[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, wherein the maintenance dose is 6 mg/kg of

the antibody and it is to be administered to the subject every four weeks in one single dose, 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, wherein the maintenance dose is 6 mg/kg of the antibody and it is to be administered to the subject every four weeks in one single dose,

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 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.