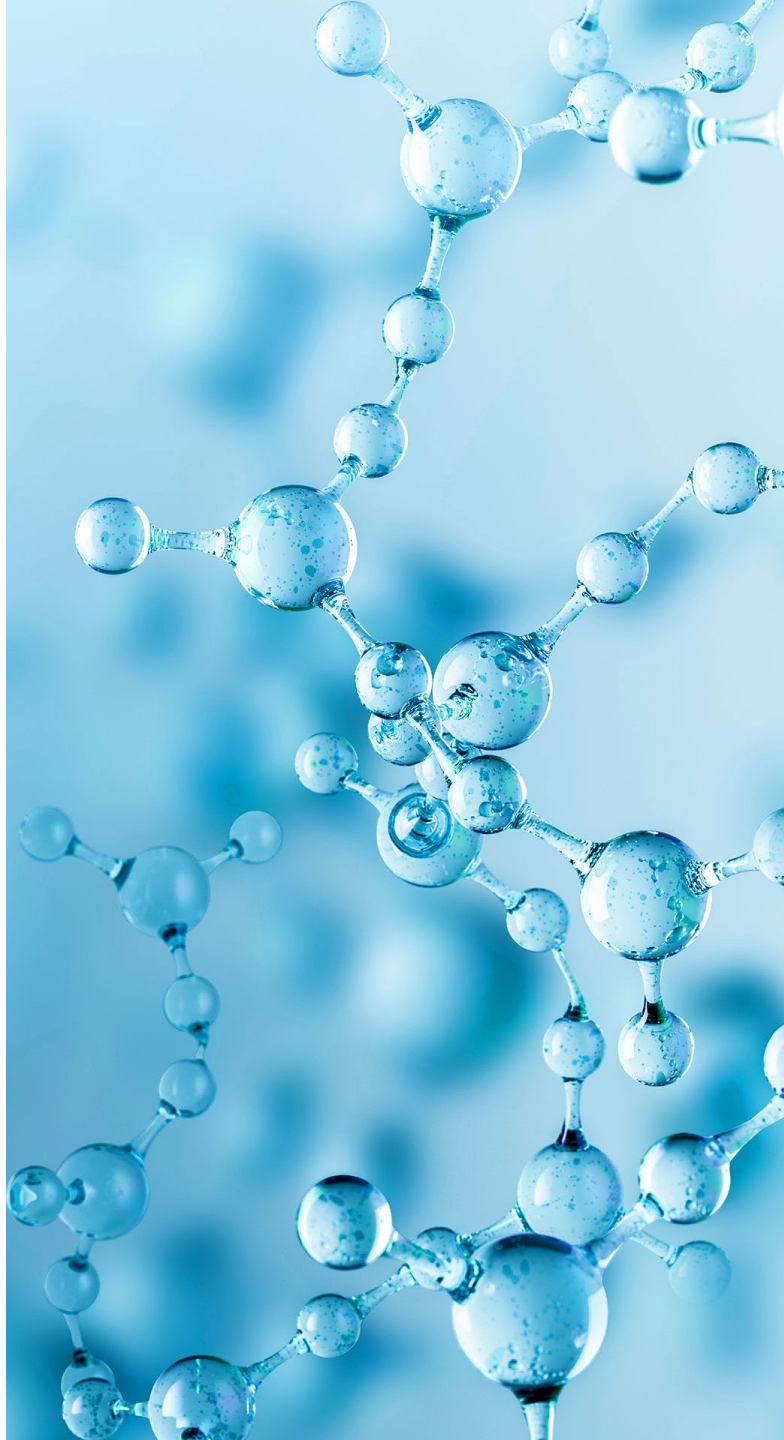
pH-Dependent Binding Humanized Anti-complement (C5) Monoclonal Antibody

Information Meeting on PiaSky®

Chugai Pharmaceutical Co., Ltd.

June 27, 2024



Important Reminders

This presentation may include forward-looking statements pertaining to the business and prospects of Chugai Pharmaceutical Co., Ltd. (the “Company”). These statements reflect the Company’s current analysis of existing information and trends. Actual results may differ from expectations based on risks and uncertainties that may affect the Company’s businesses.

Information regarding pharmaceuticals (including products under development) is included in this presentation, but is not intended as advertising or medical advice.

Please note that Japanese is the preferred language in expression and content, since the official language of this presentation is Japanese.

Agenda

01 **Overview of PiaSky® for Injection 340 mg**

PiaSky Lifecycle Leader,
Chugai Pharmaceutical Co., Ltd.
Kumi Miura

02 **Clinical Significance of PiaSky® in the Treatment of Paroxysmal Nocturnal Hemoglobinuria (PNH)**

Professor,
Department of Medical Sciences,
Faculty of Medicine, University of Tsukuba
Naoshi Obara, M.D., Ph.D.

03 **Q&A session**

Overview of PiaSky® for Injection 340 mg

Standard Commodity Classification No. of Japan	876399

pH-Dependent Binding Humanized Anti-complement (C5) Monoclonal Antibody

Listed in the NHI drug price list

PIASKY® for Injection 340 mg

Newly launched

Crovalimab (Genetical Recombination) for Intravenous and Subcutaneous Injection

Biological product, powerful drug, prescription drug (Caution: Use only as prescribed by a physician, etc.)

® Registered trademark

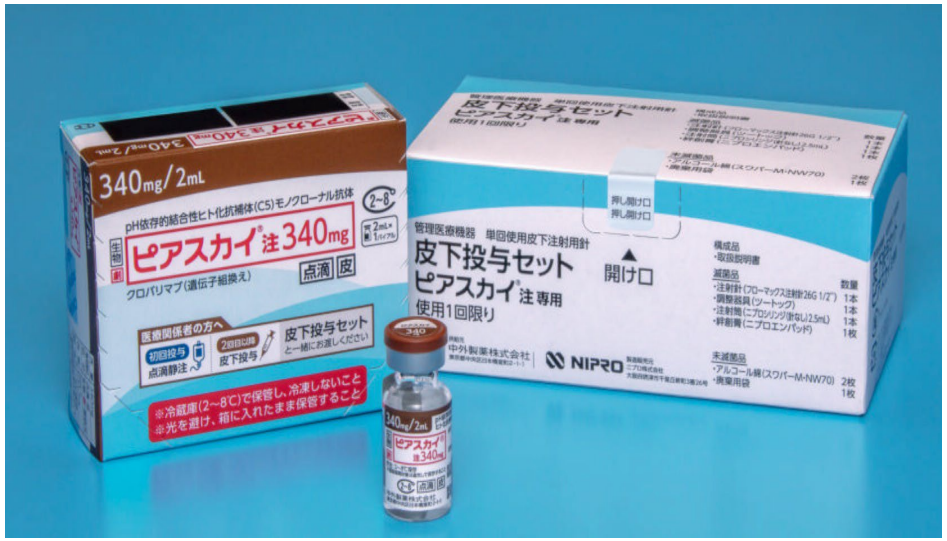
Kumi Miura
PiaSky Lifecycle Leader,
Chugai Pharmaceutical Co., Ltd.

PiaSky® (Generic name: Crovalimab) Basic Information

- A pH-dependent binding humanized anti-complement (C5) monoclonal antibody created using Chugai's Recycling Antibody® technology.
- The first antibody developed at Chugai Pharmabody Research Pte. Ltd., our drug discovery and development center in Singapore, and the fifth antibody drug created by Chugai to be launched.
- In Japan, the application for marketing approval was filed in June 2023, and approved in March 2024 (the second country after China) and launched in May 2024 (the first in the world).
- Applications for marketing approval were submitted in Europe and the U.S. at about the same time as in Japan, and approval was obtained in June 2024 in the U.S. In China, it was approved in February 2024. Approval reviews by other regulatory authorities, including Taiwan, are also ongoing.
- Indication: Paroxysmal nocturnal hemoglobinuria (PNH).

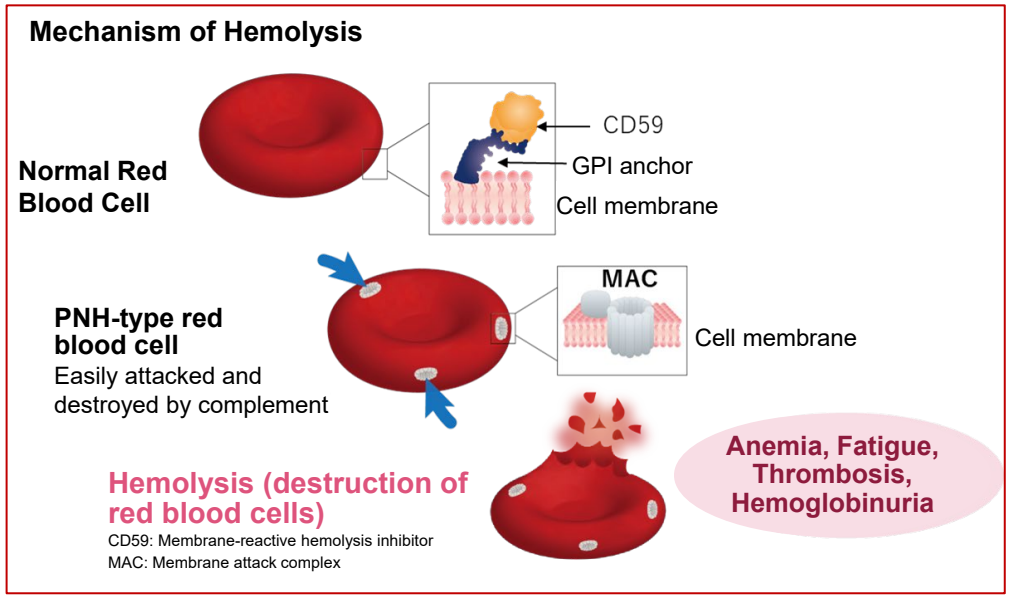
PIASKY

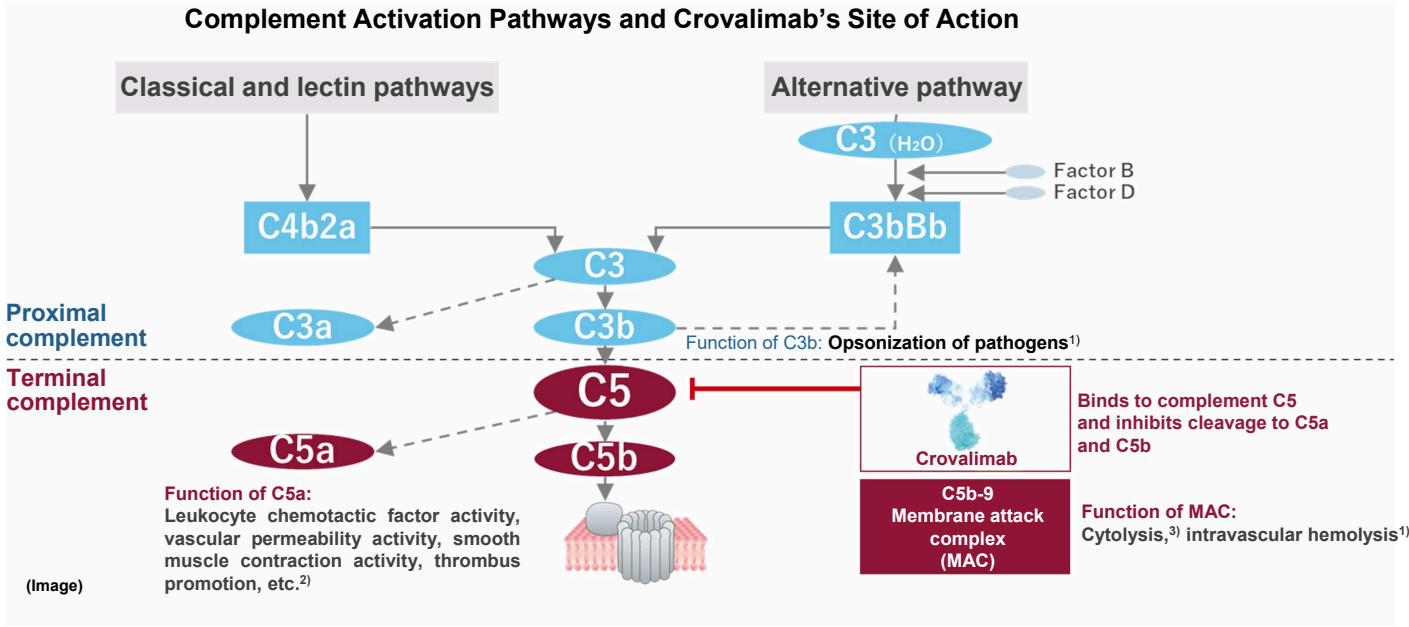
PIA: Derived from surface charge improvement technology used in crovalimab, developed from the isoelectric point (pI) adjustment technology.
SKY: Superior Kinetics antibodY
Derived from the development code, expressing the characteristics of this drug achieved by introducing antibody technologies.



Hemolysis Mechanism of Paroxysmal Nocturnal Hemoglobinuria and PiaSky's Mode of Action

- **Crovalimab binds to complement C5, and inhibits the cleavage of C5 into C5a and C5b. This inhibits activation of the terminal complement and suppresses formation of the terminal complement complex C5b-9 (membrane attack complex; MAC), thereby suppressing complement-mediated intravascular hemolysis in PNH patients.**





Working group for the development of the reference guide revision of diagnostic criteria and practice for paroxysmal nocturnal hemoglobinuria (PNH)
Reference Guidelines for the Diagnosis and Treatment of Paroxysmal Nocturnal Hemoglobinuria: FY2022 revision (in Japanese)

1) Ueda Y. The Japanese Association for Complement Research. FOCUS Complement Series, 4th Report. 2018:18-23.
2) Miyata T. et al.: Japanese Journal of Thrombosis and Hemostasis. 2021; 32:695-707.3) Wakamiya N. The Japanese Association for Complement Research. FOCUS Complement Series First Edition. 2018:2-5.

Three Antibody Technologies and C5 Recognition Site Different from Existing Anti-C5 Antibodies

pH-dependent Antigen Binding Technology (Recycling Antibody Technology) [1),2)]

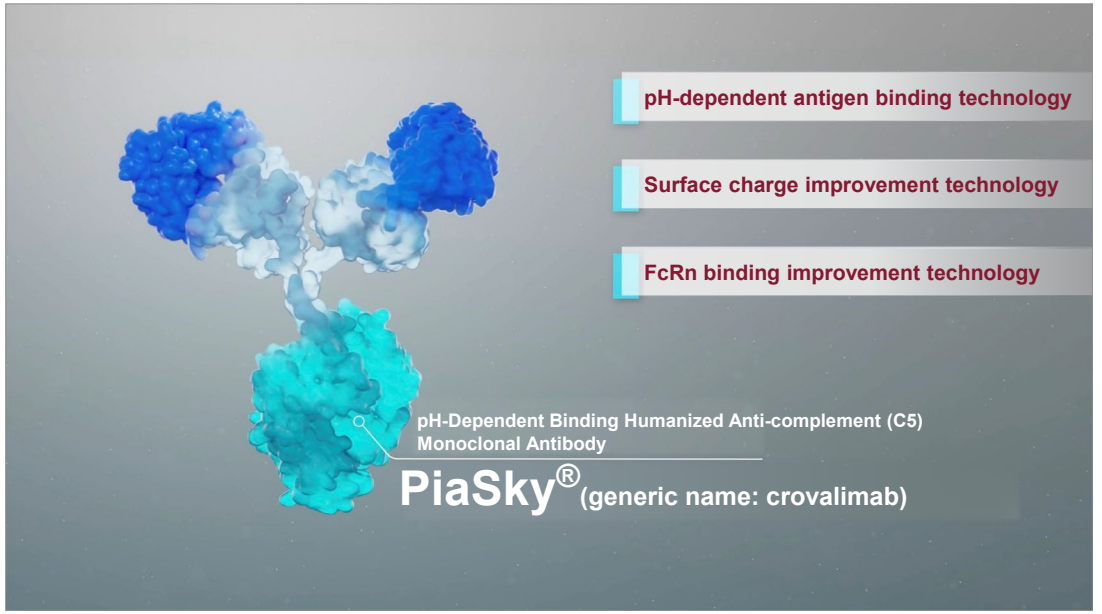
Crovalimab is designed to improve the binding affinity to C5 in an environment of pH 7.4 , and to dissociate C5 in an acidic environment with pH of 5.8 by introducing mutations into the complementarity determining region (CDR).

Surface Charge Improvement Technology[1),2)]

Crovalimab is designed to promote their uptake into cells by electrostatic effects due to negative charge on the cell membrane surface, by optimizing the surface charge of immune complexes.

FcRn Binding Improvement Technology [1-3)]

Crovalimab is designed to avoid the degradation of many antibodies in lysosomes, by modifying the Fc region to improve affinity for FcRn in endosomes.



(Image)

✓ Recognizes the MG1 domain (20-124) located on the β chain of complement C5

There is p.Arg885His polymorphism due to heterozygous mutation in the complement C5α chain (c.2654G→A), and a mutation is present near the epitope recognized by existing anti-C5 antibodies. Therefore, it is reported that about 3% of Japanese patients experience poor response.[4)] Since crovalimab binds to the β chain,[1)] it is expected to be effective also in patients with mutations.

1) Fukuzawa T, et al.: Sci Rep. 2017; 7: 1080. [The authors of this paper include employees of Chugai Pharmaceutical Co., Ltd.]
2) Sampei Z, et al.: PLoS One. 2018; 13: e0209509. [All authors of this paper are employees of Chugai Pharmaceutical Co., Ltd.]
3) Maeda A, et al.: MAbs. 2017; 9: 844-853. [This study was conducted with the support of Chugai Pharmaceutical Co., Ltd. The authors of this paper include employees of Chugai Pharmaceutical Co., Ltd.]
4) Nishimura J, et al. N Engl J Med 2014; 370: 632-39

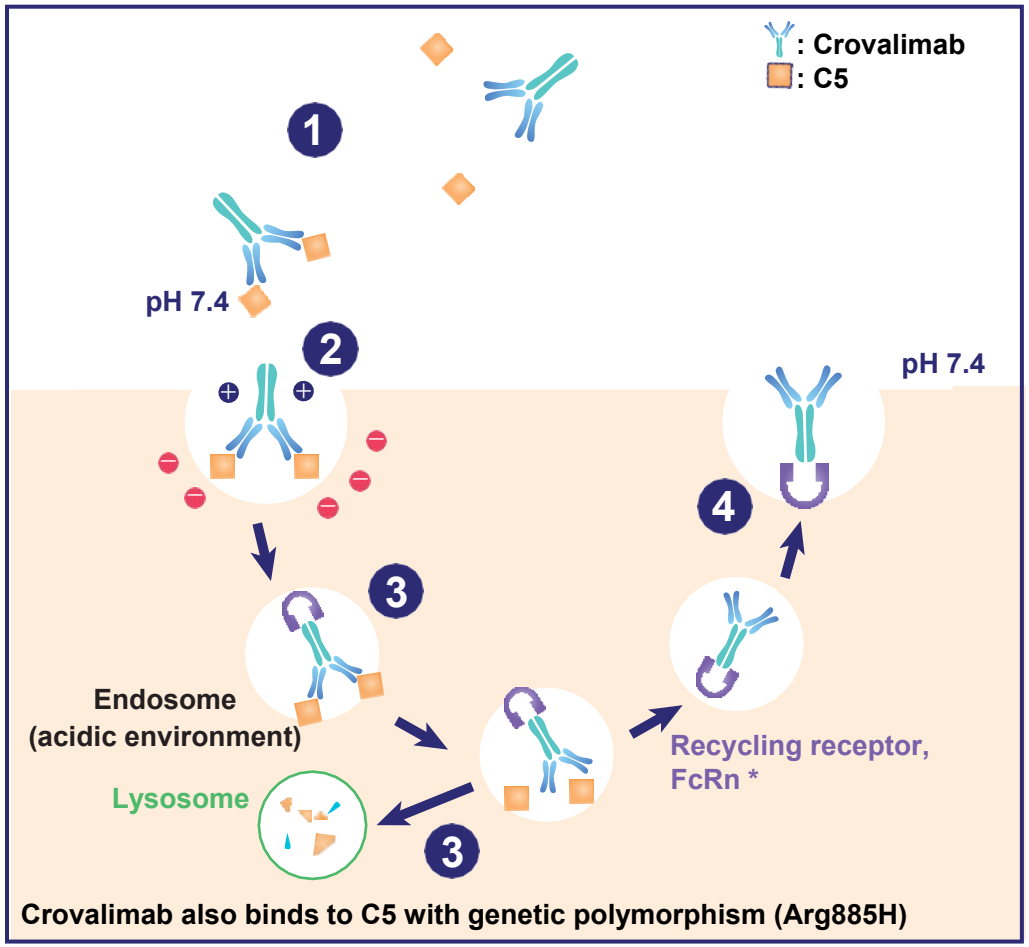
Recycling Mechanism of Crovalimab [1)2)]

1 Antigen Binding in Plasma
Crovalimab is designed to bind strongly to C5 at pH 7.4, the normal pH of the vascular compartment.

2 Endocytosis of Antigen-bound Antibodies
Crovalimab bound to C5 molecules is thought to be efficiently taken up into cells due to optimization of its surface charge.

3 Dissociation of Antigen in Endosomes
C5 dissociates from crovalimab in the acidic environment of the endosome, which is thought to promote the degradation of C5 in the lysosome.

4 Antibody Recycling by FcRn Binding
Technology that increases binding to FcRn is thought to facilitate the recycling of crovalimab back into plasma.

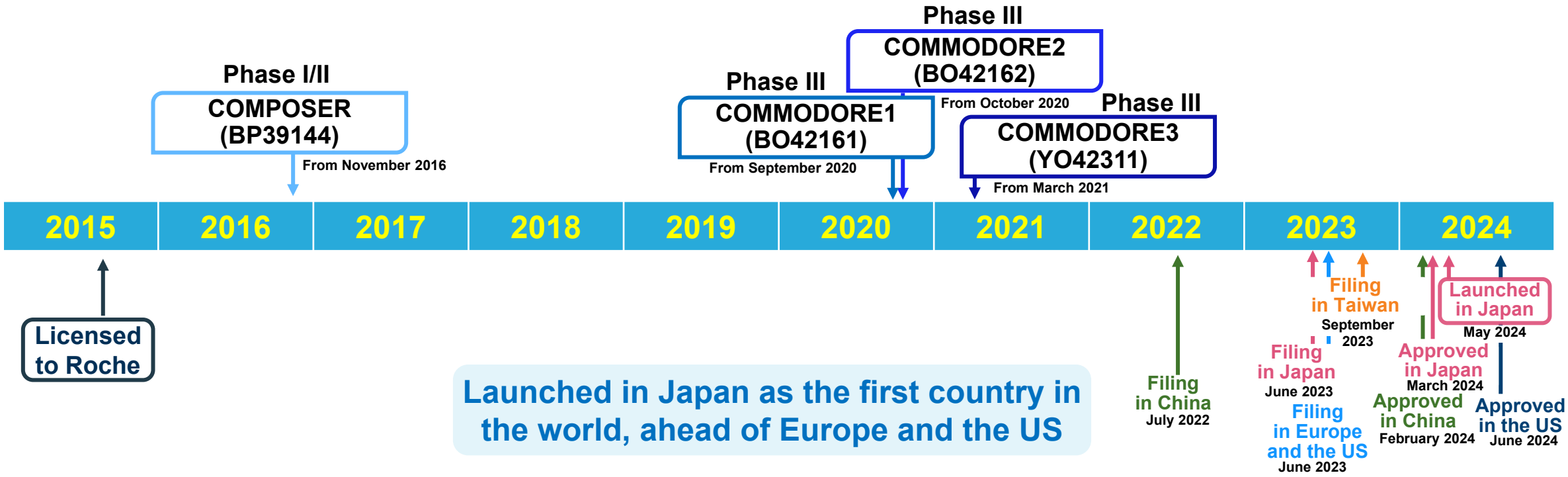


*** FcRn: neonatal Fc receptor**
(Image)

1) Fukuzawa T, et al.: Sci Rep. 2017; 7: 1080. [The authors of this paper include employees of Chugai Pharmaceutical Co., Ltd.]
2) Sampei Z, et al.: PLoS One. 2018; 13: e0209509. [All authors of this paper are employees of Chugai Pharmaceutical Co., Ltd.]

History of Development

- Started development of antibodies using recycling antibody technology following ENSPRYNG® (anti-IL-6R antibody).
- Complement C5 was selected as an antigen that may effectively exert recycling function.
  - ✓ It was expected that convenience would be improved by reducing the frequency of administration and the dosage, or by developing a subcutaneous administration, thereby improving patients' QoL.
  - ✓ By binding to the β-chain of C5 as the epitope, it was expected that a therapeutic drug could be provided for cases in which existing anti-C5 antibodies are ineffective.
- Global clinical trials were started in 2016 through joint development with Roche.



Launched in Japan as the first country in the world, ahead of Europe and the US

Clinical Studies in PNH

Evaluated in a total of over 400 patients with PNH in 4 clinical studies

Data evaluated at approval

Phase I/II COMPOSER [1)]

4-part adaptive study in C5 inhibitor-naive and experienced patients

- 15 healthy adults enrolled
- 44 PNH patients enrolled
- Confirmation of dosage and administration for Phase III clinical study

Global

Phase III COMMODORE 3 [2)]

Single-arm study in C5 inhibitor-naive patients

- 51 patients enrolled
- Adults or adolescents (≥ 12 years old)
- Single-arm, open-label
- Maintenance dosing by subcutaneous injection every 4 weeks

China only

Phase III COMMODORE 2 [3)4)]

Randomized study in C5 inhibitor-naive patients

- 204 patients enrolled in randomized arm
- 2:1 randomization
- Maintenance dosing by subcutaneous injection every 4 weeks

Primary study objective: Verify non-inferiority to eculizumab

Global

Phase III COMMODORE 1 [5)]

Randomized study in C5 inhibitor-experienced patients

- 89 patients enrolled in randomized arm
- 1:1 randomization
- Plan to enroll 100 patients in descriptive analysis arm
- Maintenance dosing by subcutaneous injection every 4 weeks

Primary objective: Safety in PNH patients switching from other C5 inhibitors (eculizumab)

Global

1) Data evaluated at approval: Global Phase I/II Study (Study BP39144) , 2) Reference data at the time of approval: Foreign phase III study (Study YO42311), 3) Data evaluated at approval: Global Phase III Study (Study BO42162), 4) Röth A, He G, Tong H, et al. Phase 3 randomized COMMODORE 2 trial: Crovalimab versus eculizumab in patients with paroxysmal nocturnal hemoglobinuria naive to complement inhibition. Am J Hematol. 2024; 1-10. [The authors of this paper include employees of F. Hoffmann-La Roche], 5) Data evaluated at approval: Global Phase III Study (Study BO42161)

INDICATIONS

Indications

Paroxysmal nocturnal hemoglobinuria

Precautions Concerning Indications

- **As PIASKY inhibits the cleavage of complement C5 and is thought to inhibit the production of terminal complement complex C5b-9, susceptibility to infections caused by encapsulated bacteria such as meningococcus may increase. Therefore, PIASKY must only be administered to the appropriate target patients after they have fully understood its efficacy and safety, and once careful consideration has been given to the pros and cons of administering PIASKY. In principle, patients should be vaccinated against meningococcus at least two weeks before the start of PIASKY treatment.**
- **Administer PIASKY to patients with a definitive diagnosis of paroxysmal nocturnal hemoglobinuria via a testing method such as flow cytometry.**
- **PIASKY must only be used in patients for whom administration is considered appropriate after they have fully understood its efficacy and safety. This includes the possibility that if PIASKY treatment is discontinued, severe intravascular hemolysis may occur due to the accumulation of PNH erythrocyte clones caused by the PIASKY treatment**
- **When switching from another anti-C5 antibody preparation to PIASKY, the necessity of switching to PIASKY should be carefully determined as there is a risk of causing immune complex reactions.**

PIASKY® for Injection 340 mg. Electronic package insert. May 2024 (Version 2)

DOSAGE AND ADMINISTRATION

Dosage and Administration

The usual Day 1 dose is 1000 or 1500 mg of crovalimab (genetical recombination) once by intravenous infusion, and subsequently, 340 mg is subcutaneously administered once on Days 2, 8, 15, and 22, and 680 or 1020 mg is subcutaneously administered once every 4 weeks from Day 29 onward, taking the patient's body weight into account.

Precautions Concerning Dosage and Administration

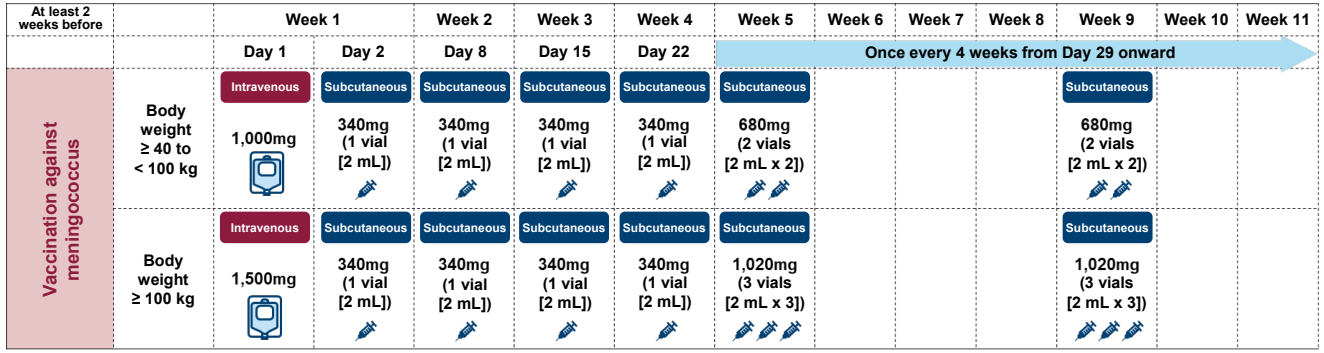
Refer to the table below for the amount per dose and method of administration of PIASKY.

Body weight	Day 1	Days 2, 8, 15, and 22	Once every 4 weeks from Day 29 onward
≥ 40 to < 100 kg	1,000 mg intravenous	340 mg subcutaneous	680 mg subcutaneous
≥ 100 kg	1,500 mg intravenous	340 mg subcutaneous	1,020 mg subcutaneous

If a dose cannot be administered on the scheduled date, it should be administered as soon as possible, and subsequent doses should be administered as prescribed.

PIASKY® for Injection 340 mg. Electronic package insert. May 2024 (Version 2)

[Reference] Treatment schedule



[Reference] Treatment scope

Intended for use by patients weighing at least 40 kg (No clinical studies have been conducted in children weighing less than 40 kg)

Significance of PiaSky Development: Contribution to the Treatment of PNH

Offering a new treatment option as the first subcutaneous C5 inhibitor for PNH patients in Japan

Improved convenience with subcutaneous administration once every 4 weeks*

Subcutaneous administration once every 4 weeks may reduce the burden of treatment on patients and caregivers, as well as on medical facilities.

- Compared to existing drugs, it reduces the frequency of administration and hospital visits, and reduces the time required for treatment due to periodic infusions.

Provides a broad range of treatment opportunities for patients with C5 gene polymorphisms

Also effective in patients with C5 gene polymorphism** that does not respond to existing anti-C5 antibody treatments

The first complement inhibitor in Japan offering treatment opportunities for PNH patients under 15 years of age***

It can be administered to patients weighing 40 kg or more regardless of age.

*: Dosing frequency in the maintenance period
**: C5 gene polymorphism is expressed in about 3% of Japanese[1)]
***: Number of pediatric cases in the clinical trial is limited

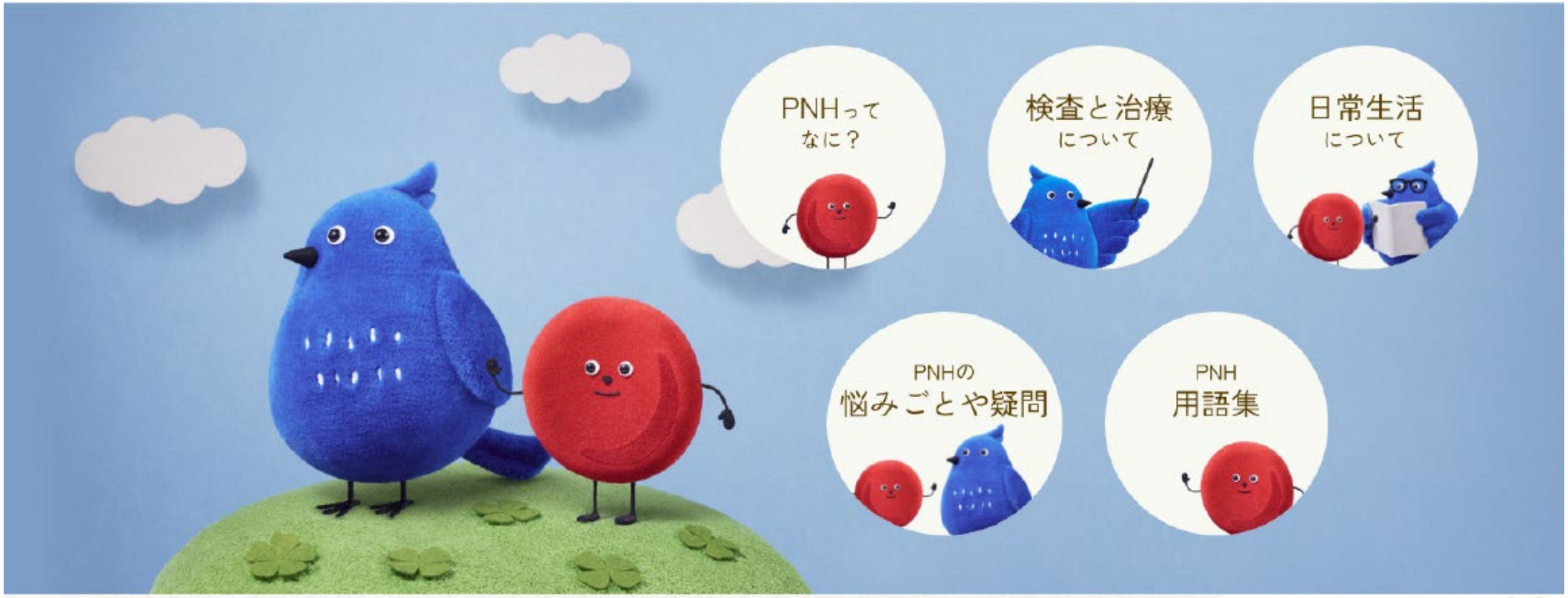
1) Nishimura J, et al. N Engl J Med 2014; 370: 632-39,

[Disease Awareness Site] Tell me about PNH

PiaSky®

おしえて PNHのコト
Paroxysmal Nocturnal Hemoglobinuria

For a better tomorrow. Let's learn about paroxysmal nocturnal hemoglobinuria (PNH).
General supervision:
Dr. Naoshi Obara, Professor, Department of Medical Sciences, Faculty of Medicine, University of Tsukuba



In collaboration with the patient group "PNH Club," we have created this disease awareness website, which aims to provide necessary information for patients and their families, and also to be useful to the general public for introducing and explaining the disease PNH to people around them. (Accessed: June 2024, Japanese only)

https://www.chugai-pharm.co.jp/ptn/oshiete-pnh/

Product Overview

Expanding options, moving to the envisioned future.

- Chugai's proprietary Recycling Antibody® technology -

- A pH-dependent binding humanized anti-complement (C5) monoclonal antibody created using Chugai's Recycling Antibody® technology
- Subcutaneous C5 inhibitor offers a new treatment option for PNH patients
- Subcutaneous administration once every 4 weeks may reduce the burden of treatment on patients and caregivers, as well as on medical facilities
- May provide new treatment to patients with C5 gene polymorphism and patients less than 15 years old weighing 40 kg or more

Clinical Significance of PiaSky® in the Treatment of Paroxysmal Nocturnal Hemoglobinuria (PNH)

Naoshi Obara, M.D., Ph.D.

Professor,
Department of Medical Sciences,
Faculty of Medicine, University of Tsukuba

COI Disclosure

Companies, etc. with COI to be disclosed by the presenter in relation to the content of the presentation:

①	**Advisor:**	**None**
②	**Shareholding and profits:**	**None**
③	**Patent royalties:**	**None**
④	**Lecture fees:**	**Novartis, Alexion Pharmaceuticals, Janssen Pharmaceutical, Asahi Kasei, Kyowa Kirin, Sobi, Chugai Pharmaceutical**
⑤	**Manuscript fees:**	**Alexion Pharmaceuticals, Novartis**
⑥	**Contract research/joint research expenses:**	**Alexion Pharmaceuticals, Kyowa Kirin**
⑦	**Scholarship donation:**	**None**
⑧	**Affiliation of endowed course:**	**None**
⑨	**Remuneration including gifts:**	**None**
⑩	**Employee of a company or for-profit organization:**	**None**
⑪	**Provision of specimens, drugs, etc.:**	**None**
⑫	**OFF LABEL USE:**	**None**

1. Complement and PNH
2. Introduction of PiaSky Clinical Study
3. Case Presentation

1. **Complement and PNH**
2. **Introduction of PiaSky Clinical Study**
3. **Case Presentation**

What is PNH?

Paroxysmal

Nocturnal

Hemoglobinuria

[Definition (disease concept)]
Paroxysmal nocturnal hemoglobinuria (PNH), which occurs due to the clonal expansion of hemopoietic stem cells with a mutation in a gene involved in the synthesis of GPI anchors, including *PIGA*, is a **hemopoietic stem cell disorder** characterized by complement-mediated intravascular hemolysis. PNH is often complicated by or develops into acquired bone marrow failure such as aplastic anemia (AA). Thrombosis is rare in Japan, but is a characteristic complication of PNH. Although rare, progression to acute leukemia also occurs.

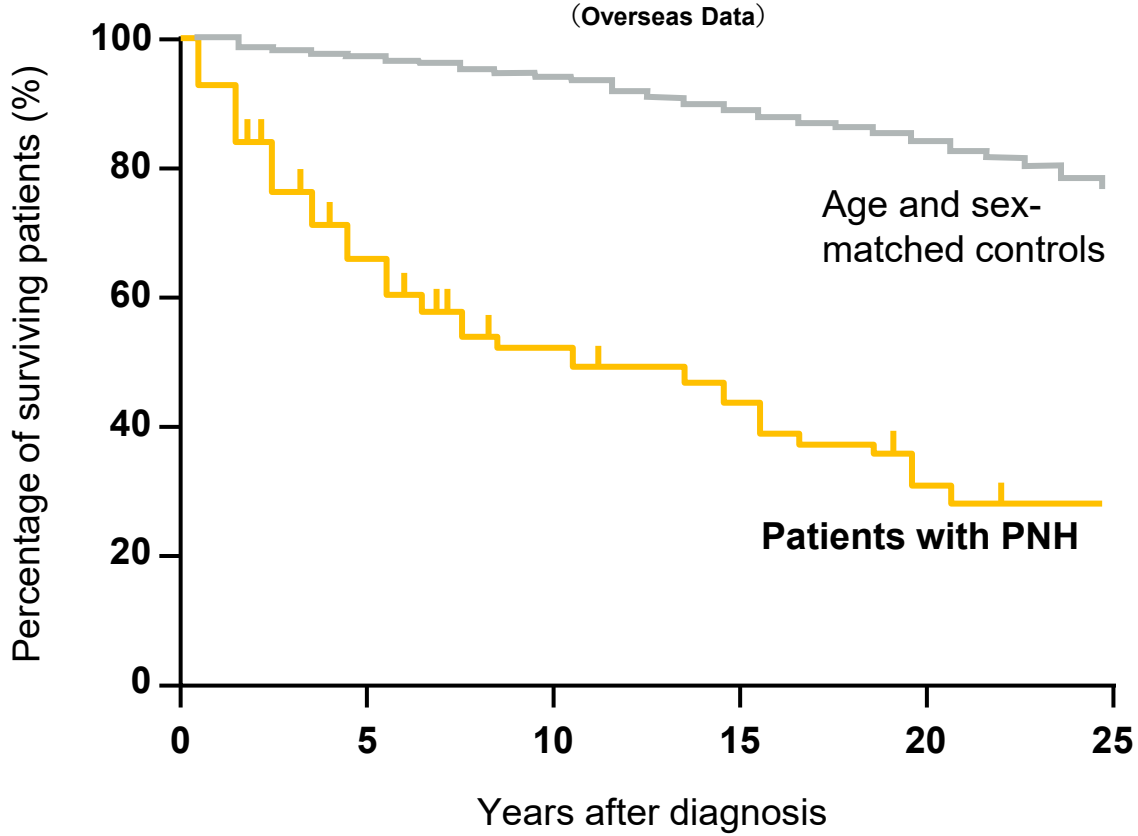
Prepared from the Reference Guidelines for the Diagnosis and Treatment of Paroxysmal Nocturnal Hemoglobinuria: FY2022 revision (in Japanese), page 4.

PNH is a Progressive and Potentially Life-Threatening Disease

- Prevalence: 3.6/1 million[1)]
  (About 900-1,000 patients are receiving anti-complement therapy in Japan. If follow-up observation is included, the actual number is about 1 in 100,000?)

- Average age at diagnosis[2)]:
  - 32.8 years old (overseas data)
  - 45.1 years old (Japanese data)
- 35% of PNH patients receiving supportive care die within 5 years of diagnosis.
- About 1 in 5 Japanese PNH patients die within 10 years of diagnosis.
- **Progressive disease: characterized by chronic complement-mediated hemolysis**
- Designated intractable disease. Medical expenses are subsidized for patients who require treatment.

Estimated Survival Rate from the Time of Diagnosis in 80 Patients PNH[3)]
(Overseas Data)



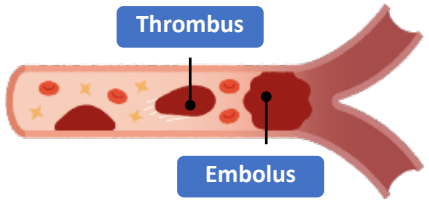
＊Data summary: A group of 80 consecutive PNH patients referred to Hammersmith Hospital, London, between 1940 and 1970 were followed. The patients were treated with supportive care after thrombus formation, including oral anticoagulation and blood transfusion[3)].

1) Yoshiyuki Ohno: "Research Group for Understanding the Epidemiological Profile of Diseases Not Covered by the Specific Disease Treatment Research Program" FY 1999 Research Achievements Collection - Final Report - Published March 2000.
2) Nishimura J, et al.Medicine. 2004;83:193-207.
3) Hillmen P, et al. *N Engl J Med.* 1995;333(19):1253-1258.

Three Major Signs of PNH[1)]

Hemolysis

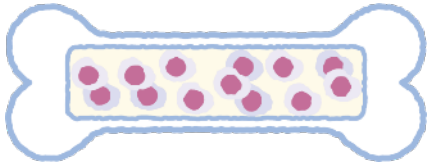
Symptoms due to hemolysis
- Renal disorder
- Thrombosis
- Abdominal pain
- Dysphagia (esophageal spasm)
- Pulmonary hypertension
- Anemia
- Fatigue



Thrombosis

Venous
- Deep vein thrombosis (DVT)
- Liver (Budd-Chiari)
- Brain

Arterial
- Cerebrovascular disorder (CVA)/ Transient ischemic attack (TIA)



Bone marrow failure

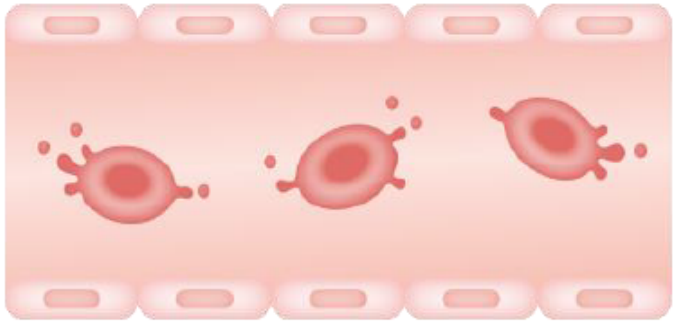
Aplastic anemia (AA)/ Myelodysplastic syndrome (MDS)
- Often transitions to PNH
- Selection mechanism of PNH clone

1）Working group for the development of the reference guide revision of diagnostic criteria and practice for paroxysmal nocturnal hemoglobinuria (PNH). Reference Guidelines for the Diagnosis and Treatment of Paroxysmal Nocturnal Hemoglobinuria: FY2022 revision (in Japanese)

Intravascular and Extravascular Hemolysis Due to Hemolytic Anemia

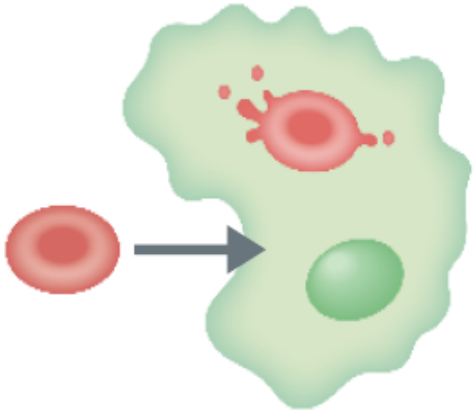
- In hemolytic anemia, erythrocyte destruction is accompanied by various findings.
- Although intravascular and extravascular hemolysis share many common findings, hemoglobinuria and urinary hemosiderin are specific to intravascular hemolysis.
- PNH mainly causes intravascular hemolysis.

Intravascular Hemolysis



Erythrocytes are destroyed in blood vessels before the end of their physiological life.

Extravascular Hemolysis



Erythrocytes are destroyed in the reticuloendothelial system (outside blood vessels), such as the spleen, before the end of their physiological life.

Prepared based on Institute for Health Care Information Sciences, ed. Medical Disease: An Illustrated Reference vol. 5, 2nd Edition, Medic Media, 2017, p. 64.65

Why Nocturnal?

1) Decreased respiratory rate during sleep → CO_2 accumulation → Acidosis
   → Increased complement activity

2) Decreased intestinal peristalsis during sleep
   → Increased LPS (polysaccharide, endotoxin) absorption → Increased activity of complement activation pathways (lectin pathway, etc.)

* Because of drinking less water and urinating less at night, urine is often concentrated in the early morning, making it more noticeable.

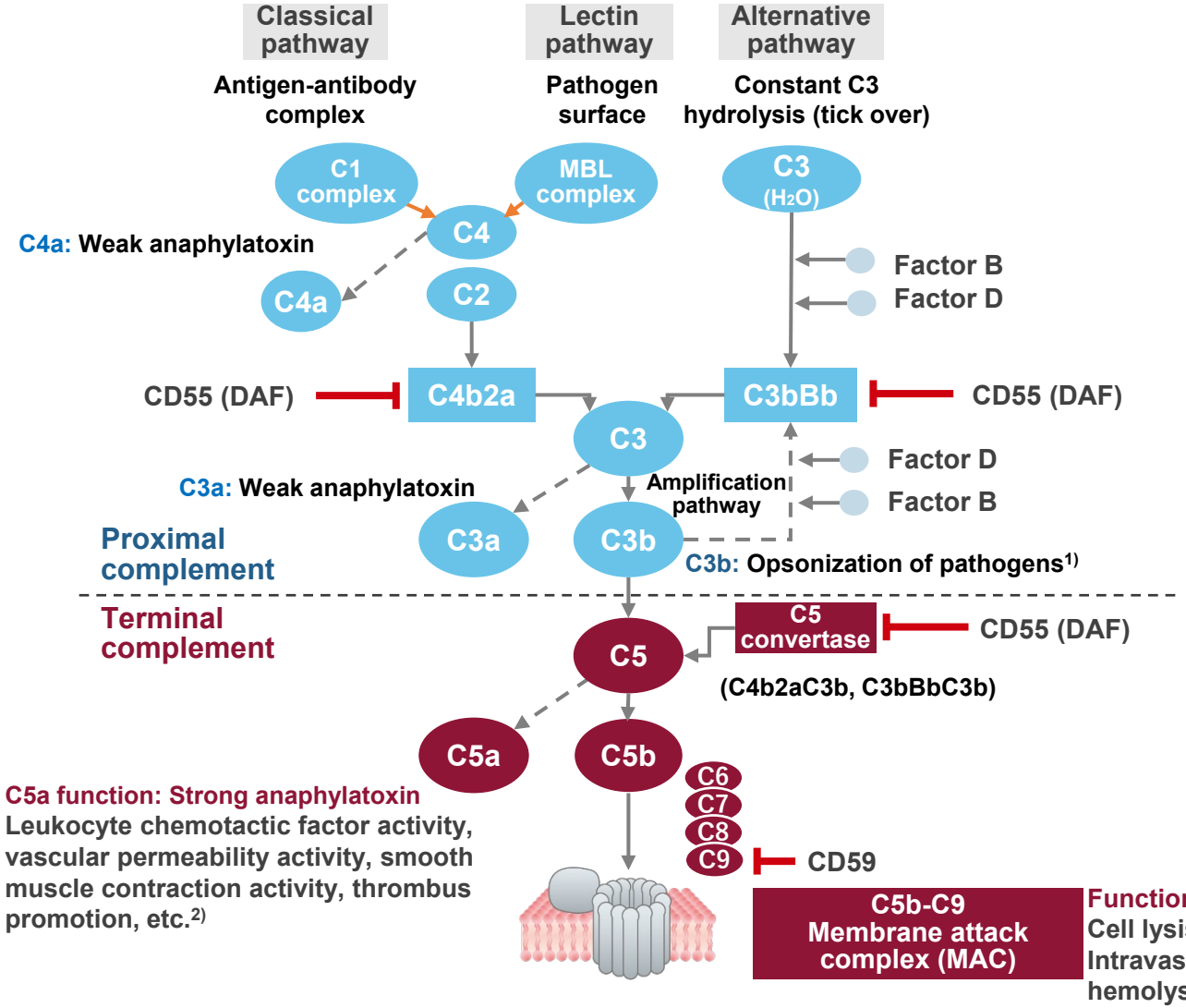
Prepared from the Working group for the development of the reference guide revision of diagnostic criteria and practice for paroxysmal nocturnal hemoglobinuria (PNH). Reference Guidelines for the Diagnosis and Treatment of Paroxysmal Nocturnal Hemoglobinuria: FY2022 revision (in Japanese)

Misconceptions about PNH

- Not **paroxysmal**
  - PNH is characterized by chronic hemolysis, which may lead to acute attacks.
- Not necessarily **at night**
  - Patients with PNH may experience hemolytic episodes at any time of the day.
- Not always accompanied by **hemoglobinuria**
  - Approximately 75% of patients do not have hemoglobinuria at hospital visit.

Rother RP, et al. *Nat Biotechnol.* 2007; 25 (11): 1256-1264.
Hill A, et al. *Br J Haematol.* 2007;137(3):181-192.
Brodsky RA. Paroxysmal nocturnal hemoglobinuria. In: Hoffman R, et al, eds. *Hematology : Basic Principles and Practice*. 4th ed. Philadelphia, PA: Elsevier Churchill Livingstone; 2005:419-427.
Parker C, et al. *Blood.* 2005;106(12):3699-3709.

What is the Complement System?



- **Identified more than 100 years ago as a protein that supports the activity of antibodies**
- **It is an immune system that has been preserved in the course of biological evolution.**
- **Constituent factors cause a cascade reaction and act in the body's defense.**
- **Major complement factors are numbered C1 to C9. Breakdown products formed during complement activation are assigned a to the smaller molecular weight, and b to the larger molecular weight (C3a, C3b, etc.).**

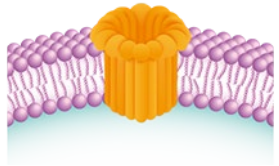
1) Ueda Y, The Japanese Association for Complement Research. FOCUS Complement Series, 4th Report. 2018:18-23., 2) Miyata T. et al.: Japanese Journal of Thrombosis and Hemostasis. 2021; 32:695-707., 3) Wakamiya N. The Japanese Association for Complement Research. FOCUS Complement Series First Edition. 2018:2-5.

The Role of Complement

1) Opsonization (pathogens are marked)

2) Induction of inflammation
(attracting white blood cells)

3) Membrane attack complex
(directly kills pathogens)



⇒ Since the body's own cells are also attacked, the body has a defense mechanism.

Wakamiya N. The Japanese Association for Complement Research. FOCUS Complement Series First Edition. 2018:2-5.

CD59 and CD55 Protect the Body's Own Cells from Complement Attack

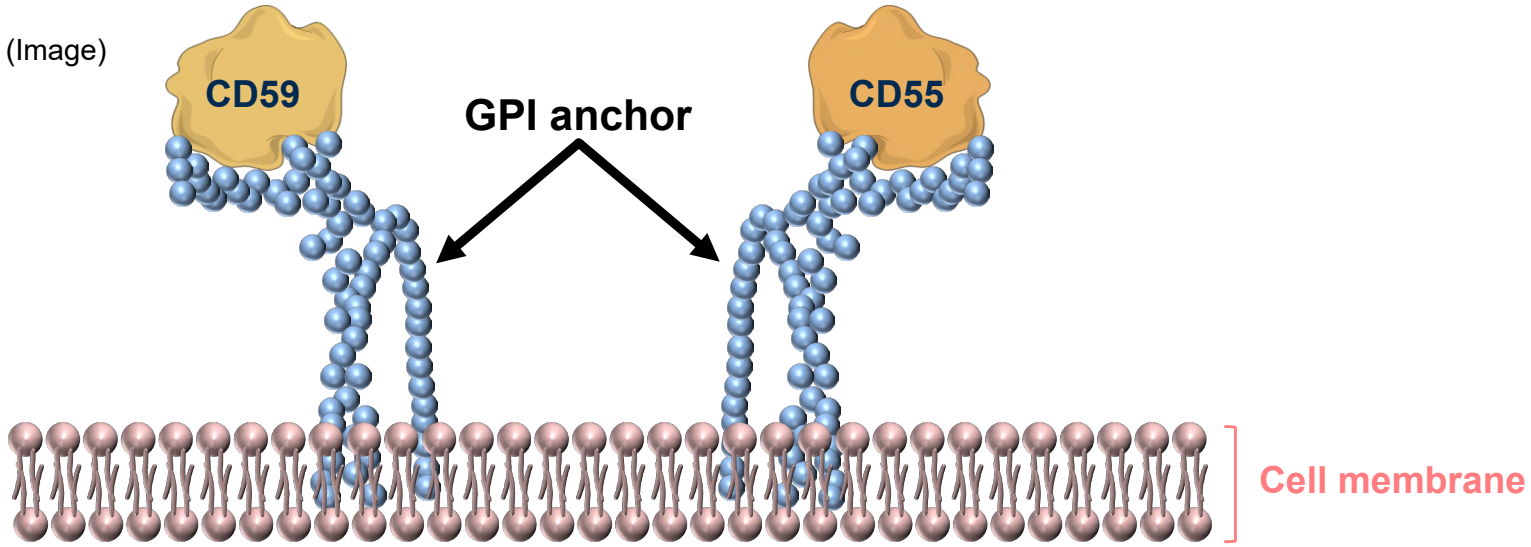
CD59 (MIRL)

- Protects red blood cells from complement-mediated hemolysis
- Inhibits the assembly of membrane attack complexes

CD55 (DAF)

- Inhibits C3 cleavage enzymes and attenuates the complement cascade

(Image)



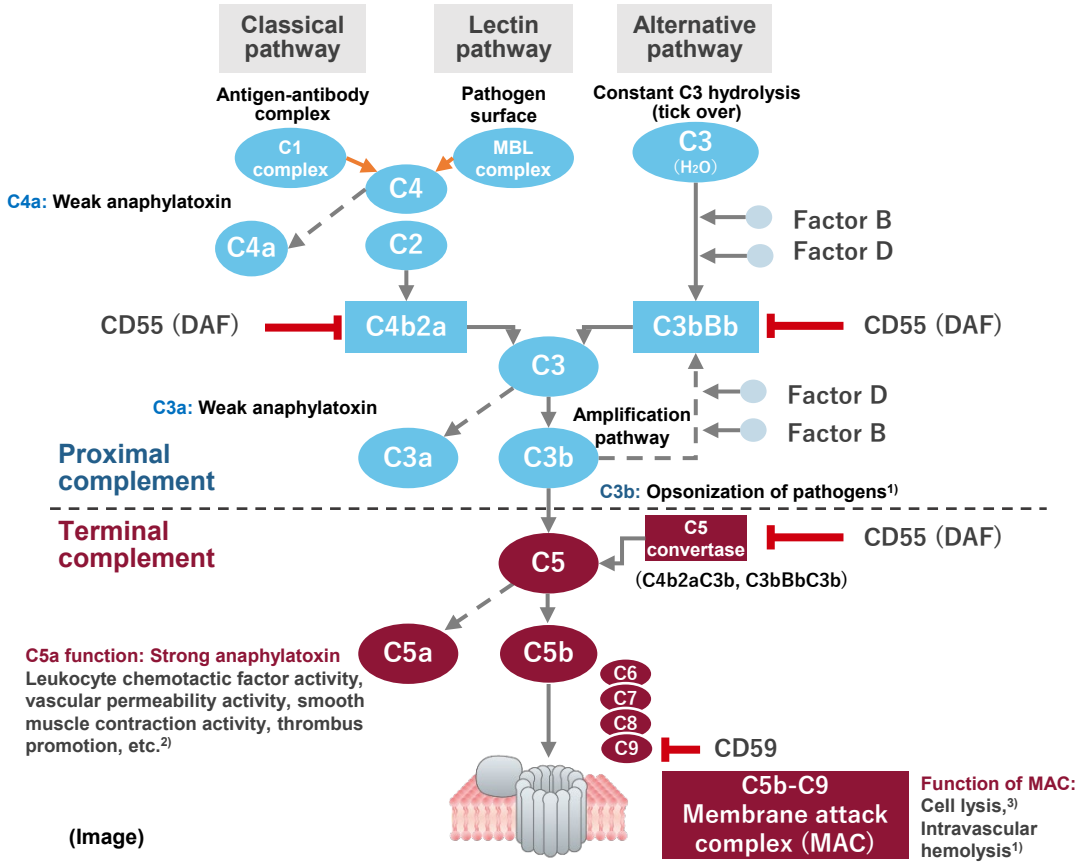
The *PIGA* gene encodes GPI anchors
⇒ PNH cells lack CD59 and CD55 expression

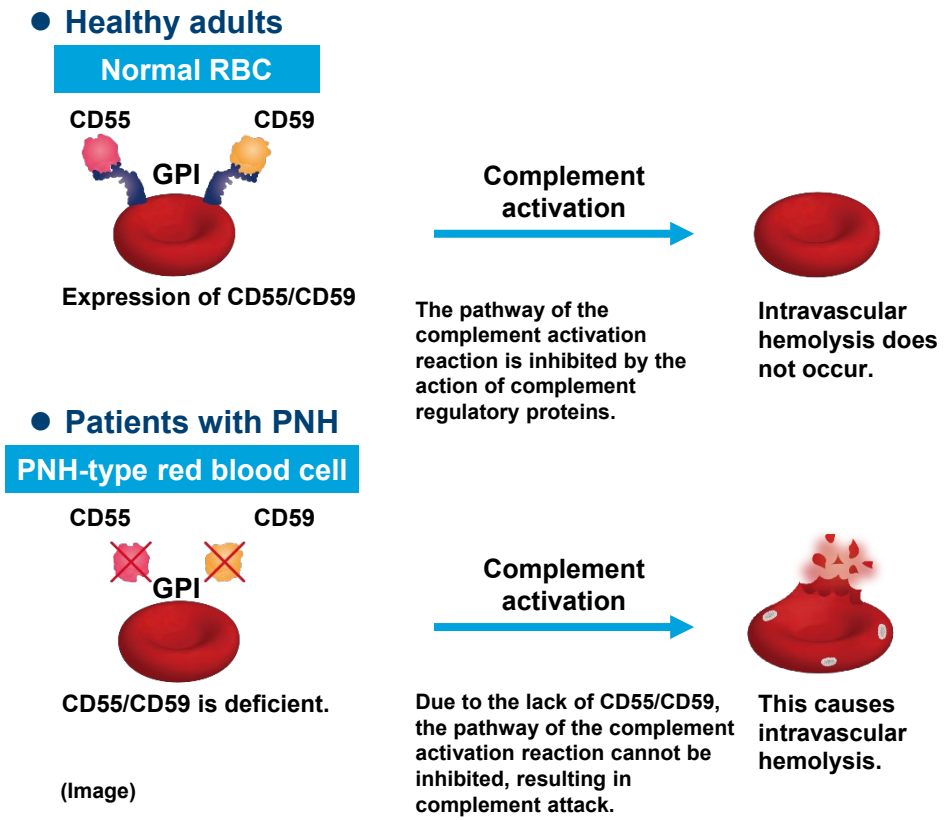
GPI: Glycosylphosphatidylinositol, GPI-AP: GPI-anchored protein, DAF: Decay-accelerating factor, MIRL: Membrane inhibitor of reactive lysis

Brodsky RA. Paroxysmal nocturnal hemoglobinuria. In: Hoffman R, et al, eds. Hematology : Basic Principles and Practice. 4th ed. Philadelphia, PA: Elsevier Churchill Livingstone; 2005:419-427.

Mechanism of PNH Hemolysis from the Perspective of Complement Activation Pathway

- **PNH-type red blood cells, which are increased due to acquired somatic mutations such as the *PIGA* gene, lack the complement regulatory proteins CD55 and CD59, and are thought to be attacked by complement, thereby causing intravascular hemolysis.[1)]**
- **Deficiency of CD59, which is involved in the "terminal complement pathway" that mainly involves C5 activation, is considered to be particularly important in the hemolytic mechanism of PNH.**



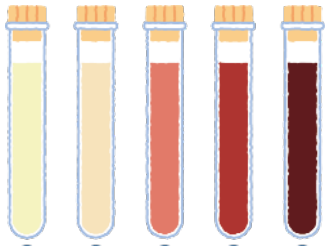


1) Working group for the development of the reference guide revision of diagnostic criteria and practice for paroxysmal nocturnal hemoglobinuria (PNH). Reference Guidelines for the Diagnosis and Treatment of Paroxysmal Nocturnal Hemoglobinuria: FY2022 revision (in Japanese), 2) Ueda Y, The Japanese Association for Complement Research. FOCUS Complement Series, 4th Report. 2018:18-23., 3) Miyata T. et al.: Japanese Journal of Thrombosis and Hemostasis. 2021; 32:695-707., 4) Wakamiya N. The Japanese Association for Complement Research. FOCUS Complement Series First Edition. 2018:2-5.

Symptoms of PNH

Major symptoms caused by hemolysis

Haemoglobinuria



Anaemia

Jaundice

Major complications of hemolysis
→Various complications occur when hemoglobin binds to nitric oxide (NO) in blood vessels, making blood vessels and muscles stiff.

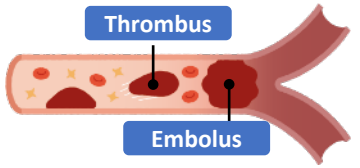
Chronic kidney disease

Acute kidney injury

Pulmonary hypertension

Dysphagia/ odynophagia

Thrombosis



Prepared from the Working group for the development of the reference guide revision of diagnostic criteria and practice for paroxysmal nocturnal hemoglobinuria (PNH). Reference Guidelines for the Diagnosis and Treatment of Paroxysmal Nocturnal Hemoglobinuria: FY2022 revision (in Japanese) Accessed May 21, 2024 http://zoketsushogaihan.umin.jp/file/2022/Paroxysmal_nocturnal_hemoglobinuria.pdf

Reference Guidelines for the Diagnosis and Treatment of Paroxysmal Nocturnal Hemoglobinuria [FY2022 Revision/Summary]

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Health and Labour Sciences Research Grant: Refractory Disease Policy Research Project
Research Group on Idiopathic Hematopoietic Disorders

Research Director: Kinuko Mitani

March 2023

Diagnostic Criteria for PNH

- **A. Test Findings**

The following 1) and 2) are met.

1) PNH-type red blood cells (types II and III) account for ≥ 1% in the detection and quantification of glycosylphosphatidylinositol (GPI)-anchored membrane protein-deficient red blood cells (PNH-type red blood cells).

2) Serum LDH level is ≥ 1.5 times the upper limit of normal.

<Diagnostic Category> Definite: A is met.

- **B. Ancillary Test Findings**

The following laboratory findings are common:

1) Anemia and decreased white blood cells and platelets

2) Reference findings for hemolysis include elevated serum LDH, increased reticulocyte, increased indirect bilirubin, and decreased serum haptoglobin.

3) Urine supernatant positive for hemoglobin, and urine sediment positive for hemosiderin

4) Decreased neutrophil alkaline phosphatase score, decreased erythrocyte acetylcholinesterase

5) Increased bone marrow erythroblasts (bone marrow is often hyperplastic, but sometimes hypoplastic)

6) Positive Ham (acidified serum hemolysis) test or sugar water test

7) Negative direct Coombs test *

*** The direct Coombs test may be positive in patients receiving eculizumab or ravulizumab, or in PNH patients with autoimmune hemolytic anemia.**

- **C. Reference Findings**

1) The following disease types are classified by bone marrow aspiration, bone marrow biopsy, chromosome test, etc., but they do not necessarily need to be classified as one of them.
(1) Classical PNH
(2) Bone marrow failure PNH
(3) Mixed PNH *
*** Mixed PNH is used for convenience in cases where both classical PNH and bone marrow failure PNH are combined, or when characteristics are insufficient for classification as either.**

2) PNH Definite is synonymous with clinical PNH, and is differentiated from bone marrow failure with minimal PNH-type cells without evidence of hemolysis (subclinical PNH).

Reference Guidelines for the Diagnosis and Treatment of Paroxysmal Nocturnal Hemoglobinuria: FY2022 revision (in Japanese). 2023, p. 4

Consideration of Severity and Anti-Complement Therapy

Mild	**Other than the following**
Moderate	**Any of the following is observed:** **Hemolysis** • Moderate hemolysis[*1] or occasional hemolytic episode[*2]
Severe	**Any of the following is observed:** **Hemolysis** • Severe hemolysis,[*3] or constant macroscopic hemoglobinuria, frequent hemolytic episodes[*2] • Requiring regular blood transfusions[*4] **The following organ disorders/symptoms associated with hemolysis** • Thrombosis or history of thrombosis (including pregnancy[*5]) • Renal disorder requiring dialysis • Smooth muscle regulation disorder: thoracoabdominal pain or dysphagia (odynophagia, difficulty swallowing) that make daily life difficult and require hospitalization • Pulmonary hypertension[*6]

Criteria for certification of designated intractable diseases

*1 Moderate hemolysis refers to serum LDH level about 3-5 times the upper limit of normal.
*2 Hemolytic episode refers to a condition in which macroscopic hemoglobinuria is observed. Occasional means about 1-2 times a year, and frequent means more than that.
*3 Severe hemolysis refers to serum LDH level about 8-10 times the upper limit of normal.
*4 Regular red blood cell transfusion refers to the case where 2 units or more of blood transfusion is required every month.
*5 Since pregnancy increases the risk of hemolytic episodes and thrombosis, it is handled as severe.
*6 Mean pulmonary artery pressure of ≥ 25 mmHg in the supine position at rest in a right heart catheterization test

Prepared from the Reference Guidelines for the Diagnosis and Treatment of Paroxysmal Nocturnal Hemoglobinuria: FY2022 revision (in Japanese)

Treatment Strategy for Each PNH Pathology

Hemolysis (hemoglobinuria)

Chronic hemolysis
- **Eculizumab or ravulizumab**
- Corticosteroids
- Transfusion
- Supportive care (folic acid, iron supplement, etc.)
- Follow-up observation

Hemolytic attack
- Trigger removal
- Blood transfusion/haptoglobin
- Corticosteroid pulse

Thrombosis

Acute phase
- Thrombolytic agent
- Heparin

Prophylaxis
- Warfarin Potassium
- DOAC

Thrombosis prevention/ improvement
- Eculizumab or ravulizumab

Bone marrow failure

Same as for aplastic anemia
- Immunosuppressive therapy
- Corticosteroids
- Anabolic hormones
- TPO-RA
- Transfusion
- G-CSF
- Iron chelator
- Follow-up observation

Condition related to life prognosis

↓

Hematopoietic stem cell transplantation

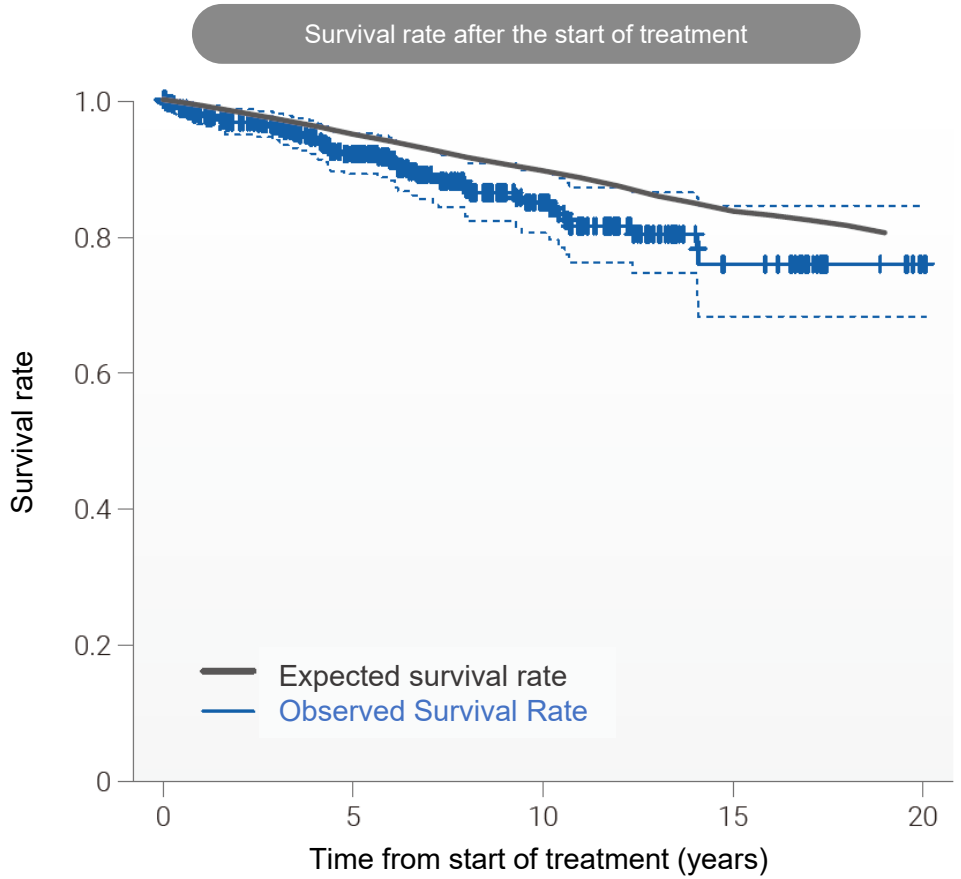
*This section includes some off-label information.

Prepared from the Reference Guidelines for the Diagnosis and Treatment of Paroxysmal Nocturnal Hemoglobinuria: FY2022 revision (in Japanese)

PNH Prognosis After the Introduction of C5 Inhibitors

■ Impact on survival after initiation of C5 inhibitor therapy in UK PNH Registry data (overseas data)

- **In patients with PNH treated with C5 inhibitors (Patients undergoing allogeneic bone marrow transplantation, excluding immunosuppressed patients), the 10-year and 19-year cumulative relative survival rates were 0.9585 (95%CI: 0.8912-1.007) and 0.9624 (95%CI: 0.8317-1.0562), respectively.**



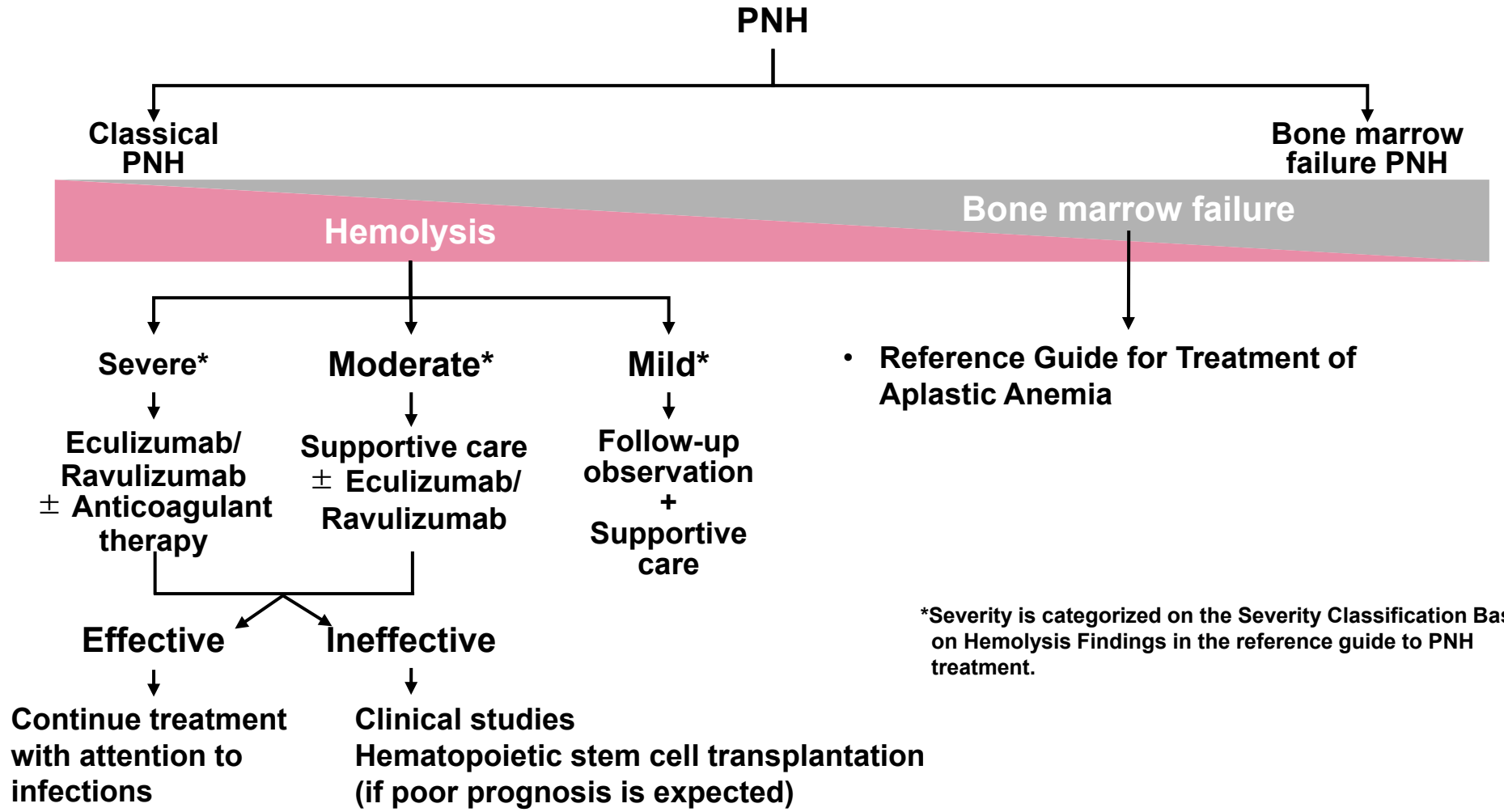
Study overview

[Purpose]	To explore improved survival and durable responses in patients treated with C5 inhibitors.
[Subjects]	PNH patients treated with C5 inhibitors (eculizumab, ravulizumab) in the UK between May 2002 and July 2022: 509
[Method]	Eculizumab was administered as an IV infusion at 600 mg/week for 4 doses followed by a 900 mg dose 1 week later. Thereafter, 900 mg was continued every 14 days. Complement regulation is induced by the patient's condition immediately before administration. In patients with a suggested effect, 1,200 mg was administered every 14 days. Ravulizumab was administered as an intravenous infusion according to the patient's body weight, then 2 and 8 weeks later. Survival on Overall Survival (OS) in PNH Cohort after Initiation of C5 Inhibitor Therapy The survival rate to overall survival (OS) in the PNH Cohort after the start of treatment with C5 inhibitors was estimated by the Kaplan-Meier method. A population deemed equivalent in age and sex to the PNH Cohort was extracted from the healthy general population included in the Human mortality database (1841 to 2020) in the UK, and the relative survival rate of the PNH Cohort to the general population was calculated based on the expected survival rate in the extracted population. Relative and expected survival rates were estimated using the EdererII method.
[Limitation]	This is a retrospective study in patients reviewed at two reference centres in the UK.

●Eculizumab
6. Dosage and administration < Inhibition of hemolysis in patients with paroxysmal nocturnal hemoglobinuria >
The usual initial adult dosage is 600 mg of Eculizumab (Genetical Recombination) per dose. After the initial dose, the drug should be intravenously infused once weekly for a total of 4 doses, followed 1 week later (4 weeks after the initial dose) by 900 mg once every 2 weeks.
●Ravulizumab
6. Dosage and administration < Paroxysmal nocturnal hemoglobinuria >
The usual initial adult dosage of Ravulizumab (Genetical Recombination) is 2,400~3,000 mg per dose, based on the patient's body weight.
After 2 weeks, administer 3,000~3,600 mg as an intravenous infusion, and then 3,000~3,600 mg as an intravenous infusion every 8 weeks.

1)Kelly RJ, et al. Blood. 2011; 117: 6786-92.
2)Kelly RJ, et al. Blood. 2024; 143(12): 1157-1166.
[The authors of this paper include those funded by Roche.]

PNH Treatment Flowchart



*Severity is categorized on the Severity Classification Based on Hemolysis Findings in the reference guide to PNH treatment.

Working group for the development of the reference guide revision of diagnostic criteria and practice for paroxysmal nocturnal hemoglobinuria (PNH)
Reference Guidelines for the Diagnosis and Treatment of Paroxysmal Nocturnal Hemoglobinuria: FY2022 revision (in Japanese)

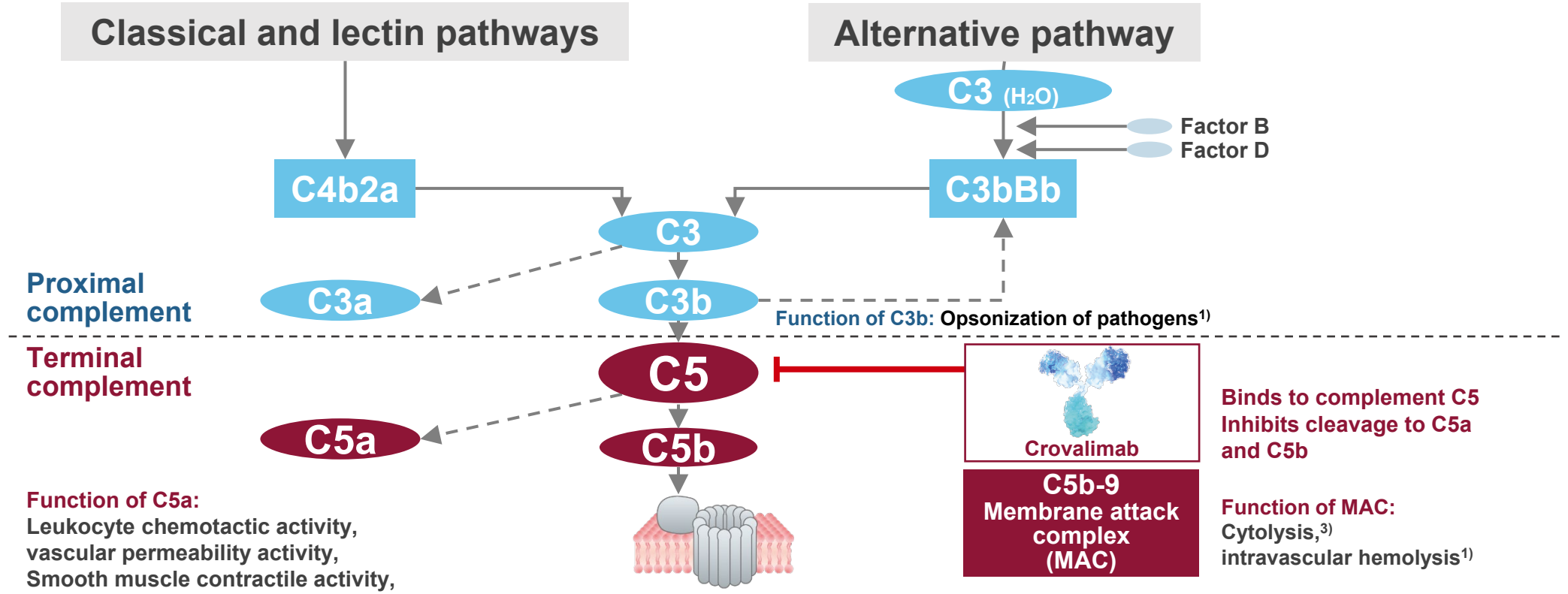
1. About PNH

2. **Introduction of PiaSky Clinical Study**

3. Case Presentation

Complement Activation Pathway and Site of Action of Crovalimab (PiaSky)

- **Crovalimab binds to complement C5 in a pH-dependent manner, and inhibits the cleavage of C5 into C5a and C5b. This is thought to inhibit complement activation and suppress formation of the terminal complement complex C5b-9 (membrane attack complex; MAC), thereby controlling complement-mediated intravascular hemolysis in PNH patients.**



(Conceptual Image)

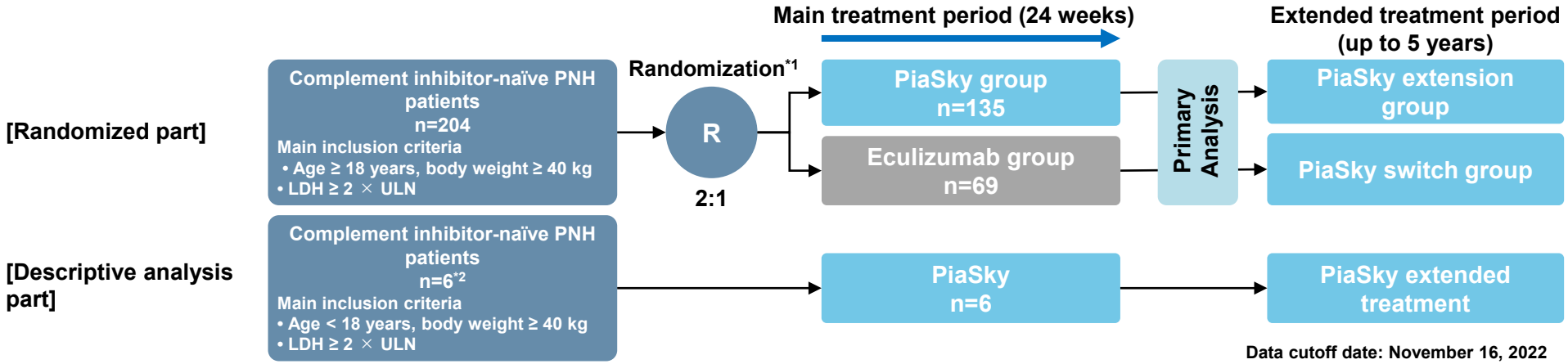
Data evaluated at approval: Pharmacology study, summary, 1) Ueda Y. The Japanese Association for Complement Research. FOCUS Complement Series, 4th Report. 2018:18-23., 2) Miyata T. et al.: Japanese Journal of Thrombosis and Hemostasis. 2021; 32:695-707., 3) Wakamiya N. The Japanese Association for Complement Research. FOCUS Complement Series First Edition. 2018:2-5.

Global Phase III Study (Study BO42162 [COMMODORE 2])

- Untreated Patients -

Study Methods

[Objective] To verify the non-inferiority of the efficacy of PiaSky to eculizumab in PNH patients with no history of treatment with complement inhibitors. Safety is also assessed.
[Design] Randomized part: Global, randomized, open-label, active-controlled
Descriptive analysis part: Global, open-label
[Subjects] Randomized part: 204 complement inhibitor-naïve PNH patients aged ≥ 18 years and weighing ≥ 40 kg [135 patients (2 Japanese) in the PiaSky group, 69 patients (3 Japanese) in the eculizumab group]
Descriptive analysis part: 6 complement inhibitor-naïve PNH patients aged < 18 years and weighing ≥ 40 kg
[Analysis set*] Safety analysis set: 135 patients in the PiaSky group and 69 patients in the eculizumab group
Efficacy analysis set: 134 patients in the PiaSky group and 69 patients in the eculizumab group



Data cutoff date: November 16, 2022

*1 Stratification factors: Last LDH value before randomization (> 2× to ≤ 4× ULN, > 4× ULN), History of packed red blood cell transfusion within 6 months before randomization (0, 0-6 units, >6 units)
*2 n indicates actual enrolled patients

[Methods] [Randomized part] Patients were randomized to PiaSky or eculizumab in a 2:1 ratio.
PiaSky Group: Patients weighing ≥40 to < 100 kg received 1,000 mg by intravenous infusion over 60 minutes (±10 minutes) on Day 1, followed by 340 mg on Days 2, 8, 15, and 22, and 680 mg on Day 29 and every 4 weeks thereafter by subcutaneous injection. Patients weighing ≥ 100 kg received a single dose of 1,500 mg by intravenous infusion over 90 minutes (±10 minutes) on Day 1, followed by 340 mg on Days 2, 8, 15, and 22, and 1,020 mg on Day 29 and every 4 weeks thereafter by subcutaneous injection.
Eculizumab arm: 600 mg was administered intravenously on days 1, 8, 15, and 22, and 900 mg was administered intravenously every 2 weeks from day 29 onwards.
The treatment period was 24 weeks as the main treatment period, and then (after the visit at Week 25) treatment with PiaSky (the PiaSky group continued to receive PiaSky, and the eculizumab group switched to PiaSky) was continued as the extended treatment period (up to 5 years).

[Descriptive analysis part] All patients received PiaSky at the same dosage and administration as the PiaSky group in the randomized part.

The treatment period was 24 weeks as the main treatment period, and then after the visit at Week 25 treatment with PiaSky was continued as the extended treatment period (up to 5 years).

[All patients] Vaccination against *Neisseria meningitidis* was mandatory before starting treatment with the study drug. An antibacterial agent was administered if the study drug was administered before or within 2 weeks after vaccination against *Neisseria meningitidis*.

*Randomized part

Data evaluated at approval: Global Phase III Study (Study BO42162)

Study Methods (2)

[Endpoints]

Primary Endpoints: [Randomized part]
- Mean proportion of patients achieving hemolysis control [*1] from Week 5 to Week 25 < confirmatory analysis item >
- Proportion of patients achieving [*2] avoidance of transfusion from baseline to Week 25 < confirmatory analysis item >

Secondary Endpoints: [Randomized part]
- Proportion of patients with breakthrough hemolysis [*3] from baseline through Week 25
- Proportion of patients with stabilization of hemoglobin [*4] from baseline to Week 25
- Mean change from baseline in FACIT-Fatigue score at Week 25 (patients ≥ 18 years)

Safety Endpoints: [Randomized part] [Descriptive analysis part]
- Adverse events, adverse events leading to treatment discontinuation, laboratory test values, vital signs, etc.

Additional Endpoints:
- Time course of complement activity (CH50) measured by liposomal immunoassay
- Changes in free C5 concentrations over time in patients treated with PiaSky

*1 Achievement of hemolysis control defined as LDH ≤ 1.5 × ULN (measured centrally)
*2 Transfusion: Packed red blood cell transfusion was recommended for any of the following; (1) hemoglobin ≤ 9 g/dL with signs or symptoms of such severity that, in the opinion of the Investigator, a transfusion is clinically indicated; or (2) hemoglobin ≤ 7 g/dL with or without clinical signs or symptoms.
*3 Hemolytic crisis defined as the appearance or worsening of at least 1 new symptom or sign of intravascular hemolysis (Fatigue, hemoglobinuria, abdominal pain, shortness of breath (dyspnea), anemia (hemoglobin < 10 g/dL), major adverse vascular events (including thrombosis), dysphagia, erectile dysfunction) in the setting of an LDH value < 1.5 × ULN and subsequently ≥ 2 × ULN during the treatment period
*4 Stabilization of hemoglobin level, defined as no decrease from baseline in hemoglobin level ≥ 2 g/dL without transfusion

Data cutoff date: November 16, 2022

Study Methods (3)

[Analysis plan] ○Efficacy

Efficacy analysis set:

[Randomized part] The primary analysis set for evaluating the non-inferiority of PiaSky to eculizumab included all randomized patients who received at least 1 dose of randomized study drug and had at least 1 LDH value (measured centrally) after the first dose.

For the efficacy in the PiaSky group who switched from eculizumab to PiaSky after completing the main treatment period, patients who switched to PiaSky at least 24 weeks before the data cutoff date and had LDH measured at least once were included in the efficacy analysis set.

[Descriptive analysis part] The efficacy analysis set was defined as all patients who received at least 1 dose of PiaSky and had at least 1 LDH value (measured centrally) after the first dose.

Analysis Methods:

[Randomized part] Verification of non-inferiority of PiaSky to eculizumab was to be achieved by demonstrating non-inferiority for both primary efficacy endpoints.

If noninferiority was demonstrated for both primary endpoints, the other efficacy endpoints were to be tested according to the prespecified order below. If noninferiority was demonstrated for the 2 primary endpoints and all secondary endpoints (except FACIT-Fatigue), then superiority was also to be tested. The order of testing is as follows;

Endpoints	Type of test
Proportion of patients achieving TA from baseline through Week 25 *1	Non-inferior
Average Proportion of Patients Achieving Hemolysis Control From Week 5 Through Week 25 *1	Non-inferior
Proportion of patients with breakthrough hemolysis from baseline to Week 25 *2	Non-inferior
Proportion of patients with stabilized hemoglobin level from baseline to Week 25 *2	Non-inferior
Proportion of patients achieving TA from baseline through Week 25	Superiority
Proportion of patients achieving hemolysis control from Week 5 through Week 25	Superiority
Proportion of patients with breakthrough hemolysis from baseline through Week 25	Superiority
Proportion of patients with stabilized hemoglobin level from baseline to Week 25	Superiority
Mean change from baseline in FACIT-Fatigue score at Week 25 (≥ 18 years) *2	Non-inferior
Mean change from baseline in FACIT-Fatigue score at Week 25 (≥ 18 years)	Superiority

*1 Primary endpoint, *2 Secondary endpoints

Data cutoff date: November 16, 2022

Study Methods (4)

[Analysis plan]

< Analytical method for primary endpoint and rationale for non-inferiority margin >

- **Proportion of patients achieving transfusion avoidance from baseline through Week 25:**
  Adjusted treatment difference (≥ 2 × ULN but ≤ 4 × ULN; > 4 × ULN) was calculated by the Mantel-Haenszel method using LDH level before randomization and history of packed red blood cell transfusion within 6 months before randomization (0, 0~6 units, >6 units) as stratification factors. Non-inferiority was to be declared if the lower limit of the 95%CI for the adjusted difference was greater than -20%. The noninferiority margin of -20% was established as the difference between eculizumab-treated and eculizumab-untreated patients, adjusted for transfusion history in the 12 months prior to enrollment, of 38.5% to maintain at least 50% of the difference between eculizumab-treated and eculizumab-untreated patients in the comparison of eculizumab-treated patients in the ALXN1210 PNH-301 treatment-naïve PNH study and eculizumab-untreated patients in the Global PNH Registry.
- **Average proportion of patients achieving hemolysis control from Week 5 through Week 25:**
  The odds ratio (PiaSky group/eculizumab group) was calculated using a generalized estimating equation (GEE) model with the logit link function (first-order autoregressive covariance structure), using treatment group, evaluation time point (every 2 weeks from Week 5 to Week 25), interaction between treatment group and evaluation time point, history of packed RBC transfusion within 6 months before randomization (0, 0~6 units, >6 units), and LDH level at baseline as explanatory variables. Non-inferiority was to be declared if the lower limit of the 95%CI for the odds ratio of the PiaSky group to the eculizumab group was greater than 0.2. The non-inferiority margin of 0.2 was calculated as the odds ratio (ORecu/pbo) of eculizumab over placebo for hemolysis control in Study ALXN1210-PNH-301 in treatment-naïve patients with PNH of 24.6 and maintained ≥ 50% of this treatment effect.

< Analysis of secondary endpoints and rationale for non-inferiority margin >

- **Proportion of patients with breakthrough hemolysis from baseline through Week 25:**
  The adjusted difference was calculated using the same analysis methodology as for the proportion of patients achieving transfusion avoidance, with non-inferiority declared if the upper bound of the 95%CI for the difference was less than 20%. The noninferiority margin of 20% was selected based on data from the eculizumab group in ALXN1210 PNH-301 treatment-naïve patients with PNH compared to eculizumab-naïve patients from the Global PNH Registry.
- **Proportion of patients with stabilized hemoglobin levels from baseline to Week 25:**
  The adjusted difference was calculated using the same analysis methodology as for the proportion of patients achieving transfusion avoidance, where non-inferiority was to be declared if the lower limit of the 95%CI for the difference was greater than -20%. The noninferiority margin of -20% was selected based on data from the eculizumab group in ALXN1210 PNH-301 treatment-naïve patients with PNH compared to eculizumab-naïve patients from the Global PNH Registry.
- **Mean change from baseline in FACIT-Fatigue at Week 25 (≥ 18 years):**
  The difference in mean change was calculated using a mixed-effects model for repeated measures (MMRM) treatment group, evaluation time point, interaction between treatment group and evaluation time point, FACIT-Fatigue score at baseline, LDH value closest to randomization (≥ 2 × ULN but ≤ 4 × ULN; > 4 × ULN), and history of packed RBC transfusion within 6 months (0, 0~6 units, >6 units) as explanatory variables (unstructured covariance structure). The test for non-inferiority of FACIT-F fatigue was designed to be performed if non-inferiority and superiority were demonstrated for all other primary and secondary efficacy endpoints. However, according to the prespecified order of testing, as PiaSky was not superior to eculizumab in the proportion of patients achieving transfusion avoidance from baseline through Week 25, noninferiority testing of FACIT-Fatigue was not conducted and assessments were descriptive in nature.

○Safety
Safety Analysis Set:
The safety population included all patients who received at least 1 dose of PiaSky.
Analysis Methods:
Data were summarized descriptively separately for the PiaSky and eculizumab groups in the randomized part and for the descriptive analysis part. Safety summaries for the PiaSky and eculizumab treatment groups in the randomized part included data from the main treatment period (the main safety evaluation period). All other safety analyses included all available data as of the data cutoff date.

Data cutoff date: November 16, 2022

Patient Background [Randomized Part]

		PiaSky group n=135	Eculizumab group n=69
Age[*1] (years)	Mean (SD)	40.5 (15.2)	41.9 (16.0)
	Median (range)	36.0 (18-76)	38.0 (17-78)
Age group,[*1] n (%)	< 18 years	0	2 (2.9)
	≥ 18 to < 65 years	122 (90.4)	58 (84.1)
	≥ 65 years	13 (9.6)	9 (13.0)
Sex, n (%)	Male	77 (57.0)	35 (50.7)
	Female	58 (43.0)	34 (49.3)
Race, n (%)	Asian	86 (63.7)	51 (73.9)
	Caucasian	45 (33.3)	16 (23.2)
	Black or African American	3 (2.2)	1 (1.4)
	Unknown	1 (0.7)	1 (1.4)
Region, n (%)	Other Asia-Pacific regions	83 (61.5)	48 (69.6)
	Europe	36 (26.7)	12 (17.4)
	Latin America	12 (8.9)	2 (2.9)
	Japan	2 (1.5)	3 (4.3)
	North America	2 (1.5)	4 (5.8)
	Africa and Middle East	0	0
Baseline weight (kg)	Mean (SD)	68.32 (15.76)	67.13 (15.26)
	Median (range)	66.10 (42.0-140.3)	62.20 (47.0-122.0)
Time from PNH diagnosis to enrollment (years)	Mean (SD)	5.22 (7.42)	4.97 (5.91)
	Median (range)	2.56 (0.0-48.5)	2.93 (0.0-31.0)
History of aplastic anemia, n (%)	Yes	53 (39.3)	26 (37.7)
	No	82 (60.7)	43 (62.3)

		PiaSky group n=135	Eculizumab group n=69
History of myelodysplastic syndrome, n (%)	Yes	6 (4.4)	6 (8.7)
	No	129 (95.6)	63 (91.3)
History of major vascular event, n (%)	Yes	21 (15.6)	10 (14.5)
	No	114 (84.4)	59 (85.5)
History of packed red blood cell transfusion,[*2] n (%)	Yes	103 (77.4)	50 (73.5)
	No	30 (22.6)	18 (26.5)
Number of units of packed red blood cell transfusion[*2] (units)	Mean (SD)	6.47 (8.27)	6.63 (8.70)
	Median (range)	3.75 (0.0-43.5)	3.00 (0.0-41.0)
PNH granulocyte clone size (%)	Mean (SD)	55.77 (26.72)	61.74 (29.50)
	Median (range)	60.32 (0.83-96.09)	74.58 (1.30-95.21)
PNH monocyte clone size (%)	Mean (SD)	84.80 (16.16)	88.08 (15.81)
	Median (range)	90.79 (42.54-99.95)	95.12 (41.49-99.92)
PNH RBC clone size (%)	Mean (SD)	29.13 (17.50)	43.20 (24.85)
	Median (range)	25.13 (3.48-96.02)	44.63 (0.11-88.87)
Baseline hemoglobin level (g/L)	Mean (SD)	87.18 (14.06)	99.69 (87.86)
	Median (range)	85.00 (63.0-135.0)	87.00 (58.0-810.0[*4])
Baseline LDH level (× ULN)[*3]	Mean (SD)	7.57 (3.38)	7.77 (3.54)
	Median (range)	7.00 (2.0-16.3)	7.74 (2.0-20.3)

SD: Standard deviation
*1 Until the descriptive analysis part was established in Protocol Version 3, patients aged 12 years or older were enrolled in the randomized part, so 2 patients aged less than 18 years were enrolled in the eculizumab group.
*2 Packed red blood cell transfusion within 12 months before screening
*3 Baseline LDH value is the mean of all LDH values obtained during screening and LDH values obtained on Day 1 before the first dose.
*4 The maximum hemoglobin value of 810 g/L was due to incorrect data entry.

Data cutoff date: November 16, 2022

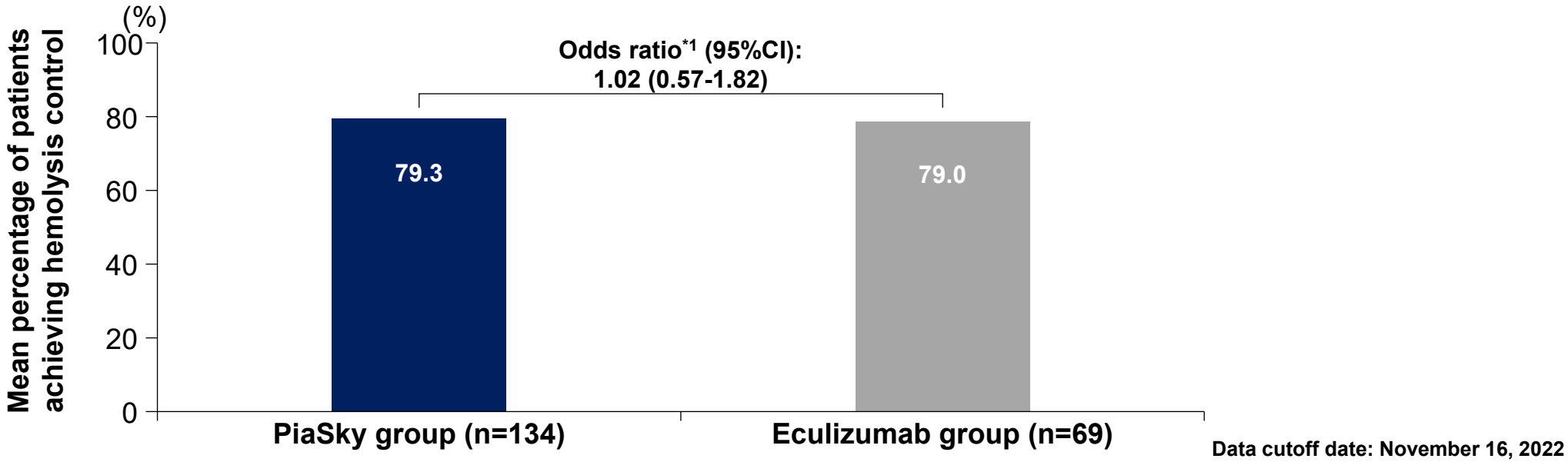
Data evaluated at approval: Global Phase III Study (Study BO42162)

Efficacy [Randomized Part] < Primary Analysis >

Mean Proportion of Patients Who Achieved Hemolysis Control from Week 5 to Week 25

[Primary Endpoint] < Confirmatory Analysis Results >

- **The mean percentage of patients who achieved hemolysis control from week 5 to week 25 was 79.3% (95%CI: 72.86 to 84.48) in the PiaSky group and 79.0% (95%CI: 69.66 to 85.99) in the eculizumab group. The odds ratio[*1] (PiaSky group/eculizumab group) was 1.02 (95%CI: 0.57 to 1.82), and the lower limit of the 95%CI exceeded the pre-specified non-inferiority margin of 0.2.[*2]**



Data cutoff date: November 16, 2022

The non-inferiority of PiaSky to eculizumab was demonstrated for both primary endpoints, hemolysis control and transfusion avoidance, as the lower limit of the 95%CI exceeded the pre-specified non-inferiority margin of 0.2 for hemolysis control and -20% for transfusion avoidance. In this study, the non-inferiority of PiaSky to eculizumab was verified by achieving the two primary efficacy endpoints.

*1 The odds ratio (PiaSky group/eculizumab group) was calculated using a generalized estimating equation (GEE) model (covariance structure was first-order autoregression) using a logit link function with the treatment group, time point (every 2 weeks from Week 5 to Week 25), interaction between treatment group and time point, history of packed red blood cell transfusion (0, 0-6 units, >6 units) within 6 months before randomization, and LDH level at baseline as explanatory variables.

*2 The odds ratio (ORecu/pbo) of eculizumab to placebo for hemolysis control in Study ALXN1210-PNH-301 in untreated PNH patients was calculated to be 24.6, and the non-inferiority margin was set at 0.2 to maintain ≥ 50% of the treatment effect.[1)]

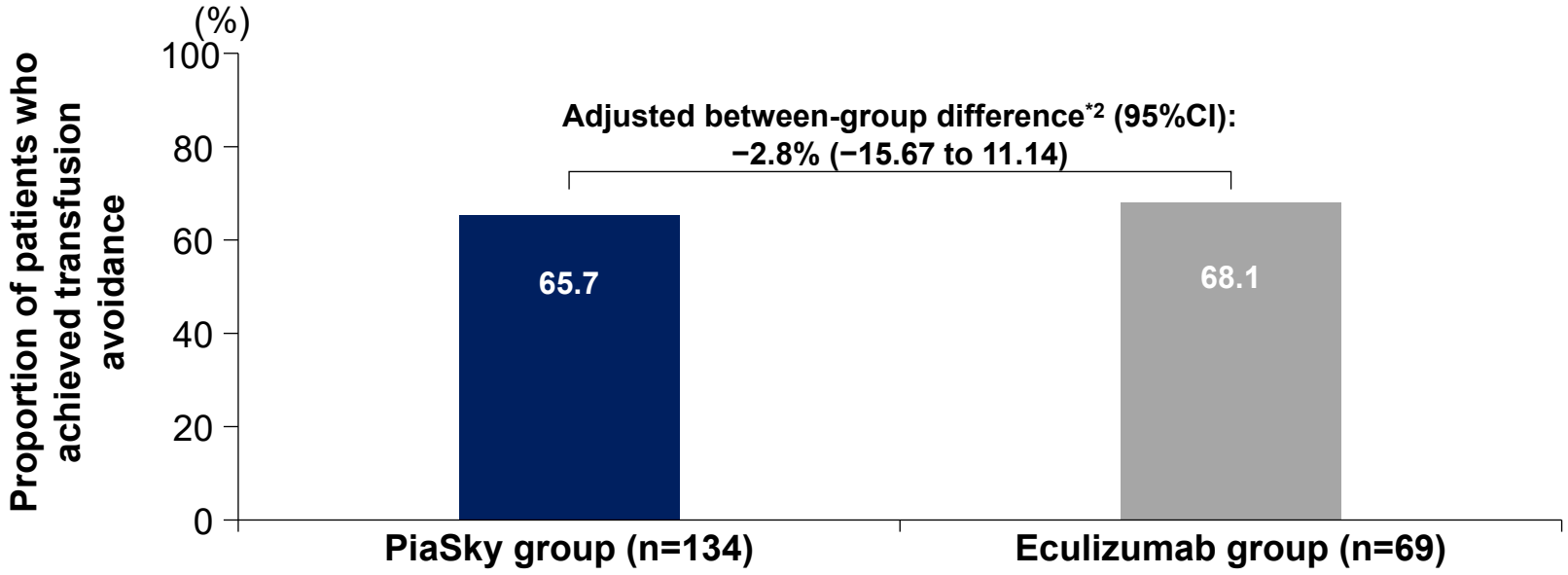
Data evaluated at approval: Global Phase III Study (Study BO42162) 1) Company data: Study BO42162 protocol, Version 6

Efficacy [Randomized Part] < Primary Analysis >

Proportion of Patients Who Achieved Transfusion Avoidance from Baseline to Week 25

[Primary Endpoint] < Confirmatory Analysis Results >

- **The proportion of patients who achieved transfusion avoidance from baseline to Week 25*1 was 65.7% (88/134 patients, 95%CI: 56.91 to 73.52) in the PiaSky group and 68.1% (47/69 cases, 95% CI: 55.67 to 78.53) in the eculizumab group. The adjusted between-group difference*2 in the proportion of patients who achieved transfusion avoidance was -2.8% (95%CI, −15.67 to 11.14), and the lower limit of the 95%CI exceeded the pre-specified non-inferiority margin of −20%.*3**



Data cutoff date: November 16, 2022

The non-inferiority of PiaSky to eculizumab was demonstrated for both primary endpoints, hemolysis control and transfusion avoidance, as the lower limit of the 95%CI exceeded the pre-specified non-inferiority margin of 0.2 for hemolysis control and -20% for transfusion avoidance. In this study, the non-inferiority of PiaSky to eculizumab was verified by achieving the two primary efficacy endpoints.

If non-inferiority was demonstrated for the two primary endpoints and all secondary endpoints (except FACIT-Fatigue), superiority testing was to be performed in the order specified by this endpoint. However, since the superiority of PiaSky to eculizumab was not demonstrated by this endpoint, the test was terminated (Mantel-Haenszel method).

*1 One patient in the PiaSky group discontinued the study before Week 25 without receiving blood transfusion, but was assumed to receive blood transfusion as a conservative approach.

*2 The adjusted between-group difference (PiaSky group - Eculizumab group) was calculated using the Mantel-Haenszel method with the pre-randomization LDH levels (≥ 2× to ≤ 4× the ULN, >4× the ULN) and history of packed red blood cell transfusion within 6 months before randomization (0, 0-6 units, >6 units) as stratification factors.

*3 In comparison between the data of the eculizumab group in Study ALXN1210-PNH-301 in untreated PNH patients and the eculizumab-naïve patients in the International PNH Registry, the difference between the eculizumab treatment group and eculizumab-naïve patients after adjustment for blood transfusion history in the 12 months before enrollment was 38.5%, and a non-inferiority margin of -20% was set to maintain at least 50% of this difference.[1)]

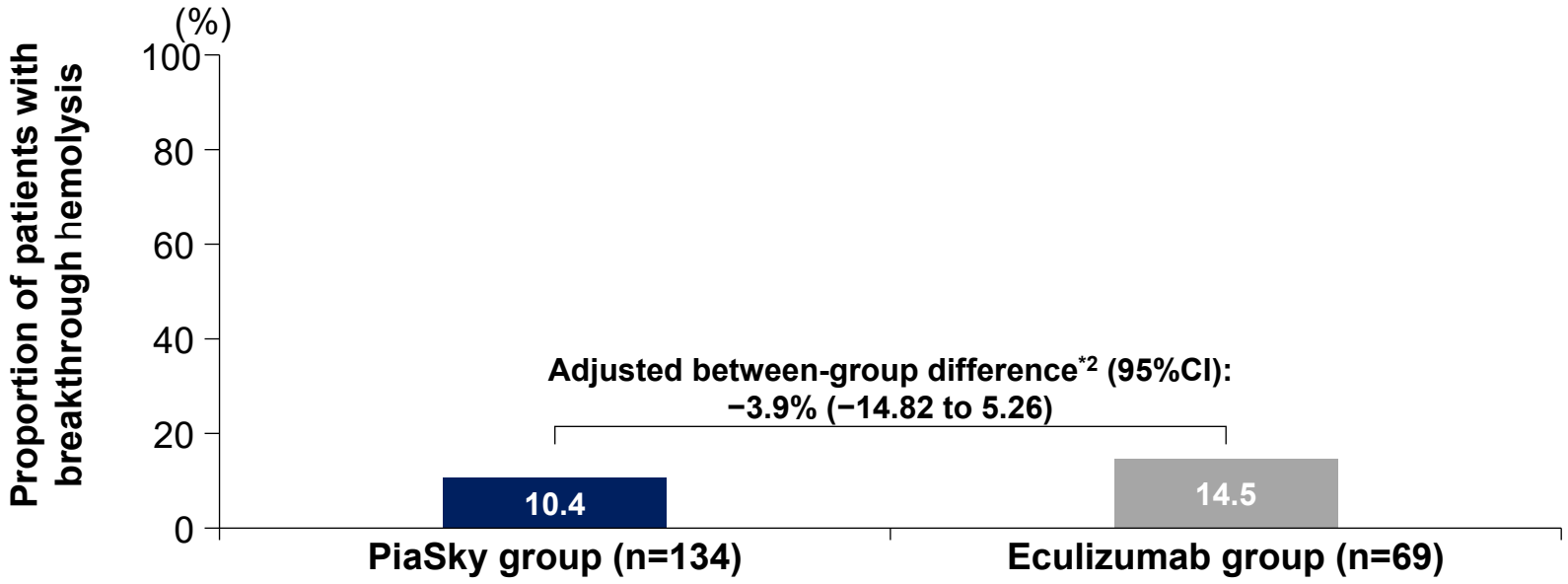
Data evaluated at approval: Global Phase III Study (Study BO42162), 1) Company data: Study BO42162 protocol, Version 6

Efficacy [Randomized Part] < Primary Analysis >

Proportion of Patients Who Experienced Breakthrough Hemolysis from Baseline through Week 25

[Secondary Endpoint]

- **The proportion of patients who experienced breakthrough hemolysis from baseline to Week 25[*1] was 10.4% (14/134 patients) in the PiaSky group and 14.5% (10/69 patients) in the eculizumab group. The adjusted between-group difference in the proportion of patients who experienced breakthrough hemolysis[*2] was -3.9% (95% CI: -14.82 to 5.26), and the upper limit of the 95% CI was below the pre-specified non-inferiority margin of 20%.[*3]**



Data cutoff date: November 16, 2022

*1 Four patients in the PiaSky group and one patient in the eculizumab group discontinued the study before week 25 without experiencing breakthrough hemolysis, but it was assumed that a breakthrough hemolysis occurred as a conservative approach.

*2 The adjusted between-group difference (PiaSky group - Eculizumab group) was calculated using the Mantel-Haenszel method with the pre-randomization LDH levels (≥ 2× to ≤ 4× the ULN, >4× the ULN) and history of packed red blood cell transfusion within the past 6 months (0, 0-6 units, >6 units) as stratification factors.

*3 A non-inferiority margin of 20% was set based on comparison of the data of the eculizumab group in Study ALXN1210-PNH-301 in treatment-naïve PNH patients with data from the International PNH Registry for treatment-naïve eculizumab patients.[1)]

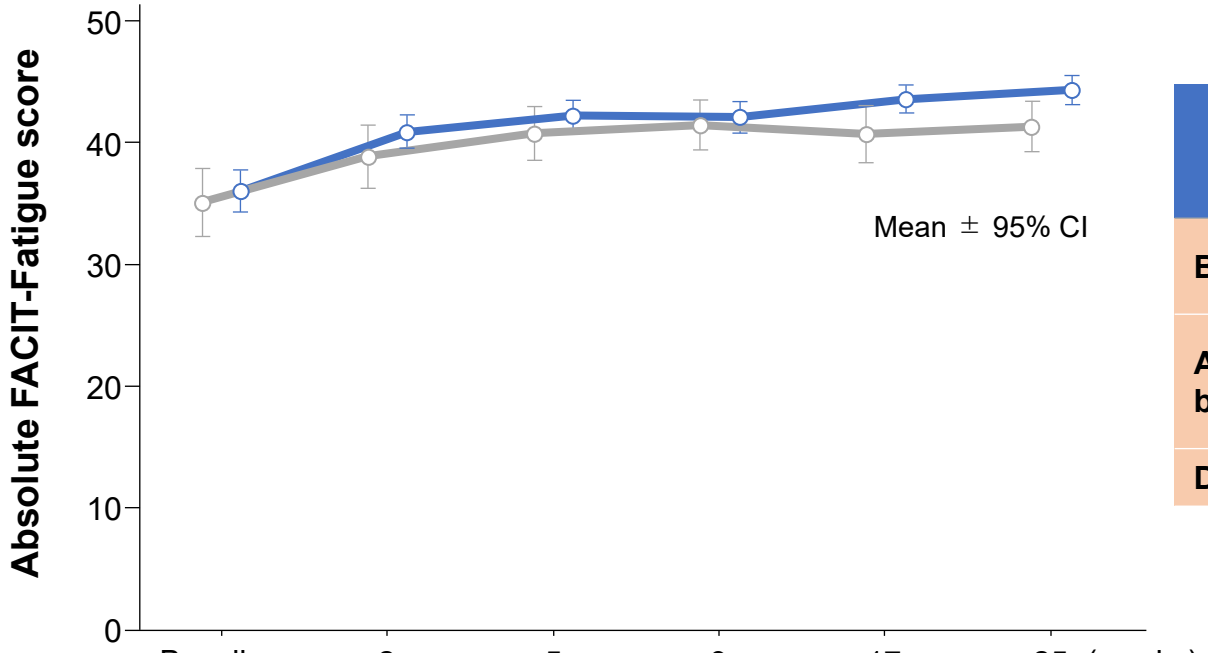
Data evaluated at approval: Global Phase III Study (Study BO42162), 1) Company data: Study BO42162 protocol, Version 6

Efficacy [Randomized Part] < Primary Analysis >

Mean Change in FACIT-Fatigue Score from Baseline to Week 25 (Patients Aged 18 Years or Older)*1

[Secondary Endpoint]

- The adjusted mean change from baseline to 25 weeks in the FACIT-Fatigue score*2 was 7.8 (95%CI: 6.49 to 9.09) in the PiaSky group, 5.2 (95%CI: 3.42 to 6.89) in the eculizumab group, and the difference in the mean change*3 was 2.6 (95%CI: 0.68 to 4.60).



Number of cases	Baseline	2	5	9	17	25
PiaSky group	134	132	130	132	129	128
Eculizumab group	67	67	66	66	66	66

	PiaSky group (n=134)	Eculizumab group (n=69)
Baseline mean (standard error)	36.0 (0.9) n=134	35.1 (1.4) n=67
Adjusted mean change from the baseline to Week 25 (SD),*1 [95%CI]	7.8 (0.7) [6.49-9.09] n=128	5.2 (0.9) [3.42-6.89] n=66
Difference in mean change*3 (95%CI)	2.6 (0.68-4.60)	

Data cutoff date: November 16, 2022

Test for non-inferiority of FACIT-Fatigue was to be performed if non-inferiority and superiority of all other primary and secondary efficacy endpoints were demonstrated. However, as PiaSky was not superior to eculizumab in the proportion of patients who achieved transfusion avoidance from baseline to 25 weeks, in accordance with the pre-specified order of testing, non-inferiority testing for FACIT-F was not performed, and evaluation was descriptive

*1 Until the descriptive analysis part was established in Protocol Version 3, patients aged 12 years or older were enrolled in the randomized part, so 2 patients aged less than 18 years were enrolled in the eculizumab group. FACIT-Fatigue scores were collected only in patients aged ≥ 18 years, and were assessed in 134 patients in the PiaSky group and 67 patients in the eculizumab group, excluding two patients <18 years.
*2 The FACIT-Fatigue total score ranges from 0 to 52, with a higher score indicating less fatigue (threshold for clinically significant change: ≥5)[1)]
*3 Difference in mean change was calculated by using the mixed-effects model for repeated measures (MMRM) (covariance structure was unstructured) with the treatment group, evaluation time point, interaction between treatment group and evaluation time point, FACIT-Fatigue score at baseline, LDH level just before randomization (≥ 2× to ≤ 4× the ULN, > 4× the ULN), and history of packed red blood cell transfusion within 6 months (0, 0-6 units, >6 units) as explanatory variables.

Data evaluated at approval: Global Phase III Study (Study BO42162),

1) Cella D, et al. J Patient Rep Outcomes. 2023; 7: 63. [The authors of this article include those funded by F. Hoffmann-La Roche AG and Chugai Pharmaceutical Co., Ltd.]

Safety

- **Safety Analysis Set**
  PiaSky group 135 patients, Eculizumab group 69 patients

Safety [Primary safety evaluation period *1] [randomized part]

Common Adverse Events (incidence ≥ 5% in any group)

	PiaSky group (n=135)	Eculizumab group (n=69)
Any adverse events	105 (77.8%)	55 (79.7%)
Infections and infestations		
Upper respiratory tract infection	11 (8.1%)	9 (13.0%)
COVID-19	11 (8.1%)	4 (5.8%)
Urinary tract infection	2 (1.5%)	4 (5.8%)
Metabolism and nutrition disorders		
Hypokalaemia	15 (11.1%)	9 (13.0%)
Hyperuricaemia	11 (8.1%)	6 (8.7%)
Hypocalcaemia	8 (5.9%)	7 (10.1%)
Injury, poisoning and procedural complications		
Infusion related reaction	21 (15.6%)	9 (13.0%)
Injection related reaction	7 (5.2%)	0
Gastrointestinal disorders		
Diarrhoea	10 (7.4%)	0
General disorders and Administration site conditions		
Pyrexia	12 (8.9%)	7 (10.1%)
Investigations		
Neutrophil count decreased	17 (12.6%)	7 (10.1%)
White blood cell count decreased	16 (11.9%)	7 (10.1%)
Nervous system disorders		
Headache	11 (8.1%)	3 (4.3%)

MedDRA version 25.1.

*1The primary safety evaluation period was defined as the period from the start date of treatment with PiaSky to the date of treatment discontinuation, the date of study discontinuation, or the date of last evaluation before treatment with PiaSky at Week 25, whichever came first for the PiaSky group and the period from the start date of treatment with eculizumab to the date of treatment discontinuation, the date of study discontinuation, or the date of last evaluation before switching from eculizumab treatment to PiaSky, whichever came first for the eculizumab group.

Data cutoff date: November 16, 2022

Safety [Primary Safety Evaluation Period*1] [Randomized Part]

Serious Adverse Events

	PiaSky group (n=135)	Eculizumab group (n=69)
Serious adverse events	14 (10.4%)	9 (13.0%)
Infections and infestations	4 (3.0%)	5 (7.2%)
COVID-19	1 (0.7%)	1 (1.4%)
Pneumonia	2 (1.5%)	0
Central nervous system infection	0	1 (1.4%)
Pyelonephritis	1 (0.7%)	0
Sepsis	0	1 (1.4%)
Tuberculosis	0	1 (1.4%)
Urinary tract infection	0	1 (1.4%)
Blood and lymphatic system disorders	3 (2.2%)	3 (4.3%)
Aplastic anemia	2 (1.5%)	1 (1.4%)
Thrombocytopenia	1 (0.7%)	1 (1.4%)
Febrile neutropenia	0	1 (1.4%)
Respiratory, thoracic and mediastinal disorders	3 (2.2%)	0
Epistaxis	2 (1.5%)	0
Respiratory tract hemorrhage	1 (0.7%)	0
Cardiac disorders	1 (0.7%)	1 (1.4%)
Heart failure	0	1 (1.4%)
Myocardial infarction	1 (0.7%)	0
General disorders and administration site conditions	1 (0.7%)	1 (1.4%)
Pyrexia	1 (0.7%)	1 (1.4%)

	PiaSky group (n=135)	Eculizumab group (n=69)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.7%)	1 (1.4%)
Myelodysplastic syndrome	0	1 (1.4%)
Thyroid cancer	1 (0.7%)	0
Gastrointestinal disorders	1 (0.7%)	0
Small intestinal hemorrhage	1 (0.7%)	0
Hepatobiliary disorders	0	1 (1.4%)
Cholecystitis chronic	0	1 (1.4%)
Injury, poisoning and procedural complications	1 (0.7%)	0
Infusion-related reaction	1 (0.7%)	0
Nervous system disorders	0	1 (1.4%)
Ischemic stroke	0	1 (1.4%)
Neurological disorders	1 (0.7%)	0
Affective disorder	1 (0.7%)	0
Skin and subcutaneous tissue disorders	1 (0.7%)	0
Henoch-Schonlein purpura	1 (0.7%)	0
Vascular disorders	1 (0.7%)	0
Hypovolemic shock	1 (0.7%)	0

MedDRA version 25.1.

*1 The primary safety evaluation period for the PiaSky group was the period from the date of the start of PiaSky administration to the date of discontinuation of administration, the date of study discontinuation, or the date of the last evaluation before administration of PiaSky in Week 25, whichever came first, and for the eculizumab group was the period from the date of the start of administration of eculizumab to the date of discontinuation of administration, the date of study discontinuation, or the date of the last evaluation before switching from administration of eculizumab to PiaSky, whichever came first.

Data cutoff date: November 16, 2022

Data evaluated at approval: Global Phase III Study (Study BO42162)

Safety [Primary Safety Evaluation Period*1] [Randomized Part]

Adverse Events Leading to Discontinuation or Death

- **Adverse events leading to treatment discontinuation**

During the primary safety evaluation period for this study, 1 of 135 patients (0.7%) in the PiaSky group and 1 of 69 patients (1.4%) in the eculizumab group experienced an adverse event that led to discontinuation of study drug. One patient in the PiaSky group had Grade 4 thrombocytopenia, which was determined to be related to the study drug. One patient in the eculizumab group had a Grade 5 ischemic stroke which was determined to be unrelated to the study drug.

- **Adverse events leading to death**

During the primary safety evaluation period for this study, 2 of 135 patients (1.5%) in the PiaSky group and 1 of 69 patients (1.4%) in the eculizumab group died. Respiratory tract hemorrhage and myocardial infarction each occurred in 1 patient in the PiaSky group, and ischemic stroke occurred in 1 patient in the eculizumab group, all of which were determined to be unrelated to the study drug.

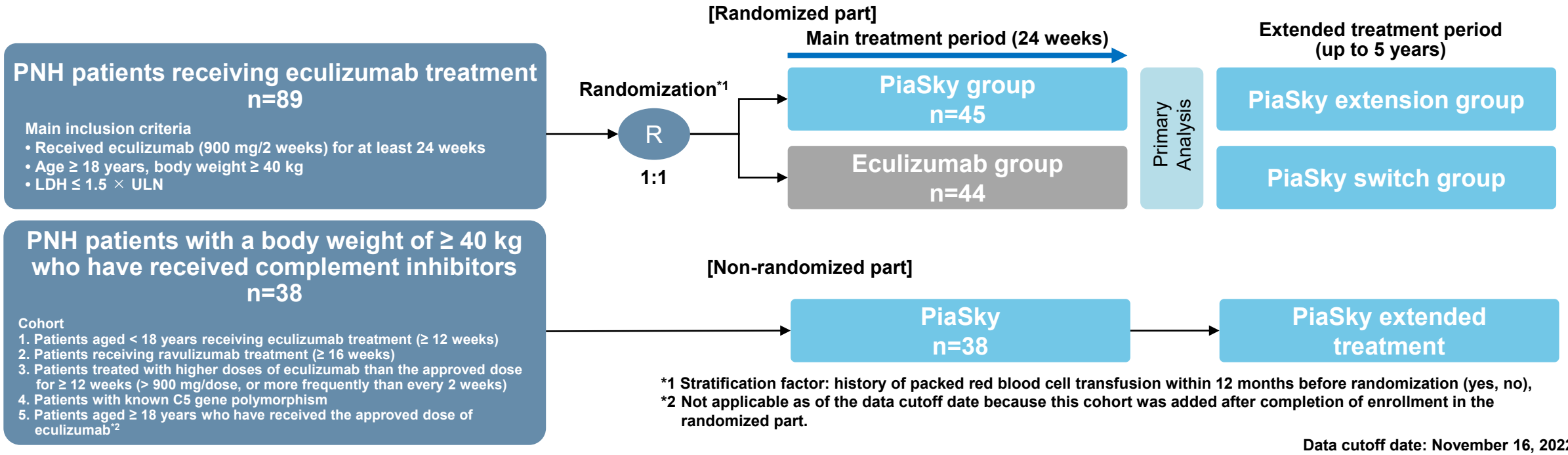
*1 The primary safety evaluation period for the PiaSky group was the period from the date of the start of PiaSky administration to the date of discontinuation of administration, the date of study discontinuation, or the date of the last evaluation before administration of PIASKY in Week 25, whichever came first, and for the eculizumab group was the period from the date of the start of administration of eculizumab to the date of discontinuation of administration, the date of study discontinuation, or the date of the last evaluation before switching from administration of eculizumab to PiaSky, whichever came first.

Data cutoff date: November 16, 2022

Global Phase III Study (Study BO42161 [COMMODORE 1])

- Switching from previously treated patients -

Study Methods



*1 Stratification factor: history of packed red blood cell transfusion within 12 months before randomization (yes, no),
*2 Not applicable as of the data cutoff date because this cohort was added after completion of enrollment in the randomized part.

Data cutoff date: November 16, 2022

[Objective] To assess the safety, pharmacokinetics, pharmacodynamics, and efficacy of PiaSky versus eculizumab in PNH patients previously treated with complement inhibitors.

[Study design] Randomized part: Global, randomized, open-label, active-controlled
Non-randomized part: Global, non-randomized, open-label

[Analysis set] Safety analysis set: [Randomized part] 44 patients in the PiaSky group and 42 patients in the eculizumab group
[Non-randomized part] Cohort 1: 1 patient, Cohort 2: 21 patients, Cohort 3: 10 patients, Cohort 4: 6 patients
Efficacy analysis set: [Randomized part] 44 patients in the PiaSky group and 42 patients in the eculizumab group
[Non-randomized part] Cohort 2: 19 patients, Cohort 3: 9 patients, Cohort 4: 6 patients

Eculizumab Dosage and Administration
The usage and dosage of eculizumab approved in Japan for the suppression of hemolysis in paroxysmal nocturnal hemoglobinuria is as follows: "For adults, the first dose is normally 600 mg of eculizumab (genetical recombination). Then, the drug is administered intravenously once a week for a total of four doses, including the first dose. Starting one week later (four weeks after the first dose), 900 mg of the drug is administered intravenously once every two weeks." [From the electronic package insert of eculizumab, revised in August 2023 (Version 6, dose change)]

Data evaluated at approval: Global Phase III Study (Study BO42161)

Study Methods (2)

[Endpoints]

Primary Endpoint:

○Safety

[Randomized part], [Non-randomized part]

- Adverse events, adverse events leading to treatment discontinuation, laboratory test values, vital signs, etc.
- Incidence and severity of injection site reactions, infusion-related reactions, hypersensitivity, and infections (including meningococcal meningitis)
- Occurrence of clinical symptoms due to immune complex formation in patients switching from eculizumab or ravulizumab to PiaSky.

Exploratory Endpoints:

○Efficacy *1

[Randomized part] < Primary treatment period >, [Non-randomized part]

- Average proportion of patients with hemolysis control*2 from baseline to Week 25
- Proportion of patients achieving avoidance of transfusion*3 from baseline through Week 25
- Proportion of patients with a breakthrough hemolysis*4 from baseline through Week 25
- Proportion of patients with stabilization of hemoglobin level*5 from baseline to Week 25
- Mean change from baseline in FACIT-Fatigue score at Week 25 (patients aged ≥ 18 years), etc.

[Randomized part] < PiaSky switch group in the extension period >

- Average proportion of patients with hemolysis control*2 from baseline to Week 25 after switching to PiaSky
- Proportion of patients achieving avoidance of transfusion*3 from baseline to Week 25 after switching to PiaSky
- Proportion of patients with breakthrough hemolysis*4 from baseline to Week 25 after switching to PiaSky
- Proportion of patients achieving stabilization of hemoglobin level*5 from baseline to Week 25 after switching to PiaSky
- Mean changes in FACIT-Fatigue score from baseline to Week 25 after switching to PiaSky

*1 This study initially planned to enroll 200 patients in the randomized part with sufficient power to verify the efficacy of this drug. However, due to feasibility reasons, the efficacy assessment was changed to an exploratory objective and the randomized part has been closed to enrollment.
*2 Achievement of hemolysis control, defined as LDH ≤ 1.5 × ULN (measured at the central laboratory)
*3 Transfusion: Packed red blood cell transfusion was recommended in any of the following cases.; (1) hemoglobin ≤ 9 g/dL with signs or symptoms of such severity that, in the opinion of the Investigator, a transfusion is clinically indicated; or (2) hemoglobin ≤ 7 g/dL with or without clinical signs or symptoms.
*4 Breakthrough hemolysis defined as at least one new or worsening symptom or sign of intravascular hemolysis (fatigue, hemoglobinuria, abdominal pain, shortness of breath [dyspnea], anemia [hemoglobin < 10 g/dL], major adverse vascular events [including thrombosis], dysphagia, erectile dysfunction) in the presence of an elevation of LDH ≥ 2 × ULN after prior reduction of LDH levels to ≤ 1.5 × ULN during the treatment period.
*5 Stabilization of hemoglobin level defined as avoidance of a ≥ 2 g/dL decrease in hemoglobin level from baseline in the absence of transfusion

Eculizumab Dosage and Administration
The usage and dosage of eculizumab approved in Japan for the suppression of hemolysis in paroxysmal nocturnal hemoglobinuria is as follows: "For adults, the first dose is normally 600 mg of eculizumab (genetical recombination). Then, the drug is administered intravenously once a week for a total of four doses, including the first dose. Starting one week later (four weeks after the first dose), 900 mg of the drug is administered intravenously once every two weeks." [From the electronic package insert of eculizumab, revised in August 2023 (Version 6, dose change)]

Data cutoff date: November 16, 2022

Data evaluated at approval: Global Phase III Study (Study BO42161)

Study Methods (3)

[Analysis plan]

○Safety
Safety Analysis Set:
The safety population included all patients who received at least 1 dose of PiaSky.

Analysis Methods:
All safety endpoints were analyzed descriptively by treatment received. Safety summaries for the PiaSky and eculizumab groups in the randomized part only included data from the main treatment period (primary safety period). All other safety analyses included all available data as of the data cutoff date.

○Efficacy
Efficacy analysis set:
[Randomized part] The efficacy analysis set included all randomized patients who were enrolled at least 24 weeks before the data cutoff date, received at least 1 dose of randomized study drug, and had at least 1 LDH value (measured centrally) after the first dose. Patients who switched from eculizumab to PiaSky after completing the main treatment period (PiaSky switch group) were included in the efficacy analysis set if they switched to PiaSky at least 24 weeks prior to the data cutoff date and had at least 1 measurement of LDH (measured centrally).
[Non-randomized part] The efficacy analysis set included all patients who received at least 1 dose of PiaSky and had at least 1 LDH value (measured centrally) after the first dose.
Analysis Methods:
[Randomized part] All analyses of this study efficacy endpoints were exploratory and descriptive, no formal statistical tests were performed, summary statistics were provided by treatment group, and proportions of patients were presented with 95% CI. The mean proportion of patients achieving hemolysis control was estimated as odds ratio (PiaSky group / Eculizumab group) using a generalized estimating equation (GEE) model with a logit link function (first-order autoregressive covariance structure), using treatment group, time point (every 2 weeks at Weeks 2, 3, 4, and 5 to 25), history of packed RBC transfusions within 12 months prior to randomization (Yes, No), and LDH level at baseline as explanatory variables. The adjusted difference between treatment groups (PiaSky group - Eculizumab group) in the proportion of patients who avoided transfusion was calculated using the Mantel-Haenszel method with the presence or absence of a history of packed red blood cell transfusion within 12 months before randomization as a stratification factor.
[Non-randomized part] Endpoint results were descriptive; no formal statistical testing was performed.

Eculizumab Dosage and Administration
The usage and dosage of eculizumab approved in Japan for the suppression of hemolysis in paroxysmal nocturnal hemoglobinuria is as follows: "For adults, the first dose is normally 600 mg of eculizumab (genetical recombination). Then, the drug is administered intravenously once a week for a total of four doses, including the first dose. Starting one week later (four weeks after the first dose), 900 mg of the drug is administered intravenously once every two weeks." [From the electronic package insert of eculizumab, revised in August 2023 (Version 6, dose change)]

Data cutoff date: November 16, 2022

Safety [Primary endpoint]

Summary of Safety

[Randomized part] [Primary safety evaluation period] *1

	PiaSky group (n=44)	Eculizumab group (n=42)
Adverse Events		
Adverse Events	34(77.3%)	28(66.7%)
Adverse events of Grade 3 *2 or higher	8(18.2%)	1(2.4%)
Serious Adverse Events	6(13.6%)	1(2.4%)
Adverse events leading to treatment discontinuation	0	0
Adverse Events Leading to Dose Modification or Interruption	1(2.3%)	0
Adverse events leading to death	0	0

*1 The period from Day 1 of treatment with PiaSky to the day of last evaluation before treatment at Week 25 or study discontinuation, whichever comes earlier, for the PiaSky group, and the period from Day 1 of treatment with eculizumab to the day of last evaluation before switching to PiaSky or study discontinuation, whichever comes earlier, for the eculizumab group; *2 NCI CTCAE v5

Adverse events were reported in 77.3% of patients in the PiaSky group and 66.7% of patients in the eculizumab group during the Primary Safety Period of this study. Major adverse events (Top 3 events in the PiaSky group and the same rate for the third event) were Type 3 immune complex mediated reaction (15.9% in PiaSky group, 0 in eculizumab group, the same order hereinafter), pyrexia (15.9%, 2.4%), COVID-19(13.6%, 16.7%), and infusion related reaction (13.6%, 0). Serious adverse events were reported in 13.6% of patients in the PiaSky group and 2.4% of patients in the eculizumab group. There were no adverse events leading to treatment discontinuation or adverse events leading to death in either group.

Eculizumab Dosage and Administration
The usage and dosage of eculizumab approved in Japan for the suppression of hemolysis in paroxysmal nocturnal hemoglobinuria is as follows: "For adults, the first dose is normally 600 mg of eculizumab (genetical recombination). Then, the drug is administered intravenously once a week for a total of four doses, including the first dose. Starting one week later (four weeks after the first dose), 900 mg of the drug is administered intravenously once every two weeks." [From the electronic package insert of eculizumab, revised in August 2023 (Version 6, dose change)]

Data cutoff date: November 16, 2022

Safety [primary endpoint]

Serious Adverse Events [Randomized part] [Primary safety evaluation period][*1]

	PiaSky group (n=44)	Eculizumab group (n=42)
Serious adverse events	6 (13.6%)	1 (2.4%)
Infections and infestations		
Pneumonia	1 (2.3%)	1 (2.4%)
Nasopharyngitis	1 (2.3%)	0
Pyelonephritis	0	1 (2.4%)
Urinary tract infection	1 (2.3%)	0
Blood and lymphatic system disorders		
Neutropenia	1 (2.3%)	0
General systemic disorders and administration site conditions		
Pyrexia	1 (2.3%)	0
Biliary disorders		
Hyperbilirubinemia	1 (2.3%)	0
Injury, poisoning and procedural complications		
Skin laceration	1 (2.3%)	0
Nervous system disorders		
Transient ischemic attack	0	1 (2.4%)
Reproductive system and breast disorders		
Cervical dysplasia	1 (2.3%)	0

MedDRA version 25.1.

*1 The period for the PiaSky group was from day 1 of PiaSky administration to the last evaluation date before 25 weeks of administration or study discontinuation, whichever came first. The period for the eculizumab group was from day 1 of eculizumab administration to the last evaluation date before switching to PiaSky or study discontinuation, whichever came first.

Eculizumab Dosage and Administration
The usage and dosage of eculizumab approved in Japan for the suppression of hemolysis in paroxysmal nocturnal hemoglobinuria is as follows: "For adults, the first dose is normally 600 mg of eculizumab (genetical recombination). Then, the drug is administered intravenously once a week for a total of four doses, including the first dose. Starting one week later (four weeks after the first dose), 900 mg of the drug is administered intravenously once every two weeks." [From the electronic package insert of eculizumab, revised in August 2023 (Version 6, dose change)]

Data cutoff date: November 16, 2022

Data evaluated at approval: Global Phase III Study (Study BO42161)

Safety [primary endpoint]

Adverse Events Leading to Treatment Discontinuation or Death

- **Adverse events leading to treatment discontinuation [randomized part]**

During the primary safety evaluation period for this study, there were no adverse events leading to discontinuation of study drug in either the PiaSky or eculizumab group.
There were no adverse events leading to discontinuation of PiaSky during the entire treatment period in the PiaSky group of this study. In the eculizumab group, type 3 immune complex reaction was observed in one patient (2.9%) after switching to PiaSky, which led to discontinuation of PiaSky.

- **Adverse events leading to death [randomized part]**

No deaths were reported in either group during the primary safety evaluation period for this study.
During the entire treatment period, 1 patient in the PiaSky group died of colorectal cancer, which was judged to be unrelated to PiaSky.

Eculizumab Dosage and Administration
The usage and dosage of eculizumab approved in Japan for the suppression of hemolysis in paroxysmal nocturnal hemoglobinuria is as follows: "For adults, the first dose is normally 600 mg of eculizumab (genetical recombination). Then, the drug is administered intravenously once a week for a total of four doses, including the first dose. Starting one week later (four weeks after the first dose), 900 mg of the drug is administered intravenously once every two weeks." [From the electronic package insert of eculizumab, revised in August 2023 (Version 6, dose change)]

Data cutoff date: November 16, 2022

Data evaluated at approval: Global Phase III Study (Study BO42161)

Efficacy

- **Efficacy Analysis Set**

[Randomized part] 44 patients in the PiaSky group and 42 patients in the eculizumab group

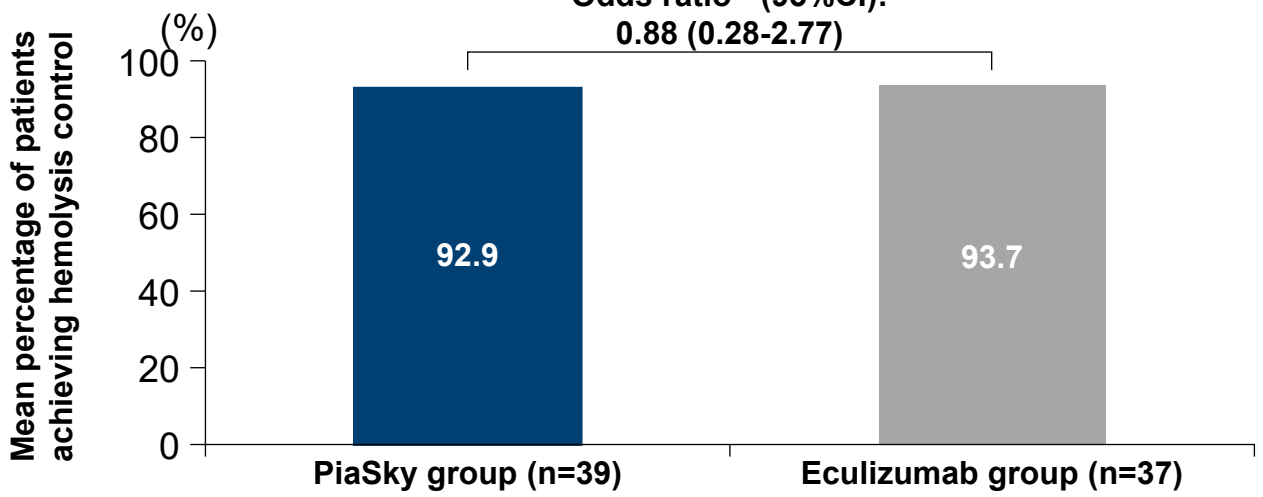
Global Phase III Study
(Study BO42161 [COMMODORE 1])

Mean Percentage of Patients Achieving Hemolysis Control

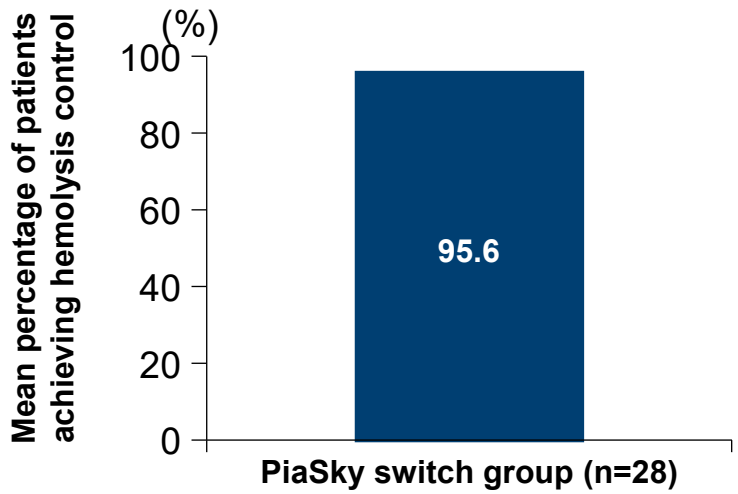
< Main treatment period: From baseline to Week 25 >
< PiaSky switch group in the extended treatment period: from baseline to Week 25 after switching to PiaSky > [Exploratory endpoint] [randomized part]

- **The mean proportion of patients who achieved hemolysis control (LDH ≤ 1.5 × ULN) from baseline to Week 25[*1] was 92.9% (95%CI: 86.62-96.39) in the PiaSky group and 93.7% (95%CI: 87.26-97.04) in the eculizumab group (odds ratio[*2] 0.88, 95%CI: 0.28-2.77) in the main treatment period.**
- **The mean proportion of patients in the PiaSky switch group[*3] in the extended treatment period who achieved hemolysis control from baseline to Week 25 after switching was 95.6% (95%CI: 87.32-98.58).**

Mean Percentage of Patients Achieving Hemolytic Control from Baseline to Week 25



Mean Percentage of Patients Achieving Hemolytic Control from Baseline to Week 25 after Switching to PiaSky



Data cutoff date: November 16, 2022

***1 The evaluation period for the PiaSky group and eculizumab group during the main treatment period was from Week 2 to Week 25.**
***2 Odds ratio (PiaSky group/eculizumab group) was estimated using a generalized estimating equation (GEE) model (covariance structure was first order autoregression) using a logit link function, with the treatment group, evaluation time point (Week 2, Week 3, Week 4, and every 2 weeks from Week 5 to Week 25), history of packed red blood cell transfusion within 12 months before randomization (yes, no), and baseline LDH level as explanatory variables.**
***3 In the PiaSky switch group, 28 patients were evaluated who entered the extended study period and switched from eculizumab to PiaSky treatment at least 24 weeks prior to the data cut-off date**

Eculizumab Dosage and Administration
The usage and dosage of eculizumab approved in Japan for the suppression of hemolysis in paroxysmal nocturnal hemoglobinuria is as follows: "For adults, the first dose is normally 600 mg of eculizumab (genetical recombination). Then, the drug is administered intravenously once a week for a total of four doses, including the first dose. Starting one week later (four weeks after the first dose), 900 mg of the drug is administered intravenously once every two weeks." [From the electronic package insert of eculizumab, revised in August 2023 (Version 6, dose change)]

Data evaluated at approval: Global Phase III Study (Study BO42161)

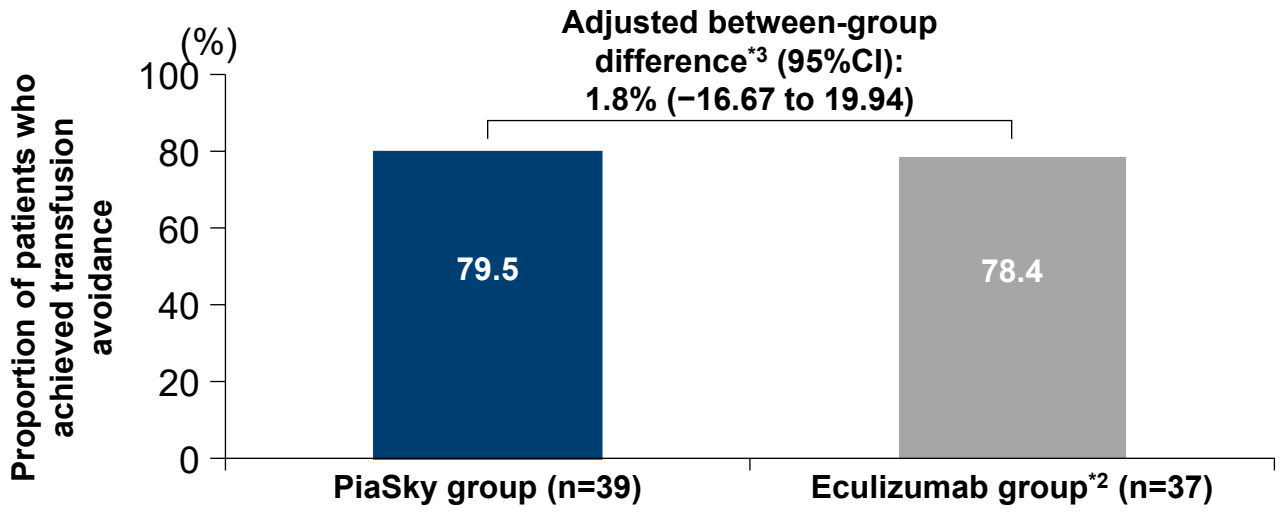
Efficacy

Proportion of Patients Achieved Transfusion Avoidance

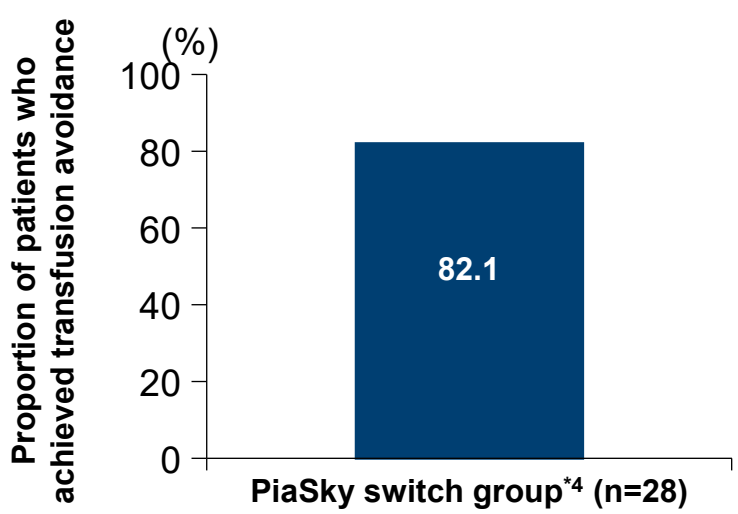
< Main treatment period: From baseline to Week 25 >
< PiaSky switch group in the extended treatment period: from baseline to Week 25 after switching to PiaSky > [Exploratory endpoint] [randomized part]

- **The proportion of patients who achieved transfusion avoidance from baseline to Week 25[*1] was 79.5% (95%CI: 63.06-90.13) in the PiaSky group and 78.4% (95%CI: 61.34-89.58) in the eculizumab group[*2] in the main treatment period (adjusted between-group difference in the proportion of patients who achieved transfusion avoidance[*3]: 1.8%, 95%CI: −16.67 to 19.94).**
- **The mean proportion of patients in the PiaSky switch group[*4] in the extended treatment period who achieved transfusion avoidance from baseline to Week 25 after switching was 82.1% (95%CI: 62.42-93.23).**

Proportion of patients who achieved transfusion avoidance from baseline to Week 25



Proportion of patients who achieved transfusion avoidance from baseline to Week 25 after switching to PiaSky



Data cutoff date: November 16, 2022

***1 The evaluation period for the PiaSky group and eculizumab group during the main treatment period was from Week 2 to Week 25.**
***2 One patient in the eculizumab group discontinued the study before Week 25 without receiving blood transfusion, but was assumed to receive blood transfusion as a conservative approach.**
***3 The adjusted between-group difference (PiaSky group - eculizumab group) was calculated using the Mantel-Haenszel method with the presence or absence of a history of packed red blood cell transfusion within 12 months before randomization as a stratification factor.**
***4 In the PiaSky switch group, 28 patients were evaluated who entered the extended study period and switched from eculizumab to PiaSky treatment at least 24 weeks prior to the data cut-off date.**

Eculizumab Dosage and Administration
The usage and dosage of eculizumab approved in Japan for the suppression of hemolysis in paroxysmal nocturnal hemoglobinuria is as follows: "For adults, the first dose is normally 600 mg of eculizumab (genetical recombination). Then, the drug is administered intravenously once a week for a total of four doses, including the first dose. Starting one week later (four weeks after the first dose), 900 mg of the drug is administered intravenously once every two weeks." [From the electronic package insert of eculizumab, revised in August 2023 (Version 6, dose change)]

Data evaluated at approval: Global Phase III Study (Study BO42161)

- **Immune Complex Reactions (When switching anti-C5 antibody preparations)**

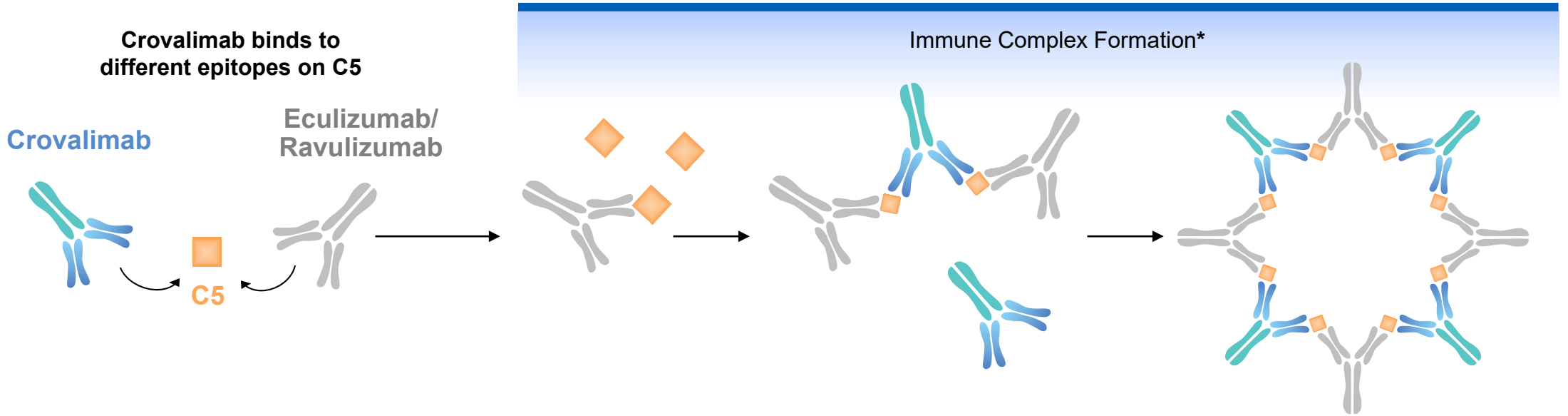
Immune Complex Reactions (When Switching Anti-C5 Antibody Preparations)

- **Immune complex reactions may occur when patients using another anti-C5 antibody preparation start receiving PiaSky or when patients using PiaSky start receiving another anti-C5 antibody preparation.**
- **It is important to monitor closely for about 30 days after switching anti-C5 antibody preparations, and take appropriate measures if any finding is observed in the skin, joints, lymph nodes/spleen, kidneys, etc.**

Mechanism of onset

Since crovalimab binds to a different C5 epitope than other anti-C5 antibody products (eculizumab or ravulizumab), when both are present in the circulating blood, transient immune complexes are formed, and their deposition in tissues is thought to cause immune complex reactions which are type III hypersensitivity reactions.

Mechanism of immune Complex Formation (Image)



*** Immune complexes vary in size according to the number of molecules of crovalimab, C5 and eculizumab/ravulizumab, and the largest immune complex may be formed consisting of 4 molecules of crovalimab, 8 molecules of C5, and 4 molecules of eculizumab/ravulizumab.**

Prepared by Röth A, et al. Blood. 2020; 135: 912–920. [This study was conducted with support from F. Hoffmann-La Roche AG and Chugai Pharmaceutical Co., Ltd. Authors of this paper include employees of F. Hoffmann-La Roche AG, Chugai Pharmaceutical Co., Ltd., and Genentech, Inc., and recipients of honoraria and other funding from F. Hoffmann-La Roche AG, Chugai Pharmaceutical Co., Ltd., and Genentech.] and Nishimura J, et al.: Clin Pharmacol Ther. 2023; 113:904-15. [This study was conducted with support from F. Hoffmann-La Roche AG and Chugai Pharmaceutical Co., Ltd. Authors of this paper include employees of F. Hoffmann-La Roche AG, Chugai Pharmaceutical Co., Ltd., and Genentech, Inc., and recipients of funding from F. Hoffmann-La Roche AG and Chugai Pharmaceutical Co., Ltd.]

Summary of PiaSky Integrated Safety Analysis

Objectives	The primary safety evaluation period results of Japanese and non-Japanese Phase 3 studies (COMMODORE1 Study *1, COMMODORE2 Study *2, COMMODORE3 Study *3) were used to demonstrate the safety of PiaSky compared with eculizumab and to comprehensively evaluate the safety of PiaSky in PNH patients.
Subjects	All 377 patients with PNH who received at least 1 dose of PiaSky (see table below)
Method	The integrated analysis results of safety data from baseline to the data cut-off date of *4 in each study are presented. Pooled data are presented by treatment group (eculizumab or PiaSky) and further divided into the PiaSky group by prior complement inhibitor use (naïve or switched) and total (naïve plus switched) (see table below).

*1 COMMODORE 1 (Study BO 42161): An open-label, randomized, global Phase 3 study to compare the safety, pharmacokinetics, pharmacodynamics, and efficacy of PiaSky with eculizumab in patients with PNH
*2 COMMODORE 2 (Study BO 42162): An open-label, randomized, global Phase 3 study to evaluate the efficacy and safety of PiaSky versus eculizumab in patients with previously untreated PNH
*3 COMMODORE 3 Study YO 42311: A Single-Arm, Multicenter, Phase 3 Study to Evaluate the Efficacy, Safety, Pharmacokinetics, and Pharmacodynamics of PiaSky in Treatment-Naïve, Chinese Patients ≥ 12 Years of Age with PNH
*4 [Cut-off date for each study] COMMODORE1: November 16, 2022, COMMODORE2: November 16, 2022, COMMODORE3: August 10, 2022

Safety analysis set for integrated analysis (integrated analysis set)

<table>
<tr><th>Eculizumab (n=111)</th><th>PiaSky (treatment naive) group (n=192)</th><th>PiaSky (conversion) group (n=185)</th><th>PiaSky (total) group (n=377)</th></tr>
<tr><td>COMMODORE 2 (n=69)</td><td>COMMODORE 2 Study
[Randomized part] (n=135)
[Non-randomized part] (n=6)</td><td></td><td rowspan="2">PiaSky (treatment naive) group (n=192)</td></tr>
<tr><td></td><td>COMMODORE 3 Study (n=51)</td><td></td></tr>
<tr><td>COMMODORE 1 (n=42)</td><td></td><td>COMMODORE 1 Study
[Randomized part] (n=44)
[Non-randomized part] (n=38)</td><td rowspan="2">PiaSky (conversion) group (n=185)</td></tr>
<tr><td></td><td></td><td>COMMODORE 2 (n=68)
COMMODORE 1 study (n=35) *5</td></tr>
</table>

*5 Patients who switched to piercing after receiving eculizumab for at least 24 weeks. Patients in the eculizumab group who were treated with eculizumab during the main treatment period and then switched to treatment with PiaSky treatment were counted twice, once in the eculizumab group and once in the PiaSky treatment group.

Evaluation data at the time of approval: Global phase III study (Study BO 42161), evaluation data at the time of approval: Global phase III study (Study BO 42162), reference data at the time of approval: Foreign phase III study (Study YO 42311), Data for evaluation at the time of approval: Summary of studies for safety evaluation, Data for evaluation at the time of approval: Pooling and presentation of safety data

Immune Complex Reactions (When Switching Anti-C5 Antibody Preparations)

Frequency [PiaSky Switch Group]

- **In Phase III studies in PNH patients conducted in Japan and overseas (Study BO42162, Study BO42161, and Study YO 42311), immune complex reactions were observed as an adverse event in 17.8% (33/185) of patients who switched from other anti-C5 antibody preparations to crovalimab. In two of these cases, reactions occurred twice, once when switching from eculizumab or ravulizumab to crovalimab, and once when switching to ravulizumab after discontinuing crovalimab.**

MedDRA System Organ Class MedDRA Preferred Term	Grade 1	Grade 2	Grade 3	Total (n=185)
All adverse events	9 (4.9%)	11 (5.9%)	13 (7.0%)	33 (17.8%)
Immune system disorders	9 (4.9%)	11 (5.9%)	13 (7.0%)	33 (17.8%)
Type III immune complex mediated reaction	9 (4.9%)	11 (5.9%)	13 (7.0%)	33 (17.8%)
Nervous system disorders	0	0	1 (0.5%)	1 (0.5%)
Axonal neuropathy	0	0	1 (0.5%)	1 (0.5%)

MedDRA version 25.1.

Data evaluated at approval: Type III hypersensitivity reaction

Safety [primary endpoint]

In Patients Who Switched from Eculizumab or Ravulizumab to PiaSky Development of Clinical Symptoms due to Immune Complex Formation [Non-randomized phase] (continued)

- The incidence of adverse events corresponding to type III hypersensitivity reactions due to immune complex formation was 23.8% (5 cases) in Cohort 2 (ravulizumab-experienced) and 20.0% (2 cases) in Cohort 3 (high-dose eculizumab-experienced), and all of the events that occurred were type III immune complex reactions.

● Incidence of adverse events corresponding to type III hypersensitivity reactions due to immune complex formation and associated clinical symptoms (by organ classification) (entire treatment period[*1])

	Cohort 1 < 18 years old, eculizumab-experienced (n=1)	Cohort 2 Ravulizumab-experienced (n=21)	Cohort 3 High dose[*2] eculizumab-experienced (n=10)	Cohort 4 C5 gene polymorphism carrier (n=6)
Adverse events corresponding to type III hypersensitivity reactions	0	5 (23.8%)	2 (20.0%)	0
Type III immune complex mediated reaction	0	5 (23.8%)	2 (20.0%)	0
Associated clinical symptoms				
Skin and subcutaneous tissue disorders	0	3 (14.3%)	0	0
Erythema	0	1 (4.8%)	0	0
Petechia	0	1 (4.8%)	0	0
Rash	0	1 (4.8%)	0	0
Nervous system disorders	0	1 (4.8%)	1 (10.0%)	0
Axonal neuropathy	0	1 (4.8%)	0	0
Headache	0	0	1 (10.0%)	0
Gastrointestinal disorders	0	0	1 (10.0%)	0
Abdominal pain upper	0	0	1 (10.0%)	0
Renal and urinary disorders	0	0	1 (10.0%)	0
Chromaturia	0	0	1 (10.0%)	0

MedDRA version 25.1.
*1 The evaluation period is the period from Day 1 of PiaSky treatment to the data cutoff date or discontinuation of PiaSky treatment, whichever comes first (including the extended treatment period).*2 More than 900 mg/dose, or more than once every 2 weeks

Eculizumab Dosage and Administration
The usage and dosage of eculizumab approved in Japan for the suppression of hemolysis in paroxysmal nocturnal hemoglobinuria is as follows: "For adults, the first dose is normally 600 mg of eculizumab (genetical recombination). Then, the drug is administered intravenously once a week for a total of four doses, including the first dose. Starting one week later (four weeks after the first dose), 900 mg of the drug is administered intravenously once every two weeks." [From the electronic package insert of eculizumab, revised in August 2023 (Version 6, dose change)]

Data cutoff date: November 16, 2022

Data evaluated at approval: Global Phase III Study (Study BO42161)

1. About PNH

2. Introduction of PiaSky Clinical Study

3. Case Presentation

Case

[Case] At the introduction of crovalimab (year X), in his 50s

[Family history] None [Past history] Diabetes mellitus

[History of present illness]

In X-27, anemia was diagnosed at a local hospital, and an iron preparation was prescribed.

In X-26, as his anemia did not improve, the patient was referred to our hospital. PNH was diagnosed based on LDH3979, negative Coombs test, positive Ham test, positive sugar water test, and 46.47% CD59 negative red blood cells.

The patient's subjective symptoms and anemia were relatively mild, and the LDH level remained at 1000 or lower. Therefore, he was placed under observation.

LDH and anemia gradually worsened in year X-1.

In year X, the patient became aware of frequent hemoglobinuria, and anti-complement therapy was considered appropriate.

Important Note: This is a single case, and not all patients will follow a similar course.

Case provided by: Naoshi Obara, University of Tsukuba

Before Starting Crovalimab

Blood Count	
WBC	4000/μL
Seg	58%
Lym	29.2%
Eosino	0.4%
Mono	11.0%
Baso	0.6%
RBC	260 × 10^4 /μL
Hb	7.9 g/dL
Ht	25.7%
MCV	98.8 fL
MCH	30.4 pg
MCHC	30.7%
PLT	12.8 × 10^4 /μL
Reticulocytes	253200/μL

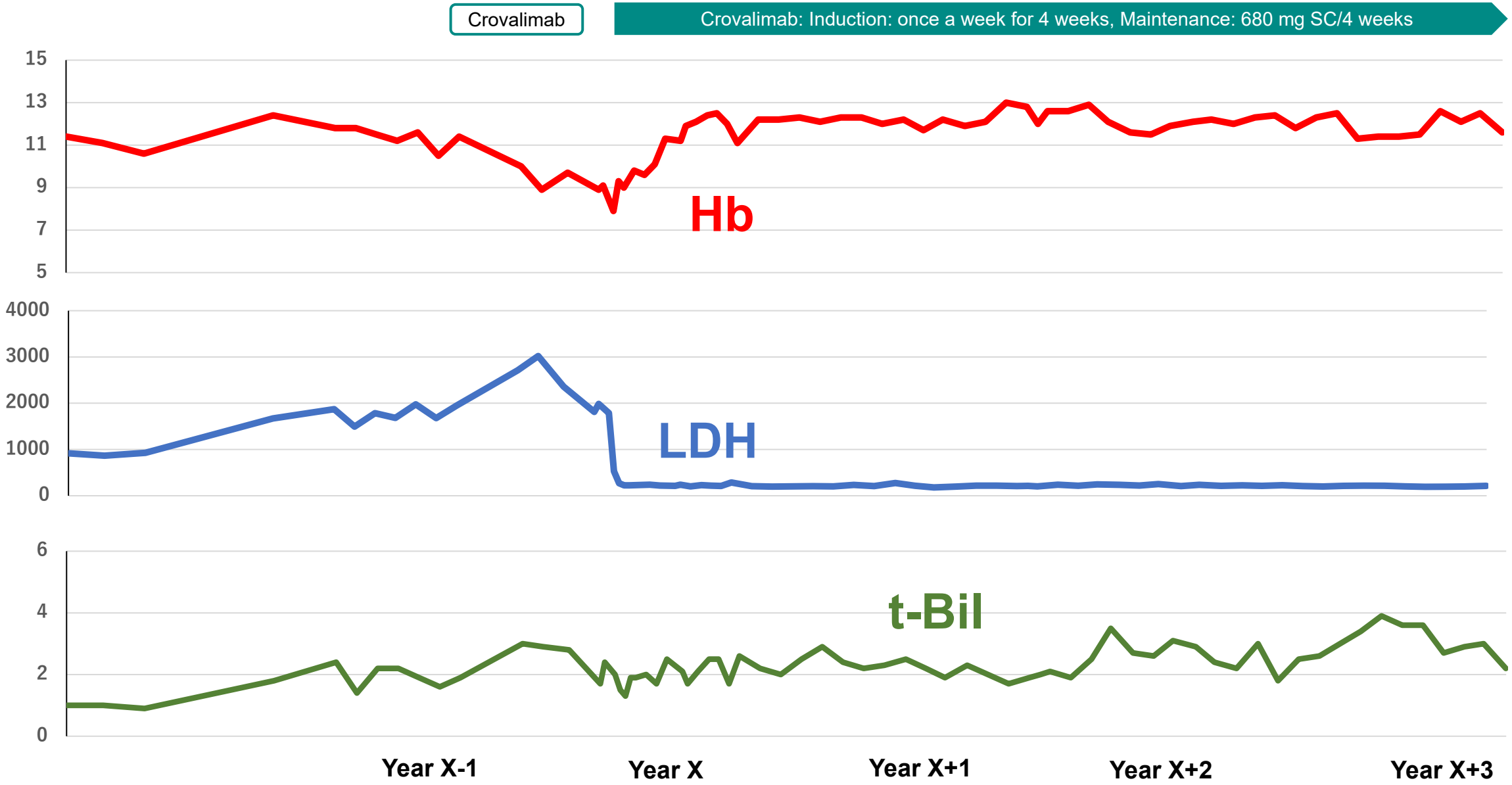
Biochemical Tests	
AST	52 U/L
ALT	32 U/L
LDH	1985 U/L
T-Bil	2.4 mg/dL
D-Bil	0.5 mg/dL
γGTP	38 U/L
TP	7.1 g/dL
Alb	4.7 g/dL
BUN	7.4 mg/dL
Cre	0.64 mg/dL
Na	143 mmol/L
K	3.9 mmol/L
Cl	106 mmol/L
D-dimer	0.3 μg/mL
Haptoglobin	≤ Detection sensitivity

Urine findings	
Specific gravity	1.008
pH	7.0
Glu	1+
Urine protein	-
Urine occult blood	3+

PNH blood cells	
PNH-type red blood cells	42.94%
PNH granulocytes	88.64%

Important Note: This is a single case, and not all patients will follow a similar course.

Treatment Course After Administration of Crovalimab



Important Note: This is a single case, and not all patients will follow a similar course.

PNH Medications Available in Japan

	Crovalimab (PiaSky®)	Eculizumab	Ravulizumab	Pegcetacoplan	Danicopan
Launch in Japan	May 2024	June 2010	September 2019	September 2023	April 2024
Therapeutic category	pH-dependent binding human anti-human complement (C5) monoclonal antibody	Anti- complement (C5) monoclonal antibodies	Anti- complement (C5) monoclonal antibodies	Complement (C3) inhibitor	Complement factor D inhibitor
Dosage and administration	The usual Day 1 dose is 1000 or 1500 mg of crovalimab (genetical recombination) once by intravenous infusion, and subsequently, 340 mg is subcutaneously administered once on Days 2, 8, 15, and 22, and 680 or 1020 mg is subcutaneously administered once every 4 weeks from Day 29 onward, taking the patient's body weight into account.	The usual initial dose for adults is 600 mg of eculizumab (genetical recombination) per dose. After the initial dose, the drug should be intravenously infused once weekly for a total of 4 doses, followed 1 week later (4 weeks after the initial dose) by 900 mg/dose intravenously infused once every 2 weeks.	The usual adult starting dose is 2,400~3,000 mg of ravulizumab (genetical recombination) per dose, taking the patient's body weight into consideration, followed by 3,000~3,600 mg per dose at 2 weeks after the initial dose and 3,000~3,600 mg every 8 weeks thereafter by intravenous infusion.	The usual dosage for adults is 1080 mg of pegcetacoplan administered subcutaneously twice weekly. For patients with inadequate response, 1080 mg of pegcetacoplan may be administered subcutaneously every 3 days.	The usual adult dosage is 150 mg of danicopan administered orally 3 times daily after meals in combination with a complement (C5) inhibitor. The dose may be increased up to 200 mg if the effect is insufficient.

Anti-complement C5 antibody

Expectations for PiaSky

- Patient options for administration method are expanded
- Can be administered to patients with C5 gene polymorphisms
- Potential for shorter administration time and hospital time per session (good news for busy patients)
- Eliminates the need for intravenous injections in the maintenance period (good news for patients with difficulty in finding a blood vessel)
- Reduces the burden on the infusion room

Thank you for your attention.

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INNOVATION BEYOND IMAGINATION

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