Pop-PK analysis. Hepatic impairment (mild) was not identified as a significant covariate on crovalimab systemic exposure.

Gender

The effect of sex on the PKs of crovalimab was evaluated in Pop-PK analysis. Approximately, 55% and 52% of the treatment-naïve patients (n= 115 of 210) and switch patients (n= 109 of 211) included in the dataset were male. The covariate analyses showed that sex had no significant effect on PK parameters of crovalimab.

Race

A formal and dedicated phase 3 Study YO42311 was performed to evaluate the efficacy, safety and PKPD of crovalimab in Chinese treatment-naïve patients with PNH. Race /ethnicity effect on the PKs of crovalimab was also investigated using the Pop-PK approach.

Study YO42311

In Chinese patients (n=51), following administration of the recommended dosing schema, mean crovalimab concentrations reached a plateau around week 9 and remained stable up to Week 49. In a subset of patients (n=17) who had intensive PK sampling at steady state conditions (between Week 21 and Week 25), NCA showed a tmax between 3 to 7 days and means of Cmax, Ctrough and AUCtau were 267 µg/mL, 179 µg/mL and 6390 µg/mL.day, respectively. These results appears comparable (within the range of 20%) to the secondary parameters predicted based on the Pop-PK model: mean Ctrough,ss and AUCtau,ss of 214 µg/mL and 7070 µg/mL.day, respectively; and also similar to those from the pivotal study BO42162 (that included both Asian and non-Asian treatment-naïve patients) with mean Ctrough,ss and AUCtau,ss of 241 µg/mL and 7810 µg/mL, respectively. Overall, no significant shift on the PK characteristics is noted in the Chinese population.

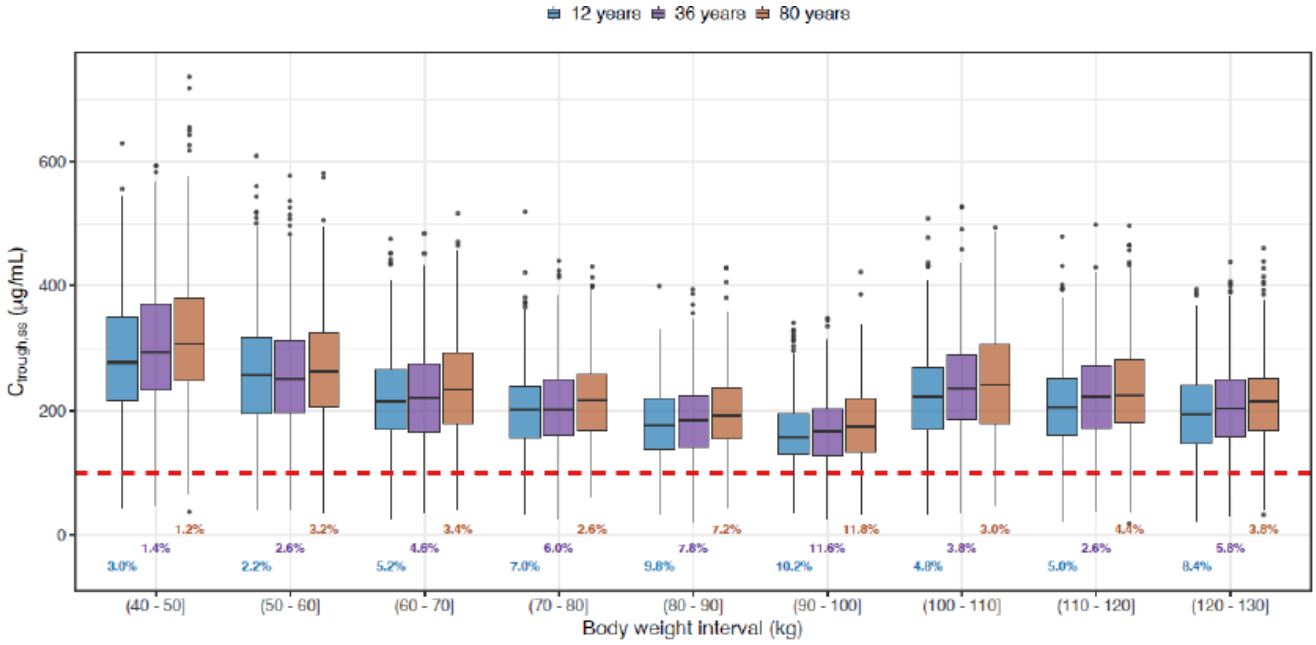
Pop-PK model

In the Pop-PK analysis, race or ethnicity was not identified to significantly influence the PKs of crovalimab. The majority of patients included in the analysis dataset were Asian: 242 of 421 (57.4%) then Caucasian n= 156 (37%). There were n= 149 Asian (71%) and 55 Caucasian (26%) of the 210 treatment-naïve patients; n= 93 Asian (44%) and 101 Caucasian (48%) of the 211 switch patients. Very few black (n= 7, 1.7%) were included patients and others or unknown race (n= 16) represented 3.8%.

Weight

In the Pop-PK analysis, BW effect was included as allometric scaling component on the total clearance of crovalimab (both the linear and time-varying terms) and on volumes of distribution parameters with fixed and estimated exponents of 0.75 and 0.684, respectively. Pop-PK model-based simulations showed that the proposed dosing regimen ensured the maintenance of $C_{trough,ss}$ above the target of 100 µg/mL across the BW continuum in approximately 90% of patients (**Figure 15**).

Figure 15: Distribution of Simulated Ctrough,ss Across Body Weight and Age for a PNH Patient Population with the Recommended Dosing Regimen



Predicted Ctrough,ss were 353 ng/mL and 219 ng/mL in a typical patient with 75 kg (the reference weight) and in a patient with low BW of [40-50 kg]. Thus, a significant increase on the systemic exposure to crovalimab, in average of 61%, is expected in patients with lower BW relative to reference BW. However, no exposure-safety relationships were identified in this specific subgroup of BW this overexposure appears not to be of a clinical concern. Regarding patients with high BW ≥ 100 kg, the BW effect is taken into account by use of higher IV and maintenance SC doses (1020 mg versus 680 mg for 40 to < 100 kg). As such 94.2% of patients weighing 120−130 kg are expected to have Ctrough,ss above 100 µg/mL. Overall, this supports the appropriateness of the proposed BW-based two-tiered dosing regimen.

Elderly/age

No formal investigations with regards to age/elderly have been performed.
The effect of age on crovalimab PK was assessed in the Pop-PK analysis. In the population dataset, the medians (min-max) of age were 35.5 years (13-76 y) in treatment-naïve PNH patients and 44 years (16-85 y) in switch patients. The majority of patients were adults between aged [18 - 64] years. There were n= 181 (86%) in treatment-naïve PNH patients and n= 184 (88%) in switch patients. Only n= 44 elderly patients ≥ 65 years were available (17 treatment-naïve patients and 27 switch patients).
Age was found to have a statistically significant effect on ka, with ka decreasing with age. In comparison to the reference value of 0.126 day^{-1} in an adult patient, ka was estimated at 0.0875 and 0.209 day^{-1} in elderly and adolescent patients, respectively. This effect does not appear to result in a significant impact on the systemic exposure to crovalimab. Indeed, no significant difference in PK profiles was observed when comparing elderly and adult [18-64 years] patients. In addition, Pop-PK model-based predictions indicate similar Ctrough,ss in elderly and adult patients.

Children

No formal dedicated studies in children have been performed.

Across studies, a limited number n= 11 of adolescent patients with PNH (> 12 to < 18 years) were enrolled (9 treatment-naïve patients and 2 switch patients).

No relevant difference in the PK profiles was observed between adolescent and adult patients aged [18-64 years] and no clinically significant impact on achievement of target Ctrough,ss concentrations is expected based on the Pop-PK model. Nevertheless, as age and BW are correlated, younger patients are expected to have lower BW and therefore may experience higher drug exposure in the BW range of [40-50 kg].

Exposure-response analysis

PK/PD relationship and ER-efficacy analysis were only graphically explored and clearly show that reaching and maintaining a crovalimab concentration of 100 µg/mL is associated to a sustained decrease of CH50 (< 30 U/mL), Free C5 (< 0.0001 g/L) and LDH.

ER safety analysis investigated using logistic regression analysis with predicted PK metrics from the PPK model, identified only a decrease of infections occurrence with increased Cmaxss and AUCs,ss, and an increase of TH3 occurrence with DTDC % levels.

The C-Qtc analysis revealed a statistically significant decrease in ΔQTcF with increasing crovalimab concentrations. However, the effect was very small (ΔQTcF of − 5.42 ms at crovalimab concentration of 600 µg/mL) in relation to the overall variability, and not in the direction of a clinical concern.

2.6.2.2. Pharmacodynamics

Mechanism of action

Crovalimab is a novel humanised anti-complement component 5 (C5) monoclonal antibody of the immunoglobulin G1 (IgG1) subtype. It binds specifically and with high affinity to C5 and blocks its cleavage into subunits C5a and C5b, thus preventing the formation of the membrane attack complex (MAC), membrane disruption, and consequently cell lysis. Crovalimab is engineered with pH-dependent antigen binding and enhancement of neonatal Fc receptor (FcRn) binding to improve antigen disposal and antibody recycling efficiency. This results in prolonged functional half-life and reduced free target accumulation (C5).

As crovalimab was developed to enable rapid and sustained terminal complement activity inhibition, terminal complement activity inhibition (CH50 assessed with an *ex-vivo* liposome immunoassay [LIA], hereinafter referred to as CH50) and free C5 concentration were chosen as PD biomarkers in all studies.

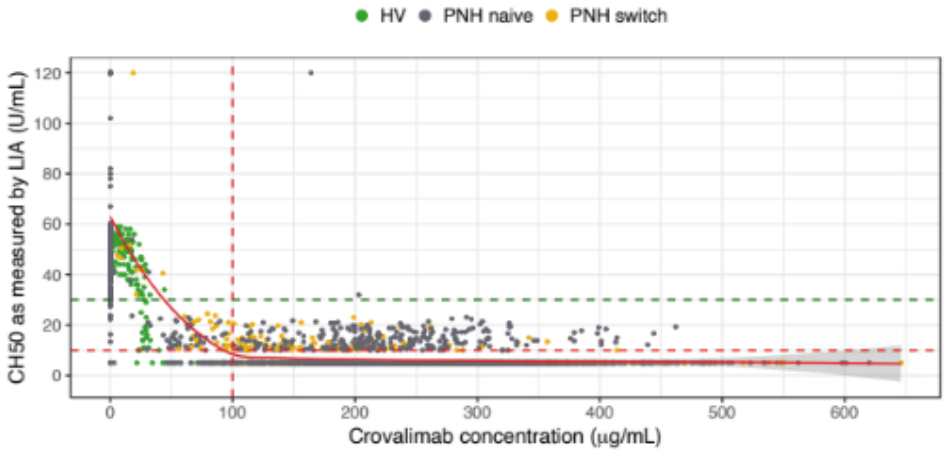
Primary and Secondary pharmacology

Primary pharmacology

The relationship between crovalimab observed concentrations and PD markers of terminal complement activity (CH50 and free C5) were graphically explored in HVs, treatment-naïve, and switch patients with PNH.

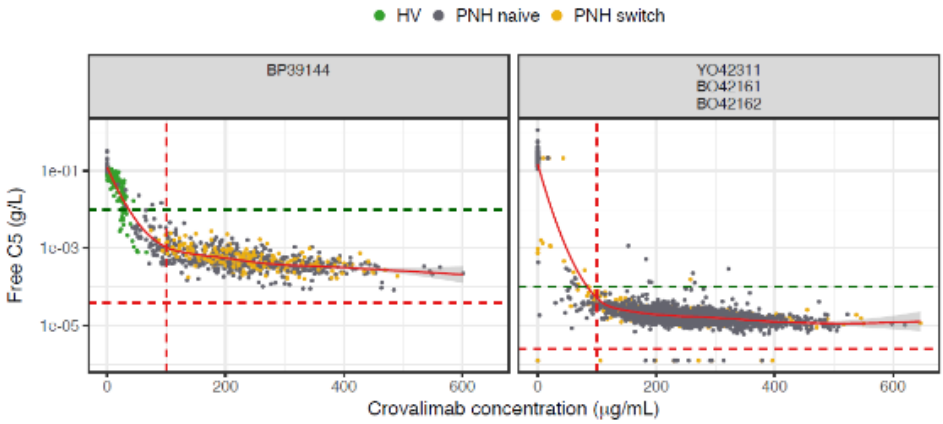
Complement activity (LIA)

Figure 16: Scatter Plot of Individual Observed CH50 Versus Time-Matched Observed Crovalimab Concentrations



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.
The red curve is a LOESS regression together with the 90% CI as shaded area. The red dashed horizontal line shows the LLOQ. The green dashed horizontal line represents the threshold for complete inhibition of terminal complement activity. The red dashed vertical line shows the crovalimab concentration threshold expected to lead to complete complement C5 inhibition. The first 12 weeks are excluded in switch patients.
Source: Report 1119749, Figure 14.

Figure 17: Scatter Plot of Individual Observed Free C5 Versus Time-Matched



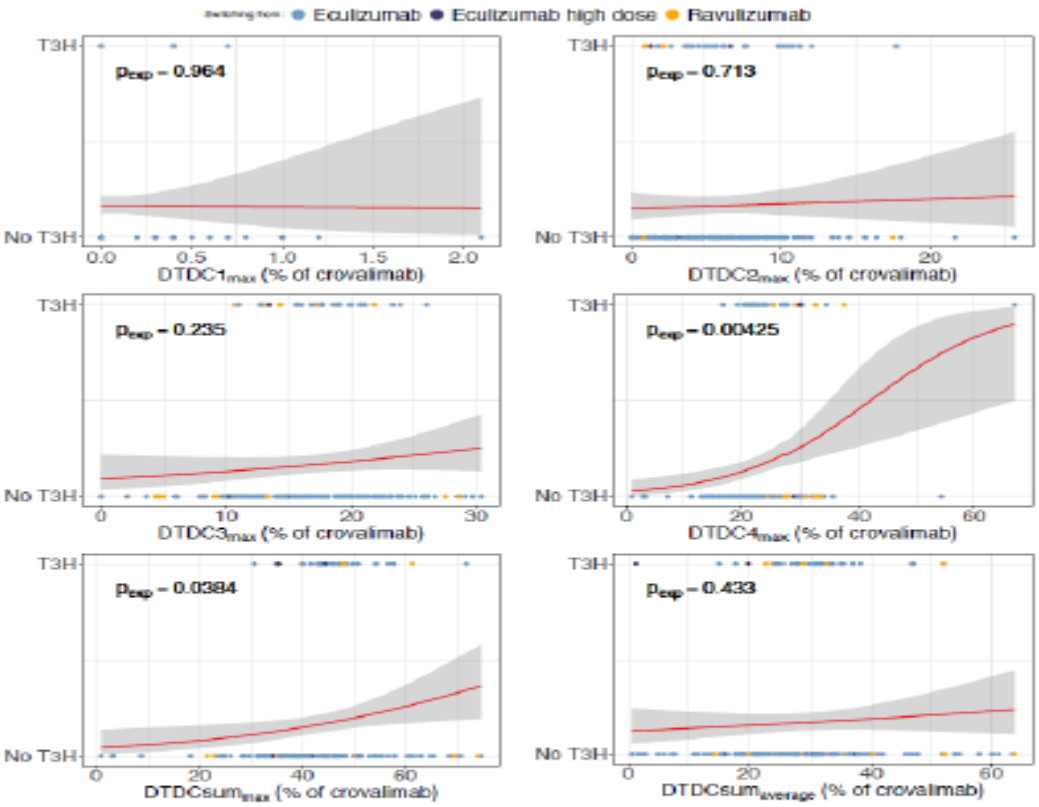
C5 = complement component 5; CI = confidence interval; HV = healthy volunteer; LLOQ = lower limit of quantification; LOESS = locally estimated scatterplot smoothing; PNH = paroxysmal nocturnal hemoglobinuria.
Different free C5 assays were used in Study BP39144 and the Phase III studies, therefore C5 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 patients.
Source: Report 1119749, Figure 20.

Secondary pharmacology

No dedicated thorough QT study was conducted.

DTDCs may have an impact on safety as they can trigger T3H reactions. Type III hypersensitivity reactions are immune complex-mediated reactions, due to the deposition in tissues of immune complex (small blood vessels, joints or glomeruli) which may cause inflammatory damages. The relationship between DTDC and the occurrence of T3H reactions in switch patients was assessed graphically.

Figure 18: Scatter plot of individual observed occurrence of Type III hypersensitivity reaction at any time during treatment versus titre for switch patients in the crovalimab safety analysis data set



CI – confidence interval; DTDC – drug-target-drug complex; $DTDC1_{max}$ – maximum DTDC Fraction 1, $DTDC2_{max}$ – maximum DTDC Fraction 2; $DTDC3_{max}$ – maximum DTDC Fraction 3; $DTDC4_{max}$ – maximum DTDC Fraction 4; $DTDCsum_{max}$ – maximum of the sum of DTDC Fractions 1-4; $DTDCsum_{average}$: average DTDC Fraction 1-4; T3H – Type III hypersensitivity. Observations before the first crovalimab administration as well as observations associated with PK BLQ within 24 h after first crovalimab dose are not included. The red curve is a logistic regression fit together with the 90% CI as shaded area. The p value for exposure is given in the respective panel.

2.6.3. Discussion on clinical pharmacology

Bioanalysis

Crovalimab ADA detection

The detection of ADAs across the clinical development programme was performed using validated analytical methods.

it can be agreed that pooled results can be used to inform about the immunogenicity in the SmPC.

Crovalimab NAbs detection

NAb assay was validated at different laboratories to evaluate NAbs in studies BO42161, BO42162 and YO42311. The applicant was asked to discuss the sensitivity and drug tolerance performance of the assay and to provide the validation report of the Roche CH assay. Validation report 1121262 was provided. As per the provided results, the method in both laboratories performed similarly in terms of sensitivity and low drug tolerance (0.5 µg/mL crovalimab at the 2500 ng/mL positive control level at both laboratories). The assay also failed selectivity assessment in switch PNH patients showing false positive results in 5/9 samples The applicant acknowledged limitations of the assay to detect neutralising ADA at therapeutic concentrations of crovalimab >100 µg/mL and therefore the NAb results obtained by this method from both laboratories should be interpreted with caution since number of NAb-positive samples could be underestimated. Instead of improving the assay, the applicant proposed to assess the clinical impact of ADA on PK, PD and efficacy regardless of NAb status. The approach analysed the impact of ADA on loss of exposure (crovalimab concentrations <100 µg/mL), loss of pharmacological activity (CH50 >30 U/mL) and loss of efficacy (3 consecutive assessments of LDH 2-fold ULN that persisted for at least 4 weeks). As such, 11 (2.9%) patients were identified with clinically meaningful impact of ADA on PK, PD, and variable impact on efficacy (6 out of 11 (1,6%) with documented loss of efficacy in the absence of confounding factors). All of them were ADA-positive (5 NAb-positive and 6 NAb-negative).

It is agreed that this approach can be accepted to evaluate clinically relevant impact of immunogenicity regardless of the NAb status.

LDH

LDH was used as a primary efficacy endpoint. However, initially no information regarding the performance of the assay could be found. In response to the CHMP request, the applicant provided details of the development and validation of the assay. The LDH Bioanalytical report for the specific study was provided and showed acceptable performance.

ADME / dose proportionality

The PKs of crovalimab (PK parameters and exposures metrics at steady state) is essentially described based on the Pop-PK approach. NCA analyses could be conducted only in Part 1 of Study BP39144 (Healthy volunteers [HV], N = 9, 3 subjects in each arm: 75, 125 mg IV and 100 mg SC) and in a subset of PNH patients in Study YO42311 (N = 17) who had rich blood sampling at steady state up to 4 weeks post-dose. Considering the sparse PK sampling in parts 2, 3 and 4 of Study BP39144 and the expected added value of the NCA estimates from part 1 (healthy volunteers receiving low doses in comparison to the therapeutic range) the request of NCA and dose proportionality analyses from Study BP39144 are no further pursued.

Immunogenicity

To characterise possible loss of efficacy in more detail, the applicant was asked to discuss whether some cut-off in ADA titres was observed to be associated with loss of exposure/pharmacological

activity/efficacy, to summarise data on time to loss of response from the start of treatment and to discuss practical measures when loss of response is observed. In response, the applicant stated that within the eleven patients with observed loss of exposure and loss of pharmacological activity, the range of measured ADA titres was large (median 25600 (range from 400 to 1640000)) and time to onset of loss of PK or PD response was variable (median 16 weeks after the start of treatment (range from 6 to 40 weeks). Due to limited data available and variable outcomes, no recommendation can be given on dose adjustment in case of loss of exposure. Wording in SmPC section 4.4 was adapted to consider development of ADAs leading to loss of exposure and efficacy in patients presenting with persistent serious intravascular haemolysis despite compliant treatment with crovalimab and to consider switch to an alternative therapy.

Population PK analysis

The methods used for model development and model evaluation are acceptable. Goodness-of-fit plots showed that the model described the data reasonably well. However, there are some deviations from the line of identity noted on DV vs. PRED and DV vs. IPRED plots. The applicant confirmed that these deviations correspond mainly to the patients with complete loss of exposure (n=8). Sensitivity analysis was performed excluding those 8 subjects, and there was no significant effect on the population PK model parameter estimates. VPCs generally show that the model is able to reproduce both the central trend and variability in the observed data. The applicant acknowledged that the median percentiles of the observed concentrations up to Week 14 in switch patients are underpredicted, mostly for pivotal study BO42162. Additional analyses performed with different transient clearance and exponential decay constant across studies could not explain the observed underprediction. The model has the slight tendency to overestimate the impact of the transient clearance, which is acceptable to describe the data. However, it should be considered if the intended use of the model changes in the future.

Hepatic impairment

Instead of the recommended Child-Pugh (CP) classification, patients were categorised with regards to hepatic status using baseline alanine aminotransferase (ALT) levels. Based on the Pop-PK approach, mild hepatic impairment was found to not significantly impact the PKs of crovalimab. To further investigate the impact of hepatic impairment on the PKs of crovalimab, the applicant was asked to grade patients (numbers and PK observations per each group) according to the Child-Pugh (CP) classification and to provide the relevant PK data and analyses. In response, the applicant highlights that key intrinsic features of PNH disease (elevated bilirubin levels due to haemolysis) and its treatment (prolongation of coagulation parameters caused by anticoagulants) interfere with some of the criteria used in the Child-Pugh classification, which may lead to misclassification of the hepatic status. Therefore, it is accepted that use of the CP classification, in this specific patient population, could be considered of limited value and no further analyses are needed. As requested, the SmPC wording in section 4.2 was amended to reflect the lack of PK data in PNH patients with moderate or severe hepatic impairment as well as the metric (i.e., ALT levels) used to grade hepatic function.

Weight / Paediatric population

No clinical (efficacy, safety and PK) data are available for children <12 years and for patients with a body weight (BW) under <40 kg. Therefore, the applicant was asked to restrict the current indication to adults and adolescents > 12 years weighting more than 40 kg which is reflected in section 4.1 of the SmPC.

BW was found to have a significant effect on crovalimab PK. Patients with lower BW will have relatively higher exposure but since no exposure-safety relationship is identified, this is not expected to lead to safety issues. Patients with BW weights will have lower exposure. Therefore, for patients with BW ≥100 kg, higher IV loading (1500 mg) and SC maintaining doses (1020 mg) are recommended. With

such dosing regimen adjusted on BW, it is expected that approximately 90% patients will have crovalimab $C_{trough,ss}$ above 100 µg/mL. However, PK simulations for the last BW category in the investigated body weight range (130 - 140 kg) was not performed and the applicant was asked to present these simulations. As per the CHMP request, the applicant provided the additional simulations of $C_{trough,ss}$ for the [130-140 kg] BW subgroup. It was confirmed that also in this weight range, more than 90% of patients would have crovalimab concentrations above the efficacy threshold of 100 µg/mL.

Interactions

No dedicated DDI studies have been performed and this is acceptable for a monoclonal antibody. This is also in line with the scientific advice received from the CHMP.

Crovalimab and other C5 inhibitors (eculizumab and ravulizumab) bind to different epitopes of C5 and can form large drug-target-drug complexes (DTDCs) upon patients switching from one to another C5 inhibitor. Based on Pop PK analysis, formation of DTDCs causes a transient increase in crovalimab clearance. Due to higher loading dose, a similar proportion of treatment-naïve and switch patients are expected to achieve crovalimab concentrations above 100 µg/mL and no dose adjustment is considered necessary for the switch patients. Peak of large DTDCs is expected around 2 weeks following switch and DTDCs in patients switching from eculizumab are expected to be cleared within 8 weeks. In patients switching from ravulizumab, a longer presence of DTDCs is possible due to longer ravulizumab half-life.

Occurrence of DTDCs may impact safety since they can cause Type III hypersensitivity reactions. For assessment of safety and T3H reactions, please see clinical safety section.

SmPC section 4.5 adequately describes formation of DTDCs and safety issues are further described in sections 4.4 and 4.8.

In study BP39144, size distribution of DTDCs was compared between treatment-naïve (Part 4a) and switch (Part 4b) patients. Further clarifications were asked since DTDCs are expected only in switch patients. It was stated that in study BP39144, in both treatment-naïve and switch patients, SEC fractions 4, 5 and 6 were detected, with peak observed at fraction 6. The applicant clarified that SEC assay is also able to detect crovalimab drug-target complexes (which would correspond to crovalimab-C5 or C5-crovalimab-C5, i.e. fraction 5) and free crovalimab (i.e. fraction 6). In treatment-naive patients, fraction 4 may contain crovalimab bound to two C5 (as a residual not in Fraction 5 due to the spillover effect in the SEC), while in switch patients it can also contain the smallest DTDC. The figure presenting SEC fractions distribution in study BP39144 was aimed to show that after 29 days of treatment large DTDC fractions in switch patients were cleared and SEC profile between treatment-naïve and switch patients was similar.

In study BO42162, DTDC data were available for 39 patients out of 68 Arm B switch patients. The applicant was asked to provide updated DTDC data for the remaining 29 patients from study BO42162, Arm B. DTDC profiles are now presented for all 68 switch patients from Arm B and are consistent with the earlier description: "Mean DTDC profiles over time in Arm B Switch patients showed that large DTDCs (Fractions 1 to 4) increased rapidly after crovalimab initiation with a peak achieved 2 weeks after switch; then cleared by Week 9."

Pharmacodynamics

Crovalimab is a recombinant humanised immunoglobulin G1 (IgG1)-based monoclonal antibody that specifically binds with high affinity to component 5 (C5) of the complement system, inhibiting its cleavage into C5a and C5b and thus preventing the formation of the membrane attack complex (MAC).

Crovalimab causes terminal complement activity inhibition. In patients with PNH, crovalimab inhibits terminal complement-mediated intravascular haemolysis.

The mechanism of action of crovalimab is adequately described in SmPC section 5.1.

In clinical studies with PNH patients, complete inhibition of terminal complement activity (CH50) was achieved rapidly following administration of initial IV dose and was sustained throughout the treatment period. Free C5 concentrations decreased from baseline to low levels (< 0.0001 g/L) early during the treatment, providing evidence of complete inhibition of free C5, and were sustained throughout the treatment period. Complete inhibition of the terminal complement activity was generally achieved with crovalimab concentrations above approximately 100 µg/mL.

Inhibition was similar between treatment-naïve and switch patients.

In a limited number of paediatric patients (>12 years with body weight ≥40 kg, n=6), CH50 and free C5 levels were similar to the levels observed in adult patients.

The pharmacodynamic effects are adequately described in SmPC section 5.1.

No dedicated tQT study was performed and this is acceptable. This was also accepted in the scientific advice by the CHMP (EMA/CHMP/SAWP/493953/2019). 12-lead ECG data was collected concomitantly with PK sampling in studies BP39144, BO42162, YO42311, and BO42161. The analysis of those data did not show any clinically relevant concerns with regards to potential prolongation of ΔQTcF or ΔQTcB.

Exploratory evaluation of efficacy was performed in a limited number of patients with C5 polymorphism (n=10). Crovalimab concentrations in those subjects and terminal complement activity inhibition was similar to the rest of the study population. One of those 10 patients had loss of exposure and loss of pharmacological activity.

Exposure-PD analyses showed a concentration-dependent inhibition of terminal complement activity. Crovalimab concentrations > 100 µg/mL were associated with complete terminal complement activity inhibition, based on both CH50 and free C5. Based on data from patients with loss of exposure, CH50<30 U/mL and free C5<0.0001 g/L were used as thresholds for complete terminal complement activity inhibition.

No relevant exposure-efficacy relationship was found between steady state crovalimab concentrations and LDH values indicating that no further reduction in LDH is expected when Ctrough,ss > 100 µg/mL.

Also, no relevant relationship was found between exposure parameters Cmax, Cmax,ss, AUC $_{\tau,ss}$, AUC28days,ss and occurrence of SAEs, AESIs, AEs G3+ and any infections.

A statistically significant relationship was found between maximum DTDCs and the occurrence of T3H reactions in the logistic regression for Fraction 4 (p= 0.00425) and the sum of Fractions 1-4 (p= 0.0384).

2.6.4. Conclusions on clinical pharmacology

Crovalimab PK following subcutaneous administration has been characterised using a Pop-PK model developed based on pooled data from HVs (n=9) and treatment-naïve (n=210) and switch patients with PNH (n=211) in the phase 1/2 study BP39144 and 3 phase 3 studies BO42162, YO42311, and BO42161.

Several other issues were raised and essentially pertain to the bioanalytical performances (low drug tolerance) for the ADAs and NAbs detection methods and posology in special populations. All these issues were sufficiently resolved either by providing the complementary requested analyses or by

implementing the appropriate wordings in the SmPC. Overall, no further issue is identified from a PKPD perspective.

2.6.5. Clinical efficacy

2.6.5.1. Dose response study

No dedicated dose study was performed. Analyses of exposure-efficacy relationship across studies COMMODORE 1-3 are briefly presented in the clinical AR, section 2.6.5.7. Supportive study(ies).

2.6.5.2. Main study

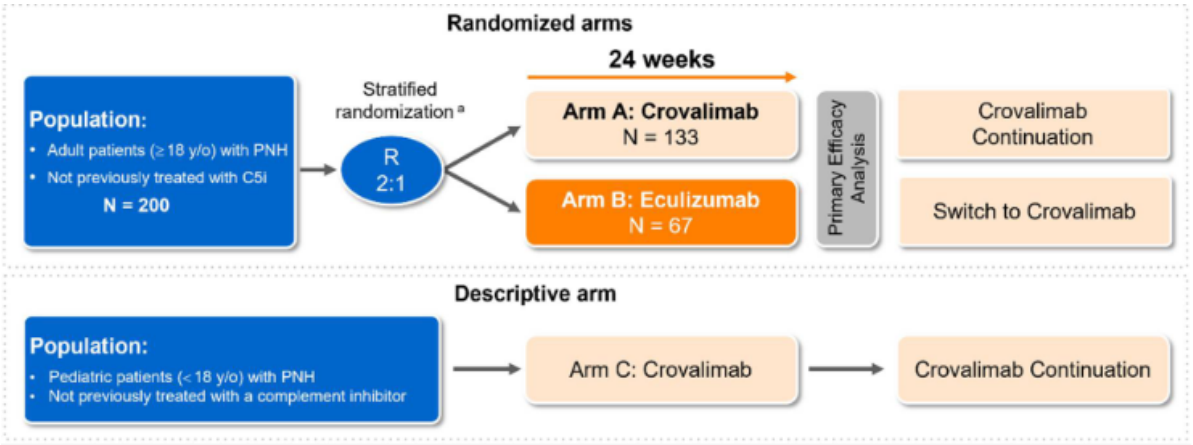
Study BO42162 (Study 162 or COMMODORE 2): a Phase III, multicentre, open-label, active-controlled study designed to evaluate the efficacy, safety, pharmacokinetics, pharmacodynamics, and impact on health-related quality of life of crovalimab vs. eculizumab in patients with PNH who were not previously treated with a complement-inhibitor therapy.

Methods

Adult patients were randomised 2:1 to either receive crovalimab (Arm A) or eculizumab (Arm B) for 24 weeks. Paediatric patients were included in descriptive Arm C and all received crovalimab for the same treatment duration.

If eligible, adult and paediatric patients initially allocated to crovalimab could enter the subsequent crovalimab extension period (up to 5 years). Patients who initially received eculizumab had the option to switch to crovalimab treatment after the 24-week treatment period. Patients not eligible or not willing to enter crovalimab extension period entered the 10 week-end safety follow up.

Figure 19: Study design for COMMODORE 2



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

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

[a] Randomization was stratified based on the most recent local LDH value (≥2 to ≤4 × ULN, and >4 × ULN) and packed RBC transfusion history (0, >0 to ≤6, and >6 units) within 6 months. Patients were randomized 2:1 to crovalimab or eculizumab, respectively.

Study Participants

Main inclusion criteria

- Documented diagnosis of PNH, confirmed by high sensitivity flow cytometry evaluation of WBCs with granulocyte or monocyte clone size of ≥10%, within 6 months prior to randomisation
- LDH level ≥2 × ULN at screening (as per local assessment)
- Presence of one or more of the following PNH-related signs or symptoms within 3 months prior to screening: fatigue, haemoglobinuria, abdominal pain, shortness of breath (dyspnoea), anaemia (haemoglobin < 10 g/dL), history of a major adverse vascular event (including thrombosis), dysphagia, or erectile dysfunction; or history of pRBC transfusion because of PNH
- Platelet count ≥ 30,000/mm3 at screening without transfusion support within 7 days of lab testing
- Absolute neutrophil granulocyte count (ANC) > 500/µL at screening
- 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
- Vaccination against *Haemophilus influenzae* type B and *Streptococcus pneumonia* according to national vaccination recommendations
- Body weight ≥ 40 kg at screening

The patients enrolled into the randomised Arms A and B had to be ≥ 18 years old at the time of signing the ICF. The paediatric patients recruited into the descriptive Arm C had to be < 18 years old at the time of signing the ICF. Otherwise, the inclusion criteria were identical across the 3 arms.

Main exclusion criteria

- Current or previous treatment with a complement inhibitor
- Pre-enrolment haemoglobin value ≤ 7 g/dL, or pre-enrolment haemoglobin value >7 g/dL and ≤9 g/dL with concurrent signs and symptoms of anaemia
- History of allogeneic bone marrow transplantation
- History of *Neisseria meningitidis* infection within 6 months prior to screening and up to first study drug administration
- Known or suspected immune deficiency (e.g., history of frequent recurrent infections)
- Known or suspected hereditary complement deficiency
- History of myelodysplastic syndrome with Revised International Prognostic Scoring System (IPSS-R) prognostic risk categories of intermediate, high and very high Additional exclusion criteria are listed in detail in the protocol

- **Treatments**

Treatment was to be administered as follows:

Arm A (crovalimab): 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 will continue Q4W thereafter, for a total of at least 24 weeks of primary treatment period, followed by the treatment extension period of no more than 5 years. All patients who received crovalimab as part of this study did according to the following weight-based tiered dosing approach schedule.

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

QW = every week; Q4W = every 4 weeks.

For those patients receiving an initial IV loading dose of 1000 mg, the infusion was delivered over 60 (± 10) minutes. For those patients receiving an initial IV loading dose of 1500 mg, the infusion was delivered over 90 (±10) minutes. Patients should have been observed by a health care professional (HCP) during the IV infusion and for 60 minutes following the completion of IV infusion.

The first 5 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 centre, clinic, or hospital. For the first 3 SC doses (Day 2 of Week 1, and Week 2 and Week 3), patients were observed by a health care professional for 60 minutes following the drug administration.

Crovalimab may be administered within ± 2 days of the scheduled dose, except the Week 1 Day 1 and Week 1 Day 2 doses, which should be administered on the scheduled day.

Arm B (eculizumab): dosing followed local prescribing information or, if enrolled in a country without access to commercial eculizumab, the pharmacy manual. Initial weekly 600 mg doses were followed by Q2W maintenance doses of 900 mg starting on Week 5.

Eculizumab may also be administered within ± 2 days of the scheduled dose, except for the doses administered in the first 4 weeks, which should be administered on the scheduled day.

Arm C (crovalimab): Paediatric patients received a loading series of crovalimab doses comprised of an IV dose on Day 1 of Week 1, followed by weekly crovalimab SC doses for 4 weeks, at Week 1 (Day 2) and then at Weeks 2, 3, and 4. Maintenance doses began at Week 5 and were administered Q4W thereafter.

If a dose of crovalimab was missed, the dose should be administered as soon as possible and then resume usual doing schedule. Two doses should not be administered on the same day to make up for missing doses. Resuming treatment after longer than 28 days of interruption should be done in consultation with the Medical Monitor.

Dose modifications

Criteria for dose modifications

Dose modification to comply with the weight-based crovalimab regimen was only required if the patient's body weight changed by 10% or more (compared with screening or the visit when the latest dose modification occurred, whichever was later), to exceed or become equal to 100 kg or to fall below 100 kg during the course of therapy.

Patients with two or more qualifying intravascular haemolysis events occurring within 24 weeks without an identifiable trigger (such as an infectious trigger) and patients with sustained intravascular haemolysis also occurring without an identifiable trigger could be considered for an increased maintenance dose of crovalimab in consultation with the Medical Monitor. Sustained intravascular haemolysis was defined as LDH ≥ 2 x ULN measured at 3 consecutive assessments and persisting for at least 4 weeks, where each LDH ≥ 2 x ULN measurement was accompanied by at least one sign or symptom of intravascular haemolysis, during the maintenance phase of crovalimab treatment (Week 5 or thereafter)

Rescue crovalimab IV dosing

If a patient who received crovalimab experiences signs and symptoms of his or her underlying PNH, such as BTH, which could be due to an acute event such as acute illness, trauma, or surgery, one or more additional IV doses of crovalimab may be administered based on investigator assessment. Prior to this IV dose, unscheduled laboratory assessments (e.g., LDH, PK, ADA, biomarker and other appropriate clinical investigations) should have been done to further characterize the BTH and evaluate the underlying cause, unless samples had been already collected within 24 hours of the IV rescue dose. The recommended dose to be administered was crovalimab IV 340 mg (regardless of body weight) to be infused over 30 minutes.

The investigator should inform the Sponsor within 24h of the time of the decision to administer a rescue IV dose and record this additional dose on the eCRF. For situations in which a patient requires

more than one additional dose in less than 1 month, the investigator needs to justify the need with the Sponsor before initiation of another dose.

Crovalimab rescue doses may only be used for patients currently receiving crovalimab treatment.

- **Objectives**

Primary efficacy objective (randomised arms)

- To evaluate the efficacy of crovalimab compared to eculizumab, based on the non-inferiority assessment of the co-primary endpoints

Secondary efficacy objectives

- To evaluate efficacy of crovalimab compared with eculizumab, based on the non-inferiority assessment of the secondary endpoints

Exploratory efficacy objectives (randomised arms)

Randomised arms

- To evaluate the efficacy of crovalimab compared to eculizumab on the basis of the exploratory endpoints

Arm C

- To evaluate the efficacy of crovalimab on the basis of the corresponding endpoints

Arm B (patients switching to crovalimab following the 24-week primary treatment period)

- To evaluate the efficacy of crovalimab on the basis of the corresponding endpoints

Safety objectives (all arms)

- To evaluate the overall safety of crovalimab compared to eculizumab, on the basis of the corresponding endpoints

Pharmacokinetic (PK) objectives (all arms)

- To evaluate the PK of crovalimab and eculizumab on the basis of the corresponding endpoints
- To evaluate potential relationships between drug exposure and the efficacy and safety of crovalimab

Immunogenicity objectives (all arms)

- To evaluate the immune response to crovalimab
- To evaluate the potential effects of ADA on PK, PD, efficacy and safety endpoints

Biomarkers objectives (all arms)

- To identify and/or evaluate biomarkers that can potentially provide evidence of crovalimab and eculizumab activity (i.e., PD biomarkers), are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation (i.e., safety biomarkers), or can increase the knowledge and understanding of disease biology and drug safety

Health status utility objective (all arms)

- To evaluate health status utility scores of paediatric (aged ≥12 years and <18 years) and adult (aged ≥18 years) patients treated with crovalimab compared to eculizumab

- **Outcomes/endpoints**

Co-primary endpoints (randomised arms)

- Proportion of patients who achieve Transfusion Avoidance (TA) from baseline through Week 25 (after 24 weeks on treatment).

  TA is defined as patients who are packed RBC (pRBC) transfusion-free and do not require transfusion per protocol-specified guidelines

- Proportion of patients with haemolysis control, measured by LDH ≤1.5 x ULN from Week 5 through Week 25 (as measured at the central laboratory)

Secondary endpoints (randomised arms)

- Proportion of patients with BTH from baseline through Week 25.

  BTH is defined as at least one new or worsening symptom or sign of intravascular haemolysis (fatigue, haemoglobinuria, abdominal pain, shortness of breath [dyspnoea], anaemia [haemoglobin <10 g/dL], a major adverse vascular event [MAVE; as defined in protocol, Appendix 4, including thrombosis], dysphagia, or erectile dysfunction) in the presence of elevated LDH ≥2 x ULN after prior reduction of LDH to ≤1.5 x ULN on treatment.

- Proportion of patients with stabilisation of haemoglobin from baseline through Week 25

  Stabilised haemoglobin is defined as avoidance of a ≥2 g/dL decrease in haemoglobin level from baseline, in the absence of transfusion

- Mean change from baseline to Week 25 in fatigue, as assessed by the FACIT-Fatigue

Main exploratory endpoints

Randomised arms

- Total number of units (based on local equivalent) of pRBCs transfused per patient by Week 25
- Proportion of patients with central LDH ≤1 x ULN from Week 5 through Week 25
- Proportion of patients experiencing a major adverse vascular event (MAVE) from baseline through Week 25
- Proportion of patients with a ≥ 5-point improvement from baseline in the FACIT-Fatigue at Week 25 (for adults aged ≥ 18 years)
- Mean change over time in quality of life, as assessed by Quality of Life Questionnaire – Aplastic Anaemia/Paroxysmal Nocturnal Haemoglobinuria (QLQ AA/PNH), and in overall health status, as assessed by Patient Global Impression of Severity Survey (PGIS) (for patients aged ≥ 18 years)

Arm C (main objectives)

- Proportion of patients who achieve TA, from baseline through Week 25 (after 24 weeks on treatment)
- Proportion of patients with haemolysis control, measured by LDH ≤1.5 x ULN from Week 5 through Week 25 (as measured at the central laboratory)
- Proportion of patients with stabilisation of haemoglobin from baseline through Week 25

- Total number of units (based on local equivalent) of pRBCs transfused per patient by Week 25
- Proportion of patients with central LDH ≤ 1 x ULN from Week 5 through Week 25
- Proportion of patients experiencing MAVE from baseline through Week 25

Arm B (patients switching to crovalimab following the 24-week primary treatment period)

- Proportion of patients who achieve TA from the first dose of crovalimab through 24 weeks of treatment with crovalimab
- Proportion of patients with central LDH ≤ 1.5 x ULN from the first dose of crovalimab through 24 weeks of treatment with crovalimab
- Proportion of patients with stabilisation of haemoglobin from the first dose of crovalimab through 24 weeks of treatment with crovalimab
- Mean change in fatigue from the first dose of crovalimab through 24 weeks of treatment with crovalimab, as assessed by the FACIT-Fatigue
- Proportion of patients with preference for crovalimab or eculizumab at Week 41, for patients randomised to eculizumab who switch to crovalimab after completing at least 24 weeks of eculizumab treatment, as assessed through use of the Patient Preference Questionnaire developed by the Sponsor (for patients aged ≥ 18 years)

Safety endpoints (all arms)

- Incidence and severity of adverse events, with severity determined according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events, Version 5 (CTCAE v5)
- Change from baseline in targeted vital signs
- Change from baseline in targeted clinical laboratory test results
- Incidence and severity of injection-site reactions, infusion-related reactions, hypersensitivity, and infections (including meningococcal meningitis)
- Incidence of adverse events leading to study drug discontinuation
- Incidence and severity of clinical manifestations of drug-target-drug-complex (DTDC) formation in patients who switched to crovalimab treatment from eculizumab treatment

Pharmacokinetic endpoints (all arms)

- Serum concentrations of crovalimab and eculizumab over time
- To evaluate potential relationships between drug exposure and the efficacy and safety of crovalimab (patients randomised to crovalimab)
- To evaluate potential relationships between drug exposure and the efficacy and safety of eculizumab (patients randomised to eculizumab)
- To evaluate relationship between DTDC size and kinetics and PK parameters of crovalimab and eculizumab (for patients randomised to eculizumab who switch to crovalimab after completion of eculizumab treatment)

Immunogenicity endpoints (all arms)

- Prevalence of ADAs at baseline and incidence of ADAs during the study
- To evaluate the potential effects of ADA on PK, PD, efficacy and safety endpoints

Main biomarker endpoints (all arms)

- Change over time in PD biomarkers, including complement activity (CH50) measured by a liposome immunoassay (LIA) and total C5 concentration
- Change over time in free C5 concentration in crovalimab-treated patients.
- Observed value and absolute change from baseline to Week 25 in parameters reflecting haemolysis (e.g., reticulocyte count, free haemoglobin, haptoglobin).

Additional endpoints are details in the clinical AR

Health status utility endpoints (all arms), according to EuroQoL 5-Dimension Questionnaire, 5-level version (EQ-5D-5L) index based and visual analog scale (VAS) scores at specified timepoints

- **Sample size**

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

The NIM for TA was determined based on the data reported in protocol ALXN1210-PNH301, comparing eculizumab-treated patients with untreated patients from the global PNH Registry for eculizumab-treated patients, i.e., 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 enrolment. Hence, 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. A more conservative NIM would have resulted in the estimated sample size being too large and infeasible. Lee et al., (2019) reported a proportion of patients with TA of 66.1% (95%CI: 57.7% to 74.6%) in treatment-naive patients in eculizumab.

With regards to haemolysis control, 116 patients were required in a 2:1 ratio to test the non-inferiority of crovalimab vs. eculizumab, with a non-inferiority margin of 0.2 in the odds ratio (OR) scale, 80% power, and 1-sided test at 0.025 Type I error rate.

Incidentally, a similar sample size was required to test for non-inferiority in the probability scale when the NIM is -0.2. Lee et al., (2019) also reported a proportion of LDH normalisation below 1 x ULN of 49.4%. Under the assumption of LDH being log-normally distributed, the expected proportion below 1.5 x ULN is 86%. The same proportion was assumed for crovalimab. The NIM in the OR scale was obtained as $1/OR^{0.5}$, where OR = 24.6 assuming 86% of patients receiving eculizumab will reach LDH ≤ 1.5 x ULN compared to an upper bound of the 95% CI of the proportion among placebo-treated patients of 20%. Note that both proportions are approximately twice the ones used in protocol ALXN1210-PNH-301 for LDH ≤ 1 x ULN), and a fraction of 0.5 of that effect is retained (Ng 2008). Assuming a 10% drop-out, the total needed sample size would be 128 patients (85 randomised to crovalimab and 43 to eculizumab). With 180 evaluable patients expected in the study, the power for this endpoint will be 94%. Hence, the joint power for both TA and LDH would be 75% if they were

uncorrelated. It is likely that co-primary endpoints are correlated and hence joint power would be higher. If there were no dropouts and all 200 patients contributed at least one LDH sample, then the power for TA would be 84% and for LDH 96%.

Table 9: Sample-Size Estimation for the Co-Primary Endpoints of Transfusion Avoidance and Haemolysis Control (LDH ≤ 1.5 x ULN)

	Crovalimab	Eculizumab	Total
Transfusion Avoidance	67%	66%	
Required N	120	60	180
N with 10% drop-out	133	67	200
Hemolysis Control	86%	86%	
Required N	77	39	116
N with 10% drop-out	85	43	128

ULN = upper limit of normal.
Note: Operating characteristics: one-sided non-inferiority testing, margin = –20%, power = 80%, Type I error rate = 0.025, drop-out = 10%, 2:1 randomization ratio.

Paediatric patients will be enrolled in the descriptive arm (Arm C) throughout the duration of the study. No target sample size is specified.

There were no planned interim analyses.

- **Randomisation and Blinding (masking)**

This was an open-label study. The study was not blinded to patients and investigators.

In order to maximise the integrity of the study, the Sponsor had no access to aggregated data by treatment until the time of the primary analysis.

Statistical methods

Analysis populations

The analysis population for the primary and secondary efficacy analyses to evaluate the non-inferiority of crovalimab compared with eculizumab will be the Primary Analysis Population as defined below.

Primary Analysis Population

The Primary Analysis Population (PAP) to evaluate the non-inferiority of crovalimab compared with eculizumab includes all randomised patients receiving at least one dose of the assigned treatment and having at least one centrally processed LDH level assessment after the first intravenous (IV) infusion.

Randomised Population

The randomised population (intent-to-treat [ITT]) is defined as all randomised patients, with analyses performed as randomised.

Per Protocol Population

The per protocol population is comprised of all randomised patients who fulfilled a selection of per protocol criteria.

Efficacy Analysis Population for Patients Switching from Eculizumab to Crovalimab

For patients in Arm B switching from eculizumab to crovalimab after completing the primary treatment period, the efficacy analysis population is defined as all patients receiving at least one dose of crovalimab and having at least one centrally processed LDH level assessment after the first crovalimab IV infusion.

Multiplicity adjustment

If non-inferiority is established for the co-primary endpoints then the secondary endpoints (see below), including superiority testing of primary and secondary endpoints, were tested following a hierarchical order. The testing hierarchy was to ensure that the family-wise one-sided Type I error rate was controlled at the 2.5% level.

Table 10: Hierarchical testing procedure

Endpoint	Test
[a]Proportion of patients with TA from baseline through Week 25	Non-Inferiority
[a]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	Non-Inferiority
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	Superiority
Mean change from baseline to Week 25 in FACIT-Fatigue scale (for adults aged ≥ 18 years)	Non-Inferiority
Mean change from baseline to Week 25 in FACIT-Fatigue scale (for adults aged ≥ 18 years)	Superiority

[a] Denotes co-primary efficacy endpoints.

Primary endpoints

Primary estimand

In alignment with the addendum to International Council for Harmonisation (ICH) Guideline E9 on statistical principles for clinical trials, the primary efficacy estimand is defined by the four attributes summarised below.

- Population: The treatment-naive PNH population, as defined through the inclusion and exclusion criteria, randomised either to crovalimab or to eculizumab, receiving at least one dose of the assigned treatment and providing at least one centrally processed LDH level assessment after the first intravenous (IV) infusion.
- Variables:
  - Transfusion avoidance: categorical indicator
  - Haemolysis control: categorical indicator based on centrally processed bi-weekly LDH measured from Week 5 to Week 25
- Intercurrent Events (ICEs):
  - TA:
    - Early withdrawal from study treatment
  - Haemolysis control:
    - Early withdrawal from study treatment

- Dose modification due to experiencing two or more qualifying intravascular haemolysis events or sustained intravascular haemolysis

- Handling of ICEs:
  - TA:
    - Composite strategy:

      Patients with data missing due to an ICE will be hypothetically assumed to have experienced an unfavourable outcome, i.e., have required transfusion in the unobserved period, assuming transfusion had not been observed prior to the ICE.
  - Haemolysis control:
    - Early withdrawal from treatment: hypothetical strategy

      Any data missing due to an ICE will not be imputed for the primary analysis; rather, the generalised estimating equation (GEE) model uses all observed data in order to provide estimates for the full 24 week period.
    - Dose modification due to experiencing two or more qualifying intravascular haemolysis events or sustained intravascular haemolysis: treatment policy strategy

      Per treatment policy strategy, data collected after dose modification due to sustained or qualifying intravascular haemolysis will be included in the primary analysis.

- Population-level Summary (Estimate):
  - TA: the difference in proportion of TA, from baseline through Week 25, between crovalimab and eculizumab arms.
  - Haemolysis control: the odds ratio for haemolysis control between crovalimab and eculizumab arms, as assessed from Week 5 through Week 25.

Transfusion avoidance

The percentage of patients with TA was computed for the two randomised arms. Patients who prematurely withdrew from study treatment before Week 25 were assumed to have undergone a transfusion. The difference in the percentage of patients with TA in the two treatment arms was calculated, along with a 95% Confidence Interval (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 crovalimab and eculizumab arms within the stratification indicators of transfusion history and baseline LDH categories using Mantel-Haenszel weights (Agresti 2013).

Non-inferiority with respect to TA was to be concluded if the lower limit (LL) of the 95% CI for the difference between crovalimab and eculizumab for TA is greater than the pre-defined non-inferiority margin (NIM) of −20%.

Haemolysis control

A GEE model is used to estimate the adjusted log-odds ratio of LDH ≤ 1.5 x ULN due to treatment, and taking account of the intra-individual correlation between LDH control statuses across visits. The dependent variable is the binary indicator for haemolysis control. Independent covariates are

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 randomisation. Data hierarchy is specified at the patient (subject ID) level.

Baseline LDH is defined as the mean of all central LDH values: 1) taken during screening, i.e., within 28 days prior to first on study drug administration of either crovalimab or eculizumab; and 2) the LDH value at Week1 Day 1 collected prior to first dose administration of either crovalimab or eculizumab.

The primary analysis was to apply an unstructured (UN) correlation matrix. This correlation structure imposes minimal assumptions; however, it requires estimating a large number of parameters which may prevent model convergence. If this is the case, other structures would be applied.

All centrally processed LDH measurements, i.e., taken Q2W from Week 5 up to Week 25, were used in the statistical model assessing non-inferiority of crovalimab compared with eculizumab. Unscheduled central LDH measurements were mapped to the nearest scheduled assessment using windowing. Where more than one measurement is attributed to a visit window, then the average was taken.

It was anticipated that a small proportion of central LDH samples would be affected by tabletop haemolysis (TTH), and such samples were excluded from analyses. Samples suspected to be affected by TTH were identified via potassium concentration ≥ 6 mmol/L and LDH ≥ 2 x ULN.

The non-inferiority hypothesis to assess the non-inferiority of crovalimab relative to eculizumab was tested by comparing the LL of the two-sided 95% CI for the odds ratio (OR) of crovalimab versus eculizumab to the pre-defined non-inferiority margin of 0.2

Sensitivity analyses

Various sensitivity analyses were performed to assess the robustness of the co-primary endpoint results against:

1. Efficacy population definition: Haemolysis Control and TA were assessed in the following alternative efficacy populations:

- Randomised/ITT population
- Per Protocol population

2. Impact of Missing Data: The following multiple imputation approaches were performed to assess the robustness of the GEE model against various missing data assumptions in the analysis of haemolysis control:

- Using MCMC assuming missing data are missing at random
- Using pattern mixture models and tipping point analyses assuming data are Missing Not at Random (MNAR). Given that the pattern mixture model imputes missing observations to follow the distribution of the control arm, the approach is considered anti-conservative. The tipping point analysis was performed by first assuming a worst-case scenario (LDH ≤ 1.5 x ULN not met for all missing central LDH values) in crovalimab arm and the reverse for the eculizumab arm (LDH ≤ 1.5 x ULN met for all missing central LDH values). Only if this worst-case scenario was not consistent with the primary analysis would intermediary imputations be performed.

Secondary endpoints

Breakthrough Haemolysis

The secondary endpoint of breakthrough haemolysis (BTH) investigated the proportion of patients with BTH from baseline through Week 25. BTH was defined as at least one new or worsening symptom or sign of intravascular haemolysis (fatigue, haemoglobinuria, abdominal pain, shortness of breath

[dyspnoea], anaemia [haemoglobin < 10 g/dL], a major adverse vascular event [MAVE; as defined in the protocol, including thrombosis], dysphagia, or erectile dysfunction) in the presence of elevated LDH ≥ 2 x ULN after prior reduction of LDH to ≤ 1.5 x ULN on treatment.

The proportion of patients with BTH from baseline through Week 25 was analysed using the same methodology as for TA. As a conservative approach, patients withdrawing from study treatment before Week 25 were assumed to have experienced a BTH event in the unobserved period.

If the upper limit (UL) of the 95% CI for the difference between crovalimab and eculizumab in the proportion of patients with BTH was less than the pre-defined noninferiority margin (NIM) of 20%, then crovalimab was to be declared non-inferior to eculizumab and the next endpoint to be tested.

Haemoglobin Stabilisation

The secondary endpoint of haemoglobin stabilisation investigated the proportion of patients with stabilisation of haemoglobin from baseline through Week 25. Stabilised haemoglobin is defined as avoidance of a ≥ 2 g/dL decrease in haemoglobin level from baseline, in the absence of transfusion. Baseline haemoglobin was defined as the latest available haemoglobin measurement prior to the first on-study drug administration of the study drug.

Stabilisation of haemoglobin was analysed using approaches similar to those for TA. As a conservative approach, patients who withdrew from study treatment before Week 25 were assumed to not have met haemoglobin stabilisation criteria.

If the LL of the 95% CI for the difference between crovalimab and eculizumab in the proportion of patients with stabilised haemoglobin was greater than the pre-defined NIM of −20%, then crovalimab was to be declared non-inferior to eculizumab and the next endpoint to be tested.

FACIT-Fatigue

The secondary endpoint of fatigue investigated the mean change from baseline to Week 25 in fatigue, as assessed by the FACIT-Fatigue.

The change from baseline to Week 25 in fatigue, as assessed by the FACIT-Fatigue questionnaire was analysed using a mixed model for repeated measures (MMRM) assuming normally distributed scores, with adjustment for stratification factors, and baseline FACIT-Fatigue score. An unstructured covariance matrix will be used to model the within-patient errors. In the event that the model does not converge with unstructured covariance matrix, a more parsimonious structure will be considered in the following order until model convergence is achieved: Toeplitz, First order Autoregressive (AR1) and Compound Symmetry (CS).

If the LL of the 95% CI for the difference between crovalimab and eculizumab in the mean change from baseline to Week 25 in fatigue was greater than the pre-defined NIM of −5 points, then crovalimab was to be declared non-inferior to eculizumab and the endpoint was to be tested for superiority.

Subgroup analyses

The treatment effect of crovalimab versus eculizumab in terms of the co-primary efficacy endpoints of haemolysis control and TA was investigated in predefined subgroups: age, sex, region, eculizumab available region, race, pRBC units transfused in the 6 months prior to baseline, local LDH level at randomisation, body weight, and prior diagnosis of aplastic anaemia.

Changes to planned analyses

Several changes to the planned analyses were made as part of the following protocol amendments.

Protocol amendment	Changes
Version 3, 20 November 2020	A separate descriptive arm (Arm C) was created to enrol all paediatric patients (< 18 years). Text was added clarifying that paediatric patients enrolled in Arm C will not be part of the primary efficacy analysis. Estimand section was updated with clarification of ICEs and their handling. Early withdrawal was defined as the only ICE and the corresponding strategy was specified for haemolysis control (hypothetical) and transfusion avoidance (composite)
Version 4, 16 July 2021	The proportion of patients with a 3+ point improvement in FACIT-Fatigue at week 25 was added as an exploratory endpoint. Exploratory intra-patient analyses for patients who switch to crovalimab were added. The text on estimand analysis was edited. The hypothetical and composite strategies for haemolysis control and transfusion avoidance (respectively) were further clarified.
Version 5, 24 January 2022	The list of ICEs was expanded to include modifications due to experiencing two or more qualifying intravascular haemolysis or sustained intravascular haemolysis. The analysis strategy for the list of ICEs was updated.
Version 6, 30 September 2022	The efficacy objectives were clarified to state that lactate dehydrogenase values from the central laboratory will be utilised

Changes in Planned Analyses Prior to Unblinding or Database Lock

For subgroup analyses of the co-primary efficacy endpoints by body weight (kg) at baseline, the SAP pre-defined categories of "40 to < 60" and of "60 to < 100" were merged to "40 to < 100" so as to align with weight categories used in crovalimab weight-based dosing, i.e. 40 kg to < 100 kg and ≥ 100 kg.

Changes Following Study Unblinding/Database Lock and Post-Hoc Analyses

The following changes to the analysis plan were made after study unblinding:

- The sensitivity analysis for TA, where only study drug related discontinuations are imputed with unfavourable outcomes, was not performed as nearly all but one reasons for discontinuation were classified as study drug related based on the predefined conservative SAP criteria (SAP Table 1). The expected results from this sensitivity analysis would therefore not differ meaningfully from the results of the main analysis of the co-primary TA efficacy endpoint where all patients who discontinue study drug are conservatively assumed to have been transfused.
- A summary of the proportion of patients without two consecutive crovalimab serum concentrations < 100 µg/mL was added.
- Summary of patients with neutralising ADAs was only performed for China patients as the assay results were not available for the rest of the countries.
- Categories for subgroup analyses of the co-primary efficacy endpoints (haemolysis control and TA) by region (North America, Central and South America, Europe, Africa and Middle East,

Japan, Rest of Asia Pacific) were merged to form: "Europe/Central, South and North America" and "Japan and rest of Asia pacific". This was done due to model convergence issues caused by a limited number of patients in some of the original categories.

The only statistical analysis plan (SAP) provided is SAP version 3, dated 19 October. The two previous versions were finalised on 4 September 2020 (v1) and 8 June 2021 (v2).

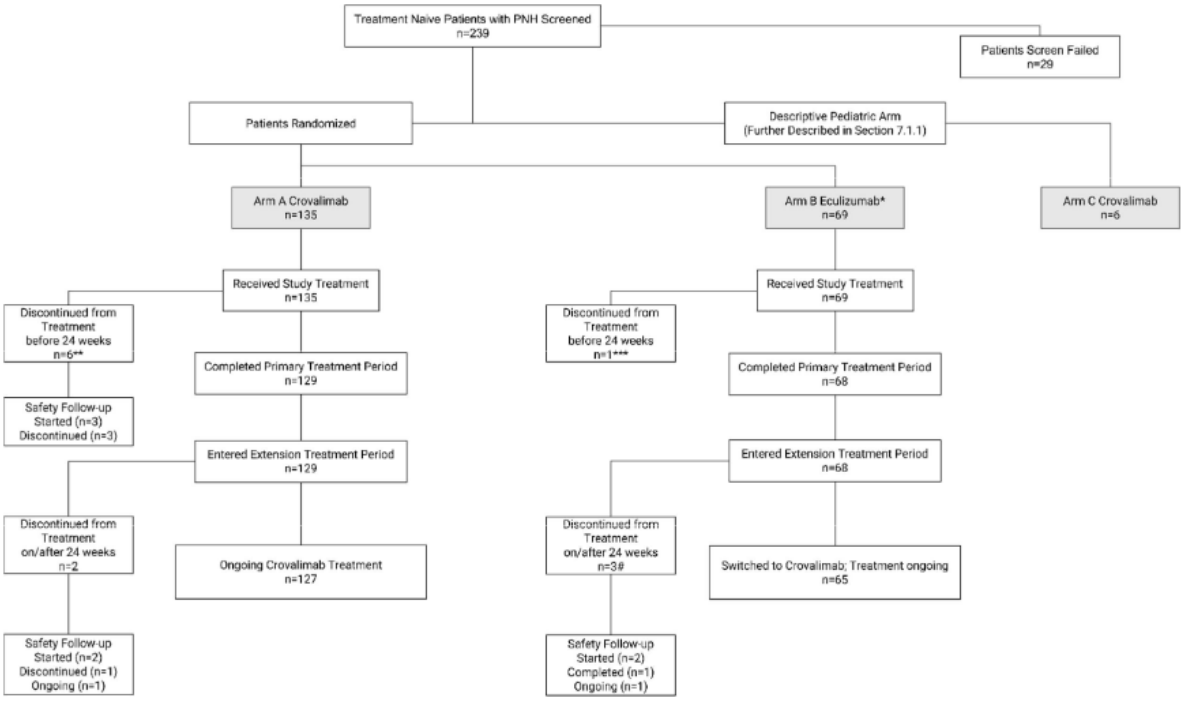
Results

- **Participant flow**

Randomised arms

Participant flow

Figure 20: Patient disposition (all patients population)



Notes:
* Two pediatric patients were in enrolled in the randomized Arm B prior to a separate descriptive Arm C being opened in Protocol V3.
** Three patients did not enter the safety follow-up.
***Patient did not enter safety follow-up.

A total of 210 patients were enrolled in Study 162. Adult patients (n=204) were randomised to crovalimab (Arm A, n=135) or to eculizumab (Arm B, n=69). Six paediatric patients entered the paediatric descriptive Arm C.

Most patients received their allocated treatment and completed the core treatment period: 95.6% in Arm A and 98.6% in Arm B. Most of them continued to receive crovalimab up to the CCOD of 16 November 2022 (94.1% and 95.6%, respectively). Treatment discontinuations were more frequent in Arm A during this time, same as treatment discontinuations after crovalimab administration (11/12), driven by withdrawal by subject and physician decision. Those that occurred following an AE (1 in each arm) were all considered unrelated to treatment. During crovalimab extension period, 4 discontinuations (2 in each arm) were due to withdrawal by subject for unspecified reasons.

- **Recruitment**

First patient was enrolled on 08 October 2020. A total of 204 adult and 6 paediatric subjects were randomised in numerous sites in 25 countries. Countries with the highest number of sites were Spain (9 sites) and China (7 sites). The highest number of patients were enrolled in China (82 patients, 39%) and Thailand (19 patients, 9%).

- **Conduct of the study**

Protocol amendments

The first version of the global protocol was issued on 13 March 2020 and was amended 5 times. The key changes to the protocol along with the rationale are summarised in the table below. First patients were included under protocol version 2.

Table 11: Protocol amendments (extracted from CSR, Table 2)

Version	Date	Amendments
1	13 Mar 2020	Original protocol
2	8 May 2020	Version under which first patients were recruited - Amended to clarify methods and mode of administration of crovalimab (crovalimab vials). - Capped country-specific enrolment at 30% of total study population - Removed AST ≤ 3 x ULN as inclusion criterion, given confounding by intravascular haemolysis
3	20 Nov 2020	- Introduction of a separate descriptive Arm C that allowed the enrolment of paediatric patients of all ages weighing 40 kg or more. *Prior to this amendment, the study enrolled patients ≥ 12 years and a minimum weight of 40 kg.* - The lower age limit for paediatric patients was removed to allow children <12 years who weigh ≥40kg to be included in Arm C. - Added clarification that SC injections should be performed by a caregiver for patients <12 years of age. - Added language regarding maintaining currency of *N. meningitidis* vaccination - Added clarifications to 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 participants
4	16 Jul 2021	- The possibility of conducting exploratory analyses in the Arm B patients switching from eculizumab to crovalimab after the primary treatment period - The 30% cap on recruitment in any country was removed to allow potential enrolment flexibility in an ultra-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

5	24 Jan 2022	Ą The primary reason for the amendment was to include guidance for dose escalation in patients treated with crovalimab who experience sustained intravascular haemolysis. Ą An exploratory endpoint introduced in version 4 to summarise the proportion of patients showing an improvement in FACIT-Fatigue was updated to use a threshold of 5 points (rather than 3 points) Ą Prohibited therapy has been extended from "ravulizumab" to "other complement inhibitors" to account for recent marketing authorisation of non-C5 inhibitor therapies Ą Clarification was provided that if transfusions are given to allow patients to meet the protocol specific haemoglobin eligibility criterion, the patient's post-transfusion haemoglobin value had to be confirmed prior to randomisation/enrolment Ą Pre-enrolment haemoglobin ≤ 7 g/dL or >7 and ≤9 g/dL with signs or symptoms of anaemia was added as an exclusion criteria Ą Vaccination requirements for *S. pneumoniae* and *H. influenza* (where required by local guidelines) clarified to be performed within one week of first study drug administration Ą Intravenous rescue dose updated from 375 mg to 340mg Ą Prohibited therapy updated to include any complement inhibitor Ą "Treatment discontinuation from crovalimab without switching to another complement inhibitor" as well as "immunogenicity" have been added as new risks associated with crovalimab therapy and corresponding guidance was provided Ą The list of inter-current events (ICEs) in the estimand section has been expanded to include dose modifications due to experiencing two or more qualifying intravascular haemolysis or sustained intravascular haemolysis. The analysis strategy for the list of ICEs have been updated
6	30 Sep 2022	Ą The primary reason for the amendment was to address the impact of the longer than originally expected half-life of crovalimab that had emerged from ongoing analyses of data across the development programme. 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 patients (from 24 to 46 weeks), and duration of reporting for pregnancies (from 24 to 46 weeks). Ą Clarification was provided that transfusions during the screening period were not mandatory. Rather, transfusions could be given to allow patients to meet the protocol specific haemoglobin eligibility criterion prior to randomisation/enrolment

Protocol deviations

Table 12: Major protocol deviations (randomised population)

Sub Category	B: Ecu (N=69)	A: Crova (N=135)
Total number of patients with at least one major protocol deviation	36 (52.2%)	84 (62.2%)
Total number of major protocol deviations	59	182
EXCLUSION CRITERIA		
Failure to meet Hb enrollment requirements OR failure to measure Hb ? 5 days pre-randomization	1 (1.4%)	3 (2.2%)
History of malignancy within 5 years	0	1 (0.7%)
Other exclusion criteria	1 (1.4%)	1 (0.7%)
INCLUSION CRITERIA		
Adequate hepatic or renal function criteria not met	0	1 (0.7%)
Failure to use contraception with failure rate <1%/year	2 (2.9%)	2 (1.5%)
LDH criteria (>=2 x ULN) not met	0	1 (0.7%)
Other Inclusion criteria	2 (2.9%)	4 (3.0%)
Vaccination criteria not met	1 (1.4%)	5 (3.7%)
MEDICATION		
Dose missed or out of window	9 (13.0%)	15 (11.1%)
Received incorrect dose of the study medication (includes overdose)	1 (1.4%)	2 (1.5%)
Use of protocol-prohibited therapy	0	1 (0.7%)
PROCEDURAL		
Any visit occurring outside of the specified time window	8 (11.6%)	9 (6.7%)
Cardiac assessment not performed	0	3 (2.2%)
Failure to collect laboratory samples	5 (7.2%)	28 (20.7%)
Failure to obtain signature of updated ICF	5 (7.2%)	9 (6.7%)
Failure to report SAE, AESI and pregnancy per protocol	0	1 (0.7%)
Missed baseline labs	3 (4.3%)	7 (5.2%)
Missed 2 or more efficacy assessments	1 (1.4%)	5 (3.7%)
Missing > 2 PD biomarkers or ADA samples	0	8 (5.9%)
Missing >1 PK samples in first 4 weeks	1 (1.4%)	1 (0.7%)
Missing >2 PK samples from Wk 5-25	0	6 (4.4%)
Missing PD biomarkers or ADA samples	2 (2.9%)	8 (5.9%)
Missing PRO questionnaires at Day 1	2 (2.9%)	0
Other significant GCP violations	0	1 (0.7%)
Other significant procedural deviation	7 (10.1%)	22 (16.3%)
Samples for wrong treatment arm collected/submitted	0	1 (0.7%)
Vitals not obtained before first infusion or missed vitals for two consecutive visits	0	4 (3.0%)
vaccination deviation other than inclusion criteria	1 (1.4%)	1 (0.7%)

Percentages are based on the total number of treated patients in the study.
For frequency counts by deviation, multiple occurrences of the same deviation in an individual are counted only once. For frequency counts of "Total number of major protocol deviations", multiple occurrences of the same deviation in an individual are counted separately.
COOD: 16NOV2022 Data Extract Date: 23JAN2023

Table 13: Major protocol deviations related to COVID-19

Primary Reason Description	B: Ecu (N=69)	A: Crova (N=135)
Total number of patients with at least one major protocol deviation related to epidemic/pandemic	5	29
Total number of major protocol deviations related to epidemic/ pandemic	9	64
Confirmed epidemic/pandemic infection	1	3
Any visit occurring outside of the specified time window	1 (1.4%)	1 (0.7%)
Dose missed or out of window	0	1 (0.7%)
Other significant procedural deviation	0	1 (0.7%)
Suspected epidemic/pandemic infection	0	1
Failure to collect laboratory samples	0	1 (0.7%)
Subject movement restricted due to epidemic/pandemic	1	24
Any visit occurring outside of the specified time window	1 (1.4%)	3 (2.2%)
Dose missed or out of window	1 (1.4%)	3 (2.2%)
Failure to collect laboratory samples	0	14 (10.4%)
Missed 2 or more efficacy assessments	0	2 (1.5%)
Missing > 2 PD biomarkers or ADA samples	0	4 (3.0%)
Missing >2 PK samples from Wk 5-25	0	3 (2.2%)
Missing PD biomarkers or ADA samples	0	5 (3.7%)
Other significant procedural deviation	0	1 (0.7%)
Vitals not obtained before first infusion or missed vitals for two consecutive visits	0	3 (2.2%)
IMP shipping delayed/blocked due to epidemic/pandemic	1	3
Dose missed or out of window	1 (1.4%)	3 (2.2%)
Site action due to epidemic/pandemic	2	5
Any visit occurring outside of the specified time window	0	1 (0.7%)
Dose missed or out of window	1 (1.4%)	0
Missed 2 or more efficacy assessments	0	1 (0.7%)
Missing > 2 PD biomarkers or ADA samples	0	3 (2.2%)
Missing >1 PK samples in first 4 weeks	1 (1.4%)	1 (0.7%)
Missing >2 PK samples from Wk 5-25	0	1 (0.7%)
Missing PD biomarkers or ADA samples	1 (1.4%)	2 (1.5%)
Vitals not obtained before first infusion or missed vitals for two consecutive visits	0	1 (0.7%)

Percentages are based on the total number of treated patients in the study.
For frequency counts by deviation, multiple occurrences of the same deviation in an individual are counted only once. For frequency counts of "Total number of major protocol deviations", multiple occurrences of the same deviation in an individual are counted separately.
CCOD: 16NOV2022 Data Extract Date: 23JAN2023

Ą Baseline data

Demographics

Table 14: Demographics and baseline characteristics (randomised population)

	B: Ecu (N=69)	A: Crova (N=135)
Age (years)		
n	69	135
Mean (SD)	41.9 (16.0)	40.5 (15.2)
Median	38.0	36.0
Min - Max	17 - 78	18 - 76
Age group (years)		
n	69	135
<18	2 (2.9%)	0
18 - 64	58 (84.1%)	122 (90.4%)
>=65	9 (13.0%)	13 (9.6%)
Sex		
n	69	135
Male	35 (50.7%)	77 (57.0%)
Female	34 (49.3%)	58 (43.0%)
Race		
n	69	135
Asian	51 (73.9%)	86 (63.7%)
White	16 (23.2%)	45 (33.3%)
Black or African American	1 (1.4%)	3 (2.2%)
American Indian or Alaska Native	0	0
Native Hawaiian or other Pacific Islander	0	0
Unknown	1 (1.4%)	1 (0.7%)
Ethnicity		
n	69	135
Hispanic or Latino	6 (8.7%)	18 (13.3%)
Not Hispanic or Latino	61 (88.4%)	114 (84.4%)
Not Stated	2 (2.9%)	3 (2.2%)
Weight (kg) at Baseline		
n	69	135
Mean (SD)	67.13 (15.26)	68.32 (15.76)
Median	62.20	66.10
Min - Max	47.0 - 122.0	42.0 - 140.3
Weight (kg) category at Baseline		
n	69	135
< 40kg	0	0
>= 40kg - <100kg	66 (95.7%)	131 (97.0%)
>= 100kg	3 (4.3%)	4 (3.0%)

Baseline is the patient's last observation prior to initiation of study drug in the primary treatment period.
CCOD: 16NOV2022 Data Extract Date: 23JAN2023

Baseline disease characteristics

Table 15: Summary of PNH history (randomised population)

	B: Ecu (N=69)	A: Crova (N=135)
Age at PNH diagnosis (yr)		
n	69	135
Mean (SD)	37.41 (16.39)	35.81 (15.53)
Median	32.11	30.97
Min - Max	11.2 - 76.8	11.5 - 74.7
Time from PNH diagnosis to enrollment (yr)		
n	69	135
Mean (SD)	4.97 (5.91)	5.22 (7.42)
Median	2.93	2.56
Min - Max	0.0 - 31.0	0.0 - 48.5
History of PNH-relevant conditions prior to enrollment (n, %)		
History of aplastic anemia		
n	69	135
Yes	26 (37.7%)	53 (39.3%)
No	43 (62.3%)	82 (60.7%)
History of myelodysplastic syndrome		
n	69	135
Yes	6 (8.7%)	6 (4.4%)
No	63 (91.3%)	129 (95.6%)
History of renal impairment		
n	69	135
Yes	6 (8.7%)	11 (8.1%)
No	63 (91.3%)	124 (91.9%)
History of major vascular events		
n	69	135
Yes	10 (14.5%)	21 (15.6%)
No	59 (85.5%)	114 (84.4%)

History of pRBC transfusion within 12 months prior to screening		
Number of patients with pRBC transfusion		
n	68	133
Yes	50 (73.5%)	103 (77.4%)
No	18 (26.5%)	30 (22.6%)
Number of units of pRBC transfused		
n	67	132
Mean (SD)	6.63 (8.70)	6.47 (8.27)
Median	3.00	3.75
Min - Max	0.0 - 41.0	0.0 - 43.5
Number of units of pRBC transfused		
n	67	132
0	18 (26.9%)	30 (22.7%)
0> to <4	16 (23.9%)	36 (27.3%)
>=4 to <14	22 (32.8%)	47 (35.6%)
>=14	11 (16.4%)	19 (14.4%)
Hemoglobin value at Baseline (g/L)		
n	69	135
Mean (SD)	99.68 (87.86)	87.18 (14.06)
Median	87.00	85.00
Min - Max	58.0 - 810.0	63.0 - 135.0
Haptoglobin value at Baseline (g/L)		
n	42	85
Mean (SD)	0.050 (0.000)	0.050 (0.000)
Median	0.050	0.050
Min - Max	0.05 - 0.05	0.05 - 0.05
LDH Value at Baseline (U/L)*		
n	69	134
Mean (SD)	1817.50 (829.09)	1770.61 (790.02)
Median	1811.00	1638.00
Min - Max	475.5 - 4761.5	458.0 - 3804.0
LDH value at Baseline (xULN)*		
n	69	134
Mean (SD)	7.77 (3.54)	7.57 (3.38)
Median	7.74	7.00
Min - Max	2.0 - 20.3	2.0 - 16.3
LDH Level at Baseline		
n	69	134
<2xULN	0	1 (0.7%)
>=2-<=4xULN	10 (14.5%)	22 (16.4%)
>4xULN	59 (85.5%)	111 (82.8%)

Baseline is the patient's last observation prior to initiation of study drug in the primary treatment period.
* Baseline LDH is defined as the mean of all central LDH values, collected within 28 days prior to the first on-study drug administration including the predose value from Day 1.
CCOD: 16NOV2022 Data Extract Date: 23JAN2023

Program: root/clinical_studies/RO7112689/CDT70115/share/data_analysis/prod/program/t_dm_pnh.sas
Output: root/clinical_studies/RO7112689/CDT70115/BO42162/data_analysis/CSR_1/prod/output/t_dm_pnh_RND1_16NOV2022_42162.out
01MAR2023 10:32
Adapted from t_dm_pnh_RND1_16NOV2022_42162.

Upon request, the applicant amended the table with data on PNH related symptoms.

Table 16: Summary of PNH history (amended)

Summary of PNH History incl. Baseline Laboratory Parameters and PNH Clone Sizes, Randomized Population
Protocol: BO42162

	B: Ecu (N=69)	A: Crova (N=135)

PNH-related signs or symptoms within 3 months prior to screening		
Abdominal Pain	11 (15.9%)	21 (15.6%)
Anemia	57 (82.6%)	109 (80.7%)
Dysphagia	2 (2.9%)	8 (5.9%)
Erectile Dysfunction	4 (5.8%)	13 (9.6%)
Fatigue	63 (91.3%)	113 (83.7%)
Hemoglobinuria	45 (65.2%)	79 (58.5%)
MAVE (including Thrombosis)	5 (7.2%)	9 (6.7%)
Shortness of Breath (Dyspnea)	14 (20.3%)	29 (21.5%)

Upon request, the summary of PNH History output for Study BO42161 has been updated to include central erythrocyte, granulocyte and monocyte clone sizes showing mean (SD), median, and minimum and maximal clone sizes.

Table 17: PNH history for Study BO42161

	B: Ecu (N=44)	A: Crova (N=45)
Type II Erythrocytes Clone Size (%)		
n	36	39
Mean (SD)	20.40 (27.20)	12.34 (17.95)
Median	4.87	5.21
Min - Max	0.1 - 81.1	0.1 - 76.8
Type III Erythrocytes Clone Size (%)		
n	36	41
Mean (SD)	35.56 (26.37)	38.35 (28.59)
Median	33.01	29.01
Min - Max	0.7 - 99.6	2.5 - 100.0
Total Erythrocytes Clone Size (%)		
n	36	41
Mean (SD)	55.96 (33.19)	50.09 (30.92)
Median	54.22	44.62
Min - Max	1.3 - 100.0	2.6 - 100.0
Monocyte PNH clone size (%) **		
n	37	40
Mean (SD)	86.96 (21.51)	80.84 (22.12)
Median	96.38	88.62
Min - Max	7.6 - 99.9	13.8 - 100.0
Granulocyte PNH clone size (%) **		
n	37	40
Mean (SD)	84.21 (25.16)	74.44 (28.40)
Median	95.67	88.07
Min - Max	7.9 - 99.9	5.2 - 100.2

Baseline is the patient's last observation prior to initiation of study drug in the primary treatment period.
* Baseline LDH is defined as the mean of all central LDH values, collected within 28 days prior to the first on-study drug administration including the predose value from Day 1.
** Monocyte PNH clone size (%) and Granulocyte PNH clone size (%) are Central lab data.
CCOD: 16NOV2022 Data Extract Date: 23JAN2023

- **Numbers analysed**

Table 18: Analysis populations (randomised population)

	B: Ecu (N=69)	A: Crova (N=135)
All Patients Population	69	135
Randomized Safety Population	69	135
Crovalimab Safety Population *	68	135
Primary Analysis Population	69	134
Per Protocol Population	59	112
Crovalimab efficacy Population, Arm B switch patients *	68	0
24-week Crovalimab Efficacy Population, Arm B switch patients ^	43	0
Biomarker-Evaluable Population	69	134
Crovalimab Pharmacokinetic-Evaluable Population *	68	135
Eculizumab Pharmacokinetic-Evaluable Population	69	0
Immunogenicity Population *	67	134

* For Arm B Eculizumab, the number represents patients who meet the criteria for the populations once they have switched to Crovalimab.
^ Includes all Arm B Eculizumab patients who switched to Crovalimab at least 24 weeks before CCOD.
CCOD: 16NOV2022 Data Extract Date: 23JAN2023

In both arms, all randomised patients were included in the randomised safety population. One patient was not included in the primary analysis population in the crovalimab arm due to death (Day 2) and therefore no post-baseline LDH assessment being available. The per protocol population included 112 and 59 patients in the randomised crovalimab and eculizumab arms, respectively.

Ą Outcomes and estimation

Exposure and study treatment compliance

Table 19: Study drug exposure (primary safety period, randomised safety population)

	B: Ecu (N=69)	A: Crova (N=135)
Treatment duration (weeks)		
n	69	135
Mean (SD)	22.02 (2.01)	19.72 (2.77)
25%-ile	22.14	20.00
Median	22.14	20.14
75%-ile	22.29	20.29
Min - Max	6.1 - 26.1	0.1 - 23.1
Treatment duration (weeks) categories		
n	69	135
>0 - <12 weeks	1 (1.4%)	3 (2.2%)
12 - <24 weeks	67 (97.1%)	132 (97.8%)
24 - <36 weeks	1 (1.4%)	0
Total cumulative dose (mg)		
n	69	135
Mean (SD)	11226.1 (933.8)	5714.4 (776.3)
Median	11400.0	5760.0
Min - Max	4200 - 13200	1000 - 9390
Total IV Dose intensity (%)		
n	69	135
Mean (SD)	100.00 (0.00)	101.46 (8.93)
Median	100.00	100.00
Min - Max	100.0 - 100.0	95.0 - 175.0
Total SC Dose intensity (%)		
n	0	134
Mean (SD)	NE (NE)	99.99 (2.12)
Median	NE	100.00
Min - Max	NE - NE	82.1 - 116.7
Number of doses		
n	69	135
Mean (SD)	13.80 (1.05)	9.84 (1.11)
Median	14.00	10.00
Min - Max	6.0 - 16.0	1.0 - 12.0
Sum	952.0	1328.0
Number of scheduled doses (intravenous, IV)		
n	69	135
Mean (SD)	13.80 (1.05)	1.01 (0.09)
Median	14.00	1.00
Min - Max	6.0 - 16.0	1.0 - 2.0
Sum	952.0	136.0
Number of unscheduled doses (intravenous, IV)		
n	69	135
0 doses	69 (100%)	131 (97.0%)
1 dose	0	2 (1.5%)
2 doses	0	2 (1.5%)
Number of doses (subcutaneous, SC)		
n	0	134
Mean (SD)	NE (NE)	8.85 (0.74)
Median	NE	9.00
Min - Max	NE - NE	3.0 - 10.0
Sum	NE	1186.0

IV dose intensity is a percentage based on actual intravenous dose / total planned intravenous dose.
SC dose intensity is a percentage based on actual subcutaneous dose / total planned subcutaneous dose.
CCOD: 16NOV2022 Data Extract Date: 23JAN2023

Crovalimab self-administration or administration by a caregiver was permitted in Study BO42162 starting at Week 9, after training and confirmation of proficiency by the health care provider.

Table 20: Summary of Crovalimab Administration by Healthcare Professional or Self-Administration (Crovalimab Safety Period, Arm A Crovalimab Safety Population)

Visit Name	By Healthcare Professional n(%)	By Patient/Caregiver n(%)		All Patients
		At site	Off site	
Week 9	108 (82.4%)	20 (15.3%)	3 (2.3%)	131
Week 13	108 (82.4%)	20 (15.3%)	3 (2.3%)	131
Week 17	107 (82.9%)	17 (13.2%)	5 (3.9%)	129
Week 21	91 (70.5%)	31 (24.0%)	7 (5.4%)	129
Week 25	89 (69.0%)	40 (31.0%)	0	129
Week 29	67 (54.5%)	13 (10.6%)	43 (35.0%)	123
Week 33	75 (61.5%)	32 (26.2%)	15 (12.3%)	122
Week 37	41 (41.0%)	13 (13.0%)	46 (46.0%)	100
Week 41	57 (61.3%)	24 (25.8%)	12 (12.9%)	93
Week 45	35 (40.7%)	13 (15.1%)	38 (44.2%)	86
Week 49	51 (64.6%)	14 (17.7%)	14 (17.7%)	79
Week 53	29 (50.0%)	4 (6.9%)	25 (43.1%)	58
Week 57	24 (49.0%)	4 (8.2%)	21 (42.9%)	49
Week 61	30 (71.4%)	7 (16.7%)	5 (11.9%)	42
Week 65	18 (56.3%)	3 (9.4%)	11 (34.4%)	32
Week 69	17 (70.8%)	1 (4.2%)	6 (25.0%)	24
Week 73	12 (75.0%)	2 (12.5%)	2 (12.5%)	16
Week 77	6 (60.0%)	0	4 (40.0%)	10
Week 81	6 (75.0%)	0	2 (25.0%)	8
Week 85	5 (83.3%)	0	1 (16.7%)	6
Week 89	4 (80.0%)	0	1 (20.0%)	5
Week 93	4 (100.0%)	0	0	4
Week 97	3 (100.0%)	0	0	3
Week 101	2 (100.0%)	0	0	2
Week 105	1 (100.0%)	0	0	1
Week 109	1 (100.0%)	0	0	1

Self administration information is summarized from Week 9 according to the self-administration guidance specified in the protocol.
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, patients and/or patient caregiver(s) were trained in SC administration of crovalimab by a health care provider.
Percentages are calculated based on number of patients given in "All patients" column of the same line.
CCOD: 16NOV2022 Data Extract Date: 23JAN2023

- Co-primary endpoint: Transfusion avoidance (TA)

Transfusion avoidance (TA) was defined as patients who are packed RBC (pRBC) transfusion-free and do not require transfusion per protocol-specified guidelines.

Table 21: Proportion of Patients who Achieve Transfusion Avoidance from Baseline through Week 25 (Primary Analysis Population)

	B: Ecu (N=69)	A: Crova (N=134)
Patients with TA, n (%)	47 (68.1%)	88 (65.7%)
95% CI for proportion *	(55.67, 78.53)	(56.91, 73.52)
Weighted difference in proportion (Crova - Ecu)		-2.8%
95% CI for difference in proportion (Crova - Ecu) **		(-15.67, 11.14)
p-Value (Mantel-Haenszel)		0.6655

* 95% CI for proportion is calculated using the Wilson's method with continuity correction.
** 95% CI for the difference in proportions of patients with Transfusion avoidance is calculated by Stratified Newcombe CI method (Yan and Su, 2010); non-inferiority is met when the lower limit of the 95% CI is greater than -20%. p-Value evaluates the superiority test.
Patients who discontinued treatment before Week 25 are assumed to have had a Transfusion.
Only patients that were recruited at least 24 weeks before CCOD are included.
CCOD: 16NOV2022 Data Extract Date: 23JAN2023

Table 22: Overview of Transfusion Avoidance Co-Primary Efficacy Endpoint Sensitivity Analyses

Co-Primary Efficacy Endpoints – TA	Eculizumab	Crovalimab
Primary Analysis[a] – Primary Analysis Population	N = 69	N = 134
Proportion of patients with TA, % (95% CI)	68.1 (55.67, 78.53)	65.7 (56.91, 73.52)
Difference in proportions, % (95% CI)	−2.8 (−15.67, 11.14) *NIM for lower 95% CI limit = −20%*	
Per-Protocol Population	N = 59	N = 112
Proportion of patients with TA, % (95% CI)	67.8 (54.24, 79.03)	66.1 (56.44, 74.58)
Difference in proportions, % (95% CI)	−4.4 (−18.31, 10.78)	
Randomized Population	N = 69	N = 135
Proportion of patients with TA, % (95% CI)	68.1 (55.67, 78.53)	65.2 (56.45, 73.04)
Difference in proportions, % (95% CI)	−3.3 (−16.19, 10.61)	

NIM = non-inferiority margin; TA = transfusion avoidance.
[a] Transfusion avoidance assessed from baseline through Week 25.
Sources: t_ef_PAP1_TRANFR25_OCM24P1_16NOV2022_42162; t_ef_PP1_TRANFR25_16NOV2022_42162; t_ef_RND1_TRANFR25_16NOV2022_42162.

A Co-primary endpoint: Haemolysis control

Haemolysis control was measured by central LDH ≤1.5 x ULN from Week 5 through Week 25.

Figure 21: Proportion of Patients and 95% CI with haemolysis control through Week 25 by Visit (Primary Analysis Population)

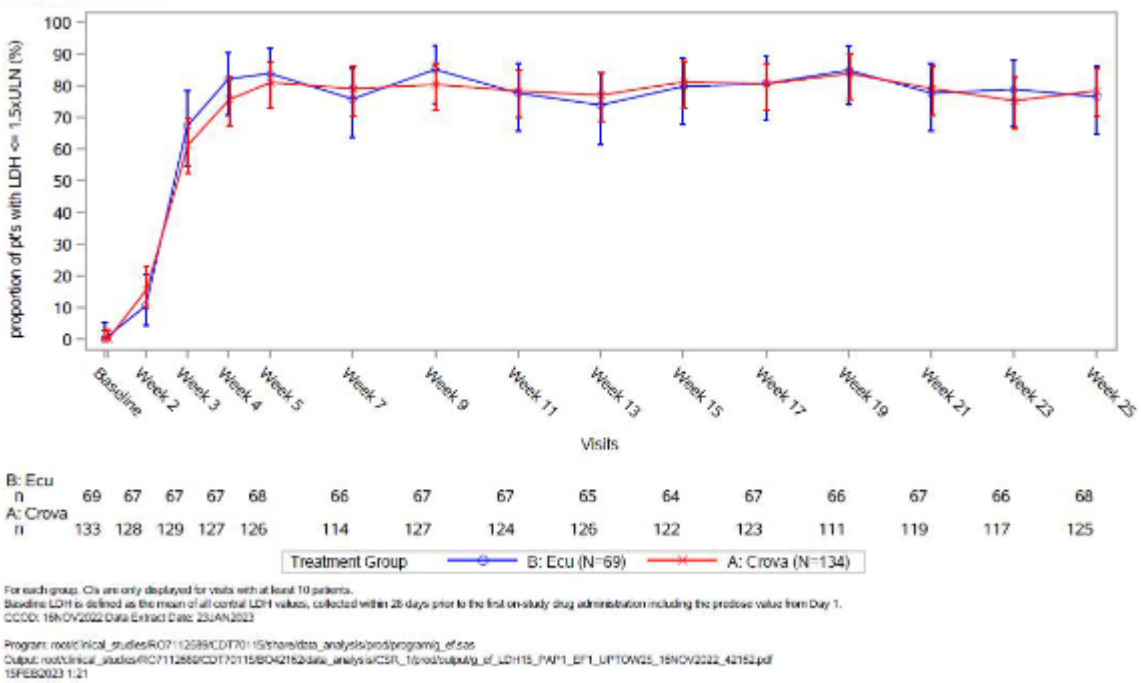


Table 23: Mean Proportion of Patients Achieving Haemolysis Control from Week 5 through Week 25 (Primary Analysis Population)

	B: Ecu (N=69)	A: Crova (N=134)
Mean Proportion of Patients Achieving Hemolysis Control	78.96%	79.27%
95% CI	(69.66, 85.99)	(72.86, 84.48)
Odds Ratio (95% CI)		1.02 (0.57, 1.82)
p-Value		0.9504

Estimates are based on GEE model.
Odds ratio greater than 1 favours Crovalimab. Non-inferiority is met when the lower limit of the 95% CI is greater than 0.2. p-Value evaluates the superiority test.
Only patients that were recruited at least 24 weeks before CCOD are included.
CCOD: 16NOV2022 Data Extract Date: 23JAN2023

Table 24: Overview of Haemolysis Control Co-Primary Efficacy Endpoint Sensitivity Analyses

Co-Primary Efficacy Endpoints – Hemolysis Control	Eculizumab	Crovalimab
Primary analysis[a] – Primary Analysis Population	N=69	N=134
Mean proportion of patients achieving hemolysis control, % (95% CI)	79.0 (69.66, 85.99)	79.3 (72.86, 84.48)
Odds Ratio (95% CI)	1.02 (0.57, 1.82)	
	NIM for lower 95% CI limit=0.2	
Per-Protocol Population	N=59	N=112
Mean proportion of patients achieving hemolysis control, % (95% CI)	79.7 (72.64, 85.32)	80.3 (70.43, 87.46)
Odds Ratio (95% CI)	0.96 (0.51, 1.81)	
Randomized Population	N=69	N=135
Mean proportion of patients achieving hemolysis control, % (95% CI)	79.0 (69.66, 85.99)	79.3 (72.86, 84.48)
Odds Ratio (95% CI)	1.02 (0.57, 1.82)	
MCMC Algorithm[b]	N=69	N=134
Mean proportion of patients achieving hemolysis control, % (95% CI)	78.0 (69.67, 86.33)	77.5 (71.69, 83.37)
Odds Ratio (95% CI)	0.97 (0.55, 1.71)	
PMM Algorithm[b]	N=69	N=134
Mean proportion of patients achieving hemolysis control, % (95% CI)	78.1 (69.80, 86.47)	77.6 (71.69, 83.41)
Odds Ratio (95% CI)	0.97 (0.55, 1.70)	
Tipping Point Analysis[b]	N=69	N=134
Mean proportion of patients achieving hemolysis control, % (95% CI)	80.4 (71.46, 87.09)	72.0 (65.64, 77.62)
Odds Ratio (95% CI)	0.63 (0.36, 1.08)	

MCMC=Markov Chain Monte Carlo; NIM=non-inferiority margin; PPM=Pattern Mixture Model.

[a] Hemolysis control measured as central LDH ≤ 1.5x ULN from Week 5 through Week 25.

[b] Sensitivity analyses assessing the impact of missing central LDH values.

Sources: t_ef_odds_PAP1_OCM24P1_16NOV2022_42162; t_ef_odds_PP1_OCM24P1_16NOV2022_42162; t_ef_odds_RND1_OCM24P1_16NOV2022_42162; t_ef_odds_mcmc_PAP1_16NOV2022_42162; t_ef_odds_pmm_PAP1_16NOV2022_42162; t_ef_odds_sens_PAP1_OCM24P1_16NOV2022_42162.

- Secondary endpoint: Breakthrough haemolysis (BTH)

BTH was defined as at least one new or worsening symptom or sign of intravascular haemolysis (fatigue, haemoglobinuria, abdominal pain, shortness of breath [dyspnoea], anaemia [haemoglobin <10 g/dL], a major adverse vascular event [MAVE, including thrombosis], dysphagia, or erectile dysfunction) in the presence of elevated LDH ≥2 x ULN after prior reduction of LDH to ≤1.5 x ULN on treatment.

Table 25: Proportion of Patients with Breakthrough Haemolysis from Baseline through Week 25 (Primary Analysis Population)

	B: Ecu (N=69)	A: Crova (N=134)
Patients with at least one BTH, n (%)	10 (14.5%)	14 (10.4%)
95% CI for proportion *	(7.54, 25.50)	(6.04, 17.21)
Weighted difference in proportion (Crova - Ecu)		-3.9%
95% CI for difference in proportion (Crova - Ecu) **		(-14.82, 5.26)
p-Value (Mantel-Haenszel)		0.4358

* 95% CI for BTH proportion is calculated using the Wilson's method with continuity correction.
** 95% CI for the difference in proportions is calculated by Stratified Newcombe CI method (Yan and Su, 2010); non-inferiority is met when the upper limit of the 95% CI is less than 20%. p-Value tests for superiority.
Patients who discontinued treatment before Week 25 are considered to have a BTH event.
Only patients that were recruited at least 24 weeks before CCOD are included.
CCOD: 16NOV2022 Data Extract Date: 23JAN2023

A Secondary endpoint: Stabilised Hb

Stabilised haemoglobin is defined as avoidance of a ≥2 g/dL decrease in haemoglobin level from baseline, in the absence of transfusion.

Table 26: Proportion of Patients with Stabilised Haemoglobin from Baseline through Week 25 (Primary Analysis Population)

	B: Ecu (N=69)	A: Crova (N=134)
Patients with Hemoglobin Stabilization, n (%)	42 (60.9%)	85 (63.4%)
95% CI for proportion *	(48.35, 72.17)	(54.63, 71.45)
Weighted difference in proportion (Crova - Ecu)		2.2%
95% CI for difference in proportion (Crova - Ecu) **		(-11.37, 16.31)
p-Value (Mantel-Haenszel)		0.7496

Stabilized hemoglobin is defined as avoidance of a >=2 g/dL decrease in hemoglobin level from baseline, in the absence of transfusion.
* 95% CI for Proportion of patients with Stabilized Hemoglobin is calculated using the Wilson's method with continuity correction.
** 95% CI for the difference in proportions of patients with Stabilized Hemoglobin calculated by Stratified Newcombe CI method (Yan and Su, 2010); non-inferiority is met when the lower limit of the 95% CI is greater than -20%.
Patients who discontinued treatment before Week 25 are considered to not have had stabilized hemoglobin.
Only patients that were recruited at least 24 weeks before CCOD are included.
CCOD: 16NOV2022 Data Extract Date: 23JAN2023

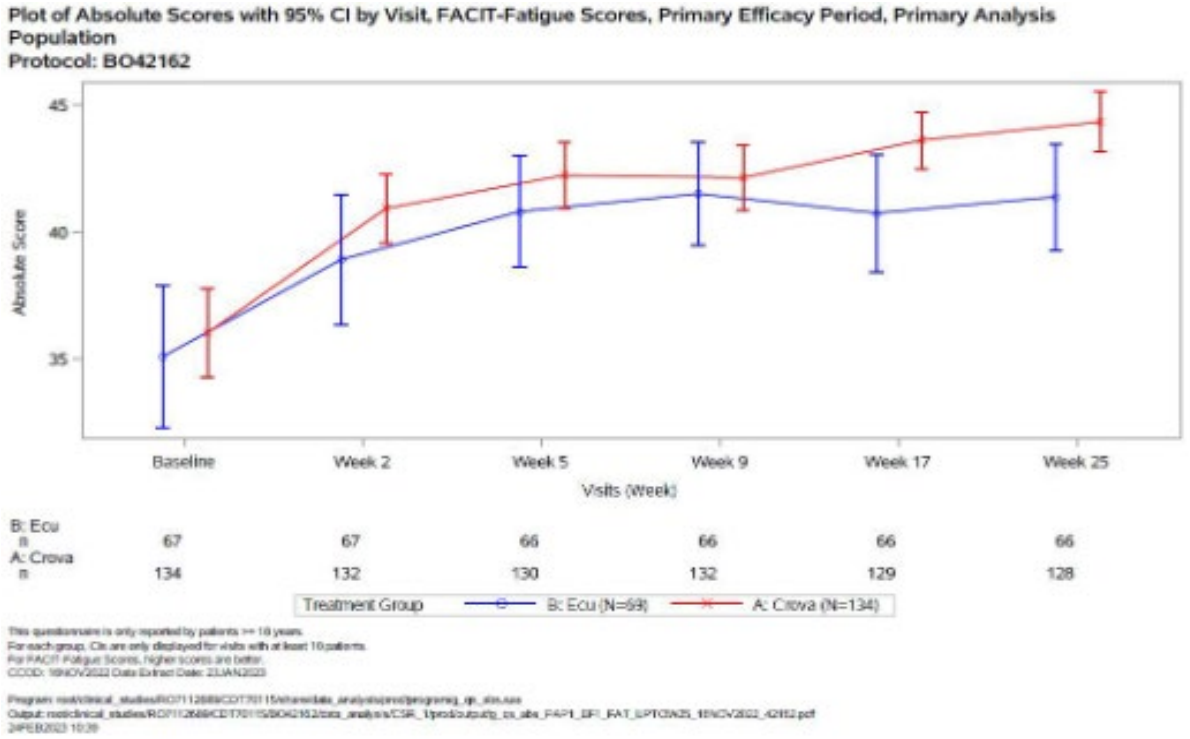
- Exploratory endpoint: change in FACIT-Fatigue

Table 27: Mean Change from Baseline to Week 25 in FACIT-Fatigue Scores (Primary Analysis Population)

Visit	Statistics	B: Ecu (N=69)	A: Crova (N=134)
Baseline	n	67	134
	Mean (SE)	35.09 (1.408)	36.02 (0.877)
Week 25	n	66	128
	Adjusted Mean (SE)	5.15 (0.880)	7.79 (0.661)
	95% CI for Adjusted Mean	(3.42, 6.89)	(6.49, 9.09)
	Difference in Adjusted Means (SE)		2.64 (0.993)
	95% CI for Difference in Adjusted Means		(0.68, 4.60)
	p-value		0.0087

Baseline is the patient's last observation prior to initiation of study drug in the primary treatment period.
Estimates include patients with an assessment at baseline. Estimates are from analysis based on mixed-effect model of repeated measures (MMRM) using unstructured covariance matrix.
Only patients that were recruited at least 24 weeks before CCOD are included.
Non-inferiority is met when the lower limit of the 95% CI is greater than -5.
p-Value tests for superiority.
CCOD: 16NOV2022 Data Extract Date: 23JAN2023

Figure 22: FACIT-Fatigue Scores through to Week 25 by Visit (Primary Analysis Population)



Ą Exploratory endpoint: red blood cell transfusions

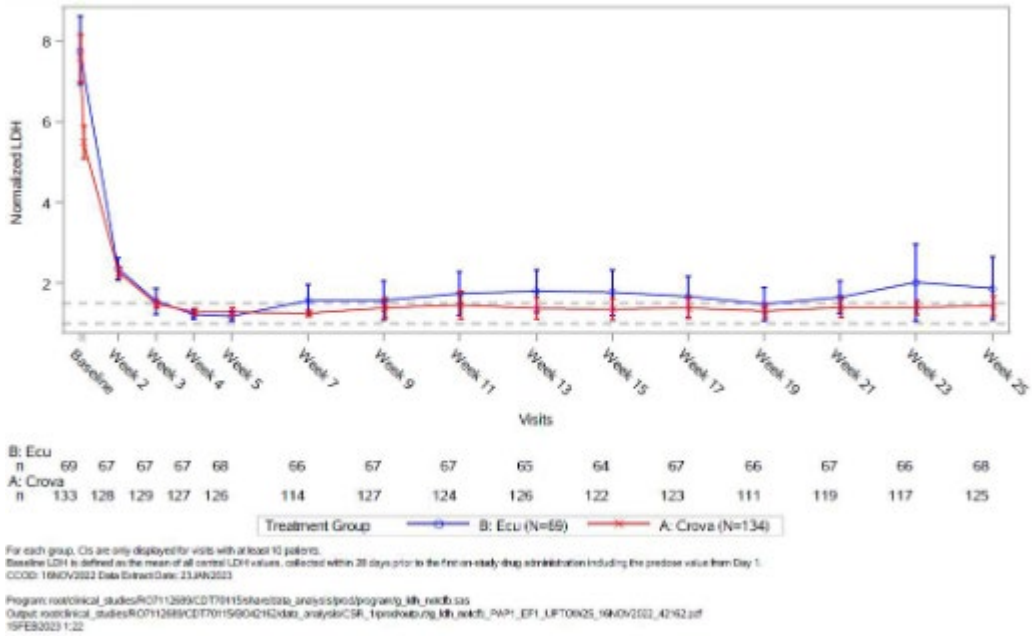
Table 28: Total Number of Units of Packed Red Blood Cells Transfused from Baseline to Week 25 (Primary Analysis Population)

	B: Ecu (N=69)	A: Crova (N=134)
Patients with at least one transfusion, n (%)	22 (31.9%)	45 (33.6%)
Total number of units of pRBC transfused		
n	69	134
Mean (SD)	2.20 (4.83)	2.33 (6.02)
95% CI for Mean	(1.04, 3.36)	(1.30, 3.36)
Median	0.00	0.00
Min - Max	0.0 - 25.0	0.0 - 55.0

Only patients that were recruited at least 24 weeks before CCOD are included.
CCOD: 16NOV2022 Data Extract Date: 23JAN2023

- Additional exploratory LDH-related endpoints
    - Mean normalised LDH levels from baseline to week 25

Figure 23: Mean Normalised Central LDH with 95% CIs from Baseline to Week 25 by Visit (Primary Analysis Population)

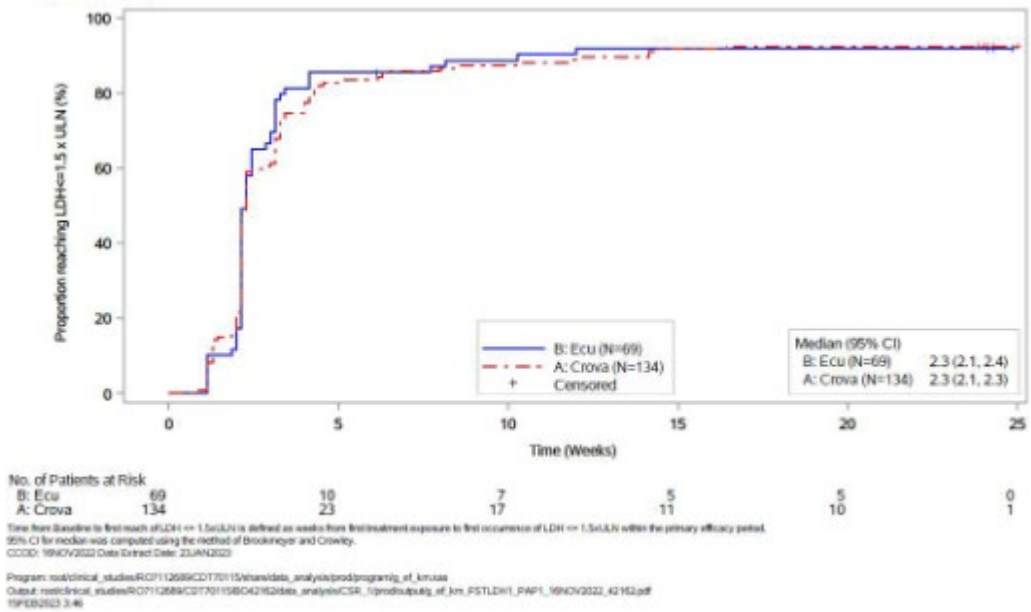


- Percent Change from Baseline to Week 25 in LDH Levels

Mean percent reduction in LDH levels (central assessment) from baseline to Week 25 was -73.6% (95% CI: -78.95, -68.22) in the crovalimab arm compared with -64.1% (95% CI: -71.36, -56.75) in the eculizumab arm.

- Time to First Reach Central LDH ≤1.5 x ULN

Figure 24: Time from Baseline to the First Reach of Central LDH ≤ 1.5 x ULN through Week 25 (Primary Analysis Population)

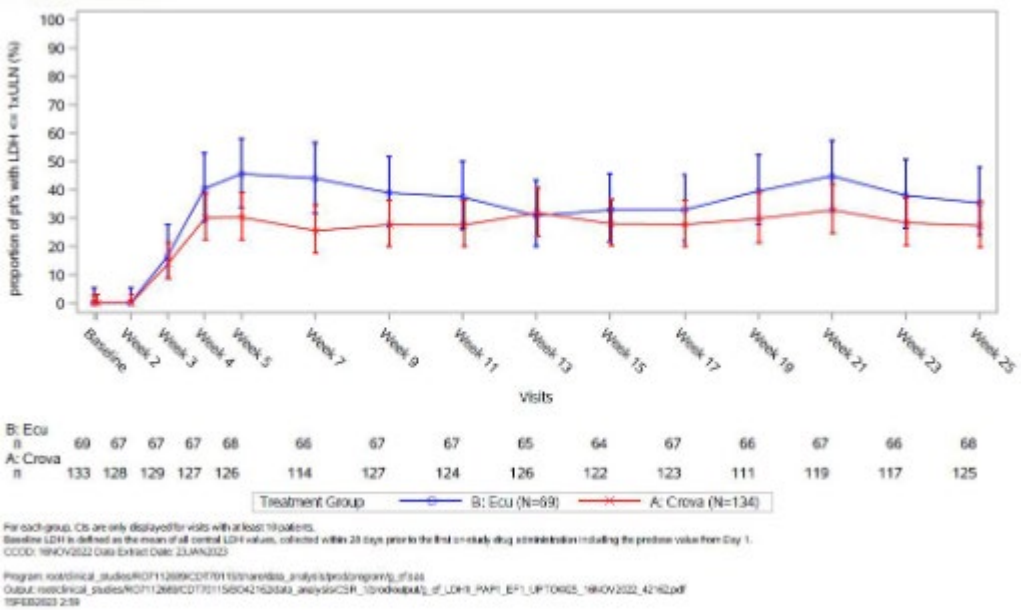


- Mean Proportion of Patients with Central LDH ≤ 1.0 x ULN from Week 5 through to Week 25

The mean proportion of patients with haemolysis control as measured by central LDH ≥ 1.0 x ULN from Week 5 through Week 25 was 28.8% (95% CI: 22.67, 35.71) for the crovalimab arm and 37.8% (95% CI: 28.77, 47.65) for the eculizumab arm. The odds ratio for haemolysis control (crovalimab versus eculizumab) was 0.67 (95% CI: 0.40, 1.11).

By visit, the proportion of patients achieving LDH ≥ 1.0 x ULN increased from 0% at baseline (both arms) to 30.2% in the crovalimab arm and 45.6% in the eculizumab arm by Week 5, and remained between 25.4% to 32.8% for crovalimab and 30.8% to 44.8% for eculizumab, from Week 7 through to Week 25.

Figure 25: Proportion of Patients and 95% CI with Central LDH ≤ 1 x ULN from Baseline through Week 25 by Visit (Primary Analysis Population)



The mean proportion of patients at each visit reaching LDH ≤ 1.0 x ULN was higher in the eculizumab arm starting from Week 3 to Week 25 compared with the crovalimab arm.

- Time to First Reach Central LDH ≤1.0 x ULN

The proportion of patients reaching central LDH ≤ 1.0 x ULN before Week 25 was 47.8% in the crovalimab arm compared to 62.3% in the eculizumab arm.

Less than 50% of the patients in the crovalimab arm achieved central LDH ≤ 1.0 x ULN during the primary treatment period, and therefore the median time to haemolysis control was not reached for crovalimab as of the primary analysis CCOD. The median time to first reach central LDH ≤ 1.0 x ULN for eculizumab was 4.1 weeks.

- Exploratory endpoint: Maintenance of haemoglobin ≥ 10 g/dL without subsequent decrease below 9 g/dL

Table 29: Summary of Proportion of Patients Who Reach and Maintain a Minimum Hb level from Baseline through to Week 25, Primary Analysis Population

	B: Ecu (N=69)	A: Crova (N=134)
Patients Who Reach and Maintain a Minimum Hgb level, n (%)	30 (43.5%)	61 (45.5%)
95% CI for proportion *	(31.77, 55.92)	(36.98, 54.33)
Weighted difference in proportion (Crova - Ecu)		1.8%
95% CI for difference in proportion (Crova - Ecu) **		(-12.52, 15.70)

Patients who reach and maintain a minimum hgb level is defined as patients who reach a Hemoglobin Level of at least 10 g/dL, without Subsequent Decrease below 9 g/dL, in Absence of Transfusion
* 95% CI for proportion of patients who reach and maintain a minimum hgb level is calculated using the Wilson's method with continuity correction.
** 95% CI for the difference between the proportions of patients with who reach and maintain a minimum hgb level is calculated by using the Stratified Newcombe method (Yan and Su, 2010), non-inferiority margin: -20%.
Patients who discontinued treatment before Week 25 are considered to not have had minimum hemoglobin level.
Only patients that were recruited at least 24 weeks before CCOD are included.
CCOD: 16NOV2022 Data Extract Date: 23JAN2023

- MAVE

  The symptoms of MAVE in 2 patients (treated with crovalimab and eculizumab respectively) were myocardial infarction and TIA. These events occurred on day 1 and 49 respectively.

- Patient-reported outcomes

Results from EORTC QLQ-C30, EORTC IL40, TSQM-9, QLQ AA/PNH, PGIS, Patient Preference questionnaire are detailed in the clinical AR.

Ancillary analyses

Subgroup analyses

Table 30: Subgroup Analyses of Proportion of Patients with TA with 95% CI (Primary Analysis Population)

Subgroup	Total n	B: Ecu (N=69) n	B: Ecu (N=69) proportion (95% CI)	A: Crova (N=134) n	A: Crova (N=134) proportion (95% CI)	Difference in Proportion (95% CI)
Age Group (yr)						
<18	2	2	50.00% (2.67 , 97.33)	0	NE	NE
18 - 64	180	58	72.41% (58.89 , 82.95)	122	66.39% (57.20 , 74.53)	-6.02(-19.20 , 8.80)
>=65	21	9	44.44% (15.34 , 77.35)	12	58.33% (28.60 , 83.50)	13.89(-25.23 , 47.84)
Sex						
Female	91	34	64.71% (46.47 , 79.70)	57	59.65% (45.84 , 72.16)	-5.06(-23.99 , 15.43)
Male	112	35	71.43% (53.48 , 84.76)	77	70.13% (58.47 , 79.75)	-1.30(-17.75 , 17.51)
Region						
Europe / Central, South and North America	67	18	66.67% (41.15 , 85.64)	49	63.27% (48.25 , 76.21)	-3.40(-25.47 , 22.50)
Japan and Rest of Asia Pacific	136	51	68.63% (53.97 , 80.48)	85	67.06% (55.92 , 76.64)	-1.57(-16.83 , 14.82)
Eculizumab available Region						
Yes	81	26	69.23% (48.10 , 84.91)	55	63.64% (49.51 , 75.86)	-5.59(-25.04 , 16.77)
No	122	43	67.44% (51.34 , 80.46)	79	67.09% (55.50 , 77.00)	-0.35(-16.64 , 17.26)
Race						
Asian	137	51	68.63% (53.97 , 80.48)	86	66.28% (55.19 , 75.90)	-2.35(-17.59 , 14.06)
Black Or African American	4	1	100% (5.46 , 100)	3	100% (31.00 , 100)	NE
White	60	16	68.75% (41.48 , 87.87)	44	61.36% (45.51 , 75.25)	-7.39(-29.95 , 20.17)
Unknown	2	1	0% (0.00 , 94.54)	1	100% (5.46 , 100)	100 (-12.21 , 100)
Stratification factor: Number of pRBC Transfusions in 6 Months Prior to Randomization						
0 UNITS	50	17	82.35% (55.80 , 95.33)	33	87.88% (70.86 , 96.04)	5.53(-13.51 , 30.02)
>0 TO<=6 UNITS	101	34	73.53% (55.35 , 86.49)	67	70.15% (57.57 , 80.40)	-3.38(-20.12 , 15.85)
>6 UNITS	52	18	44.44% (22.40 , 68.65)	34	35.29% (20.30 , 53.53)	-9.15(-34.99 , 16.88)
Stratification factor: Local LDH Level at Randomization						
>=2 TO <=4 X ULN	35	11	63.64% (31.61 , 87.63)	24	79.17% (57.29 , 92.06)	15.53(-13.36 , 46.07)
>4 X ULN	168	58	68.97% (55.31 , 80.10)	110	62.73% (52.95 , 71.61)	-6.24(-20.21 , 9.08)
Aplastic Anaemia						
Yes	78	26	76.92% (55.92 , 90.25)	52	65.38% (50.84 , 77.67)	-11.54(-29.69 , 10.63)
No	125	43	62.79% (46.72 , 76.61)	82	65.85% (54.47 , 75.74)	3.06(-13.69 , 20.68)
Body Weight (kg)						
40 - <100	196	66	66.67% (53.88 , 77.50)	130	65.38% (56.48 , 73.37)	-1.28(-14.55 , 12.95)
>=100	7	3	100% (31.00 , 100)	4	75.00% (21.94 , 98.68)	-25.00(-69.94 , 34.75)

95% CI for proportion is calculated using the Wilson's method with continuity correction.
Only patients that were recruited at least 24 weeks before CCOD are included.
CCOD: 16NOV2022 Data Extract Date: 23JAN2023

Table 31: Subgroup Analyses of Proportion of Patients Achieving Haemolysis Control (Central LDH <= 1.5 x ULN), Primary Analysis Population

Subgroup	Total n	B: Ecu (N=69) n	proportion (95% CI)	A: Crova (N=134) n	proportion (95% CI)	Odds Ratio (95% CI)
Age Group (yr)						
<18	2	2	62.15% (43.66 , 77.68)	0	NE	NE
18 - 64	180	58	82.82% (73.40 , 89.38)	122	80.95% (74.98 , 85.77)	0.88 (0.46, 1.70)
>=65	21	9	78.88% (49.50 , 93.43)	12	69.73% (45.13 , 86.58)	0.62 (0.11, 3.34)
Sex						
Female	91	34	92.23% (85.10 , 96.10)	57	78.45% (68.83 , 85.71)	0.31 (0.13, 0.74)
Male	112	35	71.14% (56.92 , 82.14)	77	81.22% (73.62 , 87.02)	1.76 (0.82, 3.76)
Region						
Europe / Central, South and North America	67	18	85.78% (69.09 , 94.21)	49	76.25% (64.89 , 84.80)	0.53 (0.17, 1.66)
Japan and Rest of Asia Pacific	136	51	77.26% (66.85 , 85.13)	85	81.56% (74.67 , 86.90)	1.30 (0.67, 2.52)
Eculizumab available Region						
Yes	81	26	81.81% (65.54 , 91.40)	55	79.41% (69.34 , 86.80)	0.86 (0.31, 2.36)
No	122	43	81.80% (71.24 , 89.07)	79	80.43% (72.98 , 86.21)	0.91 (0.44, 1.90)
Race						
Asian	137	51	80.96% (70.71 , 88.22)	86	82.88% (76.17 , 88.00)	1.14 (0.56, 2.30)
Black Or African American	4	1	74.03% (NE , NE)	3	83.98% (65.20 , 93.62)	1.84 (0.66, 5.14)
White	60	16	87.17% (64.93 , 96.14)	44	74.41% (61.88 , 83.90)	0.43 (0.10, 1.78)
Unknown	2	1	69.47% (NE , NE)	1	81.98% (81.98 , 81.98)	2.00 (NE , NE)
Stratification factor: Number of pRBC Transfusions in 6 Months Prior to Randomization						
0 UNITS	50	17	77.57% (56.32 , 90.27)	33	83.42% (67.65 , 92.37)	1.45 (0.39, 5.45)
>0 TO<=6 UNITS	101	34	88.98% (78.26 , 94.77)	67	82.38% (75.00 , 87.93)	0.58 (0.23, 1.46)
>6 UNITS	52	18	71.98% (53.11 , 85.36)	34	71.56% (59.36 , 81.26)	0.98 (0.37, 2.62)
Stratification factor: Local LDH Level at Randomization						
>=2 TO <=4 X ULN	35	11	64.78% (40.15 , 83.45)	24	75.23% (55.83 , 87.95)	1.65 (0.43, 6.29)
>4 X ULN	168	58	85.18% (76.41 , 91.08)	110	81.16% (75.23 , 85.93)	0.75 (0.38, 1.47)
Aplastic Anaemia						
Yes	78	26	83.60% (68.06 , 92.42)	52	81.22% (71.79 , 88.02)	0.85 (0.31, 2.35)
No	125	43	80.79% (69.85 , 88.42)	82	79.17% (71.37 , 85.28)	0.90 (0.44, 1.88)
Body Weight (kg)						
40 - <100	196	66	82.68% (74.25 , 88.78)	130	79.98% (74.10 , 84.80)	0.84 (0.46, 1.53)
>=100	7	3	63.83% (16.10 , 94.20)	4	79.74% (31.87 , 97.07)	2.23 (0.10, 48.29)

Estimates are based on GEE model.
Odds ratio greater than 1 favours Crovalimab.
Only patients that were recruited at least 24 weeks before CCOD are included.
CCOD: 16NOV2022 Data Extract Date: 23JAN2023

Descriptive arm C

Participant flow

Figure 26: Patient disposition (descriptive Arm C)

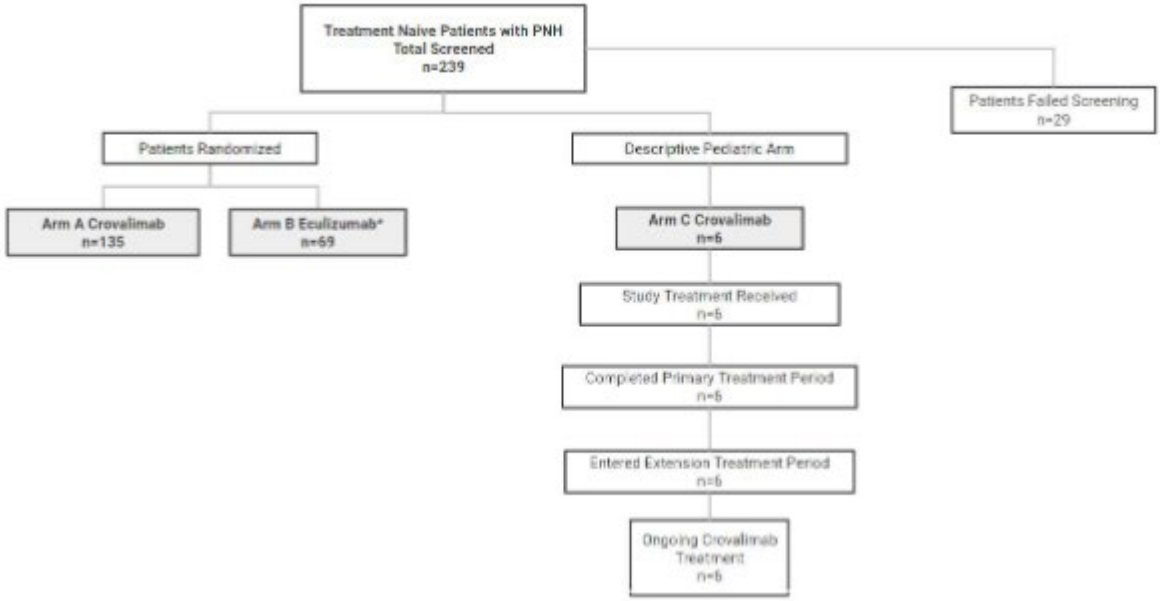


Table 32: Listing of major protocol deviations in Arm C

Treatment Group: Arm C Crovalimab (N=6)

Center/Patient ID - Age/Sex/Race	Category	Description	Date	Study Day of Start of Deviation	Actual Treat.
	MEDICATION	Dose missed or out of window			CROVA
	PROCEDURAL	Failure to collect laboratory samples			CROVA
	PROCEDURAL	Failure to collect laboratory samples			CROVA
	PROCEDURAL	Failure to collect laboratory samples			CROVA
	MEDICATION	Dose missed or out of window			CROVA
	PROCEDURAL	Failure to collect laboratory samples			CROVA
	PROCEDURAL	Missing >2 PK samples from Wk 5-25			CROVA
	PROCEDURAL	Any visit occurring outside of the specified time window			CROVA
	PROCEDURAL	Failure to collect laboratory samples			CROVA
	PROCEDURAL	Missed 2 or more efficacy assessments			CROVA
	PROCEDURAL	Missing >1 PK samples in first 4 weeks			CROVA
	PROCEDURAL	Failure to collect laboratory samples			CROVA
	MEDICATION	Received incorrect dose of the study medication (includes overdose)			CROVA
	PROCEDURAL	Failure to obtain signature of updated ICF			CROVA

CCOD: 16NOV2022 Data Extract Date: 23JAN2023

Table 33: Demographics and baseline characteristics in Arm C

Treatment Group: Arm C Crovalimab (N=6)

Center/Patient ID - Age/Sex/Race	Weight (kg)	Height (cm)	BMI (kg/m2)	Ethnicity	Number of Screenings	Num pRBCs in 6 Mths Pr to Rnd	Baseline LDH (U/L)
	80.0	182.0	24.2		1	Missing	1432.5
	54.0	173.0	18.0		1	Missing	1950.5
	50.0	170.0	17.3		1	Missing	811.5
	67.5	170.0	23.4		1	Missing	1171.5
	68.0	176.0	22.0		2	Missing	6118.5
	98.5	186.0	28.5		1	Missing	2047

CCOD: 16NOV2022 Data Extract Date: 23JAN2023

Table 34: Listing of PNH history in Arm C

Treatment Group: Arm C Crovalimab (N=6)

Center/Patient ID - Age/Sex/Race	Date of PNH Diagnosis	Age at PNH Diagnosis (years)	Time from PNH Diag. to enrollment (years)	History of				pRBC Transf. 12 Mths Prior to Screen.	No. of pRBCs Transf. 12 Mths Prior to Screen.
				Aplastic Anemia	Renal Impair-ment	MAVE	MDS		
		16.28	1.26	No	No	No	No	Yes	1.5
		13.67	0.19	Yes	No	No	No	No	0
		15.25	1.42	Yes	No	No	No	Yes	40.5
		15.43	2.56	No	No	No	No	Yes	1
		11.54	5.76	Yes	No	No	No	Yes	26
		16.98	0.10	No	No	No	No	No	0

MAVE = Major Vascular Event, MDS = Myelodysplastic Syndrome
CCOD: 16NOV2022 Data Extract Date: 23JAN2023

Numbers analysed

All 6 paediatric patients were included in the Arm C All Patients, Efficacy, Crovalimab Safety, Pharmacokinetic-Evaluable, Immunogenicity and Biomarker-Evaluable populations.

Outcomes and estimation

Exposure and treatment compliance

Treatment duration in the 6 paediatric patients ranged between 21 and 57 weeks. All patients completed the primary treatment period and are ongoing in the crovalimab extension period as of the CCOD.

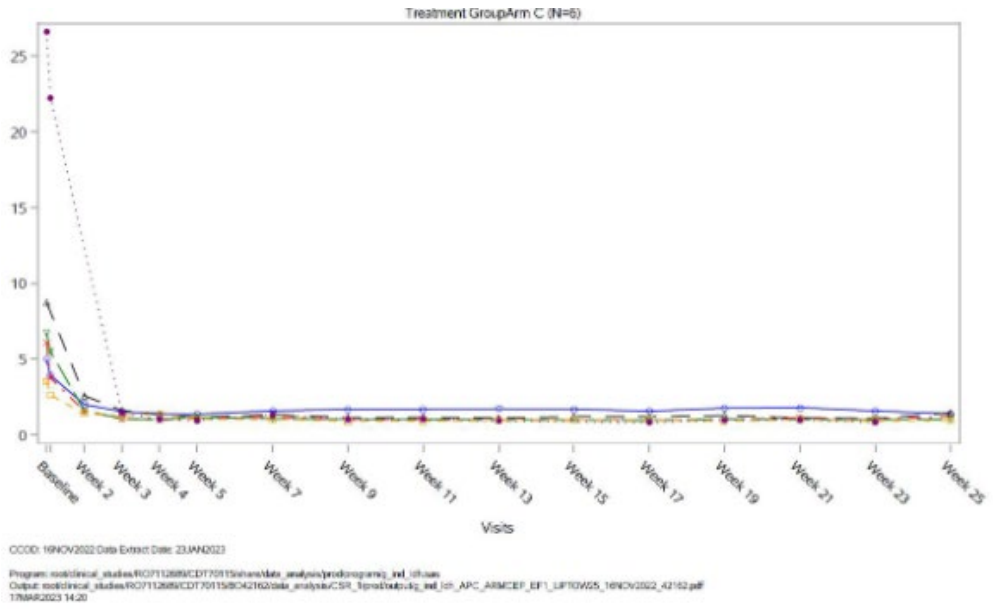
For one patient, the SC dose of crovalimab was increased from 680 mg to 1020 mg from Week 13 onward, in the context of weight increase to > 100 kg (from 98.5 kg at baseline); however, this weight increase did not meet the >10% change criterion and a major protocol deviation in relation to this modification was recorded; no new safety signal was detected in relation to this increased crovalimab dose. The patient remained on the 1020 mg dose at the time of CCOD.

Self-administration or drug administration by a caregiver was also permitted in the descriptive arm of paediatric patients at Week 9, after training and confirmation of proficiency by the health care provider. Between Weeks 9 and 25, SC injections were administered by healthcare professionals to 3 of the paediatric patients, of which one patient had not yet reached Week 25 at the COOD. In the case of the other 3 patients, SC injections of crovalimab were administered by the patients or by their

caregiver. After Week 25, administration by patient/caregiver increased, with an increase in off-site administration.

Co-primary endpoint: haemolysis control

Figure 27: Plot of Individual Patient Profiles, Normalised LDH (Arm C Efficacy Analysis Population)



Other efficacy endpoints

Table 35: Listing of Haemoglobin Stabilisation, Breakthrough Haemolysis and Transfusion Avoidance by Patient in Arm C

Center/Patient ID - Age/Sex/Race	Had the Opportunity to Complete First 24 Weeks	Had the Opportunity to Complete 24 Weeks Post Switch	Stabilized Hemoglobin			Breakthrough Hemolysis			Transfusion Free		
			Baseline to Week 25	On Crova	Switch to Week 25 Post Switch	Baseline to Week 25	On Crova	Switch to Week 25 Post Switch	Baseline to Week 25	On Crova	Switch to Week 25 Post Switch
	Y	NA	Yes	Yes	NA#	No	No	NA#	Yes	Yes	NA#
	Y	NA	Yes	Yes	NA#	No	No	NA#	Yes	Yes	NA#
	Y	NA	Yes	Yes	NA#	No	No	NA#	Yes	Yes	NA#
	Y	NA	No	No	NA#	No	No	NA#	No	No	NA#
	Y	NA	No	No	NA#	No	No	NA#	No	No	NA#
	N	NA	Yes	Yes	NA#	No	No	NA#	Yes	Yes	NA#

* Worst Case Scenario forced since the patient discontinued study treatment before the end of the applicable period.
\# Not applicable either for the patient or for the entire treatment group.
** Patient excluded from Primary Analysis Population.
CCOD: 16NOV2022 Data Extract Date: 23JAN2023

Summary of main efficacy results

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 36: Summary of efficacy for trial BO42162

Title: A Phase III, Randomised, Open-Label, Active-Controlled, Multicentre Study Evaluating The Efficacy And Safety Of Crovalimab Versus Eculizumab In Patients With Paroxysmal Nocturnal Haemoglobinuria Not Previously Treated With Complement Inhibitors		
Study identifier	Protocol number: BO42162; Protocol name: COMMODORE 2 ; EudraCT number: 2019-004931-21 ; NCT number: NCT004434092	
Design	Randomised, multicentre, open-label, active-controlled Phase III clinical study which enrolled patients with a body weight ≥40 kg, who had been diagnosed with PNH, and who had not been previously treated with a complement-inhibitor therapy. The study is divided in two parts: 2 randomised arms (Arms A and B), and a descriptive arm (Arm C), consisting of paediatric patients (<18 years old). The randomised arms aimed to randomise approximately 200 patients in a 2:1 ratio to crovalimab (Arm A) or eculizumab (Arm B). Paediatric patients were enrolled in the descriptive arm (Arm C) where they received crovalimab. No target sample size was specified for Arm C due to the rarity of the disease in this age group. Efficacy data are presented for arm C even if < 10 patients were enrolled (N=6).	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	24 weeks not applicable not applicable
Hypothesis	Non-inferiority The primary efficacy objective for this study was to evaluate the efficacy of crovalimab compared to eculizumab, based on the non-inferiority assessment of the following co-primary efficacy endpoints: • Proportion of patients who achieve transfusion avoidance from baseline through Week 25 (after 24 weeks on treatment), with patients having achieved TA defined as patients who are pRBC transfusion-free and do not require transfusion per protocol-specified guidelines. • Proportion of patients with haemolysis control, defined as LDH ≤1.5XULN, from Week 5 through Week 25 (as measured at the central laboratory). Both co-primary efficacy endpoints needed to be met in order to conclude non-inferiority of crovalimab to eculizumab	
Treatments groups	Arm A: Crovalimab	Crovalimab 340 mg/2 mL as per the weight-based tiered crovalimab dosing schedule IV loading dose on day 1 SC loading doses on days 2, 8, 15 and 22 SC maintenance doses at Week 5 and every 4 weeks (Q4W) thereafter 24 weeks N=135 randomised

Title: A Phase III, Randomised, Open-Label, Active-Controlled, Multicentre Study Evaluating The Efficacy And Safety Of Crovalimab Versus Eculizumab In Patients With Paroxysmal Nocturnal Haemoglobinuria Not Previously Treated With Complement Inhibitors			
Study identifier	Protocol number: BO42162; Protocol name: COMMODORE 2 ; EudraCT number: 2019-004931-21 ; NCT number: NCT004434092		
	Arm B: Eculizumab		Eculizumab 600 mg iv induction doses on days 1, 8, 15 and 22 and 900 mg maintenance doses on day 29 and every 2 weeks (Q2W) thereafter 24 weeks N=69
	Arm C: Crovalimab		Same as Arm A 6 paediatric patients included
Endpoints and definitions	Co-Primary endpoint	Proportion of patients with transfusion avoidance (TA)	Proportion of patients who achieve Transfusion Avoidance (TA) from baseline through Week 25 (after 24 weeks on treatment)
	Co-primary endpoint	Mean proportion of patients achieving haemolysis control	Proportion of patients with haemolysis control, measured by LDH≤1.5 X ULN, from Week 5 through Week 25 (as measured at the central laboratory)
	Secondary endpoint	Proportion of patients with Breakthrough Haemolysis (BTH)	Proportion of patients with BTH from baseline through Week 25
	Secondary endpoint	Proportion of patients with stabilised haemoglobin	Proportion of patients with stabilisation of haemoglobin from baseline through Week 25
	Secondary endpoint	Adjusted mean change from baseline in FACIT-fatigue at Week 25	Mean change from baseline to Week 25 in fatigue, as assessed by the FACIT-Fatigue.
Database lock	Database lock has not yet occurred; study is ongoing. The summary is based on a database snapshot with a clinical cut-off date of 16 November 2022 for the primary analysis of efficacy data through Week 25.		
Results and Analysis			
Analysis description	**Primary Analysis**		

Title: A Phase III, Randomised, Open-Label, Active-Controlled, Multicentre Study Evaluating The Efficacy And Safety Of Crovalimab Versus Eculizumab In Patients With Paroxysmal Nocturnal Haemoglobinuria Not Previously Treated With Complement Inhibitors				
Study identifier	Protocol number: BO42162; Protocol name: COMMODORE 2 ; EudraCT number: 2019-004931-21 ; NCT number: NCT004434092			
Analyses population and time point description	*Primary Analysis Population* The Primary Analysis Population is defined as all randomised patients in Arms A and B who received at least one dose of the originally assigned treatment and having at least one valid LDH level assessment by the central laboratory after the first intravenous (IV) infusion by planned treatment. One patient randomised to crovalimab did not have post-baseline LDH and was not included in the primary efficacy analysis.			
Descriptive statistics and estimate variability	Treatment group	Arm A	Arm B	Arm C (descriptive)
	Number of subjects	N=135	N=69	N=6
	Proportion of patients with TA, %(95%CI)	65.7 (56.91, 73.52)	68.1 (55.67,78.53)	66.7 NA
	Mean proportion of patients achieving haemolysis control, % *(95% CI)*	79.3 *(72.86, 84.48)*	79.0 *(69.66, 85.99)*	83.3 NA
	Proportion of patients with Breakthrough Haemolysis, % *(95% CI)*	10.4 *(6.04, 17.21)*	14.5 *(7.54, 25.50)*	66.7 NA
	Mean proportion of patients achieving haemolysis control, % *(95% CI)*	63.4 *(54.63, 71.45)*	60.9 *(48.35, 72.17)*	66.7 NA
Effect estimate per comparison	Co-Primary endpoint: Proportion of patients with TA	Comparison groups	Crovalimab Arm A Eculizumab Arm B	
		Difference in proportions, % (95% CI) Note: difference calculated as crovalimab minus eculizumab	-2.8% (-15.67, 11.14) NIM for 95%CI lower limit = -20%	

Title: A Phase III, Randomised, Open-Label, Active-Controlled, Multicentre Study Evaluating The Efficacy And Safety Of Crovalimab Versus Eculizumab In Patients With Paroxysmal Nocturnal Haemoglobinuria Not Previously Treated With Complement Inhibitors			
Study identifier	Protocol number: BO42162; Protocol name: COMMODORE 2 ; EudraCT number: 2019-004931-21 ; NCT number: NCT004434092		
	Co-Primary Endpoint: Mean proportion of patients achieving haemolysis control	Comparison groups	Crovalimab Arm A Eculizumab Arm B
		Odds ratio (95%CI)	*1.02 (0.57, 1.82)* *NIM for 95% CI lower limit = 0.2*
	Secondary endpoint: Proportion of patients with Breakthrough Haemolysis	Comparison groups	Crovalimab Arm A Eculizumab Arm B
		Difference in proportions, % (95% CI)	*-3.9% (-14.62, 5.26)* *NIM for 95% CI upper limit =20%*
	Secondary endpoint: Proportion of patients with stabilised haemoglobin	Comparison groups	Crovalimab Arm A Eculizumab Arm B
		Difference in proportions, % (95% CI)	*2.2% (-11.37, 16.31)* *NIM for 95% CI upper limit =-20%*
Notes	Non-inferiority remains to be demonstrated in the co-primary endpoint (haemolysis control and in the secondary endpoint (BTH and haemoglobin stabilisation). FACIT-fatigue results were not presented as this secondary endpoint was not tested for inferiority due to the break in the statistical testing hierarchy. 95%CIs and NIMs are in italic pending on discussion of selected non-inferiority margins (see LoQ).		

2.6.5.3. Clinical studies in special populations

No dedicated clinical studies in special populations were performed. But children, elderly and patients with renal or hepatic impairment have been included in presented trials.

2.6.5.4. In vitro biomarker test for patient selection for efficacy

Not Applicable.

2.6.5.5. Analysis performed across trials (pooled analyses and meta-analysis)

Not Applicable.

2.6.5.6. Supportive study(ies)

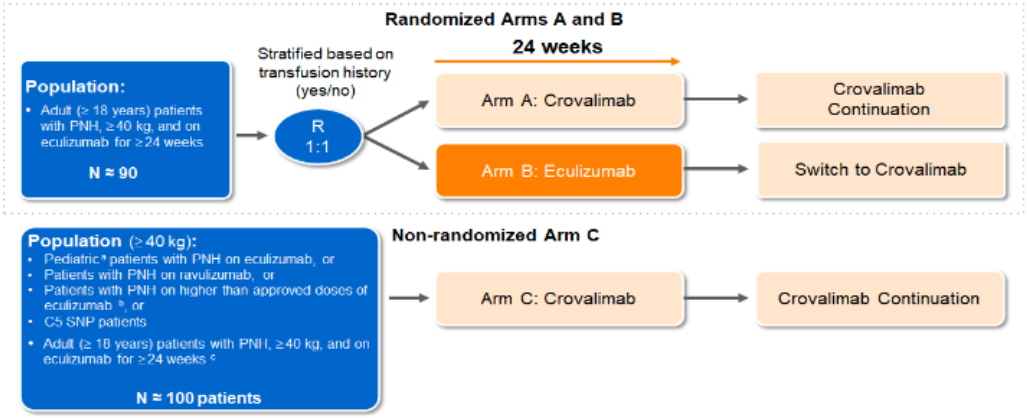
Study BO42161 (COMMODORE 1): Phase III, randomised, open-label, active-controlled, multicentre study to evaluate the safety, pharmacokinetics, pharmacodynamics, and efficacy in patients with switching from eculizumab.

Methods

Randomised adult subjects over 40 kg either received crovalimab or eculizumab (Arms A and B respectively, ratio 1:1) while subjects from Arm C all received crovalimab for 24 weeks. Arm C is a descriptive cohort which included paediatric patients, patients currently treated with ravulizumab, eculizumab at higher-than-approved doses or with C5 polymorphisms and poorly controlled haemolysis by either of approved anti-C5.

Adult and paediatric subjects initially allocated to crovalimab could enter the subsequent crovalimab extension period if eligible. Patients who initially received eculizumab had the option to switch to crovalimab after 24 weeks. Safety follow-up was 46 weeks for patients who discontinue crovalimab and 10 weeks for other patients. This is supported along with the crovalimab extension period.

Figure 28: Study schema for Study 161 (COMMODORE 1)



PNH = paroxysmal nocturnal hemoglobinuria; Q2W = every 2 weeks; R = randomization; SNP = single nucleotide polymorphism.

[a] Patients < 18 years old.

[b] Higher-than-approved doses of eculizumab: > 900 mg per dose and/or more frequently than Q2W.

[c] *This cohort 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 least 24 weeks and have LDH ≤1.5 x ULN at screening*

Study participants

Main inclusion criteria

All arms (A, B and C)

- Documented diagnosis of PNH, confirmed by high sensitivity flow cytometry evaluation of WBCs, with granulocyte or monocyte clone size ≥10%, within 6 months prior to randomisation (Arm A and B) or enrolment (Arm C)
- Vaccination against *Neisseria meningitidis* serotypes A, C, W, and Y < 3 years prior to initiation of study treatment. Vaccination against serotype B should be administered in accordance with the most current local guidelines or standard of care, as applicable in patients with complement deficiency

- Vaccination against *Haemophilus influenzae* type B and *Streptococcus pneumonia* according to national vaccination recommendations
- Platelet count ≥ 30,000/mm3 at screening without transfusion support within 7 days of lab testing
- ANC > 500/µL at screening
- Body weight ≥ 40 kg at screening

Arms A and B

Age ≥ 18 years at the time of signing the ICF

- Documented treatment with eculizumab according to the approved dosing recommended for PNH (900 mg Q2W) and completion of a minimum of 24 weeks of treatment prior to Day 1
- LDH level ≤ 1.5 × ULN at screening (as per local assessment; samples had to be obtained on a scheduled eculizumab-dosing day prior to eculizumab administration)

Arm C

For paediatric patients currently treated with eculizumab:

- Age < 18 years at time of signing of Informed Consent Form
- Documented treatment with eculizumab for a minimum of 12 weeks prior to Day 1
- LDH ≤ 2 × ULN at screening (as per local assessment; samples had to be obtained on a scheduled eculizumab dosing day prior to eculizumab administration.)
- For patients (regardless of age) currently treated with ravulizumab:
- Documented treatment with ravulizumab for a minimum of 16 weeks prior to Day 1
- LDH ≤ 2 × ULN at screening (as per local assessment)

For patients (regardless of age) currently treated with higher-than-approved doses of eculizumab:

- Documented treatment with eculizumab at > 900 mg per dose and/or more frequently than Q2W and completion of a minimum of 12 weeks of treatment prior to Day 1
- LDH ≤ 2 × ULN at screening (as per local assessment; samples had to be obtained on a scheduled eculizumab dosing day prior to eculizumab administration.)

For patients (regardless of age) with known C5 polymorphism:

- Known C5 polymorphism (e.g., Arg885)
- Poorly controlled haemolysis by eculizumab or ravulizumab, per investigator's assessment

For adult patients currently treated with approved doses of eculizumab:

- Age ≥18 years at time of signing Informed Consent Form
- Documented treatment with eculizumab according to the approved dosing recommended for PNH (900 mg Q2W) and completion of a minimum of 24 weeks of treatment prior to Day 1
- LDH level ≤ 1.5 × ULN at screening (as per local assessment; samples had to be obtained on a scheduled eculizumab-dosing day prior to eculizumab administration)

Main exclusion criteria

- Pre-enrolment haemoglobin value ≤ 7 g/dL, or pre-enrolment haemoglobin value > 7 g/dL and ≤ 9 g/dL with concurrent signs and symptoms of anaemia
- MAVE within 6 months prior to first drug administration (Day 1)
- History of allogeneic bone marrow transplantation
- History of *Neisseria meningitidis* infection within 6 months prior to screening and up to first study drug administration
- Known or suspected immune deficiency (e.g., history of frequent recurrent infections)
- Known or suspected hereditary complement deficiency
- History of myelodysplastic syndrome with Revised International Prognostic Scoring System (IPSS-R) prognostic risk categories of intermediate, high and very high

Treatments

Schedule of study treatments, along with dose modifications was identical to those from Study COMMODORE 2. Self-administration or administration by a patient caregiver was possible.

Objectives and endpoints

Table 37: Objectives and endpoints for Study 161

Objectives	Endpoints/outcomes measures
Safety objectives (all arms)	
Ą To evaluate the safety and tolerability of crovalimab compared to eculizumab, on the basis of the endpoints shown to the right	Ą Incidence and severity of adverse events, with severity determined according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events, Version 5 (CTCAE v5) Ą Change from baseline in targeted vital signs Ą Change from baseline in targeted clinical laboratory test results Ą Incidence and severity of injection-site reactions, infusion-related reactions, hypersensitivity, and infections (including meningococcal meningitis) Ą Incidence of adverse events leading to study drug discontinuation Ą Incidence and severity of clinical manifestations of drug-target-drug complex (DTDC) formation in patients who switched to crovalimab treatment from eculizumab or ravulizumab treatment
Pharmacokinetic objectives (all arms)	
Ą To characterise the crovalimab, eculizumab, and ravulizumab PK profiles on the basis of the endpoints shown to the right Ą To evaluate potential relationships between drug exposure and the safety and efficacy of crovalimab in patients who switched to crovalimab treatment from eculizumab treatment (Arm A) or ravulizumab treatment (Arm C) – exploratory PK objective	Ą Serum concentrations of crovalimab and eculizumab over time Ą Serum concentrations of ravulizumab at the time of crovalimab initiation
Immunogenicity objectives (all arms)	
Ą To evaluate the immune response to crovalimab on the basis of the endpoints shown to the right Ą To evaluate the potential effects of ADA on PK, PD, safety, or efficacy (exploration immunogenicity objective)	Ą Prevalence of ADAs at baseline and incidence of ADAs during the study

Biomarker objectives (all arms)	
Ą To identify and/or evaluate biomarkers that can potentially provide evidence of crovalimab, and eculizumab activity (i.e., PD biomarkers). Additionally, the relationship between blood biomarkers and safety, pharmacokinetics, immunogenicity, and efficacy will be investigated Biomarkers will also be descriptively summarised for patients switching from ravulizumab in Arm C	Ą Change over time in PD biomarkers, including complement activity (CH50) measured by a liposome immunoassay (LIA) and total C5 concentration Ą Change over time in free C5 concentration in crovalimab-treated patients Ą Observed value and absolute change from baseline to Week 25 in parameters reflecting haemolysis (e.g., reticulocyte count, free haemoglobin, haptoglobin) Ą Change over time in additional exploratory biomarkers, including but not limited to PNH clone size, markers from the complement system, and markers for intra- and extra-vascular haemolysis (e.g., complement components C3, C4, C3d on RBCs, and sC5b9 complex), as well as markers of endothelial cell activation and markers from the coagulation system (e.g., von Willebrand factor [vWF], P-selectin, D-dimer, thrombin-anti-thrombin complexes, thrombin generation) may also be evaluated Ą To investigate potential treatment resistance mechanisms, Arg885 and additional polymorphisms in C5 and in other complement-related genes may be analysed. Human leukocyte antigen (HLA) typing to investigate potential mechanisms of immunogenicity may also be performed
Exploratory efficacy objectives	
<u>Randomised arms</u> Ą To evaluate the efficacy of crovalimab compared with eculizumab on the basis of the endpoints shown to the right	Ą Percent change from baseline in LDH levels averaged over Weeks 21, 23, and 25 based on central laboratory LDH measurements Ą Proportion of patients who achieve transfusion avoidance (TA) from baseline through Week 25 (after 24 weeks on treatment) Ą Proportion of patients with central LDH ≤ 1.5 × ULN from baseline through Week 25 Ą Proportion of patients with breakthrough haemolysis (BTH) from baseline through Week 25 Ą Proportion of patients with stabilisation of haemoglobin from baseline through Week 25 Ą Mean change from baseline to Week 25 in fatigue, as assessed by the FACIT-Fatigue (for adults aged ≥ 18 years)

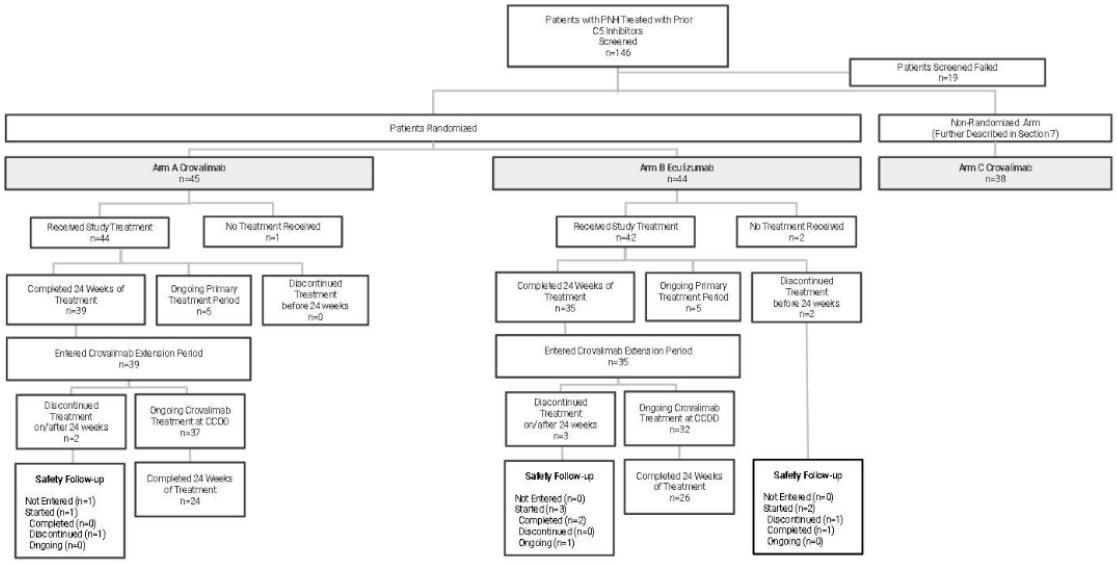
	Ą Total number of units (based on local equivalent) of pRBCs transfused per patient by Week 25 Ą Proportion of patients with central LDH ≤ 1 x ULN from baseline through Week 25 Ą Proportion of patients who reach or maintain a haemoglobin level of at least 10 g/dL, without subsequent decrease below 9 g/dL, in the absence of a transfusion Ą Proportion of patients who have experienced a MAVE from baseline through Week 25 Ą Mean change from baseline to Week 25 in Physical Functioning, Role Functioning, and Global Health Status (GHS)/Quality of Life (QoL) scales of the EORTC QLQ-C30, and select disease-related symptoms (abdominal pain, headaches, dyspnoea, dysphagia, chest pain, and erectile dysfunction) of the EORTC Item Library (for patients aged ≥ 18 years) Ą Mean treatment satisfaction with crovalimab or eculizumab at Week 25, as assessed by the Treatment Satisfaction Questionnaire for Medication-9 (TSQM-9) (for patients aged ≥ 18 years) Ą Proportion of patients with preference for crovalimab after switching from eculizumab or ravulizumab at Week 17 (Arm A), as assessed through use of a Patient Preference Questionnaire developed by the Sponsor (for patients aged ≥ 12 years)
Arm C Ą To evaluate the efficacy of crovalimab in on the basis of the endpoints shown to the right	Ą Proportion of patients who achieve TA from baseline through Week 25 (after 24 weeks on treatment) Ą Proportion of patients with central LDH ≤ 1.5 x ULN from baseline through Week 25 Ą Proportion of patients with BTH from baseline through Week 25 Ą Proportion of patients with stabilisation of haemoglobin from baseline through Week 25 Ą Mean change from baseline to Week 25 in fatigue, as assessed by the FACIT-Fatigue (for adults aged ≥ 18 years) Ą Total number of units (based on local equivalent) of pRBCs transfused per patient by Week 25 Ą Proportion of patients who have experienced a MAVE from baseline through Week 25

	Ą Mean change from baseline to Week 25 in Physical Functioning, Role Functioning, and Global Health Status (GHS)/Quality of Life (QoL) scales of the EORTC QLQ-C30, and select disease-related symptoms (abdominal pain, headaches, dyspnoea, dysphagia, chest pain, and erectile dysfunction) of the EORTC Item Library (for patients aged ≥ 18 years)
<u>Arm B (patients switching to crovalimab following the 24-week primary treatment period</u> Ą To evaluate the efficacy of crovalimab on the basis of the endpoints shown to the right	Ą Proportion of patients who achieve TA from the first dose of crovalimab through 24 weeks of treatment with crovalimab Ą Proportion of patients with central LDH ≤ 1.5 x ULN from the first dose of crovalimab through 24 weeks of treatment with crovalimab Ą Proportion of patients with BTH from the first dose of crovalimab through 24 weeks of treatment with crovalimab Ą Proportion of patients with stabilisation of haemoglobin from the first dose of crovalimab through 24 weeks of treatment with crovalimab Ą Mean change in fatigue from the first dose of crovalimab through 24 weeks of treatment with crovalimab, as assessed by the FACIT-Fatigue
<u>Health Status Utility objective</u> Ą To evaluate health status utility scores of paediatric (aged ≥12 years and <18 years) and adult (aged ≥ 18 years) patients treated with crovalimab compared to eculizumab, on the basis of the endpoint shown to the right	Ą Health status of patients according to EuroQoL 5-Dimension Questionnaire, 5-level version (EQ-5D-5L) index based and visual analog scale (VAS) scores at specified timepoints

Results

Participant flow

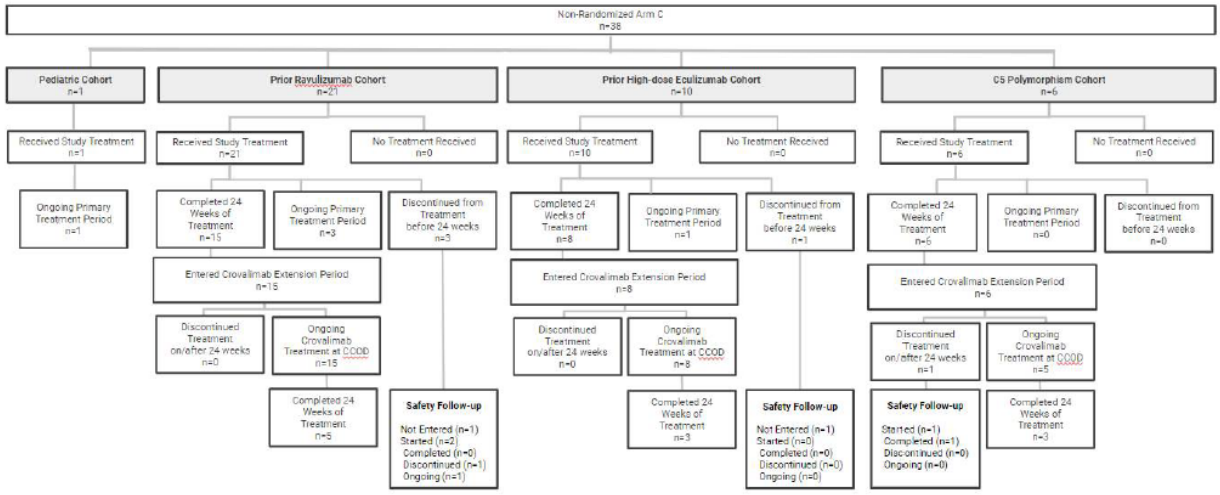
Figure 29: Summary of patient disposition (all patients population)



Note: In Arm A, 3 patients discontinued the study, 1 patient discontinued the study before receiving a dose of crovalimab, another discontinued the study during safety follow-up, and the third did not enter safety follow-up. In the Arm B, 3 patients discontinued study including 2 patients who discontinued the study before receiving a dose of eculizumab. One patient in Arm B discontinued the study during safety follow-up and then enrolled in Arm C (n=38). More details are provided in Section 4.1.1, Section 4.2.1, and Section 7.1.2.1.

Source: t_ds_RND1_PALL_16NOV2022_42161, t_ds_ARMC_PALL_16NOV2022_42161

Figure 30: Summary of patient disposition, full reporting period (Arm C population)



Note: In the prior ravulizumab cohort, 2 patients discontinued the study including 1 patient who never entered safety follow-up and 1 patient discontinued during safety follow-up. In the prior high-dose eculizumab cohort, 1 patient discontinued the study and didn't enter the safety follow-up. In the C5 polymorphism cohort, none of the patient discontinued the study.

Source: t_ds_ARMC_PALL_16NOV2022_42161

Recruitment

First patient was enrolled on 29 September 2020. A total of 127 patients were included in Study BO42161 (COMMODORE 1) across 25 countries. The geographical regions are presented below in descending order:

- Western Europe: Spain (14 patients, 11.0%), Poland (11 patients, 8.7%), Italy (7 patients, 5.5%), Portugal (6 patients, 4.7%), Belgium (5 patients, 3.9%), Greece (4 patients, 3.1%), Netherlands (4 patients, 3.1%) France (2 patients, 1.6%), Ireland (2 patients, 1.6%), Czech Republic (1 patient, 0.8%), Estonia (1 patient, 0.8%) Germany (1 patient, 0.8%), Hungary (1 patient, 0.8%) and United Kingdom (1 patient, 0.8%);
- Asia: Japan (17 patients, 13.4%), Republic of Korea (9 patients, 7.1%), Taiwan (3 patients, 2.4%), Hong Kong (1 patient, 0.8%), Singapore (1 patient, 0.8%);
- Latin America: Brazil (15 patients, 11.8%);
- Middle East: Turkey (10 patients, 7.9%) and Saudi Arabia (1 patient, 0.8%);
- North America: United States (2 patients, 1.6%), Canada (1 patient, 0.8%).

Baseline data

Demographic characteristics

Table 38: Summary of demographics (randomised population)

	B: Ecu (N=44)	A: Crova (N=45)
Age (years)		
n	44	45
Mean (SD)	49.5 (14.8)	44.4 (15.6)
Median	49.0	42.0
Min - Max	22 - 85	21 - 81
Age group (years)		
n	44	45
<18	0	0
18 - 64	37 (84.1%)	40 (88.9%)
>=65	7 (15.9%)	5 (11.1%)
Sex		
n	44	45
Male	22 (50.0%)	21 (46.7%)
Female	22 (50.0%)	24 (53.3%)
Race		
n	44	45
Asian	7 (15.9%)	9 (20.0%)
White	32 (72.7%)	34 (75.6%)
Black or African American	1 (2.3%)	2 (4.4%)
American Indian or Alaska Native	0	0
Native Hawaiian or other Pacific Islander	0	0
Unknown	4 (9.1%)	0
Ethnicity		
n	44	45
Hispanic or Latino	8 (18.2%)	8 (17.8%)
Not Hispanic or Latino	31 (70.5%)	36 (80.0%)
Not Stated	5 (11.4%)	1 (2.2%)
Weight (kg) at Baseline		
n	42	44
Mean (SD)	76.54 (18.03)	77.01 (17.47)
Median	75.10	80.00
Min - Max	47.2 - 126.4	45.2 - 120.0
Weight (kg) category at Baseline		
n	42	44
< 40kg	0	0
>= 40kg - <100kg	38 (90.5%)	41 (93.2%)
>= 100kg	4 (9.5%)	3 (6.8%)

Baseline is the patient's last observation prior to initiation of study drug in the primary treatment period.
CCOD: 16NOV2022 Data Extract Date: 23JAN2023

Table 39: Summary of demographics (Arm C All Patients Population)

	Crova [<18 years] (N=1)	Crova [Prior Ravu] (N=21)	Crova [Prior High-dose Ecu] (N=10)	Crova [C5 SNP] (N=6)	All Arm C (N=38)
Age (years)					
n	1	21	10	6	38
Mean (SD)	16.0 (NE)	45.5 (11.6)	35.5 (13.6)	58.2 (17.3)	44.1 (15.2)
Median	16.0	45.0	32.0	58.0	42.5
Min - Max	16 - 16	27 - 70	20 - 58	38 - 80	16 - 80
Age group (years)					
n	1	21	10	6	38
<18	1 (100%)	0	0	0	1 (2.6%)
18 - 64	0	20 (95.2%)	10 (100%)	3 (50.0%)	33 (86.8%)
>=65	0	1 (4.8%)	0	3 (50.0%)	4 (10.5%)
Sex					
n	1	21	10	6	38
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%)
Race					
n	1	21	10	6	38
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%)
American Indian or Alaska Native	0	0	0	0	0
Native Hawaiian or other Pacific Islander	0	0	0	0	0
Unknown	0	1 (4.8%)	3 (30.0%)	0	4 (10.5%)
Ethnicity					
n	1	21	10	6	38
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 Stated	0	0	4 (40.0%)	0	4 (10.5%)
Weight (kg) at Baseline					
n	1	21	10	6	38
Mean (SD)	53.00 (NE)	69.22 (13.90)	67.95 (11.15)	65.88 (19.57)	67.93 (13.93)
Median	53.00	69.50	65.95	66.15	68.50
Min - Max	53.0 - 53.0	46.0 - 91.0	48.1 - 82.0	44.0 - 89.2	44.0 - 91.0
Weight (kg) category at Baseline					
n	1	21	10	6	38
< 40kg	0	0	0	0	0
>= 40kg - <100kg	1 (100%)	21 (100%)	10 (100%)	6 (100%)	38 (100%)
>= 100kg	0	0	0	0	0

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

The baseline disease characteristics are presented in the table below.

Table 40: Summary of PNH history

	B: Ecu (N=44)	A: Crova (N=45)
Age at PNH diagnosis (yr)		
n	42	43
Mean (SD)	39.13 (14.76)	36.22 (15.38)
Median	37.45	31.53
Min - Max	20.0 - 83.7	17.2 - 79.3
Time from PNH diagnosis to enrollment (yr)		
n	42	43
Mean (SD)	11.17 (7.05)	8.03 (6.56)
Median	10.43	6.34
Min - Max	0.8 - 28.0	0.0 - 26.8
History of PNH-relevant conditions prior to enrollment (n, %)		
History of aplastic anemia		
n	44	45
Yes	16 (36.4%)	15 (33.3%)
No	28 (63.6%)	30 (66.7%)
History of myelodysplastic syndrome		
n	44	45
Yes	0	0
No	44 (100%)	45 (100%)
History of renal impairment		
n	44	45
Yes	8 (18.2%)	7 (15.6%)
No	36 (81.8%)	38 (84.4%)
History of major vascular events		
n	44	45
Yes	10 (22.7%)	10 (22.2%)
No	34 (77.3%)	35 (77.8%)
History of pRBC transfusion within 12 months prior to screening		
Number of patients with pRBC transfusion		
n	44	44
Yes	11 (25.0%)	10 (22.7%)
No	33 (75.0%)	34 (77.3%)
Number of units of pRBC transfused		
n	44	44
Mean (SD)	2.32 (5.43)	1.55 (3.72)
Median	0.00	0.00
Min - Max	0.0 - 24.0	0.0 - 14.0

Number of units of pRBC transfused		
n	44	44
0	33 (75.0%)	34 (77.3%)
0> to <4	3 (6.8%)	4 (9.1%)
>=4 to <14	5 (11.4%)	4 (9.1%)
>=14	3 (6.8%)	2 (4.5%)
Hemoglobin value at Baseline (g/L)		
n	42	44
Mean (SD)	107.27 (17.66)	109.74 (19.96)
Median	106.50	112.50
Min - Max	68.0 - 144.0	72.0 - 153.0
Haptoglobin value at Baseline (g/L)		
n	42	43
Mean (SD)	0.198 (0.269)	0.265 (0.447)
Median	0.050	0.050
Min - Max	0.05 - 1.09	0.05 - 2.18
LDH Value at Baseline (U/L)*		
n	42	44
Mean (SD)	234.20 (55.27)	249.16 (65.54)
Median	225.50	237.50
Min - Max	155.5 - 455.5	138.0 - 406.0
LDH value at Baseline (xULN)*		
n	42	44
Mean (SD)	1.00 (0.24)	1.06 (0.28)
Median	0.96	1.01
Min - Max	0.7 - 1.9	0.6 - 1.7
LDH Level at Baseline		
n	42	44
<ULN	24 (57.1%)	20 (45.5%)
>=ULN<=1.5xULN	16 (38.1%)	21 (47.7%)
>1.5xULN	2 (4.8%)	3 (6.8%)

Baseline is the patient's last observation prior to initiation of study drug in the primary treatment period.
* Baseline LDH is defined as the mean of all central LDH values, collected within 28 days prior to the first on-study drug administration including the predose value from Day 1.
CCOD: 16NOV2022 Data Extract Date: 23JAN2023

Table 41: Baseline disease characteristics - Arm C

	Crova [<18 years] (N=1)	Crova [Prior Ravu] (N=21)	Crova [Prior High-dose Ecu] (N=10)	Crova [C5 SNP] (N=6)
Age at PNH diagnosis (yr)				
n	1	20	10	6
Mean (SD)	13.04 (NE)	34.27 (12.12)	24.68 (9.11)	53.30 (19.54)
Median	13.04	33.26	23.44	52.28
Min - Max	13.0 - 13.0	11.4 - 61.4	15.0 - 42.2	25.9 - 80.1
Time from PNH diagnosis to enrollment (yr)				
n	1	20	10	6
Mean (SD)	3.80 (NE)	12.31 (11.62)	11.39 (10.57)	5.34 (4.78)
Median	3.80	9.62	6.52	5.81
Min - Max	3.8 - 3.8	0.6 - 50.3	0.8 - 27.1	0.1 - 13.0
History of PNH-relevant conditions prior to enrollment (n, %)				
History of aplastic anemia				
n	1	21	10	6
Yes	0	9 (42.9%)	2 (20.0%)	1 (16.7%)
No	1 (100%)	12 (57.1%)	8 (80.0%)	5 (83.3%)
History of myelodysplastic syndrome				
n	1	21	10	6
Yes	0	0	0	0
No	1 (100%)	21 (100%)	10 (100%)	6 (100%)
History of renal impairment				
n	1	21	10	6
Yes	0	4 (19.0%)	1 (10.0%)	2 (33.3%)
No	1 (100%)	17 (81.0%)	9 (90.0%)	4 (66.7%)

History of major vascular events				
n	1	21	10	6
Yes	0	2 (9.5%)	0	3 (50.0%)
No	1 (100%)	19 (90.5%)	10 (100%)	3 (50.0%)
History of pRBC transfusion within 12 months prior to screening				
Number of patients with pRBC transfusion				
n	1	21	10	6
Yes	0	3 (14.3%)	4 (40.0%)	3 (50.0%)
No	1 (100%)	18 (85.7%)	6 (60.0%)	3 (50.0%)
Number of units of pRBC transfused				
n	1	21	10	6
Mean (SD)	0.00 (NE)	0.57 (1.80)	1.80 (3.08)	14.00 (21.39)
Median	0.00	0.00	0.00	4.00
Min - Max	0.0 - 0.0	0.0 - 8.0	0.0 - 8.0	0.0 - 54.0
Number of units of pRBC transfused				
n	1	21	10	6
0	1 (100%)	18 (85.7%)	6 (60.0%)	3 (50.0%)
0> to <4	0	2 (9.5%)	2 (20.0%)	0
>=4 to <14	0	1 (4.8%)	2 (20.0%)	1 (16.7%)
>=14	0	0	0	2 (33.3%)
Hemoglobin value at Baseline (g/L)				
n	1	21	10	6
Mean (SD)	149.00 (NE)	109.76 (20.02)	97.36 (19.47)	89.83 (19.50)
Median	149.00	108.00	103.50	83.00
Min - Max	149.0 - 149.0	76.0 - 151.0	59.6 - 119.0	78.0 - 129.0
Haptoglobin value at Baseline (g/L)				
n	1	21	10	6
Mean (SD)	0.050 (NE)	0.157 (0.183)	0.154 (0.223)	0.050 (0.000)
Median	0.050	0.050	0.050	0.050
Min - Max	0.05 - 0.05	0.05 - 0.64	0.05 - 0.74	0.05 - 0.05
LDH value at Baseline (xULN)*				
n	1	21	10	6
Mean (SD)	1.53 (NE)	1.00 (0.20)	0.98 (0.22)	7.80 (6.78)
Median	1.53	1.01	0.94	6.14
Min - Max	1.5 - 1.5	0.6 - 1.4	0.7 - 1.3	1.8 - 20.7
LDH Level at Baseline				
n	1	21	10	6
<ULN	0	10 (47.6%)	5 (50.0%)	0
>=ULN<=1.5xULN	0	11 (52.4%)	5 (50.0%)	0
>1.5xULN	1 (100%)	0	0	6 (100%)

Baseline is the patient's last observation prior to initiation of study drug in the primary treatment period.
* Baseline LDH is defined as the mean of all central LDH values, collected within 28 days prior to the first on study drug administration including the predose value from Day 1. Switch Baseline LDH is defined as the mean of all central LDH values, collected within 28 days of first dose of Crova including the predose value from switch Day 1.
CCOD: 16NOV2022 Data Extract Date: 23JAN2023

Number analysed

Table 42: Summary of Analysis Populations (Randomised Population)

	B: Ecu (N=44)	A: Crova (N=45)
All Patients Population	44	45
Randomized Safety Population	42	44
Crovalimab Safety Population *	35	44
Efficacy Population	42	44
24-week Efficacy Population #	37	39
Crovalimab efficacy Population, Arm B switch patients *	35	0
24-week Crovalimab Efficacy Population, Arm B switch patients ^	28	0
Biomarker-Evaluable Population	42	44
Crovalimab Pharmacokinetic-Evaluable Population *	35	44
Eculizumab Pharmacokinetic-Evaluable Population	42	0
Immunogenicity Population *	35	44

* For Arm B Eculizumab, the number represents patients who meet the criteria for the populations once they have switched to Crovalimab.
# Includes all patients of the efficacy population who were enrolled at least 24 weeks before CCOD.
^ Includes all Arm B Eculizumab patients who switched to Crovalimab at least 24 weeks before CCOD.
CCOD: 16NOV2022 Data Extract Date: 23JAN2023

Table 43: Summary of analysis populations (Arm C All Patients Population)

	Crova [<18 years] (N=1)	Crova [Prior Ravu] (N=21)	Crova [Prior High-dose Ecu] (N=10)	Crova [C5 SNP] (N=6)	All Arm C (N=38)
All Patients Population	1	21	10	6	38
Crovalimab Safety Population	1	21	10	6	38
Efficacy Population	1	21	10	6	38
24-week Efficacy Population #	0	19	9	6	34
Biomarker-Evaluable Population	1	21	10	6	38
Crovalimab Pharmacokinetic-Evaluable Population	1	21	10	6	38
Immunogenicity Population	1	21	10	6	38

Includes all patients of the efficacy population who were enrolled at least 24 weeks before CCOD.
CCOD: 16NOV2022 Data Extract Date: 23JAN2023

For Arm C, the efficacy analyses were performed on the 24-week efficacy population - Arm C. This principle was applied for the analysis of haemolysis control, TA, BTH, stabilised Hgb, and MAVE (prior ravulizumab: 19, prior high-dose eculizumab: 9, C5 polymorphism: 6). For the endpoints of FACIT-Fatigue, EORTC QLQ C30, EORTC IL40, TSQM-9, Patients Preference, and EQ-5D-5L, efficacy population -Arm C was applied (prior ravulizumab: 21, prior high-dose eculizumab: 10, C5 polymorphism: 6).

Outcomes and estimations

An overview of the exploratory efficacy results is provided in the table below.

Table 44: Overview of exploratory efficacy (24-week efficacy population)

	Eculizumab N=37	Crovalimab N=39
Mean Proportion of Patients with Hemolysis Control (Central LDH ≤ 1.5 x ULN) from Baseline through Week 25		
Mean Proportion of Patients Achieving Controlled Hemolysis (Central LDH ≤ 1.5 x ULN) (95% CI)	93.7% (87.26, 97.04)	92.9% (86.62, 96.39)
Odds Ratio (95% CI)	0.88 (0.28, 2.77)	
Proportion of Patients with TA from Baseline through Week 25		
Patients with TA, n (%)	29 (78.4%)	31 (79.5%)
Weighted Difference in Proportion, % (95% CI)	1.8 (-16.67, 19.94)	
Proportion of Patients with BTH from Baseline through Week 25		
Patients with at least one BTH, n (%)	5 (13.5%)	4 (10.3%)
Weighted Difference in Proportion, (95% CI)	-3.5 (-19.20, 11.68)	
Proportion of Patients with Stabilized Hemoglobin from Baseline through Week 25		
Patients with Stabilized Hemoglobin, n (%)	26 (70.3%)	23 (59.0%)
Weighted Difference in Proportion (95% CI)	-10.8 (-30.84, 10.39)	

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

Table 45: Overview of exploratory efficacy for Arm C

	Crova [prior ravu] N=19	**Crova [prior HD ecu] N=9**	**Crova [C5 SNP] N=6**
Mean proportion of patients achieving controlled haemolysis (95% CI)	95.8% (95% CI: 89.11, 98.43)	91.0% (95% CI: 71.49, 97.60)	58.3% (95% CI: 29.68, 82.22)
Patients with TA, n (%; 95% CI)	11 (57.9%; 95% CI: 33.97, 78.88)	3 (33.3%; 95% CI: 9.04, 69.08)	3 (50.0%; 95% CI: 13.95, 86.05)
Patients with at least one transfusion, n (%)	6 (31.6%)	5 (55.6%)	3 (50.0%)
Mean pRBC units transfused (95% CI)	1.5 (95% CI: 0.13, 2.82)	2.0 (95% CI:-0.61, 4.61)	4.7 (95% CI:- 2.44, 11.77
Patients with at least one BTH, n (%; 95% CI)	7 (36.8%; 95% CI: 17.23, 61.37)	3 (33.3%; 95% CI: 9.04, 69.08)	1 (16.7%; 95% CI: 0.88, 63.52)

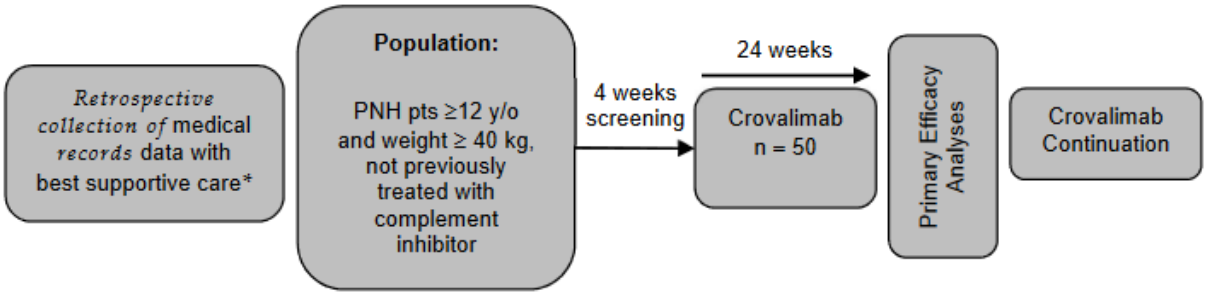
Patients with Stabilised Haemoglobin, n (%; 95% CI)	10 (52.6%; 29.50, 74.79)	2 (22.2%; 95% CI: 3.95, 59.81)	3 (50.0%; 95% CI: 13.95, 86.05)

Study YO42311 (COMMODORE 3): Phase III, multicentre, single-arm study evaluating the efficacy, safety, pharmacokinetics and pharmacodynamics of crovalimab in patients with PNH not previously treated with complement inhibitors.

Methods

Adolescents (≥12 years old) and adult patients were to receive crovalimab for 24 weeks and eligible patients were then allowed to enter the crovalimab continuation period. This single-arm study design is acceptable for a supportive study considering the comparison with retrospective collection of medical data with best supportive care for the 24 weeks prior to enrolment.

Figure 31: Study design for Study 311 (COMMODORE 3)



PNH = paroxysmal nocturnal hemoglobinuria; pts = patients.

**Note: Retrospective collection of medical data with best supportive care for the 24 weeks prior to enrollment.*

Study participants

Main inclusion criteria

- Age ≥12 years at time of signing ICF or Assent Form
- Body weight ≥40 kg at screening
- Documented diagnosis of PNH, confirmed by high sensitivity flow cytometry evaluation of WBCs with granulocyte or monocyte clone size of ≥10%, within 6 months prior to screening
- LDH level ≥2 × Upper Limit Normal (ULN) at screening (as per central assessment).
- Patients who had at least 4 transfusions during 12 months prior to screening (documented in the medical record)
- Presence of 1 or more of the following PNH-related signs or symptoms within 3 months of screening: fatigue, haemoglobinuria, abdominal pain, shortness of breath (dyspnoea), anaemia (haemoglobin <10 g/dL), history of a major adverse vascular event (MAVE) (including thrombosis), dysphagia, or erectile dysfunction, or history of pRBC transfusion because of PNH
- Vaccination against *Neisseria meningitidis* <3 years prior to initiation of study treatment (Day 1) or within 7 days after the first drug administration, in accordance with most current local guidelines or standard-of-care as applicable in patients with complement deficiency.
- Vaccination against *Haemophilus influenzae* type B and *Streptococcus pneumonia* according to national vaccination recommendations

- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception

Main exclusion criteria

- Current or previous treatment with a complement inhibitor
- History of allogeneic bone marrow transplantation
- History of *N. meningitidis* infection within 6 months prior to screening and up to first drug administration
- Known or suspected immune deficiency (e.g., history of frequent recurrent infections)
- Known or suspected hereditary complement deficiency
- Splenectomy <6 months before screening
- History of malignancy within 5 years prior to screening and up to the first drug administration, with the following exceptions:
  - Patients with any malignancy treated with curative intent and the malignancy was 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 were eligible.

Treatments

Crovalimab was to be administered consistently with studies COMMODORE 1 and 3. Dose modifications and the possibility of self-administration or administration by a patient caregiver was also aligned.

Objectives and endpoints

Table 46: Objectives and endpoints for Study 311

Objectives	Endpoints
Efficacy objectives Primary efficacy objective - To evaluate the efficacy of crovalimab based on crossing the threshold of the co-primary endpoint haemolysis control and the superiority intra-patient assessment of the co-primary endpoint of TA	- Mean proportion of patients with haemolysis control, measured by LDH ≤1.5×ULN from Week 5 through Week 25 (as measured at the central laboratory) - The difference in the proportion of patients who achieve TA from baseline through Week 25 (after 24 weeks of treatment) and the proportion of patients who achieved TA within 24 weeks prior to screening
Secondary efficacy objectives	

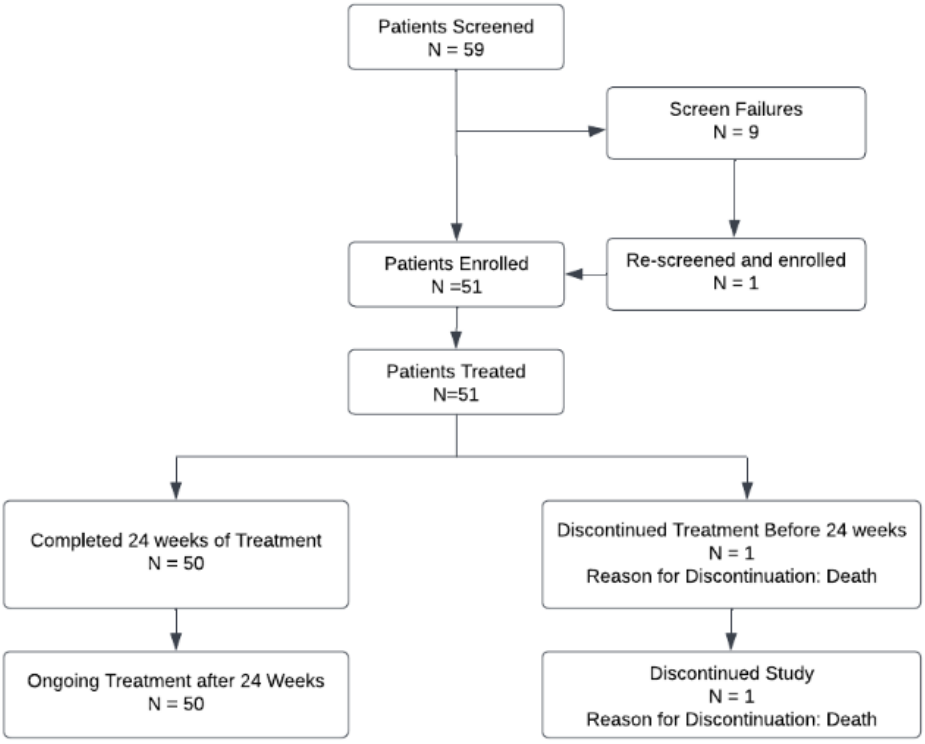
Ą To evaluate the efficacy of crovalimab	Ą Proportion of patients with BTH from baseline through Week 25 Ą Proportion of patients with stabilised haemoglobin from baseline through Week 25 Ą Mean change from baseline to Week 25 in fatigue as assessed through the use of the FACIT-Fatigue (adults aged ≥18 years)
Exploratory efficacy objectives Ą To evaluate the efficacy of crovalimab	Ą Total number of units of pRBCs transfused per patient from baseline to Week 25 Ą Mean proportion of patients with LDH ≤1×ULN from Week 5 through Week 25 (as measured at the central laboratory) Ą Mean LDH levels from baseline to Week 25 by visit Ą Percent change from baseline to Week 25 in LDH levels by visit Ą Time from baseline to first reach of LDH ≤1×ULN Ą Time from baseline to first reach of LDH ≤1.5×ULN Ą Proportion of patients who reach a haemoglobin level of at least 10 g/dL, without subsequent decrease below 9 g/dL, in the absence of a transfusion from baseline to Week 25. Ą Proportion of patients with MAVE from baseline to Week 25 Ą Mean change from baseline to Week 25 in Physical Function, Role Function, and Global Health Status/QoL scales of the EORTC QLQ-C30 (for adults aged ≥18 years) Ą Mean change from baseline to Week 25 in PedsQL MFS, and the Physical Functioning scale of the PedsQL Core (for adolescents aged 12-17 years) Ą Proportion of patients with a ≥3 point improvement from baseline in the FACIT-Fatigue at Week 25 (for adults aged ≥18 years).
Supportive historical efficacy objectives Ą To chacterise the efficacy of best supportive care and intra-patient comparison	Ą Mean LDH, and haemoglobin within 24 weeks prior to screening Ą Mean number of blood transfusions and number of units of pRBC transfused within 24 weeks prior to screening Ą Proportion of patients who had MAVE as documented in the medical records within 24 weeks prior to screening
Safety objectives Ą To evaluate the overall safety of crovalimab	Ą Incidence and severity of adverse events, with severity determined according to NCI CTCAE, Version 5 Ą Change from baseline in targeted vital signs Ą Change from baseline in targeted clinical laboratory test results

	Ą Incidence and severity of injection-site reactions, infusion-related reactions, hypersensitivity, and infections (including meningococcal meningitis) Ą Incidence of adverse events leading to study drug discontinuation
Pharmacokinetic objectives Ą To evaluate the pharmacokinetics of crovalimab	Ą Trough serum concentrations of crovalimab over time Ą Serum concentrations of crovalimab at specified time points
Immunogenicity objectives Ą To evaluate the immune response to crovalimab	Ą Prevalence of ADAs at baseline and incidence of ADAs during the study
Biomarker objectives Ą To identify and/or evaluate biomarkers that could have provided evidence of crovalimab activity (i.e., PD biomarkers)	Ą Change over time in PD biomarkers, including complement activity measured by LIA Ą Change over time in total and free C5 concentration Ą Observed value and absolute change from baseline to Week 25 in parameters reflecting haemolysis (reticulocyte count, free haemoglobin, haptoglobin) Ą To evaluate the change over time in red cell clone size by flow cytometry and markers from the coagulation system (D-dimer) Ą To evaluate the change over time in additional biomarkers of the complement system and markers for intra- and extra-vascular haemolysis (e.g., C3d on RBCs).
Health status utility objective Ą To evaluate health status utility scores of adolescent and adult patients treated with crovalimab	Ą Health status of patients according EQ-5D-5L index based and VAS scores at specified time points

Results

Participant flow

Figure 32: Patient disposition for Study 311 (full analysis population [FAP])



Recruitment

First patient was enrolled on 17 March 2021. The study was conducted at 5 centres in China. Fifty-one patients have been enrolled.

Baseline data

Demographics

Table 47: Demographics characteristics for Study 311 (FAP)

	Crova (N=51)
Age (yr)	
n	51
Mean (SD)	33.0 (9.4)
Median	31.0
Min - Max	15 - 58
Age group (yr)	
n	51
< 18	3 (5.9%)
18 - 64	48 (94.1%)
Sex	
n	51
Male	22 (43.1%)
Female	29 (56.9%)
Race	
n	51
Asian	51 (100%)
Weight (kg) at baseline	
n	51
Mean (SD)	63.68 (11.07)
Median	60.00
Min - Max	48.9 - 96.0
Weight (kg) category at baseline	
n	51
< 100	51 (100%)

Percentages are based on the total number of treated patients in the study.
CCOD: 10FEB2022 Data Extract Date: 23MAR2022

Baseline disease characteristics

Table 48: PNH history and baseline characteristics (FAP)

	Crova (N=51)
Time from PNH diagnosis to enrollment (yr)	
n	51
Mean (SD)	7.04 (4.31)
Median	7.14
Min - Max	0.7 - 18.2
History of PNH-relevant conditions prior to enrollment (n, %)	
History of aplastic anemia	
n	51
Yes	19 (37.3%)
No	32 (62.7%)
History of myelodysplastic syndrome	
n	51
Yes	1 (2.0%)
No	50 (98.0%)
History of renal impairment*	
n	51
Yes	2 (3.9%)
No	49 (96.1%)
History of major vascular events	
n	51
Yes	5 (9.8%)
No	46 (90.2%)
History of pRBC transfusion within 12 months prior to screening	
Number of patients with pRBC transfusion	
n	51
Yes	51 (100%)
Number of units of pRBC transfused	
n	51
Mean (SD)	20.83 (10.55)
Median	16.00
Min - Max	8.0 - 50.5
Number of units of pRBC transfused	
n	51
>=4 to < 14	12 (23.5%)
>= 14	39 (76.5%)

PNH clone size (granulocytes)**: %	
n	51
Mean (SD)	88.85 (13.73)
Median	95.01
Min - Max	40.4 - 99.7
PNH clone size (monocytes)**: %	
n	21
Mean (SD)	96.10 (4.36)
Median	97.37
Min - Max	79.0 - 99.6
PNH clone size (erythrocytes)**: %	
n	40
Mean (SD)	46.73 (26.68)
Median	45.86
Min - Max	9.5 - 98.8
Hemoglobin value at baseline (g/L)	
n	51
Mean (SD)	83.90 (9.77)
Median	81.00
Min - Max	71.0 - 112.0
Haptoglobin value at baseline (g/L)	
n	49
Mean (SD)	0.05 (0.00)
Median	0.05
Min - Max	0.1 - 0.1
LDH Value at baseline (U/L)***	
n	51
Mean (SD)	2175.72 (660.70)
Median	2171.00
Min - Max	928.7 - 4203.0
LDH value at baseline (xULN)***	
n	51
Mean (SD)	9.30 (2.83)
Median	9.28
Min - Max	4.0 - 18.0
LDH Level at baseline	
n	51
2-4xULN	1 (2.0%)
>4xULN	50 (98.0%)

* Defined as eGFR < 60
** Within 6 months prior to screening.
*** Baseline LDH is defined as the mean of all LDH values taken during screening and the LDH value at Week 1 Day 1 collected prior to the first dose of crovalimab.
CCOD: 10FEB2022 Data Extract Date: 23MAR2022

Number analysed

The number of patients included in the full, primary, safety, PK, and immunogenicity analysis populations are detailed in the table below.

Table 49: Analysis populations for Study 311 (all patients)

	Crova (N=51)
Full Analysis Population	51
Primary Analysis Population	51
Safety Population	51
PK Evaluable Population	51
Immunogenicity Population	51

CCOD: 10FEB2022 Data Extract Date: 23MAR2022

Outcomes and estimation

An overview of the co-primary and secondary efficacy endpoint results is provided in the table below.

Table 50: Overview of co-primary and secondary efficacy endpoint results

	Crovalimab N=51
Co-Primary Efficacy Endpoints	
Mean Proportion of Patients with Hemolysis Control from Week 5 through Week 25[a]	
Mean Proportion of Patients Achieving Controlled Hemolysis (95% CI)	78.7% (67.8%, 86.6%)
Difference in Proportion of Patients with TA from Baseline through Week 25 and Within 24 Weeks Prior to Screening	
Patients with TA Pre-screening	0/51 (0%)
Patients with TA Post-baseline	26/51 (51.0%)
Difference in Proportion (95% CI)	51.0% (34.3%, 65.1%)
p-Value (Paired McNemar Test)[b]	<.0001
Secondary Efficacy Endpoints	
Proportion of Patients with Breakthrough Hemolysis from Baseline through Week 25	
Number of Patients with at least one BTH	2/51[c]
Proportion of Patients with at least one BTH (95% CI)	3.9% (0.7%, 14.6%)
Proportion of Patients with Stabilized Hemoglobin from Baseline through Week 25[d]	
Number of Patients with Hemoglobin Stabilization	26/51
Proportion of Patients with Hemoglobin Stabilization (95% CI)	51.0% (36.8%, 65.1%)
Change from Baseline to Week 17 in FACIT-Fatigue[e]	
Baseline	
n	48[f]
Mean Score (95% CI)	31.77 (29.30, 34.25)
Week 17	
n	48[f]
Mean Score (95% CI)	40.54 (38.55, 42.54)
Mean Change from Baseline (95% CI)	8.77 (5.97, 11.57)

Study BP39144 (COMPOSER): Phase I/II study to assess safety, efficacy, PK and PD of crovalimab in healthy volunteers and patients with PNH.

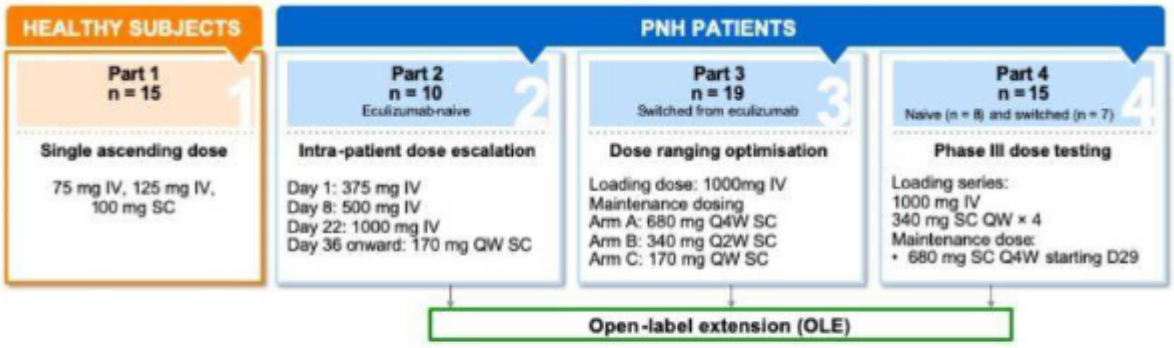
Methods

Study COMPOSER is a first-in-human study consisting of four sequential parts and an open label extension (OLE) designed to evaluate:

- the safety and tolerability, PK, and PD of crovalimab in HVs (Part 1);
- the safety and tolerability, PK and, PD of crovalimab in patients with PNH (Parts 2, 3, and 4 and OLE).

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 chacterise the PK/PD relationship in HVs and patients with PNH. In Part 3, the aim was to establish a low frequency SC dosing regimen that inhibits complement activity in PNH patients with low treatment burden. In Part 4, the aim was to establish a safe and efficacious dosing regimen in treatment-naïve PNH patients and in PNH patients switching from eculizumab that completely inhibits complement activity with low treatment burden.

Figure 33: Overall study design for Study 144



IV=intravenous; PNH=paroxysmal nocturnal hemoglobinuria; QW=weekly; Q2W=biweekly; Q4W=every 4 weeks; SC=subcutaneous.

Study participants

Main inclusion criteria

Parts 2, 3 and 4

- Male or female patients between the age of 18 and 75, inclusive, with a diagnosis of PNH.
- A documented GPI-deficient PNH clone size of ≥10% by RBCs and/or granulocytes within the last 3 months of enrolment/randomisation.
- Platelet counts >30 x 10^9/L.
- Absolute neutrophil count >0.5 x 10^9/L.
- *Neisseria meningitidis* vaccination in accordance with most current local guidelines or SOC for patients at increased risk for meningococcal disease.

Part 2 and Part 4 Arm A only - currently untreated PNH patients who are candidates for treatment with complement inhibitors only:

- PNH patients who have not been treated with any complement inhibitor or if previously treated stopped treatment due to lack of efficacy based on a single missense C5 heterozygous mutation.
- Hepatitis B patients can be enrolled if their LFT values are less than 2 × ULN and there is no liver function impairment.
- Serum LDH levels at least 1.5-fold above the ULN at screening.

Part 3 and Part 4 Arm B only - PNH patients currently treated with eculizumab only:

- Subjects with a negative hepatitis B surface antigen, hepatitis B core antibody, hepatitis C antibody, and HIV test result are eligible for the study.

- Subjects seropositive for HCV but adequately treated without detectable HCV RNA are eligible (assay sensitivity ≤25 IU/mL).
- Subjects who have been vaccinated against hepatitis B are eligible
- Subjects seropositive for HBV but adequately treated without detectable HBV DNA are eligible (assay sensitivity ≤10 IU/mL).
- PNH patients who have been treated continuously with eculizumab for at least 3 months preceding enrolment in the trial. Patients receive regular infusions of eculizumab.

OLE only - PNH patients:

- PNH patients who have completed Parts 2, 3 and 4 respectively.
- PNH patients who derived, in the Investigator's opinion, benefit from treatment with crovalimab.

Main exclusion criteria

All parts

- Known or suspected hereditary complement deficiency. History of meningococcal meningitis.
- History of allergic or anaphylactic reactions to human, humanised, or murine monoclonal antibodies or known hypersensitivity to any constituent of the product.
- Any major episode of infection requiring hospitalisation or treatment with IV antibiotics within 28 days prior to screening or oral antibiotics within 2 weeks prior to screening and up to first study drug administration.
- History of or currently active primary or secondary immunodeficiency, including known history of HIV infection.
- Evidence of chronic active hepatitis C infection.

Parts 2, 3 and 4

- History of bone marrow transplantation.
- Treatment with azathioprine or erythrocyte-stimulating agents within 14 days prior to first study drug administration.
- Splenectomy <1 year before start of crovalimab

Part 3 and Part 4 Arm B only - PNH patients currently treated with eculizumab only:

- Any evidence of seropositive autoimmune connective tissue diseases (such as systemic lupus erythematosus, or rheumatoid arthritis).
- Any evidence of active inflammatory conditions (including inflammatory bowel disease, or cryoglobulinemia).

Treatments

Treatment was to be administered as depicted in the study design presented in the figure above.

Objectives and endpoints

Table 51: Objectives and endpoints for Parts 2, 3 and 4 of Study 144

Objectives	Outcome measures
Primary	
Safety and tolerability of crovalimab for a total duration of 20 weeks in treatment-naïve patients with PNH and PNH patients switching treatment to crovalimab	Incidence of DLEs Incidence and severity of adverse events, serious adverse events and adverse events leading to withdrawal Incidence and severity of laboratory abnormalities Incidence of ADAs Physical examination findings Triplicate 12-lead ECGs Vital signs PNH clone size Exploratory assessment of DTDC (Parts 3 and 4 only)
PD effect of multiple doses of crovalimab on complement activity in patients with PNH at specified timepoints outlined in the Protocol	Total and target engaged C5 concentration Ex vivo lysis in serum (measurement of terminal complement activity
Secondary	
Describe the multiple-dose PK properties of crovalimab in treatment-naïve patients with PNH and PNH patients switching treatment to crovalimab at specified timepoints	AUC_{inf} AUC_{0-t} AUC_{tau} C_{min}, trough concentration C_{max}, peak concentration T_{max} CL after IV and CL/F after SC administration V_{ss} V/F after SC administration k: terminal elimination rate constant $t_{1/2}$ Accumulation Ratio

Ą Chacterise other PD effects of crovalimab (i.e., other than effects on complement activity) at specified timepoints outlined in the Protocol	Ą Serum LDH
Ą Chacterise the exposure-response relationship of crovalimab following different SC dosing regimens (Part 3)	Ą Bioavailability of SC administration
Ą Explore the PK/PD relationship of multiple doses of crovalimab on complement activity and other related biomarkers at specified timepoints outlined in the Protocol	Ą Other exploratory biomarkers including markers from the complement systems and markers for intra- and extravascular haemolysis (e.g., complement components C4, C3a, C3d on RBCs, and sC5b-9 complex) may be measured in blood samples
Ą Evaluate the immunogenicity of crovalimab in patients with PNH at specified timepoints outlined in the Protocol	Ą Incidence of ADAs
Ą Assess the efficacy, patient-reported outcomes and treatment satisfaction of crovalimab in treatment-naïve patients with PNH, and PNH patients switching treatment to crovalimab over a treatment period of 20 weeks.	Ą Change in LDH Ą Change in free haemoglobin Ą Proportion of patients with stabilised haemoglobin levels Ą Change in fatigue as measured by the FACIT-Fatigue Ą Change in HRQoL as measured by the EORTC QLQ-C30 Ą Comparison of patient treatment satisfaction between IV and SC modes of administration Ą Number of packed RBC (pRBC) units transfused per patient Ą Monthly rate of pRBC transfusions per patient Ą Proportion of transfusion-free patients Ą Annual rate of transfusion avoidance per patient Ą Proportion of patients with pRBC units transfused Ą Time to (1) first transfusion or (2) persistent elevation of LDH Ą Proportion of patients with LDH below ULN Ą Proportion of patients with complement suppression throughout the dosing interval Ą Annual rate of breakthrough haemolysis

ADA=anti-drug antibody; AUC_{0-t} area under the serum concentration-time profile from time 0 to time t; AUC_{inf}= area under the serum concentration versus time curve extrapolated to infinity; AUC_{tau}= area under the serum concentration-time profile within a dosing interval; C_{max}=Maximum concentration observed; Cmin =Minimum concentration observed; CL=total clearance of drug; CL/F=apparent clearance; DLE=dose-limiting event; EORTC QLQ-C30=European Organization for Research and Treatment of Cancer- Quality of Life Questionnaire-Core 30; FACIT=functional assessment of chronic illness therapy; HRQoL=health-related quality of life; IV=intravenous; PD=pharmacodynamic; PK=pharmacokinetic; PNH=paroxysmal nocturnal

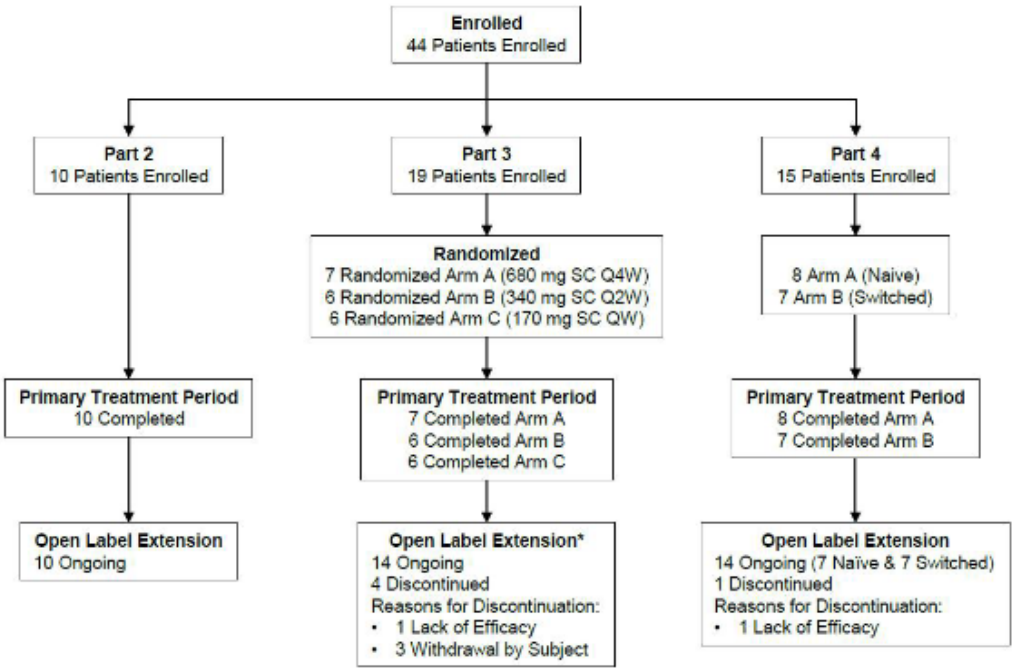
haemoglobinuria; pRBC=packed red blood cells; SC=subcutaneous; t1/2=half-life; ULN=upper limit of normal; Vss =Volume of distribution under steady-state conditions; V/F= apparent volume of distribution

Results

Participant flow

Patient disposition for Parts 3, 4 and 5 of Study 144 as of the CCOD of 01 November 2021 is presented below.

Figure 34: Parts 2, 3, 4 Patient Disposition



*Note: One patient in Part 3 completed the primary treatment period but did not enroll into the open-label extension period; this is not captured as a study discontinuation.

Recruitment

As of 29 January 2020, a total of 44 PNH patients in Parts 2 (10 eculizumab-naïve patients), 3 (19 patients who switched from eculizumab), and 4 (15 patients [8 patients in Arm A and 7 patients in Arm B]) have been enrolled.

Patients were enrolled at 14 sites in the following countries: Germany (12 patients at 3 sites), Japan (11 patients at 5 sites), France (7 patients at 1 site), Hungary (7 patients at 2 sites), Korea (4 patients at 2 sites), and Italy (3 patients at 1 site).

Baseline data

Demographic and baseline characteristics are presented in the tables below.

Table 52: Demographic and baseline characteristics for Parts 2 and 3 patients (safety-evaluable patients)

	Part 2 (N=10)	Part 3 (N=19)	All (2 & 3) (N=29)
Age (yr)			
n	10	19	29
Mean (SD)	53.9 (11.8)	49.5 (11.0)	51.0 (11.2)
Median	52.5	46.0	48.0
Min - Max	35 - 74	33 - 69	33 - 74
Sex			
n	10	19	29
Male	6 (60.0%)	13 (68.4%)	19 (65.5%)
Female	4 (40.0%)	6 (31.6%)	10 (34.5%)
Race			
n	10	19	29
Asian	3 (30.0%)	7 (36.8%)	10 (34.5%)
White	7 (70.0%)	9 (47.4%)	16 (55.2%)
Unknown	0	3 (15.8%)	3 (10.3%)
Ethnicity			
n	10	19	29
Not Hispanic or Latino	10 (100%)	15 (78.9%)	25 (86.2%)
Not Stated	0	3 (15.8%)	3 (10.3%)
Unknown	0	1 (5.3%)	1 (3.4%)
Weight (kg) at baseline			
n	10	19	29
Mean (SD)	75.11 (15.76)	80.11 (26.03)	78.39 (22.83)
Median	66.85	78.20	76.50
Min - Max	58.9 - 98.0	40.6 - 131.5	40.6 - 131.5
Height (cm) at baseline			
n	10	19	29
Mean (SD)	169.80 (10.43)	173.74 (12.77)	172.38 (11.97)
Median	170.00	172.00	170.00
Min - Max	153.0 - 184.0	156.0 - 205.0	153.0 - 205.0
History of RBC Transfusion *			
Yes	3 (30.0%)	8 (42.1%)	11 (37.9%)
No	7 (70.0%)	11 (57.9%)	18 (62.1%)
Number of RBC Transfused units *			
n	3	8	11
Mean (SD)	3.3 (2.3)	7.3 (7.0)	6.2 (6.2)
Median	2.0	5.0	2.0
Min - Max	2 - 6	1 - 21	1 - 21
Baseline PNH Granulocytes (%)			
n	10	18	28
Mean (SD)	70.60 (27.77)	90.22 (9.37)	83.21 (20.10)
Median	82.18	92.40	88.00
Min - Max	14.3 - 94.4	71.6 - 99.9	14.3 - 99.9
Baseline PNH Erythrocytes (%)			
n	9	12	21
Mean (SD)	45.51 (17.71)	64.42 (30.10)	56.32 (26.75)
Median	49.00	64.80	50.40
Min - Max	14.3 - 71.4	12.4 - 99.1	12.4 - 99.1
History of Aplastic Anemia			
Yes	1 (10.0%)	4 (21.1%)	5 (17.2%)
No	9 (90.0%)	15 (78.9%)	24 (82.8%)
Baseline Normalized LDH (U/L)			
n	9	19	28
Mean (SD)	5.59 (3.06)	1.56 (1.11)	2.85 (2.70)
Median	4.73	1.17	1.34
Min - Max	1.9 - 12.1	0.9 - 4.8	0.9 - 12.1
Baseline Hemoglobin (g/L)			
n	10	19	29
Mean (SD)	95.20 (14.70)	104.68 (17.66)	101.41 (17.06)
Median	96.00	99.00	99.00
Min - Max	77.0 - 122.0	77.0 - 149.0	77.0 - 149.0

Table 53: Demographic and baseline characteristics for Part 4 patients (safety-evaluable patients)

	Naive (N=8)	Switched (N=7)	Total (N=15)
Age (yr)			
n	8	7	15
Mean (SD)	56.6 (10.6)	44.0 (11.0)	50.7 (12.3)
Median	55.5	44.0	51.0
Min - Max	42 - 73	29 - 57	29 - 73
Sex			
n	8	7	15
Male	6 (75.0%)	6 (85.7%)	12 (80.0%)
Female	2 (25.0%)	1 (14.3%)	3 (20.0%)
Race			
n	8	7	15
Asian	4 (50.0%)	2 (28.6%)	6 (40.0%)
White	3 (37.5%)	3 (42.9%)	6 (40.0%)
Unknown	1 (12.5%)	2 (28.6%)	3 (20.0%)
Ethnicity			
n	8	7	15
Not Hispanic or Latino	7 (87.5%)	5 (71.4%)	12 (80.0%)
Not Stated	1 (12.5%)	0	1 (6.7%)
Unknown	0	2 (28.6%)	2 (13.3%)
Weight (kg) at baseline			
n	8	7	15
Mean (SD)	76.58 (15.98)	81.56 (19.19)	78.90 (17.09)
Median	80.10	79.80	79.80
Min - Max	56.7 - 100.0	60.4 - 114.0	56.7 - 114.0
Height (cm) at baseline			
n	8	7	15
Mean (SD)	170.50 (10.46)	171.29 (8.48)	170.87 (9.26)
Median	170.50	172.00	172.00
Min - Max	151.0 - 185.0	156.0 - 180.0	151.0 - 185.0
History of RBC Transfusion *			
Yes	4 (50.0%)	2 (28.6%)	6 (40.0%)
No	4 (50.0%)	5 (71.4%)	9 (60.0%)
Number of RBC Transfused units *			
n	4	2	6
Mean (SD)	53.5 (96.4)	3.0 (2.8)	36.7 (79.1)
Median	7.0	3.0	5.5
Min - Max	2 - 198	1 - 5	1 - 198
Baseline PNH Granulocytes (%)			
n	7	7	14
Mean (SD)	80.73 (20.38)	77.64 (30.90)	79.18 (25.20)
Median	86.00	92.32	88.69
Min - Max	37.0 - 97.0	17.9 - 99.6	17.9 - 99.6
Baseline PNH Erythrocytes (%)			
n	6	4	10
Mean (SD)	22.39 (18.71)	35.75 (36.37)	27.73 (26.13)
Median	17.00	23.42	17.00
Min - Max	5.0 - 58.4	8.7 - 87.4	5.0 - 87.4
History of Aplastic Anemia			
Yes	3 (37.5%)	2 (28.6%)	5 (33.3%)
No	5 (62.5%)	5 (71.4%)	10 (66.7%)
Baseline Normalized LDH (U/L)			
n	8	7	15
Mean (SD)	6.99 (5.86)	1.09 (0.19)	4.24 (5.15)
Median	5.15	1.13	2.32
Min - Max	2.3 - 20.4	0.7 - 1.3	0.7 - 20.4
Baseline Hemoglobin (g/L)			
n	8	7	15
Mean (SD)	96.38 (14.91)	106.29 (20.81)	101.00 (17.97)
Median	89.50	105.00	99.00
Min - Max	80.0 - 121.0	78.0 - 145.0	78.0 - 145.0

Number analysed

The analysis populations used for this study are listed in the table below.

Table 54: Analysis populations for Study 144

Population label	Description
Safety Analysis Population	All healthy volunteers/patients who receive at least one administration of the study drug (crovalimab or placebo)
PK/PD Analysis Population	All HVs and patients with at least one time-point with a measurable concentration will be included in the PK analysis data set
Efficacy Analysis Population	For Parts 2, 3, and 4 of the study, the efficacy analysis population will be the same as the safety analysis population.
Immunogenicity Analysis Population	All patients with at least one pre-dose and one post-dose ADA assessment. Patients were grouped according to treatment received or, if no treatment is received prior to study discontinuation, according to treatment assigned. All patients were included in the immunogenicity analysis population.

Outcomes and estimation

Summary of evaluation response to study treatment

Core treatment period (CCOD: 29 January 2020):

- The mean normalised LDH ≤1.5 x ULN was reached by Day 15 and maintained through Week 20 in treatment-naïve patients. The mean normalised LDH ≤1.5 x ULN was maintained through Week 20 in switch patients.
- Eight out of 10 patients in Part 2, 14/19 patients in Part 3, 5/8 patients in Part 4 Arm A, and 6/7 patients in Part 4 Arm B achieved transfusion avoidance up to Week 20.
- Eight out of 10 patients in Part 2, 12/19 patients in Part 3, 5/8 patients in Part 4 Arm A, and 5/7 patients in Part 4 Arm B achieved haemoglobin stabilisation up to Week 20.
- A total of 5 patients in Part 3 each had a single event that fulfilled the post-hoc criteria for BTH. No BTH events were observed in Part 2 or Part 4 patients.
- Naïve patients in Part 2 and Part 4 Arm A experienced mean clinically meaningful improvement from baseline in fatigue, physical functioning, role functioning, and GHS/QoL. On average, switching patients in Part 3 and Part 4 Arm B maintained baseline levels.

Open-label extension (OLE; CCOD: 01 November 2021):

- The proportion of patients reaching LDH ≤ 1.5 × ULN per visit remained relatively stable during the OLE, with 80% to 100% of the evaluable patients at each visit having LDH ≤1.5 x ULN.
- Mean normalised LDH was generally maintained below 1.5 × ULN during the OLE phase.
- The proportion of patients achieving transfusion avoidance (82.9% to 91.7%) and haemoglobin stabilisation (79.5% to 87.5%) remained relatively stable across the 24-week intervals during the OLE.
- The proportion of patients with breakthrough haemolysis (BTH) events was low over time during the OLE, with 0.0% to 4.9% of all patients reporting a BTH event across the 24-week intervals. The overall BTH rate in the OLE, across all patients, is 0.05 events per patient year (95% CI: 0.01-0.11).

2.6.6. Discussion on clinical efficacy

Design and conduct of clinical studies

This MAA for crovalimab in treatment of adult and paediatric patients with PNH is mainly based on the primary results from the pivotal phase III Study BO42162 (COMMODORE 2) in patients with PNH and not previously treated with complement inhibitors.

Supportive data come from additional 3 studies:

- Study YO42311 (COMMODORE 3); a phase III, single-arm study in patients not previously treated with complement inhibitor, conducted exclusively in China
- Study BO42161 (COMMODORE 1); a phase III, randomised, actively controlled study in patients currently treated with eculizumab. Additional small cohorts of patients treated with ravulizumab were included in uncontrolled arm C.
- Study BP39144 (COMPOSER, a phase I/II dose-ranging study, in complement inhibitor naïve and patients currently treated with eculizumab), a 4-part study which assessed the tolerability of crovalimab in healthy volunteers and allowed to determine the dosing schedule used in the 3 above mentioned PNH Phase 3 studies. Due to limited number of patients and different dosing regimens in each cohort, overall added value of this study for efficacy assessment is considered limited. However, this study provided longer-term data (exceeding 5 years) for a small sample of the target population (i.e. complement inhibitor-naive and switch adult patients), with a limited number of patients treated at the appropriate dosing schedule.

According to the Sponsor, all studies were GCP-compliant.

Both controlled phase III studies (BO42162 and BO42161) were open-label and consisted of a 4-week screening period followed by a 24-week primary treatment period. If eligible, adult patients initially allocated to crovalimab could enter the subsequent crovalimab extension period (up to 5 years). Patients who initially received eculizumab had the option to switch to crovalimab treatment after 24 weeks. Patients not eligible or not willing to enter crovalimab extension period entered the 10-week safety follow-up.

Open-label design is acceptable due to marked differences in route and administration schedule of IMP and control drug rendering blinded trials unfeasible. Duration and design of pivotal study is overall in line with previous registrational trials in similar setting.

Single-arm study YO42311 was conducted in China where complement inhibitor therapy is unavailable. Pivotal study BO42162 and supportive study BO42161 were actively controlled studies, which was expected considering the available PNH treatments in the EU. Eculizumab, first approved C5 inhibitor and established therapy for PNH since 2007, is an acceptable choice of comparator. Indeed, at the time of crovalimab development, ravulizumab was a relatively new therapy.

Initially, the applicant was seeking approval for "*treatment of adult and paediatric patients with paroxysmal nocturnal haemoglobinuria (PNH)*", i.e. crovalimab was intended for use in:

- the first-line setting as an alternative to eculizumab and ravulizumab, which is now clearly mentioned in the SmPC;
- an option for switch from the above mentioned C5 inhibitors.

As such, the clinical development programme can be considered is in line with the claimed indication.

In the treatment-naive setting, it is also overall in line with suggestions of several scientific advice procedures. Major deviation from the EMA scientific advice relates to the study in patients currently

treated with C5 inhibitors as the applicant was not able to properly conduct the dedicated 'switch study' providing a robust comparison of switch patients against patients continuing eculizumab (or ravulizumab).

Populations

The proposed main inclusion and exclusion criteria are considered standard for investigating complement inhibitors in PNH and are overall acceptable in all studies.

Patients in all studies were required to have body weight ≥ 40 kg, and except for single-arm study YO42311, there were no requirements regarding prior transfusions. Also, patients included across studies were 12 years old or older. As there are no dosing recommendations for patients with body weight of less than 40 kg, nor are there any data in paediatric subjects below 12 years of age, the indication has been updated to reflect the studied population.

All studies included adult patients, while non-randomised Arm C of pivotal study BO42162, and Study YO42311 also included complement inhibitor-naive paediatric patients. One additional paediatric patient was included in non-randomised Arm C of study BO42161, however no efficacy results were available for this patient at the time of CCOD. Before establishing separate paediatric Arm C in pivotal study BO42162, 2 adolescent patients were also included in eculizumab Arm B and subsequently switched to crovalimab after primary treatment period.

Patients with active disease despite treatment with C5 inhibitor or non-responding patients were not included in development programme, except for 6 patients with C5 SNP polymorphism and poor haemolysis control (per investigator) who were included in uncontrolled Arm C of study BO42161.

Pivotal study BO42162 (COMMODORE 2)

COMMODORE 2 is a Phase 3, open-label, multicentre study aimed to demonstrate the efficacy of crovalimab compared to eculizumab in complement-inhibitor naïve subjects with PNH, which covers only a part of the claimed indication. Overall, the list of eligibility criteria properly reflects this subgroup of the target population. The absence of data in patients with allogeneic bone marrow transplantation has been reflected in SmPC.

A total of 210 patients were enrolled, the majority of them being from Asia: 67.1% compared to 23.3% patients from Western Europe and 9.5% from Latin America.

Adult patients (n=204) were randomised in a 2:1 ratio to crovalimab (Arm A, n=135) or to eculizumab (Arm B, n=69) and 6 paediatric patients entered the paediatric descriptive Arm C.

Baseline demographic characteristics were generally balanced between treatment arms, with median age and time from PNH diagnosis of 30.97 years at diagnosis and 2.56 years since then in the crovalimab group compared to 32.11 and 2.93 years in the control group. Few exceptions were observed: eculizumab arm included somewhat higher proportions of older patients (≥65; 13% vs 9.6%), females (49.3% vs 43%), and Asian race (73.9% vs 63.7%).

Baseline disease characteristics were also generally balanced between the treatment arms. The mean LDH values (xULN) at baseline were about 7.6 x ULN, about 83% of patients had baseline levels of LDH in range of > 4 x ULN, median baseline Hgb levels were about 85 g/L. About 75% of patients had pRBC transfusions within 12 months prior to screening, about 30% of patients had history of aplastic anaemia, and about 15% had history of MAVE. More patients in eculizumab arm had history of MDS compared to crovalimab (8.7% vs 4.4%). Fatigue, anaemia and haemoglobinuria were most common PNH symptoms at baseline (>50% of patients). Baseline PNH symptoms were generally balanced between groups, except for dysphagia and erectile dysfunction which were somewhat more common in crovalimab arm, and fatigue and haemoglobinuria being more common in eculizumab arm.

Overall, included population is considered representative of patients naive to complement inhibitor therapy with active haemolysis and anaemia. Also, patients in both groups had large median PNH clone sizes of >90% for monocytes and granulocytes.

Endpoints

Pivotal study BO42162 (COMMODORE 2)

The pivotal study BO42162 aimed to demonstrate that in complement inhibitor naive PNH patients, crovalimab is non-inferior to eculizumab based on the co-primary efficacy endpoints: **proportion of patients who achieve transfusion avoidance** (**TA**) and **haemolysis control defined as LDH ≤ 1.5xULN**. Serum LDH is commonly used as a clinical measure for intravascular haemolysis, and TA is a disease-related event for patients with PNH and less need for transfusions indicates better disease control. Proposed co-primary endpoints integrate the effect of crovalimab on haemolysis with important clinical outcome and are therefore considered appropriate to demonstrate crovalimab efficacy in treatment of PNH patients who are complement inhibitor naïve and have active disease.

Secondary endpoints – **proportion of patients with breakthrough haemolysis** (**BTH**), **proportion of patients with stabilised haemoglobin** and **mean change in FACIT-Fatigue score** – are also considered clinically important. Exploratory endpoints investigated occurrence of MAVEs, units of pRBC transfused, changes in LDH levels up to week 25, time to first reach haemolysis control, maintenance of haemoglobin ≥ 10 g/dL in the absence of transfusion and QoL questionnaires (health status of patients based on EQ-5L-5D scores, EORTC QLQ-C30, FACIT-Fatigue, EORTC IL40, TSQM-9, QLQ AA/PNH, PGIS, patient preference and PedsQL Core for paediatric patients only).

Overall, all selected primary and secondary endpoints are clinically meaningful and in line with endpoints used in prior registrational studies in this setting.

In the paediatric population (descriptive Arm C), all above-mentioned endpoints were exploratory. For patients from Arm B who switched to crovalimab (Arm B switch patients) after 24 weeks, endpoints and patient reported outcomes (PROs) were also exploratory. Corresponding results allowed to gather additional data in the switch setting.

Superiority of crovalimab vs. eculizumab was to be evaluated provided that non-inferiority had first been demonstrated.

Study conduct

In the context of a single pivotal trial, results of Study BO42162 are expected to be "particularly compelling with respect to internal and external validity, clinical relevance, statistical significance, data quality, and internal consistency." (CPMP/EWP/2330/99).

The randomisation procedure is deemed appropriate with relevant prognostic factors. Although the study is open-label and the actual treatment assignment was available for individual patients, the study report stated that aggregated data was not accessible by the applicant.

It is acknowledged that the NIM for the co-primary endpoint transfusion avoidance (-20%) is the same as used for protocol ALXN1210-PNH301 (ravulizumab vs eculizumab pivotal trial in complement inhibitor-naïve patients). This was based on a comparison between eculizumab-treated patients and untreated patients from the PNH registry of eculizumab-treated patients. The margin was said to approximately preserve 50% of the control treatment effect. Although an alternative approach for justifying the NIM based on the eculizumab TRIUMPH study was discussed as part of the public assessment report for ravulizumab (EMA/CHMP/220699/2019), the -20% margin for the endpoint of transfusion avoidance was found to be acceptable in this previous procedure.

The applicant was requested to provide a further detailed justification of the NIM for LDH normalisation, as the argumentation and calculation provided in the initial dossier could not be followed. It is apparent from the applicant's explanation that the historical data in eculizumab and placebo patients for LDH normalisation, particularly when using a 1.5 x ULN threshold, was difficult to retrieve. In the absence of direct historical estimates, the applicant had to rely on the visual inspection of topline results material provided by Alexion from the ALXN-301 study, showing LDH results over time (in ULN units). Based on this graph, and assuming the log-normality of LDH, an average proportion of patients with LDH ≤ 1.5 x ULN was derived for eculizumab-treated patients. For placebo patients, the assumption was based on information from the TRIUMPH trial (only RCT to provide placebo data). The applicant's argumentation could be followed, and the 20% assumption for the placebo group, which is then used to derive the NIM, should represent a sufficiently conservative estimate. Nevertheless, the absence of direct historical estimates has made this justification more uncertain. In addition, the applicant provided an indirect treatment effect estimate between crovalimab and a putative placebo. Although such exploratory analysis should be interpreted with caution, it is acknowledged that its results would indicate a superior efficacy of crovalimab over placebo.

The NIMs used for secondary endpoints in Study BO42162 were the same NIMs as used in Study ALXN 301, which shared a similar MoA between crovalimab and ravulizumab and a similar NI study design versus eculizumab. As described by the applicant, there were some uncertainties associated with these derivations, which were based on the randomised and placebo-controlled TRIUMPH trial. Indeed, the derivation of the NIM for BTH could only be based on the LDH portion of the definition as not all relevant data were collected in TRIUMPH. For the proportion of patients with stabilised haemoglobin, the NIM was derived as a 50% preservation of the eculizumab effect, but it did not use the lower 95% CL for the difference, due to the likely prohibitive sample size. A similar assumption was made for the change in FACIT-Fatigue, which was not formally tested due to the break in testing strategy. Nevertheless, it is acknowledged that the corresponding NIMs were previously accepted for the presentation of NI analyses of the ALXN 301 trial.

The applicant provided further details regarding the sensitivity analyses that were performed to assess the impact of missing data on the co-primary endpoint haemolysis control, including the analysis using MCMC imputation under MAR and the PMM analysis under MNAR. Together with the tipping point analysis, they constitute a reasonable set of sensitivity analyses to assess the potential impact of missing data. Their consistency with the primary analysis results provides some reassurance on its statistical robustness.

The protocol was amended 5 times during study, the first patient being recruited in the version 2 of the protocol. Overall, except for the ICEs, the main protocol amendments listed are not considered to have affected study integrity.

In pivotal study BO42162, there was a high proportion of major, mainly procedural, protocol deviations during the primary treatment period in both arms (62.2% in Arm B vs 52.2% in Arm B); failure to collect laboratory samples was dominant in crovalimab arm and much higher than in eculizumab arm. Provided explanation (restrictions due to COVID-19 pandemic rendering regular laboratory assessments difficult to obtain and patients recruited in Ukraine) could be accepted, however, numerous patients had a protocol deviation of 'dose missed' or 'dose out of window' and those were rarely considered related to COVID-19 in both arms (4.0% and 1.5%, respectively). Based on the complementary data provided, no impact of efficacy and safety is expected. Clarifications regarding reasons for exclusion from PP set were also provided upon request and indicate no major discrepancies between treatment arms regarding proportion of excluded patients or reasons for exclusion.

Supportive studies

Similar endpoints were used in supportive studies BO42161 and YO42311.

Treatments

Adult patients in the pivotal study BO42162 and in study BO42161 were randomly assigned to crovalimab or eculizumab. Paediatric patients and patients from single-arm supportive study YO42311 all patients received crovalimab.

Eculizumab was administered according to the SmPC i.e. 600 mg IV induction doses on days 1, 8, 15 and 22 and 900 mg IV maintenance doses on day 29 and every 2 weeks (Q2W) thereafter.

Crovalimab was dosed based on patient's weight, i.e. higher doses were required for patients with body weight above 100 kg in all studies: 340 mg/2 mL for patients weighing ≥40 kg and more as per the weight-based tiered crovalimab dosing schedule with a IV loading dose on day 1, SC loading doses on days 2, 8, 15 and 22 and SC maintenance doses Week 5 and every 4 weeks (Q4W) thereafter.

In case of switch from eculizumab to crovalimab, the first crovalimab dose was to be administered at the visit when the next scheduled administration of eculizumab would have occurred, which ensured continuity of treatment.

Over the 5 first SC doses of crovalimab, patients over 12 years old and patient caregivers were trained for off-site SC administrations by a health care provider (HCP). Use of an anti-C5 subcutaneous formulation with the possibility of self-administration could represent a real gain in autonomy and considerably improve the quality of life of PNH patients.

Also, it was also possible for patients with persistent signs and symptoms of PNH to receive a rescue IV dose of 340 mg crovalimab. The corresponding cases were further discussed to support the language present in the SmPC. The majority of patients who received a rescue dose during primary treatment period were anyways considered to be 'non-responders' as they either did not achieve TA (5 out of 6 patients) or had experienced a BTH event (5 out of 6 patients), and none achieved haemoglobin stabilisation. Also, in 5 out of the 6 patients, crovalimab exposure was already above 100 µg/mL and had a complete terminal complement activity inhibition (as measured by CH50 and free C5) at the time of the IV rescue dose. Overall, it is not considered that any additional doses of crovalimab had any additional benefit with regards to LDH and haemolysis control in any of above mentioned cases, and therefore there is no clear evidence to support the benefit of rescue dosing in patients in the study and no need for inclusion of rescue dosing in the label. No safety issues were identified in regard to rescue doses.

Additional discussion on efficacy and safety in patients whose dose was modified due to sustained IVH or qualifying BTH events was also provided, however due to small number of events, heterogeneity of response after increase in dose and confounding factors related to ADA positivity, no recommendation regarding increase in dose could be given, except those related to weight increase.

The most common concomitant medications were ophthalmological (crovalimab: 78.5%; eculizumab: 87.5%), followed by antibacterials for systemic use (76.3% vs 75.4%) and ontological (62.2% vs 68.1%) and anti-anaemic preparations (59.5% vs 59.4%). It was clarified upon request that these high reported frequencies for concomitant ophthalmological and ontological drugs were due to the listing of the same treatments into multiple ATC classes. The applicant provided a thorough analysis in which, *in fine,* no ontological drug has been administered and only 11 patients received an ophthalmological therapy when deemed necessary.

Moreover, use of immunosuppressive therapies, antithrombotic agents and systemic corticosteroids was also frequent, with comparable rates in the crovalimab and eculizumab both arms: 17.0% vs 18.8%; 25.9% vs 24.6 and 34.1% vs 36.2%, respectively.

Following enrolment, dose changes/initiation of the medications of interest (immunosuppressants, systemic corticosteroids, danazol/androgens), were permitted at the investigator's discretion. This is

not a usual approach, as it would be expected to implement some rules regarding initiation of new therapies or dose changes of concomitant therapies that are expected to have an effect on parameters of interest and to plan their handling in the efficacy analysis. Consequently, patients used different types and doses of medications, with variable duration and for different indications (not always PNH related), which makes it difficult to draw any clear conclusion. Overall small number of patients in crovalimab and eculizumab arm, respectively, initiated or had dose increase in therapies of interest during primary treatment period in COMMODORE 2 study – systemic corticosteroids 5 (3.7%) and 4 (5.8%) patients; systemic immunosuppressants 6 (4.4%) and 2 (2.9%) patients; danazol/androgens 2 (1.5%) and 1 (1.5%) patient, respectively. Considering the lack of rules regarding concomitant therapies upon enrolment, it remains difficult to disentangle the possible impact of concomitant therapies on observed efficacy results. However, given the small number of patients who experienced an initiation or dose change in the medications of interest, and the relatively balanced distribution of those patients between the randomised treatment arms, no major effect on efficacy results is expected.

More pronounced imbalance was reported regarding erythropoietin use in COMMODORE 2 – 7 patients in crovalimab arm vs 0 patients in eculizumab group initiated erythropoietin or its derived products prior to study entry or during primary treatment period. The applicant provided thorough evaluation of those patients showing that only two of those 7 patients were finally considered responders in co-primary analysis, with one of them discontinuing epoetin beta on Day31, i.e. long before primary analysis. Based on provided information, it can be agreed that use of erythropoietin and its derivatives had no major impact on overall efficacy results.

Efficacy data and additional analyses

Efficacy of crovalimab in adult complement inhibitor naive patients

Pivotal study BO42162 (COMMODORE 2)

Patients were randomised in a 2:1 ratio to receive crovalimab (Arm A) or eculizumab (arm B) and were stratified based on LDH level (≥ 2 to ≤ 4 x ULN, or > 4 x ULN) and number of pRBC units administered within 6 months prior to randomisation (0 units, or > 0 - ≤ 6 units, or > 6 units). The stratification factors are considered relevant prognostic factors, therefore seem acceptable. All paediatric patients in the arm C received crovalimab.

Treatment compliance was high in both arms, with a comparable median treatment duration between arms: 20.1 weeks in the crovalimab arm, compared to 22.1 weeks in the eculizumab arm. In addition, the number of self-administrations and administration by patient caregivers increased during the core treatment period.

First patient was enrolled on 08 October 2020. As of the CCOD of 16 November 2022, the study was still ongoing.

Co-primary endpoints

Crovalimab demonstrated non-inferiority compared with eculizumab for the co-primary endpoint of transfusion avoidance (TA): 65.7% (95% CI: 56.91, 73.52) of patients in the crovalimab arm were transfusion-free from baseline through Week 25 compared to 68.1% (95% CI: 55.67, 78.53) of patients in the eculizumab arm. The weighted difference (crovalimab - eculizumab) was -2.8% with a lower limit of the 95% CI of -15.67%, which was higher than the pre-defined NIM of -20%. This was supported by the corresponding sensitivity analyses and data in Arm B Switch patients: 33 out of 43 achieved TA in the period after switching to crovalimab (76.7%, 95% CI: 61.00, 87.72).

Although criteria for transfusion, including symptom descriptions, were pre-defined in the protocol, the final decision was left to the clinical judgment of the investigator. Considering TA was one of the co-

primary endpoints of this open-label study, potential of bias was discussed, especially in cases of haemoglobin values between 7-9 g/dL, when the decision was based on investigators assessment of severity of symptoms. Provided additional data and sensitivity analysis in which the data of 6 patients (5 patients in crovalimab arm and 1 in eculizumab arm) who met the protocol-specified criteria for pRBC transfusion but were not transfused was imputed as if they had a transfusion event (i.e., considered not transfusion avoidant instead of transfusion avoidant) supported robustness of TA endpoint.

The mean proportion of patients with haemolysis control from Week 5 through Week 25 was 79.3% (95% CI: 72.86, 84.48) for the crovalimab arm and 79.0% (95% CI: 69.66, 85.99) for the eculizumab arm. Median time to first reach haemolysis control, i.e. LDH ≤ 1.5xULN was 2.3 weeks in both groups.

The choice of margins for this co-primary endpoint has been clarified and the provided sensitivity analyses were confirmed as conclusive.

Secondary endpoints

The proportion of patients with a BTH event from baseline through Week 25 was 10.4% (95% CI: 6.04, 17.21) in the crovalimab arm compared with 14.5% (95% CI: 7.54, 25.50) in the eculizumab arm. The proportion of patients reaching haemoglobin stabilisation from baseline through Week 25 was 63.4% (95% CI: 54.63, 71.45) in the crovalimab arm compared to 60.9% (95% CI: 48.35, 72.17) in the eculizumab arm.

Non-inferiority of crovalimab was confirmed for the secondary endpoints of BTH and haemoglobin stabilisation: the chosen NIMs are in line with previous clinical trials with C5 inhibitors. In addition, further discussion was provided regarding each event of BTH in respect to possible underlying aetiology and including review of possibility of suboptimal complement inhibition or other relevant PD parameters. Overall, in study BO42162, there were 10 patients (7.5%) in crovalimab and 9 patients (13%) in eculizumab arm who reported BTH events. About 60% of BTH events in each arm was temporally associated with a complement activating condition, most usual infection or surgery. All patients in crovalimab arm maintained crovalimab concentrations above 100 µg/mL resulting in complete inhibition of terminal complement activity as evidenced by CH50 levels < 30 U/mL. Additional two patients had no apparent reason provoking BTH event, while being ADA negative and also maintaining complete inhibition of terminal complement activity. In 2 patients in crovalimab arm at least 1 BTH event was associated with suboptimal PK/PD in the context of being ADA-positive.

Consistent results indicating no significant difference between treatment arms were shown also regarding number of units of pRBCs transfused, and majority of endpoints related to changes of LDH.

Due to the break in the statistical testing hierarchy, non-inferiority testing for FACIT-Fatigue was not performed and the results are considered descriptive only. The adjusted mean CFB in FACIT-Fatigue score at Week 25 was 7.8 points in the crovalimab arm compared with 5.2 points in the eculizumab arm. By Week 25, there was 58.6% and 54.5% of patients with an improvement in fatigue severity of ≥ 5 points in respective groups, which is considered a clinically meaningful change. Although results might be less reliable due to the patient's awareness of treatment assignment in an open label study, it is reasonable to assume that less fatigue is linked to achieved haemolysis control and increase in haemoglobin which were comparable between groups. It should also be noted that PROs were evaluable in a great number of patients, allowing to observe beneficial effects of crovalimab treatment on the overall QoL of PNH patients.

One patient in crovalimab and one in eculizumab arm had a MAVE on study – myocardial infarction and TIA, respectively. Both patients died and both had a prior history of MAVE.

Subgroup analyses

Acknowledging the limitations pertinent to subgroup analyses based on key baseline demographic and disease characteristics, overall efficacy of crovalimab was generally consistent with primary analysis across all subgroups for haemolysis control (about 80% of patients) and for TA (about 60-70%).

Data suggest that in patients with a history of aplastic anaemia, transfusion history (>6 units of pRBC transfusions) or profound haemolysis, the effect of crovalimab treatment on the need for transfusion is reduced. It was not possible to establish trends according to age (over or under 65 years) or weight (between 40 and 100 kg or over 100 kg), as the sample sizes were not comparable.

Interestingly, subgroup analyses did not show any clear differences depending on race, which was of concern given the large proportion of Asian patients included in the pivotal study. This is reassuring in terms of the representativeness of the complement inhibitor-naive target population.

Clinical studies in special populations

No dedicated clinical studies in special populations were performed. But children, elderly and patients with renal or hepatic impairment have been included in presented trials and corresponding results are discussed in the dedicated sections.

Considering the low proportion of subjects over 65 years of age included in the pivotal study (12 in the crovalimab arm, 9 in the eculizumab arm, all under 85 years old), it will be difficult to draw any meaningful conclusions. As available data are limited, section 4.2 of the SmPC has been updated accordingly.

Supportive study YO42311 (COMMODORE 3)

Study YO42311 was a single-arm study conducted in complement inhibitor naïve PNH patients in China and included patients ≥ 12 years of age. Overall inclusion criteria were very similar to those implemented in pivotal study BO42162, except age limit and requirement of at least 4 transfusions during 12 months prior to screening. Efficacy assessment was based on intra-patient comparison with retrospective collection of medical data with best supportive care for the 24 weeks prior to enrolment.

First patient was enrolled on 17 March 2021. As of 10 February 2022, 51 patients have been enrolled in Study 311. Median age was 31 years (range: 15-58 years), with 3 patients (5.9%) being < 18 years at study enrolment (ages: 15, 17 and 17 years), 56.9% of the patients were female.

A total of 50 patients completed 24 weeks of treatment. Again, treatment compliance was high with an increased number of crovalimab self-administrations and administration by patient caregivers from Week 5 to Week 29.

Efficacy results regarding haemolysis control were generally comparable to those observed in crovalimab Arm A of the pivotal study – 78.7% compared to 79.3%. The median time to first reach LDH ≤ 1.5 x ULN was 2.71 weeks.

Compared to Study BO42162, lower efficacy was observed regarding TA. This could be expected as the transfusion burden was higher in this study population. Nevertheless, 26 patients (51.0%) were transfusion-free from baseline through Week 25. Compared to the 24 weeks prior to screening (mean number of transfused units 10.8), the mean reduction in the number of units transfused was 6.14. Both findings are considered clinically relevant in patients who are transfusion dependent.

Lower efficacy was also observed regarding stabilisation of haemoglobin, again possibly due to inclusion of transfusion dependent patients, as opposed to the population of the pivotal study.

Proportion of patients with BTH event was 3.9%, compared to 10.4% in the crovalimab arm A of Study BO42162.

Fatigue score improved for average of 8.77 points (compared to 7.8 points in crovalimab arm of pivotal study). No MAVEs were reported.

Interpretation of efficacy data obtained in study YO42311 is hampered by uncontrolled study design and efficacy analyses based on intrapatient comparison using retrospective data. At baseline, 20 patients (39.2%) received corticosteroids for systemic use, eight patients (15.7%) received at least one immunosuppressive therapy, including ciclosporin and tacrolimus. It is hard to distinguish between the effect of crovalimab and effect of concomitant immunosuppressive therapies on observed efficacy results, especially considering high proportion of patients with aplastic anaemia (37%) who could benefit from immunosuppression. This will not be pursued further as it is deemed that discussion will not be able to alleviate this concern and, although observed results are considered supportive, the contribution of this study to the efficacy assessment of crovalimab in complement inhibitor naive PNH patients is considered of overall limited added value.

Exploratory efficacy results for patients currently receiving C5 inhibitor

Pivotal study BO42162 (COMMODORE 2) – Arm B switch

After primary treatment period of pivotal study BO42162, 68 patients from eculizumab Arm B were switched to crovalimab. Data supporting the 'switch indication' come from 43 of those 68 patients who received crovalimab for at least 24 weeks after the switch, regardless of whether they achieved haemolysis control during eculizumab treatment. There was no comparator for Arm B switch patients. This exploratory analysis of Arm B switch patients was added after enrolment in the study was completed (July 2021).

Presented results at week 25 after the switch indicate overall better effect of crovalimab after the switch compared to results observed in treatment-naïve population:

- mean proportion of patients with haemolysis control was 87.6% (vs 79.3% in complement inhibitor naive patients)
- proportion of patients with TA was 76.7% (vs 65.7% in complement inhibitor naive patients)
- proportion of patients with BTH was 7/43 (16.3%) (vs 14/134 (10.4%) in complement inhibitor naive patients). Of note, 3 out of those 7 patients discontinued crovalimab treatment before switch Week 25 and were therefore considered to have had a BTH event as a conservative analysis approach, i.e. observed BTH occurred in 4/43 patients (9%).
- proportion of patients with stabilised haemoglobin was 62.8% (vs 63.4% in complement inhibitor naive patients)
- no MAVEs were reported.

However, few uncertainties were identified in presented efficacy result in switched patients in Arm B switch of pivotal study BO42162:

- No subgroup analyses of efficacy results and no data on percent change in LDH levels from switch baseline to week 25 were provided.
- At switch baseline, 50/68 patients (73.5%) had haemolysis control, however exploratory efficacy data are presented for 43/68 switched patients who had the opportunity to receive crovalimab for at least 24 weeks post-switch. It is not clear how many of those 43 patients had haemolysis control at switch baseline, therefore the ability of crovalimab to maintain achieved haemolysis control is hard to interpret.

- Results on haemolysis control after the switch indicate that as soon as day 2 of crovalimab treatment, number of patients with haemolysis control increased from 50 to 57, and at week 2 increased to 59 patients. Starting from week 3 after the switch, number of patients with haemolysis control was stabilised and similar to switch baseline, i.e. between 50-53 patients (mean proportion of 77% - 90%). Nevertheless, the mean proportion of patients achieving haemolysis control during 24 weeks of crovalimab treatment after the switch was overall higher compared to treatment-naïve patients treated with crovalimab (primary analysis) – 88.6% vs 79.3%. Similarly, proportion of transfusion free patients was numerically higher compared to treatment-naïve population treated with crovalimab (76.7% vs 65.7%). The duration and influence of dual complement inhibition after the switch on efficacy results observed in switch population was not addressed in the dossier.
- After the switch, about 27% of patients started systemic corticosteroids and 9% started using immunosuppressants, of which 3 patients used ciclosporin, one patient used ravulizumab and one used eculizumab. Considering there was no comparator for crovalimab after the switch, it is not possible to distinguish between the effect of concomitant medications and crovalimab on observed efficacy results. The confounding effect of immunosuppressives and corticosteroids is especially problematic in patients with aplastic anaemia (38% of patients). Of note, there were no specific requirements regarding concomitant medications after the switch.

Upon request, changes in LDH following switch in stable patients were further discussed by the applicant. Overall, the mean and median percent change in LDH at each visit in the clinically stable eculizumab switch arm of Study BO42162 (n=29) remained stable across visits. The mean and median LDH values at each visit, including at Switch Week 25, remained relatively close to Switch baseline values and below 1.5 x ULN, showing maintenance of disease control.

Study BO42161 (COMMODORE 1)

Data supporting switch indication come from study BO42161 which was originally planned as dedicated 'switch study' in adult and paediatric patients. Primary and secondary endpoints were initially identical as in pivotal study BO42162.

However, due to recruitment issues, enrolment was prematurely stopped, and the applicant was unable to provide sufficiently powered randomised controlled study evaluating efficacy of crovalimab in patients switching from eculizumab compared to patients continuing eculizumab. Study thereafter focused on safety assessments; efficacy results were described only as exploratory and should be interpreted as purely descriptive.

There is no non-inferiority or superiority hypothesis testing, and no plan for control of the study type I error. The exploratory nature of all Study BO42161 efficacy analyses leads to obvious uncertainties for the benefit/risk assessment of crovalimab in patients currently treated with complement inhibitors, which are part of the claimed indication. The efforts of the applicant to gather clinically meaningful data in subgroups of the target population (i.e., addition of 'cohorts of clinical relevance' to Arm C, initially limited to paediatric patients) are acknowledged and the descriptive data presented for stable switch patients are considered acceptable given the LoOI responses that support maintenance of disease control and transfusion avoidance in this population.

Study enrolled patients who were currently receiving label-dose eculizumab treatment for at least 24 weeks before screening. Eligible patients (n=89) were randomised to switch to crovalimab or to continue on eculizumab, and 24-weeks efficacy results are available for 35 patients continuing on eculizumab (arm B) and 39 patients who switched to crovalimab (arm A). Uncontrolled arm C recruited 4 different cohorts of special interest - paediatric patients (n=1), patients treated with ravulizumab (n=21), eculizumab at higher-than-approved doses (n=10) and patients with C5 polymorphisms and poorly controlled haemolysis on eculizumab or ravulizumab (n=6). All patients were required to have

haemolysis control, however LDH ≤ 1.5xULN was requested for arm A and B, and LDH ≤ 2xULN for Arm C (except for patients with C5 SNP polymorphism). As stated before, treatment compliance was high in all groups, with a great number of crovalimab self-administrations or administrations given by patient caregivers.

Unlike in pivotal study, most patients were White (about 75%), and from Europe (about 65%). After 24 weeks of treatment, patients who switched to crovalimab (Arm A) achieved results numerically comparable to those continuing on eculizumab (Arm B) for all co-primary and secondary endpoints, except for haemoglobin stabilisation which was achieved in greater proportion of patients in eculizumab group (70.3% vs 59%). Results were also overall similar to those observed in Arm B switch patients in pivotal study. The mean percentage change in LDH from baseline was higher in the crovalimab arm compared to eculizumab arm (16.6% vs 4.5%), however, the mean LDH remained ≤ 1.5 x ULN in both treatment arms throughout the primary treatment period.

Significant imbalance was reported regarding use of immunosupressive therapy: 42.2% of patients in the crovalimab arm vs 27.3% of patients in the eculizumab arm. Ciclosporin use was reported in 15.6% of patients in the crovalimab arm and 9.1% of patients in the eculizumab arm. The influence of this imbalance on observed efficacy results is unclear, especially given very similar proportions of patients with aplastic anaemia in both groups (crovalimab: 33.3% and eculizumab: 36.4%).

Nonrandomised Arm C - special populations of interest

At the time of primary analysis, 38 patients were enrolled in the non-randomised Arm C of the study BO42161. 24-week efficacy results are available for 19 patients who received prior ravulizumab, 9 patients who received prior high-dose eculizumab and 6 patients with C5 SNP polymorphism. Patients in the Arm C cohorts were required to have an LDH level ≤2×ULN at screening, with the exception of C5 SNP patients who were required to have poorly controlled haemolysis by eculizumab or ravulizumab per the investigator's assessment.

Patients who switched from ravulizumab appear to have consistent efficacy than that observed for patients who switched from eculizumab in Arm B switch of pivotal study and Arm A of study BO42161. In patients switched from higher doses of eculizumab, lower efficacy point estimates are observed (possibly indicating hard to treat disease). Clinical benefit is also observed in patients with C5 polymorphism which is encouraging considering those patients could have poor haemolysis control with eculizumab or ravulizumab treatment. But the number of patients in each cohort was very low and the data presented are only considered descriptive.

Exploratory efficacy results in paediatric patients

Efficacy results obtained in paediatric patients are exploratory and descriptive, which is acceptable for this population as powered analysis would not be feasible due to rarity of disease. Inclusion of paediatric patients in descriptive uncontrolled arms is also in line with previous registrational trials in PNH and was agreed in PIP (EMEA-002709-PIP01-19). Indeed, results from the modelling and simulation study to evaluate the use of crovalimab in children from 2 to less than 18 years of age and weighing 5 kg or over are expected by March 2028. Until then, a minimum of 9 paediatric patients aged less than 18 years and weighing 40 kg or over is to be included in studies BO42161 and BO42162 (studies 2 and 3 of the PIP, respectively). At time of the CCOD, 1 and 6 paediatric subjects have been included in studies BO42161 and BO42162, respectively.

Complement inhibitor-naïve paediatric patients (Arm C of study BO42162 and study YO42311)

Efficacy data for complement inhibitor naive patients under 18 years of age is available for total of 9 patients - 6 patients included in nonrandomised Arm C of pivotal study BO42162, and 3 patients included in single-arm study YO42311. For a better overview of paediatric data, all important PK/PD

parameters, baseline demographic and disease characteristics, efficacy and safety analyses for 9 complement inhibitor naive paediatric patients were summarised upon request.

Pharmacokinetics/Pharmacodynamics

The crovalimab concentrations of the 9 paediatric treatment-naive patients during the primary treatment period were within the range of variability of crovalimab concentrations in adult treatment-naive patients (from studies BO42162 and YO42311), and all paediatric patients achieved concentrations > 100 µg/mL (threshold for complete inhibition of terminal complement inhibition) and maintained above this level throughout the treatment duration. The PD response in the paediatric patients was similar to adult patients; all paediatric patients achieved and maintained a complete inhibition of terminal complement activity as evidenced by CH50 values < 30 U/mL. The PD response resulted in a decrease of normalised LDH values < 1.5 x ULN in all paediatric patients. Overall, the PK and the PD profiles were similar between adults and paediatric patients.

Concomitant Medications (Immunosuppressive Therapy)

During primary treatment period (baseline to Week 25), 4 out of the 9 (44.4%) treatment-naive paediatric patients are reported to have received immunosuppressive therapy that either started prior to study entry or while on study. One additional patient had their immunosuppressive therapies both started and ended prior to study entry. The drugs used included prednisone acetate, ciclosporin, dexamethasone sodium phosphate, methylprednisolone, and tacrolimus. The indications for these drugs included PNH, allergic reaction prevention (e.g., use in association with pRBC transfusions), haemolysis control, fever, and immunosuppression.

Demographics and Baseline PNH History

In the 9 treatment-naive paediatric patients, the age range at baseline was 13 - 17 years. Five out of the 9 patients were female (55.6%), 8 patients were Asian (88.9%), and 1 indicated unknown race. All 9 patients were within the weight category of ≥ 40 kg - < 100 kg.

At baseline, median normalised LDH was 7.33 x ULN (range: 3.5 x ULN to 26.6 x ULN), and median baseline haemoglobin was 76 g/L (range: 66.0 g/L to 96.0 g/L). Seven of the 9 (77.8%) paediatric patients had a history of pRBC transfusion within 12 months prior to screening, with a median number of 18 pRBC units (range: 0 units to 40.5 units). Five patients (55.6%) had a history of aplastic anaemia and no patients had a history of myelodysplastic symptoms, history of renal impairment or a history of MAVE. Compared to naive adult patients from crovalimab Arm A of study BO42162, paediatric patients received more pRBC transfusions prior to enrolment.

The median PNH erythrocyte clone size was 53.74% (range: 37.1% to 76.6%); median monocyte clone size was 94.7% (range: 14.0% to 98.6%), and median granulocyte clone size was 94.5% (range: 13.0% to 98.3). While median monocyte clone was similar, somewhat larger median erythrocyte and granulocyte PNH clone size was observed in paediatric patients compared to adults (Arm A of COMMODORE 2 study): median erythrocyte clone size was 53.74% vs 25.13%; median granulocyte clone size was 94.5% vs 60.32%.

The majority of the 9 patients had baseline PNH signs/symptoms of anaemia (9 patients; 100%), fatigue (8 patients; 88.9%) and haemoglobinuria (8 patients; 88.9%). Other signs/symptoms included dyspnoea and abdominal pain in 2 patients each (22.2%). Overall, the 9 paediatric patients generally had similar baseline disease characteristics with regards to baseline LDH, haemoglobin, and PNH sign and symptoms as compared to the overall adult treatment-naive population.

Efficacy

Overall, efficacy results in complement inhibitor naïve paediatric patients are consistent with results observed in complement inhibitor naïve adult patients treated with crovalimab (Arm A of pivotal study BO42162):

- All 9 patients reached haemolysis control by Week 4, and this was sustained across the first 24 weeks of treatment for all except 2 patients. Other 2 patients also maintained good clinical response despite some fluctuations of LDH above 1.5xULN. Mean proportion of patients with haemolysis control in adult complement inhibitor naive patients receiving crovalimab was 79%.
- 6 of 9 patients (66.6%) achieved TA and haemoglobin stabilisation from baseline through Week 25, similar to results observed in complement inhibitor naive adult patients (65.7% and 63.4%, respectively).
- No BTH events were observed from baseline to Week 25 (compared to 10.4% in complement inhibitor naive adult patients).
- No MAVEs were reported.
- PedsQL MFS fatigue scores were too variable for 6 paediatric patients in study BO42162 and indicated overall improvement for 3 patients in study YO42311. No meaningful conclusion could be made but the limited and exploratory paediatric data suggest that crovalimab treatment could be associated with a relative improvement of QoL in this PNH subgroup. Indeed, most patients experienced an overall improvement in physical functioning. Similarly, most patients experienced an overall improvement in fatigue over the course of treatment.

Assessment of paediatric data on clinical efficacy

In study BO42162, 1 adolescent patient received eculizumab during the primary treatment period and was then switched to crovalimab during the extension period. This patient had not received a transfusion within the 12 months prior to randomisation but had a history of aplastic anaemia. At switch baseline, this patient had a haemoglobin level of 107 g/L, and normalised LDH value of 1.34×ULN. This patient maintained central LDH≤ 1.5×ULN and achieved TA and haemoglobin stabilisation from switch baseline to switch Week 25.

One paediatric patient was included in Study BO42161 two weeks before the CCOD and was therefore excluded from the primary analysis.

2.6.7. Conclusions on the clinical efficacy

Given the need for lifelong therapy in PNH, currently available therapies are still burdensome to patients due to the route and schedule of administration. As there is still a need for more convenient treatment options than regular hospital infusions (eculizumab), frequent dosing schedules or large volume home infusions (ravulizumab and pegcetacoplan SC applications, respectively), the Q4W low-volume SC self-administration of crovalimab could represent an additional and desirable option for PNH patients.

The data presented for patients not previously treated with a complement inhibitor (studies BO42162 and YO42311) are acceptable considering that the indication reflects the study population (i.e. crovalimab use as monotherapy in adult and paediatric patients weighing over 40 kg and aged 12 years and older) and that the justifications provided regarding the chosen non-inferiority margins have been adequately justified. Although formal non-inferiority testing was not possible due to the break in hierarchical testing, the submitted data were supportive also of an effect in alleviating fatigue. Also, no

discrepancies were observed between the adult and the paediatric complement inhibitor-naive populations.

While data regarding the use of crovalimab in the 'switch' setting (study BO42161) in adult patients were considered exploratory and descriptive, there is a difference between patients with good disease control and patients with suboptimal disease control on current anti-C5 treatment. The presented data are considered appropriate to support an approval in the claimed indication.

2.6.8. Clinical safety

2.6.8.1. Patient exposure

Safety data up to the latest clinical cut-off date (CCOD) of the studies BO42162 (CCOD: 16 Nov 2022), BO42161 (CCOD: 16 Nov 2022) and YO42311 (CCOD: 10 Aug 2022) were pooled and analysed, in order to perform a comprehensive assessment of the safety profile of crovalimab for the treatment of PNH.

Table 55: Safety-evaluable population

	Study and Treatment Arms	Description of Patient Population
Total Crovalimab (N = 377)	Crovalimab (Naive) (192 patients) Crovalimab (Switch) (185 patients)	Total Crovalimab Patients: Patients with PNH previously not treated with complement inhibitors (treatment-naive population), as well as those previously treated with complement inhibitors, before switching to crovalimab (treatment-switch population). Safety data up to CCOD are pooled from Studies BO42161, BO42162 and YO42311.
Crovalimab (Naive) (N = 192)	Study BO42162 Arms A and C (141 patients) Study YO42311 (51 patients)	Treatment-naive Patients: Patients with PNH previously not treated with complement inhibitors, who received crovalimab. Safety data up to CCOD are pooled from Studies BO42162 and YO42311.
Crovalimab (Switch) (N = 185)	Study BO42161 Arms A and C (82 patients) Study BO42162 Arm B-switch [a] (68 patients) Study BO42161 Arm B-switch [a] (35 patients)	Treatment-switch Patients: Patients with PNH previously treated with complement inhibitors, who received crovalimab. Safety data up to CCOD are pooled from Studies BO42161 and BO42162.
Total Eculizumab (N = 111)	Study BO42162 Arm B (69 patients) Study BO42161 Arm B (42 patients)	Total Eculizumab Patients: Patients with PNH previously not treated with complement inhibitors, as well as those previously treated with eculizumab and continued receiving it during the primary treatment period of 24 weeks. Safety data up to CCOD are pooled from Studies BO42161 and BO42162.
Eculizumab naive (N = 69)	Study BO42162 Arm B (69 patients) [a]	Eculizumab naive: Patients with PNH from Study BO42162 previously not treated with complement inhibitors and continued receiving it during the primary treatment period of 24 weeks.
Eculizumab experienced (N = 42)	Study BO42161 Arm B (42 patients) [a]	Eculizumab experienced: Patients with PNH from Study BO42161 previously treated with eculizumab and continued receiving it during the primary treatment period of 24 weeks.

[a] Arm B patients who were randomized to eculizumab had the opportunity to switch to crovalimab once they had completed at least 24 weeks of treatment with eculizumab (i.e., the last dose of eculizumab will have been received at the Week 23 visit). The first crovalimab dose was administered at the visit when the next scheduled administration of eculizumab would have occurred (Week 25 or Week 29 visit).

Table 56: Summary of study drug exposure (safety-evaluable patients)

Summary of Study Drug Exposure, Safety-Evaluable Patients
Protocols: BO42161, BO42162, YO42311

	Ecu (N=111)	Crova [Naive] (N=192)	Crova [Switch] (N=185)	Crova Total (N=377)
Treatment duration (weeks)				
n	111	192	185	
Mean (SD)	21.40 (3.89)	50.88 (16.96)	36.60 (24.27)	43.87 (22.03)
25%-ile	22.14	40.00	20.14	28.43
Median	22.14	52.14	32.29	44.43
75%-ile	22.29	60.29	52.14	56.29
Min - Max	0.1 - 26.1	0.1 - 107.9	0.3 - 108.4	0.1 - 108.4
Treatment duration (weeks) categories				
n	111	192	185	377
0 - <12 weeks	5 (4.5%)	3 (1.6%)	31 (16.8%)	34 (9.0%)
12 - <24 weeks	102 (91.9%)	5 (2.6%)	21 (11.4%)	26 (6.9%)
24 - <48 weeks	4 (3.6%)	56 (29.2%)	77 (41.6%)	133 (35.3%)
48 - <72 weeks	0	109 (56.8%)	36 (19.5%)	145 (38.5%)
72 - <96 weeks	0	16 (8.3%)	15 (8.1%)	31 (8.2%)
>= 96 weeks	0	3 (1.6%)	5 (2.7%)	8 (2.1%)
Total cumulative dose (mg)				
n	111	192	185	377
Mean (SD)	10756.8 (1841.3)	11120.7 (3196.9)	8735.1 (4286.8)	9950.1 (3951.0)
Median	11400.0	11200.0	7800.0	10520.0
Min - Max	900 - 13200	1000 - 25300	1340 - 20720	1000 - 25300
Total IV Dose intensity (%)				
n	111	192	185	377
Mean (SD)	100.00 (0.00)	102.14 (11.37)	102.13 (9.38)	102.14 (10.43)
Median	100.00	100.00	100.00	100.00
Min - Max	100.0 - 100.0	95.0 - 202.0	99.7 - 175.0	95.0 - 202.0

IV dose intensity is a percentage based on actual intravenous dose / total planned intravenous dose.
SC dose intensity is a percentage based on actual subcutaneous dose / total planned subcutaneous dose.
CCODs: BO42161/BO42162: 16NOV2022, YO42311: 10AUG2022
Data Extract Dates: BO42161/BO42162: 23JAN2023, YO42311: 26OCT2022

Program: root/clinical_studies/RO7112689/CDT70115/share/data_analysis/prod/program/t_ex.sas
Output: root/clinical_studies/RO7112689/CDT70115/share/pool_global_filing/prod/output/t_ex_SCS_SE.out
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	Ecu (N=111)	Crova [Naive] (N=192)	Crova [Switch] (N=185)	Crova Total (N=377)
Total SC Dose intensity (%)				
n	0	191	185	376
Mean (SD)	NE (NE)	100.02 (0.78)	99.93 (1.08)	99.97 (0.94)
Median	NE	100.00	100.00	100.00
Min - Max	NE - NE	93.4 - 108.3	85.7 - 102.4	85.7 - 108.3
Number of doses				
n	111	192	185	377
Mean (SD)	12.77 (2.34)	17.66 (4.38)	14.08 (6.20)	15.90 (5.64)
Median	14.00	18.00	13.00	16.00
Min - Max	1.0 - 16.0	1.0 - 32.0	2.0 - 32.0	1.0 - 32.0
Sum	1418.0	3391.0	2604.0	5995.0
Number of scheduled doses (intravenous, IV)				
n	111	192	185	377
Mean (SD)	12.77 (2.34)	1.01 (0.07)	1.00 (0.00)	1.00 (0.05)
Median	14.00	1.00	1.00	1.00
Min - Max	1.0 - 16.0	1.0 - 2.0	1.0 - 1.0	1.0 - 2.0
Sum	1418.0	193.0	185.0	378.0
Number of unscheduled doses (intravenous, IV)				
n	111	192	185	377
0 doses	111 (100%)	184 (95.8%)	175 (94.6%)	359 (95.2%)
1 dose	0	5 (2.6%)	9 (4.9%)	14 (3.7%)
2 doses	0	2 (1.0%)	1 (0.5%)	3 (0.8%)
3 doses	0	1 (0.5%)	0	1 (0.3%)

IV dose intensity is a percentage based on actual intravenous dose / total planned intravenous dose.
SC dose intensity is a percentage based on actual subcutaneous dose / total planned subcutaneous dose.
CCODs: BO42161/BO42162: 16NOV2022, YO42311: 10AUG2022
Data Extract Dates: BO42161/BO42162: 23JAN2023, YO42311: 26OCT2022

Program: root/clinical_studies/RO7112689/CDT70115/share/data_analysis/prod/program/t_ex.sas
Output: root/clinical_studies/RO7112689/CDT70115/share/pool_global_filing/prod/output/t_ex_SCS_SE.out
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	Ecu (N=111)	Crova [Naive] (N=192)	Crova [Switch] (N=185)	Crova Total (N=377)
Number of doses (subcutaneous, SC)				
n	0	191	185	376
Mean (SD)	NE (NE)	16.68 (4.22)	13.02 (6.18)	14.88 (5.58)
Median	NE	17.00	12.00	15.00
Min - Max	NE - NE	3.0 - 31.0	1.0 - 31.0	1.0 - 31.0
Sum	NE	3186.0	2408.0	5594.0

IV dose intensity is a percentage based on actual intravenous dose / total planned intravenous dose.
SC dose intensity is a percentage based on actual subcutaneous dose / total planned subcutaneous dose.
CCODs: BO42161/BO42162: 16NOV2022, YO42311: 10AUG2022
Data Extract Dates: BO42161/BO42162: 23JAN2023, YO42311: 26OCT2022

Program: root/clinical_studies/RO7112689/CDT70115/share/data_analysis/prod/program/t_ex.sas
Output: root/clinical_studies/RO7112689/CDT70115/share/pool_global_filing/prod/output/t_ex_SCS_SE.out
17FEB2023 17:36

2.6.8.2. Adverse events

Table 57: Overview of adverse events (safety-evaluable population)

Overview of Adverse Events, Safety-Evaluable Patients
Protocols: BO42161, BO42162, YO42311

	Ecu (N=111)	Crova [Naive] (N=192)	Crova [Switch] (N=185)	Crova Total (N=377)
Total number of patients with at least one AE	83 (74.8%)	174 (90.6%)	152 (82.2%)	326 (86.5%)
Total number of AEs	290	1063	692	1755
Total number of deaths	1 (0.9%)	3 (1.6%)	1 (0.5%)	4 (1.1%)
Total number of patients withdrawn from study due to an AE	0	0	0	0
Total number of patients with at least one				
AE with fatal outcome	1 (0.9%)	3 (1.6%)	1 (0.5%)	4 (1.1%)
Serious AE	10 (9.0%)	28 (14.6%)	29 (15.7%)	57 (15.1%)
Related Serious AE	1 (0.9%)	7 (3.6%)	5 (2.7%)	12 (3.2%)
Related AE	24 (21.6%)	93 (48.4%)	70 (37.8%)	163 (43.2%)
Related AE leading to withdrawal from treatment	0	1 (0.5%)	2 (1.1%)	3 (0.8%)
Related AE leading to dose modification/interruption	0	2 (1.0%)	4 (2.2%)	6 (1.6%)
Grade 3-5 AE	18 (16.2%)	50 (26.0%)	46 (24.9%)	96 (25.5%)
AE leading to withdrawal from treatment	1 (0.9%)	1 (0.5%)	3 (1.6%)	4 (1.1%)
AE leading to dose modification/interruption	3 (2.7%)	8 (4.2%)	8 (4.3%)	16 (4.2%)

Percentages are based on N in the column headings. Only treatment emergent AEs are displayed.
Multiple occurrences of the same AE in one individual are counted only once except for "Total number of AEs" row in which multiple occurrences of the same AE are counted separately.
CCODs: BO42161/BO42162: 16NOV2022, YO42311: 10AUG2022
Data Extract Dates: BO42161/BO42162: 23JAN2023, YO42311: 26OCT2022

Program: root/clinical_studies/RO7112689/CDT70115/share/data_analysis/prod/program/t_ae_oview.sas
Output: root/clinical_studies/RO7112689/CDT70115/share/pool_global_filing/prod/output/t_ae_oview_SCS_SE.out

Table 58: Overview of adverse events per 100 patients-years (safety-evaluable population)

Summary of Adverse Events per 100 Patient-Years: Adverse Event Overview, Safety-Evaluable Patients
Protocols: BO42161, BO42162, YO42311

	Ecu (N=111) (PY=49.77)			Crova [Naive] (N=192) (PY=196.13)			Crova [Switch] (N=185) (PY=139.85)		
	No. of AEs	AEs per 100PY	95% CI	No. of AEs	AEs per 100PY	95% CI	No. of AEs	AEs per 100PY	95% CI
All Events	290	582.73	(517.58,653.80)	1063	542.00	(509.90,575.59)	692	494.80	(458.61,533.08)
AE with fatal outcome	1	2.01	(0.05, 11.20)	3	1.53	(0.32, 4.47)	1	0.72	(0.02, 3.98)
Serious AE	16	32.15	(18.38, 52.21)	41	20.90	(15.00, 28.36)	43	30.75	(22.25, 41.41)
Related serious AE	1	2.01	(0.05, 11.20)	7	3.57	(1.43, 7.35)	7	5.01	(2.01, 10.31)
Related AE	70	140.66	(109.65,177.71)	423	215.68	(195.61,237.24)	155	110.83	(94.07,129.72)
Related AE leading to withdrawal from treatment	0	0	(NE , 7.41)	1	0.51	(0.01, 2.84)	2	1.43	(0.17, 5.17)
Related AE leading to dose modification/ interruption	0	0	(NE , 7.41)	2	1.02	(0.12, 3.68)	4	2.86	(0.78, 7.32)
Grade 3-5 AE	25	50.24	(32.51, 74.16)	120	61.19	(50.73, 73.16)	76	54.34	(42.82, 68.02)
AE leading to withdrawal from treatment	1	2.01	(0.05, 11.20)	1	0.51	(0.01, 2.84)	3	2.15	(0.44, 6.27)
AE leading to dose modification/ interruption	3	6.03	(1.24, 17.62)	10	5.10	(2.45, 9.38)	8	5.72	(2.47, 11.27)

PY = Patient years, calculated as last day of follow-up or CCOD (if still ongoing) - date of first dose of study medication + 1 day.
Investigator text for AEs encoded using MedDRA version 25.1. Only treatment emergent AEs are displayed.
Multiple occurrences of the same AE in one patient are counted multiple times.
95% CI is calculated using exact method based on the Poisson distribution.
CCODs: BO42161/BO42162: 16NOV2022, YO42311: 10AUG2022
Data Extract Dates: BO42161/BO42162: 23JAN2023, YO42311: 26OCT2022

Program: root/clinical_studies/RO7112689/CDT70115/share/data_analysis/prod/program/t_ae_oview_100py.sas
Output: root/clinical_studies/RO7112689/CDT70115/share/pool_global_filing/prod/output/t_ae_oview_100py_SCS_SE.out

Summary of Adverse Events per 100 Patient-Years: Adverse Event Overview, Safety-Evaluable Patients
Protocols: BO42161, BO42162, YO42311

	Crova Total (N=377) (PY=335.98)		
	No. of AEs	AEs per 100PY	95% CI
All Events	1755	522.35	(498.20,547.37)
AE with fatal outcome	4	1.19	(0.32, 3.05)
Serious AE	84	25.00	(19.94, 30.95)
Related serious AE	14	4.17	(2.28, 6.99)
Related AE	578	172.03	(158.29,186.65)
Related AE leading to withdrawal from treatment	3	0.89	(0.18, 2.61)
Related AE leading to dose modification/ interruption	6	1.79	(0.66, 3.89)
Grade 3-5 AE	196	58.34	(50.46, 67.10)
AE leading to withdrawal from treatment	4	1.19	(0.32, 3.05)
AE leading to dose modification/ interruption	18	5.36	(3.18, 8.47)

PY = Patient years, calculated as last day of follow-up or CCOD (if still ongoing) - date of first dose of study medication + 1 day.
Investigator text for AEs encoded using MedDRA version 25.1. Only treatment emergent AEs are displayed.
Multiple occurrences of the same AE in one patient are counted multiple times.
95% CI is calculated using exact method based on the Poisson distribution.
CCODs: BO42161/BO42162: 16NOV2022, YO42311: 10AUG2022
Data Extract Dates: BO42161/BO42162: 23JAN2023, YO42311: 26OCT2022

Program: root/clinical_studies/RO7112689/CDT70115/share/data_analysis/prod/program/t_ae_oview_100py.sas
Output: root/clinical_studies/RO7112689/CDT70115/share/pool_global_filing/prod/output/t_ae_oview_100py_SCS_SE.out

Common Adverse events

Table 59: Summary of adverse events with an incidence rate ≥5% by SOC (safety-evaluable patients)

Summary of Adverse Events with an Incidence Rate of at Least 5% by System Organ Class,
Safety-Evaluable Patients
Protocols: BO42161, BO42162, YO42311

MedDRA System Organ Class MedDRA Preferred Term	Ecu (N=111)	Crova [Naive] (N=192)	Crova [Switch] (N=185)	Crova Total (N=377)
Infections and infestations				
COVID-19	11 (9.9%)	29 (15.1%)	32 (17.3%)	61 (16.2%)
Upper respiratory tract infection	10 (9.0%)	45 (23.4%)	10 (5.4%)	55 (14.6%)
Urinary tract infection	7 (6.3%)	13 (6.8%)	9 (4.9%)	22 (5.8%)
Nasopharyngitis	2 (1.8%)	7 (3.6%)	10 (5.4%)	17 (4.5%)
Investigations				
Neutrophil count decreased	7 (6.3%)	36 (18.8%)	5 (2.7%)	41 (10.9%)
White blood cell count decreased	7 (6.3%)	31 (16.1%)	8 (4.3%)	39 (10.3%)
Alanine aminotransferase increased	3 (2.7%)	17 (8.9%)	5 (2.7%)	22 (5.8%)
Blood bilirubin increased	2 (1.8%)	18 (9.4%)	2 (1.1%)	20 (5.3%)
Bilirubin conjugated increased	0	16 (8.3%)	0	16 (4.2%)
Blood alkaline phosphatase increased	0	16 (8.3%)	0	16 (4.2%)
Blood bilirubin unconjugated increased	0	16 (8.3%)	0	16 (4.2%)
Alpha hydroxybutyrate dehydrogenase increased	0	11 (5.7%)	0	11 (2.9%)
Weight increased	0	10 (5.2%)	0	10 (2.7%)
Gastrointestinal disorders				
Diarrhoea	1 (0.9%)	12 (6.3%)	9 (4.9%)	21 (5.6%)
General disorders and administration site conditions				
Pyrexia	8 (7.2%)	22 (11.5%)	21 (11.4%)	43 (11.4%)
Injury, poisoning and procedural complications				
Infusion related reaction	9 (8.1%)	23 (12.0%)	17 (9.2%)	40 (10.6%)
Injection related reaction	0	7 (3.6%)	17 (9.2%)	24 (6.4%)
Metabolism and nutrition disorders				
Hypokalaemia	9 (8.1%)	18 (9.4%)	5 (2.7%)	23 (6.1%)
Hyperuricaemia	6 (5.4%)	18 (9.4%)	4 (2.2%)	22 (5.8%)
Hypocalcaemia	7 (6.3%)	9 (4.7%)	3 (1.6%)	12 (3.2%)
Musculoskeletal and connective tissue disorders				
Arthralgia	3 (2.7%)	6 (3.1%)	12 (6.5%)	18 (4.8%)

Investigator text for AEs encoded using MedDRA version 25.1. Only treatment emergent AEs are displayed.
Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once.
Displayed are MedDRA preferred terms that occurred in >= 5% of patients in at least one of the treatment groups displayed.
Events are sorted by descending overall total frequency.
CCODs: BO42161/BO42162: 16NOV2022, YO42311: 10AUG2022
Data Extract Dates: BO42161/BO42162: 23JAN2023, YO42311: 26OCT2022

Summary of Adverse Events with an Incidence Rate of at Least 5% by System Organ Class,
Safety-Evaluable Patients
Protocols: BO42161, BO42162, YO42311

MedDRA System Organ Class MedDRA Preferred Term	Ecu (N=111)	Crova [Naive] (N=192)	Crova [Switch] (N=185)	Crova Total (N=377)
Nervous system disorders				
Headache	4 (3.6%)	16 (8.3%)	21 (11.4%)	37 (9.8%)
Blood and lymphatic system disorders				
Neutropenia	2 (1.8%)	10 (5.2%)	3 (1.6%)	13 (3.4%)
Immune system disorders				
Type III immune complex mediated reaction	0	0	33 (17.8%)	33 (8.8%)

Investigator text for AEs encoded using MedDRA version 25.1. Only treatment emergent AEs are displayed.
Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once.
Displayed are MedDRA preferred terms that occurred in >= 5% of patients in at least one of the treatment groups displayed.
Events are sorted by descending overall total frequency.
CCODs: BO42161/BO42162: 16NOV2022, YO42311: 10AUG2022
Data Extract Dates: BO42161/BO42162: 23JAN2023, YO42311: 26OCT2022

Adverse Events Related to Treatment

Crovalimab Population vs Total Eculizumab Population

The overall incidence rate of treatment-related AEs was higher in the total crovalimab population (43.2%) compared to the total eculizumab population. In addition, the incidence of related AEs in patients who were naive to eculizumab treatment was higher compared to patients who were eculizumab experienced. This is most likely due to the latter group being stabilised on treatment prior to enrolment.

The most frequently reported treatment-related AEs were comparable between total crovalimab and total eculizumab populations and even more so with patients who were naive to treatment with eculizumab. The most frequent treatment-related AEs (with an incidence rate of ≥5% in either population) in the total crovalimab and total eculizumab arms respectively were:

• Infusion related reaction (10.1% vs 8.1%)

• White blood cell count decreased (9.8% vs 6.3%)

• Neutrophil count decreased (9.5% vs 6.3%)

Some notable differences between total crovalimab and total eculizumab populations (>10% difference) were observed in the incidence of the treatment-related laboratory abnormality AEs (PTs from the Investigations System Organ Class [SOC]) which were higher in the total crovalimab population (17.2%) compared to the total eculizumab population (6.3%). Generally, these AEs were not associated with other AEs and/or a change in clinical management. Additionally, PTs of Type III immune complex mediated reaction (8.8%) and injection related reaction which were unique to the total crovalimab population (6.1%) were also reported.

In the total crovalimab population, the number of treatment-related AEs per 100 PYs was 172.0 (95% CI: 158.29, 186.65), which was comparable to the total eculizumab population where it was 140.7 (95% CI: 109.65, 177.71).

Crovalimab Naive Population vs Crovalimab Switch Population

A higher proportion of patients experienced treatment-related AEs in the crovalimab naive population (48.4%) compared to the crovalimab switch population (37.8%). The most frequent treatment-related AEs by PT (with an incidence rate of ≥10% in either population) in the crovalimab naive and crovalimab switch populations, respectively were:

• Neutrophil count decreased (16.7% and 2.2%)

• White blood cell count decreased (15.6% and 3.8%)

• Infusion related reaction (11.5% and 8.6%)

• Type III immune complex mediated reaction (0 patients and 17.8%)

Of these above, AEs with notable differences (≥10% difference) between the crovalimab naive and crovalimab switch populations were:

• AEs of neutrophil count decrease and white blood cell count decrease, reported at a higher incidence in the crovalimab naive compared to the crovalimab switch population. For most of the laboratory abnormalities AEs the Sponsor's medical review has shown that the majority of these events can be explained by laboratory abnormalities present already at baseline, relevant medical history, underlying disease, and concurrent medications, and that generally those worsening laboratory abnormalities were not associated with other AEs and/or a change in clinical management.

• Additionally, Type III immune complex mediated reactions due to DTDC formation were expected to occur only in patients who switched to crovalimab (crovalimab switch population).

Adverse Events by Intensity

Total Crovalimab Population vs Total Eculizumab Population

The majority of AEs reported in the total crovalimab population (61.0%) and the total eculizumab population (58.5%) were grade 1−2 in severity (t_ae_ctc_SCS_SE). The proportion of patients who experienced at least one grade 3−5 AE in the total crovalimab population was 25.5% and in the total eculizumab population was 16.2%. The majority of these were grade 3 AEs (19.9% vs 12.6%, respectively).

In the total crovalimab and total eculizumab populations respectively, grade 4 AEs were experienced in 4.5% and 2.7% of patients, whereas 1.1% (4 patients) and 0.9% (1 patient) experienced grade 5 AEs. Incidence of grade 3−5 AEs in patients who were naive to eculizumab treatment was higher (24.6%) compared to patients who were eculizumab experienced (2.4%), most likely due to the latter group being stabilised on treatment prior to enrolment.

The number of grade 3−5 AEs per 100 PYs was 58.3 (95% CI: 50.46, 67.10) in the total crovalimab population, which was comparable to 50.2 (95% CI: 32.51, 74.16) in the total eculizumab population.

Crovalimab Naive Population vs Crovalimab Switch Population

Overall, the majority of AEs were grade 1−2 in both the crovalimab naive (64.6%) and crovalimab switch populations (57.3%).

The proportion of patients with at least one grade 3−5 AE was similar in the crovalimab naive (26.0%) and crovalimab switch (24.9%) populations, and most were grade 3 events. Grade 4 events were experienced in 5.7% and 3.2% of patients in the crovalimab naive and crovalimab switch populations, respectively. Three patients (1.6%) in the crovalimab naive population and one patient (0.5%) in the crovalimab switch population experienced grade 5 AEs.

2.6.8.3. Serious adverse event/deaths/other significant events

Table 60: Summary of deaths (safety-evaluable patients)

Summary of Deaths, Safety-Evaluable Patients
Protocols: BO42161, BO42162, YO42311

	Ecu (N=111)	Crova [Naive] (N=192)	Crova [Switch] (N=185)	Crova Total (N=377)
Total Number of Deaths	1 (0.9%)	3 (1.6%)	1 (0.5%)	4 (1.1%)
Primary Cause of Death				
Adverse event	1 (100%)	3 (100%)	1 (100%)	4 (100%)

Table summarises all the deaths occurring during the studies including safety follow-up period.
CCODs: BO42161/BO42162: 16NOV2022, YO42311: 10AUG2022
Data Extract Dates: BO42161/BO42162: 23JAN2023, YO42311: 26OCT2022

Program: root/clinical_studies/RO7112689/CDT70115/share/pool_global_filing/prod/program/t_dd.sas
Output: root/clinical_studies/RO7112689/CDT70115/share/pool_global_filing/prod/output/t_dd_SCS_SE.out

Table 61: Summary of serious adverse events (safety-evaluable patients)

Summary of Serious Adverse Events, Safety-Evaluable Patients
Protocols: BO42161, BO42162, YO42311

MedDRA System Organ Class MedDRA Preferred Term	Ecu (N=111)	Crova [Naive] (N=192)	Crova [Switch] (N=185)	Crova Total (N=377)
Total number of patients with at least one adverse event	10 (9.0%)	28 (14.6%)	29 (15.7%)	57 (15.1%)
Overall total number of events	16	41	43	84
Infections and infestations				
Total number of patients with at least one adverse event	6 (5.4%)	11 (5.7%)	12 (6.5%)	23 (6.1%)
Total number of events	7	12	13	25
Pneumonia	1 (0.9%)	4 (2.1%)	1 (0.5%)	5 (1.3%)
COVID-19	1 (0.9%)	1 (0.5%)	2 (1.1%)	3 (0.8%)
Urinary tract infection	1 (0.9%)	0	2 (1.1%)	2 (0.5%)
Infection	0	1 (0.5%)	1 (0.5%)	2 (0.5%)
Upper respiratory tract infection	0	2 (1.0%)	0	2 (0.5%)
Pyelonephritis	1 (0.9%)	1 (0.5%)	0	1 (0.3%)
Sepsis	1 (0.9%)	0	1 (0.5%)	1 (0.3%)
Bacteraemia	0	1 (0.5%)	0	1 (0.3%)
Dengue fever	0	1 (0.5%)	0	1 (0.3%)
Gastroenteritis	0	0	1 (0.5%)	1 (0.3%)
Influenza	0	1 (0.5%)	0	1 (0.3%)
Nasopharyngitis	0	0	1 (0.5%)	1 (0.3%)
Respiratory tract infection	0	0	1 (0.5%)	1 (0.3%)
Septic shock	0	0	1 (0.5%)	1 (0.3%)
Systemic bacterial infection	0	0	1 (0.5%)	1 (0.3%)
Viral infection	0	0	1 (0.5%)	1 (0.3%)
Central nervous system infection	1 (0.9%)	0	0	0
Tuberculosis	1 (0.9%)	0	0	0
Blood and lymphatic system disorders				
Total number of patients with at least one adverse event	3 (2.7%)	5 (2.6%)	7 (3.8%)	12 (3.2%)
Total number of events	3	7	8	15
Breakthrough haemolysis	0	1 (0.5%)	2 (1.1%)	3 (0.8%)
Aplastic anaemia	1 (0.9%)	2 (1.0%)	0	2 (0.5%)
Thrombocytopenia	1 (0.9%)	2 (1.0%)	0	2 (0.5%)
Febrile neutropenia	1 (0.9%)	0	1 (0.5%)	1 (0.3%)
Anaemia	0	0	1 (0.5%)	1 (0.3%)
Autoimmune haemolytic anaemia	0	0	1 (0.5%)	1 (0.3%)
Extravascular haemolysis	0	0	1 (0.5%)	1 (0.3%)
Haemolysis	0	0	1 (0.5%)	1 (0.3%)
Neutropenia	0	0	1 (0.5%)	1 (0.3%)

Investigator text for AEs encoded using MedDRA version 25.1. Only treatment emergent AEs are displayed.
Percentages are based on N in the column headings

MedDRA System Organ Class MedDRA Preferred Term	Ecu (N=111)	Crova [Naive] (N=192)	Crova [Switch] (N=185)	Crova Total (N=377)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)				
Total number of patients with at least one adverse event	1 (0.9%)	3 (1.6%)	3 (1.6%)	6 (1.6%)
Total number of events	1	3	3	6
Myelodysplastic syndrome	1 (0.9%)	0	1 (0.5%)	1 (0.3%)
Colorectal cancer	0	0	1 (0.5%)	1 (0.3%)
Desmoid tumour	0	1 (0.5%)	0	1 (0.3%)
Mantle cell lymphoma	0	0	1 (0.5%)	1 (0.3%)
Melanocytic naevus	0	1 (0.5%)	0	1 (0.3%)
Thyroid cancer	0	1 (0.5%)	0	1 (0.3%)
Immune system disorders				
Total number of patients with at least one adverse event	0	0	5 (2.7%)	5 (1.3%)
Total number of events	0	0	5	5
Type III immune complex mediated reaction	0	0	5 (2.7%)	5 (1.3%)
Hepatobiliary disorders				
Total number of patients with at least one adverse event	1 (0.9%)	1 (0.5%)	3 (1.6%)	4 (1.1%)
Total number of events	1	1	4	5
Bile duct stone	0	1 (0.5%)	0	1 (0.3%)
Cholangitis	0	0	1 (0.5%)	1 (0.3%)
Cholangitis acute	0	0	1 (0.5%)	1 (0.3%)
Cholelithiasis	0	0	1 (0.5%)	1 (0.3%)
Hyperbilirubinaemia	0	0	1 (0.5%)	1 (0.3%)
Cholecystitis chronic	1 (0.9%)	0	0	0
Injury, poisoning and procedural complications				
Total number of patients with at least one adverse event	0	3 (1.6%)	1 (0.5%)	4 (1.1%)
Total number of events	0	3	2	5
Infusion related reaction	0	1 (0.5%)	0	1 (0.3%)
Limb traumatic amputation	0	1 (0.5%)	0	1 (0.3%)
Open globe injury	0	0	1 (0.5%)	1 (0.3%)
Skin laceration	0	0	1 (0.5%)	1 (0.3%)
Subdural haematoma	0	1 (0.5%)	0	1 (0.3%)

Investigator text for AEs encoded using MedDRA version 25.1. Only treatment emergent AEs are displayed.
Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once.
For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Events are sorted by descending overall total frequency.
CCODs: BO42161/BO42162: 16NOV2022, YO42311: 10AUG2022
Data Extract Dates: BO42161/BO42162: 23JAN2023, YO42311: 26OCT2022

MedDRA System Organ Class MedDRA Preferred Term	Ecu (N=111)	Crova [Naive] (N=192)	Crova [Switch] (N=185)	Crova Total (N=377)
Nervous system disorders				
Total number of patients with at least one adverse event	2 (1.8%)	1 (0.5%)	2 (1.1%)	3 (0.8%)
Total number of events	2	1	2	3
Axonal neuropathy	0	0	1 (0.5%)	1 (0.3%)
Demyelinating polyneuropathy	0	0	1 (0.5%)	1 (0.3%)
Seizure	0	1 (0.5%)	0	1 (0.3%)
Ischaemic stroke	1 (0.9%)	0	0	0
Transient ischaemic attack	1 (0.9%)	0	0	0
Gastrointestinal disorders				
Total number of patients with at least one adverse event	0	1 (0.5%)	2 (1.1%)	3 (0.8%)
Total number of events	0	1	2	3
Ileus	0	0	1 (0.5%)	1 (0.3%)
Obstructive pancreatitis	0	0	1 (0.5%)	1 (0.3%)
Small intestinal haemorrhage	0	1 (0.5%)	0	1 (0.3%)
Respiratory, thoracic and mediastinal disorders				
Total number of patients with at least one adverse event	0	3 (1.6%)	0	3 (0.8%)
Total number of events	0	4	0	4
Epistaxis	0	2 (1.0%)	0	2 (0.5%)
Respiratory tract haemorrhage	0	1 (0.5%)	0	1 (0.3%)
Cardiac disorders				
Total number of patients with at least one adverse event	1 (0.9%)	2 (1.0%)	0	2 (0.5%)
Total number of events	1	2	0	2
Coronary artery disease	0	1 (0.5%)	0	1 (0.3%)
Myocardial infarction	0	1 (0.5%)	0	1 (0.3%)
Cardiac failure	1 (0.9%)	0	0	0
General disorders and administration site conditions				
Total number of patients with at least one adverse event	1 (0.9%)	1 (0.5%)	1 (0.5%)	2 (0.5%)
Total number of events	1	2	1	3
Pyrexia	1 (0.9%)	1 (0.5%)	1 (0.5%)	2 (0.5%)

Investigator text for AEs encoded using MedDRA version 25.1. Only treatment emergent AEs are displayed.
Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once.
For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Events are sorted by descending overall total frequency.
CCODs: BO42161/BO42162: 16NOV2022, YO42311: 10AUG2022
Data Extract Dates: BO42161/BO42162: 23JAN2023, YO42311: 26OCT2022

MedDRA System Organ Class MedDRA Preferred Term	Ecu (N=111)	Crova [Naive] (N=192)	Crova [Switch] (N=185)	Crova Total (N=377)
Renal and urinary disorders				
Total number of patients with at least one adverse event	0	0	2 (1.1%)	2 (0.5%)
Total number of events	0	0	2	2
Calculus urinary	0	0	1 (0.5%)	1 (0.3%)
Paroxysmal nocturnal haemoglobinuria	0	0	1 (0.5%)	1 (0.3%)
Reproductive system and breast disorders				
Total number of patients with at least one adverse event	0	1 (0.5%)	1 (0.5%)	2 (0.5%)
Total number of events	0	1	1	2
Breast disorder	0	1 (0.5%)	0	1 (0.3%)
Cervical dysplasia	0	0	1 (0.5%)	1 (0.3%)
Investigations				
Total number of patients with at least one adverse event	0	1 (0.5%)	0	1 (0.3%)
Total number of events	0	1	0	1
Platelet count decreased	0	1 (0.5%)	0	1 (0.3%)
Psychiatric disorders				
Total number of patients with at least one adverse event	0	1 (0.5%)	0	1 (0.3%)
Total number of events	0	1	0	1
Affective disorder	0	1 (0.5%)	0	1 (0.3%)
Skin and subcutaneous tissue disorders				
Total number of patients with at least one adverse event	0	1 (0.5%)	0	1 (0.3%)
Total number of events	0	1	0	1
Henoch-Schonlein purpura	0	1 (0.5%)	0	1 (0.3%)
Vascular disorders				
Total number of patients with at least one adverse event	0	1 (0.5%)	0	1 (0.3%)
Total number of events	0	1	0	1
Hypovolaemic shock	0	1 (0.5%)	0	1 (0.3%)

Investigator text for AEs encoded using MedDRA version 25.1. Only treatment emergent AEs are displayed.
Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once.
For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Events are sorted by descending overall total frequency.
CCODs: BO42161/BO42162: 16NOV2022, YO42311: 10AUG2022
Data Extract Dates: BO42161/BO42162: 23JAN2023, YO42311: 26OCT2022

Selected Adverse Events

Injection Site Reactions

Table 62: Injection site reactions (safety-evaluable patients)

Summary of Selected Adverse Events, Safety-Evaluable Patients
Protocols: BO42161, BO42162, YO42311

Selected Group MedDRA Preferred Term	Ecu (N=111)	Crova [Naive] (N=192)	Crova [Switch] (N=185)	Crova Total (N=377)
Injection Site Reaction				
Total number of patients with at least one adverse event	0	7 (3.6%)	18 (9.7%)	25 (6.6%)
Total number of events	0	15	30	45
Injection related reaction	0	6 (3.1%)	17 (9.2%)	23 (6.1%)
Injection site reaction	0	1 (0.5%)	1 (0.5%)	2 (0.5%)

Investigator text for AEs encoded using MedDRA version 25.1. Only treatment emergent AEs are displayed.
Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Events are sorted by descending overall total frequency.
CCODs: BO42161/BO42162: 16NOV2022, YO42311: 10AUG2022
Data Extract Dates: BO42161/BO42162: 23JAN2023, YO42311: 26OCT2022

Summary of Symptoms of Injection-Site Reactions, Safety-Evaluable Patients
Protocols: BO42161, BO42162, YO42311

MedDRA System Organ Class MedDRA Preferred Term	Ecu (N=111)	Crova [Naive] (N=192)	Crova [Switch] (N=185)	Crova Total (N=377)
Total number of patients with at least one symptom	0	7 (3.6%)	18 (9.7%)	25 (6.6%)
Overall total number of symptoms	0	33	39	72
General disorders and administration site conditions				
Total number of patients with at least one symptom	0	3 (1.6%)	9 (4.9%)	12 (3.2%)
Total number of symptoms	0	29	15	44
Injection site erythema	0	2 (1.0%)	2 (1.1%)	4 (1.1%)
Injection site pain	0	1 (0.5%)	1 (0.5%)	2 (0.5%)
Injection site pruritus	0	1 (0.5%)	1 (0.5%)	2 (0.5%)
Injection site swelling	0	1 (0.5%)	1 (0.5%)	2 (0.5%)
Malaise	0	0	2 (1.1%)	2 (0.5%)
Injection site discomfort	0	0	1 (0.5%)	1 (0.3%)
Injection site haematoma	0	0	1 (0.5%)	1 (0.3%)
Injection site rash	0	0	1 (0.5%)	1 (0.3%)
Injection site warmth	0	0	1 (0.5%)	1 (0.3%)
Nervous system disorders				
Total number of patients with at least one symptom	0	3 (1.6%)	6 (3.2%)	9 (2.4%)
Total number of symptoms	0	3	7	10
Headache	0	3 (1.6%)	6 (3.2%)	9 (2.4%)
Skin and subcutaneous tissue disorders				
Total number of patients with at least one symptom	0	0	4 (2.2%)	4 (1.1%)
Total number of symptoms	0	0	8	8
Erythema	0	0	2 (1.1%)	2 (0.5%)
Pruritus	0	0	2 (1.1%)	2 (0.5%)
Cutaneous vasculitis	0	0	1 (0.5%)	1 (0.3%)
Rash	0	0	1 (0.5%)	1 (0.3%)
Urticaria	0	0	1 (0.5%)	1 (0.3%)
Musculoskeletal and connective tissue disorders				
Total number of patients with at least one symptom	0	0	3 (1.6%)	3 (0.8%)
Total number of symptoms	0	0	3	3
Myalgia	0	0	2 (1.1%)	2 (0.5%)
Pain in extremity	0	0	1 (0.5%)	1 (0.3%)

MedDRA System Organ Class MedDRA Preferred Term	Ecu (N=111)	Crova [Naive] (N=192)	Crova [Switch] (N=185)	Crova Total (N=377)
Gastrointestinal disorders				
Total number of patients with at least one symptom	0	0	2 (1.1%)	2 (0.5%)
Total number of symptoms	0	0	2	2
Dyspepsia	0	0	1 (0.5%)	1 (0.3%)
Nausea	0	0	1 (0.5%)	1 (0.3%)
Injury, poisoning and procedural complications				
Total number of patients with at least one symptom	0	0	1 (0.5%)	1 (0.3%)
Total number of symptoms	0	0	1	1
Injection related reaction	0	0	1 (0.5%)	1 (0.3%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)				
Total number of patients with at least one symptom	0	0	1 (0.5%)	1 (0.3%)
Total number of symptoms	0	0	1	1
Neoplasm	0	0	1 (0.5%)	1 (0.3%)
Psychiatric disorders				
Total number of patients with at least one symptom	0	0	1 (0.5%)	1 (0.3%)
Total number of symptoms	0	0	1	1
Insomnia	0	0	1 (0.5%)	1 (0.3%)
Respiratory, thoracic and mediastinal disorders				
Total number of patients with at least one symptom	0	0	1 (0.5%)	1 (0.3%)
Total number of symptoms	0	0	1	1
Oropharyngeal discomfort	0	0	1 (0.5%)	1 (0.3%)
Vascular disorders				
Total number of patients with at least one symptom	0	1 (0.5%)	0	1 (0.3%)
Total number of symptoms	0	1	0	1
Hypertension	0	1 (0.5%)	0	1 (0.3%)

Signs and symptoms of patients who have a confirmed Injection-Site Reaction event are shown, given that at least one sign / symptom was recorded for this event.
Investigator text for symptoms encoded using MedDRA version 25.1.
Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same symptom in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same symptom in an individual are counted separately.

Infusion Related Reactions

Table 63: Infusion related reactions (safety-evaluable patients)

Summary of Selected Adverse Events, Safety-Evaluable Patients
Protocols: BO42161, BO42162, YO42311

Selected Group MedDRA Preferred Term	Ecu (N=111)	Crova [Naive] (N=192)	Crova [Switch] (N=185)	Crova Total (N=377)
Infusion Related Reaction				
Total number of patients with at least one adverse event	9 (8.1%)	23 (12.0%)	17 (9.2%)	40 (10.6%)
Total number of events	10	25	17	42
Infusion related reaction	9 (8.1%)	23 (12.0%)	17 (9.2%)	40 (10.6%)
Diarrhoea	0	1 (0.5%)	0	1 (0.3%)

Investigator text for AEs encoded using MedDRA version 25.1. Only treatment emergent AEs are displayed.
Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Events are sorted by descending overall total frequency.
CCODs: BO42161/BO42162: 16NOV2022, YO42311: 10AUG2022
Data Extract Dates: BO42161/BO42162: 23JAN2023, YO42311: 26OCT2022

Summary of Symptoms of Infusion-Related Reactions, Safety-Evaluable Patients
Protocols: BO42161, BO42162, YO42311

MedDRA System Organ Class MedDRA Preferred Term	Ecu (N=111)	Crova [Naive] (N=192)	Crova [Switch] (N=185)	Crova Total (N=377)
Total number of patients with at least one symptom	8 (7.2%)	23 (12.0%)	17 (9.2%)	40 (10.6%)
Overall total number of symptoms	10	34	20	54
Nervous system disorders				
Total number of patients with at least one symptom	6 (5.4%)	19 (9.9%)	11 (5.9%)	30 (8.0%)
Total number of symptoms	7	21	11	32
Headache	6 (5.4%)	18 (9.4%)	9 (4.9%)	27 (7.2%)
Dizziness	0	1 (0.5%)	2 (1.1%)	3 (0.8%)
Paraesthesia	0	1 (0.5%)	0	1 (0.3%)
Skin and subcutaneous tissue disorders				
Total number of patients with at least one symptom	0	2 (1.0%)	4 (2.2%)	6 (1.6%)
Total number of symptoms	0	2	5	7
Rash	0	2 (1.0%)	2 (1.1%)	4 (1.1%)
Erythema	0	0	1 (0.5%)	1 (0.3%)
Pruritus	0	0	1 (0.5%)	1 (0.3%)
Rash pruritic	0	0	1 (0.5%)	1 (0.3%)
Gastrointestinal disorders				
Total number of patients with at least one symptom	2 (1.8%)	2 (1.0%)	1 (0.5%)	3 (0.8%)
Total number of symptoms	2	4	1	5
Abdominal pain	1 (0.9%)	2 (1.0%)	0	2 (0.5%)
Nausea	0	1 (0.5%)	1 (0.5%)	2 (0.5%)
Vomiting	1 (0.9%)	1 (0.5%)	0	1 (0.3%)
Musculoskeletal and connective tissue disorders				
Total number of patients with at least one symptom	1 (0.9%)	2 (1.0%)	1 (0.5%)	3 (0.8%)
Total number of symptoms	1	2	1	3
Arthralgia	0	1 (0.5%)	0	1 (0.3%)
Muscle spasms	0	0	1 (0.5%)	1 (0.3%)
Pain in extremity	0	1 (0.5%)	0	1 (0.3%)
Back pain	1 (0.9%)	0	0	0

Signs and symptoms of patients who have a confirmed Infusion-Related Reaction event are shown, given that at least one sign / symptom was recorded for this event.
Investigator text for symptoms encoded using MedDRA version 25.1.
Percentages are based on N in the column headings.

Summary of Symptoms of Infusion-Related Reactions, Safety-Evaluable Patients
Protocols: BO42161, BO42162, YO42311

MedDRA System Organ Class MedDRA Preferred Term	Ecu (N=111)	Crova [Naive] (N=192)	Crova [Switch] (N=185)	Crova Total (N=377)
General disorders and administration site conditions				
Total number of patients with at least one symptom	0	3 (1.6%)	0	3 (0.8%)
Total number of symptoms	0	3	0	3
Pyrexia	0	2 (1.0%)	0	2 (0.5%)
Chills	0	1 (0.5%)	0	1 (0.3%)
Vascular disorders				
Total number of patients with at least one symptom	0	1 (0.5%)	1 (0.5%)	2 (0.5%)
Total number of symptoms	0	1	1	2
Haematoma	0	1 (0.5%)	0	1 (0.3%)
Hyperaemia	0	0	1 (0.5%)	1 (0.3%)
Eye disorders				
Total number of patients with at least one symptom	0	1 (0.5%)	0	1 (0.3%)
Total number of symptoms	0	1	0	1
Dry eye	0	1 (0.5%)	0	1 (0.3%)
Respiratory, thoracic and mediastinal disorders				
Total number of patients with at least one symptom	0	0	1 (0.5%)	1 (0.3%)
Total number of symptoms	0	0	1	1
Oropharyngeal discomfort	0	0	1 (0.5%)	1 (0.3%)

Signs and symptoms of patients who have a confirmed Infusion-Related Reaction event are shown, given that at least one sign / symptom was recorded for this event.
Investigator text for symptoms encoded using MedDRA version 25.1.
Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same symptom in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same symptom in an individual are counted separately.
Events are sorted by descending overall total frequency.
CCODs: BO42161/BO42162: 16NOV2022, YO42311: 10AUG2022
Data Extract Dates: BO42161/BO42162: 23JAN2023, YO42311: 26OCT2022

Infections

Total crovalimab population vs total eculizumab population

The proportion of patients who experienced at least one infection was 46.9% in the total crovalimab population and 36.0% in the total eculizumab population.

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

Table 64: Overview of infections (safety-evaluable patients)

Overview of Infections, Safety-Evaluable Patients
Protocols: BO42161, BO42162, YO42311

	Ecu (N=111)	Crova [Naive] (N=192)	Crova [Switch] (N=185)	Crova Total (N=377)
Total number of patients with at least one AE	40 (36.0%)	98 (51.0%)	79 (42.7%)	177 (46.9%)
Total number of AEs	60	149	124	273
Total number of patients with at least one				
AE with fatal outcome	0	0	0	0
Serious AE	6 (5.4%)	11 (5.7%)	12 (6.5%)	23 (6.1%)
Related Serious AE	0	3 (1.6%)	1 (0.5%)	4 (1.1%)
Related AE	2 (1.8%)	22 (11.5%)	4 (2.2%)	26 (6.9%)
Related AE leading to withdrawal from treatment	0	0	1 (0.5%)	1 (0.3%)
Related AE leading to dose modification/interruption	0	0	0	0
Grade 3-5 AE	5 (4.5%)	10 (5.2%)	9 (4.9%)	19 (5.0%)
AE leading to withdrawal from treatment	0	0	1 (0.5%)	1 (0.3%)
AE leading to dose modification/interruption	2 (1.8%)	4 (2.1%)	3 (1.6%)	7 (1.9%)

Percentages are based on N in the column headings. Only treatment emergent AEs are displayed.
Multiple occurrences of the same AE in one individual are counted only once except for "Total number of AEs" row in which multiple occurrences of the same AE are counted separately.
CCODs: BO42161/BO42162: 16NOV2022, YO42311: 10AUG2022
Data Extract Dates: BO42161/BO42162: 23JAN2023, YO42311: 26OCT2022

Table 65: Summary of adverse events per 100 patients-years: adverse event overview - infections (safety-evaluable patients)

Summary of Adverse Events per 100 Patient-Years: Adverse Event Overview - Infections, Safety-Evaluable Patients
Protocols: BO42161, BO42162, YO42311

	Ecu (N=111) (PY=49.77)			Crova [Naive] (N=192) (PY=196.13)			Crova [Switch] (N=185) (PY=139.85)		
	No. of AEs	AEs per 100PY	95% CI	No. of AEs	AEs per 100PY	95% CI	No. of AEs	AEs per 100PY	95% CI
All Events	60	120.56	(92.00,155.19)	149	75.97	(64.26, 89.20)	124	88.66	(73.75,105.71)
AE with fatal outcome	0	0	(NE , 7.41)	0	0	(NE , 1.88)	0	0	(NE , 2.64)
Serious AE	7	14.07	(5.66, 28.98)	12	6.12	(3.16, 10.69)	13	9.30	(4.95, 15.90)
Related serious AE	0	0	(NE , 7.41)	3	1.53	(0.32, 4.47)	1	0.72	(0.02, 3.98)
Related AE	2	4.02	(0.49, 14.52)	29	14.79	(9.90, 21.24)	5	3.58	(1.16, 8.34)
Related AE leading to withdrawal from treatment	0	0	(NE , 7.41)	0	0	(NE , 1.88)	1	0.72	(0.02, 3.98)
Related AE leading to dose modification/ interruption	0	0	(NE , 7.41)	0	0	(NE , 1.88)	0	0	(NE , 2.64)
Grade 3-5 AE	6	12.06	(4.42, 26.24)	11	5.61	(2.80, 10.04)	10	7.15	(3.43, 13.15)
AE leading to withdrawal from treatment	0	0	(NE , 7.41)	0	0	(NE , 1.88)	1	0.72	(0.02, 3.98)
AE leading to dose modification/ interruption	2	4.02	(0.49, 14.52)	4	2.04	(0.56, 5.22)	3	2.15	(0.44, 6.27)

PY = Patient years, calculated as last day of follow-up or CCOD (if still ongoing) - date of first dose of study medication + 1 day.
Investigator text for AEs encoded using MedDRA version 25.1. Only treatment emergent AEs are displayed.
Multiple occurrences of the same AE in one patient are counted multiple times.
95% CI is calculated using exact method based on the Poisson distribution.
CCODs: BO42161/BO42162: 16NOV2022, YO42311: 10AUG2022
Data Extract Dates: BO42161/BO42162: 23JAN2023, YO42311: 26OCT2022

Summary of Adverse Events per 100 Patient-Years: Adverse Event Overview - Infections, Safety-Evaluable Patients
Protocols: BO42161, BO42162, YO42311

	Crova Total (N=377) (PY=335.98)		
	No. of AEs	AEs per 100PY	95% CI
All Events	273	81.25	(71.90, 91.49)
AE with fatal outcome	0	0	(NE , 1.10)
Serious AE	25	7.44	(4.82, 10.98)
Related serious AE	4	1.19	(0.32, 3.05)
Related AE	34	10.12	(7.01, 14.14)
Related AE leading to withdrawal from treatment	1	0.30	(0.01, 1.66)
Related AE leading to dose modification/ interruption	0	0	(NE , 1.10)
Grade 3-5 AE	21	6.25	(3.87, 9.55)
AE leading to withdrawal from treatment	1	0.30	(0.01, 1.66)
AE leading to dose modification/ interruption	7	2.08	(0.84, 4.29)

PY = Patient years, calculated as last day of follow-up or CCOD (if still ongoing) - date of first dose of study medication + 1 day.
Investigator text for AEs encoded using MedDRA version 25.1. Only treatment emergent AEs are displayed.
Multiple occurrences of the same AE in one patient are counted multiple times.
95% CI is calculated using exact method based on the Poisson distribution.
CCODs: BO42161/BO42162: 16NOV2022, YO42311: 10AUG2022
Data Extract Dates: BO42161/BO42162: 23JAN2023, YO42311: 26OCT2022

Table 66: time to onset of first infection (Safety-evaluable patients)

Time to Onset of First Infection, Safety-Evaluable Patients
Protocols: BO42161, BO42162, YO42311

	Ecu (N=111)	Crova [Naive] (N=192)	Crova [Switch] (N=185)	Crova Total (N=377)
Total number of patients with at least one adverse event	40 (36.0%)	98 (51.0%)	79 (42.7%)	177 (46.9%)
Time to onset of first adverse event (weeks)*				
n	40	96	79	175
Mean (SD)	9.46 (6.36)	24.25 (18.03)	13.34 (13.26)	19.32 (16.91)
Median	7.21	22.50	10.29	15.14
Min - Max	0.1 - 23.6	0.3 - 98.0	0.1 - 59.7	0.1 - 98.0
Time to onset of first adverse event (category)*				
n	40	96	79	175
<1 week	1 (2.5%)	1 (1.0%)	5 (6.3%)	6 (3.4%)
1-<3 weeks	3 (7.5%)	5 (5.2%)	14 (17.7%)	19 (10.9%)
3-<6 weeks	9 (22.5%)	9 (9.4%)	11 (13.9%)	20 (11.4%)
6-<12 weeks	15 (37.5%)	14 (14.6%)	17 (21.5%)	31 (17.7%)
12-<18 weeks	6 (15.0%)	11 (11.5%)	9 (11.4%)	20 (11.4%)
18-<28 weeks	6 (15.0%)	19 (19.8%)	13 (16.5%)	32 (18.3%)
>=28 weeks	0	37 (38.5%)	10 (12.7%)	47 (26.9%)

* Only events with complete AE start dates were included.
The time to onset of first adverse event was calculated from the time of first dose of the respective study treatment to the time of onset of the first event.
CCODs: BO42161/BO42162: 16NOV2022, YO42311: 10AUG2022
Data Extract Dates: BO42161/BO42162: 23JAN2023, YO42311: 26OCT2022

Table 67: Duration of adverse events, infections (safety-evaluable patients)

Duration of Adverse Events: Infections, Safety-Evaluable Patients
Protocols: BO42161, BO42162, YO42311

	Ecu (N=111)	Crova [Naive] (N=192)	Crova [Switch] (N=185)	Crova Total (N=377)
Total number of events	60	145	120	265
Total number of resolved events*	56	138	116	254
Duration (weeks)*				
n	56	138	116	254
Mean (SD)	2.01 (1.67)	1.91 (4.36)	2.16 (2.94)	2.02 (3.77)
Median	1.57	1.07	1.43	1.29
Min - Max	0.3 - 7.7	0.1 - 49.1	0.1 - 21.6	0.1 - 49.1
Duration (category)*				
n	56	138	116	254
<1 week	13 (23.2%)	58 (42.0%)	33 (28.4%)	91 (35.8%)
1-<2 weeks	23 (41.1%)	52 (37.7%)	46 (39.7%)	98 (38.6%)
2-<4 weeks	13 (23.2%)	13 (9.4%)	25 (21.6%)	38 (15.0%)
4-<8 weeks	7 (12.5%)	12 (8.7%)	8 (6.9%)	20 (7.9%)
8-<12 weeks	0	2 (1.4%)	2 (1.7%)	4 (1.6%)
>=12 weeks	0	1 (0.7%)	2 (1.7%)	3 (1.2%)

Only events with complete start and end dates are included.
* Resolved events refer to events with outcome "Recovered/Resolved" or "Recovered/Resolved with Sequelae".
Duration of each resolved event was calculated as the event end date minus the event start date plus one day converted to weeks.
CCODs: BO42161/BO42162: 16NOV2022, YO42311: 10AUG2022
Data Extract Dates: BO42161/BO42162: 23JAN2023, YO42311: 26OCT2022

Crovalimab Naive Population vs Crovalimab Switch Population

Overall, a similar proportion of patients experienced infections in the crovalimab naïve population (51.0%) compared to the crovalimab switch population (42.7%).

The most frequent infections (≥5% in either population) were (crovalimab naive and crovalimab switch, respectively):

- Upper respiratory tract infection (23.4% and 5.4%)
- COVID-19 (15.1% and 17.3%)
- Urinary tract infection (6.8% and 4.9%)
- Nasopharyngitis (3.6% and 5.4%)

Patients in the crovalimab naive population had a higher incidence of upper respiratory tract infection compared to the crovalimab switch population. However, the overall incidence rate (naive: 51.0%; switch: 42.7% in switch) and occurrence per 100 PYs of infections (naive: 76.0, 95% CI: 64.26, 89.20; switch: 88.7, 95% CI: 73.75, 105.71) between the two populations were comparable, and incidence of PTs similar to upper respiratory tract infection such as nasopharyngitis and pharyngitis were also balanced between the two groups. In addition, the majority of these AEs were grade 1−2 and resolved on continued treatment with crovalimab. As such this imbalance is unlikely to be clinically significant.

Table 68: Hypersensitivity Reactions Other than Type III Hypersensitivity Reactions

Selected Group MedDRA Preferred Term	Most Extreme Intensity	Ecu (N=111)	Crova [Naive] (N=192)	Crova [Switch] (N=185)	Crova Total (N=377)
Hypersensitivity Other than T3H					
- Overall -	- Any Grade -	0	11 (5.7%)	20 (10.8%)	31 (8.2%)
	1	0	7 (3.6%)	11 (5.9%)	18 (4.8%)
	2	0	4 (2.1%)	7 (3.8%)	11 (2.9%)
	3	0	0	2 (1.1%)	2 (0.5%)
Injection related reaction	- Any Grade -	0	7 (3.6%)	17 (9.2%)	24 (6.4%)
	1	0	7 (3.6%)	10 (5.4%)	17 (4.5%)
	2	0	0	6 (3.2%)	6 (1.6%)
	3	0	0	1 (0.5%)	1 (0.3%)
Hypersensitivity	- Any Grade -	0	4 (2.1%)	1 (0.5%)	5 (1.3%)
	2	0	4 (2.1%)	0	4 (1.1%)
	3	0	0	1 (0.5%)	1 (0.3%)
Type IV hypersensitivity reaction	- Any Grade -	0	0	2 (1.1%)	2 (0.5%)
	1	0	0	1 (0.5%)	1 (0.3%)
	2	0	0	1 (0.5%)	1 (0.3%)
Injection Site Reaction					
- Overall -	- Any Grade -	0	7 (3.6%)	18 (9.7%)	25 (6.6%)
	1	0	6 (3.1%)	11 (5.9%)	17 (4.5%)
	2	0	1 (0.5%)	6 (3.2%)	7 (1.9%)
	3	0	0	1 (0.5%)	1 (0.3%)
Injection related reaction	- Any Grade -	0	6 (3.1%)	17 (9.2%)	23 (6.1%)
	1	0	6 (3.1%)	10 (5.4%)	16 (4.2%)
	2	0	0	6 (3.2%)	6 (1.6%)
	3	0	0	1 (0.5%)	1 (0.3%)
Injection site reaction	- Any Grade -	0	1 (0.5%)	1 (0.5%)	2 (0.5%)
	1	0	0	1 (0.5%)	1 (0.3%)
	2	0	1 (0.5%)	0	1 (0.3%)

Investigator text for AEs is coded using MedDRA version 25.1. Only treatment emergent AEs are displayed.

Type III Hypersensitivity Reactions

Type III hypersensitivity reactions were expected only in patients switching from eculizumab or ravulizumab to crovalimab (and vice versa). This is due to crovalimab and eculizumab (or ravulizumab) binding to different epitopes on C5, and the fact that DTDCs may form when both are present in the circulation. Therefore, patients who switched from eculizumab or ravulizumab to crovalimab (and vice versa) are at risk of developing DTDC-associated Type III hypersensitivity reactions.

Table 69: Summary of Type III hypersensitivity reactions by intensity (safety-evaluable patients)

Summary of Type III Hypersensitivity Reactions by Intensity, Safety-Evaluable Patients
Protocols: BO42161, BO42162, YO42311

MedDRA System Organ Class MedDRA Preferred Term	Most Extreme Intensity	Ecu (N=111)	Crova [Naive] (N=192)	Crova [Switch] (N=185)	Crova Total (N=377)
- Any adverse events -	- Any Grade -	0	0	33 (17.8%)	33 (8.8%)
	1	0	0	9 (4.9%)	9 (2.4%)
	2	0	0	11 (5.9%)	11 (2.9%)
	3	0	0	13 (7.0%)	13 (3.4%)
Immune system disorders					
- Overall -	- Any Grade -	0	0	33 (17.8%)	33 (8.8%)
	1	0	0	9 (4.9%)	9 (2.4%)
	2	0	0	11 (5.9%)	11 (2.9%)
	3	0	0	13 (7.0%)	13 (3.4%)
Type III immune complex mediated reaction	- Any Grade -	0	0	33 (17.8%)	33 (8.8%)
	1	0	0	9 (4.9%)	9 (2.4%)
	2	0	0	11 (5.9%)	11 (2.9%)
	3	0	0	13 (7.0%)	13 (3.4%)
Nervous system disorders					
- Overall -	- Any Grade -	0	0	1 (0.5%)	1 (0.3%)
	3	0	0	1 (0.5%)	1 (0.3%)
Axonal neuropathy	- Any Grade -	0	0	1 (0.5%)	1 (0.3%)
	3	0	0	1 (0.5%)	1 (0.3%)

Investigator text for AEs is coded using MedDRA version 25.1. Only treatment emergent AEs are displayed.
All counts represent patients. Multiple occurrences of the same AE in one individual are counted once at the highest grade for this preferred term.
To the SOC Overall row counts, a patient contributes once for each grade for which at least one AE with the corresponding highest grade is reported.
CCODs: BO42161/BO42162: 16NOV2022, YO42311: 10AUG2022
Data Extract Dates: BO42161/BO42162: 23JAN2023, YO42311: 26OCT2022

Table 70: Summary of symptoms of type III hypersensitivity reactions by intensity (safety-evaluable patients)

Summary of Symptoms of Type III Hypersensitivity Reactions by Intensity, Safety-Evaluable Patients
Protocols: BO42161, BO42162, YO42311

MedDRA System Organ Class MedDRA Preferred Term	Most Extreme Intensity	Ecu (N=111)	Crova [Naive] (N=192)	Crova [Switch] (N=185)	Crova Total (N=377)
- Any symptoms -	- Any Grade -	0	0	33 (17.8%)	33 (8.8%)
	1	0	0	10 (5.4%)	10 (2.7%)
	2	0	0	11 (5.9%)	11 (2.9%)
	3	0	0	12 (6.5%)	12 (3.2%)
Musculoskeletal and connective tissue disorders					
- Overall -	- Any Grade -	0	0	21 (11.4%)	21 (5.6%)
	1	0	0	6 (3.2%)	6 (1.6%)
	2	0	0	6 (3.2%)	6 (1.6%)
	3	0	0	9 (4.9%)	9 (2.4%)
Arthralgia	- Any Grade -	0	0	17 (9.2%)	17 (4.5%)
	1	0	0	6 (3.2%)	6 (1.6%)
	2	0	0	4 (2.2%)	4 (1.1%)
	3	0	0	7 (3.8%)	7 (1.9%)
Myalgia	- Any Grade -	0	0	6 (3.2%)	6 (1.6%)
	1	0	0	1 (0.5%)	1 (0.3%)
	2	0	0	3 (1.6%)	3 (0.8%)
	3	0	0	2 (1.1%)	2 (0.5%)
Pain in extremity	- Any Grade -	0	0	2 (1.1%)	2 (0.5%)
	2	0	0	2 (1.1%)	2 (0.5%)
Joint stiffness	- Any Grade -	0	0	1 (0.5%)	1 (0.3%)
	3	0	0	1 (0.5%)	1 (0.3%)
Joint swelling	- Any Grade -	0	0	1 (0.5%)	1 (0.3%)
	2	0	0	1 (0.5%)	1 (0.3%)
Muscular weakness	- Any Grade -	0	0	1 (0.5%)	1 (0.3%)
	2	0	0	1 (0.5%)	1 (0.3%)
Neck pain	- Any Grade -	0	0	1 (0.5%)	1 (0.3%)
	2	0	0	1 (0.5%)	1 (0.3%)
Skin and subcutaneous tissue disorders					
- Overall -	- Any Grade -	0	0	20 (10.8%)	20 (5.3%)
	1	0	0	6 (3.2%)	6 (1.6%)
	2	0	0	10 (5.4%)	10 (2.7%)
	3	0	0	4 (2.2%)	4 (1.1%)
Rash	- Any Grade -	0	0	11 (5.9%)	11 (2.9%)
	1	0	0	3 (1.6%)	3 (0.8%)
	2	0	0	6 (3.2%)	6 (1.6%)
	3	0	0	2 (1.1%)	2 (0.5%)
Erythema	- Any Grade -	0	0	2 (1.1%)	2 (0.5%)
	2	0	0	2 (1.1%)	2 (0.5%)
Petechiae	- Any Grade -	0	0	2 (1.1%)	2 (0.5%)
	1	0	0	2 (1.1%)	2 (0.5%)

Summary of Symptoms of Type III Hypersensitivity Reactions by Intensity, Safety-Evaluable Patients
Protocols: BO42161, BO42162, YO42311

MedDRA System Organ Class MedDRA Preferred Term	Most Extreme Intensity	Ecu (N=111)	Crova [Naive] (N=192)	Crova [Switch] (N=185)	Crova Total (N=377)
Henoch-Schonlein purpura	- Any Grade -	0	0	1 (0.5%)	1 (0.3%)
	3	0	0	1 (0.5%)	1 (0.3%)
Purpura	- Any Grade -	0	0	1 (0.5%)	1 (0.3%)
	3	0	0	1 (0.5%)	1 (0.3%)
Rash erythematous	- Any Grade -	0	0	1 (0.5%)	1 (0.3%)
	1	0	0	1 (0.5%)	1 (0.3%)
Rash macular	- Any Grade -	0	0	1 (0.5%)	1 (0.3%)
	2	0	0	1 (0.5%)	1 (0.3%)
Rash maculo-papular	- Any Grade -	0	0	1 (0.5%)	1 (0.3%)
	2	0	0	1 (0.5%)	1 (0.3%)
Rash papular	- Any Grade -	0	0	1 (0.5%)	1 (0.3%)
	1	0	0	1 (0.5%)	1 (0.3%)
General disorders and administration site conditions					
- Overall -	- Any Grade -	0	0	10 (5.4%)	10 (2.7%)
	1	0	0	3 (1.6%)	3 (0.8%)
	2	0	0	4 (2.2%)	4 (1.1%)
	3	0	0	3 (1.6%)	3 (0.8%)
Pyrexia	- Any Grade -	0	0	7 (3.8%)	7 (1.9%)
	1	0	0	3 (1.6%)	3 (0.8%)
	2	0	0	1 (0.5%)	1 (0.3%)
	3	0	0	3 (1.6%)	3 (0.8%)
Asthenia	- Any Grade -	0	0	2 (1.1%)	2 (0.5%)
	2	0	0	1 (0.5%)	1 (0.3%)
	3	0	0	1 (0.5%)	1 (0.3%)
Fatigue	- Any Grade -	0	0	2 (1.1%)	2 (0.5%)
	1	0	0	1 (0.5%)	1 (0.3%)
	3	0	0	1 (0.5%)	1 (0.3%)
Chills	- Any Grade -	0	0	1 (0.5%)	1 (0.3%)
	2	0	0	1 (0.5%)	1 (0.3%)
Oedema	- Any Grade -	0	0	1 (0.5%)	1 (0.3%)
	2	0	0	1 (0.5%)	1 (0.3%)
Oedema peripheral	- Any Grade -	0	0	1 (0.5%)	1 (0.3%)
	1	0	0	1 (0.5%)	1 (0.3%)
Nervous system disorders					
- Overall -	- Any Grade -	0	0	8 (4.3%)	8 (2.1%)
	1	0	0	1 (0.5%)	1 (0.3%)
	2	0	0	2 (1.1%)	2 (0.5%)
	3	0	0	5 (2.7%)	5 (1.3%)
Headache	- Any Grade -	0	0	5 (2.7%)	5 (1.3%)
	2	0	0	2 (1.1%)	2 (0.5%)
	3	0	0	3 (1.6%)	3 (0.8%)

MedDRA System Organ Class MedDRA Preferred Term	Most Extreme Intensity	Ecu (N=111)	Crova [Naive] (N=192)	Crova [Switch] (N=185)	Crova Total (N=377)
Axonal neuropathy	- Any Grade -	0	0	1 (0.5%)	1 (0.3%)
	3	0	0	1 (0.5%)	1 (0.3%)
Dizziness	- Any Grade -	0	0	1 (0.5%)	1 (0.3%)
	3	0	0	1 (0.5%)	1 (0.3%)
Dysaesthesia	- Any Grade -	0	0	1 (0.5%)	1 (0.3%)
	1	0	0	1 (0.5%)	1 (0.3%)
Gastrointestinal disorders					
- Overall -	- Any Grade -	0	0	4 (2.2%)	4 (1.1%)
	1	0	0	1 (0.5%)	1 (0.3%)
	2	0	0	1 (0.5%)	1 (0.3%)
	3	0	0	2 (1.1%)	2 (0.5%)
Abdominal pain upper	- Any Grade -	0	0	3 (1.6%)	3 (0.8%)
	2	0	0	1 (0.5%)	1 (0.3%)
	3	0	0	2 (1.1%)	2 (0.5%)
Nausea	- Any Grade -	0	0	2 (1.1%)	2 (0.5%)
	2	0	0	1 (0.5%)	1 (0.3%)
	3	0	0	1 (0.5%)	1 (0.3%)
Lip erosion	- Any Grade -	0	0	1 (0.5%)	1 (0.3%)
	1	0	0	1 (0.5%)	1 (0.3%)
Vascular disorders					
- Overall -	- Any Grade -	0	0	2 (1.1%)	2 (0.5%)
	1	0	0	1 (0.5%)	1 (0.3%)
	3	0	0	1 (0.5%)	1 (0.3%)
Vasculitis	- Any Grade -	0	0	2 (1.1%)	2 (0.5%)
	1	0	0	1 (0.5%)	1 (0.3%)
	3	0	0	1 (0.5%)	1 (0.3%)
Renal and urinary disorders					
- Overall -	- Any Grade -	0	0	1 (0.5%)	1 (0.3%)
	3	0	0	1 (0.5%)	1 (0.3%)
Chromaturia	- Any Grade -	0	0	1 (0.5%)	1 (0.3%)
	3	0	0	1 (0.5%)	1 (0.3%)

Signs and symptoms of patients who have a confirmed Type III Hypersensitivity event are shown, given that at least one sign / symptom was recorded for this event.
Investigator text for symptoms is coded using MedDRA version 25.1.
All counts represent patients. Multiple occurrences of the same symptom in one individual are counted once at the highest grade for this preferred term.
To the SOC Overall row counts, a patient contributes once for each grade for which at least one symptom with the corresponding highest grade is reported.
Events are sorted by descending overall total frequency.
CODDs: BO42161/BO42162: 16NOV2022, YO42311: 10AUG2022
Data Extract Dates: BO42161/BO42162: 23JAN2023, YO42311: 26OCT2022

Table 71: Time to onset of first type III hypersensitivity reaction (safety-evaluable patients)

Time to Onset of First Type III Hypersensitivity Reaction, Safety-Evaluable Patients
Protocols: BO42161, BO42162, YO42311

	Ecu (N=111)	Crova [Naive] (N=192)	Crova [Switch] (N=185)	Crova Total (N=377)
Total number of patients with at least one adverse event	0	0	33 (17.8%)	33 (8.8%)
Time to onset of first adverse event (weeks)*				
n	0	0	33	33
Mean (SD)	NE (NE)	NE (NE)	1.94 (0.96)	1.94 (0.96)
Median	NE	NE	1.57	1.57
Min - Max	NE - NE	NE - NE	0.7 - 4.4	0.7 - 4.4
Time to onset of first adverse event (category)*				
n	0	0	33	33
<1 week	0	0	3 (9.1%)	3 (9.1%)
1-<2 weeks	0	0	16 (48.5%)	16 (48.5%)
2-<4 weeks	0	0	12 (36.4%)	12 (36.4%)
4-<6 weeks	0	0	2 (6.1%)	2 (6.1%)
>=6 weeks	0	0	0	0

* Only events with complete AE start dates were included.
The time to onset of first Type III Hypersensitivity Reaction was calculated from the time of first dose of study treatment to the time of onset of the first event.
CCODs: BO42161/BO42162: 16NOV2022, YO42311: 10AUG2022
Data Extract Dates: BO42161/BO42162: 23JAN2023, YO42311: 26OCT2022

Table 72: Duration of adverse events, Type II hypersensitivity reactions (safety-evaluable patients)

Duration of Adverse Events: Type III Hypersensitivity Reactions, Safety-Evaluable Patients
Protocols: BO42161, BO42162, YO42311

	Ecu (N=111)	Crova [Naive] (N=192)	Crova [Switch] (N=185)	Crova Total (N=377)
Total number of events	0	0	36	36
Total number of resolved events*	0	0	31	31
Duration (weeks)*				
n	0	0	31	31
Mean (SD)	NE (NE)	NE (NE)	4.06 (6.44)	4.06 (6.44)
Median	NE	NE	1.86	1.86
Min - Max	NE - NE	NE - NE	0.4 - 34.1	0.4 - 34.1
Duration (category)*				
n	0	0	31	31
<1 week	0	0	4 (12.9%)	4 (12.9%)
1-<2 weeks	0	0	13 (41.9%)	13 (41.9%)
2-<4 weeks	0	0	6 (19.4%)	6 (19.4%)
4-<8 weeks	0	0	4 (12.9%)	4 (12.9%)
8-<12 weeks	0	0	2 (6.5%)	2 (6.5%)
>=12 weeks	0	0	2 (6.5%)	2 (6.5%)

Only events with complete start and end dates are included.
* Resolved events refer to events with outcome "Recovered/Resolved" or "Recovered/Resolved with Sequelae".
Duration of each resolved event was calculated as the event end date minus the event start date plus one day converted to weeks.
CCODs: BO42161/BO42162: 16NOV2022, YO42311: 10AUG2022
Data Extract Dates: BO42161/BO42162: 23JAN2023, YO42311: 26OCT2022

-Abnormal Liver Function Tests (Hy's Law)

No AESIs of abnormal liver function tests were reported.

-Suspected Transmission of an Infectious Agent by the Study Drug

No AESIs of suspected transmission of an infectious agent by the study drug were reported.

Safety in patients switching from ravulizumab treatment

As of the CCOD, 21 ravulizumab treated patients were enrolled in the Arm C of Study BO42161. Key safety results for these patients are provided:

• Overall, 85.7% of prior ravulizumab treated patients experienced at least one AE.

•The most frequently reported (≥ 10%) PTs were: Pyrexia (28.6%), Type III immune complex mediated reaction (23.8%), headache (19.0%), injection related reaction (19.0%), myalgia (19.0%), nausea (19.0%), arthralgia (14.3%), COVID-19 (14.3%), haemolysis (14.3%) and infusion related reaction (14.3%).

• Related AEs were reported in 47.6% of prior ravulizumab treated patients. The only PTs reported as treatment-related in ≥10% of patients were Type III immune complex mediated reaction (23.8%) and injection related reaction (19.0%).

• No fatal AEs (grade 5 AEs) occurred in prior ravulizumab treated patients. One patient discontinued from study treatment due to AE (PT: sepsis) and two patients experienced an AE leading to dose modification/interruption (PT: nasopharyngitis and infusion related reaction). Grade 3-5 AEs were reported in 42.9% of prior ravulizumab treated patients, with the only PT reported as grade 3−5 in more than 1 patient being Type III immune complex mediated reaction (14.3%).

• SAEs were reported in 33.3% of prior ravulizumab treated patients, with the only PT reported as an SAE in more than 1 patient being Type III immune complex mediated reaction (14.3%), all of which were considered related to treatment. The only other serious treatment-related AEs were sepsis and axonal neuropathy (which was indicated as being a Type III hypersensitivity reaction), which occurred in 1 patient each.

Long-Term Safety

BP39144 Phase I/II Study – Open-Label Extension

Long-term safety analyses were conducted covering both the primary treatment period (20 weeks) as well as the OLE period of Study BP39144. Safety analyses report cumulative results from baseline up to a CCOD of 1 November 2021 are provided in Report 1112075.

Forty-three of the 44 patients that were enrolled in Parts 2−4 of the study entered the OLE, and 38 patients were ongoing on crovalimab treatment at the time of the CCOD (17 naive patients and 21 patients who switched from eculizumab). Overall, a total of 5 patients discontinued from the OLE (4 patients originally enrolled to Part 3 [switch] and 1 patient originally enrolled to Part 4, Arm A [naive]). No patients discontinued from the study due to safety reasons. The median treatment duration from baseline to the CCOD was 3.03 years.

Overall, the long-term safety results from Study BP39144 indicate that crovalimab was well tolerated in patients with PNH, irrespective of naive or switch status at time of enrolment onto the study. The key safety results in Study BP39144 are as follows:

• A total of 42 (95.5%) patients experienced at least one AE from baseline to CCOD. The total number of patients with at least one AE of any grade was comparable between the treatment-naive patients (94.4%) and patients who switched from eculizumab (96.2%).

• The most frequently reported AEs by SOC (≥50% incidence in the total population) were infections and infestations (81.8%) and general disorders and administration site conditions (50.0%).

• AEs that were considered by the Investigator to be related to study treatment were reported in 14 (31.8%) patients (4 [22.2%] treatment-naive patients and 10 [38.5%] switched patients) from baseline to CCOD.

• Overall, the majority of AEs (77.3%) were of mild or moderate intensity.

• No deaths were reported.

• A total of 14 (31.8%) patients experienced at least one SAE over a median treatment duration of 3.03 years. SAEs were reported in 33.3% of patients in the treatment-naive group and 30.8% of patients in the switched from eculizumab group. In the treatment-naive patients, 1 patient (5.6%) experienced 1 SAE of breakthrough haemolysis assessed as related to study treatment by the Investigator. In the patients who switched from eculizumab, 1 patient (3.8%) experienced 1 SAE of upper respiratory tract infection assessed as related to study treatment by the Investigator.

• No patients experienced AEs leading to study treatment discontinuation.

• One out of 18 patients (5.6%) in the treatment-naive group experienced an AE that led to dose interruption. No patients who switched from eculizumab experienced an AE that resulted in a dose modification or interruption.

• Two AESIs of abnormal liver function tests were reported in 2 (4.5%) patients with PNH (1 treatment-naive patient and 1 switched patient). These AESIs were not considered related to study treatment, as assessed by the Investigator.

• Two out of 26 patients (7.7%) in the patients who switched from eculizumab experienced AESIs of Type III hypersensitivity reactions. One patient in the treatment-naive group experienced an AESI of Type III hypersensitivity at time of switch from crovalimab to eculizumab, after discontinuing from the study due to a lack of efficacy.

• No AESIs of suspected transmission of an infectious agent by the study drug were reported.

• There were no cases of Meningococcal meningitis.

A total of 36 (81.8%) patients (77.8% of treatment-naive patients and 84.6% of switched patients) experienced at least one infection up to the CCOD.

• No hypersensitivity other than Type III hypersensitivity reactions were reported.

• A total of 4.5% of patients (5.6% of treatment-naive patients and 3.8% of switched patients) experienced at least one injection site reaction up to CCOD.

• No treatment-naive patients reported infusion related reactions. Three (11.5%) patients who switched from eculizumab reported 5 events of infusion related reaction during the primary treatment period.

• Individual patients showed isolated marked laboratory abnormalities; however, no pattern in the parameters were observed with respect to time or dose, and these changes were not considered associated with crovalimab.

• No clinically significant changes were observed in the treatment-naive or switched patients in vital signs and ECG parameters.

• There were three pregnancies in partners of patients reported in the study, with no reported detectable detrimental consequences to the infants.

2.6.8.4. Laboratory findings

Vital signs

Total Crovalimab vs Total Eculizumab Population

Up to CCOD, no clinically significant changes in vital signs were observed in the total crovalimab and total eculizumab populations. Individual patients showed various vital sign abnormalities. However, there was no apparent pattern of clinically significant changes in vital signs compared to baseline.

Crovalimab Naive Population vs Crovalimab Switch Population

Up to CCOD, no notable imbalances were observed between the treatment-naive or treatment-switch crovalimab populations.

Electrocardiography

Summary of QTcF and QTcB Actual Values and Absolute Changes from Baseline, Safety-Evaluable Patients
Protocols: BO42161, BO42162, YO42311

Assessment: QTcF - Fridericia's Correction Formula (msec)

Visit Category	Ecu (N=111)	Crova [Naive] (N=192)	Crova [Switch] (N=185)	Crova Total (N=377)
Baseline				
Value at Visit				
n	110	191	184	375
<=450 msec	97 (88.2%)	175 (91.6%)	172 (93.5%)	347 (92.5%)
>450 to <=480 msec	12 (10.9%)	13 (6.8%)	11 (6.0%)	24 (6.4%)
>480 to <=500 msec	1 (0.9%)	2 (1.0%)	1 (0.5%)	3 (0.8%)
>500 msec	0	1 (0.5%)	0	1 (0.3%)
Post-Baseline				
Value at Visit				
n	105	189	166	355
<=450 msec	92 (87.6%)	176 (93.1%)	153 (92.2%)	329 (92.7%)
>450 to <=480 msec	10 (9.5%)	13 (6.9%)	13 (7.8%)	26 (7.3%)
>480 to <=500 msec	3 (2.9%)	0	0	0
>500 msec	0	0	0	0
Change from Baseline				
n	104	188	166	354
<=30 msec	95 (91.3%)	173 (92.0%)	152 (91.6%)	325 (91.8%)
>30 to <=60 msec	7 (6.7%)	13 (6.9%)	13 (7.8%)	26 (7.3%)
>60 msec	2 (1.9%)	2 (1.1%)	1 (0.6%)	3 (0.8%)

Baseline is the patient's last observation prior to initiation of the respective study drug, i.e. for patients in Arm and BO42162 who become part of the CROVALIMAB [Switch] population after the primary treatment period, baseline is the observation prior to initiation of Crovalimab in the extension period.
Post-baseline is the worst (longest) post-baseline value.
Percentages are calculated using n as the denominator.
CCODs: BO42161/BO42162: 16NOV2022, YO42311: 10AUG2022
Data Extract Dates: BO42161/BO42162: 23JAN2023, YO42311: 26OCT2022

2.6.8.5. In vitro biomarker test for patient selection for safety

Not applicable.

2.6.8.6. Safety in special populations

Intrinsic factors

-Age

Table 73: Overview of adverse events by age group at baseline (safety-evaluable patients)

Overview of Adverse Events by Age Group at Baseline, Safety-Evaluable Patients
Protocols: BO42161, BO42162, YO42311

	Ecu (N=111)			Crova [Naive] (N=192)		
	<18 (N=2)	18 - 64 (N=93)	>=65 (N=16)	<18 (N=9)	18 - 64 (N=170)	>=65 (N=13)
Total number of patients with at least one AE	2 (100%)	72 (77.4%)	9 (56.3%)	8 (88.9%)	156 (91.8%)	10 (76.9%)
Total number of AEs	6	255	29	33	976	54
Total number of deaths	0	1 (1.1%)	0	0	1 (0.6%)	2 (15.4%)
Total number of patients withdrawn from study due to an AE	0	0	0	0	0	0
Total number of patients with at least one						
AE with fatal outcome	0	1 (1.1%)	0	0	1 (0.6%)	2 (15.4%)
Serious AE	1 (50.0%)	8 (8.6%)	1 (6.3%)	0	25 (14.7%)	3 (23.1%)
Related Serious AE	0	1 (1.1%)	0	0	6 (3.5%)	1 (7.7%)
Related AE	1 (50.0%)	21 (22.6%)	2 (12.5%)	4 (44.4%)	85 (50.0%)	4 (30.8%)
Related AE leading to withdrawal from treatment	0	0	0	0	1 (0.6%)	0
Related AE leading to dose modification/interruption	0	0	0	0	2 (1.2%)	0
Grade 3-5 AE	1 (50.0%)	15 (16.1%)	2 (12.5%)	2 (22.2%)	44 (25.9%)	4 (30.8%)
AE leading to withdrawal from treatment	0	1 (1.1%)	0	0	1 (0.6%)	0
AE leading to dose modification/interruption	1 (50.0%)	2 (2.2%)	0	0	7 (4.1%)	1 (7.7%)

Age group is given in years and based on Age at initiation of the respective study drug, i.e. for patients in Arm B of BO42161 and BO42162 who become part of the CROVALIMAB [Switch] population after the primary treatment period, baseline is the time point of initiation of Crovalimab in the extension period.
Percentages are based on N in the column headings. Only treatment emergent AEs are displayed.
Multiple occurrences of the same AE in one individual are counted only once except for "Total number of AEs" row in which multiple occurrences of the same AE are counted separately.
CCODs: BO42161/BO42162: 16NOV2022, YO42311: 10AUG2022
Data Extract Dates: BO42161/BO42162: 23JAN2023, YO42311: 26OCT2022

Overview of Adverse Events by Age Group at Baseline, Safety-Evaluable Patients
Protocols: BO42161, BO42162, YO42311

	Crova [Switch] (N=185)			Crova Total (N=377)		
	<18 (N=2)	18 - 64 (N=157)	>=65 (N=26)	<18 (N=11)	18 - 64 (N=327)	>=65 (N=39)
Total number of patients with at least one AE	1 (50.0%)	127 (80.9%)	24 (92.3%)	9 (81.8%)	283 (86.5%)	34 (87.2%)
Total number of AEs	1	550	141	34	1526	195
Total number of deaths	0	1 (0.6%)	0	0	2 (0.6%)	2 (5.1%)
Total number of patients withdrawn from study due to an AE	0	0	0	0	0	0
Total number of patients with at least one						
AE with fatal outcome	0	1 (0.6%)	0	0	2 (0.6%)	2 (5.1%)
Serious AE	0	21 (13.4%)	8 (30.8%)	0	46 (14.1%)	11 (28.2%)
Related Serious AE	0	4 (2.5%)	1 (3.8%)	0	10 (3.1%)	2 (5.1%)
Related AE	1 (50.0%)	57 (36.3%)	12 (46.2%)	5 (45.5%)	142 (43.4%)	16 (41.0%)
Related AE leading to withdrawal from treatment	0	1 (0.6%)	1 (3.8%)	0	2 (0.6%)	1 (2.6%)
Related AE leading to dose modification/interruption	0	3 (1.9%)	1 (3.8%)	0	5 (1.5%)	1 (2.6%)
Grade 3-5 AE	0	34 (21.7%)	12 (46.2%)	2 (18.2%)	78 (23.9%)	16 (41.0%)
AE leading to withdrawal from treatment	0	1 (0.6%)	2 (7.7%)	0	2 (0.6%)	2 (5.1%)
AE leading to dose modification/interruption	0	5 (3.2%)	3 (11.5%)	0	12 (3.7%)	4 (10.3%)

Age group is given in years and based on Age at initiation of the respective study drug, i.e. for patients in Arm B of BO42161 and BO42162 who become part of the CROVALIMAB [Switch] population after the primary treatment period, baseline is the time point of initiation of Crovalimab in the extension period.
Percentages are based on N in the column headings. Only treatment emergent AEs are displayed.
Multiple occurrences of the same AE in one individual are counted only once except for "Total number of AEs" row in which multiple occurrences of the same AE are counted separately.
CCODs: BO42161/BO42162: 16NOV2022, YO42311: 10AUG2022
Data Extract Dates: BO42161/BO42162: 23JAN2023, YO42311: 26OCT2022

Safety in Paediatric Patients

Of the total crovalimab population, 2.9% of patients were <18 years at study enrolment. Across the Phase III studies, a total of 11 paediatric patients (9 treatment-naive and 2 switch patients with PNH), ≥40 kg were treated with crovalimab up to CCOD:

• One patient in Arm B (eculizumab) of Study BO42162 who received crovalimab in the extension period (switch patient)

• Six treatment-naive patients in Arm C of Study BO42162

• Three treatment-naive patients in Study YO42311

• One switch patient in Arm C of Study BO42161

Enrolment into Arm C of BO42161 is still ongoing.

In the 11 paediatric patients, the age range and body weight range at baseline was 13−17 years and 48.9−98.5 kg, respectively, 6 were female and 9 were Asian. These patients had similar baseline disease characteristics as the adult patients enrolled in the respective studies.

Of the total 11 paediatric patients, 9 (81.8%) paediatric patients reported at least one AE, and the majority of AEs were of grade 1-2. Two (18.2%) patients experienced AEs of grade 3−5. Five (45.5%) patients experienced AEs that were assessed as related to study treatment by the Investigator. No paediatric patient reported a fatal AE, an SAE or an AE that led to drug interruption/ modification or withdrawal.

While no serious meningococcal infections were reported across all of the studies in the crovalimab PNH development programme, of note, there was one case of Meningococcal meningitis in Study BO42354, a study evaluating the efficacy, safety, PK and PD of crovalimab in paediatric patients with atypical haemolytic uremic syndrome. The patient experienced Meningococcal meningitis on Day 430 (grade 3). The pathogen was identified as Neisseria meningitidis serotype X (the patient was vaccinated against serotype ACWY). The event subsequently resolved after 4 days, with no change to crovalimab treatment.

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

Race

Table 74: Overview of adverse events by race (safety-evaluable patients)

Overview of Adverse Events by Race, Safety-Evaluable Patients
Protocols: BO42161, BO42162, YO42311

	Ecu (N=111)				Crova [Naive] (N=192)			
	Asian (N=58)	Black or African American (N=2)	White (N=46)	Unknown (N=5)	Asian (N=142)	Black or African American (N=8)	White (N=45)	Unknown (N=2)
Total number of patients with at least one AE	47 (81.0%)	2 (100%)	30 (65.2%)	4 (80.0%)	128 (90.1%)	3 (100%)	41 (91.1%)	2 (100%)
Total number of AEs	190	7	81	12	852	20	185	6
Total number of deaths	0	0	1 (2.2%)	0	2 (1.4%)	0	1 (2.2%)	0
Total number of patients withdrawn from study due to an AE	0	0	0	0	0	0	0	0
Total number of patients with at least one								
AE with fatal outcome	0	0	1 (2.2%)	0	2 (1.4%)	0	1 (2.2%)	0
Serious AE	7 (12.1%)	0	2 (4.3%)	1 (20.0%)	22 (15.5%)	0	6 (13.3%)	0
Related Serious AE	1 (1.7%)	0	0	0	7 (4.9%)	0	0	0
Related AE	20 (34.5%)	0	4 (8.7%)	0	77 (54.2%)	2 (66.7%)	13 (28.9%)	1 (50.0%)
Related AE leading to withdrawal from treatment	0	0	0	0	1 (0.7%)	0	0	0
Related AE leading to dose modification/interruption	0	0	0	0	2 (1.4%)	0	0	0
Grade 3-5 AE	15 (25.9%)	0	2 (4.3%)	1 (20.0%)	41 (28.9%)	0	9 (20.0%)	0
AE leading to withdrawal from treatment	0	0	1 (2.2%)	0	1 (0.7%)	0	0	0
AE leading to dose modification/ interruption	2 (3.4%)	0	1 (2.2%)	0	4 (2.8%)	0	4 (8.9%)	0

Percentages are based on N in the column headings. Only treatment emergent AEs are displayed.
Multiple occurrences of the same AE in one individual are counted only once except for "Total number of AEs" row in which multiple occurrences of the same AE are counted separately.
CCODs: BO42161/BO42162: 16NOV2022, YO42311: 10AUG2022
Data Extract Dates: BO42161/BO42162: 23JAN2023, YO42311: 26OCT2022

Overview of Adverse Events by Race, Safety-Evaluable Patients
Protocols: B042161, B042162, Y042311

	Crova [Switch] (N=185)				Crova Total (N=377)			
	Asian (N=84)	Black or African American (N=4)	White (N=89)	Unknown (N=8)	Asian (N=226)	Black or African American (N=7)	White (N=134)	Unknown (N=10)
Total number of patients with at least one AE	68 (81.0%)	4 (100%)	73 (82.0%)	7 (87.5%)	196 (86.7%)	7 (100%)	114 (85.1%)	9 (90.0%)
Total number of AEs	320	13	309	50	1172	33	494	56
Total number of deaths	0	0	1 (1.1%)	0	2 (0.9%)	0	2 (1.5%)	0
Total number of patients withdrawn from study due to an AE	0	0	0	0	0	0	0	0
Total number of patients with at least one								
AE with fatal outcome	0	0	1 (1.1%)	0	2 (0.9%)	0	2 (1.5%)	0
Serious AE	15 (17.9%)	1 (25.0%)	13 (14.6%)	0	37 (16.4%)	1 (14.3%)	19 (14.2%)	0
Related Serious AE	1 (1.2%)	1 (25.0%)	3 (3.4%)	0	8 (3.5%)	1 (14.3%)	3 (2.2%)	0
Related AE	36 (42.9%)	3 (75.0%)	27 (30.3%)	4 (50.0%)	113 (50.0%)	5 (71.4%)	40 (29.9%)	5 (50.0%)
Related AE leading to withdrawal from treatment	0	0	2 (2.2%)	0	1 (0.4%)	0	2 (1.5%)	0
Related AE leading to dose modification/interruption	3 (3.6%)	0	0	1 (12.5%)	5 (2.2%)	0	0	1 (10.0%)
Grade 3-5 AE	22 (26.2%)	2 (50.0%)	21 (23.6%)	1 (12.5%)	63 (27.9%)	2 (28.6%)	30 (22.4%)	1 (10.0%)
AE leading to withdrawal from treatment	0	0	3 (3.4%)	0	1 (0.4%)	0	3 (2.2%)	0
AE leading to dose modification/interruption	4 (4.8%)	0	3 (3.4%)	1 (12.5%)	8 (3.5%)	0	7 (5.2%)	1 (10.0%)

Percentages are based on N in the column headings. Only treatment emergent AEs are displayed.
Multiple occurrences of the same AE in one individual are counted only once except for "Total number of AEs" row in which multiple occurrences of the same AE are counted separately.
CCODs: B042161/B042162: 16NOV2022, Y042311: 10AUG2022
Data Extract Dates: B042161/B042162: 23JAN2023, Y042311: 26OCT2022

Sex

Table 75: Overview of adverse events by sex (safety-evaluable patients)

Overview of Adverse Events by Sex, Safety-Evaluable Patients
Protocols: B042161, B042162, Y042311

	Ecu (N=111)		Crova [Naive] (N=192)		Crova [Switch] (N=185)		Crova Total (N=377)	
	Male (N=66)	Female (N=65)	Male (N=103)	Female (N=89)	Male (N=90)	Female (N=95)	Male (N=193)	Female (N=184)
Total number of patients with at least one AE	46 (82.1%)	37 (67.3%)	89 (86.4%)	85 (95.5%)	71 (78.9%)	81 (85.3%)	160 (82.9%)	166 (90.2%)
Total number of AEs	181	109	488	575	305	387	793	962
Total number of deaths	1 (1.8%)	0	2 (1.9%)	1 (1.1%)	0	1 (1.1%)	2 (1.0%)	2 (1.1%)
Total number of patients withdrawn from study due to an AE	0	0	0	0	0	0	0	0
Total number of patients with at least one								
AE with fatal outcome	1 (1.8%)	0	2 (1.9%)	1 (1.1%)	0	1 (1.1%)	2 (1.0%)	2 (1.1%)
Serious AE	5 (8.9%)	5 (9.1%)	15 (14.6%)	13 (14.6%)	14 (15.6%)	15 (15.8%)	29 (15.0%)	28 (15.2%)
Related Serious AE	1 (1.8%)	0	4 (3.9%)	3 (3.4%)	2 (2.2%)	3 (3.2%)	6 (3.1%)	6 (3.3%)
Related AE	14 (25.0%)	10 (18.2%)	40 (38.8%)	53 (59.6%)	30 (33.3%)	40 (42.1%)	70 (36.3%)	93 (50.5%)
Related AE leading to withdrawal from treatment	0	0	1 (1.0%)	0	0	2 (2.1%)	1 (0.5%)	2 (1.1%)
Related AE leading to dose modification/interruption	0	0	2 (1.9%)	0	1 (1.1%)	3 (3.2%)	3 (1.6%)	3 (1.6%)
Grade 3-5 AE	9 (16.1%)	9 (16.4%)	19 (18.4%)	31 (34.8%)	22 (24.4%)	24 (25.3%)	41 (21.2%)	55 (29.9%)
AE leading to withdrawal from treatment	1 (1.8%)	0	1 (1.0%)	0	0	3 (3.2%)	1 (0.5%)	3 (1.6%)
AE leading to dose modification/interruption	0	3 (5.5%)	6 (5.8%)	2 (2.2%)	4 (4.4%)	4 (4.2%)	10 (5.2%)	6 (3.3%)

Percentages are based on N in the column headings. Only treatment emergent AEs are displayed.
Multiple occurrences of the same AE in one individual are counted only once except for "Total number of AEs" row in which multiple occurrences of the same AE are counted separately.
CCODs: B042161/B042162: 16NOV2022, Y042311: 10AUG2022
Data Extract Dates: B042161/B042162: 23JAN2023, Y042311: 26OCT2022

-Weight

Table 76: Overview of adverse events by weigh at baseline (safety-evaluable patients)

Overview of Adverse Events by Weight at Baseline, Safety-Evaluable Patients
Protocols: BO42161, BO42162, YO42311

	Ecu (N=111)		Crova [Naive] (N=192)		Crova [Switch] (N=185)		Crova Total (N=377)	
	>=40kg - <100kg (N=104)	>=100kg (N=7)	>=40kg - <100kg (N=188)	>=100kg (N=4)	>=40kg - <100kg (N=174)	>=100kg (N=11)	>=40kg - <100kg (N=362)	>=100kg (N=15)
Total number of patients with at least one AE	78 (75.0%)	5 (71.4%)	170 (90.4%)	4 (100%)	144 (82.8%)	8 (72.7%)	314 (86.7%)	12 (80.0%)
Total number of AEs	270	20	1054	9	670	22	1724	31
Total number of deaths	1 (1.0%)	0	3 (1.6%)	0	1 (0.6%)	0	4 (1.1%)	0
Total number of patients withdrawn from study due to an AE	0	0	0	0	0	0	0	0

Weight at Baseline refers to the patient's last observation prior to initiation of the respective study drug, i.e. for patients in Arm B of BO42161 and BO42162 who become part of the CROVALIMAB [Switch] population after the primary treatment period, baseline is the patient's last observation prior to initiation of Crovalimab in the extension period.
Percentages are based on N in the column headings. Only treatment emergent AEs are displayed.
Multiple occurrences of the same AE in one individual are counted only once except for "Total number of AEs" row in which multiple occurrences of the same AE are counted separately.
CCODs: BO42161/BO42162: 16NOV2022, YO42311: 10AUG2022
Data Extract Dates: BO42161/BO42162: 23JAN2023, YO42311: 26OCT2022

Adverse drug reactions

Adverse Drug Reactions (ADRs) were determined with consideration of relationship to -study drug, AE incidence rate and medical concept of the observed AE. ADR assessment was based on the pivotal study (BO42162) and the supportive Studies YO42311 and BO42161. Patients who are treatment-naive and patients who switched from another C5 inhibitor were pooled for the purpose of ADR assessment as these patients are biologically identical to each other, and the safety profile in both patient groups is comparable apart from Type III hypersensitivity reactions, which is exclusive to the switch population.

Any adverse event (preferred term) occurring at an incidence rate of ≥5% and grade 3−5 adverse events (preferred term) with any incidence were reviewed. In addition, the following criteria were applied:

a) Events with an incidence lower than 5% (All grades) could be considered an ADR if there was a medical rationale supporting the assessment, such as a known class effect / known effect from mechanism of action and at least one of the observed events was assessed by the Sponsor as related to crovalimab.

b) Sponsor Medical judgement was to be further applied to a potential ADR, taking into consideration the extent to which the adverse event was consistent with the pharmacology of the drug, apparent dose response trend, re-challenge response, temporality and the consistency of the pattern of symptoms across studies/ indications, confounders, and quality of information.

Safety data from Study BP39144 (n= 44) were not pooled with the safety data from the other three studies (BO42162, YO42311, and BO42161) and are presented separately.

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

Table 77: Crovalimab adverse drug reactions

MedDRA Preferred Term	All Grades (%[a])	Grade 3–5[b] (%[a])	Frequency category
General disorders and administration site conditions			
Pyrexia	43 (11.4%)	1 (0.3%)	Very common
Immune System Disorders SOC			
Hypersensitivity	5 (1.3%)	1 (0.3%)	Common
Type III immune complex mediated reaction[c]	33 (8.8%)	13 (3.4%)	Common
Infections and infestations SOC			
Bacteraemia	1 (0.3%)	1 (0.3%)	Uncommon
Pneumonia	7 (1.9%)	4 (1.1%)	Common
Pyelonephritis	2 (0.5%)	2 (0.5%)	Uncommon
Nasopharyngitis	17 (4.5%)	0	Common
Sepsis	1 (0.3%)	1 (0.3%)	Uncommon
Septic shock	1 (0.3%)	1 (0.3%)	Uncommon
Respiratory tract infection	2 (0.5%)	1 (0.3%)	Uncommon
Upper respiratory tract infection	55 (14.6%)	3 (0.8%)	Very common
Urinary tract infection	22 (5.8%)	4 (1.1%)	Common
Injury, poisoning and procedural complications SOC			
Infusion related reaction	40 (10.6%)	0	Very common
Injection related reaction	24 (6.4%)	1 (0.3%)	Common
Musculoskeletal and connective tissue disorders			
Arthralgia	18 (4.8%)	0	Common
Nervous System Disorders			
Headache	37 (9.8%)	0	Common

[a] Frequency was calculated as the number of patients who experienced an ADR out of the Total Crovalimab Population enrolled in Studies BO42161, BO42162 and YO42311 (n = 377).

Withdrawal and rebound

Based on experience with other C5 inhibitors, it is known that patients treated with C5 inhibitors who discontinue treatment and do not switch to an alternative therapy, are at risk of serious haemolysis when C5 inhibition is stopped.

No events of serious haemolysis were reported in patients who discontinued from crovalimab treatment across the Phase III PNH studies. Of note, patients discontinuing from study may become lost to follow-up in a clinical trial setting or switch to another complement inhibitor therapy.

In case of crovalimab discontinuation in patients with PNH, patients must be closely monitored, as per the study protocol, for signs and symptoms of serious intravascular haemolysis, identified by elevated LDH levels, along with sudden decrease in haemoglobin, or re-appearance of symptoms such as fatigue, haemoglobinuria, abdominal pain, shortness of breath (dyspnoea), major adverse vascular events (including thrombosis), dysphagia, or erectile dysfunction.

Additionally, patients who discontinue treatment with crovalimab and start treatment with either eculizumab or ravulizumab would be at risk of DTDC-associated Type III hypersensitivity reactions. Two patients in the pooled safety dataset who discontinued treatment with crovalimab and switched to treatment with ravulizumab experienced Type III hypersensitivity reactions.

2.6.8.7. Immunological events

summary results of immunogenicity analyses for Studies BP39144 (CCOD: 01 November 2021), BO42162 (CCOD: 16 November 2022), YO42311 (CCOD: 10 August 2022), and BO42161 (CCOD: 16November 2022).

The immunogenicity analysis population consisted of all crovalimab treated patients with at least one ADA assessment. The numbers and proportions of ADA-positive patients and ADA-negative patients at baseline (baseline prevalence) and after baseline (post-baseline incidence) were summarised by treatment group.

Study BP39144

Table 78: Summary of baseline prevalence and post-baseline incidence of ADAs (Study BP39144 parts 2, 3 and 4)

Summary of Baseline Prevalence and Post-Baseline Incidence of ADAs, Immunogenicity Population, Part 2, 3 & 4 Patients Protocol: BP39144 Snapshot Date: 11JAN2022 Cutoff Date: 01NOV2021

	Part 2 (N=10)	Part 3 (N=19)	Part 4A (N=8)	Part 4B (N=7)	All Naive (N=18)	All Switched (N=26)	All (N=44)
Baseline Prevalence of ADAs							
Baseline evaluable Subjects	10	19	8	7	18	26	44
Number of Subjects with a positive sample at Baseline	0	12 (63.2%)	0	2 (28.6%)	0	14 (53.8%)	14 (31.8%)
Number of Subjects with no positive sample at Baseline	10 (100%)	7 (36.8%)	8 (100%)	5 (71.4%)	18 (100%)	12 (46.2%)	30 (68.2%)
Post-Baseline Incidence of ADAs							
Post-Baseline evaluable Subjects	10	19	8	7	18	26	44
Number of Subjects with treatment-emergent ADAs	6 (60.0%)	4 (21.1%)	4 (50.0%)	4 (57.1%)	10 (55.6%)	8 (30.8%)	18 (40.9%)
Treatment-induced ADAs	6 (60.0%)	1 (5.3%)	4 (50.0%)	3 (42.9%)	10 (55.6%)	4 (15.4%)	14 (31.8%)
Transient ADAs	1	0	1	0	2	0	2
Persistent ADAs	5	1	3	3	8	4	12
Treatment-enhanced ADAs	0	3 (15.8%)	0	1 (14.3%)	0	4 (15.4%)	4 (9.1%)
Number of Subjects with no treatment-emergent ADAs	4 (40.0%)	15 (78.9%)	4 (50.0%)	3 (42.9%)	8 (44.4%)	18 (69.2%)	26 (59.1%)
Subjects negative for ADAs	4	6	4	2	8	8	16
Treatment unaffected	0	9	0	1	0	10	10

The immunogenicity analyses will include all patients with at least one ADA assessment.
Patients in Part 2 and Part 4A are naive patients.
Patients in Part 3 and Part 4B are switched patients.

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15MAR2022 14:51 Page 1 of 1

Table 79: Time to development of first post-baseline ADA (study BP39144 Parts 2, 3 and 4)

Time to Development of First Post-Baseline ADA, Immunogenicity Population, Part 2, 3 & 4 Patients
Protocol: BP39144 Snapshot Date: 11JAN2022 Cutoff Date: 01NOV2021

	Part 2 (N=10)	Part 3 (N=19)	Part 4A (N=8)	Part 4B (N=7)	All Naive (N=18)	All Switched (N=26)	All (N=44)
Time to development of first post-baseline ADA (weeks)							
n	6	4	4	4	10	8	18
Mean (SD)	39.14 (43.16)	14.39 (14.03)	13.89 (6.65)	42.64 (49.02)	29.04 (34.92)	28.52 (36.64)	28.81 (34.62)
Median	15.14	9.14	16.14	19.14	15.64	17.64	16.14
Min - Max	7.1 - 115.1	4.1 - 35.1	4.1 - 19.1	16.1 - 116.1	4.1 - 115.1	4.1 - 116.1	4.1 - 116.1
Time to development of first post-baseline ADA (category)							
n	6	4	4	4	10	8	18
<12 weeks	1 (16.7%)	3 (75.0%)	1 (25.0%)	0	2 (20.0%)	3 (37.5%)	5 (27.8%)
12-<24 weeks	3 (50.0%)	0	3 (75.0%)	3 (75.0%)	6 (60.0%)	3 (37.5%)	9 (50.0%)
24-<48 weeks	0	1 (25.0%)	0	0	0	1 (12.5%)	1 (5.6%)
48-<96 weeks	1 (16.7%)	0	0	0	1 (10.0%)	0	1 (5.6%)
>=96 weeks	1 (16.7%)	0	0	1 (25.0%)	1 (10.0%)	1 (12.5%)	2 (11.1%)

Program: root/clinical_studies/RO7112689/CDT70115/BP39144/data_analysis/CSR_November2021/prod/program/t_pd_tte.sas
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15MAR2022 15:41 Page 1 of 1

Table 80: Overview of adverse events by ADA status (study BP39144, Parts 2, 3 and 4)

Overview of Adverse Events by ADA Status, Immunogenicity Population, Safety-Evaluable Patients, Part 2, 3 & 4 Patients
Protocol: BP39144 Snapshot Date: 11JAN2022 Cutoff Date: 01NOV2021

	Naive (N=18)		Switched (N=26)		Total (N=44)	
	ADA+ (N=10)	ADA- (N=8)	ADA+ (N=8)	ADA- (N=18)	ADA+ (N=18)	ADA- (N=26)
Total number of patients with at least one AE	10 (100%)	7 (87.5%)	8 (100%)	17 (94.4%)	18 (100%)	24 (92.3%)
Total number of AEs	74	50	96	156	170	206
Total number of deaths	0	0	0	0	0	0
Total number of patients withdrawn from study due to an AE	0	0	0	0	0	0
Total number of patients with at least one						
AE with fatal outcome	0	0	0	0	0	0
Serious AE	4 (40.0%)	2 (25.0%)	4 (50.0%)	4 (22.2%)	8 (44.4%)	6 (23.1%)
Serious AE leading to withdrawal from treatment	0	0	0	0	0	0
Serious AE leading to dose modification/interruption	1 (10.0%)	0	0	0	1 (5.6%)	0
Related Serious AE	1 (10.0%)	0	0	1 (5.6%)	1 (5.6%)	1 (3.8%)
AE leading to withdrawal from treatment	0	0	0	0	0	0
AE leading to dose modification/interruption	1 (10.0%)	0	0	0	1 (5.6%)	0
Related AE	2 (20.0%)	2 (25.0%)	2 (25.0%)	8 (44.4%)	4 (22.2%)	10 (38.5%)
Related AE leading to withdrawal from treatment	0	0	0	0	0	0
Related AE leading to dose modification/interruption	0	0	0	0	0	0

Investigator text for AEs encoded using MedDRA version 24.1. Percentages are based on N in the column headings.
Multiple occurrences of the same AE in one individual are counted only once except for "Total number of AEs" row in which multiple occurrences of the same AE are counted separately.
The immunogenicity analyses will include all patients 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.

Program: root/clinical_studies/RO7112689/CDT70115/BP39144/data_analysis/CSR_November2021/prod/program/t_ae_oview_prism13743.sas
Output: root/clinical_studies/RO7112689/CDT70115/BP39144/data_analysis/CSR_November2021/prod/output/
t_ae_oview_prism13743_ADA_SE_NS_01NOV2021_39144.out
23MAR2022 7:56

Studies BO42162, YO42311, and BO42161

Table 81: Summary of crovalimab ADA status (studies BO42162, YO42311, and BO42161)

Summary of Crovalimab Anti-Drug Antibody Status, Immunogenicity Population
Protocols: BO42161, BO42162, YO42311

	BO42162 Crova [Naive] (N=140)	BO42162 Crova [Switch] (N=67)	BO42161 Crova [Switch] (N=117)	YO42311 Crova [Naive] (N=51)	Crova [Naive] Total (N=191)	Crova [Switch] Total (N=184)	Crova Total (N=375)
Baseline Prevalence of ADAs							
Baseline Evaluable Patients	139	65	116	51	190	181	371
Number of Patients with a Positive Sample at Baseline	6 (4.3%)	29 (44.6%)	1 (0.9%)	1 (2.0%)	7 (3.7%)	30 (16.6%)	37 (10.0%)
Number of Patients with no Positive Samples at Baseline	133 (95.7%)	36 (55.4%)	115 (99.1%)	50 (98.0%)	183 (96.3%)	151 (83.4%)	334 (90.0%)
Post-Baseline Incidence of ADAs							
Post-Baseline Evaluable Patients	140	67	117	51	191	184	375
Number of Patients with Treatment-emergent ADAs	42 (30.0%)	23 (34.3%)	20 (17.1%)	18 (35.3%)	60 (31.4%)	43 (23.4%)	103 (27.5%)
Treatment-induced ADAs	40 (28.6%)	16 (23.9%)	19 (16.2%)	17 (33.3%)	57 (29.8%)	35 (19.0%)	92 (24.5%)
Transient	7	1	2	1	8	3	11
Persistent	33	15	17	16	49	32	81
Treatment-enhanced ADAs	2 (1.4%)	7 (10.4%)	1 (0.9%)	1 (2.0%)	3 (1.6%)	8 (4.3%)	11 (2.9%)
Neutralizing Antibody+	2 (4.8%)	0	0	0	2 (3.3%)	0	2 (1.9%)
Neutralizing Antibody-	17 (40.5%)	12 (52.2%)	0	18 (100%)	35 (58.3%)	12 (27.9%)	47 (45.6%)
Neutralizing Antibody Missing	23 (54.8%)	11 (47.8%)	20 (100%)	0	23 (38.3%)	31 (72.1%)	54 (52.4%)
Number of Patients with no Treatment-emergent ADAs	98 (70.0%)	44 (65.7%)	97 (82.9%)	33 (64.7%)	131 (68.6%)	141 (76.6%)	272 (72.5%)
Patients Negative for ADAs	94	22	97	33	127	119	246
Treatment Unaffected	4	22	0	0	4	22	26

For calculation of percentages for Neutralising Antibody +/-, the number of patients with treatment-emergent ADAs was used as the denominator.
Baseline is the patient's last observation prior to initiation of Crovalimab.
The immunogenicity population consists of all patients with at least one ADA assessment.
Patients with treatment-emergent ADAs are considered ADA positive. Patients with no treatment-emergent ADAs are considered ADA negative. All ADA assessments up to CCOD are included to determine ADA status.
CCODs: BO42161/BO42162: 16NOV2022, YO42311: 10AUG2022
Data Extract Dates: BO42161/BO42162: 23JAN2023, YO42311: 26OCT2022

Program: root/clinical_studies/RO7112689/CDT70115/share/pool_global_filing/prod/program/t_pd_ada.sas
Output: root/clinical_studies/RO7112689/CDT70115/share/pool_global_filing/prod/output/t_pd_ada_ISI_IM.out
21FEB2023 17:19

Table 82: Time to development of first post-baseline ADA (studies BO42162, YO42311, and BO42161)

Time to Development of First Post-Baseline Crovalimab ADA, Immunogenicity Population
Protocols: BO42161, BO42162, YO42311

	BO42162 Crova [Naive] (N=140)	BO42162 Crova [Switch] (N=67)	BO42161 Crova [Switch] (N=117)	YO42311 Crova [Naive] (N=51)	Crova [Naive] Total (N=191)	Crova [Switch] Total (N=184)	Crova Total (N=375)
Time to development of first post-baseline ADA (weeks)							
n	42	23	20	18	60	43	103
Mean (SD)	16.98 (13.31)	15.87 (8.41)	17.39 (9.69)	15.41 (12.89)	16.51 (13.10)	16.58 (8.95)	16.54 (11.50)
Median	12.86	13.43	14.29	12.21	12.29	13.43	12.43
Min - Max	1.1 - 48.1	2.1 - 36.3	8.1 - 40.1	1.1 - 59.9	1.1 - 59.9	2.1 - 40.1	1.1 - 59.9
Time to development of first post-baseline ADA (category)							
n	42	23	20	18	60	43	103
<4 weeks	6 (14.3%)	3 (13.0%)	0	2 (11.1%)	8 (13.3%)	3 (7.0%)	11 (10.7%)
4 - <12 weeks	7 (16.7%)	2 (8.7%)	4 (20.0%)	3 (16.7%)	10 (16.7%)	6 (14.0%)	16 (15.5%)
12 - <24 weeks	21 (50.0%)	13 (56.5%)	13 (65.0%)	11 (61.1%)	32 (53.3%)	26 (60.5%)	58 (56.3%)
24 - <36 weeks	3 (7.1%)	4 (17.4%)	1 (5.0%)	1 (5.6%)	4 (6.7%)	5 (11.6%)	9 (8.7%)
>= 36 weeks	5 (11.9%)	1 (4.3%)	2 (10.0%)	1 (5.6%)	6 (10.0%)	3 (7.0%)	9 (8.7%)

n refers to the number of patients with treatment-emergent ADAs. Percentages are calculated using n as the denominator.
The immunogenicity population consists of all patients with at least one ADA assessment.
Patients with treatment-emergent ADAs are considered ADA positive. Patients with no treatment-emergent ADAs are considered ADA negative. All ADA assessments up to CCOD are included to determine ADA status.
CCODs: BO42161/BO42162: 16NOV2022, YO42311: 10AUG2022
Data Extract Dates: BO42161/BO42162: 23JAN2023, YO42311: 26OCT2022

Potential Impact on Safety

Table 83: Overview of adverse events by Crovalimab ADA status (studies BO42162, YO42311, and BO42161)

Overview of Adverse Events by Crovalimab ADA Status, Immunogenicity Population
Protocols: BO42161, BO42162, YO42311

	Crova [Naive] (N=191)		Crova [Switch] (N=184)		Crova Total (N=375)	
	ADA NEGATIVE (N=131)	ADA POSITIVE (N=60)	ADA NEGATIVE (N=141)	ADA POSITIVE (N=43)	ADA NEGATIVE (N=272)	ADA POSITIVE (N=103)
Total number of patients with at least one AE	118 (90.1%)	55 (91.7%)	115 (81.6%)	37 (86.0%)	233 (85.7%)	92 (89.3%)
Total number of AEs	731	331	490	202	1221	533
Total number of deaths	1 (0.8%)	1 (1.7%)	1 (0.7%)	0	2 (0.7%)	1 (1.0%)
Total number of patients withdrawn from study due to an AE	0	0	0	0	0	0
Total number of patients with at least one						
AE with fatal outcome	1 (0.8%)	1 (1.7%)	1 (0.7%)	0	2 (0.7%)	1 (1.0%)
Serious AE	17 (13.0%)	10 (16.7%)	20 (14.2%)	9 (20.9%)	37 (13.6%)	19 (18.4%)
Related Serious AE	6 (4.6%)	1 (1.7%)	3 (2.1%)	2 (4.7%)	9 (3.3%)	3 (2.9%)
Related AE	65 (49.6%)	28 (46.7%)	48 (34.0%)	22 (51.2%)	113 (41.5%)	50 (48.5%)
Related AE leading to withdrawal from treatment	1 (0.8%)	0	2 (1.4%)	0	3 (1.1%)	0
Related AE leading to dose modification/interruption	1 (0.8%)	1 (1.7%)	3 (2.1%)	1 (2.3%)	4 (1.5%)	2 (1.9%)
Grade 3-5 AE	31 (23.7%)	18 (30.0%)	27 (19.1%)	19 (44.2%)	58 (21.3%)	37 (35.9%)
AE leading to withdrawal from treatment	1 (0.8%)	0	2 (1.4%)	1 (2.3%)	3 (1.1%)	1 (1.0%)
AE leading to dose modification/interruption	5 (3.8%)	3 (5.0%)	5 (3.5%)	3 (7.0%)	10 (3.7%)	6 (5.8%)

Percentages are based on N in the column headings. Only treatment emergent AEs are displayed.
Multiple occurrences of the same AE in one individual are counted only once except for "Total number of AEs" row in which multiple occurrences of the same AE are counted separately.
The immunogenicity population consists of all patients with at least one ADA assessment.
Patients with treatment-emergent ADAs are considered ADA positive. Patients with no treatment-emergent ADAs are considered ADA negative. All ADA assessments up to CCOD are included to determine ADA status.
CCODs: BO42161/BO42162: 16NOV2022, YO42311: 10AUG2022
Data Extract Dates: BO42161/BO42162: 23JAN2023, YO42311: 26OCT2022

Table 84: Summary of adverse events of special interest by Crovalimab ADA status (studies BO42162, YO42311, and BO42161)

Summary of Adverse Events of Special Interest by Crovalimab ADA Status, Immunogenicity Population
Protocols: BO42161, BO42162, YO42311

AESI category MedDRA Preferred Term	Crova [Naive] (N=191)		Crova [Switch] (N=184)		Crova Total (N=375)	
	ADA NEGATIVE (N=131)	ADA POSITIVE (N=60)	ADA NEGATIVE (N=141)	ADA POSITIVE (N=43)	ADA NEGATIVE (N=272)	ADA POSITIVE (N=103)
Case of an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined in protocol						
Total number of patients with at least one adverse event	0	0	0	0	0	0
Total number of events	0	0	0	0	0	0
Suspected transmission of an infectious agent by the study drug						
Total number of patients with at least one adverse event	0	0	0	0	0	0
Total number of events	0	0	0	0	0	0
Type III hypersensitivity reactions						
Total number of patients with at least one adverse event	0	0	23 (16.3%)	10 (23.3%)	23 (8.5%)	10 (9.7%)
Total number of events	0	0	26	10	26	10
Type III immune complex mediated reaction	0	0	23 (16.3%)	10 (23.3%)	23 (8.5%)	10 (9.7%)
Axonal neuropathy	0	0	1 (0.7%)	0	1 (0.4%)	0

Investigator text for AEs encoded using MedDRA version 25.1. Only treatment emergent AEs are displayed.
Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once.
For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Events are sorted by descending overall total frequency.
The immunogenicity population consists of all patients with at least one ADA assessment.
Patients with treatment-emergent ADAs are considered ADA positive. Patients with no treatment-emergent ADAs are considered ADA negative. All ADA assessments up to COOD are included to determine ADA status.
CCODs: BO42161/BO42162: 14NOV2022, YO42311: 10AUG2022
Data Extract Dates: BO42161/BO42162: 23JAN2023, YO42311: 26OCT2022

2.6.8.8. Safety related to drug-drug interactions and other interactions

No formal drug-drug or drug-food interaction assessments were conducted.

2.6.8.9. Discontinuation due to adverse events

Adverse Events that Led to Withdrawal of Treatment

Table 85: Summary of adverse events leading to treatment discontinuation (safety-evaluable patients)

Summary of Adverse Events Leading to Treatment Discontinuation, Safety-Evaluable Patients
Protocols: BO42161, BO42162, YO42311

MedDRA System Organ Class MedDRA Preferred Term	Ecu (N=111)	Crova [Naive] (N=192)	Crova [Switch] (N=185)	Crova Total (N=377)
Total number of patients with at least one adverse event	1 (0.9%)	1 (0.5%)	3 (1.6%)	4 (1.1%)
Overall total number of events	1	1	3	4
Nervous system disorders				
Total number of patients with at least one adverse event	1 (0.9%)	0	1 (0.5%)	1 (0.3%)
Total number of events	1	0	1	1
Demyelinating polyneuropathy	0	0	1 (0.5%)	1 (0.3%)
Ischaemic stroke	1 (0.9%)	0	0	0
Blood and lymphatic system disorders				
Total number of patients with at least one adverse event	0	1 (0.5%)	0	1 (0.3%)
Total number of events	0	1	0	1
Thrombocytopenia	0	1 (0.5%)	0	1 (0.3%)
Immune system disorders				
Total number of patients with at least one adverse event	0	0	1 (0.5%)	1 (0.3%)
Total number of events	0	0	1	1
Type III immune complex mediated reaction	0	0	1 (0.5%)	1 (0.3%)
Infections and infestations				
Total number of patients with at least one adverse event	0	0	1 (0.5%)	1 (0.3%)
Total number of events	0	0	1	1
Sepsis	0	0	1 (0.5%)	1 (0.3%)

Investigator text for AEs encoded using MedDRA version 25.1. Only treatment emergent AEs are displayed.
Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once.
For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

Adverse Events that Led to Dose Modification

Table 86: Summary of adverse events leading to treatment modification/interruption (safety-evaluable patients)

Summary of Adverse Events Leading to Treatment Modification/Interruption, Safety-Evaluable Patients
Protocols: BO42161, BO42162, YO42311

MedDRA System Organ Class MedDRA Preferred Term	Ecu (N=111)	Crova [Naive] (N=192)	Crova [Switch] (N=185)	Crova Total (N=377)
Total number of patients with at least one adverse event	3 (2.7%)	8 (4.2%)	8 (4.3%)	16 (4.2%)
Overall total number of events	3	10	8	18
Infections and infestations				
Total number of patients with at least one adverse event	2 (1.8%)	4 (2.1%)	3 (1.6%)	7 (1.9%)
Total number of events	2	4	3	7
COVID-19	1 (0.9%)	4 (2.1%)	1 (0.5%)	5 (1.3%)
Nasopharyngitis	0	0	1 (0.5%)	1 (0.3%)
Pneumonia	0	0	1 (0.5%)	1 (0.3%)
Sepsis	1 (0.9%)	0	0	0
Gastrointestinal disorders				
Total number of patients with at least one adverse event	0	1 (0.5%)	1 (0.5%)	2 (0.5%)
Total number of events	0	1	1	2
Abdominal pain	0	0	1 (0.5%)	1 (0.3%)
Nausea	0	1 (0.5%)	0	1 (0.3%)
Immune system disorders				
Total number of patients with at least one adverse event	0	0	2 (1.1%)	2 (0.5%)
Total number of events	0	0	2	2
Type III immune complex mediated reaction	0	0	2 (1.1%)	2 (0.5%)
Injury, poisoning and procedural complications				
Total number of patients with at least one adverse event	0	1 (0.5%)	1 (0.5%)	2 (0.5%)
Total number of events	0	1	1	2
Infusion related reaction	0	1 (0.5%)	1 (0.5%)	2 (0.5%)
Hepatobiliary disorders				
Total number of patients with at least one adverse event	1 (0.9%)	1 (0.5%)	0	1 (0.3%)
Total number of events	1	1	0	1
Hepatic function abnormal	0	1 (0.5%)	0	1 (0.3%)
Cholecystitis chronic	1 (0.9%)	0	0	0
Blood and lymphatic system disorders				
Total number of patients with at least one adverse event	0	1 (0.5%)	0	1 (0.3%)
Total number of events	0	1	0	1
Pancytopenia	0	1 (0.5%)	0	1 (0.3%)

Investigator text for AEs encoded using MedDRA version 25.1. Only treatment emergent AEs

MedDRA System Organ Class MedDRA Preferred Term	Ecu (N=111)	Crova [Naive] (N=192)	Crova [Switch] (N=185)	Crova Total (N=377)
General disorders and administration site conditions				
Total number of patients with at least one adverse event	0	1 (0.5%)	0	1 (0.3%)
Total number of events	0	1	0	1
Feeling cold	0	1 (0.5%)	0	1 (0.3%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)				
Total number of patients with at least one adverse event	0	0	1 (0.5%)	1 (0.3%)
Total number of events	0	0	1	1
Mantle cell lymphoma	0	0	1 (0.5%)	1 (0.3%)
Vascular disorders				
Total number of patients with at least one adverse event	0	1 (0.5%)	0	1 (0.3%)
Total number of events	0	1	0	1
Peripheral coldness	0	1 (0.5%)	0	1 (0.3%)

Investigator text for AEs encoded using MedDRA version 25.1. Only treatment emergent AEs are displayed.
Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once.
For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Events are sorted by descending overall total frequency.
CCODs: BO42161/BO42162: 16NOV2022, YO42311: 10AUG2022
Data Extract Dates: BO42161/BO42162: 23JAN2023, YO42311: 26OCT2022

2.6.8.10. Post marketing experience

At the time of the initial MAA submission, crovalimab was not approved in any country, therefore no post-marketing data are available.

2.6.9. Discussion on clinical safety

Safety data from the pivotal study BO42162 was pooled with the safety data from the supportive studies BO42161 and YO42311, using data through to the latest CCOD of each study (studies BO42162 (CCOD: 31 MAY 2023), BO42161 (CCOD: 31 MAY 2023) and YO42311 (CCOD: 10 Aug 2022)). The pooled safety database comprises 393 patients in the total crovalimab population (192 in the crovalimab naive and 201 in the crovalimab switch population) and 111 patients in the total eculizumab population.

Safety data from the subset of patients of the total crovalimab population who were previously treated with ravulizumab and then switched to crovalimab in Arm C of study BO42161, as well as long-term safety data from study BP39144 are discussed separately.

The median treatment duration in total crovalimab population (64 weeks, range: 0.1−136.4 weeks) was longer compared to the total eculizumab population (22.1 weeks, range: 0.1−26.1 weeks). This difference in treatment duration was taken into consideration by calculating time adjusted incidence rate for comparing AEs incidence between both arms.

The median treatment duration was 68 weeks (range: 0.1−136 weeks) for the crovalimab naive population and was 56.3 weeks (range: 0.3−136 weeks) for the crovalimab switch population.

A higher proportion of patients were Asian in the crovalimab naive population (74.0%) compared with the crovalimab switch population (45.4%), which was driven by the crovalimab naive population including study YO42311, which enrolled only Chinese patients, as well as study BO42162, in which China was the highest recruiting country. The crovalimab naive population included more paediatric patients (naive: 4.7%, switch: 1.1%) and less patients ≥ 65 years (naive: 6.8%, switch: 14.1%) compared with the crovalimab switch population.

The baseline disease characteristics were generally balanced between the total crovalimab and total eculizumab populations. Prior to enrolment, 37.7% and 36.9% of patients had a history of aplastic anaemia, 3.4% and 5.4% had a history of myelodysplastic syndrome, 10.1% and 11.7% had a history of renal impairment, and 15.1% and 17.1% had a history of MAVE in the total crovalimab and total eculizumab populations, respectively.

The median time from PNH diagnosis to enrolment was 3.5 years (range: 0.0−48.5 years) and 6.3 years (range: 0.0−50.3 years) in the crovalimab naïve population and crovalimab switch population, respectively. Prior to enrolment, a history of aplastic anaemia was reported in 39.1% and 36.2% of patients, a history of myelodysplastic syndrome in 3.6% and 3.2% of patients, a history of renal impairment in 6.8% and 13.5% of patients, and a history of MAVE in 13.5% and 16.8% of patients in the crovalimab naive and the crovalimab switch populations, respectively.

Although most overall safety parameters seem to be similar for crovalimab and eculizumab, some trends for higher event frequencies with crovalimab for treatment time adjusted grade 3−5 AEs (58. vs 49 per 100 PYs) were reported.

Overall incidence (time adjusted) of AEs, AEs with fatal outcome, and related AEs in patients who were crovalimab naive was higher (497, 2.25, and 173 per 100 PYs, respectively) compared to patients who were crovalimab switch (430, 0.84 and 83 per 100 PYs, respectively). The incidence of serious AEs was

higher in patients who were crovalimab switch (31 per 100 PYs) compared to crovalimab naïve patients (25 per 100 PYs).

The most frequent AEs (≥ 10%) in the total crovalimab were COVID-19 (332%), upper respiratory tract infection (18.6%), pyrexia (13.4%), neutrophil count decreased (11.2%), infusion related reaction (10.6%) and white blood cell count decreased (10.3%).

The most common AEs in the total crovalimab compared to eculizumab group were: COVID-19 (33% vs 9.9%), **upper respiratory tract infection** (18.6% vs 9.9%), **pyrexia** (13.5% vs 6.3%), neutrophil count decreased (11.2% vs 6.3%), **infusion related reaction** (10.2% vs 8.1%), white blood cell count decreased (10.4% vs 6.3%), **headache** (9.8% vs 3.6%), **type 3 immune complex mediated reaction** (9.7% vs 0), **injection related reaction** (7.9% vs 0), ALT increased (6.1% vs 2.7%), hyperuricaemia (5.8% vs 5.4%), diarrhoea (6.6% vs 0.9%), blood bilirubin increased (4.8% vs 0.9%), **arthralgia** (5.9% vs 2.7%), **nasopharyngitis** (5.1% vs 1.8%), bilirubin conjugated increased, ALP increased, blood bilirubin unconjugated increased (4.1% vs 0%), neutropenia (3.4% vs 1.8%), alpha hydroxybutyrate dehydrogenase increased (2.9% vs 0%) and weight increased (2.5% vs 0%). **Urinary tract infection** was reported in 8.7% in the total crovalimab group compared with 6.3% in the eculizumab group. AEs in bold have been included as ADRs. Diarrhoea, fatigue and asthenia, and abdominal pain events are added as ADRs to the section 4.8 of SmPC.

Among the adverse events that the investigator considered to be treatment-related, the most common were in the total crovalimab compared to eculizumab group: infusion related reaction (9.7% vs 8.1%), white blood cell count decreased (9.9% vs 6.3%), neutrophil count decreased (9.2% vs 6.3%), type 3 immune complex mediated reaction (9.7% vs 0%), injection related reaction (7.6% vs 0%), bilirubin conjugated increased, ALP increased (4.4% vs 0%), upper respiratory tract infection (3.6% vs 0.9%), blood bilirubin increased (3.3% vs 0%), ALT increased (2.8% vs 0%), platelet count decreased (3.3% vs 0%), GGT increased (1.8% vs 0%), urinary tract infection (1.3% vs 0%), nasopharyngitis (1.3% vs 0%), blood bilirubin unconjugated increased (1% vs 0%), pyrexia, arthralgia (1.5% vs 0%).

The number of grade 3−5 AEs per 100 PYs was 57.5 (95% CI: 51.34, 64.78) in the total crovalimab population, compared to 48.9 (95% CI: 31.67, 72.25) in the total eculizumab population. The proportion of patients with at least one grade 3−5 AE was similar in the crovalimab naive (37.0%) and crovalimab switch (33.8%) populations, and most were grade 3 events. Grade 4 events were experienced in 7.3% and 3.5% of patients in the crovalimab naive and crovalimab switch populations, respectively.

The number of SAEs per 100 PYs in the total crovalimab population was 28.0 (95% CI: 24, 33) and 31.32 (95% CI: 18, 50.86) in the total eculizumab population. SAEs considered by the investigator as possibly related to crovalimab treatment include: type 3 immune complex mediated reaction (8 patients, 2%), upper respiratory tract infection (2 patients, 0.5%), bacteraemia, sepsis, thrombocytopenia, pyrexia, infusion related reaction, axonal neuropathy, epistaxis (single cases, 0.3%).

In the total crovalimab population, the number of deaths due to AEs per 100 PYs was 1.6 (95% CI: 0.69, 3.13) versus 2.0 (95% CI: 0.05, 10.91) in the total eculizumab population. Three patients in the crovalimab naive population experienced grade 5 AEs of subdural haematoma, respiratory tract haemorrhage, and myocardial infarction. One patient in the crovalimab switch population died due to a colorectal cancer AE. 8 patients in the total crovalimab population experienced grade 5 AEs of subdural haematoma, respiratory tract haemorrhage, myocardial infarction, colorectal cancer, COVID-19, COVID-19 pneumonia, pneumonia aspiration and death (unexplained cause; patient died in his sleep and had no symptoms in the days preceding death, with normal haematologic laboratory data. An autopsy was not performed, considered natural death). One patient in the total eculizumab population died. This patient died on Study Day 71 due to an ischaemic stroke, which occurred 28 days after the

last study drug administration. All these cases were assessed as not related to crovalimab by the Investigator. After the SRR CCOD for Studies BO42161 and BO42162 (31 May 2023), one additional death occurred in the crovalimab switch population in Study BO42162. This patient experienced a fatal subdural haematoma on 9 June 2023. This AE was assessed as not related to crovalimab treatment by the Investigator and the patient had many risk factors (MDS, low platelet count at baseline...).

The proportion of patients who experienced injection site reactions was 4.7% in the crovalimab naive population and 11.9% in the crovalimab switch population. The majority of events were grade 1−2 in severity. Three grade 3 injection related reactions were reported in two patients in the crovalimab switch population. These AEs of injection site reactions, resolved with no dose modification/interruption. The most frequently reported symptoms of injection site reactions were (crovalimab naive and crovalimab switch population, respectively), headache (2.1% and 3%), injection site erythema (1.0% and 1.0%), malaise (0% and 1%), erythema (0% and 1.1%), pruritus (0% and 1%) and myalgia (0% and 1.0%). However, it remains unclear if the ADR "injection related reactions" in section 4.8 of SmPC encompasses systemic and local injection related reactions. Injection reactions type local site was then added as ADR in the section 4.8 of the SmPC.

The proportion of patients who experienced infusion related reactions was 10.6% in the total crovalimab and 8.1% in the total eculizumab populations. All events were grade 1-2. The most frequently reported symptoms of infusion related reactions in the crovalimab naive and crovalimab switch populations, respectively were headache (9.4% and 4.9%), rash (1.0% and 1.1%), abdominal pain (1.0% and 0%), pyrexia (1.0% and 0%) and dizziness (0.5% and 1.1%).

Overall, the number of reported infections per 100 PYs was lower in the total crovalimab population (91.5, 95% CI: 83.33, 100.24) compared to the total eculizumab population (123.3, 95% CI: 94.77, 157.79). The most frequently reported infections in the total crovalimab and total eculizumab populations were COVID-19 (33% vs 9.9%), upper respiratory tract infection (18.6% vs 9.9 %), and urinary tract infection (8.7% vs 6.3%), respectively. The majority were grade 1−2 events. In the total crovalimab and total eculizumab populations, grade 3 events were experienced in 9.4% and 3.6% of patients. One patient in the total eculizumab population experienced a grade 4 infection (central nervous system infection). In the total crovalimab population, 2 patients experienced grade 4 infections (pyelonephritis and COVID-19), and 3 patients experienced grade 5 infections (COVID - 19, COVID - 19 pneumonia, and pneumonia aspiration) considered unrelated to treatment. The incidence rate of grade 3-5 infection AEs per 100PY in the total crovalimab (9.7, 95% CI: 7.19, 12.86) is comparable to the total eculizumab population (11.8, 95% CI: 4.31, 25.57).
There were no cases of infection with N. meningiditis (including Meningococcal meningitis) in studies with PNH. But there was one case of meningococcal meningitis in study BO42354, in paediatric patients with atypical haemolytic uremic syndrome. The patient experienced Meningococcal meningitis on Day 430 (grade 3). The pathogen was identified as Neisseria meningitidis serotype X (the patient was vaccinated against serotype ACWY). The event subsequently resolved after 4 days, with no change to crovalimab treatment.

The median time to onset of the first infection was longer in the total crovalimab population (22.1 weeks) compared to the total eculizumab population (7.9 weeks). The median duration of infections was comparable between the total crovalimab population (1.3 weeks) and the total eculizumab population (1.6 weeks).

Up to updated CCODs, the number of reported infections and SAEs per 100 PYs respectively was comparable between the crovalimab naive (88.5, 95% CI: 77.53, 100.50) (7.9, 95% CI: 4.87, 12.03) and crovalimab switch populations (94.9, 95% CI: 82.90, 108.14) (9.7, 95% CI: 6.15, 14.56).

The median time to onset of the first infection was longer in the crovalimab naïve population (30.4 weeks) compared to the crovalimab switch population (13.7 weeks). The median time to onset of the

first serious infection was also longer in the crovalimab naive population (40.8 weeks) compared to the crovalimab switch population (16.6 weeks). This difference may have been due to patients who switched to crovalimab and were already exposed to a C5 inhibitor prior to the start of treatment. Increased susceptibility to infections is a known risk associated with C5 inhibitors. In Study YO42311, one patient was diagnosed with serious grade 3 bacteraemia, and Neisseria subflava was the pathogen confirmed in blood cultures. The applicant clarified that this infection was not a meningococcal infection and described the occurrence of the single case of serious grade 3 bacteraemia with Neisseria subflava in Section 4.8 of SmPC.

There were 2 cases of opportunistic infections assessed as not related to crovalimab and did not require change to study treatment and resolve in a timely manner when appropriate treatment is administered.

Up to CCOD, 9.9% of patients in the total crovalimab population experienced hypersensitivity other than type III hypersensitivity reactions (crovalimab naive (6.3 %) and crovalimab switch (13.4 %)). The most frequently reported event in the crovalimab naive population and crovalimab switch population was injection related reaction (4.2 % and 11.4 %). Two patients in the crovalimab switch population had grade 3 events (hypersensitivity and circulatory collapse) which resolved with no dose modification/interruption. Two patients (1.1%) in the crovalimab switch population reported Type IV hypersensitivity reaction; both were grade 1−2.

Patients who switched from eculizumab or ravulizumab to crovalimab (and vice versa) are at risk of developing DTDC-associated type III hypersensitivity reactions (19.4%) because crovalimab binds to a different epitope than eculizumab and ravulizumab. In the eculizumab switch population, the proportion of patients who experienced Type III hypersensitivity reactions was 17.2%. In these 30 patients, 19 patients (63.3%) had a grade 1-2 event, and 11 patients (36.7%) had grade 3 events. In the ravulizumab switch population, the proportion of patients who experienced Type III hypersensitivity reactions increased from 23.8% as reported in the SCS to 33.3% at the SRR CCODs. In these 9 patients, four patients (44.4%) had a grade 1 or 2 event, and 5 patients (55.6%) had grade 3 events.

One patient (0.5%) each also reported a PT of grade 3 axonal neuropathy and grade 2 injection related reaction. Axonal neuropathy occurred at the same time with other symptoms (arthralgia, myalgia…) indicative of type III immune complex mediated reaction in a patient after switching from crovalimab to ravulizumab. Peripheral neuropathy could be a symptom of drug induced hypersensitivity vasculitis. Axonal neuropathy has been added among symptoms of type III hypersensitivity reactions in section 4.4 of the SmPC.

The most frequently reported symptoms of T3H reactions were arthralgia (8.5 %), rash (6.5 %), pyrexia (4%) myalgia (3%), and abdominal pain upper (1.5%). None of the T3H reactions had renal manifestations. Most symptoms were grade 1−2. Grade 3 symptoms were experienced in 6.5% of patients and there were no grade 4 symptoms. Note, three patients had unresolved Type III hypersensitivity reactions up to SRR CCODs.

Median time to onset and median duration were comparable between patients who switched from eculizumab and ravulizumab. Median time to onset for eculizumab switch patients was 1.5 weeks (range: 0.7-4.4 weeks) and median duration was 1.7 weeks (range: 0.4-34.1), whereas in ravulizumab switch patients median time to onset was 2.0 weeks (range: 1.3-4.3 weeks) and median duration was 1.7 weeks (range: 0.6-11.9). The applicant updated the SmPC section 4.8 to inform prescribers that 6.1% of patients (2 of 33) experienced an immune complex reaction with a time to onset that exceeded 4 weeks. This is endorsed.

Safety in patients switching from ravulizumab is based on only 21 patients. Overall, safety data seems consistent with the safety profile observed for the total crovalimab population, with the exception of type III hypersensitivity reactions which was consistent with the general crovalimab switch population. No fatal AEs (grade 5 AEs) occurred in prior ravulizumab treated patients. One patient discontinued from study treatment due to AE (PT: sepsis) and two patients experienced an AE leading to dose modification/interruption (PT: nasopharyngitis and infusion related reaction). Given eculizumab and ravulizamab are both C5 inhibitors which binds to the same C5 epitope, it is not expected the safety profile of switch patients to be different.

At post-baseline, abnormal ECG data (QTcF values) were comparable between the total crovalimab and total eculizumab populations. Change from baseline of > 60 ms was reported in 0.8% of total crovalimab and 1.9% of total eculizumab populations.

Of the total crovalimab population, 10.3% of patients were ≥65 years of age. Incidence of safety parameters was higher in patients ≥65 years of age compared to patients aged 18−64, namely SAEs (42% and 21%, respectively), fatal AEs (9.3% and 1.2%), AEs leading to dose modification/ interruption and withdrawal from treatment and grade 3−5 AEs (55.8.0% and 33.4%, respectively). This is in part could be due to a higher number of co-morbidities in this patient subgroup. Notably, 97.4% of crovalimab treated patients aged ≥65 years had a condition as part of their medical history, compared to 77.4% of crovalimab treated patients aged 18-64. Furthermore, the imbalance is not really driven by a specific safety concern that is occurring in elderly patients, and instead relates to a broad range of SOCs and PTs. Last, the number of elderly patients (n=39) is considerably smaller than the size of the 18-64 years population (n =327). As such, imbalances in safety parameters between these two groups should be interpreted with caution.

Given the very limited number of patients in the ≥ 100 kg weight cohort, no firm conclusion could be drawn on the impact of body weight on the safety profile.

There was no evidence from clinical trials to properly assess haemolysis risk and the known manifestations of untreated PNH and to allow to propose a time frame to detect haemolysis symptoms in patients who do not start treatment with other complement inhibitors after discontinuation of crovalimab. The SmPC was updated to consider restarting appropriate treatment if signs and symptoms of haemolysis occur after discontinuation, including elevated LDH.

Overall, across the crovalimab naive and crovalimab switch populations, the baseline prevalence was 9.6% (37 patients out of 387) and the incidence of treatment-emergent ADA was 30.1% (118 patients out of 392) at the updated CCODs, compared with a baseline prevalence of 10% (37 patients out of 371) and an incidence of treatment-emergent ADA of 27% (103 patients out of 375). At the SRR CCODs, the number of patients with transient ADA was low (17 patients); most of the patients had persistent ADA (91 patients), and the median time to ADA onset was 15.9 weeks (range 1.1 to 72.3 weeks).

Neutralising ADAs were detected in 5 patients out of 111 ADA-positive patients (nAb status missing in 7 patients). It should be however noted that the current assay may underestimate the number of patients with positive nAbs, given that the drug tolerance (which is the crovalimab concentration that still results in detectable ADA signal) does not cover the therapeutic concentrations of crovalimab.

Imbalances were noted in safety parameters between ADA-positive and ADA-negative patients. Specifically, the incidence of grade 3-5 AEs was higher in ADA-positive patients (46.0%) compared to ADA-negative patients (30.6%) in the total crovalimab population. the main contributors for this imbalance are AEs from Investigations and Infections and Infestations SOC. Conversely, reported incidence rates of AEs which are typically associated with immunogenicity (injection site reactions,

infusion related reactions) are either comparable or lower in ADA-positive compared to ADA-negative patients.

In the total crovalimab population, the number of AEs leading to dose modification/ interruption per 100 PYs (5.36 (95% CI: 3.18, 8.47)) was similar compared to the total eculizumab population (6.03 (95% CI: 1.24, 17.62)). The most frequently reported AEs in the total crovalimab population were COVID-19 (1.3%), type III immune complex mediated reaction (0.5%) and infusion related reaction (0.5%).

1.1% (4 patients) of the total crovalimab population and 0.9% (1 patient) of the total eculizumab population experienced at least one AE leading to treatment discontinuation. The 4 AEs leading to treatment discontinuation in the total crovalimab population were demyelinating polyneuropathy, thrombocytopenia, type III immune complex mediated reaction, and sepsis.

Long-term safety results are limited, based on 44 patients from study BP39144 with median treatment duration of 4.69 years. No patients discontinued from the study due to an adverse event. A total of 43 (97.7%) patients experienced at least one AE. There was one death (in a patient who switched from eculizumab). No AEs resulted in withdrawal of a patient from the study. 43.2% of patients experienced at least one SAE. 31.8% of patients experienced AEs that were considered by the investigator to be related to crovalimab treatment. One (2.3%) patient experienced a serious AE not related to crovalimab that led to dose interruption.

The most frequently reported AEs were nasopharyngitis (38.6%), Covid-19 (34.1%), upper respiratory tract infection (29.5%) headache (25.0%), back pain (22.7%), pyrexia (22.7%), arthralgia (20.5%) cough (20.5%). Two out of 26 patients (7.7%) who switched from eculizumab experienced AESIs of Type III hypersensitivity reactions. Both of these AESIs were mild to moderate in intensity and occurred during the primary treatment period. 6.8% of patients experienced at least one infusion-related reaction and 4.5% of patients (5.6% of treatment-naïve patients and 3.8% of switched patients) experienced at least one injection-site reaction up to the CCOD. All events were mild in intensity. Two AESI of abnormal liver function tests were reported in one naïve and one switch PNH patient but were not related to treatment with crovalimab. Based on the long-term data presented, no new safety issues are raised and the safety profile of crovalimab is consistent with the safety data presented in the SCS in the initial submission.

Assessment of paediatric data on clinical safety

Of the total crovalimab population, 3% of patients were paediatrics aged <18 years. This represents only 12 paediatric patients (9 treatment-naive and 3 switch patients with PNH). Of these 12 paediatric patients, 9 patients were Asian. All 12 (100%) paediatric patients reported at least one AE, and the majority of AEs (83.3%) were of grade 1-2. Two (16.7%) patients experienced grade 3-5 AEs. Six (50.0%) patients experienced AEs that were assessed as related to study treatment by the Investigator. No paediatric patient reported a fatal AE, an SAE or an AE that led to drug interruption/modification or withdrawal.

There was one case of meningococcal meningitis (grade 3) in study BO42354, evaluating crovalimab in paediatric patients with atypical haemolytic uremic syndrome.

Main AEs reported in paediatrics were related to investigations SOC and GI disorders. One renal injury event was reported in a paediatric patient naïve to crovalimab. This case was described and considered not related to treatment. The number of patients is small in each group based on race (White n=2, Asian n=9 and 1 unknown), it is then difficult to have a clear conclusion on the relevance of safety findings observed in Asian patients to the white paediatric patients.

From the safety database all the adverse reactions reported in clinical trials have been included in the

Summary of Product Characteristics.

2.6.10. Conclusions on the clinical safety

Overall, the safety profile of crovalimab appears similar to that of eculizumab in patients with PNH, both in treatment naïve patients and in patients already on treatment with eculizumab or ravulizumab.

The most commonly reported adverse events with crovalimab were pyrexia, headache, infections, infusion related reactions, injection related reactions (only crovalimab due to SC administration) and type III hypersensitivity only in switch patients. Meningococcal infection is an important risk of crovalimab related to its mode of action.

2.7. Risk Management Plan

2.7.1. Safety concerns

The applicant proposed the following summary of safety concerns in the RMP:

Table 87: Summary of safety concerns

Summary of safety concerns	
Important identified risks	Serious infections Infusion and injection-related reactions Type III immune complex reactions (patients switching from eculizumab or ravulizumab to crovalimab (and vice versa)) Meningococcal infection Immunogenicity
Important potential risks	Serious haemolysis after drug discontinuation Malignancies and haematological abnormalities
Missing information	Use in pregnancy and/or breastfeeding

2.7.2. Pharmacovigilance plan

Table 88: On-going and planned additional pharmacovigilance activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Date(s)
Category 1—Imposed mandatory additional pharmacovigilance activities that are conditions of the marketing authorization				
Not applicable.				
Category 2—Imposed mandatory additional pharmacovigilance activities that are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
Not applicable.				
Category 3—Required additional pharmacovigilance activities (by a competent authority such as CHMP/PRAC or NCA)—i.e., studies that investigate a safety concern or evaluate the effectiveness of risk minimization activities				
Study MO45473: Crovalimab Safety Study to Characterize Safety Events and Special Conditions Including Pregnancy and Infant Outcomes in the IPIG Registry **Planned**	The primary objectives for this study are as follows: • To estimate the frequency of adverse events among patients exposed to crovalimab (i.e. cases of serious hemolysis in patients who discontinue crovalimab, serious infections, meningococcal infection, and malignancies and hematologic abnormalities) • To evaluate pregnancy and infant outcomes in crovalimab-exposed PNH patients To estimate the frequency of adverse pregnancy outcomes (during pregnancy and during 1 year postpartum) and birth outcomes (i.e., live births, spontaneous abortions, stillbirths, elective terminations, and preterm births) To estimate the frequency of adverse fetal/neonatal/infant outcomes (i.e., major and minor congenital malformations, gestational age , postnatal growth and development) and serious safety events at birth and through at least the first year of life of infants Estimate the frequency of serious safety event and infant outcomes among women treated with crovalimab by breastfeeding status	**Important Risks:** Serious infections, Meningococcal infection, Serious hemolysis after crovalimab discontinuation, Malignancies and hematological abnormalities **Missing information:** Pregnancy and/or breastfeeding	Final Protocol First Interim Report Final Clinical Study Report	31 December 2024 31 October 2026 (subsequent interim reports to be provided every 2 years thereafter with the PBRER) 31 December 2036

IPIG=International PNH Interest Group; PBRER=Periodic Benefit-Risk Evaluation Report; PNH=paroxysmal nocturnal hemoglobinuria.

2.7.3. Risk minimisation measures

Table 89: Risk minimisation measures

Safety concern	Risk minimization measures	Pharmacovigilance activities
Serious infections	**Routine risk minimization measures:** Routine risk communication is described in: • SmPC Section 4.4 – Special warnings and precautions for Use Recommendation to vaccinate patient per local guidelines to prevent *Streptococcus pneumoniae* and *Haemophilus influenzae* type b infections. Recommendation to monitor patients closely with an active systemic infection for signs and symptoms of worsening infection. **Additional risk minimization measures:** Education materials: guides for prescribing HCPs and patients/caregivers.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Study MO45473
Infusion- and injection-related reactions	**Routine risk-minimization measures:** Routine risk communication is described in: • SmPC Section 4.2 – Posology and method of administration • SmPC Section 4.4 – Special warnings and precautions for use Recommendation that patient/caregiver may administer SC dosing without HCP supervision after appropriate training, if determined by the treating physician to be appropriate. Recommendation to slow down or interrupt IV loading dose infusion in case of an IRR or discontinue immediately if the patient experiences a serious hypersensitivity reaction. Recommendation for patient/ caregiver to seek immediate medical attention if the patient develops symptoms of serious allergic reactions, including to confirm with the HCP regarding crovalimab treatment continuation, and administration of appropriate therapy. **Additional risk minimization measures:** Education materials: guides for prescribing patients/caregivers. Additionally, patient cards will be provided	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** None.

Safety concern	Risk minimization measures	Pharmacovigilance activities
Type III immune complex reactions patients switching from eculizumab or ravulizumab to crovalimab (and vice versa)	**Routine risk-minimization measures:** Routine risk communication is described in: • SmPC Section 4.4 – Special warnings and precautions for use Recommendation to monitor for the first 30 days after switching from eculizumab or ravulizumab to crovalimab for occurrence of the symptoms of Type III immune complex reactions. Guidance provided for appropriate treatments in the event of mild/moderate or severe reactions. **Additional risk minimization measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** None
Meningococcal Infection	**Routine risk-minimization measures:** Routine risk communication is described in: • SmPC Section 4.3 – Contraindications • SmPC Section 4.4 – Special warnings and precautions for use Requirement to vaccinate patient with a tetravalent meningococcal vaccine at least 2 weeks prior to receiving the first dose of crovalimab treatment; or if immediate therapy with crovalimab is indicated in an unvaccinated patient, the required vaccination should be administered as soon as possible and patients should receive prophylactic antibiotics from the time they start crovalimab treatment until 2 weeks after vaccination; and to maintain up to date vaccinations according to current local guidelines. Recommendation to closely monitor patient for worsening of PNH symptoms (including hemolysis) upon vaccination. Recommendation to monitor patient for early signs of meningococcal infection and consider use of antibiotics based on local guidance, to inform patient of these signs and symptoms and steps and urge them to seek medical care immediately. Physician must discuss the benefits and risks of crovalimab treatment with patients. Recommendation to provide patient with a patient card and patient guide.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Guided questionnaire **Additional pharmacovigilance activities:** Study MO45473

Safety concern	Risk minimization measures	Pharmacovigilance activities
Meningococcal Infection (cont.)	**Additional risk minimization measures:** • Education materials: guides for prescribing HCPs and patients/caregivers • Patient card • Controlled access program • Vaccination/re-vaccination reminder	
Serious hemolysis after drug discontinuation	**Routine risk-minimization measures:** Routine risk communication is described in: • SmPC Section 4.4 – Special warnings and precautions for use Requirement to closely monitor patient for signs and symptoms of serious intravascular hemolysis upon treatment discontinuation if patient does not switch to another treatment for PNH. **Additional risk minimization measures:** Education materials: guides for prescribing HCPs and patients/caregivers.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** Study MO45473
Malignancies and hematological abnormalities	**Routine risk-minimization measures:** None **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** Study MO45473
Immunogenicity	**Routine risk-minimization measures:** Routine risk communication is described in: • SmPC Section 4.4 – Special warnings and precautions for use • SmPC Section 4.8– Undesirable Effects	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** None.

2.7.4. Conclusion

The CHMP considers that the risk management plan version 1.0 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 06.02.2024.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Piasky (Crovalimab) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU and it is also a biological product.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The agreed indication for crovalimab is Piasky as monotherapy is indicated for the treatment of adult and paediatric patients 12 years of age or older with a weight of 40 kg and above with paroxysmal nocturnal haemoglobinuria (PNH):

- In patients with haemolysis with clinical symptom(s) indicative of high disease activity.
- In patients who are clinically stable after having been treated with a complement component 5 (C5) inhibitor for at least the past 6 months.

PNH is an acquired, rare, clonal and potentially life-threatening non-malignant haematologic disease characterised by complement-mediated red blood cell (RBC) haemolysis, with or without haemoglobinuria, an increased susceptibility to thrombotic episodes, and/or some degree of bone marrow dysfunction.

While spontaneous remission has been reported, the disease generally follows a clinically progressive course.

3.1.2. Available therapies and unmet medical need

Historically, management of PNH was limited to the use of supportive treatments, such as blood transfusions and anticoagulation therapy. Other supportive treatments are now part of the therapeutic landscape to reduce symptoms, stimulate haematopoiesis and limit complications.

Allogeneic bone marrow transplantation (BMTx) is the only curative treatment but is associated with substantial morbidity and mortality. Complement inhibitor therapies such Soliris and Ultomiris, two C5 inhibitors approved in 2007 and 2019 respectively are symptomatic treatments aimed to improve the quality of life (QoL) of adult patients with PNH. Recently, new medicines have been authorised such as Aspaveli, a C3 inhibitor targeting the proximal complement, Fabhalta, a proximal complement inhibitor that specifically binds to FB to inhibit the activation of the AP and amplification loop and Voydeya an oral small molecule reversible inhibitor of complement factor D (FD) that selectively blocks the complement alternative pathway (AP).

3.1.3. Main clinical studies

The main evidence for efficacy and safety is based on the pivotal study BO42162 (hereafter mentioned as Study 162 or COMMODORE 2), a Phase 3, randomised, eculizumab-controlled study in PNH paediatric and adult subjects not previously treated with complement inhibitors.

Supportive data were provided from study BO42161 (hereafter mentioned as Study 161 or COMMODORE 1), a randomised, eculizumab-controlled supportive study in PNH paediatric and adult subjects currently treated with complement inhibitors and Study YO42311 (hereafter mentioned as Study 311 or COMMODORE 3), a single-arm supportive study in Chinese PNH adult and adolescent subjects not previously treated with complement inhibitors. Longer-term data were provided from an ongoing Phase I/II adaptive study BP39144 (hereafter mentioned as Study 144) aimed to assess safety, efficacy, PK and PD in healthy volunteers and patients with PNH (all adults).
As of 16 November 2022, a total of 204 adult patients were randomised in Study 162 to crovalimab (Arm A, n=135) or to eculizumab (Arm B, n=69). 6 paediatric patients entered the paediatric descriptive Arm C.

Randomised treatment arms were overall balanced in terms of age and weight, baseline medians being comparable between both arms: 37 years and 66.1 kg in the crovalimab arm and 38 years old and 62.2 kg in the eculizumab arm. Baseline disease characteristics were also balanced as median age and time from PNH diagnosis were also comparable: 30.97 years at diagnosis and 2.56 years since then in the crovalimab group compared to 32.11 and 2.93 years in the control group).

Regarding exposure, median treatment duration was similar between both arms: 20.1 weeks (range: 0.1-23.1 weeks) in the crovalimab arm (Arm A), compared to 22.1 weeks (range: 6.1-26.1 weeks) in the eculizumab arm (Arm B). Treatment compliance was high in both arms.

Crovalimab self-administration or drug administration by a caregiver was permitted starting at Week 9, after training and confirmation of proficiency by the healthcare provider. Overall, this was not associated with medication error leading to dose modification nor major protocol deviations.

Major protocol deviations were more frequent in the crovalimab arm when compared to the eculizumab (62.2% vs 52.2%, respectively), the majority of them being about procedural deviations due to COVID-19 restrictions according to the applicant. However, numerous patients had a protocol deviation of 'dose missed or out of window' and those were rarely considered related to COVID-19 in both arms (4.0% and 1.5%, respectively). Based on the complementary data provided, no impact of efficacy and safety is expected. Clarifications regarding reasons for exclusion from PP set were provided upon request and indicate no major discrepancies between treatment arms regarding proportion of excluded patients or reasons for exclusion.

Requirements regarding use of concomitant therapies during treatment period were lacking, i.e. no stable dose of concomitant therapies was required after randomisation. The potential influence of immunosuppressants, corticosteroids, androgens and erythropoietin on efficacy results was discussed. Due to the lack of rules regarding concomitant therapies upon enrolment, it remains difficult to disentangle the possible impact of concomitant therapies on observed efficacy results. However, given the small number of patients who experienced an initiation or dose change in the medications of interest, and the relatively balanced distribution of those patients between the randomised treatment arms, no major effect on efficacy results is expected. Regarding erythropoietin, a more pronounced imbalance was reported regarding erythropoietin use in COMMODORE 2: 7 patients in crovalimab arm vs 0 patients in eculizumab group initiated erythropoietin or its derived products prior to study entry or during primary treatment period. Based on provided information, it can be agreed that the use of erythropoietin and its derivatives had no major impact on overall efficacy results.

Resue crovalimab doses were allowed per protocol. Four patients from Arm A received one or two 340 mg IV crovalimab rescue doses, along with 2 Arm B Switch patients. The corresponding cases were further discussed to support the language present in the SmPC. The majority of patients who received a rescue dose during primary treatment period were considered to be 'non-responders' as they either did not achieve TA (5 out of 6 patients) or had experienced a BTH event (5 out of 6 patients), and none achieved haemoglobin stabilisation. Overall, it is considered that the additional doses of

crovalimab did not provide any additional benefit in terms of LDH and haemolysis control in any of the above-mentioned cases. Therefore, there is no clear evidence to support the benefit of rescue dosing in patients in the study and no need for inclusion of rescue dosing in the label.

3.2. Favourable effects

In the crovalimab arm, 65.7% (95% CI: 56.91, 73.52) of patients were transfusion-free from baseline through Week 25 compared to 68.1% (95% CI: 55.67, 78.53) of patients in the eculizumab arm. Non-inferiority was demonstrated with a weighted difference of - 2.8% and a lower limit of the 95% CI of -15.67%. This was supported by the sensitivity analyses and data in Arm B Switch patients: 33 out of 43 achieved transfusion avoidance through switch Week 25 (76.7%, 95% CI: 61.00, 87.72).

Criteria for transfusion, including symptom descriptions, were pre-defined in the protocol, for patients who had haemoglobin values of 7-9 g/dL. The final decision was left to the clinical judgment of the investigator and depended on assessment of severity of symptoms. Considering the open-label design of the study, possibility of bias for the co-primary endpoint of transfusion avoidance was discussed upon requested and ruled out.

The mean proportion of patients with haemolysis control from Week 5 through Week 25 was 79.3% (95% CI: 72.86, 84.48) for the crovalimab arm and 79.0% (95% CI: 69.66, 85.99) for the eculizumab arm.

There was a large proportion of Asian patients enrolled in the pivotal study, however subgroup analyses for co-primary endpoints did not show any clear differences according to the race of the subjects included. This was reassuring in terms of the representativeness of the complement inhibitor-naive target population.

The proportion of patients with a BTH event from baseline through Week 25 was 10.4% (95% CI: 6.04, 17.21) in the crovalimab arm compared with 14.5% (95% CI: 7.54, 25.50) in the eculizumab arm.

The proportion of patients reaching haemoglobin stabilisation from baseline through Week 25 was 63.4% (95% CI: 54.63, 71.45) in the crovalimab arm compared to 60.9% (95% CI: 48.35, 72.17) in the eculizumab arm.

Patient reported outcomes were evaluable in a great number of patients, allowing to adequately appreciate the effects of crovalimab treatment on PNH patients' QoL. Improvement in fatigue was observed by Week 2, with the mean score increasing to 40.9 points (95% CI: 39.57, 42.28) in the crovalimab arm compared with 38.9 points (95% CI: 36.35, 41.47) in the eculizumab arm. Further improvement in levels of fatigue were reported up to Week 25, with the mean score increasing to 44.3 points (95% CI: 43.15, 45.52) in the crovalimab arm compared with 41.4 points (95% CI: 39.29, 43.47) in the eculizumab arm at Week 25.

Results from supportive study COMMODORE 3 (also in complement inhibitor-naïve subjects) were overall consistent with results presented in the pivotal study.

Data in patients who switched to crovalimab (COMMODORE 1) are purely descriptive, as efficacy endpoints were downgraded to exploratory endpoints due to recruitment challenges. However, consistency is observed with results in complement inhibitor-naïve patients: the mean proportion of patients treated with crovalimab achieving haemolysis control (central LDH ≤ 1.5 × ULN) through Week 25 was 92.9% (vs. 79.3% [95%CI: 72.86, 84.48] in COMMODORE 2), 79.5% (vs. 65.7% [95% CI: 56.91, 73.52]) of patients avoided transfusion. At least one BTH event was reported in 10.3% of patients (vs. 10.4% [95% CI: 6.04, 17.21]) and 59.0% (vs. 65.7% [95% CI: 56.91, 73.52]) of patients presented stabilised haemoglobin.

Results in Arm B switch patients of study BO42162 are also globally in line with those results. Acknowledging the similar PK, PD and safety profile and the absence of evidence towards differences in PNH pathogenesis and response to treatment between complement inhibitor-naïve and switch patients, it is considered that the data could be extrapolated from the former subpopulation to the latter.

Although extrapolation is supported and similar efficacy responses were observed in both settings, further clarifications were requested, considering the limited pool of ravulizumab switch patients. The applicant presented thorough analyses of LDH fluctuations and BTH events for ravulizumab switch patients compared to eculizumab switch patients. Despite difference in sample sizes and indirect comparison bias, no major differences were observed. These findings were reinforced by data supportive of the overall benefit of crovalimab treatment in terms of transfusion avoidance in both switch subpopulations.

This extrapolation also covers the PNH adolescents ≥12 years of age and ≥40 kg, as available paediatric data are limited to the complement inhibitor-naïve population (9 patients among studies COMMODORE 2 and 3, aged 13-17 years and of body weight ≥40 kg). Further results are expected by March 2028, date of completion of the PIP for crovalimab (EMEA/002709/PIP01/19/M01). Efficacy results obtained in paediatric patients are only exploratory and descriptive which is acceptable as powered analysis would not be feasible due to rarity of disease in this subgroup. All treatment-naive paediatric patients reached central LDH < 1.5 x ULN by Week 4 and this was maintained at each visit during the primary treatment period in 7 out of the 9 patients. Other 2 patients also maintained good clinical response despite some fluctuations of LDH above 1.5xULN.

Six out of the 9 paediatric treatment-naive patients achieved transfusion avoidance and haemoglobin stabilisation from baseline to Week 25.

No BTH events were reported from baseline to Week 25. Overall, presented results pointed to a favourable effect of crovalimab treatment of paediatric patients and are consistent with results observed in complement inhibitor naïve adult patients treated with crovalimab (Arm A of pivotal study BO42162).

3.3. Uncertainties and limitations about favourable effects

In the context of a single pivotal trial, results of Study BO42162 are expected to be "particularly compelling with respect to internal and external validity, clinical relevance, statistical significance, data quality, and internal consistency." (CPMP/EWP/2330/99).

However, no data are available in PNH patients aged less than 13 years and weighing less than 40 kg since no patients under 12 years of age or weighing less than 40 kg were included in the studies presented. Besides, there is no posology recommendations for patients under 40 kg. This has been reflected in the amended indication, along with the use of crovalimab as a monotherapy. Mention of complement component 5 (C5) was added within the indication for clarity.

Efficacy of crovalimab in terms of haemolysis control and TA was numerically lower in elderly patients (≥65 years old). Considering the fact that only 12 elderly patients received crovalimab and 9 received eculizumab, no firm conclusions could be drawn, Section 4.2. of the SmPC has been amended in order to reflect the current knowledge and data gaps in this regard.

Additional discussion on efficacy and safety in patients whose dose was modified due to sustained IVH or qualifying BTH events was also provided, however due to small number of events, heterogeneity of response after increase in dose and confounding factors related to ADA positivity, no recommendation regarding increase in dose can be provided at this time beyond those related to weight increase.

Efficacy of crovalimab in adult patients switching from other C5 inhibitors (mainly eculizumab) is based on exploratory and descriptive data, without any data in paediatric switch patients.

Regarding QoL, assessment of FACIT-Fatigue and other PROs could be influenced by patients' knowledge of their treatment assignment.

Also, a total loss of pharmacological activity was reported in 11 patients. Despite the narratives provided, it is not possible to determine the reasons for this loss of activity due the low proportion of patients concerned and the unique clinical context of each of them.

3.4. Unfavourable effects

The median treatment duration was 68.1 weeks (range: 0.1-136.1weeks) for the crovalimab naive population and was 56.3 weeks (range: 0.3−136.4 weeks) for the crovalimab switch population.

Injection site reactions were overall reported in 4.7% of the crovalimab naive population and 11.9% of the crovalimab switch population. Only 2 patients had a grade 3 injection related reactions, which resolved with no dose modification/interruption. The most frequently reported symptoms of injection site reactions were (crovalimab naive and crovalimab switch population, respectively), headache (2.1% and 3%), injection site erythema (1.0% and 1%), malaise (0% and 1.1%), erythema (0% and 1.1%), pruritus (0% and 1.1%) and myalgia (0% and 1.1%).

Infusion related reactions were reported in 10.2% in the total crovalimab and 8.1% in the total eculizumab populations. All events were grade 1-2. The most frequently reported symptoms of infusion related reactions in the crovalimab naive and crovalimab switch populations, respectively were headache (9.4% and 4.9%), rash (1.0% and 0.5%), abdominal pain (1.0% and 0%), pyrexia (1.0% and 0%) and dizziness (0.5% and 1%).

Infections: the incidence of all grade infections was 64.6% in Crovalimab arm (number of events per 100 PYs was 91.5 (95% CI: 83.33, 100.24)) and 37.8% (number of events per 100PY was 123.3, (95% CI: 94.77, 157.79)) in eculizumab arm. Of these, 10.7% were grade 3-5 AEs (comparing to 4.5% for Ecu) and 9.7% were serious events (comparing to 5.4% for Eculizumab). The most frequently reported infections in the total crovalimab and total eculizumab populations were COVID-19 (35.4% vs 31.3%), upper respiratory tract infection (26% vs 11.4%), and urinary tract infection (10.4% vs 7%), respectively. There were no cases of infection with N. meningitidis (including Meningococcal meningitis) in studies with PNH. However, there was one case of Meningococcal meningitis in Study BO42354, in paediatric patients with atypical haemolytic uremic syndrome.

Type III hypersensitivity reactions: Patients who switched from eculizumab or ravulizumab to crovalimab (and vice versa) are at risk of developing DTDC-associated type III hypersensitivity reactions. The majority of events were grade 1−2, and 8.0% of patients had grade 3 events. One patient (0.5%) also reported a PT of grade 3 axonal neuropathy. One patient discontinued treatment due to T3H event.

In the total crovalimab population, the number of deaths due to AEs per 100 PYs was 1.6 (95% CI: 0.69, 3.13) versus 2.01 (95% CI: 0.05, 11.20) in the total eculizumab population. 8 patients in the total crovalimab population experienced grade 5 AEs of subdural haematoma, respiratory tract haemorrhage, myocardial infarction, colorectal cancer, COVID-19, COVID-19 pneumonia, pneumonia aspiration and death (unexplained cause).

In the total crovalimab population, the number of AEs leading to dose modification/ interruption per 100 PYs (3.6 (95% CI: 2.12, 5.65)) was similar compared to the total eculizumab population (5.9 (95% CI: 1.21, 17.16)). The most frequently reported AEs leading to dose modification/ interruption in the total crovalimab population were COVID-19 (1.5%), type III immune complex mediated reaction

(0.5%) and infusion related reaction (0.5%). The 4 AEs leading to treatment discontinuation in the total crovalimab population were demyelinating polyneuropathy, thrombocytopenia, type III immune complex mediated reaction, and sepsis.

Long-term safety results were overall consistent with the safety profile observed in pivotal studies.

Of the total crovalimab population, 3% of patients were <18 years. Of the total 12 paediatric patients, all paediatric patients reported at least one AE, and the majority of AEs were of grade 1-2. Two (16.7%) patients experienced AEs of grade 3−5. Six (50%) patients experienced AEs considered related to study treatment by the investigator. No paediatric patient reported a fatal AE, an SAE or an AE that led to drug interruption/ modification or withdrawal. There was one case of meningococcal meningitis (grade 3) in study BO42354, evaluating crovalimab in paediatric patients with atypical haemolytic uremic syndrome.

3.5. Uncertainties and limitations about unfavourable effects

Immune complex formation and reactions occurred in patients switching from eculizumab and ravulizumab to crovalimab (and vice-versa) given that crovalimab binds to different epitope than other C5 inhibitors. Among the 39 patients who experienced type III immune complex reactions, 23 patients (59%) had a grade 1-2 event, and 15 patients (41%) had grade 3 events. One patient discontinued treatment due to type III hypersensitivity reactions and events of type III immune complex reactions remains unresolved in 14% of cases. Some patients had relatively longer Type III hypersensitivity events (up to 34 weeks). Information on immune complex reactions has been added to section 4.4, 4.5 and 4.8 of the SmPC. In addition, type III immune complex reactions (patients switching from eculizumab or ravulizumab to crovalimab (and vice versa)) has been added as an important identified risk in the RMP.

Patients with active systemic bacterial, viral, or fungal infection within 14 days before first drug administration were excluded in phase III studies. This has also been reflected in section 4.4 of the SmPC. Serious infections have been added as an important identified risk in the RMP.

Despite there were no malignancies considered related to crovalimab and since a plausible relationship has been established for eculizumab and the risk is included in the SmPC of eculizumab, a similar pattern cannot be ruled out for crovalimab. Malignancies and haematological abnormalities have been added as an important potential risk in the RMP.

Safety data in paediatric patients is limited particularly for long-term effects given the low number of paediatric patients included in clinical studies.

Uncertainties mainly related to the observed difference in incidence of some AEs and the small sample size of paediatric patients hamper drawing clear conclusion about the risk of immunogenicity on safety. Immunogenicity has been added as an important identified risk in the RMP.

3.6. Effects Table

Table 90: Effects Table for Piasky in treatment of adults and children with PNH (data cut-off: 16 November 2022)

Effect	Short Description	Unit	Treatment N=135	Control N=69	Uncertainties/ Strength of evidence	References
Favourable Effects – treatment naïve PNH patients						
Transfusion avoidance (TA)	Proportion of patients who achieve TA from baseline through Week 25	%, (95%CI)	65.7 (56.91,73.52)	68.1 (55.67, 78.53)	Difference in proportions, % (95% CI): -2.8% (-15.67, 11.14) NIM for 95%CI lower limit = -20%	BO42162
Haemolysis control	Mean proportion of patients with central LDH ≤1.5 X ULN, from Week 5 through Week 25	% (95% CI)	79.3 (72.86, 84.48)	79.0 (69.66, 85.99)	Odds ratio (95%CI) 1.02 (0.57, 1.82) NIM for 95% CI lower limit = 0.2	BO42162
Breakthrough haemolysis (BTH)	Proportion of patients with BTH from baseline through Week 25	% (95% CI)	10.4 (6.04, 17.21)	14.5 (7.54, 25.50)	Difference in proportions, % (95% CI) -3.9% (-14.62, 5.26) NIM for 95% CI upper limit =20%	BO42162
Hb stabilisation	Proportion of patients with stabilisation of haemoglobin from baseline through Week 25	% (95% CI)	63.4 (54.63, 71.45)	60.9 (48.35, 72.17)	Difference in proportions, % (95% CI) 2.2% (-11.37, 16.31) NIM for 95% CI upper limit =-20%	BO42162
Effect	**Short Description**	**Unit**	**Treatment N= 39**	**Control N=37**	**Uncertainties/ Strength of evidence**	**References**
Favourable Effects – stable PNH patients previously treated with eculizumab						
Transfusion avoidance (TA)	Proportion of patients who achieve TA from baseline through Week 25	%, (95%CI)	79.5 (63.06, 90.13)	78.4 (61.34, 89.58)	Unc: Descriptive data only	BO42161, randomised arms

Haemolysis control	Mean proportion of patients with central LDH ≤1.5 X ULN, from Week 5 through Week 25	% (95% CI)	92.9 (86.62, 96.39)	93.7 (87.26, 97.04)		
Breakthrough haemolysis (BTH)	Proportion of patients with BTH from baseline through Week 25	% (95% CI)	10.3 (3.34, 25.16)	13.5 (5.08, 29.57)		
Hb stabilisation	Proportion of patients with stabilisation of haemoglobin from baseline through Week 25	% (95% CI)	59.0 (42.19, 74.02)	70.3 (52.83, 83.56)		
Favourable Effects – stable PNH patients previously treated with ravulizumab (n=19)						
Transfusion avoidance (TA)	Proportion of patients who achieve TA from baseline through Week 25	%, (95%CI)	57.9 (33.97, 78.88)		Unc: Descriptive data only, uncontrolled data	BO42161, Arm C
Haemolysis control	Mean proportion of patients with central LDH ≤1.5 X ULN, from Week 5 through Week 25	% (95% CI)	95.8 (89.11, 98.43)			
Breakthrough haemolysis (BTH)	Proportion of patients with BTH from baseline through Week 25	% (95% CI)	36.8 (17.23, 61.37)			
Hb stabilisation	Proportion of patients with stabilisation of haemoglobin from baseline through Week 25	% (95% CI)	52.6 (29.50, 74.79)			

Unfavourable Effects

Effect	Short Description	Unit	Treatment N= 377	Control N=111	Uncertainties/ Strength of evidence	References
Injection site reactions	Incidence	%	8.4	0	Unique to Crova, infrequent G3,higher incidence in Crova switch compared to naive	

Infusion related reactions	Incidence	%	10.2	8.1	All grade 1-2	
Infections	Incidence	%	64.6	37.8	3 patients experienced grade 5 AE, 9% grade 3-5 AE;	
Type III hypersensitivity reactions	Incidence	%	19.4 (only crova switch patients, n=185)	0	49% of events were grade 3, only in patients switching from eculizumab or ravulizumab to crovalimab (and vice versa).	

Abbreviations: ADA= anti-drug antibody; AE= adverse event; CI= confidence interval; OC= other concern; NIM = non-inferiority margin; SAE = serious adverse event

Note: Hierarchal testing was broken before the endpoint of FACIT-fatigue. Therefore, the corresponding results are not presented in the table above.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Given the need for lifelong therapy in PNH, the Q4W low-volume SC self-administration of crovalimab represents an additional therapeutic option for patients.

In the absence of PK, efficacy and safety data in subjects below 12 years of age, with a body weight ≥40 kg, the indication was amended to reflect the studied population and the use of crovalimab as monotherapy. Mention of complement component 5 (C5) within the indication was added for clarity.

The pivotal randomised Phase III study was focused on the investigation of adult patients with PNH who never received treatment with a complement inhibitor; in that setting, crovalimab was shown to be non-inferior to eculizumab in terms of transfusion avoidance and haemolysis control. Although it was not formally tested, improvement in fatigue was also observed, however, it should be noted that assessment of FACIT-Fatigue and other PROs could be influenced by patients' knowledge of their treatment assignment.

Efficacy results obtained in paediatric patients (n=9) are exploratory and descriptive, which is acceptable for this population as statistically powered analysis would not be feasible due to rarity of disease. Overall, efficacy results in complement inhibitor naïve paediatric patients are consistent with results observed in complement inhibitor naïve adult patients treated with crovalimab - all 9 paediatric patients achieved haemolysis control by Week 4, 7 of them sustained it across the first 24 weeks of treatment, and six patients (66.6%) achieved and sustained TA and haemoglobin stabilisation. Fatigue scores were variable in majority but a general improvement in fatigue could be observed. Also, the PK/PD profile is similar in both age groups. Longer-term safety data were provided, revealing no major differences in between subgroups in terms of safety profile, pathogenesis of PNH and response to treatment. Therefore, the adult treatment-naive clinical data package could be extrapolated also to the switch population within the studied age and weight limits.

Due to recruitment challenges and subsequent refocus on safety endpoints, efficacy of crovalimab in adult patients who switched from C5 inhibitor compared to continuation of C5 inhibitor therapy was

only of exploratory and descriptive nature, mainly arising from patients receiving eculizumab (descriptive results are available also for 19 patients who were switched from ravulizumab). The claimed 'switch' indication was questioned and a satisfactory extrapolation plan from complement inhibitor-naïve patients to stable switch patients was provided by the applicant. Considering the limited pool of switch patients initially treated with raviluzumab, the applicant presented thorough analyses of LDH fluctuations and BTH events in ravulizumab switch patients compared to eculizumab switch patients. Despite difference in sample sizes and indirect comparison bias, no major differences were observed. These findings were reinforced by data supportive of the overall benefit of crovalimab treatment in terms of transfusion avoidance in both switch subpopulations.

Efficacy of crovalimab in patients who have suboptimal disease control despite treatment with other C5 inhibitor was investigated only in 6 patients with C5 SNP polymorphism treated with eculizumab or ravulizumab.

From a safety point of view, while no major differences have been observed with crovalimab compared to eculizumab, safety data are still rather limited. Due to the rarity of the disease the safety programme could not identify rare adverse events. Type III immune complex reactions occurred in patients switching from eculizumab and ravulizumab to crovalimab (and vice-versa) and is considered a safety concern. Data on safety in paediatric patients are limited given the small number of paediatric patients included in trials.

3.7.2. Balance of benefits and risks

The applicant was seeking a MA for crovalimab as monotherapy for the treatment of adult and paediatric patients with paroxysmal nocturnal haemoglobinuria (PNH). The development programme was aimed at demonstrating non-inferiority of crovalimab compared to eculizumab in treatment of adult and paediatric PNH patients. Crovalimab is proposed in the first line treatment setting as an alternative to eculizumab and ravulizumab, but also as an option for patients who are clinically stable on another C5 inhibitor.

The proposed indication was amended to better reflect the study population and evidence provided, and a reference to complement component 5 (C5) was added within the indication wording for clarity. While the data provided as part of the stable switch setting are only considered descriptive, based on pathophysiology of PNH and crovalimab PK/PD data, efficacy could be extrapolated as supported by the available exploratory data since efficacy data in this patient population showed similar responses to those observed in the naive setting.

The safety of crovalimab is overall manageable and consistent with other C5 inhibitors. In patients switching from other C5 inhibitors to crovalimab, type III immune complex reactions is an expected risk that should be considered; relevant information was added to the SmPC accordingly.

3.7.3. Additional considerations on the benefit-risk balance

Not Applicable.

3.8. Conclusions

The overall benefit /risk balance of Piasky is positive in the following indication: as monotherapy for the treatment of adult and paediatric patients 12 years of age or older with a weight of 40 kg and above with paroxysmal nocturnal haemoglobinuria (PNH):

- In patients with haemolysis with clinical symptom(s) indicative of high disease activity.

- In patients who are clinically stable after having been treated with a complement component 5 (C5) inhibitor for at least the past 6 months.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Piasky is not similar to Aspaveli, Fabhalta and Voydeya within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000. See Appendix on Similarity.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Piasky is favourable in the following indication:

Piasky as monotherapy is indicated for the treatment of adult and paediatric patients 12 years of age or older with a weight of 40 kg and above with paroxysmal nocturnal haemoglobinuria (PNH):

- In patients with haemolysis with clinical symptom(s) indicative of high disease activity.
- In patients who are clinically stable after having been treated with a complement component 5 (C5) inhibitor for at least the past 6 months.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

The MAH shall ensure that in each Member State where Piasky is marketed, all healthcare professionals and patients who are expected to prescribe/dispense and use Piasky have access to/are provided with the following educational package:

- Guide for healthcare professionals
- Patient/caregiver guide
- Patient card
- Vaccination/re-vaccination reminders aimed at healthcare professionals

The guide for healthcare professionals (HCPs) will contain information about serious infections, meningococcal infection, and serious haemolysis after crovalimab discontinuation in PNH patients, and may include:

- Details on how to minimise the safety concern through appropriate vaccination, monitoring and management
- Key messages to convey in patient counselling
- Instructions on how to handle possible adverse events
- Remarks on the importance of reporting on adverse reactions

The MAH shall ensure that in each Member State where Piasky is marketed, a controlled access programme of Piasky is in place. This additional risk minimisation measure aims to manage the important risk of meningococcal infection and to specifically ensure that the patient receives the appropriate vaccination against Neisseria meningitidis infection and prophylactic antibiotics as required in the product information. The targeted audience for this additional risk minimisation measure is the HCP/pharmacist who prescribes/dispenses crovalimab to the patients.

The MAH shall send annually to prescribers or and pharmacists who prescribe/dispense crovalimab, a reminder to ensure that patients receiving crovalimab have been vaccinated (using the tetravalent vaccine) against Neisseria meningitidis infections.

The patient/carer guide will contain information about serious infections, infusion- and injection related reactions meningococcal infection, and serious haemolysis after crovalimab discontinuation in PNH patients, , and may include:

- A description of the signs and symptoms of the risks
- A description of the best course of action if signs and symptoms of those risks present themselves
- A description of when to seek urgent attention from the health care provider should signs and symptoms of these risks present themselves
- Remarks on the importance of reporting on adverse reactions

Patients will be given a card that they should always carry with them with information about the key signs and symptoms of meningococcal infections and severe allergic reactions, and instructions to seek emergency medical care if they experience symptoms of meningococcal infections and/or severe allergic reactions.

The patient card also includes a warning message for healthcare professionals treating the patient stating that the patient is receiving crovalimab.

The key elements of the patient card provide:

- A description of the key signs and symptoms of meningococcal infections and severe allergic reactions
- A statement that the patient card should be retained for 11 months after last dose of crovalimab
- A description of when to seek urgent medical care, should signs and symptoms of these risks present themselves
- The treating physician's contact details

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that crovalimab is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.

Paediatric Data

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision EMEA-002709-PIP01-M01 the agreement of a paediatric investigation plan (PIP) and on the granting of a class waiver.

At the time of submission of the application, the PIP EMEA-002709-PIP01-19-M01 was not yet completed as some measures were deferred.