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# Novel therapeutic approaches for treatment of COVID-19

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#### **Abstract**

To date, there is no licensed treatment or approved vaccine to combat the coronavirus disease of 2019 (COVID-19), and the number of new cases and mortality multiplies every day. Therefore, it is essential to develop an effective treatment strategy to control the virus spread and prevent the disease. Here, we summarized the therapeutic approaches that are used to treat this infection. Although it seems that antiviral drugs are effective in improving clinical manifestation, there is no definite treatment protocol. Lymphocytopenia, excessive inflammation, and cytokine storm followed by acute respiratory distress syndrome are still unsolved issues causing the severity of this disease. Therefore, immune response modulation and inflammation management can be considered as an essential step. There is no doubt that more studies are required to clarify immunopathogenesis and immune response; however, new therapeutic approaches including mesenchymal stromal cell and immune cell therapy showed inspiring results.

**Keywords** COVID-19 · Coronavirus · Therapeutic approaches · Severe acute respiratory syndrome · Acute respiratory distress syndrome · Cell therapy

### Introduction

Corona viruses are a large family of enveloped, positive-sense RNA viruses that have the largest RNA genome (rage from 26 to 32 kb) [1, 2]. Several coronavirus epidemics such as Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) and Middle East Respiratory Syndrome Coronavirus (MERS-CoV) have occurred during the past years [2, 3]. At the end

of 2019, a novel coronavirus infection named coronavirus disease of 2019 (COVID-19) was first identified in Wuhan, China [4–7]. Due to the fast transmission, it is reported in almost all countries and has become a global crisis. Therefore, COVID-19 pandemic becomes an international threat for human health and economy [1, 8].

COVID-19 spreads fast among people and the mortality rate is controversial; however, it was less than 2% in some

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studies. The main manifestations of the disease include fever, dry caught, headache, shortness of breath, pneumonia, acute respiratory distress syndrome (ARDS), septic shock, and even death [3, 11, 12].

The genome sequencing of this virus revealed more than 82% identity to SARS-CoV [9]. Analysis indicated that the binding affinity of virus S protein to the angiotensin-converting enzyme 2 (ACE2) receptor on human alveolar epithelial cells is higher compared with the SARS-CoV [10].

Since SARS-CoV-2 is a new pathogen, little is known about it. Moreover, there is no licensed treatment or approved vaccine and the number of new cases and mortality multiplies daily [8]. Therefore, it is vital to develop an effective treatment strategy to control the virus spread and prevent the disease [1, 11].

## **Immunopathogenesis of COVID-19**

Although the pathogenesis of this disease has not been fully understood, it seems that the host immune responses play an important role. Aberrant host immune response causes lung tissue damage, reduced lung capacity, and finally respiratory failure [4]. Studies indicated that dendritic cells (DCs) and macrophages are playing crucial role in innate immune responses [12, 13]. These cells produce inflammatory cytokines and chemokines including TNF- $\alpha$ , IL-12, IL-6, IFN $\gamma$ , and IL-8, and monocyte chemoattractant protein (MCP-1), macrophage colony-stimulating factor (GM-CSF), and granulocyte-colony-stimulating factor (G-CSF) [6, 14]. These inflammatory responses may lead to systemic inflammation [6, 7, 13, 14].

Adoptive immunity plays a major role in viral infections [15]. Cytotoxic T cells (CD8+ T cells) are the main T cell subsets that destroy infected cells [16]. Therefore, the number of these cells is one of the major factors for clearance of the viral infection [17, 18]. Preliminarily, it was indicated that the number of total T cells, CD4+ and CD8+ T cells, reduced significantly in COVID-19 patients. This decrease was more intensive in ICU admitted patients compared with that in non-ICU admitted individuals [19]. It is also reported that T cell clonal exhaustion occurred during the infection and the expression of certain T cell surface markers like PD1 (programmed cell death protein 1) and TIM-3 (T cell immunoglobulin and mucin domain-containing molecule-3) markedly increased [19, 20]. The cytokine storm occurred in response to SARS-CoV-2 infection that led to increased expression of NKG2A (natural-killer group 2, member A) on cytotoxic T cells (CTLs) and NK cells. This upregulation suppressed CTL and NK function and cytokine secretion [19, 21, 22]. It is suggested that inflammatory cytokines, TNF- $\alpha$  and IL-6, mainly originated from apoptotic monocytes (CD14+CD16+ ) and macrophages and induced T CD4+ and T CD8+ cells [19, 23]. These excessive inflammatory responses might result in respiratory system pathology and dysfunction [23].

Perhaps it takes many years to achieve a specific and effective therapeutic protocol, efficient vaccine, or suitable medicine for the treatment of COVID-19. There is a wide range of existing and current treatment strategies categorized into antiviral drugs, immunotherapy protocols including convalescent serum and monoclonal antibodies, cell-based therapies, hydroxychloroquine, Chinese medicine, and steroids (just for patients who suffer from ARDS) [24]. A schematic figure (Fig. 1) summarized the novel therapeutic approaches in treatment of COVID-19 patients. Moreover, there are a growing number of clinical trials registered for the treatment of COVID-19 (Table 1).

## **Passive immunotherapy**

#### Convalescent serum

Antibody injection to the patients and susceptible people provides rapid immunity to treat or prevent the disease [25–27]. Past experiences from SARS and MERS viral infections indicated that passive immunotherapy could be a potential treatment strategy for the patients [27–29]. It is considered that passive immunotherapy could also be beneficial in SARS-CoV-2 infection [30]. Extracting neutralizing antibodies from recovered individuals with high titer of antibodies in sera and transfusion to infected patient could deactivate the virus. However, neutralization activity of these antibodies is not fully understood. It has been showed that neutralizing antibodies are not long lasting and only the recently recovered patients are suitable candidates [31]. It has also been reported that the neutralizing antibody titers vary among the patients and elderly patients had higher antibody titer compared with young recovered individuals [32]. It is supposed that convalescent serum administration may induce phagocytosis and antibody-mediated cellular cytotoxicity [25, 27]. One important implications for using convalescent serum is the risk for antibody-dependent enhancement (ADE) [33]. It is supposed that these neutralizing antibodies may enhance other viral infections [34]. Another major limitation of this strategy is donor shortage. However, by increasing the number of recovered individuals, this limitation would be solved [25].

## Monoclonal antibodies

It has been shown that monoclonal antibodies (mAbs) could be an effective tool for the treatment of viral infectious diseases [35–37]. Different techniques have been used to develop mAbs including phage display library, hybridoma, single B cell isolation, and transgenic mice [37]. Various monoclonal antibodies developed against MERS and SARS infections include m396, 80R, and S3.1 against SARS and LCA60 for the



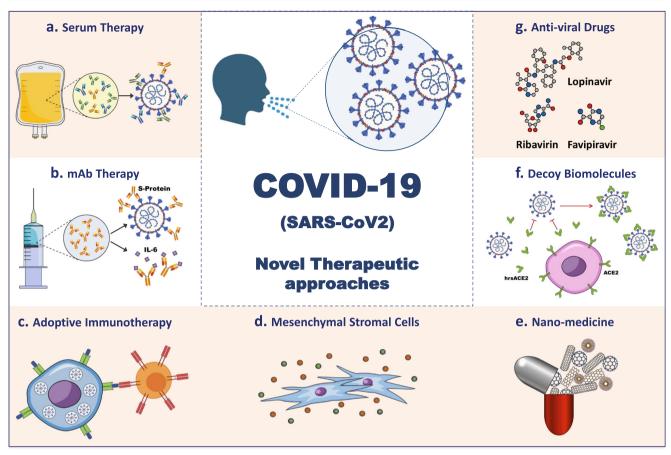


Fig. 1 Novel therapeutic strategies for treatment of clinical complications of COVID-19. (a) Passive immunotherapy using serum of immunized individuals. (b) Monoclonal antibodies can directly target virus particles. Also, mAbs can be used to eliminate crucial cytokines in progression of inflammation, e.g., IL-6. (c) The effector cells in adoptive immunotherapy can be used to specifically target infected cells and enhance anti-viral

immune responses. (d) Mesenchymal stromal cells are key players in immunomodulation of severe immune response. The paracrine effect of these cells can tune down immune reaction. (e) Using nanostructures for drug delivery in different medical applications. (f) Recombinant ACE2 receptor protein in soluble form attaches to viral particles. (g) Antiviral medicines can prohibit viral proliferation

treatment of MERS disease [29, 37–41]. These mAbs limited virus replication and facilitated lung recovery in animal models [42–44]. S protein is also the most immunogenic determinant of coronaviruses [40]. Several mAbs target receptor-binding domain (RBD) in the virus spike (S) glycoprotein and inhibit the virus to invade the host cell [9]. It is reported that mAbs against SARS-CoV-1 could cross react with SARS-CoV-2 [45]. It is indicated in the preprint that mAb 1A9 that targets the S protein of SARS-CoV-1 could interact with SARS-CoV-2 [46].

Tocilizumab is a humanized monoclonal antibody against IL-6 receptor cytokine. Tocilizumab targets both membrane and soluble-bound IL-6 receptors. This mAb is used for the treatment of COVID-19 patients [47]. It is shown that the IL-6 level is considerably high in severe COVID-19 cases. Treatment of 21 severe COVID-19 cases with tocilizumab indicated that using this monoclonal antibody is an effective treatment and well tolerated in these patients. In the preprinted study, tocilizumab caused body temperature and CRP returned to the normal levels and improved lung function

[48]. There are also many registered clinical trials on efficiency and safety of tocilizumab for the treatment of COVID-19 (Table 1).

VEGF is one of the main mediators of vascular permeability and progression of ARDS. Bevacizumab is a humanized monoclonal antibody that targets VEGF and employed in a phase II/III clinical trial for the treatment of COVID-19 patients (NCT04275414).

As described earlier, during the SARS-CoV-2 infection, exhaustion of T and NK cells happens. In order to restore these cells, using monoclonal antibodies to block the PD-1/PD-L1 and TIM3 pathways may have beneficial therapeutic effects as well [49].

## **Kinase inhibitors**

It is suggested that an inhibitor of Janus kinase (JAK) called baricitinib could prevent the entry of SARS-CoV-2 into the host cells and also inhibit the inflammation [50, 51]. Cyclin Gassociated kinase (GAK) and AP2-associated protein kinase 1



Phase II/III Phase II/III Phase II/III Phase II/III Phase II/III Phase II/III Phase II Phase III Phase I Phase III Phase III Phase III Phase II Phase III Phase II Phase II Phase II Phase III Phase II Phase I Phase II Phase I Phase II Phase II Phase II NA NA ΑN Enrolling by invitation Recruitment status Not yet recruiting Available Available Example of clinical trials registered at ClinicalTrials.gov USA, Spain, UK Malaysia Country Denmark Sweden Mexico Sweden France France France China Russia France China China China Spain USA USA Italy ítaly JSA JSA JSA JSA USA JSA JSA USA ítaly JSA JSA NCT04327349 NCT04372979 NCT04343755 NCT04363034 NCT04292340 NCT04322773 NCT04317092 NCT04331795 NCT04345445 NCT04315298 NCT04351243 NCT04275414 NCT04288713 NCT04362813 NCT04348448 NCT04380519 NCT04351152 NCT04369469 NCT04343144 NCT04275245 NCT04333355 NCT04264858 NCT04346589 NCT04377659 NCT04324073 NCT04371367 NCT04329650 NCT04324021 NCT04381052 NCT04376684 NCT04324021 NCT04343651 NCT04380961 CT number Table 1 Variety of therapeutic agents used in clinical trials registered to treat COVID-19 Immunoglobulins obtained with DFPP Immunoglobulin of cured patients nactivated convalescent plasma Convalescent plasma Convalescent serum Therapeutic agent Clazakizumab Canakinumab Bevacizumab Emapalumab Ravulizumab Avdoralimab Emapalumab Meplazumab **Tocilizumab** Gimsilumab Eculizumab Olokizumab Lenzilumab Leronlimab Siltuximab Nivolumab Sirukumab Sarilumab Otilimab Monoclonal antibodies Group Serum



Table 1 (continued)

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Acalabrutinib         NCT04346147         Spain         Recruiting           Acalabrutinib         NCT04346199         Spain         Not yet recruiting           Duvelisib         NCT04330688         USA         Not yet recruiting           Tofacitinib         NCT04332042         Italy         Not yet recruiting           Imatinib         NCT04346147         Spain         Recruiting           NCT04375397         USA         Not yet recruiting           Nintedanib         NCT04338802         China         Not yet recruiting           Fingolimod         NCT0438058         China         Recruiting           Sirolimus         NCT04341675         USA         Recruiting		Baricitinib	NCT04340232	USA	Not yet recruiting	Phase II/III
Acalabrutinib         NCT04346147         Spain         Recruiting           Duvelisib         NCT04380688         USA         Not yet recruiting           Tofacitinib         NCT04332042         Italy         Not yet recruiting           Imatinib         NCT04346147         Spain         Recruiting           NCT04375397         USA         Not yet recruiting           Nintedanib         NCT04375397         USA         Not yet recruiting           Nintedanib         NCT04338802         China         Not yet recruiting           NCT04280588         China         Recruiting           NCT04341675         USA         Recruiting			NCT04358614	Italy	Completed	Phase II/III
Acalabrutinib NCT04346199 Spain Not yet recruiting NCT04372602 USA Not yet recruiting NCT04372602 USA Not yet recruiting NCT04372602 USA Not yet recruiting NCT04346147 Spain NCT04346147 Spain NCT04375397 USA Not yet recruiting NCT04375397 USA Not yet recruiting NCT04338802 China Not yet recruiting NCT04280588 China Recruiting NCT04280588 China Recruiting NCT04341675 USA Recruiting Recruiting NCT04341675 USA Recruiting			NCT04346147	Spain	Recruiting	Phase II
Duvelisib         NCT04372602         USA         Not yet recruiting           Tofacitinib         NCT04332042         Italy         Not yet recruiting           Imatinib         NCT04346147         Spain         Recruiting           Not yet recruiting         NCT04345397         USA         Not yet recruiting           Nintedanib         NCT04338802         China         Not yet recruiting           Fingolimod         NCT04280588         China         Recruiting           Sirolimus         NCT04341675         USA         Recruiting		Acalabrutinib	NCT04346199	Spain	Not yet recruiting	Phase II
DuvelisibNCT04372602USANot yet recruitingTofacitinibNCT04346147SpainRecruitingImatinibNCT04375397USANot yet recruitingNintedanibNCT04338802ChinaNot yet recruitingFingolimodNCT04280588ChinaRecruitingSirolimusNCT04341675USARecruiting			NCT04380688	USA	Not yet recruiting	Phase II
Tofacitinib         NCT04332042         Italy         Not yet recruiting           Imatinib         NCT04375397         USA         Not yet recruiting           Ibrutinib         NCT04375397         USA         Not yet recruiting           Nintedanib         NCT04338802         China         Not yet recruiting           Fingolimod         NCT04280588         China         Recruiting           NCT04341675         USA         Recruiting		Duvelisib	NCT04372602	USA	Not yet recruiting	Phase II
ImatinibNCT04346147SpainRecruitingIbrutinibNCT04375397USANot yet recruitingNintedanibNCT04338802ChinaNot yet recruitingFingolimodNCT04280588ChinaRecruitingSirolimusNCT04341675USARecruiting		Tofacitinib	NCT04332042	Italy	Not yet recruiting	Phase II
Ibrutinib NCT04378397 USA Nintedanib NCT04338802 China Not yet recruiting NCT04280588 China Recruiting NCT04280588 China Recruiting		Imatinib	NCT04346147	Spain	Recruiting	Phase II
NintedanibNCT04338802ChinaNot yet recruitingFingolimodNCT04280588ChinaRecruitingSirolimusNCT04341675USARecruiting		Ibrutinib	NCT04375397	USA	Not yet recruiting	Phase II
Fingolimod NCT04280588 China Recruiting NCT04341675 USA Recruiting		Nintedanib	NCT04338802	China	Not yet recruiting	Phase II
NCT04341675 USA Recruiting	Other immunosuppressors	Fingolimod	NCT04280588	China	Recruiting	Phase II
		Sirolimus	NCT04341675	USA	Recruiting	Phase II



Champing         Enumble of chinical finish trighstered at Clinical finish registered at Clini						
CT number         CT number         CC number         Recruitment status           Leanlidounide         NCT04341088         Spain         Recruiting           Methorexade         NCT043401088         Spain         Not yet recruiting           Methorexade         NCT04320899         USA         Recruiting           NCT04320810         LSA         Recruiting           NCT04340648         Table         Available           NCT04340649         LBA         Available           NCT04340649         LBA         Activity on tercruiting           NCT04340649         LBA         Available           NCT04340641         Egypt         Available           NCT04340645         LBA         Available           NCT04340649         Chan         Recruiting           NCT04340641         Egypt         Available           Damospecir, inconserve         NCT04340647         China         Recruiting           NCT04340647         Spain         Recruiting         Recruiting           Number of trionwer         NCT04340647         Spain         Recruiting           Number of trionwer         NCT04340647         Spain         Recruiting           Number of trionwer         NCT04340647         China<	Group	Therapeutic agent	Example of clinic	cal trials registered at ClinicalTria	ls.gov	
Parcolimas   Pacolimas   NCT0434108   Spain   Recruiting     McHortecate   NCT0435246   Brazil   Not yet recruiting     Remaissivi			CT number	Country	Recruitment status	Phase
Methotrewate   NCT04359665   Spain   Not yet recruiting		Tacrolimus	NCT04341038	Spain	Recruiting	Phase III
Remdesive         NCT0435546         Bazal         NO yet recruting           NCT04366725         France         Available         Recruting           NCT04366725         France         Available         Recruting           NCT04366725         France         Available         Available           NCT0436672         Span         Recruting         Available           NCT0434662         Unificonoir         NCT0434664         Inaly         Available           Abldel Apdecabloride vs. ceclamivir         NCT0434692         Inal         Recruting           NCT0434664         Inal         Recruting         Recruting           NCT0434664         Inal         Recruting         Recruting           NCT0434640         Rome         Recruting         Recruting           NCT0434640         Spain         Recruting         Recruting </td <td></td> <td>Lenalidomide</td> <td>NCT04361643</td> <td>Spain</td> <td>Not yet recruiting</td> <td>Phase IV</td>		Lenalidomide	NCT04361643	Spain	Not yet recruiting	Phase IV
Remdesivir         NCT04292890         USA         Recruiting           NCT04286704         L85A         Recruiting           NCT043466724         Bay         Available           NCT04346724         L85A         NO yet recruiting           NCT0434678         L85A         NO yet recruiting           NCT0434678         L85P         NO yet recruiting           NCT0434678         Lapina virticonavir         NCT04336690         Canada         Recruiting           NCT04336680         Canada         Recruiting         Recruiting           NCT04336681         NCT04336690         Canada         Recruiting           NCT04336680         Canada         Recruiting         Recruiting           NCT0434681         Spain         Recruiting         Recruiting           NCT0434681         NCT0434647         Spain         Recruiting           NCT0434681         NCT0434697         Recruiting         Recruiting           NTACO-duine         NCT0435667         China         Recruiting           NTACO-duine         NCT0432661         Canada         Recruiting           NTACO-duine         NCT0432661         Canada         Recruiting           NCT0434605         USA         NO yet recruiting		Methotrexate	NCT04352465	Brazil	Not yet recruiting	Phase I/II
Revipiravir         NCTQ4380705         USA         Recruiting           NCTQ434628         USA         Advisible           NCTQ434628         USA         Not yet recruiting           NCTQ434628         USA         Not yet recruiting           Abidol bydrochloride vs. osellamivir         NCTQ4349241         Egypt         Not yet recruiting           Asidol bydrochloride vs. osellamivir         NCTQ4340241         Egypt         Not yet recruiting           Asidol bydrochloride vs. osellamivir         NCTQ4320691         Korea         Recruiting by invitation           Asidol bydrochloride vs. osellamivir         NCTQ432041         Spain         Recruiting           NCTQ432045         Canada         Recruiting         Recruiting           NCTQ432045         China         Recruiting           Nurzole         NCTQ4324241         Spain         Recruiting           Nurzole         NCTQ432431         Korea         Not yet recruiting           Nurzole         NCTQ4324301         Brazil         Recruiting           Nurzole         NCTQ4324301         Strain         Not yet recruiting           Nurzole         NCTQ4324301         Strain         Not yet recruiting           Nurzole         NCTQ4324301         Not yet recruiting	Antivirals	Remdesivir	NCT04292899	USA	Recruiting	Phase III
NCT04365725         France         Available           NCT04365904         Italy         Available           NCT04365904         Italy         Available           Umifenovir         NCT04340241         Egypt         Not yet recuting           Abidol hydrochloride vs. osetlamivir         NCT04350641         Iran         Ecrutining           vs. lopinavirritonavir         NCT04350691         China         Recrutining           NCT0432607         China         Recrutining           NCT0432691         Spani         Recrutining           NCT0432691         Spani         Recrutining           NCT0432691         Spani         Recrutining           NCT0432691         China         Recrutining           NCT0432691         China         Recrutining           NCT0432661         China         Recrutining           NCT0432661         China         Recrutining           NCT0432661         China         Recrutining           NCT0434791         Roca         Recrutining           NCT0434791         Roca         Recrutining           NCT0434602         USA         Not yet recrutining           NCT0434602         USA         Not yet recrutining           NCT043			NCT04280705	USA	Recruiting	Phase III
Eavipinevir   NCT04346624   1845   Section   Not yet recruting			NCT04365725	France	Available	NA
Unificatorit         NCT0434628         USA         Not yet recruiting           Abidol hydrochloride vs. coeltamivir         NCT0435084         Ian         Brouling by invitation           vs. lopinavirritionavir         NCT04330600         Canada         Recruiting           vs. lopinavirritionavir         NCT04330600         Canada         Recruiting           NCT0433012         Kina         Recruiting           NCT04340503         Korea         Recruiting           NCT04345473         Spain         Recruiting           NCT04345473         Spain         Recruiting           NCT04345473         China         Recruiting           Virazole         NCT0434567         China         Recruiting           Virazole         NCT0434567         China         Recruiting           Ninezokamide         NCT0434567         China         Recruiting           Ninezokamide         NCT0434569         USA         Not yet recruiting           Ninezokamide         NCT0434560         USA         Not yet recruiting           Ninezokamide         NCT0434560         USA         Not yet recruiting           Ninezokamide         NCT0434620         USA         Recruiting           National         NCT0434620		Favipiravir	NCT04336904	Italy	Active, not recruiting	Phase III
OCTO434924           Egypt         Not yet recruiting           Abidol bydochloride vs. oselamivir         NCTO4359045         Inn         Eurolling by invitation           vs. bopinavirritonavir         NCTO435064         Inn         Eurolling by invitation           vs. bopinavirritonavir         NCTO435063         Canada         Recruiting           NCTO437693         Korea         Recruiting           NCTO4346147         Spain         Recruiting           NCTO4346147         Spain         Recruiting           NCTO43426252         France         Recruiting           NCTO432627         China         Recruiting           NCTO433667         China         Recruiting           NCTO43267         China         Recruiting           NCTO432661         Korea         Not yet recruiting           NCTO432661         Corea         Not yet recruiting           NCTO432961         Canada         Recruiting           NCTO432961         Canada         Not yet recruiting           NCTO432361         Canada         Not yet recruiting           NCTO432361         Canada         Not yet recruiting           NCTO432662         UsaA         Not yet recruiting           NCTO432662         China			NCT04346628	USA	Not yet recruiting	Phase II
Umifenovir         NCT04350684         Inan         Enrolling by invitation           vs. lopinavir/itonavir         NCT0435077         China         Recruiting           vs. lopinavir/itonavir         NCT04340690         Cranda         Recruiting           Danoprevir, ritonavir         NCT043407693         Korea         Recruiting           Danoprevir, ritonavir         NCT04349176         Brazil         Recruiting           NCT0434076         China         Recruiting           NCT0434507         Usha         Recruiting           NCT0434507         China         Recruiting           NCT0434507         China         Recruiting           NCT0434507         China         Recruiting           NCT04347915         Korea         Not yet recruiting           NCT0434507         Usha         Recruiting           NCT0434507         China         Not yet recruiting           NCT0434507         China			NCT04349241	Egypt	Not yet recruiting	Phase III
Abidol Pydrochloride vs. oseltamivir a NCT04255017 China Recruiting		Umifenovir	NCT04350684	Iran	Enrolling by invitation	Phase IV
vs. lopmaviritionavir         NCT04330600         Canada         Recruiting           NCT04340147         Spain         Recruiting           NCT04328285         France         Recruiting           Danoprevir, ritonavir         NCT0434257         China         Recruiting           Danoprevir, ritonavir         NCT0434257         China         Recruiting           Virazole         NCT0434574         China         Recruiting           Virazole         NCT0434840         Brazil         Recruiting           Nitazovanide         NCT0434840         Brazil         Not yet recruiting           Nitazovanide         NCT0434840         Brazil         Recruiting           NGT0434840         Brazil         Recruiting           NCT0434840         Brazil         Not yet recruiting           NCT0434861         Brazil         Not yet recruiting           Carrimycin         NCT04346632		Abidol hydrochloride vs. oseltamivir	NCT04255017	China	Recruiting	Phase IV
NCT0430647   Spain   NCT0430648   Grand   NCT0430649   Contained   NCT043064647   Spain   Recruiting   NCT04326284   France   Recruiting   NCT04326274   China   Recruiting   NCT04326374   China   Recruiting   NCT04326374   China   Recruiting   NCT04326410   Brazil   Recruiting   NCT0433680   USA   Not yet recruiting   NCT0433681   Israel   Not yet recruiting   NCT0433691   Israel   Not yet recruiting   NCT0434640   USA   Recruiting   NCT0434664   China   Not yet recruiting   NCT0438663   China   Not yet recruiting   NCT0438663   China   Not yet recruiting   NCT0438664   China   Not yet recruiting   NAMEZ   NOT yet recruiting   NCT0438668   China   Not yet recruiting   NAMEZ   NOT yet recruiting   NAMEZ   NOT yet recruiting   NOT yet recruiting   NAMEZ   NOT yet recruiting   NOT yet recruiting   NAMEZ   NOT yet recruiting   NOT yet		vs. lopinavii/ritonavii Loninavii/ritonavii	NCT04330690	Canada	Recmiting	Phase II
Calidesivir			NCT04307693	Korea	Pecruiting	Dhase II
NCTO4328285   France   Recruiting			NCT04346147	Snain	Recruiting	Dhase II
Classification   Classification   China   China   Recruiting			TO COCCO COLOR	J. J	rectuling F ::	I mase II
Galidesivir         NCT0389120         Brazil         Recruiting           Danoprevir, ritonavir         NCT04342276         China         Recruiting           Virazole         NCT04335677         USA         Not yet recruiting           Clevudine         NCT04348409         Brazil         Not yet recruiting           Nitazoxanide         NCT04348409         Brazil         Not yet recruiting           Hydroxychloroquine         NCT04339680         USA         Not yet recruiting           NCT04345691         Canada         Recruiting           NCT04345692         USA         Not yet recruiting           NCT04345691         Cermany         Not yet recruiting           NCT04345692         USA         Not yet recruiting           NCT04345632         USA         Not yet recruiting           NCT04345632         USA         Not yet recruiting           NCT04345632         China         Not yet recruiting           NCT04286503         China         Withdrawn           NCT04351364         China         Withdrawn           NCT04351364         China         Not yet recruiting           NCT04351364         China         Withdrawn           NCT04351364         China         Not yet recruiting			NCI 04328285	France	Recruiting	Phase III
Danoprevir, ritonavir         NCT04342276         China         Recruiting           Darumavir/cobkistat         NCT04252274         China         Recruiting           Virazole         NCT04347915         Korea         Not yet recruiting           Clevudine         NCT04348409         Brazil         Not yet recruiting           Nitazoxanide         NCT04348409         Brazil         Not yet recruiting           Hydroxychloroquine         NCT04359680         USA         Not yet recruiting           NCT043361         Camada         Recruiting           NCT04345692         USA         Not yet recruiting           NCT04345692         USA         Recruiting           NCT04345692         USA         Recruiting           NCT04345692         USA         Recruiting           NCT04350107         USA         Not yet recruiting           NCT0438603         China         Not yet recruiting           rhACE2, rhACE2         NCT04287686         China         Not yet recruiting           rhACE2         NCT0437696         China         Not yet recruiting           NCT0437604         Reppt         Not yet recruiting		Galidesivir	NCT03891420	Brazil	Recruiting	Phase I
Darumavit/cobicistat         NCT04252274         China         Recruiting           Virazole         NCT04356677         USA         Not yet recruiting           Clevudine         NCT04348409         Brazil         Not yet recruiting           Nitazoxanide         NCT04348409         Brazil         Recruiting           Hydroxychloroquine         NCT04329611         Canada         Not yet recruiting           NCT04329611         Canada         Recruiting           NCT04329611         Canada         Recruiting           NCT04329611         Canada         Not yet recruiting           NCT04329611         Canada         Not yet recruiting           NCT0433202         USA         Recruiting           NCT04362332         Netherlands         Recruiting           NCT04362332         Netherlands         Not yet recruiting           NCT0436503         China         Not yet recruiting           Austria, Denmark, Germany         Not yet recruiting           rbACE2, rhACE2         NCT04285696         China         Withdrawn           NCT04335136         Austria, Denmark, Germany         Not yet recruiting           RbACE2         NCT042875046         Egypt         Not yet recruiting		Danoprevir, ritonavir	NCT04345276	China	Recruiting	Phase IV
Virazole         NCT04356677         USA         Not yet recruiting           Clevudine         NCT043491915         Korea         Not yet recruiting           Nitazoxanide         NCT04348409         Brazil         Not yet recruiting           Hydroxychloroquine         NCT04329681         Canada         Not yet recruiting           NCT04323631         Israel         Not yet recruiting           NCT04345692         USA         Not yet recruiting           NCT04345692         China         Not yet recruiting           Carrimycin         NCT04286503         China         Not yet recruiting           nhACE2, rhACE2         NCT04287686         China         Not yet recruiting           hAACE2         NCT04287686         China         Not yet recruiting           NCT04375046         Egypt         Not yet recruiting		Darunavir/cobicistat	NCT04252274	China	Recruiting	Phase III
Clevudine         NCT04348409         Brazil         Not yet recruiting           Nitazoxanide         NCT04348409         Brazil         Recruiting           Hydroxychloroquine         NCT04329611         Canada         Not yet recruiting           NCT0432461         Canada         Recruiting           NCT04325611         Israel         Not yet recruiting           NCT04345622         USA         Recruiting           NCT04345632         USA         Recruiting           NCT0435107         USA         Not yet recruiting           NCT0435107         USA         Not yet recruiting           NCT0435107         USA         Not yet recruiting           NCT043660         China         Not yet recruiting           NCT04286503         China         Withdrawn           NCT04335136         Austria, Denmark, German         Withdrawn           NCT04335136         Egypt         Not yet recruiting		Virazole	NCT04356677	USA	Not yet recruiting	Phase I
Nitazoxanide         NCT04348409         Brazil         Recruiting           Hydroxychloroquine         NCT04329611         Canada         Not yet recruiting           NCT04322611         Israel         Not yet recruiting           NCT04345621         USA         Not yet recruiting           NCT04345692         USA         Recruiting           NCT04362332         Netherlands         Recruiting           NCT0436232         Netherlands         Not yet recruiting           NCT0436232         NCT0436232         Netherlands         Not yet recruiting           NCT0436232         NCT04371952         France         Not yet recruiting           NCT04286503         China         Not yet recruiting           NCT04287686         China         Withdrawn           NCT04335136         Austria, Denmark, Germany         Recruiting           rbACE2         NCT04335136         Austria, Denmark, Germany         Not yet recruiting		Clevudine	NCT04347915	Korea	Not yet recruiting	Phase II
Hydroxychloroquine         NCT04329611         Canada         Not yet recruiting           NCT04323631         Israel         Not yet recruiting           NCT04345692         USA         Not yet recruiting           NCT04345692         USA         Recruiting           NCT04345692         USA         Recruiting           NCT04345692         USA         Not yet recruiting           NCT04323107         USA         Not yet recruiting           NCT04371952         France         Not yet recruiting           NCT04286503         China         Not yet recruiting           NCT0428660         China         Withdrawn           NCT04287686         China         Withdrawn           NCT04287687         China         Withdrawn           NCT04287688         China         Not yet recruiting		Nitazoxanide	NCT04348409	Brazil	Recruiting	NA
Hydroxychloroquine         NCT04329611         Canada         Recruiting           NCT0432631         Israel         Not yet recruiting           NCT0434694         Germany         Not yet recruiting           NCT04345692         USA         Recruiting           NCT04345693         USA         Recruiting           NCT04332107         USA         Not yet recruiting           NCT0433190         China         Not yet recruiting           NCT04286503         China         Not yet recruiting           NCT04286503         China         Withdrawn           NCT0428660         China         Withdrawn           NO yet recruiting         Not yet recruiting			NCT04359680	USA	Not yet recruiting	Phase III
NCT0432631         Israel         Not yet recruiting           NCT04340544         Germany         Not yet recruiting           NCT04345692         USA         Recruiting           NCT0436233         Netherlands         Recruiting           NCT04332107         USA         Not yet recruiting           NCT04331952         France         Not yet recruiting           NCT04286503         China         Not yet recruiting           NCT04287686         China         Withdrawn           NCT04335136         Austria, Denmark, Germany         Recruiting           NCT04335136         Egypt         Not yet recruiting		Hydroxychloroquine	NCT04329611	Canada	Recruiting	Phase III
NCT04340544         Germany         Not yet recruiting           NCT04345692         USA         Recruiting           NCT04362332         Netherlands         Recruiting           NCT04332107         USA         Not yet recruiting           Doxycycline         NCT04371952         France         Not yet recruiting           NCT04286503         China         Not yet recruiting           NCT04287686         China         Withdrawn           NCT04335136         Austria, Denmark, Germany         Recruiting           PACE2         NCT04335136         Egypt         Not yet recruiting			NCT04323631	Israel	Not yet recruiting	Early Phase I
NCT04345692         USA         Recruiting           NCT0436233         Netherlands         Recruiting           Doxycycline         NCT04332107         USA         Not yet recruiting           Carrimycin         NCT04286503         China         Not yet recruiting           nolecules         rhACE2, rhACE2         NCT04287686         China         Withdrawn           NCT0438135136         Austria, Denmark, Germany         Recruiting           rbACE2         NCT04375046         Egypt         Not yet recruiting			NCT04340544	Germany	Not yet recruiting	Phase III
NCT0436232 Netherlands Recruiting NCT04332107 USA Not yet recruiting NCT04332107 USA Not yet recruiting NCT04371952 France Not yet recruiting NCT04286503 China Not yet recruiting NCT04286503 China Withdrawn NCT04287686 China Withdrawn NCT04335136 Austria, Denmark, Germany Recruiting NCT04335136 Austria, Denmark, Germany Recruiting NCT04335136 Egypt Not yet recruiting			NCT04345692	USA	Recruiting	Phase III
Azithromycin Doxycycline  Carrimycin nolecules  rhACE2, rhACE2  rbACE2  rbACE2  Austria, Denmark, Germany NCT04335136  NCT04335136  NCT0433504  NCT04335136  NCT0433504  NCT0433504  NCT0433504  NCT0433504  NCT0433504  NCT0433504  NOT yet recruiting			NCT04362332	Netherlands	Recruiting	Phase IV
Doxycycline NCT04371952 France Not yet recruiting Carrimycin rhACE2, rhACE2 RACE2, rhACE2 RACE2, rhACE2 RACE2, rhACE2 RACE2, rhACE2 RACE2, rhACE2 RACE2 RACE2 RACE35136 RASTINA Recruiting Recruiting Recruiting Recruiting Recruiting RACE2 RACE2 RACE35136 RASTINA RACE3 RACE35136 RASTINA RACE3 RACE35136 RASTINA RACE35136 RASTINA RACE35136	Antibiotics	Azithromycin	NCT04332107	USA	Not yet recruiting	Phase III
Cartimycin NCT04286503 China Not yet recruiting nCT04287686 China Withdrawn NCT04335136 Austria, Denmark, Germany Recruiting NCT04335136 Austria, Denmark, Germany Recruiting NCT04375046 Egypt Not yet recruiting		Doxycycline	NCT04371952	France	Not yet recruiting	Phase III
rhACE2, rhACE2 NCT04287686 China Withdrawn NCT04335136 Austria, Denmark, Germany Recruiting rbACE2 NCT04375046 Egypt Not yet recruiting		Carrimycin	NCT04286503	China	Not yet recruiting	Phase IV
NCT04335136 Austria, Denmark, Germany Recruiting NCT04375046 Egypt Not yet recruiting	Decoy biomolecules	rhACE2, rhACE2	NCT04287686	China	Withdrawn	NA
NCT04375046 Egypt Not yet recruiting			NCT04335136	Austria, Denmark, Germany	Recruiting	Phase II
		rbACE2	NCT04375046	Egypt	Not yet recruiting	Phase I



Table 1 (continued)

Compy         Descriptions         Post Colinical Units registered at Clinical Units registered units registered at Clinical Units registered at Clinical Units registered at Clinical Units registered units registered at Clinical Units registered units registered at Clinical Units registered u	Table 1 (continued)					
PUL-042. PUL-042         NCT04313927         USA         Not yet recuting           Rhar-pGSN         NCT04313927         USA         Not yet recuting           Peidkenessen         NCT04312997         USA         Not yet recuting           Peidkenessen         NCT0431297         USA         Not yet recuting           Peidkenessen         NCT04356650         USA         Not yet recuting           Ramipell         NCT04356650         USA         Not yet recuting           Loeartan         NCT04356651         USA         Recruting           Cardissphere-derived cells         NCT04360551         USA         Not yet recruting           Denial pulp mesenchymal stem cells         NCT04360551         USA         Not yet recruting           MSC         NCT04360551         USA         Not yet recruting           MSC         NCT04360518         Spain         Not yet recruting           MSC         NCT04360521         China         Not yet recruting           MSC         NCT0436638         China         Not yet recruting           MSC         NCT04345661         Spain         Not yet recruting           NCT0434568         China         Not yet recruting           NCT0434568         China         Not yet recruti	Group	Therapeutic agent	Example of clini -	cal trials registered at ClinicalT	rials.gov	
PUL-042, PUL-042         NCT04313973         USA         Not yet recruting           Rhu-pGSN         NCT04358405         USA         Not yet recruting           Picilatenoson         NCT04331429         USA         Not yet recruting           Valsartan         NCT0433475         USA         Not yet recruting           Valsartan         NCT0433375         USA         Not yet recruting           Valsartan         NCT0433375         Not pat recruting         Not yet recruting           Cardiosphere-derived cells         NCT0433375         USA         Available           Dental pulp nesenchymal sem cells         NCT0433242         China         Not yet recruting           MSC         NCT0433259         China         Not yet recruting           MSC         NCT0433243         China         Not yet recruting           MSC         NCT04322519         China         Not yet recruting           MSC         NCT04322518         China         Not yet recruting           NGC         NCT04323363         Spain         Not yet recruting           NGC         NCT043234364         China         Not yet recruting           NGC         NCT04343666         China         Not yet recruting           NGC         NGC			CT number	Country	Recruitment status	Phase
Rin-JGSN         NCT04312997         USA         Not yet recruting           Picificanoson         NCT04333472         Israel         Not yet recruting           Ramipril         NCT04333472         Israel         Not yet recruting           Losartan         NCT0433378         Netherlands         Recruting           Losartan         NCT0433378         Netherlands         Recruting           Losartan         NCT0433378         Ageatina         Recruting           NCT0433378         USA         Recruting           NCT0433379         USA         Recruting           NCT0433379         USA         Recruting           NCT0433379         USA         Recruting           NCT0430259         China         Not yet recruting           NCT0430259         China         Not yet recruting           MSC         NCT0430259         China         Not yet recruting           NCT04325018         China         Not yet recruting           NCT0435032         Spain         Not yet recruting           NCT0435032         Spain         Not yet recruting           NCT04366329         China         Not yet recruting           NCT04366021         USA         Not yet recruting		PUL-042, PUL-042	NCT04313023	USA	Not yet recruiting	Phase II
Rhu-pGSN         NCT04358406         USA         Not yet recruting           Ramipul         NCT043360505         USA         Not yet recruting           Valsaran         NCT04335786         Netherlands         Recruting           Losurtan         NCT04335736         Agentina         Recruting           Losurtan         NCT043360531         USA         Recruting           Dental pulp messendymal stem cells         NCT04302519         China         Not yet recruting           MSC         Cacdisaphere-derived cells         NCT0430254         China         Not yet recruting           MSC         Cacosomes         NCT0430254         China         Not yet recruting           MSC         Cacosomes         NCT04302518         China         Not yet recruting           MSC         NCT04302518         China         Not yet recruting           MSC         NCT04302518         China         Not yet recruting           MSC         NCT04352803         USA         Not yet recruting           MSC         NCT04352803         USA         Not yet recruting           NCT04352804         NGT04352803         China         Not yet recruting           NGC         NCT04352504         China         Not yet recruting			NCT04312997	USA	Not yet recruiting	Phase II
Picifienoson         NCT0433372         Israel         Not yet recruiting           Vakartan         NCT0433578         Neherlands         Recruiting           Losartan         NCT0433578         Agenita         Recruiting           Losartan         NCT0433578         LiSA         Not yet recruiting           Cardissphere-derived cells         NCT0435393         Agenita         Recruiting           Dental pulp mesenchymal stem cells         NCT0430251         China         Not yet recruiting           MSC         NCT0430251         China         Not yet recruiting           MSC         NCT0430251         China         Not yet recruiting           MSC         NCT0430530         China         Not yet recruiting           MSC         NCT0436192         USA         Not yet recruiting           NCT0436192         USA         Not yet recruiting           NCT04366192         USA         Not yet recruiting           NCT043466192         USA         Not yet recruiting           NCT043466192         USA         Not yet recruiting           NCT04346610         USA         Not yet recruiting           NCT04346610         USA         Not yet recruiting           NCT04346610         USA         Recruiting<		Rhu-pGSN	NCT04358406	USA	Not yet recruiting	Phase II
Ramipril         NCT04356050         USA         Not yet recruiting           Usharan         NCT04335123         USA         Recruiting           Losartan         NCT0433523         USA         Recruiting           Tehnisartan         NCT0433534         USA         Recruiting           Cardiosphere-derived cells         NCT04336551         USA         Available           Dental pulp inesenchymal stem cells         NCT0433624         China         Not yet recruiting           MSC         NCT0435624         China         Recruiting           MSC         NCT0425118         China         Recruiting           MSC         NCT0436192         Spain         Not yet recruiting           AD MSC         NCT04456192         Spain         Not yet recruiting           NCT04362189         USA         Not yet recruiting           NCT04352803         USA         Not yet recruiting           NCT04363280         USA         Recruiting           NCT04352803         USA         Recruiting           NCT04363280         China         Not yet recruiting           NCT04353640         China         Recruiting           NCT04366271         Spain         Not yet recruiting           NCT04366271		Piclidenoson	NCT04333472	Israel	Not yet recruiting	Phase II
Valsartan         NCT04335780         Netherlands         Recruting           Losartan         NCT04335793         Agentaa         Recruting           Telmisartan         NCT04335936         Agentaa         Recruting           Ocardisephere-derived cells         NCT0433834         USA         Available           Dental pulp mesendymal stem cells         NCT0433824         China         Not yet recruting           MSC         NCT043218         China         Not yet recruting           NCT0432238         USA         Not yet recruting           NCT04345280         USA         Not yet recruting           NCT04345368         USA         Not yet recruting           NCT04345369         USA         Not yet recruting           NCT04345601         USA         Not yet recruting           NCT04345602         China         Recruting           NCT04353366         China         Recruting           NCT04354566         China         Not yet recruting           NCT0436086	ACE inhibitors and AR blockers	Ramipril	NCT04366050	USA	Not yet recruiting	Phase II
Losartun         NCT04335123         USA         Recruting           Tehnisartun         NCT04360551         LQA         NO yet recruting           Cardiosphere-derived cells         NCT04302519         China         Not yet recruting           Denal pulp mesenchymal stem cells         NCT04302519         China         Not yet recruting           MSC         NCT042762418         China         Recruting           MSC         NCT04356925         China         Not yet recruting           MSC         NCT0437694         China         Not yet recruting           MSC         NCT04356925         China         Not yet recruting           NCT04356623         Spain         Not yet recruting           NCT04366323         Spain         Not yet recruting           NCT04366323         Spain         Not yet recruting           NCT04366323         Spain         Not yet recruting           NCT04366223         Spain         Not yet recruting           NCT04366223         China         Recruting           NCT04366224         China         Recruting           NCT04366225         China         Recruting           NCT04366226         China         Recruting           NCT0436627         Spain		Valsartan	NCT04335786	Netherlands	Recruiting	Phase IV
Telmisartan         NCT04385536         Argentina         Recruiting           Cardiosphero-derived cells         NCT04380251         USA         Noy or recruiting           Dental pulp mesenethymal stem cells         NCT043302519         China         Noy or recruiting           MSC exosomes         NCT04276987         China         Noy or recruiting           MSC         NCT04276987         China         Noy or recruiting           MSC         NCT04276987         China         Noy or recruiting           MSC         NCT04276987         China         Noy or recruiting           NCT0437218         China         Noy or recruiting           NCT0437289         USA         Noy or recruiting           NCT04372803         USA         Noy or recruiting           NCT04345601         USA         Noy or recruiting           NCT04345601         USA         Recruiting           NCT04355728         China         Noy or recruiting           NCT04366021         Spain         Noy or recruiting           NCT04366021         Spain         Noy or recruiting           NCT04368671         Spain         Noy or recruiting           NCT04366071         Spain         Noy or recruiting           NCT04368076		Losartan	NCT04335123	USA	Recruiting	Phase I
Cardiosphere-derived cells         NCT04360551         USA         Not yet recruiting           Denal pulp mesenchymal stem cells         NCT0433547         China         Not yet recruiting           Denal pulp stem cells         NCT04276987         China         Not yet recruiting           MSC exosomes         NCT04276987         China         Not yet recruiting           MSC         NCT04276987         China         Not yet recruiting           NGC exosomes         NCT0437694         Spain         Not yet recruiting           NGC exosomes         NCT0437694         Spain         Not yet recruiting           NCT04372780         USA         Not yet recruiting           NCT04352803         USA         Not yet recruiting           NCT0435604         China         Not yet recruiting           NCT0435605         China         Not yet recruiting           NCT0436605         China         Recruiting           NCT0436600         China         Not yet recruiting           NCT043660         China         Not yet recruiting		Telmisartan	NCT04355936	Argentina	Recruiting	Phase II
Cardiosphere-derived cells         NCT04338347         USA         Available           Dental pulp mesenchymal stem cells         NCT04330251         China         Not yet recruting           Dental pulp stem cells         NCT04330251         China         Not yet recruting           MSC         NCT0436194         Spain         Not yet recruting           MSC         NCT0436194         Spain         Not yet recruting           NCT0436194         Spain         Not yet recruting           NCT0436218         USA         Not yet recruting           NCT0436219         USA         Not yet recruting           NCT0436218         China         Not yet recruting           NCT043628         China         Not yet recruting           NCT043668         China         Not yet recruting           NCT0433568         China         Not yet recruting           NCT04345601         USA         Not yet recruting           NCT04335678         China         Recruting           NCT04335679         China         Not yet recruting           NCT0433660         China         Recruting           NCT0433667         China         Not yet recruting           NCT04331325         China         Not yet recruting			NCT04360551	USA	Not yet recruiting	Phase II
Dental pulp mesenchymal stem cells         NCT04302519         China         Not yet recruting           MSC         NCT04276887         China         Not yet recruting           MSC         NCT0427334         China         Not yet recruting           MSC         NCT04361942         Spain         Not yet recruting           NCT04361942         Spain         Not yet recruting           NCT04362189         USA         Not yet recruting           NCT04362819         USA         Not yet recruting           NCT0436282         China         Not yet recruting           NCT0436283         Spain         Not yet recruting           NCT0436284         China         Not yet recruting           NCT0436385         China         Not yet recruting           NCT0433536         China         Not yet recruting           NCT0433566         China         Not yet recruting           NCT0433660         China         Recruting           NCT0433660         China         Recruting           NCT0433660         China         Recruting           NCT0433660         China         Not yet recruting           NCT0433660         China         Not yet recruting           NCT0433660         China	MSC and other cells	Cardiosphere-derived cells	NCT04338347	USA	Available	NA
Denial pulp stem cells         NCT04336254         China         Recruiting           MSC exosomes         NCT04276987         China         Not yet recruiting           MSC         NCT04322118         China         Not yet recruiting           AD MSC         NCT04377334         Germany         Not yet recruiting           NCT0437734         USA         Not yet recruiting           NCT0437739         USA         Not yet recruiting           NCT04346368         China         Not yet recruiting           NCT04346368         China         Not yet recruiting           NCT04346369         USA         Not yet recruiting           NCT04346369         China         Not yet recruiting           NCT0434601         USA         Recruiting           NCT04336969         China         Not yet recruiting           NV-MSC         NCT043366         China         Recruiting           NV-MSC         NCT043366         China         Recruiting           NCT0434060         China         Recruiting           NCT0434060         China         Not yet recruiting           NCT0434060         Spain         Not yet recruiting           Budseonide         NCT0433607         Spain         Not yet recruiting		Dental pulp mesenchymal stem cells	NCT04302519	China	Not yet recruiting	Phase I
MSC exosomes         NCT04276987         China         Not yet recruiting           MSC         NCT04252118         China         Recruiting           AD MSC         NCT0435192         Spain         Not yet recruiting           AD MSC         NCT04352189         USA         Not yet recruiting           NCT0436532         Spain         Not yet recruiting           NCT0436532         Spain         Not yet recruiting           NCT0434568         China         Not yet recruiting           NCT04345691         USA         Not yet recruiting           NCT04355728         USA         Not yet recruiting           NCT04355691         USA         Not yet recruiting           NCT04355671         USA         Not yet recruiting           NCT0435660         China         Recruiting           NCT0435660         China         Recruiting           NCT04366271         Spain         Not yet recruiting           NCT0438660         China         Recruiting           NCT0438660         China         Recruiting           NG yet recruiting         Not yet recruiting           NG yet recruiting         Not yet recruiting           Dexamethasone         NCT04360825         Spain         Not yet		Dental pulp stem cells	NCT04336254	China	Recruiting	Phase I/II
MSC         NCT04252118         China         Recruiting           AD MSC         NCT04361942         Spain         Not yet recruiting           AD MSC         NCT04362389         USA         Not yet recruiting           NCT04362380         USA         Not yet recruiting           NCT04362380         USA         Not yet recruiting           NCT0436380         China         Not yet recruiting           NCT0436380         China         Not yet recruiting           NCT0437640         China         Not yet recruiting           NCT0437640         China         Not yet recruiting           NCT0437640         China         Recruiting           NCT0437640         China         Recruiting           NCT0437660         China         Recruiting           NCT0438760         China         Recruiting           NCT043880         China         Recruiting           NCT04386087         Not yet recruiting           NCT04386087         Spain         Not yet recruiting           NCT04386087         Spain         Not yet recruiting           NCT04380886         Spain         Not yet recruiting           NCT04380886         Spain         Not yet recruiting           NCT04380		MSC exosomes	NCT04276987	China	Not yet recruiting	Phase I
NCT04361942         Spain         Not yet recruiting           NCT04377334         Germany         Not yet recruiting           NCT04362218         USA         Not yet recruiting           NCT0434636         USA         Not yet recruiting           NCT0434636         China         Not yet recruiting           NCT0434508         China         Not yet recruiting           NCT04335728         USA         Not yet recruiting           NCT0423546         China         Not yet recruiting           NCT0423364         China         Recruiting           NCT04233568         France         Recruiting           NCT0433368         China         Recruiting           NCT0433660         China         Recruiting           NCT0433667         China         Recruiting           NCT0433667         Spain         Not yet recruiting           NCT04335667         Spain         Not yet recruiting           NCT04335667         Spain         Not yet recruiting           NCT04343667         Spain         Not yet recruiting		MSC	NCT04252118	China	Recruiting	Phase I
AD MSC         NCT04362189         USA         Not yet recruiting           NCT04362323         USA         Not yet recruiting           NCT0436686         China         Not yet recruiting           NCT0434668         China         Not yet recruiting           NCT0434660         USA         Not yet recruiting           NCT04334601         USA         Not yet recruiting           NCT0433368         China         Not yet recruiting           NCT0433366         China         Not yet recruiting           NCT0433366         China         Not yet recruiting           NCT0433366         China         Recruiting           NCT0433660         China         Recruiting           NCT0433660         China         Recruiting           NCT0433366         China         Recruiting           NCT0433660         China         Recruiting           NCT0433663         Korea         Not yet recruiting           Budesonide         NCT0433656         Korea         Not yet recruiting           Dexamethasone         NCT0435667         Spain         Not yet recruiting           NCT04360876         USA         Not yet recruiting			NCT04361942	Spain	Not yet recruiting	Phase II
AD MSC         NCT04362189         USA         Not yet recruiting           NCT04352803         USA         Not yet recruiting           NCT04366323         Spain         Not yet recruiting           NCT0436632         Spain         Not yet recruiting           NCT04345601         USA         Not yet recruiting           NCT04335728         USA         Not yet recruiting           NCT04333646         China         Not yet recruiting           NCT0433366         China         Not yet recruiting           NCT0433366         China         Recruiting           NCT04339660         China         Recruiting           NCT0431322         Jordan         Not yet recruiting           NCT0431322         Jordan         Not yet recruiting           NCT0431322         Jordan         Not yet recruiting           NCT0431322         Spain         Not yet recruiting           Dexamethasone         NCT04385637         Spain         Not yet recruiting           NCT04325061         Spain         Not yet recruiting           NCT0431322         Spain         Not yet recruiting           NCT04380876         Spain         Not yet recruiting           NCT0435061         Spain         Not yet recruiting </td <td></td> <td></td> <td>NCT04377334</td> <td>Germany</td> <td>Not yet recruiting</td> <td>Phase II</td>			NCT04377334	Germany	Not yet recruiting	Phase II
NCT04352803         USA         Not yet recruiting           NCT04366323         Spain         Not yet recruiting           NCT04346601         USA         Not yet recruiting           NCT04345601         USA         Not yet recruiting           NCT0435728         USA         Not yet recruiting           NCT0435364         China         Not yet recruiting           NCT0433368         France         Recruiting           NCT04339660         China         Recruiting           NCT04330566         Korea         Not yet recruiting           NCT04330566         Korea         Not yet recruiting           NcT04330567         Spain         Not yet recruiting           NcT0435637         Spain         Not yet recruiting           NcT0435637         Spain         Not yet recruiting           Not yet recruiting         Not yet recruiting </td <td></td> <td>AD MSC</td> <td>NCT04362189</td> <td>USA</td> <td>Not yet recruiting</td> <td>Phase II</td>		AD MSC	NCT04362189	USA	Not yet recruiting	Phase II
MCT04366323         Spain         Not yet recutifing           NCT04345601         USA         Not yet recutifing           NCT04345601         USA         Not yet recutifing           NCT04355728         USA         Not yet recutifing           NCT04273646         China         Not yet recutifing           NCT04269525         China         Recruiting           NCT04269525         China         Recruiting           NCT04339660         China         Recruiting           NCT04366271         Spain         Not yet recruiting           NCT04313322         Jordan         Not yet recruiting           NCT0431342         Sweden         Not yet recruiting           NCT0431352         Spain         Not yet recruiting           NCT0431366         Spain         Not yet recruiting           NCT04315661         Spain         Not yet recruiting           NCT0435667         Spain         Not yet recruiting           NCT0435667         Spain         Not yet recruiting           NCT0435667         Spain         Not yet recruiting           NCT043666         USA         Not yet recruiting			NCT04352803	USA	Not yet recruiting	Phase I
BM-MSC         NCT04345601         USA         Not yet recruiting           UC-MSC         NCT04355728         USA         Not yet recruiting           NCT0435364         China         Not yet recruiting           NCT04273646         China         Not yet recruiting           NCT04233368         France         Recruiting           NCT04269525         China         Recruiting           NCT04339660         China         Recruiting           NCT04339660         China         Not yet recruiting           NCT04339660         China         Not yet recruiting           NCT04339660         China         Not yet recruiting           NCT04333563         Korea         Not yet recruiting           NCT04335637         Spain         Not yet recruiting           NCT0435661         Spain         Not yet recruiting           NCT04360876         USA         Not yet recruiting			NCT04366323	Spain	Not yet recruiting	Phase I/II
NCT04345601         USA         Not yet recruiting           NCT04235728         USA         Recruiting           NCT04273646         China         Not yet recruiting           NCT04245652         China         Not yet recruiting           NCT0433368         France         Recruiting           NCT0433660         China         Recruiting           NCT043366271         Spain         Not yet recruiting           NCT0431332         Jordan         Not yet recruiting           NCT0431356         Korea         Not yet recruiting           NCT0431365         Spain         Not yet recruiting           NCT04385637         Spain         Not yet recruiting           NCT04355637         Spain         Not yet recruiting           NCT04356697         Spain         Not yet recruiting           NCT04360876         USA         Not yet recruiting		BM-MSC	NCT04346368	China	Not yet recruiting	Phase I/II
UC-MSC         NCT04355728         USA         Recruiting           NCT04273646         China         Not yet recruiting           NCT0433368         France         Recruiting           NCT04269525         China         Recruiting           NCT04339660         China         Recruiting           NCT0433060         China         Recruiting           NCT04330560         China         Not yet recruiting           NCT04313322         Jordan         Not yet recruiting           NCT04331364         Sweden         Not yet recruiting           NCT04355637         Spain         Not yet recruiting           NCT0435061         Spain         Not yet recruiting           NCT0435061         Spain         Not yet recruiting			NCT04345601	USA	Not yet recruiting	Early Phase I
NCT04273646         China         Not yet recruiting           NCT0433368         France         Recruiting           NCT04269525         China         Recruiting           NCT0433660         China         Recruiting           NCT0433660         China         Recruiting           NCT04313322         Jordan         Not yet recruiting           NCT04313322         Jordan         Not yet recruiting           NCT04330586         Korea         Not yet recruiting           NCT0433134         Sweden         Not yet recruiting           NCT04355637         Spain         Not yet recruiting           NCT04325661         Spain         Not yet recruiting           NCT04360876         USA         Not yet recruiting		UC-MSC	NCT04355728	USA	Recruiting	Phase I/II
NCT04269525         China         Recruiting           NCT04269525         China         Recruiting           NCT04339660         China         Recruiting           NCT04339660         China         Recruiting           NCT04313322         Jordan         Not yet recruiting           NCT04330586         Korea         Not yet recruiting           NCT04330586         Spain         Not yet recruiting           NCT04325637         Spain         Not yet recruiting           NCT04325661         Spain         Not yet recruiting           NCT04360876         USA         Not yet recruiting			NCT04273646	China	Not yet recruiting	NA
NCT04269525         China         Recruiting           NCT04339660         China         Recruiting           NCT04366271         Spain         Not yet recruiting           NCT04313322         Jordan         Recruiting           NCT04330586         Korea         Not yet recruiting           NCT04381364         Sweden         Not yet recruiting           NCT04385637         Spain         Not yet recruiting           Dexamethasone         NCT04325061         Spain         Not yet recruiting           NCT04360876         USA         Not yet recruiting			NCT04333368	France	Recruiting	Phase I/II
NCT04339660         China         Recruiting           NCT04366271         Spain         Not yet recruiting           NCT04313322         Jordan         Recruiting           NCT04330586         Korea         Not yet recruiting           NCT04381364         Sweden         Not yet recruiting           NCT04355637         Spain         Not yet recruiting           Dexamethasone         NCT0435061         Spain         Not yet recruiting           NCT04360876         USA         Not yet recruiting			NCT04269525	China	Recruiting	Phase II
WJ-MSC         NCT0431332         Spain         Not yet recruiting           Ciclesonide         NCT04313322         Jordan         Recruiting           NCT04330586         Korea         Not yet recruiting           NCT04381364         Sweden         Not yet recruiting           NCT04355637         Spain         Not yet recruiting           NCT04325061         Spain         Not yet recruiting           NCT04360876         USA         Not yet recruiting			NCT04339660	China	Recruiting	Phase I/II
WJ-MSC         NCT04313322         Jordan         Recruiting           Ciclesonide         NCT04330586         Korea         Not yet recruiting           NCT04381364         Sweden         Not yet recruiting           NCT04325637         Spain         Recruiting           NCT04325061         Spain         Not yet recruiting           NCT04360876         USA         Not yet recruiting			NCT04366271	Spain	Not yet recruiting	Phase II
CiclesonideNCT04330586KoreaNot yet recruitingNCT04381364SwedenNot yet recruitingBudesonideNCT04355637SpainRecruitingDexamethasoneNCT04325061SpainNot yet recruitingNCT04360876USANot yet recruiting		WJ-MSC	NCT04313322	Jordan	Recruiting	Phase I
NCT04381364         Sweden         Not yet recruiting           NCT04355637         Spain         Recruiting           NCT04325061         Spain         Not yet recruiting           NCT04360876         USA         Not yet recruiting	Corticosteroids	Ciclesonide	NCT04330586	Korea	Not yet recruiting	Phase II
NCT04355637 Spain Recruiting NCT04325061 Spain Not yet recruiting NCT04360876 USA Not yet recruiting			NCT04381364	Sweden	Not yet recruiting	Phase II
NCT0435061 Spain Not yet recruiting NCT04360876 USA Not yet recruiting		Budesonide	NCT04355637	Spain	Recruiting	Phase IV
USA Not yet recruiting		Dexamethasone	NCT04325061	Spain	Not yet recruiting	Phase IV
			NCT04360876	USA	Not yet recruiting	Phase II



Cr number         Cr number         Cuanty         Recruitment status         Phase II           Preditione         NCT04344288         France         Recruiting         Phase II           Methylpedusislone         NCT04342381         France         Nay Set encuting         Phase II           Methylpedusislone vs. hechecorrisone         NCT0434329         Brazil         Recruiting         Phase II           Nation of the comment         NCT0434329         France         Nay Set encuting         Phase II           Nation of the comment         NCT04343673         France         Nay Set encuting         Phase II           Pluckers         NCT0434372         Egypt         Nay Set encuting         Phase II           Pluckers         Avanine bromble         NCT04343663         USA         Recruiting         Phase II           Pluckers         Avanine bromble         NCT04343663         USA         Recruiting         Phase II           Bealtmand         NCT04343663         USA         Recruiting         Phase II           Macklybysteine         NCT04343669         USA         Recruiting         Phase II           Macklybysteine         NCT04343669         USA         Recruiting         Phase II           Macklybysteine         NCT04343669	Group	Therapeutic agent	Example of clinic	Example of clinical trials registered at ClinicalTrials.gov	rials.gov	
Predinisone         NCT04544288         France         Recruiting           Methylpredinisone vs. hydroconisone         NCT04535211         France         Not yst exertining           Methylpredinisolone sodlum succinate         NCT0454279         Brazal         Completed           NCT0454279         Brazal         Completed           NCT0454279         Brazal         Not yet recruiting           NCT0454679         Brazal         Not yet recruiting           NCT0454679         Brazal         Not yet recruiting           NCT0454676         Brazal         Not yet recruiting           NCT0454676         USA         Recruiting           Place control         NCT0454666         USA         Recruiting           Ascoriner benaise         NCT0454669         USA         Not yet recruiting           Ascoriner benaise         NCT0454669         USA         Not yet recruiting           Schinesco         NCT0454669         USA         Not yet recruiting           Medplalam         NCT0454669         USA         Not yet recruiting           Medplalam         NCT0454669         USA         Not yet recruiting           Meacylic-steine         NCT045380376         Rassia         Recruiting           Augenousin peptide (1-7) de			CT number	Country	Recruitment status	Phase
Se, antidepressurs, neurologies         NCT04337321         France         Not yet recruiting           Se, antidepressurs, neurologies         NCT043437323         China         Superabled           Se, antidepressurs, neurologies         Chioppromuzione         NCT04343729         Brazil         Recruiting           Se, antidepressurs, neurologies         Chioppromuzione         NCT0434366329         France         Not yet recruiting           Planovatine         NCT0434366329         Clina         Not yet recruiting           Planovatine         NCT043342663         USA         Recruiting           Planovatine         NCT043342663         USA         Recruiting           Belanovate thomide         NCT04336607         USA         Recruiting           Belanovate thomide         NCT0433609         Slowenia         Recruiting           Avaignation of the control         NCT0433509         Slowenia         Recruiting           Avaignation of the control         NCT04335200         Indy         Recruiting <t< td=""><td></td><td>Prednisone</td><td>NCT04344288</td><td>France</td><td>Recruiting</td><td>Phase II</td></t<>		Prednisone	NCT04344288	France	Recruiting	Phase II
Se, amble pressurits, neurolegicis Solure de l'Activité processurits, neurolegicis Chlorpomuzine continum succinate         NCT04273731         Clinn         Completed           ce, amble pressants, neurolegicis Chlorpomuzine         NCT04367393         France         Not yet recruiting           Recruité provincie         NCT04373529         China         Not yet recruiting           Pluoxetime         NCT04373529         China         Not yet recruiting           Pluoxetime         NCT04373529         China         Not yet recruiting           Azoxame bennidine         NCT0437359         USA         Recruiting           Azoxame bennidine         NCT0437429         USA         Not yet recruiting           Azoxame bennidine         NCT0437429         USA         Not yet recruiting           Benlatumide         NCT04338027         Spain         Not yet recruiting           Maphalam         NCT04348026         USA         Recruiting           Maphalam         NCT04348026         USA         Recruiting           Maphalam         NCT04348026         USA         Recruiting           Amende, circ         NCT04348026         USA         Recruiting           Amende, circ         NCT04348026         USA         Recruiting           Amende, circ         NCT0434		Prednisone vs. hydrocortisone	NCT04359511	France	Not yet recruiting	Phase III
Se, antidepressants, neurolepties         Methylprechtisotone sodium succinate         NCT04234873         Bazzil         Recruiting           Se, antidepressants, neurolepties         Chlospronazine         NCT043454875         Egypt         Noy yet recruiting           Pluvocamine         NCT043424863         Usha         Recruiting           Pluvocamine         NCT04342663         Usha         Recruiting           Pluvocamine         NCT04342663         Usha         Recruiting           Accommedenonidine         NCT04342663         Usha         Recruiting           Decembedoundine         NCT04342663         Usha         Recruiting           Billinecor         NCT04342663         Usha         Recruiting           Ascept/cysteine         NCT04342669         Usha         Recruiting           Ascept/cysteine         NCT04342690         Usha         Recruiting           Ascept/cysteine         NCT043435609         Usha         Recruiting           Ascept/cysteine         NCT04343500         Usha         Recruiting           Ascept/cysteine         NCT04343500         Usha         Recruiting           Ascept/cysteine         NCT04343500         Usha         Recruiting           Ascept/cysteine         NCT04343500         Usha </td <td></td> <td>Methylprednisolone</td> <td>NCT04273321</td> <td>China</td> <td>Suspended</td> <td>NA</td>		Methylprednisolone	NCT04273321	China	Suspended	NA
e., antidepressums, neuroleptics         MCT04345729 Tennee         Razeil         Recruiting           e., antidepressums, neuroleptics         Choppromazine         NCT04373529 China         Noy of recruiting           Pluvoxamirie         NCT04373529 China         Noy of recruiting           Fluvoxamirie         NCT0437350 China         Noy of recruiting           Pouvoxeline         NCT0437350 China         Noy of recruiting           Acoximer bromide         NCT0437370 Spain         Noy of recruiting           Acoximer bromide         NCT0438177 Russia         Recruiting           Acoximer bromide         NCT0438177 Russia         Recruiting           Molphala         NCT0438075 Russia         Recruiting           Molphala         NCT0438075 Russia         Recruiting           N-acetyleysteine         NCT0435020 Belgium         Recruiting           N-acetyleysteine         NCT0435027 Belgium         Recruiting           N-acetyleysteine         NCT0435020 Belgium         Recruiting           N-acetyleysteine         NCT0435520 Belgium         Recruiting           N-acetyleysteine         NCT0435520 Belgium         Recruiting           N-acetyleysteine         NCT0435520 Belgium         Recruiting           Nationesta mesilate         NCT0435520 Belgium         <			NCT04274071	USA	Completed	NA
es, amidepressants, neuroloptics         Chloppromazine         NCT04354603         Egapt both         Not yet recruiting           Ruvoxamine         NCT043542663         USA         Not recruiting           Fluvoxamine         NCT04317368         USA         Recruiting           Pluvoxamine         NCT04317368         USA         Recruiting           Azoximer bronnied         NCT04317368         USA         Recruiting           Bioposide         NCT04317368         USA         Recruiting           Bronneamine         NCT043175660         USA         Not yet recruiting           Metphalan         NCT04317660         USA         Not yet recruiting           Metphalan         NCT04317610         USA         Not yet recruiting           Metphalan         NCT04316098         USA         Recruiting           Ameetycysteine         NCT04316098         USA         Recruiting           Amgiorassin poptide (1-7) derived plasma         NCT0431609         USA         Not yet recruiting           Avipadal         NCT0431609         USA         Not yet recruiting           Avipadal         NCT0431609         USA         Not yet recruiting           Not yet recruiting         NCT04315340         USA         Not yet recruiting <td></td> <td>Methylprednisolone sodium succinate</td> <td>NCT04343729</td> <td>Brazil</td> <td>Recruiting</td> <td>Phase II</td>		Methylprednisolone sodium succinate	NCT04343729	Brazil	Recruiting	Phase II
NCT043754805         Egypt         Not yet recunting           Fluvoxamine         NCT04275293         China         Not yet recunting           Fluvoxamine         NCT04375673         USA         Recruting           Pluoxetine         NCT04375672         Spain         Not yet recunting           Accounted bennide         NCT04387677         Spain         Not yet recunting           Accounted bennide         NCT04387677         Spain         Not yet recunting           Bical transide         NCT04387677         Spain         Not yet recunting           Sclinexor         NCT043426903         USA         Recruting           Macphalan         NCT04342079         USA         Recruting           Macphalan         NCT04342090         USA         Recruting           Macphalan         NCT04352090         Bedgium         Recruting           Macphalan         NCT04352090         Bedgium         Recruting           Macphalan         NCT04352090         Bedgium         Recruting           Macphalan         NCT04352090         Bedgium         Recruting           Macphalan         NCT04353200         Bedgium         Recruting           Avipadil         Aripadil         NCT04353249         USA	Sedatives, antidepressants, neuroleptics	Chlorpromazine	NCT04366739	France	Not yet recruiting	Phase III
Thaltdomide			NCT04354805	Egypt	Not yet recruiting	Phase I/II
Pluvosamine   NCT0437505   USA   Recruting		Thalidomide	NCT04273529	China	Not yet recruiting	Phase II
Decemberation         NCT04377308         USA         Recruiting           Dexamedetomidine         NCT0435867         Spain         Not yet recruiting           Azoximer bromide         NCT0435867         USA         Not yet recruiting           Etoposide         NCT0434098         USA         Not yet recruiting           Selinevor         NCT0434029         USA         Not yet recruiting           Mobbalan         NCT04342729         USA         Not yet recruiting           Bromhexine         NCT0434269         Slovania         Recruiting           Avacyleyseine         NCT0434461         USA         Recruiting           Avagotuesin peptide (1-7) derived plasma         NCT04326920         Belgium         Recruiting           Avigutali         NCT04335721         Turkey         Recruiting           Avigutali         NCT04335721         Turkey         Not yet recruiting           Avigutali         NCT04335240         USA         Not yet recruiting           Avigutali         NCT0435240         UsA         Not yet recruiting           Amitrine         NCT0435240         UsA         Not yet recruiting           Almitrine         NCT04354313         Chance         Not yet recruiting           Progesterone		Fluvoxamine	NCT04342663	USA	Recruiting	Phase II
Dexmedetomidine         NCT0438777         Russia         Not yet recruiting           Eoposide         NCT0438177         Russia         Recruiting           Bicalutamide         NCT0434098         USA         Not yet recruiting           Selinexor         NCT0434098         USA         Recruiting           Melphalan         NCT0434098         USA         Recruiting           Maceyleyseine         NCT0435026         Slovenia         Recruiting           Aaceyleyseine         NCT0435020         Belgium         Recruiting           Sargamostim         NCT0435201         Indx         Recruiting           Angiotensin peptide (1-7) derived plasma         NCT0435201         Indx         Not yet recruiting           Angiotensin peptide (1-7) derived plasma         NCT0431697         USA         Not yet recruiting           Aviptadil         Avigidensi         NCT0435201         Indx         Not yet recruiting           Aviptadil         NCT0435240         Demase apha         NCT0435240         Not yet recruiting           Camostat mesilate         NCT0435249         Demase         Not yet recruiting           Sildenafil citrate         NCT04304313         China         Recruiting           Progesterone         NCT04304313         C		Fluoxetine	NCT04377308	USA	Recruiting	Phase IV
Azonimer bromide         NCT0438177         Russia         Recruting           Bolposide         NCT04345669         USA         Not yet recruting           Selinexor         NCT04344909         USA         Not yet recruting           Melphalam         NCT04344909         USA         Recruting           Bromhexine         NCT04349376         Slovenia         Recruting           Aseckylcysteine         NCT0434620         Slovenia         Recruting           Aseckylcysteine         NCT0434620         Slovenia         Recruting           Aseckylcysteine         NCT0434461         USA         Recruting           Amgiotensin peptide (1-7) derived plasma         NCT0435520         Belgium         Recruting           Avipadil         Avipadil         NCT0435520         USA         Recruting           Avipadil         Avipadil         NCT0435240         USA         Not yet recruting           Andmostat mesilate         NCT0432106         Demmark         Not yet recruting           Almitrine         NCT04345534         Prance         Not yet recruting           Progesterone         NCT0434545         Prance         Not yet recruting           NCT0434661         USA         Recruting           NCT0434661		Dexmedetomidine	NCT04358627	Spain	Not yet recruiting	NA
e         NCT04356690         USA         Not yet recruiting           NCT04374279         USA         Not yet recruiting           NCT04380376         Russia         Recruiting           NCT04380376         Russia         Recruiting           NCT04355026         Slovenia         Recruiting           NCT04337461         USA         Recruiting           NCT043326920         Belgium         Recruiting           NCT04335201         Italy         Not yet recruiting           NCT04335201         Italy         Not yet recruiting           NCT04353540         Italy         Not yet recruiting           NCT04353240         Italy         Not yet recruiting           NCT04353240         Italy         Not yet recruiting           NCT04353240         Italy         Not yet recruiting           NCT04353247         France         Not yet recruiting           NCT04365127         USA         Recruiting           NCT04365127         USA         Recruiting           NCT04365127         USA         Recruiting           NCT0436612         USA         Recruiting           NCT0436615         USA         Recruiting           NCT0436615         USA         Recruiting<	Others	Azoximer bromide	NCT0438177	Russia	Recruiting	Phase II/III
e         NCT04374279         USA         Not yet recruiting           NCT04349098         USA         Recruiting           NCT04380376         Russia         Recruiting           leine         NCT04355026         Slovenia         Recruiting           m         NCT04374461         USA         Recruiting           peptide (1-7) derived plasma         NCT04375124         Turkey         Recruiting           na         NCT04335201         Italy         Not yet recruiting           na silate         NCT0435546         France         Recruiting           nesilate         NCT0435240         Italy         Not yet recruiting           nCT0435240         Italy         Not yet recruiting           nCT0435247         France         Not yet recruiting           nCT0435224         USA         Not yet recruiting           nCT0435457         France         Not yet recruiting           nCT0435517         USA         Recruiting           nCT0435517         USA         Recruiting           nCT04355143         USA         Recruiting           nCT0436615         USA         Recruiting           nCT0436615         USA         Recruiting           nCT0436615         <		Etoposide	NCT04356690	USA	Not yet recruiting	Phase II
NCT04349098         USA         Recruiting           NCT04380376         Russia         Recruiting           leine         NCT04355026         Slovenia         Recruiting           m         NCT04374461         USA         Recruiting           peptide (1-7) derived plasma         NCT04326920         Belgium         Recruiting           NCT04335201         Italy         Not yet recruiting           NCT04311697         USA         Not yet recruiting           NCT04353544         France         Not yet recruiting           NCT0435284         Denmark         Not yet recruiting           NCT0435284         USA         Not yet recruiting           NCT0435284         USA         Not yet recruiting           NCT04353284         USA         Not yet recruiting           NCT04364517         USA         Recruiting           NCT04365127         USA         Recruiting           NCT04365127         USA         Recruiting           NCT04365137         China         Recruiting           NCT0436615         USA         Recruiting           NCT0436615         USA         Recruiting		Bicalutamide	NCT04374279	USA	Not yet recruiting	Phase II
NCT04380376         Russia         Recruiting           leine         NCT04352026         Slovenia         Recruiting           m         NCT04374461         USA         Recruiting           peptide (1-7) derived plasma         NCT04326920         Belgium         Recruiting           ha         NCT04335201         Italy         Not yet recruiting           ha         NCT04311697         USA         Not yet recruiting           nesilate         NCT04352400         Italy         Not yet recruiting           NCT0435240         Ltaly         Not yet recruiting           NCT0435240         Denmark         Not yet recruiting           NCT0435240         Denmark         Not yet recruiting           NCT04352475         France         Not yet recruiting           NCT043513         China         Recruiting           NCT04355143         USA         Recruiting           NCT04355143         USA         Recruiting           NCT0436615         USA         Recruiting           NCT04346615         USA         Recruiting		Selinexor	NCT04349098	USA	Recruiting	Phase II
ceine         NCT04355026         Slovenia         Recruiting           m         NCT04374461         USA         Recruiting           m         NCT04326920         Belgium         Recruiting           peptide (1-7) derived plasma         NCT04335201         Italy         Not yet recruiting           NCT04311697         USA         Not yet recruiting           NCT04355364         France         Recruiting           NCT04355364         France         Not yet recruiting           NCT04352400         Italy         Not yet recruiting           NCT0435240         Italy         Not yet recruiting           NCT04353244         USA         Not yet recruiting           NCT0436317         China         Recruiting           NCT04365127         USA         Recruiting           NCT04365127         USA         Recruiting           NCT04365143         USA         Recruiting           NCT04308317         China         Recruiting           NCT04308317         China         Recruiting           NCT0436615         USA         Recruiting		Melphalan	NCT04380376	Russia	Recruiting	Phase II
m         NCT04374461         USA         Recruiting           m         NCT04326920         Belgium         Recruiting           peptide (1-7) derived plasma         NCT04335124         Turkey         Recruiting           NCT04335201         Italy         Not yet recruiting           NCT04311697         USA         Not yet recruiting           NCT0435240         Italy         Not yet recruiting           NCT04352284         USA         Not yet recruiting           NCT04353284         USA         Not yet recruiting           NCT04352284         USA         Not yet recruiting           NCT04365127         USA         Not yet recruiting           NCT04365127         USA         Recruiting           NCT04365127         USA         Recruiting           NCT04365127         USA         Recruiting           NCT0436817         China         Recruiting           NCT04308317         China         Bercuiting           NCT04346615         USA         Recruiting		Bromhexine	NCT04355026	Slovenia	Recruiting	Phase IV
m         NCT04326920         Belgium         Recruiting           peptide (1-7) derived plasma         NCT04375124         Turkey         Recruiting           NCT04335201         Italy         Not yet recruiting           ha         NCT04355364         France         Recruiting           ncsilate         NCT04352400         Italy         Not yet recruiting           NCT04351096         Denmark         Not yet recruiting           NCT04351284         USA         Not yet recruiting           NCT0435127         USA         Not yet recruiting           NCT04365127         USA         Not yet recruiting           NCT04365127         USA         Recruiting           NCT04355143         USA         Recruiting           NCT04355143         USA         Recruiting           NCT04365127         USA         Recruiting           NCT04365143         China         Enrolling by invitation           NCT0436615         USA         Recruiting		N-acetylcysteine	NCT04374461	USA	Recruiting	Phase IV
peptide (1-7) derived plasma         NCT04335201         Turkey         Recruiting           NCT04312697         USA         Not yet recruiting           NCT04352364         France         Recruiting           NCT04352364         France         Recruiting           NCT04352364         Italy         Not yet recruiting           NCT04352400         Denmark         Not yet recruiting           NCT0435284         USA         Not yet recruiting           NCT04357457         France         Not yet recruiting           NCT04357457         France         Not yet recruiting           NCT04357457         France         Recruiting           NCT04355127         USA         Recruiting           NCT04355143         USA         Recruiting           NCT04355143         USA         Recruiting           NCT04355143         China         Enrolling by invitation           NCT0436615         USA         Recruiting		Sargramostim	NCT04326920	Belgium	Recruiting	Phase IV
ha         NCT04335201         Italy         Not yet recruiting           NCT04355364         France         Recruiting           mesilate         NCT04352400         Italy         Not yet recruiting           NCT04321096         Denmark         Not yet recruiting           NCT0435284         USA         Not yet recruiting           NCT04357457         France         Not yet recruiting           NCT04365127         USA         Not yet recruiting           NCT04365127         USA         Recruiting           NCT04355143         USA         Recruiting           NCT04355143         USA         Recruiting           NCT04355143         USA         Recruiting           NCT04365117         China         Enrolling by invitation           NCT04365117         USA         Recruiting		Angiotensin peptide (1-7) derived plasma	NCT04375124	Turkey	Recruiting	NA
ha         NCT04311697         USA         Not yet recruiting           mesilate         NCT0435240         Italy         Not yet recruiting           esilate         NCT0431096         Denmark         Not yet recruiting           NCT0435284         USA         Not yet recruiting           NCT04357457         France         Not yet recruiting           NCT04304313         China         Recruiting           NCT04365127         USA         Recruiting           NCT0435543         USA         Recruiting           NCT04355143         USA         Recruiting           NCT0436615         USA         Recruiting           NCT04346615         USA         Recruiting		Defibrotide	NCT04335201	Italy	Not yet recruiting	Phase II
ha         NCT04355364         France         Recruiting           mesilate         NCT04352400         Italy         Not yet recruiting           nCT04353284         USA         Not yet recruiting           nCT04357457         France         Not yet recruiting           nCT04304313         China         Recruiting           nCT04365127         USA         Recruiting           nCT04355143         USA         Recruiting           nCT04355143         USA         Recruiting           nCT04368317         China         Enrolling by invitation           nCT04346615         USA         Recruiting		Aviptadil	NCT04311697	USA	Not yet recruiting	Phase II
mesilate         NCT04352400         Italy         Not yet recruiting           esilate         NCT0433284         USA         Not yet recruiting           NCT04353284         USA         Not yet recruiting           NCT04357457         France         Not yet recruiting           NCT04304313         China         Recruiting           NCT04365127         USA         Recruiting           NCT04355143         USA         Recruiting           NCT04355143         USA         Recruiting           NCT04308317         China         Enrolling by invitation           NCT04346615         USA         Recruiting		Dornase alpha	NCT04355364	France	Recruiting	Phase III
sesilate         NCT04321096         Denmark         Not yet recruiting           NCT0435284         USA         Not yet recruiting           NCT04357457         France         Not yet recruiting           NCT04304313         China         Recruiting           NCT04365127         USA         Recruiting           NCT04355143         USA         Recruiting           NCT04365143         USA         Recruiting           NCT04365143         USA         Recruiting           NCT04308317         China         Enrolling by invitation           NCT04346615         USA         Recruiting		Nafamostat mesilate	NCT04352400	Italy	Not yet recruiting	Phase II/III
NCT04353284         USA         Not yet recruiting           NCT04357457         France         Not yet recruiting           NCT04304313         China         Recruiting           NCT04365127         USA         Recruiting           NCT04375202         Italy         Recruiting           NCT04355143         USA         Recruiting           NCT04308317         China         Enrolling by invitation           NCT04346615         USA         Recruiting		Camostat mesilate	NCT04321096	Denmark	Not yet recruiting	Phase I/II
NCT04357457         France         Not yet recruiting           NCT04304313         China         Recruiting           NCT04365127         USA         Recruiting           NCT04375202         Italy         Recruiting           NCT04355143         USA         Recruiting           NCT04308317         China         Enrolling by invitation           NCT04346615         USA         Recruiting			NCT04353284	USA	Not yet recruiting	Phase II
trate         NCT04304313         China         Recruiting           NCT04365127         USA         Recruiting           NCT04375202         Italy         Recruiting           NCT04308317         China         Enrolling by invitation           NCT04346615         USA         Recruiting		Almitrine	NCT04357457	France	Not yet recruiting	Phase III
e         NCT04365127         USA         Recruiting           NCT04375202         Italy         Recruiting           NCT04355143         USA         Recruiting           NCT04308317         China         Enrolling by invitation           NCT04346615         USA         Recruiting		Sildenafil citrate	NCT04304313	China	Recruiting	Phase III
NCT04375202 Italy Recruiting NCT04355143 USA Recruiting NCT04308317 China Enrolling by invitation NCT04346615 USA Recruiting		Progesterone	NCT04365127	USA	Recruiting	Phase I
NCT04365143 USA Recruiting NCT04308317 China Enrolling by invitation NCT04346615 USA Recruiting		Colchicine	NCT04375202	Italy	Recruiting	Phase II
NCT04308317 China Enrolling by invitation NCT04346615 USA Recruiting			NCT04355143	USA	Recruiting	Phase II
NCT04346615 USA Recruiting		Tetrandrine	NCT04308317	China	Enrolling by invitation	Phase IV
		Vazegepant	NCT04346615	USA	Recruiting	Phase II/III



Table 1 (continued)

Table 1 (continued)					
Group	Therapeutic agent	Example of clinic	Example of clinical trials registered at ClinicalTrials.gov	ls.gov	
		CT number	Country	Recruitment status	Phase
	Dapagliflozin	NCT04350593	USA	Recruiting	Phase III
	Isotretinoin	NCT04361422	Egypt	Not yet recruiting	Phase III
	Deferoxamine	NCT04333550	Iran	Recruiting	Phase I/II
	SnPP protoporphyrin	NCT04371822	Egypt	Not yet recruiting	Phase I
	Ascorbic acid	NCT04363216	USA	Not yet recruiting	Phase II
	BACTEK-R	NCT04363814	Spain	Not yet Recruiting	Phase III
	Traditional Chinese medicine	NCT04323332	China	Not yet recruiting	Phase III
	Huaier granule	NCT04291053	China	Not yet recruiting	Phase II/III
Combined	Favipiravir, hydroxychloroquine	NCT04359615	Iran	Not yet recruiting	Phase IV
		NCT04376814	Iran	Enrolling by invitation	NA
	Favipiravir, tocilizumab	NCT04310228	China	Recruiting	NA
	Hydroxychloroquine, azithromycin	NCT04328272	Pakistan	Not yet Recruiting	Phase III
		NCT04329832	USA	Recruiting	Phase II
		NCT04359316	Iran	Not yet recruiting	Phase IV
	Hydroxychloroquine, nitazoxanide	NCT04361318	Egypt	Not yet recruiting	Phase II/III
	Hydroxychloroquine, azithromycin, tocilizumab	NCT04332094	Spain	Recruiting	Phase II
	Hydroxychloroquine vs. hydroxychloroquine, loninavir/ritonavir vs. hydroxychloroquine, azithromycin	NCT04359095	Colombia	Not yet recruiting	Phase II/III
	Hydroxychloroquine, famotidine	NCT04370262	USA	Recruiting	Phase III
	Ivermectin, Nitazoxanide	NCT04360356	Egypt	Not yet recruiting	Phase II/III
	Lopinavir/ritonavir, ribavirin, interferon beta-1B	NCT04276688	China	Completed	Phase II

ACE angiotensin-converting enzyme; AR angiotensin receptor; DFPP double-filtration plasmapheresis; MSC mesenchymal stem (stromal) cells; AD MSC adipose-derived MSC; BM-MSC bone marrow-derived MSC; UC-MSC umbilical cord-derived MSC; WJ-MSC Wharton jelly-derived MSC; NK cells natural killer cells; rhACE2 recombinant human angiotensin-converting enzyme 2; rbACE2 recombinant bacterial angiotensin-converting enzyme 2; Rhu-pGSN recombinant human plasma gelsolin

Phase II/III Phase II

Completed Recruiting

Bosnia and Herzegovina

NCT04276688 NCT04374032

Met-enkephalin, tridecactide



(AAK1) are endocytosis regulators. Baricitinib might inhibit SARS COV-2 entry by disruption of these regulators. Other JAK inhibitors such as fedratinib and ruxolitinib are also candidates for decreasing inflammatory cytokines in COVID-19 individuals [51]. Although JAK inhibitors have wide effects and can inhibit cytokine secretion such as IFN- $\alpha$ , more studies need to confirm their safety and efficiency [14].

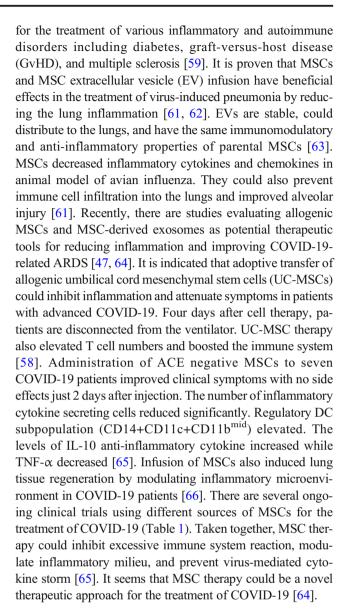
## **Adoptive immunotherapy**

Adoptive transfer of antigen-specific T cells has been developed for the treatment of cancers, autoimmunity, and viral infections including hepatitis B virus (HBV), hepatitis C virus (HCV), and cytomegalovirus (CMV) [24-26]. In this approach, anti-viral-specific T cell clones are generated, expanded, and purified in vitro [26]. It is shown that engineered SARS-specific CD8+ T cells had normal activity and function and may be a potential therapeutic tool for SARS infection [27]. Recently, it has been indicated that the number of CD8+ T cells decreased dramatically and the ratio of CD4+/CD8+ T cells increased during the SARS-CoV-2 infection. This decrease in the number of CD8+ lymphocytes has been correlated with the disease severity and clinical outcome [52]. It has also indicated that CD8+ T cells and the CD4+/CD8+ ratio decreased and increased respectively after the treatment. It seems that CD8+ T cells play an important role in COVID-19 and could be a potential biomarker of the disease [52, 53]. Due to these findings, adoptive transfer of COVID-19-specific CD8+ T cells may be an effective treatment strategy [28]. NK cells are innate immune cells that play a crucial role in host immune response after viral infections [54]. Preprinted studies indicated that NK cell population decreased remarkably during the disease [55, 56]. It has been indicated that during SARS-CoV-2 infection, increased amount of IL-6 inflammatory cytokine had negative correlation with the number of NK cells [52]. Thus, it is assumed that adoptive transfer of NK cells may have an effective therapeutic approach. Therefore, recently, an ongoing phase I clinical trial has been registered in which NK cell therapy in combination with conventional therapies for COVID-19 patients was proposed (NCT04280224). Altogether, it seems that cell-mediated immunity plays an important role in host immune response against SARS-CoV-2 [57].

## Mesenchymal stromal cells

Persistence of inflammatory cytokines in COVID-19 patients leads to lung dysfunction and even death. Using corticosteroids for dampening cytokine storm suppresses immune system and makes delay in virus elimination [58].

Mesenchymal stromal cells (MSCs) are characterized with their immunomodulatory and anti-inflammatory properties [59, 60]. Because of these characteristics, they have been used



#### **Nanomedicine**

LIF (leukemia inhibitory factor) is one of the important cytokines to protect the respiratory system and promote lung homeostasis during viral infections [67, 68]. This cytokine modulates severe adverse events during ARDS [67]. Up to now, there is no study investigating the role of LIF in SARS-CoV-2 infection. However, in respiratory syncytial virus (RSV) model, it has been shown that overexpression of LIF enhanced the recovery of lungs during pneumonia. Neutralization of the LIF induced alveolar damage and chemokine secretion [69]. According to these data, LIF might also have protective effects in SARS-CoV-2 infection.

LIF nanoparticles (LIF-NPs) indicated clinical benefits in experimental autoimmune encephalomyelitis (EAE) animal models. LIF-NPs possessed immunomodulatory effects and increased self-tolerance in animal models for ARDS [70].



These inhalable NPs could be a novel strategy for lung tissue repair and cytokine storm inhibition [64]. Activation and polarization of macrophages play a major role in the initiation and intensity of inflammation, respectively, in ALI/ARDS. Peptide-coated gold nanoparticles could alleviate lung inflammation through inducing M1-to-M2 macrophage phenotype transition and increasing the anti-inflammatory cytokine (IL-10) in the lung of acute lung injury (ALI) mice [71].

#### **Decoy biomolecules**

As mentioned above, SARS-COV-2 attaches to ACE2 receptor to invade the host cells, particularly alveolar epithelial cells. SARS-CoV-2 spike protein has strong affinity to ACE2 receptor [72–74]. This attachment may enhance viral entry and replication [74, 75]. It is assumed that targeting this interaction and using soluble form of ACE2 could be a potential therapeutic approach [76]. Studies on COVID-19 indicated that ACE2 injection could competitively neutralize the virus and improve lung injury [77]. Recently, a novel therapeutic approach was developed based on soluble ACE2 interaction with the virus. It has been shown that human recombinant soluble ACE2 (hrsACE2) could inhibit SARS-CoV-2 from entering the host cells, decreasing the viral load in a dosedependent manner. This molecule inhibits viral infection of human blood vessels and kidney organoids. These data indicated that hrsACE2 was effective in early-stage patients [78]. Since the inhibitory effects of hrsACE2 were not complete, it is preliminarily considered that the virus may use a second receptor or co-factor such as transmembrane protease serine 2 (TMPRSS2) [79]. In this regard, TMPRSS2 inhibitor was approved for clinical application in COVID-19 to inhibit the entry of virus [74].

#### **Antiviral drugs**

Remdesivir is claimed to be an option to treat COVID-19 [80]. It is a nucleoside analog and has broad-spectrum activities against RNA viruses such as MERS; remdesivir can effectively diminish the viral load in lung tissue infected with MERS-CoV and improve lung function in animal model [81]. The in vitro study revealed that, compared with ribavirin or favipiravir, remdesivir in combination with emetine showed the inhibition in viral yield that might achieve 64.9% [82]. Regarding its clinical application, Grein et al. reported the good improvement among severe COVID-19 cases (68%, n = 53) after treatment with remdesivir [83]. It also showed promising results in the treatment of a patient with COVID-19 in the USA [84]. However, its efficacy is doubted because, e.g., in a randomized, double-blind, placebo-controlled, multicenter trial, Wang et al. reported no statistically significant clinical benefits [85].

Chloroquine is a drug used to treat malaria [86]. It is taught that chloroquine has a great potential to treat COVID-19 [87]; chloroquine can prevent pH-dependent steps of the replication of several viruses such as SARS-CoV [88]. Additionally, chloroquine has immunomodulatory effects by suppressing the production/release of TNF- $\alpha$  and IL-6. It also might interfere with viral infection and replication, as an autophagy inhibitor [89]. In preprinted paper, Chen et al. showed that hydroxychloroquine use can shorten the time to clinical recovery in COVID-19 patients [90]. Gautret et al. claimed that the treatment of COVID-19 patients with hydroxychloroguine (chloroquine analog) caused the significant viral load reduction/disappearance [91]. However, other researchers did not reveal the same effect. Moreover, high-dose chloroquine diphosphate in combination with azithromycin or oseltamivir resulted in high rates of death and adverse cardiac events [92]. Clinicians also cautioned that the increased consumption of chloroquine and hydroxychloroquine can lead to their shortage that might create a problem for people suffering systemic lupus erythematosus, other rheumatological disorders, primary Sjögren syndrome, dermatological diseases, and antiphospholipid syndrome [93].

It has been previously reported that the protease inhibitors such as lopinavir and ritonavir, used to treat infection with human immunodeficiency virus (HIV) [94], could improve the outcome of MERS-CoV- [95] and SARS-CoV [96]-infected patients. Initially, lopinavir and ritonavir were hypothesized to inhibit the 3-chymotrypsin-like protease of SARS and MERS, and seemed to be associated with improved outcomes of patients with SARS in a non-randomized open-label trial. In a case report from Korea, it has been shown that the viral loads of a SARS-CoV-2 significantly decreased after lopinavir/ ritonavir treatment [97]. However, it is controversial whether HIV protease inhibitors could effectively inhibit the 3-chymotrypsin-like and papain-like proteases of SARS-CoV-2. HIV protease belongs to the aspartic protease family, whereas the two coronavirus proteases are from the cysteine protease family. Moreover, HIV protease inhibitors were specifically optimized to fit the C2 symmetry in the catalytic site of the HIV protease dimer; however, this C2-symmetric pocket is absent in coronavirus proteases. If HIV protease inhibitors alter host pathways to indirectly interfere with coronavirus infections, their potency remains a concern [98].

Favipiravir is a new type of RNA-dependent RNA polymerase inhibitor. Additionally, it is capable of blocking the replication of other RNA viruses [99]. Favipiravir is converted into an active phosphoribosylated form (favipiravir-RTP) in cells and is recognized as a substrate by viral RNA polymerase, therefore inhibiting RNA polymerase activity [100]. Favipiravir may have potential antiviral action on SARS-CoV-2, which is a RNA virus. In a clinical trial on favipiravir



for the treatment of COVID-19, the preliminary results indicated that favipiravir had more potent antiviral action than lopinavir/ritonavir [101].

#### **BCG** vaccine

Bacillus Calmette-Guérin (BCG; weakened strain of Mycobacterium bovis) vaccination could have protective effects against COVID-19 infection. There are several mechanisms that ensure BCG-induced non-specific protection and are actively studied. BCG and viral antigens have similar molecular structure; so after vaccination, B and T cells can recognize both pathogen types. Moreover, BCG vaccination results in the so-called trained immunity—epigenetic reprogramming of innate immune cell types [102]. Monocytes of vaccinated individuals had higher expression of different surface markers of activation and synthesis of cytokines (IL-1β, IL-6, IFNγ, and TNF) in response to infection than those of non-vaccinated ones; so nonmycobacterium pathogens, e.g., staphylococci, yellow fever virus, and influenza, can be removed faster [103]. In several preprints, it is claimed that BCG vaccination program could reduce the number of SARS-CoV-2-infected individuals and their mortality [104, 105]. However, the WHO does not recommend BCG vaccination to prevent COVID-19 because there is still no direct evidence that it can protect against SARS-CoV-2 infection, and all related clinical trials are ongoing [106].

#### **Corticosteroids**

Corticosteroids are well-known with their immunosuppressive activity, which are essential to stop or delay the progression of the pneumonia and have been proved to be beneficial for the treatment of ARDS [107]. Additionally, corticosteroids have an anti-inflammatory effect to diminish systemic inflammation, reduce exudative fluid in the lung tissue, and inhibit further diffused alveolar damage, which can relieve hypoxemia which can protect the lungs effectively and prevent further progression of respiratory insufficiency [108]. The use of corticosteroids for the treatment of COVID-19 is controversial due to their negative impact on anti-viral immune responses [109]. However, it has been shown that corticosteroids could improve mortality in severe COVID-19 patients with systemic hyperinflammation [110]. It is supposed that patient selection, half-life, formulation, and dosage of the corticosteroids are important factors determining the clinical outcome. In this regard, a preprinted study indicated that in severe COVID-19 patients with ARDS early short-term and low dose of corticosteroid (methylprednisolone) improved clinical manifestation and long lesions [111].



Although it seems that antiviral drugs are effective in improving clinical manifestation and controlling the SARS-CoV-2 infection, until now, there is no definite treatment protocol for this novel virus infection. Lymphocytopenia alongside with excessive inflammation and cytokine storm followed by ARDS in these patients are still unsolved problems that cause severity of the disease [14]. Therefore, it is considered that immune response modulation and inflammation management are essential steps. Based on the abovementioned, more studies needed to be conducted on immunopathogenesis and immune response during the SARS-CoV-2 infection. In this regard, new therapeutic approaches including mesenchymal stromal cell therapy and immune cell therapy showed promising results.

#### Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

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