Patent Right	Date	March 28, 2018	Court	Tokyo District Court, 29th Civil Division
	Case Number	2016 (Wa) 11475		
- A case in which, with regard to the case of seeking injunction against infringement of the Patent Right titled "Factor IX/factor IXa-antibodies and antibody derivatives," the target product cannot be said to belong to the technical scope of the Invention stated in the Patent.				

Case type : Injunction, etc.

Result : Dismissed

References : Article 70 of the Patent Act

Number of related rights, etc.:Patent No. 4313531, Correction 2017-390031, Correction 2017-390088

Summary of the Judgment

1. The present case is a case in which the plaintiffs allege that the acts of the defendant of manufacturing and assigning the defendant's product are acts of infringing on the Patent Right and demands the prohibition of manufacture and transfer of defendant products and disposal of the product under the provisions of Article 100, paragraphs(1) and (2) of the Patent Act.

2. The court decision judged that the defendant's product cannot be said to belong to the technical scope of the Invention.

The scope of claims is written in abstractive and functional expressions. In such a case, the technical scope of the Invention cannot be clarified only by its statement. In addition to the statements in claims, the statements in the specification and the drawings shall be taken into consideration. The technical scope of the invention should be determined based on the technical idea shown in the concrete configuration disclosed therein. However, this does not limit the technical scope of the Patent Invention to concrete examples. Any constituent feature that could be implemented by a person skilled in the art in view of the statements in the specification and the drawings should be recognized as being included in the technical scope of the Patent Invention.

When considering the constituent feature that could be implemented by a person skilled in the art based on the statement in the present specification, in order that the defendant's product can be said to be in the technical scope of the Patent Invention, it is required that antibodies should be "monoclonal antibodies (monospecific antibodies) against Factor IX or Factor IXa, which can substantially increase the

procoagulant activity of factor IXa, or antibody derivatives prepared by modifying the antibodies while retaining the activities thereof." In this context, the defendant's product cannot be said as any of "monoclonal antibodies (monospecific antibodies) against Factor IX or Factor IXa, which can substantially increase the procoagulant activity of factor IXa, or antibody derivatives prepared by modifying the antibodies while retaining the activities thereof" and thus cannot be recognized as one belonging to the technical scope of the Patent Invention.

Judgment rendered on March 28, 2018, the original of the judgment was received by the court clerk on the same day

2016 (Wa) 11475 Case of seeking injunction of patent infringement, etc.

Date of conclusion of oral argument: December 20, 2017

Judgment

Indication of the parties: As enumerated in the attached list

Main text

1 All of the plaintiffs' claims are dismissed.

2 The plaintiffs shall bear the court costs.

3 The additional period for filing an appeal against this judgment shall be 30 days.

Facts and reasons

I. **Demand**

1. The defendant shall not manufacture, use, assign, export, or offer an assignment of any product stated in the attached Defendant's product list.

2 The defendant must dispose of any product stated in the attached Defendant's product list.

II. **Outline of the case**

1 Summary of the case

In this case, the plaintiffs who share the patent right of Patent No. 4313531 in which the title of the invention is "FACTOR IX/FACTOR IXa ANTIBODIES AND ANTIBODY DERIVATIVES" (hereinafter, this patent right is referred to as " **Present Patent Right,**" this patent is referred to as " **Present Patent**," and the specification (including the scope of claims) and drawings considered as attached to the application of Present Patent is collectively referred to as "**Present Specification,**" and the scope of claims stated in the specification is referred to as "Present Scope of Claims or simply "Scope of Claims") allege that any product stated in the attached Defendant's product list (hereinafter, the product is referred to as "**the Defendant's product**") falls within the technical scope of each of the inventions stated in claims 1 and 4 of Present Scope of Claims in the case (hereinafter, respectively referred to as "Present **Invention 1**" and "Present **Invention 4**" and collectively referred to as "**Present Inventions**"). Then, the plaintiffs request the defendant to not manufacture, use, assign, export, or offer an assignment of any Defendant's product (hereinafter, collectively referred to

"**the production, etc.**") as under the provisions of Article 100, paragraph (1) of the Patent Act and seeks the disposal of the product under the provisions of Article 100, paragraph (2) of the Patent Act.

2 The facts used as premise (facts without conflict between the parties and the stated evidences as well as facts easily recognized by the stated evidences and the entire import of the oral argument; incidentally, for the documentary evidence, the description of the branch number is omitted unless otherwise specified)

(1) Parties

The plaintiff Baxalta Incorporated as an U.S. corporation and the plaintiff Baxalta GmbH as a Swiss corporation are foreign companies involved in development, manufacture, and sale of therapeutic drugs against rare diseases in hematology immunology, and oncology (Exhibits Ko 1 to 3).

The defendant is a corporation aimed at research, development, manufacture, sale, import and export, etc. of medicines.

(2) Present Patent Right

A. The plaintiffs have received the transfer of registration received on December 21, 2015 for the right of the patent (Present Patent Right) specified by the following matters and subsequently have shared the Patent Right (Exhibits Ko 3 and 4).

Patent number: Patent 4313531

Title of the invention: FACTOR IX/FACTOR IXa ANTIBODIES AND ANTIBODY DERIVATIVES

Date of registration: May 22, 2009

Date of filing: September 13 2000

(hereinafter, referred to as "**the filing date of Present Application**")

Application number: Japanese Patent Application No. 2001-523763

International filing application number PCT/EP2000/008936

Priority date: September 14, 1999

Priority claim number: A1576/99

Priority country: Austria

B. Present Scope of Claims at the time of the registration of establishment was as stated in the pertinent column of the attached patent gazette (Exhibit Ko 4).

On April 28, 2017, the plaintiffs requested a trial for correction (Correction 2017-390031) for requesting to (i) correct claims 1 to 13 after correction from "an antibody or antibody derivative" in claim 1 to "an antibody or antibody derivative (except for antibody clone AHIX-5041: manufactured by Haematologic Technologies, Inc., and antibody clone HIX-1: manufactured by SIGMA-ALDRICH, Inc.)"; and (ii)

correct claims 15 to 18 after correction to "a pharmaceutical preparation comprising an antibody or antibody derivative according to claim l and a pharmaceutically acceptable carrier" to "a pharmaceutical preparation comprising an antibody or antibody derivative against factor IX or factor IXa, which increases procoagulant activity and a pharmaceutically acceptable carrier." The appeal decision dated August 21, 2017 approved the correction including the above (i) and (ii) as its contents (hereinafter, collectively referred to as "**Correction 1**") and then the appeal decision became final and binding on August 31, 2017 (Exhibits Ko 130 and 167).

Subsequently, on September 4, 2017, the plaintiffs requested a trial for correction for correcting claim 1 after correction from "an antibody or antibody derivative (except for antibody clone AHIX-5041: manufactured by Haematologic Technologies, Inc., and antibody clone HIX-1: manufactured by SIGMA-ALDRICH, Inc.)" to "an antibody or antibody derivative (except for antibody clone AHIX-5041: manufactured by Haematologic Technologies, Inc., antibody clone HIX-1: manufactured by SIGMA-ALDRICH, Inc., antibody clone ESN-2: manufactured by American Diagnostica Inc., and antibody clone ESN-3: manufactured by American Diagnostica Inc., and antibody derivatives thereof)." The appeal decision dated October 31, 2017 approved the correction including the above contents (hereinafter, collectively referred to as "**Correction 2**") and then the appeal decision became final and binding on November 9, 2017 (Exhibits Ko 168 and 191).

As stated above, as the appeal decisions admitting Corrections 1 and 2 (hereinafter, correctively referred to as "**the respective Corrections**") have become final and binding, the present scope of the claims in the Patent has been corrected to the statements in the attached "[Name of Document] Scope of Claims."

(3) Separate statements of the constituent components of Present Inventions

A. Constituent components of Present Invention 1 (the invention recited in claim 1) can be separately stated as follows (hereinafter, each constituent component to be separately stated is referred to as, for example, "**constituent component 1A**" in correspondence with a reference symbol; and also "AHIX-5041: manufactured by Haematologic Technologies, Inc., antibody clone HIX-1: manufactured by SIGMA-ALDRICH, Inc., antibody clone ESN-2: manufactured by American Diagnostica Inc., and antibody clone ESN-3: manufactured by American Diagnostica Inc." are collectively referred to as "**the antibodies excluded from the case**").

1A. An antibody or antibody derivative against factor IX or factor IXa,

1B. which increases procoagulant activity,

1C. an antibody or antibody derivative (except for AHIX-5041: manufactured

by Haematologic Technologies, Inc., antibody clone HIX-1: manufactured by SIGMA-ALDRICH, Inc., antibody clone ESN-2: manufactured by American Diagnostica Inc., and antibody clone ESN-3: manufactured by American Diagnostica Inc., and antibody derivatives thereof).

B. Present Invention 4 (the invention recited in claim 4) can be separately stated as follows and constituent component 4D can be further separately stated as constituent components 1A to 1C (the constituent components of the invention recited in claim 1 on which it depends).

4D. An antibody or antibody derivative according to claim 1,

4E. wherein an antibody or antibody derivative is selected from the group consisting of monoclonal antibodies, antibody fragments, chimeric antibodies, humanized antibodies, single chain antibodies, bispecific antibodies, diabodies, and di-, oligo-, or multimers thereof.

4F. an antibody or antibody derivative.

3. Issues

(1) Whether the Defendant's product falls within the technical scope of Present Inventions (Issue 1)

(2) Whether the production, etc. of the Defendant's product infringes or is likely to infringe on Present Patent Right (Issue 2)

(3) Whether the production, etc. of the Defendant's product for clinical trials falls under the category of "the working of the patented invention for experimental or research purposes" (Article 69(1) of the Patent Act) (Issue 3)

(4) Whether Present Patent is recognized as one that should be invalidated by a trial for patent invalidation (Issue 4)

A. Whether Invalidation Reason 1 (violation of enablement requirement [Article 36(4) of the Patent Act before revision by the Act No. 24 of 2002]) is recognized (Issue 4-1)

B. Whether Invalidation Reason 2 (violation of supporting requirement [Article 36(1) of the Patent Act before revision by the Act No. 24 of 2002]) is recognized (Issue 4-2)

C. Whether Invalidation Reason 3 (violation of clarity requirement [Article 36(6)(ii) of the Patent Act before revision by the Act No. 24 of 2002]) is recognized (Issue 4-3)

D. Whether Invalidation Reason 4 (violation of correction requirement) is recognized (Issue 4-4)

(omitted)

IV. **Court decision**

1. Regarding the significance of Present Inventions

(1) Statements in Present Specification

The Detailed Description of the Invention in Present Specification generally includes the following statements (Exhibit Ko 4; regarding the drawings, see the attached patent gazette).

A. The art to which Present Inventions pertains

"[0001]

The present invention relates to factor IX/factor IXa-antibodies and antibody derivatives."

B. Prior Art

"[0003]

Activation of factor X by the complex of activated factor IX (FIXa) and activated factor VIII (FVIIIa) is a key step in coagulation. The absence of the components of this complex or a disturbance of their function is associated with the blood coagulation disorder called hemophilia --- . Hemophilia A denotes a (functional) absence of factor VIII activity, while Hemophilia B is characterized by the absence of factor IX activity. At present, treatment of Hemophilia A is effected via a substitution therapy by administering factor VIII concentrates. However, approximately 20-30% of Hemophilia A patients develop factor VIII inhibitors (i.e., antibodies against factor VIII), whereby the effect of administered factor VIII preparations is inhibited. Treatment of factor VIII inhibitor patients is very difficult and involves risks, and so far there exist only a limited number of treatments for these patients."

C. Problems to be solved by Present Inventions

"[0004]

In the case of patients having a low FVIII inhibitor level, it is possible, although expensive, to administer high doses of factor VIII to such patients and thus to neutralize the antibodies against factor VIII. The amount of factor VIII beyond that needed to neutralize the inhibitor antibodies then has hemostatic action. In many cases, desensitization can be effected, whereupon it is then possible to again apply standard factor VIII treatments. Such high dose factor VIII treatments require, however, large amounts of factor VIII, are time-consuming, and may involve severe anaphylactic side reactions. ---

[0005]

A further high-cost method involves removing factor VIII inhibitors through extra corporeal immunoadsorption on lectins which bind to immunoglobulins (protein A, protein G) or to immobilized factor VIII. Since the patient must be connected to an apheresis machine during this treatment, the treatment also constitutes a great burden on the patient. It is also not possible to treat an acute hemorrhage in this way."

D. Purpose of the Invention

"[0010]

(Summary of Present Inventions)

With a view to the possible risks and side effects which may occur in the treatment of hemophilia patients, there is a need for a therapy which allows for the effective treatment of FVIII inhibitor patients. Therefore, it is an object of the present invention to provide a preparation for the treatment of blood coagulation disorders which has particular advantages for factor VIII inhibitor patients."

E. Means for solving the problem

"[0007]

In the intravascular system of blood coagulation, the last step is the activation of factor X. This reaction is stimulated by the binding of factor VIIIa to factor IXa and the formation of a "tenase"-complex consisting of the factors IXa, VIIIa, X, and phospholipid. Without the binding of FVIIIa, FIXa exhibits no or only a very slight enzymatic activity relative to FX."

"[0011]

According to the present invention, this object is achieved through the use of antibodies or antibody derivatives against factor IX/factor IXa which have factor VIIIa-cofactor activity or factor IXa-activating activity and lead to an increase in the procoagulant activity of factor IXa. Surprisingly, the action of these inventive factor IX/factor IXa-activating antibodies and antibody derivatives is not negatively affected by the presence of inhibitors, such as inhibitors against factor VIII/factor VIIIa, but instead the procoagulant activity of factor IXa in this case is also increased."

F. Effects of Present Inventions

"[0012]

A further advantage of this invention is that the administration of the preparation according to the invention allows for rapid blood coagulation even in the absence of factor VIII or factor VIIIa, even in the case of FVIII inhibitor patients. Surprisingly, these agents are also effective in the presence of factor VIIIa."

G. Methods for producing antibodies or antibody derivatives

"[0030]

(Methods of Production)

The antibodies of the present invention can be prepared by methods known from the prior art, e.g., by conventional hybridoma techniques, or by means of phage display gene libraries, immunoglobulin chain shuffling or humanizing techniques --- . The production of the inventive antibodies and antibody derivatives may, for instance, be made by conventional hybridoma techniques --- . According to the present invention, human and also non-human species may be employed therefor, such as cattle, pigs, monkeys, chickens, and rodents (mice, rats). Normal, immunocompetent Balb/c mice or FIX-deficient mice may, e.g., be used --- . Immunization may, e.g., be effected with factor IX, factor IXaα or completely activated factor IXaβ, or with fragments thereof."

H. Evaluation method for procoagulant activity

"[0013]

The antibodies and antibody derivatives according to the present invention thus have an FVIII-cofactor-like activity which, in an FVIII assay (e.g. a COATEST[R] assay or Immunochrom test) after 2 hours of incubation exhibits a ratio of background (basic noise) to measured value of at least 3. Calculation of this ratio may, e.g., be effected after two hours of incubation according to the following scheme:

[0014]

[Equation 1]

$$\frac{\text{Antibody measurement (OD 405) - blank value from reagent}}{\text{Mouse-IgG-measurement (OD 405) - blank value from reagent}} > 3$$

"[0037]

The purification of the inventive antibodies and antibody derivatives may also be carried out by methods described in the prior art, e.g., by ammonium sulfate precipitation, affinity purification (protein G-Sepharose), ion exchange chromatography, or gel chromatography. The following methods may be used as the test methods to show that the antibodies and antibody derivatives of the present invention bind to factor IX/factor IXa, increase the procoagulant activity of factor IXa or have factor VIII-like activity: the one step coagulation test (Mikaelsson and Oswaldson, Scand. J. Haematol., Suppl., 33, pp. 79-86, 1984) or the chromogenic tests, such as COATEST VIII: C[R] (Chromogenix) or Immunochrom (IMMUNO). In principle, all the methods used for determining factor VIII activity may be used. As

the control blank value for the measurements, e.g., unspecific mouse-IgG antibody may be used."

I. Antibodies or antibody derivatives

"[0019]

The inventive antibodies and antibody derivatives and organic compounds derived there from comprise human and animal monoclonal antibodies or fragments thereof, single chain antibodies and fragments thereof and mini-antibodies, bispecific antibodies, diabodies, triabodies, or di-, oligo- or multimers thereof. Also included are peptidomimetics or peptides derived from the antibodies according to the invention, e.g., they comprise one or several CDR regions, preferably the CDR3 region."

"[0021]

The term factor IX/IXa activating antibodies and antibody derivatives may also include proteins produced by expression of an altered, immunoglobulin-encoding region in a host cell, e.g., "technically modified antibodies" such as synthetic antibodies, chimeric or humanized antibodies, or mixtures thereof, or antibody fragments which partially or completely lack the constant region, e.g., Fv, Fab, Fab' or F(ab)'2, etc. In these technically modified antibodies, e.g., a part or parts of the light and/or heavy chain may be substituted. Such molecules may, e.g., comprise antibodies consisting of a humanized heavy chain and an unmodified light chain (or chimeric light chain), or vice versa. The terms Fv, Fc, Fd, Fab, Fab' or F(ab)2 are used as described in the prior art (Harlow E. and Lane D., in 'Antibodies, A Laboratory Manual,' Cold Spring Harbor Laboratory, 1988)."

"[0024]

The humanized antibody according to the present invention preferably has the structure of a human antibody or of a fragment thereof and comprises the combination of characteristics necessary for a therapeutic application, e.g., the treatment of coagulation disorders in patients, preferably factor VIII inhibitor patients."

"[0026]

Bispecific antibodies are macromolecular, heterobifunctional cross-linkers having two different binding specificities within one single molecule. In this group belong, e.g., bispecific (bs) IgGs, bs IgM-IgAs, bs IgA-dimers, bs $(Fab')_2$, bs $(scFv)_2$, diabodies, and bs bis Fab Fc --- ."

J. Statements in working examples

(a) Example 1

Paragraphs [0043] to [0046] generally state a working example in which a mouse was immunized with either factor IX or factor IXa to produce hybridoma cells

secreting antibody against factor IX or factor IXa.

(b) Example 2

Paragraphs [0047] to [0055] generally state a working example in which hybridoma cells were screened by chromogenic assay and those producing antibodies having factor VIII-like activity were selected.

(c) Example 3

Paragraphs [0056] to [0061] generally state a working example in which ELISA confirmed the activity against factor X or factor IXa of the hybridoma supernatant containing the antibody having the factor V factor-like activity obtained in Example 2.

(d) Example 4

"[0062]

(Example 4: Anti-FIX/FIXa antibodies exhibiting FVIII-like activity in a chromogenic FVIII assay)

Several anti-FIX/FIXa antibody producing hybridoma clones were subcloned up to four times and the resulting monoclonal hybridoma cell line used to produce monoclonal antibody containing supernatant. IgG isotype antibodies derived from these supernatants were purified over affinity columns and dialyzed against TBS (see above). IgM antibodies were used as unpurified supernatant fractions. The following experiments were done with two sets of representative antibodies: 193/AD3 and 198/AC1/1 (IgG isotype, the antibody 198/AC1/1 is a preparation from the parent 198/AC1 hybridoma clone; i.e., that a (frozen) vial containing 198/AC1 cells is cultivated and antibodies are produced. The supernatant is then used for these experiments.) and 196/AF2 and 196/AF1 (IgM isotype) (Fig. 6A and Fig. 6B). Briefly, 25µl aliquots of monoclonal antibody containing sample (unpurified hybridoma supernatant or, where indicated, a certain amount of FIX specific antibody) were transferred to microtiter plate wells and warmed to 37°C. Chromogenic substrate (S-2222), synthetic thrombin inhibitor (1-2581), factor (F) IXa and FX were reconstituted in sterile water and FIXa/FX was mixed with phospholipids according to the supplier's protocol. Per reaction, 50µl of the phospholipid/FIXa/FX solution were combined with 25µl CaCl2 (25mM) and 50µl of the substrate/inhibitor cocktail. To start the reaction, 125µl of the premix were added to the monoclonal antibody solution in the microtiter plates and incubated at 37°C. Absorbance at 405 nm and 490 nm of' the samples was read at various times (5min to 6h) against a reagent blank (cell culture medium instead of hybridoma supernatant) in a Labsystems iEMS Reader MF[TM] microtiter plate reader using GENESIS[TM] software.)"

(e) Example 5

"[0065]

(Example 5: FVIII-like activity exhibited by anti- FIX/FIXa-antibodies generates factor Xa and is phospholipid, FIXa/FX and Ca2+ dependent.)

Factor VIII activity is usually determined with a chromogenic assay and/or an APTT-based clotting assay. Both types of assays rely on FVIIIa/FIXa-mediated factor Xa generation. In the case of a chromogenic FVIII assay, the factor Xa produced will subsequently react with a chromogenic substrate, which can be monitored spectroscopically, e.g., in an ELISA reader. In an APTT based clotting assay free factor Xa will assemble with FVa on a phospholipid surface in the so-called prothrombinase complex and activate prothrombin to thrombin. Thrombin in turn gives rise to fibrin generation and finally to clot formation. Central to the two assay systems is generation of factor Xa by the FVIIIa/FIXa complex."

"[0067]

The results of the factor IXa stimulation by the FVIII-like activity exhibited by the IgM anti- FIX/FIXa- antibody 196/AF2 in generating actor Xa as judged by the readily measurable cleavage of the chromogenic substrate S-2222 (compare '16mU FVIII' and '196/AF2') is shown in Fig. 7A. Factor Xa activity is effectively blocked by the FXa specific inhibitor 'Pefabloc Xa[R]' (compare '196/AF2' versus '196/AF2 35µM Pefabloc Xa[R]') indicating that indeed FXa was generated.

[0068]

The same experiment was performed using purified IgG preparations of clone 198/AM1 (Fig. 7B). Purified IgG was diluted in TBS to a final concentration of 0,4mg/ml and 25µl (i.e., a total of 10 µg), transferred to microtiter plate wells, and warmed to 37°C. As a positive control, 6mU plasma- derived FVIII was used. 10 µg unspecific mouse IgG (Sigma I-5381) served as a negative control. The assay was performed as described above."

(f) Example 6

"[0073]

(Example 6: Certain anti-FIX/FIXa-antibodies are procoagulant in the presence of FIXa)

During normal hemostasis, FIX becomes initially activated either by the tissue factor (TF) /factor Vila pathway or later on by activated factor XI (FXIa). Subsequent to its activation, FIXa associates on the platelet surface in a membrane bound complex with activated FVIII. Factor IXa by itself has little or no enzymatic activity towards FX, but becomes highly active in the presence of FVIIIa. To demonstrate that certain anti-FIX/FIXa antibodies have FVIII-like activity and hence

are procoagulant in a FVIII deficient human plasma, the following experiment was carried out. --- ."

(g) Example 7

"[0076]

(Example 7: Anti-FIX/FIXa-antibodies are procoagulant in the presence of FVIII inhibitors and FIXa)

A severe complication of the standard FVIII substitution therapy is the development of alloantibodies directed against FVIII, leading to FVIII neutralization and a condition where the patient's blood will not clot.

[0077]

To demonstrate that certain anti-FIXa-antibodies have FVIII-like activity even in the presence of FVIII inhibitors, the following experiment was carried out. Different amounts of antibody 193/AD3 or, as a control, mouse IgG were used in a standard APTT based one-stage clotting assay. Briefly, 100-µl antibody samples were incubated with either 100 µl of FVIII deficient plasma (Fig. 10A) or FVIII inhibitor plasma (inhibitor potency 400BU/ml), Fig. 10B) as well as with 100 µl of DAPTTIN reagent, in a KC10A clotting analyzer. In addition, a total amount of 50 ng activated FIXa was included in the reaction mixture. After a 4-minute incubation, the reaction was started by the addition of 100-µl $CaCl_2$ (25mM). To ensure equal conditions, the experiments employing FVIII deficient plasma and FVIII inhibitor plasma were done side by side. The results are shown in Fig. 10A and 10B. As already shown in Example 6, there is a clear dose-dependent reduction of the clotting time in samples supplemented with antibody 193/AD3 in the presence of FVIII inhibitors."

(h) Example 8

"[0078]

(Example 8: Anti-FIX/FIXa-antibodies are procoagulant in the presence of defective FVIII and FIXa)

To demonstrate that certain anti-FIXa-antibodies have FVIII-like activity in the presence of defective FVIII, the following experiment may be carried out. ---"

(i) Example 9

"[0079]

(Example 9: Anti-FIX/FIXa-antibodies with procoagulant activity in the presence of FIXa distinguish between human and bovine FIXa)

FIX/FIXa specific monoclonal antibodies selected from the 198th fusion experiment were purified from the respective hybridoma supernatant and quantified as

described in Example 3. These antibodies were analyzed in a modified one-stage clotting assay (as described in Example 6) and some showed procoagulant activity."

"[0081]

Fig. 11 shows the time course of the FVIII-like activity exhibited by the monoclonal antibodies 198/A1, 198/B1, and 198/AP1 with (+) and without (-) addition of 50 ng human FIXaβ. Non-specific polyclonal mouse IgG was used as a control. 198/A1 and 198/B1 show procoagulant activity (similar as 193/AD3 in example 6) whereas 198/AP1 does not. Antibody 198/BB1 had the same activity pattern (data not shown)."

(j) Example 10

"[0083]

(Example 10: Structure and procoagulant activity of antibody derivatives derived from anti-FIX/FIXa-antibodies; Subcloning antibody variable domains from hybridoma cell lines 193/AD3, 193/K2, 198/A1 and 198/B1 (clone AB2) ---"

"[0084]

--- The resultant vectors were designated pDAP2- 193/AD3scFv, pDAP2-198/A1scFv, pDAP2-198/AB2scFv (derived from antibody 198/B1), and pDAP2-193/K2scFv. They encode the VH-gene and the VL-gene of the monoclonal antibodies 193/AD3, 198/A1, 198/AB2 (derived from antibody 198/B1), and 193/K2."

(k) Example 11

"[0089]

(Example 11: procoagulant activity of peptides derived from CDR3 regions of anti-FIX/FIXa-antibodies) ---"

"[0094]

The principle of such a study is exemplified by a series of peptides derived from CDR3H region of antibodies 198/A1 and 198/B1. The original peptide A1 (see table 2) is derived from the CDR3H region of antibody 198/A1 and peptide B1 is derived from the CDR3H region of antibody 198/B1 (see example 10, Figs. 16 and 17). The term "scrambled version" means that a peptide has the same amino acids but in random order. ---"

"[0105]

Fig. 20 demonstrates the unchanged chromogenic activity of peptide A1/3-Rd. Peptides at a final concentration of 12 μM or the buffer control (IZ) were incubated in the presence of 2.3 nM human FIXa (+). The chromogenic activity of peptide A1/3 and A1/3-Rd was found to be virtually unchanged and gave almost identical results in the chromogenic assay. The scrambled version of peptide A1/3, A1/5 as well as the

buffer gave no significant FXa generation."

(l) Example 12

"[0123]

(Example 12: procoagulant activity of peptide derivatives obtained from CDR3 regions of anti- FIX/FIXa-antibodies in FVIII inhibitor plasma)

To assay for the procoagulant activity of peptide A1/3 in FVIII inhibitor plasma the following experiment was carried out. ---"

(m) Example 13

"[0125]

(Example 13: Conversion of the 196/C4 IgM into IgG1)

Since some IgM antibodies demonstrate high FVIII-like activity in chromogenic assays, attempts were made to convert such IgM antibodies into IgG antibodies (though antibody derivatives such as Fab, F(ab)2, scFv, etc. could also be produced). ---"

(n) Example 14

"[0130]

(Example 14: Activation of FIXa amydolytic activity by anti-FIXa antibodies:)

"--- Specific cleavage of FIXa substrate was monitored at 405 nm in an ELISA reader. The presence of the anti-FIX antibodies enhanced the amydolytic activity of FIXa at least 2 fold. Fig. 24 shows the increase of the amidolytic activity of FIXa in the presence of antibody 198/B1 (Fig. 24A) and antibody 198/AF1 (Fig. 24B). ---"

(o) Example 15

"[0131]

(Example 15: FVIII-like activity exhibited by Fab fragments derived from anti-FIX/FIXa-antibodies)

Fab fragments of anti-FIX/FIXa antibodies were prepared and purified according to standard protocols. ---"

(p) Example 16

"[0133]

(Example 16: FVIII-like activity exhibited by fusion proteins between scFv fragments of anti-FIX/FIXa antibodies and E. coli alkaline phosphatase)

The single chain Fv fragment (see example 10) of antibody 198/B1 (subclone AB2) was fused to the N- terminus of E. coli alkaline phosphatase employing the pDAP2 vector system ---."

(r) Example 17

"[0134]

(Example 17: FVIII-like activity exhibited by a bivalent miniantibody)

In order to obtain a bivalent miniantibody, the scFv fragment of antibody 198/B1 (subclone AB2) was fused to an amphipathic helical structure employing the pZip1 vector system ---."

(s) Example 18

"[0139]

(Example 18: FVIII-like activity exhibited by anti- FIXa/FIX antibody scFv fragments)

The single chain Fv fragment of antibody 198/B1 (subclone AB2) as well as the scFv fragment of antibody #8860 were expressed employing the pMycHis6 vector system. ---"

(2) Significance of Present Inventions

According to the above statements in the Detailed Description of the Invention in Present Specification, the significance of Present Inventions is recognized to be as follows:

Specifically, the conventional treatment for patients with haemophilia A was replacement therapy by administration of factor VIII concentrates to the patients to compensate for the lack or deficiency of factor VIII (paragraph [0003]). As treatment for such patients, there are several treatment methods, such as administration of high dose factor VIII. However, the methods had problems of being expensive (paragraphs [0004] and [0005]), taking a lot of time (paragraph [0004]), having possibility of involving serious side reactions (paragraph [0004]), placing a large burden on patients (paragraph [0005]), and so on. An object of Present Inventions is to provide a preparation for the treatment of blood coagulation disorders which has a particular advantage for factor VIII inhibitor patients (paragraph [0010]). This is achieved by an antibody or antibody derivative thereof which binds to factor XX or factor IXa and increases the procoagulant activity of factor IXa (paragraph [0001]).

Specifically, the antibodies or antibody derivatives are those obtained by preparing monoclonal antibodies (monospecific antibodies) against Factor IX or Factor IXa (Examples 1 to 3); evaluating the degree of procoagulant activity by a method such as chromogenic assay (Examples 4 to 9 and 14); and preparing various antibody derivatives (for example, CDR3 region-derived peptides and their derivatives (Examples 11 and 12), chimeric antibodies (Example 13), Fab fragments (Example 15), single-chain antibodies (ScFv, Examples 10, 16, and 18), and miniantibodies (Example 17).

2. Regarding the configuration of the Defendant's product

(1) The configuration of the Defendant's product

The Defendant's product is an asymmetric bispecific antibody having the amino acid sequence stated in the attached Defendant's product manual and the attached "Amino acid sequence of the Defendant's product," and is classified as IgG antibody among antibodies. The Defendant's product has two antigen binding sites, one of which recognizes factor IXa and the other recognizes factor X. (Exhibit Ko 23, Exhibits Otsu 28, and 38, and the entire import of the oral argument)

(2) Development history of the Defendant's product

During the development of the Defendant's product, the screened monospecific anti-factor Xa factor antibody used by the defendant in making bispecific antibodies is a monoclonal antibody that specifically binds to human factor IXa and has as little inhibitory activity as possible against the enzymatic activity of factor IXa. Then, among the prepared bispecific antibodies, the antibody with the highest factor VIII cofactor activity is XB12/SB04, which is prepared from a monospecific anti-factor Xa factor antibody having no factor V factor cofactor activity. It is therefore recognized that the monospecific anti-factor Xa factor antibody selected in the development of the Defendant's product was screened regardless of whether or not the procoagulant activity of factor IXa was increased. In addition, there is no correlation between factor VIII cofactor activity of monospecific anti-factor Xa factor antibody and the factor VIII cofactor activity of bispecific antibody prepared therefrom. The factor VIII cofactor activity of the bispecific antibody is not only the structure derived from the anti-factor Xa factor antibody but also by the structure derived from the anti-factor X antibody. (Exhibits Otsu 55, 57, and 75)

Then, the Defendant's product controls the spatial orientation of Factor IXa and Factor X in a suitable situation, making the active site of the enzyme and the substrate more easily accessible each other in an accurate manner and thereby promoting factor VIII cofactor activity to be catalyzed by factor IXa. Such a mechanism enhances the procoagulant activity of the Defendant's product. (Exhibit Otsu 33 and Exhibit Ko 165). The degree of such an increase is superior to that of any of antibodies (198A1, 198B3, and 224F3) prepared by the same method as in the working example of Present Specification (according to Exhibits Otsu 6 and 36, it is said that it works about 1000 times more effectively than others).

(2) Regarding the experimental results of the defendant (Exhibits Otsu 36 and 38)

A. Exhibit Otsu 38 intended to evaluate, with respect to the monospecific antibody (Qhomo) prepared by the defendant and composed of left and right arms each

binding to factor IXa of the Defendant's product, the degree of increasing procoagulant activity using a chromogenic assay kit for measuring blood coagulation factor VIII factor; and the ratio thereof to the Qhomo's negative control was 1.36 to 1.48 (The same values of the Defendant's product were from ● omitted ● to ● omitted ●).

B. Exhibit Otsu 36 includes the experimental results of the enzyme reaction kinetics analysis for the factor X activation reaction of factor IXa on the Defendant's product, Qhomo, and so on.

The plaintiffs allege that the experimental results show that Qhomo has a higher Km (Michaelis-Menten constant) value, a higher kcat (enzyme reaction rate) value, and a higher kcat/Km (enzyme reaction efficiency) value, compared to blank values; and thus Qhomo has a high affinity for the substrate (factor X), a high production rate, and a high enzyme reaction efficiency. Then, the plaintiffs allege in conclusion that Qhomo increases procoagulant activity of factor IXa (enzyme).

However, these values cannot be employed to immediately evaluate the ability of "increasing procoagulant activity procoagulant activity" as stated in the corresponding Inventions, because Present Specification does not mention any enzyme kinetic analysis as an index for evaluating the ability of "increasing procoagulant activity procoagulant activity," and also neither describes nor suggests the relationship between the increase in procoagulant activity and the enzymatic kinetics. Moreover, as far as the affinity to the substrate, production rate, and enzyme reaction efficiency are improved, there is no technical common sense as to whether it can be evaluated as "increasing procoagulant activity procoagulant activity." Rather, when compared with the values of the positive control (factor VIIIa factor) of Exhibits Otsu 36, the numerical values of Qhomo are very close to the blank values. Thus, such experimental results cannot allow us to admit that Qhomo is an antibody "increasing procoagulant activity."

C. The plaintiffs insist that, according to the articles on the Defendant's product published by the defendant (Exhibits Ko 110 and 112), the defendant himself has confirmed that the Defendant's product has the effect of increasing procoagulant activity of factor IXa. However, even if the Defendant's product has the effect of increasing procoagulant activity of factor IXa, the Defendant's product and Qhomo have their own structures different from each other. Thus, Qhomo cannot be recognized as an antibody increasing procoagulant activity procoagulant activity.

(3) Regarding the results of experiments conducted by the plaintiffs (Exhibits Ko 114, 163, and 164)

A. Exhibit Ko 114 states the results of an experiment using anti-IXa

monospecific antibody (MonoBM) produced by plaintiffs, the antibody having the same amino acid sequence as Qhomo. In this experiment, parameters (kinetic parameters) of enzyme substrate reaction by Michaelis-Menten equation were calculated. In addition, the experiment carried out the measurement of APTT to determine the degree of increasing procoagulant activity increase. Exhibit Ko 163 states the results of an experiment using the Biacore system utilizing the surface plasmon resonance (SPR) phenomenon to determine the state in which MonoBM and others bind to human factor X and bovine factor X. In Exhibit Ko 164, furthermore, human Factor X was added to the TECHNOCHROM kit (including human Factor IXa and bovine factor X) to determine a change in absorbance over time for each of the Defendant's product and MonoBM.

B. Based on these experimental results, the plaintiffs allege that Qhomo is an antibody that increases procoagulant activity (Exhibit Ko 114) and the increased procoagulant activity of the Defendant's product was brought about by the contribution of only the arm binding to factor IXa (Exhibits Ko 163 and 164).

However, Exhibits Otsu 79 and 80 state that, unlike low molecular weight active ingredients, biopharmaceuticals (including antibody drugs as well) are difficult to guarantee the identity between a biosimilar and the original drug thereof. Exhibit Otsu 92 makes a remark that MonoBM and Qhomo are not the same. Thus, the above experimental results (Exhibits Ko 114, 163, and 164) cannot allow MonoBM and Qhomo to be considered to be identical with each other. On the basis of such identity, therefore, Qhomo cannot be recognized as an antibody that increases procoagulant activity or an antibody where only its arm binding to factor IXa of the Defendant's product can increase procoagulant activity.

On the other hand, based on Exhibits Ko 162, the plaintiffs allege as follows: There is an established generality of the principle in which the information necessary to identify the catalytic enzyme activity is contained in the amino acid sequence and the sequence specifies a higher order structure. If the amino acid sequences are the same, their higher-order structures are also identical with each other, and thus MonoBM and Qhomo are the same. However, on page 50 of Exhibits Ko 162 there is a statement that "Similar refolding experiments were also performed on many other proteins. In many cases, the natural structure was reproduced under optimum conditions. However, some proteins were not folded efficiently again." It means that higher order structures are reproduced under "optimum conditions," but some of them may not be reproduced. Even if the amino acid sequences are identical, therefore, the higher-order structures are not necessarily the same.

3 Regarding the technical common sense at the filing date of Present Application

(1) A plurality of methods for preparing bispecific antibodies against Factor IX or Factor IXa were known at the time of the filing date of Present Application. Among them, the quadroma technique is a simple method. This technique was a procedure capable of producing bispecific antibodies within the confines of reasonable time and effort for a person skilled in the art at the time of the filing date of Present Application. Various methods and protocols for fusing and selecting quadromas producing bispecific antibodies were available in 1999 and have been widely used and well established to create bispecific IgG molecules (Present Specification, paragraph [0026] and Exhibits Ko 97 and 140-1).

Thus, a person skilled in the art could recognize that bispecific antibodies against factor IX or factor IXa could be prepared, from the technical common sense at the time of the filing date of Present Application.

(2) As stated in the above 2(2), it is not recognized that there is a correlation between the factor VIII cofactor activity of monospecific anti-factor IXa factor antibody and the factor VIII cofactor activity of bispecific antibody prepared therefrom. The factor VIII cofactor activity of the bispecific antibody is influenced by not only the structure derived from the anti-factor IXa factor antibody but also the structure derived from the anti-factor X antibody (see, Exhibits Otsu 55, 57, and 75).

However, when converting from a monospecific antibody to a bispecific antibody, the binding site for factor IX or factor IXa becomes monovalent. Even a monovalent has the effect of increasing procoagulant activity procoagulant activity (Present Specification, Examples 10 to 12, 15, 16, and 18). Unless steric interference occurs between the two antigens of the bispecific antibody, the activity of the monospecific antibody is maintained Exhibit Ko 140-1). Assuming that the binding site other than factor IX or factor IXa is factor X, the structures of factor IXa and factor Xa could be revealed at the time of the filing date of Present Application. From the three-dimensional structures of factor IXa and factor Xa, a person skilled in the art could predict that a bispecific antibody biding to factor IXa and factor could hardly cause any interference with the activity of factor IXa binding site (Exhibits Ko 140-1).

Thus, it is recognized that, from the technical common sense at the time of the filing date of Present Application, a person skilled in the art could predict that bispecific antibodies are capable of maintaining the effect of increasing procoagulant activity possessed by monospecific antibody derived from mono-specific antibody against factor IX or factor IXa.

4. Issue 1 (whether the Defendant's product falls within the technical scope of Present Inventions)

(1) Claim 1 of Present Scope of Claims in the Patent (the scope of claims for Present Invention 1) states that "an antibody or antibody derivative against factor IX or factor IXa, which increases the procoagulant activity of FIXa (except for antibody clone AHIX-5041: manufactured by Haematologic Technologies, Inc., and antibody clone HIX-1: manufactured by SIGMA-ALDRICH, Inc.)." Claim 4 (the scope of the invention for Present Invention 4) depends on claim 1. Here, the meaning of the statement "increases the procoagulant activity of FIXa" is not defined in Present Specification. Thus, such a statement is just an object of Present Inventions "to provide a preparation for the treatment of blood coagulation disorders" (paragraph [0010]) and only represents an antibody or antibody derivative in Present Inventions. Accordingly, it does not make clear a specific configuration required for attaining the object or effect of Present Inventions.

Exclusive right under the patent right is given as compensation for disclosing a new and inventive patented invention to the public. Thus, when the entire configuration that can exert the function and working effect of the invention is recognized to be included in the technical scope, the case where the statement in the scope of the claims remains functional and abstract representation may lead to giving an exclusive right based on the patent right, including a configuration belonging to a technical idea not disclosed in the specification. Such interpretation should not be allowed unless it violates the purpose of the patent system that grants an exclusive right in exchange for disclosure of the invention to public.

Thus, where the scope of claims is stated in abstract and functional expression as stated above, the technical scope of the invention cannot be clarified only by such a statement. In addition to the above statement, the statements in the specification and the drawings shall be taken into consideration. Based on the technical idea shown in the concrete configuration disclosed therein, the technical scope of the invention should be determined. However, this does not limit the technical scope of the patented invention to concrete working examples. It can be recognized to be included in the technical scope as long as it is configured to be implemented by a person skilled in the art in view of the statements in the specification and the drawings.

(2) Then, the technical idea stated in the concrete configuration disclosed in Present Specification will be examined below.

A. As assays for indicating that an antibody binds to factor IX or factor IXa and increases the procoagulant activity of factor IXa or has factor VIII-like activity, there

are coagulation assay, chromogenic assay, and so on, which are capable of evaluating such properties of the antibody (paragraphs [0013], [0014], [0037], and [0065]). A plurality of monoclonal antibodies (monospecific antibodies) having factor VIII-like activity is prepared by screening antibodies against factor IXa and subjecting them to chromogenic assay (Examples 4 and 9). Among them, antibody (193/AD3) having factor VIII inhibitor, which causes blood clotting, has also been confirmed (Example 7). Thus, it is recognized that a person skilled in the art could prepare monoclonal antibody (monospecific antibody) that increases procoagulant activity at a constant rate by screening antibodies against factor IXa.

In addition, several derivatives from monoclonal antibodies (monospecific antibodies) that increase procoagulant activity have also been produced. Examples of such derivatives include CDR3 region-derived peptides and derivatives thereof (Examples 11 and 12), chimeric antibodies (scFv. Examples 10, 16, and 18), and miniantibodies (Example 17). It is recognized that derivatives from monoclonal antibodies (monospecific antibodies) that increase procoagulant activity could also be prepared.

Regarding the degree of "increases procoagulant activity," it is not evaluated as "increases procoagulant activity" when the ratio to the negative control in the chromogenic assay is about 1.7 (for example, in paragraph [0081] and FIG. 11, the ratio of antibody 198/API to negative control is about 1.7, but 198/API does not exert procoagulant activity. Paragraph [0067], FIG. 7A (35 μM of 196/AF2, Perfablock Xa (registered trademark), paragraph [0068], FIG. 7B (35 μM of 196/AF1, Perfablock Xa (registered trademark) or about 2 (in paragraph [0105], FIG. 20, the ratio of A1/5 to negative control is about 2, but there is no significant procoagulant activity assessed) in Present Specification. Thus, "increases procoagulant activity" is equivalent to understanding that at least the ratio with the negative control must be of more than about 2. Then, those with little increase in procoagulant activity are not evaluated as "increases procoagulant activity." The degree of increasing must be substantial. It should be therefore recognized that the phrase "increases procoagulant activity" requires a ratio thereof to negative control of at least more than about 2.

B. Regarding bispecific antibodies, an exemplified bispecific antibody prepared as a working example is not stated in Present Specification, and also no disclosure is made on the characteristic features of any antigen of interest to which an arm other than the arm binding to factor XX or factor IXa. However, the bispecific antibody itself is specified as one aspect of an antibody derivative (paragraphs [0019] and [0026]). Then, a plurality of derivatives are prepared from monospecific antibodies,

which increase procoagulant activity, have also been prepared (Examples 10 to 13 and 15 to 18). The technical common sense at the time of the filing date of at the time of the filing date of Present Application would allow a person skilled in the art to prepare bispecific antibodies against factor IX or factor IXa. The bispecific antibodies derived from monospecific antibodies against factor IX or factor IXa can be recognized as those capable of maintaining the effect of increasing the procoagulant activity of monospecific antibody. Then, it is recognized that bispecific antibodies can be also included in "antibody derivatives" as one aspect of the antibody derivatives in which the antibody is modified while maintaining the activity of the monospecific antibody.

C. Thus, in order to be included in the technical scope of Present Inventions, it is necessary to be "a monoclonal antibody (monospecific antibody) against factor IX or factor IXa, which substantially increases the procoagulant activity of factor IXa or an antibody derivative obtained by modifying the antibody while maintaining its activity." It should be therefore recognized that bispecific antibodies can be included as an aspect of "antibody derivatives."

D. The defendant alleges that they are limited to monospecific antibodies and their derivatives that have a ratio of greater than 3 to negative control in the chromogenic assay.

For considering such a fact, Present Specification states that, in a factor VIII assay after 2-hour incubation, it can be evaluated as "increases procoagulant activity" when it has a ratio of more than 3 to the negative control (paragraphs [0013] and [0014]). On the other hand, in Present Specification, as a procoagulant activity assay, all of assays including a coagulation assay other than a chromogenic assay can be used (paragraphs [0037] and [0065]). Even with the same chromogenic assay, an example in which an incubation time of 2 hours is not employed is stated (Example 11, Figs. 18 to 20). Then, it can be said that there are multiple methods for evaluating procoagulant activity stated in Present Specification. Generally, different evaluation methods do not always use different standards. In Present Specification, it cannot be immediately recognized that "an increase in procoagulant activity" is uniquely determined to have a ratio of more than 3 to negative control in the chromogenic assay.

E. The plaintiffs allege that "increases procoagulant activity" is sufficient if a ratio of more than 2 to negative control can be attained.

However, in Present Specification, even in the case of a ratio of about 1.7 or about 2 to negative control, it cannot be evaluated as "increases procoagulant activity." Thus, it is already stated that it cannot be said that a ratio of more than 1 to negative

control is not always sufficient. The above plaintiffs' allegation cannot be adopted.

(3) On the other hand, if the monoclonal antibody (monospecific antibody) against factor IX or factor IXa does not substantially increase the procoagulant activity of factor IXa, it should be recognized differently. In other words, for belonging to the technical scope of Present Inventions, it is recognized that the antibody should be "a monoclonal antibody (monospecific antibody) against factor IX or factor IXa, which substantially increases the procoagulant activity of factor IXa or an antibody derivative obtained by modifying the antibody while maintaining its activity."

It should be said that such a requirement does not include monoclonal antibodies (monospecific antibodies) against factor IX or factor IXa, which do not substantially increase the procoagulant activity of factor IXa, and also include antibody derivatives (bispecific antibodies derived from such monoclonal antibodies (monospecific antibodies). Even if such an antibody derivative (bispecific antibody) itself has the effect of increasing the procoagulant activity of factor IXa, the antibody derivative is provided with an effect of increasing procoagulant activity by means different from the means of solving the problem of Present Inventions. Thus, it should be said that a person skilled in the art could not make them based on the statements in Present Specification.

(4) As stated in the above (2), it is recognized that "substantially increase the procoagulant activity" must exhibit at least a ratio of 2 to the negative control. As acknowledged in the above 2, the ratio of monospecific antibody (Qhomo) constituted of the left and right arms each binding to factor IXa of the Defendant's product to the negative control was 1.36 to 1.48 as measured by a chromogenic assay kit (Exhibit Otsu 38). Thus, it cannot be said that Qhomo is a monospecific antibody that substantially increases the procoagulant activity of factor IXa. Then, the Defendant's product is a bispecific antibody (antibody derivative) which modified one arm of Qhomo to one for factor X. It can be therefore a derivative from a monospecific antibody that does not substantially increase the procoagulant activity of factor IXa.

Hence, the binding site for factor IXa is removed from the monospecific antibody, which is not a product of substantially increasing the procoagulant activity of factor IXa, and combined with a specific factor X-binding site to convert it into a bispecific antibody to cause an increase in procoagulant activity. The Defendant's product is therefore not admitted to "a monoclonal antibody (monospecific antibody) against factor IX or factor IXa, which substantially increases the procoagulant activity of factor IXa or an antibody derivative obtained by modifying the antibody while maintaining its activity."

(5) It should be therefore said that the Defendant's product cannot be admitted as one falling within the technical scope of Present Inventions.

5. Conclusion

According to the above statements, all the claims of the plaintiffs are without reason and should be dismissed without need to decide the other issues. Accordingly, the court decides as in the main text.

Tokyo District Court, 29th Civil Division

Presiding Judge

SHIMASUE Kazuhide

Judge

ITO Kiyotaka

Judge

NISHIYAMA Yoshiki

(Attachment)

List of parties

Plaintiff: Baxalta Incorporated
Plaintiff: Baxalta GmbH
Defendant: CHUGAI PHARMACEUTICAL CO., LTD.

(Attachment)

List of the Defendant's product

1. Product name

Antibody (development code: ACE910 / non-proprietary name: emicizumab)

2. Category

Medicine

3. Manufacturer

CHUGAI PHARMACEUTICAL CO., LTD.

4. Clinical trial start-up time

At the latest around August, 2012

5. Summary

A bispecific antibody that binds simultaneously with active-type factor IX factor and factor X

(Attachment)
Exhibit Ko 4: Patent gazette, omitted

(Attachment)
Exhibit Ko 168: "[Title of Document] Scope of Claims," omitted

(Attachment)

Explanatory document for the Defendant's product

The Defendant's product is an antibody with development code ACE 910, generic name emicizumab, which binds simultaneously with active type IX factor and factor X.

Specifically, the Defendant's product is a bispecific antibody (an antibody designed to bind to two antigens with different antigen binding sites), which is a medicine intended for the treatment of hemophilia A and exerts factor VIII-like functions by binding simultaneously with active type IX factor and factor X to enhance the coagulation.

(Attachment)

Amino acid sequences of the Defendant's product

An antibody comprising amino acids as H chains of

QVQLVESGGGLVQPGGSLRLSCAASGFTFSYYDIQWVRQAPGKGLEWVSSISPSGQSTYYRREVKGRFTISRD

NSKNTLYLQMNSLRAEDTAVYYCARRTGREYGGGWYFDYWGQGTLVTVSS ("IXa-side H chain") and

QVQLVQSGSELKKPGASVKVSCKASGYTFTDNNMDWVRQAPGQGLEWMGDINTRSGGSIYNEEFQDRVIMTVD

KSTDTAYMELSSLRSEDTATYHCARRKSYGYYLDEWGEGTLVTVSS ("X-side H chain")

and an amino acid as a common L chain of

DIQMTQSPSSLSASVGDRVTITCKASRNIERQLAWYQQKPGQAPELLIYQASRKESGVPDRFSGSRYGTDFTL

TISSLQPEDIATYYCQQYSDPPLTFGGGTKVEIK

wherein an antigen-binding site ("IXa-binding site") derived from the IXa-side H chain and the L chain binds to factor IXa, while an antigen-binding site ("X-binding site") derived from the X-side H chain and the L chain binds to factor X.