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Monthly update

# Research & development of treatments for COVID-19

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Updated September 2020

## Disclaimer

**No product against COVID-19 is approved. This document does not provide guidance on what medicines to take. Please avoid self-prescription and always refer to your doctor before making any treatment decision.**

This document provides a selection of updates on the research and development of treatments for COVID-19. Those highlights are for the information of patient organisations/ groups, advocates and people living with a rare disease. EURORDIS takes reasonable steps to verify the accuracy of the information presented. This document does not constitute, and shall not be deemed or construed as, any approval or endorsement by EURORDIS of such product or entity.

## Contents [\(click to navigate in document\)](#)

A 'must-read' introduction .....	4
Resources .....	5
Products in development .....	6
Summary Table .....	7
Latest news.....	9
Hydroxychloroquine: Lack of efficacy - stopped .....	9
Lopinavir / ritonavir: lack of efficacy - stopped.....	9
Remdesivir (Veklury®): authorised .....	9
Dexamethasone: under evaluation by EMA .....	9
Discovery and Solidarity Trials ADAPTED .....	10
Products to reduce SARs-coV2 viral growth .....	11
Azithromycin: lack of efficacy.....	11
Convalescent plasma transfusion: contradictory results .....	12
Plasma derived medicinal products: in progress .....	14
Polyclonal antibodies.....	15
Favipiravir: peer-reviewed results not yet published .....	16
Hydroxychloroquine: Lack of efficacy .....	17
Interferon-Beta-1a (Rebif®, Avonex®) and Interferon-Beta-1b (Betaferon®, Extavia®): in progress.....	17
Lopinavir / ritonavir: lack of efficacy .....	19
Remdesivir (Veklury®): authorised .....	20
Products to treat inflammation and/or respiratory illness.....	23

<b>Dexamethasone: under evaluation by EMA</b> .....	23
<b>Tocilizumab</b> .....	24
Other products not in this document .....	26
.....	27
Initiatives of interest .....	27
<b>Therapeutic trials</b> .....	28
<b>Discovery Trial ADAPTED</b> .....	28
<b>Solidarity trial</b> .....	30
<b>For all other clinical trials</b> .....	31

## A 'must-read' introduction

This document provides a selection of updates on the research and development of treatments for COVID-19. Those highlights are for the information of patient organisations/groups, advocates and people living with a rare disease. EURORDIS takes reasonable steps to verify the accuracy of the information presented. This document does not constitute, and shall not be deemed or construed as, any approval or endorsement by EURORDIS of such product or entity.

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EURORDIS has a role in disseminating up-to-date information that could be useful for people living with a rare disease, who are exposed to the SARS-coV2 virus infection. Some rare diseases constitute an aggravated risk when infected by C-19. Some products being studied for C-19 are already approved or used off-label for some rare diseases, with potential information confusion and shortages risks. In other rare diseases, some products being studied for C-19 may have medicinal products interactions with medicines used in the care of these diseases. All good reasons to inform patient advocates with curated though raw information material to empower their respective actions. EURORDIS's Task Force on Drug Information, Transparency and Access (DITA) was tasked to prepare and regularly

update this document. This task force is composed of EURORDIS volunteers and staff.

This document is an editorial selection and highlights the most recent developments for products being currently tested in phase III clinical trials, measuring their efficacy and toxicity. It is by no mean an exhaustive list of all therapeutic research. To avoid repeating the same situation than for the last Ebola outbreak, where the evaluation of potential treatments could not be completed (not enough participants as the trials were started too late), clinical trials against COVID-19 were authorised very soon after the epidemic started. The priority is to enrol participants in authorised trials.

For any questions or clarification, please contact François Houyez: [francois.houyez@eurordis.org](mailto:francois.houyez@eurordis.org)

## Resources

- EUnetHTA Covid-19 Rolling Collaborative Reviews <https://eunethta.eu/rcro1-rcrxx/>
- Horizon scanning for treatments and vaccines by the Austrian HTA institute GÖG <https://eprints.aihta.at/1234/>
- World Health Organization: [https://www.who.int/blueprint/priority-diseases/key-action/Table\\_of\\_therapeutics\\_Appendix\\_17022020.pdf?ua=1](https://www.who.int/blueprint/priority-diseases/key-action/Table_of_therapeutics_Appendix_17022020.pdf?ua=1)  
All trials for COVID-19: [https://www.who.int/docs/default-source/coronaviruse/covid-19-trials.xls?sfvrsn=a8be2a0a\\_6&ua=1](https://www.who.int/docs/default-source/coronaviruse/covid-19-trials.xls?sfvrsn=a8be2a0a_6&ua=1)
- The NIH register of clinical trials includes 210 clinical trials to treat COVID 19 (as of 30 March 2020). You can consult here: <https://clinicaltrials.gov>

And also

- A review of the most advanced research was published here in March 2020:  
Research and Development on Therapeutic Agents and Vaccines for COVID-19 and Related Human Coronavirus Diseases. Cynthia Liu et al. ACS Cent. Sci., 315-331. Published 12/03/2020  
<https://pubs.acs.org/doi/10.1021/acscentsci.0c00272>
- Other information (infography): <https://www.visualcapitalist.com/every-vaccine-treatment-covid-19-so-far>
- Video on the pathophysiology of the virus, the dynamic of the pandemic and how to fight it  
<https://youtu.be/BtN-goy9VOY>

## Products in development

This document is a summary of information on products in development to treat COVID-19, intended for people living with a rare disease. Sources include the European Medicines Agency and EUnetHTA, the European Network of HTA Agencies that publishes rolling collaborative reviews and horizon scanning reports.

Of all products in development to treat COVID-19, the EURORDIS's Drug Information, Transparency and Access Task Force decided the following selection for its own review:

1. The most advanced treatments or vaccines: products in clinical development already, with emphasis on products in phase II, phase II/III and/or phase III.
2. Products with specific issues on efficacy or safety for some groups of rare diseases (e.g. drug-drug interaction between a product to treat COVID-19 and other medicines used to treat a rare disease)
3. Possible supply tensions, when a product already used to treat a rare disease is now tested to treat COVID-19, thus creating potential tensions on the supply

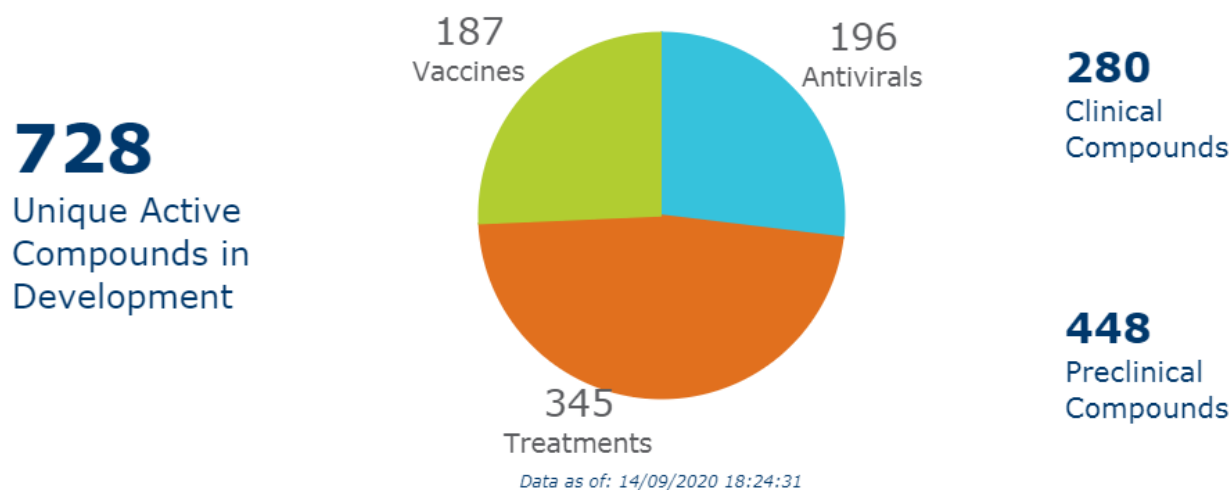


Figure 1: <https://www.bio.org>

## Summary Table

	<i>Authorisation holder or developer</i>	<i>Generic forms</i>	<i>Mechanism of action for COVID-19</i>	<i>Available evidence</i>	<i>Status</i>
<a href="#"><i>Azithromycin</i></a>	Hundreds different MAHs in EU/EEA	Yes	Some broad-spectrum antiviral activity in vitro. Often added to Hydroxychloroquine in trials and compassionate use programmes	Weak. Published: One open label non-randomised trial <sup>1</sup> , and one cohort <sup>2</sup>	Clinical research stopped
<a href="#"><i>Convalescent plasma</i></a>	NA	NA	Antibodies from healed COVID-19 patients, re-injected to active COVID-19 patients	Large hospital datasets, cohorts studies, randomised trials, few results published	In progress
<a href="#"><i>Favipiravir</i></a>	Toyama Chemical	No	Broad antiviral activity against RNA viruses. Targets RdRp (the RNA-dependent RNA polymerase), leading to inaccurate viral RNA synthesis	Weak. One publication on interim results from a randomised, phase 2/3 clinical trial	In progress Authorised in Russia
<a href="#"><i>Interferon-Beta</i></a>	Several MAHs in the EU/EEA	Yes	It could help controlling the inflammatory response during COVID-19	Published results for 3 randomised controlled trials combination of interferon beta-1b with other products	Unclear if an effect
<a href="#"><i>Hydroxychloroquine</i></a>	21 different MAHs in EU/EEA	Yes	Clinical research stopped for lack of efficacy	All arms in randomised clinical trials were interrupted	stopped
<a href="#"><i>Lopinavir / ritonavir</i></a>	9 different MAHs in EU/EEA	Yes	Clinical research stopped for lack of efficacy	Studied in a number of clinical trials with overall no virological or clinical effect	stopped
<a href="#"><i>Polyclonal antibodies</i></a>	Takeda, Regeneron	NA	Antibody concentrates from convalescent patients' plasma		
<a href="#"><i>Remdesivir (Veklury®)</i></a>	Gilead Sciences	No	Broad-spectrum antiviral, with activity against RNA viruses such as coronaviruses. It targets the SARS-coV- RNA-dependent RNA polymerase needed for the virus replication	One main randomised clinical trial with published results, results are preliminary though (conditional authorisation)	authorised

<sup>1</sup> Gautret P. et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents. 2020:105949. Epub 2020/03/25. DOI: 10.1016/j.ijantimicag.2020.105949.

<sup>2</sup> Lane J. et al. Safety of hydroxychloroquine, alone and in combination with azithromycin, in light of rapid wide-spread use for COVID-19: a multinational, network cohort and self-controlled case series study. medRxiv. 2020:2020.2004.2008.20054551. DOI: 10.1101/2020.04.08.20054551

<a href="#"><u>Tocilizumab (has results)</u></a>	Roche	No	Some patients with severe COVID-19 might have a cytokine storm syndrome. Hyper-inflammation could be treated with therapies with proven safety profiles	Several RCTs and interventional studies with tocilizumab alone or in combination are ongoing	In progress
<a href="#"><u>Dexamethasone (marketing authorisation application submitted)</u></a>	Taw, Mylan....	yes	The proposed mechanism of glucocorticoids involves the mitigation of an excessive immune response that can lead to acute respiratory distress syndrome (ARDS) and multi-organ failure	Several randomised trials in progress, in particular the RECOVERY trial	Evaluation in progress by EMA



## Latest news

### Hydroxychloroquine: Lack of efficacy - stopped

Due to the lack of effectiveness of chloroquine and Hydroxychloroquine in treating COVID-19 patients and in light of serious adverse effects as well as the decisions to stop enrolling participants in the Hydroxychloroquine arm of the RECOVERY and SOLIDARITY trials, reporting related to these two pharmaceuticals was stopped.

### Lopinavir / ritonavir: lack of efficacy - stopped

The University of Oxford, the WHO and INSERM publicly announced that the lopinavir-ritonavir (Kaletra®) arms of the RECOVERY, SOLIDARITY and DISCOVERY studies in adults hospitalised with severe COVID-19 will be stopped given the data showed no beneficial effect.<sup>3</sup>

### Remdesivir (Veklury®): authorised

Patients who received remdesivir had a 31% faster time to recovery than those who received placebo ( $p < 0.001$ ). Specifically, the median time to recovery was 11 days for patients treated with remdesivir compared with 15 days for those who received placebo. Results also suggested a survival benefit, with a mortality rate of 8.0% for the group receiving remdesivir versus 11.6% for the placebo group ( $p = 0.059$ ).<sup>4</sup>

Remdesivir is authorised to treat COVID-19 in the European Union (conditional marketing authorisation, 03 July 2020).<sup>5</sup>

### Dexamethasone: under evaluation by EMA<sup>6</sup>

The EMA is currently evaluating a marketing authorisation for Dexamethasone Taw. Should the available data show that the benefits of Dexamethasone Taw outweigh its risks in the treatment of hospitalised adults with COVID-19, EMA will issue a positive recommendation on the medicine's new use in patients with COVID-19. The agency will then liaise with the European Commission to fast-track the authorisation.

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<sup>3</sup> <https://www.recoverytrial.net/news/no-clinical-benefit-from-use-of-lopinavir-ritonavir-in-hospitalised-covid-19-patients-studied-in-recovery>

<sup>4</sup> <https://www.niaid.nih.gov/news-events/nih-clinical-trial-shows-remdesivir-accelerates-recovery-advanced-covid-19>

<sup>5</sup> [https://ec.europa.eu/commission/presscorner/detail/en/mex\\_20\\_1266](https://ec.europa.eu/commission/presscorner/detail/en/mex_20_1266).

<sup>6</sup> <https://www.ema.europa.eu/en/news/ema-receives-application-marketing-authorisation-dexamethasone-taw-covid-19>

## Discovery and Solidarity Trials ADAPTED

**31 July 2020:** both in Discovery and in Solidarity trial, lopinavir/ritonavir with or without  $\beta$ -interferon arms were interrupted, due to lack of efficacy. Discussions have started to decide on how to adapt the trial and to test other treatments, and which ones.<sup>7</sup>

Hydroxychloroquine was abandoned mid-June, due to lack of efficacy.

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<sup>7</sup> <https://www.inserm.fr/actualites-et-evenements/actualites/covid-19-inserm-sur-tous-fronts>

## Products to reduce SARs-coV2 viral growth

### Azithromycin: lack of efficacy

#### Rational

Proposed as an add-on treatment for its action against bacterial pneumopathies, and also as it showed some broadspectrum antiviral activity in vitro.

#### Results

Results from a large cohort of patients treated either with Hydroxychloroquine alone or azithromycin alone or with a combination of Hydroxychloroquine and azithromycin are **disappointing**: among patients hospitalised with COVID-19, **treatment with Hydroxychloroquine, azithromycin, or both was not associated with significantly lower in-hospital mortality**.<sup>8</sup> These negative results are consistent with other similar observational studies.<sup>9-10-11</sup>

<i>Adjusted Cox proportional hazards models, relative risk compared to receiving neither drugs</i>		<i>Hydroxychloroquine</i>	<i>Azithromycin</i>	<i>Hydroxychloroquine + azithromycin</i>
<i>Mortality</i> <i>No statistically significant difference</i>  <i>Cardiac arrest*</i>		Hazard ratio 1.08 [95% CI, 0.63-1.85] (not significant)	Hazard ratio 0.56 [95% CI, 0.26-1.21] (not significant)	Hazard ratio 1.35 [95% CI, 0.76-2.40] (not significant)
		adjusted OR, 1.91 [95% CI, 0.96-3.81] (not significant)	adjusted OR, 0.64 [95% CI, 0.27-1.56] (not significant)	adjusted <b>OR 2.13</b> [95% CI, 1.12-4.05] (significant difference compared to neither drugs)

\* No significant differences in the relative likelihood of abnormal electrocardiogram findings, e.g. no arrhythmias

<sup>8</sup> Rosenberg ES, Dufort EM, Udo T, et al. Association of Treatment With Hydroxychloroquine or Azithromycin With In-Hospital Mortality in Patients With COVID-19 in New York State. JAMA. May 11, 2020. doi:10.1001/jama.2020.8630

<sup>9</sup> Magagnoli J et al Outcomes of hydroxychloroquine usage in United States veterans hospitalized with Covid-19. medRxiv. Preprint posted April 23, 2020. doi:10.1101/2020.04.16.20065920

<sup>10</sup> Mahevas M, Tran V-T, Roumier M, et al. No evidence of clinical efficacy of hydroxychloroquine in patients hospitalized for COVID-19 infection with oxygen requirement: results of a study using routinely collected data to emulate a target trial. medRxiv. Preprint posted April 14, 2020. doi:10.1101/2020.04.10.20060699

<sup>11</sup> Geleris J, Sun Y, Platt J, et al. Observational study of hydroxychloroquine in hospitalized patients with Covid-19. N Engl J Med. May 7, 2020. doi:10.1056/NEJMoa2012410PubMed

## Convalescent plasma transfusion: contradictory results

### Rational

Convalescent plasma is plasma collected from patients that have recovered from an infectious disease and can be transfused to patients fighting an infection or can be used to manufacture immune globulin concentrates (plasma derived medicinal products). Possible explanations for the efficacy are that the antibodies from convalescent plasma might suppress viraemia and activate the complement system, thus promoting viral elimination.

Antibody is most effective when administered shortly after the onset of symptoms, and a sufficient amount of antibody must be administered. Plasma transfusions may be associated with transfusion reactions such as allergic reactions, antibody-mediated enhancement of infection, transfusion-related acute lung injury (TRALI) and circulatory overload.

Convalescent plasma was previously used for treatment of severe acute respiratory syndrome (SARS), pandemic 2009 influenza A (H1N1), avian influenza A (H5N1), several haemorrhagic fevers such as Ebola, and other viral infections with positive results related to different clinical outcomes.<sup>12 13 14</sup>

Six conditions must be met to deploy convalescent plasma treatment for COVID-19:

1. availability of a population of donors who have recovered from the disease and can donate convalescent serum
2. blood banking facilities to process the serum donations
3. availability of assays, including serological assays, to detect SARS-CoV-2 in serum and virological assays to measure viral neutralisation
4. virology laboratory support to perform these assays
5. prophylaxis and therapeutic protocols, which should ideally include randomised clinical trials to assess the efficacy of any intervention and measure immune responses
6. and regulatory compliance, including institutional review board approval

### Clinical experience against COVID-19

The clinical experience is limited, and first results are contradictory.

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<sup>12</sup> Casadevall A. and Pirofski L. The convalescent sera option for containing COVID-19. *J Clin Invest.* 2020;Mar 13(pii: 138003. doi: 10.1172/JCI138003

<sup>13</sup> Roback J. and Guarner J. Convalescent Plasma to Treat COVID-19 Possibilities and Challenges. *JAMA.* 2020;Mar 27(doi: 10.1001/jama.2020.4940

<sup>14</sup> Chen L., Xiong J., Bao L. and Shi Y. Convalescent plasma as a potential therapy for COVID-19. *Lancet Infect Dis.* 2020;Apr; 20(4):398–400. Published online 2020 Feb 2027. doi: 2010.1016/S1473-3099(2020)30141-30149.

### A large expanded access programme in the USA

As of August 15, 2020 one observational study was published by Joyner et al. 2020<sup>15</sup> from an open-label, Expanded Access Program (EAP) for the treatment of COVID-19 patients with human convalescent plasma (NCT04338360). They evaluated seven and 30-day mortality in 35,322 hospitalised adults transfused with COVID-19 convalescent plasma. This cohort included a high proportion of critically-ill patients, with 52.3% in the intensive care unit (ICU) and 27.5% receiving mechanical ventilation at the time of plasma transfusion. The seven-day mortality rate was 8.7% [95% CI 8.3%-9.2%] in patients transfused within 3 days of COVID-19 diagnosis but 11.9% [11.4%-12.2%] in patients transfused 4 or more days after diagnosis ( $p < 0.001$ ). Similar findings were observed in 30-day mortality (21.6% vs. 26.7%,  $p < 0.0001$ ). **Importantly, a gradient of mortality was seen in relation to IgG antibody levels in the transfused plasma. For patients who received high IgG plasma ( $>18.45$  S/Co), seven-day mortality was 8.9% (6.8%, 11.7%); for recipients of medium IgG plasma (4.62 to 18.45 S/Co) mortality was 11.6% (10.3%, 13.1%); and for recipients of low IgG plasma ( $<4.62$  S/Co) mortality was 13.7% (11.1%, 16.8%) ( $p = 0.048$ ).**

Authors concluded that the relationships between reduced mortality and both earlier time to transfusion and higher antibody levels provide signatures of efficacy for convalescent plasma in the treatment of hospitalised COVID-19 patients.

### Preprint from the ConCOVID trial

One randomised clinical trial appeared as preprint (NCT04342182), performed on 86 patients with COVID-19 (moderate-critical) admitted to 14 centres in the Netherlands, but halted prematurely.<sup>16</sup> ConCOVID was a randomised trial comparing convalescent plasma with standard of care therapy in Dutch patients hospitalised for COVID-19. Patients were randomised 1:1 and received 300ml of plasma with anti-SARSCoV-2 neutralising antibody titres of at least 1:80.

The primary endpoint was day-60 mortality and key secondary endpoints were hospital stay and WHO 8-point disease severity scale improvement on day 15.

The trial was halted prematurely after 86 patients were enrolled. Although symptomatic for only 10 days (IQR 6-15) at the time of inclusion, 53 of 66 patients tested had anti-SARS-CoV-2 antibodies at baseline. A SARS-CoV-2 plaque reduction neutralisation test showed neutralising antibodies in 44 of the 56 (79%) patients tested with median titres comparable to the 115 donors (1:160 vs 1:160,  $p = 0.40$ ).

Because these observations caused concerns about the potential benefit of convalescent plasma in the study population, after discussion with the data safety monitoring board, the study was discontinued. No difference in mortality ( $p = 0.95$ ), hospital stay ( $p = 0.68$ ) or day-15 disease severity ( $p = 0.58$ ) was observed between plasma treated patients and patients on standard of care. The authors concluded that most COVID-19 patients already have high neutralising antibody titres at hospital admission.

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<sup>15</sup> European Commission (EC). Coronavirus: European Commission strengthens support for treatment through convalescent plasma. 2020. Available from: [https://ec.europa.eu/commission/presscorner/detail/en/ip\\_20\\_1435](https://ec.europa.eu/commission/presscorner/detail/en/ip_20_1435)

<sup>16</sup> Gharbharan A. et al. Convalescent Plasma for COVID-19. A randomized clinical trial. MedRxiv.DOI: 10.1101/2020.07.01.20139857

## Caution

Plasma transfusions are generally safe and well-tolerated by most patients, but can cause allergic reactions and other side effects. It is also not known if patients with COVID-19 might have other types of reactions to convalescent plasma.<sup>17</sup>

Among plasma donors (people who fully recovered from COVID-19), there are some people also infected with HIV (they were infected before). Like for organ donations, discussions are taking place for HIV people to donate their blood to other HIV people suffering from COVID-19 (USA, Switzerland), but not to other COVID-19 patients.

## Plasma derived medicinal products: in progress

### Rational

Neutralising monoclonal antibodies to SARS-CoV-2 have the potential to be used for both prevention and treatment of infection. They can help to guide vaccine design and development as well.

The main target of SARS-CoV-2 neutralizing monoclonal antibodies is the surface spike glycoprotein that mediates viral entry into host cells. Some products will include of a combination of two monoclonal antibodies targeting different sites on the spike protein. Due to long half-life of most monoclonal antibodies (approximately 3 weeks for IgG1), a single infusion should be sufficient. A potential limitation of monoclonal antibodies for treatment of COVID-19 is the unknown bioavailability of passively infused IgG in tissues affected by the disease, especially the lungs, which serve as a key target of SARS-CoV-2 infection.

Due to the effect of viral diversity, it will be important to monitor for the emergence of resistant viral mutations under selective pressure of monoclonal antibody treatment.

To block disease progression, therapeutic trials will include treatment of patients with varying degrees of illness. In the prevention of COVID-19, passive infusion of monoclonal antibodies as pre-exposure or post-exposure prophylaxis might offer immediate protection from infection that could last weeks or months.

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<sup>17</sup> US Food and Drugs Administration, Investigational COVID-19 Convalescent Plasma - Emergency INDs Frequently Asked Questions. 26.03.2020, available online: <https://www.fda.gov/media/136470/download>

### Clinical research

In a press release on July 06, 2020, Regeneron Pharmaceuticals announced the initiation of late-stage clinical trials evaluating REGN-COV2, Regeneron's investigational double antibody cocktail for the treatment and prevention of COVID-19.<sup>18</sup>

1. A Phase 3 prevention trial will evaluate REGNCOV2's ability to prevent infection among uninfected people who have had close exposure to a COVID-19 patient (such as the patient's housemate). It is being run jointly with the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health (NIH). The Phase 3 prevention trial is being conducted at approximately 100 sites and is expected to enrol 2,000 patients in the U.S.
2. REGN-COV2 has also moved into the Phase 2/3 portion of two adaptive Phase 1/2/3 trials testing the cocktail's ability to treat hospitalised and non-hospitalised (or "ambulatory") patients with COVID-19. The two Phase 2/3 treatment trials in hospitalised (estimated enrolment =1,850) and non-hospitalised (estimated enrolment =1,050) patients are planned to be conducted at approximately 150 sites in the U.S., Brazil, Mexico and Chile, and will evaluate virological and clinical endpoints.

### Status

Current US NIH COVID-19 Treatment Guidelines state that there are insufficient clinical data to recommend either for or against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) immunoglobulins for the treatment of COVID-19.<sup>19</sup>

## Polyclonal antibodies

### Rational

TAK-888: Takeda initiated the development of an anti-SARS-CoV-2 polyclonal hyper-immune globulin (H-IG) to treat high-risk individuals with COVID-19, while also studying whether Takeda's currently marketed and pipeline products may be effective treatments for infected patients.<sup>20</sup>

Testing of antibody concentrates from convalescent patients' plasma by Takeda could take 10-12 months to complete.

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<sup>18</sup> <https://investor.regeneron.com/news-releases/news-release-details/regeneron-announces-start-regn-cov2-phase-3-covid-19-prevention>

<sup>19</sup> National Institute of Health (NIH). COVID-19 Treatment Guidelines. 2020. Available from: <https://covid19treatmentguidelines.nih.gov/introduction>

<sup>20</sup> Takeda Initiates Development of a Plasma-Derived Therapy for COVID-19. Published on 4th of March, 2020: <https://www.takeda.com/newsroom/newsreleases/2020/takeda-initiates-development-of-a-plasma-derived-therapy-for-covid-19/>

## Favipiravir: peer-reviewed results not yet published

### Rational

Medicine authorised as Avigan, Toyama Chemical, in Japan and China for flu (influenza). The active substance belongs to a class of products called pyrazinecarboxamide derivative, with a broad antiviral activity against many RNA viruses: flavi-, alpha-, filo-, bunya-, arena-, noro-, and other RNA viruses and may have antiviral action against Covid-19 disease (caused by SARS-CoV-2, which is a RNA virus).<sup>21</sup>

It targets the RdRp (the RNA-dependent RNA polymerase), its mechanism of action consists in a purine nucleoside that acts as an alternate substrate leading to inaccurate viral RNA synthesis.

### Clinical experience against COVID-19

As of 08/06/2020 two publications about the efficacy and safety of favipiravir to treat Covid-19 patients could be identified, in comparison with baloxavir marboxil (ChiCTR2000029544) or with umifenovir (ChiCTR2000030254). However, these publications are not peer-reviewed yet.

### Availability

Authorised only in Japan and China (for Influenza) but only if other treatments fails, as only studied in non-clinical against avian H5N1 and H7N9.

Based on interim results, the Russian Ministry of Health granted a conditional marketing authorisation to favipiravir (AVIFAVIR®), which makes it the only approved oral drug for treatment of moderate COVID-19 to date in Russia.

### Caution

Teratogenic product, restricted use.

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<sup>21</sup> Li G, De Clercq E. Therapeutic options for the 2019 novel coronavirus (2019-nCoV). Nature Reviews Drug Discovery 2020 Feb <https://www.nature.com/articles/d41573-020-00016-0>



## Hydroxychloroquine: Lack of efficacy

Due to the lack of effectiveness of chloroquine and Hydroxychloroquine in treating COVID-19 patients and in light of serious adverse effects as well as the decisions to stop enrolling participants in the Hydroxychloroquine arm of the RECOVERY and SOLIDARITY trials, reporting related to these two pharmaceuticals was stopped.

## Interferon-Beta-1a (Rebif®, Avonex®) and Interferon-Beta-1b (Betaferon®, Extavia®): in progress

### Rational

The possible use of Interferon- $\beta$  to treat patients with COVID-19 was first proposed by Chinese researchers, who published a list of treatments possibly effective. It could help controlling the inflammatory response during COVID-19. Interferon- $\beta$  balances the expression of pro- and anti-inflammatory agents in the brain, leading to a reduction of neuron inflammation. Clinical observations in mammals infected with the Middle East respiratory syndrome coronavirus (MERS-CoV) have shown clinical improvements with the use of INF- $\beta$ .

### Clinical evidence against COVID-19

In most clinical trials, interferon is tested in combination with other products such as lopinavir-ritonavir.

On May 30, 2020, a preprint was identified (medRxiv platform) related to the results from RCT on Interferon beta-1a treatment (n=46) vs the standard of care (n=46), in 92 patients with severe COVID-19 in Iran (IRCT20100228003449N28).<sup>22</sup>

81 patients (42 in the IFN and 39 in the control group) completed the study. On day 14, 66.7% vs. 43.6% of patients in the IFN group and the control group were discharged, respectively (OR= 2.5; 95% CI: 1.05- 6.37). The 28-day overall mortality was significantly lower in the IFN then the control group (19% vs. 43.6% respectively, p= 0.015). Early administration significantly reduced mortality (OR=13.5; 95% CI: 1.5-118).

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<sup>22</sup> Davoudi-Monfared E.et al. Efficacy and safety of interferon beta-1a in treatment of severe COVID-19: A randomized clinical trial. medRxiv. 2020. DOI: 10.1101/2020.05.28.20116467

For alpha-interferon:<sup>23</sup>

Results of a single-centre, randomised, open-label, prospective clinical trial that enrolled 101 patients with mild to moderate COVID-19 were published.

	Three arms tested			<i>p</i>
	Ribavirin plus Interferon- $\alpha$	Lopinavir/ritonavir plus Interferon- $\alpha$	Ribavirin plus Interferon- $\alpha$ plus lopinavir/ritonavir	
Median interval from baseline to no more virus detected (SARS-CoV-2 nucleic acid negativity)	13 days	12 days	15 days	0.23 (not significant)
% negative SARS-coV2 nucleic acid at day 14	51.5%	61.1%	46.9%	Not significant
Incidence of gastrointestinal adverse events			higher	

Conclusions: the results indicate that there are no significant differences among the three regimens in terms of antiviral effectiveness in patients with mild to moderate COVID-19.

### Status

Interferon-Beta-1a is already authorised to treat multiple sclerosis (Avonex®, Rebif®, Pregridy® ...), as a chronic treatment. When used long-term, it is contra-indicated in patients who have severe depression or have thoughts of suicide.

The US COVID-19 Treatment Guidelines Panel recommends **against the use** of the interferons (alfa or beta) for the treatment of severely or critically ill patients with COVID-19, **except in the context of a clinical trial**.<sup>24</sup>

There are insufficient data for the Panel to recommend either for or against the use of the Interferon-beta for the treatment of early (i.e., <7 days from symptom onset) mild and moderate COVID-19.

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<sup>23</sup> Hung I. al. Triple combination of interferon beta-1b, lopinavir–ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomised, phase 2 trial. The Lancet. 2020. DOI: 10.1016/S0140-6736(20)31042-4.

<sup>24</sup> National Institutes of Health (NIH). COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. 2020 [cited 13/07/2020]. <https://www.covid19treatmentguidelines.nih.gov>

## Lopinavir / ritonavir: lack of efficacy

### Rational

It is a combination of 2 HIV protease inhibitors, ritonavir being used as a booster to enhance lopinavir activity. Several HIV inhibitors such as lopinavir, ritonavir, and saquinavir produce strong interaction with the active site of SARS-CoV-2 main protease *in silico*.<sup>25</sup>

From SCIENCE, "The combination can inhibit the protease of other viruses as well, specifically coronaviruses. It has shown efficacy in marmosets infected with the MERS virus, and has also been tested in SARS and MERS patients, though results from those trials are ambiguous." In advanced COVID19 patients, the lack of efficacy was probably due to the fact it was used too late.

It targets coronavirus main protease 3CLpro, a protease for the proteolysis of viral polyprotein into functional units. And also PLpro, papain-like protease PLpro a protease for the proteolysis of viral polyprotein into functional units.

### Clinical experience against COVID-19

One Chinese trial showed no benefit, but it enrolled too few patients for statistical analysis (underpowered). In adults with severe COVID-19 hospitalised in Wuhan, China, treatment using a combination of antiviral drugs –lopinavir–ritonavir (HIV/AIDS therapies) –provided no benefit.<sup>26</sup>

The University of Oxford, the WHO and INSERM publicly announced that the lopinavir-ritonavir (Kaletra®) arms of the RECOVERY, SOLIDARITY and DISCOVERY studies in adults hospitalised with severe COVID-19 will be stopped given the data showed no beneficial effect.<sup>27</sup>

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<sup>25</sup> Ortega JT, Serrano ML, Pujol FH, Rangel HR. Unrevealing sequence and structural features of novel coronavirus using *in silico* approaches: The main protease as molecular target. *EXCLI J*. 2020;19:400–409. Published 2020 Mar 17. doi:10.17179/excli2020-1189

<sup>26</sup> <https://www.nejm.org/doi/full/10.1056/NEJMoa2001282>

<sup>27</sup> <https://www.recoverytrial.net/news/no-clinical-benefit-from-use-of-lopinavir-ritonavir-in-hospitalised-covid-19-patients-studied-in-recovery>

## Remdesivir (Veklury®): authorised

### Rational

Remdesivir is an investigational broad-spectrum antiviral, developed by Gilead Sciences as a treatment for Ebola virus disease and Marburg virus infections, with antiviral activity against other single stranded RNA viruses such as respiratory syncytial virus, Junin virus, Lassa fever virus, Nipah virus, Hendra virus, and the coronaviruses (including MERS and SARS viruses). It targets the SARs-coV- RNA-dependent RNA polymerase for replicating viral genome.

Intellectual property rights: Gilead Sciences owns the patent US20170071964 for a “Preparation of amino acid-containing nucleotides and methods for treating arenaviridae and coronaviridae virus infections”.<sup>28</sup>

### First results

#### NIH Clinical Trial Shows Remdesivir Accelerates Recovery from Advanced COVID-19

Preliminary results indicate that patients who received remdesivir had a 31% faster time to recovery than those who received placebo ( $p < 0.001$ ). Specifically, the median time to recovery was 11 days for patients treated with remdesivir compared with 15 days for those who received placebo. Results also suggested a survival benefit, with a mortality rate of 8.0% for the group receiving remdesivir versus 11.6% for the placebo group ( $p = 0.059$ ).<sup>29</sup>

#### What benefits of Veklury® have been shown in studies?<sup>30</sup>

A main study (NIAID-ACTT-1) involving 1,063 hospitalised patients with COVID-19 (120 with mild to moderate disease and 943 with severe disease) showed that Veklury® can speed up the recovery time in some patients, allowing them to spend less time in hospital or on treatment

The study showed that, in the overall study population, patients treated with Veklury® recovered after about 11 days, compared with 15 days for patients given placebo. For patients with severe disease requiring supplemental oxygen, time to recovery was 12 days for patients given remdesivir, compared with 18 days for patients on placebo. However, no difference was seen in time to recovery in the subgroup of patients with severe disease who started remdesivir

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<sup>28</sup> ACS Cent. Sci. 2020, 6, 315–331

<sup>29</sup> <https://www.niaid.nih.gov/news-events/nih-clinical-trial-shows-remdesivir-accelerates-recovery-advanced-covid-19>

<sup>30</sup> [https://www.ema.europa.eu/en/documents/overview/veklury-epar-medicine-overview\\_en.pdf](https://www.ema.europa.eu/en/documents/overview/veklury-epar-medicine-overview_en.pdf)

when they were already on mechanical ventilation or ECMO (extracorporeal membrane oxygenation). No difference was also observed in patients with mild/moderate disease not requiring supplemental oxygen: time to recovery was 5 days for both the remdesivir group and the placebo group.

### Status

#### In the European Union

Remdesivir is authorised to treat COVID-19 (conditional marketing authorisation, 03 July 2020),<sup>31</sup> mainly based on preliminary data published by Beigel et al.<sup>32</sup>

Remdesivir (Veklury®) is subject to additional monitoring for safety and Gilead should submit additional data before December 2020.

Remdesivir is indicated for the treatment of coronavirus disease 2019 (COVID-19) in adults and adolescents (aged 12 years and older with body weight at least 40 kg) with pneumonia requiring supplemental oxygen. The drug is for administration by intravenous infusion after further dilution. The recommended dosage of remdesivir is: Day 1 – single loading dose of remdesivir 200 mg (intravenous), Day 2 onwards – 100 mg given once daily (intravenous).

The total duration of treatment should be at least 5 days and not more than 10 days. **Concomitant use of remdesivir with chloroquine phosphate or hydroxychloroquine sulphate is not recommended due to antagonism observed in vitro.**

The most common adverse reaction in healthy volunteers is increased transaminases (14%) (a sign of liver problems). The most common adverse reaction in patients with COVID-19 is nausea (4%).

#### In the USA

On May 1, 2020 the U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) to permit the emergency use of the unapproved product remdesivir for treatment of suspected or laboratory confirmed coronavirus disease 2019 (COVID-19) in adults and children hospitalized with severe disease.

**On June 15, 2020 FDA issued the warning about co-administration of remdesivir and chloroquine phosphate or hydroxychloroquine sulphate which may result in reduced antiviral activity of remdesivir.**

US COVID-19 Treatment Guidelines Panel issued recommendations on remdesivir treatment for patients with COVID-19 (as of July 24, 2020):

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<sup>31</sup> [https://ec.europa.eu/commission/presscorner/detail/en/mex\\_20\\_1266](https://ec.europa.eu/commission/presscorner/detail/en/mex_20_1266).

<sup>32</sup> Beigel J., Tomashek K., Dodd L., Mehta A., Zingman B., Kalil A., et al. Remdesivir for the Treatment of Covid-19 — Preliminary Report. New England Journal of Medicine. 2020. DOI: 10.1056/NEJMoa2007764

1. Recommendation for Prioritizing Limited Supplies of Remdesivir: remdesivir be prioritized for use in hospitalized patients with COVID-19 who require supplemental oxygen but who are not on high-flow oxygen, non-invasive ventilation, mechanical ventilation, or extracorporeal membrane oxygenation (ECMO)
2. Recommendation for Patients with Mild or Moderate COVID-19: There are insufficient data for the Panel to recommend either for or against the use of remdesivir in patients with mild or moderate COVID-19.
3. Recommendation for Patients with COVID-19 Who Are on Supplemental Oxygen but Who Do Not Require High-Flow Oxygen, Non-invasive or Invasive Mechanical Ventilation, or ECMO: The Panel recommends using remdesivir for 5 days or until hospital discharge, whichever comes first (AI). If a patient who is on supplemental oxygen while receiving remdesivir progresses to requiring high-flow oxygen, non-invasive or invasive mechanical ventilation, or ECMO, the course of remdesivir should be completed.
4. Recommendation for Patients with COVID-19 Who Require High-Flow Oxygen, Non-invasive Ventilation, Mechanical Ventilation, or ECMO: Because there is uncertainty regarding whether starting remdesivir confers clinical benefit in these groups of patients, the Panel cannot make a recommendation either for or against starting remdesivir. In a randomized clinical trial, there was no observed difference between the remdesivir and placebo groups in time to recovery or mortality rate in these subgroups. However, because the trial was not powered to detect differences in outcomes in these subgroups, there is uncertainty as to the effect of remdesivir on the course of COVID-19 in these patients.

Gilead Sciences Inc. said it plans to start human trials of an inhaled version of its anti-Covid-19 drug remdesivir. An inhaled version, through a nebulizer, could allow Gilead to give the drug to a broader group of patients, including those with milder symptomatic cases who do not need to be hospitalised.<sup>33</sup>

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<sup>33</sup> <https://www.pharmacist.com/article/gilead-begin-human-testing-inhaled-version-covid-19-drug-remdesivir>

## Products to treat inflammation and/or respiratory illness

<https://www.nytimes.com/2020/06/11/health/coronavirus-cytokine-storm.html?smid=em-share>

### Dexamethasone: under evaluation by EMA<sup>34</sup>

#### Rational

The proposed mechanism of dexamethasone and glucocorticoids in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) involves the mitigation of an excessive immune response that can lead to acute respiratory distress syndrome (ARDS) and multi-organ failure. ARDS develops in approximately 20% of COVID-19 patients and is linked to multi-organ failure through cytokine release syndrome.

#### Clinical experience against COVID-19

In June, a university news release reported results of dexamethasone as 1 of 6 possible treatments tested in a randomized trial: a 17% reduction in 28-day mortality in 6,425 hospitalised patients with COVID-19.<sup>35</sup>

In patients on invasive mechanical ventilation, 29% of those treated with dexamethasone died within 28 days of starting dexamethasone treatment compared with 41% of patients receiving usual care, **a relative reduction of about 35%.**

In patients receiving oxygen without mechanical ventilation, the figures were 23% with dexamethasone and 26% with usual care. No reductions in death occurred in patients who were not receiving oxygen therapy or mechanical ventilation.

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<sup>34</sup> <https://www.ema.europa.eu/en/news/ema-receives-application-marketing-authorisation-dexamethasone-taw-covid-19>

<sup>35</sup> Low-cost dexamethasone reduces death by up to one third in hospitalised patients with severe respiratory complications of COVID-19 (RECOVERY). Oxford University. June 16, 2020. Accessed June 24, 2020. <https://www.recoverytrial.net/news/low-cost-dexamethasone-reduces-death-by-up-to-one-third-in-hospitalised-patients-with-severe-respiratory-complications-of-covid-19>

## Status

Dexamethasone is authorised at national level in the EU and is used in a wide range of conditions, including rheumatic problems, skin diseases, severe allergies, asthma and chronic obstructive lung disease.

The EMA is currently evaluating a marketing authorisation for Dexamethasone Taw. Should the available data show that the benefits of Dexamethasone Taw outweigh its risks in the treatment of hospitalised adults with COVID-19, EMA will issue a positive recommendation on the medicine's new use in patients with COVID-19. The agency will then liaise with the European Commission to fast-track the authorisation.

## Tocilizumab

### Rational

Tocilizumab, is a monoclonal antibody, a type of protein that has been designed to recognise and attach to a specific target (called an antigen) in the body. Tocilizumab attaches to the receptor for a messenger molecule or 'cytokine' called interleukin-6 (IL6). This messenger is involved with inflammation and is found at high levels in patients with rheumatoid arthritis, systemic juvenile idiopathic arthritis, juvenile idiopathic polyarthritis, giant cell arteritis and cytokine release syndrome. Tocilizumab reduces the inflammation and other symptoms of these diseases.

Accumulating evidence suggests that a subgroup of patients with severe COVID-19 might have a cytokine storm syndrome. A recent study recommends identification and treatment of hyper-inflammation using existing, approved therapies with proven safety profiles to address the immediate need to reduce the rising mortality. Therapeutic options include selective cytokine blockade (e.g. Anakinra or Tocilizumab)<sup>36</sup>.

### Clinical experience against COVID-19

In February 2020, first clinical trials in China investigated Tocilizumab as experimental treatment of pneumonia in COVID-19. On April 10<sup>th</sup> 2020, 43 trials are registered by WHO. Different populations are investigated: patients with inflammatory rheumatic diseases, patients with advanced or metastatic cancer and COVID-19 (not listed here).

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<sup>36</sup> Puja Mehta, Daniel F McAuley, Michael Brown, Emilie Sanchez, Rachel S Tattersall, Jessica J Manson et al. "COVID-19: consider cytokine storm syndromes and immunosuppression" – The Lancet - Published: March 16, 2020 - DOI: [https://doi.org/10.1016/S0140-6736\(20\)30628-0](https://doi.org/10.1016/S0140-6736(20)30628-0)



### First results

#### [A Study to Evaluate the Safety and Efficacy of Tocilizumab in Patients With Severe COVID-19 Pneumonia \(COVACTA\)](#)

Phase 3 randomized, Double-Blind, Placebo-Controlled. 450 participants.

Treatment group: Tocilizumab

Control group: IV placebo

The phase III COVACTA (NCT04320615) study of Tocilizumab **did not meet its primary endpoint** of improved clinical status in hospitalised adult patients with severe COVID-19 associated pneumonia. In addition, the key secondary endpoints, which included the difference in patient mortality at week four, were not met; however, **there was a positive trend in time to hospital discharge** in patients treated with Tocilizumab. The COVACTA study did not identify any new safety signals for Tocilizumab.<sup>37</sup>

### Status

Tocilizumab is not approved by the European Medicines Agency (EMA) or the American Food and Drug Administration (FDA) for COVID-19 patients.

Tocilizumab is indicated (EMA-approved) for the treatment of

- rheumatoid arthritis in adults
- giant cell arteritis in adults
- active systemic juvenile idiopathic-arthritis in patients aged  $\geq 2$  years
- juvenile idiopathic polyarthritis in patients aged  $\geq 2$  years
- chimeric antigen receptor (CAR) T cell-induced severe or life-threatening cytokine release syndrome (CRS) in patients aged  $\geq 2$  years

Tocilizumab is available as a solution to be injected under the skin and as a concentrate for making a solution for infusion (drip) into a vein under the brand name RoActemra® by Roche in Europe.

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<sup>37</sup> EUnetHTA Joint Action 3: Tocilizumab for the treatment of COVID-19

[https://eunetha.eu/wp-content/uploads/2020/08/EUnetHTA-Covid-19\\_RCR03\\_TOCILIZUMAB.pdf](https://eunetha.eu/wp-content/uploads/2020/08/EUnetHTA-Covid-19_RCR03_TOCILIZUMAB.pdf)

## Caution

The most serious side effects are serious infections, complications of diverticulitis and allergic reactions. For the full list of side effects, see the [Summary of product characteristics](#).

Tocilizumab must not be used in patients who have an active, severe infection.

During the 10-day follow-up Toniati et al. 2020 recorded **three cases of severe adverse events**: two patients developed septic shock and died, one had gastrointestinal perforation requiring urgent surgery and was alive at day 10.<sup>38</sup>

## Other products not in this document

Darunavir

- Camostat Mesilate (Foipan®)
- APN01 / Recombinant human Angiotensin-converting Enzyme 2 (rhACE2)
- Sarilumab (Kevzara®)
- Solnatide
- Umifenovir (Arbidol®)
- Anakinra (Kineret®)
- Colchicine

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<sup>38</sup> Toniati P et al. Tocilizumab for the treatment of severe COVID-19 pneumonia with hyper-inflammatory syndrome and acute respiratory failure: A single center study of 100 patients in Brescia, Italy. Autoimmunity Reviews. 2020. DOI: <https://doi.org/10.1016/j.autrev.2020.102568>

# Initiatives of interest

## Therapeutic trials

### Discovery Trial<sup>39</sup> ADAPTED

EudraCT Number: 2020-000936-23

**Objective:** to evaluate the efficacy and safety of four experimental therapeutic strategies which might be effective against COVID-19

**Principal investigator:** Florence Ader, infectiologist, Infectious and Tropical Diseases Department of the Croix-Rousse Hospital of Lyon University Hospital and researcher at the CIRI International Research Centre in Infectiology (Inserm/CNRS / Claude Bernard University Lyon 1

**Sponsors:** INSERM, COMBACTE, PREPARE and RECOVER

**Adaptive trial design:** ineffective experimental treatments can very quickly be dropped and replaced by other molecules that emerge from research efforts

**31 July 2020:** both in Discovery and in Solidarity trial, lopinavir/ritonavir with or without  $\beta$ -interferon arms were interrupted, due to lack of efficacy. Discussions have started to decide on how to adapt the trial and to test other treatments, and which ones.<sup>40</sup>

Earlier in May, based on the article in the Lancet with higher mortality in Hydroxychloroquine arms, this product was interrupted both in Discovery and in Solidarity trials. Early June 2020 the Lancet article was retracted, Hydroxychloroquine trials started again but were thereafter abandoned mid-June, due to lack of efficacy.

**Number of participants:** 3200, 800 in France (20 centres)

<sup>39</sup> Launch of a European clinical trial against COVID-19

<https://presse.inserm.fr/en/launch-of-a-european-clinical-trial-against-covid-19/38737/>

<sup>40</sup> <https://www.inserm.fr/actualites-et-evenements/actualites/covid-19-inserm-sur-tous-fronts>

### Discovery, Contact: INSERM

Christelle DELMAS  
8 rue de la Croix Jarry  
75013 Paris - France  
+331 82 53 33 68  
[rqrc.siege@inserm.fr](mailto:rqrc.siege@inserm.fr)

**Starting date:** 22 March 2020

**Update:** as of 29 March, 123 enrolled in France (objective 800) in 7 centres (objective: 20).<sup>41</sup> As of 5 April, 600 enrolled in France.

As of July, around 763 enrolled, for an expected total of 3,200.

**Participating countries:** Belgium, France, Germany, Luxembourg, the Netherlands, Spain, Sweden, and the United Kingdom

In fact only France and Luxembourg recruited patients in this trial. The cost per patient, organisational aspects and diplomatic ones can explain the situation.<sup>42</sup>

**Design:** randomised, open-label trial (participants will know which treatment they receive).

**Arms:**

- ▶ standard of care
- ▶ standard of care plus remdesivir

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<sup>41</sup> <https://www.latribune.fr/economie/international/covid-19-a-lyon-la-professeure-ader-dirige-un-essai-clinique-crucial-et-loin-du-buzz-843707.html>

<sup>42</sup> Coronavirus : l'essai clinique Discovery englué faute de coopération européenne », *Le Monde.fr*, 7 mai 2020.

[https://www.lemonde.fr/planete/article/2020/05/07/coronavirus-l-essai-clinique-discovery-englue-faute-de-cooperation-europeenne\\_6038909\\_3244.html](https://www.lemonde.fr/planete/article/2020/05/07/coronavirus-l-essai-clinique-discovery-englue-faute-de-cooperation-europeenne_6038909_3244.html)

## Solidarity trial<sup>43</sup>

<http://www.isrctn.com/ISRCTN83971151>

### Sponsor

World Health Organization

### Participating countries

Argentina, Bahrain, Canada, France, Iran, Norway, South Africa, Spain, Switzerland and Thailand have confirmed that their participation.

USA and United Kingdom are not involved.

### Arms: similar to European Discovery Trial, chloroquine instead of hydroxychloroquine

- ▶ standard of care
- ▶ standard of care plus remdesivir

**Starting date:** 26 March 2020

### Inclusion

Adults (aged over 18 years) hospitalized with definite COVID-19 and not already receiving any of the study drugs. Patients invited to join the study will be those who are admitted to a collaborating hospital

### Evolution

End May 2020, Hydroxychloroquine was interrupted (as in Discovery trial)

On 17 June, the Hydroxychloroquine arm was definitely stopped.

On 4 July, WHO stopped testing the association of lopinavir-ritonavir with or without  $\beta$ -interferon.

As of today, only remdesivir continues to be compared to placebo, as it hasn't yet demonstrated a reduction in mortality.

## Solidarity, Contact: WHO Switzerland

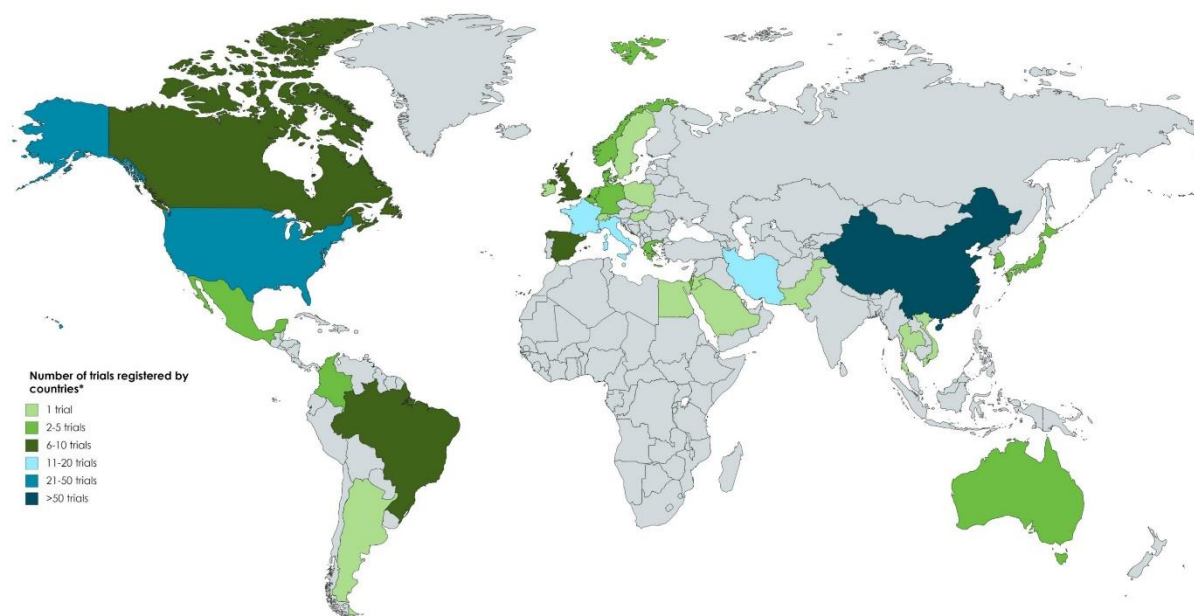
Medical Officer  
HQ/RDB R&D Blue Print  
World Health Organization HQ  
Geneva 1211, Switzerland  
+41 795130039  
[henaorestrepoa@who.int](mailto:henaorestrepoa@who.int)

<sup>43</sup> <https://www.who.int/thailand/news/detail/20-03-2020-thailand-joins-the-who-solidarity-trial-global-testing-of-effective-treatments-of-covid-19-across-8-countries-an-aggressive-effort-to-save-lives-from-the-pandemic>

## For all other clinical trials

You can consult the Anti-Cancer Fund database:

<http://www.redo-project.org/COVID-19db>



\* For international trials, only the country of the primary sponsor is indicated. This causes an underestimation of the number of trials running in each country. For instance, the WHO Solidarity trial is running at least in Argentina, Brazil, Canada, Germany, Indonesia, Iran, Norway, Peru, Qatar, South Africa, Spain, Switzerland & Thailand but is attributed to Switzerland as the WHO Swiss headquarters registered the trial.

Paris hospitals (39 hospitals) participate in many clinical trials, read here (in French): <https://www.aphp.fr/contenu/covid-19-plusieurs-essais-cliniques-promotion-ap-hp-ont-ete-lances-en-moins-dun-mois>