

Summary of the Invention

[Problems to be solved by the Invention]

The present invention was achieved in view of the above circumstances. An objective of the present invention is to provide multispecific antigen-binding molecules having blood coagulation factor VIII (FVIII) cofactor function-substituting activity and pharmaceutical formulations containing such a molecule as an active ingredient.

Furthermore, the present invention was achieved in view of the above circumstances. Another objective of the present invention is to provide antibodies in which association between a heavy chain and a light chain is regulated, methods for producing an antibody in which association between a heavy chain and a light chain is regulated, and methods for regulating association between a heavy chain and a light chain of an antibody.

[Means for Solving the Problems]

To obtain bispecific antibodies with high specific activity and maximum FVIII cofactor function-substituting activity, the present inventors obtained from a human antibody library, novel light chains having sequences different from those of ACE910 (Eminicizumab), which have FVIII cofactor function-substituting activity, and prepared bispecific antibodies in which amino acid substitutions have been introduced at various sites of the light chains and ACE910 (Eminicizumab) heavy chains. Then, they found that blood coagulation factor IX (FIX) activation-inhibiting activity increases with increase in the FVIII cofactor function-substituting activity.

As a result of dedicated examination, the present inventors succeeded in finding bispecific antibodies whose FIX activation-inhibiting activity is not elevated and whose FVIII cofactor function-substituting activity is elevated.

Furthermore, the present inventors selected a heavy chain constant region CH1 and a light chain constant region (CL) as heavy-chain and light-chain regions to be subjected to association regulation, and conducted dedicated studies on the regulation of association between the CH1 and CL. As a result, the present inventors succeeded in discovering that undesirable CH1 and CL association can be suppressed by substituting specific amino acid residues present at the interface between CH1 and CL with amino acid residues which electrostatically repel each other, and that heterogeneous molecules are formed more efficiently than by using the above-described modifications that only introduce a knob and hole into CH3.

In one aspect, the present invention refers to a bispecific antibody comprising a first antibody heavy chain and a first antibody light chain which bind to blood coagulation factor IX and/or activated blood coagulation factor IX, and a second antibody heavy chain and a second antibody light chain which bind to blood coagulation factor X, wherein the bispecific antibody is

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comprising the amino acid sequence of SEQ ID NO: 60, a first antibody light chain variable region comprising the amino acid sequence of SEQ ID NO: 69, a second antibody heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 79, and a second antibody light chain variable region comprising the amino acid sequence of SEQ ID NO: 90;

- 5 (p) a bispecific antibody which comprises a first antibody heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 59, a first antibody light chain variable region comprising the amino acid sequence of SEQ ID NO: 70, a second antibody heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 80, and a second antibody light chain variable region comprising the amino acid sequence of SEQ ID NO: 91;
- 10 (q) a bispecific antibody which comprises a first antibody heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 60, a first antibody light chain variable region comprising the amino acid sequence of SEQ ID NO: 71, a second antibody heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 79, and a second antibody light chain variable region comprising the amino acid sequence of SEQ ID NO: 90;
- 15 (r) a bispecific antibody which comprises a first antibody heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 60, a first antibody light chain variable region comprising the amino acid sequence of SEQ ID NO: 71, a second antibody heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 81, and a second antibody light chain variable region comprising the amino acid sequence of SEQ ID NO: 92;
- 20 (s) a bispecific antibody which comprises a first antibody heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 60, a first antibody light chain variable region comprising the amino acid sequence of SEQ ID NO: 69, a second antibody heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 82, and a second antibody light chain variable region comprising the amino acid sequence of SEQ ID NO: 93;
- 25 (t) a bispecific antibody which comprises a first antibody heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 105, a first antibody light chain variable region comprising the amino acid sequence of SEQ ID NO: 72, a second antibody heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 83, and a second antibody light chain variable region comprising the amino acid sequence of SEQ ID NO: 94.

30 In another aspect, the present invention refers to a bispecific antibody comprising a first antibody heavy chain and a first antibody light chain which bind to blood coagulation factor IX and/or activated blood coagulation factor IX, and a second antibody heavy chain and a second antibody light chain which bind to blood coagulation factor X, wherein the bispecific antibody is any of (a) to (t) below:

- 35 (a) a bispecific antibody which comprises a first antibody heavy chain comprising the amino acid sequence of SEQ ID NO: 120, a first antibody light chain comprising the amino acid sequence of

sequence of SEQ ID NO: 155;

(p) a bispecific antibody which comprises a first antibody heavy chain comprising the amino acid sequence of SEQ ID NO: 123, a first antibody light chain comprising the amino acid sequence of SEQ ID NO: 135, a second antibody heavy chain comprising the amino acid sequence of SEQ ID NO: 145, and a second antibody light chain comprising the amino acid sequence of SEQ ID NO: 156;

(q) a bispecific antibody which comprises a first antibody heavy chain comprising the amino acid sequence of SEQ ID NO: 124, a first antibody light chain comprising the amino acid sequence of SEQ ID NO: 136, a second antibody heavy chain comprising the amino acid sequence of SEQ ID NO: 144, and a second antibody light chain comprising the amino acid sequence of SEQ ID NO: 155;

(r) a bispecific antibody which comprises a first antibody heavy chain comprising the amino acid sequence of SEQ ID NO: 124, a first antibody light chain comprising the amino acid sequence of SEQ ID NO: 136, a second antibody heavy chain comprising the amino acid sequence of SEQ ID NO: 146, and a second antibody light chain comprising the amino acid sequence of SEQ ID NO: 157;

(s) a bispecific antibody which comprises a first antibody heavy chain comprising the amino acid sequence of SEQ ID NO: 124, a first antibody light chain comprising the amino acid sequence of SEQ ID NO: 134, a second antibody heavy chain comprising the amino acid sequence of SEQ ID NO: 147, and a second antibody light chain comprising the amino acid sequence of SEQ ID NO: 158;

(t) a bispecific antibody which comprises a first antibody heavy chain comprising the amino acid sequence of SEQ ID NO: 125, a first antibody light chain comprising the amino acid sequence of SEQ ID NO: 137, a second antibody heavy chain comprising the amino acid sequence of SEQ ID NO: 148, and a second antibody light chain comprising the amino acid sequence of SEQ ID NO: 159.

In yet another aspect, the present invention refers to an isolated nucleic acid which encodes the bispecific antibody of the present disclosure.

In yet another aspect, the present invention refers to a host cell which comprises the nucleic acid of the present disclosure.

In yet another aspect, the present invention refers to a pharmaceutical formulation which comprises the bispecific antibody of the present disclosure, and a pharmaceutically acceptable carrier.

The present disclosure has been made based on such findings, and specifically provides [1] to [25] below:

[1] a multispecific antigen-binding molecule which has a function to substitute for the function of blood coagulation factor VIII, wherein the molecule comprises a first antigen-binding site

bleeding, or the disease caused by bleeding is a disease which develops and/or progresses due to a decrease or deficiency in the activity of blood coagulation factor VIII and/or activated blood coagulation factor VIII;

[25] the pharmaceutical formulation of [24], wherein the disease which develops and/or

- 5 progresses due to a decrease or deficiency in the activity of blood coagulation factor VIII and/or activated blood coagulation factor VIII is hemophilia A, a disease with emergence of an inhibitor against blood coagulation factor VIII and/or activated blood coagulation factor VIII, acquired hemophilia, or von Willebrand disease.

Furthermore, the present disclosure relates to the following:

- 10 [26] the multispecific antigen-binding molecule of any one of [1] to [9], the multispecific antibody of [10], the bispecific antibody of [10], [11], or [16], or the antigen-binding molecule of any one of [12] to [15], which is for use as a medicament;

[27] the multispecific antigen-binding molecule of any one of [1] to [9], the multispecific antibody of [10], or the bispecific antibody of [10] or [11], which is for use in prevention and/or

- 15 treatment of bleeding, a disease involving bleeding, or a disease caused by bleeding;

[28] the multispecific antigen-binding molecule of any one of [1] to [9], the multispecific antibody of [10], or the bispecific antibody of [10] or [11], which is for use in substituting for the cofactor function of FVIII;

[29] use of the multispecific antigen-binding molecule of any one of [1] to [9], the multispecific

- 20 antibody of [10], or the bispecific antibody of [10] or [11] in the manufacture of a medicament for treating bleeding, a disease involving bleeding, or a disease caused by bleeding;

[30] use of the multispecific antigen-binding molecule of any one of [1] to [9], the multispecific antibody of [10], or the bispecific antibody of [10] or [11] in the manufacture of a medicament for substituting for the cofactor function of FVIII ;

[31] a method for treating an individual with bleeding, a disease involving bleeding, or a disease caused by bleeding, wherein the method comprises administering to the individual an effective amount of the multispecific antigen-binding molecule of any one of [1] to [9], the multispecific antibody of [10], or the bispecific antibody of [10] or [11]; and

- 25 [32] a method for substituting for the cofactor function of FVIII in an individual, wherein the method comprises the step of administering to the individual an effective amount of the multispecific antigen-binding molecule of any one of [1] to [9], the multispecific antibody of [10], or the bispecific antibody of [10] or [11] for substituting for the cofactor function of FVIII .

[32] a method for substituting for the cofactor function of FVIII in an individual, wherein the

- 30 method comprises the step of administering to the individual an effective amount of the multispecific antigen-binding molecule of any one of [1] to [9], the multispecific antibody of [10], or the bispecific antibody of [10] or [11] for substituting for the cofactor function of FVIII .

Furthermore, the present disclosure relates to the following:

[33] the antigen-binding molecule production method of [17], which comprises in step (1), the

- 35 step of modifying a nucleic acid such that the amino acid residues which electrostatically repel each other are selected from the amino acid residues included in either group of (X) or (Y)

position 44 according to Kabat numbering; and

[40] the method of [38] or [39], wherein the amino acid residues which electrostatically repel each other are selected from the amino acid residues included in either set of (X) or (Y) below:

(X) glutamic acid (E) and aspartic acid (D); and

5 (Y) lysine (K), arginine (R), and histidine (H).

Furthermore, the present disclosure relates to the following:

[41] the multispecific antigen-binding molecule of any one of [1] to [7], which is any of (a) to (v) below:

(a) a multispecific antigen-binding molecule which comprises a first antibody heavy chain
10 variable domain comprising the amino acid sequence of SEQ ID NO: 56, a first antibody light chain variable domain comprising the amino acid sequence of SEQ ID NO: 61, a second antibody heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 73, and a second antibody light chain variable domain comprising the amino acid sequence of SEQ ID NO: 84 (QH01/QL21//JH01/JL01);

15 (b) a multispecific antigen-binding molecule which comprises a first antibody heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 57, a first antibody light chain variable domain comprising the amino acid sequence of SEQ ID NO: 62, a second antibody heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 73, and a second antibody light chain variable domain comprising the amino acid sequence of SEQ
20 ID NO: 84 (QH02/QL22//JH01/JL01);

(c) a multispecific antigen-binding molecule which comprises a first antibody heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 58, a first antibody light chain variable domain comprising the amino acid sequence of SEQ ID NO: 63, a second antibody heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 74,
25 and a second antibody light chain variable domain comprising the amino acid sequence of SEQ ID NO: 85 (QH03/QL23//JH02/JL02);

(d) a multispecific antigen-binding molecule which comprises a first antibody heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 58, a first antibody light chain variable domain comprising the amino acid sequence of SEQ ID NO: 64, a second
30 antibody heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 74, and a second antibody light chain variable domain comprising the amino acid sequence of SEQ ID NO: 85 (QH03/QL24//JH02/JL02);

(e) a multispecific antigen-binding molecule which comprises a first antibody heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 57, a first antibody light
35 chain variable domain comprising the amino acid sequence of SEQ ID NO: 62, a second antibody heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 75,

CLAIMS

1. A bispecific antibody comprising a first antibody heavy chain and a first antibody light chain which bind to blood coagulation factor IX and/or activated blood coagulation factor IX,
5 and a second antibody heavy chain and a second antibody light chain which bind to blood coagulation factor X, wherein the bispecific antibody is any of (a) to (t) below:
- (a) a bispecific antibody which comprises a first antibody heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 56, a first antibody light chain variable region comprising the amino acid sequence of SEQ ID NO: 61, a second antibody heavy chain
10 variable region comprising the amino acid sequence of SEQ ID NO: 73, and a second antibody light chain variable region comprising the amino acid sequence of SEQ ID NO: 84;
- (b) a bispecific antibody which comprises a first antibody heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 57, a first antibody light chain variable region comprising the amino acid sequence of SEQ ID NO: 62, a second antibody heavy chain
15 variable region comprising the amino acid sequence of SEQ ID NO: 73, and a second antibody light chain variable region comprising the amino acid sequence of SEQ ID NO: 84;
- (c) a bispecific antibody which comprises a first antibody heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 58, a first antibody light chain variable region comprising the amino acid sequence of SEQ ID NO: 63, a second antibody heavy chain
20 variable region comprising the amino acid sequence of SEQ ID NO: 74, and a second antibody light chain variable region comprising the amino acid sequence of SEQ ID NO: 85;
- (d) a bispecific antibody which comprises a first antibody heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 58, a first antibody light chain variable region comprising the amino acid sequence of SEQ ID NO: 64, a second antibody heavy chain
25 variable region comprising the amino acid sequence of SEQ ID NO: 74, and a second antibody light chain variable region comprising the amino acid sequence of SEQ ID NO: 85;
- (e) a bispecific antibody which comprises a first antibody heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 57, a first antibody light chain variable region comprising the amino acid sequence of SEQ ID NO: 62, a second antibody heavy chain
30 variable region comprising the amino acid sequence of SEQ ID NO: 75, and a second antibody light chain variable region comprising the amino acid sequence of SEQ ID NO: 86;
- (f) a bispecific antibody which comprises a first antibody heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 57, a first antibody light chain variable region comprising the amino acid sequence of SEQ ID NO: 62, a second antibody heavy chain variable
35 region comprising the amino acid sequence of SEQ ID NO: 76, and a second antibody light chain variable region comprising the amino acid sequence of SEQ ID NO: 87;

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comprising the amino acid sequence of SEQ ID NO: 59, a first antibody light chain variable region comprising the amino acid sequence of SEQ ID NO: 68, a second antibody heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 78, and a second antibody light chain variable region comprising the amino acid sequence of SEQ ID NO: 89;

- 5 (o) a bispecific antibody which comprises a first antibody heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 60, a first antibody light chain variable region comprising the amino acid sequence of SEQ ID NO: 69, a second antibody heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 79, and a second antibody light chain variable region comprising the amino acid sequence of SEQ ID NO: 90;
- 10 (p) a bispecific antibody which comprises a first antibody heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 59, a first antibody light chain variable region comprising the amino acid sequence of SEQ ID NO: 70, a second antibody heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 80, and a second antibody light chain variable region comprising the amino acid sequence of SEQ ID NO: 91;
- 15 (q) a bispecific antibody which comprises a first antibody heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 60, a first antibody light chain variable region comprising the amino acid sequence of SEQ ID NO: 71, a second antibody heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 79, and a second antibody light chain variable region comprising the amino acid sequence of SEQ ID NO: 90;
- 20 (r) a bispecific antibody which comprises a first antibody heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 60, a first antibody light chain variable region comprising the amino acid sequence of SEQ ID NO: 71, a second antibody heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 81, and a second antibody light chain variable region comprising the amino acid sequence of SEQ ID NO: 92;
- 25 (s) a bispecific antibody which comprises a first antibody heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 60, a first antibody light chain variable region comprising the amino acid sequence of SEQ ID NO: 69, a second antibody heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 82, and a second antibody light chain variable region comprising the amino acid sequence of SEQ ID NO: 93;
- 30 (t) a bispecific antibody which comprises a first antibody heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 105, a first antibody light chain variable region comprising the amino acid sequence of SEQ ID NO: 72, a second antibody heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 83, and a second antibody light chain variable region comprising the amino acid sequence of SEQ ID NO: 94.

- 35 2. The bispecific antibody of claim 1, wherein the first antibody heavy chain and antibody

light chain comprise constant regions comprising the amino acid sequences set forth in (1) below, and the second antibody heavy chain and antibody light chain comprise constant regions comprising the amino acid sequences set forth in (2) below: (1) SEQ ID NO: 119 as a heavy chain constant region and SEQ ID NO: 100 as a light chain constant region

5 (2) SEQ ID NO: 118 as a heavy chain constant region and SEQ ID NO: 102 as a light chain constant region.

3. A bispecific antibody comprising a first antibody heavy chain and a first antibody light chain which bind to blood coagulation factor IX and/or activated blood coagulation factor IX, and a second antibody heavy chain and a second antibody light chain which bind to blood coagulation factor X, wherein the bispecific antibody is any of (a) to (t) below:

10 (a) a bispecific antibody which comprises a first antibody heavy chain comprising the amino acid sequence of SEQ ID NO: 120, a first antibody light chain comprising the amino acid sequence of SEQ ID NO: 126, a second antibody heavy chain comprising the amino acid sequence of SEQ ID NO: 138, and a second antibody light chain comprising the amino acid sequence of SEQ ID NO: 149;

(b) a bispecific antibody which comprises a first antibody heavy chain comprising the amino acid sequence of SEQ ID NO: 121, a first antibody light chain comprising the amino acid sequence of SEQ ID NO: 127, a second antibody heavy chain comprising the amino acid sequence of SEQ ID NO: 138, and a second antibody light chain comprising the amino acid sequence of SEQ ID NO: 149;

(c) a bispecific antibody which comprises a first antibody heavy chain comprising the amino acid sequence of SEQ ID NO: 122, a first antibody light chain comprising the amino acid sequence of SEQ ID NO: 128, a second antibody heavy chain comprising the amino acid sequence of SEQ ID NO: 139, and a second antibody light chain comprising the amino acid sequence of SEQ ID NO: 150;

(d) a bispecific antibody which comprises a first antibody heavy chain comprising the amino acid sequence of SEQ ID NO: 122, a first antibody light chain comprising the amino acid sequence of SEQ ID NO: 129, a second antibody heavy chain comprising the amino acid sequence of SEQ ID NO: 139, and a second antibody light chain comprising the amino acid sequence of SEQ ID NO: 150;

(e) a bispecific antibody which comprises a first antibody heavy chain comprising the amino acid sequence of SEQ ID NO: 121, a first antibody light chain comprising the amino acid sequence of SEQ ID NO: 127, a second antibody heavy chain comprising the amino acid sequence of SEQ ID NO: 140, and a second antibody light chain comprising the amino acid sequence of SEQ ID NO: 151;

5 NO: 152;

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10    sequence of SEQ ID NO: 150;
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15 sequence of SEO ID NO: 150;

20 NO: 150;

25 NO: 153;

30 sequence of SEO ID NO: 153;

35 NO: 154;

(m) a bispecific antibody which comprises a first antibody heavy chain comprising the amino

acid sequence of SEQ ID NO: 123, a first antibody light chain comprising the amino acid sequence of SEQ ID NO: 133, a second antibody heavy chain comprising the amino acid sequence of SEQ ID NO: 142, and a second antibody light chain comprising the amino acid sequence of SEQ ID NO: 153;

- 5 (n) a bispecific antibody which comprises a first antibody heavy chain comprising the amino acid sequence of SEQ ID NO: 123, a first antibody light chain comprising the amino acid sequence of SEQ ID NO: 133, a second antibody heavy chain comprising the amino acid sequence of SEQ ID NO: 143, and a second antibody light chain comprising the amino acid sequence of SEQ ID NO: 154;
- 10 (o) a bispecific antibody which comprises a first antibody heavy chain comprising the amino acid sequence of SEQ ID NO: 124, a first antibody light chain comprising the amino acid sequence of SEQ ID NO: 134, a second antibody heavy chain comprising the amino acid sequence of SEQ ID NO: 144, and a second antibody light chain comprising the amino acid sequence of SEQ ID NO: 155;
- 15 (p) a bispecific antibody which comprises a first antibody heavy chain comprising the amino acid sequence of SEQ ID NO: 123, a first antibody light chain comprising the amino acid sequence of SEQ ID NO: 135, a second antibody heavy chain comprising the amino acid sequence of SEQ ID NO: 145, and a second antibody light chain comprising the amino acid sequence of SEQ ID NO: 156;
- 20 (q) a bispecific antibody which comprises a first antibody heavy chain comprising the amino acid sequence of SEQ ID NO: 124, a first antibody light chain comprising the amino acid sequence of SEQ ID NO: 136, a second antibody heavy chain comprising the amino acid sequence of SEQ ID NO: 144, and a second antibody light chain comprising the amino acid sequence of SEQ ID NO: 155;
- 25 (r) a bispecific antibody which comprises a first antibody heavy chain comprising the amino acid sequence of SEQ ID NO: 124, a first antibody light chain comprising the amino acid sequence of SEQ ID NO: 136, a second antibody heavy chain comprising the amino acid sequence of SEQ ID NO: 146, and a second antibody light chain comprising the amino acid sequence of SEQ ID NO: 157;
- 30 (s) a bispecific antibody which comprises a first antibody heavy chain comprising the amino acid sequence of SEQ ID NO: 124, a first antibody light chain comprising the amino acid sequence of SEQ ID NO: 134, a second antibody heavy chain comprising the amino acid sequence of SEQ ID NO: 147, and a second antibody light chain comprising the amino acid sequence of SEQ ID NO: 158;
- 35 (t) a bispecific antibody which comprises a first antibody heavy chain comprising the amino acid sequence of SEQ ID NO: 125, a first antibody light chain comprising the amino acid sequence of

SEQ ID NO: 137, a second antibody heavy chain comprising the amino acid sequence of SEQ ID NO: 148, and a second antibody light chain comprising the amino acid sequence of SEQ ID NO: 159.

- 5 4. An isolated nucleic acid which encodes the bispecific antibody of any one of claims 1-3.
5. A host cell which comprises the nucleic acid of claim 4.
6. A pharmaceutical formulation which comprises the bispecific antibody of any one of
10 claims 1-3, and a pharmaceutically acceptable carrier.
7. The pharmaceutical formulation of claim 6, which is for use in prevention and/or
treatment of bleeding, a disease involving bleeding, or a disease caused by bleeding.
- 15 8. The pharmaceutical formulation of claim 7, wherein the bleeding, the disease involving
bleeding, or the disease caused by bleeding is a disease which develops and/or progresses due to
a decrease or deficiency in the activity of blood coagulation factor VIII and/or activated blood
coagulation factor VIII.
- 20 9. The pharmaceutical formulation of claim 8, wherein the disease which develops and/or
progresses due to a decrease or deficiency in the activity of blood coagulation factor VIII and/or
activated blood coagulation factor VIII is hemophilia A, a disease with emergence of an inhibitor
against blood coagulation factor VIII and/or activated blood coagulation factor VIII, acquired
hemophilia, or von Willebrand disease.