[PTL 2] WO 2005/035756
[PTL 3] WO 2006/109592
[PTL 4] WO 2012/067176
[PTL 5] WO 2015/194233

Non-Patent Literature

[0010]

[NPL 1] Blood 58, 1-13 (1981)
[NPL 2] Nature 312, 330-337 (1984)
[NPL 3] Nature 312, 337-342 (1984)
[NPL 4] Biochim.Biophys.Acta 871, 268-278 (1986)
[NPL 5] Nature Medicine 18, 1570-1574(2012)
[NPL 6] PLOS ONE 8, 1-13(2013)
[NPL 7] J Thromb Haemost. 12, 206-213(2014)
[NPL 8] Blood 127(13), 1633-1641(2016)
[NPL 9] N Engl J Med. 374(21), 2044-2053(2016)
[NPL 10] XXV Congress of the International Society on Thrombosis and Haemostasis, Toronto, Canada, June 20-25, 2015. Abstr AS017.

Summary of Invention

[Technical Problem]

[0011]

An objective of the present invention is to provide another effective pharmaceutical composition or a dosage regimen for treating and/or reducing the incidence of a disease that develops and/or progresses due to a decrease or deficiency in the activity of FVIII and/or activated blood coagulation factor VIII (FVIIIa).

[Solution to Problem]

[0012]

As a result of dedicated research, the present inventors succeeded in discovering an effective dosage regimen for a pharmaceutical composition containing a bispecific antigen-binding molecule (antibody) that recognizes (a) FIX and/or FIXa and (b) FX and/or FXa for treating and/or reducing the incidence of a disease that develops and/or progresses due to a decrease or deficiency in the activity of FVIII and/or FVIIIa.

[0012a]

In one aspect, the present invention refers to use of a bispecific antibody that recognizes (a) blood coagulation factor IX and/or activated blood coagulation factor IX and (b) blood coagulation factor X and/or activated blood coagulation factor X in the manufacture of a medicament for treating and/or reducing the incidence of 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 (FVIIIa), wherein the bispecific antibody is to be administered to a subject at a weekly loading dose of 3 mg/kg or 4.5 mg/kg of the antibody for one or more weeks or at an every-two-week loading dose of 6 mg/kg of the antibody for two or more weeks; and, after the loading dose administration(s) are complete, a maintenance dose of

the antibody is to be administered to the subject one or more times, the maintenance dose being 6 mg/kg of the antibody. In another aspect, the present invention refers to use of a bispecific antibody that recognizes (a) blood coagulation factor IX and/or activated blood coagulation factor IX and (b) blood coagulation factor X and/or activated blood coagulation factor X in the manufacture of a medicament for treating and/or reducing the incidence of 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 (FVIIIa), wherein the bispecific antibody is to be administered to a subject at a weekly loading dose of 4.5 mg/kg of the antibody for four weeks; and thereafter a maintenance dose of the antibody is to be administered to the subject one or more times, the maintenance dose being 9 mg/kg of the antibody which is administered every four weeks or every month in two or four divided doses. In yet another aspect, the present invention refers to use of a bispecific antibody that recognizes (a) blood coagulation factor IX and/or activated blood coagulation factor IX and (b) blood coagulation factor X and/or activated blood coagulation factor X in the manufacture of a medicament for treating and/or reducing the incidence of 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 (FVIIIa), wherein the bispecific antibody is to be administered to a subject at a weekly loading dose of 6 mg/kg of the antibody for four weeks; and thereafter a maintenance dose of the antibody is to be administered to the subject one or more times, the maintenance dose being 12 mg/kg of the antibody which is administered every four weeks or every month in two or four divided doses.

[0013]

Specifically, the present disclosure relates to a pharmaceutical composition or a dosage regimen used for treating and/or reducing the incidence of a disease that develops and/or progresses due to a decrease or deficiency in the activity of FVIII and/or FVIIIa, and specifically relates to the following:

[1] a method for treating and/or reducing the incidence of 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 (FVIIIa), the method comprising: administering to a subject a bispecific antibody that recognizes (a) blood coagulation factor IX and/or activated blood coagulation factor IX and (b) blood co-

the antibody for four weeks; and thereafter administering a maintenance dose of the antibody to the subject one or more times, the maintenance dose being 9 mg/kg of the antibody which is administered every four weeks or every month in two or four divided doses;
[11] a method for treating and/or reducing the incidence of 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 (FVIIIa), the method comprising: administering to a subject a bispecific antibody that recognizes (a) blood coagulation factor IX and/or activated blood coagulation factor IX and (b) blood coagulation factor X and/or activated blood coagulation factor X at a weekly loading dose of 6 mg/kg of the antibody for four weeks; and thereafter administering a maintenance dose of the antibody to the subject one or more times, the maintenance dose being 12 mg/kg of the antibody which is administered every four weeks or every month in two or four divided doses;
[12] the method of [10] further comprising, in a case of no or insufficient effect of treating and/or reducing the incidence of the disease by administering the maintenance dose of the antibody, stopping administering the maintenance dose of the antibody and starting administering an alternative maintenance dose of the antibody to the subject, the alternative maintenance dose being a weekly dose of 4.5 mg/kg of the antibody;
[13] the method of [11] further comprising, in a case of no or insufficient effect of treating and/or reducing the incidence of the disease by administering the maintenance dose of the antibody, stopping administering the maintenance dose of the antibody and starting administering an alternative maintenance dose of the antibody to the subject, the alternative maintenance dose being a weekly dose of 6 mg/kg of the antibody;
[14] the method of any one of [1] to [13], wherein the antibody is emicizumab; and
[15] the method of [14], wherein the 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 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.
[0014]
Furthermore, the present disclosure relates to:
[16] a pharmaceutical composition for use in treating and/or reducing the incidence of 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 (FVIIIa), wherein the composition comprises a bispecific antibody that recognizes (a) blood coagulation factor IX and/or activated blood coagulation factor IX and (b) blood coagulation factor X and/or activated blood coagulation factor X, wherein the

[CLAIMS]

[Claim 1]

Use of a bispecific antibody that recognizes (a) blood coagulation factor IX and/or activated blood coagulation factor IX and (b) blood coagulation factor X and/or activated blood coagulation factor X in the manufacture of a medicament for treating and/or reducing the incidence of 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 (FVIIIa), wherein the bispecific antibody is to be administered to a subject at a weekly loading dose of 3 mg/kg or 4.5 mg/kg of the antibody for one or more weeks or at an every-two-week loading dose of 6 mg/kg of the antibody for two or more weeks; and, after the loading dose administration(s) are complete, a maintenance dose of the antibody is to be administered to the subject one or more times, the maintenance dose being 6 mg/kg of the antibody.

[Claim 2]

The use of claim 1, wherein the maintenance dose of 6 mg/kg of the antibody is to be administered to the subject every four weeks or every month in a single dose or multiple divided doses.

[Claim 3]

The use of claim 1 or 2, wherein the antibody is to be administered at the weekly loading dose of 3 mg/kg of the antibody for four weeks, followed by the maintenance dose.

[Claim 4]

The use of claim 1 or 2, wherein the antibody is to be administered at the weekly loading dose of 4.5 mg/kg of the antibody for two weeks, followed by the maintenance dose.

[Claim 5]

The use of claim 1 or 2, wherein the antibody is to be administered at the every-two-week loading dose of 6 mg/kg of the antibody for four weeks, followed by the maintenance dose.

[Claim 6]

The use of any one of claims 1 to 5, wherein the maintenance dose is to be administered in one single dose at 6 mg/kg of the antibody monthly or every four weeks.

[Claim 7]

The use of any one of claims 1 to 5, wherein the maintenance dose is to be administered in two single doses of the antibody, each at 3 mg/kg, monthly or every four weeks, wherein one single dose of the maintenance dose at 3 mg/kg of the antibody is to be administered once every two weeks.

[Claim 8]

The use of any one of claims 1 to 5, wherein the maintenance dose is to be administered in four single doses each at 1.5 mg/kg of the antibody monthly or every four weeks, wherein one single dose of the maintenance dose at 1.5 mg/kg of the antibody is to be administered once every week.

[Claim 9]

The use of any one of claims 1 to 8 further comprising, in a case wherein the incidence of the disease is not reduced when using the maintenance dose of the antibody, the maintenance dose of the antibody is stopped and an alternative maintenance dose of the antibody is to be administered to the subject, the alternative maintenance dose being a weekly dose of 3 mg/kg of the antibody or an every-two-week dose of 6 mg/kg of the antibody.

[Claim 10]

Use of a bispecific antibody that recognizes (a) blood coagulation factor IX and/or activated blood coagulation factor IX and (b) blood coagulation factor X and/or activated blood coagulation factor X in the manufacture of a medicament for treating and/or reducing the incidence of 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 (FVIIIa), wherein the bispecific antibody is to be administered to a subject at a weekly loading dose of 4.5 mg/kg of the antibody for four weeks; and thereafter a maintenance dose of the antibody is to be administered to the subject one or more times, the maintenance dose being 9 mg/kg of the antibody which is administered every four weeks or every month in two or four divided doses.

[Claim 11]

Use of a bispecific antibody that recognizes (a) blood coagulation factor IX and/or activated blood coagulation factor IX and (b) blood coagulation factor X and/or activated blood coagulation factor X in the manufacture of a medicament for treating and/or reducing the incidence of 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 (FVIIIa), wherein the bispecific antibody is to be administered to a subject at a weekly loading dose of 6 mg/kg of the antibody for four weeks; and thereafter a maintenance dose of the antibody is to be administered to the subject one or more times, the maintenance dose being 12 mg/kg of the antibody which is administered every four weeks or every month in two or four divided doses.

[Claim 12]

The use of claim 10 further comprising, in a case wherein the incidence of the disease is not reduced when using the maintenance dose of the antibody, the maintenance dose of the antibody is stopped and an alternative maintenance dose of the antibody is to be administered to the subject, the alternative maintenance dose being a weekly dose of 4.5 mg/kg of the antibody.

[Claim 13]

The use of claim 11 further comprising, in a case wherein the incidence of the disease is not reduced when using the maintenance dose of the antibody, the maintenance dose of the antibody is stopped and an alternative maintenance dose of the antibody is to be administered to the subject, the alternative maintenance dose being a weekly dose of 6 mg/kg of the antibody.

[Claim 14]

The use of any one of claims 1 to 13, wherein the antibody is emicizumab.

[Claim 15]

The use of claim 14, wherein the 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 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.