

CLAIMS

1. Use of an anti-adrenomedullin (ADM) antibody or anti-ADM antibody fragment or anti-ADM non-Ig scaffold in the manufacture of a medicament for treatment of a critically ill patient suffering from an acute disease or condition selected from the group comprising: severe infections (e.g., meningitis, systemic inflammatory response syndrome (SIRS), sepsis), shock (e.g., septic shock, cardiogenic shock), acute heart failure (including acute decompensated heart failure, chronic heart failure with worsening signs and symptoms), myocardial infarction, stroke, organ dysfunction (e.g., kidney, liver, heart, lung) or dementia in order to accelerate the conversion of ADM-Gly to ADM-NH₂ of circulating ADM-Gly in said patient, wherein said patient is characterized by having a ratio of pro-Adrenomedullin or a fragment thereof to ADM-NH₂ (SEQ ID No. 20) above a certain threshold in a sample of bodily fluid, wherein said pro-Adrenomedullin or fragment thereof is selected from the group consisting of PAMP (SEQ ID No. 32), MR-proADM (SEQ ID No. 33), ADM-Gly (SEQ ID No. 21) and CT-proADM (SEQ ID No. 34) and wherein said anti-ADM antibody or anti-ADM fragment or anti-ADM non-Ig scaffold binds to the N-terminal and/ or mid-regional part (aa 1-42) of ADM-Gly and/ or ADM-NH₂:
YRQSMNNFQGLRSFGCRFGTCTVQKLAHQIYQFTDKDKDNVA (SEQ ID No. 23).
2. The use according to claim 1, wherein said anti-ADM antibody or anti-ADM fragment or anti-ADM non-Ig scaffold is for treatment of a critically ill patient suffering from an acute disease or condition selected from the group comprising: severe infections (e.g., meningitis, systemic inflammatory response syndrome (SIRS), sepsis), shock (e.g., septic shock, cardiogenic shock), acute heart failure (including acute decompensated heart failure, chronic heart failure with worsening signs and symptoms), myocardial infarction, stroke or organ dysfunction (e.g., kidney, liver, heart, lung), and wherein said anti-ADM antibody or anti-ADM fragment or anti-ADM non-Ig scaffold binds to the N-terminal part (amino acid 1-21) of ADM-Gly and/ or ADM-NH₂:
YRQSMNNFQGLRSFGCRFGTC (SEQ ID No. 14).

3. The use according to claims 1 or 2, wherein said anti-ADM antibody or anti-ADM antibody fragment or anti-ADM non-Ig scaffold recognizes and binds to the N-terminal end (amino acid 1) of ADM-Gly and/ or ADM-NH₂.
- 5 4. The use according to claim 1, wherein said anti-ADM antibody or anti-ADM fragment or anti-ADM non-Ig scaffold binds to the mid-regional part (amino acid 21-42) of ADM-Gly and/ or ADM-NH₂: CTVQKLAHQIYQFTDKDKDNVA (SEQ ID No. 48).
- 10 5. The use according to claim 4, wherein said anti-ADM antibody or anti-ADM fragment or anti-ADM non-Ig scaffold binds to the mid-regional part (amino acid 21-32) of ADM-Gly and/ or ADM-NH₂: CTVQKLAHQIYQ (SEQ ID No.: 15).
- 15 6. The use according to claim 1, wherein said anti-ADM antibody or anti-ADM fragment or anti-ADM non-Ig scaffold is for treatment of a critically ill patient suffering from dementia, and wherein said anti-ADM antibody or anti-ADM fragment or anti-ADM non-Ig scaffold binds to the mid-regional part (amino acid 21-42) of ADM-Gly and/ or ADM-NH₂: CTVQKLAHQIYQFTDKDKDNVA (SEQ ID No. 48).
- 20 7. The use according to claim 6, wherein said anti-ADM antibody or anti-ADM fragment or anti-ADM non-Ig scaffold binds to the mid-regional part (amino acid 21-32) of ADM-Gly and/ or ADM-NH₂: CTVQKLAHQIYQ (SEQ ID No.: 15).
- 25 8. The use according to claim 6, wherein said anti-ADM antibody or anti-ADM fragment or anti-ADM non-Ig scaffold binds to the mid-regional part (amino acid 27-39) of ADM-Gly and/ or ADM-NH₂: AHQIYQFTDKDKD (SEQ ID No.: 49).
- 30 9. The use according to any one of claims 1 - 8, wherein in a sample of bodily fluid of said patient the level of pro-Adrenomedullin or a fragment thereof consisting of the group of PAMP (SEQ ID No. 32), MR-proADM (SEQ ID No. 33), ADM-Gly (SEQ ID No. 21) and CT-proADM (SEQ ID No. 34) and ADM-NH₂ (SEQ ID No. 20) is determined.
- 35 10. The use according to any one of claims 1 - 9, wherein in a sample of bodily fluid of said patient a ratio of the level of ADM-Gly (SEQ ID No. 21) and ADM-NH₂ (SEQ ID No. 20) is determined and the patient is to be treated with said anti-ADM antibody or an anti-ADM antibody fragment or anti-ADM non-Ig scaffold if the ratio is above a certain

threshold, wherein the ADM-Gly/ ADM-NH₂ ratio is in a range between 1 and 10, preferably between 1.5 and 7.5, preferably between 2 and 5, most preferred the threshold is 2.5.

- 5 11. The use according to any one of claims 1 - 9, wherein the sample of bodily fluid of said patient is selected from the group of blood, serum, plasma, urine, cerebrospinal fluid (CSF), and saliva.
- 10 12. The use according to claim 11, wherein said sample is selected from the group comprising human citrate plasma, heparin plasma and EDTA plasma.
- 15 13. The use according to any one of claims 1 - 12, wherein an immunoassay is used for determining the ratio of pro-Adrenomedullin or a fragment thereof and ADM-NH₂, wherein said pro-Adrenomedullin or fragment thereof is selected from the group consisting of PAMP (SEQ ID No. 32), MR-proADM (SEQ ID No. 33), ADM-Gly (SEQ ID No. 21) and CT-proADM (SEQ ID No. 34).
- 20 14. The use according to claim 13, wherein said immunoassay is a sandwich immunoassay, preferably a fully automated assay.
- 25 15. The use according to any one of claims 1 - 14, wherein the assay sensitivity of said assay for the detection of ADM-NH₂ is able to quantify ADM-NH₂ of healthy subjects and is < 70 pg/ml, preferably < 40 pg/ml and more preferably < 10 pg/ml.
- 30 16. The use according to any one of claims 1 - 14, wherein the assay sensitivity of said assay for ADM-Gly is able to quantify ADM-Gly of healthy subjects and is 20 pg/ml, preferably 15 pg/ml and more preferably 10 pg/ml.
- 35 17. The use according to any one of claims 1 -16, wherein the level of pro-Adrenomedullin or a fragment thereof and ADM-NH₂ (SEQ ID No. 20) is determined by using one binder to said pro-Adrenomedullin or a fragment thereof and a second binder to ADM-NH₂ (SEQ ID No. 20), wherein said proAdrenomedullin or a fragment thereof is selected from the group consisting of PAMP (SEQ ID No. 32), MR-proADM (SEQ ID No. 33), ADM-Gly (SEQ ID No. 21) and CT-proADM (SEQ ID No. 34), and wherein both binders are selected from the group comprising an antibody, an antibody fragment

or a non-Ig-Scaffold binding to said pro-Adrenomedullin or a fragment thereof and ADM-NH₂.

18. Use of an anti-adrenomedullin (ADM) antibody or anti-ADM antibody fragment or anti-ADM non-Ig scaffold in the manufacture of a medicament for therapy of a patient, wherein said anti-ADM antibody or anti-ADM fragment or anti-ADM non-Ig scaffold binds to the N-terminal and/ or mid-regional part (amino acid 1-42) of ADM-Gly and/ or ADM-NH₂:

YRQSMNNFQGLRSFGCRFGTCTVQKLAHQIYQFTDKDKDNVA (SEQ ID No. 23), wherein in a sample of bodily fluid of said patient the level of peptidylglycine alpha-amidating monooxygenase (PAM) and/or its isoforms and/or fragments thereof is determined and the patient is to be treated with said anti-ADM antibody or an anti-ADM antibody fragment or anti-ADM non-Ig scaffold, if the level of peptidylglycine alpha-amidating monooxygenase (PAM) is below a threshold.

19. The use according to claim 18, wherein said level of PAM and/or its isoforms and/or fragments thereof is the total concentration of PAM and/or its isoforms and/or fragments thereof having at least 12 amino acids or the activity of PAM and/or its isoforms and/or fragments thereof comprising the sequences SEQ ID No. 39, SEQ ID No. 40, SEQ ID No. 41, SEQ ID No. 42, SEQ ID No. 43, SEQ ID No. 44, SEQ ID No. 45, SEQ ID No. 46 and SEQ ID No. 47.

20. Use of an anti-Adrenomedullin (ADM) antibody or anti-ADM antibody fragment or anti-ADM non-Ig scaffold in combination with L-ascorbic acid in the manufacture of a medicament for:

- a. therapy of an acute disease or acute condition of a patient for stabilizing the systemic circulation of said patient wherein said patient is in need of stabilizing the systemic circulation and exhibits a heart rate of > 100 beats /min and/ or < 65 mm Hg mean arterial pressure and wherein stabilizing the systemic circulation means increasing the mean arterial pressure over 65 mmHg, or
- b. prevention of a heart rate increase to > 100 beats/min and/or a mean arterial pressure decrease to < 65 mm Hg in patients having an acute disease or acute condition, or
- c. therapy of an acute disease or acute condition of a patient that suffers from a chronic and/or acute disease or acute condition for prevention or reduction of organ

dysfunction or prevention of organ failure in said patient and wherein said organ is selected from the group comprising heart, kidney, liver, lungs, pancreas, small intestines and spleen, or

- 5 d. therapy or prevention of SIRS, meningitis, sepsis, shock, *e.g.*, septic shock in a patient, or
- e. reduction of the mortality risk in a patient with SIRS, meningitis, sepsis, shock, *e.g.*, septic shock,

wherein said anti-ADM antibody or anti-ADM fragment or anti-ADM non-Ig scaffold binds to the N-terminal and/ or mid-regional part (amino acid 1-42) of ADM-Gly and/ or ADM-NH₂:

10

YRQSMNNFQGLRSFGCRFGTCTVQKLAHQIYQFTDKDKDNVA (SEQ ID No. 23).

21. The use according to claim 20, wherein said L-ascorbic acid is a single enantiomer, a mixture of enantiomers, a mixture of diastereomers or a pharmaceutically acceptable salt, solvate, hydrate or prodrug thereof.

15