About Hemophilia A[1,2]

Hemophilia is classified into two types, hemophilia A and hemophilia B. Hemophilia A is a bleeding disorder caused by a deficiency of a protein called coagulation factor VIII (FVIII), which is essential for normal blood clotting. As a result, people with hemophilia A have difficulty forming blood clots. Hemophilia A can be either congenital, caused by an inherited genetic abnormality, or acquired, which develops later in life. Congenital hemophilia A predominantly affects males and occurs in approximately one in 5,000 male births. Occurrence in females is extremely rare because congenital hemophilia A is an X-linked recessive disorder.

Symptoms associated with bleeding in hemophilia A vary, but a characteristic feature of the disease is the frequent occurrence of internal bleeding that is not externally visible. Internal bleeding can lead to the formation of hematomas, or localized collections of blood, which may compress surrounding nerves and blood vessels, causing pain and functional impairment. Bleeding commonly occurs in joints such as the elbows, knees, and ankles, as well as in muscles, often resulting in swelling, warmth, and severe pain. In patients with severe hemophilia A, bleeding into joints and muscles can occur even during normal daily activities. Repeated joint bleeding may lead to progressive joint damage, significantly affecting quality of life.

Since around 2000, prophylactic treatment with regular replacement of the missing factor VIII has become widely adopted. However, this approach requires intravenous infusions as frequently as once to several times per week. In addition, people with hemophilia A who developed an immune response to factor VIII, a non-self protein, resulting in the formation of factor VIII inhibitors, faced significant treatment challenges due to the limited treatment options available to them.

Sources:

1. Michael U. Callaghan, et al. Long-term outcomes with emicizumab prophylaxis for hemophilia A with or without FVIII inhibitors from the HAVEN 1-4 studies https://ashpublications.org/blood/article/137/16/2231/474603/Long-term-outcomes-with-emicizumab-prophylaxis-for (accessed September 2026)
2. Japanese Society on Thrombosis and Hemostasis (JSTH), Clinical Practice Guidelines https://www.jsth.org/wordpress/guideline/index.html (in Japanese only, accessed September 2026)

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Number of People with Hemophilia
According to the World Federation of Hemophilia (WFH) Annual Global Survey 2024, a total of 224,353 people with hemophilia A were reported across 135 countries worldwide, comprising 202,548 males, 8,223 females, and 13,557 individuals of unspecified sex. Considering the global population and limitations in diagnosis and reporting, the actual number of people with hemophilia A is estimated to be several times higher than the reported figure.[1]

In Japan, Nationwide Survey of Patients with Coagulation Disorders 2025 reported 3,813 people with hemophilia A, including 3,685 males and 128 females.[2]

Congenital hemophilia A follows an X-linked recessive pattern of inheritance and therefore predominantly affects males, occurring in approximately 1 in 5,000 male births. Females are usually carriers, although rare cases of affected females have been reported.

Sources

1. World Federation of Hemophilia (WFH), Annual Global Survey 2024 https://www1.wfh.org/publications/files/pdf-2588.pdf (accessed September 2026)
2. Nationwide Survey of Patients with Coagulation Disorders 2025 (Japan) https://api-net.jfap.or.jp/image/data/blood/r07_research/r07_research.pdf (accessed September 2026; in Japanese only)

Symptoms
The severity of hemophilia A is classified according to the activity level of coagulation factor VIII. With normal factor VIII activity in healthy individuals defined as 100%, hemophilia is categorized as severe when factor VIII activity is less than 1%, moderate when it is 1% to 5%, and mild when it is more than 5% to less than 40%. Hemophilia A can cause a variety of bleeding symptoms, but internal bleeding is particularly characteristic of the disease. Internal bleeding can lead to the accumulation of blood within tissues, forming hematomas that may compress surrounding nerves and blood vessels, causing pain and functional impairment. Bleeding frequently occurs in joints such as the elbows, knees, and ankles, as well as within muscles. These bleeding episodes may result in swelling, warmth, and severe pain. In people with severe hemophilia A who do not receive preventive treatment, bleeding into joints and muscles can occur during ordinary daily activities. Repeated joint bleeding is known to cause progressive joint damage (hemophilic arthropathy), which can significantly impair quality of life (QOL).

Treatment
Hemophilia A is usually diagnosed during childhood, and treatment generally continues throughout life. Historically, the standard treatment has been factor replacement therapy, in which the missing coagulation factor VIII is administered intravenously. Factor replacement therapy can be categorized into:
- On-demand treatment: administration of factor VIII in response to a bleeding episode.
- Pre-event prophylaxis: administration before activities associated with a high risk of bleeding, such as sports events or excursions.
- Regular prophylaxis: routine administration regardless of whether bleeding has occurred.

Before the introduction of emicizumab, the majority of people with hemophilia A in developed countries received regular prophylaxis.

Regular prophylaxis with factor VIII products typically requires intravenous injections administered at home once or multiple times per week. However, because factor VIII is absent in people with hemophilia A, the administered factor VIII may be recognized as a foreign substance by the immune system. This can lead to the development of neutralizing antibodies against factor VIII, known as factor VIII inhibitors. When inhibitors develop, the effectiveness of factor VIII products is reduced, and conventional prophylactic treatment may no longer be effective. To address these challenges, newer subcutaneous therapies that do not rely on factor VIII itself have emerged. The first of these was Hemlibra (emicizumab), an antibody drug designed to substitute for the function of factor VIII.

On-Demand Treatment
On-demand treatment involves administering coagulation factor products after a bleeding episode has occurred. For bleeding into joints or muscles, treatment is often combined with the RICE approach: Rest, Ice, Compression (using bandages or supportive devices), Elevation. The dose of coagulation factor required to achieve hemostasis varies depending on the patient's body weight, the location and severity of bleeding, and the individual's coagulation factor activity level.

Regular Prophylaxis
Regular prophylaxis involves scheduled administration of coagulation factor products. Depending on the product used, treatment may be given once every few weeks, once per week, several times per week, or even daily. The goal of prophylactic treatment is to maintain coagulation factor activity above a predetermined threshold, generally at least within the moderate disease range, in order to prevent bleeding. Regular prophylaxis has been shown to reduce the frequency of joint bleeding and lower the risk of hemophilic arthropathy. As a result, many people with hemophilia are able to lead more active school, work, and social lives.

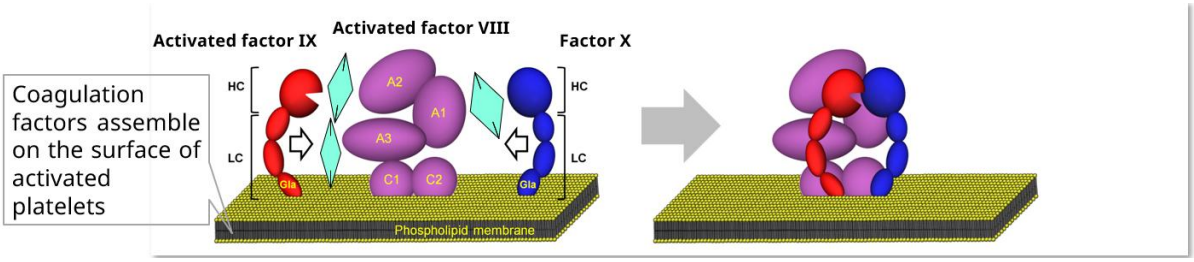
Reference
Smile-On: Hemophilia Information Website (Chugai Pharmaceutical)
https://smile-on.jp/ (In Japanese only)

Research Overview
The achievement recognized by this award is the creation of Hemlibra (emicizumab), the world’s first recombinant full-length IgG bispecific antibody designed to substitute for the function of coagulation Factor VIII, providing a new treatment option for people with hemophilia A.

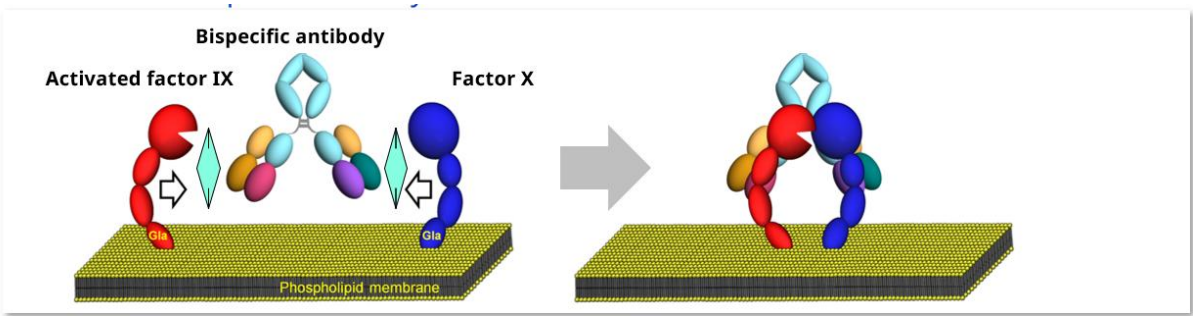
In 2000, Dr. Kunihiro Hattori, who led Chugai’s coagulation research group, conceived an unconventional idea: using an antibody to substitute for the function of Factor VIII. Activated Factor VIII normally serves as a cofactor that facilitates the interaction between activated Factor IX and Factor X on the surface of activated platelets, thereby promoting Factor X activation. Based on his hypothesis regarding this molecular mechanism, the

team developed a novel drug discovery concept: a bispecific antibody designed to bind activated Factor IX with one arm and Factor X with the other, thereby reproducing the function of Factor VIII.

Function of factor VIII: Promotes the reaction in which activated factor IX activates factor X



Could we create an antibody that performs the function of factor VIII?
Reproducing this function with a bispecific antibody that binds activated factor IX with one arm and factor X with the other



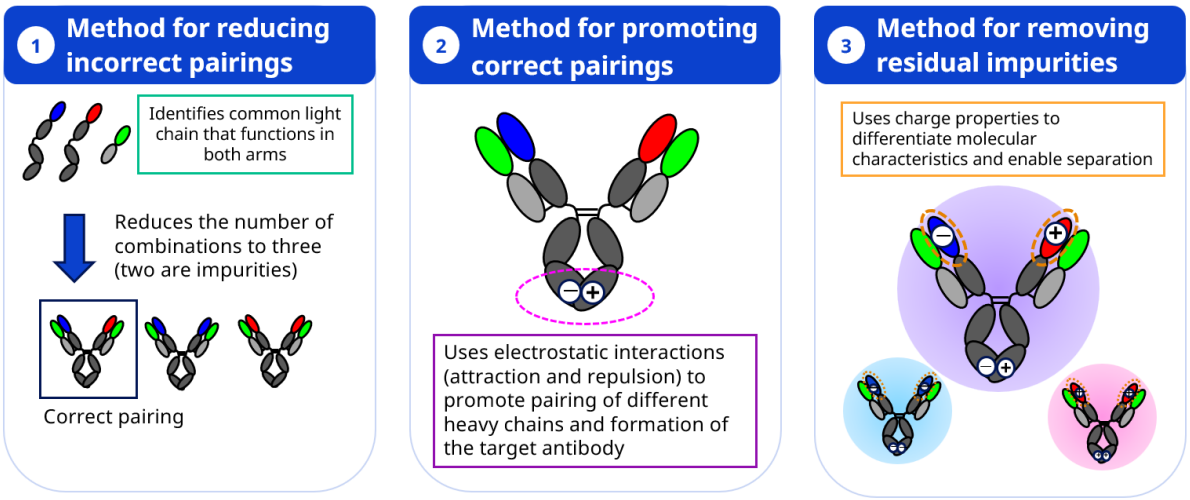
Kitazawa, Igawa...., Hattori. ***Nat Med.*** 18(10) 1570 (2012)

Research on bispecific antibodies began in 2002. Through the screening of approximately 460 bispecific antibodies, the team identified an antibody (XB12/SB04) that enabled them to qualitatively validate this concept, representing a critical "zero-to-one" breakthrough.

Subsequently, after screening approximately 4,000 antibodies, the first clinical candidate was identified. However, because it failed to demonstrate clear hemostatic activity in disease models and raised safety concerns, the program was terminated in 2006. Rather than abandoning the concept, the research team led by Dr. Hattori and Dr.Takehisa Kitazawa chose to start again, driven by the conviction that if they gave up, no one would be able to deliver this drug to patients. Building on lessons from the initial program, they conducted a 10-fold larger screening campaign involving approximately 40,000 bispecific antibodies and identified a lead antibody (BS15). Dr. Tomoyuki Igawa and team then carried out repeated engineering optimization, including sequence design and evaluation. In 2010, this effort resulted in ACE910 (later named emicizumab), a bispecific antibody that demonstrated sufficient hemostatic activity in disease models together with favorable safety, pharmacokinetic properties, physicochemical stability, low immunogenicity, and suitability for commercial manufacturing.

A major challenge in developing recombinant full-length IgG bispecific antibodies was the complexity of manufacturing. When two different heavy chains and two different light

chains are combined, numerous unwanted byproducts can be generated, making the efficient, stable, and high-purity production of the desired antibody extremely difficult. To overcome this challenge, Chugai established its proprietary antibody engineering platform, ART-Ig, by integrating three key technologies: FR/CDR shuffling technology for common light-chain generation, isoelectric point engineering technology that enables byproduct separation, and electrostatic interaction-based chain association control technology to promote heavy-chain heterodimerization. This innovation enabled the successful commercial-scale production of recombinant full-length IgG bispecific antibodies.



The discovery and development of emicizumab was made possible through the dedication and collaboration of many partners. In 2003, Chugai initiated a research collaboration with Nara Medical University, a pioneering institution in hemophilia research and treatment in Japan. Nara Medical University made significant contributions through coagulation assays using patient plasma and support for clinical development. Subsequently, a domestic Phase I study consisting of a healthy volunteer cohort and a hemophilia A cohort was initiated in 2012. In the hemophilia A cohort, which began in 2013, results suggested a reduction in bleeding events[1,2]. Building on these findings, Phase III studies were initiated in 2015. Across multiple global Phase III studies (HAVEN 1-4) and a domestic Phase III study, Hemlibra demonstrated favorable prophylactic efficacy against bleeding regardless of inhibitor status, along with the convenience of subcutaneous administration[3-7]. These studies were conducted through collaboration among Nara Medical University, Roche, and Genentech.

Hemlibra was approved in the United States in 2017 and subsequently in Japan and Europe in 2018. Today, it is approved in more than 120 countries and has been administered to more than 30,000 people with hemophilia A worldwide (as of June 2026).

The significance of this achievement extends beyond reducing the treatment burden for people with hemophilia A. Traditionally, most antibody drugs have worked by inhibiting or eliminating disease-related targets. Emicizumab demonstrated a fundamentally new concept: restoring a missing biological function through an antibody. This achievement not only transformed hemophilia A treatment but also established a new paradigm for antibody therapeutics and represents a major advancement in antibody drug discovery.

Sources

1. Shima et al. N Engl J Med. 374(21) 2044 (2016)
2. Shima et al. Blood Adv. 1(22) 1891 (2017)
3. Oldenburg J, et al: N Engl J Med. 377(9): 809-18, 2017
4. Young G, et al: Blood. 134(24): 2127-38, 2019
5. Mahlangu J, et al: N Engl J Med. 379(9): 811-22, 2018
6. Pipe SW, et al: Lancet Haematol. 6(6): e295-e305, 2019
7. Shima et al. Haemophilia. 25(6) 979 (2019)

Supplementary Note[1] on the HAVEN 1-4 Studies

Objective	To evaluate the long-term safety, efficacy, and pharmacokinetics of Hemlibra in people with hemophilia A through an integrated analysis of the HAVEN 1–4 studies
Subjects	HAVEN 1[1]: 113 people aged ≥12 years with inhibitors HAVEN 2[2]: 88 children aged <12 years with inhibitors HAVEN 3[3]: 152 people aged ≥12 years with severe hemophilia A without inhibitors HAVEN 4[4]: 48 people aged ≥12 years with or without inhibitors
Analysis population	Enrolled: 401 Efficacy analysis population (ITT): 400 Safety analysis population: 399
Results	[Efficacy] The primary endpoint, annualized bleeding rate (ABR) for treated bleeds over 24-week intervals throughout the study, was 1.4 events/year. For the secondary endpoint, 70.8% (277/391) had zero treated bleeds during Weeks 1–24, increasing to 82.4% (140/170) during Weeks 121–144. [Safety] No new safety signals were identified. The most common adverse event was injection-site reactions (27.8%).

*This product was approved based on a clinical data package that included results from clinical studies conducted using dosage regimens and administration methods that were not approved in Japan at the time. Therefore, some descriptions may reflect dosing regimens and administration methods that differ from those currently approved in Japan.

1. Michael U, et al. Blood (2021) 137 (16): 2231–2242, 2021
2.Oldenburg J, et al: N Engl J Med. 377(9): 809-18, 2017
3.Young G, et al: Blood. 134(24): 2127-38, 2019
4.Mahlangu J, et al: N Engl J Med. 379(9): 811-22, 2018
5.Pipe SW, et al: Lancet Haematol. 6(6): e295-e305, 2019

Development History

- 2000: Dr. Kunihiro Hattori of Chugai Pharmaceutical conceived the original concept
- 2002: Research on bispecific antibody generation commenced
- 2003: Joint research collaboration between industry (Chugai Pharmaceutical) and academia (Nara Medical University) was initiated
- From 2005: A series of patent applications were filed for proprietary antibody engineering technologies enabling the manufacture of bispecific antibodies
- 2006: The first clinical candidate antibody was discontinued; the research team decided to restart the program
- 2010: Selection of development candidate ACE910 (generic name: emicizumab; product name: Hemlibra)
- 2012: Initiation of the healthy volunteer cohort of the Phase I study in Japan
- 2013: Initiation of the hemophilia A cohort of the Phase I study in Japan, followed by an extension study (Phase I/II)
- 2015: Initiation of global Phase III clinical trials

- 2017: Approved in the United States (November 2017)
- 2018: Approved in Japan (March 2018) and launched in Japan (May 2018); approved in Europe (February 2018)
- Today: Approved in more than 120 countries worldwide and used by more than 30,000 people with hemophilia A globally

Other Awards related to this Research
- 2018: Prix Galien France
- 2018: Prix Galien Germany
- 2020: 4th Japan Bioindustry Award (Japan Bioindustry Association)
- 2020: Minister of Health, Labour and Welfare Award at the 4th Japan Medical Research and Development Grand Prize
- 2021: 6th JBDA Drug Discovery Award (Japan Bio-Venture Development Organization)
- 2023: 15th Ernest Beutler Lecture and Prize (American Society of Hematology)

Sources

1. Shima et al. N Engl J Med. 374(21) 2044 (2016)
2. Shima et al. Blood Adv. 1(22) 1891 (2017)
3. Oldenburg J, et al: N Engl J Med. 377(9): 809-18, 2017
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6. Pipe SW, et al: Lancet Haematol. 6(6): e295-e305, 2019
7. Shima et al. Haemophilia. 25(6) 979 (2019)

Reference Materials
News Releases
- Chugai's HEMLIBRA® Receives the World's First Regulatory Approval from FDA for Hemophilia A with Inhibitors (Nov 17, 2017)
  https://www.chugai-pharm.co.jp/english/news/detail/20171117083000_53.html?year=2017&category=
- Launch of HEMLIBRA® Subcutaneous Injection for the Treatment of Hemophilia A (May 22, 2018)
  https://www.chugai-pharm.co.jp/english/news/detail/20180522113000_14.html?year=2018&category=
- Chugai and Nara Medical University Jointly Win the 4th Japan Bioindustry Award for Discovery and Development of Hemlibra for the Treatment of Hemophilia A (Jul 15, 2020)
  https://www.chugai-pharm.co.jp/english/news/detail/20200715150001_739.html?year=2020&category=
- Chugai's Hemlibra Wins the MHLW Minister's Award at the Fourth Japan Medical Research and Development Grand Prize (Dec 25, 2020)
  https://www.chugai-pharm.co.jp/english/news/detail/20201225113000_788.html?year=2020&category=

Media Conference
- HEMLIBRA Subcutaneous Injection Product Overview (June 1, 2018)

https://www.chugai-pharm.co.jp/english/profile/media/conference/files/180601eHEMLIBRA.pdf
Please note that the information reflects the status as of the briefing date.

*Please refer to the electronic package insert for detailed information regarding the indications, dosage, and administration of Hemlibra.

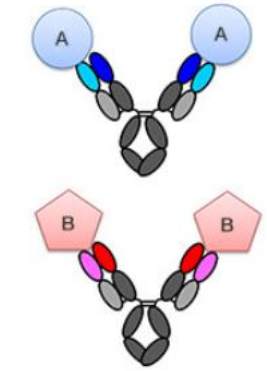
Glossary

- Antibody
  Antibodies play a central role in humoral immunity, a key component of the body's immune system, and are essential for protecting the body against pathogens. Antibodies are a type of protein known as immunoglobulins. When a foreign substance enters the body, antibodies are produced that specifically bind to antigens on that substance, helping to eliminate it. The human body is capable of producing antibodies that precisely recognize and bind to virtually any foreign substance it encounters.

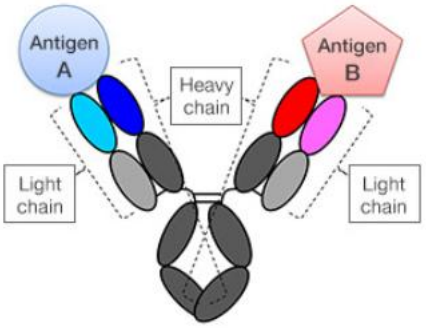
- **Antibody Structure**
  The basic structure of an antibody resembles a Y shape and consists of two heavy (H) chains and two light (L) chains. It contains regions that bind to foreign substances and regions that interact with immune cells. The upper arms of the Y-shaped structure form the antigen-binding region. Because this region varies in structure to recognize different antigens, it is known as the variable region. The remainder of the antibody is known as the constant region.

- **Antibody Drugs**
  Antibody drugs are medicines that utilize antibodies. Because antibody drugs can specifically target antigens on the surface of cells, such as cancer cells, they are expected to provide high therapeutic efficacy while reducing side effects. Some antibody drugs recognize and bind to proteins that are overproduced in tissues responsible for disease.

- **Bispecific Antibodies**
  Conventional antibodies bind to a single type of antigen per antibody. In contrast, bispecific antibodies can bind to two different antigens through two distinct antigen-binding sites. This enables the simultaneous modulation of two targets and offers mechanisms of action that cannot be achieved with conventional antibodies.



Conventional IgG antibody



Asymmetric bispecific IgG antibody (BiAb)

Reference Materials

Platforms & Technologies (Chugai Pharmaceutical)
https://www.chugai-pharm.co.jp/english/innovation/rd/technologies.html