AMENDED CLAIMS
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Claims

1. A polypeptide comprising at least one immunoglobulin single variable domain (ISVD) against von Willebrand Factor (vWF) for use in reducing the risk of and/or preventing an acute episode of a vWF-related disease in a human in need thereof, comprising the steps of
   (i) measuring the ADAMTS13 activity of said human;
   (ii) comparing said ADAMTS13 activity with a reference ADAMTS13 activity; and
   (iii) if said ADAMTS13 activity is lower than 30%, such as 20%, 15%, 10% or 5% of said reference ADAMTS13 activity, then administering to said human a dose of 5-40 mg of said polypeptide, preferably 10 mg.

2. The polypeptide according to claim 1, wherein said risk of an acute episode of a vWF-related disease, such as TTP, is reduced by factor of at least 1.2.

3. The polypeptide according to claim 2, wherein the risk is reduced by a factor 1.2, 1.3, 1.4, 1.5, 1.6, 1.75, 1.8, 2 or more, such as 3, 4, 5, 6, 7, 8, 9, or even 10, or even more such as 20, 50 or even 100.

4. The polypeptide according to any of claims 1 to 3, further comprising
   - measuring the platelet number; and
   - if said platelet number is lower than 150,000/µl, then repeating administering to said human a dose of 5-40 mg of said polypeptide, preferably 10 mg.

5. A polypeptide comprising at least one immunoglobulin single variable domain (ISVD) against von Willebrand Factor (vWF) for use in treating a vWF-related disease in a human in need thereof, comprising administering said polypeptide until the ADAMTS13 activity is at least 10% such as at least 15%, 20%, 25%, 30%, 35%, 45% or even 50% of a ADAMTS13 reference activity.

6. A polypeptide comprising at least one immunoglobulin single variable domain (ISVD) against von Willebrand Factor (vWF) for use in treating a vWF-related disease in a human in need thereof, comprising at least the following steps;
   (i) performing a Plasma Exchange (PE);
   (ii) administering to said human a dose of 5-40 mg, preferably 10 mg of said polypeptide;
   (iii) measuring the ADAMTS13 activity of said patient;

(iv) comparing said ADAMTS13 activity with a reference ADAMTS13 activity; and

(v) if said ADAMTS13 activity is lower than 30%, such as 20%, 15%, 10% or 5% of said reference ADAMTS13 activity, then repeating said step (ii) and optionally step (i), wherein said step (i) and/or said step (ii) are repeated once or twice per day.

7. The polypeptide according to claim 6, wherein said step (i) is repeated once or twice per day, for at most for 7 days such as at most 6, 5, 4, 3, or 2 days.

8. A polypeptide comprising at least one immunoglobulin single variable domain (ISVD) against von Willebrand Factor (vWF) for use in reducing and/or preventing ischaemic organ damage by a vWF-related disease in a human in need thereof, comprising at least the following steps;

(i) administering to said human a dose of 5-40 mg/day, preferably 10 mg/day of said polypeptide;

(ii) optionally measuring the level of an organ damage marker; and

(iii) optionally repeating step (i) and step (ii) until the level of said organ damage marker is at least 20% of a reference level.

9. The polypeptide according to claim 8, wherein the risk of organ damage, ischaemic damage and/or microthrombi formation is reduced by 10%, 20%, 30%, preferably by at least 40%, or even at least 50%, such as 60%, 70%, 80%, 90% or even to 100%.

10. The polypeptide according to claim 8, wherein the risk of organ damage, ischaemic damage and/or microthrombi formation is reduced by a factor 1.2, 1.3, 1.4, 1.5, 1.75, 2 or more, such as 3, 4, 5, 6, 7, 8, 9, or even 10, or even more such as 20, 50 or even 100.

11. The polypeptide according to claim 8, wherein organ damage, ischaemic damage and/or microthrombi formation is reduced preferably by at least 10%, 20%, 30%, 40%, or even at least 50%, such as 60%, 70%, 80%, 90% or even to 100%.

12. The polypeptide according to claim 8, wherein organ damage, ischaemic damage and/or microthrombi formation is reduced by a factor 2 or more, such as 3, 4, 5, 6, 7, 8, 9, or even 10, or even more such as 20, 50 or even 100.

13. The polypeptide according to any of claims 8 to 12, wherein organ damage markers, such as LDH levels, troponin T, troponin I levels, and/or creatinine levels, return to at least 40%, or even at least 50%, such as 60%, 70%, 80%, 90% or even to 100% of normal levels.

14. The polypeptide according to any of claims 8 to 12, wherein said organ damage markers, such as LDH levels, troponin T, troponin I levels, and/or creatinine levels, improve by at least 20%, such 30% or even higher, such as 40%, or even at least 50%, such as 60%, 70%, 80%, 90% or even to 100% of normal levels.

15. The polypeptide according to any of claims 8 to 14, wherein said organ damage, such as LDH levels, troponin T, troponin I levels, and/or creatinine levels, markers improve in less than 30 days of treatment, preferably, in less than 20 days of treatment, such as, less than 15, 10, 9, 8, 7, 6, 5, 4, 3, 2 days or even within 1 day.

16. The polypeptide according to any of claims 1 to 15, wherein said the ISVD against vWF essentially consists of 4 framework regions (FR1 to FR4, respectively) and 3 complementarity determining regions (CDR1 to CDR3, respectively), in which:

a) CDR1 comprises or essentially consists of:
- the amino acid sequence YNPMG; or
- an amino acid sequence that has 2 or only 1 amino acid difference(s) with the amino acid sequence YNPMG;

and

b) CDR2 comprises or essentially consists of:
- the amino acid sequence AISRTGGSTYYPDSVEG; or
- an amino acid sequence that has at least 80%, preferably at least 90%, more preferably at least 95%, even more preferably at least 99% sequence identity with the amino acid sequence AISRTGGSTYYPDSVEG; or
- an amino acid sequence that has 2 or only 1 amino acid difference(s) with the amino acid sequence AISRTGGSTYYPDSVEG;

and

c) CDR3 comprises or essentially consists of:
- the amino acid sequence AGVRAEDGRVRTLPSEYTF; or
- an amino acid sequence that has at least 80%, preferably at least 90%, more preferably at least 95%, even more preferably at least 99% sequence identity with the amino acid sequence AGVRAEDGRVRTLPSEYTF; or

- an amino acid sequence that has 2 or only 1 amino acid difference(s) with the amino acid sequence AGVRAEDGRVRTLPSEYTF.

17. The polypeptide according to any of claims 1 to 16, wherein said polypeptide comprises or consists of SEQ ID NO:s 1-19.

Claims

1. A polypeptide comprising at least one immunoglobulin single variable domain (ISVD) against von Willebrand Factor (vWF) for use in reducing the risk of and/or preventing an acute episode of a vWF-related disease in a human in need thereof, comprising step
   (i) administering to said human a dose of 5-40 mg of said polypeptide.

2. The polypeptide according to claim 1, further comprising
   (ii) measuring the ADAMTS13 activity of said patient;
   (iii) comparing said ADAMTS13 activity with a reference ADAMTS13 activity; and
   (iv) if said ADAMTS13 activity is lower than 30%, such as 20%, 15%, 10% or 5% of said reference ADAMTS13 activity, then repeating said step (i).

3. The polypeptide according to claim 1 or 2, wherein said risk of an acute episode of a vWF-related disease, such as TTP, is reduced by factor of at least 1.2.

4. The polypeptide according to claim 1 or 2, wherein the risk of organ damage, ischaemic damage and/or microthrombi formation is reduced by a factor 1.2, 1.3, 1.4, 1.5, 1.6, 1.75, 1.8, 2 or more, such as 3, 4, 5, 6, 7, 8, 9, or even 10, or even more such as 20, 50 or even 100.

5. The polypeptide according to claim 1, further comprising
   - measuring the platelet number; and
   - if said platelet number is lower than 150,000/µl, then repeating said step (i).

6. A polypeptide comprising at least one immunoglobulin single variable domain (ISVD) against von Willebrand Factor (vWF) for use in treating a vWF-related disease in a human in need thereof, comprising administering to said human a first dose of 5-40 mg, preferably 10 mg of said polypeptide.

7. The polypeptide according to claim 6, wherein said administering said polypeptide is followed within 5 min to 8 h by performing a first Plasma Exchange (PE).

8. The polypeptide according to claim 7, wherein said administering of said polypeptide is preceded by performing a preceded Plasma Exchange (PE), preferably within 24h of said first PE.

9. The polypeptide according to any of claims 6 to 8, wherein said first PE is followed by administering a second dose of 10 mg of said polypeptide within 30 min of said first PE.

10. The polypeptide according to any one of claims 6 to 9, wherein said treating a vWF-related disease in a human in need thereof, further comprises:

(i) performing a PE; and

(ii) administering a dose of 10 mg of said polypeptide 15 min to 4 h after said PE of step (i), wherein step (i) and step (ii) are repeated once per day until the platelet count of said patient is $\geq$150000/µl.

11. The polypeptide according to claim 10, further comprising administering once per day a dose of 10 mg of said polypeptide for at least 30 days after the platelet count of said patient was for the first time $\geq$150.000/µl.

12. The polypeptide according to any of claims 6 to 9, comprising administering said polypeptide until ADAMTS13 activity is at least 5%, such 10% or even 15% of a reference ADAMTS13 activity.

13. A polypeptide comprising at least one immunoglobulin single variable domain (ISVD) against von Willebrand Factor (vWF) for use in treating a vWF-related disease in a human in need thereof according to claim 6, comprising at least the following steps;

(i) performing a Plasma Exchange (PE);

(ii) administering to said human a dose of 5-40 mg, preferably 10 mg of said polypeptide;

wherein said step (i) and said step (ii) are repeated once or twice per day.

14. The polypeptide according to claim 13, wherein said step (i) and said step (ii) are repeated once or twice per day, for at most for 7 days such as at most 6, 5, 4, 3, or 2 days.

15. The polypeptide according to claim 13 or 14, further comprising

(iii) measuring the ADAMTS13 activity of said patient;

(iv) comparing said ADAMTS13 activity with a reference ADAMTS13 activity; and

(v) if said ADAMTS13 activity is lower than 30%, such as 20%, 15%, 10% or 5% of said reference ADAMTS13 activity, then repeating said step (ii) and optionally step (i).

16. The polypeptide according to any of claims 1 to 15, wherein said the ISVD against vWF essentially consists of 4 framework regions (FR1 to FR4, respectively) and 3 complementarity determining regions (CDR1 to CDR3, respectively), in which:

a) CDR1 comprises or essentially consists of:

- the amino acid sequence YNPMG; or
- an amino acid sequence that has 2 or only 1 amino acid difference(s) with the amino acid sequence YNPMG;

and

b) CDR2 comprises or essentially consists of:

- the amino acid sequence AISRTGGSTYYPDSVEG; or
- an amino acid sequence that has at least 80%, preferably at least 90%, more preferably at least 95%, even more preferably at least 99% sequence identity with the amino acid sequence AISRTGGSTYYPDSVEG; or
- an amino acid sequence that has 2 or only 1 amino acid difference(s) with the amino acid sequence AISRTGGSTYYPDSVEG;

and

c) CDR3 comprises or essentially consists of:

- the amino acid sequence AGVRAEDGRVRTLPSEYTF; or
- an amino acid sequence that has at least 80%, preferably at least 90%, more preferably at least 95%, even more preferably at least 99% sequence identity with the amino acid sequence AGVRAEDGRVRTLPSEYTF; or
- an amino acid sequence that has 2 or only 1 amino acid difference(s) with the amino acid sequence AGVRAEDGRVRTLPSEYTF.

17. The polypeptide according to any of claims 1 to 16, wherein said polypeptide comprises or consists of SEQ ID NO:s 1-19.

18. A kit or an article of manufacture, comprising a container containing the polypeptide according to any claims 1 to 17, and instructions for use.