CLAIMS

1. 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 for the regulation of fluid balance.

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 according to claim 1 wherein said patient is a patient in need of regulating the fluid balance.

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 according to claim 1 or 2, wherein said anti ADM antibody or an anti adrenomedullin antibody fragment or anti-ADM non Ig scaffold is a non neutralizing anti ADM antibody or a non neutralizing anti adrenomedullin antibody fragment or a non neutralizing anti ADM non Ig scaffold.

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 according to any of claims 1 to 3 for preventing or reducing edema in said patient.

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 according to any of claims 1 to 4, wherein said antibody or antibody fragment or non Ig scaffold is monospecific.

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 according to any of claims 1

to 5, characterized in that said antibody or fragment or scaffold exhibits a binding affinity to ADM of at least 10^{-7} M.

7. 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 according to any of claims 1 to 6, wherein said antibody or fragment or scaffold is not ADM binding Protein 1 (complement factor H).

8. 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 according to any of claims 1 to 7, wherein said antibody or antibody fragment or non-Ig scaffold binds to a region of preferably at least 4 or at least 5 amino acids within the sequence of aa 1-42 of mature human ADM:

YRQSMNNFQGLRSFGCRFGTCTVQKLAHQIYQFTDKDKDNVA
(SEQ ID No. 24).

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 according to any of claims 1 to 8, wherein said antibody or antibody fragment or non-Ig scaffold binds to a region of at least 4 or 5 amino acids within the sequence of aa 1-21 of mature human ADM:

YRQSMNNFQGLRSFGCRFGTC
(SEQ ID No. 23).

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 according to any of claims 1 to 9, wherein said antibody or fragment scaffold recognizes and binds to an epitope containing the N-terminal end amino acid 1 of mature human ADM and wherein said

antibody or fragment or scaffold would neither bind N-terminal extended nor N-terminal modified Adrenomedullin nor N-terminal degraded adrenomedullin.

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 according to any of claims 1 to 10, wherein said antibody or fragment or scaffold is an ADM stabilizing antibody or ADM stabilizing antibody fragment or ADM stabilizing non-Ig scaffold that enhances the half-life ($t_{1/2}$-half-retention time) of adrenomedullin in serum, blood, plasma at least 10 %, preferably at least 50 %, more preferably >50 %, most preferably >100 %.

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 according to any of claims 1 to 11, wherein said antibody or fragment blocks the circulating ADM bioactivity not more than 80 %, preferably not more than 50%.

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 according to any of claims 1 to 12, wherein said disease is selected from the group comprising SIRS, sepsis, diabetes, cancer, heart failure, shock and kidney dysfunction.

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 according to any of claims 1 to 13, wherein said antibody or fragment is an antibody or fragment that binds to ADM or an antibody fragment thereof that binds to ADM 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 according to claim 14 wherein said antibody or fragment comprises the sequences:~~

~~SEQ ID NO: 7 (AM-VH-C)~~

~~QVQLQQSGAELMKPGASVKISCKATGYTFSRYWIEWVKQRPGHGLEWIGEIL PGSGSTNYNEKFKGKATITADTSSNTAYMQLSSLTSEDSAVYYCTEGYEYDGF DYWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTK VDKRVEPKHHHHHHH~~

~~SEQ ID NO: 8 (AM-VH1)~~

~~QVQLVQSGAEVKKPGSSVKVSCKASGYTFSRYWISWVRQAPGQGLEWMGRI LPGSGSTNYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCTEGYEYDG FDYWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTV SWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNT KVDKRVEPKHHHHHHH~~

~~SEQ ID NO: 9 (AM-VH2-E40)~~

~~QVQLVQSGAEVKKPGSSVKVSCKASGYTFSRYWIEWVRQAPGQGLEWMGRI LPGSGSTNYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCTEGYEYDG FDYWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTV SWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNT KVDKRVEPKHHHHHHH~~

SEQ ID NO: 10 (AM-VH3-T26-E55)

QVQLVQSGAEVKKPGSSVKVSCKATGYTFSRYWISWVRQAPGQGLEWMGEI
LPGSGSTNYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCTEGYEYDG
FDYWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTV
SWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNT
KVDKRVEPKHHHHHH

SEQ ID NO: 11 (AM-VH4-T26-E40-E55)

QVQLVQSGAEVKKPGSSVKVSCKATGYTFSRYWIEWVRQAPGQGLEWMGEI
LPGSGSTNYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCTEGYEYDG
FDYWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTV
SWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNT
KVDKRVEPKHHHHHH

SEQ ID NO: 12 (AM-VL-C)

DVLLSQTPLSLPVSLGDQATISCRSSQSIVYSNGNTYLEWYLQKPGQSPKLLIY
RVSNRFSGVPDRFSGSGSGTDFTLKISRVEAEDLGVYYCFQGSHIPYTFGGGTK
LEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQS
GNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSF
NRGEC

SEQ ID NO: 13 (AM-VL1)

DVVMTQSPLSLPVTLGQPASISCRSSQSIVYSNGNTYLNWFQQRPGQSPRRLIY
RVSNRDSGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCFQGSHIPYTFGQGT
KLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQ
SGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKS
FNRGEC

SEQ ID NO: 14 (AM-VL2-E40)

DVVMTQSPLSLPVTLGQPASISCRSSQSIVYSNGNTYLEWFQQRPGQSPRRLIY
RVSNRDSGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCFQGSHIPYTFGQGT
KLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQ
SGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKS
FNRGEC

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 according to any of claims 1 to 15, wherein said antibody or fragment or scaffold is a modulating antibody or modulating fragment or modulating scaffold that enhances the half life ($t_{1/2}$ 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 bioactivity of ADM 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 according to any of the claims 1 to 16, characterized in that said antibody, antibody fragment or non-Ig scaffold does not bind to the C-terminal portion of ADM, being it aa 43-52 of ADM (SEQ ID NO: 25)

PRSKISPQGY-NH2
(SEQ ID NO:25).

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 according to any of the claims 1 to 17 to be used in combination with catecholamine and/ or fluids administered intravenously.

19. 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 according to any of the claims 1 to 17 or a combination according to claim 18 to be used in combination with ADM binding protein and/or further active ingredients.

20. 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 for the regulation of fluid balance according to any of the preceding claims, characterized in that said therapy is not a method of primary treatment to said acute disease or acute condition.

21. Pharmaceutical formulation comprising an 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 according to any of claims 1 to 20.

~~22. Pharmaceutical formulation comprising an 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 according to claim 21, wherein said pharmaceutical formulation is a solution, preferably a ready-to-use solution.~~

~~23. Pharmaceutical formulation comprising an 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 according to claim 22, wherein said pharmaceutical formulation is in a freeze-dried state.~~

~~24. Pharmaceutical formulation comprising an 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 according to any of the claims 21 to 23, wherein said pharmaceutical formulation is to be administered to a patient for regulating the systemic fluid balance with the proviso that said patient is in need of regulating the fluid balance.~~

1. Use of an anti-Adrenomedullin (ADM) antibody, anti-ADM antibody fragment binding to adrenomedullin or anti-ADM non-Ig protein scaffold binding to adrenomedullin in the manufacture of a medicament for regulating fluid balance in a patient in need thereof by preventing or treating an acute disease or acute condition of the patient, wherein said antibody, antibody fragment or non-Ig scaffold binds to a region of at least 4 amino acids within the sequence of amino acids 1-42 of mature human ADM as set out in SEQ ID NO: 24.

2. The use of claim 1, wherein the acute disease or condition is edema.

3. The use of claim 1 or 2, wherein said antibody, antibody fragment or non-Ig scaffold is monospecific.

4. The use of any one of claims 1 to 3, wherein said antibody, antibody fragment or non-Ig scaffold exhibits a binding affinity to ADM of at least 10^{-7} M.

5. The use of any one of claims 1 to 4, wherein said antibody, antibody fragment or non-Ig scaffold is not ADM-binding-Protein-1 (complement factor H).

6. The use of any one of claims 1 to 5, wherein said antibody, antibody fragment or non-Ig scaffold binds to a region of at least 4 or 5 amino acids within the sequence of amino acids 1-21 of mature human ADM:

YRQSMNNFQGLRSFGCRFGTC (SEQ ID No. 23).

7. The use of any one of claims 1 to 6, wherein said antibody, antibody fragment or non-Ig scaffold recognizes and binds to an epitope comprising the N-terminal end amino acid of mature human ADM and wherein said antibody, antibody fragment or non-IG scaffold does not bind N-tenninal extended, N-terminal modified Adrenomedullin or N-terminal degraded adrenomedullin.

8. The use of any one of claims 1 to 7, wherein said antibody, antibody fragment or non-Ig scaffold is an ADM stabilizing antibody, antibody fragment or non-Ig scaffold that enhances the half life ($t_{1/2}$ half retention time) of adrenomedullin in serum, blood or plasma by at least 10 %, at least 50 %, greater than 50 %, or greater than 100 %.

9. The use of any one of claims 1 to 8, wherein said antibody, antibody fragment or non-Ig scaffold blocks the circulating ADM bioactivity not more than 80 %, or not more than 50%, wherein the bioactivity of ADM is determined in a human recombinant Adrenomedullin receptor cAMP functional assay.

10. The use of any one of claims 1 to 9, wherein the patient suffers from one or more of SIRS, sepsis, diabetes, cancer, heart failure, shock or kidney dysfunction.

11. The use of any one of claims 1 to 10, wherein said antibody, or antibody fragment is an antibody or antibody fragment that binds to ADM or a fragment thereof that binds

to ADM, wherein the heavy chain of said antibody or antibody fragment 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.

12. The use of claim 11, wherein said antibody or antibody fragment comprises at least one of the sequences:

SEQ ID NO: 7 (AM-VH-C)
QVQLQQSGAELMKPGASVKISCKATGYTFSRYWIEWVKQRPGHGLEWIGEIL
PGSGSTNYNEKFKGKATITADTSSNTAYMQLSSLTSEDSAVYYCTEGYEYDGF
DYWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS
WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTK
VDKRVEPKHHHHHH

SEQ ID NO: 8 (AM-VHJ)

QVQLVQSGAEVKKPGSSVKVSCKASGYTFSRYWISWVRQAPGQGLEWMGRI
LPGSGSTNYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCTEGYEYDG
FDYWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTV
SWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNT
KVDKRVEPKHHHHHH

SEQ ID NO: 9 (AM-VH2-E40)
QVQLVQSGAEVKKPGSSVKVSCKASGYTFSRYWIEWVRQAPGQGLEWMGRI
LPGSGSTNYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCTEGYEYDG
FDYWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTV
SWNSGALTSGVHTFPAVLQSSGLYSLSSVVIPSSSLGTQTYICNVNHKPSNTKV
DKRV EPKHHHHHH

SEQ ID NO: 10 (AM-VH3-T26-E55)
QVQLVQSGAEVKKPGSSVKVSCKATGYTFSRYWISWVRQAPGQGLEWMGEI
LPGSGSTNYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCTEGYEYDG
FDYWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTV
SWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNT
KVDKRVEPKHHHHHH

SEQ ID NO: 11 (AM-VH4-T26-E40-E55)
QVQLVQSGAEVKKPGSSVKVSCKATGYTFSRYWIEWVRQAPGQGLEWMGEI
LPGSGSTNYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCTEGYEYDG
FDYWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTV
SWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNT
KVDKRVEPKHHHHHH

SEQ ID NO: 12 (AM-VL-C)
DVLLSQTPLSLPVSLGDQATISCRSSQSIVYSNGNTYLEWYLQKPGQSPKLLIY
RVSNRFSGVPDRFSGSGSGTDFTLKISRVEAEDLGVYYCFQGSHIPYTFGGGTK
LEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQS
GNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSF
NRGEC

SEQ ID NO: 13 (AM-VL1)
DVVMTQSPLSLPVTLGQPASISCRSSQSIVYSNGNTYLNWFQQRPGQSPRRLIY
RVSNRDSGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCFQGSHIPYTFGQGT
KLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQ
SGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKS
FNRGEC
or
SEQ ID NO: 14 (AM-VL2-E40)
DVVMTQSPLSLPVTLGQPASISCRSSQSIVYSNGNTYLEWFQQRPGQSPRRLIY
RVSNRDSGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCFQGSHIPYTFGQGT
KLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQ
SGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKS
FNRGEC

13. The use of any one of claims 1 to 12, wherein said antibody, antibody fragment or non-Ig scaffold is a modulating antibody, modulating antibody fragment or modulating non-Ig scaffold that enhances the half life ($t_{1/2}$ half retention time) of adrenomedullin in serum, blood or plasma by at least 10 %, at least 50 %, greater than 50 %, or greater than 100% and that blocks the bioactivity of ADM not more than 80 %, or not more than 50%, wherein the bioactivity of ADM is determined in a human recombinant Adrenomedullin receptor cAMP functional assay.

14. The use of any one of claims 1 to 13, wherein said antibody, antibody fragment or non-Ig scaffold does not bind to the C-terminal portion of ADM, amino acids 43-52 of ADM

PRSKISPQGY-NH2
(SEQ ID NO:25).

15. The use of any one of claims 1 to 14, wherein the medicament is to be administered with catecholamine and/or one or more fluids, wherein the catecholamine and/or fluids are to be administered intravenously.

16. The use of any one of claims 1 to 15, wherein the medicament is to be administered with ADM binding protein and/or one or more further active ingredient.

17. The use of any one of claims 1 to 16, wherein the medicament is not for primary treatment of said acute disease or acute condition.

18. The use of any one of claims 1 to 17, wherein said medicament is formulated as a solution or in a freeze-dried state.

19. The use of claim 18, wherein the solution is a ready-to-use solution.

20. The use of any one of claims 1 to 19, wherein said medicament is for regulating the systemic fluid balance in the patient.