[Non-patent Document 4] Biochim.Biophys.Acta 871, 268-278 (1986)
[Non-patent Document 5] Nature Medicine 18, 1570-1574(2012)
[Non-patent Document 6] PLOS ONE 8, 1-13(2013)
[Non-patent Document 7] J Thromb Haemost. 12, 206-213(2014)

Summary of the Invention

[Problems to be solved by the Invention]

An objective of the present invention is to provide a more effective pharmaceutical composition or a dosage regimen for preventing and/or treating a disease that 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.

[Means for Solving the Problems]

As a result of dedicated research, the present inventors succeeded in discovering a more effective dosage regimen for a pharmaceutical composition containing a bispecific antigen-binding molecule that recognizes blood coagulation factor IX and/or activated blood coagulation factor IX and blood coagulation factor X and/or activated blood coagulation factor X for preventing and/or treating a disease that 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.

Specifically, the present invention relates to the use of a composition comprising a bispecific antigen-binding molecule that recognizes blood coagulation factor IX and/or activated blood coagulation factor IX and blood coagulation factor X and/or activated blood coagulation factor X in the manufacture of a medicament for preventing and/or treating a disease that 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, wherein the antigen-binding molecule is to be administered at an initial dose of approximately 0.001 to 100 mg/kg and is to be continually administered several times at continued doses that are nearly the same as or less than the initial dose, wherein the interval between individual administrations is at least one day or longer. In another aspect, the present invention refers to a product comprising (i) a container; (ii) a pharmaceutical composition in the container, wherein the composition comprises a bispecific antigen-binding molecule that recognizes blood coagulation factor IX and/or activated blood coagulation factor IX and blood coagulation factor X and/or activated blood coagulation factor X; and (iii) a document instructing administration of the antigen-binding molecule at an initial dose of approximately 0.001 to 100 mg/kg and several continued administrations of continued doses that are nearly the same as or less than the initial dose, wherein the interval between

individual administrations is at least one day or longer. Also described herein is a pharmaceutical composition or a dosage regimen used for preventing and/or treating a disease that 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, and specifically relates to the following:

[1] a pharmaceutical composition for use in preventing and/or treating a disease that 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, wherein the composition comprises a bispecific antigen-binding molecule that recognizes blood coagulation factor IX and/or activated blood coagulation factor IX and blood coagulation factor X and/or activated blood coagulation factor X, wherein the antigen-binding molecule is administered at an initial dose of approximately 0.001 to 100 mg/kg and is continually administered several times at continued doses that are nearly the same as or less than the initial dose, wherein the interval between individual administrations is at least one day or longer;

[2] the pharmaceutical composition of [1], wherein the continued dose is a dose selected from the group consisting of the same dose as the initial dose, and approximately one-half, approximately one-third, approximately 0.3-times, approximately one-fourth, approximately

of blood coagulation factor VIII and/or activated blood coagulation factor VIII;

[14] the product of [13], wherein the label indicates that the pharmaceutical composition can be used for the treatment of hemophilia A, acquired hemophilia A, von Willebrand disease, and hemophilia A with emergence of an inhibitor against blood coagulation factor VIII and/or activated blood coagulation factor VIII; and

[15] the product of any one of [10] to [14], wherein the antigen-binding molecule is the bispecific antibody described below, wherein the first polypeptide and the third polypeptide are associated and the second polypeptide and the fourth polypeptide are associated:

a bispecific antibody comprising a first polypeptide which is an H chain comprising the amino acid sequence of SEQ ID NO: 20; a second polypeptide which is an H chain comprising the amino acid sequence of SEQ ID NO: 25; and a third polypeptide and a fourth polypeptide which are commonly shared L chain comprising the amino acid sequence of SEQ ID NO: 32.

Furthermore, the present disclosure relates to:

[16] a method for preventing and/or treating a disease that 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, which comprises administering a bispecific antigen-binding molecule which recognizes blood coagulation factor IX and/or activated blood coagulation factor IX and blood coagulation factor X and/or activated blood coagulation factor X at an initial dose of approximately 0.001 to 100 mg/kg and continually administering the antigen-binding molecule several times at continued doses that are nearly the same as or less than the initial dose, wherein the interval between administrations is at least one day or longer;

[17] an antigen-binding molecule for use in preventing and/or treating a disease that 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, wherein the bispecific antigen-binding molecule recognizes blood coagulation factor IX and/or activated blood coagulation factor IX and blood coagulation factor X and/or activated blood coagulation factor X and is administered at an initial dose of approximately 0.001 to 100 mg/kg and then continually administered several times at continued doses that are nearly the same as or less than the initial dose, wherein the interval between administrations is at least one day or longer; and

[18] use of an antigen-binding molecule in the manufacture of a pharmaceutical composition used for preventing and/or treating a disease that 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, wherein the bispecific antigen-binding molecule recognizes blood coagulation factor IX and/or activated blood coagulation factor IX and blood coagulation factor X and/or activated blood coagulation factor X and is administered at an initial dose of approximately 0.001 to 100 mg/kg and then continually administered several times at continued doses that are nearly the

CLAIMS

1. Use of a composition comprising a bispecific antigen-binding molecule that recognizes blood coagulation factor IX and/or activated blood coagulation factor IX and blood coagulation factor X and/or activated blood coagulation factor X in the manufacture of a medicament for preventing and/or treating a disease that 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, wherein the antigen-binding molecule is to be administered at an initial dose of approximately 0.001 to 100 mg/kg and is to be continually administered several times at continued doses that are nearly the same as or less than the initial dose, wherein the interval between individual administrations is at least one day or longer.

2. The use of claim 1, wherein the continued dose is a dose selected from the group consisting of the same dose as the initial dose, and approximately one-half, approximately one-third, approximately 0.3-times, approximately one-fourth, approximately one-fifth, and approximately one-tenth the initial dose.

3. The use of claim 2, wherein the initial dose is 1 mg/kg and at least one of the continued doses is 0.3 mg/kg.

4. The use of claim 2, wherein the initial dose is 3 mg/kg and at least one of the continued doses is 1 mg/kg.

5. The use of claim 2, wherein the initial dose is 3 mg/kg and at least one of the continued doses is 3 mg/kg.

6. The use of any one of claims 1 to 5, wherein at least one of the intervals between individual administrations is one week.

7. The use of any one of claims 1 to 6, wherein the disease is selected from the group consisting of hemophilia A, acquired hemophilia A, von Willebrand disease, and hemophilia A with emergence of an inhibitor against blood coagulation factor VIII and/or activated blood coagulation factor VIII.

8. The use of any one of claims 1 to 7, wherein the antigen-binding molecule is the bispecific antibody described below, wherein the first polypeptide and the third polypeptide are associated and the second polypeptide and the fourth polypeptide are associated:

a bispecific antibody comprising a first polypeptide which is an H chain comprising the amino acid sequence of SEQ ID NO: 20; a second polypeptide which is an H chain comprising the amino acid sequence of SEQ ID NO: 25; a third polypeptide and a fourth polypeptide which are a commonly shared L chain comprising the amino acid sequence of SEQ ID NO: 32.

9. The use of any one of claims 1 to 8, wherein the antigen-binding molecule is to be administered subcutaneously.

10. A product comprising (i) a container; (ii) a pharmaceutical composition in the container, wherein the composition comprises a bispecific antigen-binding molecule that recognizes blood coagulation factor IX and/or activated blood coagulation factor IX and blood coagulation factor X and/or activated blood coagulation factor X; and (iii) a document instructing administration of the antigen-binding molecule at an initial dose of approximately 0.001 to 100 mg/kg and several continued administrations of continued doses that are nearly the same as or less than the initial dose, wherein the interval between individual administrations is at least one day or longer.

11. The product of claim 10, wherein the initial dose is 1 mg/kg and at least one of the continued doses is 0.3 mg/kg.

12. The product of claim 10 or 11, wherein at least one of the intervals between individual administrations is one week.

13. The product of any one of claims 10 to 12, which further comprises a label attached to the container which indicates that the pharmaceutical composition can be used for preventing and/or treating a disease that 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.

14. The product of claim 13, wherein the label indicates that the pharmaceutical composition can be used for the treatment of hemophilia A, acquired hemophilia A, von Willebrand disease, and hemophilia A with emergence of an inhibitor against blood coagulation factor VIII and/or activated blood coagulation factor VIII.

15. The product of any one of claims 10 to 14, wherein the antigen-binding molecule is the bispecific antibody described below, wherein the first polypeptide and the third polypeptide are associated and the second polypeptide and the fourth polypeptide are associated:

a bispecific antibody comprising a first polypeptide which is an H chain comprising the amino acid sequence of SEQ ID NO: 20; a second polypeptide which is an H chain comprising the amino acid sequence of SEQ ID NO: 25; and a third polypeptide and a fourth polypeptide which are commonly shared L chain comprising the amino acid sequence of SEQ ID NO: 32.