Dandekar (2005) Nat. Rev. Immunol. 5(12): 917-927; Chen et al. (2020) Current Tropical Medicine Reports 3:1-4).

Tada et al. (2020), available at https://www.biorxiv.org/content/10.1101/2020.09.16.300319v1.full, disclose an "ACE2 microbody" in which the extracellular domain of catalytically inactive ACE2 is fused to Fc domain 3 of the immunoglobulin heavy chain.

Svilenov et al. (2020), available at https://www.researchsquare.com/article/rs-459941/v1 and PCT/EP2021/063692 describe ACE2 fusion proteins with the Fc domain of IgG1 and IgG4.

European patent application EP21188832.6 discloses ACE2 fusion proteins with the Fc domain of IgM and IgG2.

WO 2021/170113, WO 2021/183404, US 2021/0284716 and WO 2021/189772 also disclose fusion proteins of ACE2 with the Fc part of different immunoglobulins.

Zhang et al. (2021) Cell Discovery 7: 65 describe that a fusion protein of the extracellular domain of ACE2 with the Fc part of IgG1 protected mice from SARS-CoV2 infection, as determined by reduced viral replication, weight loss, histological changes and inflammation in the lungs. Additionally, it is shown that unlike antibodies targeting the receptor-binding domain of SARS-CoV2 treatment with the fusion protein does not induce the development of escape mutants.

Hence, there is still a need for agents which can be used for the treatment and/or prevention of infections with coronaviruses, in particular with SARS-CoV-2.

SUMMARY

In one aspect, the present disclosure provides a fusion protein comprising a first part comprising a fragment of human ACE2 or a variant of said fragment, said human ACE2 having the amino acid sequence according to SEQ ID No. 1, and a second part comprising a variant of the Fc portion of human IgG1, said variant having the amino acid sequence according to SEQ ID No. 19.

In one example the first part and the second part are linked by the amino acid sequence according to SEQ ID No. 15.

The fragment of human ACE2 may consist of a protein with the amino acid sequence according to SEQ ID No. 2 or may be the extracellular domain of ACE2 consisting of a protein with the amino acid sequence according to SEQ ID No. 3.

In one example the variant of the human ACE2 fragment is an enzymatically inactive variant of human ACE2.

The enzymatically inactive variant of human ACE2 may comprise a H374N and a H378N mutation, the numbering referring to SEQ ID No. 1.or a mutation at position 273, preferably a R273A mutation, the numbering referring to SEQ ID No. 1.

In one example, the enzymatically inactive variant of human ACE2 consists of a protein having the amino acid sequence according to SEQ ID No. 91 or 92.

In one example, the enzymatically inactive variant of human ACE2 consists of a protein having the amino acid sequence according to SEQ ID No. 24 or 25.

In one example, the variant of the human ACE2 fragment comprises a S645C mutation, the numbering referring to SEQ ID No. 1. In particular, the variant of the human ACE2 fragment may consist of a protein having the amino acid sequence according to SEQ ID No. 28 or 29.

In one example, the variant of the human ACE2 fragment further comprises a H374N and a H378N mutation, the numbering referring to SEQ ID No. 1. In particular, the variant of the human ACE2 fragment may consist of a protein having the amino acid sequence according to SEQ ID No. 32 or 33.

In one example, the variant of the human ACE2 fragment further comprises a mutation at position 273, preferably a R273A mutation, the numbering referring to SEQ ID No. 1. In particular, the variant of the human ACE2 fragment may consist of a protein having the amino acid sequence according to SEQ ID No. 36 or 37.

In another aspect, the present disclosure further provides a fusion protein comprising:

(a) a first part comprising a variant of a fragment of human ACE2, said human ACE2 having the amino acid sequence according to SEQ ID No. 1, wherein the variant of the human ACE2 fragment comprises a S645C mutation, the numbering referring to SEQ ID No. 1, and (b) a second part comprising the Fc portion of human IgG or a variant of the Fc portion of human IgG.

In one example, the variant of a fragment of human ACE2 consists of a protein having the amino acid sequence according to SEQ ID No. 28 or 29.

In one example, the variant of a fragment of human ACE2 further comprises a H374N and a H378N mutation, the numbering referring to SEQ ID No. 1. In particular, the variant of the human ACE2 fragment may consist of a protein having the amino acid sequence according to SEQ ID No. 32 or 33.

In one example, the variant of a fragment of human ACE2 further comprises a mutation at position 273, preferably a R273A mutation, the numbering referring to SEQ ID No. 1. In particular, the variant of the human ACE2 fragment may consist of a protein having the amino acid sequence according to SEQ ID No. 36 or 37.

In one example, the second part comprises the Fc part of human IgG1 or IgG4 or a variant of the Fc part of human IgG1 or IgG4.

In one example, the second part comprises the Fc part of human IgG1 according to SEQ ID No. 16, preferably the first part and the second part are linked by the amino acid sequence according to SEQ ID No. 15.

In another example, the second part comprises the Fc part of human IgG4 according to SEQ ID No. 5, preferably the first part and the second part are linked by the amino acid sequence according to SEQ ID No. 4.

In another example, the second part comprises a variant of the Fc portion of human IgG4 having the sequence according to SEQ ID No. 44, preferably the first part and the second part are linked by the amino acid sequence according to SEQ ID No. 4.

In another example, the second part comprises a variant of the Fc portion of human IgG1 having the sequence according to SEQ ID No. 59 or a variant of the Fc portion of human IgG4 having the sequence according to SEQ ID No. 60.

In one example, the second part comprises a variant of the Fc portion of human IgG1 having the sequence according to SEQ ID No. 59 and the first part and the second part are linked by the amino acid sequence according to SEQ ID No. 15.

In another example, the second part comprises a variant of the Fc portion of human IgG4 having the sequence according to SEQ ID No. 60 and the first part and the second part are linked by the amino acid sequence according to SEQ ID No. 4.

In another aspect, the present disclosure further provides a fusion protein comprising a first part comprising a fragment of human ACE2 or a variant of said fragment, said human ACE2 having the amino acid sequence according to SEQ ID No. 1, and a second part comprising a variant of the Fc portion of human IgG1, said variant having the sequence according to SEQ ID No. 59 or a variant of the Fc portion of human IgG4, said variant having the sequence according to SEQ ID No. 60.

The second part may comprise a variant of the Fc portion of human IgG1 having the sequence according to SEQ ID No. 59 and the first part and the second part are linked by the amino acid sequence according to SEQ ID No. 15 or the second part may comprise a variant of the Fc portion of human IgG4 having the sequence according to SEQ ID No. 60 and the first part and the second part are linked by the amino acid sequence according to SEQ ID No. 4.

The fragment of human ACE2 may consist of a protein having the amino acid sequence according to SEQ ID No. 2 or may be the extracellular domain of ACE2 consisting of a protein having the amino acid sequence according to SEQ ID No. 3.

In one example. the variant of the human ACE2 fragment is an enzymatically inactive variant of human ACE2.

The enzymatically inactive variant of human ACE2 may comprise a H374N and a H378N mutation, the numbering referring to SEQ ID No. 1 or a mutation at position 273, preferably a R273A mutation, the numbering referring to SEQ ID No. 1.

In another aspect, the present disclosure further provides a fusion protein comprising:
(a) a first part comprising a variant of a fragment of human ACE2, said human ACE2 having the amino acid sequence according to SEQ ID No. 1, wherein the variant of the human ACE2 fragment comprises a R273A mutation, the numbering referring to SEQ ID No. 1, and
(b) a second part comprising the Fc portion of human IgG or a variant of the Fc portion of human IgG.

In one example, the variant of a fragment of human ACE2 consists of a protein having the amino acid sequence according to SEQ ID No. 24 or 25.

The second part may comprise the Fc part of human IgG1 or IgG4.

In one example, the second part comprises the Fc part of human IgG1 according to SEQ ID No. 16, preferably the first part and the second part are linked by the amino acid sequence according to SEQ ID No. 15.

In an alternative example, the second part comprises the Fc part of human IgG4 according to SEQ ID No. 5, preferably the first part and the second part are linked by the amino acid sequence according to SEQ ID No. 4.

In an alternative example, the second part comprises a variant of the Fc portion of human IgG4 having the sequence according to SEQ ID No. 44.

The fusion protein of the present disclosure may have an amino acid sequence selected from the group of amino acid sequences according to SEQ ID Nos. 20, 21, 22, 23, 26, 27, 30, 31, 34, 35, 38, 39, 40, 41, 42, 43, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 93 and 94.

In further aspects, the present disclosure also relates to a nucleic acid molecule comprising a nucleic acid sequence encoding said fusion protein, an expression vector comprising said nucleic acid molecule and a host cell comprising said nucleic acid molecule or said expression vector.

Further, in another aspect, the present disclosure relates to a method for producing said fusion protein, comprising culturing said host cell in a suitable culture medium.

In yet another aspect, the present disclosure provides a fusion protein as described herein for use in therapy. In yet another aspect, the present disclosure provides a use of a fusion protein as described herein in the manufacture of a medicament for preventing and/or treating an infection with a coronavirus binding to ACE2. In yet another aspect, the present disclosure provides a use of a fusion protein as described herein in the manufacture of a medicament for treating hypertension (including high blood pressure), congestive heart failure, chronic heart failure, acute heart failure, contractile heart failure, myocardial infarction, arteriosclerosis, kidney failure, renal failure, Acute Respiratory Distress Syndrome (ARDS), Acute Lung Injury (ALI), chronic obstructive pulmonary disease (COPD), pulmonary hypertension, renal fibrosis, chronic renal failure, acute renal failure, acute kidney injury, inflammatory bowel disease and multi-organ dysfunction syndrome.

The present disclosure also relates to said fusion protein for medical use, in particular for use in preventing and/or treating an infection with a coronavirus binding to ACE2.

In one example, the coronavirus binding to ACE2 is selected from the group consisting of SARS, SARS-CoV-2 and NL-63, preferably is SARS-CoV-2.

Said fusion protein may be administered in combination with an anti-viral agent which may be selected from the group consisting of remdesivir, arbidol HCl, ritonavir, lopinavir, darunavir, ribavirin, chloroquin and derivatives thereof, nitazoxanide, camostat mesilate, tocilizumab, siltuximab, sarilumab and baricitinib phosphate.

Said fusion protein may also be administered in combination with an antibody which may be selected from the group consisting of bamlanivimab, etesevimab, casirivimab, imdevimab, sotrovimab and mixtures thereof.

The present disclosure also relates to said fusion protein for use in treating hypertension (including high blood pressure), congestive heart failure, chronic heart failure, acute heart failure, contractile heart failure, myocardial infarction, arteriosclerosis, kidney failure, renal failure, Acute Respiratory Distress Syndrome (ARDS), Acute Lung Injury (ALI), chronic obstructive pulmonary disease (COPD), pulmonary hypertension, renal fibrosis, chronic renal

failure, acute renal failure, acute kidney injury, inflammatory bowel disease and multi-organ dysfunction syndrome.

In a further aspect, the present disclosure also relates to a pharmaceutical composition comprising said fusion protein and a pharmaceutically acceptable carrier or excipient. The pharmaceutical composition may further comprise an anti-viral agent.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1: Protein yield of different fusion proteins after protein A chromatography as determined by slope spectroscopy

CLAIMS

1. A fusion protein comprising a first part comprising a fragment of human ACE2 or a variant of said fragment, said human ACE2 having the amino acid sequence according to SEQ ID No. 1, and a second part comprising a variant of the Fc portion of human IgG1, said variant having the amino acid sequence according to SEQ ID No. 19.

2. Fusion protein according to claim 1, wherein the first part and the second part are linked by the amino acid sequence according to SEQ ID No. 15.

3. Fusion protein according to claim 1 or 2, wherein the fragment of human ACE2 consists of a protein with the amino acid sequence according to SEQ ID No. 2.

4. Fusion protein according to claim 1 or 2, wherein the fragment of human ACE2 is the extracellular domain of ACE2 consisting of a protein with the amino acid sequence according to SEQ ID No. 3.

5. Fusion protein according to claim 1 or 2, having the amino acid sequence according to SEQ ID No. 20 or 21.

6. Fusion protein according to any one of claims 1 to 5, wherein the variant of the human ACE2 fragment is an enzymatically inactive variant of human ACE2.

7. Fusion protein according to claim 6, wherein the enzymatically inactive variant of human ACE2 comprises a H374N and a H378N mutation, the numbering referring to SEQ ID No. 1.

8. Fusion protein according to claim 6 or 7, wherein the enzymatically inactive variant of human ACE2 consists of a protein having the amino acid sequence according to SEQ ID No. 91 or 92.

9. Fusion protein according to any one of claims 6 to 8, having the amino acid sequence according to SEQ ID No. 22 or 23.

10. Fusion protein according to claim 6, wherein the enzymatically inactive variant of human ACE2 comprises a mutation at position 273, the numbering referring to SEQ ID No. 1.

11. Fusion protein according to claim 10, wherein the mutation at position 273 is a R273A mutation.

12. Fusion protein according to claim 10 or 11, wherein the enzymatically inactive variant of human ACE2 consists of a protein having the amino acid sequence according to SEQ ID No. 24 or 25.

13. Fusion protein according to any one of claims 10 to 12, having the amino acid sequence according to SEQ ID No. 26 or 27.

14. Fusion protein according to any one of claims 1 to 5, wherein the variant of the human ACE2 fragment comprises a S645C mutation, the numbering referring to SEQ ID No. 1.

15. Fusion protein according to claim 14, wherein the variant of the human ACE2 fragment consists of a protein having the amino acid sequence according to SEQ ID No. 28 or 29.

16. Fusion protein according to claim 14 or 15, having the amino acid sequence according to SEQ ID No. 30 or 31.

17. Fusion protein according to claim 14, wherein the variant of the human ACE2 fragment further comprises a H374N and a H378N mutation, the numbering referring to SEQ ID No. 1.

18. Fusion protein according to claim 17, wherein the variant of the human ACE2 fragment consists of a protein having the amino acid sequence according to SEQ ID No. 32 or 33.

19. Fusion protein according to claim 17 or 18, having the amino acid sequence according to SEQ ID No. 34 or 35.

20. Fusion protein according to claim 14, wherein the variant of the human ACE2 fragment further comprises a mutation at position 273, the numbering referring to SEQ ID No. 1.

21. Fusion protein according to claim 20, wherein the mutation at position 273 is a R273A mutation.

22. Fusion protein according to claim 20 or 21, wherein the variant of the human ACE2 fragment consists of a protein having the amino acid sequence according to SEQ ID No. 36 or 37.

23. Fusion protein according to claim 20 to 22, having the amino acid sequence according to SEQ ID No. 38 or 39

24. A fusion protein comprising:
(a) a first part comprising a variant of a fragment of human ACE2, said human ACE2 having the amino acid sequence according to SEQ ID No. 1, wherein the variant of the human ACE2 fragment comprises a S645C mutation, the numbering referring to SEQ ID No. 1, and
(b) a second part comprising the Fc portion of human IgG or a variant of the Fc portion of human IgG.

25. Fusion protein according to claim 24, wherein the variant of a fragment of human ACE2 consists of a protein having the amino acid sequence according to SEQ ID No. 28 or 29.

26. Fusion protein according to claim 24 or 25, wherein the variant of a fragment of human ACE2 further comprises a H374N and a H378N mutation, the numbering referring to SEQ ID No. 1.

27. Fusion protein according to claim 26, wherein the variant of a fragment of human ACE2 consists of a protein having the amino acid sequence according to SEQ ID No. 32 or 33.

28. Fusion protein according to claim 24 or 25, wherein the variant of a fragment of human ACE2 further comprises a mutation at position 273, the numbering referring to SEQ ID No. 1.

29. Fusion protein according to claim 28, wherein the mutation at position 273 is a R273A mutation.

30. Fusion protein according to claim 28 or 29, wherein the variant of a fragment of human ACE2 consists of a protein having the amino acid sequence according to SEQ ID No. 36 or 37.

31. Fusion protein according to any one of claims 24 to 30, wherein the second part comprises the Fc part of human IgG1 or IgG4 or a variant of the Fc part of human IgG1 or IgG4.

32. Fusion protein according to claim 31, wherein the second part comprises the Fc part of human IgG1 according to SEQ ID No. 16.

33. Fusion protein according to claim 32, wherein the first part and the second part are linked by the amino acid sequence according to SEQ ID No. 15.

34. Fusion protein according to claim 32 or 33, having the amino acid sequence according to SEQ ID No. 40 or 41.

35. Fusion protein according to claim 31 wherein the second part comprises the Fc part of human IgG4 according to SEQ ID No. 5.

36. Fusion protein according to claim 35, wherein the first part and the second part are linked by the amino acid sequence according to SEQ ID No. 4.

37. Fusion protein according to claim 35 or 36, having the amino acid sequence according to SEQ ID No. 42 or 43.

38. Fusion protein according to claim 31, wherein the second part comprises a variant of the Fc portion of human IgG4 having the sequence according to SEQ ID No. 44.

39. Fusion protein according to claim 38, wherein the first part and the second part are linked by the amino acid sequence according to SEQ ID No. 4.

40. Fusion protein according to claim 38 or 39, having the amino acid sequence according to SEQ ID No. 45 or 46.

41. Fusion protein according to any one of claims 26 and 31 to 33, having the amino acid sequence according to SEQ ID No. 47 or 48.

42. Fusion protein according to any one of claims 28, 29 and 31 to 33, having the amino acid sequence according to SEQ ID No. 49 or 50.

43. Fusion protein according to any one of claims 26, 31, 35 and 36, having the amino acid sequence according to SEQ ID No. 51 or 52.

44. Fusion protein according to any one of claims 28, 29, 35 and 36, having the amino acid sequence according to SEQ ID No. 53 or 54.

45. Fusion protein according to any one of claims 26, 31, 38 and 39, having the amino acid sequence according to SEQ ID No. 55 or 56.

46. Fusion protein according to any one of claims 28, 29, 38 and 39, having the amino acid sequence according to SEQ ID No. 57 or 58.

47. Fusion protein according to claim 31, wherein the second part comprises a variant of the Fc portion of human IgG1 having the sequence according to SEQ ID No. 59 or a variant of the Fc portion of human IgG4 having the sequence according to SEQ ID No. 60.

48. Fusion protein according to claim 47, wherein the second part comprises a variant of the Fc portion of human IgG1 having the sequence according to SEQ ID No. 59 and the first part and the second part are linked by the amino acid sequence according to SEQ ID No. 15.

49. Fusion protein according to any one of claims 24, 25, 47 and 48, having the amino acid sequence according to SEQ ID No. 61 or 62.

50. Fusion protein according to any one of claims 26, 47 and 48, having the amino acid sequence according to SEQ ID No. 63 or 64.

51. Fusion protein according to any one of claims 28, 29, 47 and 48, having the amino acid sequence according to SEQ ID No. 65 or 66.

52. Fusion protein according to claim 47, wherein the second part comprises a variant of the Fc portion of human IgG4 having the sequence according to SEQ ID No. 60

and the first part and the second part are linked by the amino acid sequence according to SEQ ID No. 4.

53. Fusion protein according to any one of claims 24, 25, 47 and 50, having the amino acid sequence according to SEQ ID No. 67 or 68.

54. Fusion protein according to any one of claims 26, 47 and 50, having the amino acid sequence according to SEQ ID No. 69 or 70.

55. Fusion protein according to any one of claims 28, 29, 47 and 50, having the amino acid sequence according to SEQ ID No. 71 or 72.

56. A fusion protein comprising a first part comprising a fragment of human ACE2 or a variant of said fragment, said human ACE2 having the amino acid sequence according to SEQ ID No. 1, and a second part comprising a variant of the Fc portion of human IgG1, said variant having the sequence according to SEQ ID No. 59 or a variant of the Fc portion of human IgG4, said variant having the sequence according to SEQ ID No. 60.

57. Fusion protein according to claim 56, wherein the second part comprises a variant of the Fc portion of human IgG1 having the sequence according to SEQ ID No. 59 and the first part and the second part are linked by the amino acid sequence according to SEQ ID No. 15.

58. Fusion protein according to claim 56, wherein the second part comprises a variant of the Fc portion of human IgG4 having the sequence according to SEQ ID No. 60 and the first part and the second part are linked by the amino acid sequence according to SEQ ID No. 4.

59. Fusion protein according to any one of claims 56 to 58, wherein the fragment of human ACE2 consists of a protein having the amino acid sequence according to SEQ ID No. 2.

60. Fusion protein according to claim 56 to 58, wherein the fragment of human ACE2 is the extracellular domain of ACE2 consisting of a protein having the amino acid sequence according to SEQ ID No. 3.

61. Fusion protein according to any one of claims 56, 57, 59 or 60, having the amino acid sequence according to SEQ ID No. 73 or 74.

62. Fusion protein according to any one of claims 56 or 58 to 60, having the amino acid sequence according to SEQ ID No. 75 or 76.

63. Fusion protein according to any one of claims 56 to 60, wherein the variant of the human ACE2 fragment is an enzymatically inactive variant of human ACE2.

64. Fusion protein according to claim 63, wherein the enzymatically inactive variant of human ACE2 comprises a H374N and a H378N mutation, the numbering referring to SEQ ID No. 1.

65. Fusion protein according to claim 63 or 64, wherein the enzymatically inactive variant of human ACE2 consists of a protein having the amino acid sequence according to SEQ ID No. 91 or 92.

66. Fusion protein according to any one of claims 63 to 65, having the amino acid sequence according to any one of SEQ ID Nos. 77 to 80.

67. Fusion protein according to claim 63, wherein the enzymatically inactive variant of human ACE2 comprises a mutation at position 273, the numbering referring to SEQ ID No. 1.

68. Fusion protein according to claim 67, wherein the mutation at position 273 is a R273A mutation.

69. Fusion protein according to claim 67 or 68, having the amino acid sequence according to any one of SEQ ID Nos. 81 to 84.

70. A fusion protein comprising:

(a) a first part comprising a variant of a fragment of human ACE2, said human ACE2 having the amino acid sequence according to SEQ ID No. 1, wherein the variant of the human ACE2 fragment comprises a R273A mutation, the numbering referring to SEQ ID No. 1, and

(b) a second part comprising the Fc portion of human IgG or a variant of the Fc portion of human IgG.

71. Fusion protein according to claim 70, wherein the variant of a fragment of human ACE2 consists of a protein having the amino acid sequence according to SEQ ID No. 24 or 25.

72. Fusion protein according to claim 70 or 71, wherein the second part comprises the Fc part of human IgG1 or IgG4.

73. Fusion protein according to claim 72, wherein the second part comprises the Fc part of human IgG1 according to SEQ ID No. 16.

74. Fusion protein according to claim 73, wherein the first part and the second part are linked by the amino acid sequence according to SEQ ID No. 15.

75. Fusion protein according to any one of claims 70 to 74, having the amino acid sequence according to SEQ ID No. 85 or 86.

76. Fusion protein according to claim 72, wherein the second part comprises the Fc part of human IgG4 according to SEQ ID No. 5.

77. Fusion protein according to claim 76, wherein the first part and the second part are linked by the amino acid sequence according to SEQ ID No. 4.

78. Fusion protein according to claim 76 or 77, having the amino acid sequence according to SEQ ID No. 87 or 88.

79. Fusion protein according to claim 72, wherein the second part comprises a variant of the Fc portion of human IgG4 having the sequence according to SEQ ID No. 44.

80. Fusion protein according to claim 79, wherein the first part and the second part are linked by the amino acid sequence according to SEQ ID No. 4.

81. Fusion protein according to claim 79 or 80, having the amino acid sequence according to SEQ ID No. 89 or 90.

82. Fusion protein having the amino acid sequence according to SEQ ID No. 93 or 94.

83. Nucleic acid molecule comprising a nucleic acid sequence encoding the fusion protein according to any one of claims 1 to 82.

84. Expression vector comprising the nucleic acid molecule according to claim 83.

85. Host cell comprising the nucleic acid molecule according to claim 83 or the expression vector according to claim 84.

86. Method for producing the fusion protein according to any one of claims 1 to 82, comprising culturing the host cell according to claim 85 in a suitable culture medium.

87. Fusion protein according to any one of claims 1 to 82 for use in therapy.

88. Use of a fusion protein according to any one of claims 1 to 82 in the manufacture of a medicament for preventing and/or treating an infection with a coronavirus binding to ACE2.

89. The use according to claim 88, wherein the coronavirus binding to ACE2 is selected from the group consisting of SARS, SARS-CoV-2 and NL63, preferably it is SARS-CoV-2.

90. The use according to claim 88 or 89, wherein the fusion protein is to be administered in combination with an anti-viral agent.

91. The use according to claim 90, wherein the anti-viral agent is selected from the group consisting of remdesivir, arbidol HCl, ritonavir, lopinavir, darunavir, ribavirin, chloroquin and derivatives thereof, nitazoxanide, camostat mesilate, tocilizumab, siltuximab, sarilumab and baricitinib phosphate.

92. The use according to claim 88 or 89, wherein the fusion protein is to be administered in combination with an antibody.

93. The use according to claim 92, wherein the antibody is selected from the group consisting of bamlanivimab, etesevimab, casirivimab, imdevimab, sotrovimab and mixtures thereof.

94. Use of a fusion protein according to any one of claims 1 to 82 in the manufacture of a medicament for treating hypertension (including high blood pressure), congestive heart failure, chronic heart failure, acute heart failure, contractile heart failure, myocardial infarction, arteriosclerosis, kidney failure, renal failure, Acute Respiratory Distress Syndrome (ARDS), Acute Lung Injury (ALI), chronic obstructive pulmonary disease (COPD), pulmonary hypertension, renal fibrosis, chronic renal failure, acute renal failure, acute kidney injury, inflammatory bowel disease and multi-organ dysfunction syndrome.

95. Pharmaceutical composition comprising an effective amount of the fusion protein according to any one of claims 1 to 82 and a pharmaceutically acceptable carrier or excipient.

96. Pharmaceutical composition according to claim 95, further comprising an anti-viral agent.