

CLAIMS

1. A method for (a) diagnosing or predicting the risk of life-threatening deterioration or an adverse event or (b) diagnosing or prognosing the severity or (c) predicting or monitoring the success of a therapy or intervention or (d) therapy guidance or therapy stratification or (e) patient management in a patient infected with a Corona virus, the method comprising:
- determining the level of pro-Adrenomedullin (SEQ ID No. 31) or fragment thereof in a sample of bodily fluid of said patient,
 - comparing said level of pro-Adrenomedullin or fragment thereof to a pre-determined threshold or to a previously measured level of pro-Adrenomedullin or fragment thereof, and
 - correlating said level of pro-Adrenomedullin or fragment thereof with the risk of life-threatening deterioration or an adverse event, or
 - correlating said level of pro-Adrenomedullin or fragment thereof with the severity, or
 - correlating said level of pro-Adrenomedullin or fragment thereof with the success of a therapy or intervention, or
 - correlating said level of pro-Adrenomedullin or fragment thereof with a certain therapy or intervention, or
 - correlating said level of pro-Adrenomedullin or fragment thereof with the management of said patient,
- 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-NH₂ (SEQ ID No. 20), ADM-Gly (SEQ ID No. 21) and CT-proADM (SEQ ID No. 34).
2. A method for (a) diagnosing or predicting the risk of life-threatening deterioration or an adverse event or (b) prognosing the severity or (c) predicting or monitoring the success of a therapy or intervention in a patient infected with a Corona virus according to claim 1, wherein said Corona Virus is selected from the group comprising Sars-CoV-1, Sars-CoV-2, MERS-CoV, in particular Sars-CoV-2.
3. A method for (a) diagnosing or predicting the risk of life-threatening deterioration or an adverse event or (b) prognosing the severity or (c) predicting or monitoring the success of a therapy or intervention in a patient infected with a Corona virus according to claim

1 or 2, wherein said adverse event is selected from the group comprising death, organ dysfunction, shock.

4. A method for (a) diagnosing or predicting the risk of life-threatening deterioration or an adverse event or (b) prognosing the severity or (c) predicting or monitoring the success of a therapy or intervention in a patient infected with a Corona virus according to claims 1 to 3, wherein said level of pro-Adrenomedullin or fragment thereof is above a pre-determined threshold.
5. A method for (a) diagnosing or predicting the risk of life-threatening deterioration or an adverse event or (b) prognosing the severity or (c) predicting or monitoring the success of a therapy or intervention in a patient infected with a Corona virus according to claims 1 to 4, wherein said patient has a level of D-dimer equal or greater than 0.5 $\mu\text{g/ml}$, preferably equal or greater than 1.0 $\mu\text{g/ml}$.
6. A method for (a) diagnosing or predicting the risk of life-threatening deterioration or an adverse event or (b) prognosing the severity or (c) predicting or monitoring the success of a therapy or intervention in a patient infected with a Corona virus according to claims 1 to 5, wherein the level of pro-Adrenomedullin or fragment thereof is determined by contacting said sample of bodily fluid with a capture binder that binds specifically to pro-Adrenomedullin or fragment thereof.
7. A method for (a) diagnosing or predicting the risk of life-threatening deterioration or an adverse event or (b) prognosing the severity or (c) predicting or monitoring the success of a therapy or intervention in a patient infected with a Corona virus according to claims 1 to 6, wherein said determination comprises the use of a capture-binder that binds specifically to pro-Adrenomedullin or fragment thereof wherein said capture-binder may be selected from the group of antibody, antibody fragment or non-IgG scaffold.
8. A method for (a) diagnosing or predicting the risk of life-threatening deterioration or an adverse event or (b) prognosing the severity or (c) predicting or monitoring the success of a therapy or intervention in a patient infected with a Corona virus according to claims 1 to 7, wherein said patient is treated with an Anti-adrenomedullin (ADM) antibody or anti-ADM antibody fragment or anti-ADM non-Ig scaffold 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).

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9. Anti-adrenomedullin (ADM) antibody or anti-ADM antibody fragment or anti-ADM non-Ig scaffold for use in therapy or intervention in a patient infected with a Corona virus.

10. Anti-adrenomedullin (ADM) antibody or anti-ADM antibody fragment or anti-ADM non-Ig scaffold for use in therapy or intervention in a patient infected with a Corona virus according to claim 9, wherein said Corona Virus is selected from the group comprising Sars-CoV-1, Sars-CoV-2, MERS-CoV, in particular Sars-CoV-2.

11. Anti-adrenomedullin (ADM) antibody or anti-ADM antibody fragment or anti-ADM non-Ig scaffold for use in therapy or intervention in a patient infected with a Corona virus according to claim 9 or 10, wherein said patient has a level of pro-Adrenomedullin or fragment thereof in a sample of bodily fluid of said subject that is above a predetermined threshold or higher than a previously measured level of pro-Adrenomedullin when determined by a method according to any of claims 1 – 8.

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12. Anti-adrenomedullin (ADM) antibody or anti-ADM antibody fragment or anti-ADM non-Ig scaffold for use in therapy or intervention in a patient infected with a Corona virus according to claims 9 to 11, wherein said patient has a level of D-dimer equal or greater than 0.5 µg/ml, preferably equal or greater than 1.0 µg/ml.

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13. Anti-adrenomedullin (ADM) antibody or anti-ADM antibody fragment or anti-ADM non-Ig scaffold for use in therapy or intervention in a patient infected with a Corona virus according to claims 9 to 12, wherein said anti-ADM antibody or anti-ADM fragment or anti-ADM non-Ig scaffold binds to the N-terminal (amino acid 1-21) of ADM-Gly and/ or ADM-NH₂: YRQSMNNFQGLRSFGCRFGTC (SEQ ID No. 14).

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14. Anti-adrenomedullin (ADM) antibody or anti-ADM antibody fragment or anti-ADM non-Ig scaffold for use in therapy or intervention in a patient infected with a Corona virus

according to claims 9 – 13, wherein said antibody is a monoclonal antibody or monoclonal antibody fragment.

15. Anti-adrenomedullin (ADM) antibody or anti-ADM antibody fragment or anti-ADM non-Ig scaffold for use in therapy or intervention in a patient infected with a Corona virus according to claim 14, wherein the complementarity determining regions (CDR's) in the heavy chain comprises the sequences:

CDR1: SEQ ID NO: 1

GYTFSRYW

CDR2: SEQ ID NO: 2

ILPGSGST

CDR3: SEQ ID NO: 3

TEGYEYDGFYD

and the complementarity determining regions (CDR's) in the light chain comprises the sequences:

CDR1: SEQ ID NO: 4

QSIVYSNGNTY

CDR2:

RVS

CDR3: SEQ ID NO: 5

FQGSHIPYT

16. Anti-adrenomedullin (ADM) antibody or anti-ADM antibody fragment or anti-ADM non-Ig scaffold for use in therapy or intervention in a patient infected with a Corona virus according to claim 15, wherein said antibody or fragment comprises a sequence selected from the group comprising as a VH region:

SEQ ID NO: 6 (AM-VH-C)

5 QVQLQQSGAELMKPGASVKISCKATGYTFSRYWIEWVKQRPGHGLEWIGEILP
GSGSTNYNEKFKGKATITADTSSNTAYMQLSSLTSEDSAVYYCTEGYEYDGFD
YWGQGTTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWN
SGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKR
VEPK

SEQ ID NO: 7 (AM-VH1)

10 QVQLVQSGAEVKKPGSSVKVSCKASGYTFSRYWISWVRQAPGQGLEWMGRIL
PGSGSTNYAQKFQGRVTITADESTSTAYMELSSLRSEDYAVYYCTEGYEYDGFD
YWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWN
SGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKR
15 VEPK

SEQ ID NO: 8 (AM-VH2-E40)

20 QVQLVQSGAEVKKPGSSVKVSCKASGYTFSRYWIEWVRQAPGQGLEWMGRIL
PGSGSTNYAQKFQGRVTITADESTSTAYMELSSLRSEDYAVYYCTEGYEYDGFD
YWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWN
SGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKR
VEPK

25 SEQ ID NO: 9 (AM-VH3-T26-E55)

30 QVQLVQSGAEVKKPGSSVKVSCKATGYTFSRYWISWVRQAPGQGLEWMGEIL
PGSGSTNYAQKFQGRVTITADESTSTAYMELSSLRSEDYAVYYCTEGYEYDGFD
YWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWN
SGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKR
VEPK

SEQ ID NO: 10 (AM-VH4-T26-E40-E55)

5 QVQLVQSGAEVKKPGSSVKVSCKATGYTFSRYWIEWVRQAPGGLEWMGEIL
PGSGSTNYAQKFQGRVTITADESTSTAYMELSSLRSED TAVYYCTEGYEYDGFD
YWGQGT TTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVT VSWN
SGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKR
VEPK

10 or a sequence that is > 80% identical to each of the above depicted sequences
respectively, and

comprises a sequence selected from the group comprising the following sequence as a
VL region:

15 SEQ ID NO: 11 (AM-VL-C)

DVLLSQTPLSLPVSLGDQATISCRSSQSIVYSNGNTYLEWYLQKPGQSPKLLIYR
VSNRFSGV PDRFSGSGSGTDFTLKISRVEAEDLGVYYCFQGSHIPYTFGGG TKLE
IKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNS
20 QESVTEQDSKDYSLSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGE
C

SEQ ID NO: 12 (AM-VL1)

25 DVVMTQSPLSLPVTLGQPASISCRSSQSIVYSNGNTYLNWFQQRPGQSPRRLIYR
VSNRDSGV PDRFSGSGSGTDFTLKISRVEAEDVGVYYCFQGSHIPYTFGQGTKL
EIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGN
SQESVTEQDSKDYSLSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRG
EC

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SEQ ID NO: 13 (AM-VL2-E40)

DVVMTQSPLSLPVTLGQPASISCRSSQSIVYSNGNTYLEWFQQRPGQSPRRLIYR
VSNRDSGV PDRFSGSGSGTDFTLKISRVEAEDVGVYYCFQGSHIPYTFGQGTKL

EIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGN
SQESVTEQDSKDYSLSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRG
EC

5 or a sequence that is > 80% identical to each of the above depicted sequences.

17. Adrenomedullin (ADM) antibody or anti-ADM antibody fragment or anti-ADM non-Ig
scaffold for use in therapy or intervention in a patient infected with a Corona virus
according to any of claims 15 to 16, wherein said antibody or fragment comprises the
10 following sequence as a heavy chain:

SEQ ID NO: 35

QVQLVQSGAEVKKPGSSVKVSCKASGYTFSRYWIEWVRQAPGQGLEWIGEILPG
15 SGSTNYNQKFQGRVTITADTSTSTAYMELSSLRSEDVAVYYCTEGYEYDGFYD
GQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGA
LTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPK
SCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVK
FNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
20 ALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWE
SNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHY
TQKSLSLSPGK

or a sequence that is > 95% identical to it,
25 and comprises the following sequence as a light chain:

SEQ ID NO: 36

DVVLTSQPLSLPVTLGQPASISCRSSQIVYSNGNTYLEWYLQRPQGSPRLLIYRV
30 NRFSGVDPDRFSGSGSGTDFTLKISRVEAEDVGVYYCFQGSHIPYTFGGGTKLEIKR
TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESV
TEQDSKDYSLSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

or a sequence that is > 95% identical to it.

18. Anti-adrenomedullin (ADM) antibody or anti-ADM antibody fragment or anti-ADM non-Ig scaffold for use in therapy or intervention in a patient with compromised lung function and/or acute respiratory distress syndrome (ARDS).
- 5
19. Anti-adrenomedullin (ADM) antibody or anti-ADM antibody fragment or anti-ADM non-Ig scaffold for use in therapy or intervention in a patient with compromised lung function and/or acute respiratory distress syndrome (ARDS) according to claim 18, wherein said patient has a Horowitz index below 300, in particular below 200, in
- 10 particular below 100 and/or said patient is in need of mechanical ventilation.
20. Anti-adrenomedullin (ADM) antibody or anti-ADM antibody fragment or anti-ADM non-Ig scaffold for use in therapy or intervention in a patient with compromised lung function and/or acute respiratory distress syndrome (ARDS) according to claim 18 or 19,
- 15 wherein said patient has a level of pro-Adrenomedullin or fragment thereof in a sample of bodily fluid of said subject that is above a predetermined threshold or higher than a previously measured level of pro-Adrenomedullin when determined by a method according to any of claims 1 – 8.
- 20 21. Anti-adrenomedullin (ADM) antibody or anti-ADM antibody fragment or anti-ADM non-Ig scaffold for use in therapy or intervention in a patient with compromised lung function and/or acute respiratory distress syndrome (ARDS) according to claims 18 - 20, wherein the complementarity determining regions (CDR's) in the heavy chain comprises the sequences:
- 25
- CDR1: SEQ ID NO: 1
GYTFSRYW
- CDR2: SEQ ID NO: 2
- 30 ILPGSGST
- CDR3: SEQ ID NO: 3
TEGYEYDGFY

and the complementarity determining regions (CDR's) in the light chain comprises the sequences:

CDR1: SEQ ID NO: 4

5 QSIVYSNGNTY

CDR2:

RVS

10 CDR3: SEQ ID NO: 5

FQGSHIPYT

22. Anti-adrenomedullin (ADM) antibody or anti-ADM antibody fragment or anti-ADM non-Ig scaffold for use in therapy or intervention in a patient with compromised lung function and/or acute respiratory distress syndrome (ARDS) according to claim 21, wherein said antibody or fragment comprises a sequence selected from the group comprising as a VH region:
- 15

SEQ ID NO: 6 (AM-VH-C)

20

QVQLQQSGAELMKPGASVKISCKATGYTFSRYWIEWVKQRPGHGLEWIGEILP
GSGSTNYNEKFKGKATITADTSSNTAYMQLSSLTSEDSAVYYCTEGYEYDGFD
YWGQGTTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWN
SGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKR
25 VEPK

SEQ ID NO: 7 (AM-VH1)

30

QVQLVQSGAEVKKPGSSVKVSCKASGYTFSRYWISWVRQAPGGLEWMGRIL
PGSGSTNYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCTEGYEYDGFD
YWGQGTTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWN
SGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKR
VEPK

SEQ ID NO: 8 (AM-VH2-E40)

QVQLVQSGAEVKKPGSSVKVSCKASGYTFSRYWIEWVRQAPGQGLEWMGRIL
PGSGSTNYAQKFQGRVTITADESTSTAYMELSSLRSEDТАVYYCTEGYEYDGFD
5 YWGQGTТTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWN
SGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKR
VEPK

SEQ ID NO: 9 (AM-VH3-T26-E55)

10 QVQLVQSGAEVKKPGSSVKVSCKATGYTFSRYWISWVRQAPGQGLEWMGEIL
PGSGSTNYAQKFQGRVTITADESTSTAYMELSSLRSEDТАVYYCTEGYEYDGFD
YWGQGTТTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWN
SGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKR
15 VEPK

SEQ ID NO: 10 (AM-VH4-T26-E40-E55)

20 QVQLVQSGAEVKKPGSSVKVSCKATGYTFSRYWIEWVRQAPGQGLEWMGEIL
PGSGSTNYAQKFQGRVTITADESTSTAYMELSSLRSEDТАVYYCTEGYEYDGFD
YWGQGTТTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWN
SGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKR
VEPK

25 or a sequence that is > 80% identical to each of the above depicted sequences
respectively, and

comprises a sequence selected from the group comprising the following sequence as a
VL region:

30

SEQ ID NO: 11 (AM-VL-C)

DVLLSQTPSLPVS LGDQATISCRSSQSIVYSNGNTYLEWYLQKPGQSPKLLIYR
VSNRFSGV PDRFSGSGSGTDFTLKISRVEAEDLGVYYCFQGSHIPYTFGGGTKLE

IKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNS
QESVTEQDSKDSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGE
C

5 SEQ ID NO: 12 (AM-VL1)

DVVMTQSPLSLPVTLGQPASISCRSSQSIVYSNGNTYLNWFQQRPGQSPRRLIYR
VSNRDSGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCFQGSHIPYTFGQGTKL
EIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGN
10 QESVTEQDSKDSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRG
EC

SEQ ID NO: 13 (AM-VL2-E40)

DVVMTQSPLSLPVTLGQPASISCRSSQSIVYSNGNTYLEWFQQRPGQSPRRLIYR
VSNRDSGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCFQGSHIPYTFGQGTKL
EIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGN
15 QESVTEQDSKDSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRG
EC

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or a sequence that is > 80% identical to each of the above depicted sequences.

23. Adrenomedullin (ADM) antibody or anti-ADM antibody fragment or anti-ADM non-Ig
scaffold for use in therapy or intervention in a patient with compromised lung function
25 and/or acute respiratory distress syndrome (ARDS) according to any of claims 21 to 22,
wherein said antibody or fragment comprises the following sequence as a heavy chain:

SEQ ID NO: 35

30 QVQLVQSGAEVKKPGSSVKVSCKASGYTFSRYWIEWVRQAPGQGLEWIGEILPG
SGSTNYNQKFQGRVTITADTSTSTAYMELSSLRSEDVAVYYCTEGYEYDGFYD
GQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGA
LTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPK
SCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVK

FNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWE
SNGQPENNYKTTTPVLDSGGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHY
TQKSLSLSPGK

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or a sequence that is > 95% identical to it,
and comprises the following sequence as a light chain:

SEQ ID NO: 36

10

DVVLTSQSPLSLPVTLGQPASISCRSSQSIVYSNGNTYLEWYLQRPQGSPRLLIYRVS
NRFSGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCFQGSHIPYTFGGGTKLEIKR
TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESV
TEQDSKDSSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

15

or a sequence that is > 95% identical to it.