Report on the Deliberation Results

March 6, 2024

Pharmaceutical Evaluation Division, Pharmaceutical Safety Bureau
Ministry of Health, Labour and Welfare

Brand Name	Piasky for Injection 340 mg
Non-proprietary Name	Crovalimab (Genetical Recombination) (JAN*)
Applicant	Chugai Pharmaceutical Co., Ltd.
Date of Application	June 14, 2023

Results of Deliberation

In its meeting held on February 29, 2024, the First Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The product is classified as a biological product. The re-examination period is 8 years. The drug product and its drug substance are both classified as powerful drugs.

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Because only a limited number of Japanese patients participated in the clinical studies, the applicant is required to conduct a use-results survey covering all patients treated with the product in the post-marketing settings until data are obtained from a specified number of patients, to clearly understand the characteristics of patients treated with the product and promptly collect safety and efficacy data so as to take appropriate measures that ensure proper use of the product.
3. Prior to the product launch, the applicant is required to take necessary measures that will ensure the use of the product only by physicians and at medical institutions with adequate expertise in the diagnosis and treatment of paroxysmal nocturnal hemoglobinuria and competence in the management of product-associated risks, and only in cooperation with physicians with expertise in the diagnosis and treatment of *Neisseria meningitidis* infection.

**Japanese Accepted Name (modified INN)*

Review Report

February 15, 2024
Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following pharmaceutical product submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Brand Name	Piasky for Injection 340 mg
Non-proprietary Name	Crovalimab (Genetical Recombination)
Applicant	Chugai Pharmaceutical Co., Ltd.
Date of Application	June 14, 2023
Dosage Form/Strength	Injection: each vial contains 340 mg of crovalimab (genetical recombination)
Application Classification	Prescription drug, (1) Drug with a new active ingredient

Definition

Crovalimab is a recombinant anti-human complement C5 monoclonal antibody, the complementarity-determining regions of which are derived from rabbit antibody and other regions are derived from human IgG1. In the H-chain, the amino acid residues at positions 241, 242, 245, 333, 336, 337, 434, 440, 444 and 446 are substituted by Arg, Arg, Lys, Gly, Ser, Ser, Leu, Ala, Arg and Glu, respectively, and Gly and Lys at the C-terminus are deleted. Crovalimab is produced in Chinese hamster ovary cells. Crovalimab is a glycoprotein (molecular weight: ca. 148,000) composed of 2 H-chains (γ1-chains) consisting of 451 amino acid residues each and 2 L-chains (κ-chains) consisting of 217 amino acid residues each.

Structure

Amino acid sequence:

Light (L) chain

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DIQMTQSPSS LSASVGDRVT ITCRASQGIS SSLAWYQQKP GKAPKLLIYG
ASETESGVPS RFSGSGSGTD FTLTISSLQP EDFATYYCQN TKVGSSYGNT
FGGGTKVEIK RTVAAPSVFI FPPSDEQLKS GTASVVCLLN NFYPREAKVQ
WKVDNALQSG NSQESVTEQD SKDSTYSLSS TLTLSKADYE KHKVYACEVT
HQGLSSPVTK SFNRGEC
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Heavy (H) chain

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QVQLVESGGG LVQPGRSLRL SCAASGFTVH SSYYMAWVRQ APGKGLEWVG
AIFTGSGAEY KAEWAKGRVT ISKDTSKNQV VLTMTNMDPV DTATYYCASD
AGYDYPTHAM HYWGQGTLVT VSSASTKGPS VFPLAPSSKS TSGGTAALGC
LVKDYFPEPV TVSWNSGALT SGVHTFPAVL QSSGLYSLSS VVTVPSSSLG
TQTYICNVNH KPSNTKVDKK VEPKSCDKTH TCPPCPAPEL RRGPKVFLFP
PKPKDTLMIS RTPEVTCVVV DVSHEDPEVK FNWYVDGVEV HNAKTKPREE
QYNSTYRVVS VLTVLHQDWL NGKEYKCKVS NKGLPSSIEK TISKAKGQPR
EPQVYTLPPS REEMTKNQVS LTCLVKGFYP SDIAVEWESN GQPENNYKTT
PPVLDSDGSF FLYSKLTVDK SRWQQGNVFS CSVLHEALHA HYTRKELSLS
P
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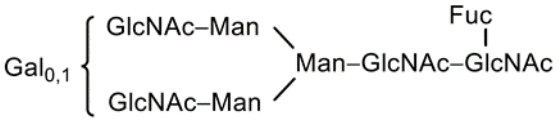
Intra-chain disulfide bonds: solid lines in the figure

Inter-chain disulfide bonds: L-chain C217–H-chain C226, H-chain C232–H-chain C232, H-chain C235–H-chain C235

Pyroglutamic acid (partial): H-chain Q1, Glycosylation: H-chain N303

Deduced structure of major glycan:



Gal, galactose; GlcNAc, *N*-acetylglucosamine; Man, mannose; Fuc, fucose

Molecular formula: $C_{6430}H_{9974}N_{1726}O_{2026}S_{46}$ (protein moiety, 4 chains)
(H-chain) $C_{2199}H_{3404}N_{588}O_{672}S_{17}$
(L-chain) $C_{1016}H_{1587}N_{275}O_{341}S_{6}$
Molecular weight: Approximately 148,000

Items Warranting Special Mention None
Reviewing Office Office of New Drug I

Results of Review
On the basis of the data submitted, PMDA has concluded that the product has efficacy in the treatment of paroxysmal nocturnal hemoglobinuria, and that the product has acceptable safety in view of its benefits (see Attachment).

As a result of its review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following conditions.

Indication
Paroxysmal nocturnal hemoglobinuria

Dosage and Administration
The usual dosage is 1,000 or 1,500 mg of crovalimab (genetical recombination) administered by intravenous infusion on Day 1, followed by 340 mg of crovalimab on Days 2, 8, 15, and 22 by subcutaneous injection. At Day 29 and thereafter, 680 or 1,020 mg of crovalimab is administered every 4 weeks by subcutaneous injection. The dosage should be determined based on the patient's body weight.

Approval Conditions
1. The applicant is required to develop and appropriately implement a risk management plan.
2. Because only a limited number of Japanese patients participated in the clinical studies, the applicant is required to conduct a use-results survey covering all patients treated with the product in the post-marketing settings until data are obtained from a specified number of patients, to clearly understand the characteristics of patients treated with the product and promptly collect safety and efficacy data so as to take appropriate measures that ensure that proper use of the product.
3. Prior to the product launch, the applicant is required to take necessary measures that will ensure the use of the product only by physicians and at medical institutions with adequate expertise in the diagnosis and treatment of paroxysmal nocturnal hemoglobinuria and competence in the management of product-associated risks, and only in cooperation with physicians with expertise in the diagnosis and treatment of *Neisseria meningitidis* infection.

Attachment

Review Report (1)

January 12, 2024

The following is an outline of the data submitted by the applicant and content of the review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Product Submitted for Approval	
Brand Name	Piasky for Injection 340 mg
Non-proprietary Name	Crovalimab (Genetical Recombination)
Applicant	Chugai Pharmaceutical Co., Ltd.
Date of Application	June 14, 2023
Dosage Form/Strength	Injection: each vial contains 340 mg of crovalimab (genetical recombination)
Proposed Indication	Paroxysmal nocturnal hemoglobinuria
Proposed Dosage and Administration	The usual initial dose is 1,000 or 1,500 mg of crovalimab (genetical recombination) administered by intravenous infusion on Day 1, followed by 340 mg of crovalimab on Days 2, 8, 15, and 22 administered by subcutaneous injection. At Day 29 and thereafter, 680 or 1,020 mg of crovalimab is administered every 4 weeks by subcutaneous injection. The dosage should be determined based on the patient's body weight.

Table of Contents

List of Abbreviations

See Appendix.

1. Origin or History of Discovery, Use in Foreign Countries, and Other Information

Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired clonal hematopoietic stem cell disorder, caused by an acquired mutation of the *phosphatidylinositol glycan class A* (*PIGA)* gene, which leads to a loss of cluster of differentiation (CD) 55 and CD59, terminal complement regulators on the erythrocyte surface, resulting in complement-mediated intravascular hemolysis (*Cell.* 1993;73:703-11, *N Engl J Med.* 1994;330:249-55). In Japan, PNH is a designated intractable disease (No. 62, Ministerial Announcement of the Ministry of Health, Labour and Welfare, dated on January 1, 2015). Currently approved PNH treatment drugs in Japan include eculizumab (genetical recombination) and ravulizumab (genetical recombination), which are humanized anti-complement component 5 (C5) monoclonal antibodies, and pegcetacoplan, a complement component 3 (C3) inhibitor for patients with an inadequate response to C5 inhibitors.

Crovalimab (genetical recombination) (hereinafter referred to as "crovalimab") is a novel humanized anti-C5 monoclonal antibody developed by the applicant. Crovalimab binds to C5, which blocks C5 cleavage into its active metabolites C5a and C5b, inhibiting the formation of membrane attack complex (MAC). Crovalimab is therefore expected to prevent the development of complement-mediated intravascular hemolysis in patients with PNH.

Recently, the applicant filed an application for marketing approval of crovalimab based on data from the global studies in patients with PNH because the study data demonstrated the efficacy and safety of crovalimab.

Outside Japan, approval applications of crovalimab have been filed in the US and Europe. As of December 2023, crovalimab has not been approved in any country or region.

2. Quality and Outline of the Review Conducted by PMDA

2.1 Drug substance

2.1.1 Generation and control of cell substrate

Human C5 was administered to rabbits to obtain antibodies, one of which with binding capacity to pH-dependent human C5 was then selected and humanized. Mutations were introduced into the variable regions to improve the C5 binding activity, [redacted] solubility and to [redacted]. The constant regions were replaced with constant regions of modified human immunoglobulin G1 (IgG1) heavy chains and human κ-type light chains for the purpose of [redacted]. The expression construct for crovalimab was created by inserting a gene fragment encoding this antibody into the expression vector.

Characterization, purity tests, and genetic stability tests were performed on the master cell bank (MCB), working cell bank (WCB), and cells cultured beyond the limit of *in vitro* cell age (LIVCA) in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for

Human Use (ICH) Guidelines Q5A (R1), Q5B, and Q5D. The test results demonstrated genetic stability during production. In the tested items, no viral or non-viral adventitious agents were detected, other than endogenous retrovirus-like particles commonly found in rodent-derived cell lines.

Both the MCB and WCB are stored in the gas phase of liquid nitrogen. While [redacted], WCB is newly prepared as-needed.

2.1.2 Manufacturing process

The manufacturing process of the drug substance consists of thawing of WCB, seed culture, inoculation culture, production culture, harvesting, [redacted] chromatography, [redacted] treatment (viral inactivation), [redacted] filtration, [redacted] chromatography, [redacted] filtration 1, [redacted] chromatography, virus removal [redacted], [redacted] filtration 2/[redacted] filtration, [redacted] filtration 3 and conditioning/filtration/filling, storage/testing, and storage.

Critical steps are [redacted].

Process validation is performed on the drug substance manufacturing process on a commercial scale.

2.1.3 Safety evaluation of adventitious agents

With the exception of CHO cell lines, the host cells, no raw materials of biological origin are used in the process of manufacturing the drug substance.

Impurities were studied on the MCB, WCB, and cells cultured beyond LIVCA [see Section 2.1.1]. Microbial limit testing, [redacted] testing, mycoplasma testing, [redacted] testing, *in vitro* virus testing, and transmission electron microscopy were performed on pre-harvest unprocessed bulk manufactured on a commercial scale. In the tested items no viral or non-viral adventitious agents were detected. These tests performed on pre-harvest unprocessed bulk, except for [redacted] tests and [redacted], are specified as in-process control tests.

The viral clearance study was performed using model viruses, and the results demonstrated a certain capability of purification process in viral clearance (Table 1).

Table 1. Results of viral clearance studies

Manufacturing process	Virus reduction factor (log_{10})		
	Xenotropic murine leukemia virus	Minute virus of mice	Simian virus 40
[redacted] chromatography	[redacted]	[redacted]	[redacted]
[redacted] treatment (virus inactivation)	[redacted]	[redacted]	[redacted]
[redacted] chromatography	[redacted]	[redacted]	[redacted]
Virus removal [redacted] [a)]	[redacted]	[redacted]	[redacted]
Overall reduction factor	≥10.64	≥7.61	3.80

a) The virus removal [redacted] was performed only [redacted]. The applicant explained that when the virus reduction factors for [redacted] are [redacted], overall reduction factors for [redacted] and [redacted] are [redacted] and [redacted], respectively.

2.1.4 Manufacturing process development

The major changes to the manufacturing process during the development of the drug substance are shown below (the manufacturing processes are referred to as Process 1, Process 2, Process 3, and the proposed commercial process). The formulations produced from the drug substances derived from the Process 3 or the proposed commercial process were used in the phase III studies.

- From Process 1 to Process 2: changes in [redacted], [redacted] step, [redacted], and [redacted]
- From Process 2 to Process 3: introduction of [redacted], changes in [redacted], [redacted] step, [redacted] step, formulation, and [redacted]
- From Process 3 to the proposed commercial process: changes in [redacted], [redacted], [redacted] step, and [redacted]

According to these changes in the manufacturing process, comparability was evaluated with respect to the quality attributes. The results demonstrated the comparability of the drug substance before and after the change.

2.1.5 Characterization

2.1.5.1 Structure and properties

Table 2 summarizes the characterization performed.

Table 2. Evaluation items for characterization

Primary/higher-order structure	Amino acid sequence, molecular weight, disulfide bonds, free thiol groups, N- and C-terminal amino acid sequence, glycation, higher-order structure
Physicochemical properties	Size variants, charge variants, absorption coefficient
Carbohydrate structure	N-linked oligosaccharide
Biological properties	Binding affinity for C5
	Binding affinity for FcγR (FcγRIa, FcγRIIa [redacted] and [redacted], FcγRIIb, FcγRIIIa [redacted] and [redacted], FcγRIIIb [redacted] and [redacted]), binding affinity for FcRn, C1q binding activity
	Activity to inhibit cell membrane attack, hemolysis inhibition activity

Main results of the investigation of biological properties are as follows.

- The binding affinity for C5 was evaluated by surface plasmon resonance (SPR). The results showed that crovalimab binds to human C5 and cynomolgus monkey C5 in antigen concentration-dependent and [redacted]-dependent manners.
- The binding affinity for fragment crystallisable (Fc) γ receptor (FcγR) was evaluated by SPR. The binding affinity of crovalimab for FcγR was significantly [redacted] compared to that of the antibodies with the Fc region of the native human IgG1. Based on the results, the applicant explained that the main mechanism of action associated with the efficacy of crovalimab [redacted]

[redacted].

- The binding affinity for neonatal Fc receptor (FcRn) was evaluated by SPR. The results showed that the binding affinity of crovalimab for FcRn was [redacted] as compared to that of the antibodies with the Fc region of the native human IgG1.
- Complement component C1q (C1q) binding activity was evaluated by enzyme-linked immunosorbent assay (ELISA). The results showed that the C1q binding activity of crovalimab was significantly [redacted] as compared to that of the antibodies with the Fc region of human IgG1. Based on the results, the applicant explained that crovalimab is [redacted].
- The activities to inhibit cell membrane attack were evaluated by the test system using [redacted]. In this assay, the reaction of [redacted] in plasma released to [redacted] from [redacted] after adding [redacted] was quantitatively determined using [redacted] as an indicator. The complement-dependent inhibition activities of crovalimab against cell membrane attack were detected.
- A chicken red blood cell assay was performed using human, cynomolgus monkey, rabbit, and rat sera. Crovalimab inhibited chicken red blood cell hemolysis induced by the complement system in human and cynomolgus monkey sera.

2.1.5.2 Product-related substances/Product-related impurities

No product-related substances were identified. Based on the characterization results and other data in Section 2.1.5.1, Impurity A, Impurity B, Impurity C, Impurity D, Impurity E, Impurity F, Impurity G, Impurity H, Impurity I, Impurity J, and Impurity K were identified as product-related impurities. Of these, Impurities A and B are controlled by the specifications for the drug substance and the drug product, while Impurity K is controlled by the specifications for the drug substance. The rest of the product-related impurities are confirmed to be controlled at a low level or a specified level in the manufacturing process, and are not controlled by routine testing.

2.1.5.3 Process-related impurities

Host cell protein (HCP), host cell deoxyribonucleic acid (DNA), Impurity N, Impurity O, Impurity P, and Impurity Q were identified as process-related impurities. Impurity L, Impurity M, Impurity N, and Impurity O are confirmed to be adequately removed during the manufacturing process. The risk assessment found that Impurities P and Q do not require control. Impurities L and M are controlled by the in-process testing.

2.1.6 Control of drug substance

The proposed specifications for the drug substance include content, description, identification (peptide mapping), osmolality, pH, purity test (ion exchange chromatography [IEC], non-reduced capillary electrophoresis sodium dodecyl sulfate [CE-SDS], size exclusion liquid chromatography [SEC]), bacterial endotoxins, microbial limits, [redacted] poloxamer 188, potency ([redacted]), and assay (ultraviolet visible spectrophotometry).

2.1.7 Stability of drug substance

Table 3 shows the main stability studies for the drug substance.

Table 3. Summary of main stability studies for the drug substance

	Number of batches[a)]	Storage condition	Study period	Storage container
Long-term	**4**	**[redacted] ± [redacted]°C**	**[redacted] months[b)]**	**[redacted]**
Accelerated	**4**	**[redacted] ± [redacted]°C**	**[redacted] months**	**[redacted] bag**
Stress	**2**	**[redacted] ± [redacted]°C/[redacted]% RH**	**[redacted] weeks**	**[redacted] container**

a) The drug substance was manufactured by the proposed commercial process.
b) The stability testing is ongoing up to [redacted] months.

The long-term study showed no changes in quality attributes throughout the test period.

The accelerated testing revealed the following tendencies: an increase in [redacted] in [redacted], a decrease in [redacted], an increase in [redacted] in [redacted], an increase in [redacted] in [redacted], an increase in [redacted], and an increase in [redacted].

In the stress testing, [redacted] tended to decrease. The changes in [redacted], [redacted], and [redacted] were greater than those observed in the accelerated testing.

Based on the above results, a shelf life of [redacted] months was proposed for the drug substance when stored at [redacted] ± [redacted]°C using [redacted] bags.

2.2 Drug product

2.2.1 Description and composition of drug product and formulation development

The drug product is an aqueous injection solution in a 2-mL glass vial containing crovalimab 340 mg/2 mL. The drug product contains L-histidine, L-aspartic acid, L-arginine hydrochloride, poloxamer 188, and water for injection as excipients.

2.2.2 Manufacturing process

The manufacturing process for the drug product consists of drug solution preparation, aseptic filtration, filling/capping, tightening, inspection, storage, packaging/labeling, and storage/testing.

[redacted] and [redacted] are defined as critical steps.

Process validation is performed on a commercial scale for the manufacturing process of the drug product.

2.2.3 Manufacturing process development

The major changes to the manufacturing process during the development of the drug product are as follows (the manufacturing processes are referred to as Process A, Process B, Process C, Process D,

Process E, the proposed commercial process 1, and proposed commercial process 2). In the phase III studies, formulations produced by Process E or by the proposed commercial process 1 were used.

- From Process A to Process B: changes in formulation, [redacted], and [redacted]
- From Process B to Process C: changes in [redacted] and [redacted]
- From Process C to Process D: changes in [redacted] and [redacted]
- From Process D to Process E: changes in [redacted]
- From Process E to the proposed commercial process 1: Changes in [redacted]
- From the proposed commercial process 1 to proposed commercial process 2: Addition of [redacted]

With these manufacturing process changes, comparability was evaluated with respect to the quality attributes. The results demonstrated the comparability of the drug product before and after the changes.

2.2.4 Control of drug product

The proposed specifications for the drug product include strength, description, identification (peptide mapping), osmolality, pH, purity tests (IEC, non-reduced CE-SDS, and SEC), bacterial endotoxins, extractable volume, foreign insoluble matter, insoluble particulate matter, sterility, potency ([redacted]), and assay (ultraviolet visible spectrophotometry).

2.2.5 Stability of drug product

Table 4 shows main stability studies for the drug product.

Table 4. Summary of main stability studies for the drug product

	Number of batches[a)]	Storage condition	Study period	Storage container
Long-term	**3**	**5 ± 3°C**	**30 months[b)]**	**Glass vial and butyl rubber stopper**
Accelerated	**7**	**25 ± [redacted]°C/60% RH**	**6 months**	
Stress	**10**	**40 ± [redacted]°C/75% RH**	**4 weeks**	
Photostability	**1**	**Overall illumination of ≥1.2 million lux·h and integrated near ultraviolet energy of ≥200 W·h/m^2**		

a) The drug substance and the drug product were produced using the proposed commercial processes.
b) The stability testing is ongoing up to [redacted] months.

The long-term testing revealed the following tendencies: increased [redacted] and decreased [redacted] in [redacted], increased [redacted] in [redacted], and increased [redacted] in [redacted].

The changes observed in the accelerated testing and stress testing were greater than those observed in the long-term testing.

Photostability testing showed that the drug product is photolabile.

Based on the above, a shelf life of 30 months was proposed for the drug product when stored at 2°C to 8°C in a glass vial with a butyl rubber stopper (primary packaging) in a paper box protected from light.

2.3 Quality control strategy

Based on the following analyses, the control method for the quality attributes of crovalimab was formulated. The control method consists of the control of process parameters, in-process control testing,

and specifications [for product-related impurities and process-related impurities, see Sections 2.1.5.2 and 2.1.5.3].

- Identification of critical quality attributes (CQAs)

  The following CQAs were identified based on the information obtained during the development of crovalimab and relevant findings.

  CQAs: Description (color, clarity, and appearance), [redacted], bacterial endotoxins, microbial limits, content of formulation buffer solution, [redacted], poloxamer 188 content, [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], host cell DNA, HCP, identity (being identical to those of the intended product), [redacted], [redacted], mycoplasma, osmolality, [redacted], pH, potency ([redacted]), [redacted] and [redacted], protein content, purity, [redacted], [redacted], [redacted], sterility, insoluble particulate matter, virus, foreign insoluble matter, extractable volume

- Characterization of the processes

  Based on the risk assessment on the process parameters, critical process parameters which affect CQAs and critical performance indicators were identified.

2.R Outline of the review conducted by PMDA

Based on the submitted data and the review in the following section, PMDA concluded that the quality of the drug substance and drug product is adequately controlled.

2.R.1 Novel excipients

The drug product contains L-histidine, L-aspartic acid, and L-arginine hydrochloride, which maximum daily doses are greater than existing subcutaneous injection. Therefore, all these substances were considered new excipients and subjected to the following assessments.

2.R.1.1 Specifications and stability

L-histidine, L-aspartic acid, and L-arginine hydrochloride conform to in the Japanese Pharmacopoeia. PMDA concluded that there are no problems with specifications and stability.

2.R.1.2 Safety

Based on the results of toxicity studies of crovalimab, which used vehicles containing L-histidine, L-aspartic acid, or L-arginine hydrochloride, the results of clinical studies with the proposed commercial formulation or formulations identical to it, and literature data, PMDA concluded that the maximum daily doses of L-histidine, L-aspartic acid, and L-arginine hydrochloride contained in the subcutaneous formulation are unlikely to pose safety problems.

3. Non-clinical Pharmacology and Outline of the Review Conducted by PMDA

Studies of primary pharmacodynamics assessed binding affinity of crovalimab for C5 and the inhibition of complement activity *in vitro* and *in vivo*. The secondary pharmacodynamic study were conducted on the interaction of crovalimab binding to the Fc region or to C1q. Safety pharmacology studies included the investigation of effects on the cardiovascular system, central nervous system, and respiratory system. Pharmacodynamic drug interaction studies were performed to investigate the interaction with other anti-C5 antibodies.

3.1 Primary pharmacodynamics

3.1.1 *In vitro* studies

3.1.1.1 Binding affinity for C5 (CTD 4.2.1.1-1, 4.2.1.1-2)

The binding affinity of crovalimab for human C5 or cynomolgus monkey C5 was assessed by SPR. The equilibrium dissociation constant (K_D) of crovalimab at pH 7.4 was 0.172 nmol/L for human C5 and 0.200 nmol/L for cynomolgus monkey C5. The dissociation rates of crovalimab from human C5 and that from cynomolgus monkey C5 were faster at pH 6.0 compared to at pH 7.4 for both species.

The binding affinity of crovalimab for mouse C5 or rat C5 was assessed by SPR. The K_D of crovalimab for mouse C5 was 14.6 nmol/L at pH 7.4, while that for rat C5 was incalculable.

3.1.1.2 Inhibition of complement activity (CTD 4.2.1.1-3)

Crovalimab was added to human, cynomolgus monkey, rabbit, or rat serum, and antibody-sensitized chicken red blood cells were added to the serum to investigate the inhibition of complement activity by crovalimab. Crovalimab inhibited antibody-sensitized chicken red blood cell hemolysis in a dose-dependent manner in human and cynomolgus monkey sera, with a half maximal inhibitory concentration (IC_{50}) of 0.834 and 0.958 μg/mL, respectively. The inhibition of hemolysis by crovalimab was <50% in rats or rabbits at the highest concentration studied (301 μg/mL).

3.1.2 *In vivo* studies

3.1.2.1 Inhibition of complement activity (CTD 4.2.2.2-1, 4.2.3.2-1, 4.2.3.2-2, 4.2.3.2-3)

In a pharmacokinetic study in cynomolgus monkeys [see Section 4.1.1], the inhibition of complement activity by crovalimab was investigated using antibody-sensitized chicken red blood cells. While no inhibitory effect of crovalimab was observed on complement activity at a single intravenous dose of crovalimab 0.8 mg/kg, a single intravenous dose of crovalimab 4 or 20 mg/kg and a single subcutaneous dose of crovalimab 4 mg/kg inhibited complement activity. The inhibition increased in a dose-dependent manner during a period in which the complement activity was ≤20% the baseline level.

In a 2-week repeated dose toxicity study in cynomolgus monkeys, the inhibition of complement activity by crovalimab was investigated using antibody-sensitized chicken red blood cells. The inhibition of complement activity was observed at the every-other-week intravenous doses of crovalimab 4 or

100 mg/kg (2 doses in total) and at the once-weekly subcutaneous doses of crovalimab 4 or 40 mg/kg (3 doses in total).

In 4-week intravenous and 21-week subcutaneous dose toxicity studies in cynomolgus monkeys [see Section 5.2], crovalimab 10, 40, or 160 mg/kg was administered intravenously once weekly for 4 weeks, followed by once weekly subcutaneous crovalimab 40 mg/kg for 21 weeks, and complement activity levels were measured. Complement activity levels decreased in all treatment groups of crovalimab. In the group that had a 17-week recovery period, without subcutaneous administration, after repeated intravenous doses of crovalimab, complement activity levels tended to recover in 2 of 3 males and 2 of 3 females in the crovalimab 10 mg/kg group, and 1 of 3 males in the 40 mg/kg group, while complement activity levels remained low in the rest of the animals during the recovery period.

In a 26-week repeated dose toxicity study in cynomolgus monkeys [see Section 5.2], crovalimab 10, 40, or 100 mg/kg was administered subcutaneously once weekly for 26 weeks (only the initial dose was 100 mg/kg, administered intravenously) or crovalimab 160 mg/kg was administered intravenously every 2 weeks for 26 weeks, and complement activity levels were measured. Complement activity levels decreased in all crovalimab groups. During the 26-week recovery period, complement activity levels recovered or tended to recover in 1 of 2 males and 2 of 2 females in the 10 mg/kg subcutaneous group, and 2 of 2 females in the 40 mg/kg subcutaneous group.

3.2 Secondary pharmacodynamics

3.2.1 Binding affinity for Fc region (CTD 4.2.1.2-1)

The binding affinity of crovalimab for human FcγR and cynomolgus monkey FcγR at pH 7.4 was investigated by SPR. The binding affinity of crovalimab for human FcγR and cynomolgus monkey FcγR was almost undetectable, and lower than that of trastuzumab (genetical recombination), the control. The binding affinity of crovalimab for human FcRn and cynomolgus monkey FcRn at pH 6.0 was investigated by SPR. The K_D values of crovalimab for human FcRn and cynomolgus monkey FcRn were 0.170 and 0.178 μmol/L, respectively, which were approximately 1/10 of those of trastuzumab (genetical recombination) (1.73 and 1.98 μmol/L, respectively).

3.2.2 Binding activity to C1q (CTD 4.2.1.2-2)

The binding activity of crovalimab to human C1q was investigated by ELISA. Rituximab (genetical recombination), the control, showed concentration-dependent binding activity to C1q, while the binding activities of crovalimab and natalizumab (genetical recombination) to C1q were significantly lower than that of rituximab (genetical recombination).

3.3 Safety pharmacology

Table 5 summarizes the results of safety pharmacology studies.

Table 5. Summary of safety pharmacology studies

Category	Test system	Evaluation items/methods	Crovalimab regimen	Findings	CTD
Cardiovascular system	Cynomolgus monkeys (1) 2-week IV and SC administration (2) 4-week IV and 21-week SC administration (3) 26-week IV and SC administration	Electrocardiogram (telemetry), blood pressure	(1) IV: 4 or 100 mg/kg every 2 weeks SC: 4 or 10 mg/kg once weekly (2) IV: 10, 40, or 160 mg/kg once weekly SC: 40 mg/kg once weekly (3) IV: 160 mg/kg every 2 weeks SC: initial dose 100 mg/kg IV dose followed by once weekly SC doses of 10, 40, or 100 mg/kg	No effects	(1) 4.2.3.2-1 (2) 4.2.3.2-2 (3) 4.2.3.2-3
Central nervous system		Clinical signs, functional observational battery		No effects	
Respiratory system		Respiratory state observation		No effects	

3.4 Pharmacodynamic drug interactions

3.4.1 Interaction with other anti-C5 antibodies (CTD 4.2.1.4-2)

The characteristics of the drug-target-drug complex (DTDC) formed with crovalimab and anti-C5 antibody (ECZ)[1)] were investigated at pH 7.4 or pH 6.0 by SEC. Crovalimab and ECZ recognize different C5 epitopes. The molar ratio of crovalimab to C5, which are DTDC components, changed in a crovalimab concentration-dependent manner. It was estimated that when the mixture ratio of crovalimab, recombinant human C5, and ECZ were roughly equimolar, DTDC would be largest, consisting of 8 antibodies and ≥8 recombinant human C5 molecules. Crovalimab dissociated at pH 6.0 from the DTDC formed at pH 7.4.

3.R Outline of the review conducted by PMDA

3.R.1 Pharmacological action

The applicant's explanation about the pharmacological action of crovalimab:

PNH is an extremely rare, acquired clonal hematopoietic stem cell disorder. Patients with PNH carry *PIGA* gene mutation, which causes their red blood cells to lose glycosyl-phosphatidylinositol-anchored proteins, including complement regulators CD55 and CD59(*Cell.* 1993;73:703-11, *N Engl J Med.* 1994;330:249-55). The complement regulator CD59 blocks MAC formation on the cell surface, thereby preventing complement-mediated red blood cell and platelet from being damaged. This mechanism causes patients with red blood cells deficiency in CD59 to have intravascular hemolysis, leading to anemia, hemoglobinuria, and life-threatening thromboembolic events.

Crovalimab is a humanized anti-C5 monoclonal antibody that binds to C5 with high affinity, inhibiting its cleavage to C5a and C5b and preventing MAC formation, thereby inhibiting intravascular hemolysis in patients with PNH.

In primary pharmacodynamic studies, crovalimab bound to human C5 and cynomolgus monkey C5 in a pH-dependent manner, and inhibited antibody-sensitized chicken red blood cell hemolysis in human and cynomolgus monkey sera in a concentration-dependent manner. In pharmacokinetic studies and

[1)] An anti-C5 antibody synthesized at a laboratory, which has the same amino acid sequence as eculizumab (genetical recombination).

toxicity studies in cynomolgus monkeys, crovalimab 4 to 160 mg/kg inhibited complement activity. Therefore, crovalimab is expected to have efficacy against PNH through the inhibition of C5.

PMDA's view:

Based on the submitted data from the primary pharmacodynamic studies, the applicant's explanation is reasonable, and crovalimab has promising efficacy in the treatment of PNH. Based on the submitted safety pharmacology study data, clinical use of crovalimab is unlikely to affect the cardiovascular, central nervous, or respiratory system significantly.

4. Non-clinical Pharmacokinetics and Outline of the Review Conducted by PMDA

The pharmacokinetics of intravenous or subcutaneous crovalimab was evaluated in monkeys. The plasma concentrations of crovalimab were measured by ELISA with a lower limit of quantitation of 0.05 μg/mL.

4.1 Absorption

4.1.1 Single-dose studies (CTD 4.2.2.2-1)

Table 6 shows plasma pharmacokinetic parameters of a single intravenous or subcutaneous dose of crovalimab in male monkeys.

Table 6. Plasma pharmacokinetic parameters after single administration of crovalimab to monkeys

Route of administration	Dose (mg/kg)	C_{max}[a)] (μg/mL)	t_{max} (day)	$AUC_{0-\infty}$ (μg·day/mL)	$t_{1/2}$ (day)	Bioavailability[b)] (%)
IV	0.8	19.1	–	305	19.9	–
	20	457	–	7,040	12.0	–
SC	4	41.9	2	1,010	15.0	69.1

Mean of data from 2 animals; "–," not applicable

a) In intravenous administration data, plasma crovalimab concentration C_0 at t = 0 was obtained by extrapolation

b) Calculated using dose-corrected $AUC_{0-\infty}$ after intravenous or subcutaneous administration

4.1.2 Repeated dose studies (CTD 4.2.3.2-2 and 4.2.3.2-3)

Toxicokinetics of crovalimab was investigated in male and female monkeys treated once weekly for 4 weeks intravenously or for 21 weeks subcutaneously. Table 7 shows plasma pharmacokinetic parameters. The C_{max} and AUC_{0-7day} values of intravenous doses increased in a generally dose-proportional manner, with higher values on Day 22 than at the initial dose. The toxicokinetics study suggested that C_{max} and AUC_{0-7day} would reach a steady state on Day 71 or later by subcutaneous administration. No clear sex differences were noted by route of administration.

Table 7. Plasma crovalimab pharmacokinetic parameters after 4-week intravenous or 21-week subcutaneous administration to monkeys

Route of administration	Crovalimab dose (mg/kg)	Sex	N	Timepoint (Day)	C_{max} [a)] (μg/mL)	t_{max} (days)	$AUC_{0\text{-}7day}$ (μg·day/mL)
IV	10	M	4	1	235 ± 39	–	846 ± 127
			4	22	449 ± 51	–	2,310 ± 310
		F	5	1	196 ± 23	–	729 ± 80
			3	22	380 ± 41	–	1,940 ± 90
	40	M	5	1	940 ± 90	–	3,330 ± 300
			5	22	1,630 ± 130	–	7,740 ± 1,030
		F	5	1	811 ± 60	–	3,010 ± 230
			5	22	1,750 ± 90	–	8,340 ± 500
	160	M	6	1	3,300 ± 290	–	12,200 ± 1,300
			6	22	5,800 ± 630	–	29,900 ± 4,100
		F	6	1	2,740 ± 280	–	10,300 ± 700
			5	22	5,690 ± 640	–	29,100 ± 1,000
SC	40	M	1	1	452 [b)]	3.0 [b)]	2,930 [b)]
			2	71	2,070 [c)]	3.0 [c)]	14,100 [c)]
			1	141	2,160 [b)]	7.0 [b)]	14,500 [b)]
		F	3	1	384 ± 25	3.0	2,200 ± 80
			3	71	1,450 ± 490	2.0	9,330 ± 3,140
			2	141	1,680 [c)]	0.7 [c)]	9,700 [c)]

Mean ± standard deviation; "–," not applicable
a) In intravenous administration data, plasma crovalimab concentration C_0 at t = 0 was obtained by extrapolation
b) Individual value (N = 1)
c) Mean of 2 animals

The toxicokinetics of crovalimab was investigated in male and female monkeys treated every 2 weeks for 26 weeks intravenously or once weekly for 26 weeks subcutaneously. Table 8 shows plasma pharmacokinetic parameters. The study suggested that C_{max} and $AUC_{0\text{-}14day}$ increased generally in a dose-proportional manner and crovalimab exposure reached a steady state on Day 113 or later in the intravenous group and on Day 57 or later in the subcutaneous group. No clear sex differences were noted.

Table 8. Plasma crovalimab pharmacokinetic parameters after 26-week administration of crovalimab to monkeys

Route of administration	Crovalimab dose (mg/kg)	Sex	N	Timepoint (Day)	C_{max} [a)] (μg/mL)	$AUC_{0\text{-}14day}$ (μg·day/mL)	$t_{1/2}$ (days)
IV	160	M	5	1	3,720 ± 490	23,900 ± 1,900	NC
			5	57	5,610 ± 1,150	55,600 ± 17,300	NC
			5	113	7,070 ± 1,070	63,600 ± 15,200	NC
			5	169	8,180 ± 2,360	68,300 ± 17,700	NC
			2	351	NC	NC	77.3 [c)]
		F	5	1	2,910 ± 390	19,000 ± 1,600	NC
			5	57	6,060 ± 1,080	54,400 ± 13,100	NC
			4	113	6,710 ± 280	66,300 ± 7,200	NC
			4	169	7,570 ± 510	69,100 ± 9,200	NC
			2	351	NC	NC	37.6 [c)]
SC [b)]	10	M	4	1	2,270 ± 400	10,600 ± 1,700	NC
			4	8	1,030 ± 200	6,370 ± 720	NC
			3	57	877 ± 37	5,390 ± 510	NC
			2	120	995 [c)]	6,060 [c)]	NC
			2	176	1,070 [c)]	6,610 [c)]	NC
		F	5	1	1,820 ± 130	8,470 ± 1,150	NC
			5	8	967 ± 90	6,070 ± 620	NC
			5	57	834 ± 104	4,580 ± 560	NC
			3	120	874 ± 93	5,200 ± 150	NC
			3	176	786 ± 84	5,180 ± 480	NC
	40	M	5	1	2,130 ± 310	9,730 ± 2,040	NC
			5	8	1,230 ± 180	7,900 ± 1,190	NC
			5	57	1,900 ± 710	11,900 ± 4,100	NC
			5	120	2,580 ± 820	16,000 ± 4,200	NC
			5	176	2,500 ± 420	16,400 ± 2,700	NC
		F	5	1	1,570 ± 90	7,880 ± 580	NC
			5	8	1,050 ± 140	6,660 ± 960	NC
			4	57	1,950 ± 310	11,700 ± 2,500	NC
			4	120	2,290 ± 250	14,400 ± 2,100	NC
			4	176	2,370 ± 100	14,700 ± 800	NC
	100	M	4	1	2,390 ± 300	10,800 ± 900	NC
			4	8	1,600 ± 80	9,780 ± 280	NC
			4	57	4,550 ± 750	29,800 ± 4,000	NC
			4	120	5,700 ± 700	36,800 ± 4,400	NC
			4	176	5,430 ± 660	36,100 ± 4,900	NC
		F	5	1	1,830 ± 190	8,480 ± 490	NC
			5	8	1,680 ± 30	10,500 ± 200	NC
			5	57	4,160 ± 600	25,400 ± 3,300	NC
			5	120	4,050 ± 560	26,200 ± 4,400	NC
			5	176	4,960 ± 1,060	31,600 ± 5,300	NC

Mean ± standard deviation; NC, not calculated

a) In intravenous administration data, plasma crovalimab concentration C_0 at t = 0 was obtained by extrapolation

b) As the initial dose, 100 mg/kg was administered intravenously. On Day 8 and thereafter, each dose level was administered subcutaneously once weekly.

c) Mean of 2 animals

4.2 Distribution

For being a humanized IgG1 monoclonal antibody, crovalimab's antigen-nonspecific distribution was assumed to be similar to that of endogenous IgG1. Distribution volume of crovalimab in monkeys[2)] indicated the unlikeliness of tissue migration. For these reasons, no non-clinical pharmacokinetic studies were conducted on the distribution of crovalimab.

4.3 Metabolism

Crovalimab, a humanized IgG1 monoclonal antibody, was assumed to be degraded into peptides and amino acids after intravenous or subcutaneous administration. Therefore, no non-clinical pharmacokinetic studies were conducted on the metabolism of crovalimab.

[2)] In a single-dose study in male monkeys [see Section 4.1.1], a volume of distribution of 69.5 to 71.8 mL/kg at steady state was calculated after intravenous administration of crovalimab 0.8 to 20 mg/kg.

4.4 Excretion

Because crovalimab is a humanized IgG1 monoclonal antibody, peptides and amino acids are produced during its metabolization and excreted or used for new protein production via normal metabolic pathways. Therefore, no non-clinical pharmacokinetic studies were conducted on the excretion of crovalimab.

Although yet to be studied, the excretion of crovalimab into breast milk is possible as crovalimab is an IgG antibody, according to a report on the distribution of IgG antibodies in human breast milk (*Vaccine.* 2003;21:3374-6).

4.R Outline of the review conducted by PMDA

Based on the submitted non-clinical pharmacokinetic study data and the applicant's explanation, PMDA has concluded that non-clinical pharmacokinetics of crovalimab were evaluated appropriately.

5. Toxicity and Outline of the Review Conducted by PMDA

The applicant conducted repeated-dose toxicity studies, reproductive and developmental toxicity studies, and other toxicity studies. The following sections describe the results of the main studies.

5.1 Single-dose toxicity

No single-dose toxicity studies were conducted.

In the repeated-dose toxicity studies in cynomolgus monkeys, the evaluation data after the initial dose indicated no toxicity changes associated with crovalimab treatment.

5.2 Repeated-dose toxicity

A repeated-dose toxicity study was conducted in cynomolgus monkeys for up to 26 weeks (Table 9). The findings include arteritis and glomerulonephritis, which are considered to be caused by the formation of an immune complex consisting of crovalimab and the anti-drug antibody (ADA). However, protein structure varies across species, and the structure of crovalimab, an anti-human C5 antibody, is recognized as foreign body in cynomolgus monkeys. Therefore, the extrapolability of ADA-related findings from immunogenicity in animals to humans was considered low, which led to the conclusion that there were no toxicological findings possibly affecting human risk evaluation. The AUC at the maximum dose level in the 26-week repeated-dose toxicity study in cynomolgus monkeys was approximately 17 times the AUC at the subcutaneous doses (only the initial dose was administered intravenously) and approximately 18 times the AUC at the intravenous doses in clinical use.

Table 9. Summary of repeated-dose toxicity study results

Test system	Route of administration	Treatment duration	Dose	Major findings[a)]	No-observed adverse effect level (mg/kg/week)	CTD
Male/female cynomolgus monkeys	**IV or SC**	**IV[b)]: 4 weeks (5 doses in total), 17-week recovery period** **SC[b)]: 21 weeks (22 doses in total)**	**IV: 0,[c)] 10, 40, 160 mg/kg/week** **SC: 0,[c)] 40 mg/kg/week**	**At the end of treatment period** **IV:** **At ≥10, arteritis in multiple organs, immune complex deposition in arteritis lesion sites** **SC:** **At 40, inflammatory changes at the injection site of crovalimab (mononuclear cell infiltration)** **At the end of recovery period** **IV:** **At ≥10, arteritis in multiple organs, immune complex deposition in arteritis lesion sites**	**<10**	**4.2.3.2-2**
Male/female cynomolgus monkeys	**IV/SC or IV**	**26 weeks[d)] (SC,[e)] 27 doses in total; IV, 14 doses in total), 26-week recovery period**	**SC: 0,[c)] 10, 40, 100 mg/kg/week** **IV: 0,[c)] 160 mg/kg/2 weeks**	**At the end of treatment period** **SC:** **At ≥10, inflammatory changes at the injection site of crovalimab (mononuclear cell infiltration)** **At 100, arteritis in multiple organs (males)[f)]** **IV:** **At 160, arteritis in multiple organs,[f)] high creatinine, glomerulonephritis accompanied by urinary occult blood (males)** **At the end of recovery period** **SC:** **At 40, arteritis in multiple organs[g)]** **IV:** **At 160, arteritis in multiple organs (females)[g)]**	**10**	**4.2.3.2-3**

a) The studies detected blood ADAs and crovalimab-ADA immune complexes in blood of animals receiving crovalimab.
b) In the IV necropsy group, control animals were necropsied after receiving vehicle once weekly for 4 weeks intravenously. In the IV post-recovery necropsy group and the SC necropsy group, control animals were necropsied after concurrently receiving vehicle once weekly intravenously for 4 weeks and once weekly subcutaneously for 21 weeks.
c) A [redacted] mmol/L histidine-aspartate buffer (pH 6.0) containing [redacted] mmol/L arginine aspartate and [redacted] mg/mL poloxamer 188
d) In the control group, the first dose of vehicle was given intravenously. From the second dose onwards, doses were given subcutaneously once weekly and intravenously every 2 weeks.
e) In the crovalimab group, the first dose crovalimab 100 mg/kg was administered intravenously. From the second dose onwards, crovalimab was given subcutaneously.
f) Arteritis was noted in the heart and uterine cervix of 1 female animal in the control group.
g) Arteritis was noted in the kidney of 1 male animal in the control group.

5.3 Genotoxicity

Because crovalimab is an antibody produced by genetic engineering, no genotoxicity studies were conducted.

5.4 Carcinogenicity

Because crovalimab is an antibody produced by genetic engineering, no carcinogenicity studies were conducted.

5.5 Reproductive and developmental toxicity

An enhanced pre- and postnatal development (ePPND) study was conducted in cynomolgus monkeys (Table 10), which revealed no effects on the growth and development of pups. In the study, the AUC of crovalimab was approximately 13 times that in clinical use.

Table 10. Summary of reproductive and developmental toxicity study data

Study type	Test system	Route of administration	Treatment period	Dose	Major findings	No-observed adverse effect level (mg/kg/week)	CTD
ePPND	**Female Cynomolgus monkeys**	**IV and SC**	**Dams: Gestation day 20 to birth (once weekly)**	**First IV dose: 0,[a] 100 mg/kg Second dose onwards, SC: 0,[a] 10, 100 mg/kg/week**	**None[b]**	**100**	**4.2.3.5.3-1**

a) A [redacted] mmol/L histidine-aspartate buffer (pH 5.8) containing [redacted] mmol/L arginine hydrochloride, [redacted] mmol/L sodium chloride, and [redacted] mg/mL poloxamer 188.
b) Blood ADAs were detected in dams in the crovalimab group. Plasma crovalimab exposure and blood ADAs were noted in their F1 offspring.

5.6 Local tolerance

In the repeated-dose toxicity study in cynomolgus monkeys, crovalimab was well tolerated locally at intravenous and subcutaneous administration sites.

5.7 Other toxicity studies

A tissue cross-reactivity study and an *in vitro* cytokine release study were conducted. The findings indicated no toxicological concerns (Table 11).

Table 11. Summary of other toxicity study data

Study type	Test system	Test method	Major findings	CTD
Cross-reactivity	**Cynomolgus monkeys and human tissue panel**	**Cross reactivity was evaluated by immunostaining using crovalimab.**	**Crovalimab binding was observed in the blood vessel walls or around blood vessels, which was considered indicative of cross reactivity against secreted C5 protein present in plasma and extracellular matrix.**	**4.2.3.7.7-2**
***In vitro* cytokine release**	**Human blood**	**Crovalimab was added to human blood and concentrations of IL-6, IL-8, TNF-α, and IFN-γ were measured.**	**The levels of crovalimab-induced cytokines were comparable to those of cetuximab (genetical recombination), the low-risk comparator.**	**4.2.3.7.7-5**

5.R Outline of the review conducted by PMDA

Based on the submitted data, PMDA concluded that there are no toxicological concerns associated with the clinical use of crovalimab.

6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA

6.1 Summary of biopharmaceutic studies and associated analytical methods

Table 12 shows the formulations used in the clinical studies data, which were submitted as evaluation data for the present application.

Table 12. Formulations used in clinical studies

Clinical study	Formulation
Global phase I/II study (BP39144)	**Formulation A:** **A vial formulation containing 170 mg of crovalimab**
Global phase I/II study (BP39144)	**Formulation B:** **A prefilled syringe containing 340 mg of crovalimab**
Global phase I/II study (BP39144) **Global phase III study (BO42162)** **Global phase III study (BO42161)**	**Formulation C [a]:** **A vial formulation containing 170 mg of crovalimab**
Global phase I/II study (BP39144) **Global phase III study (BO42162)** **Global phase III study (BO42161)**	**Formulation D (proposed commercial formulation):** **A vial formulation containing 340 mg of crovalimab**

a) A vial formulation (1 mL) that has the same compositions and manufacturing process as the proposed commercial formulation (2 mL)

Crovalimab concentrations in human serum were measured by ELISA, with a lower limit of quantitation of 0.05 µg/mL. Complement activity levels in human serum were measured by immunoassay using liposome. Free C5 concentrations in human serum were determined by electrochemiluminescence immunoassay (ECLIA) and flow-through fluorescence immunoassay. Anti-drug antibodies, neutralizing antibodies, and total C5 concentrations in human serum were measured by ELISA.

6.2 Clinical pharmacology

6.2.1 Global phase I/II study in healthy adults and patients with PNH (CTD 5.3.3.1-1 and 5.3.3.1-2, Study BP39144 [(as of December 2023) ongoing since November 2016, data cut-off on November 1, 2021])

This study investigated pharmacokinetics and pharmacodynamics in healthy adults and patients with PNH following intravenous and subcutaneous administration of crovalimab. The study consisted of 4 parts. Part 1 involved healthy adults receiving single-dose treatment, while Parts 2, 3, and 4 targeted patients with PNH treated by multiple-dose administration [see Section 7.1.1 for the outline of studies and the efficacy and safety results].

Part 1: single-dose administration to healthy adults

Patients received a single intravenous dose of crovalimab 75 or 125 mg or placebo, or a single subcutaneous dose of crovalimab 100 mg or placebo.

All 15 patients who received the study drug (4 patients [placebo IV], 2 patients [placebo SC], 3 patients [75 mg IV], 3 patients [125 mg IV], and 3 patients [100 mg SC]) were included in the pharmacodynamic analysis set. A total of 9 patients with evaluable pharmacokinetic data were included in the pharmacokinetic analysis set.

Table 13 shows the pharmacokinetic parameters of crovalimab in serum.

Table 13. Serum pharmacokinetic parameters following single-dose administration of crovalimab to healthy adults

Route of administration	Crovalimab dose (mg)	N	C_{max} (µg/mL)	t_{max} [a] (day)	AUC_{last} (µg·day/mL)
IV	75	3	28.5 ± 1.95	0.0424 (0.0417, 0.500)	844 ± 183
	125	3	47.3 ± 17.8	0.084 (0.0424, 2.00)	962 ± 236
SC	100	3	15.6 ± 3.30	18.1 (4.00, 19.1)	672 ± 160

Mean ± standard deviation
a) Median (Min, Max)

Pharmacodynamic data showed the following: the complement activity levels (mean ± standard deviation) before the single-dose intravenous administration of crovalimab 75 mg and 125 mg were 51.0 ± 2.7 and 48.3 ± 7.1 U/mL, respectively, and 19.0 ± 11.5 and 10.3 ± 0.6 U/mL, respectively, at the end of intravenous administration. In the intravenous group, complement activity inhibition peaked at the end of intravenous administration. In contrast, in the subcutaneous group, no clear suppression of complement activity by crovalimab was noted.

After the administration of crovalimab, ADAs were detected in 33.3% (1 of 3) of patients in the 125-mg IV group and 33.3% (1 of 3) of patients in the 100-mg SC group. Neutralizing antibodies were not measured.

Parts 2, 3, and 4: multiple-dose administration to patients with PNH

Patients received intravenous and subcutaneous doses of crovalimab in accordance with the dosage regimens in Table 14.

Table 14. Dosage regimens

Part (Treatment group)	Study population	Dosage regimen
2	Complement inhibitor-naïve patients with PNH	Day 1: 375 mg IV Day 8: 500 mg IV Day 22: 1,000 mg IV From Day 36 onwards: 170 mg SC once weekly
3 (Arm A)	Patients with PNH switching from eculizumab to crovalimab	Day 1: 1,000 mg IV From Day 8 onwards: 170 mg SC once weekly[a)] From Day 64 onwards: 680 mg SC every 4 weeks
3 (Arm B)		Day 1: 1,000 mg IV From Day 8 onwards: 340 mg SC every 2 weeks
3 (Arm C)		Day 1: 1,000 mg IV From Day 8 onwards: 170 mg SC once weekly
4 (Arm A)	Complement inhibitor-naïve patients with PNH	Day 1: 1,000 mg IV Days 2, 8, 15, and 22: 340 mg SC From Day 29 onwards: 680 mg SC every 4 weeks
4 (Arm B)	Patients with PNH who switched from eculizumab to crovalimab	

a) Because the first 2 patients experienced suspected DTDC-related adverse events, 680 mg SC every 4 weeks was changed to 170 mg SC once weekly.

All 44 patients receiving the study drug (Part 2: 10 patients; Part 3: 7 patients in Arms A, 6 patients in Arm B, and 6 patients in Arm C; Part 4: 8 patients in Arm A and 7 patients in Arm B) were included in the pharmacokinetic analysis set and pharmacodynamic analysis set.

Table 15 shows the pharmacokinetic parameters of crovalimab in serum (estimated values) calculated based on the population pharmacokinetic analysis [see Section 6.2.4].

Table 15. Pharmacokinetic parameters in serum following multiple doses of crovalimab in patients with PNH (estimated values)

Part (Treatment group)	N	$C_{max,ss}$ (μg/mL)	$t_{max,ss}$ (day)	$AUC_{28day,ss}$ (μg·day/mL)	$C_{trough,ss}$ (μg/mL)
2	10	174 ± 69.5	5.1 ± 0.92	4,820 ± 1,930	173 ± 69.3
3 (Arm A)	7	203 ± 76.1	9.0 ± 1.3	5,200 ± 1,880	160 ± 54.7
3 (Arm B)	6	169 ± 46.6	6.3 ± 0.85	4,620 ± 1,290	159 ± 45.4
3 (Arm C)	6	254 ± 64.3	3.8 ± 0.66	7,060 ± 1,790	251 ± 62.9
4 (Arm A)	8	294 ± 78.7	9.0 ± 0.50	7,700 ± 1,970	244 ± 56.9
4 (Arm B)	7	242 ± 66.7	8.6 ± 1.1	6,130 ± 1,780	185 ± 60.2

Mean ± standard deviation

Pharmacodynamic data show that the complement activity levels remained near or below the lower limit of quantitation (10 U/mL) up to 20 weeks after the first dose both in treatment-naïve patients (Part 2 and Arm A in Part 4) and patients switching from eculizumab (Part 3 and Arm B in Part 4).

After the administration of crovalimab, ADAs were detected in 55.6% (10 of 18)[3)] of treatment-naïve patients and in 30.8% (8 of 26)[4)] of switching patients. Neutralizing antibodies were not measured.

DTDCs were detected in all patients switching from eculizumab to crovalimab (Part 3 and Arm B in Part 4). As of Day 22, the mean proportion of patients experiencing DTDC formation was lower by 56% in Part 4 Arm B than in Part 3 Arm A.

6.2.2 Global phase III study (CTD 5.3.5.1-1, Study BO42162 [(as of December 2023) ongoing since October 2020, data cut-off on May 31, 2023])

This study investigated pharmacokinetics and pharmacodynamics in complement inhibitor-naïve Japanese patients and non-Japanese patients with PNH following intravenous and subcutaneous administration of crovalimab [see Section 7.2.1 for the outline of studies and the efficacy and safety results].

The study consisted of 2 parts, the 24-week primary evaluation period (crovalimab or eculizumab treatment) and the extension period of up to 5 years (crovalimab treatment).

Patients received intravenous and subcutaneous crovalimab or intravenous eculizumab in the primary evaluation period through Week 24 (Day 169), and subcutaneous crovalimab for up to 5 years in the extension period according to the dosage regimens in Table 16.

[3)] Anti-drug antibodies were not detected in any patients at baseline.
[4)] At baseline, ADAs were detected in 4 of 8 patients.

Table 16. Dosage regimens

Body weight	Crovalimab			Eculizumab	
	Day 1	Days 2, 8, 15, and 22	Day 29 onwards every 4 weeks	Days 1, 8, 15, and 22 (once weekly)	Day 29 onwards every 2 weeks
≥40 kg and <100 kg	1,000 mg IV	340 mg SC	680 mg SC	600 mg IV	900 mg IV
≥100 kg	1,500 mg IV	340 mg SC	1,020 mg SC		

Table 17 shows the serum crovalimab concentrations. Based on the results, serum crovalimab concentrations reached a steady state by 13 weeks after the first dose and would remain stable up to Week 25 in all treatment groups.

Table 17. Serum crovalimab concentrations (trough concentrations) following multiple dose administration of crovalimab in patients with PNH (μg/mL)

		Crovalimab	Eculizumab	Arm C[a)]
Primary evaluation period	Day 1	362 [316, 407] (134)	–[b)]	281 [118, 443] (6)
	Day 8	253 [240, 266] (128)	–[b)]	238 [169, 308] (5)
	Day 15	260 [248, 273] (127)	–[b)]	287 [197, 376] (6)
	Day 29	298 [283, 314] (125)	–[b)]	349 [244, 453] (6)
	Day 57	283 [267, 299] (126)	–[b)]	293 [220, 366] (5)
	Day 85	262 [246, 277] (128)	–[b)]	268 [170, 366] (4)
	Day 169	241 [226, 256] (121)	–[b)]	267 [212, 321] (5)
Extension period	Day 1[c)]	–	348 [317, 378] (65)[d)]	–
	Day 8[c)]	–	272 [254, 290] (67)[d)]	–
	Day 15[c)]	–	262 [240, 284] (60)[d)]	–
	Day 29[c)]	–	274 [253, 296] (64)[d)]	–
	Day 57[c)]	235 [221, 248] (113)	273 [215, 330] (59)[d)]	–
	Day 85[c)]	–	233 [210, 255] (43)[d)]	–
	Day 169[c)]	232 [211, 254] (72)	235 [213, 257] (36)[d)]	–

Mean [95% CI] (N); "–," not applicable

a) The descriptive analysis part in which crovalimab was administered to complement inhibitor-naïve patients with PNH aged <18 years

b) Eculizumab was administered.

c) The number of days from the start of crovalimab treatment in the extension period. Day 1 in the extension period for the crovalimab group and Arm C was the same day as Day 169 in the primary evaluation period.

d) Crovalimab was administered (see Table 16 for the dosage regimens).

Table 18 shows the complement activity levels in each treatment group. In all treatment groups, complement activity levels decreased to below the lower limit of quantitation (10 U/mL) by Week 2 in the primary evaluation period. In the eculizumab group, and the effect lasted even after switching from eculizumab to crovalimab.

Table 18. Complement activity levels (U/mL)[a)]

		Crovalimab	Eculizumab	Arm C[b)]
Primary evaluation period	Day 1	49.7 [47.7, 51.8] (130)	48.8 [45.7, 51.9] (68)	49.2 [36.8, 61.6] (6)
	Day 8	5.76 [5.19, 6.33] (128)	13.8 [10.7, 16.8] (67)	5.00 [c)] (5)
	Day 15	5.72 [5.27, 6.18] (129)	9.18 [7.01, 11.4] (66)	5.00 [c)] (6)
	Day 29	5.69 [5.22, 6.15] (125)	9.72 [6.88, 12.6] (67)	5.00 [c)] (6)
	Day 57	5.95 [5.24, 6.67] (126)	9.85 [6.73, 13.0] (67)	5.00 [c)] (5)
	Day 85	6.59 [5.45, 7.74] (126)	9.77 [6.59, 12.9] (66)	5.00 [c)] (4)
	Day 169	6.57 [5.52, 7.63] (127)	10.3 [7.05, 13.5] (64)	5.00 [c)] (5)
Extension period	Day 1 [d)]	–	10.1 [7.02, 13.1] (68)	–
	Day 8 [d)]	–	5.55 [5.04, 6.07] (66)	–
	Day 15 [d)]	–	5.83 [5.07, 6.59] (60)	–
	Day 29 [d)]	8.25 [−33.1, 49.6] (2)	5.48 [4.85, 6.12] (63)	–
	Day 57 [d)]	5.95 [5.00, 6.89] (111)	5.44 [5.00, 5.88] (60)	–
	Day 85 [d)]	5.00 [e)]	6.40 [3.86, 8.93] (44)	–
	Day 169 [d)]	5.67 [5.10, 6.23] (74)	7.15 [4.13, 10.2] (38)	–

Mean [95% CI] (N); "–," not applicable

a) Values below the lower limit of quantitation (10 U/mL) were imputed as 5.0 U/mL.

b) The descriptive analysis part in which crovalimab was administered to complement inhibitor-naïve patients with PNH aged <18 years

c) Mean (N)

d) Number of days from the start of crovalimab treatment in the extension period. Day 1 in the extension period for the crovalimab group and Arm C was the same day as Day 169 in the primary evaluation period.

e) An individual value from 1 patient

ADAs were detected after the administration of crovalimab in 29.1% (39 of 134) of patients[5)] in the crovalimab group, 34.3% (23 of 67) of patients[6)] in the eculizumab group, and 50.0% (3 of 6) of patients[7)] in Arm C. Neutralizing antibodies were detected in 5.7% (2 of 35) of ADA-positive patients in the crovalimab group and 4.35% (1 of 23) of ADA-positive patients[8)] in the eculizumab group.

(DTDCs) were detected in all patients switching from eculizumab to crovalimab. The results showed that large DTDCs had disappeared by Week 9.

6.2.3 Global phase III study (CTD 5.3.5.1-2, Study BO42161 [September 2020 to November 2022])

This study investigated pharmacokinetics and pharmacodynamics after intravenous and subcutaneous administration of crovalimab to Japanese and non-Japanese patients with PNH who had been on complement inhibitor treatment [see Section 7.2.2 for the outline of study and the efficacy and safety results].

[5)] ADAs were detected in 2 of 39 patients at baseline.
[6)] ADAs were detected in 7 of 23 patients at baseline.
[7)] ADAs were not detected in any patients at baseline.
[8)] Data for 4 of 39 patients who tested positive for ADAs in the crovalimab group were missing. There were no missing data in the eculizumab group and Arm C.

The study consisted of 2 parts, a 24-week primary evaluation period (crovalimab or eculizumab treatment) and an extension period (crovalimab treatment) lasting up to 5 years.

Through Week 24 (Day 169), patients received intravenous and subcutaneous crovalimab or intravenous eculizumab in the primary evaluation period and subcutaneous of crovalimab for up to 5 years in the extension period, according to the dosage regimens in Table 16 as in Study BO42162.

Table 19 shows serum crovalimab concentrations. In all treatment groups, serum crovalimab concentrations reached a steady state by 9 weeks after the first dose and remained stable through Week 25.

Table 19. Serum crovalimab concentrations (trough concentrations) following multiple dose administration of crovalimab in patients with PNH (μg/mL)

		Crovalimab	Eculizumab	Arm C (descriptive analysis part)			
				Cohort (1)[a)]	Cohort (2)[b)]	Cohort (3)[c)]	Cohort (4)[d)]
Primary evaluation period	Day 1	344 [313, 376] (42)	–[e)]	295[g)]	363 [290, 436] (21)	355 [287, 423] (10)	314 [195, 437] (6)
	Day 8	238 [218, 259] (43)	–[e)]	357[g)]	280 [249, 311] (21)	275 [214, 337] (8)	211 [155, 268] (6)
	Day 15	224 [196, 253] (44)	–[e)]	327[g)]	253 [213, 294] (21)	270 [213, 327] (9)	221 [163, 279] (6)
	Day 29	249 [222, 276] (42)	–[e)]	–	252 [200, 303] (19)	291 [206, 377] (9)	274 [179, 369] (6)
	Day 57	218 [198, 239] (42)	–[e)]	–	243 [185, 300] (18)	221 [189, 253] (9)	204 [43.1, 365] (6)
	Day 85	222 [196, 247] (41)	–[e)]	–	197 [149, 246] (17)	238 [199, 277] (9)	208 [51.9, 364] (6)
	Day 169	214 [190, 238] (38)	–[e)]	–	201 [142, 260] (15)	224 [180, 268] (7)	213 [71.3, 355] (6)
Extension period	Day 1[f)]	–	348 [313, 383] (34)[h)]	–	–	–	–
	Day 8[f)]	114[g)]	240 [220, 261] (33)[h)]	–	–	–	–
	Day 15[f)]	–	227 [208, 246] (34)[h)]	–	–	–	–
	Day 29[f)]	–	246 [217, 274] (32)[h)]	–	–	–	–
	Day 57[f)]	215 [192, 237] (33)	225 [194, 256] (29)[h)]	–	206 [142, 270] (12)	225 [158, 293] (7)	251 [40.9, 461] (5)
	Day 85[f)]	–	218 [189, 246] (28)[h)]	–	–	–	–
	Day 169[f)]	244 [188, 300] (24)	239 [203, 276] (26)[h)]	–	179 [86.2, 271] (5)	283[g)]	282 [174, 390] (3)

Mean [95% CI] (N); "–," not applicable

a) Crovalimab was administered to patients with PNH aged <18 years (body weight ≥40 kg) who had been receiving eculizumab.

b) Crovalimab was administered to patients with PNH who had been receiving ravulizumab.

c) Crovalimab was administered to patients with PNH who had been receiving eculizumab at a higher dose than that approved for PNH.

d) Crovalimab was administered to patients with known C5 genetic polymorphism and hemolysis poorly controlled with eculizumab or ravulizumab.

e) Eculizumab was administered.

f) The number of days from the start of crovalimab treatment in the extension period. Day 1 in the extension period for the crovalimab group and Arm C was the same day as Day 169 in the primary evaluation period.

g) An individual value from 1 patient; h) Crovalimab was administered (see Table 16 for the dosage regimens).

Table 20 shows the complement activity levels in each treatment group. In all treatment groups, complement activity levels decreased to below the lower limit of quantitation (10 U/mL) by 2 weeks after the first dose.

Table 20. Complement activity levels (U/mL)[a)]

		Crovalimab	Eculizumab	Arm C (descriptive analysis part)			
				Cohort (1)	Cohort (2)	Cohort (3)	Cohort (4)
Primary evaluation period	Day 1	9.89 [7.91, 11.9] (42)	8.96 [6.41, 11.5] (40)	5.0 [b)]	10.3 [6.99, 13.7] (21)	6.56 [2.97, 10.1] (9)	41.3 [27.7, 54.8] (6)
	Day 8	5.79 [4.83, 6.76] (43)	7.71 [6.04, 9.37] (34)	5.0 [b)]	5.0 [5.0, 5.0] (21)	5.0 [5.0, 5.0] (8)	5.0 [5.0, 5.0] (6)
	Day 15	7.37 [5.76, 8.99] (43)	10.3 [7.29, 13.3] (37)	5.0 [b)]	5.0 [5.0, 5.0] (21)	5.0 [5.0, 5.0] (9)	5.0 [5.0, 5.0] (6)
	Day 29	6.16 [5.31, 7.01] (42)	8.96 [6.45, 11.5] (37)	–	6.08 [4.49, 7.66] (19)	5.0 [5.0, 5.0] (9)	5.0 [5.0, 5.0] (6)
	Day 57	6.05 [5.21, 6.89] (40)	11.0 [7.79, 14.2] (33)	–	5.76 [4.16, 7.35] (18)	5.0 [5.0, 5.0] (9)	10.1 [−3.04, 23.3] (6)
	Day 85	6.19 [5.24, 7.14] (41)	8.85 [5.98, 11.7] (35)	–	6.71 [3.85, 9.57] (16)	6.78 [3.83, 9.72] (9)	12.8 [−7.22, 32.8] (6)
	Day 169	7.65 [5.46, 9.84] (39)	7.21 [5.66, 8.76] (30)	–	9.56 [2.87, 16.3] (15)	5.79 [3.93, 7.65] (8)	12.6 [−3.68, 28.8] (6)
Extension period	Day 1 [c)]	–	8.00 [5.97, 10.0] (35)	–	–	–	–
	Day 8 [c)]	–	5.0 [5.0, 5.0] (33)	–	–	–	–
	Day 15 [c)]	–	5.17 [4.83, 5.51] (35)	–	–	–	–
	Day 29 [c)]	10.2 [−55.9, 76.3] (2)	5.68 [4.87, 6.48] (30)	–	–	–	–
	Day 57 [c)]	6.52 [5.27, 7.77] (31)	5.64 [4.32, 6.95] (26)	–	–	–	–
	Day 85 [c)]	–	6.07 [4.59, 7.55] (28)	–	10.5 [2.43, 18.5] (12)	5.0 [5.0, 5.0] (7)	13.7 [−10.5, 37.9] (5)
	Day 169 [c)]	6.30 [4.66, 7.95] (23)	7.96 [4.00, 11.9] (26)	–	8.28 [−0.83, 17.4] (5)	7.60 [−25.4, 40.6] (2)	5.0 [5.0, 5.0] (3)

Mean [95% CI] (N); "–," not applicable

a) Values below the lower limit of quantitation (10 U/mL) were imputed as 5.0 U/mL.

b) An individual value from 1 patient

c) The number of days from the start of crovalimab treatment in the extension period. Day 1 in the extension period for the crovalimab group and Arm C was the same day as Day 169 in the primary evaluation period.

ADAs were detected in 13.6% (6 of 44) of patients in the crovalimab group, 11.4% (4 of 35) of patients in the eculizumab group, and 28.6% (6 of 21) of patients in Arm C Cohort (2), 10.0% (1 of 10) of patients in Cohort (3), and 50.0% (3 of 6) of patients in Cohort (4). Neutralizing antibodies were detected in 25% (1 of 4) of ADA-positive patients in the eculizumab group and 33.3% (1 of 3) of ADA-positive patients in Cohort (4) of Arm C.[9)]

DTDCs were detected in all patients switching from eculizumab to crovalimab. The mean percentage of the formation of large DTDCs in the crovalimab group, eculizumab group and Arm C Cohort (3) peaked at Week 2 post-switch to crovalimab and DTDCs nearly disappeared by Week 9. In Arm C Cohort (2), the mean percentage of the formation of large DTDCs peaked at Week 2 post-switch, and decreased at Week 21, but DTDCs were detected even at Week 25 post-switch.

[9)] One of 6 patients in Cohort (2) in Arm C had missing data. There were no missing data in the crovalimab group, eculizumab group, Cohorts (1), (3), and (4) of Arm C.

6.2.4 Population pharmacokinetic analysis (CTD 5.3.3.5-2)

Population pharmacokinetic analyses were performed based on serum crovalimab concentration data (N = 430; 6,115 timepoints) from a global phase I/II study in healthy adults and patients with PNH (Study BP39144), a global phase III study in complement inhibitor-naïve patients with PNH (Study BO42162), a global phase III study in patients with PNH who had been previously treated with complement inhibitors (Study BO42161), and a foreign phase III study in complement inhibitor-naïve Chinese patients with PNH (Study YO42311). The analyses employed a nonlinear mixed effect model (software, NONMEM Version 7.5). The pharmacokinetics of crovalimab in patients with PNH was described by a linear 2-compartment model with a first-order elimination process as well as a first-order absorption process after subcutaneous administration.

Based on the analyses,[10)] the following covariates were chosen for the model: (1) age on the absorption rate constant (ka) of crovalimab; (2) body weight on overall clearance (clearance [CL] + clearance decreasing over time [CLs]), CLs, inter-compartmental clearance (Q), volume of distribution of central compartment (V2), and volume of distribution of peripheral compartment (V3); (3) ADAs on CL.

Figure 1 shows the estimated trough serum concentration at steady state ($C_{trough,\ ss}$) of crovalimab by body weight category following the administration of subcutaneous crovalimab as per the proposed dosage regimen (for details of the regimen, see Table 44) to patients with PNH. The applicant explained that when crovalimab was administered according to the proposed regimen for patients with PNH aged 12, 36, and 80 years, >88.2% of the patients in all age categories had $C_{trough,\ ss}$ >100 μg/mL, a concentration that would completely inhibit complement activity.

[10)] The following parameters were tested as covariates: age and race on ka of crovalimab; body weight, sex, race, and total C5 concentration on V2; body weight, race, and total C5 concentration on V3; body weight, ADAs, sex, race, total C5 concentration, albumin, creatinine clearance (CL_{cr}), AST, and ALT on CL + CLs; treatment switching status information on CLs and equilibrium dissociation constant (Kd); body weight, race, and total C5 concentration on Q.

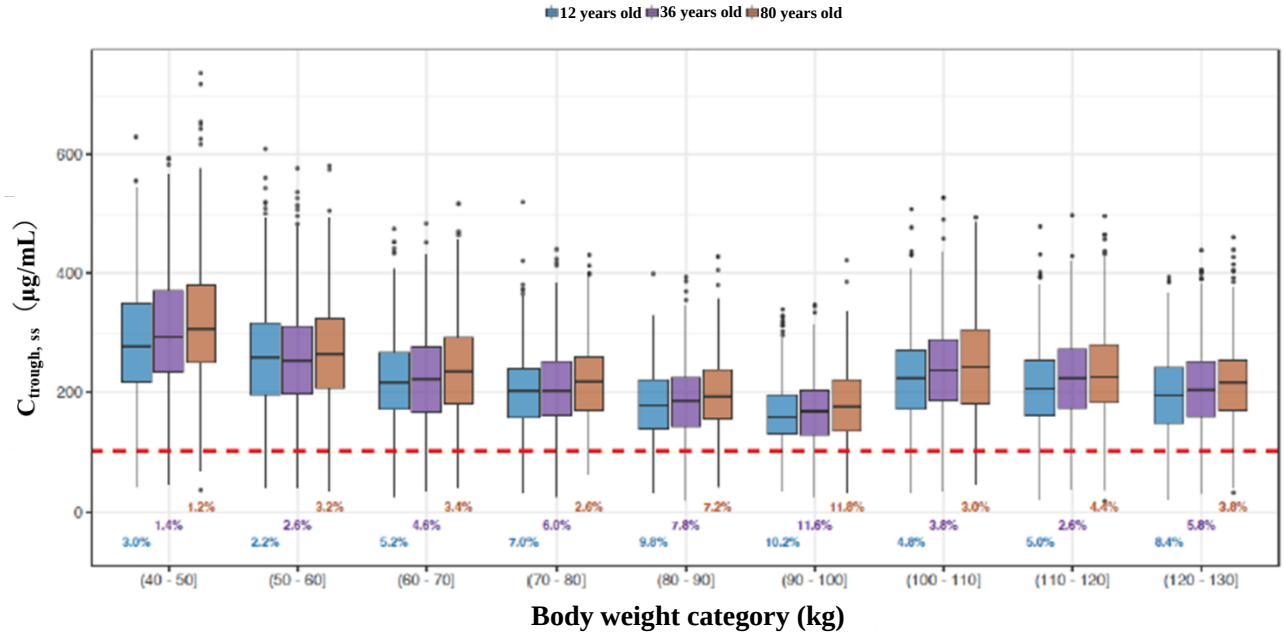


Figure 1. Estimated $C_{trough, ss}$ of crovalimab by body weight category following multiple subcutaneous dose administration of crovalimab in patients with PNH according to the proposed dosage regimen

The red dotted line (horizontal) indicates 100 μg/mL. The percentage shown below the box plot indicates the proportion of patients with a trough concentration <100 μg/mL.

The bottom end, middle, and upper end of the box correspond to the 25th, 50th, and 75th percentile data points. The lower whisker is drawn from the 25th percentile down to the lowest data point that falls within the range between the 25th percentile and the 1.5 interquartile range (IQR) value"; similarly, the upper whisker is drawn from the 75th percentile up to the highest data point that falls within the range between the 75th percentile and the 1.5 IQR value. Outliers are plotted as dots.

6.2.5 Exposure-response analyses (CTD 5.3.3.5-3)

The exposure-response relationship was investigated using pharmacodynamic, efficacy, and serum crovalimab concentration data obtained from a global phase I/II study in healthy adults (Study BP39144), a global phase III study in complement inhibitor-naïve patients with PNH (Study BO42162), a global phase III study in patients with PNH who had been previously treated with complement inhibitors (Study BO42161), and a foreign phase III study in complement inhibitor-naïve, Chinese patients with PNH (Study YO42311).

Figure 2 shows the relationship between serum crovalimab concentration and complement activity level following intravenous and subcutaneous administration of crovalimab to healthy adults, complement inhibitor-naïve patients with PNH, and patients with PNH who had previously been treated with complement inhibitor. According to the applicant, the results suggest that complement activity can be completely inhibited (threshold <30 U/mL)[11)] at a serum crovalimab concentration of approximately >100 μg/mL regardless of prior complement inhibitor treatment.

[11)] In all patients with PNH who exhibited a decrease in serum crovalimab concentration (serum crovalimab concentrations <100 μg/mL in ≥2 consecutive timepoints) and elevated LDH (>2 × ULN), the complement activity levels increased to >30 U/mL. Therefore, a threshold of 30 U/mL was selected as the value at which complement activity is completely inhibited.

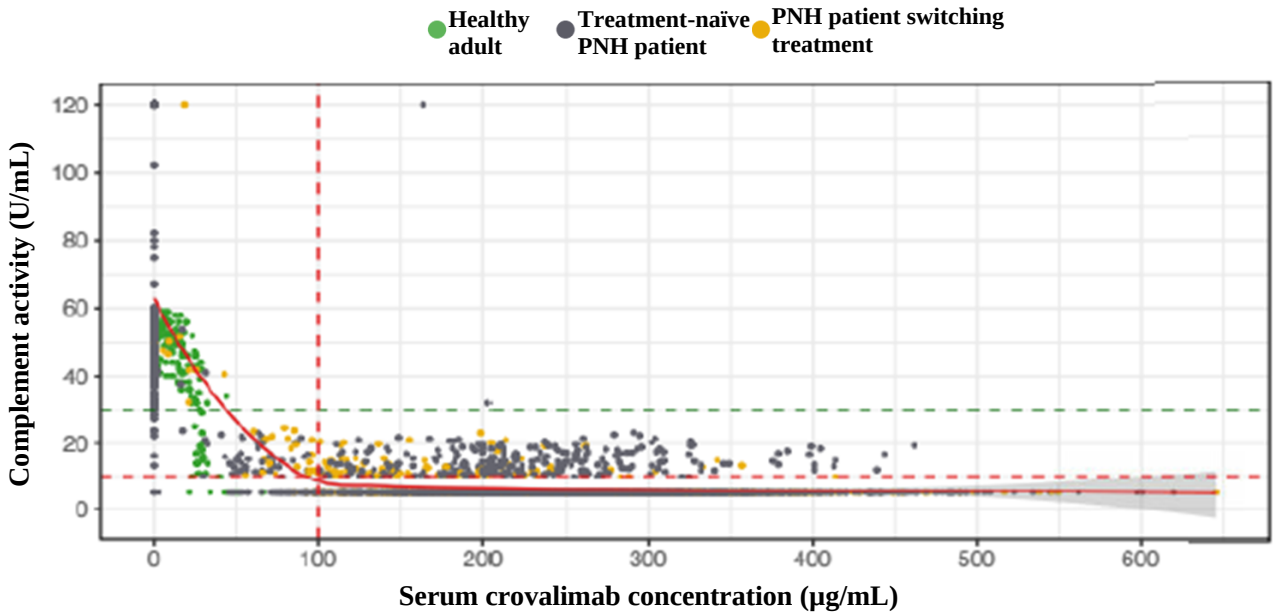


Figure 2. Exposure-response relationship between the crovalimab concentration and complement activity in healthy adults and patients with PNH

The red curve is the locally estimated scatterplot smoothing regression. The shaded area indicates the 90% confidence interval.
The red dotted line (horizontal) indicates the lower limit of quantitation. The green dotted line (horizontal) indicates 30 U/mL, below which complement activity is considered to be completely inhibited.
The red dotted line (vertical) indicates 100 µg/mL.

Figure 3 shows the relationship between the serum crovalimab concentration at Week 10 and the efficacy endpoint (lactate dehydrogenase [LDH] standardized by the upper limit of normal [ULN]). The applicant explained that the results indicated no exposure-response relationship between the serum crovalimab concentration at Week 10 and the standardized LDH and that LDH levels remained roughly constant at concentrations approximately >100 µg/mL.

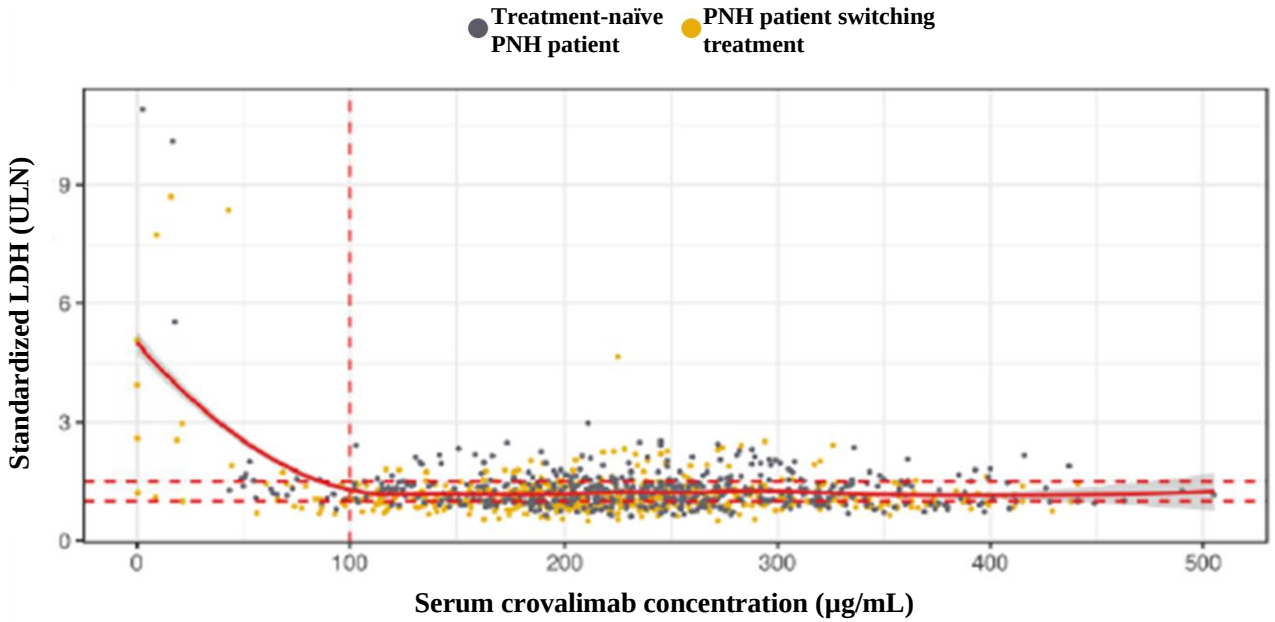


Figure 3. Exposure-response relationship between the crovalimab concentration and efficacy at Week 10 in patients with PNH

The red curve is the locally estimated scatterplot smoothing regression. The shaded area indicates the 90% confidence interval.
The red dotted lines (horizontal) indicate ULN and 1.5 × ULN.
The red dotted line (vertical) indicates 100 µg/mL.

6.R Outline of the review conducted by PMDA

Based on the submitted data and discussions in Sections 6.R.1 and 6.R.2, there were no pharmacokinetic concerns that could affect the efficacy and safety of crovalimab administered to patients with PNH.

6.R.1 Differences in pharmacokinetics of crovalimab between Japanese and non-Japanese patients with PNH

The applicant's explanation about the differences in pharmacokinetics of crovalimab between Japanese and non-Japanese patients with PNH:

Figure 4 and Figure 5 show over-time serum crovalimab concentrations following intravenous and subcutaneous administration of crovalimab to Japanese and non-Japanese patients with PNH in Studies BO42162 and BO42161, respectively. In Study BO42162, over-time serum crovalimab concentrations were similar between Japanese patients and non-Japanese patients with PNH, while Study BO42161 showed a tendency of serum crovalimab concentrations higher in Japanese patients than in non-Japanese patients. In Study BO42162, there was no difference in body weight between Japanese and non-Japanese patients, while a difference in body weight was observed between Japanese and non-Japanese patients in Study BO42161 (mean weight ± standard deviation: in the Japanese population, 53.4 ± 8.51 kg in the crovalimab group and 55.9 ± 9.09 kg in the eculizumab group; in the non-Japanese population, 80.0 ± 16.0 kg in the crovalimab group and 78.7 ± 17.4 kg in the eculizumab group), which may be one of the factors contributing to the difference in serum crovalimab concentrations. However, given the simulation results [see Section 6.2.4] by age category based on the population pharmacokinetic analysis, the difference in crovalimab exposure between Japanese and non-Japanese patients observed in Study BO42161 is not considered of clinical concern. In addition, there are no particular safety concerns in patients weighing close to the lower limit [see Section 7.R.5.1]. The results of covariate analysis in the population pharmacokinetic analyses indicated that ethnic difference was not a covariate of pharmacokinetic parameters [see Section 6.2.4].

Based on the above, the difference in crovalimab exposure between Japanese and non-Japanese patients with PNH is unlikely to have a significant clinical impact.

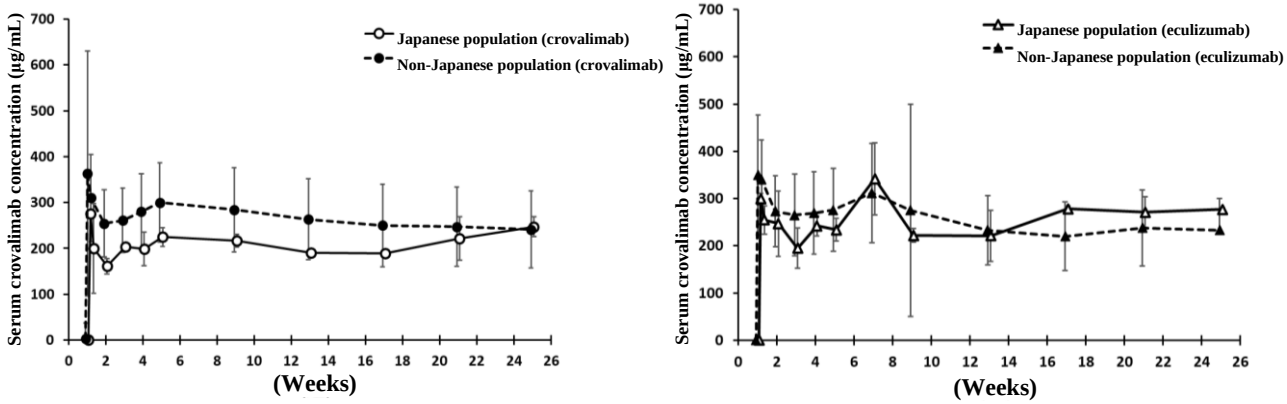


Figure 4. Serum crovalimab concentrations over time in Japanese and non-Japanese patients with PNH in Study BO42162 (mean ± standard deviation)

Left, Serum crovalimab concentrations over time in the crovalimab group (2 Japanese and 132 non-Japanese patients).
Right, Serum crovalimab concentrations over time in patients switching to crovalimab in the eculizumab group (3 Japanese and 64 non-Japanese patients). The number of weeks after switching to crovalimab are shown.

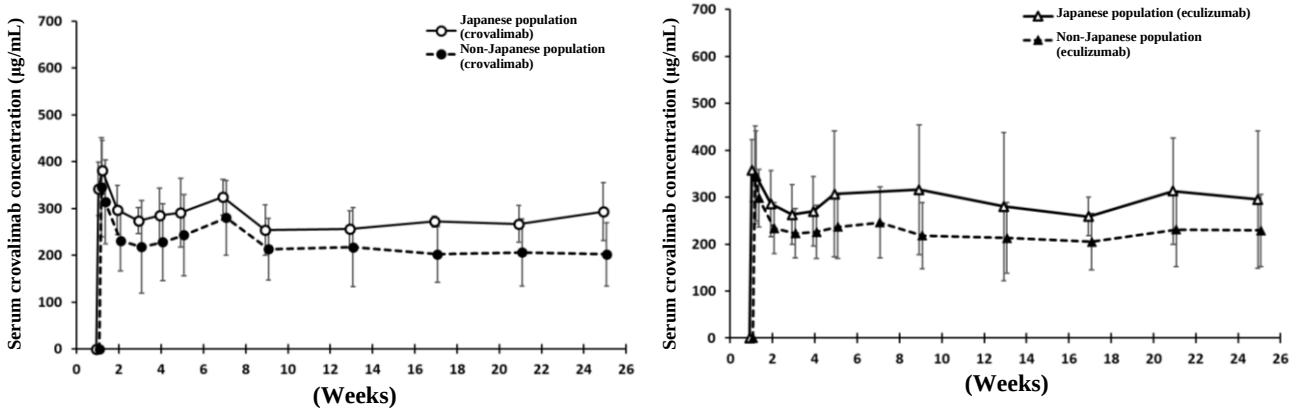


Figure 5. Serum crovalimab concentrations over time in Japanese and non-Japanese patients with PNH in Study BO42161 (mean ± standard deviation)

Left, Serum crovalimab concentrations over time in the crovalimab group (5 Japanese and 39 non-Japanese patients).
Right, Serum crovalimab concentrations over time in patients switching to crovalimab in the eculizumab group (4 Japanese and 30 non-Japanese patients). The number of weeks after switching to crovalimab are shown.

PMDA's view:

The applicant explains that body weight is one of the factors contributing to the difference in crovalimab exposure between Japanese and non-Japanese patients with PNH in Study BO42161, which is reasonable. The simulation results by body weight category based on the population pharmacokinetic analysis [see Section 6.2.4] indicated no significant difference in the $C_{trough, ss}$ of crovalimab in all body weight categories ≥40 kg. Therefore, the difference in body weight is unlikely to cause clinical problems.

6.R.2 Immunogenicity

The applicant's explanation about the incidence of ADAs and its effects on the pharmacokinetics of crovalimab:

In the global phase III studies in patients with PNH (Studies BO42162, BO42161, and YO42311), ADAs were detected following crovalimab treatment in 31.4% (60 of 191) of treatment-naïve patients and 23.4% (43 of 184) of patients switching from eculizumab or ravulizumab.

Figure 6 shows serum crovalimab concentrations in ADA-positive treatment-naïve patients and ADA-positive switching patients. Serum crovalimab concentrations tended to be lower in the ADA-positive patients than in ADA-negative patients. However, in both ADA-positive patients and ADA-negative patients, the median serum crovalimab concentrations at all timepoints exceeded 100 μg/mL, the threshold for complement activity inhibition [see Section 6.2.5]. The median complement activity levels both in ADA-positive patients and in ADA-negative patients were around the lower limit of quantitation (10 U/mL), indicating that inhibition of complement activity generally remained constant throughout the crovalimab treatment period regardless of ADA status. Therefore, treatment-emergent ADAs following crovalimab treatment are unlikely to have significant clinical impacts in most patients.

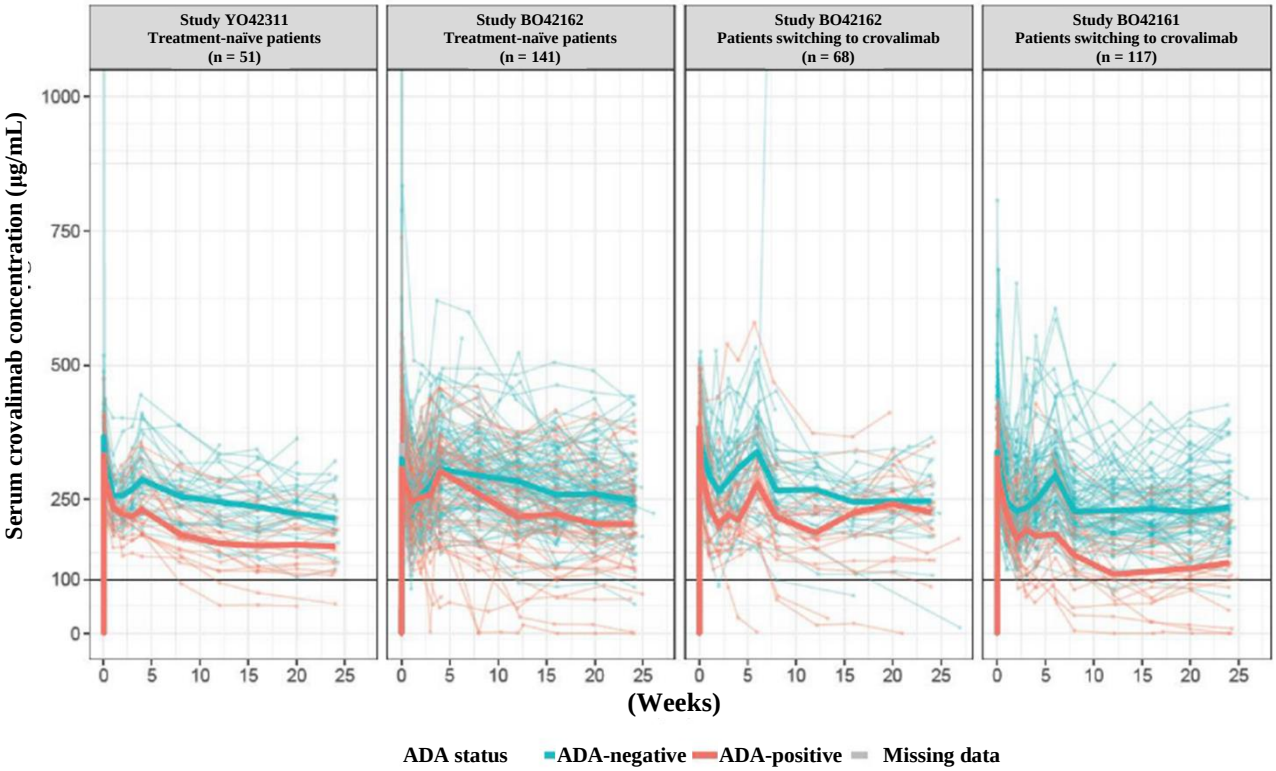


Figure 6. Serum crovalimab concentrations over time in patients with PNH (by ADA status) in global phase III studies (Studies BO42162, BO42161, and YO42311) (mean ± standard deviation)

Bold curves indicate median serum crovalimab concentrations over time; thin curves indicate individual values; black horizontal lines indicate 100 µg/mL.

At the same time, some ADA-positive patients (5.3% [20 of 375] receiving crovalimab) had decreased serum crovalimab concentrations (serum crovalimab concentration <100 µg/mL in 2 consecutive measurements), and in 11 patients of these (accounting for 2.9% of patients receiving crovalimab), decreased serum crovalimab concentration was accompanied by loss of pharmacodynamic activity (complement activity level and free C5 concentration). In 6 patients (accounting for 1.6% of patients receiving crovalimab) of the 11 patients, loss of clinical effects (defined as LDH is ≥2 × ULN in 3 consecutive measurements for ≥4 weeks) was not noted. In the remaining 5 patients, a relationship between the development of ADAs and attenuated clinical effect remained inconclusive.

Taken together, ADAs developing after crovalimab treatment will not affect most patients clinically significantly but may decrease crovalimab exposure and efficacy in some cases. Therefore, the package insert will caution about the need for close monitoring for serious intravascular hemolysis and associated changes in clinical symptoms during crovalimab treatment.

PMDA's view:

It is difficult to determine a relationship between the development of ADAs or neutralizing antibodies and their impacts on the efficacy and safety of crovalimab based on data from the limited number of ADA-positive patients. Nevertheless, the emergence of ADAs during crovalimab treatment can attenuate or decrease the efficacy of crovalimab, in view that crovalimab exposure tended to decrease in some patients with PNH who turned ADA-positive after crovalimab treatment, and that decreased efficacy of crovalimab was suggested in some of these ADA-positive patients with decreased exposure

to crovalimab. Therefore, it is reasonable to caution about the need for close monitoring for serious intravascular hemolysis and associated changes in clinical symptoms during crovalimab treatment.

7. Clinical Efficacy and Safety and Outline of the Review Conducted by PMDA

The applicant submitted efficacy and safety evaluation data, in the form of results from 1 global phase I/II study and 2 global phase III studies (Table 21).

Table 21. Outline of clinical studies on efficacy and safety

Phase Study ID	Study population	Study design	Study period, group, number of patients enrolled	Primary efficacy endpoint
Global phase I/II study BP39144	Part 1: Healthy adults Parts 2, 3, 4: Complement inhibitor-naïve patients with PNH and patients with PNH receiving C5 inhibitor (eculizumab)	Part 1: randomized, investigator/subject-blind, placebo-controlled Part 2: open-label, multiple-dose, intrapatient dose escalation Part 3: randomized, open-label, multiple-dose Part 4: open-label, multiple-dose	Primary evaluation period, 13 weeks (Part 1), 20 weeks (Parts 2, 3, and 4) • Part 1: 15 subjects (0 Japanese subjects) • Part 2: 10 subjects (1 Japanese subject) • Part 3: 19 subjects (6 Japanese subjects) • Part 4: 15 subjects (4 Japanese subjects) Extension part[a]: 5 years maximum • Extension part: 43 subjects	–
Global phase III study BO42162	Complement inhibitor-naïve patients with PNH	Randomized, open-label, active-controlled	Primary evaluation period, 24 weeks • Randomized part Arm A (crovalimab), 135 subjects (2 Japanese subjects) Arm B (eculizumab), 69 subjects (3 Japanese subjects) • Descriptive analysis part Arm C, 6 subjects (0 Japanese subjects) Extension part (5 years maximum) • 203 subjects The crovalimab group and Arm C continued crovalimab treatment The eculizumab group switched to crovalimab	The proportion of patients achieving transfusion avoidance from baseline to Week 25 and the proportion of patients achieving hemolysis control from Week 5 to Week 25
Global phase III study BO42161	Patients with PNH receiving another C5 inhibitor (eculizumab or ravulizumab)	Randomized, open-label, active-controlled	Primary evaluation period, 24 weeks • Randomized part Arm A (crovalimab), 45 subjects (5 Japanese subjects) Arm B (eculizumab), 44 subjects (4 Japanese subjects) • Non-randomized part Arm C, 38 subjects (8 Japanese subjects) Extension part (5 years maximum) • 103 subjects The crovalimab group and Arm C continued crovalimab treatment The eculizumab group switched to crovalimab	–

a) Continued treatment from Part 2, 3, or 4

7.1 Phase I/II study

7.1.1 Global phase I/II study (CTD 5.3.3.1-1, 5.3.3.1-2, Study BP39144 [(as of December 2023) ongoing since November 2016, data cut-off on November 1, 2021])

A multi-center, open-label study[12)] was conducted at 15 study centers in 7 countries including Japan (5 study centers in Japan) to evaluate the efficacy, safety, pharmacokinetics, etc. of crovalimab in healthy adults and patients with PNH (Table 22) (target sample size, approximately 25 healthy adults, approximately 34 patients with PNH[13)]).

Table 22. Key inclusion/exclusion criteria

Key inclusion criteria for patients with PNH
• Aged ≥18 and ≤75 years
• Documented PNH diagnosis based on glycosylphosphatidylinositol (GPI)-deficient erythrocyte or granulocyte clone size of ≥10% within 3 months prior to randomization/enrollment
• Platelet counts ≥30,000/mm^3 at screening
• Absolute neutrophil counts >500/μL at screening
• Vaccinated with *Neisseria meningitidis* vaccine according to with latest guidelines or standard of care for patients at increased risk for meningococcal disease
(See Table 23 for Part 2 and Arm A in Part 4)
• LDH ≥1.5 × ULN at screening
• Naïve to treatment with complement inhibitor, or previously discontinued due to lack of efficacy because of single missense C5 heterozygous mutation
(See Table 23 for Part 3 and Arm B in Part 4)
• Receiving eculizumab for ≥3 months
Key exclusion criteria for patients with PNH
•History of or currently active primary or secondary immunodeficiency, including history of human immunodeficiency virus (HIV) infection
• History of meningococcal meningitis
• History of bone marrow transplantation
• Confirmed or suspected hereditary complement deficiency
• Evidence of malignant disease including myelodysplastic syndrome
(See Table 23 for Part 2 and Arm A in Part 4)
• Current or previous treatment with complement inhibitor

The study consisted of Part 1 in healthy adults treated with a single dose, Parts 2, 3, and 4 in patients with PNH treated for 20 weeks, and the extension part lasting for up to 5 years. Table 23 shows the dosage regimens.

[12)] Part 1 is an investigator/subject-blind study.

[13)] The target sample sizes sufficient for the objectives: Part 1, ≤25 healthy adults for safety and pharmacokinetic/pharmacodynamic analyses; Part 2, 6 patients with PNH for pharmacokinetic/pharmacodynamic analyses of dose-escalation treatment; Part 3, 18 patients with PNH, for the determination of dosage regimen; Part 4, 5 complement inhibitor-naïve patients with PNH and 5 patients with PNH previously treated with eculizumab for the investigation of safety and tolerability

Table 23. Parts of the study and dosage regimens

Part	Study population	Dosage regimen
1	Healthy adults	A single-dose of 75 mg IV, 125 mg IV, 100 mg SC, or placebo (IV, SC)
2	Treatment-naïve patients with PNH	Crovalimab 375 mg IV on Day 1, 500 mg IV on Day 8, 1,000 mg IV on Day 22, and from Day 36 onwards, 170 mg SC once weekly
3	Patients with PNH currently receiving eculizumab	All arms: crovalimab 1,000 mg IV on Day 1 From Day 8 onwards: Arm A: (before modification) 680 mg SC every 4 weeks (after modification[a]) 170 mg SC once weekly for 8 weeks. 680 mg SC every 4 weeks from Day 64 onwards Arm B: 340 mg SC every 2 weeks Arm C: 170 mg SC once weekly
4	Arm A: treatment-naïve patients with PNH Arm B: patients with PNH currently receiving eculizumab	Arms A and B: 1,000 mg IV on Day 1, 340 mg SC on Days 2, 8, 15, and 22 680 mg SC every 4 weeks from Day 29 onwards
Extension	Patients with PNH who completed 20-week treatment in Part 2, 3, or 4, and responded to treatment	At the start of study: continue with the dosage regimen in the previous part From protocol sixth version (dated in September 2022): body weight ≥40 kg and <100 kg, 680 mg SC; body weight ≥100 kg, 1,020 mg SC every 4 weeks

a) Because the first 2 patients developed events suspected of DTDC-related adverse events, the dosage regimen for Arm A was modified.

In Part 1, all 15 healthy adults enrolled (0 Japanese subject) completed the study. In Parts 2, 3, and 4, a total of 44 patients with PNH were enrolled (10 [1 Japanese] in Part 2; 19 [6 Japanese] in Part 3; 15 patients in Part 4 [8 (3 Japanese) in Arm A; 7 (1 Japanese) in Arm B]). A total of 18 treatment-naïve patients with PNH (hereinafter referred to as "treatment-naïve patients") (10 in Part 2; 8 in Part 4 Arm A) completed 20 weeks of treatment and started the extension part. All 26 patients with PNH who had been treated with another C5 inhibitor (hereinafter referred to "patients switching to crovalimab"; 19 in Part 3 and 7 in Part 4 Arm B) completed 20 weeks of treatment. Of the 26 patients, 25 patients started the extension part (1 patients in Part 3 did not wish to enter the extension part). In the extension part, 5 patients discontinued treatment due to "withdrawal of consent" (3 patients) and "inadequate response" (2 patients).

In treatment-naïve patients (Arm A in Parts 2 and 4), the mean LDH levels decreased to ≤1.5 × ULN by Day 15 and were maintained through Week 20. In patients switching to crovalimab (Arm B in Parts 3 and 4), the mean LDH levels were maintained ≤1.5 × ULN through Week 20. Up to Week 20, 8 of 10 patients in Part 2, 13 of 19 patients in Part 3, 5 of 8 patients in Part 4 Arm A, 6 of 7 patients in Part 4 Arm B achieved transfusion avoidance. Hemoglobin (Hb) levels were stabilized[14)] by Week 20 in 8 of 10 patients in Part 2, 12 of 19 patients in Part 3, 5 of 8 patients in Part 4 Arm A, and 5 of 7 patients in Part 4 Arm B. In the extension part, LDH levels decreased to ≤1.5 × ULN in 80% to 100% of patients, and mean LDH levels generally remained ≤1.5 × ULN. The proportions of patients who achieved transfusion avoidance and stabilized Hb, respectively, in 24-week periods were 82.9% to 91.7% and 79.5% to 87.5%.

In Part 1, adverse events occurred in 4 of 6 patients (66.7%) in the placebo group and in 8 of 9 patients (88.9%) in the crovalimab group. Adverse events occurring in ≥2 patients were myalgia (2 of 6 patients)

[14)] A condition in which blood Hb does not decrease by ≥2 g/dL from baseline without receiving transfusion

in the placebo group and rhinitis (2 of 9 patients) in the crovalimab group. An adverse drug reaction occurred in 1 patient (skin disorder) in the crovalimab group. Adverse events reported in Part 1 were all mild or moderate in severity.

In Parts 2, 3, 4, and the extension part, adverse events occurred in 42 of 44 patients (95.5%) (17 of 18 treatment-naïve patients and 25 of 26 patients switching to crovalimab). Adverse drug reactions occurred in 14 of 44 patients (31.8%) (4 of 18 treatment-naïve patients and 10 of 26 patients switching to crovalimab). There were no adverse events leading to death or study treatment discontinuation. Serious adverse events occurred in 14 of 44 patients (31.8%) (6 of 18 treatment-naïve patients [hypertensive crisis, breakthrough haemolysis, myocardial infarction, coronary artery stenosis, atrial fibrillation, abdominal pain, cardiac failure, hyperglycaemia, dyspnoea, bile duct stone, and cholelithiasis in 1 patient each; some patients were counted more than once] and 8 of 26 patients switching to crovalimab [breakthrough haemolysis (2 patients); erysipelas, nephrolithiasis, muscle injury, respiratory tract infection, device related infection, platelet count decreased, and upper respiratory tract infection (1 patient each); some patients were counted more than once]). Serious adverse drug reactions occurred in 1 treatment-naïve patient (breakthrough haemolysis) and 1 patient switching to crovalimab (upper respiratory tract infection), both of which resolved.

In the Japanese subpopulation, adverse events occurred in 10 of 11 patients (90.9%) (4 of 4 treatment-naïve patients and 6 of 7 patients switching to crovalimab), and adverse drug reactions occurred in 6 of 11 patients (54.5%) (2 of 4 treatment-naïve patients and 4 of 7 patients switching to crovalimab). There were no adverse events leading to death or study treatment discontinuation. Serious adverse events occurred in 4 of 11 patients (36.4%) (2 of 4 treatment-naïve patients and 2 of 7 patients switching to crovalimab). While there were no reports of serious adverse drug reactions in treatment-naïve patients, a serious adverse drug reaction occurred in 1 patient switching to crovalimab (upper respiratory tract infection) and resolved.

7.2 Phase III studies

7.2.1 Global phase III study (CTD5.3.5.1.1, Study BO42162 [(as of December 2023) ongoing since October 2020, data cut-off on May 31, 2023])

A multi-center, randomized, open-label, active-controlled study was conducted at 67 study centers in 25 countries including Japan (4 study centers in Japan) to investigate the efficacy and safety of crovalimab in complement inhibitor-naïve patients with PNH (Table 24) (target sample size in the randomized part, approximately 200 subjects[15)]).

[15)] To determine the proportion of patients achieving transfusion avoidance from baseline to Week 25, when approximately 200 patients were randomized in the ratio of 2 to1 (crovalimab to eculizumab) to secure approximately 180 evaluable patients with a drop-off rate of 10%, a statistical power of 80% would be secured to demonstrate the non-inferiority of crovalimab to eculizumab with a one-sided significance level of 2.5%, assuming a non-inferiority margin of −20% between the groups and achievement rate of 66.1% for both groups. To determine the mean proportion of patients achieving hemolysis control from Week 5 to Week 25, 128 patients would be required to secure a statistical power of 80% to demonstrate the non-inferiority of crovalimab to eculizumab, at the randomization ratio of 2 to 1 (crovalimab to eculizumab), assuming a mean achievement rate of 86% in both groups, non-inferiority odds ratio of 0.2, with a one-sided significance level of 2.5% and a drop-off rate of 10%. Accordingly, the sample size of approximately 200 patients, the larger of the 2 sample sizes calculated, was selected as the target sample size.

Table 24. Key inclusion/exclusion criteria

Key inclusion criteria **• Aged ≥18 years (randomized part) or <18 years (Arm C)** **• No prior treatment with complement inhibitor and body weight ≥40 kg at screening** **• Confirmed PNH by white blood cell assessment (granulocyte or monocyte clone size of ≥10%) using high-sensitivity flow cytometry in 6 months prior to randomization (Arms A and B) or enrollment (Arm C)** **• PNH-related signs or symptoms observed in 3 months prior to screening, i.e., fatigue, hemoglobinuria, abdominal pain, shortness of breath (dyspnea), Hb <10 g/dL, history of major adverse vascular events, dysphagia, erectile dysfunction, history of packed red blood cell transfusion associated with PNH** **• LDH ≥2 × ULN at screening at screening** **• Platelet counts ≥30,000/mm^3 at screening without transfusion in 7 days before clinical testing** **• Absolute neutrophil counts >500/μL at screening** **• Vaccinated against *Neisseria meningitidis* serotypes A, C, W, and Y in 3 years prior to study treatment** **• Vaccinated against *Haemophilus influenzae* b and *Streptococcus pneumoniae* prior to study treatment or in 1 week after first administration of the study drug according to latest guidelines** **Key exclusion criteria** **• Current or previous treatment with complement inhibitor** **• Hb concentration ≤7 g/dL before enrollment, or >7 g/dL and ≤9 g/dL with signs and symptoms of anemia** **• Confirmed or suspected hereditary complement deficiency** **• History of allogeneic bone marrow transplantation** **• History of *Neisseria meningitidis* infection in 6 months prior to screening and before the initial dose of study drug** **• Confirmed or suspected immunodeficiency (e.g., frequent recurrent infections)** **• History of myelodysplastic syndrome with an intermediate, high, or very high prognosis risk according to the International Prognostic Scoring System-Revised (IPSS-R)**

The study consisted of a randomized part in patients with PNH aged ≥18 years (Arm A [crovalimab group] and Arm B [eculizumab group]) and a descriptive analysis part in patients aged <18 years (Arm C), with a 24-week primary evaluation period and an extension period up to 5 years.

In the primary evaluation period (24 weeks), patients received crovalimab or eculizumab. In the extension period, all patients received crovalimab for ≤ 5 years in accordance with the dosage regimen in Table 25.

Table 25. Dosage regimens

Body weight	Arm A (crovalimab)				Arm B (eculizumab)	
	Day 1	Day 2	Weeks 2, 3, and 4	From Week 5 onwards every 4 weeks	Day 1, Weeks 2, 3, and 4	From Week 5 onwards every 2 weeks
≥40 kg and <100 kg	1,000 mg IV	340 mg SC	340 mg SC	680 mg SC	600 mg IV	900 mg IV
≥100 kg	1,500 mg IV	340 mg SC	340 mg SC	1,020 mg SC		

A total of 204 patients were enrolled in the randomized part and randomized in a ratio of 2 to 1, 135 patients (2 Japanese) in the crovalimab group and 69 patients (3 Japanese) in the eculizumab group. Patients aged ≥12 years and <18 years had also been enrolled in the randomized part before Arm C was added to the third version of the protocol, and 2 patients aged ≥12 years and <18 years were enrolled in the eculizumab group. All randomized patients received the study drug and were included in the randomized safety population (RSP) and the safety analysis set. Of the 204 randomized, 1 patient was excluded due to death on Day 2 with no LDH measurements, and the remaining 203 patients (134 [2 Japanese] in the crovalimab group and 69 patients [3 Japanese] in the eculizumab group were included in the primary analysis population (PAP), which was the main efficacy analysis set. By Week 24, the primary efficacy period, 6 patients in the crovalimab group ("adverse events" and "lost to follow-up" [1 patient each], "investigator's decision" and "withdrawal of consent by the patient" [2 patients each]) and 1 patient in the eculizumab group ("adverse event") discontinued from the study. No Japanese patients discontinued from the study by Week 24. In the 24-week primary evaluation period, 95.6% (129

of 135) of patients in the crovalimab group (Arm A) and 98.6% (68 of 69) of patients in the eculizumab group (Arm B) completed treatment and entered the extension period. In Arm C, 6 patients (0 Japanese) were enrolled.

In the randomized part, the co-primary efficacy endpoints were "the mean proportion of patients achieving hemolysis control[16] from Week 5 to Week 25" and "the proportion of patients achieving transfusion avoidance from baseline to Week 25." Table 26 shows the results. The lower limit of the 95% confidence interval for the odds ratio of the mean proportion of patients achieving hemolysis control from Week 5 to Week 25 in the crovalimab group compared to that of the eculizumab group exceeded the prespecified non-inferiority margin of 0.2.[17] Figure 7 shows the proportion of patients whose LDH remained ≤1.5 × ULN over time. The lower limit of the 95% confidence interval for the between-group difference (crovalimab group minus eculizumab group) in the proportion of patients achieving transfusion avoidance from baseline to Week 25 exceeded the prespecified non-inferiority margin of −20%.[18] These results have demonstrated the non-inferiority of crovalimab to eculizumab.

In Arm C, all 6 patients aged <18 years showed decreased LDH levels to ≤1.5 × ULN following treatment with crovalimab from Week 2 to Week 4, which lasted through Week 25 in 5 of 6 patients. A total of 4 out of the 6 patients remained transfusion-free from baseline to Week 25.

Table 26. Results of primary endpoints (PAP)

Primary endpoint	Arm A (crovalimab) (N = 134)	Arm B (eculizumab) (N = 69)
Mean proportion of patients who achieved hemolysis control from Week 5 to Week 25 (LDH ≤1.5 × ULN), % [95% CI][a)]	**79.3 [72.86, 84.48]**	**79.0 [69.66, 85.99]**
Odds ratio [95% CI][a)]	**1.02 [0.57, 1.82]**	
Proportion of patients who achieved transfusion avoidance from baseline to Week 25,[b)] % (N)	**65.7 (88)**	**68.1 (47)**
Adjusted between-group difference [95% CI][c)]	**−2.8 [−15.67, 11.14]**	

a) Calculated based on the generalized estimating equation (GEE) approach using the logit link function, with treatment, timepoint (once every 2 weeks from Week 5 to Week 25), treatment-timepoint interaction, transfusion units within 6 months prior to randomization (0, >0 and ≤6, or >6), and baseline LDH as explanatory variables (the covariance structure is first-order autoregressive).

b) One patient in the crovalimab group discontinued from the study before Week 25 without receiving transfusions. It was assumed that the patient had received a transfusion as conservative approach.

c) Calculated based on a stratified Newcombe method (*Stat Biopharm Res.* 2010;2:329-335) with pre-randomization LDH (≥2 × ULN and ≤4 × ULN, or >4 × ULN), and transfusion units within 6 months prior to randomization (0, >0 and ≤6, or >6) as stratification factors.

16) Defined as LDH, a main biochemical marker for intravascular hemolysis, reaching ≤1.5 × ULN.

17) Based on the LDH levels in the eculizumab group in a global phase III study that evaluated the non-inferiority of ravulizumab to eculizumab (Study ALXN1210-PNH-301), it was assumed that LDH levels would follow a lognormal distribution. Thus, the proportion of patients who achieve LDH levels ≤1.5 × ULN after eculizumab treatment was estimated to be 86%. Based on the results from a foreign phase III study that evaluated superiority of eculizumab to placebo (TRIUMPH study), the proportion of patients who achieve LDH levels ≤1.5 × ULN after placebo treatment was conservatively assumed to be 20%. Assuming an odds ratio for eculizumab to placebo (ORecu/pbo) of 24.6, a non-inferiority margin of 0.2 was calculated using $1/ORecu/pbo^{0.5}$.

18) Based on the data from the eculizumab group in Study ALXN1210-PNH-301 and on eculizumab treatment-naïve patients from the Global PNH Registry (patients treated with eculizumab who achieved transfusion avoidance, 57.1%; patients not treated with eculizumab who achieved transfusion avoidance, 18.6%; between-group difference, 38.5%), the half of the between-group difference, 20%, was selected.

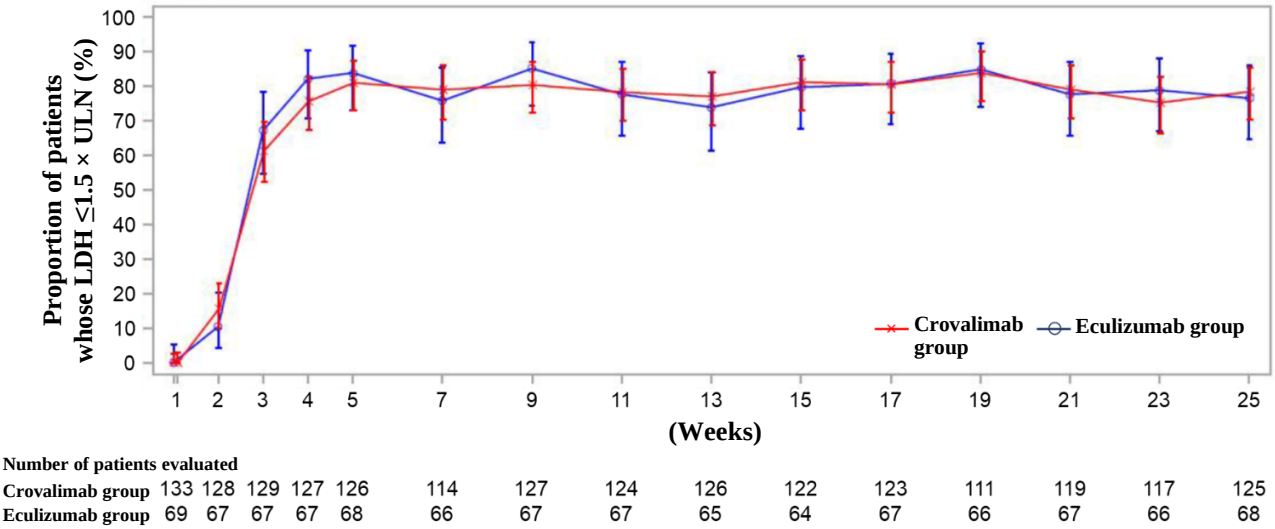


Figure 7. Proportion of patients with LDH levels ≤1.5 × ULN over time (point estimate ± 95% CI, PAP)

Table 27 summarizes adverse events reported in the primary evaluation period. Adverse events occurred in 105 of 135 patients (77.8%) in the crovalimab group and 55 of 69 patients (79.7%) in the eculizumab group. Adverse drug reactions occurred in 45 of 135 patients (33.3%) in the crovalimab group and 24 of 69 patients (34.8%) in the eculizumab group.

Table 27. Adverse events in the primary evaluation period (RSP)

	Primary evaluation period (24 weeks)	
	Arm A (crovalimab) (N = 135)	Arm B (eculizumab) (N = 69)
Adverse events	**77.8 (105)**	**79.7 (55)**
Adverse drug reactions	**33.3 (45)**	**34.8 (24)**
Death	**1.5 (2)**	**1.4 (1)**
Serious adverse events	**10.4 (14)**	**13.0 (9)**
Serious adverse drug reactions	**3.0 (4)**	**1.4 (1)**
Adverse events leading to study treatment discontinuation	**0.7 (1)**	**1.4 (1)**
Adverse events occurring in ≥5% of patients in either group		
Infusion related reaction	**15.6 (21)**	**13.0 (9)**
Neutrophil count decreased	**12.6 (17)**	**10.1 (7)**
White blood cell count decreased	**11.9 (16)**	**10.1 (7)**
Hypokalaemia	**11.1 (15)**	**13.0 (9)**
Pyrexia	**8.9 (12)**	**10.1 (7)**
Upper respiratory tract infection	**8.1 (11)**	**13.0 (9)**
Hyperuricaemia	**8.1 (11)**	**8.7 (6)**
COVID-19	**8.1 (11)**	**5.8 (4)**
Headache	**8.1 (11)**	**4.3 (3)**
Diarrhoea	**7.4 (10)**	**0**
Hypocalcaemia	**5.9 (8)**	**10.1 (7)**
Injection related reaction	**5.2 (7)**	**0**
Urinary tract infection	**1.5 (2)**	**5.8 (4)**

Medical Dictionary for Regulatory Activities Japanese version (MedDRA/J) ver. 25.1; incidence, % (n)

Deaths of 2 patients in the crovalimab group (respiratory tract haemorrhage[19)] and myocardial infarction[20)] [1 patient each]) and 1 patient in the eculizumab group (ischaemic stroke[21)]) were reported. A causal relationship to the study drug was ruled out for all these events.

[19)] The Asian man aged 6[redacted] years developed fever on Day 8 of study treatment. He was diagnosed as having bilateral pneumonia and received corticosteroid and antibiotic therapy. After that, while intermittent fever persisted, small intestinal haemorrhage occurred on Day 38 and COVID-19 infection on Day 140. The patient died on Day 151 due to respiratory tract haemorrhage.

[20)] The white women aged 6[redacted] years became unconscious in a vehicle on the way back home from the hospital 2 to 3 hours after receiving IV crovalimab 1,000 mg on Day 1 of study treatment. The patient was sent to an emergency room by ambulance due to ventricular fibrillation. The patient once resuscitated from cardiac arrest and was placed under mechanical ventilation management in the ICU, but died on Day 2.

[21)] The white man aged 4[redacted] years had an epileptic seizure on Day 48. A head MRI scan indicated an ischemic change and brain edema. Based on the cerebrospinal fluid tests and culture tests, the patient was diagnosed as having meningitis caused by streptococcal infection, and was treated with an antibacterial agent. The patient, however, died of ischemic stroke on Day 71.

In the primary evaluation period, serious adverse events occurred in 14 of 135 patients (10.4%) in the crovalimab group (aplastic anaemia, pneumonia, epistaxis [2 patients each], COVID-19, thrombocytopenia, pyelonephritis, respiratory tract haemorrhage, myocardial infarction, pyrexia, thyroid cancer, small intestinal haemorrhage, infusion-related reaction, affective disorder, Henoch-Schonlein purpura, and hypovolaemic shock [1 patient each]; some patients were counted more than once) and 9 of 69 patients (13.0%) in the eculizumab group (COVID-19, central nervous system infection, sepsis, tuberculosis, urinary tract infection, aplastic anaemia, thrombocytopenia, febrile neutropenia, cardiac failure, pyrexia, myelodysplastic syndrome, cholecystitis chronic, and ischaemic stroke [1 patient each]; some patients were counted more than once). Serious adverse drug reactions occurred in 4 of 135 patients (3.0%) in the crovalimab group (thrombocytopenia, pyrexia, infusion-related reaction, and epistaxis [1 patient each]) and 1 of 69 patients (1.4%) in the eculizumab group (thrombocytopenia), all of which resolved or were resolving. Adverse events leading to study treatment discontinuation occurred in 1 of 135 patients (0.7%) in the crovalimab group (thrombocytopenia) and 1 of 69 patients (1.4%) in the eculizumab group (ischaemic stroke), one of which in 1 patient in the crovalimab group was determined to be related to the study drug but resolved.

In the safety analysis for the extension period, patients who had been in Arm A (crovalimab group) in the primary evaluation period (hereinafter referred to as "the crovalimab continuation group") were evaluated for the "overall treatment period," from the start of the primary evaluation period through the data cut-off date, and patients who had been in Arm B (eculizumab group) in the primary evaluation period (hereinafter referred to as "the crovalimab-switch group") were evaluated for the "post-switch period" after the start of the extension period up to the data cut-off date.

Adverse events occurred in 118 of 135 patients (87.4%) in the crovalimab continuation group and 50 of 68 patients (73.5%) in the crovalimab-switch group. Adverse drug reactions occurred in 48 of 135 patients (35.6%) in the crovalimab continuation group and 25 of 68 patients (36.8%) in the crovalimab-switch group. Table 28 shows adverse events occurring in ≥5% of patients in either group. Adverse drug reactions occurring in ≥5% of patients in either group were infusion-related reaction (14.8%; 20 of 135 patients), white blood cell count decreased (12.6%; 17 of 135 patients), and neutrophil count decreased (11.9%; 16 of 135 patients) in the crovalimab continuation group; type III immune complex mediated reaction (16.2%; 11 of 68 patients), white blood cell count decreased (10.3%; 7 of 68 patients), neutrophil count decreased (5.9%; 4 of 68 patients), and injection-related reaction (5.9%; 4 of 68 patients) in the crovalimab-switch group.

Death was reported in 2 patients, both were in the crovalimab continuation group and occurred during the primary evaluation period. Serious adverse events occurred in 22 of 135 patients (16.3%) in the crovalimab continuation group in the overall treatment period (pneumonia [4 patients], upper respiratory tract infection, aplastic anaemia, epistaxis [2 patients each], COVID-19, dengue fever, infection, influenza, breakthrough haemolysis, thrombocytopenia, pyelonephritis, respiratory tract haemorrhage,

coronary artery disease, limb traumatic amputation, myocardial infarction, infusion-related reaction, pyrexia, thyroid cancer, small intestinal haemorrhage, seizure, affective disorder, Henoch-Schonlein purpura, hypovolaemic shock [1 patient each]; some patients were counted more than once) and 6 of 18 patients (8.8%) in the crovalimab-switch group during the post-switch period (gastroenteritis, septic shock, mantle cell lymphoma, myelodysplastic syndrome, anaemia, cholelithiasis, demyelinating polyneuropathy, and paroxysmal nocturnal haemoglobinuria [1 patient each]; some patients were counted more than once). Serious adverse drug reactions occurred in 6 of 135 patients (4.4%) only in the crovalimab continuation group (upper respiratory tract infection [2 patients], thrombocytopenia, pyrexia, infusion-related reaction, and epistaxis [1 patient each]), and the outcomes were reported as resolved for all events. Adverse events leading to study treatment discontinuation occurred in 1 patient in the crovalimab continuation group during the primary evaluation period and 1 of 68 patients (1.5%) in the crovalimab-switch group (demyelinating polyneuropathy). A causal relationship to the study drug was ruled out for the event in the patient in the crovalimab-switch group.

Table 28. Adverse events occurring in ≥5% of patients in either group (crovalimab safety population[a])

Type of adverse events	Crovalimab continuation group (N = 135)	Crovalimab-switch group (N = 68)
	Overall treatment period (treatment duration[b]: 48.29 weeks)	Post-switch period (treatment duration [b]: 24.14 weeks)
Adverse events occurring in ≥5% of patients in either group		
COVID-19	**21.5 (29)**	**8.8 (6)**
Infusion related reaction	**15.6 (21)**	**2.9 (2)**
Upper respiratory tract infection	**14.1 (19)**	**4.4 (3)**
Neutrophil count decreased	**13.3 (18)**	**5.9 (4)**
White blood cell count decreased	**12.6 (17)**	**11.8 (8)**
Pyrexia	**11.9 (16)**	**5.9 (4)**
Hypokalaemia	**11.1 (15)**	**4.4 (3)**
Headache	**9.6 (13)**	**5.9 (4)**
Hyperuricaemia	**8.1 (11)**	**4.4 (3)**
Diarrhoea	**8.1 (11)**	**2.9 (2)**
Hypocalcaemia	**5.9 (8)**	**4.4 (3)**
Injection related reaction	**5.2 (7)**	**5.9 (4)**
Cough	**5.2 (7)**	**0**
Type III immune complex mediated reaction	**0**	**16.2 (11)**

MedDRA/J ver. 25.1; incidence, % (n)
a) The crovalimab safety population is defined as all patients who received ≥1 dose of crovalimab in the randomized part.
b) Median

In Arm C, adverse events occurred in 5 of 6 patients (83.3%) in the overall treatment period (hyperuricaemia [2 patients], hypocalcaemia, hypokalaemia, hypomagnesaemia, aphthous ulcer, fatigue, pyrexia, urinary tract infection, contusion, and headache [1 patient each]; some patients were counted more than once). An adverse drug reaction (fatigue) occurred in 1 of 6 patients (16.7%) but resolved. There were no reports of death, serious adverse events, or adverse events leading to study treatment discontinuation.

In the Japanese population, during the primary evaluation period, no adverse events occurred in the crovalimab group and adverse events occurred in 2 of 3 patients (66.7%) in the eculizumab group (COVID-19, oral herpes, pyrexia, febrile neutropenia, infusion-related reaction [1 patient each]; some patients were counted more than once). An adverse drug reaction occurred in 1 patient in the eculizumab group (infusion-related reaction), with the outcome being reported as resolved. There were

no reports of death in the Japanese subpopulation. Serious adverse events occurred in 1 of 3 patients (33.3%) in the eculizumab group (COVID-19 and febrile neutropenia) only. A causal relationship to the study drug was ruled out for these events. No adverse events led to study treatment discontinuation.

In the Japanese population, during the extension period, adverse events occurred in 1 of 2 patients (50.0%) in the crovalimab continuation group and 3 of 3 patients (100%) in the crovalimab-switch group. While no adverse drug reactions occurred in the crovalimab continuation group, adverse drug reactions occurred in 2 of 3 patients (66.7%) in the crovalimab-switch group. The adverse drug reaction occurring in ≥2 patients was type III immune complex mediated reaction (2 patients) (2 cases resolved and 1 case unresolved). There were no reports of death, serious adverse events, or adverse events leading to study treatment discontinuation.

7.2.2 Global phase III study (CTD 5.3.5.1.2, Study BO42161 [(as of December 2023) ongoing since September 2020, data cut-off on May 31, 2023])

A multi-center, randomized, open-label, active-controlled, parallel-group study was conducted at 70 study centers (14 study centers in Japan) in 25 countries including Japan to investigate the safety, efficacy, and pharmacokinetics of crovalimab in patients with PNH who had been previously treated with another complement inhibitor (Table 29), with a target sample size of approximately 200 patients[22)] in the randomized part.

Table 29. Key inclusion/exclusion criteria

Key inclusion criteria
• Prior treatment with complement inhibitor and body weight ≥40 kg at screening
• Confirmed PNH by white blood cell assessment (granulocyte or monocyte clone size of ≥10%) using high-sensitivity flow cytometry in 6 months prior to randomization (Arms A and B) or enrollment (Arm C)
• Platelet counts ≥30,000/mm^3 at screening without transfusion within 7 days before clinical testing
• Absolute neutrophil counts >500/μL at screening
• Vaccinated against *Neisseria meningitidis* serotypes A, C, W, and Y within 3 years prior to study treatment
• Vaccinated against *Haemophilus influenzae* b and *Streptococcus pneumoniae* according to latest local guidelines
(Key inclusion criteria for the randomized part)
• LDH ≤1.5 × ULN at screening
• Documented treatment with eculizumab (900 mg every 2 weeks) for ≥24 weeks before Day 1
(Key inclusion criteria for Arm C, Cohort [1])
• Aged <18 years
• Treated with eculizumab for≥12 weeks before Day 1
• LDH ≤2 × ULN at screening
(Key inclusion criteria for Arm C, Cohort [2])
• Treated with ravulizumab for ≥16 weeks before Day 1
• LDH ≤2 × ULN at screening
(Key inclusion criteria for Arm C, Cohort [3])
• Treated with eculizumab for ≥12 weeks before Day 1 at >900 mg/dose or more frequently than every 2 weeks
• LDH ≤2 × ULN at screening
(Key inclusion criteria for Arm C, Cohort [4])
• Confirmed C5 genetic polymorphism with poor hemolysis control with eculizumab or ravulizumab as determined by the investigator
(Key inclusion criteria for Arm C, Cohort [5])
• Aged ≥18 years
• Treated with eculizumab at the approved dosage level for ≥24 weeks before Day 1
• Patients with LDH ≤1.5 × ULN at screening

22) For the evaluation of the percentage change from baseline in LDH at Week 25, in order to demonstrate the non-inferiority of crovalimab to eculizumab with a statistical power of at least 90%, 172 patients would be required based on assumed mean between-group difference of 0%, a common standard deviation of 30%, a non-inferiority margin of 15%, a one-sided significance level of 2.5%, and a randomization ratio of 1:1. A target sample size of approximately 200 patients was determined at the beginning, with a drop-off rate of 15% taken into account. After that, however, due to anticipated difficulty in enrolling sufficient number of patients that assures adequate statistical power, study design modification was decided in September 2022. Namely, efficacy evaluation was changed to exploratory objective and safety evaluation to the primary objective. The modification was reflected in the sixth version of the protocol. Approximately 90 patients were expected to be enrolled in the randomized part.

Key exclusion criteria
- **Hemoglobin concentration ≤7 g/dL before enrollment, or >7 g/dL and ≤9 g/dL with signs and symptoms of anemia**
- **History of *Neisseria meningitidis* infection**
- **History of allogeneic bone marrow transplantation**
- **Confirmed or suspected immunodeficiency (e.g., frequent recurrent infections)**
- **History of myelodysplastic syndrome with intermediate, high, or very high prognosis risk according to the IPSS-R**

This study consisted of 2 parts, a randomized part (Arm A [crovalimab group] and Arm B [eculizumab group]) and a non-randomized part (Arm C comprising 5 cohorts; see Table 31). A 24-week primary evaluation period and a 5-year maximum extension period were established. Patients were to receive crovalimab or eculizumab according to the dosage regimens in Table 30 in the primary evaluation period (up to Week 24), and crovalimab was to be administered subcutaneously in the extension period up to of 5 years.

Table 30. Dosage regimens

Body weight	Arm A (crovalimab)				Arm B (eculizumab)
	Day 1	Day 2	Weeks 2, 3, and 4	From Week 5 onwards every 4 weeks	Every 2 weeks[a)]
≥40 kg and <100 kg	1,000 mg IV	340 mg SC	340 mg SC	680 mg SC	900 mg IV
≥100 kg	1,500 mg IV	340 mg SC	340 mg SC	1,020 mg SC	

a) The approved maintenance dose level (900 mg) of eculizumab was administered, with Day 1 being 2 weeks after the last dose. Thereafter, doses were intravenously administered every 2 weeks. Dose change was not allowed during the study period.

The number of patients treated with eculizumab decreased over time with changing circumstances in clinical settings. It was therefore considered difficult to enroll the target sample size planned earlier that would secure the required statistical power to demonstrate efficacy. Accordingly, in September 2022, confirmatory efficacy evaluation was changed to an exploratory and descriptive evaluation, and enrollment in the randomized part (crovalimab and eculizumab groups) was terminated. In the randomized part, 89 patients were enrolled and randomized at 1:1 to crovalimab (45 including 5 Japanese) and eculizumab (44 including 4 Japanese). Of the 89 randomized patients, 3 patients (1 in the crovalimab group and 2 in the eculizumab group) discontinued the study before receiving study treatment. All 86 randomized patients who received the study drug in the randomized part (44 in the crovalimab group and 42 in the eculizumab group) were included in the randomized safety population (RSP), which was the safety analysis set. Of the randomized patients, 76 patients who had been enrolled in the study ≥24 weeks before the data cut-off date (39 patients [including 5 Japanese] in the crovalimab group and 37 patients [including 4 Japanese] in the eculizumab group) were included in the 24-week efficacy population. Up to Week 24, the primary evaluation period, 2 patients in the eculizumab group were discontinued from the study (due to "protocol deviation" and "other reasons" in 1 patient each). No Japanese patients were discontinued from the study by Week 24. In the primary evaluation period, 39 of 45 patients (86.7%) in the crovalimab group (Arm A) and 35 of 44 patients (79.5%) in the eculizumab group (Arm B) completed treatment and entered the extension period.

In Arm C, the non-randomized part, 38 patients (including 8 Japanese) were enrolled. Table 31 shows the 5 cohorts of Arm C and the number of patients enrolled. All patients enrolled were included in the safety analysis set. A total of 34 patients who had been enrolled in the study ≥24 weeks before the data

cut-off date (19 in Cohort [2], 9 in Cohort [3], and 6 in Cohort [4]) were included in the 24-week efficacy population.

Table 31. Five cohorts of Arm C and number of patients enrolled

Arm C cohorts	Patients enrolled (Japanese patients)
(1) Patients aged <18 years who have been receiving eculizumab (body weight ≥40 kg)	1 (0)
(2) Patients who have been treated with ravulizumab	21 (3)
(3) Patients who have been treated with eculizumab at a dose level higher than the approved dose level for PNH	10 (0)
(4) Patients with known C5 genetic polymorphism whose hemolysis control was poor with eculizumab or ravulizumab	6 (5)
(5) Patients aged ≥18 years who have been treated with eculizumab at the approved dosage level [a)]	0 (0)

a) The cohort added after the termination of enrollment in the randomized part in September 2022.

In Arm C, 3 patients in Cohort (2) and 1 patient in Cohort (3) discontinued the study before completing the 24-week treatment period. In the primary evaluation period, 15 patients in Cohort (2), 8 patients in Cohort (3), and 6 patients in Cohort (4) completed treatment and entered the extension period. No Japanese patients discontinued the study.

Table 32 shows the efficacy results in the 24-week efficacy population. The efficacy in hemolysis control from Week 2 to Week 25,[23)] transfusion avoidance from baseline to Week 25, and breakthrough hemolysis from baseline to Week 25[24)] in the crovalimab group were comparable to those in the eculizumab group. The proportion of patients whose Hb levels were stable from baseline to Week 25[25)] tended to be higher in the eculizumab group than in the crovalimab group. The adjusted mean change from baseline on the functional assessment of chronic illness therapy-fatigue (FACIT-Fatigue)[26)] scale at Week 25 improved in the crovalimab group compared to that in the eculizumab group.

Table 32. Efficacy results (24-week efficacy population)

	Crovalimab (Arm A) (N = 39)	Eculizumab (Arm B) (N = 37)
Mean proportion of patients achieving hemolysis control from Week 2 to Week 25, % [95% CI][a)]	92.9 [86.62, 96.39]	93.7 [87.26, 97.04]
Odds ratio [95% CI][a)]	0.88 [0.28, 2.77]	
Proportion of patients achieving transfusion avoidance, % (n)	79.5 (31)	78.4 (29)
Adjusted between-group difference [95% CI][b)]	1.8 [−16.67, 19.94]	
Proportion of patients with breakthrough hemolysis, % (n)	10.3 (4)	13.5 (5)
Adjusted between-group difference [95% CI][b)]	−3.5 [−19.20, 11.68]	
Proportion of patients with stabilized Hb, % (n)	59.0 (23)	70.3 (26)
Adjusted between-group difference [95% CI][b)]	−10.8 [−30.84, 10.39]	
Adjusted mean change from baseline in FACIT-Fatigue score [c)]	1.09	−2.61
Difference in mean change [95% CI][c)]	3.71 [0.05, 7.36]	

a) Calculated based on the GEE approach using the logit link function, with treatment, evaluation timepoint (Week 2, Week 3, Week 4, and from Week 5 onwards, once every 2 weeks up to Week 25), transfusion history in the 12 months prior to randomization, and baseline LDH as explanatory variables (the covariance structure is first-order autoregressive).
b) Calculated based on a stratified Newcombe method (*Stat Biopharm Res.* 2010;2:329-335) with transfusion history in the 12 months prior to randomization as stratification factor.
c) Calculated based on the mixed-effects model for repeated measures (MMRM) with treatment, timepoint, treatment-timepoint interaction, transfusion history in the 12 months prior to randomization, and baseline FACIT-Fatigue score as explanatory variables (the covariance structure is unstructured).

[23)] The mean proportion of patients achieving LDH ≤1.5 × ULN
[24)] At least one of the following events emerged or worsened, in the presence of elevated LDH levels ≥2 × ULN after prior reduction of LDH levels to <1.5 × ULN following study drug treatment:
fatigue, hemoglobinuria, abdominal pain, shortness of breath (dyspnoea), Hb <10 g/dL, major adverse vascular events, dysphagia, erectile dysfunction
[25)] A condition in which blood Hb levels have not decreased ≥2 g/dL from baseline without receiving transfusion
[26)] The FACIT-Fatigue scale is a 13-item measure that assesses fatigue for the 7 most recent days, in which higher scores indicate better functioning (less fatigue). The total score was considered evaluable when answers to >50% of questions (≥7 out of 13 questions) are obtained.

In Arm C, the mean proportion of patients achieving hemolysis control from baseline to Week 25 [95% confidence interval (CI)] was 95.8% [89.11%, 98.43%] in Cohort (2) and 91.0% [71.49%, 97.60%] in Cohort (3). The mean LDH at baseline for 6 patients in Cohort (4) was 7.8 × ULN. The LDH levels in 3 patients decreased to ≤1.5 × ULN by Week 5, while 2 patients maintained LDH levels at ≤2 × ULN from Week 5 through Week 25. The proportions of patients achieving transfusion avoidance from baseline to Week 25 were 57.9% (11 of 19 patients), 33.3% (3 of 9 patients), and 50.0% (3 of 6 patients) in Cohorts (2), (3), and (4), respectively.

In the primary evaluation period in the randomized part, adverse events occurred in 34 of 44 patients (77.3%) in the crovalimab group and 28 of 42 patients (66.7%) in the eculizumab group. Adverse drug reactions occurred in 14 of 44 patients (31.8%) in the crovalimab group and 0 of 42 patients (0%) in the eculizumab group. Table 33 shows adverse events occurring in ≥5% of patients in either group during the primary evaluation period. Adverse drug reactions occurring in ≥5% of patients in the crovalimab group were type III immune complex mediated reaction (15.9%; 7 of 44 patients), infusion-related reaction (13.6%; 6 of 44 patients), and injection-related reaction (6.8%; 3 of 44 patients).

Table 33. Adverse events occurring in ≥5% of patients in either group (RSP)

	Primary evaluation period (24 weeks)	
	Crovalimab (Arm A) (N = 44)	Eculizumab (Arm B) (N = 42)
All adverse events	**77.3 (34)**	**66.7 (28)**
Pyrexia	**15.9 (7)**	**2.4 (1)**
Type III immune complex mediated reaction	**15.9 (7)**	**0**
COVID-19	**13.6 (6)**	**16.7 (7)**
Infusion related reaction	**13.6 (6)**	**0**
Headache	**11.4 (5)**	**2.4 (1)**
Nausea	**6.8 (3)**	**4.8 (2)**
Asthenia	**6.8 (3)**	**4.8 (2)**
Diarrhoea	**6.8 (3)**	**2.4 (1)**
Upper respiratory tract infection	**6.8 (3)**	**2.4 (1)**
Oedema peripheral	**6.8 (3)**	**2.4 (1)**
Injection related reaction	**6.8 (3)**	**0**
Arthralgia	**6.8 (3)**	**0**
Rash	**6.8 (3)**	**0**
Influenza	**4.5 (2)**	**7.1 (3)**
Urinary tract infection	**4.5 (2)**	**7.1 (3)**

MedDRA/J ver. 25.1; incidence, % (n)

In the primary evaluation period, there were no reports of death. Serious adverse events occurred in 6 of 44 patients (13.6%) in the crovalimab group (pneumonia, nasopharyngitis, urinary tract infection, neutropenia, pyrexia, hyperbilirubinaemia, skin laceration, and cervical dysplasia [1 patient each]; some patients were counted more than once) and 1 of 42 patients (2.4%) in the eculizumab group (pyelonephritis and transient ischaemic attack). There were no serious adverse drug reactions or adverse events leading to study treatment discontinuation in either group.

In the extension period, adverse events occurred in 39 of 44 patients (88.6%) in the crovalimab continuation group and 30 of 35 patients (85.7%) in the crovalimab-switch group. Adverse drug reactions occurred in 14 of 44 patients (31.8%) in the crovalimab continuation group and 16 of 35 patients (45.7%) in the crovalimab-switch group. Table 34 shows adverse events occurring in ≥5% of patients in either group. Adverse drug reactions occurring in ≥5% of patients in either group were type

III immune complex mediated reaction (15.9%; 7 of 44 patients), infusion-related reaction (13.6%; 6 of 44 patients), and injection-related reaction (6.8%; 3 of 44 patients) in the crovalimab continuation group and type III immune complex mediated reaction (22.9%; 8 of 35 patients), injection-related reaction (14.3%; 5 of 35 patients), and infusion-related reaction (11.4%; 4 of 35 patients) in the crovalimab-switch group.

Table 34. Adverse events occurring in ≥5% of patients in either group (extension period; crovalimab safety population)

	Crovalimab continuation group (N = 44)	Crovalimab-switch group (N = 35)
	Overall treatment period (treatment duration[a]: 52.00 weeks)	Post-switch period (treatment duration[a]: 32.14 weeks)
All adverse events	**88.6 (39)**	**85.7 (30)**
COVID-19	**22.7 (10)**	**25.7 (9)**
Pyrexia	**18.2 (8)**	**5.7 (2)**
Type III immune complex mediated reaction	**15.9 (7)**	**22.9 (8)**
Headache	**15.9 (7)**	**8.6 (3)**
Infusion related reaction	**13.6 (6)**	**11.4 (4)**
Arthralgia	**9.1 (4)**	**8.6 (3)**
Upper respiratory tract infection	**9.1 (4)**	**2.9 (1)**
Injection related reaction	**6.8 (3)**	**14.3 (5)**
Asthenia	**6.8 (3)**	**5.7 (2)**
Urinary tract infection	**6.8 (3)**	**2.9 (1)**
Diarrhoea	**6.8 (3)**	**2.9 (1)**
Nasopharyngitis	**6.8 (3)**	**2.9 (1)**
Oedema peripheral	**6.8 (3)**	**0**
Neutrophil count decreased	**6.8 (3)**	**0**
Rash	**6.8 (3)**	**0**
Pruritus	**6.8 (3)**	**0**
Nausea	**6.8 (3)**	**0**
Influenza	**4.5 (2)**	**5.7 (2)**
Back pain	**4.5 (2)**	**8.6 (3)**
Muscle spasms	**2.3 (1)**	**5.7 (2)**
Odynophagia	**2.3 (1)**	**5.7 (2)**
Contusion	**0**	**5.7 (2)**
Thrombocytopenia	**0**	**5.7 (2)**
Pharyngitis	**0**	**5.7 (2)**

MedDRA/J ver. 25.1; incidence, % (n)
a) Median

In the extension period, 1 patient in the crovalimab continuation group died (colorectal cancer[27)]), of which a causal relationship to crovalimab was ruled out. Serious adverse events occurred in 10 of 44 patients (22.7%) in the crovalimab continuation group (urinary tract infection [2 patients], COVID-19, pneumonia, nasopharyngitis, respiratory tract infection, systemic bacterial infection, breakthrough haemolysis, febrile neutropenia, neutropenia, ileus, pyrexia, hyperbilirubinaemia, skin laceration, open globe injury, cervical dysplasia, and colorectal cancer [1 patient each]; some patients were counted more than once) and 4 of 35 patients (11.4%) in the crovalimab-switch group (breakthrough haemolysis, obstructive pancreatitis, type III immune complex mediated reaction, and COVID-19 [1 patient each]). Among these events, type III immune complex mediated reaction occurring in 1 patient in the crovalimab-switch group was considered to be a serious adverse drug reaction, with the outcome being reported as resolved. An adverse event leading to study treatment discontinuation was reported

27) The white female aged 5[redacted] years visited a clinic on Day 198 for difficulty in food intake. The patient was diagnosed as having colorectal cancer based on the pathological biopsy. The CT scan performed concurrently indicated peritoneal dissemination, and palliative treatment was selected. On Day 211, the patient died of colorectal cancer.

only in the crovalimab-switch group (2.9%, 1 of 35 patients; type III immune complex mediated reaction).

In Arm C, in the overall treatment period, adverse events occurred in 33 of 38 patients (86.8%) in total, and on a cohort-by-cohort basis, 0 of 1 patient (0%) in Cohort (1), 18 of 21 patients (85.7%) in Cohort (2), 10 of 10 patients (100%) in Cohort (3), and 5 of 6 patients (83.3%) in Cohort (4). Adverse drug reactions occurred in 15 of 38 patients (39.5%) in total, including 0 of 1 patient (0%) in Cohort (1), 10 of 21 patients (47.6%) in Cohort (2), 3 of 10 patients (30.0%) in Cohort (3), and 2 of 6 patients (33.3%) in Cohort (4).

In Arm C, there were no reports of death in the overall treatment period. Serious adverse events occurred in 9 of 38 patients (23.7%) in total, including, 7 of 21 patients (33.3%) in Cohort (2) (type III immune complex mediated reaction [3 patients each], extravascular haemolysis, haemolysis, infection, sepsis, viral infection, cholangitis, cholangitis acute, axonal neuropathy, and calculus urinary [1 patient each]; some patients were counted more than once) and 2 of 10 patients (20.0%) in Cohort (3) (type III immune complex mediated reaction and autoimmune haemolytic anaemia [1 patient each]). Type III immune complex mediated reaction (3 patients), sepsis, axonal neuropathy in Cohort (2), and type III immune complex mediated reaction (1 patient each) in Cohort (3) were classified as serious adverse drug reactions, which resolved or were resolving. No serious adverse events occurred in Cohort (1) or (4). Adverse events leading to study treatment discontinuation occurred only in Cohort (2) (1 of 21 patients, 4.8%; type III immune complex mediated reaction).

In the Japanese subpopulation, during the primary evaluation period, adverse events occurred in 4 of 5 patients (80.0%) in the crovalimab group and 3 of 4 patients (75.0%) in the eculizumab group. Adverse drug reactions occurred only in the crovalimab group in 2 of 5 patients (40.0%). There were no reports of death. Serious adverse events occurred in 2 of 5 patients (40.0%) in the crovalimab group (nasopharyngitis, pyrexia, cervical dysplasia [1 patient each]; 1 patient was counted twice), and a causal relationship to the study drug was ruled out for all events. No adverse events led to study treatment discontinuation.

In the Japanese subpopulation, during the extension period, adverse events occurred in 4 of 5 patients (80.0%) in the crovalimab continuation group and 4 of 4 patients (100%) in the crovalimab-switch group. Adverse drug reactions occurred in 3 of 4 patients (75.0%) in the crovalimab-switch group. Adverse drug reactions occurring in ≥2 patients were type III immune complex mediated reaction, injection-related reaction, and infusion-related reaction. While the outcomes for type III immune complex mediated reaction and infusion-related reaction were reported as resolved, the outcomes of injection-related reaction in 2 patients were reported as not resolved. During the extension period, serious adverse events occurred in 2 of 5 patients (40%) in the crovalimab continuation group (systemic bacterial infection, nasopharyngitis, pyrexia, and cervical dysplasia [1 patient each]; some patients were counted more than once) and 1 of 4 patients (25.0%) in the crovalimab-switch group (breakthrough

haemolysis). A causal relationship to the study drug was ruled out for all events. No adverse events led to study treatment discontinuation.

In Arm C in the Japanese subpopulation, during the overall treatment period, adverse events occurred in 8 of 8 patients (100%) and adverse drug reactions in 5 of 8 patients (62.5%). There were no reports of death, and serious adverse events occurred in 2 of 3 patients (66.7%) in Cohort (2) (calculus urinary, extravascular haemolysis, and infection [1 patient each]; 1 patient was counted twice). A causal relationship to crovalimab was ruled out for all events. No adverse events led to study treatment discontinuation.

7.R Outline of the review conducted by PMDA

7.R.1 Efficacy

Based on the discussions in Sections 7.R.1.1 through 7.R.1.4, PMDA has concluded that the efficacy of crovalimab has been demonstrated in the treatment of PNH and is promising in Japanese patients as well.

7.R.1.1 Efficacy in complement inhibitor-naïve patients with PNH

The applicant's explanation about efficacy in complement inhibitor-naïve patients with PNH:

Eculizumab had been the standard of care for patients with PNH in many countries and regions. Therefore, for the global phase III study (Study BO42162) in complement inhibitor-naïve patients with PNH (Table 24) eculizumab was selected as the comparator to investigate the non-inferiority of crovalimab to eculizumab. The study had 2 primary endpoints of "the proportion of patients with transfusion avoidance from baseline to Week 25" and "the mean proportion of patients achieving hemolysis control from Week 5 to Week 25." The co-endpoints were expected to allow the demonstration of clinically meaningful efficacy by evaluating not only transfusion avoidance but also hemolysis control as objective indicator, LDH. The non-inferiority margin for transfusion avoidance was selected as follows. Based on the data from the eculizumab group in a global phase III study that evaluated the non-inferiority of ravulizumab to eculizumab (Study ALXN1210-PNH-301), and data on eculizumab treatment-naïve patients from the Global PNH Registry, eculizumab-treated patients showed a benefit over eculizumab treatment-naïve patients in terms of transfusion avoidance with a difference of approximately 40%. A non-inferiority margin of "−20%" was determined to preserve approximately 50% of eculizumab's therapeutic effect compared to eculizumab treatment-naïve patients. The non-inferiority margin for hemolysis control was selected as follows. Based on the data from Study ALXN1210-PNH-301, the proportion of patients achieving hemolysis control after receiving eculizumab was assumed to be 86%, and based on the results of a foreign phase III study (TRIUMPH study) that evaluated the superiority of eculizumab over to placebo, the proportion of patients achieving hemolysis control after receiving placebo was conservatively assumed to be 20%. A non-inferiority margin of "0.2" was selected to preserve approximately 50% of eculizumab's treatment effect compared to placebo.

In both primary endpoints of Study BO42162, the lower bounds for the 95% confidence interval exceeded the non-inferiority margin, demonstrating the non-inferiority of crovalimab to eculizumab [see Section 7.2.1]. In the Japanese population, 2 of 2 patients in the crovalimab group and 1 of 3 patients in the eculizumab group achieved hemolysis control from Week 5 to Week 25, while 2 of 2 patients in the crovalimab group and 3 of 3 patients in the eculizumab group achieved transfusion avoidance from baseline to Week 25. Although the limited number of Japanese patients in the study precludes strict interpretation of the results, efficacy in the Japanese population did not tend to differ from that in the overall population.

Table 35 shows key secondary endpoints of Study BO42162: "the proportion of patients with breakthrough hemolysis[24)] from baseline to Week 25," "the proportion of patients with stabilized Hb levels[25)] from baseline to Week 25," and "the adjusted mean change from baseline in FACIT-Fatigue score[26)] to Week 25" The results suggest the consistent efficacy of crovalimab. The results of key secondary endpoints in the Japanese population showed that 0 of 2 patients in the crovalimab group and 1 of 3 patients in the eculizumab group experienced breakthrough hemolysis from baseline to Week 25; 2 of 2 patients in the crovalimab group and 3 of 3 patients in the eculizumab group had stabilized Hb levels from baseline to Week 25; and the mean change from baseline in FACIT-Fatigue score up to Week 25 was 13.0 in the crovalimab group and 5.7 in the eculizumab group. Although the limited number of Japanese patients in the study precludes strict interpretation of the results, there was no difference between the overall population and the Japanese population that could cause clinical problems

Taken together, the efficacy of crovalimab has been demonstrated in complement inhibitor-naïve patients with PNH, and crovalimab is expected to effective in Japanese patients.

Table 35. Results for key secondary endpoints in the global phase III study (Study BO42162) (PAP)

	Crovalimab (Arm A) (N = 134)	Eculizumab (Arm B) (N = 69)
Proportion of patients with breakthrough hemolysis from baseline to Week 25, % (n)	**10.4 (14)**	**14.5 (10)**
Adjusted between-group difference [95% CI][a)]	**−3.9 [−14.82, 5.26]**	
Proportion of patients with stabilized Hb levels from baseline to Week 25, % (n)	**63.4 (85)**	**60.9 (42)**
Adjusted between-group difference [95% CI][a)]	**2.2 [−11.37, 16.31]**	
Adjusted mean change in FACIT-Fatigue score from baseline to Week 25	**7.8**	**5.2**
Difference in mean change [95% CI][b)]	**2.6 [0.68, 4.60]**	

a) Calculated based on a stratified Newcombe method (*Stat Biopharm Res.* 2010;2:329-335) with pre-randomization LDH (≥2 × ULN and ≤4 × ULN, or >4 × ULN) and transfusion units within 6 months prior to randomization (0, >0 and ≤6, or >6) as stratification factors.
b) Calculated based on the MMRM with treatment, timepoint, treatment-timepoint interaction, baseline FACIT-Fatigue score, pre-randomization LDH (≥2 × ULN and ≤4 × ULN, or >4 × ULN), and transfusion units within 6 months prior to randomization (0, >0 and ≤6, or >6) as explanatory variables (the covariance structure is unstructured).

In Study BO42162, 6 complement inhibitor-naïve patients aged <18 years (13-17 years) were enrolled in Arm C. Although the limited number of patients evaluated allowed limited interpretation of the data, the results suggest promising efficacy of crovalimab in both hemolysis control and transfusion avoidance, the primary endpoints [see Section 7.2.1]. The pathophysiology of PNH is consistent regardless of age (*Blood*. 2011;118:2102). The steady state trough concentration of crovalimab in any

body weight category of patients aged 12 years, 36 years, and 80 years exceeded the concentration which allows complete inhibition of complement activity [see Section 6.2.4]. These findings further support crovalimab's potential efficacy in complement inhibitor-naïve patients with PNH aged <18 years as in those aged ≥18 years.

PMDA's view:
Given that Study BO42162 aimed to investigate the efficacy of crovalimab in complement inhibitor-naïve patients with PNH, it is reasonable to use eculizumab, the standard of care, as a comparator, and co-primary endpoints to evaluate hemolysis and transfusion. In addition, the non-inferiority margins were within a clinically reasonable range based on the information available at the time of study planning, and thus the non-inferiority margins set were appropriate. Both primary endpoints of Study BO42162, "the mean proportion of patients achieving hemolysis control from Week 5 to Week 25" and "the proportion of patients with transfusion avoidance from baseline to Week 25," demonstrated the non-inferiority of crovalimab to eculizumab by the lower bounds for the 95% confidence interval greater than the pre-specified non-inferiority margin. The key secondary endpoints supported the primary endpoint outcomes. Therefore, crovalimab has promising efficacy in the treatment of complement inhibitor-naïve patients with PNH. In Japanese population evaluated, although limited in number, 2 patients in the crovalimab group achieved both primary endpoints and the key secondary endpoints yielded outcomes tending to similar to those in the overall population. Thus, the results in the Japanese population are considered consistent with those of the overall population, and that crovalimab is expected to show its efficacy in Japanese patients.

Crovalimab is also expected to have efficacy in complement inhibitor-naïve patients with PNH aged <18 years, based on the results in Arm C, which did not tend to contradict the results in those aged ≥18 years in the crovalimab group and the applicant's explanation about the disease state of PNH by age group and the pharmacokinetics of crovalimab.

7.R.1.2 Efficacy in patients with PNH switching from another complement inhibitor to crovalimab

The applicant's explanation about efficacy in patients with PNH switching from another complement inhibitor (eculizumab or ravulizumab) to crovalimab:
The randomized part of the global phase III study (Study BO42161) enrolled patients who had been treated with eculizumab for ≥24 weeks whose screening LDH levels were ≤1.5 × ULN (Table 29). However, because of over-time decrease in the number of patients treated with eculizumab with changing circumstances in clinical settings, it was difficult to enroll the target number of patients as originally planned to ensure the statistical power required to demonstrate efficacy in Study BO42161. Accordingly, the efficacy evaluation was performed for exploratory purpose. For this reason, the endpoints pertaining to "hemolysis control," "transfusion avoidance," "breakthrough hemolysis," "Hb levels," and "FACIT-Fatigue score" were evaluated, albeit exploratory. The efficacy in the crovalimab group was similar to that in the eculizumab group (Table 36). In the Japanese population,

the limited number of patients evaluated precluded adequate interpretation of data. However, the efficacy results in the Japanese population did not tend to differ markedly from those in the overall population (Table 36).

Table 36. Results of efficacy endpoints in the global phase III study (Study BO42161) (24-week efficacy population)

	Overall population		Japanese population	
	Crovalimab (N = 39)	Eculizumab (N = 37)	Crovalimab (N = 5)	Eculizumab (N = 4)
Mean proportion of patients achieving hemolysis control, %	92.9	93.7	_[b)]	_[b)]
Odds ratio [95% CI]	0.88 [0.28, 2.77]		_[b)]	
Proportion of patients achieving transfusion avoidance, % (n)	79.5 (31)	78.4 (29)	80.0 (4)	75.0 (3)
Between-group difference[a)] [95% CI]	1.8 [−16.67, 19.94]		5.0 [−42.11, 52.83]	
Proportion of patients with breakthrough hemolysis, % (n)	10.3 (4)	13.5 (5)	20.0 (1)	0.0 (0)
Between-group difference[a)] [95% CI]	−3.5 [−19.20, 11.68]		20.0 [−31.65, 62.45]	
Proportion of patients with stabilized Hb, % (n)	59.0 (23)	70.3 (26)	40.0 (2)	75.0 (3)
Between-group difference[a)] [95% CI]	−10.8 [−30.84, 10.39]		−35.0 [−69.86, 23.16]	
Adjusted mean change from baseline in FACIT-Fatigue score	1.09	−2.61	−3.28	−7.35
Difference in mean change from baseline [95% CI]	3.71 [0.05, 7.36]		4.06 [−8.28, 16.41]	

a) In the analysis of the overall population, the adjusted between-group difference was calculated with the presence/absence of transfusion history in the 12 months prior to randomization as a stratification factor, while in the analysis of the Japanese subpopulation, due to the limited number of patients evaluated, the between-group difference was calculated without using a stratification factor.

b) All Japanese patients who achieved hemolysis control had maintained LDH ≤1.5 × ULN at all timepoints except for 1 timepoint in 1 patient (crovalimab group, Week 13; 1.56 × ULN). For this reason, it was determined that calculation of odds ratio based on the GEE approach, equivalent to that implemented for the overall population, was not possible for the Japanese subpopulation.

The pathophysiological mechanism of PNH involves hematopoietic stem cell clones deficient in GPI-anchored proteins (*Nat Rev Dis Primers*. 2017;3:17028). Even when treatment with a complement inhibitor improves intravascular hemolysis, anemia, or thrombosis is improved after treatment with, PNH clone size of hematopoietic stem cells as measured in granulocyte clones does not change over time (*Blood*. 2008;111:1840-7). Therefore, the basic pathophysiological mechanism of PNH should be the same regardless of prior treatment with a complement inhibitor, and crovalimab is expected to show its efficacy in patients with PNH who have been previously treated with a complement inhibitor as in treatment-naïve patients.

PMDA's view:

Patient enrollment in the randomized part of Study BO42161, which targeted patients with PNH whose LDH levels were controlled ≤1.5 × ULN with eculizumab or ravulizumab, was discontinued due to the failure to enroll the number of patients sufficient to assure adequate statistical power for efficacy assessments. Therefore, it is difficult to reach a conclusion on the efficacy of crovalimab in patients who were previously treated with another C5 inhibitor based on the study results. However, the exploratory assessment of efficacy data from the study showed no tendency of significant inconsistency in overall efficacy between crovalimab and eculizumab in the randomized part of Study BO42161. Although the limited number of Japanese patients precluded adequate interpretation, the results did not tend to differ significantly from those in the overall population. The applicant's explanation, i.e., there is no pathological difference between complement inhibitor-naïve patients with PNH and patients with PNH with prior treatment with another complement inhibitor, is reasonable. In addition, the efficacy of

crovalimab has been demonstrated in complement inhibitor-naïve patients with PNH, and crovalimab is expected to have efficacy in Japanese patients [see Section 7.R.1.1]. In these views, there is no need to restrict patients in stable condition with another C5 inhibitor from switching to crovalimab. Such restriction is unnecessary in Japanese patients as well.

7.R.1.3 Efficacy by patient characteristics

The applicant's explanation about the efficacy of crovalimab by patient characteristics:

The co-primary endpoint results from the global phase III study (Study BO42162), hemolysis control and transfusion avoidance by patient characteristics, are shown in Table 37 and Table 38, respectively. Some of the subgroups have limited number of patients, which precluded adequate interpretation of the results. However, there were no differences in the efficacy of crovalimab between subgroups except for sex. The odds ratio [95% CI] of hemolysis control for crovalimab to eculizumab was 0.31 [0.13, 0.74] in female patients and 1.76 [0.82, 3.76] in male patients. The upper bound of the 95% CI for the odds ratio was <1 in female patients. Conversely, efficacy pertaining to transfusion avoidance in the crovalimab group was similar to that in the eculizumab group in both male and female subgroups (Table 38). There were no differences in the efficacy of crovalimab between the sexes in secondary endpoints, i.e., the proportion of patients with stabilized Hb, breakthrough hemolysis, and mean change in FACIT-Fatigue score from baseline. There were no differences between the sexes in terms of the change from baseline in complement activity levels or exposure-response relationship. In summary, other than sex difference in hemolysis control, there was no consistent trend in other efficacy endpoints, and the observed difference is not considered clinically meaningful.

Table 37. Mean proportion of patients achieving hemolysis control from Week 5 to Week 25 by patient characteristics (PAP)

		Crovalimab (N = 134)	Eculizumab (N = 69)	Odds ratio [95% CI]
Age	<18 years	– (0)	62.2 [43.7, 77.7] (2)	–
	≥18 and <65 years	81.0 [75.0, 85.8] (122)	82.8 [73.4, 89.4] (58)	0.88 [0.46, 1.70]
	≥65 years	69.7 [45.1, 86.6] (12)	78.9 [49.5, 93.4] (9)	0.62 [0.11, 3.34]
Sex	Female	78.5 [68.8, 85.7] (57)	92.2 [85.1, 96.1] (34)	0.31 [0.13, 0.74]
	Male	81.2 [73.6, 87.0] (77)	71.1 [56.9, 82.1] (35)	1.76 [0.82, 3.76]
Transfusion history (number of units administered within 6 months prior to screening)	No transfusion	83.4 [67.7, 92.4] (33)	77.6 [56.3, 90.3] (17)	1.45 [0.39, 5.45]
	≤6 units	82.4 [75.0, 87.9] (67)	89.0 [78.3, 94.8] (34)	0.58 [0.23, 1.46]
	>6 units	71.6 [59.4, 81.3] (34)	72.0 [53.1, 85.4] (18)	0.98 [0.37, 2.62]
LDH at randomization	≥2 × ULN and ≤4 × ULN	75.2 [55.8, 88.0] (24)	64.8 [40.2, 83.5] (11)	1.65 [0.43, 6.29]
	>4 × ULN	81.2 [75.2, 85.9] (110)	85.2 [76.4, 91.1] (58)	0.75 [0.38, 1.47]
Aplastic anemia	Present	81.2 [71.8, 88.0] (52)	83.6 [68.1, 92.4] (26)	0.85 [0.31, 2.35]
	Absent	79.2 [71.4, 85.3] (82)	80.8 [69.9, 88.4] (43)	0.90 [0.44, 1.88]

Mean proportion of patients [95% CI] (N)

Table 38. The proportion of patients achieving transfusion avoidance at Week 24 by patient characteristics (PAP)

		Crovalimab (N = 134)	Eculizumab (N = 69)	Between-group difference [95% CI]
Age	<18 years	– (0/0)	50.0 (1/2)	–
	≥18 and <65 years	66.4 (81/122)	72.4 (42/58)	−6.02 [−19.2, 8.80]
	≥65 years	58.3 (7/12)	44.4 (4/9)	13.9 [−25.2, 47.8]
Sex	Female	59.7 (34/57)	64.7 (22/34)	−5.06 [−24.0, 22.5]
	Male	70.1 (54/77)	71.4 (25/35)	−1.30 [−17.8, 17.5]
Transfusion history (number of units administered within 6 months prior to screening)	No transfusion	87.9 (29/33)	82.4 (14/17)	5.53 [−13.5, 30.0]
	≤6 units	70.2 (47/67)	73.5 (25/34)	−3.38 [−20.1, 15.9]
	>6 units	35.3 (12/34)	44.4 (8/18)	−9.15 [−35.0, 16.9]
LDH at randomization	≥2 × ULN and ≤4 × ULN	79.2 (19/24)	63.6 (7/11)	15.53 [−13.4, 46.1]
	>4 × ULN	62.7 (69/110)	69.0 (40/58)	−6.24 [−20.2, 9.08]
Aplastic anemia	Present	65.4 (34/52)	76.9 (20/26)	−11.5 [−29.7, 10.6]
	Absent	65.9 (54/82)	62.8 (27/43)	3.06 [−13.7, 20.7]

Proportion of patients [95% CI] (patients achieving transfusion avoidance/N)

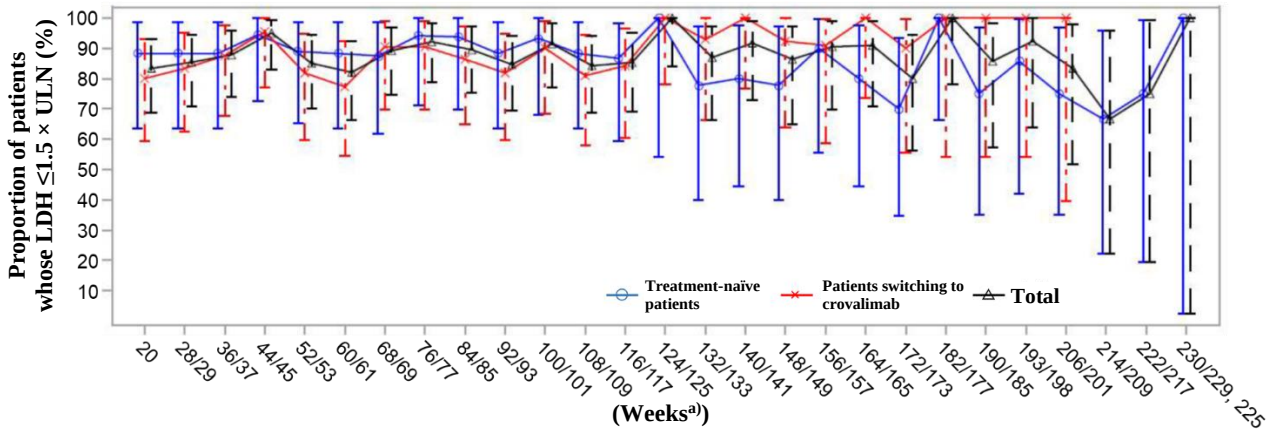
PMDA's view:

The efficacy data by patient characteristics showed a low proportion of female patients on crovalimab achieving hemolysis control, one of the primary endpoints as compared to eculizumab. However, such tendency was not noted in the results of transfusion avoidance, the other primary endpoint, or subgroup analysis results of the secondary endpoints, and thus the efficacy of crovalimab is not markedly low in female patients. Some of the subgroups by patient characteristics were small in size, but did not show a tendency towards a decrease in efficacy in the crovalimab group as compared to the eculizumab group. Any of the evaluated differences in patient characteristics is unlikely to have significant impacts on the efficacy of crovalimab.

7.R.1.4 Long-term efficacy

The applicant's explanation about the long-term efficacy of crovalimab:

Figure 8 shows the proportion of patients with LDH ≤1.5 × ULN in the extension part (38 patients; median treatment duration, 3.0 years) of the global phase I/II study (Study BP39144) over time, which remained roughly in the range of 80% to 100% throughout the treatment period. Table 39 shows the proportion of patients achieving transfusion avoidance in 24-week periods. Throughout the treatment period, the proportion remained roughly in the range of 80% to 90%. The proportion of patients with breakthrough hemolysis and that of stabilized Hb also remained roughly in the ranges of 0% to 5% and 80% to 88%, respectively, in 24-week periods throughout the treatment period. Study BP394144 enrolled 11 Japanese patients (4 treatment-naïve patients and 7 patients switching to crovalimab). In all 4 treatment-naïve patients, LDH decreased to ≤1.5 × ULN by Day 15 and maintained LDH ≤1.5 × ULN through the data cut-off date. In 6 of the 7 patients switching to crovalimab, LDH remained ≤1.5 × ULN for the most part after baseline. In the remaining 1 patient, although LDH was >1.5 × ULN, ≤2.0 × ULN was maintained at all timepoints. Eight of the 11 Japanese patients stayed transfusion-free up to the data cut-off date. These results demonstrated continued efficacy of crovalimab, which is expected to be shown in Japanese patients as well.



Number of patients evaluated																											
Treatment-naïve patients	17	17	17	18	18	17	16	17	16	17	15	17	15	6	9	10	9	10	10	10	9	8	7	8	6	4	1
Patients switching to crovalimab	25	24	24	22	22	22	21	21	22	22	20	21	19	15	14	14	13	11	12	10	6	6	6	4	0	0	0
Total	42	41	41	40	40	39	37	38	38	39	35	38	34	21	23	24	22	21	22	20	15	14	13	12	6	4	1

Figure 8. Proportion of patients with LDH ≤1.5 ×ULN over time (the median and the interquartile range; extension part in Study BP39144)

a) Weeks are expressed as Week number X/Y. X represents the week number for patients who started the extension period after Part 2 or Part 3, while Y represents the week number for patients who started the extension period after Part 4.

Table 39. Proportion of patients who achieved transfusion avoidance in 24-week periods (Study BP39144, extension part)

	Treatment-naïve patients (N = 18)	Patients switching to crovalimab (N = 25)	Overall (N = 43)
Weeks 20-43	**77.8 (14/18)**	**87.0 (20/23)**	**82.9 (34/41)**
Weeks 44-67	**94.1 (16/17)**	**81.8 (18/22)**	**87.2 (34/39)**
Weeks 68-91	**82.4 (14/17)**	**86.4 (19/22)**	**84.6 (33/39)**
Weeks 92-115	**80.0 (12/15)**	**94.7 (18/19)**	**88.2 (30/34)**
Weeks 116-139	**90.0 (9/10)**	**92.9 (13/14)**	**91.7 (22/24)**
Weeks 140-163	**90.0 (9/10)**	**91.7 (11/12)**	**90.9 (20/22)**
Weeks 164-187	**87.5 (7/8)**	**83.3 (5/6)**	**85.7 (12/14)**
Weeks 188-212	**83.3 (5/6)**	**NE (0)**	**83.3 (5/6)**

Proportion, % (patients achieving transfusion avoidance/N); NE, not evaluable

Based on the results from the extension part of Study BP39144, the efficacy of crovalimab will generally last in long-term use, and long-lasting efficacy of crovalimab will be expected in Japanese patients as well.

7.R.2 Safety

Based on the discussions in Sections 7.R.2.1, 7.R.2.2, and 7.R.2.3, in the clinical studies of crovalimab, the safety data of crovalimab including infection risks in patients with PNH did not tend to differ particularly from those of eculizumab. The safety profile of crovalimab is not considered to differ significantly from that of other existing C5 inhibitors. Although small size of the Japanese population precluded adequate interpretation of the results, there were no safety concerns specific to Japanese patients. In addition, for being a subcutaneous formulation, crovalimab must be used with caution due to possible injection site-related adverse events observed frequently as compared to eculizumab for intravenous infusion. However, most of the adverse events were mild or moderate in severity and did not interrupt the treatment; Thus, tolerability at the injection site will not compromise the usefulness of crovalimab. Furthermore, cautionary advice should be offered concerning immune complex reactions induced by DTDC formation for patients switching to crovalimab from an existing C5 inhibitor.

Accordingly, the applicant is required to take necessary measures in preparation for the launch of crovalimab, to ensure that crovalimab is administered only by physicians and at medical institutions with expertise in the diagnosis and treatment of PNH and capability to manage the risks associated with crovalimab, and only in cooperation with a physician expert in diagnosis and treatment of meningococcal infection, as practiced in the use of other approved complement inhibitors.

Only a small number of Japanese patients were evaluated in the clinical studies. Thus, the applicant is required to conduct post-marketing surveillance covering all patients treated with crovalimab to evaluate the safety of crovalimab in Japanese patients with PNH as proposed, and thereby take necessary actions according to the obtained data.

7.R.2.1 Adverse events reported in global phase III studies

The applicant's explanation about the safety of crovalimab in patients with PNH in comparison with eculizumab:

The summaries of adverse events in the randomized part of the primary evaluation period in the global phase III studies (Studies BO42162 and BO42161) are shown in Table 40 and Table 41, respectively. In the overall population, the incidences of adverse events were similar between the crovalimab group and the eculizumab group in both studies, while the incidence of adverse drug reactions was higher in the crovalimab group than in the eculizumab group in Study BO42161. In Study BO42161, the incidence of type III immune complex mediated reaction was higher in the crovalimab group than in the eculizumab group, which was attributable to DTDC formation caused by switching to crovalimab from eculizumab. In both studies, the incidence of injection-related reactions was higher in the crovalimab group than in the eculizumab group, which is considered a reaction specific to crovalimab subcutaneous formulation. The limited sample size in Japanese population precluded adequate interpretation of the occurrence of adverse events and adverse drug reactions. However, there was no trend towards an increased risk in the Japanese population as compared to the overall population in both studies.

In Arm C (patients with PNH aged <18 years) of Study BO42162, the incidence of adverse events was 83.3% (5 of 6 patients), and the incidence of adverse drug reactions was 16.7% (1 of 6 patients). In Arm C of Study BO42161 (Table 31), the incidence of adverse events was 0% (0 of 1 patient) in Cohort (1), 85.7% (18 of 21 patients) in Cohort (2), 100% (10 of 10 patients) in Cohort (3), and 83.3% (5 of 6 patients) in Cohort (4); the incidence of adverse drug reactions was 0% (0 of 1 patient) in Cohort (1), 47.6% (10 of 21 patients) in Cohort (2), 30% (3 of 10 patients) in Cohort (3), and 33.3% (2 of 6 patients) in Cohort (4). Although the limited number of patients enrolled in Arm C in both studies precluded adequate interpretation of results, in both the overall population and Japanese population, the incidences of adverse events and adverse drug reactions in Arm C did not differ significantly from those in the crovalimab group, the randomized part (Arm A) of the studies.

Table 40. Summary of adverse events in Study BO42162 (RSP, primary evaluation period)

	Overall population		Japanese population	
	Crovalimab (N = 135)	Eculizumab (N = 69)	Crovalimab (N = 2)	Eculizumab (N = 3)
Adverse events	77.8 (105)	79.7 (55)	0	66.7 (2)
Adverse drug reactions	33.3 (45)	34.8 (24)	0	33.3 (1)
Death	1.5 (2)	1.4 (1)	0	0
Serious adverse events	10.4 (14)	13.0 (9)	0	33.3 (1)
Serious adverse drug reactions	3.0 (4)	1.4 (1)	0	0
Adverse events leading to study treatment discontinuation	0.7 (1)	1.4 (1)	0	0
Adverse events occurring in ≥5% of patients in either group of the overall population				
Infusion related reaction	15.6 (21)	13.0 (9)	0	33.3 (1)
Neutrophil count decreased	12.6 (17)	10.1 (7)	0	0
White blood cell count decreased	11.9 (16)	10.1 (7)	0	0
Hypokalaemia	11.1 (15)	13.0 (9)	0	0
Pyrexia	8.9 (12)	10.1 (7)	0	33.3 (1)
Upper respiratory tract infection	8.1 (11)	13.0 (9)	0	0
Hyperuricaemia	8.1 (11)	8.7 (6)	0	0
COVID-19	8.1 (11)	5.8 (4)	0	0
Headache	8.1 (11)	4.3 (3)	0	0
Diarrhoea	7.4 (10)	0	0	0
Hypocalcaemia	5.9 (8)	10.1 (7)	0	0
Injection related reaction	5.2 (7)	0	0	0
Urinary tract infection	1.5 (2)	5.8 (4)	0	0
Adverse drug reactions occurring in ≥5% of patients in either group of the overall population				
Infusion related reaction	14.8 (20)	13.0 (9)	0	33.3 (1)
White blood cell count decreased	11.9 (16)	10.1 (7)	0	0
Neutrophil count decreased	11.1 (15)	10.1 (7)	0	0

MedDRA/J ver. 25.1; incidence, % (n)

Table 41. Summary of adverse events in Study BO42161 (RSP, primary evaluation period)

	Overall population		Japanese population	
	Crovalimab (N = 44)	Eculizumab (N = 42)	Crovalimab (N = 5)	Eculizumab (N = 4)
Adverse events	77.3 (34)	66.7 (28)	80.0 (4)	75.0 (3)
Adverse drug reactions	31.8 (14)	0	40.0 (2)	0
Death	0	0	0	0
Serious adverse events	13.6 (6)	2.4 (1)	40.0 (2)	0
Serious adverse drug reactions	0	0	0	0
Adverse events leading to study treatment discontinuation	0	0	0	0
Adverse events occurring in ≥5% of patients in either group of the overall population				
Pyrexia	15.9 (7)	2.4 (1)	20.0 (1)	0
Type III immune complex mediated reaction	15.9 (7)	0	20.0 (1)	0
COVID-19	13.6 (6)	16.7 (7)	0	33.3 (1)
Infusion related reaction	13.6 (6)	0	20.0 (1)	0
Headache	11.4 (5)	2.4 (1)	20.0 (1)	25.0 (1)
Nausea	6.8 (3)	4.8 (2)	20.0 (1)	0
Asthenia	6.8 (3)	4.8 (2)	0	0
Upper respiratory tract infection	6.8 (3)	2.4 (1)	0	0
Diarrhoea	6.8 (3)	2.4 (1)	0	25.0 (1)
Oedema peripheral	6.8 (3)	2.4 (1)	20.0 (1)	0
Injection related reaction	6.8 (3)	0	20.0 (1)	0
Arthralgia	6.8 (3)	0	20.0 (1)	0
Influenza	4.5 (2)	7.1 (3)	0	0
Urinary tract infection	4.5 (2)	7.1 (3)	0	0
Rash	6.8 (3)	0	0	0
Adverse drug reactions occurring in ≥5% of patients in either group of the overall population				
Type III immune complex mediated reaction	15.9 (7)	0	20.0 (1)	0
Infusion related reaction	13.6 (6)	0	20.0 (1)	0
Injection related reaction	6.8 (3)	0	20.0 (1)	0

MedDRA/J ver. 25.1; incidence, % (n)

Based on the adverse events and adverse drug reactions occurring in the global phase III studies (Studies BO42162 and BO42161), PMDA concluded that, with the exception of injection site reaction and immune complex reactions in patients switching from eculizumab to crovalimab, there are no differences in the safety profiles between crovalimab and eculizumab that would give rise to differences in clinical outcomes. Furthermore, although the limited number of patients in the Japanese

subpopulation precluded adequate interpretation of results, PMDA concluded that there were no safety concerns specific to Japanese patients. The details of immune complex reactions and injection site reactions are discussed in Sections 7.R.2.3.2 and 7.R.2.3.4, respectively.

7.R.2.2 Long-term safety

The applicant's explanation about the long-term safety of crovalimab:

Table 42 shows the incidence of adverse events by time period in patients who continued with crovalimab treatment (in Parts 2, 3, and 4, and the extension part) in the global phase I/II study (Study BP39144). Up to Week 129, there was no trend towards an increase in the incidence of adverse events with prolonged crovalimab treatment. At Week 130 and thereafter, no trend towards an increase in the incidence of adverse events was observed with prolonged crovalimab treatment.

Table 42. Summary of adverse events by time period in patients who continued to receive crovalimab treatment (in Parts 2, 3, and 4, and the extension part) in Study BP39144

	Primary evaluation period		Extension part				
	Weeks 0-9 (N = 44)	Weeks 10-19 (N = 44)	Weeks 20-29 (N = 44)	Weeks 30-39 (N = 44)	Weeks 40-49 (N = 41)	Weeks 50-59 (N = 40)	Weeks 60-69 (N = 39)
Adverse events	70.5 (31)	54.5 (24)	34.1 (15)	27.3 (12)	26.8 (11)	25.0 (10)	33.3 (13)
Adverse drug reactions	20.5 (9)	9.1 (4)	20.5 (9)	0	0	5.0 (2)	5.1 (2)
Serious adverse events	4.5 (2)	2.3 (1)	4.5 (2)	2.3 (1)	2.4 (1)	2.5 (1)	5.1 (2)
Serious infections	2.3 (1)	0	0	0	0	0	0
	Extension part						Overall treatment period
	Weeks 70-79 (N = 39)	Weeks 80-89 (N = 39)	Weeks 90-99 (N = 39)	Weeks 100-109 (N = 38)	Weeks 110-119 (N = 38)	Weeks 120-129 (N = 31)	Weeks 0 to >230 (N = 44)
Adverse events	35.9 (14)	30.8 (12)	33.3 (13)	34.2 (13)	31.6 (12)	12.9 (4)	95.5 (42)
Adverse drug reactions	2.6 (1)	5.1 (2)	0	0	0	0	31.8 (14)
Serious adverse events	5.1 (2)	5.1 (2)	2.6 (1)	7.9 (3)	0	3.2 (1)	31.8 (14)
Serious infections	0	2.6 (1)	0	2.6 (1)	0	0	9.1 (4)

Incidence, % (n)

PMDA's view:

Based on the incidence of adverse events by time period of crovalimab treatment in Study BP39144, the incidence of adverse events is unlikely to increase with increasing in treatment duration, and therefore, the safety of crovalimab will not change significantly over time.

7.R.2.3 Adverse events of special interest

The applicant explains observations on infections (including meningococcal infection), immune complex reactions, infusion-related reactions, and injection site reactions, all of which are defined as adverse events of special interest based on the mechanism of action of crovalimab, known safety profiles of C5 inhibitors, route of administration, and other factors as follows.

7.R.2.3.1 Meningococcal infections and other infections

The applicant's explanation about meningococcal infection and other infections:

Because crovalimab, as with eculizumab, is a C5 inhibitor, patients treated with crovalimab are at higher risk for meningococcal infections. The clinical study protocols of crovalimab required study participants to be vaccinated against *Neisseria meningitidis* serotypes A, C, W, and Y within 3 years prior to the start of study treatment in accordance with the safety measures against meningococcal infections implemented for eculizumab. The protocol also required study participants who had been vaccinated <2 weeks prior to or after the start of study treatment to receive an appropriate antibacterial agent from the start of study treatment for ≥2 weeks after the completion of vaccination.

In the global phase III studies (Studies BO42162 and BO42161) and foreign phase III study (Study YO42311),[28)] neither the crovalimab nor eculizumab group reported meningococcal infections.[29)]

Infections[30)] occurred in 23.7% (32 of 135) of patients in the crovalimab group and 36.2% (25 of 69) of patients in the eculizumab group in Study BO42162; 40.9% (18 of 44) of patients in the crovalimab group and 35.7% (15 of 42) of patients in the eculizumab group in Study BO42161. The main infection events were upper respiratory tract infection (11 patients, 9 patients, 3 patients, and 1 patient in the crovalimab group [BO42162], eculizumab group [BO42162], crovalimab group [BO42161], and eculizumab group [BO42161], respectively; the same applies hereinafter), COVID-19 (11, 4, 6, and 7 patients), urinary tract infection (2, 4, 2, and 3 patients), influenza (4, 0, 2, and 3 patients). Serious infections occurred in 4 patients in the crovalimab group in Study BO42162 (pneumonia [2 patients], COVID-19 and pyelonephritis [1 patient each]), 5 patients in the eculizumab group in Study BO42162 (COVID-19, central nervous system infection, sepsis, tuberculosis, and urinary tract infection [1 patient each]), 2 patients in the crovalimab group in Study BO42161 (urinary tract infection, nasopharyngitis, and pneumonia [1 patient each]; some patients were counted more than once), 2 patients in the eculizumab group in Study BO42161 (pyelonephritis and pneumonia [1 patient each]). These results indicated no tendency towards an increase in the incidence of infections in the crovalimab group compared to the eculizumab group. In the Japanese subpopulation, infections occurred in 0 of 2 patients in the crovalimab group [BO42162], 1 of 3 patients in the eculizumab group [BO42162], 1 of 5 patients in the crovalimab group [BO42161], and 0 of 4 patients in the eculizumab group [BO42161]. These results showed no tendency indicative of clinical concerns in the Japanese subpopulation as compared to the overall population.

Based on the above, patients who intend to start crovalimab treatment in post-marketing settings should also be vaccinated against *Neisseria meningitidis* beforehand as practiced in the clinical studies, which should be advised via the package insert. The package insert should further advise that crovalimab be

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[28)] An open-label, uncontrolled phase III study conducted in complement inhibitor-naïve Chinese patients with PNH aged ≥12 years to evaluate the efficacy, safety, pharmacokinetics, and pharmacodynamics of crovalimab. By the data cut-off date (August 10, 2022), 51 patients were enrolled and the median treatment duration was 56.14 weeks.

[29)] Events that are classified as the following MedDRA Preferred Terms (PTs):
encephalitis meningococcal, endocarditis meningococcal, meningitis meningococcal, meningococcal carditis, meningococcal infection, meningococcal sepsis, myocarditis meningococcal, optic neuritis meningococcal, pericarditis meningococcal, Waterhouse-Friderichsen syndrome, and meningococcal bacteraemia

[30)] Events that are classified as MedDRA System Organ Class (SOC) "infections and infestations"

administered under appropriate meningococcal infection control, in cooperation with other emergency-prepared medical facilities where possible, along with a caution against other infections.

PMDA's view:
As practiced in the use of eculizumab, the administration of crovalimab warrants due attention to infections, with appropriate measures against meningococcal infections. The provision of such cautionary advice is necessary, and in this view, applicant has taken the appropriate action.

7.R.2.3.2 Immune complex reactions

The applicant's explanation about immune complex reactions:
DTDCs are formed when both crovalimab and eculizumab (or ravulizumab), which bind to different C5 epitopes, are present in circulating blood, and DTDC deposition onto tissue may cause an immune complex reaction, which is a type III hypersensitivity reaction. Therefore, patients switching from another C5 inhibitor to crovalimab or vice versa are at risk of DTDC-associated immune complex reactions.

In the global phase III studies (Studies BO42162 and BO42161), the incidence of immune complex reactions[31)] in patients switching from another C5 inhibitor to crovalimab was 17.8% (33 of 185 patients), of which 33 patients had type III immune complex mediated reactions and 1 patient developed axonal neuropathy. Main symptoms included arthralgia in 17 patients, rash in 11 patients, pyrexia in 7 patients, myalgia in 6 patients, headache in 5 patients, abdominal pain upper in 3 patients. Of patients who developed immune complex reactions, 2 patients experienced 2 episodes of reactions, the first one after switching from another C5 inhibitor to crovalimab, and the second one after discontinuing crovalimab and switching to another C5 inhibitor.

Serious adverse events occurred in 5 patients (Grade 3 type III immune complex mediated reaction [5 patients], Grade 3 axonal neuropathy [1 patient]), and 1 adverse event led to treatment discontinuation of crovalimab in 1 patient (Grade 3 type III immune complex mediated reaction). Adverse events leading to dose interruption of crovalimab occurred in 2 patients (Grade 3 and Grade 2 type III immune complex mediated reaction in 1 patient each), with the outcome reported as resolving or resolved.

Table 43 shows the time to onset of immune complex reaction in patients switching treatment from another C5 inhibitor to crovalimab. The median time to onset was 1.57 weeks with the longest case being 4.4 weeks.

Table 43. Time to onset of immune complex reaction (pooled analysis set)

	Patients who developed immune complex reactions (N = 33)
<7 days	**9.1 (3)**
≥7 days and <14 days	**48.5 (16)**
≥14 days and <28 days	**36.4 (12)**
≥28 days	**6.1 (2)**

Incidence, % (n)

[31)] Events identified by the investigator as immune complex reactions.

Based on the above, when switching from another C5 inhibitor to crovalimab or vice versa, patients are at risk of immune complex reactions and should be closely monitored for immune complex reactions for approximately 30 days after treatment switch. The package insert should offer this advice.

PMDA's view:
Based on the incidence of immune complex reactions in the clinical studies, switching from an approved C5 inhibitor to crovalimab require careful consideration of its necessity, taking into account the possibility of an immune complex reaction. The provision of cautionary advice in the package insert on close monitoring for immune complex reactions for approximately 30 days after switching from another C5 inhibitor is appropriate.

7.R.2.3.3 Infusion-related reactions

The applicant's explanation about infusion-related reactions:
The incidence of infusion-related reactions[32)] was 15.6% (21 of 135 patients) in the crovalimab group (BO42162) and 13.0% (9 of 69 patients) in the eculizumab group (BO42162), 13.6% (6 of 44 patients) in the crovalimab group (BO42161), and 0% (0 of 42 patients) in the eculizumab group (BO42161). Reported events were infusion-related reaction (21 patients in the crovalimab group and 9 patients in eculizumab group [BO42162], 6 patients in crovalimab group and 0 patients in the eculizumab group [BO42161]) and diarrhoea (1 in the crovalimab group, 0 in eculizumab group [BO42162], 0 in crovalimab group, and 0 in the eculizumab group [BO42161]). These events were Grade 1 or 2 in severity. A serious adverse event (infusion-related reaction) occurred in 1 patient in the crovalimab group in Study BO42162 on Day 1, which resolved.

Accordingly, infusion-related reactions can be controlled by advising in the package insert.

PMDA's view:
Infusion-related reactions were reported in the clinical studies and may be a potential safety concern with crovalimab. However, in the clinical studies, serious adverse events associated with infusion-related reaction occurred in only 1 patient on Day 1 and resolved. Given that all the reported infusion-related reactions were Grade 1 or 2, infusion-related reactions are unlikely to compromise the clinical usefulness of crovalimab. Nevertheless, the package insert should strongly urge caution against infusion-related reactions.

7.R.2.3.4 Injection site reactions

The applicant's explanation about injection site reactions:
The incidence of injection site reactions[33)] was 5.2% (7 of 135 patients) in the crovalimab group (BO42162), 0% (0 of 69 patients) in the eculizumab group (BO42162), 9.1% (4 of 44 patients) in the crovalimab group (BO42161), and 0% (0 of 42 patients) in the eculizumab group (BO42161). In both

[32)] Events assessed by the investigator as infusion-related reactions (including local and systemic reactions)
[33)] Events assessed by the investigator as injection site reactions (including local and systemic reactions)

studies, injection site reactions were reported only in the crovalimab group, in which the crovalimab was administered subcutaneously. Reported events were injection-related reaction (6 patients in the crovalimab group in Study BO42162 and 3 patients in the crovalimab group in Study BO42161) and injection site reaction (1 patient each in the crovalimab group in Studies BO42162 and BO42161). There were no serious adverse events or adverse events leading to study treatment discontinuation. These events were all Grade 1 or 2 in severity. A Grade 3 injection site reaction occurred in 1 patient in Arm C, Cohort (2) in Study BO42161. However, this event resolved without modifying or interrupting doses.

Therefore, it is considered that injection site reactions can be controlled by the provision of cautionary advice in the package insert.

PMDA's view:
Based on the route of administration of crovalimab and injection site reactions reported only in the crovalimab group, injection site reactions are currently a risk factor specific to crovalimab among similar drugs. However, given no serious adverse events or adverse events leading to treatment discontinuation in the clinical studies and the severity of events being Grade 1 or 2, except for 1 patient, injection site reactions is not considered to compromise the clinical usefulness of crovalimab. Nevertheless, the package insert should strongly urge caution against injection site reactions.

7.R.3 Clinical positioning and indication

The applicant's explanation about the clinical positioning and indication of crovalimab:
In Japan, common pharmacotherapies for PNH are C5 inhibitors (eculizumab and ravulizumab), which has been shown to reduce symptoms and complications effectively in many patients with PNH. Crovalimab can inhibit intravascular hemolysis by inhibiting C5, in a manner similar to eculizumab and ravulizumab. Crovalimab can be self-administered subcutaneously every 4 weeks, which may help reduce the burden of hospital visits on patients and caregivers.

The global phase III study (Study BO42162) in complement inhibitor-naïve patients with PNH demonstrated the efficacy of crovalimab that was non-inferior to eculizumab [see Section 7.R.1.1]. In the global phase III study (Study BO42161) in patients with PNH who had previously been treated with complement inhibitors, switching from eculizumab to crovalimab did not tend to cause efficacy-related problems [see Section 7.R.1.2]. Furthermore, crovalimab and other approved C5 inhibitors bind to different C5 epitopes. Arm C, Cohort (4) of Study BO42161 enrolled 6 patients (including 5 Japanese patients) who had C5 genetic polymorphism poorly controlled with existing C5 inhibitors. The results suggested that crovalimab was also effective in these patients [see Section 7.2.2].

Safety profiles of the crovalimab groups in the global phase III studies (Studies BO42162 and BO42161) and the foreign phase III study (Study YO42311) were similar to that of the eculizumab group except for immune complex reactions that may develop after treatment switch from another C5 inhibitor to

crovalimab. The safety of crovalimab is controllable where it is administered only by a physician with sufficient knowledge of PNH, as required for other approved C5 inhibitors[see Section 7.R.2].

Based on the above, crovalimab can be positioned as a treatment option for patients with PNH, and "paroxysmal nocturnal hemoglobinuria" was specified as the proposed indication for crovalimab.

PMDA's view:
The results from Studies BO42162 and BO42161 in patients with PNH demonstrated the efficacy of crovalimab in complement inhibitor treatment-naïve patients with PNH and showed promising efficacy of crovalimab in patients with PNH previously treated with other complement inhibitors as well [see Section 7.R.1]. Furthermore, the safety of crovalimab is controllable where it is administered only by a physician with sufficient knowledge of PNH and a thorough understanding of the risks associated with crovalimab [see Section 7.R.2]. Therefore, crovalimab is a new treatment option for patients with PNH that can be positioned equally with the existing C5 inhibitors. The proposed indication for crovalimab "paroxysmal nocturnal hemoglobinuria" is acceptable.

7.R.4 Dosage and administration

7.R.4.1 Dosage regimen

The applicant's explanation about the dosage regimens of crovalimab:
The dosage regimens of crovalimab in the global phase III studies (Studies BO42162 and BO42161) were determined (Table 44) based on the results of the global phase I/II study (Study BP39144), aiming to maintain the concentration of free crovalimab that has a binding site for C5, while minimizing DTDC formation in patients switching from another complement inhibitor to crovalimab.

Table 44. Dosage regimen

Body weight	Day 1	Days 2, 8, 15, and 22	From Day 29 onwards, every 4 weeks
≥40 kg and <100 kg	1,000 mg IV	340 mg SC	680 mg SC
≥100 kg	1,500 mg IV	340 mg SC	1,020 mg SC

The results from Studies BO42162 and BO42161 demonstrated the efficacy of crovalimab [see Section 7.R.1], and the safety data did not reveal any clinically significant problems as compared to eculizumab [see Section 7.R.2]. In both studies, there was no difference in the efficacy or safety data between the overall population and the Japanese population that could be a clinical problem [see Sections 7.R.1 and 7.R.2].
Table **45** shows the efficacy results (hemolysis control and transfusion avoidance) by dosage (body weight category) in the randomized part of Study BO42162. Although the small number of patients weighing ≥100 kg precluded adequate interpretation of the results, the level of efficacy in the crovalimab group was similar to that in the eculizumab group at both dosage levels (body weight categories). Table 46 shows the incidences of adverse events by dosage (body weight category) in the pooled analysis on Studies BO42162, BO42161, and YO42311 (foreign phase III study). Although the limited number of patients weighing ≥100 kg precluded adequate interpretation, the estimated $C_{trough, ss}$

values of crovalimab similar between the body weight categories [see Section 6.2.4] indicated that the dosage levels (by body weight category) make no significant difference in the safety of crovalimab.

Table 45. Efficacy results by body weight category in Study BO42162 (PAP)

Endpoint	Body weight category	Crovalimab (N = 134)	Eculizumab (N = 69)
Mean proportion of patients achieving hemolysis control from Week 5 to Week 25 (LDH ≤1.5 × ULN) [95% CI] (n)	≥40 kg and <100 kg	79.98% [74.10%, 84.80%] (130)	82.68% [74.25%, 88.78%] (66)
	≥100 kg	79.74% [31.87%, 97.07%] (4)	63.83% [16.10%, 94.20%] (3)
Proportion of patients achieving transfusion avoidance from baseline to Week 25, % (n)	≥40 kg and <100 kg	65.38% (130)	66.67% (66)
	≥100 kg	75.00% (4)	100% (3)

Table 46. Summary of adverse events by body weight category in pooled analysis set

	Crovalimab		Eculizumab	
	≥40 kg and <100 kg (N = 362)	≥100 kg (N = 15)	≥40 kg and <100 kg (N = 104)	≥100 kg (N = 7)
Adverse events	86.7 (314)	80.0 (12)	75.0 (78)	71.4 (5)
Adverse drug reactions	43.9 (159)	26.7 (4)	21.2 (22)	28.6 (2)
Deaths	1.1 (4)	0	1.0 (1)	0
Serious adverse events	15.7 (57)	0	9.6 (10)	0
Adverse events leading to treatment discontinuation	1.1 (4)	0	1.0 (1)	0

Incidence, % (n)

In Studies BO42162 and BO42161, patients weighing ≥40kg were eligible and patients weighing ≥40 kg and <100 kg received the same dosage. A total of 10 patients in the crovalimab group of Study BO42162 and 5 patients in the crovalimab group of Study BO42161 weighed close to the lower limit of body weight (≥40 kg and ≤50 kg). The efficacy data of the population show that most patients retained LDH ≤1.5 × ULN at Week 5 and thereafter in Study BO42162 and after baseline in Study BO42161. The proportion of patients achieving transfusion avoidance was 30.0% (3 of 10 patients) and 80.0% (4 of 5 patients) in Study BO42161. In Study BO42162, the proportion of patients achieving transfusion avoidance tended to be lower than that in the overall population of the crovalimab group (65.7%). This result may be attributable to packed red blood cell transfusion all patients weighing close to the lower limit had undergone in 6 months prior to randomization, and to the number of transfusion units that tended to be high as compared to the overall population of the crovalimab group. In terms of safety in this population, the incidence of adverse events was 90.0% (9 of 10 patients) in Study BO42162 and 60.0% (3 of 5 patients) in Study BO42161; the incidence of adverse drug reactions was 30.0% (3 of 10 patients) in Study BO42162 and 40.0% (2 of 5 patients) in Study BO42161, most of which were mild or moderate in severity. Serious adverse drug reactions occurred in 2 patients in Study BO42162 (epistaxis and thrombocytopenia in 1 patient each), all of which resolved. Although the small sample size of patients weighing close to the lower limit precluded adequate interpretation of the results, crovalimab is expected to have efficacy without significant safety problems in patients weighing ≥40 kg.

Based on the above, the dosage regimen of crovalimab was determined based on the dosage regimens in Studies BO42162 and BO42161 with body weight taken into consideration. The initial dose is 1,000 or 1,500 mg administered by intravenous infusion on Day 1, followed by 340 mg of crovalimab on Days 2, 8, 15, and 22 by subcutaneous injection. At Day 29 and thereafter, 680 or 1,020 mg of crovalimab is administered every 4 weeks by subcutaneous injection. The dosage based on body weight category will be described in the "Precautions Concerning Dosage and Administration" section of the package insert.

PMDA's view:

The results from Studies BO42162 and BO42161 demonstrated the efficacy of crovalimab [see Section 7.R.1] and showed the safety profile in the crovalimab group similar to that in the eculizumab group. Therefore, the safety of crovalimab is controllable where crovalimab is administered only by a physician with sufficient knowledge of PNH as required for other approved complement inhibitors[see Section 7.R.2]. Although the small number of Japanese patients in these studies allowed limited evaluation of the primary endpoints, consistency in safety results between the Japanese population and the overall population was shown by the comprehensive assessment with other endpoints taken into account [see Sections 7.R.1 and 7.R.2]. Furthermore, albeit inadequate interpretation of the results by dosage due to the number of patients weighing ≥100 kg, crovalimab is expected to have efficacy at both dose levels with no particular safety concerns as compared to eculizumab. There were no efficacy or safety concerns in patients weighing close to the lower limit. Therefore, crovalimab is expected to have efficacy with controllable safety in patients weighing ≥40 kg. Give these, the dosage regimen of crovalimab for use in Japan and precautions concerning dosage and administration proposed based on Studies BO42162 and BO42161 are appropriate.

7.R.4.2 Self-administration

The applicant's explanation about efficacy and safety of self-administered crovalimab:
In the global phase III studies (Studies BO42162 and BO42161), patients or their caregivers were trained for self-treatment with subcutaneous injection of crovalimab, and patients who had been recognized by the investigators as competent were allowed to self-administer crovalimab from Week 9.

In Study BO42162Crovalimab was self-administered by patients or their caregivers, in 79 of 135 patients in the crovalimab group, 29 of 68 patients in the crovalimab-switch group in the eculizumab group, and 4 of 6 patients in Arm C, and in Study BO42161, 18 of 45 patients in the crovalimab group, 12 of 35 patients in the crovalimab-switch group in the eculizumab group, and 12 of 38 patients in Arm C. In the Japanese population, 0 of 5 patients in Study BO42162 and 3 of 17 patients in Study BO42161 self-administered crovalimab. Among these 3 Japanese patients, LDH ≤1.5 × ULN was maintained throughout the period when crovalimab was self-administered. Adverse events observed were Grade 1 or 2 in severity, with no serious adverse events or adverse events leading to treatment discontinuation of crovalimab. There were no administration errors leading to dose modification. There were no efficacy or safety concerns associated with self-administration, and crovalimab can thus be self-administered.

PMDA's view:
Based on the applicant's explanation regarding the results on self-administration in Japanese patients in the clinical studies, crovalimab can be self-administered in the clinical settings in Japan, when patients are appropriately instructed and recognized by physicians as competent in self-administration.

7.R.5 Post-marketing investigations

The applicant has planned to conduct a general use-results survey as shown in Table 47 covering all patients receiving crovalimab in post-marketing settings.

Table 47. General use-results survey plan (draft)

Objective	**To evaluate/investigate the safety, etc. in clinical use of crovalimab in patients with PNH**
Survey method	**All-case surveillance**
Population	**All patients who have received crovalimab**
Planned sample size	**100 patients (as the number of patients registered)**
Observation period	**6 months**
Main survey items	**• Baseline patient characteristics (e.g., age, sex, pregnancy status, height, body weight, PNH clone size, disease duration, breakthrough hemolysis status, severity, clinical symptoms of PNH, vaccination status [*Neisseria meningitidis*, *Streptococcus pneumoniae*, *Haemophilus influenzae*], LDH at the time of administration, medical history, comorbidities)** **• Prior treatment, concomitant drugs, concurrent therapies** **• Surgical history** **• Crovalimab treatment status (treatment duration, dosage, reason for discontinuation, history of switch to another C5 inhibitor)** **• Immune complex reactions related to DTDC (e.g., onset date, seriousness, outcome, causal relationship, symptoms)** **• Adverse events other than immune complex reactions related to DTDC (e.g., onset date, seriousness, outcome, causal relationship)**

PMDA's view:

Because only a small number of Japanese patients with PNH received crovalimab in the global phase III studies (Studies BO42162 and BO42161), the safety of crovalimab was not adequately investigated in this population. The applicant should conduct post-marketing surveillance covering all patients who are treated with crovalimab. The details of the surveillance plan including the observation period need to be further discussed.

8. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

8.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The new drug application data were subjected to a document-based inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

8.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The new drug application data (CTD 5.3.5.1-1) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

9. Overall Evaluation during Preparation of the Review Report (1)

On the basis of the data submitted, PMDA has concluded that crovalimab has efficacy in the treatment of paroxysmal nocturnal hemoglobinuria, and that crovalimab has acceptable safety in view of its benefits. Crovalimab is clinically meaningful because it offers a new treatment option in the treatment of paroxysmal nocturnal hemoglobinuria.

PMDA has concluded that crovalimab may be approved if crovalimab is not considered to have any particular problems based on comments from the Expert Discussion.

Review Report (2)

February 13, 2024

Product Submitted for Approval

Brand Name	Piasky for Injection 340 mg
Non-proprietary Name	Crovalimab (Genetical Recombination)
Applicant	Chugai Pharmaceutical Co., Ltd.
Date of Application	June 14, 2023

List of Abbreviations

See Appendix.

1. Content of the Review

Comments made during the Expert Discussion and the subsequent review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below. The expert advisors present during the Expert Discussion were nominated based on their declarations, etc. concerning the product submitted for marketing approval, in accordance with the provisions of the Rules for Convening Expert Discussions, etc. by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

1.1 Efficacy

At the Expert Discussion, the PMDA's conclusion in Section "7.R.1 Efficacy" in Review Report (1) was supported by the expert advisors.

1.2 Safety

At the Expert Discussion, the PMDA's conclusion in Section "7.R.2 Safety" in Review Report (1) was supported by the expert advisors.

In view of the discussion at the Expert discussion, PMDA has concluded that the Warnings section of the package insert should provide cautionary advice as follows. The applicant responded appropriately.

Warnings

1. Patients treated with crovalimab are at a risk of meningococcal infections, which may be fatal. The following advice must be strongly borne in mind.
   1.1 Patients on crovalimab treatment should be closely monitored for early signs and symptoms of meningococcal infection, such as fever, headache, and nuchal rigidity. Patient with suspected meningococcal infection must be examined immediately and treated appropriately with antibacterial agents, etc.

1.2 In principle, patients must be vaccinated against *Neisseria meningitidis* before starting crovalimab treatment, and be revaccinated as necessary.

1.3 Meningococcal infections may follow a life-threatening clinical course. Crovalimab must be administered only by a physician and at a medical institution well-prepared for emergencies or in cooperation with other medical facilities capable of providing diagnosis and treatment of meningococcal infection.

1.4 Patients must be explained the risk of meningococcal infection for clear understanding of early signs of the infection. They should be advised to contact their attending physicians immediately in case of a meningococcal infection-related adverse drug reaction.

2. Crovalimab must be administered only by physicians with adequate knowledge on paroxysmal nocturnal hemoglobinuria and only when its benefits are expected to outweigh the risks. Prior to the treatment, patients or their caregivers must be fully explained the efficacy and risks of crovalimab, including the fact that crovalimab is not intended for complete cure of the disease, and provide consent.

1.3 Indication

At the Expert Discussion, the expert advisors supported PMDA's conclusion in Section "7.R.3 Indication" in Review Report (1).

PMDA concluded that the indication should be defined as proposed and the "Precautions Concerning Indication" section should be described as below. The applicant responded appropriately.

Indication

Paroxysmal nocturnal hemoglobinuria

Precautions Concerning Indication

1. Crovalimab is expected to inhibit C5 cleavage and thereby prevent the formation of terminal complement complex C5b-9, which may increase susceptibility to infections with encapsulated bacteria such as *Neisseria meningitidis*. Crovalimab should be administered only to eligible patients by physicians with a good understanding of the efficacy and safety of crovalimab, and careful consideration of the necessity of the treatment. As rule, patients must be vaccinated against *Neisseria meningitidis* ≥2 weeks prior to the start of crovalimab treatment.
2. Crovalimab should be administered to patients with paroxysmal nocturnal hemoglobinuria confirmed by flow cytometry or any other reliable method.
3. The administration of crovalimab causes PNH red blood cell clones to accumulate. Discontinuation of crovalimab treatment can trigger serious intravascular hemolysis. Crovalimab should be administered only to eligible patients by physicians with a good understanding of the efficacy and safety of crovalimab.

4. Treatment switch from another anti-C5 antibody to crovalimab may cause immune complex reactions. The necessity of treatment switch to crovalimab should be carefully determined.

1.4 Dosage and administration

At the Expert Discussion, the expert advisors supported PMDA's conclusion in Section "7.R.4 Dosage and administration" in Review Report (1)t.

PMDA concluded that the dosage and administration should be defined as follows with the precautions concerning dosage and administration described as below. The applicant responded appropriately.

Dosage and administration

The usual dosage is 1,000 or 1,500 mg of crovalimab (genetical recombination) administered as an intravenous infusion on Day 1, followed by 340 mg of crovalimab on Days 2, 8, 15, and 22 administered by subcutaneous injection. At Day 29 and thereafter, 680 or 1,020 mg of crovalimab is administered every 4 weeks by subcutaneous injection. The dosage should be determined based on the patient's body weight.

Precautions Concerning Dosage and Administration

1. Consult the table below for the dosage and method of administration.

Body weight	Day 1	Days 2, 8, 15, and 22	From Day 29 onwards, every 4 weeks
≥40 kg and <100 kg	1,000 mg IV	340 mg SC	680 mg SC
≥100 kg	1,500 mg IV	340 mg SC	1,020 mg SC

If a dose is missed on a scheduled day, administer 1 dose as soon as possible. Subsequent doses should be administered according to the schedule.

1.5 Risk management plan (draft)

At the Expert Discussion, the expert advisors supported PMDA's conclusion in Section "7.R.5 Post-marketing investigations" in Review Report (1). PMDA has concluded that the risk management plan (draft) for crovalimab should include the safety and efficacy specifications presented in Table 48, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities as presented in Table 49 and a general use-results survey as presented in Table 50.

Table 48. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	**Important potential risks**	**Important missing information**
• Meningococcal infection • Serious infections (other than meningococcal infection) • Immune complex reactions • Infusion reactions, infusion-related systemic reactions • Immunogenicity leading to decreases in exposure and efficacy	• Serious hemolysis due to discontinuation of crovalimab	• None
Efficacy specification		
• None		

Table 49. Summary of additional pharmacovigilance activities and additional risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Efficacy survey and studies	Additional risk minimization activities
• Early post-marketing phase vigilance • General use-results survey (paroxysmal nocturnal hemoglobinuria) (all case surveillance)	• None	• Dissemination of data gathered during early post-marketing phase vigilance • Information provision to healthcare professionals (proper use guide) • Information provision to patients (Piasky brochure, Patient Safety Card)

Table 50. General use-results survey plan (draft)

Objective	To evaluate/investigate the safety, etc. of crovalimab in patients with PNH in clinical use
Survey method	All case surveillance
Population	All patients who have received crovalimab
Planned sample size	100 patients (as the number of patients registered)
Observation period	52 weeks
Main survey items	• Baseline demographics and disease characteristics of patients (e.g., age, sex, pregnancy status, height, body weight, PNH clone size, disease duration, breakthrough hemolysis status, severity, clinical symptoms of PNH, vaccination status [*Neisseria meningitidis*, *Streptococcus pneumoniae*, *Haemophilus influenzae*], LDH at the time of administration, medical history, comorbidities) • Prior treatment, coadministered drugs, concurrent therapies • Surgical history • Crovalimab treatment status (treatment duration, dosage, reason for discontinuation, history of switching to another C5 inhibitor) • Immune complex reactions related to DTDC (e.g., onset date, seriousness, outcome, causal relationship, symptoms) • Adverse events other than immune complex reactions related to DTDC (e.g., onset date, seriousness, outcome, causal relationship)

2. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below with the following approval conditions. Because the product is a drug with a new active ingredient, the re-examination period is 8 years. The product is classified as a biological product. The drug substance and drug product are both classified as powerful drugs.

Indication

Paroxysmal nocturnal hemoglobinuria

Dosage and Administration

The usual dosage is 1,000 or 1,500 mg of crovalimab (genetical recombination) administered by intravenous infusion on Day 1, followed by 340 mg of crovalimab on Days 2, 8, 15, and 22 administered by subcutaneous injection. At Day 29 and thereafter, 680 or 1,020 mg of crovalimab is administered every 4 weeks by subcutaneous injection. The dosage should be determined based on the patient's body weight.

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Because only a limited number of Japanese patients participated in the clinical studies, the applicant is required to conduct a use-results survey covering all patients treated with the product in the post-marketing settings until data are obtained from a specified number of patients, to clearly understand the characteristics of patients treated with the product and promptly collect safety and efficacy data so as to take appropriate measures that ensure proper use of the product.
3. Prior to the product launch, the applicant is required to take necessary measures that will ensure the use of the product only by physicians and at medical institutions with s adequate expertise in the diagnosis and treatment of paroxysmal nocturnal hemoglobinuria and competence in the management of product-associated risks, and only in cooperation with physicians with expertise in the diagnosis and treatment of *Neisseria meningitidis* infection.

Appendix

List of Abbreviations

ADA	Anti-drug antibody
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the concentration versus time curve
C1q	Complement component C1q
C3	Complement component 3
C5	Complement component 5
C5a, C5b	Active metabolites of C5
CD	Cluster of differentiation
CE-SDS	Capillary electrophoresis sodium dodecyl sulfate
CHO	Chinese hamster ovary
CL	Clearance
CL_{cr}	Creatinine clearance
C_{max}	Maximum serum concentration
$C_{trough, ss}$	Trough serum concentration at steady state
COVID-19	Coronavirus Disease 2019
CQA	Critical quality attribute
Crovalimab	Crovalimab (Genetical Recombination)
CTD	Common technical document
DNA	Deoxyribonucleic acid
[redacted]	[redacted]
DTDC	Drug-target-drug complex
ECLIA	Electrochemiluminescence immunoassay
Eculizumab	Eculizumab (Genetical Recombination)
ELISA	Enzyme-linked immunosorbent assay
ePPND	Enhanced pre- and postnatal development
[redacted]	[redacted]
FACIT-Fatigue	Functional assessment of chronic illness therapy - fatigue
FAS	Full analysis set
Fc	Fragment crystallisable
FcRn	Neonatal Fc receptor
FcγR	Fcγ receptor
[redacted]	[redacted]
GEE	Generalized estimating equation
GPI	glycosylphosphatidylinositol
Hb	Hemoglobin
HCP	Host cell protein
[redacted]	[redacted]
IC_{50}	Half maximal inhibitory concentration
ICH	International council for harmonisation of technical requirements for pharmaceuticals for human use
ICH Q5A (R1) Guidelines	"Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin" (PMSB/ELD Notification No. 329, dated February 22, 2000)
ICH Q5B Guidelines	"Quality of Biotechnological Products: Analysis of the Expression Construct in Cells Used for Production of r-DNA Derived Protein Products" (PMSB/ELD Notification No. 3, dated January 6, 1998)

ICH-Q5D Guidelines	"Derivation and Characterisation of Cell Substrates Used for Production of Biotechnological/Biological Products" (PMSB/ELD Notification No. 873, dated July 14, 2000)
IEC	Ion exchange chromatography
IFN	interferon
IgG	Immunoglobulin G
IL	Interleukin
IPSS-R	International Prognostic Scoring System-Revised
IV	Intravenous
ka	Absorption rate constant
Kd	Equilibrium dissociation constant
K_D	Equilibrium dissociation constant
[redacted]	[redacted]
LDH	Lactate dehydrogenase
LIVCA	Limit of *in vitro* cell age
[redacted]	[redacted]
MAC	Membrane attack complex
MCB	Master cell bank
MedDRA/J	Medical Dictionary for Regulatory Activities Japanese version
MMRM	Mixed-effects model for repeated measures
NA	Neutrophil antigen
PIGA	phosphatidylinositol glycan class A
PMDA	Pharmaceuticals and Medical Devices Agency
PNH	Paroxysmal nocturnal hemoglobinuria
Q	Inter-compartmental clearance
Ravulizumab	Ravulizumab (Genetical Recombination)
RH	Relative humidity
RMP	Risk management plan
SC	subcutaneous
SEC	Size exclusion liquid chromatography
SOC	System Organ Class
SPR	Surface plasmon resonance
$t_{1/2}$	Elimination half-life
t_{max}	Time to reach maximum concentration
TNF	Tumor necrosis factor
ULN	Upper limit of normal
V2	Volume of distribution of central compartment
V3	Volume of distribution of peripheral compartment
WCB	Working cell bank