Current Updates and treatment Strategy of the European and WHO Registered Clinical Trials of Coronavirus Disease 2019

Henu Kumar Verma¹, Neha Merchant², Manish Kumar Verma³, Cansu İlke Kuru⁴, Anand Narayan Singh³, Fulden Ulucan⁵, Poonam Verma⁶, Antaripa Bhattacharya⁷ and L.V.K.S Bhaskar⁸*

¹Institute of Experimental Endocrinology and Oncology CNR, Naples, Italy. Email: henu.verma@yahoo.com
²Department of Hematology and Medical Oncology, Winship Cancer Institute, Emory University, Atlanta, GA 30322
³Department of Biochemistry, G.S.V.M. Medical College, Kanpur, India. Email: manishverma8919@gmail.com, anandnarayansingh@gmail.com
⁴Ege University Faculty of Science and Buca Municipality Kızılıçulu Science and Art Center, Izmir, Turkey Email: cansuilke89@gmail.com,
⁵Department of Bioengineering, Ege University, Bornova, Izmir, Turkey Email: ulucanfulden@gmail.com
⁶Department of Biotechnology, IFTM University, Moradabad, India Email: president.ssr@gmail.com
⁷Department of Molecular Medicine and Medical Biotechnology, University of Naples “Federico II”, Naples, Italy Email: antaripa1210@gmail.com
⁸Department of Zoology, Guru Ghasidas Vishwavidyalaya, Bilaspur, India Email: lvksbhaskar@gmail.com

Conflicts of interest
The authors have declared that there are no conflicts of interest.

*Corresponding Author
Dr. L.V. K.S. Bhaskar, PhD.
Professor of Zoology
Dean, SoS in Life Sciences
Guru Ghasidas University, Bilaspur, Chhattisgarh, India
Email: lvksbhaskar@gmail.com
Mobile: 8224979600
Current Updates on the European and WHO Registered Clinical Trials of Coronavirus Disease 2019 (COVID-19)

Abstract

Background: Coronavirus disease 2019 (COVID-19) is a major public health concern currently. To date, there are no approved antiviral drugs or vaccines against this transmissible disease. This report sheds light on available information for a better understanding of clinical trials and pharmacotherapy related to COVID-19.

Methods: MEDLINE, PubMed, EMBASE, Scopus databases, Web of Science, WHO, and EU clinical trial sites were used to perform comparative analysis. Information was collected on the use of therapeutic agents for human therapy in patients with COVID-19 up to May 2020.

Results: We have extracted data from 60 clinical trials. Amongst these trials, 34 were from the European Union database of clinical trials and 26 from the National Institute of health. The data selection procedure includes active, completion, and recruitment in progress status. Most of the clinical trials are ongoing and hence, there is a lack of precise results for the treatment.

Conclusions: There is a lack of high-quality clinical evidence. The protocol to be developed requires large randomized clinical trials with a combination of available drugs and prospective therapies. We propose the usage of a large number of cases and different statistical analyses to conduct systematic clinical trials. This could provide comprehensive information about the clinical trial and potential therapeutic progress.

Keywords: COVID-19, Corona Pandemic, Vaccination, Clinical trials, Therapeutic
**Introduction**

COVID-19 is a pneumonia-like disease, which is caused by a novel coronavirus [1]. Coronavirus belongs to Orthocoronavirinae subfamily of the Coronaviridae family within the order Nidovirales. COVID-19 is the defining global health crisis that has spread over 205 countries including USA, Italy, Russia, Spain, Japan, Korea, Iran, and Germany [2, 3]. By the end of December 2019, a serious pneumonia like cluster of cases with unknown source expanded globally from Wuhan, China [4]. Various reports suggest that the novel coronavirus is 96.2% identical to a bat CoV RaTG13 [5, 6]. Evolutionary analysis of virus genome has suspected bat as a natural host of the virus origin that could have been transmitted from an unknown intermediate host to the humans [7]. The infection poses a significant risk to patients with COVID-19 due to the high frequency of pneumonia, fever, and dry cough. Additionally, patients suffer from the potential damage of vital organs, especially the lungs, heart, liver, and kidneys [8-10]. As per the latest reports from China, the mortality rate of COVID-19 disease is approximately 3-4% [11]. The latest data obtained on 30 June 2020 describes that COVID-19 has infected more than Ten million people worldwide. Amongst these cases, 5.6 million have been successfully treated and 5,08,422 has died. The number of infected people is increasing every day by one thousand worldwide.

Recently, severity model based analysis has showed that the fatality ratio for China is 0-66%, on the Diamond Princess ship is 2.3%, and the large meta-analysis of 36 European countries showed the case-fatality rate of COVID-19 range of 4% to 4.5% with an increasing profile with age [12-14]. Furthermore, in current scenario, India is ranked as the fourth highest country with positive cases and a case-fatality rate of 1.9 to 3.6 % [15]. In the current situation, a second wave of coronavirus has hit the major cities of European countries including Sao Paulo.
and Rio de Janeiro, which is the centre for pandemic. Till date, more than 1.3 million positive cases have been identified in Brazil [16]. In Russia, more than 687,862 cases and 10,296 deaths due to COVID-19 infection has been reported [17].

In order to treat COVID-19, the only available treatment currently available is the retroviral therapy. Further, it was proven that convalescent plasma transfusion (CPT) is useful against COVID-19 [18, 19]. At this crucial moment, in-depth research is essential to treat and prevent the disease. Several researchers have promptly carried out clinical research aimed towards the diagnosis, treatment, and prevention of COVID-19 [20]. However, globally there is limited information available to analyze and summarize the registered clinical trials. The purpose of this review is to summaries existing COVID-19 clinical trial data that would aid in selecting the most appropriate COVID-19 treatment.

Methods

Search strategy and selection criteria
Using various keywords related to COVID-19 including comorbidities, clinical characteristics, epidemiological, immunotherapy, vaccine, and SARS CoV-2 clinical trial data were obtained from different electronic databases. Some of these databases were European union clinical trials database, Clinical Trial Registry, Clinicatrial.gov, International Clinical Trials Registry Platform (WHO ICTRP), Chinese Biomedical Literature Database, and the Wanfang Database. Pubmed, the National Library of Medicine (NLM), and EMBASE database were also used to identify ongoing trials.

Literature inclusion and exclusion criteria
All investigators have selected only the most appropriate and suitable studies. Inclusion criteria encompasses the following: (1) studies of COVID-19 patients’ clinical trials (2) detailed protocol
of clinical trials (3) data mining (4) the original design type (Interventional or observational) (5) reports that involved the treatment of COVID-19. The exclusion criteria includes the following: (1) studies having duplicate data and (2) vague theoretical research and unregistered clinical trials.

Quality assessment

Quality of clinical data and extracted data from the literature were assessed by rigorous information cross-check. Discrepancy between the investigators was resolved and the final decisions were decided without any conflicts. Relevant data was summarized in a narrative manner and the treatment strategy was grouped. Each table was categorized according to the drug usage. Results were classified based on the type of study, country, dose, duration of administration, an indication of medication, and the number of patients included in the study.

Results

Trial search outcomes

34 clinical trials from the European Union clinical trial database and 26 clinical trials from the National Institute of Health (NIH) clinical trial database were retrieved and presented in the flow chart (figure 1). A total of 60 clinical trials of COVID-19 were classified as either active, completed, or recruiting. 8 patients used hydroxyquinone alone or in combination with other drugs, 6 used remdesivir, 5 used Tocilizumab, Lopinavir/ritonavir either single or combined, 4 used Interferon alpha and beta, and 4 patients used Plaquenil. All other remaining cases used different types of molecules or interventions (Table 1 and Table 2). Above all, most of the trials have cleared the ethical approval. Some of the case studies are still in the recruitment phase,
whereas 20 trials have begun recruiting patients. Amongst them, only 4 trials are in active phase and in the next few days, patient recruitment will begin. 2 clinical trials are still incomplete.

The first randomized controlled clinical pathways were sponsored by Dongzhimen Hospital of the Beijing University of Traditional Chinese Medicine (medical aspects of traditional knowledge that developed over generations). Those drugs were registered as "Chinese Severe Pneumonia Medicine with Severe Coronavirus Pneumonia" on 3 January 2020. In this review, we have included 60 trials in terms of clinical trial phases. Amongst them, 43 trials are in the preliminary experimental phase, 7 are in the middle phase, 8 are in phase 3 and extended for validation. 1 trial is completed with Ganovo+ritonavir+/-Interferon nebulization drugs and ready for sale as the same diagnostic kit (Quest Diagnostics, Bill and Melinda).

**Intervention and evaluation**

The leading intervention strategy of registered clinical trials consists of traditional Chinese medicine, western medicine, and conventional integrated treatment. Especially, the outcome of therapy includes treatment time, patient immunity, frequency of use of ventilation, mortality, number of complications, and virological detection indicators. Current duration of the medication is more than 10 days. Medicinal approaches include oral, injection, and inhalation. The control subject was treated regularly with a placebo. At present, 24 western medicinal treatments are registered in clinical trials. On the other hand, single or combination of biological agents such as hydroxychloroquine, camostat mesilate, sargramostim, colchicine, tocilizumab, remdesivir, Itraconazole, IFX-1, Imatinib mesilate, Interferon beta-1a (IFN-β1a), Sarilumab, Budesonide, and Nitric Oxide 0.5 % / Nitrogen 99.5 % Gas for Inhalation, Recombinant human angiotensin-converting enzyme 2, Plaquenil, lopinavir/ritonavir, RoActemra, Chloroquine
phosphate, Hydrocortisone, Levofloxacin, Emapalumab, Anakinra, Sarilumab, Danoprevir+ritonavir+/−Interferon, Emtricitabine/tenofovir are listed as intervention methods. Two clinical trials include biological agents (product mRNA, blood stem cells, cord blood mononuclear cells, mesenchymal stem cell (MSC), recombinant cytokine gene-derived vector, and immunoglobulin (IgM, IgG).

**Discussion**

Since the impact of COVID-19 is extremely severe, the development of an effective treatment strategy against the infection is very critical and concerning throughout the world. Although the molecular diagnosis, treatment, and international public health has improved after experiencing the 2003 SARS (CoV-I) epidemic, due to the new mutant form of the COVID virus, it is difficult to diagnose and treat the infection. Moreover, there is no proven or recognized licensed therapy against COVID-19. This sudden event has caused a high mortality rate in China and other countries around the world, mainly the European regions. The current situation leads us to carry out a systematic review to summarize the on-going clinical trials and possible therapeutic options against COVID-19 [1, 21, 22]. Intensive clinical trials are being conducted by many researchers to eradicate this disease.

Most of the reports demonstrate the intervention of western medicine and a combination of traditional medicine to treat COVID-19 infection. Most of the studies are still in the preliminary experimental phase of the clinical trail. There are 43 extended (Phase 1) trial studies that show the utilization of drugs (Hydroxychloroquine, Camostat mesilate, Sargramostim, Colchicine, Tocilizumab, Remdesivir, Itraconazole, IFX-1, Imatinib mesilate, Interferon beta-1a
(IFN-β1a), Kevzara, Budesonide, Lopinavir/ritonavir, RoActemra, Chloroquine phosphate, Hydrocortisone, Levofloxacin, Emapalumab, Anakinra, Sarilumab). According to the population size used in the clinical trial, 18 interventional clinical trials were carried out, which included 4 to 4000 candidates/trials and 8 observational studies, that included around 1000 to 3000000 candidates. Most of the trials are on-going; thus, the confirmation level and the clinical significance is limited (Table 1).

The alternative strategy to fight against COVID-19 is mainly based on boosting immune responses and to prevent the disease complications. This strategy improves patient immunity by predominating self-immune damage to the cytokine storm (modulating the post-infection immune response) and symptomatic treatment [23]. Although some Chinese herbs have shown both antiviral and high immune effects, current situations prove that the antiviral effect of western drugs is superior and tolerable in comparison to the traditional ayurvedic, Unani, or homeopathic medicines [24, 25]. The combination of Qingfeipaidutang and hydroxychloroquine phosphate might be a potential therapeutic strategy for the treatment and management of COVID-19 [26, 27]. Recently, an open-label, randomized clinical trial of standard medical treatment or colchicine (1.5-mg loading dose by 0.5 mg after 60 min and maintenance doses of 0.5 mg twice daily) in 105 patients showed that event-free survival time was 20.7 days in the colchicine group and 18.6 days in the control group and a significantly improved time to clinical deterioration [28]. Another multicenter, open-label randomized controlled trial in 160 patients with Shenhuang granule (50 g of Panax ginseng C. A. Mey, 40 g of Rheum palmatum L. stem, 30 g of Sargentodoxa cuneata stem, 30 g of Taraxacum mongolicum, 50 g of Aconiti Lateralis Radix Praeparata, and 6 g of Whitmania pigra Whitman) twice a day for 14 days is underway and the trail results are awaiting [29].
Still, there is a lack of high-grade substantiation evidence that demands further clinical clarification and verification. Several clinical researchers have used biological products for the treatment of COVID-19. In order to treat COVID-19 infection, Steroid-based therapy has been implemented and the result availability is limited for trials [13, 30]. The most commonly used drug is chloroquine (anti-malaria) and ribavirin with a broad-spectrum antiviral combination of Remdesivir and IFN-α2b. An interventional study based in Spain was registered at ClinicalTrials.gov on 1 April 2020 (ID: NCT04334928). Currently, this is the only clinical trial underway with Emtricitabine/tenofovir disoproxil / hydroxychloroquine against COVID-19 infection. Due to minimal interaction, the combination of baricitinib and lopinavir/ritonavir / remdeviate antivirals was used to treat the infection COVID-19 during the pandemic. The combination of baricitinib and above-mentioned drugs may reduce viral replication, infectivity, and aberrant host inflammatory response [31].

**Future Perspective**

In most trials, inclusion and exclusion criteria has eliminated children under 18 years, pregnant women, and comorbidities like liver, heart, and kidney disease. This may result in a lack of substantial clinical evidence. The quality of clinical research needs to improve drastically. Registered clinical trials must follow Observatory / Interventional Clinical Trial Guidelines. Clinical trials must not be registered without accurate drug testing. Safety guidelines for *in vitro* experiments during clinical trials are a major concern. Thus, The National Science Research Administration (NASR) should consider improving the health risks assessment, good research practice, and coordination of fewer promising drugs i.e.; Remdesivir. Moreover, a major
limitation of the registered clinical studies is that most of them follow a traditional conservative approach without considering the timeline.

**Conclusion**

Due to the lack of intensive and high-quality clinical evidence, there is no final consent to the ideal therapy for COVID-19. It is difficult to obtain reliable data even with a small sample size and prolonged study periods. There is a undoubted need for protocol development that can be used for large randomized clinical trials. In order to establish such clinical trials, prospective therapies must be designed. The NASR must improve the good clinical practice in research and coordination along as well as aid in improving the efficacy and quality of the study that could deal with current health emergencies. Besides, during clinical trials, the implementation of a variety of study designs with a large number of cases and different statistical analyses is crucial. Further; we must recognize the ancient history report of previous infectious diseases in order to implement novel conceptual health-related policies.

**Ethics approval and consent to participate**

Not applicable.

**Consent for publication**

All authors have read the manuscript and approved this submission.

**Availability of data and materials**

Not applicable.

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Not applicable
Contribution of the authors

The authors HKV have conceived the study MKV, CIK, PV, and FU have retrieved the data, HKV, ANS, AB and BLVKS wrote the manuscript and approved the final version and made manuscript technically sound.

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| NOS | NCT Number | Title                                                                 | Status      | Interventions                               | Sponsor                      | Age              | Phases | Enrollment | Study Type | Start Date | Completion |
|-----|------------|----------------------------------------------------------------------|-------------|---------------------------------------------|------------------------------|-------------------|--------|------------|------------|------------|------------|
| 1.  | NCT04333420| Open label, randomized phase ii/iii study of ifx-1 in patients with severe covid-19 pneumonia | Recruiting  | Best supportive Care (BSC) + IFX-1| InflaRx GmbH | 18-75 years and older | Phase 2 Phase 3 | 130 | Intervventional | 31-Mar-20 | 31-Dec-20 |
| 2.  | NCT04306497| Clinical Trial on Regularity of TCM Syndrome and Differentiation on Treatment of COVID- | Recruiting  | TCM prescriptions | Jiangsu Famous Medical Technology Co., Ltd. | 18-75 years | NA | 340 | Observational | 02-Mar-20 | May-20    |
| #  | Study Title                                                                 | Status   | Intervention Type | Age/Cohort       | Phase | Sample Size | Enrollment Start | Enrollment End |
|----|-----------------------------------------------------------------------------|----------|-------------------|------------------|-------|-------------|------------------|----------------|
| 3. | Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734,e) in Participants With Severe Coronavirus Disease (COVID-19) | Recruiting | Remdesivir        | Gilead Sciences  | 18 Years and older | Phase 3          | 400              | 06-Mar-20      |
| 4. | Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734,e) | Recruiting | Remdesivir        | Gilead Sciences  | 18 Years and older | Phase 3          | 600              | 15-Mar-20      |
|   |   |   |   |   |   |   |
|---|---|---|---|---|---|---|
|   |   |   |   |   |   |   |
| 5. | NCT04324489 | DAS181 for Severe COVID-19: Compassionate Use | Recruiting | DAS181 | Renmin Hospital of Wuhan University|Ansun Biopharma, Inc. | 18 Years to 70 Years | NA | 4 | Intervventional | 06-Mar-20 | 30-Apr-20 |
| 6. | NCT04330690 | Treatments for COVID-19: Canadian Arm of the | Active, not recruiting | Lopinavir/ritonavir | Sunnybrook Health Sciences Centre|AbbVie | 6 Months and | Phases 1-2 | 440 | Intervventional | 18-Mar-20 | NA |
| Nr. | Protocol ID | Study Title                                                                 | Recruitment Status | Treatment | Sponsor                        | Age Range | Intervention Phase | Duration | Clinical Status |
|-----|-------------|------------------------------------------------------------------------------|--------------------|-----------|--------------------------------|-----------|--------------------|----------|-----------------|
| 7.  | NCT04324021 | SOLIDARITY Trial: Efficacy and Safety of Emapalumab and Anakinra in Reducing Hyperinflammation and Respiratory Distress in Patients With COVID-19 Infection. | Recruiting         | Emapalumab, Anakinra | Swedish Orphan Biovitrum        | 30 Years to 79 Years | Phase 2 Phase 3 | 54       | Interventionsal  |
| 8.  | NCT04327388 | Sarilumab COVID-19: Recruiting Sarilumab | Recruiting         | Sarilumab | Sanofi|Regeneron Pharmaceuticals       | 18 Years and older | Phase 2 Phase 3 | 300      | Interventionsal  |
|   | Study Code | Title                                                                                   | Recruitment Status | Principal Investigator | No. of Participants | Study Design      | Start Date | End Date  |
|---|------------|-----------------------------------------------------------------------------------------|--------------------|------------------------|---------------------|-------------------|------------|-----------|
| 9. | NCT043 34954 | SARS-CoV2 Pandemic Serosurvey and Blood Sampling                                          | Recruiting         | NA                     | 18 Yrs and older    | Observational     | 09-Apr-20 | 31-Mar-22 |
| 10 | NCT043 25646 | Sero-epidemiological Study of the SARS-CoV-2 Virus in France: Constitution of a Collection of Human Biological Samples | Recruiting         | Institut Pasteur       | 5 Yrs and older     | Observational     | 13-Mar-20 | 28-Feb-23 |
| 11 | NCT043      | Household Recruiters Human biological samples                                           | Recruiting         | Institut Pasteur       | 5                  | Intervention      | 23         | 23-       |
|   |   | Transmissio  | Investigat  | Study for COVID-19 in French Guiana | Recrui  | Remdesivir | National Institute of Allergy and Infectious Diseases (NIAID) | Years to 99 Years | Pha  | Interventional | Years and older |   | Mar-22 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
|12 | NCT04280705 | Adaptive COVID-19 Treatment Trial (ACTT) | Recruiting | | | | | | 440 | Inter  | 21 - Feb-20 | 01- Apr-23 |
|13 | NCT04313127 | A Phase I Clinical Trial in 18-60 Adults | Active, not recruiting | Adenovirus Type 5 Vector | CanSino Biologics Inc.|Institute of Biotechnology, Academy of Military Medical Sciences. PLA of China|Jiangsu | 18 Yea  | Pha  | Interven  | 16 - Mar-20 | 20- Dec-22 |
| #  | NCT Number | Study Title                                                                 | Phase | Intervention Type    | Sample Size | Study Duration       |
|----|------------|-----------------------------------------------------------------------------|-------|----------------------|-------------|----------------------|
| 14 | NCT04321811| Behavior, Environment And Treatments for Covid-19                           | Recruiting | Human Biological samples | 18 Years and older | NA | 10000 | Observational | 21-Mar-20 | 20-Mar-22 |
| 15 | NCT04333654| Hydroxychloroquine in Outpatient, Adults With COVID-19                      | Recruiting | Hydroxychloroquine | Sanofi | 18 Years and older | Phase 1 | 210 | Interventional | 31-Mar-20 | May-20 |
|   | Study ID   | Study Title                                                                 | Phase | Intervention | Status   | Recruiting Date | Enrollment | Treatment Duration |
|---|------------|------------------------------------------------------------------------------|-------|--------------|----------|-----------------|------------|--------------------|
|16| NCT03808922| Phase III DAS181 Lower Tract PIV Infection in Immunocompromised Subjects (Substudy: DAS181 for COVID-19): RCT Study | III   | Intervenional| Recruiting|                |            | 23-May-19          |
|17| NCT04291729| Evaluation of Ganovo®Danoprevir Combined With Ritonavir in the               | IV    | Intervenional| Completed|                |            | 17-Feb-20          |
|   | Treatment of Novel Coronavirus Infection |
|---|------------------------------------------|
| 18 | Clinical Trial for the Prevention of SARS-CoV-2 Infection in Healthcare Personnel (EPICOS) |
| NCT043 34928 | Active, not recruiting |
|   | Emtricitabine/tenofovir disoproxil/Hydroxychloroquine |
|   | Plan Nacional sobre el Sida (PNS)Effice Servicios Para la Investigacion S.L. |
|   | 18 Years to 65 Years |
|   | Phase 3 |
|   | 4000 |
|   | Interventional |
|   | 01 - Apr-20 |
|   | 31-Jul-20 |
| 19 | Impact of Swab Site and Sample Collector on Testing Sensitivity for SARS-CoV-2 Virus |
| NCT043 21369 | Completed |
|   | Diagnostic tests |
|   | Dr. Deneen Vojta|Quest Diagnostics|Bill and Melinda Gates Foundation|UnitedHealth Group |
|   | 5 Years and older |
|   | NA |
|   | Observational |
|   | 09 - Mar-20 |
|   | 23-Mar-20 |
| Study ID | Title | Phase | Intervention | Duration |
|----------|-------|-------|--------------|----------|
| NCT04327804 | Longitudinal Study of SARS-CoV-2 Positive Patients Testing Nasal Swabs and Collecting Blood Samples for Research | Recruiting | Diagnostic Test | Dr. Deneen Vojta|PATH|Mayo Clinic|Bill and Melinda Gates Foundation | 5 Years and older | NA | 120 | Observational | 25 Mar-20 | 10-Apr-20 |
| NCT04283461 | Safety and Immunogenicity Study of 2019-nCoV Vaccine | Recruiting | mRNA-1273 | National Institute of Allergy and Infectious Diseases | 18 Years to 55 Years | Phase 1 | 45 | Intervventional | 03 Mar-20 | 01-Jun-21 |
| #  | Study Title                                                                 | Design                                                                 | Intervention                                                                 | Sponsor                                                                 | Phase | Intervention Type | Primary Completion Date |
|----|----------------------------------------------------------------------------|------------------------------------------------------------------------|-------------------------------------------------------------------------------|------------------------------------------------------------------------|-------|-------------------|------------------------|
| 22 | Inhaled Gaseous Nitric Oxide (gNO) Antimicrobial Treatment of Difficult Bacterial and Viral Lung (COVID-19) Infections | Active, not recruiting                                                 | Nitric Oxide 0.5% / Nitrogen 99.5% Gas for Inhalation                        | (NIAID) University of British Columbia/Mallinckrodt                  | 20    | Intervention      | 24-Oct-17              |
| 23 | Epidemiological Observation From a Smartphone                              | Recruiting                                                             | Device                                                                        | Weprom|Institut Pasteur|Assistance Publique - Hôpitaux de Paris|DOCAPOS | NA                    | 30000 00             | Observational          | 17-Mar-20              | 31-Jul-20              |
|   | Self-monitoring Application for Suspected COVID-19 Patients’ Triage | T|Direction GÂ©nÂ©rale de l'Offre de Soins |   |   |   |   |
|---|---|---|---|---|---|---|---|
| 24 | Safety and Efficacy of Hydroxychloroquine Associated With Azithromycin in SARS-CoV2 Virus (Coalition Covid-19 Brasil II) | Recruiting | Hydroxychloroquine + azithromycin | Hospital Israelita Albert Einstein|EMS|Hospital do Coracao|Hospital Sirio-Libanes|Brazilian Research in Intensive Care Network|CristÃ¡lia Produtos QuÃ­micos FarmacÃªuticos |   |   |   |   |
| NCT04321278 |   |   |   | 18 Years and older | Phase 3 | 440 | Interventional | 28-Mar-20 | 30-Aug-20 |
|   |   |   | Ltda. |   |   |   |
|---|---|---|---|---|---|---|
| 25 | Audio Data Collection for Identification and Classification of Coughing | Recruiting | NA | HealthMode Inc. | 18 Years and older | NA | 1000 | Observational | 25-Mar-20 | 25-Sep-22 |
| NCT04326309 |   |   |   |   |   |   |


| S.N. | Sponsors Name | Protocol No. | Study Title | Start Date | Ongoing / Completed | Population Age | No. of Subjects | Medical Condition | Active Substances | Level | Route | Country/ National Competent Authority |
|------|---------------|--------------|-------------|------------|---------------------|----------------|-----------------|------------------|------------------|-------|-------|------------------------------------|
| 1    | Akershus University Hospital | Ahus-NO-COVID-19 | Norwegian coronavirus disease 2019 (no covid-19) study: an open labeled randomized controlled pragmatic trial to evaluate the antiviral effect of chloroquine in adult patients with sars-cov-2 infection | 2020-03-23 | Ongoing | Adults, Elderly (18-64) | 200 | SARS-COV-2 infection | Hydroxychloroquine Sulfate 200mg | LLT | Oral | Norway |
| 2    | University of Oxford/ Clinical Trials and | PRINCIPLE | Platform Randomised trial of interventions against COVID-19 in older people | 2020-03-26 | Ongoing | Adults, Elderly (18-64) | 3000 | Suspected COVID-19 | Hydroxychloroquine Sulfate 200mg | PT | Oral | UK - MHRA |
|   | Research Governance | Study Title | Study Description | Start Date | End Date | Intervention | Comparator | Sponsor | Country |
|---|---------------------|-------------|-------------------|------------|----------|--------------|------------|---------|---------|
| 3 | Department of Infectious Diseases, Aarhus University Hospital | The Impact of Camostat Mesilate on COVID-19 Infection: An investigator-initiated randomized, placebo-controlled, phase iia trial | 2020-03-30 | Adults, Elderly (18-64) | 180 | 2019-nCoV acute respiratory disease | Camostat mesilate 100mg | Oral | Denmark - DHMA |
| 4 | University Hospital Ghent | A prospective, randomized, open-label, interventional study to investigate the efficacy of sargramostim (Leukine®) in improving oxygenation and short- and long-term outcome of COVID-19 | 2020-03-24 | Adults, Elderly (18-64) | 80 | Acute hypoxic respiratory failure of COVID-19 patients | Sargramostim 250ug | Intravenous | Belgium - FPS Health-DGM |
| No. | Sponsor | Study | Title | Start Date | End Date | Intervention | Treatment | Country | Notes |
|-----|---------|-------|-------|------------|-----------|--------------|-----------|---------|-------|
| 5   | Greek Society of Rhythmology | GRECCO-19 | The Greek study in the Effects of Colchicine in Covid-19 complications prevention | 2020-04-01 | Ongoing | Adults, Elderly (18-64) | Colchicine | Greece - EOF | Intra venous |
| 6   | Azienza Unità Sanitaria Locale -IRCCS di Reggio Emilia | RCT-TCZ-COVID-19 | Uno studio randomizzato multicentrico in aperto per valutare l’efficacia della somministrazione precoce del Tocilizumab (TCZ) in pazienti affetti da polmonite da COVID-19 | 2020-03-27 | Ongoing | Adults, Elderly (18-64) | Tocilizumab 20mg/ml | Italy - Italian Medicines Agency | Intra venous |
| 7   | CHU Angers | 49RC20_0071 | HYCOVID - Hydroxychloroquine versus placebo chez les patients ayant une infection COVID-19 à risque d’aggravation secondaire : étude | 2020-03-31 | Ongoing | Adults, Elderly (18-64) | Hydroxychloroquine 200mg | France - ANSM | LLT |
|   |   |   | prospective multicentrique randomisée en double aveugle |
|---|---|---|---------------------------------------------------------|
| 8 | F. Hoffmann-La Roche Ltd | WA42380 | A randomized, double-blind, placebo-controlled, multicenter study to evaluate the safety and efficacy of tocilizumab in patients with severe COVID-19 pneumonia. |
|   |   |   | 31-03-20 | Ongoing | Adults, Elderly (18-64) | 50 | COVID-19 pneumonia | Tocilizumab 20mg/ml | PT | Intra venous | France - ANSM |
| 9 | Regents of the University of Minnesota | 10 | A Multicenter, Adaptive, Randomised, Blinded Controlled Trial of the Safety and Efficacy of Investigational Therapeutics for the Treatment of COVID-19 in Hospitalized Adults - Version for European U... |
|   |   |   | 25-03-20 | Ongoing | Adults, Elderly (18-64) | 100, 50, 40 | Influenza COVID-19 | Remdesivir 100/200mg | HLT | Intra venous | Denmark - DHMA & UK - MHRA |
| 10 | UZLeuven | S63874 | Covid-19: A randomized, open-label, adaptive, proof-of-concept clinical |
|   |   |   | 26-03-20 | Ongoing | Adults, Elderly | 200 | COVID-19 | Itraconazole | LLT | Belgium - FPS Health- |
| #  | Sponsor                                      | Trial Name  | Description                                                                                                                                                                                                 | Duration | Phase | Study Type | Intervention                          | Country          | Route | DGM     |
|----|----------------------------------------------|-------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------|-------|------------|---------------------------------------|------------------|-------|---------|
| 11 | Sanofi - aventis recherche & développement | EFC16858    | An adaptive Phase 2/3, randomized, open-label study assessing efficacy and safety of hydroxychloroquine for hospitalized patients with moderate to severe COVID-19                                                                 | 2020-04-02 | Ongoing | Adults, Elderly (18-64) | Hydroxychloroquine 200 mg | PT Oral | UK – MHRA, France - ANSM |
| 12 | InflaRx GmbH                                 | IFX-1-P.2.9 | A pragmatic adaptive open label, randomized Phase II/III multicenter study of IFX-1 in Patients with severe COVID-19 Pneumonia - "PANAMO"                                                                                | 2020-03-29 | Ongoing | Adults, Elderly (18-64) | IFX-1 | PT Intravenous | Netherlands - Competent Authority |
| 13 | GUSTAVE ROUSSY                               | 2020/3078   | COVID-19 - Epidemiology of SARS-CoV-2 and Mortality to Covid19 Disease upon Hydroxychloroquine and Azithromycin                                                                                               | 2020-04-03 | Ongoing | Adults, Elderly (18-64) | LTT Oral | Hydroxychloroquine | France - ANSM |
| Study Number | Institution | Disease | Title | Study Type | Start Date | Duration | Eligibility | Primary Endpoint | Treatment | Location | Competency Authority |
|--------------|-------------|---------|-------|------------|-------------|----------|-------------|------------------|------------|-----------|----------------------|
| 14           | Amsterdam UMC | COVID-19 | COUNTER-COVID - Oral imatinib to prevent pulmonary vascular leak in COVID-19 – a randomized, single-blind, placebo controlled, clinical trial in patients with severe COVID-19 disease | Ongoing | Adults, Elderly (18-64) | 304 | Covid19 is characterized by hypoxemic respiratory failure, caused by extensive vascular leak and pulmonary edema early in the course of disease. | Imatinib mesilate | Oral | Netherlands - Competent Authority |
| 15           | ISTITUTO NAZIONALE PER LO STUDI O E LA CURA | COVID-19 | Multicenter study on the efficacy and tolerability of tocilizumab in the treatment of patients with COVID-19 pneumonia | Ongoing | Adults, Elderly (18-64) | 330 | COVID-19 | Tocilizumab 20mg/ml | PT | Italy - Italian Medicines Agency |
| No. | Sponsor | Study ID | Description | Start Date | Duration | Phase | Intervention Details | Location | Status | Route |
|-----|---------|----------|-------------|------------|----------|-------|----------------------|----------|--------|-------|
| 16  | Synairgen Research Limited | SG016 | A randomised double-blind placebo-controlled trial to determine the safety and efficacy of inhaled SNG001 (ifnβ-1a for nebulisation) for the treatment of patients with confirmed SARS-cov-2 infection... | 2020-03-17 | Ongoing | Adults, Elderly (18-64) | 200 | COVID-19 | Interferon beat-1a (IFN-β1a) | LLT | UK - MHRA |
| 17  | Assistance Publique - Hôpitaux de Paris | APHP200375 | Cohort Multiple randomized controlled trials open-label of immune modulatory drugs and other treatments in COVID-19 patients | 2020-03-25 | Ongoing | Adults, Elderly (18-64) | 1000 | COVID-19 | Kevzara, LLT, Intra venous | France - ANSM |
| 18  | DRCI   | APHP20039 | Protective role of inhaled steroids for... | 2020-03-25 | Ongoing | Adults, Not anno | COVID-19 | Budes, NA | | |France - |
| APHP | 4 | COVID-19 infection | 04-05 | Elderly (18-64) | onidation | Inhalation | ANSM |
|---|---|---|---|---|---|---|---|
| 19 | Gilead Sciences, Inc. | GS-US-540-5774 | A Phase 3 Randomized Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734™) in Participants with Moderate COVID-19 Compared to Standard of Care Treatment | 2020-03-18 | Ongoing | Adults, Elderly (18-64) | Remdesivir 100mg LLT | Germany - BfArM, Spain - AEMPS, France - ANSM, Netherlands - Authority, UK - MHRA, Sweden - MPA |
| 20 | Gilead Sciences, Inc. | GS-US-540-5773 | A Phase 3 Randomized Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734™) in Adolescents, Under 18, Adults, with Moderate COVID-19 Compared to Standard of Care Treatment | 2020-03-18 | Ongoing | 200, 20, 20, 45, 40, 35, 35, 40, 50, 100 | Remdesivir 100mg LLT | Germany - BfArM, Spain - AEMPS |
| N. | Sponsor | Study Code | Investigator | Study Design | Study Phase | Study Period | Patient Details | Study Intervention | Study Site |
|---|---|---|---|---|---|---|---|---|---|
| 21 | APEIRON Respiratory Therapies GmbH | APN01-01-COVID19 | | Recombinant human angiotensin-converting enzyme 2 (rhACE2) as a treatment for patients with COVID-19 | Ongoing | 2020-04-03 | Adults, Elderly (18-64) | Severe COVID-19 POSITIVE hospitalized male or female, between 35 and ≤ 80 years of age | Recombinant human angiotensin-converting enzyme | Denmark - DHMA |
| Trial ID | Sponsor | Trial Title | Participants | Intervention | Study Duration | Symptoms | Location | Comparator | Note |
|----------|---------|-------------|--------------|--------------|----------------|----------|----------|------------|------|
| 22 | Oslo University Hospital | WHO-NOR-COVID-19 | Adults, Elderly (18-64) | SARS-CoV-2 infection | 2020-03-26 | Plaquenil | Norway - NOMA |
| 23 | CHU de Saint Etienne | Evaluation of the concentration/viral effect relationship of hydroxychloroquine in COVID-19 patients in the intensive care unit | Adults, Elderly (18-64) | covid-19 | 2020-03-30 | Hydroxychloroquine sulphate 400-800mg | France - ANSM |
| 24 | University of Oxford | Randomised Evaluation of COVID-19 Therapy (RECOVERY) | Adults, Elderly (18-64) | COVID-19 (infection with SARS-CoV-2 virus) | 2020-03-17 | Lopinavir/ritonavir 200mg | UK - MHRA |
| 25 | Fondation Méditerranéenne Infections (FMI) - IHU Méditerranéenne Infections | 202002102 | Treatment of Coronavirus SARS-CoV2 Respiratory Infections with Hydroxychloroquine | 2020-03-05 | Ongoing | Adolescents, (12 to 17), Adults, Elderly (18-64) | 25 | Patients with documented respiratory infection with coronavirus SARS COV 2 | Plaquenil 200 mg | LLT, Oral | France - ANSM |
|----|-----------------------------------------------------------------------------|-----------|--------------------------------------------------------------------------------|-----------|---------|-----------------------------------------------|----|------------------------------------------------|----------------|--------|----------------|
| 26 | University Hospital Ghent | COV-AID | A prospective, randomized, factorial design, interventional study to compare the safety and efficacy of combinations of blockade of interleukin-6 pathway and interleukin-1 pathway to best standard .. | 2020-04-03 | Ongoing | Adults, Elderly (18-64) | 342 | COVID-19 patients with acute hypoxic respiratory failure and systemic cytokine release syndrome. | RoActemra | Intra venous | Belgium - FPS Health-DGM |
| No. | Institute | Trial ID | Description | Start Date | Phase | Arm 1 | Arm 2 | Treatment 1 | Treatment 2 | Treatment 3 | Treatment 4 | Treatment 5 | Treatment 6 | Outcome 1 |
|-----|-----------|----------|-------------|------------|-------|-------|-------|------------|------------|------------|------------|------------|------------|-----------|----------|
| 27  | INSERM    | C20-15   | Multi-centre, adaptive, randomized trial of the safety and efficacy of treatments of COVID-19 in hospitalized adults | 2020-03-09 | Ongoing | Adults, Elderly (18-64) | 1000 | COVID-19 | Plaquenil 200 mg | Oral | France - ANSM |
| 28  | University of Tübingen | COV-HCQ | Randomized controlled trial of hydroxychloroquine versus placebo for the treatment of adult patients with acute coronavirus disease 2019 – COVID-19 | 2020-03-25 | Ongoing | Elderly (>65) | 220 | Acute coronavirus disease 2019 | Chloroquine phosphate 200 mg | Oral | Germany - BfArM |
| 29  | University of Tübingen | UNIKINON-01/HOPE | CHROLOQUINE PHOSPHATE AGAINST INFECTION BY THE NOVEL CORONAVIRUS SARS-cov-2 (COVID-19): THE HOPE OPEN-LABEL, NON-RANDOMIZED CLINICAL TRIAL | 2020-04-02 | Ongoing | Adults, Elderly (18-64) | 60 | pneumonia from SARS-CoV-2 in patients staying home and improving symptoms of SARS-CoV-2 pneumonia in patients treated in hospital | Tocilizumab | Intra venous | Greece - EOF |
| 30  | Sanofi     | EFC16844 | An adaptive phase 2/3, randomized, | 2020-06-01 | Ongoing | Adults, 25, 40, | Corona virus | Hydrocortis | PT | Germany - |
| Study ID | Sponsor | Study Design | Intervention | Study Start | Study Duration | Study Population | Primary Outcome | Secondary Outcomes | Treatment | Comparator | Site(s) | Contact Information |
|----------|---------|--------------|--------------|-------------|----------------|------------------|-----------------|-------------------|-----------|-------------|--------|---------------------|
| 31       | University Medical Center | double-blind, placebo-controlled, study assessing efficacy and safety of sarilumab for hospitalized patients with COVID-19 | 03-26 | Elderly (18-64) | 25 | infection | one | BfArM, France - ANSM, Italy - Italian Medicines Agency | Intra venous |
| 32       | Hellenic institute for the study of ESCAPE | Reducing health care workers absenteeism in SARS-cov-2 pandemic by enhanced trained immune responses through Bacillus Calmette-Guérin vaccination, a randomized controlled trial (COVID-19). | 2020-03-17 | Ongoing | Adults, Elderly (18-64) | 1000 | SARS-CoV-2 infection | BCG-CORONA | Intra venous |
|          |         | Efficiency in management of organ dysfunction associated with infection by the novel sars-cov-2 virus (covid-19) through a | 2020-04-01 | Ongoing | Adults, Elderly (18-64) | 20 | Organ dysfunction by the novel SARS-Cov-2 virus | Tocilizumab 400mg | LTT | Greece - EOF |
| #  | Institution/Center | Study Identifier | Study Title | Start Date | Status | Eligibility | Treatment | Country(ies) |
|----|--------------------|------------------|-------------|------------|--------|-------------|-----------|-------------|
| 33 | The Parke Institute, Bispebjerg and Frederiksberg Hospital, | APPI2-CV-2020-01 | Effectiveness of Interleukin-6 Receptor Inhibitors in the Management of Patients with Severe SARS-CoV-2 Pneumonia: An Open-Label Multicenter Sequential Randomized Controlled Trial | 2020-04-3 | Ongoing | Adults, Elderly (18-64) | 200 | SARS-CoV-2 Infection | Tocilizumab 400mg | LLT | Intravenous | Denmark-DHMA |
| 34 | University Medical Center Utrecht | REMAP-CAP | Randomized, Embedded, Multifactorial, Adaptive Platform trial for Community-Acquired Pneumonia (REMAP-CAP) | 2015-09-16 | Ongoing | Adults, Elderly (18-64) | 600, 600, 40, 800, 200, 270, 600, 30, 60, 152 | Severe Community Acquired Pneumonia | Levofloxacin | LLT | Intravenous | Netherlands, Ireland, Portugal, UK-MHRA, Hungary, Belgium |
Table No 2: Characteristics of ongoing European Union Clinical Trials studying the efficacy and safety of Chloroquine, Tocilizumab, Lopinavir/ritonavir or other related formulation for patients with novel coronavirus pneumonia (COVID-19). LLT: Lowest Level Terms, PT: Preferred Terms, HLT: High-Level Terms, NA: Not Available
Fig. 1. Flowchart of study selection for the present study.
Highlight

- Clinical trials are essential for the development of new treatments for COVID-19.
- Drugs currently recommended treating COVID-19 such as hydrochloride, interferon, and Thalidomide plus can also be used with other combination.
- More clinical studies are needed to confirm the use of antiviral corticosteroids, if they prove to be effective in human clinical studies.
Conflicts of interest

All authors have declared that there are no conflicts of interest.