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).

Patients having a chronic or acute disease or acute condition, especially patients at the ICU (Intensive Care Unit), may suffer from fluid imbalance. This may cause severe adverse events such as kidney failure and mortality.

It was the subject of the present invention to provide a medicament for regulating the fluid balance and/or improving the fluid balance of such patients.

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 the regulation of fluid balance.

In another aspect, there is provided the use of a 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 in the manufacture of a medicament for therapy of an acute disease or acute condition of a patient as disclosed herein.

Detailed Description

The expression "regulating fluid balance" with the context of the instant invention is directed to any correction of a manifested – imbalance – of a patient's fluid balance due to an underlying chronic or acute disease or acute condition. Said correction is in favour of re-establishing normotension in said patients. The person skilled in the art is fully aware that blood pressure in general, as well as hyper- and hypotension is closely related to the fluid balance of a patient.
Fluid balance is the balance of the input and the output of fluids in the body to allow metabolic processes to function. Dehydration is defined as a 1% or greater loss of body mass as a result of

fluid loss. The three elements for assessing fluid balance and hydration status are: clinical assessment, body weight and urine output; review fluid balance charts and review of blood chemistry. All this is very well known to a man skilled in the art (Alison Shepherd, Nursing Tomes 19.07.11/Vol 107 No 28, pages 12 to 16).

Thus, in one embodiment a person in need of regulating the fluid balance and/or improving the fluid balance of such patients is a person that has a 1% or greater loss of body mass as a result of fluid loss. The fluid balance may be assessed according to Scales and Pilsworth (2008) Nursing Standard 22:47, 50-57. For instance, normal urine output is in the range of 0.5 to 2 ml/kg of body weight per hour. The minimum acceptable urine output for a patient with normal renal function is 0.5 ml/kg per hour. All these standards may be used to assess whether a patient is in need for regulating the fluid balance and/or improving the fluid balance.

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 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~~ The use 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~~ The use 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~~ The use according to any of claims 1 to 3, wherein the medicament is 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~~ The use 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~~ The use 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~~ The use 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~~ The use 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~~ The use 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~~ The use 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~~ The use 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~~ The use 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~~ The use 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~~ The use 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~~ 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)
QVQLQQSGAELMKPGASVKISCKATGYTFSRYWIEWVKQRPGHGLEWIGEILPGSGS
TNYNEKFKGKATITADTSSNTAYMQLSSLTSEDSAVYYCTEGYEYDGFDYWGQGTT
LTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTF
PAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKHHHHHH
SEQ ID NO: 8 (AM-VH1)
QVQLVQSGAEVKKPGSSVKVSCKASGYTFSRYWISWVRQAPGQGLEWMGRILPGSG
STNYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCTEGYEYDGFDYWGQGT
TVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHT
FPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKHHHHHH
SEQ ID NO: 9 (AM-VH2-E40)
QVQLVQSGAEVKKPGSSVKVSCKASGYTFSRYWIEWVRQAPGQGLEWMGRILPGS
GSTNYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCTEGYEYDGFDYWGQG
TTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNS

GALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKHH
HHHH

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

QVQLVQSGAEVKKPGSSVKVSCKATGYTFSRYWISWVRQAPGQGLEWMGEILPGSGST
NYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCTEGYEYDGFDYWGQGTTVTV
SSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQ
SSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKHHHHHH

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

QVQLVQSGAEVKKPGSSVKVSCKATGYTFSRYWIEWVRQAPGQGLEWMGEILPGSGST
NYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCTEGYEYDGFDYWGQGTTVTV
SSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQ
SSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKHHHHHH

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

DVLLSQTPLSLPVSLGDQATISCRSSQSIVYSNGNTYLEWYLQKPGQSPKLLIYRVSNRFS
GVPDRFSGSGSGTDFTLKISRVEAEDLGVYYCFQGSHIPYTFGGGTKLEIKRTVAAPSVFIF
PPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSS
TLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO: 13 (AM-VL1)

DVVMTQSPLSLPVTLGQPASISCRSSQSIVYSNGNTYLNWFQQRPGQSPRRLIYRVSNRDS
GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCFQGSHIPYTFGQGTKLEIKRTVAAPSVFI
FPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLS
STLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

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

DVVMTQSPLSLPVTLGQPASISCRSSQSIVYSNGNTYLEWFQQRPGQSPRRLIYRVSNRDS
GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCFQGSHIPYTFGQGTKLEIKRTVAAPSVFI
FPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLS
STLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

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 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~~ The use 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~~ The use according to any of the claims 1 to 17, wherein the medicament is 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~~ The use according to any of the claims 1 to ~~17 or a combination according to claim~~ 18, wherein the medicament is 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~~ The use 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. Use of a ~~P~~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 the manufacture of a medicament for 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~~ The use 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~~ The use 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~~ The use 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.