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An update on drugs with therapeutic potential for SARS-CoV-2 (COVID-19) treatment

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ABSTRACT

The COVID-19 pandemic is one of the greatest threats to human health in the 21st century with more than 257 million cases and over 5.17 million deaths reported worldwide (as of November 23, 2021). Various agents were initially proclaimed to be effective against SARS-CoV-2, the etiological agent of COVID-19. Hydroxychloroquine, lopinavir/ritonavir, and ribavirin are all examples of therapeutic agents, whose efficacy against COVID-19 was later disproved. Meanwhile, concentrated efforts of researchers and clinicians worldwide have led to the identification of novel therapeutic options to control the disease including PAXLOVID™ (PF-07321332). Although COVID-19 cases are currently treated using a comprehensive approach of anticoagulants, oxygen, and antibiotics, the novel Pfizer agent PAXLOVID™ (PF-07321332), an investigational COVID-19 oral antiviral candidate, significantly reduced hospitalization time and death rates, based on an interim analysis of the phase 2/3 EPIC-HR (Evaluation of Protease Inhibition for COVID-19 in High-Risk Patients) randomized, double-blind study of non-hospitalized adult patients with COVID-19, who are at high risk of progressing to severe illness. The scheduled interim analysis demonstrated an 89 % reduction in risk of COVID-19-related hospitalization or death from any cause compared to placebo in patients treated within three days of symptom onset (primary endpoint). However, there still exists a great need for the development of additional treatments, as the recommended therapeutic options are insufficient in many cases. Thus far, mRNA and vector vaccines appear to be the most effective modalities to control the pandemic. In the current review, we provide an update on the progress that has been made since April 2020 in clinical trials concerning the effectiveness of therapies available to combat COVID-19. We focus on currently recommended therapeutic agents, including steroids, various monoclonal antibodies, remdesivir, baricitinib, anticoagulants and PAXLOVID™ summarizing the latest original studies and meta-analyses. Moreover, we aim to discuss other currently and previously studied agents targeting COVID-19 that either show no or only limited therapeutic activity. The results of recent studies report that hydroxychloroquine and convalescent plasma demonstrate no efficacy against SARS-CoV-2 infection. Lastly, we summarize the studies on various drugs with incoherent or insufficient data concerning their effectiveness, such as amantadine, ivermectin, or niclosamide.

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1. Introduction

Coronaviruses (CoVs) are enveloped, spherical viruses, whose genome contains a positive-sense, single-stranded RNA (Cui et al., 2019; Pollard et al., 2020). They are responsible for respiratory and interstitial infections, whose severity varies from cold-like symptoms to severe respiratory failure (Fehr and Perlman, 2015; Giovanetti et al., 2021). The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), causes the Coronavirus Disease 2019 (COVID-19), whose symptoms can vary from mild, self-limiting respiratory distress to severe pneumonia leading to multiple organ failure and death (Huang et al., 2020). To date, the World Health Organization (WHO) has reported nearly 257 million COVID-19 cases and more than 5.17 million deaths worldwide (World Health Organization, 2021) (as of November 23, 2021).

The genome of the SARS-CoV-2 encodes multiple structural, as well as 16 non-structural proteins necessary for transcription and replication (Fehr and Perlman, 2015; Perlman and Netland, 2009), such as the membrane protein (M), spike protein (S), envelope protein (E), and nucleocapsid protein (N) (Fig. 1) (Kirtipal et al., 2020). Similar to other RNA viruses, the genome of SARS-CoV-2 is prone to random mutations that affect both structural and non-structural genes (Giovanetti et al., 2021; Aleem et al., 2021). As a result of this genetic diversity, SARS-CoV-2 variants of concern (VOC) have emerged around the world, posing a possible threat to public health. The genetic alterations change the viral phenotype and affect its transmissibility, virulence, and severity of clinical manifestation (World Health Organization, 2021; Aleem et al., 2021). Since the beginning of the pandemic, the WHO has named five variants as VOCs, namely the Alpha, Beta, Gamma, Delta, and Omicron variants, which have spread worldwide (World Health Organization, 2021). With the emergence of novel variants, the rapid evaluation of possible resistance to anti-viral therapies and vaccines against VOC is clearly insufficient. For example, the Beta and Gamma variants demonstrated decreased susceptibility in vitro to treatment with bamlanivimab and etesevimab, a combination of anti-SARS-CoV-2 monoclonal antibodies (mAb) (COVID-19 Treatment Guidelines Panel, 2021; Food and Drug Administration, 2021a). However, this combination shows no reduced susceptibility (<5-fold reduction) towards the Alpha, Delta, and Lambda variants. The clinical implication of these findings has yet to be established. Nevertheless, sotrovimab and a combination of casirivimab and imdevimab showed sufficient activity against all VOCs (COVID-19 Treatment Guidelines Panel, 2021; Food and Drug Administration, 2020, 2021b). The emergence of highly transmissible variants, combined with the easing of travel restrictions and low vaccination rates in some countries may lead to a further rise in reported cases, hospitalization rates, and deaths (World Health Organization, 2021).

Since the beginning of the pandemic, multiple antivirals, antibiotics, antimalarials, and immunomodulatory drugs were predicted to be effective against SARS-CoV-2 (Fig. 2). However, further studies reported limited or no clinical usefulness for most proposed drugs. However, identification of agents that are ineffective is of paramount importance, so that both proper and effective treatment is applied, and possible undesired side-effects of treatment are avoided. In the current review, we aim to provide an update on the advancements in clinical trials assessing the clinical efficacy of those treatment modalities that has been made since April 2020 and provide insight into future perspectives (Tables 1 and 2). The current recommendations for COVID-19 treatment are summarized in Table 3.

2. Vaccines

The introduction of COVID-19 vaccines in late 2020 has provided an opportunity to restrict the transmission of the SARS-CoV-2 virus and reduce the number of hospitalizations and deaths (Fig. 3). The US Food and Drugs Administration (FDA) has approved the Pfizer-BioNTech COVID-19 vaccine, Moderna COVID-19 Vaccine, and Janssen COVID-19 Vaccine for emergency use in the USA, while the European Medicines Agency (EMA) also authorized the vaccine developed by Astrazeneca. Furthermore, other vaccines are being used around the world and many more are still being developed. The efficacy and safety of the most frequently used vaccines are summarized in Table 4. According to the WHO, almost 7.7 billion doses of vaccines have been administered and approximately 53.2 % of the world’s population have received at least the first vaccine dose. However, most vaccines were distributed in a small number of highly developed countries, leaving most of the developing world susceptible to SARS-CoV-2 infection. Furthermore, the data evaluating the efficacy of vaccines against VOC is limited and inconsistent, yet full vaccination appears to protect against a severe course of illness and death from all occurring VOCs (World Health Organization, 2021; Fontanet et al., 2021; Lopez Bernal et al., 2021). Moreover, multiple studies have shown waning immunity acquired after vaccination, especially in immunocompromised patients, for example those undergoing hemodialysis or cytotoxic cancer drug treatment. This contributes to an increasing number of breakthrough infections (Shroff et al., 2021; Juno and Wheatley, 2021; Goldberg et al., 2021; Fowlkes et al., 2021; Davidovic et al., 2021; Campo et al., 2021). Currently, several countries have developed various strategies to tackle this problem, among which, additional doses of COVID-19 vaccines have shown to be safe and efficient in boosting immune response (Yue et al., 2021; Falsey et al., 2021; Dekervel et al., 2021; Choi et al., 2021; Barros-Martins et al., 2021). Nonetheless, the low vaccination rate, coupled with the risk of emergence of vaccine-resistant SARS-CoV-2 variants and waning immunity, emphasizes the burning need to develop novel drugs and therapeutic modalities for COVID-19 (Artese et al., 2020; Twomey et al., 2020; Drozdzal et al., 2020).

3. Recommended therapeutic agents/potential treatment

3.1. Monoclonal antibodies

Bamlanivimab (LY-CoV555) is a potent neutralizing IgG1 mAb against the SARS-CoV-2 spike protein. It is designed to block viral attachment and entry into human cells, thus neutralizing the virus and potentially preventing and treating COVID-19 (Anon, 2006; Jones et al., 2021).

Etesevimab (also known as JS016 or LY-CoV016) is a fully
humanized recombinant neutralizing mAb that specifically binds to the SARS-CoV-2 surface protein receptor-binding domain (RBD) with high affinity and can effectively block virus binding to the host angiotensin converting enzyme 2 (ACE-2) receptor on the cell surface (Anon, 2006).

In a phase 3 study, Dougan et al., randomized a 1:1 cohort of outpatients with mild to moderate COVID-19, who were at high risk of progressing to severe disease, have received a single intravenous infusion of mAbs. This therapy was administered to patients at doses of 2800 mg (bamlanivimab) and 2800 mg (etesevimab) or a placebo within 3 days following laboratory diagnosis of SARS-CoV-2 infection. The primary endpoint was the overall clinical status of the patients, defined as hospitalization for COVID-19 or all-cause death by day 29. A total of 1035 patients participated in the study, with a mean age (± SD) of 53.8 ± 16.8 years. By day 29, a total of 11 out of 518 patients (2.1 %) in the bamlanivimab-etesevimab group were hospitalized or died from COVID-19, compared with 36 of 517 patients (7.0 %) in the placebo group (absolute risk difference = -4.8 percentage points (95 % CI: -7.4 – -2.3); relative risk difference = 70 %; p < 0.001). There were no deaths in the bamlanivimab-etesevimab group, although there were 10 deaths in the placebo group, 9 of which were assessed by the investigators as related to COVID-19. At Day 7, there was a greater log reduction from baseline in viral load for patients who received bamlanivimab with etesevimab than for patients who received a placebo (p < 0.001). The authors of the study concluded that in non-hospitalized patients with mild to moderate COVID-19 disease, treatment with bamlanivimab and etesevimab compared to a placebo was associated with a statistically significant reduction in SARS-CoV-2 viral load (p = 0.002) (Anon, 2021).

**Sotrovimab** (Xevudy, GlaxoSmithKline and Vir Biotechnology, Inc.) is a recombinant engineered human IgG1 mAb that binds to a highly conserved epitope on the S protein RBD of SARS-CoV-2 with high affinity, but it does not compete with human ACE-2 receptor binding (Anon, 2021). The efficacy of sotrovimab was evaluated in an interim analysis of the ongoing COMET-ICE study. Patients were treated with a single 500 mg infusion of sotrovimab (N = 291) or a placebo (N = 292) over 1 h. The median age of the overall randomized population was 53 years (range: 18–96). The clinical progression of COVID-19 at Day 29 in recipients of sotrovimab was reduced by 85 % compared with the placebo group (p = 0.002) (Anon, 2021).

**Casirivimab** (IgG1-κ) and **imdevimab** (IgG1-λ) are recombinant human mAbs, which are unmodified in the Fc regions. The mAbs bind to non-overlapping epitopes of the spike protein RBD of SARS-CoV-2, and thereby block binding to the human ACE-2 receptor (Anon, 2020). An ongoing phase 1–3 trial in non-hospitalized COVID-19 patients investigated the effect of the mix of these antibodies (REGN–COV2) to reduce the risk of developing a refractory mutant virus. Patients were randomly assigned (1:1:1) to receive a placebo, 2.4 g of REGN–COV2, or 8.0 g of REGN–COV2 and were prospectively characterized at baseline for the
1358 patients, with nine out of ten studies found to be of high quality. We reviewed and performed a meta-analysis of observational studies evaluating the effect of tocilizumab in COVID-19 in which they allocated patients to two groups. The control group received the standard care, while the treatment group was comprised of patients who received tocilizumab in addition to standard care; the primary outcome was 28 to 30-day mortality. Secondary endpoints included progression to severe disease, defined as the need for mechanical ventilation, intensive care unit (ICU) admission, or complex disease. Out of 6493 patients, 3358 (52.2%) were allocated to tocilizumab. The results demonstrated that tocilizumab use was associated with decreased mortality (24.4% vs. 29.0%; odds ratio (OR) = 0.87 (95% CI: 0.74–1.01); p = 0.07). Tocilizumab did reduce the need for mechanical ventilation and was associated with an advantage in the composite secondary endpoint, but did not reduce the number of ICU admissions (Arthur et al., 2021).

However, the results of a phase 3 trial were contradictory. The NCT04320615 study described by Rosas et al., did not present a difference between tocilizumab and placebo groups [mortality at day 28 was 19.7% – the tocilizumab group and 19.4% – the placebo group (95% CI = -7.6–8.2; p = 0.941)] (Rosas et al., 2021). A Study authors suggests considering the use of tocilizumab in hospitalized COVID-19 patients with hypoxia and laboratory signs of significant inflammation.

3.2. Remdesivir

Remdesivir is an adenosine analogue that is metabolized to its active metabolite, remdesivir triphosphate. Remdesivir triphosphate is a structural analogue of adenosine triphosphate (ATP) and competes with the natural substrate for the incorporation by RNA polymerase into nascent viral RNA, which results in delayed chain termination during replication and consequently inhibition of viral replication (Singh et al., 2020).

One of the most recent and largest studies that describes the effectiveness of remdesivir in SARS-CoV-2 infection reports that despite its conditional recommendation, remdesivir may still be effective in achieving early clinical improvement. It reduces early-stage mortality and the need for high flow oxygen supplementation and invasive mechanical ventilation among hospitalized COVID-19 patients. Treatment with remdesivir was associated with an increase in clinical recovery rate by 21% [risk ratio (RR) = 1.21 (95% CI: 1.08–1.35)] on day 7 and 29% [RR = 1.29 (95% CI: 1.22–1.37)] on day 14. The likelihoods of requiring high-flow supplemental oxygen and invasive mechanical ventilation in the remdesivir group were lower than in the placebo group by 27% [RR = 0.73 (95% CI: 0.54 – 0.99)] and 47% [RR = 0.53 (95% CI: 0.39 – 0.72)], respectively. Remdesivir-treated patients showed a 39% [(RR = 0.61 (95% CI: 0.46 – 0.79)) reduction in the risk of mortality on day 14 compared to the control group; however, there was no significant difference on day 28 (Angamo et al., 2021). A Study authors suggests considering the use of remdesivir in patients with confirmed SARS-CoV-2 infection during the period of viral replication (i.e., not later than 5–7 days from the onset of the first symptoms of the disease) in patients with documented pneumonia and peripheral blood oxygen saturation (SpO2) ≤ 94% (when breathing atmospheric air).

3.3. Baricitinib

Baricitinib is a selective inhibitor of janus activated kinase 1 (JAK1) and janus activated kinase 2 (JAK2), the two of which mediate signaling for cytokines and growth factors involved in hematopoiesis, inflammation, and the immune response. It modulates intracellular signaling by partially inhibiting JAK1 and JAK2 enzymatic activity, thereby reducing phosphorylation and activation of STAT proteins. Baricitinib inhibits the induction of IL-6 in a dose dependent manner while also reducing the serum concentration of C-reactive protein (CRP) (Siebing et al., 2020).

In a multi-center study, the beneficial impact of baricitinib was tested in COVID-19 patients with moderate pneumonia (Cantini et al., 2020). At baseline, 113 patients were included in the baricitinib-arm, and 78 in the control-arm. The results indicate that the 2-week case fatality rate was significantly lower in the baricitinib-arm compared with controls [0% (0/113) vs. 6.4% (5/78) (p = 0.010; 95% CI: 0.0000 – 0.4569)]. ICU admission was necessary in 0.88% (1/113) patients in patients with documented pneumonia and peripheral blood oxygen saturation (SpO2) ≤ 94% (when breathing atmospheric air).

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Table 1

Summary of currently conducted studies on COVID-19 drugs according to: drugvirus.info (Andersen et al., 2020; Drugvirus.info, 2021), clinicaltrials.gov (US National Library of Medicine, 2020) (updated on – 27th of July 2021).

| Therapeutic agent | Number of phase III-IV clinical trials |
|-------------------|---------------------------------------|
| Amantadine        | 3                                     |
| ASA               | 10                                    |
| Azithromycin      | 41                                    |
| Bamlanivimab - etesevimab | 3                              |
| Baricitinib       | 13                                    |
| Camostat mesylate | 6                                     |
| Casirivimab - imdevimab | 3                              |
| Chloroquine       | 13                                    |
| Dexamethasone     | 29                                    |
| Favipiravir       | 21                                    |
| HCQ               | 117                                   |
| Imatinib          | 2                                     |
| IFN-β-1a          | 11                                    |
| Isotretinoin      | 3                                     |
| Ivermectin        | 37                                    |
| Lopinavir/ritonavir | 20                                |
| Mefloquine        | 2                                     |
| Nafamostat mesylate | 5                              |
| Nicoamide         | 4                                     |
| Nitazoxanide      | 18                                    |
| Osel tamivir      | 7                                     |
| Remdesivir        | 46                                    |
| Ribavirin         | 3                                     |
| Sofosbuvir        | 8                                     |
| Sotrovimab        | 2                                     |
| Tocilizumab       | 23                                    |
| Umifenovir        | 4                                     |

Legend: ASA – acetylsalicylic acid, aspirin; HCQ – hydroxychloroquine; IFN-interferon.
| Therapeutic agent | Clinical trial ID | Number of participants | status | Additional information |
|-------------------|-------------------|------------------------|--------|------------------------|
| Abidol            | NCT04255017       | 400                    | recruiting | compared to oseltamivir, lopinavir/ritonavir, standard of care |
| Adalimumab        | NCT04705844       | 1444                   | not yet recruiting | compared to placebo |
| Adalimumab        | ChiCTR2000030089  | 60                     | active, not recruiting | compared to standard treatment |
| Adamunab + Tozumab| NCT04952519       | 60                     | recruiting | compared to placebo |
| Amantadine        | NCT04894617       | 226                    | not yet recruiting | compared to placebo |
| Amantadine        | NCT04854795       | 200                    | recruiting | compared to placebo |
| Amiodarone        | NCT04351763       | 804                    | recruiting | compared to verapamil, standard of care |
| Anakinra          | NCT04608049       | 606                    | active | compared to placebo |
| Anakinra          | NCT04424056       | 216                    | not yet recruiting | combined with ruxolitinib; compared to tocilizumab, tocilizumab + ruxolitinib, standard of care |
| Anakinra          | NCT04362111       | 30                     | recruiting | compared to placebo |
| Anakinra          | NCT04443881       | 179                    | completed | compared to standard of care |
| Anakinra          | NCT04643678       | 80                     | recruiting | compared to standard of care |
| Anakinra          | NCT04341584       | 240                    | completed | – |
| Anakinra          | NCT04339712       | 20                     | completed | compared to tocilizumab |
| Anakinra          | NCT04324021       | 54                     | terminated | compared to emapalumab and standard treatment |
| Angiotensin 1–7   | NCT04345406       | 60                     | not yet recruiting | compared to standard of care |
| ACE-I             | NCT04353596       | 216                    | completed | stopping of ACEI/ARB treatment compared to further ACEI/ARB treatment |
| ACE-I & ARBs      | NCT04591210       | 1155                   | recruiting | compared to no treatment |
| ACE-I & ARBs      | NCT04493259       | 240                    | recruiting | compared to standard of care |
| ARBs              | NCT04394117       | 1500                   | recruiting | compared to placebo |
| Anti-SARS-CoV-2 equine hyperimmune serum | NCT04838821 | 156 | active | compared to placebo |
| Apremilast        | NCT04590586       | 516                    | active | compared to landelumab, zilucoplan, placebo |
| Arbidol           | NCT04260594       | 304                    | completed, has results | compared to standard of care |
| ASC09             | NCT04261270       | 60                     | recruiting | combined with oselamivir; compared to ritonavir + oselamivir, oselamivir |
| ASC09             | NCT04261270       | 60                     | recruiting | compared to ritonavir; combined with oselamivir |
| ASC09             | NCT04261907       | 160                    | not yet recruiting | compared to lopinavir/ritonavir; combined with ritonavir |
| ASA               | NCT04352606       | 128                    | recruiting | compared to daclatasvir, sofosbuvir + daclatasvir, placebo |
| Atazanavir        | NCT04468087       | 1005                   | recruiting | combined with azithromycin |
| Atovaquone        | NCT04339426       | 25                     | recruiting | combined with azithromycin |
| Avipitril         | NCT04311697       | 196                    | completed | compared to placebo |
| AZD7442           | NCT04723934       | 1700                   | recruiting | compared to placebo |
| Azithromycin      | NCT04359316       | 40                     | not yet recruiting | combined with HCQ |
| Azithromycin      | NCT04381962       | 298                    | completed | compared to standard of care |
| Azithromycin      | NCT04363060       | 104                    | not yet recruiting | combined with amoxicillin/clavulanate; compared to amoxicillin/clavulanate |
| Azithromycin      | NCT04341727       | 500                    | suspended | compared to chloroquine and hydroxychloroquine |
| Azithromycin      | NCT04324063       | 1500                   | recruiting | compared to chloroquine |
| Azithromycin      | NCT04339896       | 240                    | terminated | combined with hydroxychloroquine |
| Azithromycin      | NCT04336332       | 160                    | active, not recruiting | compared to hydroxychloroquine; combined with hydroxychloroquine |
| Azithromycin      | NCT04332107       | 2271                   | active, not recruiting | – |
| Azithromycin + Hydroxychloroquine | NCT04322123 | 630 | active, not recruiting | compared to HCQ |
| Azithromycin + Hydroxychloroquine | NCT04321278 | 440 | completed | compared to HCQ |
| Arzoxifer Bromide | NCT04381377       | 394                    | active | compared to placebo |
| Azudine           | NCT04668235       | 342                    | recruiting | compared to placebo |
| Azudine           | ChiCTR2000029853  | 20                     | recruiting | compared to standard treatment |
| Azudine           | ChiCTR2000030041  | 40                     | not yet recruiting | – |
| Azudine           | ChiCTR2000030424  | 30                     | not yet recruiting | – |
| Azudine           | ChiCTR2000030487  | 10                     | recruiting | – |
| Barclec-E         | NCT04363814       | 100                    | recruiting | compared to standard of care |
| Baloxavir marboxil| NCT0400029544     | 30                     | not yet recruiting | compared to favipavir and standard treatment |
| Baloxavir marboxil| NCT0400029545     | 30                     | not yet recruiting | compared to favipavir and lopinavir/ritonavir |
| Bamlanivimab      | NCT04656691       | 4000                   | completed | single group assignment |
| Bamlanivimab      | NCT04796402       | 576                    | recruiting | compared to standard of care |
| Bamlanivimab      | NCT04748588       | 648                    | recruiting | compared to standard of care |
| Bamlanivimab      | NCT04518410       | 2000                   | recruiting | compared to BRII-196/BRII-198, AZD7442, SGN001, Camostat, C135-LS + C144-LS, SAB-185, placebo, combined with remdesivir; combined to remdesivir + placebo |
| Baricitinib       | NCT04401579       | 1033                   | completed | – |
| Baricitinib       | NCT04640168       | 1010                   | active | combined with remdesivir; compared to dexamethasone and remdesivir |
| Baricitinib       | NCT04979071       | 382                    | recruiting | combined with remdesivir; compared to dexamethasone plus remdesivir |
| Baricitinib       | NCT04421027       | 1585                   | completed | compared to placebo |

(continued on next page)
### Table 2 (continued)

| Therapeutic agent | Clinical trial ID | Number of participants | status | Additional information |
|-------------------|-------------------|------------------------|--------|------------------------|
| Baricitinib       | NCT04358614       | 12                     | completed | crossover assignment |
| Baricitinib       | NCT04320277       | 60                     | not yet recruiting | – |
| Baricitinib       | NCT04340232       | 80                     | withdrawn | – |
| Baricitinib       | NCT04321993       | 1000                   | recruiting | compared to HCQ, lopinavir/ritonavir and sarilumab |
| BDB-0031          | NCT04495858       | 368                     | recruiting | compared to standard of care |
| BLD-2660          | NCT04334460       | 120                     | active, not recruiting | – |
| BNO 1030          | NCT04799796       | 133                     | completed | compared to standard of care |
| Brazilian Green Propolis Extract | NCT04480593 | 120                     | completed | compared to placebo |
| Bromocarbimid     | NCT04817332       | 400                     | completed | compared to placebo |
| Bromhexidine      | NCT04350262       | 90                     | recruiting | combined with HCQ, compared to HCQ |
| Bucillamine       | NCT04507434       | 1000                   | recruiting | compared to placebo |
| Budesonid         | NCT04361474       | 120                     | completed | compared to placebo |
| Budesonid         | NCT04355637       | 300                     | recruiting | compared to standard of care |
| C21               | NCT04880642       | 600                     | not yet recruiting | compared to placebo |
| Camostat Mesylate | NCT04680896       | 596                     | recruiting | compared to placebo |
| Camostat Mesylate | NCT04665749       | 155                     | completed | compared to placebo |
| Camostat Mesylate | NCT04321096       | 180                     | recruiting | – |
| Canakinumab       | NCT04362813       | 451                     | completed | compared to placebo |
| Canakinumab       | NCT04510493       | 116                     | recruiting | compared to placebo |
| Cannabidiol       | NCT04619718       | 100                     | active | compared to placebo |
| Cannabidiol       | NCT04615949       | 422                     | recruiting | compared to placebo |
| Carrimycin        | NCT04672564       | 300                     | recruiting | compared to placebo |
| CD24FC            | NCT04317404       | 243                     | completed | compared to placebo |
| CD24FC            | NCT04317404       | 239                     | completed | compared to placebo |
| Cefitoren pivoxil  | NCT04709172       | 30                     | recruiting | single group assignment |
| Cetirizine        | NCT04836806       | 160                     | recruiting | compared to placebo |
| Chloroquine       | ChiCTR2000029542  | 20                      | recruiting | compared to standard treatment |
| Chloroquine       | ChiCTR2000029609  | 200                     | not yet recruiting | compared to lopinavir/ritonavir |
| Chloroquine       | ChiCTR2000029741  | 112                     | recruiting | compared to lopinavir/ritonavir |
| Chloroquine       | ChiCTR2000029826  | 45                      | not yet recruiting | – |
| Chloroquine       | ChiCTR2000029837  | 120                     | not yet recruiting | – |
| Chloroquine       | ChiCTR2000029935  | 100                     | recruiting | – |
| Chloroquine       | ChiCTR2000029939  | 100                     | recruiting | compared to standard treatment |
| Chloroquine       | ChiCTR2000029975  | 10                      | not yet recruiting | – |
| Chloroquine       | ChiCTR2000029988  | 80                      | recruiting | compared to standard treatment |
| Chloroquine       | ChiCTR2000029992  | 100                     | not yet recruiting | compared to standard treatment; combined with HCQ |
| Chloroquine       | ChiCTR2000030031  | 120                     | suspended | – |
| Chloroquine       | ChiCTR2000030417  | 30                      | suspended | – |
| Chloroquine       | ChiCTR2000030718  | 80                      | recruiting | compared to standard treatment |
| Chloroquine       | NCT04333628       | 210                     | terminated | combined with hydroxychloroquine |
| Chloroquine       | NCT04331600       | 400                     | completed | – |
| Chloroquine       | NCT04328493       | 250                     | completed | compared to standard treatment |
| Chlorpromazine     | NCT04366739       | 40                      | not yet recruiting | compared to standard of care |
| Ciclesonide       | NCT04377711       | 400                     | completed | compared to placebo |
| Ciclesonide       | NCT04350386       | 141                     | completed | compared to standard treatment; combined with HCQ |
| CimiertA          | NCT04802382       | 252                     | recruiting | compared to placebo |
| Colchicine        | NCT04667780       | 102                     | completed | compared to standard of care |
| Colchicine        | NCT04350320       | 102                     | completed | compared to standard of care |
| Colchicine        | NCT04819849       | 250                     | recruiting | compared to standard of care |
| Colchicine        | NCT04726111       | 466                     | recruiting | combined with rosuvastatin; compared to standard of care |
| Colchicine        | NCT04328480       | 1279                    | completed | compared to standard of care |
| Colchicine        | NCT04492358       | 144                     | recruiting | combined with prednisone; compared to standard of care |
| Colchicine        | NCT04416334       | 954                     | recruiting | compared to standard of care |
| Colchicine        | NCT04328480       | 2500                    | completed | – |
| Colchicine        | NCT04322682       | 6000                    | completed | – |
| Colchicine        | NCT04322565       | 100                     | recruiting | – |
| Comega-3 Oil      | NCT04836052       | 372                     | recruiting | compared to standard of care |
| Convalescent Plasma Therapy | NCT04425915 | 400                     | completed | compared to standard of care |
| Convalescent Plasma Therapy | NCT04355767 | 511                     | completed | compared to placebo |
| Convalescent Plasma Therapy | NCT04547360 | 160                     | completed | compared to standard of care |
| Convalescent Plasma Therapy | NCT04589949 | 690                     | recruiting | compared to Fresh Frozen Plasma |
| Convalescent Plasma Therapy | NCT04535063 | 200                     | recruiting | single group assignment |
| Convalescent Plasma Therapy | NCT04316858 | 196                     | completed | compared to human immunoglobulin |
| Convalescent Plasma Therapy | NCT04361253 | 220                     | recruiting | compared to standard plasma |
| Convalescent Plasma Therapy | NCT04539275 | 702                     | active | compared to placebo |
| Convalescent Plasma Therapy | NCT04516811 | 600                     | recruiting | compared to standard of care |
| Convalescent Plasma Therapy | NCT04836260 | 100                     | recruiting | single group assignment |
| Convalescent Plasma Therapy | NCT04567173 | 136                     | recruiting | compared to standard of care |
| Convalescent Plasma Therapy | NCT04342899 | 1100                    | recruiting | compared to infusion placebo |
| Convalescent Plasma Therapy | NCT04747158 | 350                     | completed | single group assignment |

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| Therapeutic agent                          | Clinical trial ID     | Number of participants | status       | Additional information                                                                 |
|-------------------------------------------|-----------------------|------------------------|--------------|----------------------------------------------------------------------------------------|
| Convalescent Plasma Therapy               | NCT04385043           | 400                    | recruiting   | compared to standard of care                                                            |
| Convalescent Plasma Therapy               | NCT04388410           | 410                    | recruiting   | compared to placebo                                                                     |
| Convalescent Plasma Therapy               | NCT04873414           | 364                    | recruiting   | compared to standard of care                                                            |
| Convalescent Plasma Therapy               | NCT04342182           | 426                    | active       | compared to standard of care                                                            |
| Convalescent Plasma Therapy               | NCT04502472           | 200                    | recruiting   | single group assignment                                                                  |
| Convalescent Plasma Therapy               | NCT04374526           | 29                     | completed    | compared to standard of care                                                            |
| Convalescent Plasma Therapy               | NCT04380935           | 60                     | recruiting   | compared to standard of care                                                            |
| Convalescent Plasma Therapy               | NCT04384588           | 100                    | recruiting   | parallel assignment - cancer patients and non-cancer patients                            |
| Convalescent Plasma Therapy               | NCT04816942           | 102                    | completed    | single group assignment                                                                  |
| Convalescent Plasma Therapy               | NCT04332835           | 92                     | completed    | compared to standard of care                                                            |
| Convalescent Plasma Therapy               | NCT04376034           | 240                    | recruiting   | compared to standard of care                                                            |
| Cretan IAMA                               | NCT04705753           | 20                     | completed    | single group assignment                                                                  |
| CSA0001                                  | ChiCTR2000030939      | 10                     | recruiting   | placebo                                                                                |
| CT-950                                    | NCT04602000           | 1020                   | recruiting   | compared to standard of care                                                            |
| Cyclosporine                              | NCT04392531           | 120                    | recruiting   | compared to standard of care                                                            |
| Dalargin                                  | NCT04346693           | 320                    | completed    | compared to standard of care                                                            |
| Danoprevir/ Ritonavir                     | ChICTR2000030000      | 50                     | recruiting   | compared to IFN-α, peginterferon α-2a and standard treatment                             |
| Danoprevir/ Ritonavir                     | ChiCTR2000030259      | 60                     | recruiting   | compared to standard treatment                                                          |
| Danoprevir/ Ritonavir                     | ChiCTR2000030472      | 20                     | recruiting   | compared to standard treatment                                                          |
| Dapagliflozin                             | NCT04350593           | 1250                   | active       | placebo                                                                                |
| Dapson A                                  | NCT04935476           | 3000                   | not recruiting | placebo                                                                                 |
| Darunavir/Cobicistat                      | NCT04252274           | 30                     | recruiting   | compared to standard treatment                                                          |
| Darunavir/ Ritonavir                      | NCT04304053           | 3040                   | completed    | placebo                                                                                |
| DAS181                                    | NCT04324489           | 4                      | completed    | compared to standard treatment                                                          |
| Deferoxamine                              | NCT04333550           | 50                     | recruiting   | compared to standard treatment                                                          |
| Defibrotide                               | NCT04335201           | 50                     | recruiting   | –                                                                                       |
| Desferal                                  | NCT04389801           | 200                    | not yet recruiting | compared to placebo                                                                   |
| Dexamethasone                             | NCT04726908           | 198                    | recruiting   | high dose compared to low dose                                                           |
| Dexamethasone                             | NCT04663555           | 300                    | recruiting   | high dose compared to low dose                                                           |
| Dexamethasone                             | NCT04509973           | 1000                   | active       | high dose compared to low dose                                                           |
| Dexamethasone                             | NCT04509973           | 1000                   | active       | high dose compared to low dose                                                           |
| Dexamethasone                             | NCT04499313           | 60                     | recruiting   | compared to methylprednisolone                                                          |
| Dexamethasone                             | NCT04347980           | 122                    | recruiting   | combined with HCQ; compared to HCQ                                                       |
| Dexamethasone                             | NCT04834375           | 142                    | recruiting   | weight-based dexamethasone use compared to standard dexamethasone                        |
| Dexamethasone                             | NCT04765371           | 220                    | recruiting   | compared to prednisolone                                                                |
| Dexamethasone                             | NCT04780581           | 290                    | recruiting   | compared to methylprednisolone                                                          |
| Dexamethasone                             | NCT04327401           | 290                    | terminated   | –                                                                                       |
| Dihydropyrimidin/ Piperazine              | ChICTR2000030082      | 40                     | suspended    | compared to IFN-α + umifenovir; combined with antiviral treatment                         |
| Dipiridamole                               | NCT04410328           | 132                    | recruiting   | combined with ASA; compared to standard of care                                          |
| Dornase alfa                              | NCT04355364           | 100                    | recruiting   | compared to standard of care                                                            |
| Dornase alfa                              | NCT04402970           | 30                     | completed    | compared to standard of care                                                            |
| Doxycycline                               | NCT04715295           | 200                    | recruiting   | combined with rivaroxaban; combined to standard of care                                 |
| Doxycycline                               | NCT0485657            | 1100                   | recruiting   | monotherapy or combined with Zinc; compared to placebo                                   |
| Doxycycline                               | NCT04371952           | 330                    | not yet recruiting | compared to placebo                                                                       |
| Dutasteride                               | NCT04729491           | 138                    | completed    | combined with azithromycin + nitazoxanidine; compared to azithromycin + nitazoxanidine + placebo |
| DWU1248                                   | NCT04713176           | 1022                   | recruiting   | combined with remdesivir; compared to placebo                                           |
| Ebastine                                   | ChiCTR2000030535      | 100                    | recruiting   | combined with IFN-α and lopinavir                                                      |
| Emphalumab                                 | NCT04324021           | 54                     | terminated   | compared to dapagilofoxin + ambribentan, standard of care                                |
| Emtricitabine / Tenofovir                  | NCT04890263           | 2193                   | recruiting   | compared to anakinra and standard treatment                                             |
| Emtricitabine / Tenofovir                  | NCT04359095           | 1200                   | recruiting   | combined to baricitinib + dexamethasone, dexamethasone, standard of care                  |
| Emtricitabine / Tenofovir + Lopinavir/Ritonavir | NCT04200029468   | 120                    | not yet recruiting | –                                                                |
| Entinostat Iodide                          | NCT04682873           | 700                    | recruiting   | compared to placebo                                                                     |
| Enovipir                                  | NCT04828161           | 2100                   | recruiting   | compared to placebo                                                                     |
| Evolocumab                                | NCT04941105           | 60                     | recruiting   | compared to placebo                                                                     |
| Famositidine                              | NCT04370262           | 233                    | completed    | compared to placebo                                                                     |
| Favipiravir                                | NCT04529499           | 780                     | active       | compared to placebo                                                                     |
| Favipiravir                                | NCT04542694           | 200                    | completed    | compared to standard of care                                                            |
| Favipiravir                                | NCT04359615           | 40                     | not yet recruiting | combined with HCQ; compared to HCQ                                                      |
| Favipiravir                                | NCT04558463           | 100                    | recruiting   | combined to oseltamivir                                                                  |
| Favipiravir                                | NCT04501783           | 168                    | active       | compared to standard of care                                                            |
| Favipiravir                                | NCT04608895           | 826                    | recruiting   | compared to placebo                                                                     |
| Favipiravir                                | NCT04818220           | 500                     | active       | compared to standard of care                                                            |
| Favipiravir                                | NCT04694612           | 676                    | recruiting   | combined to remdesivir, placebo                                                         |

(continued on next page)
| Therapeutic agent | Clinical trial ID | Number of participants | status | Additional information |
|------------------|------------------|------------------------|--------|------------------------|
| Favipiravir      | NCT04425460      | 256                    | not yet recruiting | compared to placebo |
| Favipiravir      | NCT04411433      | 1008                   | active            | monotherapy or combined with HCQ or azithromycin; compared to HCQ, HCQ + azithromycin |
| Favipiravir      | NCT04605999      | 150                    | recruiting        | compared to standard of care |
| Favipiravir      | NCT04432428      | 330                    | active            | compared to standard of care |
| Favipiravir      | NCT04645408      | 576                    | recruiting        | compared to placebo |
| Favipiravir      | NCT04351295      | 90                     | recruiting        | compared to placebo |
| Favipiravir      | NCT04402203      | 50                     | recruiting        | compared to standard of care |
| Favipiravir      | NCT04373733      | 502                    | active            | compared to standard of care |
| Favipiravir      | NCT04319900      | 150                    | recruiting        | monotherapy or combined with favipiravir; compared to placebo |
| Favipiravir      | ChiCTR2000029544 | 30                     | not yet recruiting | compared to baloxavir marboxil and standard treatment |
| Favipiravir      | ChiCTR2000029548 | 30                     | not yet recruiting | compared to baloxavir marboxil and lopinavir/ritonavir |
| Favipiravir      | ChiCTR2000029600 | 90                     | recruiting        | compared to placebo |
| Favipiravir      | ChiCTR2000029986 | 60                     | recruiting        | compared to tocilizumab; combined with tocilizumab |
| Favipiravir      | ChiCTR2000030113 | 20                     | recruiting        | compared to placebo |
| Favipiravir      | ChiCTR2000030254 | 240                    | completed         | compared to umifenovir |
| Favipiravir      | ChiCTR2000029548 | 30                     | not yet recruiting | compared to baloxavir marboxil and lopinavir/ritonavir; combined with IFN-α |
| Favipiravir      | ChiCTR2000029544 | 30                     | recruiting        | combined with chloroquine |
| Favipiravir      | JPRN [RCT041190120 | 86                  | completed         | - |
| Fenofibrate      | NCT04273763      | 60                     | active, not recruiting | combined with bromhexine, IFN α-2b and umifenovir |
| Fenofibrate      | NCT04310228      | 150                    | recruiting        | compared to standard of care |
| Fenofibrate      | NCT04336904      | 100                    | active, not recruiting | - |
| Fingolimod       | NCT04280588      | 30                     | withdrawn         | compared to standard treatment |
| Fluvoxamine      | NCT04324663      | 152                    | completed, has results | - |
| Fluvoxamine      | NCT04727424      | 3645                   | recruiting        | compared to doxazosin, ivermectin, peginterferon λ-1a, peginterferon β-1A, placebo |
| Fluvoxamine      | NCT04668959      | 1100                   | active            | combined with placebo |
| Fluvoxamine      | NCT04629703      | 308                    | recruiting        | combined with placebo |
| Fluvoxamine      | NCT04750278      | 403                    | recruiting        | combined with placebo |
| Fluvoxamine      | NCT04588792      | 640                    | active            | combined with placebo |
| Fluvoxamine      | NCT04349199      | 540                    | completed         | combined with standard of care |
| Fluvoxamine      | NCT04420247      | 142                    | completed         | combined with placebo |
| Fluvoxamine      | NCT04354428      | 300                    | active            | monotherapy or combined with azithromycin; compared to placebo |
| HCO              | NCT04351724      | 500                    | recruiting        | compared to placebo |
| HCO              | NCT04353336      | 194                    | completed         | compared to standard of care |
| HCO              | NCT04652648      | 54                     | completed         | compared to placebo |
| HCO              | NCT04322123      | 630                    | completed         | monotherapy or combined with azithromycin; compared to placebo |
| HCO              | NCT04788355      | 176                    | completed         | monotherapy or combined with apixaban; compared to apixaban or placebo |
| HCO              | 2020 – 000890-25 (EU-CTR) | 25                | ongoing           | - |
| HCO              | ChiCTR2000029559 | 300                    | recruiting        | - |
| HCO              | ChiCTR2000029740 | 78                     | recruiting        | compared to standard treatment |
| HCO (Tang et al., 2020) | 2020 – 000890-25 (EU-CTR) | 25                | ongoing           | - |

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| Therapeutic agent                  | Clinical trial ID | Number of participants | status                                                                 | Additional information                                                                 |
|-----------------------------------|-------------------|------------------------|----------------------------------------------------------------------|------------------------------------------------------------------------------------------|
| **Hydroxychloroquine (HCQ)**      |                   |                        |                                                                      |                                                                                           |
| HCQ                               | NCT043343512      | 600                    | recruiting                                                          | compared with azithromycin, HCQ and standard treatment; combined with azithromycin        |
| HCQ                               | NCT04334382      | 1550                   | recruiting                                                          | combined with azithromycin                                                               |
| HCQ                               | NCT04329832      | 300                    | active, not recruiting                                               | combined with azithromycin                                                               |
| HCQ                               | NCT04329572      | 400                    | suspended                                                            | combined with azithromycin                                                               |
| HCQ                               | NCT04328272      | 75                     | not yet recruiting                                                   | combined with azithromycin                                                               |
| HCQ                               | NCT04323631      | 1116                   | withdrawn                                                            | compared to standard treatment                                                           |
| HCQ                               | NCT04321993      | 1000                   | recruiting                                                          | compared to baricitinib, lopinavir/ritonavir and sarilumab                               |
| HCQ                               | NCT04342169      | 400                    | recruiting                                                          | –                                                                                         |
| HCQ                               | NCT04341727      | 500                    | suspended                                                            | compared to azithromycin and chloroquine                                                |
| HCQ                               | NCT04341493      | 86                     | terminated                                                           | compared to nitazoxanide                                                                  |
| HCQ                               | NCT04334967      | 1250                   | suspended                                                            | compared to standard treatment                                                           |
| HCQ                               | NCT043433654     | 210                    | terminated                                                           | compared to standard treatment                                                           |
| HCQ (Self et al., 2020)           | NCT04332991      | 510                    | completed, has results                                               | –                                                                                         |
| HCQ                               | NCT04321616      | 700                    | recruiting                                                          | compared to remdesivir and standard treatment                                            |
| HCQ + IFN β-1b + Lopinavir/Ritonavir | IRTC20100228  | 30                     | completed                                                            | –                                                                                         |
| HCQ + IFN β-1b + Lopinavir/Ritonavir | 003449027       | 30                     | completed, has results (Effat et al., 2021)                         | doi: 10.1128/AAC.01061–20                                                                |
| HCQ + Lopinavir/Ritonavir         | JPRNJRCT201190227| 50                     | completed                                                            | –                                                                                         |
| HCQ + Lopinavir/Ritonavir + Sofosbuvir/Ledipivir | IRTC20100228 | 50                     | completed                                                            | –                                                                                         |
| HCQ + Camostat Mesylate           | NCT04338906      | 334                    | withdrawn                                                            | –                                                                                         |
| Hyperimmune Anti SARS-CoV-2 serum | NCT04913779      | 200                    | recruiting                                                          | compared to placebo                                                                     |
| Busprofen                         | NCT04334629      | 230                    | recruiting                                                          | compared to standard of care                                                             |
| ifenprodil (NP-120)               | NCT04382924      | 168                    | completed                                                            | –                                                                                         |
| IFN α                             | ChiCTR2000029496 | 90                     | recruiting                                                          | compared to lopinavir/ritonavir; combined with lopinavir/ritonavir                        |
| IFN α                             | ChiCTR2000029600 | 90                     | recruiting                                                          | compared to lopinavir/ritonavir and favipiravir                                         |
| IFN α                             | ChiCTR2000029638 | 100                    | recruiting                                                          | compared to rSIFN-co                                                                     |
| IFN α                             | NCT04291729      | 11                     | completed                                                            | –                                                                                         |
| IFN α-1b                          | ChiCTR2000029989 | 300                    | not yet recruiting                                                   | –                                                                                         |
| IFN α-1b                          | NCT04293887      | 328                    | not yet recruiting                                                   | compared to standard treatment                                                          |
| IFN α-1b + Lopinavir/Ritonavir    | ChiCTR2000029387 | 108                    | recruiting                                                          | –                                                                                         |
| IFN α-2b                          | NCT04273763      | 60                     | active, not recruiting                                               | combined with bromohexine, favipiravir and umifenovir                                     |
| IFN α-2b + Lopinavir/Ritonavir    | ChiCTR2000030166 | 20                     | not yet recruiting                                                   | –                                                                                         |
| IFN β-1a                          | NCT04492475      | 969                    | completed                                                            | combined with remdesivir; compared to placebo                                            |
| IFN β-1a                          | NCT04350671      | 40                     | recruiting                                                          | combined with lopinavir/ritonavir + HCQ, compared with lopinavir/ritonavir and peginterferon α-2a |
| IFN β-1a                          | 2020–001023-14 (EU-CTR) | 400               | completed, has results (Monk et al., 2021)                         | –                                                                                         |
| IFN β-1a                          | NCT04343768      | 60                     | completed                                                            | compared to HCQ + lopinavir / ritonavir and IFN β-1b; combined with HCQ + lopinavir / ritonavir |
| IFN β-1b                          | NCT04343768      | 60                     | completed                                                            | combined with HCQ + lopinavir / ritonavir and IFN β-1a; combined with HCQ + lopinavir / ritonavir |
| IFN β-1b + Ribavirin               | NCT04276688      | 70                     | completed                                                            | combined with lopinavir/ritonavir                                                        |
| IFN α and Lopinavir/Ritonavir     | NCT04251871      | 150                    | recruiting                                                          | –                                                                                         |
| IFN α and Lopinavir/Ritonavir     | NCT04275388      | 348                    | not yet recruiting                                                   | –                                                                                         |
| IFN-1                             | NCT04333420      | 130                    | recruiting                                                          | compared to standard treatment                                                          |
| Imatinib                          | NCT04394416      | 204                    | recruiting                                                          | compared to placebo                                                                     |
| Imatinib                          | NCT04422678      | 30                     | not yet recruiting                                                   | compared to standard of care                                                             |
| Imatinib                          | NCT04422678      | 30                     | not yet recruiting                                                   | compared to standard of care                                                             |
| IMU-838                           | NCT04397271      | 223                    | completed                                                            | compared to placebo                                                                     |
| INB03                             | NCT04370236      | 366                    | recruiting                                                          | combined with remdesivir and standard of care; compared to abatacept, ceniciviroc, standard of care |
| Influniximab                      | NCT04593940      | 2160                   | recruiting                                                          | compared to placebo                                                                     |
| INM005                            | NCT04494984      | 242                    | completed                                                            | compared to placebo                                                                     |
| Interleukin-2                     | ChiCTR2000030167 | 80                     | not yet recruiting                                                   | compared to standard treatment                                                          |
| Ivasuxaconazole                   | NCT04707703      | 162                    | recruiting                                                          | combined to placebo                                                                     |
| Isotretinoin                      | NCT04361422      | 300                    | not yet recruiting                                                   | combined to standard of care                                                            |
| Isotretinoin                      | NCT04353180      | 10,000                 | not yet recruiting                                                   | combined to standard of care                                                            |
| Ivermectin                        | NCT04528381      | 400                    | recruiting                                                          | combined with doxycycline; combined to standard of care                                   |
| Ivermectin                        | NCT04920942      | 500                    | recruiting                                                          | combined to standard of care                                                            |
| Ivermectin                        | NCT04646109      | 66                     | completed                                                            | combined to standard of care                                                            |
| Ivermectin                        | NCT04729140      | 150                    | recruiting                                                          | combined with doxycycline; combined to placebo                                          |
| Ivermectin                        | NCT04681053      | 80                     | recruiting                                                          | combined to standard of care                                                            |
| Ivermectin                        | NCT04793410      | 50                     | completed                                                            | combined to standard of care                                                            |
| Ivermectin                        | NCT04937569      | 1644                   | not yet recruiting                                                   | compared to standard of care                                                            |
| Ivermectin                        | NCT04885530      | 15,000                 | recruiting                                                          | compared to fluvoxamine, fluticasone, placebo                                           |

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### Table 2 (continued)

| Therapeutic agent | Clinical trial ID | Number of participants | status | Additional information |
|-------------------|-------------------|------------------------|--------|------------------------|
| Ivermectin        | NCT04716569       | 150                    | recruiting | compared to standard of care |
| Ivermectin        | NCT04915362       | 117                    | recruiting | compared to standard of care |
| Lenalidomide      | NCT04343092       | 50                     | completed, has results | combined with HCQ; compared to placebo |
| IVIG              | NCT04546581       | 593                    | active     | combined with remdesivir; compared to placebo + remdesivir |
| IVIG              | NCT04842435       | 376                    | recruiting | compared to placebo |
| IVIG              | NCT04891172       | 310                    | recruiting | compared to standard of care |
| Lenlizumab        | NCT0401689        | 306                    | not recruiting | compared to placebo |
| Levamisole        | NCT04331470       | 70                     | active, not recruiting | – |
| Levlimab          | NCT04397562       | 206                    | completed  | compared to placebo |
| Lianhuaxingwen    | NCT04433013       | 300                    | not recruiting | compared to placebo |
| Lidocaine         | NCT04609865       | 100                    | recruiting | compared to placebo |
| Lilly Bamlanivimab| NCT04790786       | 5000                   | recruiting | compared to regeneron casirivimab + imdevimab, Lilly Bamlanivimab + esevimab, sotrovimab |
| Lipid Emulsion Infusion | NCT04957940 | 90 | recruiting | compared to placebo |
| Liposomal Lactotransferrin | NCT04475120 | 92 | completed | compared to standard of care |
| Lopinavir / Ritonavir | NCT04738045    | 90                     | recruiting | combined with remdesivir; compared to remdesivir |
| Lopinavir / Ritonavir | NCT04466241   | 294                     | recruiting | monotherapy or combined with telmisartan, atorvastatin |
| Lopinavir / Ritonavir | NCT04403100  | 1968                   | recruiting | monotherapy or combined with HCQ; compared to HCQ, placebo |
| Lopinavir / Ritonavir | NCT04381936  | 45,000                 | recruiting | – |
| Lopinavir/Ritonavir | NCT04433013       | 328                    | recruiting | compared to standard treatment |
| Lopinavir/Ritonavir | NCT04738045       | 30                     | not recruiting | compared to baloxavir marboxil and favipiravir |
| Lopinavir/Ritonavir | NCT04466241       | 480                    | recruiting | combined with IFN-α and umifenovir |
| Lopinavir/Ritonavir | NCT04403100       | 90                     | recruiting | compared to favipiravir; combined with IFN-α |
| Lopinavir/Ritonavir | NCT04361643       | 120                    | not yet recruiting | compared to placebo |
| Lopinavir / Ritonavir | NCT04738045     | 480                     | recruiting | compared to standard of care |
| Liposomal Lactotransferrin | NCT04475120 | 92 | completed | compared to standard of care |
| Lopinavir / Ritonavir | NCT04250029600 | 200                    | not yet recruiting | compared to chloroquine |
| Lopinavir/Ritonavir | NCT04361643       | 200                    | completed, has results | compared to standard treatment |
| Lopinavir/Ritonavir | NCT04252885       | 80                     | recruiting | – |
| Lopinavir/Ritonavir | NCT04250029600 | 328                    | recruiting | compared to standard treatment and umifenovir |
| Lopinavir/Ritonavir | NCT04250029600 | 328                    | recruiting | compared to standard treatment and umifenovir |
| Lopinavir/Ritonavir | NCT04250029600 | 328                    | recruiting | compared to standard treatment and umifenovir |
| Lopinavir/Ritonavir | NCT04250029600 | 328                    | recruiting | compared to standard treatment and umifenovir |
| Losartan          | NCT04606563       | 1372                   | recruiting | compared to standard of care |

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| Therapeutic agent | Clinical trial ID         | Number of participants | status                  | Additional information                                           |
|-------------------|---------------------------|------------------------|-------------------------|-----------------------------------------------------------------|
| Losartan          | NCT04328012               | 100                    | recruiting              | compared to placebo                                             |
| Losartan (Geriak et al., 2021) | NCT04340557 | 200                    | completed, has results  | –                                                              |
| Losmapimod        | NCT04511189               | 410                    | active                  | compared to placebo                                             |
| LY3128542         | NCT04342987               | 200                    | terminated              | –                                                              |
| LY3819253         | NCT04501978               | 10,000                 | recruiting              | compared to remdesivir, VIR-7831, BRII-196/BRII-198, AZD7442, MP0420, placebo |
| LY3819253         | NCT04427501               | 577                    | recruiting              | monotherapy or combined with LY3832479; compared to placebo     |
| MAD0004308        | NCT04952085               | 800                    | recruiting              | compared to placebo                                             |
| Mavrilimumab      | NCT04447469               | 588                    | recruiting              | compared to placebo                                             |
| Mefloquine        | NCT04347031               | 320                    | completed, has results  | –                                                              |
| Meplaxamub        | NCT04275245               | 28                     | completed              | compared to placebo                                             |
| Mesenchymal Stem Cells | NCT04366063 | 60                     | recruiting              | combined with standard of care                                  |
| Mesenchymal Stromal Cells | NCT04371939 | 223                    | active                  | placebo                                                         |
| Metenkefalin      | NCT04342897               | 200                    | terminated              | –                                                              |
| Metformin         | NCT04510194               | 1160                   | recruiting              | compared and combined with ivermectin, fluvoxamine, placebo     |
| Methylprednisolone| NCT04673162               | 260                    | not yet recruiting      | compared to standard of care                                    |
| Methylprednisolone| NCT04438980               | 72                     | completed              | compared to placebo                                             |
| Methylprednisolone| NCT04636671               | 680                    | recruiting              | compared to dexamethasone                                       |
| Methylprednisolone| NCT04244591               | 80                     | completed              | compared to standard of care                                    |
| Methylprednisolone| NCT04263402               | 100                    | recruiting              | compared to standard treatment                                  |
| Methylprednisolone| NCT04451228               | 48                     | comparable to standard | treatment                                                      |
| Methylprednisolone| NCT04244591               | 80                     | completed              | compared to standard treatment                                  |
| Methylprednisolone| NCT04273421               | 400                    | completed              | compared to standard treatment                                  |
| Methylprednisolone| NCT04323529               | 104                    | completed, has results  | compared to standard treatment                                  |
| Molixan           | NCT0478672                | 330                    | recruiting              | compared to placebo                                             |
| Molnupiravir       | NCT04575584               | 300                    | active                  | compared to placebo                                             |
| Molnupiravir       | NCT04575597               | 1850                   | recruiting              | compared to placebo                                             |
| Montelukast       | NCT04389411               | 600                    | not yet recruiting      | compared to placebo                                             |
| MultiStem         | NCT04367077               | 400                    | recruiting              | compared to placebo                                             |
| NA-831            | NCT04452565               | 525                    | recruiting              | monotherapy or combined with atazanavir or dexamethasone        |
| N-acetylcysteine  | NCT04792021               | 60                     | recruiting              | compared to standard of care                                    |
| Nafamostat Mesilate| NCT04390594              | 186                    | recruiting              | compared to standard of care                                    |
| Nafamostat Mesilate| NCT04483960              | 2400                   | recruiting              | compared to standard of care                                    |
| Nafamostat Mesilate| NCT04352400              | 256                    | recruiting              | compared to placebo                                             |
| Nafamostat Mesilate| NCT04473053              | 60                     | recruiting              | compared to TD139, standard of care                              |
| Nangibotide       | NCT04429334               | 730                    | recruiting              | compared to placebo                                             |
| Naproxen          | NCT04325653               | 584                    | terminated              | compared to standard treatment                                  |
| Neurokinin-1 Receptor | NCT04468646         | 100                    | recruiting              | compared to placebo                                             |
| Niagen            | NCT04809974               | 100                    | recruiting              | compared to placebo                                             |
| Niclosamide       | NCT04558021               | 200                    | recruiting              | compared to placebo                                             |
| Niclosamide       | NCT04603924               | 436                    | recruiting              | compared to placebo                                             |
| Nintedanib        | NCT04541060               | 250                    | recruiting              | compared to placebo                                             |
| Nintedanib        | NCT04619060               | 120                    | recruiting              | compared to placebo                                             |
| Nitazoxanide      | NCT04462313               | 102                    | completed              | compared to placebo                                             |
| Nitazoxanide      | NCT04423861               | 380                    | not yet recruiting      | compared to placebo                                             |
| Nitazoxanide      | NCT04392427               | 100                    | not yet recruiting      | combined with ribavirin and ivermectin; compared to standard of | care                                             |
| Nitazoxanide      | NCT04382846               | 160                    | recruiting              | compared to standard of care                                    |
| Nitazoxanide      | NCT04523090               | 440                    | recruiting              | compared to placebo                                             |
| Nitazoxanide      | NCT04463264               | 135                    | recruiting              | compared to placebo                                             |
| Nitazoxanide      | NCT04920838               | 600                    | recruiting              | combined with ciclesonide; compared to paracetamol, telmisartan  |
| Nitazoxanide      | NCT04341493               | 86                     | terminated              | compared to hydroxychloroquine                                  |
| Nivolumab         | NCT04334344               | 92                     | not yet recruiting      | compared to standard treatment                                  |
| Novaferon         | NCT04669015               | 914                    | recruiting              | compared to placebo                                             |
| Octagam           | NCT04400058               | 208                    | recruiting              | compared to placebo                                             |
| Octagam           | NCT04411667               | 34                     | completed              | compared to standard of care                                    |
| Omega 3           | NCT04553705               | 200                    | recruiting              | combined with sativa oil, Indian Costus, quinine pills, anise | seed capsules                                  |
| Opaganib          | NCT04467840               | 475                    | completed              | compared to placebo                                             |
| Oseltamivir       | NCT04255017               | 400                    | recruiting              | compared to lopinavir/ritonavir and umifenovir                  |
| Oseltamivir       | NCT04261270               | 60                     | recruiting              | compared to ASC09 and ritonavir                                |
| Oseltamivir       | NCT04303299               | 80                     | recruiting              | compared to favipiravir, lopinavir/ritonavir and standard | treatment; combined with chloroquine, darunavir, | ritonavir and lopinavir/ritonavir          |
| Ozone therapy     | NCT04359030               | 50                     | not yet recruiting      | compared to standard of care                                    |
| Ozone therapy     | NCT04370223               | 208                    | not yet recruiting      | compared to standard of care                                    |
| P2E1              | NCT04410510               | 100                    | recruiting              | compared to placebo                                             |
| Pacritinib        | NCT04404361               | 200                    | active                  | compared to placebo                                             |

(continued on next page)
| Therapeutic agent                      | Clinical trial ID | Number of participants | Status                        | Additional information                                                                 |
|---------------------------------------|-------------------|------------------------|-------------------------------|----------------------------------------------------------------------------------------|
| Palmitolethanolamide                  | NCT04568876       | 40                     | recruiting                    | compared to standard of care                                                             |
| PD-1 monoclonal antibody              | ChiCTR2000030028  | 40                     | not yet recruiting            | compared to standard treatment                                                            |
| PD-1 monoclonal antibody              | NCT04268537       | 120                    | not yet recruiting            | compared to standard treatment and thymosin                                             |
| Peginterferon Lambda-1a               | NCT04311999       | 120                    | completed, has results        | doi: 10.1038/s41467–021-22177–1                                                         |
| Peginterferon α-2a                    | NCT04291729       | 11                     | completed                     | compared to darunavir/ritonavir, IFN α and lopinavir/ritonavir                           |
| Piclidenoson                           | NCT04333472       | 40                     | recruiting                    | compared to standard treatment                                                            |
| Pioglitazone                          | NCT04535700       | 76                     | recruiting                    | compared to standard of care in DM2 patients                                             |
| Pirfenidone                           | NCT04282902       | 294                    | recruiting                    | compared to standard of care                                                             |
| Piritrexin                            | NCT04784559       | 609                    | recruiting                    | combined with dexamethasone; compared to remdesivin + dexamethasone                       |
| Polyinosinic polycytidylic acid       | ChiCTR2000029776  | 40                     | recruiting                    | compared to standard treatment                                                            |
| Propolis extract                      | NCT04800224       | 200                    | recruiting                    | compared to placebo                                                                      |
| Proxalumine                           | NCT04869228       | 724                    | not yet recruiting            | compared to placebo                                                                      |
| Proxalumine                           | NCT04853134       | 200                    | active                        | compared to standard of care                                                             |
| Proxalumine                           | NCT04728802       | 645                    | completed                     | compared to placebo                                                                      |
| Proxalumine                           | NCT04870606       | 668                    | recruiting                    | compared to placebo                                                                      |
| PUL-042                               | NCT04312997       | 100                    | completed                     | –                                                                                        |
| PVP-I                                 | NCT04872686       | 798                    | recruiting                    | compared to placebo                                                                      |
| Pyridostigmine Bromide                | NCT04343963       | 436                    | recruiting                    | compared to placebo                                                                      |
| Pyronaridine-arnesunate               | NCT04701606       | 402                    | recruiting                    | compared to placebo                                                                      |
| Quercetin                             | NCT04468139       | 60                     | recruiting                    | combined with Zinc, Vitamin C, bromelain; single group assessment                        |
| Quercetin phytosome                    | NCT04578158       | 152                    | completed                     | compared to standard of care                                                             |
| Radiation Therapy                     | NCT04433949       | 52                     | recruiting                    | compared to standard of care                                                             |
| Ramdicivir                            | NCT04693026       | 150                    | recruiting                    | combined with baricitinib; compared to remdesivin + tocilizumab                          |
| Ravulizumab                           | NCT04390464       | 1167                   | recruiting                    | compared to baricitinib, standard of care                                               |
| Ravulizumab                           | NCT04369469       | 270                    | active                        | compared to standard of care                                                             |
| REGN10983 + REGN10987                 | NCT04425629       | 6420                   | recruiting                    | compared to placebo                                                                      |
| REGN10983 + REGN10987                 | NCT04452318       | 3750                   | active                        | compared to placebo                                                                      |
| Remdesivir                            | NCT04843761       | 640                    | recruiting                    | compared to aviptatidil, steroids, placebo                                              |
| Remdesivir                            | NCT04853901       | 77                     | completed                     | compared to standard of care                                                             |
| Remdesivir                            | NCT04647669       | 100                    | not yet recruiting            | compared to acalabrutinib, IFN β-1a, standard of care                                   |
| Remdesivir                            | NCT04779047       | 150                    | recruiting                    | compared to HCQ, tocilizumab, lopinavir / ritonavir, ivermectin                         |
| Remdesivir                            | NCT04745351       | 1116                   | recruiting                    | compared to standard of care                                                             |
| Remdesivir                            | NCT04610541       | 2000                   | active                        | single group assignment                                                                 |
| Remdesivir                            | NCT04431453       | 52                     | recruiting                    | single group assignment                                                                 |
| Remdesivir                            | NCT04579064       | 400                    | active                        | compared to standard of care                                                             |
| Remdesivir                            | NCT04345419       | 200                    | completed                     | compared to standard of care                                                             |
| Remdesivir                            | NCT04315948       | 2416                   | active                        | compared to standard of care                                                             |
| Remdesivir                            | NCT04252644       | 308                    | suspended                     | –                                                                                        |
| Remdesivir                            | NCT04257656       | 453                    | terminated                   | –                                                                                        |
| Remdesivir                            | NCT04280705       | 394                    | completed, has results        | –                                                                                        |
| Remdesivir (Beigel et al., 2020)      | NCT04292730;      | 600                    | completed, has results        | compared to standard treatment                                                           |
| Remdesivir (Spinler et al., 2020)    | 2020 – 000842-32  | 2416                   | active                        | compared to standard of care                                                             |
| Remdesivir                            | 2020 – 000936-23  | 3000                   | ongoing                       | compared to IFN β-1a and lopinavir/ritonavine                                           |
| Remdesivir                            | EU-CTR             |                        |                               | compared to IFN β-1a and lopinavir/ritonavine                                           |
| Remdesivir                            | NCT04252644       | 308                    | suspended                     | –                                                                                        |
| Remdesivir                            | NCT04257656       | 453                    | terminated                   | –                                                                                        |
| Remdesivir                            | NCT04280705       | 394                    | completed, has results        | –                                                                                        |
| Remdesivir                            | 2020 – 000841-15  | 600                    | completed, has results        | compared to standard treatment                                                           |
| Remdesivir                            | EU-CTR             | 2416                   | active                        | compared to standard of care                                                             |
| Remdesivir                            | NCT04315948       | 3100                   | active, not recruiting        | compared to hydroxychloroquine, IFN β-1a and lopinavir/ritonavir                       |
| Remdesivir                            | NCT04321616       | 700                    | recruiting                    | compared to hydroxychloroquine and standard treatment combined with dexamethasone; compared to remdesivin + dexamethasone, dexamethasone |
| Remdesivir + Baricitinib              | NCT04832880       | 4000                   | not yet recruiting            | compared to standard treatment                                                           |
| Remdesivir + Tocilizumab              | NCT04678739       | 205                    | completed                     | compared to standard of care                                                             |
| Reparixin                             | NCT04879055       | 312                    | recruiting                    | compared to placebo                                                                      |
| Reparixin                             | NCT04879055       | 312                    | recruiting                    | compared to placebo                                                                      |
| RESP301                               | NCT04460183       | 300                    | recruiting                    | compared to standard of care                                                             |
| tHACE2 APN01                          | NCT04353136       | 200                    | completed                     | compared to standard of care                                                             |
| hG-CSF (Cheng et al., 2021)           | ChCTR20000030007  | 200                    | completed, has results        | combined with IFN α-2a and umifenovir                                                   |
| Ribavirin                             | ChCTR2000029638   | 100                    | recruiting                    | compared to placebo                                                                      |
| Ritonavir                             | ChCTR2000030113   | 200                    | recruiting                    | compared to favipavir                                                                      |
| RO7496998                             | NCT04889040       | 1386                   | recruiting                    | compared to placebo                                                                      |
| RP4-104                               | NCT04380519       | 372                    | completed                     | compared to placebo                                                                      |
| rIFN-co                               | ChCTR2000029638   | 100                    | recruiting                    | compared to IFN α                                                                        |
| Ruconest                              | NCT04705831       | 40                     | recruiting                    | compared to placebo                                                                      |

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Table 2 (continued)

| Therapeutic agent | Clinical trial ID | Number of participants | status | Additional information |
|--------------------|-------------------|------------------------|--------|-----------------------|
| Ruoxolitinib       | NCT04362137       | 432                    | completed | compared to placebo    |
| Ruoxolitinib       | NCT043388958      | 200                    | recruiting | –                     |
| Ruoxolitinib       | NCT04331665       | 64                     | completed | –                     |
| Sargramostim       | NCT04326920       | 80                     | completed | compared to standard of care |
| Sargramostim       | NCT04629950       | 60                     | recruiting | compared to placebo |
| Sarilumab (Lencure et al., 2021a) | NCT04327398 | 300                      | completed, has results | doi: 10.1016/S2213-2600(21)00099-0 |
| Sarilumab          | NCT04322773       | 200                    | terminated | compared to standard treatment and tocilizumab |
| Sarilumab          | NCT04341870       | 60                     | suspended  | combined with azithromycin and HCQ; compared with sarilumab |
| Sarilumab          | NCT04315298       | 400                    | completed | –                     |
| Sarilumab          | NCT04321993       | 1000                   | recruiting | compared to baricitinib, HCQ, and lopinavir/ritonavir |
| SARS-CoV-2 Convalescent Plasma | NCT04372979 | 80                      | recruiting | compared to standard plasma |
| SARS-CoV-2 Convalescent Plasma | NCT04432103 | 36                      | not yet recruiting | parallel assignment - two groups depending on the stage of the disease |
| SCTA01             | NCT04644185       | 795                    | recruiting | compared to placebo |
| Sildenafil         | NCT04304313       | 10                     | recruiting | single group assignment |
| Sildenafil         | NCT04304313       | 10                     | recruiting | –                     |
| Situximab          | NCT04329650       | 100                    | recruiting | compared to methylprednisolone |
| Silymarin          | NCT04816062       | 30                     | recruiting | compared to standard of care |
| Silymarin          | NCT04394208       | 50                     | recruiting | compared to placebo |
| Sirolimus          | NCT04948203       | 60                     | recruiting | parallel assignment - varying doses of sirolimus |
| Sirolimus          | NCT04341675       | 30                     | recruiting | –                     |
| SNG001             | NCT04732949       | 610                    | recruiting | compared to placebo |
| Sodium Pyruvate    | NCT04430626       | 60                     | recruiting | compared to placebo |
| Sofosbuvir         | NCT04535869       | 50                     | recruiting | combined with daclatasvir |
| Sofosbuvir         | NCT04640443       | 60                     | recruiting | combined with ledipasvir; compared to sofosbuvir + daclatasvir, standard of care |
| Sofosbuvir + Daclatasvir | NCT04497649 | 100                    | recruiting | combined with daclatasvir; compared to standard of care |
| Sofosbuvir + Ledipasvir | NCT04530422 | 250                    | completed | compared to oseltamivir + HCQ + azithromycin |
| Sofosbuvir + Ledipasvir | NCT04498936 | 240                    | completed | compared to nitzoxanide, standard of care |
| Sofosbuvir + Ledipasvir | NCT0460443 | 60                     | recruiting | compared to sofosbuvir + daclatasvir, standard of care |
| Sofosbuvir/Daclatasvir (Simmons et al., 2021) | IRC20200128 | 70 | completed, has results | compared to standard treatment |
| Sotrovimab         | NCT04916765       | 1020                   | recruiting | i.v. administration versus i.m. administration |
| Spironolactone     | NCT04424134       | 80                     | recruiting | combined with bromhexine; compared to standard of care |
| Spironolactone     | NCT04826822       | 440                    | recruiting | combined with dexamethasone; compared to standard of care |
| Suleoxide          | NCT04483830       | 243                    | completed | compared to placebo |
| Tacrolimus         | NCT04341038       | 84                     | recruiting | compared to standard treatment; combined with methylprednisolone |
| Telmisartan        | NCT04355936       | 400                    | completed | compared to standard of care |
| Telmisartan        | NCT04356495       | 820                    | recruiting | combined to ciclosporine, IFN β-1b, vitamins |
| Tenofivir          | NCT04685512       | 60                     | recruiting | combined with emtricitabine; compared to standard of care |
| Tetrandrine        | NCT04308317       | 60                     | recruiting | compared to standard of care |
| Therapeutic Plasma Exchange | NCT04973288 | 38                     | completed | compared to standard of care |
| Thymosin           | ChICTR2000029541   | 100                    | not yet recruiting | combined with darunavir/cobicistat or lopinavir/ritonavir |
| Thymosin           | ChICTR2000029860   | 120                    | recruiting | compared to camrelizumab and conventional treatment |
| Tigerase           | NCT04450225       | 100                    | completed | compared to standard of care |
| TJ003234           | NCT04341116       | 144                    | recruiting | –                     |
| Tocilizumab        | NCT04577534       | 88                     | completed | compared to standard of care |
| Tocilizumab        | NCT04730223       | 93                     | completed | compared to methylprednisolone + standard of care |
| Tocilizumab        | NCT04600141       | 300                    | recruiting | combined with heparin |
| Tocilizumab        | NCT04377250       | 500                    | recruiting | compared to placebo |
| Tocilizumab        | NCT04412727       | 300                    | recruiting | compared to placebo |
| Tocilizumab        | NCT04372186       | 388                    | active    | compared to placebo |
| Tocilizumab        | NCT04409262       | 649                    | completed | combined with remdesivir; compared to remdesivir + placebo |
| Tocilizumab        | NCT04356937       | 243                    | completed | compared to placebo |
| Tocilizumab        | ChICTR2000029765   | 188                    | recruiting | compared to standard treatment |
| Tocilizumab        | ChICTR2000030196   | 60                     | not yet recruiting | – |
| Tocilizumab        | ChICTR2000030442   | 100                    | not yet recruiting | – |
| Tocilizumab        | NCT04310228       | 150                    | recruiting | compared to favipiravir; combined with favipiravir |
| Tocilizumab        | NCT04315480       | 30                     | active, not recruiting | – |
| Tocilizumab        | NCT04317092       | 400                    | active, not recruiting | – |
| Tocilizumab        | NCT04339712       | 20                     | completed | compared to anakirina |
| Tocilizumab        | NCT04331808       | 240                    | active, not recruiting | – |
| Tocilizumab        | NCT04322773       | 200                    | terminated | compared to sarilumab and standard treatment |
| Tocilizumab        | NCT04335305       | 24                     | recruiting | compared to standard treatment; combined with pembrolizumab |
| Tocilizumab        | NCT04335071       | 100                    | terminated | – |
| Tocilizumab        | NCT04332913       | 30                     | recruiting | – |
| Tocilizumab        | NCT04332994       | 276                    | recruiting | compared with azithromycin + hydroxychloroquine; combined with azithromycin + HCQ |

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the baricitinib-arm compared to the 17.9 % (14/78) in the control-arm in week 1 (p = 0.019; 95 % CI: 0.0092 – 0.6818), and week 2 (p < 0.0001; 95 % CI: 0.0038 – 0.2624). Discharge rate was significantly higher in the baricitinib-arm at week 1 [9.7 % (11/113) vs. 1.3 % (88/113); p = 0.039; 95 % CI: 1.41–90.71], and at week 2 [77.8 % (10/132) vs. 12.8 % (10/78); p < 0.0001; 95 % CI: 10.79–51.74] (Cantini et al., 2020).

A randomized trial, Marconi et al., demonstrated that baricitinib may be an important drug that can be used in patients hospitalized for COVID-19 (Marconi et al., 2021). In the 60-day all-cause mortality was 10 % (79) for baricitinib and 15 % (n = 116) for placebo (HR 0.62 (95 % CI 0.47–0.83); p = 0.0050). The use of this drug did not significantly increase the side effects (Marconi et al., 2021). The authors of this study recommend the use baricitinib in hospitalized patients diagnosed with COVID-19 with moderate and severe disease.

### 3.4. Tofacitinib

Tofacitinib is a potent and selective inhibitor of the JAK family of kinases. Tofacitinib has been shown to inhibit the activity of JAK1, JAK2, and JAK3, and to a lesser extent tyrosine-protein 2 kinases (TyK2). In human cells, tofacitinib inhibits the signaling of heterodimeric cytokine receptors which bind JAK3 and/or JAK1, and that possess greater functional selectivity than that of cytokine receptors that signal through JAK2 kinase pairs. Inhibition of JAK1 and JAK3 kinases by tofacitinib attenuates interleukin signaling (IL-2, IL-4, IL-6, IL-7, IL-9, IL-15, and IL-21), as well as interferon type I and type II signaling, resulting in modulation of the immune response (Maeshima et al., 2012).

Guimarães et al., assessed the efficacy and safety of tofacitinib in patients hospitalized for coronavirus pneumonia. Two groups of adult patients (n = 289 in total) with COVID-19 pneumonia were randomized...
directly induces ER stress, leading to the activation of UPR in infected tofacitinib led to a decrease in the risk of death or respiratory failure by the Treatment Guidelines Panel, 2021; Organization, 2021; Bhimraj et al., 2021).

ER stress response, apoptosis, autophagy, and innate immunity exists, ER stress and activates a pathway known as the unfolded protein response (UPR)

infection

3.5. Application of autophagy and UPR in targeting SARS-CoV-2 infection

The endoplasmic reticulum (ER) is the site of both protein translation and protein folding (Sureda et al., 2020). However, if the protein load that is shuffled into the ER exceeds its folding capacity, there is an accumulation of unfolded proteins which triggers the ER stress response, and activates a pathway known as the unfolded protein response (UPR) (Almanza et al., 2019). UPR aims to improve ER folding capacity by reducing global protein synthesis and inducing molecular chaperone expression (Hombach-Klonisch et al., 2018). However, if ER stress is not resolved, UPR directs the cell towards programmed cell death (Mehr bod et al., 2019).

Multiple studies have shown that CoV replication in the cytoplasm directly induces ER stress, leading to the activation of UPR in infected cells. As an intricate interplay between UPR and the inflammatory response, apoptosis, autophagy, and innate immunity exists, ER stress can significantly affect the patient’s antiviral response (Fung and Liu, 2019; Shi et al., 2019). Recent evidence suggests that upon coronavirus infection, ER stress and UPR are induced by excessive synthesis, modification, and folding of viral proteins that results in ER membrane restructuring and its subsequent exhaustion due to continued formation of new virions (Fung et al., 2014; Fung and Liu, 2014). Moreover, some members of the coronaviridae family are capable of utilizing certain aspects of UPR to overcome protein translation shutdown and ensure the production of their own proteins (Fung et al., 2016). Moreover, in severe COVID-19 cases, hypoxemia may trigger a response from both mitochondria and ER, which is directed towards restoring oxygen level and promoting cell survival (Bartoszewksa and Collawn, 2020). However, if this state persists, the role of UPR would then be altered from pro-survival to induction of apoptosis, which is possibly one of the molecular causes of organ damage in COVID-19 (Sureda et al., 2020).

Unsurprisingly, multiple therapeutic drug candidates for COVID-19 infection are autophagy modulators. It is therefore possible that the beneficial effect of these drugs is perhaps due to the over-accumulation of autophagosomes that can induce apoptotic cell death of virally infected cells (Shojaei et al., 2020). Further research exploring CoV-induced UPR could help identify novel therapeutic targets that are based directly on the pathogenesis of the disease.

Studies exploring UPR reveal that the inositol-requiring enzyme 1 (IRE1) axis is involved in the regulation of the secretome of cells via production of spliced XBP (Logue et al., 2018). Moreover, SARS-CoV activates NLR Family Pyrin Domain Containing 3 (NLRP3) inflammasomes in macrophages as well as induces UPR through its Open Reading Frame-8b (ORF-8b) (Shi et al., 2019). The latter is involved in autophagy flux activation and cytokine processing. Hence, targeting the RNase activity of IRE1 could potentially modulate COVID-19 infection via modulation of the macropage secretome.

In another study, SARS-CoV activated the protein kinase R-like reticulum kinase (PERK) arm of UPR, thereby increasing the phosphorylation of eukaryotic initiation factor 2 alpha (eIF2α). As PERK activation suppresses type 1 interferon signaling, it could be a potential mechanism through which innate immunity is suppressed in CoV infected cells (Minakshi et al., 2009). Therefore, PERK inhibitors could potentially aid in halting SARS-CoV-2 infection.

3.5.1. Paxlovid

Paxlovid is a therapeutic combination consisting of two compounds: PF-07,321,332, an oral covalent 3CL protease inhibitor of SARS-CoV-2 and ritonavir, an inhibitor of HIV-1 and HIV-2 protease. Ritonavir is also an inhibitor of cytochrome P450 3A and CYP2D6, thus inhibiting the metabolism of PF-07,321,332 and allowing the administration of a lower dose of the substance. In contrast, P-07,321,332 binds to the catalytic cysteine residue of CysS145 in all coronavirus proteases infecting humans (Mahase, 2021a).

In a recent study, the participants were randomized 1:1; half of which received Paxlovid and the other half received placebo administered orally every 12 h for five consecutive days (Mahase, 2021b). The study revealed that among patients who were treated with paxlovid within three days of symptom onset, 3 out of 339 (0.8 %) patients were admitted to hospital by day 28 after randomization and no deaths were reported. In comparison, 7% (27/385) of patients who received placebo were admitted to the hospital, with seven deaths reported. The statistical significance of these results was assessed as high (p < 0.0001). In subjects treated within five days of symptom onset, 1% (6/607) of those treated with paxlovid were admitted to hospital by day 28 compared to 6.7 % (41/612) of patients in the placebo group. Up to day 28, no deaths were reported in the paxlovid group as compared to 10 deaths (1.6 %) in the placebo group (Mahase, 2021b).

3.5.2. Molnupiravir

The mechanism of action of molnupiravir (Lagevrio) is based on a novel approach to fighting viruses. The compound is converted in the
patient’s body into a synthetic cytidine nucleoside. It then introduces errors into the genetic material of the viruses RNA as it replicates. The mutations lead to defective viral elements, hence neutralizing the pathogen, ultimately exerting an antiviral effect (Painter et al., 2021).

Among 202 participants of a recent study, significantly lower number of participants receiving 800 mg dose of molnupiravir (1.9 %) were carried virus that could be isolated, as compared to placebo (16.7 %) at day 3 ($p = 0.02$). At day 5, virus could not be isolated from any participants receiving 400 or 800 mg molnupiravir, versus 11.1 % of those receiving placebo ($p = 0.03$). Molnupiravir was generally well tolerated, with similar adverse events across all groups (Fischer et al., 2021).

### 3.5.3. Regdanvimab

Regdanvimab (Regkirona) is a recombinant human IgG1 monoclonal antibody. The mechanism of action for regdanvimab in treating patients with SARS-CoV-2 infection is binding of regdanvimab to the receptor binding domain (RBD) of the spike(s) protein of SARS-CoV-2 with dissociation constant $K_D = 0.065$ nM, thus, inhibiting the interaction between the SARS-CoV-2 RBD and the cellular receptor, namely the angiotensin-converting enzyme 2 (ACE2), and consequently blocking cellular entry and SARS-CoV-2 infection. Regkirona is recommended for treating COVID-19 in adults who do not require supplemental oxygen and who are at increased risk of their disease becoming severe (European Medicines Agency, 2021).

The principle, main components and mechanism of action of each vaccine type has been explained in detail in the text.

### Table 4

| Virus variant | Name of the vaccine | Alpha Variant (B.1.1.7) | Beta Variant (B.1.351) | Delta Variant (B.1.617.2) |
|---------------|---------------------|------------------------|-----------------------|--------------------------|
| Comirnaty (Pfizer BioNTech) | Vaccine effectiveness Vs symptomatic infection | Vaccine effectiveness Vs symptomatic infection | Vaccine effectiveness Vs symptomatic infection |
| Dose 1 | 95 % CI 64-68 % | 95 % CI 52-67 % | 95% CI 63-67 % | 95 % CI 64-65 % |
| Dose 2 | 95 % CI 86-91 % | 95 % CI 69-92 % | 95 % CI 64-95 % |
| Spikevax (Moderna) | Vaccine effectiveness Vs Hospitalization rate | Vaccine effectiveness Vs Hospitalization rate | Vaccine effectiveness Vs Hospitalization rate |
| Dose 1 | 95 % CI 80-86 % | 95 % CI 69-92 % | 95 % CI 78 % |
| Dose 2 | 95 % CI 86-96 % | No information | No information |
| Janssen COVID-19 Vaccine (Johnson & Johnson) | Vaccine effectiveness Vs symptomatic infection rate | Vaccine effectiveness Vs symptomatic infection rate | Vaccine effectiveness Vs symptomatic infection rate |
| Dose 1 | effective according to the manufacturer | effective according to the manufacturer | effective according to the manufacturer |

Legend: 95 % CI – 95 % confidence interval.
were hospitalized, required supplemental oxygen or died within 28 days of treatment compared with 11.1 % of patients on placebo (48 out of 434) (Kreuzberger et al., 2021).

3.5.4. Anakinra

Anakinra (Kineret) inhibits the biological activity of interleukin 1. It counteracts the production of NO, PGE2 and collagenase in the synovium, fibroblasts and chondrocytes. A systematic review and patient-level meta-analysis performed by Kyriazopoulou et al. examined pooled data for 1185 patients from nine studies, as well as individual patient data for 895 patients from six of the analyzed studies (Kyriazopoulou et al., 2021). Eight trials were observational studies, and one was a randomized controlled trial. The data taken into account were age, comorbidities, baseline partial pressure of oxygen in arterial blood, the ratio of arterial partial pressure of oxygen divided by inspired fraction of oxygen (PaO2/FiO2), C-reactive protein and lymphopenia. The mortality was significantly lower in patients treated with anakinra (38 [11 %] out of 342 patients) as compared with subjects receiving standard care with or without placebo (137 [25 %] out of 553; adjusted odds ratio [OR] 0.32 [95 % CI 0.20–0.51]). The mortality benefit was comparable between all subgroups, regardless of existing comorbidities, levels of ferritin I, or baseline PaO2/FiO2. Anakinra was more effective in reducing mortality in patients with a C-reactive protein concentration exceeding 100 mg/l (OR 0.23 [95 % CI 0.12–0.43]), but not with additional dexamethasone (0.72 [95 % CI 0.37–1.41]). The use of anakinra, as compared to standard of care was not associated with a significantly increased risk of secondary infections (OR 1.35 [95 % CI 0.59–3.10]) (Kyriazopoulou et al., 2021).

3.5.5. Sotrovimab

Sotrovimab (Xevudy, also known as VIR-7831 and GSK4182136) is a monoclonal antibody with an activity against COVID-19. Sotrovimab was designed to attach to S protein of SARS-CoV-2. When it binds to S protein, the ability of the virus to enter the cells of the body are reduced. This is expected to reduce both the severity of the disease and need for hospitalization in COVID-19 (Sotrovimab, 2021). One article reported that the drug was administered at a dose of 500 mg or placebo. The primary efficacy outcome was hospitalization exceeding 24 h for any cause or death within 29 days of randomization. In this pre-specified interim analysis, which included an intention-to-treat population of 583 patients (291 in the sotrovimab group and 292 in the placebo group), 3 patients (1%) in the sotrovimab group, as compared with 21 patients (7%) in the placebo group, experienced disease progression leading to hospitalization or death (relative risk reduction, 85 %; 97.24 % confidence interval, 44–96; p = 0.002). In the placebo group, 5 patients were admitted to the ICU, including 1 who died by day 29. The safety assessment was performed in 868 patients (430 in the sotrovimab group and 438 in the placebo group). The adverse events were reported in 17 % of subjects in the sotrovimab group and 19 % of those in the placebo group; serious adverse events were less common with sotrovimab than with placebo (in 2% and 6% of the patients, respectively) (Gupta et al., 2021).
3.5.6. Tixagevimab and cilgavimab

Tixagevimab and cilgavimab (Evusheld), two monoclonal antibodies have been designed to attach to the spike protein of SARS-CoV-2 at two different sites. By attaching to the spike protein, the medicine is expected to stop the virus from entering the body’s cells and causing infection. Because the antibodies attach to different parts of the protein, using them in a combination may be more effective than using either of them alone. The results of a recent trial funded by AstraZeneca met the primary endpoint, with a dose of 600 mg of AZD7442 given by intramuscular (IM) injection reducing the risk of developing severe COVID-19 or death (from any cause) by 50% compared to placebo in outpatients who had been symptomatic for seven days or less. The trial recorded 18 events in the AZD7442 arm (18/407) and 37 in the placebo arm (37/415). The LAAB was generally well tolerated in the trial. In a pre-specified analysis of participants who received treatment within five days of symptom onset, AZD7442 reduced the risk of developing severe COVID-19 or death (from any cause) by 67% compared to placebo, with nine events in the AZD7442 arm (9/253) and 27 in the placebo arm (27/ 251) (AstraZeneca, 2021).

4. Other agents tested for potential efficacy in treating COVID-19 infection

4.1. Hydroxychloroquine

During the early days of the COVID-19 pandemic, many scientists and physicians placed hope in hydroxychloroquine (HCQ) and other antimalarial drugs. Moreover, non-randomized studies describing the positive effects of this drug are cited more often than any subsequent randomized trials about its lack of clinical benefit or even harmful side-effects (Bellos, 2021). With time, the severity of adverse effects and long-term consequences of HCQ treatment were elucidated (Drozdżal et al., 2020; Díaz-arocuhipa and Hernandez, 2021). HCQ used both in monotherapy and in combination with azithromycin has been shown to increase the prevalence of a prolonged QTc as a side effect. An association with higher incidence of arrhythmias has not been demonstrated, although this is possibly due to underestimated reporting frequency72).

According to studies with a high level of certainty surrounding their evidence, HCQ does not reduce mortality in patients with COVID-19 (Self et al., 2020; Kashour et al., 2021). Moreover, a meta-analysis performed by Axfors et al., showed that patients had an all-cause combined mortality OR of 1.11 for hydroxychloroquine (95% CI: 1.02–1.20) (Axfors et al., 2021). The effect of pharmacological prophylaxis in COVID-19 has also been disputed. Bartoszko et al., showed that taking HCQ has practically no effect on hospital admission or mortality, but it significantly increased the incidence of side effects. A meta-analysis of the available RCTs demonstrated no positive effects of the drug, but instead the incidence of side effects increased [RR = 1.81 (95% CI: 1.36–2.42); p < 0.05] (Bartoszko et al., 2021). The study authors, do not recommend the use of chloroquine and hydroxychloroquine for either post-exposure prophylaxis or the treatment of COVID-19.

4.2. Colchicine

Colchicine may play a role in reducing the symptoms of COVID-19, as it binds to b-tubulin hence blocking microtubule polymerization. This in turn affects the spindle, and therefore reduces the movement and degranulation of intracellular lysosomes and the release of lysozymes, chemoattractants, and lactic acid. It inhibits the phagocytosis of sodium urate crystals by leukocytes, and reduces the breakdown of leukocyte cell membranes through their mobilization, migration, and the ability to adhere (Leung et al., 2015). It is characterized by anti-inflammatory effects achieved through a reduction of leukocyte migration, inhibition of endothelial adhesion, reduction in interleukin production, and cytokine storm prevention (Vitiello and Ferrara, 2021). Colchicine is a powerful anti-inflammatory agent routinely used to treat gout, viral pericarditis, coronary artery disease, and familial Mediterranean fever. Golpour et al., in a meta-analysis analyzed the effect of colchicine on the treatment of COVID-19. Colchicine was shown to be responsible for reducing mortality and length of hospitalization, and may therefore be an effective therapeutic option to improve COVID-19 treatment (Golpour et al., 2021).

4.3. Convalescent plasma

The concept of using convalescent plasma in the treatment of COVID-19 was enthusiastically received by clinicians, internationally. The premise was based on the theory that antibodies produced by convalescent patients would help the recipients’ body combat the infection and improve their prognosis. The initial results were very promising, but the intervention group not only included COVID-19 patients, but also those with SARS, MERS, and influenza (Aviani et al., 2021). In a meta-analysis of COVID-19 patients, Bansal et al., showed that adding convalescent plasma to the standard of care reduced mortality among patients (Bansal et al., 2021a). A second meta-analysis by Janiaud et al., did not demonstrate the beneficial effect of administering convalescent plasma to patients (Janiaud et al., 2021). Furthermore, Prasad et al., considered the most recent data in both randomized clinical trials and cohort studies, suggesting a possible weak association, although underlined the need for further randomized trials (Prasad et al., 2021). Finally, Korley et al., published the results of a recent trial investigating the effect of convalescent plasma on the progression of COVID-19 in high-risk patients (n = 511). This study showed no effect on disease progression and length of hospitalization (Korley et al., 2021). The study authors do not recommend the routine use of convalescent plasma in patients hospitalized with COVID-19.

4.4. Amantadine

Amantadine hydrochloride, a synthetic tricyclic amine, is an antiviral drug known since the 1960s for the treatment of influenza A. It works by blocking M2 ion channels, inhibiting viral entry into cells, and inhibiting viral replication (Raupp-Barcaro et al., 2018a).

A model was proposed by Abreu et al., in which amantadine blocks viroportin E of the SARS-CoV-2 virus, preventing the release of genetic material into the host nucleus (Aranda-Abreu et al., 2020). It was also shown to inhibit the replication of the virus in vitro, however, this occurred only at a concentration higher than that achievable with oral supplementation (Fink et al., 2021).

When discussing amantadine, it is worth mentioning the neurological complications of COVID-19, i.e. agitation, myoclonus, abulia, alogia (Baller et al., 2020), brain fog, and chronic fatigue (Graham et al., 2021). Studies are emerging to assess the effects of amantadine on alleviating theses neurological symptoms. It has been suggested that amantadine can potentially help in the treatment of catatonia, especially in patients with contraindications to benzodiazepines due to respiratory failure (Raupp-Barcaro et al., 2018b). Additionally, amantadine may support the treatment of depressive disorders (Zaidi and Dehgani-Mobaraki, 2021). The study authors did not recommend the routine use of amantadine in COVID-19 patients limiting its use to a clinical trial.

4.5. Ivermectin

Ivermectin is one of the most commonly used drugs to treat parasitic infections in humans as well as in animals in veterinary medicine. Its mechanism is based on the selective, positive allosteric modulation of glutamate chloride channels found in nematodes and insects. It acts by binding to these channels, leading to an influx of chloride ions, causing cell hyperpolarization and thus dysfunction. Moreover, at higher concentrations, ivermectin can also bind to GABA receptors (Zaidi and Dehgani-Mobaraki, 2021). Ivermectin is rapidly absorbed orally and has high liposome solubility. Moreover, it is metabolized in the liver (by the
cytochrome P450 system) and almost exclusively excreted in feces (González Canga et al., 2008). One of the main potential mechanisms of ivermectin action is based on binding to the importin-α (IMPα)/β1 heterodimer complex. IMPα/β1 participates in binding to the CoV load protein in the cytoplasm and transports it through the nuclear pore complex (NPC) into the nucleus, where it breaks down and the viral load assists in reducing the host cell’s antiviral response, thereby increasing the infection. Ivermectin binds to the IMPα/β1 and destabilizes it, thus preventing it from binding the viral protein and entering the nucleus. This likely results in decreased inhibition of the immune response, leading to a normal, more effective antiviral reaction (Wagstaff et al., 2012).

Ivermectin has been examined in several studies, including that by Zein et al., who performed a review of the meta-analyses and meta-regression of randomized controlled trials. Among the available trials, they searched for the effectiveness of ivermectin in SARS-CoV-2 virus infections as compared to control patients with standard of care or a placebo. The primary endpoint that was evaluated was mortality. In total, 9 RCTs involving 1788 patients were analyzed in this meta-analysis, revealing that ivermectin was associated with a reduction in mortality [RR = 0.39 (95% CI: 0.20–0.74); p = 0.004]. However, the benefit of ivermectin and this reduced mortality were impeded by hypotension [RR = 1.08 (95% CI: 1.03–1.13); p = 0.001]. A sensitivity analysis using the fixed effects model showed that ivermectin reduced all-cause mortality [RR = 0.43 (95% CI: 0.29–0.62); p < 0.001] and the severe COVID-19 subgroup [RR = 0.48 (95% CI: 0.32–0.72); p < 0.001] (AFMZ et al., 2021).

However, other studies did not report statistically significant differences in mortality (Ravikiri and Pattadar, 2021), length of hospitalization (Abdulamir et al., 2021a) and clinical endpoints, disease progression, recovery, the occurrence of symptoms (Okumuş et al., 2021). The study authors did not recommend the routine use of ivermectin in COVID-19 patients, limiting its use to a clinical trial.

4.6. Niclosamide

Niclosamide (NIC) is an oral chlorinated salicylanilide. In clinical practice, it is a drug used to treat tapeworm infections. Its mechanism of action is centered around decoupling the electron transport chain from ATP synthase, thereby abolishing ATP synthesis. When administered orally, NIC specifically induced the degradation of the androgen receptor variant V7 (AR-V7) via a proteasome-mediated pathway. This action decreased the expression of the AR variant, inhibiting its transcriptional activity and reducing the recruitment of AR-V7 into the prostate-specific antigen (PSA) gene promoter. NIC also prevented AR-V7-mediated phosphorylation and activation of STAT3 (Kadri et al., 2018). In addition, there are reports of the antiviral activity of NIC against the influenza virus and HRV (Jurgeit et al., 2012). Various drug repurposing screens identified NIC as a potential drug candidate against COVID-19. Prevention of viral entry by altering endosomal pH and prevention of viral replication by inhibition of autophagy are the plausible mechanisms of action of NIC against COVID-19. Therefore, the clinical efficacy of NIC against COVID-19 therefore needs to be further evaluated (Pindiprolu and Pindiprolu, 2020).

One study in an animal model assessed the efficacy of NIC-Lysozyme (NIC-hLYS) particles against the SARS-CoV-2 infection. A once-daily administration in the form of nasal NIC-hLYS particles suspended in 0.45% NaCl resulted in a 30% survival rate in fatal SARS-CoV-2 infection. Moreover, it caused a statistically significant decrease in viral load in the lung after 10 days of treatment. By day 6 of treatment with 240 µg/kg NIC, interstitial pneumonia was significantly reduced and further resolved by day 14 (Brunaugh et al., 2020).

A randomized trial by Abdulamir et al., investigated the efficacy and safety of NIC as an adjunct to the standard of care in COVID-19 infection. This study was a randomized, controlled, open-label clinical study including 75 COVID-19 patients treated with standard of care plus NIC and 75 COVID-19 patients treated only with standard care therapy. Each group consisted of 25 mild, 25 moderate, and 25 severe COVID-19 patients. The main endpoints of the analysis were survival rate, time to recovery, and adverse reactions. NIC did not increase the survival rate as three severe COVID-19 patients in the NIC and control groups died (p > 0.05). However, when compared to the control group, NIC reduced recovery time in patients with moderate and severe COVID-19 by 5 and 3 days, respectively, but not in mild patients (p ≤ 0.05). Interestingly, NIC reduced recovery time to five days in patients with comorbidities (P ≤ 0.05), while shortening it by only one day in patients without comorbidities (p > 0.05). The authors concluded that NIC speeds up recovery by approximately 3–5 days in patients with moderate to severe COVID-19, especially those with underlying medical conditions. Hence NIC achieved clinical benefits by freeing up hospital beds for more patients in a pandemic crisis (Abdulamir et al., 2021b). The authors did not recommend the routine use of NIC in COVID-19 patients, limiting its use to a clinical trial.

4.7. Sarilumab

Sarilumab (Kevzara) is a human monoclonal antibody that acts to inhibit the binding of IL-6 to its α receptor. This drug is approved for the treatment of adults with moderately to severely active rheumatoid arthritis. Due to sarilumab ability to inhibit both soluble and membrane-bound IL-6 receptor, it has the potential to exert a therapeutic effect in patients with SARS-CoV-2 infection (KEVZARA (Sarilumab), 2017). A study by Lescure et al., describes the effects of sarilumab in patients admitted to the hospital with severe or critical COVID-19. This was a phase 3 randomized, double-blind, placebo-controlled study on 416 patients allocated to 3 groups. Group one received a placebo, the second group received sarilumab at a dose of 200 mg and the third group received the drug at a dose of 400 mg. The authors concluded that the use of sarilumab was not effective in patients admitted to the hospital with COVID-19 and receiving oxygen supplementation. In patients with critical illness due to COVID-19, appropriately enhanced trials of targeted immunomodulatory therapies assessing survival as a primary endpoint, are suggested (Lescure et al., 2021a).

4.8. Chinese herbal medicine

In many environments, folk medicine plays an important role in the treatment of various diseases, especially those that people fear, or when conventional medicine is powerless or unable to propose effective treatment. This can be seen during the course of some cancers, and the beginning of the COVID-19 pandemic. Patients’ questions often relate to Chinese herbal medicine (CHM) as a popular representative of alternative medicine. Currently, protocols of systematic reviews and meta-analyses for 7 preparations have been announced: Shufeng Jiedu (Wang et al., 2020a), Xuanei Baidu (Zhao et al., 2021), Maxingshigan Decoction (Shao et al., 2020), Reyanning mixture (Li et al., 2021), Xiaqinglong decoction (Ren et al., 2020), Lianhua Qingwen (Liu et al., 2020a), and Xiyanping (Zhou et al., 2020). As the authors suggest, these drugs have been used to treat COVID-19 in China, so scientific evidence is needed to evaluate their effectiveness. The study authors did not recommend the use of CHM in COVID-19 patients.

4.9. Dietary supplements

Vitamin C has been used as a remedy for cold-like symptoms for years. Studies on animal models show that vitamin C reduces vascular permeability, improves blood circulation, and due to its antioxidant effect, reduces the amount of free radicals (Armour et al., 2001; Chakrabarty et al., 1992). Furthermore, there have been reports of vitamin C used in combination with hydrocortisone and thiamine to treat sepsis and acute respiratory distress syndrome, significantly reducing mortality (Marik et al., 2017).
Gao et al., conducted a study in which vitamin C was administered at high doses to patients with COVID-19 (n = 46) and compared them with standard treatment (n = 30). The study showed a significant reduction in mortality and a lower need for respiratory support. Given the availability of vitamin C, there is a lack of large adequately powered studies confirming or contradicting the effectiveness of this supplement in treating COVID-19 (Gao et al., 2021). Huang et al., have published a protocol for a systematic review and meta-analysis of high-dose intravenous vitamin C administration, but have not released the results as of November 2021 (Huang et al., 2021).

Vitamin D supplementation during viral infections is also very popular. Vitamin D possesses an immunomodulatory effect by altering the expression and secretion of proinflammatory cytokines (e.g. IL-6, TNF), interferon, and chemokines (Greller and Martineau, 2015). A meta-analysis published by Rawat et al., examining the use of vitamin D in patients with COVID-19 demonstrated no significant reduction in mortality, ICU admission, or the need for invasive ventilation in patients receiving vitamin D supplementation (Rawat et al., 2021).

It is also worth mentioning that zinc, one of the micronutrients, was postulated to be effective in the combat against COVID-19. It was shown that supplementation with zinc reduced mortality in pneumonia without increasing the risk of therapy failure (Wang and Song, 2018). Its role is to reduce oxidative stress and inflammation (Prasad, 2014), thereby increasing the risk of therapy failure (Wang and Song, 2018). Its role is postulated to be effective in the combat against COVID-19. It was shown that supplementation with zinc reduced mortality in pneumonia without increasing the risk of therapy failure (Wang and Song, 2018). Its role is to reduce oxidative stress and inflammation (Prasad, 2014), thereby increasing the risk of therapy failure (Wang and Song, 2018). Its role is postulated to be effective in the combat against COVID-19. It was shown that supplementation with zinc reduced mortality in pneumonia without increasing the risk of therapy failure (Wang and Song, 2018). Its role is to reduce oxidative stress and inflammation (Prasad, 2014), thereby increasing the risk of therapy failure (Wang and Song, 2018). Its role is postulated to be effective in the combat against COVID-19. It was shown that supplementation with zinc reduced mortality in pneumonia without increasing the risk of therapy failure (Wang and Song, 2018). Its role is to reduce oxidative stress and inflammation (Prasad, 2014), thereby increasing the risk of therapy failure (Wang and Song, 2018). Its role is postulated to be effective in the combat against COVID-19. It was shown that supplementation with zinc reduced mortality in pneumonia without increasing the risk of therapy failure (Wang and Song, 2018). Its role is to reduce oxidative stress and inflammation (Prasad, 2014), thereby increasing the risk of therapy failure (Wang and Song, 2018). Its role is postulated to be effective in the combat against COVID-19. It was shown that supplementation with zinc reduced mortality in pneumonia without increasing the risk of therapy failure (Wang and Song, 2018). Its role is to reduce oxidative stress and inflammation (Prasad, 2014), thereby increasing the risk of therapy failure (Wang and Song, 2018). Its role is postulated to be effective in the combat against COVID-19. It was shown that supplementation with zinc reduced mortality in pneumonia without increasing the risk of therapy failure (Wang and Song, 2018).

5. Adjuvants/supportive treatment

5.1. Steroids

5.1.1. Dexamethasone

Dexamethasone is a synthetic glucocorticoid, a fluorinated derivative of prednisone that possesses a strong and long-lasting anti-inflammatory and immunosuppressive effect. The mechanism of action is based on the reduction of accumulated leukocytes and their adhesion to the endothelium. Moreover, dexamethasone inhibits phagocytosis and lysosomal breakdown, reduces the number of lymphocytes, eosinophils, monocytes, and blocks IgE-dependent secretion of histamine and leukotrienes. Finally, it inhibits the synthesis and release of cytokines, including interferon γ, TNF-α, GM-CSF, and interleukins IL-1, IL-2, IL-3, and IL-6. By inhibiting the activity of phospholipase A2 through lipocortin, it prevents the release of arachidonic acid, therefore reducing mediators of inflammation such as leukotrienes and prostaglandins (Ahmed and Hassan, 2020; Sinner, 2019).

In one of the most comprehensive trials, patients were randomized to receive 6 mg oral or intravenous dexamethasone once daily for up to 10 days or to a control group that received the standard of care. The primary endpoint was mortality at 28 days. A total of 2104 patients were assigned to receive dexamethasone and 4321 received standard of care. Overall, 482 patients (22.9 %) in the dexamethasone group and 1110 patients (25.7 %) in the standard of care group died within 28 days after randomization [age-adjusted rate ratio = 0.83 (95 % confidence interval [CI]: 0.75–0.93); p < 0.001]. In the dexamethasone group, the death rate was lower than in the standard care group receiving invasive mechanical ventilation [29.3 % vs. 41.4 %; rate ratio = 0.64 (95 % CI: 0.51–0.81)] and receiving oxygen without invasive mechanical ventilation [23.3 % vs. 26.2 %; rate ratio = 0.82 (95 % CI: 0.72–0.94)], but not among those who did not receive respiratory support at the time of randomization [17.8 % vs. 14.0 %; rate ratio = 1.19 (95 % CI: 0.92–1.55)]. This study showed that dexamethasone treatment resulted in a lower 28-day mortality in patients hospitalized for COVID-19 who were undergoing mechanical ventilation or oxygen therapy, but not for those patients who did not receive respiratory support (Lim et al., 2021).

The results of the most recent trial pertaining the use of dexamethasone, the COVID STEROID 2 Trial provided by Munch et al. in October 2021 have shown that in COVID-19 patients with severe hypoxemia, the use of 12 mg/d of dexamethasone as compared with 6 mg/d of dexamethasone did not reduce 28-day survival without life support (Munch et al., 2021). In the 12 mg dexamethasone group the mortality at 28 days was lower (27.1 %) and in the 6 mg dexamethasone group was higher (32.3 %) (adjusted relative risk, 0.86 [99 % CI, 0.68–1.08]). Similarly, the death rate at 90 days was lower (32.0 %) in the 12 mg dexamethasone group as compared to mortality in the 6 mg dexamethasone group (37.7 %), with adjusted relative risk of 0.87 [99 % CI, 0.70–1.07]). Although the results of the by Munch et al. are supportive, but not definitive of improved outcomes when using 12 mg/d of dexamethasone, the study was underpowered. Therefore, the results of COVID STEROID 2 Trial do not satisfy the usual criteria to support change in practice, but further trials are needed to define the optimal dose of dexamethasone with definite survival benefit. The results of three on-going trials (NCT04381936, NCT04726098, NCT04663555) are highly awaited. Hence, the study authors recommended the use of dexamethasone in the routine care of patients with COVID-19, especially during hospitalization, but the optimal dose is yet to be established.

5.1.2. Budesonide

Another member of the glucocorticoid family which has recently been used to treat SARS-CoV-2 infections is budesonide. A randomized, phase 2 trial of inhaled budesonide versus standard of care (Steroids in COVID-19; STOIC study) was conducted in adults within 7 days of onset of mild COVID-19 symptoms. The dry powder of budesonide was administered via a turbine inhaler at a dose of 400μg. Participants were asked to perform two inhalations twice a day. The primary endpoint was a COVID-19 related emergency department visit. Secondary endpoints were patient-reported symptom relief, body temperature, blood oxygen saturation, and SARS-CoV-2 virus load. For the pre-protocol population (n = 139), the primary endpoint was met in 10 (14 %) of 70 participants receiving the standard of care and 1 (1%) of 69 participants receiving budesonide [difference = 0.131 (95 % CI: 0.043 – 0.218); p = 0.004]. In the intention-to-treatment population, the primary endpoint occurred in 11 (15 %) participants in the usual care group and two (3%) participants in the budesonide group [difference = 0.123 (95 % CI: 0.033 – 0.213); p = 0.009]. The number needed to treat with inhaled budesonide to reduce the worsening of COVID-19 was 8. Budesonide was also found to be safe, and only five (7%) participants reported self-limiting adverse events (Ramakrishnan et al., 2021). The study authors recommend the inhalation of steroids in the routine use in patients with COVID-19 in the early stages of the disease.

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**Table 5**

| Drug | No. patients | Outcome Effect |
|------|--------------|----------------|
| Vitamin D (Rawat et al., 2021) | 467 | Mortality No effect; R = 0.55 (95 % reduction CI: 0.22–1.39), p = 0.21 |
| HCQ (Amarni et al., 2021) | 6059 | Mortality No effect, RR = 0.7 (95 % reduction CI: 0.24–1.99) |
| HCQ (Bartoszko et al., 2021) | 8161 | Side effects RR = 1.81 (95 % CI: 1.36–2.42), p < 0.05 |
| HCQ (Afreds et al., 2021) | 10,012 | Increase of mortality OR = 1.11 (95 % CI: 1.02–1.20) |
| Convalescent plasma (Bansal et al., 2021b) | 27,706 | Mortality OR = 0.76 (95 % CI: 0.53–1.08), p = 0.13 |
| Sarilumab (Lescure et al., 2021b) | 416 | Positive Effect HR = 1.03 (95 % CI: 0.75–1.40), p = 0.96 |

Legend: HCQ – hydroxychloroquine; HR – hazard ratio; OR – odds ratio; RR – risk ratio; 95 % CI – 95 % confidence interval.
2.1. Anticoagulants

Heparin possesses potent anticoagulant activity, induced by catalyzing the thrombin-antithrombin reaction. In addition, heparin exerts an anti-inflammatory effect that may improve endothelial function, which may be beneficial for patients with COVID-19. To date, there are two studies comparing the low-molecular-weight (LMW) to unfractionated heparin, and both demonstrated a reduced risk of death with LMW compared with unfractionated heparin (Kirkup et al., 2021; Pawlowski et al., 2021). In one study, mortality for the primary population was 270/1939 vs. 390/1012 with an OR = 0.258 (95% CI: 0.215–0.309); in-hospital mortality for the matched populations was 154/711 (22%) vs. 268/733 (37%) with an OR = 0.480 (95% CI: 0.380–0.606) and 28-day mortality for matched populations 12/528 (2.3%) vs. 44/463 (9.5%) with an OR = 0.221 (95% CI: 0.115–0.425). In addition, the addition of LMW heparin reduced hospitalization (10.99 days vs. 13.33 days; p = 0.005), and ICU admission (10.7 vs. 12.16; p = 0.00008), and finally reduced the number of patients transferred to the ICU (primary populations: 988/1936 vs. 717/1009, OR = 0.424 (95% CI: 0.361–0.499); comparison of matched populations: 399/714 (56%) vs. 481/732 (66%), OR = 0.661 (95% CI: 0.534–0.817) (Kirkup et al., 2021).

In the second study, Pawlowski et al., showed that all-cause mortality for primary populations was reduced [11 (2.5%) vs. 28 (17%); RR = 6.76 (95% CI: 3.39–12.7)], with the 28-day mortality for the primary populations of 9/244 (3.7%) vs. 20/118 (17) (RR = 4.60, 95% CI: 2.13–9.29). Additionally, end-points in favor of LMW heparin were reported to decrease the risk of mechanical ventilation (48.4% non-ASA vs. 35.7% ASA; p = 0.05). After the adjustment of confounding variables, the ASA use was associated with an absolute reduction in the number of thrombotic events by 0.6% and an absolute increase in the number of major bleeding events by 0.6% (RECOVERY Collaborative Group, 2021).

In the study by Chow et al., reported promising effects of ASA in SARS-CoV-2 infection. Among the 412 patients included in the study, 314 did not receive ASA (76.3%) while 98 patients (23.7%) did. The significant differences were reported between the two groups in the ICU admission rate (51% non-ASA vs. 38.8% ASA; p < 0.05) and the rate of mechanical ventilation (48.4% non-ASA vs. 35.7% ASA; p < 0.05). After the adjustment of confounding variables, the ASA use was reported to decrease the risk of mechanical ventilation (HR = 0.56; 95% CI: 0.37–0.85; p = 0.007), admission to intensive care unit (HR = 0.57; 95% CI: 0.38–0.85; p = 0.005) and in-hospital death adjusted (HR = 0.53; 95% CI: 0.31–0.90; p = 0.02) (Chow et al., 2021).

5.2. Acetylsalicylic acid

Acetylsalicylic acid (ASA, aspirin) belongs to the group of non-steroidal anti-inflammatory drugs (NSAIDs) that possess anti-inflammatory, antipyretic, and analgesic properties. Its mechanism of action is based mainly upon inhibiting cyclooxygenases (COX) in two distinct ways. Constitutive COX (COX-1) is responsible for the synthesis of prostaglandins that fulfill physiological functions. On the other hand, inducible COX (COX-2) is responsible for the synthesis of pro-inflammatory prostaglandins at the site of inflammation. ASA mainly inhibits COX-1, and to a lesser extent, COX-2. By irreversibly inhibiting platelet COX-1 and crippling thrombogenesis, it exerts an anti-aggregating effect. At higher doses, it acts as an antithrombotic agent by antagonizing vitamin K (Tanasescu et al., 2000). Moreover, the pleiotropic effects of ASA include the modulaion of endothelial function (Sayed Ahmed et al., 2021), and therefore it may have a role in preventing COVID-19 complications (Dzeshka et al., 2016).

In the RECOVERY study, Horby et al., described the effectiveness of ASA in COVID-19 infection. In this randomized, controlled, open-label platform study, several possible treatments were compared with standard of care in patients hospitalized for COVID-19. Eligible and consenting adults were randomly assigned in a 1:1 ratio to either standard care (7541 patients) or standard care plus 150 mg of ASA (7351 patients) once a day until discharge from the hospital. The primary endpoint was mortality at 28 days. This study demonstrated that 1222 (17%) patients assigned to ASA and 1299 (17%) patients assigned to ordinary care died within 28 days (RR = 0.96; 95% CI: 0.89–1.04; p = 0.35). Among subjects who did not require invasive mechanical ventilation at baseline, there was no significant difference in the proportion meeting the composite endpoint of invasive mechanical ventilation or death (21% vs. 22%; RR = 0.96; 95% CI: 0.90–1.03; p = 0.23). The use of ASA was associated with an absolute reduction in the number of thrombotic events by 0.6% and an absolute increase in the number of major bleeding events by 0.6% (RECOVERY Collaborative Group, 2021).

5.3. Acetylsalicylic acid

Statins

Statins, 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-CoA) inhibitors, are lipid-lowering drugs that display pleiotropic effects. As acute respiratory distress syndrome (ARDS), the main cause of death from COVID-19, is caused by exaggerated inflammatory response, the immunomodulatory properties of statins have become of interest in the context of COVID-19 research, and have previously shown a beneficial
virus can damage the lungs, heart and brain, which significantly in effects might mimic COVID-19. Muscle-related symptoms especially, are by hypoxia and pathological findings (Silva Andrade et al., 2021; Zhang et al., 2020).

A meta-analysis of 4 studies showed that the use of statins is associated with a significantly reduced hazard for fatal or severe disease (pooled HR = 0.70; 95% CI: 0.53–0.94), although these results based on 8990 patients strongly highlight a need for prospective studies (Kow and Hasan, 2020).

The currently available data seems encouraging and suggests that in no case should the use of statins be abandoned during COVID-19 infection. However, it is too soon to include statins in the routine therapeutic plan for COVID-19 treatment (Subir et al., 2020). Moreover, people, who start therapy with statins due to cardiovascular diseases during the pandemic should be aware that some of the potential side effects might mimic COVID-19. Muscle-related symptoms especially, are similar when comparing the side-effects of statins or viral infection (Karalis DG, 2020).

6. Treatment of COVID-19 complications

COVID-19 symptoms can, in some cases, persist for months. The virus can damage the lungs, heart and brain, which significantly increases the risk of long-term health issues. This group of conditions has been called post–COVID-19 syndrome or long COVID-19 (Datta et al., 2020). In general, they are considered to be the effects of COVID-19 that persist for more than four weeks after diagnosis (Silva Andrade et al., 2021). SARS-CoV-2 can cause severe inflammation that is triggered by the immune system, which responds by increasing the rate of coagulation, which is triggered largely due to other systems in the body being affected by blood clots, such as the lungs, kidneys, liver, or heart. Moreover, COVID-19 can also weaken blood vessels and cause them to leak, which further contributes to the potential long-term complications affecting the kidneys and liver (Jin et al., 2020). The SARS-CoV-2 infection requires the cooperation of several essential systems to maintain homeostasis. The direct effect of SARS-CoV-2 hyperinflammation induces the production of endogenous compounds that promote the alteration of vascular hemostasis (Liu et al., 2020b). Furthermore, the release of pro-inflammatory and pro-thrombotic cytokines has a direct effect on blood coagulation. These factors result in disseminated intravascular coagulation and the formation of thromboembolic conditions that can affect various tissues, especially those which are more sensitive to ischemic processes, such as pulmonary, cardiovascular, and cerebrovascular tissues (Jin et al., 2020; Giustino et al., 2020). The cardio-pulmonary system especially is severely affected (Cobo-Siles et al., 2020). The lungs suffer from gradual functional failure, which is reflected by hypoxia and pathological findings (Silva Andrade et al., 2021; Al-Khawaga and Abdelalim, 2020). Among the most common pathologies of the lung, respiratory failure, pulmonary thromboembolism, pulmonary embolism and Abdelalim, 2020). Among the most common pathologies of the lung, respiratory failure, pulmonary thromboembolism, pulmonary embolism, pneumonia, pulmonary vascular damage, and post-viral pulmonary fibrosis should be highlighted (Sakr et al., 2020; George et al., 2020; Lechowicz et al., 2020). So far, there is no single, proper guideline for treating pulmonary complications after COVID-19. It has been suggested that physical exercise and appropriate rehabilitation, including breathing exercises, may help to resolve pulmonary symptoms (Crook et al., 2021). In more severe cases, the use of opioids may reduce respiratory effort (Jennings, 2002). However, lung fibrosis may be a long-term complication. Due to the relatively short follow-up period from the first infection, the available data on this phenomenon is limited. Therefore, it is suggested that the treatment recommendations regarding idiopathic pulmonary fibrosis be followed.152 There have been reports in the literature that the use of spironolactone during COVID-19 infection can prevent fibrosis (Kotfis et al., 2021).

The most experienced cardiac complications include angina, acute coronary syndromes, and arrhythmias. The NICE recommendations point to the use of beta blockers in these cases (National Institute for Health and Care Excellence, 2021, 2020; National Institute for Health and Care Excellence, 2016). Furthermore, remission of one complication, myocarditis, might depend on immunomodulatory effect (Sinagra et al., 2016). Complications related to the nervous system following COVID-19 infection include loss of taste, smell and hearing, headaches, spams, convulsions, confusion, visual disturbances, neuralgia, dizziness, disturbance of consciousness or delirium, nausea and vomiting, hemiplegia, ataxia, stroke, as well as cerebral hemorrhage (Favas et al., 2020; Samarayanake et al., 2020; Almufairij et al., 2020; Kennedy et al., 2020; Kotfis et al., 2020; Pun et al., 2021). According to Crook et al., chronic fatigue syndrome can be compared to the myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) so treatment may include cognitive behavioral therapy (CBT) and graded exercise therapy (GET) (Crook et al., 2021). In the case of cognitive impairment, the so-called brain fog, apart from psychological support, methylphenidate, donepezil, modafinil, and memantine may also be helpful (Crook et al., 2021; Chemo brain, 2021; Theoharides et al., 2021).

COVID-19 infections can cause macro- and micro-thromboembolic renal dysfunction as well as trigger microvascular obstruction and infarction. Idilman et al., found that a large number of patients with mild to moderate COVID-19 had perfusion deficits (PD) in their lungs and kidneys, which may be suggestive of the presence of systemic microangiopathy with microthrombosis (Acharya et al., 2020; Idilman et al., 2021). In addition to kidney damage, the other system affected by complications from COVID-19 infection is the digestive system and liver. A meta-analysis of thirty-one studies examining the incidence of gastrointestinal symptoms in 4682 patients found that diarrhea and anorexia were among the most significant gastrointestinal symptoms associated with COVID-19. In addition, it was observed that patients admitted to ICU or with high intensity were more likely to develop abdominal pain and increased hepatic inflammatory markers such as aspartate aminotransferase or alanine aminotransferase (Dong et al., 2021).

One of the other potential long-term complications of COVID-19, due to long-term persistence of viral particles in organs, is interaction with autophagy machinery (Habibzadeh et al., 2021). This interaction induces inhibition of autophagy flux, which potentially is involved in potentiation of cancer progression and metastasis and immune escape in COVID-19 survivors (Habibzadeh et al., 2021).

7. Summary

Prophylaxis with SARS-CoV-2 vaccines is the most effective modality to prevent and eliminate COVID-19. COVID-19 symptomatology varies between patients and treatment needs to be tailored towards specific symptoms, as there are many critical points of disease progression that can be targeted. The development and progression of COVID-19 can be viewed as a multi-stage process (Fig. 5) that begins with the exposure to the virus, followed by the SARS-CoV-2 infection phase, and then the initiation of COVID-19 disease processes such as early infection, pulmonary phase and inflammatory storm phase. Pharmacological...
interventions at any of these stages are required in order to minimize the effects. Moreover, the timing of the intervention is critical. Currently, behavioral modifications are necessary to prevent exposure to SARS-CoV-2, and public health guidelines for social distancing, masking, and hygiene are recommended. Rigorously tested pharmacological strategies to reduce and block SARS-CoV-2 virus infection and COVID-19 development are the subject of thousands of trials around the world to reduce and contain the global epidemic. In the latter respect, Pfizer Inc., recently announced that its investigational novel COVID-19 oral antiviral candidate, PAXLOVID™ (PF-07321332), significantly reduced hospitalization and death, based on an interim analysis of the phase 2/3 EPIC-HR (Evaluation of Protease Inhibition for COVID-19 in High-Risk Patients) randomized, double-blind study of non-hospitalized adult patients with COVID-19, who are at high risk of progressing to severe illness. The scheduled interim analysis demonstrated an 89 % reduction in risk of COVID-19-related hospitalization or death from any cause compared to placebo in patients treated within three days of symptom onset (primary endpoint); 0.8 % of patients who received PAXLOVID™ were hospitalized through Day 28 following randomization (3/389 hospitalized with no deaths), compared to 7.0 % of patients who received placebo and were hospitalized or died (27/385 hospitalized with 7 subsequent deaths). The statistical significance of these results was high (p < 0.0001). Similar reductions in COVID-19-related hospitalization or death were observed in patients treated within five days of symptom onset; 1.0 % of patients who received PAXLOVID™ were hospitalized through Day 28 following randomization (6/607 hospitalized, with no deaths), compared to 6.7 % of patients who received a placebo (41/612 hospitalized with 10 subsequent deaths), with high statistical significance (p < 0.0001). In the overall study population through Day 28, no deaths were reported in patients who received PAXLOVID™ as compared to 10 deaths (1.6 %) in patients who received placebo.

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