[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 (FVIII) 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 of the antibody for four weeks; and, after the loading dose administrations are complete, a maintenance dose of the antibody is to be administered to the subject one or more times, wherein the maintenance dose is 6 mg/kg of

the antibody and it is to be administered to the subject every four weeks in a single dose or multiple divided doses, wherein the disease is hemophilia A, acquired hemophilia A, von Willebrand disease, or hemophilia A with emergence of an inhibitor against FVIII and/or FVIIIa and wherein the bispecific antibody is: (a) a bispecific antibody comprising a first polypeptide which is an H chain containing an H chain variable region containing CDR 1, 2, and 3 amino acid sequences of SEQ ID NOs: 1, 2, and 3, respectively; a second polypeptide which is an H chain containing an H chain variable region containing CDR 1, 2, and 3 amino acid sequences of SEQ ID NOs: 6, 7, and 8, respectively; and a third and fourth polypeptide which are a commonly shared L chain containing an L chain variable region containing CDR 1, 2, and 3 amino acid sequences of SEQ ID NOs: 11, 12, and 13, respectively; (b) a bispecific antibody comprising a first polypeptide which is an H chain containing an H chain variable region amino acid sequence of SEQ ID NO: 4; a second polypeptide which is an H chain containing an H chain variable region amino acid sequence of SEQ ID NO: 9; and a third and fourth polypeptide which are a commonly shared L chain containing an L chain variable region amino acid sequence of SEQ ID NO: 14; or (c) a bispecific antibody comprising a first polypeptide which is an H chain containing the amino acid sequence of SEQ ID NO: 5; a second polypeptide which is an H chain containing the amino acid sequence of SEQ ID NO: 10; and a third and fourth polypeptide which are a commonly shared L chain containing the amino acid sequence of SEQ ID NO: 15.

[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-

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 (FVIII) 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 of the antibody for four weeks; and, after the loading dose administrations are complete, a maintenance dose of the antibody is to be administered to the subject one or more times, wherein the maintenance dose is 6 mg/kg of the antibody and it is to be administered to the subject every four weeks in a single dose or multiple divided doses,

wherein the disease is hemophilia A, acquired hemophilia A, von Willebrand disease, or hemophilia A with emergence of an inhibitor against FVIII and/or FVIIIa and

wherein the bispecific antibody is:

(a) a bispecific antibody comprising a first polypeptide which is an H chain containing an H chain variable region containing CDR 1, 2, and 3 amino acid sequences of SEQ ID NOs: 1, 2, and 3, respectively; a second polypeptide which is an H chain containing an H chain variable region containing CDR 1, 2, and 3 amino acid sequences of SEQ ID NOs: 6, 7, and 8, respectively; and a third and fourth polypeptide which are a commonly shared L chain containing an L chain variable region containing CDR 1, 2, and 3 amino acid sequences of SEQ ID NOs: 11, 12, and 13, respectively;

(b) a bispecific antibody comprising a first polypeptide which is an H chain containing an H chain variable region amino acid sequence of SEQ ID NO: 4;
a second polypeptide which is an H chain containing an H chain variable region amino acid sequence of SEQ ID NO: 9; and a third and fourth polypeptide which are a commonly shared L chain containing an L chain variable region amino acid sequence of SEQ ID NO: 14; or

(c) a bispecific antibody comprising a first polypeptide which is an H chain containing the amino acid sequence of SEQ ID NO: 5; a second polypeptide which is an H chain containing the amino acid sequence of SEQ ID NO: 10; and a third and fourth polypeptide which are a commonly shared L chain containing the amino acid sequence of SEQ ID NO: 15.

[Claim 2]
The use of claim 1, wherein the maintenance dose is selected from following a) to c):
a) the maintenance which is to be administered in one single dose at 6 mg/kg of the antibody every four weeks,
b) the maintenance dose which is to be administered in two single doses of the antibody each at 3 mg/kg 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, and
c) the maintenance dose which is to be administered in four single doses each at 1.5 mg/kg of the antibody every four weeks, wherein one single dose of the maintenance dose at 1.5mg/kg of the antibody is to be administered once every week.

[Claim 3]
The use of claim 1 or 2, wherein the 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 is emicizumab.