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CHUGAI PHARMACEUTICAL CO., LTD.

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CHUGAI PHARMACEUTICAL CO., LTD.

Information Meeting on PiaSky

June 27, 2024

Event Summary

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[Venue]	Webcast
[Venue Size]	
[Participants]	

[Number of Speakers]	3	
	Naoshi Obara, M.D., Ph.D.	Professor, Department of Medical Sciences, Faculty of Medicine, University of Tsukuba
	Kumi Miura	PiaSky Lifecycle Leader
	Kae Miyata	Head of Corporate Communications Department
[Analyst Names]*	Shinichiro Muraoka	Morgan Stanley MUFG Securities
	Hidemaru Yamaguchi	Citigroup Global Markets
	Kazuaki Hashiguchi	Daiwa Securities
	Hiroyuki Matsubara	Nomura Securities
	George Zhou	Goldman Sachs
	Koichi Mamegano	BofA Securities
	Seiji Wakao	JPMorgan Securities

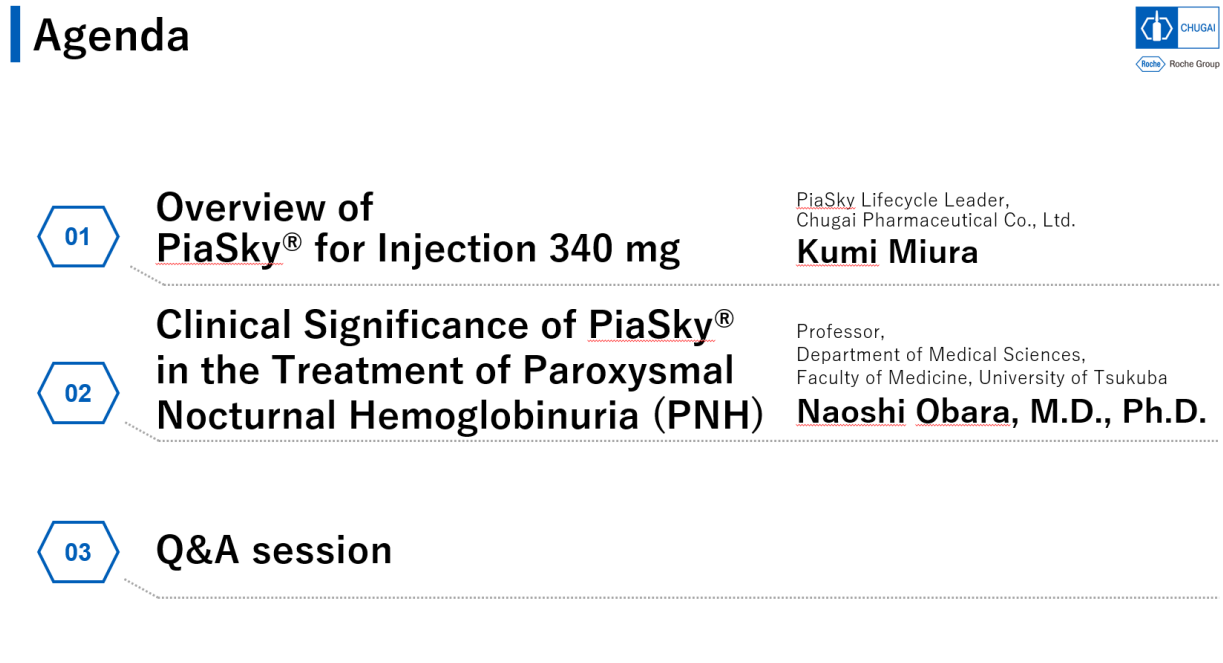
*Analysts that SCRIPTS Asia was able to identify from the audio who spoke during Q&A or whose questions were read by moderator/company representatives.

Presentation

Miyata: Thank you very much for attending today's meeting on PiaSky for Injection, a pH-dependent binding humanized anti-complement, C5, monoclonal antibody.

I'm Miyata from the corporate communications department, and I will be your facilitator today. Thank you.

Today's event is held on an on-site basis and also distributed on a Zoom webinar basis at the same time.



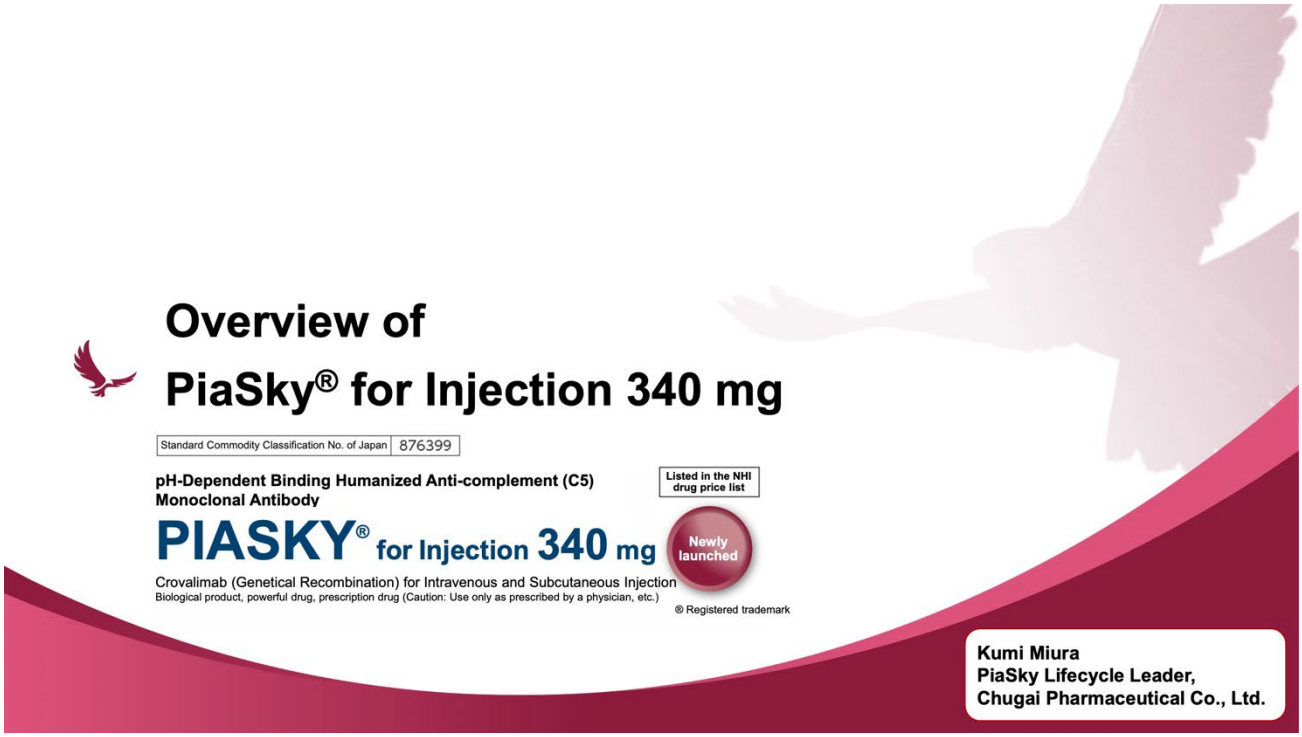
The agenda for today's meeting is shown on the venue screen, on the web screen, and on the third page of the presentation materials. I will explain the contents accordingly.

Today, we have invited as a special lecturer, Dr. Naoshi Obara, MD, PhD, Professor, Department of Medical Sciences, Faculty of Medicine, University of Tsukuba.

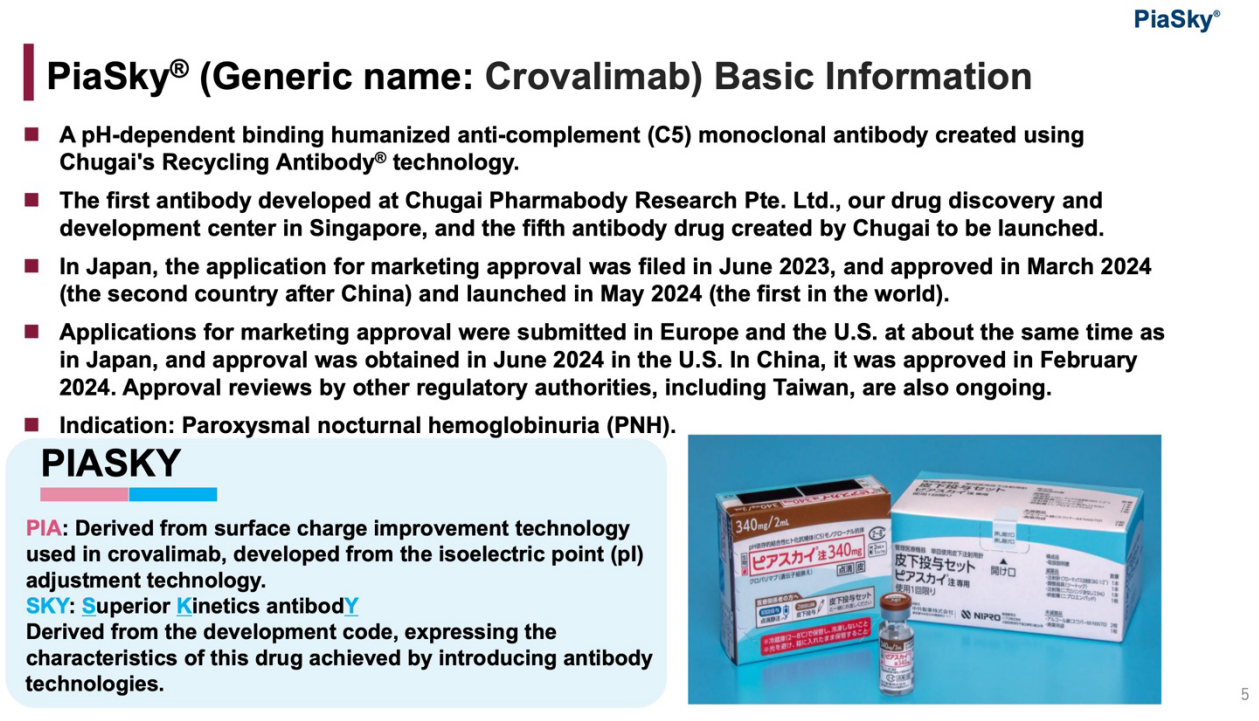
We have already sent you Dr. Obara's biography along with today's presentation materials, so due to time constraints, we will skip the introduction of his biography at this time. Please note that there will be time for screen capture before each presentation.

Questions will be taken after all presentations have been completed. The Q&A session is expected to last 30 minutes, so we hope you will be proactive and ask questions. Please note that your audio will be muted during the presentation.

Now, Miura, the PiaSky Lifecycle Leader of CHUGAI PHARMACEUTICAL, will give an overview of PiaSky. There will be a short pause at the beginning, so if you would like to take a screen capture, please use this opportunity. Ms. Miura, please see the camera. Please go ahead.



Miura: My name is Miura, the PiaSky Lifecycle Leader of CHUGAI PHARMACEUTICAL CO. Thank you. I will give a brief overview of our products.

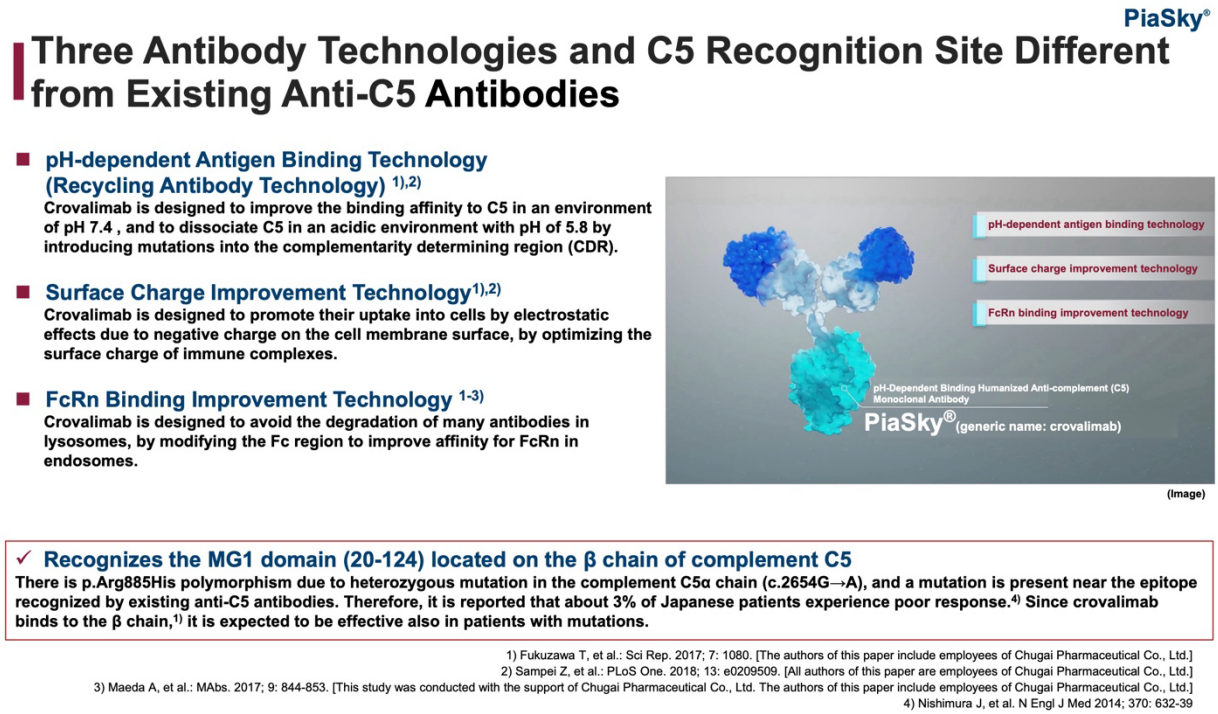


PiaSky is a pH-dependent binding humanized anti-complement, C5, monoclonal antibody using our proprietary recycling antibody technology. This is the first antibody developed at CPR, our drug discovery and development base in Singapore, and the fifth antibody drug discovered by us.

In Japan, the product was launched in 2024, in May of this year, which means that this launch is a world first. The US and Europe also applied for manufacturing and marketing approval at about the same time as Japan, and approval was received in the US on June 20.

The indication is paroxysmal nocturnal hemoglobinuria.

Dr. Obara will explain the mechanism of hemolysis and the mechanism of action of this disease later, so I will skip that part.



The drug uses antibody engineering technology, which is our specialty, and incorporates three antibody technologies that we employ.

The first is pH-dependent antigen binding technology, recycling antibody technology. The agent 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 5.8 by introducing mutations into the complementarity determining region, CDR.

The second point is the adoption of surface charge improvement technology. It 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.

Third, we have introduced FcRn binding improvement technology, and it is designed to avoid the degradation of many antibodies in lysosomes by modifying the Fc region to improve affinity for FcRn in endosomes.

Another characteristic feature is the presence of polymorphism due to a heterozygous mutation in the complement C5α chain, and it has been reported that approximately 3% of these patients in Japan have a poor response to existing drugs. The drug is expected to be effective for patients with mutations by binding to the β-chain.

PiaSky®

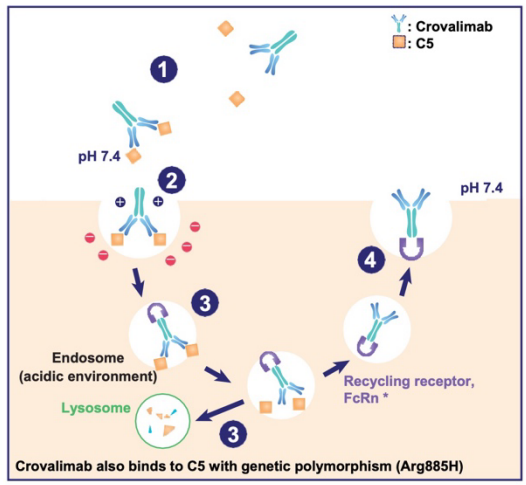
Recycling Mechanism of Crovalimab [1)2)]

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.]

8

This is the recycling mechanism of crovalimab.

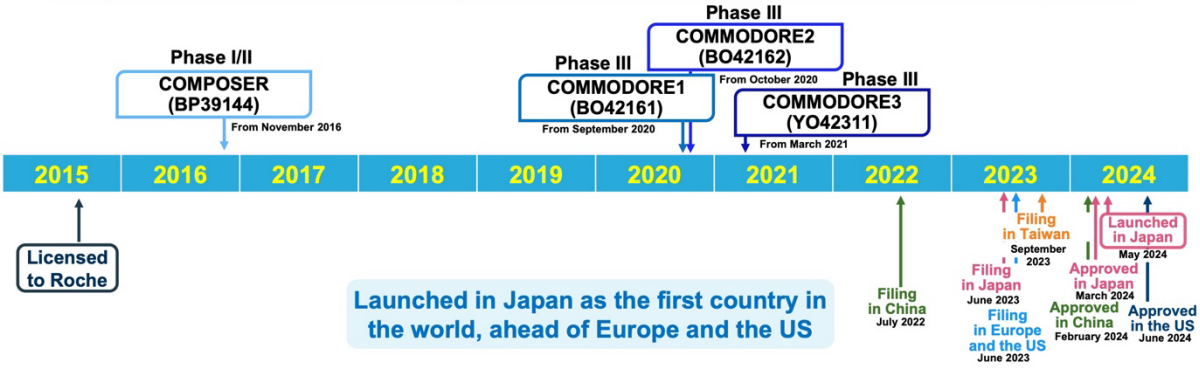
It binds to antigens in plasma. We designed the product to bind strongly to C5 at pH 7.4, which is the normal pH. It is also believed that crovalimab bound to C5 can be efficiently taken up into the cell by optimizing its surface charge.

Third, the acidic environment in the endosome dissociates C5 from crovalimab and promotes C5 separation in the lysosome. It is also believed that techniques that enhance binding to FcRn will facilitate the recycling of crovalimab back into the plasma.

PiaSky®

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.



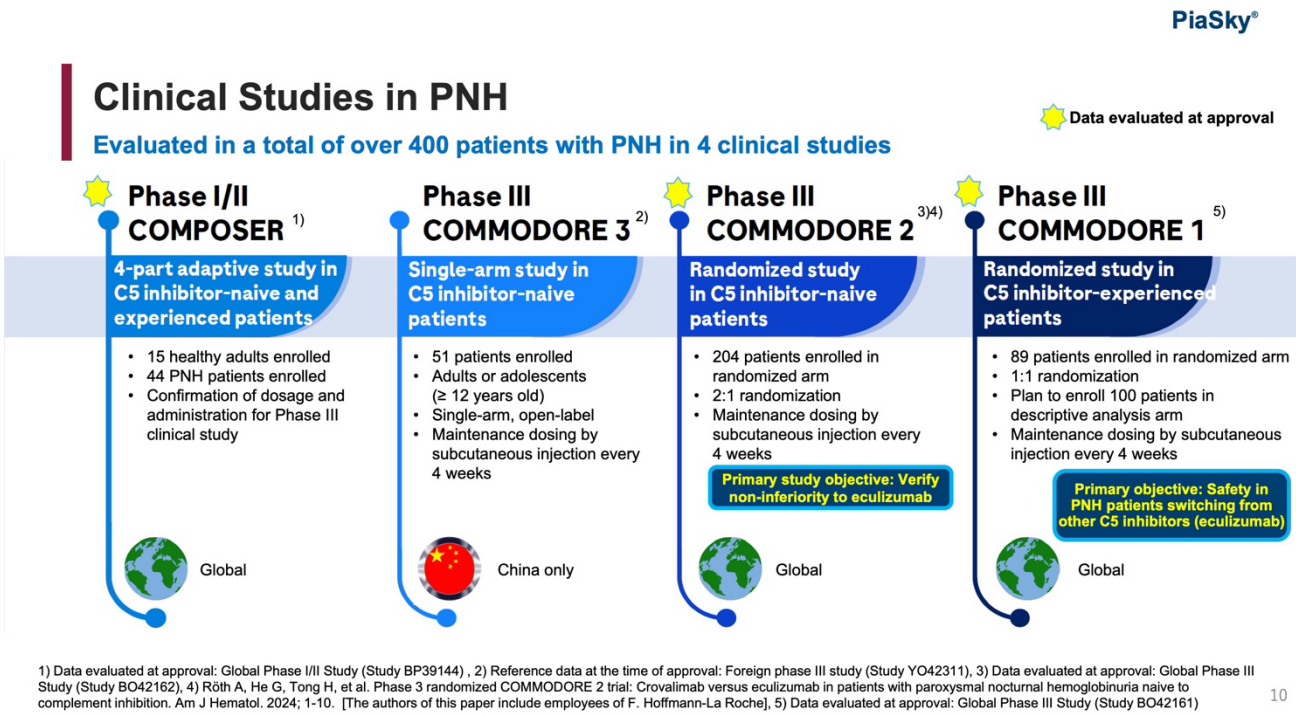
9

This is the development history.

This is the second antibody using this recycling antibody technology, following ENSPRYNG, an anti-IL-6 receptor antibody, which is already on the market. Following the development of ENSPRYNG, we decided to develop an antibody using this recycling antibody technology and reviewed antigens to target, and complement C5 was selected as the target antigen and we started the development.

The reason for this was the expectation that the convenience of administration could be improved by reducing the frequency and dosage of administration and developing subcutaneous administration, thereby improving the quality of life of patients, and that the use of a β-chain as the epitope of C5 to which the antibody binds could provide a therapeutic agent for cases of poor response to existing C5 antibodies.

We started the joint development of this drug with Roche in 2015. Subsequently, we are conducting these clinical trials globally.



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)

10

We have conducted four clinical trials listed here.

These three studies marked with yellow stars are the ones evaluated at approval.

Today, Dr. Obara will explain the results of the tests, focusing on two on the right, COMMODORE 1 and COMMODORE 2 studies.

PiaSky®

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)

11

The indication for this drug is paroxysmal nocturnal hemoglobinuria.

The above three precautions are common to all anti-C5 antibodies, but a fourth precaution has been added for this product, namely, to carefully evaluate the necessity of switching to this product when switching from another C5 antibody formulation to this product, since this product may cause immune complex reactions. We will discuss this background later in the results of the clinical trial.

PiaSky®

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

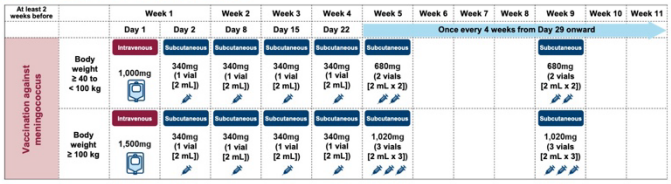
Refer to the table below for the amount per dose and method of administration of PIASKY.

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

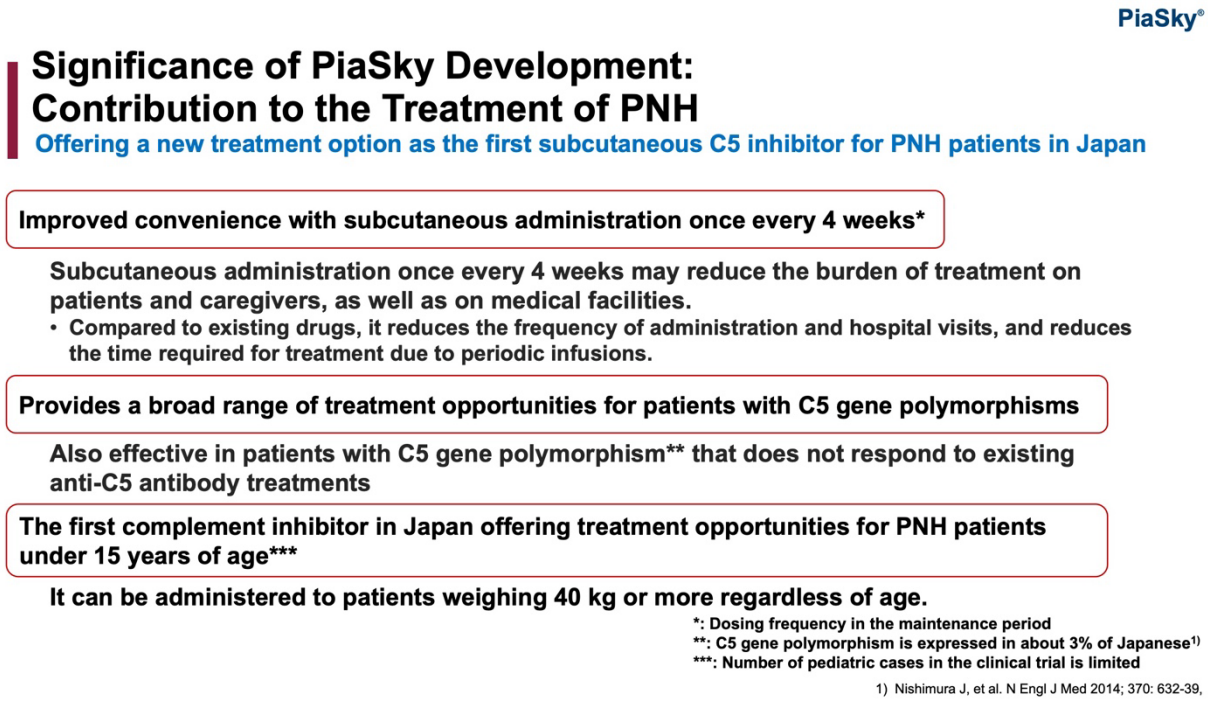
Intended for use by patients weighing at least 40 kg (No clinical studies have been conducted in children weighing less than 40 kg)

12

The dosage and administration of crovalimab will be 1,000 mg or 1,500 mg intravenously on day 1, 340 mg once on days 2, 8, 15, and 22, and 680 mg or 1,020 mg subcutaneously once every four weeks on day 29 and thereafter, depending on patient weight.

Please refer to the table below and the diagram we have included as a reference for the administration schedule for a better understanding.

The dosage is based on the patient's weight, and pediatric patients weighing 40 kg or more can also be administered.



As for the significance of the development of this product, we believe that it will provide a new treatment option as the first subcutaneously administered C5 inhibitor for patients with PNH in Japan. These three main items are listed here.

First, we believe that the once-every-four-week subcutaneous administration will improve convenience by reducing the frequency of administration, the frequency of hospital visits, and the time required for periodic infusions compared to existing drugs, thereby reducing the burden of treatment on patients and caregivers and the burden on the medical field.

Second, it is also effective for patients with C5 gene polymorphisms who do not respond to treatment with existing C5 antibodies, which we believe will provide a wide range of treatment opportunities for these patients.

Thirdly, the drug can be administered to patients weighing 40 kg or more without age restriction, and we believe that for the first time in Japan, it may also provide treatment opportunities for PNH patients younger than 15 years of age.

This is the disease awareness website that is being launched at the same time as the launch.

This is supervised by Dr. Obara, who will be speaking today. We have launched this website in cooperation with the PNH Club, a patient organization, and hope that this website will serve as an educational site for the general public to help introduce and explain the disease of PNH to those who are close to them.

The product overview can be found here.

As I mentioned earlier, this is a pH-dependent binding humanized anti-complement monoclonal antibody using recycling antibody technology developed by our company.

There are three points. As a subcutaneously administered C5 inhibitor, it offers a new treatment option, and this subcutaneous administration could reduce the burden of treatment on patients and caregivers and the burden on the medical field. This may provide new treatment to patients with gene polymorphism and patients less than 15 years old weighing 40 kg or more.

This is the summary of the product overview. Thank you.

Miyata: Thank you very much. Dr. Naoshi Obara will continue with an explanation of the clinical positioning of PiaSky. There will be a short pause at the beginning, so if you would like to take a screen capture, please use this opportunity. Now, please begin.

Obara: Thank you. I am Obara of the Department of Medical Sciences, Faculty of Medicine, University of Tsukuba. Today, I would like to talk about the pathogenesis of paroxysmal nocturnal hemoglobinuria, PNH, and then the clinical positioning of PiaSky.

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**

17

This is my COI.

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

18

Today, I will discuss three separate topics. First, I will introduce the disease of PNH and the basics of complement, a component of the immune system. After that, I will introduce the clinical trial of PiaSky, and finally, I will talk about a case of clinical trials that are being conducted at our facility.

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. 20

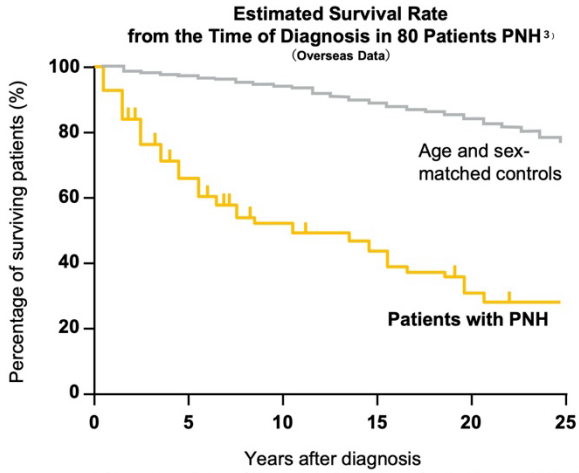
First, let me talk about the complement and PNH.

PNH has a very long name in Japanese, paroxysmal nocturnal hemoglobinuria. The pathogenesis of this disease is a disease of hematopoietic stem cells, which is caused by an acquired mutation of a gene called *PIGA* in hematopoietic stem cells, and the hematopoietic cells with the mutation proliferate and take over hematopoiesis.

It is a very rare disease, but it has been known to cross-transfer with other hematopoietic disorders such as aplastic anemia and myelodysplastic syndromes, and although it is rare, it can also progress to acute leukemia. It is a disease with such a diverse range of pathologies.

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.



＊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. 21

PNH is a fairly rare disease. According to an old data from about 20 years ago, in Japan, the prevalence number is 3.6 out of 1 million people. Today, there is a bit more awareness in the medical field, and it is likely that there are a few more.

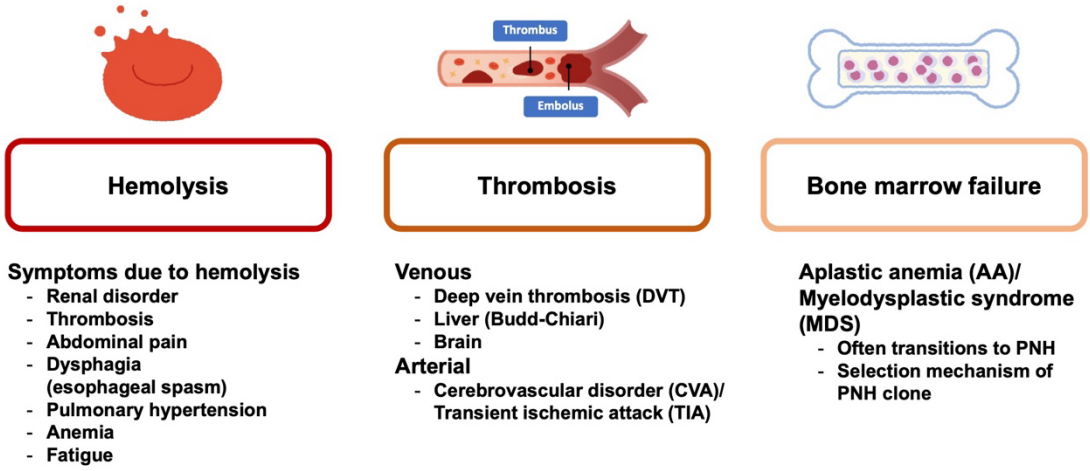
Currently, there are about 1,000 people receiving anti-complement therapy for this PNH, so including those undergoing follow-up, we estimate that there is roughly one person in every 100,000.

The average age at onset and diagnosis is said to be roughly in the 40s or around 40 years old. It is a disease with a very wide age range of onset, as it affects and is diagnosed in both relatively young and very old people.

Although PNH is a benign disease, it causes various complications, etc., and before the advent of anti-complement therapy, it was a disease with a rather poor prognosis. Roughly half of the patients died of the following complications, mainly thrombosis and renal failure, during a period of about 10 years.

Because it is an infrequent disease and requires a fairly long-term treatment, it is designated as an intractable disease. As for patients, this means the patients can receive the support for the cost of treatment.

Three Major Signs of PNH[1)]



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)

22

PNH has three main signs.

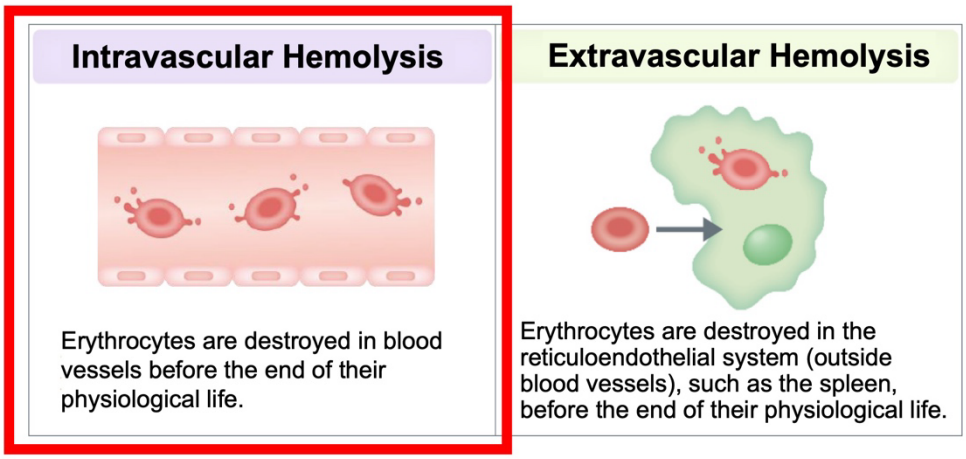
One is hemolysis. This disease causes a variety of symptoms. Blood dissolves, causing anemia and hemolysis, which may be accompanied by kidney damage, thrombosis, and also gastrointestinal problems such as abdominal pain, and also pulmonary disorder.

More characteristic or life-threatening complication is thrombosis. This is a thrombosis that can occur in both veins and arteries, which means it is one of the major causes of death in PNH.

Then there is bone marrow failure. Often there is a decrease not only in red blood cells but also in white blood cells, platelets, and all three systems. It is also a disease that is said to be a relative and mutually transferable to such hematopoietic failure diseases.

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.



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

23

One type of hemolytic anemia is PNH, and hemolysis can be divided into two major types: intravascular hemolysis and extravascular hemolysis. Hemolysis is a disease in which red blood cells are destroyed or destroyed before the end of its life.

PNH is primarily a disease of intravascular hemolysis. Intravascular hemolysis is a disease where the red cell is destroyed by a complement while flowing through blood vessels. On the other hand, extravascular hemolysis is a disease where the red cell is destroyed by old cell-eating cells, such as macrophages in the spleen or liver.

There are two types of hemolysis, but intravascular hemolysis is more severe and is characterized by very frequent organ damage. It can be said that PNH is a form of hemolysis that can be very severe in blood vessels.

PNH is called paroxysmal nocturnal hemoglobinuria, which has the strange name nocturnal, because of the historical background that the name was given to this condition when it was first noticed that hemoglobinuria, pee, urine was very red or black when the patient woke up in the morning.

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)

24

The reason why such hemolysis occurs during the night is not well understood, but there are two hypotheses.

As the respiratory rate decreases during sleep, CO_2 accumulates, and as it does so, the acidosis tends to become more acidic. Complement activity is very active in acidic conditions, which means that hemolysis may be enhanced while the patient is sleeping.

The other is intestinal peristalsis. Since intestinal peristalsis is decreased during sleep, it has been suggested that during this time, some of the toxins in the intestinal tract from intestinal bacteria may be absorbed and complement activity may be increased accordingly.

It is also said that since there is not much drinking and urinating during the night while sleeping, the urine is concentrated early in the morning, and thus the color of the urine, such as black or red, may be more noticeable.

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.

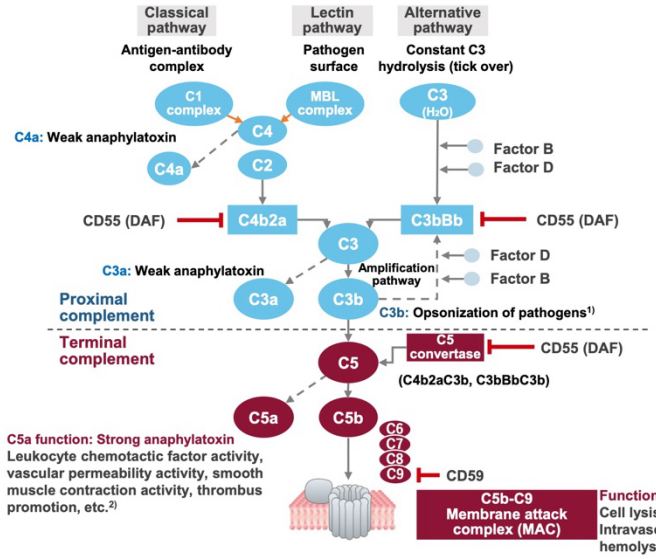
25

PNH, paroxysmal nocturnal hemoglobinuria, is the name of the disease, but the main condition of the disease is not paroxysmal. Basically, it is a chronic progressive hemolysis, not a disease that occurs suddenly or for some other reason.

However, hemolysis can be promoted as a seizure, triggered by infection or vaccines. Also, it is not necessarily at night, but when some trigger, such as infection, causes hemoglobinuria, blood or hemoglobin in pee, such attacks occur not only at night.

In addition, since the disease presents with a variety of symptoms, there are some misconceptions about the name, such as that hemoglobinuria, or the color of the urine, is not the only characteristic of the disease.

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.

26

PNH is a disease in which blood cells are destroyed by complement.

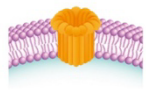
First, we can say that complement is basically one of the proteins that govern immunity and one of the systems of protein immunity. Complement is a protein that originally got its name from the fact that it assists antibodies, it is known to have a very important function.

There are various kinds of conserved systems among living organisms.

Complement is characterized in such a way that several many factors, mainly C1 to C9, react one after another to govern immunity. The main ones are named C, from the name of complement, which means that they are named C1 through C9.

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.

27

There are three major roles of complement.

The first is called opsonization in which complement attaches itself to the pathogen and acts as a marker, which is then used by one of the white blood cells or macrophages to kill the pathogen.

Next is the induction of inflammation. It works in such a way that it causes inflammation, i.e., it attracts white blood cells, which are then eliminated by the white blood cells at the pathogen.

Third is directly related to PNH, and there is something called the membrane attack complex. When all the complement reacts, it creates something like this tube in the cell membrane, and the pathogen is destroyed based on it or is directly destroyed.

However, the membrane attack complex is designed to attack its own cells, and the complement system is such that any cell can create a membrane attack complex and attack the cells. Therefore, the living body is equipped with a defense mechanism against complement to prevent its own cells from being attacked. Pathogens have no defense mechanisms, so they are attacked, and that is how the system works.

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

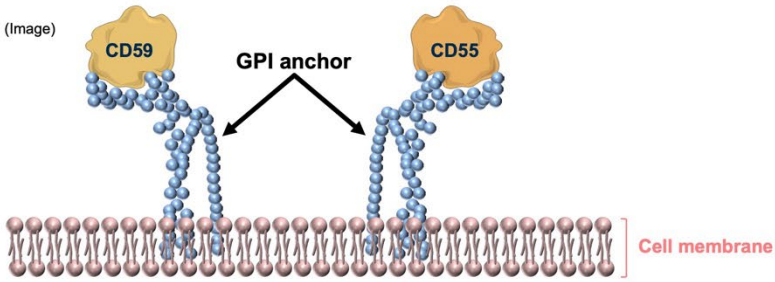
CD59 (MIRL)

- 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.

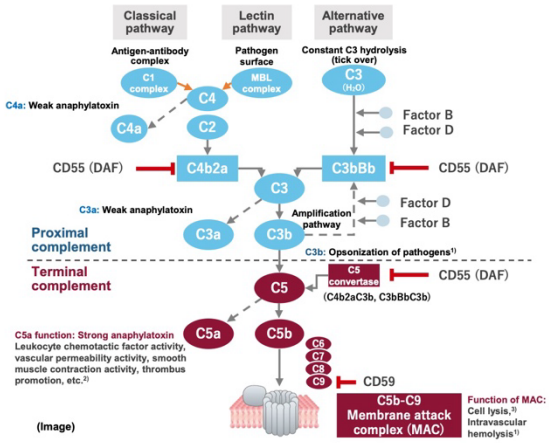
28

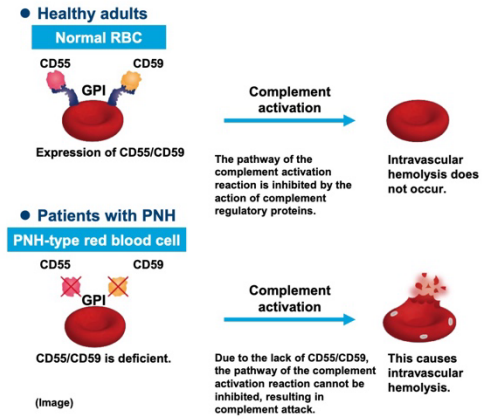
In the system, CD55 and 59 are important proteins. Each of these proteins acts in such a way as to protect the organism from complement reactions. These CD55 and 59 are connected by a chain-like structure called a GPI anchor, which is attached to the surface of the cell membrane.

In the case of PNH, a genetic abnormality occurs such that the GPI anchor cannot be formed, and CD55 and 59, which protect cells from complement, cannot attach to the cell surface. This is the reason why own cells are attacked by complements and the symptoms appear.

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.**



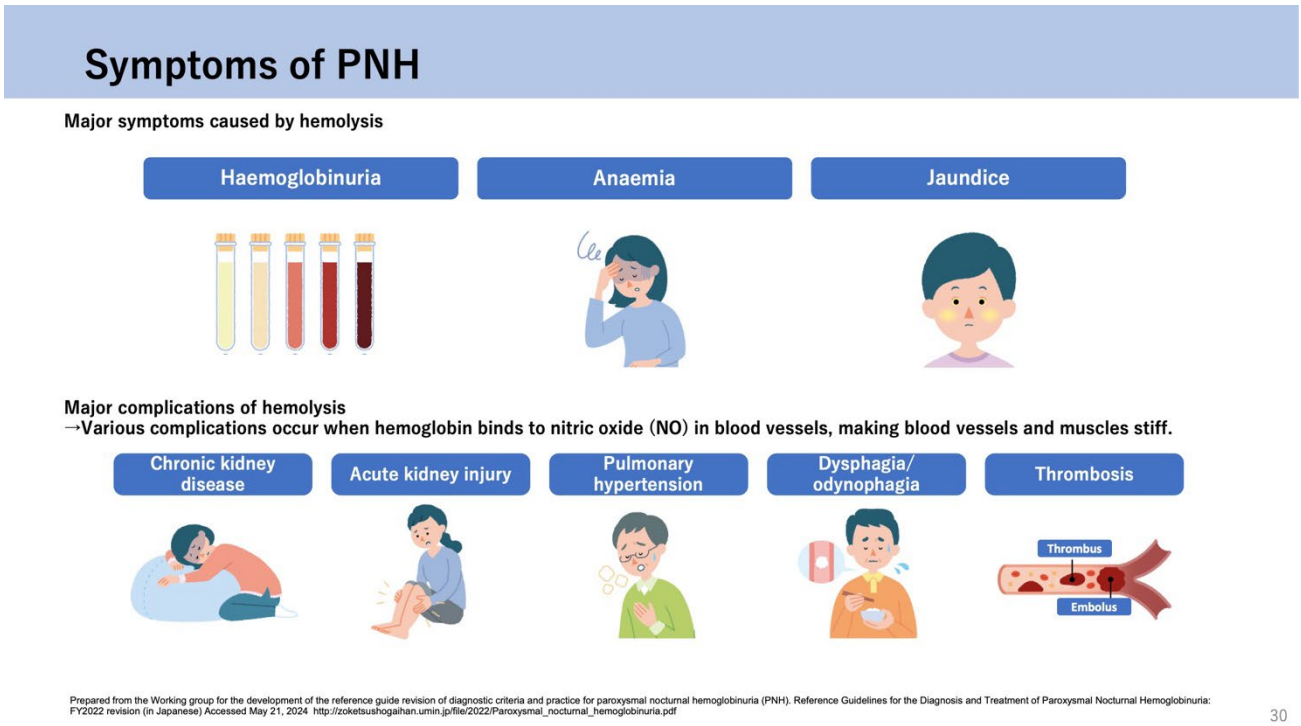


1) Working group for the development of the reference guide revision of diagnostic criteria and practice for paroxysmal nocturnal hemoglobinuria (PNH). Reference Guidelines for the Diagnosis and Treatment of Paroxysmal Nocturnal Hemoglobinuria: FY2022 revision (in Japanese),
2) Ueda Y, The Japanese Association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

29

As I mentioned earlier, the complement pathway is now a series of reactions of various proteins that eventually result in what is called the membrane attack complex, which attacks pathogens.

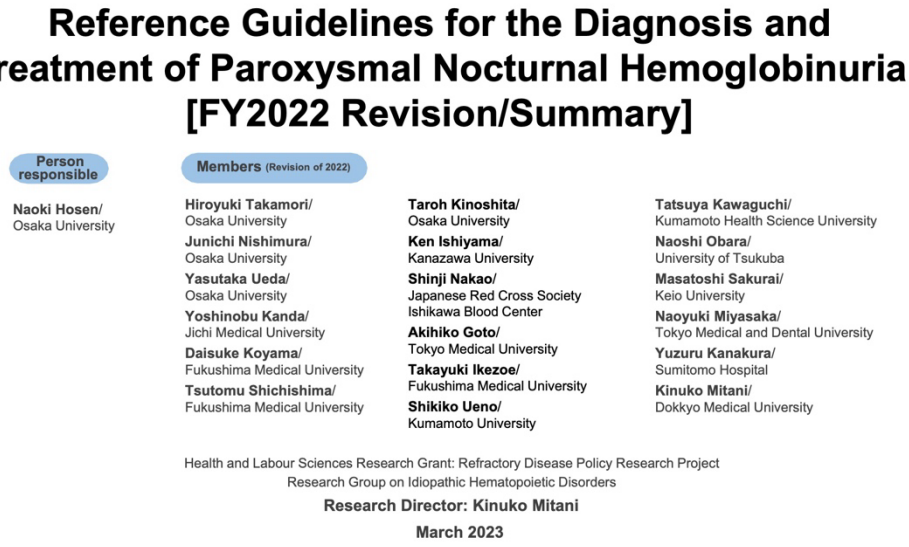
Healthy people have these CD55 and 59 on the cell surface, so even if there is this kind of complement reaction, there is no problem because they are not attacked even if they are attacked on the cell surface, but in patients with PNH, this chain-like thing called GPI is missing, so when complement is activated, the red blood cells are attacked, and hemolysis occurs.



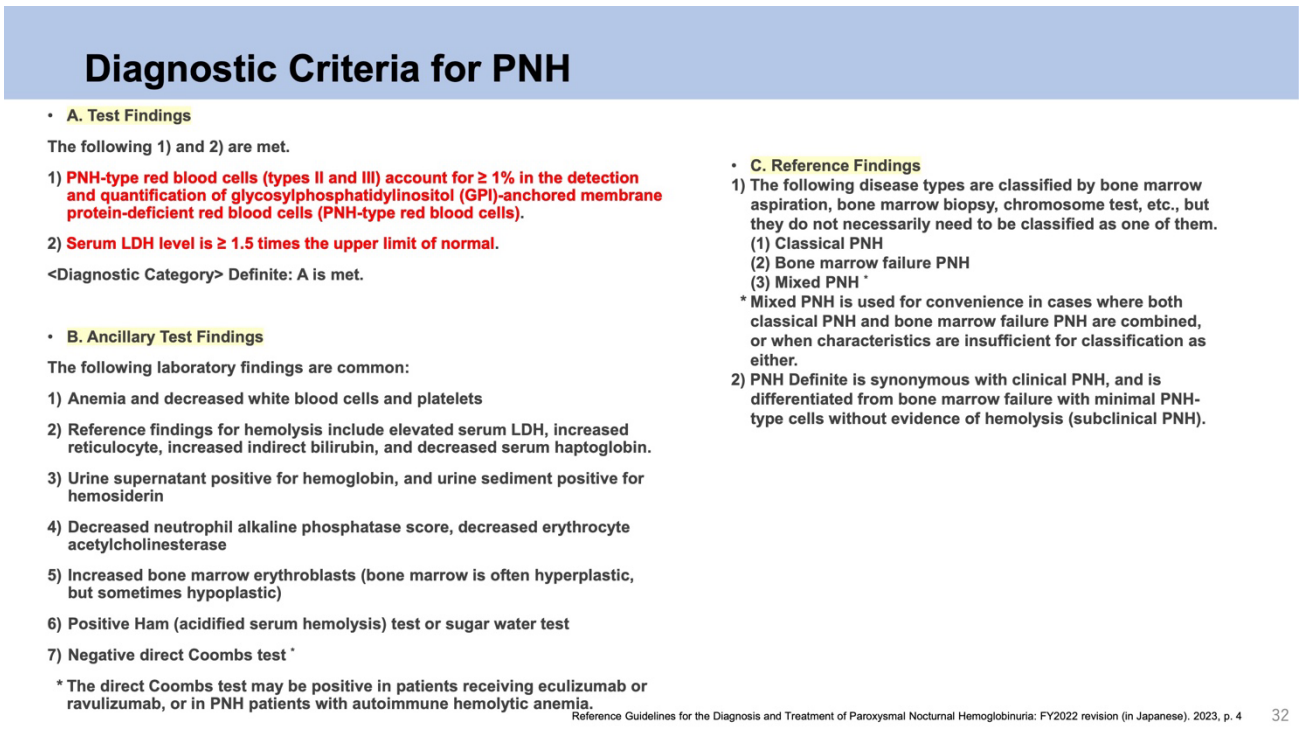
The symptoms that occur with PNH, as I have just given you, can be detailed, hemoglobinuria, for example. The hemolyzed components of the blood come out in the urine, causing the pee to turn red or, in severe cases, black.

Then there is anemia and the jaundice that accompanies it. Furthermore, the process of hemoglobin excretion from the kidneys causes damage to the kidneys, and renal disease, degradation of kidneys would occur. It can be either acute or chronic, but the kidneys deteriorate. Since the blood vessel could be contracted or damaged, if the blood vessels in the lungs are damaged, it can lead to pulmonary hypertension and respiratory failure, or if the muscles and blood vessels of the digestive tract are damaged, abdominal pain and difficulty in swallowing can occur.

More importantly, blood vessels are damaged, making it easier for clots to form on their surfaces and thrombosis to occur. This can lead to serious thrombosis such as stroke or myocardial infarction.



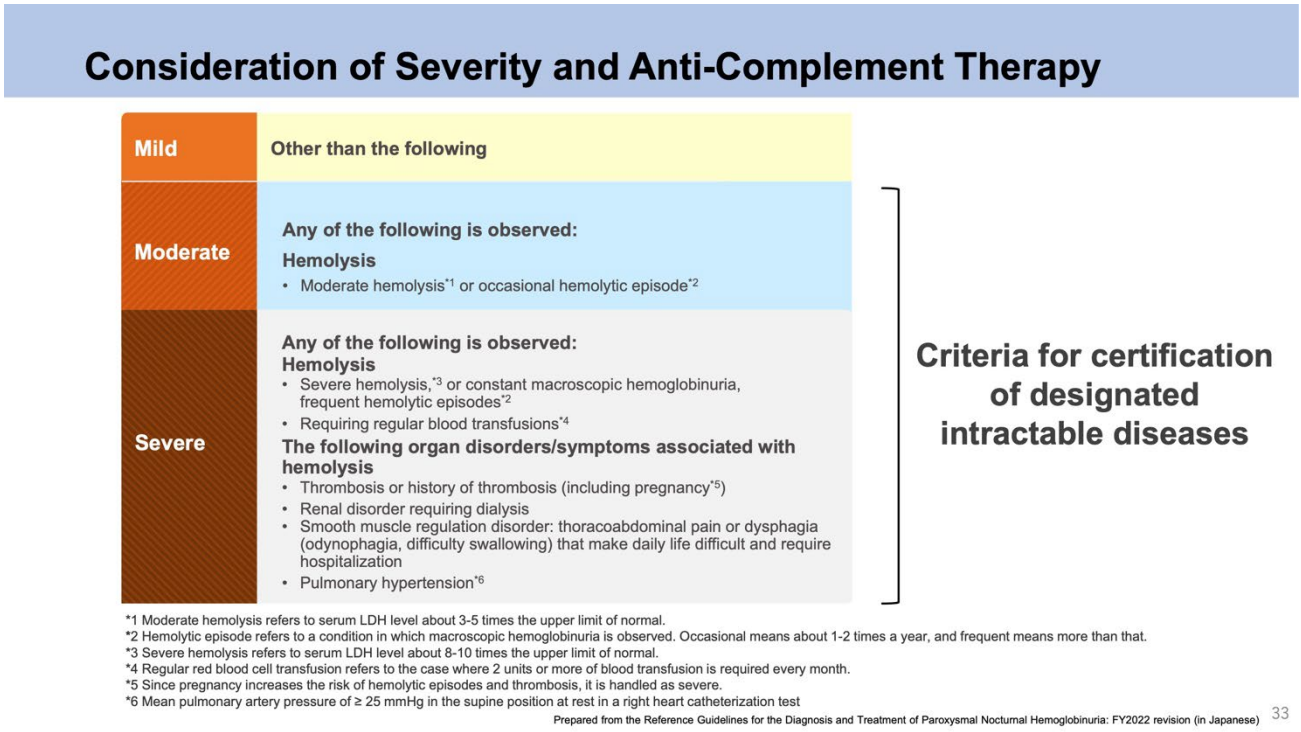
PNH is a rare disease, but we regularly produce a reference guide, which brings together doctors who see many patients in Japan. The latest version is in a form that was revised a few years ago, and we discuss diagnosis and other issues based on that.



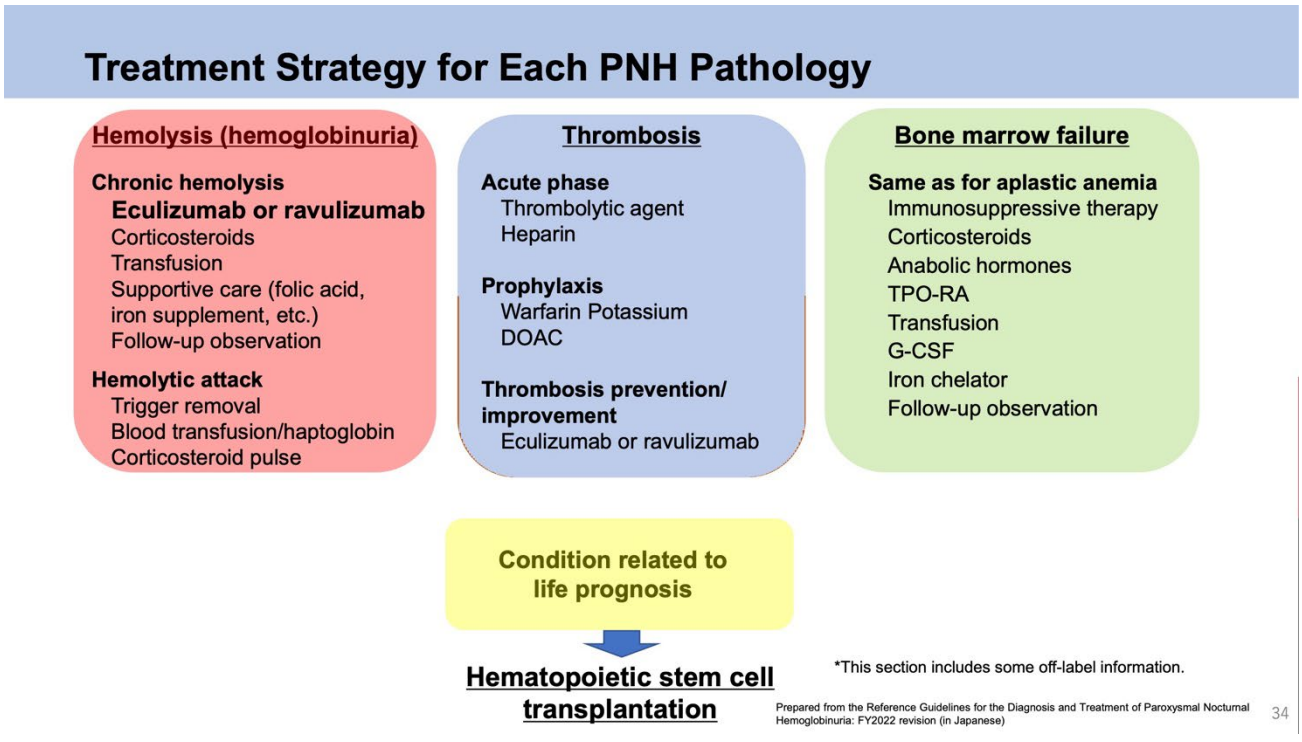
This shows the diagnostic criteria for PNH.

There are many details, but the important one is the GPI, which means that red blood cells deficient in GPI-anchored proteins are detected. The diagnostic criteria for PNH is based on the fact that if there are findings for hemolysis accompanying the detection of such red cells.

To determine the existence of hemolytic findings is to use a value of serum LDH. There are many others, but these two points are very important diagnostic findings.



PNH is classified into three levels of severity: mild, moderate, and severe. Those with moderate disease or higher are certified as a designated intractable disease, which means that the government will subsidize the cost of treatment after certification. There are various symptoms and details, but it means moderate or severe among these three levels.



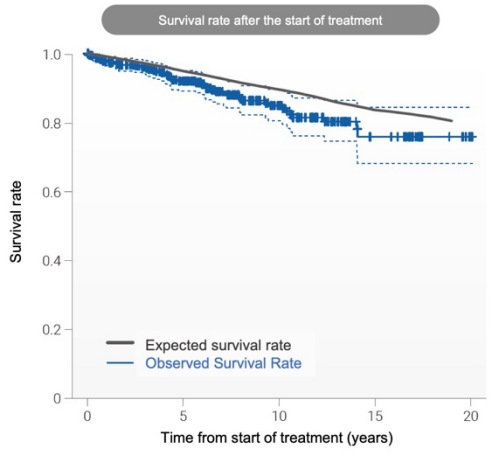
PNH can present with a wide variety of pathological conditions and pathological states, so it is necessary to treat PNH in a variety of ways accordingly.

If there is thrombosis or something similar, thrombolysis or prophylactic treatment for thrombosis will be necessary. Or if the patient has bone marrow failure, pancytopenia, or all the blood cells are going to decrease, then we would do the treatment accordingly, but if the symptoms are mainly hemolysis and anemia, there are two existing drugs that inhibit C5 and complement. Eculizumab and ravulizumab were two drugs which are most commonly used to control hemolysis.

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.**



Reprinted from Blood., 143(12), Kelly RJ, Holt M, Vidler J, et al. Treatment outcomes of complement protein C5 inhibition in 509 UK patients with paroxysmal nocturnal hemoglobinuria., 1157-1166., Copyright (2024) The American Society of Hematology, with permission from Elsevier.

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.]

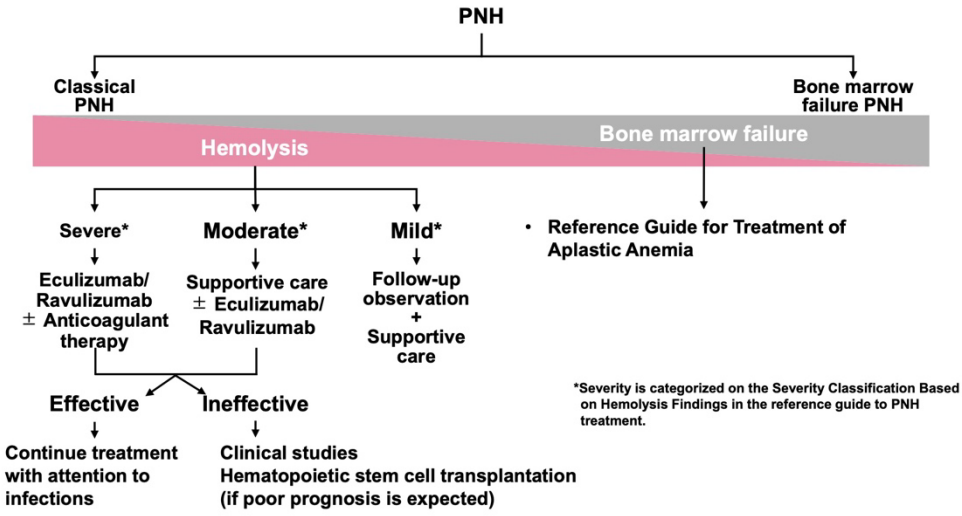
35

It has been more than a decade since the advent of eculizumab and ravulizumab, and it can be said that they have dramatically improved the prognosis for patients with PNH, as well as their symptoms and organ failure.

Here is the data on its prevention. This is the data from the UK. The expected prognosis and survival curve are shown in the black line here. This means that patients with PNH can now secure a prognosis that is comparable to the expectation. Eculizumab and ravulizumab have made it possible to ensure this.

Considering that before the introduction of these medications, half of the patients died within 10 years. This means that they have been able to achieve a very high level of effectiveness.

PNH Treatment Flowchart



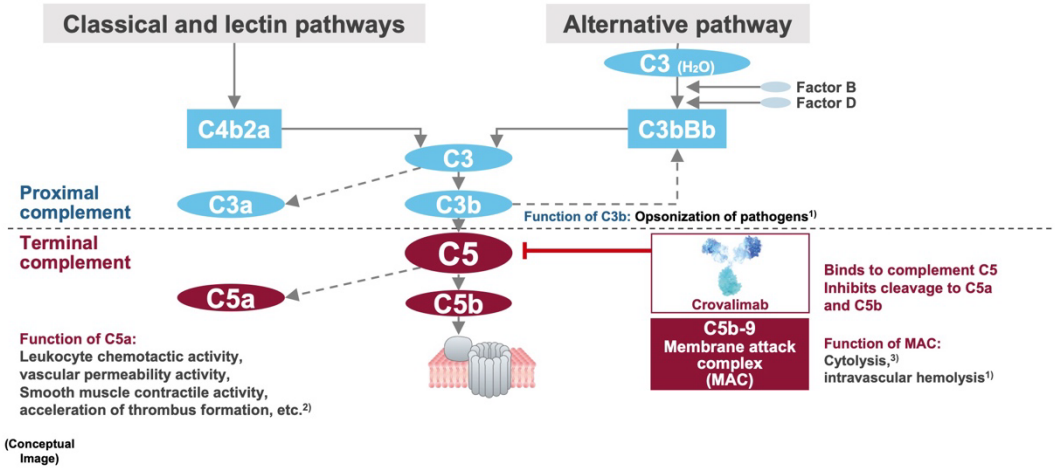
Working group for the development of the reference guide revision of diagnostic criteria and practice for paroxysmal nocturnal hemoglobinuria (PNH)
Reference Guidelines for the Diagnosis and Treatment of Paroxysmal Nocturnal Hemoglobinuria: FY2022 revision (in Japanese)

36

So, in the treatment of PNH, the current standard of care is to use eculizumab and ravulizumab when hemolysis is the main symptom.

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.**



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.

38

Next, I will introduce PiaSky clinical study.

It is crovalimab, PiaSky. Crovalimab is supposed to inhibit what is called C5 in the complement pathway. In the complement pathway, a series of reactions of several proteins occurs, but from the C5 point onward, a membrane attack complex is formed. The complex destroys red blood cells, but this drug prevents hemolysis by suppressing it with antibodies before that stage.

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

- Untreated Patients -

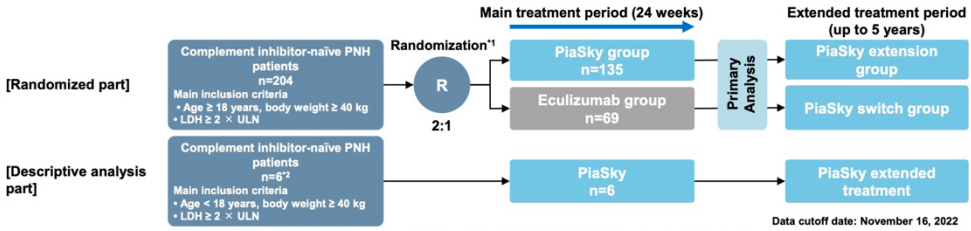
39

Here are two clinical studies I would like to introduce today. The first study is the COMMODORE 2 study with untreated patients.

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

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



*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)

40

This slide contains too much texts, but it says we have divided the untreated patients into two groups. The patients are divided 2:1 into the PiaSky and eculizumab groups, and then those in the eculizumab group are switched to PiaSky for extended treatment.

Global phase III study
(Study BO42162 [COMMODORE 2])

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

Evaluation data at the time of approval: Global phase III study (Study BO 42162) 41

The endpoints are patients who have achieved hemolytic control or avoided transfusion.

It might take time to read the test method in too much texts, but I hope you will take a look at the document you have on hand.

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

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) 44

This is the patient background.

There were not significant difference in the patient backgrounds between the PiaSky group and eculizumab group in terms of age, gender, race, and the percentage of blood cells with PNH.

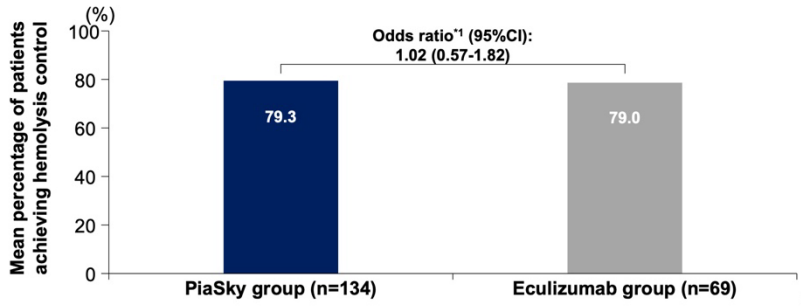
Global Phase III Study
(Study BO42162 [COMMODORE 2])

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

45

Next is the results.

This shows the percentage of patients who achieved hemolytic control from week 5 to week 25. The comparison was made between 134 patients in the PiaSky group and 69 patients in the eculizumab group, and there was no significant difference. It means that non-inferiority to the existing eculizumab was proven.

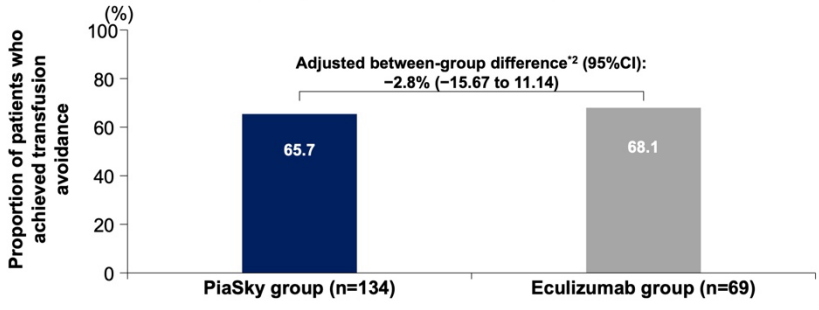
Global Phase III Study
(Study BO42162 [COMMODORE 2])

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

46

This is the percentage of patients who avoided transfusion.

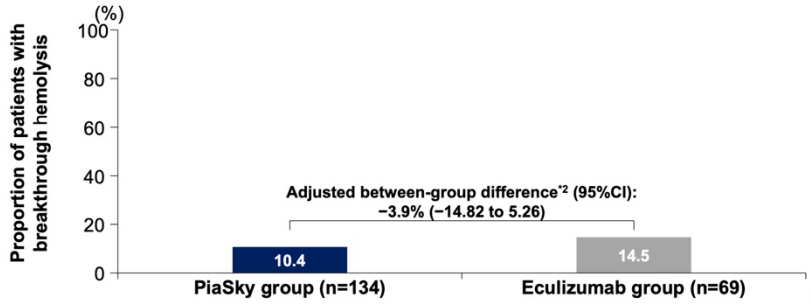
The percentage of patients who avoided transfusion during 25 weeks, which is six months, was 65.7% in the PiaSky group and 68.1% in the eculizumab group, so there was no significant difference.

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

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

47

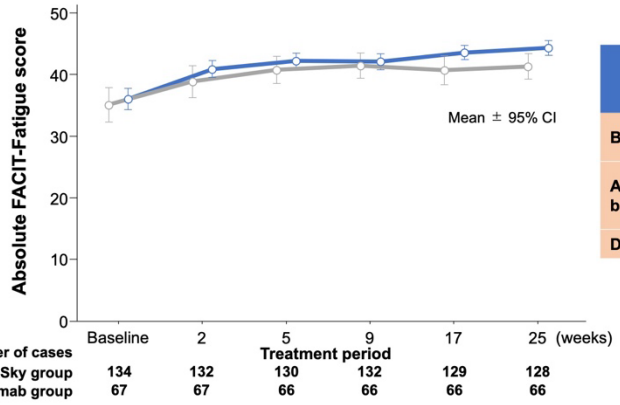
In the case of PNH, hemolysis is greatly accelerated by vaccines, infected patients, or surgery, and this is called a breakthrough hemolysis, and there was no significant difference in the percentage of such patients in the eculizumab and PiaSky groups.

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

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).**



	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.]

48

Improvement of the patient's symptoms is shown here.

The FACIT-Fatigue score, which scores patients' quality of life, symptoms, lethargy, fatigue, etc., is in gray line for the eculizumab group, but there was no significant difference between the eculizumab and PiaSky groups.

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

Safety

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

49

Next, safety.

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

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

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

50

As for the safety, eculizumab and PiaSky, both are drugs that inhibit complement. Complement is often associated with immunity, so infections can be a major problem.

Meningococcal infections are particularly problematic, and there were none regarding meningococcal infections. Otherwise, it means that there is no significant difference compared to the eculizumab group.

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

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%)
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)

51

This also means that there is no significant difference between the PiaSky group and eculizumab group in terms of serious adverse events.

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

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

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

52

There have been patients who have discontinued the drug or died.

There was one patient in the eculizumab group and one patient in the PiaSky group that resulted in discontinuation of treatment, but there was no specific relationship to the study drug. There have also been cases of death, including myocardial infarction and ischemic stroke, but all of which were determined to be unrelated to these drugs.

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

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

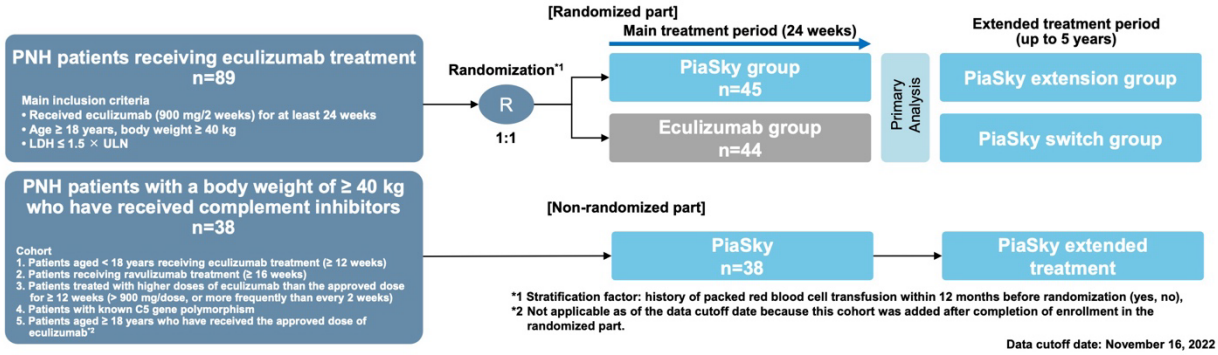
- Switching from previously treated patients -

53

The next is the study on cases switching from previously treated patients. This is a study of patients switching from previously treated with eculizumab.

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

Study Methods



[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)

54

In this study, the PNH patients on eculizumab treatment were divided into two groups. In this study, the patients were divided into 1:1, between the PiaSky group and eculizumab group, n=45 and 44, respectively.

The eculizumab group will be switched to PiaSky after 24 weeks, and receive PiaSky as extended treatment.

Please see the document at hand for details.

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

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

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

57

First, safety.

There was not much difference in the frequency of adverse events in either the PiaSky group or eculizumab group. There were no specific adverse events that led to discontinuation of these drugs.

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

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)

58

Meningococcal infection is also a very big problem here again, but neither group had meningococcal infection. It can be said that there were not so major serious infections.

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

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)

59

Adverse events that resulted in discontinuation of treatment or death.

At the time of this trial, there were no one who had to discontinue dosing in either group. No deaths have been reported.

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

Efficacy

- **Efficacy Analysis Set**

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

60

Next is efficacy. This is the efficacy in the switching group.

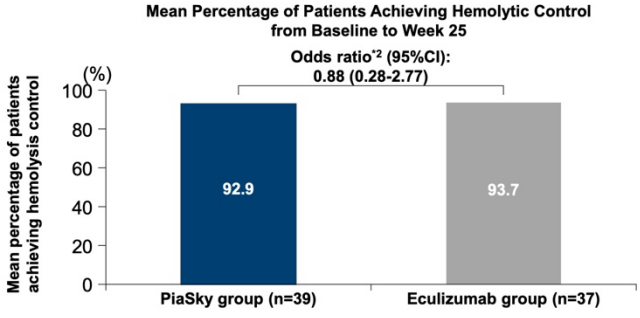
Global Phase III Study
(Study BO42161 [COMMODORE 1])

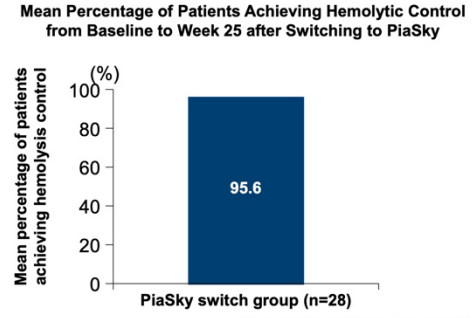
Efficacy

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).**





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)

61

The percentage of patients who achieved hemolytic control was also not significantly different between the eculizumab group and the PiaSky group.

The patients in the eculizumab group were switched to PiaSky after 25 weeks, which also shows a very high efficacy rate.

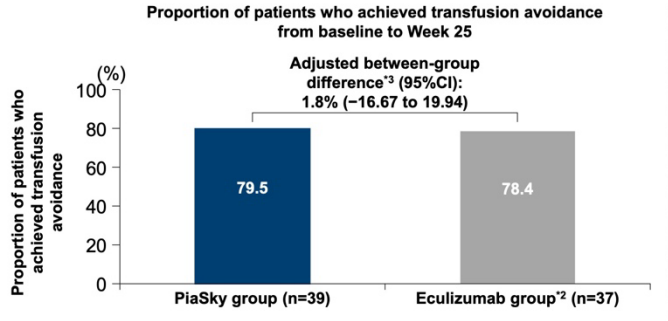
Global Phase III Study
(Study BO42161 [COMMODORE 1])

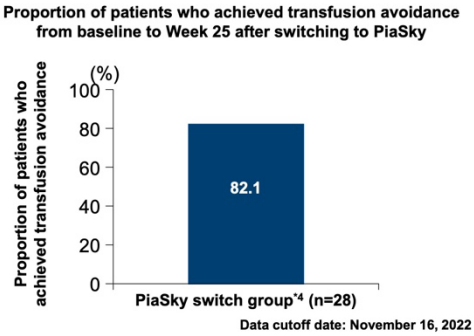
Efficacy

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).





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)

62

The same is true with respect to transfusion avoidance. This means that both the PiaSky group and the eculizumab group had similar and very high efficacy.

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

63

In the case of switching, one thing to be aware of when switching from existing eculizumab or ravulizumab to PiaSky is the immune complex reaction.

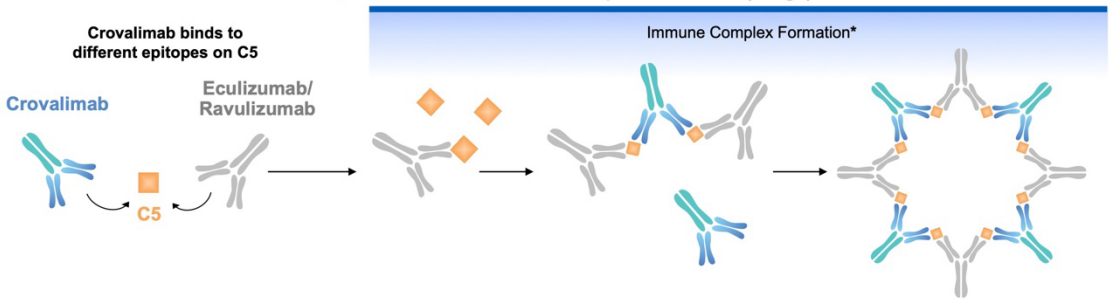
Immune Complex Reactions (When Switching Anti-C5 Antibody Preparations)

- 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.]

64

These are eculizumab/ravulizumab, and crovalimab/PiaSky, both are antibodies targeting C5, but the binding sites are different between these two drugs. If it differs, it is possible for a single C5 protein to bind both PiaSky and eculizumab.

Then, a large immune complex may form, such as this one, like holding hands. Then it might trigger a concern that this may lead to skin or kidney disorder, for example.

Integrated Safety Analysis
(COM1, COM2, COM3)

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)

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

*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

65

Here, this slide shows the safety analysis.

Integrated Safety Analysis
(COM1, COM2, COM3)

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

66

This shows the frequency of onset of this immune complex reaction.

This refers to the PiaSky switch group, but the reaction still comes out in a few percent. At grades one through three, there is no grade four, of course, but a total of a dozen percent of immune complex reactions may occur at grades one through three.

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

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)

67

Clinical symptoms due to immune complexes are skin symptoms. There is a possibility of skin disorders such as erythema, petechia, and rash, as well as nervous system disorder and renal disorders, but in each case, as

the existing eculizumab and ravulizumab disappear from the blood levels, these immune complex reactions will also disappear. Therefore, I do not think that it will be very serious.

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 69

Finally, I would like to introduce a case that participated in the clinical trial.

The case is a male patient in his 50s. He has a very long medical history and was diagnosed 26 years ago. At that time, LDH was over 3,000 and various tests were performed to diagnose PNH.

Since then, the patient had a mild disease and was followed up without treatment, but his anemia and LDH gradually worsened, and he was considered eligible for anti-complement therapy.

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+

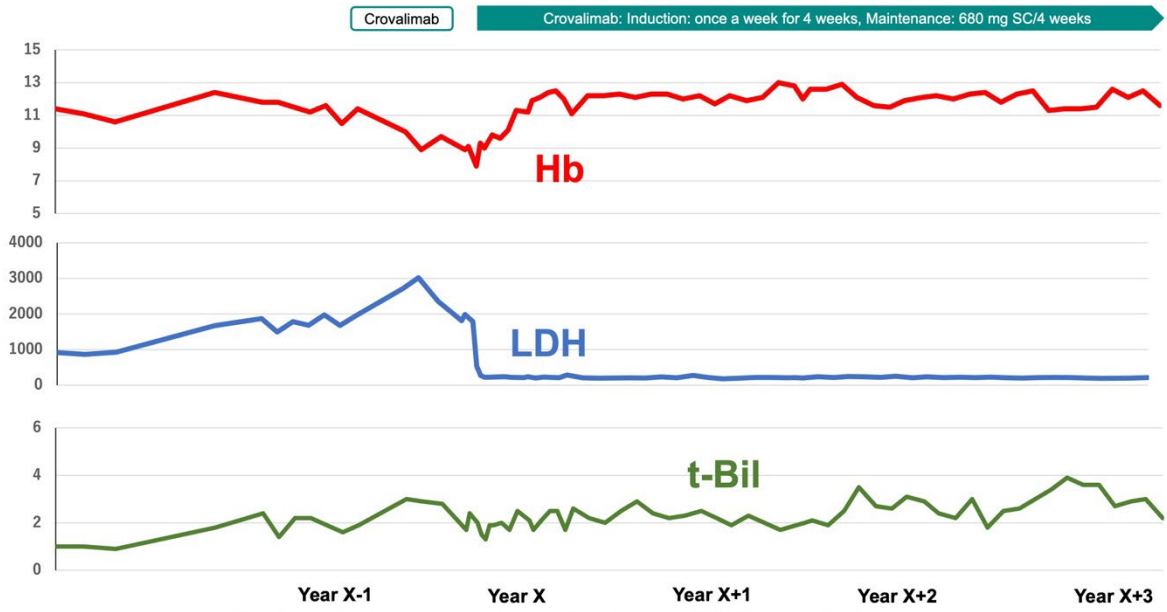
PNH blood cells	
PNH-type red blood cells	42.94%
PNH granulocytes	88.64%

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

70

Before dosing crovalimab, PiaSky, his hemoglobin level was 7.9 and LDH was about 2,000. The urine occult blood was 3+, which indicated the existence of hemoglobinuria.

Treatment Course After Administration of Crovalimab



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

71

This is the treatment course.

Before administrating crovalimab, the hemoglobin and LDH levels were very high, but after crovalimab was introduced, the hemoglobin level rose and the LDH quickly dropped to near normal range. Since then, the situation has been progressing without major problems.

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

72

The drugs currently available in Japan for the treatment of PNH are listed here.

PiaSky, eculizumab, and ravulizumab target C5. Currently, these three drugs are available as first-line treatments. Eculizumab and ravulizumab were the mainstay of existing treatments, and now PiaSky is also another option.

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**

73

Crovalimab, PiaSky, is a subcutaneous medication, whereas eculizumab and ravulizumab are administered as an intravenous infusion. The method of administration is very different from the previous medications, so here are some expectations for this drug.

It gives patients more options for the method of administration. There are patients who do not like intravenous drips, and I think it would be very good for such patients.

Then, although I did not mention it much, eculizumab and ravulizumab are ineffective for the patients with C5 gene polymorphisms. Since the binding sites are different, it can be said that PiaSky can be administered to such patients.

Then, since this drug is injected subcutaneously, it is administered immediately, thus reducing administration time and hospital stay. As PNH is a very chronic disease that requires long-term treatment, they need to be able to perform their daily routines properly. In that sense, this is very good news for busy patients.

For example, there are a certain number of people who do not have many blood vessels or who have difficulty with intravenous infusion. During the maintenance phase, PiaSky will give further benefit for these people as they do not need intravenous infusions

Also, IV rooms in large hospitals are always crowded. Patients have to wait for a long time, and it is hoped that the use of subcutaneous injections will shorten the infusion time and reduce the waiting time for other patients.

That's all from me. Thank you very much for your attention.

Miyata: Thank you very much.

Question & Answer

Miyata [M]: We are now moving on to the Q&A session.

We apologize for the inconvenience, but in order to encourage more people to ask questions, we would appreciate your cooperation in limiting the number of questions to two per person.

Please note that the audio of your questions, along with the presentation, will be posted on our website at a later date.

Muraoka [Q]: Thank you. I am Muraoka from Morgan Stanley MUFG Securities. I would like to ask Dr. Obara.

It was very informative to have a summary of the profiles of the various new drugs. In addition, how will you use the different medications, including iptacopan, which will come out in the future?

I think you probably see a lot of patients, so if you were to switch existing patients, how many of them would you want to use PiaSky, for example, and if they are new patients, how would you use it, how would you treat them, and how would you position PiaSky within that context? If possible, it would be helpful if you could tell us what percentage of patients you would like to use this.

Obara [A]: As I showed you earlier in the slides, patients who can benefit from PiaSky and subcutaneous injections are those who are busy or those who are reluctant to use intravenous infusions. I would be willing to present it to such patients.

Currently, we are treating about 22 cases of PNH at our facility, five of which are in clinical trials. We are thinking of switching one or two more patients, so it is difficult to predict what will happen in the near future. We believe that 30% to 40% of patients with PNH using C5 antibodies may be treated, as a matter of fact.

There are medications such as iptacopan, which was recently approved for refractoriness. I think that for refractory patients, other medications such as iptacopan and danicopan should be used in combination. We believe that these medications are not intended for the level of hundreds of patients as targets.

As for danicopan, it will probably go at a level of a few dozen for the time being. As for the pegcetacoplan, I guess it will also go on the level of dozens of patients.

Iptacopan is an oral medication, so there is still some unpredictability, but oral medications can be forgotten to take, and PNH can cause hemolytic attacks. For this reason, I think it may not be a good for those who are not very compliant with oral medication. I think it can be said that intravenous infusion or injections are more reliable than orals, so for such patients, PiaSky can be given once every four weeks, or ravulizumab once every eight weeks, so I think that those who continue to use the drug will continue to use it and go on with it.

Muraoka [Q]: Thank you. Is the risk of forgetting to take it still a factor of considerable concern for you?

Obara [A]: Yes, exactly.

Muraoka [Q]: Then I know this is a bit of a mean question, but PiaSky only needs to be taken once a month, right? If this frequency interval is long, something like forgetting to visit the hospital, wouldn't that be too much of a risk?

Obara [A]: In our experience, once every four weeks, there is almost no chance of forgetting to visit the hospital. One is that patients are still aware that it is an intractable disease, so many patients have a high awareness of such a disease, since many of them are quite late in discovering it. Also, this disease is designated as an intractable disease, and they will show the handbook every time they visit the hospital. Therefore, I think it is unlikely that patients will forget to visit the hospital.

Muraoka [Q]: Thank you. I was surprised when you said earlier that 30% to 40% of the patients would be eligible for crovalimab, which is a rather large number. Because of the immune complex thing, I was wondering if patients hesitate when they have that, but is that not the feeling you have? Is the ease of use of subcutaneous injections much appreciated?

Obara [A]: We have five patients in the trial, but fortunately none of them had immune complex reactions. I suspect that most immune complex reactions can probably be handled by eczema, follow-up, or steroid application.

Or, over time, the drugs such as ravulizumab and eculizumab that remained in the blood will gradually decrease, so there will be convergence. We think that it will probably take roughly a month, a month or two at the most, to converge, so while immune complex reactions may occur, we do not think it is very likely that this will be very much an obstacle as a treatment choice.

Muraoka [M]: I understand. Thank you.

Yamaguchi [Q]: Thank you very much. I'm Yamaguchi from Citigroup.

As mentioned in the presentation, there are only a few patients, but there was a discussion about genetic polymorphisms, which in Japan is 3%, but I wonder if there are ethnic differences or not. Is that something that you already know before you start the treatment, or is it something that you find out after you treat them and then switch in a hurry? Or is that pretty much the topic in terms of treatment? Please tell us this point first.

Obara [A]: It is said that there are some ethnic differences in genetic polymorphisms. In Japan, it is said to be 3% to 4%, but although I have not been able to find out the percentage worldwide, there are some ethnic differences, and it is possible that the percentage is relatively high among Japanese people.

Since genetic polymorphisms are not examined by screening tests, it means that it is not possible to know in current practice whether a patient has a genetic polymorphism before treatment, for example. If you give eculizumab or ravulizumab to a person with a genetic polymorphism, the LDH or hemolysis levels would not subside at all, which is usually the case after one or two doses, and we just guess it would be.

For those without genetic polymorphisms, eculizumab and ravulizumab are effective in significantly reducing hemolysis, so it is easy to guess whether the patient has a genetic polymorphism or not. For such people, I think PiaSky is a very good adaptation.

I don't mean that genetic polymorphisms cannot be tested, but since the screening test is a genetic test, it is not yet realistic in terms of cost and various other aspects and also in terms of frequency.

Yamaguchi [Q]: This goes along with the previous question, but I thought there is no incentive to change existing treatment for patients who have been on ravulizumab for a long time, for example, for maintenance, if they have settled down. That's why I asked the question.

Still, some may change because one of the options, subcutaneous injection, is better, but what do you think?

Obara [A]: There is quite a variety in the stability of treatment effects. I believe that many facilities have very stable patients who only come once every eight weeks for an IV. If you are a busy person and don't like the idea of monthly, I think you would probably prefer the existing treatment and ravulizumab as it is.

For those who don't like waiting for an hour IV infusion, or waiting in front of the IV room, PiaSky may be a good option. I think the strong point of PiaSky is that it can change the patient's lifestyle according to their wishes.

Yamaguchi [M]: Thank you.

Saga [Q]: I am Saga, a freelance writer. Thank you. I also have a related question.

Do you have any such data on the 900 to 1,000 patients who have been using C5 so far, and these patients are mostly already on ravulizumab nationally?

Obara [A]: I can't give you an exact figure right now because it includes data from other companies, but I think that more than 95% of them are in ravulizumab.

Saga [Q]: I see. Second, I would like to know more about hemolytic attack. You mentioned vaccines and patients forgetting taking medication, but what triggers this, and what can go wrong with a hemolytic attack? Also, since you call it an attack, does it subside spontaneously? Please tell us more about it.

Obara [A]: Hemolytic attacks occur in situations where complement activity is increased. The most common case of increased complement activity is, for example, infection. The rest is surgery. In other words, the hemolysis is enhanced in situations where immunity is needed. These days, it is vaccines. The COVID-19 vaccine or mRNA vaccine is quite potent in its ability to induce inflammation, so that it becomes a problem for both treated and untreated patients with PNH.

That is how hemolytic attacks are triggered with many reasons. Those who are prone to get anemia, for example, even a slight cold can cause anemia quite a bit. If a hemolytic attack occurs, there are some degree of problems, but in severe cases, anemia can quickly progress and several units of blood transfusion may be necessary, or the patient may develop renal failure or acute renal failure.

In some cases, patients are not aware of the disease until it has progressed to a very advanced stage, and in other cases, it occurs very quickly, so it is important to be very careful.

Saga [Q]: In the clinical trial you presented today, the frequency of hemolytic attacks was shown, but is this roughly the same as what you have seen in your actual clinical experience?

Obara [A]: Hemolytic attacks during treatment include minor hemolytic attacks, so if we include minor hemolytic attacks, the frequency of hemolytic attacks will generally look something like that.

Hashiguchi [Q]: My name is Hashiguchi from Daiwa Securities.

I think you mentioned earlier that about 30% to 40% of the patients could be treated with PiaSky, but I think you meant to include the hurdles for existing patients to switch. How would you approach for new patients? It may not be a disease that brings in so many new patients, but when you first introduce antibody therapy, what kind of option would you make?

Obara [A]: About 30% to 40% is about the future, and I don't really think about 300 or 400 out of 1,000 existing patients would be switched right away, for example. It also means that as we gradually explain the options, I wonder there might be patients who will start to think in such a way.

As for first-time applicants, we will probably show them flat. I would ask like if you prefer once every eight weeks with IV or even once every two weeks with IV. Or there is also the option of subcutaneous injections once every four weeks, which I think it would be simple like that.

For those who don't want to come too often, they might say once every eight weeks would be fine, and for those who want to finish soon, once every four weeks is fine. That's pretty much a trade-off of time and frequency, so it's hard to say. I think there are quite a lot of patients with diseases that come in once every four weeks, so I think that for those patients it would be well-balanced, or you never know until we try it.

Hashiguchi [Q]: So, you are still trying to get a feel for which is which and how much?

Obara [A]: Yes. I don't know the feeling yet, but when I refer people to clinical trials and such, there are quite a few who say it would be fine if it were injected subcutaneously once every four weeks. I do not think it is likely that the number of patients will be overwhelmingly concentrated on one side or the other.

Hashiguchi [Q]: Is my understanding correct that you do not feel there is much difference in terms of efficacy and safety?

Obara [A]: I don't think there is a difference.

Matsubara [Q]: My name is Matsubara from Nomura Securities. Thank you. I have two questions.

The first is about iptacopan. In your earlier explanation, I think you mentioned that the adherence to the medication may be a problem and that the medication may not be taken as well as it could be. On the other hand, I think you mentioned that PNH is recognized as an intractable disease and that it is possible to have a handbook. With that in mind, could you please explain again that iptacopan may not be widely used in the future?

Obara [A]: I'm not saying that the iptacopan treatment will not proceed. Our concern is that patients may forget to take their medications.

Since this is the first PNH medication that can be controlled by oral medication alone from the initial onset, it is difficult to predict what to expect.

With oral medications, it is inevitable that some patients will forget to take their medications. It is difficult to say 100%. In the case of PNH, patients are often aware that it is an intractable disease and that it is very difficult to treat, so we expect that adherence will be much better than patients with blood pressure medication, for example. I hope you understand that it is honestly impossible to know until we try.

However, the most basic pathology of PNH is to suppress the membrane attack complex, and I think that the consensus for treatment in the immediate future is likely to be to first suppress C5. Oral medication appears to be very convenient, but it is hard to predict that it will flow dramatically into iptacopan. That's all from me.

Matsubara [Q]: I understand very well. Thank you. Second, in your slide, you mentioned that hematopoietic stem cell transplantation (HSCT) is performed in patients with poor prognosis. What is the percentage of patients who do HSCT with this C5, C3, or other drugs, and as a first prescription, is the reason for not doing HSCT due to lack of donors or something like that?

Obara [A]: I think there are almost no patients who do a HSCT if they are doing well to some extent on eculizumab and ravulizumab. The most likely candidates for HSCT are those patients who have a strong hematopoietic insufficiency that is those who have very low white blood cell counts and platelets. Since eculizumab and ravulizumab do not work on platelets and white blood cells, anti-complement therapy does

not work, so such patients have to take some form of medication that stimulates hematopoiesis. The ultimate form of this process is HSCT.

I believe that those who are currently diagnosed with PNH and who will undergo a HSCT are almost always those who would be diagnosed with hematopoietic failure or aplastic anemia.

HSCT is a very high-risk treatment. Compared to eculizumab and ravulizumab, the treatment has a considerably higher risk. The treatment is such that you have to be prepared for 10% to 20% of deaths in about one to two years. In light of this, the treatment with eculizumab and ravulizumab is effective in most patients, so I think the consensus is to start with anti-complement therapy for those whose main symptom is hemolysis.

Zhou [Q]: I'm Zhou from Goldman Sachs.

I would like to ask Dr. Obara. You say that the effect was obtained even in those with genetic polymorphisms, but what percentage or how many people were included in this trial overall? This is the first point I would like to confirm.

Miura [A]: I will answer your question. We have six patients in this Phase III study.

Zhou [Q]: Thank you very much. The second question, I think it is a great result that non-inferiority was demonstrated in this non-inferiority trial design. Among them, there were still a certain number of patients who did not benefit from the treatment.

In that case, when you think about what is missing, do you have any future drug targets or molecules that you are looking forward to? That's all from me. Thank you.

Obara [A]: As with eculizumab and ravulizumab, there are a certain number of patients for whom it does not work. There are a wide variety of causes, but one of the most common causes is a severe hematopoietic deficiency, or hematopoiesis itself is so poor that even if hemolysis is suppressed, the hematopoiesis level does not rise very high.

The other is patients who have renal anemia due to the poor kidney function, patients whose anemia does not improve because they do not have much erythropoietin, patients whose anti-complement therapy medications themselves may not be somewhat effective, and so on.

I think it is the same for both eculizumab and ravulizumab that roughly 10% to 20% of the patients will have poor efficacy. I think PiaSky is also almost the same in that regard. That's all from me.

Zhou [Q]: Thank you very much. I would like to ask a follow-up question to the answer you just gave. In that case, for example, in the case of patients with severe hematopoietic insufficiency or renal anemia, do you think it will be difficult to improve the overall therapeutic effect in the future, or do you think it is possible to improve the therapeutic effect by using some kind of concomitant medication? I am sorry, but I would appreciate your confirmation.

Obara [A]: There are various measures that can be taken depending on the cause. If the patient has renal anemia, we might give erythropoietin or a HIF-PH inhibitor, which is a medication that stimulates erythropoietin. There are my patients who are doing this. I believe that some of them also use aplastic anemia treatment in combination if hematopoiesis is poor.

Also, there are some cases in which the use of C5 antibodies leads to extravascular hemolysis not intravascular hemolysis, so I think there are cases in which such patients may use iptacopan, as mentioned earlier, or other

novel antibody drugs. So the remaining 10% to 20% of patients who do not respond well are the ones that we must be looking for, I think it is quite important to understand and consider the pathophysiology of the disease, and the various types that are available.

Zhou [M]: I understand very well. Thank you.

Mamegano [Q]: Hello. My name is Mamegano from BofA Securities. Thank you.

I have two points. The first point is that ravulizumab is administered once every eight weeks, while PiaSky is administered subcutaneously once every four weeks. I heard what you said earlier about the frequency of patients coming to the hospital, but even if they come once every eight weeks, I think there are still concerns about side effects first, so I think they come once every two weeks or once every four weeks. I wonder if there is any benefit to ravulizumab once every eight weeks. Could you explain about that point? Thank you.

Obara [A]: It is true that at the beginning of anti-complement therapy, patients usually come in after two or four weeks, and in my case, for the time being, many patients come in once every four weeks even though they are administered once every eight weeks for a while. For those who are really stable, we ask them to come in roughly every eight weeks. In other words, there are many patients who come only on the day of intravenous infusion administration with blood tests may be sufficient.

The effects of PNH treatment are varied, and while there are some unstable patients, there are quite a lot who are very stable and for whom once every eight weeks is already sufficient.

Mamegano [Q]: I see. Thank you. The second point, I would also like to confirm about the iptacopan matter. Looking at the results of the clinical trials, I thought it seemed to be quite effective, even though it is an oral drug. I was wondering if patients might flow in that direction.

I think you mentioned earlier that it is quite important to suppress C5, and considering that, I wonder if the current C5 antibodies are quite sufficient in terms of efficacy. I would like to know the level of clinical demand, or rather the level of efficacy required. I was wondering if you could tell me about the C5 antibodies, if they are as effective as they are now, I thought it doesn't have to change to an oral formulation where compliance is a concern. Sorry, please reply to this question.

Obara [A]: I think you make a very perceptive point. As for the current treatment with ravulizumab and eculizumab, if we look only at the therapeutic effect, I think that basically not too many, but at least about 80% of the patients will be quite satisfied. I think PiaSky will probably be the same as well.

Therefore, if such patients, who can be controlled without fail if they receive intravenous infusion once every eight weeks, it is difficult to imagine that everyone among them will switch to oral medication.

I wonder if iptacopan could be considered to some extent in the case that it is still better to take it orally or patients who do not want to be stabbed or who do not have many blood vessels left. I think this is a good indication for those.

As I mentioned earlier, I think it might be a good idea to try it for those who have very severe extravascular hemolysis or for those for whom extravascular hemolysis would be a problem as a therapeutic effect. We are wondering whether many patients who are overwhelmingly getting satisfactory treatment results with C5 antibodies would actively change their current style of hospital visits, and we are wondering whether there are not many such patients.

Since iptacopan is taken orally, I think it has enough advantage to be switched to iptacopan, and I think there is a possibility that the switch may proceed to some extent. However, iptacopan is a very expensive drug, so

it is not likely that all out-of-hospital pharmacies will be able to prepare it, so there may be some inconvenience.

Mamegano [M]: I understand very well. Thank you.

Wakao [Q]: I'm Wakao from JPMorgan. I'm sorry, this is the similar question.

I'm afraid this is the same as the person who asked the question just now, but regarding the effectiveness of iptacopan. Can I understand that from your point of view, the clinical trial data here was not that surprising? After all, many people probably wondered if this was better when they saw this efficacy, so it would be very helpful if you could just comment on this part.

Obara [A]: Iptacopan has been very highly effective. We see from the clinical trial data that it is probably very impressive in terms of side effects. But I think that is one thing that we don't know yet because we have not directly compared the difference with the C5 antibody, the difference in efficacy. So, it is probably not very likely that patients will switch medications based solely on the data itself that is available in iptacopan.

I believe that the switch will probably be based on the patient's wishes, whether there is extravascular hemolysis and whether the hospital or pharmacy is able to accommodate the prescription, and the switch might proceed a bit. I think it is excellent data, but it is within our expectations to some extent.

Wakao [M]: I understand very well. Thank you.

Hashiguchi [Q]: I am sorry to ask questions again. I'm Hashiguchi from Daiwa Securities.

I think you mentioned that it depends on the patient as to whether they would prefer a one-hour infusion every eight weeks or a subcutaneous infusion every four weeks in comparison to eculizumab. I think that there are quite a few cases of self-injection or home injection of subcutaneous injections for the treatment of other diseases. I felt that if the patient could do it at home that would be the best.

In the case of this disease, I was wondering if it is necessary to have patients visit the hospital on a regular basis for checkups, or if there is any resistance to self-injection, or how much customary it is. There might be difference between Japan and overseas, and we are also interested in overseas sales, so I wonder if you could comment a little more on these issues.

Obara [A]: I think the future benefit of subcutaneous injections will be the possibility of self-injection, as you mentioned. Since PiaSky is a 2 cc x twice treatment with subcutaneous injection, self-injection may be feasible enough in the future. I think the younger patients will probably move onto that form.

Then, for those who are very stable, there is a possibility that, for example, they could do it once a month at their own home already, and blood sampling and blood tests could be done once every three months.

I think it is possible to have the somewhat unstable patients come in once a month, but I think that will vary somewhat from patient to patient.

Hashiguchi [Q]: How many of the 1,000 patients in your hospital would be satisfied with a visit once every three months?

Obara [A]: It depends quite a bit on the stance of the hospitals. For those who are very stable, I think that a good percentage of patients will be in a position to say that they are fine with the long-term interval. Based on my experience with ravulizumab, there are about half of the patients who are fine with once every eight weeks.

Hashiguchi [M]: Thank you very much.

Muraoka [Q]: I am Muraoka from Morgan Stanley MUFG Securities. Thank you for letting me ask questions for the second time.

This may be an off-the-cuff question, but I believe that this PiaSky, crovalimab, is also moving forward to add the indication for aHUS in the future. Sorry, I don't know if this is the disease you also cover or not, but if you see a lot of patients with aHUS, there are no data on aHUS, but what do you think is the position of easy-to-use drug in treatment?

Obara [A]: I have no patients with aHUS currently. I don't, but I think it would be a good indication. However, aHUS is often found in very serious cases at the onset, and it will need hospitalization for quite a while. I think it is still too early to say whether this would be a good indication simply because it would probably need to be considered, including whether it would be needed on a regular basis after discharge from the hospital. However, in terms of pathology, it is theoretically possible to suppress the disease by suppressing C5, so I think that in the future we may be in a situation where we can propose crovalimab alongside other options.

Muraoka [Q]: Thank you. I also have a question for Ms. Miura. What is your current image of the development schedule for the self-injection mentioned earlier?

Miura [A]: Regarding self-injection in Japan, we have been working with the authorities to enable self-injection. However, because of the 14-day prescription limit in Japan, we are currently unable to provide a once-every-four-week treatment, which means that self-administration is not possible at this time.

We would like to expand the self-injection of this drug as much as possible, considering the benefits to patients. We have been working with the authorities to adopt such a system, but we still need to go through some more procedures to completely allow self-administration at home. After proceeding with this, the ban on 14-day prescriptions will basically be lifted after one year, and we are hoping to achieve that timing. However, we have not yet reached the final stage of the process, so I hope you understand the situation.

Muraoka [Q]: I see. Do you mean that there is a possibility that in just one year, hopefully, self-injection will be possible?

Miura [A]: Yes.

Muraoka [M]: Thank you.

Saga [Q]: Excuse me. I am Saga, a freelance writer.

Regarding the survival rates, you have shown us the data from overseas, but do you have any data from Japan?

Obara [A]: There is actually no recent data on overall survival in Japan. So, I think we will be collecting them from now on.

Saga [M]: Thank you very much.

Miyata [M]: Thank you. There seems to be no question, so we will end the Q&A session.

This concludes the information meeting on PiaSky of CHUGAI PHARMACEUTICAL.

If you have additional questions, please contact the corporate communications department separately. The number and email address are provided on the last page of the presentation materials.

Please note that a survey will be available on the desk for those in the audience in the venue and on the Zoom for those participating via Zoom. We would appreciate your cooperation in this regard for future reference.

Thank you for joining us today despite your busy schedule. Thank you very much.

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