Administration of ADM in combination with ADM-binding-Protein-1 is described for treatment of sepsis and septic shock in the art. It is assumed that treatment of septic animals with ADM and ADM-binding-Protein-1 prevents transition to the late phase of sepsis. It has to be noted that in a living organism ADM binding protein (complement factor H) is present in the circulation of said organism in high concentrations (Pio *et al.*: Identification, characterization, and physiological actions of complement factor H as an Adrenomedullin binding Protein present in Human Plasma; Microscopy Res. and Technique, 55:23-27 (2002) and Martinez *et al.*; Mapping of the Adrenomedullin-Binding domains in Human Complement factor H; Hypertens Res Vol. 26, Suppl (2003), S56-59).

In accordance with the invention the ADM-binding-Protein-1 may be also referred to as ADM-binding-Protein-1 (complement factor H).

Prevention or reduction of organ dysfunction or organ failure is very important when treating a patient having a chronic or acute disease or acute condition, especially a life threatening disease or condition.

Summary

In one aspect, there is provided the use of anti-Adrenomedullin (ADM) antibody or an anti-ADM antibody fragment binding to adrenomedullin or anti-ADM non-Ig scaffold binding to adrenomedullin in the manufacture of a medicament for therapy of an acute disease or acute condition of a patient for prevention or reduction of organ dysfunction or prevention of organ failure in said patient.

In another aspect, there is provided the use of a pharmaceutical formulation comprising an anti-ADM antibody or anti-ADM antibody fragment or anti-ADM non-Ig scaffold in the manufacture of a medicament for therapy of an acute disease or acute condition of a patient as disclosed herein.

**Description of the invention**

Subject matter of the present invention is an anti-adrenomedullin (ADM) antibody or an anti-adrenomedullin antibody fragment or anti-ADM non-Ig scaffold for use in therapy of a chronic

or acute disease or acute condition of a patient for prevention or reduction of organ dysfunction or organ failure. In a preferred embodiment subject matter of the invention is an anti-ADM antibody or an anti-adrenomedullin antibody fragment or anti-ADM non-Ig scaffold for use in therapy of a chronic or acute disease or acute condition of a patient for prevention or reduction of kidney dysfunction or kidney failure or liver dysfunction or liver failure. Said organ may be selected from the group comprising heart, kidney, liver, lungs, pancreas, small intestines and spleen. Anti-ADM antibody or an anti-adrenomedullin antibody fragment or anti-ADM non-Ig scaffold may be administered at any point of time before the occurrence of dysfunction or failure or after the occurrence of dysfunction or failure.

"Organ dysfunction" denotes a condition or a state of health where an organ does not perform its expected function. "Organ failure" denotes an organ dysfunction to such a degree that normal homeostasis cannot be maintained without external clinical intervention.

**Claims**

1. Use of ~~A~~anti-Adrenomedullin (ADM) antibody or an anti-ADM antibody fragment binding to adrenomedullin or anti-ADM non-Ig scaffold binding to adrenomedullin ~~for use~~ in the manufacture of a medicament for therapy of an acute disease or acute condition of a patient for prevention or reduction of organ dysfunction or prevention of organ failure in said patient.

2. ~~Anti-Adrenomedullin (ADM) antibody or an anti-ADM antibody fragment binding to adrenomedullin or anti-ADM non-Ig scaffold binding to adrenomedullin for use in therapy of an acute disease or acute condition of a patient~~ The use according to claim 1, wherein said anti-ADM antibody or said anti-adrenomedullin antibody fragment or said anti-ADM non-Ig scaffold is a non-neutralizing ADM antibody or a non-neutralizing adrenomedullin antibody fragment or a non-neutralizing ADM non-Ig scaffold.

3. ~~Anti-Adrenomedullin (ADM) antibody or an anti-ADM antibody fragment binding to adrenomedullin or anti-ADM non-Ig scaffold binding to adrenomedullin for use in therapy of an acute disease or acute condition of a patient~~ The use according to claim 1 or 2, wherein said organ is kidney or liver.

4. ~~Anti-Adrenomedullin (ADM) antibody or an anti-ADM antibody fragment binding to adrenomedullin or anti-ADM non-Ig scaffold binding to adrenomedullin for use in therapy of an acute disease or acute condition of a patient~~ The use according to claim 1 to 3, wherein said organ is heart.

5. ~~Anti-Adrenomedullin (ADM) antibody or an anti-ADM antibody fragment binding to adrenomedullin or anti-ADM non-Ig scaffold binding to adrenomedullin for use in therapy of an acute disease or acute condition of a patient~~ The use according to any of the claims 1 to 4, wherein said antibody or fragment or scaffold binds to the N-terminal part (aa 1-21) of adrenomedullin.

6. ~~Anti-Adrenomedullin (ADM) antibody or an anti-ADM antibody fragment binding to adrenomedullin or anti-ADM non-Ig scaffold binding to adrenomedullin for use in~~

~~therapy of an acute disease or acute condition of a patient~~ 6. The use according to any of claims 1 to 5, wherein said antibody or antibody fragment or non-Ig scaffold is monospecific.

7. ~~Anti-Adrenomedullin (ADM) antibody or an anti-ADM antibody fragment binding to adrenomedullin or anti-ADM non-Ig scaffold binding for use in therapy of an acute disease or acute condition of a patient~~ The use according any of claims 1 to 6, wherein said antibody or fragment or scaffold exhibits a binding affinitity to ADM of at least $10^{-7}$ M.

8. ~~Anti-Adrenomedullin (ADM) antibody or an anti-ADM antibody fragment binding to adrenomedullin or anti-ADM non-Ig scaffold binding for use in therapy of an acute disease or acute condition of a patient~~ The use according any of claims 1 to 7, wherein said antibody or fragment or scaffold is not ADM-binding-Protein-1 (complement factor H).

9. ~~Anti-Adrenomedullin (ADM) antibody or an anti-ADM antibody fragment binding to adrenomedullin or anti-ADM non-Ig scaffold binding to adrenomedullin for use in therapy of an acute disease or acute condition of a patient~~ The use according to any of claims 1 to 8, wherein said antibody or fragment or scaffold recognizes and binds to the N-terminal end (aa1) of adrenomedullin.

10. ~~Anti-Adrenomedullin (ADM) antibody or an anti-ADM antibody fragment binding to adrenomedullin or anti-ADM non-Ig scaffold binding to adrenomedullin for use in therapy of an acute disease or acute condition of a patient~~ The use according to any of claims 1 to 9, wherein said antibody or said fragment or scaffold is an ADM stabilizing antibody or fragment or scaffold that enhances the half life (t1/2 half retention time) of adrenomedullin in serum, blood, plasma at least 10 %, preferably at least 50 %, more preferably >50 %, most preferably >100%.

11. ~~Anti-Adrenomedullin (ADM) antibody or an anti-ADM antibody fragment binding to adrenomedullin or anti-ADM non-Ig scaffold binding to adrenomedullin for use in therapy of an acute disease or acute condition of a patient~~ The use according to any of claims 1 to 10, wherein said antibody or fragment or scaffold blocks the ADM bioactivity not more than 80 %, preferably not more than 50%.

12. ~~Anti-Adrenomedullin (ADM) antibody or an anti-ADM antibody fragment binding to adrenomedullin or anti-ADM non-Ig scaffold binding to adrenomedullin for use in therapy of an acute disease or acute condition of a patient~~ The use according to any of claims 1 to 11, wherein said disease is selected from the group comprising sepsis, diabetes, cancer, heart failure, and shock.

13. ~~Anti-Adrenomedullin (ADM) antibody or an anti-ADM antibody fragment binding to adrenomedullin or anti-ADM non-Ig scaffold binding to adrenomedullin for use in therapy of an acute disease or acute condition of a patient~~ The use according to any of claims 1 to 12, wherein said disease is not SIRS, sepsis, or septic shock.

14. ~~Anti-Adrenomedullin (ADM) antibody or an anti-ADM antibody fragment binding to adrenomedullin for use in therapy of an acute disease or acute condition of a patient~~ The use according to any of claims 1 to 13, wherein said antibody or fragment is a human monoclonal antibody or fragment that binds to ADM or an antibody fragment thereof wherein the heavy chain comprises the sequences

SEQ ID NO: 1
GYTFSRYW

SEQ ID NO: 2
ILPGSGST

SEQ ID NO: 3
TEGYEYDGFDY

and wherein the light chain comprises the sequences

SEQ ID NO:4
QSIVYSNGNTY

SEQ ID NO: 5
RVS

SEQ ID NO: 6
FQGSHIPYT.

15. ~~A human monospecific anti-Adrenomedullin (ADM) antibody or an anti-ADM antibody fragment binding to adrenomedullin for use in therapy of an acute disease or acute condition of a patient~~ The use according to claim 14, wherein the anti-ADM antibody is a human monospecific anti-ADM antibody, wherein said antibody or fragment comprises the sequences:

SEQ ID NO: 7 (AM-VH-C)
QVQLQQSGAELMKPGASVKISCKATGYTFSRYWIEWVKQRPGHGLEWIGEILPGSGSTNY
NEKFKGKATITADTSSNTAYMQLSSLTSEDSAVYYCTEGYEYDGFDYWGQGTTLTVSSAS
TKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLY
SLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKHHHHHH
SEQ ID NO: 8 (AM-VH1)
QVQLVQSGAEVKKPGSSVKVSCKASGYTFSRYWISWVRQAPGQGLEWMGRILPGSGSTN
YAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCTEGYEYDGFDYWGQGTTVTVSSA
STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGL
YSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKHHHHHH
SEQ ID NO: 9 (AM-VH2-E40)
QVQLVQSGAEVKKPGSSVKVSCKASGYTFSRYWIEWVRQAPGQGLEWMGRILPGSGSTN
YAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCTEGYEYDGFDYWGQGTTVTVSSA
STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGL
YSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKHHHHHH
SEQ ID NO: 10 (AM-VH3-T26-E55)
QVQLVQSGAEVKKPGSSVKVSCKATGYTFSRYWISWVRQAPGQGLEWMGEILPGSGSTN
YAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCTEGYEYDGFDYWGQGTTVTVSSA
STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGL
YSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKHHHHHH
SEQ ID NO: 11 (AM-VH4-T26-E40-E55)

QVQLVQSGAEVKKPGSSVKVSCKATGYTFSRYWIEWVRQAPGQGLEWMGEILPGSGSTN
YAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCTEGYEYDGFDYWGQGTTVTVSSA
STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGL
YSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKHHHHHH

SEQ ID NO: 12 (AM-VL-C)
DVLLSQTPLSLPVSLGDQATISCRSSQSIVYSNGNTYLEWYLQKPGQSPKLLIYRVSNRFSG
VPDRFSGSGSGTDFTLKISRVEAEDLGVYYCFQGSHIPYTFGGGTKLEIKRTVAAPSVFIFPP
SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLT
LSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO: 13 (AM-VL1)
DVVMTQSPLSLPVTLGQPASISCRSSQSIVYSNGNTYLNWFQQRPGQSPRRLIYRVSNRDSG
VPDRFSGSGSGTDFTLKISRVEAEDVGVYYCFQGSHIPYTFGQGTKLEIKRTVAAPSVFIFPP
SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLT
LSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO: 14 (AM-VL2-E40)
DVVMTQSPLSLPVTLGQPASISCRSSQSIVYSNGNTYLEWFQQRPGQSPRRLIYRVSNRDSG
VPDRFSGSGSGTDFTLKISRVEAEDVGVYYCFQGSHIPYTFGQGTKLEIKRTVAAPSVFIFPP
SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLT
LSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

16. ~~Anti-Adrenomedullin (ADM) antibody or an anti-ADM antibody fragment binding to adrenomedullin or anti-ADM non-Ig scaffold binding to adrenomedullin for use in therapy of an acute disease or acute condition of a patient~~ The use according to any of claims 1 to 15, wherein said antibody or fragment or scaffold is a modulating antibody or fragment or scaffold that enhances the half life (t1/2 half retention time) of adrenomedullin in serum, blood, plasma at least 10 %, preferably at least 50 %, more preferably >50 %, most preferably >100% and that blocks the ADM bioactivity not more than 80 %, preferably not more than 50%.

17. ~~Anti-Adrenomedullin (ADM) antibody or an anti-ADM antibody fragment binding to adrenomedullin or anti-ADM non-Ig scaffold binding to adrenomedullin for use in therapy of an acute disease or acute condition of a patient~~ The use according to any of the claims 1 to 16, wherein the medicament is to be used in combination with vasopressors *e.g.* catecholamine and/ or fluids administered intravenously.

18. ~~Anti-Adrenomedullin (ADM) antibody or an anti-ADM antibody fragment binding to adrenomedullin or anti-ADM non-Ig scaffold binding to adrenomedullin for use in therapy of an acute disease or acute condition of a patient~~ The use according to any of the claims 1 to ~~16 or a combination according to claim~~ 17, wherein the medicament is to be used in combination with ADM binding protein and/or further active ingredients.

19. Use of a ~~P~~pharmaceutical formulation comprising an anti-ADM antibody or anti-ADM antibody fragment or anti-ADM non-Ig scaffold ~~for use~~ in the manufacture of a medicament for ~~a~~ therapy of an acute disease or acute condition of a patient according to any of claims 1 to 18.

20. ~~Pharmaceutical formulation for use in therapy of an acute disease or acute condition of a patient~~ The use according to claim 19, wherein said pharmaceutical formulation is a solution, preferably a ready-to-use solution.

21. ~~Pharmaceutical formulation for use in therapy of an acute disease or acute condition of a patient~~ The use according to claim 20, wherein said pharmaceutical formulation is in a freeze-dried state.

22. ~~Pharmaceutical formulation~~ The use according to any of claims 19 to 21, wherein said pharmaceutical formulation is to be administered intra-muscular.

23. ~~Pharmaceutical formulation~~ The use according to any of claims 19 to 21, wherein said pharmaceutical formulation is to be administered intra-vascular.

24. ~~Pharmaceutical formulation~~ The use according to claims 19 to 21, wherein said pharmaceutical formulation is to be administered via infusion.

25. ~~Pharmaceutical formulation~~ The use according to claims 19 to 21, wherein said pharmaceutical formulation is to be administered systemically to a patient for prevention or reduction of organ dysfunction or organ failure in a patient having an acute disease or acute condition.

5

26. ~~Pharmaceutical formulation~~ The use according to claims 19 to 21, wherein said pharmaceutical formulation is to be administered systemically via infusion to a patient for prevention or reduction of organ dysfunction or organ failure in a patient having an acute disease or acute condition.