SUMMARY ~~OF THE INVENTION~~

The objective is solved by the subject of the present claims and as further described herein.

The ~~invention~~present disclosure provides a pharmaceutical preparation comprising liraglutide or gefitinib or a salt, solvate or combination thereof, in an effective amount for use in prophylactic or therapeutic treatment of a disease condition which is caused by or associated with an infection by a coronavirus.

In an aspect of the present disclosure, there is provided a use of a pharmaceutical preparation comprising liraglutide, or gefitinib, or a salt, or solvate thereof, in the manufacture of a medicament for the prophylactic or therapeutic treatment of a disease condition which is caused by or associated with an infection by a coronavirus.

In another aspect of the present disclosure, there is provided a pharmaceutical preparation comprising liraglutide or gefitinib or a salt, solvate thereof, in an effective amount, further comprising an active agent selected from the group consisting of suramin, raloxifene, maraviroc, miglustat, quinacrine, glatiramer acetate, auranofin, and dexamethasone.

In a specific ~~embodiment~~example, a combination of liraglutide and gefitinib, or the salt or solvate thereof is provided herein for use in prophylactic or therapeutic treatment of a disease condition which is caused by or associated with an infection by a coronavirus.

According to a specific ~~aspect~~example, the coronavirus species are selected from human and non-human, such as zoonotic, Coronaviridae viruses, in particular naturally-occurring coronaviruses including mutants thereof which may evolve during a season of infection or a pandemic, or mutants that are artificially evolved to anticipate naturally-occurring mutants.

Specifically, the coronavirus is a β-coronavirus, more specifically a human β-coronavirus. Within the genus β-coronavirus, four lineages (i.e., A, B, C, and D) are commonly recognized. Specifically, the β-coronavirus is of the B-lineage (subgenus Sarbecovirus), such as SARS-CoV or SARS-CoV-2, or of the C-lineage (subgenus Merbecovirus), such as MERS-CoV, or of the A-lineage (subgenus Embecovirus), such as HCoV-NL63, HCoV 229E, HCoV-OC43 or HCoV-HKU1.

Specifically, the coronavirus is selected from the group consisting of SARS-CoV-2, MERS-CoV, SARS-CoV-1, HCoV-NL63, HCoV 229E, HCoV-OC43, and HCoV-

HKU1, or mutants thereof, in particular those mutants which are naturally-occurring, i.e which are not artificial (“man-made”) but found in nature.

According to a specific ~~aspect~~example, the pharmaceutical preparation is a medicinal product or a drug product, comprising liraglutide or gefitinib and a pharmaceutically acceptable carrier.

Specifically, the pharmaceutical preparation described herein is used for treatment or prevention of a disease condition which can be, but is not limited to common cold, infection of the nose, throat and larynx, sinusitis, bronchiolitis, diarrhea, rash on skin, pneumonia, or acute respiratory distress syndrome (ARDS), symptoms of the central nervous system, hepatic steatosis, portal fibrosis, occurrence of lymphocytic infiltrates and ductular proliferation, lobular cholestasis, acute liver cell necrosis, central

vein thrombosis, renal proximal tubular injury, focal pancreatitis, adrenocortical hyperplasia, and lymphocyte depletion of spleen and lymph nodes, alveolar damage specifically characterized by edema, hyaline membranes, and proliferation of pneumocytes and fibroblasts, endothelial damage.

Specifically, the effective amount is effective in preventing infection of susceptible cells by the virus, thereby treating the disease condition.

Specifically, the effective amount is effective by reducing or inhibiting inflammatory and undesired coagulation symptoms associated with virus infection.

In a specific ~~embodiment~~example, the effective amount is administered locally or systemically.

Liraglutide is a synthetic analog of human glucagon-like peptide-1(GLP-1) and acts as a GLP-1 receptor agonist. Liraglutide is 97% homologous to native human GLP-1 by substituting arginine for lysine at position 34. Liraglutide is made by attaching a C-16 fatty acid (palmitic acid) with a glutamic acid spacer on the remaining lysine residue at position 26 of the peptide precursor. Liraglutide comprises the sequence:

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys(1)-Glu-Phe-Ile-Ala-Trp-Leu-Val-Arg-Gly-Arg-Gly (SEQ ID NO: 1).

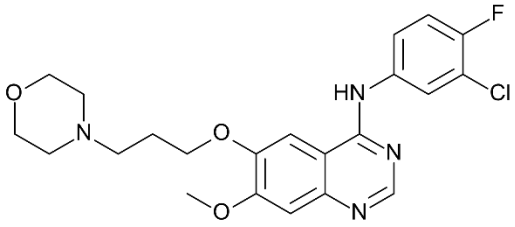
Its protein chemical formula is $C_{172}H_{265}N_{43}O_{51}$.

Liraglutide is commercially available under the trade names Saxenda® and Victoza®.

Liraglutide has cardio-, reno-, as well as neuroprotective effects. Liraglutide was also shown to counterbalance inflammatory processes and oxidative stress. Levels of TNF, IL1b, IL6, IL17 and IL21, key players in inflammatory response after COVID-19 infection, are reduced by liraglutide. In addition, liraglutide modulates DPP4 levels, a molecule potentially linked to coronavirus entry and replication.

Specifically, TNF, IL17, IL21, IL6 and/or IL1b are inhibited by liraglutide.

In a further ~~embodiment~~example, gefitinib is present in the pharmaceutical preparation described herein. Gefitinib is characterized by the structure (I)



Specifically, the preparation comprises about 50 ng to 1 g / dose of gefitinib, more specifically the preparation comprises about 100 ng to 800 mg, specifically 500 ng to 500 mg/dose.

Specifically, the daily dose is in the range of about 50 ng to 1 g of gefitinib, more specifically the preparation comprises about 100 ng to 800 mg, specifically 500 ng to 500 mg.

According to an ~~embodiment~~example, the pharmaceutical preparation is administered to the subject as a spray, a powder, a gel, an ointment, a cream, a foam, or a liquid solution, a lotion, a patch, a gargle solution, an aerosolized powder, an aerosolized liquid formulation, granules, capsules, specifically comprising nanoparticles, drops, tablet, syrup, lozenge, nano-capsule, liposomal preparation or a preparation for infusion or injection.

According to a specific ~~embodiment~~example, liraglutide can be administered by inhalation, more specifically in a dose of about 1 to 15 µg/kg, specifically 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 13, 14, 15 µg/kg.

Specifically, the preparation is administered as the sole substance, or wherein treatment is combined with a further treatment with one or more active substances, preferably selected from the group consisting of antiviral, anti-inflammatory and antibiotic substances.

In a specific ~~embodiment~~example, the preparation is administered in combination with an active agent selected from the group consisting of suramin, raloxifene, maraviroc, miglustat, quinacrine, glatiramer acetate, auranofin and dexamethasone.

Specifically, a subject is treated with the preparation described herein, who has been infected or is at risk of being infected with coronavirus.

According to a specific ~~aspect~~example, a subject is treated who has been infected or is at risk of being infected with said virus, preferably a human being, or a non-human mammal, such as a dog, cat, horse, camelids, cattle or pig.

Specifically, the subject is or has been exposed to a virus, or is otherwise at risk of being infected with the virus.

Specifically, the subject has been determined or diagnosed of being infected with the virus.

In specific ~~embodiment~~examples, a subject is treated which is a diseased subject or patient suffering from Coronaviridae virus-caused disease, such as gastroenteritis, respiratory tract disease, or severe acute respiratory syndrome (SARS). Specifically, the

disease is a β-coronavirus-caused disease e.g., a SARS virus-caused disease, upon getting in contact with the pathogen, such as COVID19, or COVID19-associated pneumonia.

According to a further ~~embodiment~~example, there is provided a pharmaceutical preparation comprising liraglutide or gefitinib or a salt, solvate or combination of liraglutide and gefitinib, in an effective amount, further comprising an active agent selected from the group consisting of suramin, raloxifene, maraviroc, miglustat, quinacrine, glatiramer acetate and auranofin.

According to a specific ~~aspect~~example, a kit is provided which comprising one or more individual dosage units of liraglutide, or gefitinib as further described herein, and directions for their use in treating a coronavirus infection or a coronavirus-caused disease, in a human or non-human mammal.

According to a specific ~~aspect~~example, the ~~invention~~present disclosure further provides for methods of treating a subject being infected or at risk of being infected with a virus such as a coronavirus, comprising administering an effective amount of liraglutide or gefitinib or combination thereof, and respective medicinal products or pharmaceutical preparations as further described herein.

According to a further specific ~~aspect~~example, the ~~invention~~present disclosure provides for an preparation of liraglutide or gefitinib as described herein (such as a medicinal product, pharmaceutical preparation or disinfectant) and methods of producing such antiviral preparation comprising formulating an antiviral effective amount of liraglutide, or gefitinib, with a pharmaceutically acceptable carrier to produce a preparation, in particular a medicinal product or pharmaceutical preparation which specifically has antiviral, anti-inflammatory and/or anti-coagulation effect.

FIGURES

Figure 1: Cytokine release assay of interleukin 6 (IL-6) in response to nucleocapsid (N) stimulation or Mock stimulation as control. Immune modulation by gefitinib (GEF) alone was significantly stronger than by dexamethasone (DEX) alone. Numbers at the bottom of the boxplot represent replicate numbers of the experiments. The strongest immunomodulatory effect was observed in combination of GEF and DEX.

Figure 2: Cytokine release assay of interleukin 17 (IL-17), tumor necrosis factor beta (TNF-beta) and IL-21 in response to nucleocapsid (N) stimulation or Mock stimulation as control. Immune modulation by gefitinib (GEF, 5 µM), liraglutide (LIR, 2

CLAIMS

1. Use of a ~~P~~pharmaceutical preparation comprising liraglutide, or gefitinib, or a salt, or solvate thereof, in ~~an effective amount for use in~~the manufacture of a medicament for the prophylactic or therapeutic treatment of a disease condition which is caused by or associated with an infection by a coronavirus.

2. The ~~pharmaceutical preparation for~~ use according to claim 1, wherein the coronavirus is a β-coronavirus, preferably selected from the group consisting of SARS-CoV-2, MERS-CoV, SARS-CoV-1, HCoV-OC43, and HCoV-HKU1, or mutants thereof.

3. The ~~pharmaceutical preparation for~~ use according to claim 1 or 2, wherein the pharmaceutical preparation is a medicinal product or a drug product, comprising liraglutide or gefitinib and a pharmaceutically acceptable carrier.

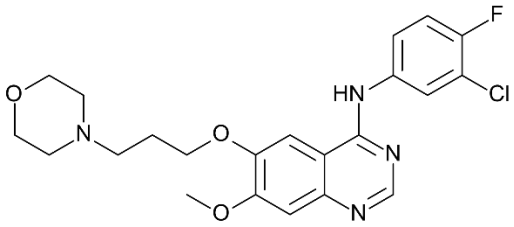
4. The ~~pharmaceutical preparation for~~ use according to any one of claims 1 to 3, wherein the disease condition is common cold, infection of the nose, throat and larynx, sinusitis, bronchiolitis, diarrhea, rash on skin, pneumonia, or acute respiratory distress syndrome (ARDS), symptoms of the central nervous system, hepatic steatosis, portal fibrosis, occurrence of lymphocytic infiltrates and ductular proliferation, lobular cholestasis, acute liver cell necrosis, central vein thrombosis, renal proximal tubular injury, focal pancreatitis, adrenocortical hyperplasia, and lymphocyte depletion of spleen and lymph nodes, alveolar damage specifically characterized by edema, hyaline membranes, and proliferation of pneumocytes and fibroblasts, endothelial damage.

5. The ~~pharmaceutical preparation for~~ use according to any one of claims 1 to 4, wherein the antiviral ~~effective amount~~ is effective in preventing infection of susceptible cells by the virus, thereby treating the disease condition.

6. The ~~pharmaceutical preparation for~~ use according to any one of claims 1 to 5, wherein liraglutide comprises the sequence His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys(1)-Glu-Phe-Ile-Ala-Trp-Leu-Val-Arg-Gly-Arg-Gly (SEQ ID NO. 1)

7. The ~~pharmaceutical preparation for~~ use according to claim 6, wherein the preparation comprises about 50 ng to 1 g of liraglutide.

8. The ~~pharmaceutical preparation for~~ use according to any one of claims 1 to 5, wherein gefitinib comprises the structure



9. The ~~pharmaceutical preparation for~~ use according to claim 8, wherein the preparation comprises about 50 ng to 1 g of gefitinib.

10. The ~~pharmaceutical preparation for~~ use according to any one of claims 1 to 9, wherein said pharmaceutical preparation is formulated for local administration, preferably for application to the upper and lower respiratory tract, nasal, pulmonary, intraoral, ocular, or dermal use, or for systemic administration, preferably for parenteral administration.

11. The ~~pharmaceutical preparation for~~ use according to any one of claims 1 to 10, wherein said pharmaceutical preparation is to be administered to ~~the~~ a subject as a spray, a powder, a gel, an ointment, a cream, a foam, or a liquid solution, a lotion, a patch, a gargle solution, an aerosolized powder, an aerosolized liquid formulation, granules, capsules, specifically comprising a preparation for parenteral administration.

12. The ~~pharmaceutical preparation for~~ use according to any one of claims 1 to 11, wherein the preparation is to be administered as the sole substance, or wherein treatment is to be combined with a further treatment with one or more active substances, selected from the group consisting of antiviral, anti-inflammatory and antibiotic substances.

13. The ~~pharmaceutical preparation for~~ use according to any one of claims 1 to 12, wherein the preparation is to be administered in combination with an active agent

selected from the group consisting of suramin, raloxifene, maraviroc, miglustat, quinacrine, glatiramer acetate, auranofin, and dexamethasone.

14. The ~~pharmaceutical preparation for~~ use according to any one of claims 1 to 13, wherein a subject is treated who has been infected or is at risk of being infected with coronavirus.

15. Pharmaceutical preparation comprising liraglutide or gefitinib or a salt, solvate thereof, in an effective amount, further comprising an active agent selected from the group consisting of suramin, raloxifene, maraviroc, miglustat, quinacrine, glatiramer acetate, auranofin, and dexamethasone.