HTA Austria
Austrian Institute for
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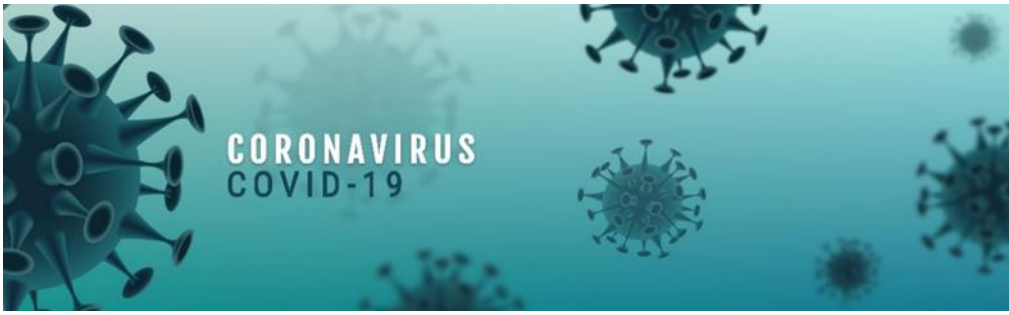
GmbH

Covid-19



HSS/ Horizon Scanning

Living Document **V02 May** 2020

AIHTA Policy Brief Nr.: 002
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HSS/ Horizon Scanning
Living Document **V02 May** 2020

Vienna, **May 2020**

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May 1st 2020	Addition chapter 3.12 (Convalescent plasma)
May 4th 2020	Update Methodology (chapter 1.2)
May 5th 2020	Update Vaccine (chapter 2)
May 7th 2020	Update Remdesivir (chapter 3.1 + Tables)
May 7th 2020	Update Hydroxychloroquine (chapter 3.6 + Tables)
May 9th 2020	Update Chloroquine (chapter 3.5 + Tables)
May 9th 2020	Update Lopinavir + Ritonavir (chapter 3.2 + Tables)
May 10th 2020	Addition chapter 3.13 (Combination therapy – results from the 1st RCT on triple combination therapy interferon beta-1b, lopinavir–ritonavir and ribavirin)
May 11th 2020	Update Tocilizumab (chapter 3.9 + Tables)
May 11th 2020	Update Sarilumab (chapter 3.10 + Tables)
May 12th 2020	Update Favipiravir (chapter 3.3 + Tables)
May 12th 2020	Update Darunavir (chapter 3.4)
May 12th 2020	Update Camostat Mesilate (chapter 3.7 + Tables)
May 12th 2020	Update APN01/rhACE2 (chapter 3.8)
May 12th 2020	Update Interferon beta (chapter 3.11 + Tables)
May 12th 2020	Update on Solnatide (Appendix)

Deutsche Zusammenfassung

Hintergrund und Methode: vgl. V1, April 2020,

Ergänzung Vignetten_NEU (Abschnitt 3.12):

Konvaleszenten-Plasma

(Re-)Konvaleszenzplasma ist Plasma, das von Patient*innen gewonnen wird, die sich von einer covid19 Erkrankung bereits erholt haben, und kann an Patient*innen abgegeben werden, die an covid19 neu erkrankt sind. Es kann auch zur Herstellung von Immunglobulinkonzentraten verwendet werden. Die mögliche Erklärung für eine Wirksamkeit ist, dass die Antikörper aus dem Konvaleszenzplasma das Immunsystem des/der Erkrankten aktivieren könnten.

Plasmaprodukte werden derzeit in 43 klinischen Studien getestet, wovon 26 RCTs sind. Die meisten Studien sind noch im Stadium der Rekrutierung. Erste Ergebnisse sind Ende 2020 zu erwarten.

Details der Updates finden sich nur im englischen Teil.

1 Background: policy question and methods“

1.1 Policy Question

On March 30th 2020, a request was raised by the Austrian Ministry of Health (BMASGK) and further Austrian policy stakeholder to set up a Horizon Scanning ystem (HSS) for medicines and vaccines. The establishment of a HSS/ Horizon Scanning System for Covid-19 interventions has the intentions of

a. informing health policy makers at an early stage which interventions (vaccinations and drugs) are currently undergoing clinical trials and
b. monitoring them over the next few months in order to support evidence-based purchasing, if necessary.

March 30th 2020:
Request to set up Covid-19 HSS
(medicines + vaccines)

information on
***status of R&D**
***evidence-based purchasing**

1.2 Methodology

To respond to this request,

1. As a first step an inventory, based on international sources, is built.
2. As a second step, selective searches by means of searches in study registries are carried out for information on clinical studies in humans and the state of research.
3. This information forms the basis for “vignettes” (short descriptions) for those products that are already in an "advanced" stage.
4. Subsequently, the products are monitored with regard to the status of the clinical studies up to approval and finally evaluated for their benefit and harm.

multistep approach:

inventory
selective searches
vignettes
monitoring

All work steps are conducted in close international (European) cooperation.

(European) cooperation

Additionally, public funding for the development of medicines and vaccines is gathered.

- Version 1(V1, April 2020): inventory + vignettes for most advanced
- Version 2+: monthly monitoring and updates

additional: monitoring of public funding R&D
V1: inventory + vignettes
V2: monthly monitoring

Table 1.2-1: International Sources

Primary sources	Link
WHO Drugs: Vaccines:	https://www.who.int/teams/blueprint/covid-19 https://www.who.int/blueprint/priority-diseases/key-action/Table_of_therapeutics_Appendix_17022020.pdf?ua=1 https://www.who.int/who-documents-detail/covid-19-candidate-treatments https://www.who.int/who-documents-detail/draft-landscape-of-covid-19-candidate-vaccines
Danish Medicine Agency Drugs: Vaccines:	https://laegemiddelstyrelsen.dk/da/nyheder/temaer/ny-coronavirus-covid-19/~/media/5B83D25935DF43A38FF823E24604AC36.ashx https://laegemiddelstyrelsen.dk/da/nyheder/temaer/ny-coronavirus-covid-19/~/media/3A4B7F16D0924DD8BD157BBE17BFED49.ashx
Pang et al. 2020 [1] Drugs: Vaccines:	https://www.mdpi.com/2077-0383/9/3/623 Table 5+6, Table 3+4
SPS HS-report (UK)	unpublished
Secondary sources	
VfA/ Verband Forschender Arzneimittelhersteller Drugs: Vaccines:	https://www.vfa.de/de/arzneimittel-forschung/woran-wir-forschen/therapeutische-medikamente-gegen-die-coronavirusinfektion-covid-19 https://www.vfa.de/de/arzneimittel-forschung/woran-wir-forschen/impfstoffe-zum-schutz-vor-coronavirus-2019-ncov
EMA/ Europen Medicines Agency Medicines:	https://www.ema.europa.eu/ https://www.ema.europa.eu/en/medicines/medicines-under-evaluation
FDA/US Food and Drug Administration	https://www.fda.gov/emergency-preparedness-and-response/counterterrorism-and-emerging-threats/coronavirus-disease-2019-covid-19
Trial Registries	
US National Library of Medicine European Union Drug Regulating Authorities Clinical Trials Database WHO International Clinical Trials Registry Platform TrialsTracker	https://clinicaltrials.gov/ https://eudract.ema.europa.eu/ https://www.who.int/ictrp/en/ http://Covid-19.trialstracker.net/
Up-to-date information on clinical trials and literature searching resources relating to COVID-19	
Cochrane COVID-19 Study Register 21/04.20	https://covid-19.cochrane.org/
Living mapping of research and a living systematic review	https://covid-nma.com/ https://covid-nma.com/dataviz/
Living listing of interventional clinical trials in Covid-19/2019-nCoV produced by the Anticancer Fund	http://www.redo-project.org/covid19db/; http://www.redo-project.org/covid19_db-summaries/
Global Coronavirus COVID-19 Clinical Trial Tracker	https://www.covid-trials.org/
LitCovid	https://www.ncbi.nlm.nih.gov/research/coronavirus/
UK NIHR Innovation Observatory NIHR COVID-19 Studies COVID-19 Therapeutics Dashboard COVID-19: a living systematic map of the evidence	https://www.nihr.ac.uk/covid-studies/ http://www.io.nihr.ac.uk/report/covid-19-therapeutics/ http://eppi.ioe.ac.uk/cms/Default.aspx?tabid=3765
WHO COVID-19 Database new search interface	https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov
COVID-evidence Database	https://covid-evidence.org/database
Medical Library Association – COVID-19 Literature search strategies	https://www.mlanet.org/page/covid-19-literature-searching
Centre of Evidence Based Dermatology (CEBD) - Coronavirus Dermatology Online Resource	https://www.nottingham.ac.uk/research/groups/cebd/resources/Coronavirus-resource/Coronavirushom
Ovid Expert Searches for COVID-19	http://tools.ovid.com/coronavirus/

EBSCO Covid-19 Portal Literature searching section of portal Information portal	 https://covid-19.ebscomedical.com/research https://covid-19.ebscomedical.com/
NIH COVID-19 Treatment Guidelines. 2020.	https://covid19treatmentguidelines.nih.gov/introduction/
Tertiary sources	
NIPHNO	https://www.fhi.no/en/qk/systematic-reviews-hta/map/
INAHTA	http://www.inahta.org/covid-19-inahta-response/

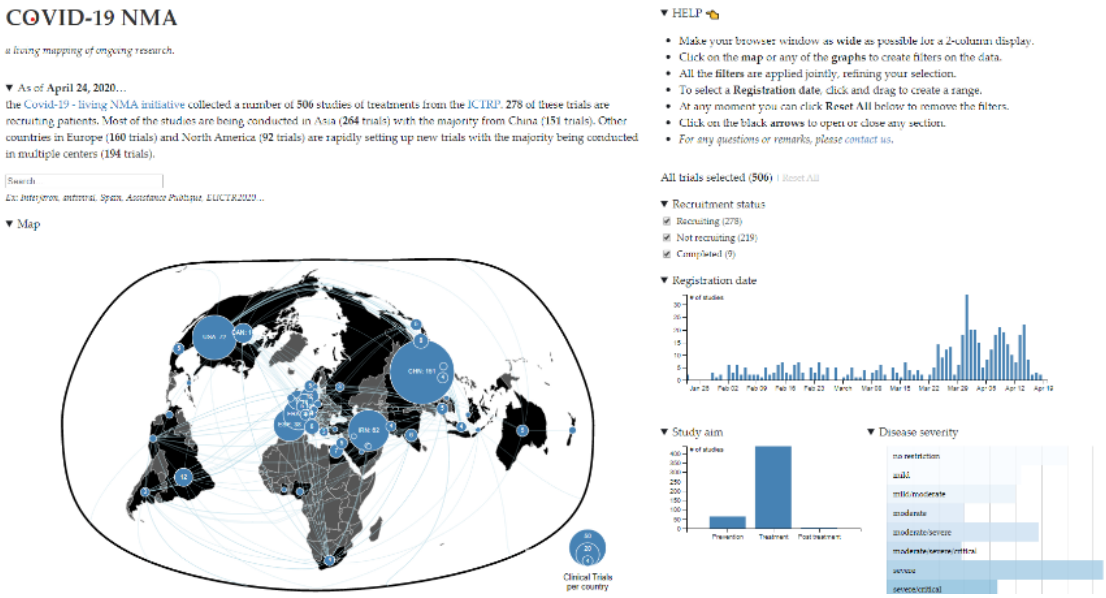
living documents: up-to-date information

Several organisations and international teams of researchers are providing up-to-date information through living listing of interventional clinical trials in Covid-19/2019-nCoV and literature resources (Table 1.2-2) [27-29]. A short description of two of such databases is presented below.

mapping of ongoing RCTs

Boutron et al., 2020 [27] are performing a living mapping of ongoing randomized trials, followed by living systematic reviews with pairwise meta-analyses and when possible, network meta-analyses focusing on two main questions: the effectiveness of preventive interventions for COVID-19 and the effectiveness of treatment interventions for COVID-19 (Figure 1.2-1).

Figure 1.2-1: A living mapping of ongoing randomized trials, living systematic reviews with pairwise meta-analyses and network meta-analyses



COVID-19 Clinical Trial Tracker

Thorlund et al., 2020 [28] developed a COVID-19 clinical trials registry to collate all trials related to COVID-19: Global Coronavirus COVID-19 Clinical Trial Tracker. Data is pulled from the International Clinical Trials Registry Platform, including those from the Chinese Clinical Trial Registry, ClinicalTrials.gov, Clinical Research Information Service - Republic of Korea, EU Clinical Trials Register, ISRCTN, Iranian Registry of Clinical Trials, Japan Primary Registries Network, and German Clinical Trials Register (Figure 1.2-2). They also use content aggregator services, such as LitCovid, to ensure that their data acquisition strategy is complete [29].

Figure 1.2-2: Global Coronavirus COVID-19 Clinical Trial Tracker - a real-time dashboard of clinical trials for COVID-19

1.3 Selection of Products for "Vignettes"

most advanced products

The following products have been selected for further investigation (searches in registry databases and description as "vignettes") for the following reasons:

- most advanced in clinical research ins humans
- most often discussed in clinical journals as potential candidates

The full inventory (list) can be found in Part 2 - Appendix A-1: vaccines, A-2, therapeutics, A3-EudraCT registry studies.

2 Results: Vaccines

Table 2-1: Most advanced vaccines in the R&D pipeline

Company/Institution/Registry number	Technology		Stage/Sponsor	Source
	Platform	**Type of candidate vaccine**		
Moderna Therapeutics—US National Institute of Allergy **NCT04283461**	RNA	LNP-encapsulated mRNA vaccine encoding S protein	Phase1 National Institute of Allergy and Infectious Diseases (NIAID)	[1, 2] SPS Coronavirus HS report (UK), GÖG [30-34]
CanSino Biological Inc. and Beijing Institute of Biotechnology **ChiCTR2000030906/ NCT04313127**	Non-Replicating Viral Vector	adenovirus Type 5 Vector that expresses S protein	Phase 1 CanSino Biologics Inc.	[2, 3] GÖG [30-35]
CanSino Biological Inc. and Beijing Institute of Biotechnology **ChiCTR2000031781**	Non-Replicating Viral Vector	adenovirus Type 5 Vector that expresses S protein	Phase 2 Jiangsu Provincial Center for Disease Control and Prevention/ Institute of Biotechnology, Academy of Military Medical Sciences, PLA of China/ CanSino Biologics Inc.	[30-32, 34, 35]
Inovio Pharmaceuticals **NCT04336410**	DNA	DNA plasmid vaccine encoding S protein delivered by electroporation	Phase 1 Inovio Pharmaceuticals	[1, 2] GÖG [30-34]
Novavax **NCT04368988**	Protein Subunit	VLP-recombinant protein nanoparticle vaccine + Matrix M	Phase 1 Novavax	[1, 2] GÖG [30-33]
University of Queensland/GSK/Dynavax	Protein Subunit	Molecular clamp stabilized Spike protein	Preclinical Funding by CEPI	[1, 2] GÖG
CureVac	RNA	mRNA	Preclinical; Phase 1 study will start in June/July 2020	[1, 2] GÖG
University of Oxford **NCT04324606/ EudraCT 2020-001072-15**	Non-Replicating Viral Vector	ChAdOx1	Phase 1/2 study University of Oxford	[2, 3] SPS Coronavirus HS report (UK), GÖG [30-33] [34, 36]

BioNTech/Fosun Pharma/Pfizer **EudraCT 2020-001038-36/ NCT04368728**	RNA	mRNA	Phase 1/2 BioNTech RNA Pharmaceuticals GmbH	[2] SPS Coronavirus HS report (UK), GÖG [30-33] [34, 36]
Shenzhen Geno-Immune Medical Institute **NCT04299724**	Synthetic mini-gene -based product	Pathogen-specific aAPC	Phase 1 Shenzhen Geno-Immune Medical Institute	[33]
Shenzhen Geno-Immune Medical Institute **NCT04276896**	Synthetic mini-gene -based product	LV-SMENP-DC	Phase 1/2 Shenzhen Geno-Immune Medical Institute	[33]
Insitute of Biotechnology, Academy of Military Medical Sciences, PLA of China **NCT04341389**	Non-Replicating Viral Vector	adenovirus Type 5 Vector that expresses S protein	Phase 2 Insitute of Biotechnology, Academy of Military Medical Sciences, PLA of China	[30-33]
vivo Corporation **NCT04334980**	DNA bacTRL platform	bacTRL-Spike	Phase 1 Symvivo Corporation	[30-33]
Sinovac **NCT04352608**	Inactivated vaccine	inactivated SARS-CoV-2 virus	Phase 1/2 Sinovac Research and Development Co., Ltd.	[30-34]
Wuhan Institute of Biological Products/Sinopharm **ChiCTR2000031809**	Inactivated vaccine	Vero cells derived (cell culture-derived inactivated vaccines)	Phase 1/2	[30-32, 34, 35]

2.1 Moderna Therapeutics—US National Institute of Allergy

About the vaccine

The **mRNA-1273** vaccine candidate developed by ModernaTX, Inc. in collaboration with NIAID and sponsored by NIAID/CEPI is an LNP-encapsulated mRNA-based vaccine (mRNA-1273) intended for prevention through full-length, perfusion stabilized spike (S) protein of SARS-CoV-2 that is the key into the human cell [37]. An mRNA-based virus has not been approved for use in humans yet [38].

Estimated timeline for approval

Currently, this is the first ongoing phase I trial with 45 healthy participants. It takes place in three centres in the US where the participants are split to 3 groups where they receive two injections of low (25 mcg), medium (100 mcg) or high doses (250 mcg) of mRNA-1273 and are monitored for any AEs and immune response [39]. Safety reviews are in place before dose escalation [39]. The primary endpoint of the study is frequency and grade of adverse reactions at 7/28/394 days post injection [37]. The secondary endpoints measure the level of antibodies at 57 days post injection. The Phase I safety study should be completed by June 2021.

To date, no completed studies in humans are available for mRNA-1273.

*Table 2.1-1: **mRNA-1273** in clinical trial registry*

Active substance	**mRNA-1273**
Sponsor	Coalition for Epidemic Preparedness Innovations (CEPI), National Institute of Allergy and Infectious Diseases (NIAID) and ModernaTX, Inc.
Mechanism of operation	Platform: messenger RNA (mRNA) Type of candidate vaccine: lipid nanoparticle (LNP)-encapsulated mRNA-based vaccine - mRNA-1273 Intended prevention through full-length, prefusion stabilized spike (S) protein of SARS-CoV-2
Regulatory status	Not approved
Trial Identifier	NCT04283461
Phase & Intention	Phase I clinical trial on safety, reactogenicity, and immunogenicity of mRNA-1273 novel coronavirus vaccine (in healthy adults aged 18-55 years old – excluding pregnant women)
Study design	Non-randomized, open-label, multi-centre, sequentially assigned, dose-escalating, phase I clinical trial
Status trial	Recruiting
Duration/ End of Study	Study start: March 3rd, 2020 Estimated Primary Completion Date: June 1st 30, 2021 Estimated Study Completion Date: June 1st, 2022
Study details	N of pts: 45 Location/ centres: United States (Georgia, Maryland, Washington) Intervention/ control: LNP-encapsulated mRNA-based vaccine - mRNA-1273/ NA Duration of observation/ follow-up: 12 months End points: Frequency and grade of safety indexes of adverse reactions 7 days post injection/28 days post injection/394 days post injection (primary endpoints). 3 further secondary endpoints measuring level of antibodies at 57 days post injection.
Results	N.A.

Sources: clinicaltrials.gov [37], Abbreviations: CEPI - Coalition for Epidemic Preparedness Innovations, LPN - lipid nanoparticle, N.A. – not applicable, NIAID - National Institute of Allergy and Infectious Diseases.

2.2 CanSino Biological Inc. and Beijing Institute of Biotechnology

About the vaccine

The **AD5-nCoV** vaccine candidate developed by CanSino Biologics Inc. and the Beijing Institute of Biotechnology is a replication-defective adenovirus type 5 that expresses SARS-CoV-2 spike proteins. The vectored vaccine is intended to prevent the disease caused by the novel coronavirus [40-42]. The platform (non-replicating viral vector) of AD5-nCoV was originally used for an Ebola vaccine (AD5-EBOV) [42, 43].

Estimated timeline for approval

Currently, the first clinical, phase I trial with 108 healthy adults is ongoing. The study is a single-centre dose-escalation study to test both the safety and tolerability of AD5-nCoV injections in three intervention groups using different dosages (low, medium and high). The primary endpoint of the trial is adverse reactions up to seven days post-vaccination. Further twelve secondary safety and immunogenetic endpoints are additionally measured. Data collection for the primary outcome is anticipated to finish in December 2020. The study is estimated to be completed in December 2022 [44]. New RCT, phase 2, started also (ChiCTR2000031781). This randomised, double-blinded, placebo-controlled, parallel, three groups trial aims to evaluate safety and immunogenicity for recombinant novel coronavirus disease vaccine (adenovirus vector) in healthy adults aged above 18 years. Two intervention groups are using middle or low dose of novel vaccine, and the third group is using placebo. The primary endpoints of the trial are adverse reactions 0-14 days post vaccination; anti-S antibody IgG titer on day 28 post vaccination and anti-SARS-CoV-2 neutralizing antibody titer on day 28 post vaccination. Six further safety-related and immunogenetic are registered as secondary endpoints [34, 35]. This RCT will be conducted from 2020-04-12 to 2021-01-31.

To date, no completed studies in humans are available for AD5-nCoV.

*Table 2.2-1: **Ad5-nCoV** in clinical trial registry*

Active substance	Ad5-nCoV	Ad5-nCoV
Sponsor	CanSino Biologics Inc.	CanSino Biologics Inc.
Mechanism of operation	Platform: non-replicating viral vector Type of candidate vaccine: adenovirus type 5 vector Intended prevention through expression of SARS-CoV-2 spike proteins	Platform: non-replicating viral vector Type of candidate vaccine: adenovirus type 5 vector Intended prevention through expression of SARS-CoV-2 spike proteins
Regulatory status	Not approved	Not approved
Trial Identifier	ChiCTR2000030906 NCT04313127	ChiCTR2000031781
Phase & Intention	Phase I clinical trial on safety, reactogenicity and immunogenicity of recombinant novel coronavirus vaccine (adenovirus type 5 vector in healthy adults aged 18-60 years old	Phase 2 clinical trial on safety and immunogenicity for recombinant novel coronavirus disease vaccine (adenovirus vector) in healthy adults aged above 18 years
Study design	Non-randomized, single-centre, sequentially assigned, dose-escalating, phase I clinical trial	Randomized, double-blinded, placebo-controlled, parallel design
Status trial	Active, not recruiting	Active, not recruiting
Duration/ End of Study	Study start: March 16, 2020 Estimated Primary Completion Date: December 30, 2020 Estimated Study Completion Date: December 20, 2022	From 2020-04-12 to 2021-01-31
Study details	N of pts: 108 Location/ centres: China, Hubei	N of pts: 500

	Intervention/ control: Recombinant Novel Coronavirus Vaccine (Adenovirus Type 5 Vector) / NA Duration of observation/ follow-up: 6 months End points: Safety indexes of adverse reactions 7 days post injection (primary endpoint). 12 further safety-related and immunogenetic secondary endpoints.	Location/ centres: China, Hubei Intervention/ control: Recombinant Novel Coronavirus Vaccine (Adenovirus Type 5 Vector) / placebo Duration of observation/ follow-up: 6 months End points: Adverse reactions 0-14 days post vaccination; Anti-S antibody IgG titer on day 28 post vaccination; Anti-SARS-CoV-2 neutralizing antibody titer on day 28 post vaccination (primary endpoint). 6 further safety-related and immunogenetic secondary endpoints.
Results	N.A.	N.A.

Sources: [40-44], [34, 35]; Abbreviation: N.A. – not applicable.

2.3 Inovio Pharmaceuticals

About the vaccine

The **INO-4800** vaccine candidate developed by Inovio Pharmaceuticals Inc. is a DNA plasmid vaccine based on a DNA platform. The DNA is hereby synthesised in a laboratory, hence, no actual virus samples are required [43, 45]. The company's DNA platform was previously utilised for a MERS-CoV vaccine (INO-4700) tested in a phase I trial [15].

Estimated timeline for approval

According to press releases from the manufacturer [14, 15], and ClinicalTrials.gov register, human testing (a phase I clinical trial) started in April 2020. The results are aimed to be presented and published thereafter (April 2021).

The phase 1, non-randomized, open-label, sequential assignment clinical trial (NCT04336410) in 40 healthy adult volunteers aims to evaluate the safety, tolerability and immunological profile of INO-4800 administered by intradermal (ID) injection followed by electroporation (EP) using CELLECTRA® 2000 device. The primary endpoints of the trial are as following: percentage of participants with adverse events (AEs); percentage of participants with administration (injection) site reactions; percentage of participants with adverse events of special interest (AESIs); change from baseline in Antigen-Specific Binding Antibody Titers; change from baseline in Antigen-Specific Interferon-Gamma (IFN-γ) Cellular Immune Response. Secondary endpoints are not provided [30-34]. This RCT will be conducted from April 2020 to April 2021. Estimated Primary Completion Date is April 2021.

To date, no ongoing or completed studies in humans are available for the INO-4800 vaccine candidate.

*Table 2.3-1: Information on **INO-4800***

Active substance	INO-4800
Sponsor	Inovio Pharmaceuticals Inc. (Funding by CEPI, up to $9 million)
Mechanism of operation	Platform: DNA Type of candidate vaccine: DNA plasmid vaccine
Regulatory status	Not approved
Trial Identifier	NCT04336410
Phase & Intention	Phase 1 open-label trial to evaluate the safety, tolerability and immunological profile of INO-4800 administered by intradermal (ID) injection followed by electroporation (EP) using CELLECTRA® 2000 device in healthy adult volunteers
Study design	Non-randomized, open-label, sequential assignment
Status trial	Recruiting
Duration/ End of Study	Study start: April 3, 2020 Estimated Primary Completion Date: April, 2021 Estimated Study Completion Date: April, 2021
Study details	N of pts: 40 Location/ centres: US Intervention: one ID injection of INO-4800 and EP using the CELLECTRA® 2000 device/ two ID injections of INO-4800 and EP using the CELLECTRA® 2000 device Duration of observation/ follow-up: 52 weeks End points: Percentage of participants with Adverse Events (AEs) [Time Frame: baseline up to week 52]; Percentage of participants with administration (Injection) site reactions [Time frame: day 0 up to week 52]; Percentage of participants with Adverse Events of Special Interest (AESIs) [Time Frame: baseline up to week 52]; Change from baseline in Antigen-Specific Binding Antibody Titers [Time frame: baseline up to week 52]; Change from baseline in Antigen-Specific Interferon-Gamma (IFN-γ) Cellular Immune Response [Time frame: baseline up to week 52] (primary endpoint). Secondary endpoints not provided.
Results	N.A:

Sources: [14, 15, 43, 45], [30-34]; Abbreviations: CEPI – Coalition for Epidemic Preparedness Innovations; N.A. – not applicable.

2.4 Novavax

About the vaccine

The Novavax COVID-19 vaccine being developed by Novavax and co-sponsored by CEPI [46] is a recombinant protein nanoparticle technology platform that is to generate antigens derived from the coronavirus spike (S) protein [47]. Novavax also expects to utilize its proprietary Matrix-M™ adjuvant in order to enhance immune responses. Matrix-M™ is Novavax patented saponin-based adjuvant that has the potential to boost the immune system by stimulating the entry of antigen-presenting cells into the injection site and enhancing antigen presentation in local lymph nodes, boosting immune responses [48, 49].

Estimated timeline for approval

Novavax has been assessing recombinant nanoparticle vaccine candidates in animal models and they aim to initiate Phase I clinical trial in May/June 2020 [46]. Novavax has previous experience with both MERS and SARS [48].

The phase 1, randomized, placebo-controled, triple-blind, parallel assignment clinical trial (NCT04368988) in 131 healthy adults aims to evaluate the immunogenicity and safety of SARS-CoV-2 rS nanoparticle vaccine with or without Matrix-M adjuvant in healthy participants ≥ 18 to 59 years of age.

The study will be conducted in 2 parts. In Part 1, at least 1 and up to two SARS-CoV-2 rS constructs will be evaluated in up to 2 cohorts, which may be enrolled in parallel. An interim analysis of Part 1 safety and immunogenicity data will be performed prior to an optional expansion to Part 2. The primary endpoints of the trial are as following: subjects with solicited AEs - Phase 1; safety Laboratory Values (serum chemistry, hematology) - Phase 1 and serum IgG antibody levels specific for the SARS-CoV-2 rS protein antigen(s) - Phase 1. Secondary endpoints are not provided [30-33]. This RCT will be conducted from May 15, 2020 to July 31, 2021. Estimated Primary Completion Date is December 31, 2020.

To date, no completed studies in humans are available for Novavax COVID-19 vaccine.

Table 2.4-1: ***Novavax COVID-19 Vaccine*** *in clinical trial registry*

Active substance	**Novavax COVID-19 Vaccine**
Sponsor	Novavax, CEPI
Mechanism of operation	Platform: protein subunit Type of candidate vaccine: Full length S trimers/ Virus-like particle (VLP) recombinant protein nanoparticle + Matrix M™
Regulatory status	Not approved
Trial Identifier	NCT04368988
Phase & Intention	*A 2-Part, phase 1/2, randomized, observer-blinded study to evaluate the safety and immunogenicity Of A SARS-CoV-2 Recombinant Spike Protein Nanoparticle Vaccine (SARS-CoV-2 rS) with or without MATRIX-M™ adjuvant in healthy subjects
Study design	Randomized, placebo-controled, triple-blind, parallel assignment
Status trial	Not yet recruiting
Duration/ End of Study	Study start: May 15, 2020 Estimated Primary Completion Date: December 31, 2020 Estimated Study Completion Date: July 31, 2021
Study details	N of pts: 131 Location/ centres: Australia Intervention/Control: SARS-CoV-2 rS - 25 µg without Matrix-M; SARS-CoV-2 rS - 5 µg with 50 µg Matrix-M; SARS-CoV-2 rS - 25 µg with 50 µg Matrix-M; SARS-CoV-2 rS - 25 µg with 50 µg Matrix-M followed by Placebo/ Placebo - Saline Duration of observation/ follow-up: 35 days End points: Subjects with solicited AEs - Phase 1 [Time frame: 28 days]; Safety Laboratory Values (serum chemistry, hematology) - Phase 1 [Time frame: 28 days]; Serum IgG antibody levels specific for the SARS-CoV-2 rS protein antigen(s) - Phase 1 [Time frame: 35 days]; Secondary endpoints not provided.
Results	N.A:

*For Phase 1 only. Additional information will be provided if Phase 2 is implemented. Sources: [46, 47], [30-33]; Abbreviations: CEPI - Coalition for Epidemic Preparedness Innovations, N.A. – not applicable, VLP - virus-like particle.

2.5 University of Queensland/GSK/Dynavax

About the vaccine

Together with DynaVax and GlaxoSmithKline (GSK)[1], The University of Queensland currently investigates on a potential vaccine using molecular clamp stabilized Spike proteins [38, 43]. The so called 'molecular clamp' technology is hereby utilised: the intended prevention is through synthesising surface proteins and „clamping" them into shape. In so doing, the immune system may induce a response, by recognising them as the correct antigen on the surface of the virus, more easily [50].

[1] Both DynaVax and GSK will provide adjuvants.

Initially, this technology was designed to be a platform for generating vaccines against different viruses such as influenza, Ebola, and the MERS coronavirus [51].

Estimated timeline for approval

At this moment in time, the vaccine candidate developed by the University of Queensland is still in the preclinical phase. According to press releases, human clinical trials may start in June 2020 [52].

To date, no ongoing or completed studies in humans are available for the candidate vaccine.

Table 2.5-1: Vaccine candidate for COVID-19 developed by the University of Queensland

Active substance	N.A.
Sponsor	University of Queensland/ GlaxoSmithKline / Dynavax Funding by CEPI (up to AU$15.4 million)
Mechanism of operation	Platform: Protein Subunit Type of candidate vaccine: Molecular clamp stabilized Spike protein
Regulatory status	Not approved
Trial Identifier	N.A.
Phase & Intention	Preclinical (human trials may start in June 2020)
Study design	N.A.
Status trial	N.A.
Duration/ End of Study	N.A.
Study details	N.A.
Results	N.A.

Sources: [38, 43, 51-53]. Abbreviations: N.A. – not applicable. CEPI - Coalition for Epidemic Preparedness Innovations.

2.6 CureVac

About the vaccine

The vaccine candidates developed by CureVac are a protamine-complexed mRNA-based vaccine expressing undisclosed SARS-CoV-2 protein(s) [38]. Each CureVac product is a tailored molecular creation that contains 5' and 3' untranslated regions and the open reading frame to make sure translation of the messenger RNA (mRNA) sequence results in appropriate levels of proteins in the body [54]. This means that CureVac's technology uses mRNA as a data carrier in order to train the human body to produce ideal levels of proteins. Thereby the immune system is stimulated and can respond to antigens [55].

Recently, CureVac reported on results from an interim analysis of a Phase 1 study on a novel prophylactic mRNA based rabies vaccine, which showed that humans were fully protected after two doses of 1μg mRNA vaccine [56]. The same concept and technology that was applied in the development of this vaccine will also be used for the vaccine against the the new coronavirus.

Estimated timeline for approval

During a press conference call on March 17, 2020, CureVac explained that they are currently encoding 1 specific protein, which is present on the surface of the new coronavirus and which is sufficient to activiate the immune system. They are currently waiting for the animal data and already started with the production of 2 vaccine candidates for use in humans [57]. Those suitable vaccine canditates were selected from several constructs. The selection criteria applied were based on quality and biological activity. CureVac is also collaborating with the German Paul Ehrlich Institute (PEI) and European health authorities. The start of the clinical trials is planned for early summer 2020 and it was reported that two primary study centers have already been determined [58].

To date, no ongoing or completed studies in humans are available for the vaccine candidates.

Table 2.6-1: ***CureVac***

Active substance	COVID-19 mRNA mobile unit
Sponsor	CureVac AG • Funding by CEPI of up to $8.3 million for accelerated vaccine development, manufacturing and clinical tests • Financial support from the European Commission of up to €80 million in form of an EU guarantee of a currently assessed European Investment Bank loan of the same amount.
Mechanism of operation	Platform: RNA Type of candidate vaccine: Protamine-complexed mRNA-based vaccine expressing undisclosed SARS-CoV-2 protein(s)
Regulatory status	Not approved
Trial Identifier	N.A.
Phase & Intention	Preclinical phase; phase 1 study will start in June/July 2020
Status design	N.A.
Status trial	N.A.
Duration/ End of Study	N.A.
Study details	N.A.
Results	N.A.

Sources: [1, 9, 19, 38, 57, 59] Abbreviations: N.A. – not applicable. CEPI - Coalition for Epidemic Preparedness Innovations

2.7 University of Oxford

About the vaccine

The **ChAdOx1 nCoV-19** vaccine candidate developed by the Jenner Institute at Oxford University is based on a non-replicating viral vector. A chimpanzee adenovirus platform is hereby used. This platform was previously utilised in clinical phase I trials for a vaccine against MERS [13, 40].

The vaccine candidate uses a genetically modified safe adenovirus that may cause a cold-like illness. The intended prevention is through the modified adenovirus producing Spike proteins, eventually leading to the formation of antibodies to the coronavirus's Spike proteins. These antibodies may bind to the coronavirus and, subsequently, stop it from causing an infection [13].

Estimated timeline for approval

Currently, the first clinical phase I/II trial in 510 healthy adults is ongoing. The study is a single-blinded, placebo-controlled, multi-centre randomised controlled trial to test efficacy, safety and immunogenicity of ChAdOx1 nCoV-19. The primary endpoints are number of virologically confirmed symptomatic cases/symptomatic cases of COVID-19 (efficacy) and occurrence of serious adverse events (safety). Primary endpoints are measured within six months and an optional follow-up visit is offered at day 364. The study is estimated to be completed in May 2021 [60].

To date, no completed studies in humans are available for the ChAdOx1 nCoV-19 vaccine candidate.

*Table 2.7-1: **ChAdOx1** in clinical trial registry*

Active substance	ChAdOx1
Sponsor	University of Oxford
Mechanism of operation	Platform: Non-Replicating Viral Vector Type of candidate vaccine: ChAdOx1 Intended prevention through antibodies to the Spike binding to the coronavirus and stopping it from causing an infection.
Regulatory status	Not approved
Trial Identifier	NCT04324606
Phase & Intention	Phase I/II To determine efficacy, safety and immunogenicity of the candidate Coronavirus Disease (COVID-19) vaccine ChAdOx1 nCoV-19 in UK healthy adult volunteers aged 18-55 years
Study design	Randomised, single-blinded, placebo-controlled, multi-centre study
Status trial	Recruiting
Duration/ End of Study	Study start: March 2020 Estimated Primary Completion Date: May 2021 Estimated Study Completion Date: May 2021
Study details	N of pts: 510 Location/ centres: United Kingdom (Southhampton, London, Oxford) Intervention/ control: ChAdOx1 nCoV-19/ Saline placebo Duration of observation/ follow-up: 6 months (optional: additional FU visit at day 364) *Primary end points:* *Efficacy:* Number of virologically confirmed (PCR positive) symptomatic cases within 6 months post injection Number of virologically confirmed (PCR positive) symptomatic cases of COVID-19 *Safety:* Occurrence of serious adverse events (SAEs) within 6 months post injection Occurrence of serious adverse events (SAEs) throughout the study duration 11 further secondary end points related to safety, immunogenicity and efficacy
Results	N.A.

Sources: [13, 40, 43, 60]. Abbreviations: FU – follow up; N.A. – not applicable.

2.8 BioNTech/Fosun Pharma/Pfizer

About the vaccine

The **BNT-162** vaccine candidate developed by BioNTech in collaboration with Fosun Pharma and Pfizer is an mRNA platform-based vaccine expressing codon-optimized undisclosed SARS-CoV-2 protein(s) encapsulated in 80-nm ionizable cationic lipid/phosphatidylcholine/cholesterol/polyethylene glycol–lipid nanoparticles [38]. In 2018, Pfizer and BioNTech collaborated on mRNA-based vaccines for the prevention of influenza and their partnership applies outside of China [61]. BioNTech's partnership with Fosun Pharma applies for China only [61, 62].

Estimated timeline for approval

Currently, BNT-162 enters clinical testing by the end of April 2020 [63] and R&D is supposed to be carried out both in the US as well as in Germany [61].

This is a phase 1/2, randomized, placebo-controlled, triple-blind, dose-finding, and vaccine candidate-selection study in healthy adults (NCT04368728/EudraCT 2020-001038-36). The study will evaluate the safety, tolerability, immunogenicity, and potential efficacy of up to 4 different SARS-CoV-2 RNA vaccine candidates against COVID-19: as a 2-dose or single-dose schedule; at up to 3 different dose levels; in 3 age groups (18 to 55 years of age, 65 to 85 years of age, and 18 to 85 years of age. The study consists of 3 stages: Stage 1: to identify preferred vaccine candidate(s), dose level(s), number of doses, and schedule of administration (with the first 15 participants at each dose level of each vaccine candidate comprising a

sentinel cohort); Stage 2: an expanded-cohort stage; and Stage 3; a final candidate/dose large-scale stage. Estimated Primary Completion Date and Study Completion Date is January 27, 2023.

To date, no completed studies in humans are available for the BNT-162 vaccine.

*Table 2.8-1: **BNT-162** in clinical trial registry*

Active substance	BNT-162
Sponsor	BioNTech/Fosun Pharma/Pfizer
Mechanism of operation	Platform: messenger RNA (mRNA) Type of candidate vaccine: mRNA vaccine (BNT162) expressing codon-optimized undisclosed SARS-CoV-2 protein(s) encapsulated in 80-nm ionizable cationic lipid/phosphatidylcholine/ cholesterol/polyethylene glycol–lipid nanoparticles
Regulatory status	Not approved
Trial Identifier	NCT04368728/EudraCT 2020-001038-36
Phase & Intention	Phase I/II study to describe the safety, tolerability, immunogenicity, and potential efficacy of SARS-COV-2 RNA vaccine candidates against COVID-19 in healthy adults
Study design	Randomized, placebo-controlled, triple-blind, parallel assignment, dose-finding and vaccine candidate-selection study in healthy adults.
Status trial	Not yet recruiting.
Duration/ End of Study	Study start: April 28, 2020 Estimated Primary Completion Date: January 27, 2023 Estimated Study Completion Date: January 27, 2023.
Study details	N of pts: 8640 Location/ centres: NA Intervention/Control: BNT 162 up to 3 diferent dose levels (low-, mid- and high-dose, as single dose or 2 doses/ Placebo Duration of observation/ follow-up: up tp 2 years End points: Percentage of participants reporting local reactions; Percentage of participants reporting systemic events; Percentage of participants reporting adverse events; Percentage of participants reporting serious adverse events; Percentage of sentinel cohort participants with abnormal hematology and chemistry laboratory values; Percentage of sentinel cohort participants with grading shifts in hematology and chemistry laboratory assessments; different immunogenetic endpoints and confirmed COVID-19 incidence as secondary endpoints.
Results	N.A.

Sources: [38, 63], [30-34, 36]; Abbreviations: N.A. – not applicable

2.9 New vaccines entered in clinical investigation in healthy volunteers, as at 05 May 2020

As at 05 May 2020, **6 new vaccines** are registered in phase 1, phase 1/2 and phase 2, by Shenzhen Geno-Immune Medical Institute (NCT04299724 and NCT04276896); Insitute of Biotechnology, Academy of Military Medical Sciences, PLA of China (NCT04341389); Symvivo Corporation (NCT04334980); Sinovac (NCT04352608) and Wuhan Institute of Biological Products/Sinopharm (ChiCTR2000031809) (Table 2-1). NCT04299724 is phase 1 study related to pathogen-specific aAPC (aAPCs modified with lentiviral vector expressing synthetic minigene based on domains of selected viral proteins) and NCT04276896 is phase 1/2 study related to LV-SMENP-DC vaccine (DCs modified with lentiviral vector expressing synthetic minigene based on domains of selected viral proteins; administered with antigen-specific CTLs). NCT04341389 is phase 2 trial related to adenovirus Type 5 Vector expressing S protein. NCT04334980 is phase 1 study, the first-in-human study of bacTRL-Spike, and the first-in-human use of orally delivered bacTRL. Two clinical trials in phase 1/2 are related to inactivated vaccine: NCT04352608 is related to inactivated SARS-CoV-2 virus and ChiCTR2000031809 to Vero cells derived (cell culture-derived inactivated) vaccine [30-35].

Clinical studies assessing BCG vaccine in prevention of COVID-19 are underway also: RCTs in Netherlands (BCG-CORONA phase 3 trial, NCT04328441) and Australia (BRACE phase 3 trial,

NCT04327206) aim to assess whether BCG-Danish reduces the incidence and severity of COVID-19 in health-care workers, and the effect this has on time away from work [64]. The same is true for US RCT (NCT04348370) [33]. The same is planned in Egypt (NCT04350931) and in Denmark (NCT04373291) (RCTs, not yet recruiting healthy volunteers) [33].

3 Results: Therapeutics

Table 3-1: Most advanced therapeutics in the R&D pipeline

Drug	Mechanism of operation	Study phase and trial identifier
Remdesivir (GS-5734)	Antiviral agent	Phase III (NCT04252664) - Suspended Phase III (NCT04257656) - Terminated Phase III (NCT04292730, EudraCT number: 2020-000841-15) Phase III (NCT04292899, EudraCT number: 2020-000842-32) Phase III (NCT04280705, EudraCT number: 2020-001052-18) Phase III (NCT04315948, EudraCT number: 2020-000936-23) Phase II / III (NCT04321616, EudraCT number: 2020-000982-18) Phase III (ISRCTN83971151) Phase IV (EudraCT number: 2020-001366-11) Phase II (NCT04330690) NCT04323761 Expanded Access NCT04302766 Expanded Access EudraCT number: 2020-001453-49 Expanded Access
Lopinavir + Ritonavir (Kaletra®)	Antiviral agent	Phase IV (NCT04255017) Phase IV (NCT04252885) Phase III (NCT04315948) Phase III (NCT04321174) Phase II (NCT04307693) Phase NA (ChiCTR2000029308) Phase NA (ChiCTR2000029539) Phase NA (ChiCTR2000029387) Phase NA (ChiCTR2000030187) Phase IV (NCT04255017) Phase II (NCT04276688, Completed) Phase II/III (NCT04328012) Phase II/III (NCT04351724) Phase III (ISRCTN83971151) Phase III (NCT04330690) Phase IV (EudraCT 2020-001366-11) Phase II/III (ISRCTN50189673, EudraCT 2020-001113-21)
Favipiravir (Avigan, T-705)	Antiviral agent	Phase NA (ChiCTR2000029548) Phase NA (ChiCTR2000029544) Phase NA (ChiCTR2000029600) Phase NA (ChiCTR2000030113) Phase NA (ChiCTR2000030254) Phase NA (NCT04333589) Phase II (NCT04358549) Phase III (2020-001449-38) Phase III (2020-001435-27) Phase NA (NCT04310228)
Darunavir (Prezista®)	Antiviral agent	Phase III (NCT04252274) Phase NA (ChiCTR2000029541)
Chloroquine Phosphate (Resochin®)	Antiviral cell-entry inhibitor	Phase IV (ChiCTR2000029988) Phase IV (ChiCTR2000029975) Phase IV (ChiCTR2000029542) Phase IV (ChiCTR2000029609) Phase IV (ChiCTR2000029741) Phase IV (ChiCTR2000029898) Phase IV (ChiCTR2000029992) Phase IV (ChiCTR2000029899) Phase 0 (ChiCTR2000030054) Phase NA (ChiCTR2000029939) Phase NA (ChiCTR2000029935) Phase II (NCT04328493)

		Phase IV (NCT04362332) Phase IV (NCT04351191) Phase II (NCT04342650) Phase II (NCT04323527) Phase II/III (NCT04351724) Phase III (NCT04341727) Phase III (ISRCTN83971151) Phase IV (EudraCT 2020-001366-11)
Hydroxychloroquine (Plaquenil®)	Antiviral cell-entry inhibitor	Phase IV (NCT04316377) Phase IV (ChiCTR2000029559) Phase IV (ChiCTR2000029992) Phase IV (ChiCTR2000029898) Phase IV (ChiCTR2000029899) Phase IV (ChiCTR2000029868, Completed) Phase IV (ChiCTR2000029740) Phase III / IV (EudraCT: 2020-000982-18) Phase III (NCT04315896) Phase III (NCT04321278) Phase III (NCT04308668) Phase III (NCT04315948, EudraCT 2020-000936-23) Phase III (EudraCT: 2020-000890-25) Phase II (EudraCT: 2020-001224-33) Phase 0 (ChiCTR2000030054) Phase II/III (EudraCT 2020-001113-21, ISRCTN50189673) Phase III (EudraCT 2020-001209-22, ISRCTN86534580) Phase IV (EudraCT 2020-001366-11) Phase III (EudraCT 2020-001333-13) Phase II (EudraCT 2020-001417-21) Phase III (ISRCTN83971151) Phase I (NCT04323631) Phase III (NCT04328272) Phase II/III (NCT04328012) Phase II (NCT04329832) Phase III (NCT04322123) Phase II/III (NCT04321616, EudraCT 2020-000982-18) Phase III (NCT04325893, EudraCT 2020-001271-33) Phase III (NCT04345692) Phase III (NCT04334382) Phase III (NCT04342221) Phase II (NCT04307693) Phase II (NCT04336332) Phase IV (NCT04362332) Phase II (NCT04369742) Phase III (NCT04261517, Completed) Phase II (NCT04335552) Phase II (NCT04330690) Phase II/III (NCT04351516) Phase II (NCT04374019) Phase III (NCT04332991) Phase III (NCT04344444) Phase II/III (NCT04328012) Phase II/III (NCT04345861) Phase I (NCT04333654) Phase II (NCT04342169) Phase III (NCT04341727) Phase II/III (NCT04351724) Phase IV (NCT04316377, EudraCT 2020-001010-38) Phase IV (NCT04351191)

Camostat Mesilate (Foipan®)	Antiviral cell-entry inhibitor	Phase II (NCT04321096, 2020-001200-42) Phase II (NCT04353284) Phase II (NCT04374019)
APN01 (rhACE2)	Antiviral cell-entry inhibitor	Phase II (NCT04335136, 2020-001172-15) Phase NA (NCT04287686) Withdrawn (Without CDE Approval)
Tocilizumab (RoActemra®)	Monoclonal antibody	Phase IV (NCT04330638) Phase III (NCT04320615, 2020-001154-22) Phase II (NCT04335071) Phase II (NCT04335305) Phase II (NCT04333914) Phase II (NCT04331808) Phase II (NCT04322773) Phase II (NCT04332094) Phase II (NCT04317092, 2020-001110-38) Phase II (NCT04331795) Phase II (NCT04315480) Phase NA (NCT04332913) Phase NA (NCT04310228) Phase NA (NCT04306705) Phase II (NCT04346355) Phase IV (NCT04377750) Phase III (NCT04361552) Phase II (2020-001275-32) Phase II (2020-001770-30) Phase II (2020-002032-69) Phase II (2020-001408-41) Phase III (2020-001500-41) Phase IV (2020-001437-12) Phase II/III (2020-001113-21) Phase II/III (2020-001246-18)
Sarilumab (Kevzara)	Monoclonal antibody	Phase II / III (NCT04324073) Phase II / III (NCT04327388, 2020-001162-12) Phase II / III (NCT04315298) Phase II (NCT04322773) Phase II (NCT04321993) Phase II (NCT04357808, 2020-001634-36) Phase II/III (NCT04341870) Suspended Phase II (NCT04359901) Phase III (2020-001367-88) Phase II (2020-001531-27) Phase III (2020-001290-74) Phase II (2020-001275-32) Phase II/III (2020-001246-18)
Interferon beta 1a (SNG001)	Interferon	Phase IV (NCT02735707) Phase III (NCT04315948) Phase II (EudraCT: 2020-001023-14) Phase NA (NCT04314817) Phase II (NCT04385095) Phase III (NCT04315948, EudraCT 2020-000936-23) Phase III (ISRCTN83971151) Phase IV (EudraCT 2020-001366-11, NCT02735707) Phase II (NCT04276688) Interferon beta 1b, Completed
Convalescent Plasma (interventional studies n =43, RCTs=26)	Convalescent Plasma	Phase 2 (EudraCT 2020-001310-38), RCT Phase Unknown (NCT04264858), nonRCT Phase Unknown (NCT04321421), single group Phase 2 (NCT04323800), RCT Phase 2 (NCT04325672), single group, Withdrawn (Study stopped due to opening Expanded Access Protocol) Phase Unknown (NCT04327349; IRCT20181104041551N1 - Registry Identifier: Iranian Registry of Clinical Trials IRCT), single group Phase 2 (NCT04332380), single group Phase 2/3 (NCT04332835), RCT Phase 1 (NCT04333251), RCT Phase 1 (NCT04333355), single group

		Phase Expanded access (NCT04338360) Phase 1 early (NCT04340050), single group Phase 2/3 (NCT04342182), RCT Phase 2 (NCT04343261), single group Phase 2 (NCT04343755), single group Phase 1/2 (NCT04344535), RCT Phase 3 (NCT04345289), RCT Phase 2 (NCT04345523), RCT Phase 1 early (NCT04345679), single group Phase 2 (NCT04346446), RCT Phase Unknown (NCT04346589), single group Phase 2 (NCT04347681), nonRCT Phase 3 (NCT04348656), RCT Phase Unknown (NCT04348877), single group Phase Unknown (NCT04352751), single group Phase 1 early (NCT04353206), single group Phase 2 (NCT04354831), nonRCT Phase 2 (NCT04355767), RCT Phase 1 early (NCT04355897), single group Phase 1/2 (NCT04356482), single group Phase Unknown (NCT04356534), RCT Phase 2 (NCT04357106), single group Phase 2 (NCT04345991), RCT NCT04358211, expanded access Phase 2 (NCT04358783), RCT Phase 2 (NCT04359810), RCT NCT04360486, expanded access Phase 3 (NCT04361253), RCT Phase 3 (NCT04362176), RCT Phase Unknown (ChiCTR2000029757), RCT Phase Unknown (ChiCTR2000029850), nonRCT Phase Unknown (ChiCTR2000030010), RCT Phase Unknown (ChiCTR2000030039), nonRCT Phase Unknown (ChiCTR2000030046), single arm Phase New Treatment (ChiCTR2000030179), RCT Phase Unknown (ChiCTR2000030627), RCT Phase Unknown (ChiCTR2000030702), RCT Phase Unknown (ChiCTR2000030929), RCT Phase 3 (IRCT20200404046948N1), RCT Phase 3 (IRCT20200413047056N1), RCT Phase 2/3 (IRCT20200310046736N1), RCT

3.1 Remdesivir/GS-5734

About the drug under consideration

Remdesivir (RDV)/GS-5734 constitutes another potential therapeutic treatment of the 2019 novel coronavirus shortly called COVID-19 or 2019-nCoV. RDV has a broad spectrum of antiviral activities against RNA viruses. RDV is a nucleotide analogue inhibitor of RNA-dependent RNA polymerases (RdRps). Originally it was utilised against the severe acute respiratory syndrome-CoV (SARS-COV) and the Middle East respiratory syndrome (MERS-COV). Research has shown that RDV could effectively inhibit MERS-COV replication in vitro, and showed efficacy against SARS-COV in animal trials. Furthermore, phase 3 clinical trials of RVD examining pharmacokinetics and safety had been completed for the treatment of Ebola [65].

In 2020 RDV has been utilised in hundreds of COVID-19 patients in the US and Europe outside of a clinical trial in what is called compassionate use [66]. One case study published in the New England Journal of Medicine (NEJM) reports the use of RDV in a patient with COVID-19. In this case report, the treatment with intravenous RVD was initiated on the evening of day 7, without observation of apparent

adverse events in association with the infusion. On the 8th day after hospitalisation (the 12th day after onset) the clinical symptoms improved on the 8th day after hospitalisation [67].

Currently, a major limitation is a lack of evidence with regard to efficacy and safety, i.e. lack of phase 1 and 2 clinical data against 2019 novel coronavirus. The majority of studies mentioning RDV propose that further assessments of this antiviral agent is needed by clinical trials.

The therapy with RVD is not approved by the **European Medicine Agency (EMA)** for COVID-19, but was recommended on compassionate use for on the 3rd of April 2020 [68]. On May 11, 2020 EMA's human medicines committee (CHMP) has recommended **expanding the compassionate use** of the investigational medicine remdesivir. In addition to patients undergoing invasive mechanical ventilation, the compassionate use recommendations now cover the treatment of hospitalised patients requiring supplemental oxygen, non-invasive ventilation, high-flow oxygen devices or ECMO (extracorporeal membrane oxygenation). More information is available in the summary on compassionate use and the conditions of use of remdesivir [69]. Furthermore, it has orphan designation for the treatment of Ebola virus disease since February 2016.

On April 30, 2020 EMA's human medicines committee (CHMP) has started a 'rolling review' of data on the use of the investigational antiviral medicine remdesivir for the treatment of coronavirus disease (COVID-19), based on preliminary results from the ACTT study, which suggest a beneficial effect of remdesivir in the treatment of hospitalised patients with mild-to-moderate or severe COVID-19. As stated, EMA has not yet evaluated the full study and it is too early to draw any conclusions regarding the benefit-risk balance of the medicine. A rolling review is one of the regulatory tools available to the Agency to speed up the assessment of a promising investigational medicine during a public health emergency, such as the ongoing pandemic. The CHMP will evaluate all data on remdesivir, including evidence from a recently published study from China and other clinical trials and conclude on the medicine's benefits and risks as soon as possible [70].

The use of RDV for COVID-19 was granted by the Food and Drug Administration (FDA) on the 19th of March in the course of the expanded access program to allow the emergency use, and in addition it has an orphan designation for Ebola since September 2015 [71].

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. Severe disease is defined as patients with an oxygen saturation (SpO2) ≤ 94% on room air or requiring supplemental oxygen or requiring mechanical ventilation or requiring extracorporeal membrane oxygenation (ECMO). EUA was based on available data from two randomized clinical trials (NIAID ACTT-1 Study, NCT04280705 and Study GS-US-540-5773, NCT04292899); a compassionate use program in patients with COVID-19; from clinical trials in healthy volunteers and subjects with Ebola virus disease [72, 73].

Ongoing studies

The search in two clinical trial registers (humans only) on 06/05/2020 yielded no completed study on the safety and efficacy of RVD in COVID-19 patients. Two phase 3 randomised controlled trials (RCT) to evaluate intravenous RVD in patients with 2019-nCoV were initiated in the beginning of February in China are now suspended (NCT04252664) or terminated (NCT04257656) because the epidemic of COVID-19 has been controlled well in China, and no eligible patients can be enrolled further. Another phase 3 multicentre RCT was started on the 21st of February with the estimated completion date in April 2023 (NCT04280705). In addition, 3 further phase 3 multicentre RCTs that start in the first (NCT04292899), third (NCT04292730), and fourth (NCT04315948) week of March respectively could be identified. Two of the trials are global multicentre RCTs in 96 (NCT04292730) and 91 (NCT04292899) centres respectively with completion dates in April 2020 and April 2023. A multicentre trial conducted in 3 centres in France (DisCoVeRy trial, NCT04315948, EudraCT 2020-000936-23) is initiated by the French Institut National de la Santé Et de la Recherche Médicale (INSERM) using a master protocol developed by WHO, with the estimated completion date in March 2023. WHO Solidarity trial (ISRCTN83971151) is an international RCT, launched by the World Health Organization and partners, with aim to assess

relative effectiveness of four treatment options (remdesivir; chloroquine or hydroxychloroquine; lopinavir with ritonavir; lopinavir with ritonavir plus interferon beta-1a) against standard of care, in COVID-19 patients. WHO Solidarity trial arms are ongoing in different countries; WHO-NOR-COVID-19 trial as Norwegian arm of SOLIDARITY trial (NCT04321616, EudraCT 2020-000982-18); Spain arm of SOLIDARITY trial (EudraCT 2020-001366-11) and Canadian arm of SOLIDARITY trial (NCT04330690). Table 3.1-1 displays more details of the identified ongoing trials.

Results of publications

At 6th of May 2020, Wang Y et al. [74] published results of the first randomised, double-blind, placebo-controlled, multicentre trial, conducted at ten hospitals in Hubei, China (NCT04257656), assessing the effect of intravenous remdesivir in adults admitted to hospital with severe COVID-19. The study was terminated before attaining the prespecified sample size (237 of the intended 453 patients were enrolled) because the outbreak of COVID-19 was brought under control in China. Patients were randomly assigned in a 2:1 ratio to intravenous remdesivir (200 mg on day 1 followed by 100 mg on days 2–10 in single daily infusions) or the same volume of placebo infusions for 10 days. Patients were permitted concomitant use of lopinavir–ritonavir, interferons, and corticosteroids. The primary endpoint was time to clinical improvement up to day 28, defined as the time (in days) from randomisation to the point of a decline of two levels on a six-point ordinal scale of clinical status (from 1=discharged to 6=death) or discharged alive from hospital, whichever came first. Primary analysis was done in the intention-to-treat (ITT) population and safety analysis was done in all patients who started their assigned treatment. Remdesivir treatment was not associated with a statistically significant difference in time to clinical improvement (hazard ratio 1·23 [95% CI 0·87–1·75]). Patients receiving remdesivir had a numerically faster time to clinical improvement than those receiving placebo among patients with symptom duration of 10 days or less, but this was not statistically significant also (hazard ratio 1·52 [0·95–2·43]). The duration of invasive mechanical ventilation was not significantly different between groups (numerically shorter in remdesivir recipients than placebo recipients). 22 (14%) of 158 patients on remdesivir died versus ten (13%) of 78 on placebo. There was no signal that viral load decreased differentially over time between remdesivir and placebo groups. Adverse events were reported in 102 (66%) of 155 remdesivir recipients versus 50 (64%) of 78 placebo recipients. Remdesivir was stopped early because of adverse events in 18 (12%) patients versus four (5%) patients who stopped placebo early (Table 3.1-3).

Table 3.1-1 : ***Remdesivir*** *in clinical trial registry*

Active substance	Remdesivir/GS-5734	Remdesivir/GS-5734	Remdesivir/GS-5734	Remdesivir/GS-5734	Remdesivir/GS-5734	Remdesivir/GS-5734
Sponsor/ Collaborator	Capital Medical University/Chinese Academy of Medical Sciences	Capital Medical University	Gilead Sciences	Gilead Sciences	National Institute of Allergy and Infectious Diseases (NIAID)	Institut National de la Santé Et de la Recherche Médicale, France
Mechanism of operation	Antiviral agent	Antiviral agent	Antiviral agent	Antiviral agent	Antiviral agent	Antiviral agent
Regulatory status EMA/FDA	**EMA:** Not approved, the compassionate use, but orphan designation for the treatment of Ebola virus disease (17/02/2016) **FDA**: Emergency Use Authorization (EUA) (01/05/2020), orphan designation for Ebola (18/09/2015)	**EMA:** Not approved, the compassionate use, but orphan designation for the treatment of Ebola virus disease (17/02/2016) **FDA**: Emergency Use Authorization (EUA) (01/05/2020), orphan designation for Ebola (18/09/2015)	**EMA:** Not approved, the compassionate use, but orphan designation for the treatment of Ebola virus disease (17/02/2016) FDA: Emergency Use Authorization (EUA) (01/05/2020), orphan designation for Ebola (18/09/2015)	**EMA:** Not approved, the compassionate use, but orphan designation for the treatment of Ebola virus disease (17/02/2016) **FDA:** Emergency Use Authorization (EUA) (01/05/2020), orphan designation for Ebola (18/09/2015)	**EMA:** Not approved, the compassionate use, but orphan designation for the treatment of Ebola virus disease (17/02/2016) **FDA:** Emergency Use Authorization (EUA), orphan designation for Ebola (18/09/2015)	**EMA:** Not approved, the compassionate use, but orphan designation for the treatment of Ebola virus disease (17/02/2016) **FDA:** Emergency Use Authorization (EUA) (01/05/2020), orphan designation for Ebola (18/09/2015)
Trial Identifier	NCT04252664 https://clinicaltrials.gov/ct2/show/study/NCT04252664	NCT04257656 https://clinicaltrials.gov/ct2/show/NCT04257656?term=NCT04257656&draw=2&rank=1	NCT04292730 https://clinicaltrials.gov/ct2/show/NCT04292730?term=NCT04292730&draw=2&rank=1	NCT04292899 https://clinicaltrials.gov/ct2/show/NCT04292899?term=NCT04292899&draw=2&rank=1	NCT04280705, ACTT trial https://clinicaltrials.gov/ct2/show/NCT04280705	NCT04315948, EudraCT 2020-000936-23, DisCoVeRy trial https://clinicaltrials.gov/ct2/show/NCT04315948
Phase & Intention	Phase 3 study to evaluate the efficacy and safety of RDV in hospitalized adult patients with mild and moderate 2019-nCoV respiratory disease	Phase 3 study to evaluate the efficacy and safety of RDV in hospitalized adult patients with severe 2019-nCoV respiratory disease	Phase 3 study to evaluate the safety and antiviral activity of RDV (GS-5734) in participants with moderate COVID-19 compared to SOC	Phase 3 study to evaluate the safety and antiviral activity of RDV (GS-5734) in participants with severe COVID-19	Phase 3 study to evaluate the safety and efficacy of investigational therapeutics for the treatment of COVID-19 in hospitalized adults	Phase 3 study to evaluate the safety and efficacy of treatments of COVID-19 in hospitalized adults
Study design	Randomised double-blind placebo-controlled multicentre study (Parallel assignment)	Randomised double-blind placebo-controlled multicentre study (Parallel assignment)	Randomised multicentre study (Parallel assignment)	Randomised multicentre study (Parallel assignment)	Adaptive randomised, double-blind placebo-controlled multicentre trial (Parallel assignment)	Multicentre adaptive randomised study that randomises participants 1:1:1:1:1 to standard of care alone (control) or with investigational product added. If

Active substance	Remdesivir/GS-5734	Remdesivir/GS-5734	Remdesivir/GS-5734	Remdesivir/GS-5734	Remdesivir/GS-5734	Remdesivir/GS-5734
						additional arms are added to or dropped from the trial, randomisation will proceed with an equal probability of assignment to each of the remaining arms (Parallel assignment)
Status trial	**Suspended**	**Terminated**	Recruiting	Recruiting	Recruiting	Recruiting
Duration/End of Study	2.5 months / Start: February 12, 2020 Primary completion date: April 10, 2020 Study completion date: April 27, 2020	~3 months / Start: February 6, 2020 Primary completion date: April 3, 2020 Study completion date: May 1, 2020	~3 months / Start: March 15, 2020 Primary completion date: May 2020 Study completion date: May 2020	~3 months / Start: March 6, 2020 Primary completion date: May 2020 Study completion date: May 2020	~3 years / Start: February 21, 2020 Primary completion date: April 1, 2023 Study completion date: April 1, 2023	~3 years / Start: March 22, 2020 Primary completion date: March 2023 Study completion date: March 2023
Study details						
Number of Patients	n = 308	n = 453	n = 600	n = 400	n = 440	n = 3100
Location/Centres	China, Jin Yin-tan hospital, Hubei, Wu Han / NA (Multicentre)	China, Bin Cao, Beijing, Beijing / NA (Multicentre)	USA, Republic of Korea, Singapore, Spain, Switzerland, Taiwan, United Kingdom / 96 study locations	USA, Germany, Hong Kong, Italy, Republic of Korea, Singapore, Spain, Switzerland, Taiwan, United Kingdom / 91 study locations	USA, Japan, Republic of Korea, Singapore / 40 study locations	France / 3 study locations (Multicentre)
Intervention	**RDV** 200 mg loading dose on day 1 is given, followed by 100 mg iv once-daily maintenance doses for 9 days (n = NR)	**RDV** 200 mg loading dose on day 1 is given, followed by 100 mg iv once-daily maintenance doses for 9 days (n = NR)	**RDV**, 5 Days, administered as an intravenous infusion, Participants will receive continued SOC therapy together with RDV 200 mg on Day 1 followed by RDV 100 mg on Days 2, 3, 4, and 5 (n = NR) **RDV**, 10 days, administered as an intravenous infusion, Participants will receive continued SOC therapy together with RDV 200 mg on day 1 followed by RDV 100 mg on days	**RDV**, 5 days, administered as an intravenous infusion, participants will receive continued SOC therapy together with RDV 200 mg on day 1 followed by RDV 100 mg on Days 2, 3, 4, and 5 (n = NR) **RDV**, 10 days, administered as an intravenous infusion, participants will receive continued standard of care therapy together with RDV 200 mg on day 1 followed by RDV 100	200 mg of **RDV** administered intravenously on day 1, followed by a 100 mg once-daily maintenance dose of RDV for the duration of the hospitalization up to a 10 days total course (n=220)	**RDV** will be administered as a 200 mg intravenous loading dose on day 1, followed by a 100 mg once-daily intravenous maintenance dose for the duration of the hospitalization up to a 10 days total course (n = 620) **Lopinavir/ritonavir** (400 lopinavir mg/100 mg ritonavir) will be administered every 12 h for 14 days in tablet form. For patients who are unable to take medications by mouth, the lopinavir/ritonavir (400 lopinavir mg/100 mg ritonavir) will be administered as a 5-ml suspension every 12 h for 14 days via a pre-existing or newly placed nasogastric tube (n=620)

Active substance	Remdesivir/GS-5734	Remdesivir/GS-5734	Remdesivir/GS-5734	Remdesivir/GS-5734	Remdesivir/GS-5734	Remdesivir/GS-5734
			2, 3, 4, 5, 6, 7, 8, 9, and 10 (n = NR)	mg on days 2, 3, 4, 5, 6, 7, 8, 9, and 10 (n = NR)		**Lopinavir/ritonavir** As written above **plus** **Interferon ß1a** will be administered subcutaneously at the dose of 44 µg for a total of 3 doses in 6 days (day 1, day 3, day 6) (n=620) **Hydroxychloroquine** will be administered orally as a loading dose of 400 mg twice daily for one day followed by 400 mg once daily for 9 days. The loading dose of hydroxychloroquine through a nasogastric tube will be increased to 600 mg twice a day for one day, followed by a maintenance dose of 400 mg once a day for 9 days (n=620)
Controls	**RDV placebo** 200 mg loading dose on day 1 is given, followed by 100 mg iv once-daily maintenance doses for 9 days (n = NR)	**RDV placebo** 200 mg loading dose on day 1 is given, followed by 100 mg iv once-daily maintenance doses for 9 days (n = NR)	Continued SOC therapy (n = NR)	NR	200 mg of **RDV placebo** administered intravenously on day 1, followed by a 100 mg once-daily maintenance dose of RDV placebo for the duration of the hospitalization up to a 10 days total course (n=220)	SOC (n = 620)
Duration of observation/Follow-up (Current Primary Outcome Measures)	Up to 28 days	Up to 28 days	Up to 14 days	Up to 14 days	15 days	15 days
Endpoints (Current Primary Outcome Measures)	Time to clinical recovery (TTCR)	Time to clinical improvement (TTCI)	Proportion of participants discharged by day 14	Proportion of participants with normalization of fever and oxygen saturation through day 14	Percentage of subjects reporting each severity rating on an 8-point ordinal scale	Percentage of subjects reporting each severity rating on a 7-point ordinal scale
Results/Publication	Not provided	Provided [74]	Not provided	Not provided	Not provided	Not provided

NR = Not reported, RDV = Remdesivir, SOC = Standard of care

*Table 3.1-2 : **Remdesivir** in clinical trial registry (Continued)*

Active substance	Remdesivir/GS-5734	Remdesivir/GS-5743	Remdesivir/GS-5734	Remdesivir/GS-5734
Sponsor/Collaborator	WHO	Oslo University Hospital	Sunnybrook Health Sciences Centre/ AbbVie; Apotex Inc.	WHO (World Health Organization)
Mechanism of operation	Antiviral agent	Antiviral agent	Antiviral agent	Antiviral agent
Regulatory status EMA/FDA	**EMA:** Not approved, the compassionate use, but orphan designation for the treatment of Ebola virus disease (17/02/2016) **FDA:** Emergency Use Authorization (EUA) (01/05/2020), orphan designation for Ebola (18/09/2015)	**EMA:** Not approved, the compassionate use, but orphan designation for the treatment of Ebola virus disease (17/02/2016) **FDA:** Emergency Use Authorization (EUA) (01/05/2020), orphan designation for Ebola (18/09/2015)	**EMA:** Not approved, the compassionate use, but orphan designation for the treatment of Ebola virus disease (17/02/2016) **FDA:** Emergency Use Authorization (EUA) (01/05/2020), orphan designation for Ebola (18/09/2015)	**EMA:** Not approved, the compassionate use, but orphan designation for the treatment of Ebola virus disease (17/02/2016) **FDA:** Emergency Use Authorization (EUA) (01/05/2020), orphan designation for Ebola (18/09/2015)
Trial Identifier	ISRCTN83971151, SOLIDARITY trial http://www.isrctn.com/ISRCTN83971151	NCT04321616, EudraCT 2020-000982-18, Norwegian arm of SOLIDARITY trial https://clinicaltrials.gov/ct2/show/NCT04321616?term=remdesivir&draw=4&rank=8	NCT04330690, Canadian arm of SOLIDARITY trial https://clinicaltrials.gov/ct2/show/record/NCT04330690?term=NCT04330690&draw=2&rank=1	EudraCT 2020-001366-11, Spain arm of SOLIDARITY trial https://www.clinicaltrialsregister.eu/ctr-search/trial/2020-001366-11/ES
Phase & Intention	Phase III study to compare different therapy (remdesivir, chloroquine or hydroxychloroquine, lopinavir plus ritonavir, and interferon-beta) with each other in hospitalized COVID-19 patients who are all receiving the local standard of care, to reduces all-cause mortality	Phase 2/3 study to evaluate the efficacy of different antiviral drugs in SARS-CoV-2 infected patients	Phase 2 study to assess the safety and efficacy of investigational therapeutics for the treatment of COVID-19 in hospitalizedpPatients (CATCO: Canadian Treatments for COVID-19), in conjunction with the public health emergency SOLIDARITY Trial (World Health Organization)	Phase IV study to compare the effects on major outcomes in hospital of the local standard of care alone versus the local standard of care plus one of four alternative anti-viral agents
Study design	**RCT**, open-label, local standard of care comparator, parallel assignment	Open randomised adaptive controlled multicentre trial (Parallel Assignment)	RCT, adaptive, open-label, local standard supportive care comparator, parallel assignment	RCT, open-label, local standard supportive care comparator, parallel assignment
Status trial	Recruiting	Recruiting	Recruiting	Ongoing
Duration/End of Study	March 2020 to March 2021	~7 months / Start: March 26, 2020 Primary completion date: August 2020 Study completion date: November 2020	~ 24 months / Start: March 18, 2020 Primary completion date: March 18, 2022 Study completion date: May 18, 2022	6 months-1 year
Study details				
Number of Patients	No specific sample size is specified - at least several thousand patients will be recruited into the trial (18 or more years old)	n = 700 (18 years and older)	N=440 (18 years and older)	N=2500 (18 years and older)

Active substance	Remdesivir/GS-5734	Remdesivir/GS-5743	Remdesivir/GS-5734	Remdesivir/GS-5734
Location/Centres	Argentina, Brazil, Canada, Germany, Honduras, India, Indonesia, Iran, Ireland, Israel, Italy, Kenya, Lebanon, Malaysia, Norway, Peru, Philippines, Qatar, Saudi Arabia, South Africa, Spain, Switzerland, Thailand	Norway	Canada	Spain
Intervention	**RDV** **Chloroquine or hydroxychloroquine** **Lopinavir + ritonavir** (Kaletra) **Lopinavir + ritonavir plus interferon-beta** together **with local standard of care**	**RDV** will be given intravenously 100 mg daily for the duration of the hospitalization and up to 10 days total course. A loading dose of 200 mg at inclusion will be given (n = NR) **Hydroxychloroquine** will be given orally (in the ICU in gastrointestinal tubes) with 800 mg x 2 loading dose followed by 400 mg x 2 every day for a total of 10 days (n=NA)	**RDV** 200mg IV on day 1, followed by 100 mg IV daily infusion for 9 days plus optimized supportive care or until discharge from hospital, whichever occurs first **Hydroxychloroquine** 800mg BID for 1 day then 400mg BID for 10 days plus optimized supportive care or until discharge from hospital, whichever occurs first **Lopinavir/ritonavir** will be administered 400 mg/100 mg orally for a 14-day course plus supportive care, or until discharge from hospital, whichever occurs first	**RDV** **Chloroquine** **Hydroxychloroquine** **Lopinavir/Ritonavir** **Interferon beta-1a**
Controls	Local standard of care	SOC (n = NA)	Standard supportive care	Local standard of care
Duration of observation/Follow-up (Current Primary Outcome Measures)	Until death or discharge from hospital	3 weeks	29 days, up to 60 days	At discharge or death
Endpoints (Current Primary Outcome Measures)	All-cause mortality, subdivided by the severity of disease at the time of randomization, measured using patient records throughout the study	All cause in-hospital mortality	All-cause mortality, assessed at hospital discharge	All-cause mortality, subdivided by severity of disease at the time of randomisation
Results/Publication	Not provided	Not provided	Not provided	Not provided

NR = Not reported, RDV = Remdesivir, SOC = Standard of care

Table 3.1-3: Publications on clinical trials on product ***remdesivir***

Author, year [Reference]	***Wang et al. 2020** [74]
Country	China
Sponsor/Funding	Chinese Academy of Medical Sciences Emergency Project of COVID-19, National Key Research and Development Program of China, the Beijing Science and Technology Project
Study design	Randomised, double-blind, placebo-controlled, multicentre trial **NCT04257656**
Number of pts	237 (RDV n=158, Placebo n=79)
Intervention/Product	Remdesivir (200 mg on day 1 followed by 100 mg on days 2–10 in single daily infusions)
Comparator	Placebo (same volume of placebo infusions for a total of 10 days)
Inclusion criteria	Men and non-pregnant women with COVID-19 who were aged at least 18 years and were RT-PCR positive for SARS-CoV-2, had pneumonia confirmed by chest imaging, had oxygen saturation of 94% or lower on room air or a ratio of arterial oxygen partial pressure to fractional inspired oxygen of 300 mm Hg or less, and were within 12 days of symptom onset
Exclusion criteria	Pregnancy or breast feeding; hepatic cirrhosis; alanine aminotransferase or aspartate aminotransferase more than five times the upper limit of normal; known severe renal impairment (estimated glomerular filtration rate <30 mL/min per 1·73 m^2) or receipt of continuous renal replacement therapy, haemodialysis, or peritoneal dialysis; possibility of transfer to a non-study hospital within 72 h; and enrolment into an investigational treatment study for COVID-19 in the 30 days before screening
Pts pretreated + previous treatment	Use of other treatments, including lopinavir–ritonavir, was permitted
Mean age of patients, yrs (SD)	RDV group (66.0); Placebo (64.0)
Sex % male (% female)	RDV group (56.0 m vs 44 f); Placebo (65.0 m vs 35 f)
Follow-up (days)	Up to 28 days
Clinical status	Most patients were in category 3 of the six-point ordinal scale of clinical status at baseline
Loss to follow-up, n (%)	One patient in the placebo group withdrew their previously written informed consent after randomisation (158 and 78 patients were included in the ITT population)
Efficacy outcomes	
Overall survival (OS), n (%)	28-day mortality: 22 [14%] died in the remdesivir group vs 10 (13%) in the placebo group; difference 1·1% [95% CI –8·1 to 10·3]
Time to clinical improvement	RDV group: median 21·0 days [IQR 13·0–28·0] vs 23·0 days [15·0–28·0] in placebo group; HR 1·23 [95% CI 0·87–1·75]
Other efficacy outcomes	No statisticaly significant differences were observed between the two groups in length of oxygen support, hospital length of stay, days from randomisation to discharge, days from randomisation to death and distribution of six-category scale at day 7, day 14, and day 28, and viral load decrease over time
Safety outcomes	
Adverse events (AEs)	RDV group 102 (66%) of 155 patients vs 50 (64%) of 78 in the control group
Serious adverse events (SAEs)	28 (18%) in the remdesivir group vs 20 (26%) in the control group
Discontinuation of study drug due to AEs or SAEs	18 [12%] in the remdesivir group *vs* four [5%] in the placebo group), among whom seven (5%) were due to respiratory failure or acute respiratory distress syndrome in the remdesivir group

*Study was terminated before attaining the prespecified sample size (237 of the intended 453 patients were enrolled) because the outbreak of COVID-19 was brought under control in China.

3.2 Lopinavir + Ritonavir (Kaletra®)

About the drug under consideration

Lopinavir and ritonavir are human immunodeficiency virus (HIV) protease inhibitors that are originally used in combination to treat HIV infection. Concerning HIV, they work by decreasing the amount of HIV in the blood. An increased amount of lopinavir can be detected in the body resulting from the treatment combination of both substances [40, 75].

The combination therapy of lopinavir and ritonavir (Kaletra) has been approved by the American Food and Drug Administration (FDA) since 15.09.2000 and by the European Medicines Agency (EMA) since 19.03.2001 as an HIV medicine to treat adults and pediatric patients (14 days and older) with HIV-1 infection.

Drug used in Covid-19 patients: ongoing studies

Recently, lopinavir in combination with ritonavir is also applied in patients with Covid-19 infection. The search in clinical trials (humans only) in April 2020 yielded no completed study on the safety and efficacy of lopinavir plus ritonavir for Covid-19 patients. Two ongoing phase IV randomised controlled trials (RCTs) (NCT04255017, NCT04252885), two ongoing phase III RCTs (NCT04315948, NCT04321174), one ongoing phase II RCT (NCT04307693) and additional ongoing Chinese RCTs with unknown study phases (ChiCTR2000029308, ChiCTR2000029387, ChiCTR2000029539, ChiCTR2000029541, ChiCTR2000030187), as well as, one ongoing non-randomised controlled trial (NRCT) with an unknown study phase (ChiCTR2000029600) could be identified.

The two phase IV RCTs are expected to be completed during summer 2020. One phase III study is expected to be completed within one year (March 2021) and the second phase III RCT will be completed by March 2023. The phase II clinical study is expected to be completed within the next month (May 2020). One of the Chinese RCTs was expected to be completed by the end of March 2020 and, but results are not available yet, and the remaining four Chinese RCTs have an estimated completion date between December 2020 and February 2021. The NRCT is expected to be completed by the end of April 2020. Table 3.2-1.

Until 09 May 2020, 8 RCTs (7 ongoing, 1 completed - NCT04276688) were found in ClinicalTrials.gov and EudraCT registers. Details are written in Table 3.2-1. The completed RCT (NCT04276688) was conducted in Hong Kong, and it results are written in part 3.13 (Combination therapy), since this is triple combination of interferon beta-1b, lopinavir–ritonavir, and ribavirin, compared with lopinavir–ritonavir alone.

Drug used in Covid-19 patients: results of publications

So far (status: May 9, 2020) only one publication [5] on the effectiveness and safety of lopinavir in combination with ritonavir in adults hospitalised with severe Covid-19 could be identified (clinical trial ChiCTR2000029308). In the study, 199 patients were randomly assigned to lopinavir/ ritonavir (n=99) or standard therapies (n=100) including supplemental oxygen, noninvasive and invasive ventilation, antibiotic agents, vasopressor support, renal-replacement therapy, and extracorporeal membrane oxygenation (ECMO) as necessary. Treatment with lopinavir/ ritonavir was not associated with a statistically significant difference from standard care in the time to clinical improvement (HR 1.31; 95% CI 0.95-1.85, p=0.09) and the 28-day mortality (19.2% vs. 25.0%, difference −5.8 percentage points; 95% CI −17.3 to 5.7, p=not reported). The percentages of patients with clinical improvement of two points on the 7-category ordinal scale at day 28 (78.8 vs. 70.0, difference 8.8 percentage points, 95% CI -3.3-20.9, p=NR) and with detectable viral RNA at various time points were similar between the two study groups. Concerning all adverse events that occurred during the follow-up of 28 days, gastrointestinal events were more common in the lopinavir/ ritonavir group, however, severe adverse events were more frequently reported in the standard therapy group. Overall, no clinical benefit could be observed with lopinavir/ ritonavir treatment beyond standard care in hospitalised adult patients with severe Covid-19. Detailed information about the study results is presented in Table 3.2-2. Details related to RCT number NCT04276688 are written in Section 3.13, related to Combination therapy.

*Table 3.2-1: **Lopinavir plus ritonavir (Kaletra®)** in clinical trial registry*

Active substance	**Lopinavir/ ritonavir** (Kaletra®)	**Lopinavir/ ritonavir** (Kaletra®)	**Lopinavir/ ritonavir** (Kaletra®) **Lopinavir/ ritonavir** plus interferon beta-1a	**Lopinavir/ ritonavir** (Kaletra®)	**Lopinavir/ ritonavir** (Kaletra®)
Sponsor	Tongji Hospital	Guangzhou 8th People's Hospital	Institut National de la Santé Et de la Recherche Médicale, France	Darrell Tan, St. Michael's Hospital, Toronto	Asan Medical Center
Mechanism of operation	Antiviral drug: protease inhibitors	Antiviral drug: protease inhibitors	Antiviral drug: protease inhibitors	Antiviral drug: protease inhibitors	Antiviral drug: protease inhibitors
Regulatory status	EMA approval since 19/03/2001: HIV medicine used in combination with other medicines to treat adults and children from over 14 days of age who are infected with HIV 1. FDA approval since 15/09/2000: KALETRA is an HIV-1 protease inhibitor indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and pediatric patients (14 days and older).	EMA approval since 19/03/2001: HIV medicine used in combination with other medicines to treat adults and children from over 14 days of age who are infected with HIV 1. FDA approval since 15/09/2000: KALETRA is an HIV-1 protease inhibitor indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and pediatric patients (14 days and older).	EMA approval since 19/03/2001: HIV medicine used in combination with other medicines to treat adults and children from over 14 days of age who are infected with HIV 1. FDA approval since 15/09/2000: KALETRA is an HIV-1 protease inhibitor indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and pediatric patients (14 days and older).	EMA approval since 19/03/2001: HIV medicine used in combination with other medicines to treat adults and children from over 14 days of age who are infected with HIV 1. FDA approval since 15/09/2000: KALETRA is an HIV-1 protease inhibitor indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and pediatric patients (14 days and older).	EMA approval since 19/03/2001: HIV medicine used in combination with other medicines to treat adults and children from over 14 days of age who are infected with HIV 1. FDA approval since 15/09/2000: KALETRA is an HIV-1 protease inhibitor indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and pediatric patients (14 days and older).
Trial Identifier	NCT04255017	NCT04252885	NCT04315948	NCT04321174	NCT04307693
Phase & Intention,	Phase IV on efficacy of three antiviral drugs in the treatment of Covid-19 pneumonia including **lopinavir plus ritonavir**.	Phase IV on efficacy of **lopinavir plus ritonavir** and arbidol for treating patients with novel Covid-19 infection.	Phase III on safety and efficacy of treatments for COVID-19 in hospitalised adults including **lopinavir plus ritonavir.**	Phase III on efficacy of oral **lopinavir/ ritonavir** as post-exposure prophylaxis against COVID-19 infection.	Phase II on whether **lopinavir plus ritonavir** or hydroxy-chloroquine reduces viral load from respiratory specimen in patients with mild COVID-19.
Study design	Prospective/ retrospective, randomised controlled clinical study	Randomised, open-label, controlled study	Multi-centre, adaptive, randomised, open clinical trial	Cluster randomised controlled trial	Multicenter, open-labelled, randomised clinical trial
Status trial	Recruiting	Recruiting	Recruiting	Not yet recruiting	Recruiting
Duration/ End of Study	4 months/ Estimated June 2020	7 months/ Estimated End of July 2020	3 years/ Estimated March 2023	1 year/ Estimated March 2021	3 months/ Estimated May 2020
Study details	Pts: n = 400 Location: China Interventions: - Abidole hydrochloride	Pts: n = 125 Group 1: n = 50 Group 2: n = 50 Group 3: n = 25	Pts: n = 3100 5 groups each n = 620 Location: France Interventions:	Pts: n = 1220 Location: Canada Intervention:	Pts: n = 150 Location: Korea Intervention:

Active substance	**Lopinavir/ ritonavir** (Kaletra®)	**Lopinavir/ ritonavir** (Kaletra®)	**Lopinavir/ ritonavir** (Kaletra®) **Lopinavir/ ritonavir** plus interferon beta-1a	**Lopinavir/ ritonavir** (Kaletra®)	**Lopinavir/ ritonavir** (Kaletra®)
	- Oseltamivir - Lopinavir/ ritonavir *(500 mg, 2/day, 2 weeks)* Control: Symptomatic supportive treatment Duration of observation/ follow-up: 2 weeks Primary outcomes: - Rate of disease remission - Time for lung recovery	Location: China Interventions: - Group 1: Standard treatment + lopinavir *(200mg)* /ritonavir *(50mg) (2/day, 7-14 days)* - Group 2: Standard treatement + arbidol Control: Standard treatment (group 3) Duration of observation/ follow-up: 21 days Primary outcome: Rate of virus inhibition	- Group 1: Remdesivir - Group 2: Lopinavir *(400 mg)* / ritonavir *(100mg) (2/day, 2 weeks)* - Group 3: Lopinavir *(400 mg)* / ritonavir *(100 mg)* plus interferon beta-1a - Group 4: Hydroxychloroquine Control: Standard of care (group 5) Duration of observation/ follow-up: 28 days Primary outcomes: Percentage of subjects reporting each severity rating on a 7-point ordinal scale: 1) Not hospitalized, no limitations on activities; 2) Not hospitalized, limitation on activities; 3) Hospitalized, not requiring supplemental oxygen; 4) Hospitalized, requiring supplemental oxygen; 5) Hospitalized, on non-invasive ventilation or high flow oxygen devices; 6) Hospitalized, on invasive mechanical ventilation or ECMO (extracorporeal membrance oxygenation); 7) Death;	Lopinavir *(400mg)* / ritonavir *(100mg) (orally 2/day, 14 days)* Control: No intervention Duration of observation/ follow-up: 14 days Primary outcome: Microbiologic evidence of infection (e.g., detection of viral RNA)	Lopinavir *(200mg)* / ritonavir *(100mg) (orally 2/day, 7-10 days)* Control: - Hydroxychloroquine - No intervention Duration of observation/ follow-up: 18 days Primary outcome: Viral load (area under the cure of Ct value or viral copies number per mL)
Results	No publications available yet.	No publications available yet.	No publications available yet.	No publications available yet.	No publications available yet.

Abbreviations: EMA – European Medicines Agency, FDA – Food and Drug Administration, Pts. - Patients

*Table 3.2-1: **Lopinavir plus ritonavir (Kaletra®)** in clinical trial registry (Continued)*

Active substance	**Lopinavir/ ritonavir** (Kaletra®)	**Lopinavir/ ritonavir** (Kaletra®)	**Lopinavir/ ritonavir** plus interferon-alpha **Lopinavir/ ritonavir** plus interferon-alpha plus ribavirin	**Lopinavir/ ritonavir** (Kaletra®)	**Lopinavir/ ritonavir** (Kaletra®)	**Lopinavir/ ritonavir plus** alpha-interferon atomisation
Sponsor	Wuhan Jinyintan Hospital (Wuhan Infectious Diseases Hospital)	Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology	Chongqing Public Health Medical Center	Jingzhou First People's Hospital	Zhongnan Hospital of Wuhan University	The Third People's Hospital of Shenzhen
Mechanism of operation	Antiviral drug: protease inhibitors	Antiviral drug: protease inhibitors	Antiviral drug: protease inhibitors	Antiviral drug: protease inhibitors	Antiviral drug: protease inhibitors	Antiviral drug: protease inhibitors
Regulatory status	EMA approval since 19/03/2001: HIV medicine used in combination with other medicines to treat adults and children from over 14 days of age who are infected with HIV 1. FDA approval since 15/09/2000: KALETRA is an HIV-1 protease inhibitor indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and pediatric patients (14 days and older).	EMA approval since 19/03/2001: HIV medicine used in combination with other medicines to treat adults and children from over 14 days of age who are infected with HIV 1. FDA approval since 15/09/2000: KALETRA is an HIV-1 protease inhibitor indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and pediatric patients (14 days and older).	EMA approval since 19/03/2001: HIV medicine used in combination with other medicines to treat adults and children from over 14 days of age who are infected with HIV 1. FDA approval since 15/09/2000: KALETRA is an HIV-1 protease inhibitor indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and pediatric patients (14 days and older).	EMA approval since 19/03/2001: HIV medicine used in combination with other medicines to treat adults and children from over 14 days of age who are infected with HIV 1. FDA approval since 15/09/2000: KALETRA is an HIV-1 protease inhibitor indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and pediatric patients (14 days and older).	EMA approval since 19/03/2001: HIV medicine used in combination with other medicines to treat adults and children from over 14 days of age who are infected with HIV 1. FDA approval since 15/09/2000: KALETRA is an HIV-1 protease inhibitor indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and pediatric patients (14 days and older).	EMA approval since 19/03/2001: HIV medicine used in combination with other medicines to treat adults and children from over 14 days of age who are infected with HIV 1. FDA approval since 15/09/2000: KALETRA is an HIV-1 protease inhibitor indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and pediatric patients (14 days and older).
Trial Identifier	ChiCTR2000029308	ChiCTR2000029539	ChiCTR2000029387	ChiCTR2000030187	ChiCTR2000029541	ChiCTR2000029600
Phase & Intention,	Study (phase not reported) on efficacy and safety of **lopinavir plus ritonavir** in hospitalised patients with novel Covid-19 pneumonia.	Study (phase not reported) on efficacy and safety of **lopinavir plus ritonavir** in patients with mild novel Covid-19 pneumonia.	Study (phase not reported) on effectiveness and safety of ribavirin plus interferon-alpha, **lopinavir/ ritonavir** plus interferon-alpha and ribavirin plus	Study (phase not reported) on efficacy and safety of **lopinavir plus ritonavir** in the treatment of novel Covid-19 pneumonia.	Study (phase unknown) on efficacy and safety of darunavir plus cobicistat or **lopinavir plus ritonavir** combined with thymosin a1 in the treatment of Covid-19.	Study (phase not reported) on safety and efficacy of **lopinavir/ ritonavir** plus alpha-interferon atomisation in the treatment of novel Covid-19.

Active substance	**Lopinavir/ ritonavir** (Kaletra®)	**Lopinavir/ ritonavir** (Kaletra®)	**Lopinavir/ ritonavir** plus interferon-alpha **Lopinavir/ ritonavir** plus interferon-alpha plus ribavirin	**Lopinavir/ ritonavir** (Kaletra®)	**Lopinavir/ ritonavir** (Kaletra®)	**Lopinavir/ ritonavir plus** alpha-interferon atomisation
			lopinavir/ritonavir plus interferon-alpha in in patients with mild to moderate novel Covid-19 pneumonia.			
Study design	Randomised, controlled open-label trial	Randomised, open-label study	Randomised controlled trial	Randomised controlled trial	Randomised, open, controlled trial	Non-randomised controlled trial
Status trial	Recruiting	Recruiting	Recruiting	Recruiting	Not recruiting yet	Recruiting
Duration/ End of Study	1 year/ Estimated January 2021	1 year/ Estimated February 2021	1 year/ Estimated End of January 2021	1 month/ Estimated End of March 2020	10 months/ Estimated December 2020	3 months/ Estimated end of April 2020
Study details	Pts: n = 160 2 groups each n = 80 Location: China, Wuhan Interventions: Lopinavir/ ritonavir Control: Conventional standardised treatment Duration of observation/ follow-up: 28 days Primary outcome: Clinical improvement time of 28 days after randomization on a 7-point scale: 1) Discharged to normal function; 2) Discharged but not restored to normal functional status; 3) Hospitalisation does not require oxygen therapy; 4) Hospitalisation for oxygen therapy; 5) Hospitalised for non-invasive ventilation and / or high-flow oxygen therapy;	Pts: n = 328 2 groups each n = 164 Location: China, Wuhan Interventions: Conventional standard treatment + lopinavir/ ritonavir Control: Conventional standard treatment Duration of observation/ follow-up: 14 days Primary outcome: Incidence of adverse outcome within 14 days after admission (Pts. with conscious dyspnea, SpO2 ≤ 94% or respiratory frequency ≥ 24 times/min in the state of resting without oxygen inhalation)	Pts: n = 108 3 groups each n = 36 Location: China Interventions: Group 1: Ribavirin + interferon alpha-1b Group 2: Lopinavir/ ritonavir + interferon alpha-1b Group 3: Ribavirin+ lopinavir/ ritonavir + interferon alpha-1b Control: Not reported Duration of observation/ follow-up: 28 days Primary outcome: Time to Covid-19 RNA negativity in patients	Pts: n = 60 2 groups each n = 30 Location: China Interventions: Lopinavir/ ritonavir Control: Routine symptomatic support treatment Duration of observation/ follow-up: 30 days Primary outcomes: - Endotracheal intubation rate - Mortality	Pts: n = 100 Group 1: n = 40 Group 2: n = 40 Group 3: n = 40 Location: China Intervention: Group 1: Darunavir *(800mg)* / cobicistat *(150mg)* + conventional treatment with thymosin *(1.6 mg)* Group 2: Lopinavir *(400mg)* / ritonavir *(100mg)* + conventional treatment with thymosin *(1.6mg)* Control: Conventional treatment with thymosin *(1.6mg)* (group 3) Duration of observation: Not reported Primary outcome: Time to conversion of Covid-19 RNA result from RI sample	Pts: n=90 Group 1: n = 30 Group 2: n = 30 Group 2: n = 30 Location: China Intervention: Group1: Alpha-interferon atomisation Group 2: Lopinavir/ ritonavir + alpha-interferon atomisation Group 3: Favipiravir + alpha-interferon atomisation Control: Not reported Duration of observation: Not reported Primary outcomes: - Declining speed of novel Covid-19 by PCR - Negative time of novel Covid-19 by PCR - Incidence rate of chest imaging - Incidence rate of liver enzymes - Incidence rate of kidney damage

Active substance	**Lopinavir/ ritonavir** (Kaletra®)	**Lopinavir/ ritonavir** (Kaletra®)	**Lopinavir/ ritonavir** plus interferon-alpha **Lopinavir/ ritonavir** plus interferon-alpha plus ribavirin	**Lopinavir/ ritonavir** (Kaletra®)	**Lopinavir/ ritonavir** (Kaletra®)	**Lopinavir/ ritonavir plus** alpha-interferon atomisation
	6) Admission to ECMO (extracorporeal membrane oxygenation) and / or mechanical ventilation; 7) Death;					
Results	Cao et al. (2020) [5]	No publications available yet.	No publications available yet.	No publications available yet.	No publications available yet.	No publication available yet.

Abbreviations: EMA – European Medicines Agency, FDA – Food and Drug Administration, Pts. – Patients

*Table 3.2-1: **Lopinavir plus ritonavir (Kaletra®)** in clinical trial registry (Continued)*

Active substance	**Lopinavir-ritonavir**	**Lopinavir-ritonavir**	**Lopinavir-ritonavir**	**Lopinavir-ritonavir**	**Lopinavir-ritonavir**
Sponsor	Tongji Hospital	The University of Hong Kong	Bassett Healthcare	Medical University of Vienna	University of Oxford
Trial Identifier	NCT04255017	NCT04276688	NCT04328012, COVID MED trial	NCT04351724	ISRCTN50189673 EudraCT 2020-001113-21, RECOVERY Trial
Phase & Intention	Phase 4, to compare the efficacy of three antiviral drugs in the treatment of 2019-nCoV pneumonia by studying the efficacy of abidol hydrochloride, oseltamivir and lopinavir/ritonavir in the treatment of 2019-nCoV viral pneumonia, and to explore effective antiviral drugs for new coronavirus	Phase 2, to evaluate the safety and efficacy in mortality reduction with a combination of lopinavir/ ritonavir, ribavirin and interferon beta-1b in the treatment of patient hospitalised for 2019-n-CoV infection and compare this to lopinavir/ ritonavir alone	Phase 2/3, to compare therapeutics for hospitalized patients infected with SARS-CoV-2 in a Pragmatic aDaptive randoMizED Clinical Trial During the COVID-19 Pandemic (COVID MED Trial)	Phase 2/3, on the efficacy and safety of experimental therapeutics for patients with COVID-19	Phase II/III, to provide reliable estimates of the effect of study treatments on death within 28 days of randomisation (with subsidiary analyses of cause of death)
Study design	RCT, single blind, placebo controlled, parallel assignment	RCT, open-label, active comparator, parallel assignment	RCT, quadruple blind, placebo controlled, parallel assignment	RCT, open-label, active comparator, parallel assignment; three main study arms (antiviral treatments) and three substudies (A, B, C) are planned	RCT, open-label, standard of care comparator, parallel assignment
Status trial	Recruiting	**Completed**	Recruiting	Recruiting	Ongoing
Duration/ End of Study	Study start: February 1, 2020 Estimated Primary Completion Date: June 1, 2020	Study start: February 10, 2020 Actual Primary Completion Date: March 30, 2020	Study start: April 6, 2020 Estimated Primary Completion Date: January 1, 2021	Study start: April 16, 2020 Estimated Primary Completion Date: December 1, 2020	Study start: 17 March 2020 Estimated Primary Completion Date: NA

Active substance	**Lopinavir-ritonavir**	**Lopinavir-ritonavir**	**Lopinavir-ritonavir**	**Lopinavir-ritonavir**	**Lopinavir-ritonavir**
	Estimated Study Completion Date: June 1, 2020	Actual Study Completion Date: March 31, 2020	Estimated Study Completion Date: April 1, 2021	Estimated Study Completion Date: December 31, 2020	Estimated Study Completion Date: NA
Study details	N of pts: 400 Location/ centres: China Intervention/control: Lopinavir/ritonavir 500mg once, twice a day, 2 weeks; Oseltamivir 75mg once, twice a day, 2 weeks; Abidol hydrochloride/ Symptomatic supportive treatment Duration of observation/follow-up: 2 weeks Primary end point(s): Rate of disease remission; Time for lung recovery (Time frame: two weeks) Secondary endpoints: Rate of no fever; Rate of respiratory symptom remission; Rate of lung imaging recovery; Rate of undetectable viral RNA, CRP,ES,Biochemical criterion(CK,ALT,Mb) recovery	N of pts: 127 Location/ centres: Hong Kong Intervention/control: Combination of lopinavir/ ritonavir, ribavirin and interferon beta-1b / Lopinavir/ritonavir Duration of observation/follow-up: 1 months Primary end point(s): Time to negative NPS [Time Frame: Up to 1 month] Secondary endpoints: Time to negative saliva, Time to clinical improvement, Hospitalisation, Mortality, Immune reaction, Adverse events, Time to negative all clinical specimens	N of pts: 4000 Location/ centres: US Intervention/control: hydroxychloroquine sulfate 400 mg BID on Day 0 200 mg BID Days 1-4, days 1-13; lopinavir/ritonavir 400mg/200mg mg po BID X 5-14 days; losartan 25 mg po QD X 5-14 days/ Placebo Duration of observation/follow-up: 60 days Primary end point(s): NIAID COVID-19 Ordinal Severity Scale (NCOSS) [Time frame: 60 days] Secondary endpoints: Hospital length of stay, Intensive care unit level LOS, Mechanical ventilation, survival	N of pts: 500 Location/ centres: Austria Intervention/control: Hydroxychloroquine 200mg 2-0-2 on day 1 followed by 200mg 1-0-1, or Chloroquine 250mg 2-0-2; Lopinavir/Ritonavir 200mg/50mg 2-0-2 / Best standard of care Duration of observation/follow-up: 29 days Primary end point(s): sustained improvement (>48h) of one point on the WHO Scale [Time frame: Inclusion to day 29, daily evaluation] Secondary endpoints: 19 listed, among Mortality, Ventilator free days until day 29, Duration of hospitalization…	N of pts: 2000 Location/ centres: UK Intervention/control: Hydroxychloroquine; Lopinavir/ritonavir/Azithromycin; Prednisolone; Hydrocortisone; Tocilizumab/Standard of care Duration of observation/follow-up: until death, discharge from hospital or 28 days post-randomisation (whichever is sooner). Longer term follow-up will be sought through linkage to electronic healthcare records and medical databases. Primary end point(s): All-cause mortality within 28 days of randomisation Secondary endpoints: Duration of hospitalisation, Use of ventilation
Results	N.A.	Please see section 3.13	N.A.	N.A.	N.A.

*Table 3.2-1: **Lopinavir plus ritonavir (Kaletra®)** in clinical trial registry (Continued)*

Active substance	**Lopinavir-ritonavir**	**Lopinavir-ritonavir**	**Lopinavir-ritonavir**
Sponsor	See Remdesivir Table 3.1-1	See Remdesivir Table 3.1-1	See Remdesivir Table 3.1-1
Trial Identifier	ISRCTN83971151, SOLIDARITY trial	NCT04330690, Canadian arm of SOLIDARITY trial	EudraCT 2020-001366-11, Spain arm of SOLIDARITY trial
Phase & Intention	See Remdesivir Table 3.1-1	See Remdesivir Table 3.1-1	See Remdesivir Table 3.1-1
Study design	See Remdesivir Table 3.1-1	See Remdesivir Table 3.1-1	See Remdesivir Table 3.1-1
Status trial	See Remdesivir Table 3.1-1	See Remdesivir Table 3.1-1	See Remdesivir Table 3.1-1
Duration/ End of Study	See Remdesivir Table 3.1-1	See Remdesivir Table 3.1-1	See Remdesivir Table 3.1-1
Study details	See Remdesivir Table 3.1-1	See Remdesivir Table 3.1-1	See Remdesivir Table 3.1-1
Results	See Remdesivir Table 3.1-1	See Remdesivir Table 3.1-1	See Remdesivir Table 3.1-1

*Table 3.2-2: Publication on clinical trial on **lopinavir plus ritonavir (Kaletra®)***

Author, year [Reference]	**Cao et al. 2020 [5]**
Country	China
Sponsor	Major Projects of National Science and Technology on New Drug Creation and Development, the Chinese Academy of Medical Sciences (CAMS) Emergency Project of Covid-19 and a National Science Grant for Distinguished Young Scholars
Study design	Open-label, individually randomised, controlled trial
Number of pts	199 (99 vs. 100)
Intervention/Product	Lopinavir (400mg) + ritonavir (100mg) twice daily + standard care for 14 days
Comparator	Standard care (as necessary): supplemental oxygen, noninvasive and invasive ventilation, antibiotic agents, vasopressor support, renal-replacement therapy, and extracorporeal membrane oxygenation (ECMO)
Inclusion criteria	- Male and nonpregnant woman ≥18 years of age - Positive reverse-transcriptase–polymerase chain-reaction (RT-PCR) assay (Shanghai ZJ Bio-Tec or Sansre Biotech) for SARS-CoV-2 S-CoV-2 - Pneumonia confirmed by chest imaging - Oxygen saturation (Sao_2) of 94% or less while breathing ambient air or a ratio of the partial pressure of oxygen (Pao_2) to the fraction of inspired oxygen (Fio_2) (Pao_2:Fio_2) at or below 300 mg Hg
Exclusion criteria	- Physician decision that involvement in the trial was not in the patient's best interest - Presence of any condition that would not allow the protocol to be followed safely - Known allergy or hypersensitivity to lopinavi/ ritonavir - Known severe liver disease - Use of medications that are contra indicated with lopinavir/ ritonavir and that could not b replaced or stopped during the trial period - Pregnancy or breast-feeding - Known HIV infection, because of concerns about the development of resistance to lopinavir/ ritonavir if used without combining with other antiretrovirals
Pts pretreated +previous treatment	NR
Median age of patients, yrs (range)	Total: 58.0 (49.0-68.0): IG: 58.0 (50.0-68.0) CG: 58.0 (48.0-68.0)
Sex % male (% female)	Total: 60.3 (39.7): IG: 61.6 (38.4) CG: 59.0 (61.0)
Follow-up (days)	7, 14, 28
Loss to follow-up, n (%)	5 vs. 0 - 3 died within 24 hours after randomisation. - 2 did not receive lopinavir/ ritonavir because the attending physician refused to describe it.
Outcomes: efficacy	
Overall survival (OS), n (%)	NR
Median time to clinical improvement (days): *Time from randomisation to an improvement of two points (from the status at randomisation) on a 7-category ordinal scale (NEWS2 score) OR live discharge from the hospital, whichever came first*	ITT population: 16 v. 16, HR 1.31; 95% CI 0.95-1.85, p=0.09 Modified ITT population: 15 vs. 16, HR 1.39, 95% CI 1.00-1.91, p=NR No significant differences were observed when the time to clinical improvement was assessed by NEWS2 score at entry in the ITT population.

Author, year [Reference]	Cao et al. 2020 [5]
Clinical improvement, n (%) *Improvement of two points (from the status at randomisation) on a 7-category ordinal scale (NEWS2 score)*	ITT population: Day 7: 6 (6.1) vs. 2 (2.0), difference 4.1 percentage points, 95% CI -1.4-9.5, p=NR Day 14: 45 (45.5) vs. 30 (30.0), difference 15.5 percentage points, 95% CI 2.2-28.8, p=NR Day 28: 78 (78.8) vs. 70 (70.0), difference 8.8 percentage points, 95% CI -3.3-20.9, p=NR
Mortality at day 28 (%)	ITT population: 19.2 vs. 25.0, difference −5.8 percentage points; 95% CI −17.3 to 5.7, p=NR Modified ITT population: 16.7 vs. 25.0, difference -8.3 percentage points; 95% CI -19.6 to 3.0, p=NR
Median duration of invasive mechanical ventilation (days)	ITT population: 4 vs. 5, difference -1; 95% CI -4-2, p=NR
Median duration of hospitalisation (days)	ITT population: 14 vs. 16, difference 1; 95% CI 0-2, p=NR
Median time from treatment initiation to death (days)	ITT population: 9 vs. 12, difference -3, 95% -6-2, p=NR
Proportions with viral RNA detection over time (%)	Day 5: 34.5 vs. 32.9 Day 10: 50.0 vs. 48.6 Day 14: 55.2 vs. 57.1 Day 21: 58.6 vs. 58.6 Day 28, 60.3 vs. 58.6
Outcomes: safety	
Serious adverse events (SAE), n	Total: 19 (20.0) vs. 32 (32.3) Respiratory failure or ARDS: 12 (12.6) vs. 27 (27.3) Acute kidney injury: 3 (3.2) vs. 6 (6.1) Secondary infection: 1 (1.1) vs. 6 (6.1) Shock: 2 (2.1) vs. 2 (2.0) Severe anemia: 3 (3.2) vs. 0 (0.0) Acute gastritis: 2 (2.1) vs. 0 (0.0) Hemorrhage of lower digestive tract: 2 (2.1) vs. 0 (0.0) Pneumothorax: 0 (0.0) vs. 2 (2.0) Unconsciousness: 1 (1.1) vs. 0 (0.0) Disseminated intravascular coagulation: 1 (1.1) vs. 1 (1.0) Sepsis: 0 (0.0) vs. 1 (1.0) Acute heart failure: 0 (0.0) vs. 1 (1.0)
Adverse events (AE) that occurred during treatment, n (%) *5 most common AEs*	Total: 46 (48.4) vs. 49 (49.5) Lymphopenia: 16 (16.8) vs. 12 (12.1) Nausea: 9 (9.5) vs. 0 (0.0) Thrombocytopenia: 6 (6.3) vs. 10 (10.1) Leukopenia: 7 (7.4) vs. 13 (13.1) Vomiting: 6 (6.3) vs. 0 (0.0)
Premature discontinuation of treatment due to AEs, n (%)	13 (13.8)

Abbreviations: ARDS – Acute Respiratory Distress Syndrom, CI – Confidence interval, HR – Hazard ratio, ITT – Intionen-to-treat, NR – Not reported

3.3 Favipiravir (Avigan®)

About the drug under consideration

Favipiravir (Avigan®), an antiviral drug, is a new type of RNA-dependent RNA polymerase (RdRp) inhibitor. In addition to its anti-influenza virus activity, favipiravir is capable of blocking the replication of 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) [76, 77].

In 2014, it was approved in Japan for the treatment of novel or re-emerging pandemic influenza virus infections. However, use has been limited to cases, in which other influenza antiviral drugs are not sufficiently effective because favipiravir was only investigated in non-clinical studies in avian influenza A (H5N1 and H7N9) and efficacy against seasonal influenza A or B has not been sufficiently demonstrated. Furthermore, favipiravir was also trialled for treating Ebola; however, evidence on the effectiveness was lacking [76]. Favipiravir (Avigan®) has not been approved by the European Medicines Agency (EMA) or the American Food and Drug Administration (FDA).

Drug used in Covid-19 patients: ongoing studies

Recently, favipiravir (Avigan®) is also applied in patients with Covid-19 infection. The search in clinical trials (humans only) in April 2020 yielded one completed multicenter, randomised, open, positive, parallel-controlled clinical study (ChiCTR2000030254). Besides, three ongoing randomised controlled trials (RCTs) with unknown study phases (ChiCTR2000029548, ChiCTR2000029544, ChiCTR2000030113) and one ongoing non-randomised controlled trial (NRCT) with an unknown study phase (ChiCTR2000029600) could be identified. The three ongoing RCTs are expected to be completed between May and June 2020 and the ongoing NRCT is expected to be completed by the end of April 2020.

Until May 12, 2020 five ongoing RCTs are found in ClinicalTrial.gov and EudraCT registers (NCT04333589; NCT04358549; 2020-001449-38; 2020-001449-38, and RCT number NCT04310228, already described in Table 3.9-3 related to tocilizumab). Number of patients included in these trials is ranging from 50 to 1057. Details of these RCTs are visible in Table 3.3-1.

Drug used in Covid-19 patients: results of publications

So far (status: 12/05/2020), only one publication [78] on the completed RCT (ChiCTR2000030254) about the efficacy and safety of favipiravir, in comparison with umifenovir, to treat Covid-19 patients could be identified; however, currently the publication is available just as pre-print but not yet peer-reviewed, thus it has not been extracted.

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*Table 3.3-1: **Favipiravir** in clinical trial registry*

Active substance	**Favipiravir** (Avigan, T-705)	**Favipiravir** (Avigan, T-705)	**Favipiravir** (Avigan, T-705)	**Favipiravir** (Avigan, T-705)	**Favipiravir** (Avigan, T-705)
Sponsor	Zhongnan Hospital of Wuhan University	The First Affiliated Hospital, Zhejiang University School of Medicine	The First Hospital Affiliated to Zhejiang University's Medical School	The Third People's Hospital of Shenzhen	The Third People's Hospital of Shenzhen
Mechanism of operation	Antiviral drug	Antiviral drug	Antiviral drug	Antiviral drug	Antiviral drug
Regulatory status	EMA: Not approved but it was an experimental Ebola treatment. FDA: Not approved. Approved in Japan since 2014 for the treatment of novel or re-emerging pandemic influenza virus infections.	EMA: Not approved but it was an experimental Ebola treatment. FDA: Not approved. Approved in Japan since 2014 for the treatment of novel or re-emerging pandemic influenza virus infections.	EMA: Not approved but it was an experimental Ebola treatment. FDA: Not approved. Approved in Japan since 2014 for the treatment of novel or re-emerging pandemic influenza virus infections.	EMA: Not approved but it was an experimental Ebola treatment. FDA: Not approved. Approved in Japan since 2014 for the treatment of novel or re-emerging pandemic influenza virus infections.	EMA: Not approved but it was an experimental Ebola treatment. FDA: Not approved. Approved in Japan since 2014 for the treatment of novel or re-emerging pandemic influenza virus infections.
Trial Identifier	ChiCTR2000030254	ChiCTR2000029548	ChiCTR2000029544	ChiCTR2000030113	ChiCTR2000029600
Phase & Intention	Study (phase not reported) on the efficacy and safety of favipiravir compared to arbidol for adult patients with novel Covid-19 pneumonia.	Study (phase not reported) on evaluating of the efficacy and safety of baloxavir marboxil, favipiravir, and lopinavir/ ritonavir in the treatment of novel Covid-19 patients.	Study (phase not reported) on efficacy and safety of baloxavir marboxil, favipiravir tablets in novel Covid-19 patients who are still positive on virus detection under the current antiviral therapy.	Study (phase not reported) on safety and efficacy of favipiravir in the treatment of novel Covid-19 with poorly responsive ritonavir.	Study (phase not reported) on safety and efficacy of favipiravir in the treatment of novel Covid-19.
Study design	Multicenter, randomised, open, positive, parallel-controlled clinical study	Randomised, open-label, controlled trial	Randomised controlled trial	Randomised controlled trial	Non-randomised controlled trial
Status trial	Completed	Not recruiting yet	Not recruiting yet	Recruiting	Recruiting
Duration/ End of Study	1 month/ Estimated March 2020	5 months/ Estimated June 2020	4 months/ Estimated end of May 2020	4 months/ Estimated end of May 2020	3 months/ Estimated end of April 2020

Active substance	**Favipiravir** (Avigan, T-705)	**Favipiravir** (Avigan, T-705)	**Favipiravir** (Avigan, T-705)	**Favipiravir** (Avigan, T-705)	**Favipiravir** (Avigan, T-705)
Study details	Pts: n=240 Group 1: n = 120 Group 2: n = 120 Location: China Intervention: Farpiravir tablets (group 1) Control: Abidole tablets (group 2) Duration of observation: 7 days Primary outcome: Clinical recovery rate of day 7	Pts: n=30 Group 1: n = 10 Group 2: n = 10 Group 3: n = 10 Location: China Intervention: Group 1: Baloxavir marboxil Group 2: Favipiravir *(600 mg tid with 1600mg first loading dosage for no more than 14 days)* Group 3: Lopinavir/ ritonavir Control: Not reported Duration of observation: 14 days Primary outcomes: - Time to viral negativity by RT-PCR - Time to clinical improvement (time from start of study drug to hospital discharge or an improvement of two points of the NEWS2 score for 24 hours).	Pts: n=30 Group 1: n = 10 Group 2: n = 10 Group 3: n = 10 Location: China Intervention: Group 1: Current antiviral treatment + baloxavir marboxil Group 2: Current antiviral treatment + favipiravir tablets Control: Current antiviral treatment (group 3) Duration of observation: 14 and/or 28 days Primary outcomes: - Time to viral negativity by RT-PCR - Time to clinical improvement (time from start of study drug to hospital discharge or an improvement of two points of the NEWS2 score for 24 hours).	Pts: n=30 Group 1: n = 15 Group 2: n = 15 Location: China Intervention: Favipiravir (group 1) Control: Ritonavir (group 2) Duration of observation: Not reported Primary outcomes: - Blood routine tests - Liver function examination - Renal function examination - Blood gas analysis - Chest CT examination	Pts: n=90 Group 1: n = 30 Group 2: n = 30 Group 2: n = 30 Location: China Intervention: Group1: Alpha-interferon atomisation Group 2: Lopinavir/ ritonavir + alpha-interferon atomisation Group 3: Favipiravir + alpha-interferon atomisation Control: Not reported Duration of observation: Not reported Primary outcomes: - Declining speed of novel Covid-19 by PCR - Negative time of novel Covid-19 by PCR - Incidence rate of chest imaging - Incidence rate of liver enzymes - Incidence rate of kidney damage
Results	Publication available: [78]; pre-print not peer-reviewed	No publications available yet.	No publications available yet.	No publications available yet.	No publication available yet.

Abbreviations: EMA – European Medicines Agency, FDA – Food and Drug Administration, PCR - Polymerase chain reaction, Pts. – Patients

*Table 3.3-2: **Favipiravir** in clinical trial registry (Continued)*

Active substance	**Favipiravir**	**Favipiravir**	**Favipiravir**	**Favipiravir**	**Favipiravir**
Sponsor	Peking University First Hospital	Fujifilm Pharmaceuticals U.S.A., Inc.	Chelsea and Westminster Hospital NHS Foundation Trust	CENTRE HOSPITALIER UNIVERSITAIRE DE BORDEAUX, ETABLISSEMENT PUBLIC	See Table 3.3-3: Tocilizumab
Trial Identifier	NCT04333589	NCT04358549	2020-001449-38	2020-001449-38	NCT04310228
Phase & Intention	Phase NA, to investigate the mechanism, clinical outcome and therapeutic efficacy with favipiravir of Corona Virus Disease 2019 patients whose nucleic acids changed from negative to positive	Phase 2, to determine the effect of favipiravir + standard of care vs. standard of care on COVID-19 viral clearance	Phase III, to determine whether early intervention with either a combination of hydroxychloroquine, azithromycin and zinc or favipirivir improves time to significant improvement in clinical status	Phase III, to estimate the efficacy of several specific experimental treatments, compared to standard care, to prevent hospitalization or death at D14 in adults over 65 years of age, with documented SARS-CoV-2 infection, with symptoms lasting less than 72 hours and not meeting any hospitalization criteria	See Table 3.3-4: Tocilizumab
Study design	RCT, open-label, regular treatment group comparator, parallel assignment	RCT, open-label, standard of care comparator, parallel assignment	RCT, open-label, standard of care comparator, parallel assignment	RCT, open-label, vitamins suplements comparator, parallel assignment	See Table 3.3-5: Tocilizumab
Status trial	Recruiting	Recruiting	Ongoing	Ongoing	See Table 3.3-6: Tocilizumab
Duration/ End of Study	Study start: April 1, 2020 Estimated Primary Completion Date: June 1, 2020 Estimated Study Completion Date: September 15, 2020	Study start: April 17, 2020 Estimated Primary Completion Date: August 2020 Estimated Study Completion Date: December 2020	Study start: 29/04/2020 Estimated Primary Completion Date: NA Estimated Study Completion Date: NA	Study start: 10/04/2020 Estimated Primary Completion Date: NA Estimated Study Completion Date: NA	See Table 3.3-7: Tocilizumab
Study details	N of pts: 210 Location/ centres: China Intervention/control: Favipiravir (1st day, 1600mg each time, twice a day; from the 2nd to the 7th day, 600mg	N of pts: 50 Location/ centres: US Intervention/control: Favipiravir + Standard of care / Standard of Care	N of pts: 450 Location/ centres: UK Intervention/control: Favipiravir vs Hydroxycholorquine &	N of pts: 1057 Location/ centres: France Intervention/control: Favipiravir; Imatinib; Hydroxichloroquine;	See Table 3.3-8: Tocilizumab

	each time, twice a day not more than 14 days) / Treatments other than lopinavir and ritonavir, chloroquine phosphate, hydroxychloroquine sulfate, arbidol, and colomycin Duration of observation/follow-up: 5 months Primary end point(s): Viral nucleic acid test negative conversion rate [Time frame: 5 months] Secondary endpoints: Clinical cure rate [Time frame: 5 months]	Duration of observation/follow-up: 46 days Primary end point(s): Time to viral clearance [Time frame: Day 29] Secondary endpoints: Status of clinical recovery as measured by the study-specific 6-point ordinal scale on Day 15; Clinical effect measured by the National Early Warning Score 2 (NEWS2); Characterize the pharmacokinetics (PK) of favipiravir in plasma	Azithromycin & Zinc vErsEs vs Standard CaRe Duration of observation/follow-up: until death, or 28 days post-randomisation Primary end point(s): Time to clinical improvement (post randomisation) by two points on a seven-category ordinal scale or live discharge from the hospital, whichever comes first Secondary endpoints: 16 listed, among All cause in hospital mortality; Number of participants requiring intensive care admission; Number of participants requiring mechanical ventilation; Duration of mechanical ventilation	Telmisartan / Vitamins suplements Duration of observation/follow-up: 28 days Primary end point(s): Proportion of participants with an occurrence of hospitalization and/or death between D0 and D14 in each arm Secondary endpoints: The analyzes on the secondary endpoints, with the exception of the toxicity results, will be carried out with the intention of treating on the available data	
Results	N.A.	N.A.	N.A.	N.A.	See Table 3.3-9: Tocilizumab

*Table 3.3-10: Publications on clinical trials on product **favipiravir (Avigan®)** – publication forthcoming*

Author, year [Reference]	Chen et al. 2020 [78]
Country	China
Sponsor	
Study design	
Number of pts	
Intervention/Product	
Comparator	
Inclusion criteria	
Exclusion criteria	
Pts pretreated +previous treatment	
Mean age of patients, yrs (SD)	
Sex % male (% female)	
Follow-up (days)	
Clinical status: asymptomatic/ URTI/ LRTI (proportion)	
Loss to follow-up, n (%)	
Overall survival (OS), n (%)	

3.4 Darunavir

About the drug under consideration

Darunavir is an antiviral agent from the group of human immunodeficiency virus (HIV) protease inhibitors for the treatment of HIV-1 infections. The effects are based on the inhibition of the HIV protease, which plays a central role in the maturation of the virus and virus replication. Darunavir is combined with a pharmacokinetic booster such as ritonavir or cobicistat [79].

Darunavir (Prezista®) has been approved by the American Food and Drug Administration (FDA) on the 23th of June 2006 and by the European Medicines Agency (EMA) on the 11t^{h} of February /2007 for the treatment of HIV-1 infection in adult and pediatric patients three years of age and older in combination with ritonavir or other antiretroviral agents such as cobicistat. Currently, there are three generics available: Darunavir Krka, Darunavir Mylan, Darunavir Krka d.d.

Drug used in Covid-19 patients: ongoing studies

Recently, darunavir (Prezista®) has also been considered as a treatment option in patients with Covid-19 infection. Its inhibitory effect on SARS-CoV-2 and its potential therapeutic effect may be mainly due to its inhibitory effect on papain-like viral protease [40]. So far (status 07/04/2020) the search in clinical trials (humans only) yielded no completed clinical trial, but two ongoing randomised controlled trials (RCTs) (NCT04252274, ChiCTR2000029541), both with an estimated completion date in December 2020. Detailed information about the two ongoing RCTs is given in Table 3.4-1.

Until May 12, 2020 no aditional ongoing RCTs are found in ClinicalTrial.gov and EudraCT registers, except one RCT (NCT04303299), in which darunavir is applied in various combination with different pharmaceuticals (like ritonavir, oseltamivir, hydroxychloroquine and favipiravir), not listed here.

Drug used in Covid-19 patients: results of publications

Until now (status: 12/05/2020) no scientific publication on RCTs of darunavir (Prezista®) in Covid-19 patients could be identified.

*Table 3.4-1: **Darunavir** in clinical trial registry*

Active substance	**Darunavir** (Prezista®) plus cobicistat	**Darunavir** (Prezista®) plus cobicistat
Sponsor	Shanghai Public Health Clinical Center	Zhongnan Hospital of Wuhan University
Mechanism of operation	Antiviral drug: HIV protease inhibitor	Antiviral drug: HIV protease inhibitor
Regulatory status	EMA approved since 11/02/2007: Darunavir (Prezista®) is used together with low-dose ritonavir and other HIV medicines to treat adults and children aged three years or over who are infected with human immunodeficiency virus (HIV-1). In adults, darunavir is also used with another medicine, cobicistat, in combination with other HIV medicines to treat HIV-1 infection. 3 Generics are available: Darunavir Krka, Darunavir Mylan, Darunavir Krka d.d. FDA approved since 23/06/2006: Darunavir (Prezista®) is indicated for the treatment of HIV-1 infection in adult and pediatric patients three years of age and older. It must be co-administered with ritonavir and with other antiretroviral agents.	EMA approved since 11/02/2007: Darunavir (Prezista®) is used together with low-dose ritonavir and other HIV medicines to treat adults and children aged three years or over who are infected with human immunodeficiency virus (HIV-1). In adults, darunavir is also used with another medicine, cobicistat, in combination with other HIV medicines to treat HIV-1 infection. 3 Generics are available: Darunavir Krka, Darunavir Mylan, Darunavir Krka d.d. FDA approved since 23/06/2006: Darunavir (Prezista®) is indicated for the treatment of HIV-1 infection in adult and pediatric patients three years of age and older. It must be co-administered with ritonavir and with other antiretroviral agents.
Trial Identifier	NCT04252274	ChiCTR2000029541
Phase & Intention	Phase III on efficacy and safety of darunavir plus cobicistat for treatment of pneumonia caused by Covid-19.	Study (phase unknown) on efficacy and safety of darunavir plus cobicistat or lopinavir/ ritonavir combined with thymosin a1 in the treatment of Covid-19.
Study design	Open-label randomised controlled trial	Randomised, open, controlled trial
Status trial	Recruiting	Not recruiting yet
Duration/ End of Study	10 months/ Estimated end of December 2020	10 months/ Estimated December 2020
Study details	Pts: n = 30 Location: China Intervention: Darunavir + cobicistat *(each one tablet/day for 5 days)* + conventional treatments Control: Conventional treatments Duration of observation: 7, 14 days Primary outcome: Virological clearance rate of throat swabs, sputum, or lower respiratory tract secretions at day 7	Pts: n = 100 Group 1: n = 40 Group 2: n = 40 Group 3: n = 40 Location: China Intervention: Group 1: Darunavir *(800mg)* / cobicistat *(150mg)* + conventional treatment with thymosin *(1.6 mg)* Group 2: Lopinavir *(400mg)* / ritonavir *(100mg)* + conventional treatment with thymosin *(1.6mg)* Control: Conventional treatment with thymosin *(1.6mg)* (group 3) Duration of observation: Not reported Primary outcome: Time to conversion of Covid-19 RNA result from RI sample
Results	No publications available yet.	No publications available yet.

Abbreviations: EMA – European Medicines Agency, FDA – Food and Drug Administration, HIV - Human immunodeficiency virus, Pts. - Patients

3.5 Chloroquine (Resochin®)

About the drug under consideration

Chloroquine is a anti-malarial drug with theraputic as well as prophylactic indication. It has due to its anti-inflammatory and immunomodulating effects, further therapeutic indications for rheumatoid arthritis and lupus. In recent in-vitro studies it is indicated, that the drug has also anti-viral effects, e.g. on the cell-entry mechanism of coronavirus like SARS-CoV-2, which is causing Covid-19 [80]. Chloroquine is closely related to hydroxychloroquine and shares the same pharmacokinetics, but showing a lower safety level and more concerns in drug-drug interactions.

Chloroquine has been approved by the American Food and Drug Administration (FDA) since 09/07/1975 as suppressive treatment and for acute attacks of malaria due to *P. vivax*, *P. malariae*, *P. ovale*, and susceptible strains of *P. falciparum*. It is also indicated for the treatment of extraintestinal amebiasis. Further it has an **Emergency Use Authorization for Covid-19**. By the European Medicines Agency (EMA) it is not approved (but has an orphan designation for the treatment of glioma since 19/11/2014), whereas it is national approved in Austria since 19/10/1959 for prevention and treatment of malaria due to *P. vivax*, *P. malariae*, *P. ovale*, and susceptible strains of *P. falciparum*. It is also indicated for treatment of (juvenile) chronic rheumatoid arthritis and systemic lupus.

Recently, EMA issued a reminder on the risk of serious side effects with chloroquine and hydroxychloroquine because recent studies have reported serious, in some cases fatal, heart rhythm problems with chloroquine or hydroxychloroquine, particularly when taken at high doses or in combination with the antibiotic azithromycin [81]. As EMA pointed out, some clinical trials currently investigating the effectiveness of chloroquine or hydroxychloroquine in treating COVID-19 use higher doses than those recommended for the authorised indications. While serious side effects can occur with recommended doses, higher doses can increase the risk of these side effects, including abnormal electrical activity that affects the heart rhythm (QT-prolongation).

Also the FDA issued reminders on reports of serious heart rhythm problems in patients with COVID-19 treated with hydroxychloroquine or chloroquine, often in combination with azithromycin and other QT prolonging medicines. Both drugs can cause abnormal heart rhythms such as QT interval prolongation and a dangerously rapid heart rate called ventricular tachycardia. Patients who also have other health issues such as heart and kidney disease are likely to be at increased risk of these heart problems when receiving these medicines [82].

Drug used in Covid-19 patients: ongoing studies

Recently, chloroquine is also applied in patients with Covid-19 infection. The search in clinical trials (humans only) in April 2020 yielded no completed study on the safety and efficacy chloroquine for Covid-19 patients. Eight ongoing phase IV controlled trials (ChiCTR2000029988, ChiCTR2000029975, ChiCTR2000029542, ChiCTR2000029609, ChiCTR2000029741, ChiCTR2000029898, ChiCTR2000029992, ChiCTR2000029899), one ongoing Chinese controlled trial with phase 0 (ChiCTR2000030054), and two additional controlled trails with not reported phases (ChiCTR2000029939, ChiCTR2000029935) could be identified.

The eight phase IV controlled trials are expected to be completed in spring/early summer 2020, but no results are availabe yet. The controlled trial in phase 0 is expected to be completed in May 2020 and the two controlled trials with no defined phase are expected to be finished in February 2021. Table 3.5-1.

Until 09 May 2020, an additional nine ongoing RCTs are registered (ClinicalTrial.gov and EudraCT); details could be seen in Table 3.5-1.

Drug used in Covid-19 patients: results of publications

So far (status: 09/05/2020) one publication [8] [ChiCTR2000029542]) on the effectiveness and safety of chloroquine in adults hospitalised with Covid-19 could be identified. Also, authors of a RCT with registry number NCT04323527 published preliminary results onsafety issues [82].

In [8] 22 hospitalised Covid-19 patients were assigned to chloroquine (n=10) or comparator treatment lopinavir/ritonavir (n=12). Comparing the virological cure (RT-PCR negative) of the chloroquine intervention group to the lopinavir/ritonavir comparator group, the percentages of patients who became SARS-CoV-2 negative were slightly higher at day 7 (70.0% vs. 58.33%, RR= 1.20 [CI: 0.60, 2.40]), day 10 (90.0% vs. 75.0%, RR= 1.20 [CI: 0.84, 2.00]), and day 14 (100.0% vs. 91.67%, RR= 1.09 [CI: 1.00, 1.33]). Also the proportion of CT-scan improvement of the chloroquine intervention group compared to the lopinavir/ritonavir comparator group, was higher at day 10 (20.0% vs. 8.33%, RR=2.4 (CI: 0.14, 12.32) and day 14 (100.0% vs. 75.0%, RR=1.33 [CI: 1.00, 2.00]). In addition, patients treated with chloroquine were discharged from hospital much earlier than patients treated with lopinavir/ritonavir (clinical recovery at day 10: 80.0% vs. 58.33%, RR= 1.37 [CI: 0.80, 2.80]; hospital discarge at day 14: 100.0% vs. 50.0%, RR= 2.0 [CI: 1.33,4.00]). Concerning all adverse events that occured during the follow-up of 14 days, the intervention group showed 9 different adverse events, the comparator group 10. Neurological events were more common in the lopinavir/ ritonavir comparator group. Severe adverse events were not reported. Overall, a slight clinical benefit could be observed with chloroquine treatment beyond lopinavir/ ritonavir treatment in hospitalised adult patients with Covid-19. Detailed information about the study results are presented in Table 3.5-2.

Borba et al. 2020 (NCT04323527) [82] [83] presented preliminary safety results of a randomised, double-blind, phase IIb clinical trial with 81 adult patients who were hospitalized with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection at a tertiary care facility in Manaus, Brazilian Amazon. Patients were allocated to receive high-dosage CQ (ie, 600 mg CQ twice daily for 10 days) or low-dosage CQ (ie, 450 mg twice daily on day 1 and once daily for 4 days). Primary outcome was reduction in lethality by at least 50% in the high-dosage group compared with the low-dosage group. Out of a predefined sample size of 440 patients, 81 were enrolled (41 [50.6%] to high-dosage group and 40 [49.4%] to low-dosage group). Enrolled patients had a mean (SD) age of 51.1 (13.9) years, and most (60 [75.3%]) were men. Older age (mean [SD] age, 54.7 [13.7] years vs 47.4 [13.3] years) and more heart disease (5 of 28 [17.9%] vs 0) were seen in the high-dose group. Lethality until day 13 was 39.0% in the high-dosage group (16 of 41) and 15.0% in the low-dosage group (6 of 40). The high-dosage group presented more instances of QTc interval greater than 500 milliseconds (7 of 37 [18.9%]) compared with the low-dosage group (4 of 36 [11.1%]). Respiratory secretion at day 4 was negative in only 6 of 27 patients (22.2%). The authors concluded that the preliminary findings of their study suggest that the higher CQ dosage should not be recommended for critically ill patients with COVID-19 because of its potential safety hazards, especially when taken concurrently with azithromycin and oseltamivir. The authors pointed out that these findings cannot be extrapolated to patients with nonsevere COVID-19.

*Table 3.5-1: **Chloroquine** in clinical trial registry*

Active substance	**Chloroquine Phosphate**	**Chloroquine Phosphate**	**Chloroquine Phosphate**	**Chloroquine Phosphate**
Sponsor	HwaMei Hospital, University of Chinese Academy of Sciences, Zhejiang, China	HwaMei Hospital, University of Chinese Academy of Sciences, Zhejiang, China	Zhongnan Hospital of Wuhan University, Wuhan, China	The First Hospital of Jilin University, Jilin, China
Mechanism of operation	Antiviral cell-entry inhibitor: endocytosis inhibitor	Antiviral cell-entry inhibitor: endocytosis inhibitor	Antiviral cell-entry inhibitor: endocytosis inhibitor	Antiviral cell-entry inhibitor: endocytosis inhibitor
Regulatory status	EMA: Not approved. Orphan designation for the treatment of glioma since 19/11/2014. Austria: National approval since 19/10/1959, indicated for prevention and treatment of malaria due to *P. vivax*, *P. malariae*, *P. ovale*, and susceptible strains of *P. falciparum*. Also indicated for treatment of (juvenile) chronic rheumatoid arthritis and systemic lupus. FDA: Approved since 09/07/1975: Chloroquine Phosphate is indicated for suppressive treatment and for acute attacks of malaria due to *P. vivax*, *P. malariae*, *P. ovale*, and susceptible strains of *P. falciparum*. It is also indicated for the treatment of extraintestinal amebiasis. **Emergency use authorization for Covid-19.**	EMA: Not approved. Orphan designation for the treatment of glioma since 19/11/2014. Austria: National approval since 19/10/1959, indicated for prevention and treatment of malaria due to *P. vivax*, *P. malariae*, *P. ovale*, and susceptible strains of *P. falciparum*. Also indicated for treatment of (juvenile) chronic rheumatoid arthritis and systemic lupus. FDA: Approved since 09/07/1975: Chloroquine Phosphate is indicated for suppressive treatment and for acute attacks of malaria due to *P. vivax*, *P. malariae*, *P. ovale*, and susceptible strains of *P. falciparum*. It is also indicated for the treatment of extraintestinal amebiasis. **Emergency use authorization for Covid-19.**	EMA: Not approved. Orphan designation for the treatment of glioma since 19/11/2014. Austria: National approval since 19/10/1959, indicated for prevention and treatment of malaria due to *P. vivax*, *P. malariae*, *P. ovale*, and susceptible strains of *P. falciparum*. Also indicated for treatment of (juvenile) chronic rheumatoid arthritis and systemic lupus. FDA: Approved since 09/07/1975: Chloroquine Phosphate is indicated for suppressive treatment and for acute attacks of malaria due to *P. vivax*, *P. malariae*, *P. ovale*, and susceptible strains of *P. falciparum*. It is also indicated for the treatment of extraintestinal amebiasis. **Emergency use authorization for Covid-19.**	EMA: Not approved. Orphan designation for the treatment of glioma since 19/11/2014. Austria: National approval since 19/10/1959, indicated for prevention and treatment of malaria due to *P. vivax*, *P. malariae*, *P. ovale*, and susceptible strains of *P. falciparum*. Also indicated for treatment of (juvenile) chronic rheumatoid arthritis and systemic lupus. FDA: Approved since 09/07/1975: Chloroquine Phosphate is indicated for suppressive treatment and for acute attacks of malaria due to *P. vivax*, *P. malariae*, *P. ovale*, and susceptible strains of *P. falciparum*. It is also indicated for the treatment of extraintestinal amebiasis. **Emergency use authorization for Covid-19.**
Trial Identifier	ChiCTR2000029939	ChiCTR2000029935	ChiCTR2000029988	ChiCTR2000029975
Phase & Intention	Study (phase not reported) on the clinical effect of oral administration of the active substance Chloroquine Phosphate in patients with confirmed Covid-19 pneumonia	Study (phase not reported) on the clinical effect of oral administration of the active substance Chloroquine Phosphate in patients with confirmed Covid-19 pneumonia	Phase IV on safety and efficacy of oral administration of the active substance Chloroquine Phosphate in patients with severe confirmed Covid-19 pneumonia	Phase IV on safety and efficacy of aerosol administration of the active substance Chloroquine Phosphate in patients with confirmed Covid-19 pneumonia
Study design	Randomised, parallell assigned, single-blinded study	Single arm, open-label, case series study	Randomised, parallell assigned, open-label study	Single-arm, open-label study

Active substance	**Chloroquine Phosphate**	**Chloroquine Phosphate**	**Chloroquine Phosphate**	**Chloroquine Phosphate**
Status trial	Recruiting	Recruiting	Recruiting	Not yet recruiting
Duration/ End of Study	12 months/ Estimated February 6, 2021	12 months/ Estimated February 6, 2021	3 months/ Estimated May 31, 2020	3 months/ Estimated May 31, 2020
Study details	Pts: n = 100 Location: China Intervention: Chloroquine Phosphate *(not specified)* Control: Standard of care Duration of observation: up to 30 days Primary outcome: Length of hospital stay	Pts: n = 100 Location: China Intervention: Chloroquine Phosphate *(not specified)* Control: none Duration of observation: up to 30 days Primary outcome: Length of hospital stay	Pts: n = 80 Location: China Intervention: Chloroquine Phosphate *(not specified)* Control: no treatment Duration of observation: not given Primary outome: Time to clinical recovery	Pts: n = 10 Location: China Intervention: Chloroquine *(150 mg dissolved in 5 ml of normal saline, q12h, inhaled by atomization for one week)* Control: none Duration of observation: up to 30 days Primary outcome: - Viral negative-transforming time - 30-day cause-specific mortality - Co-infections - Time from severe and critical patients to clinical improvement
Results	No publications available yet.	No publications available yet.	No publications available yet.	No publications available yet.

*Table 3.5-1: **Chloroquine** in clinical trial registry (Continued)*

Active substance	**Chloroquine**	**Chloroquine Phosphate** vs. Lopinavir/ritonavir	**Chloroquine Phosphate** vs. Lopinavir/ritonavir	**Chloroquine Phosphate** vs. Hydroxychloroquine Sulfate
Sponsor	Sun Yat sen Memorial Hospital of Sun Yat sen University, China	The Fifth Affiliated Hospital of Sun Yat-Sen University, China	The Fifth Affiliated Hospital of Sun Yat-Sen University, China	Peking University Third Hospital, China
Mechanism of operation	Antiviral cell-entry inhibitor: endocytosis inhibitor	Antiviral cell-entry inhibitor: endocytosis inhibitor	Antiviral cell-entry inhibitor: endocytosis inhibitor	Antiviral cell-entry inhibitor: endocytosis inhibitor
Regulatory status	EMA: Not approved. Orphan designation for the treatment of glioma since 19/11/2014. Austria: National approval since 19/10/1959, indicated for prevention and treatment of malaria due to *P. vivax*, *P. malariae*, *P. ovale*, and susceptible strains of *P. falciparum*. Also indicated for treatment of (juvenile) chronic rheumatoid arthritis and systemic lupus. FDA: Approved since 09/07/1975: Chloroquine Phosphate is indicated for suppressive treatment and for acute attacks of malaria due to *P. vivax*, *P. malariae*, *P. ovale*, and susceptible strains of *P. falciparum*. It	EMA: Not approved. Orphan designation for the treatment of glioma since 19/11/2014. Austria: National approval since 19/10/1959, indicated for prevention and treatment of malaria due to *P. vivax*, *P. malariae*, *P. ovale*, and susceptible strains of *P. falciparum*. Also indicated for treatment of (juvenile) chronic rheumatoid arthritis and systemic lupus. FDA: Approved since 09/07/1975: Chloroquine Phosphate is indicated for suppressive treatment and for acute attacks of malaria due to *P. vivax*, *P. malariae*, *P. ovale*, and susceptible strains of *P. falciparum*. It is also indicated for the treatment of extraintestinal amebiasis.	EMA: Not approved. Orphan designation for the treatment of glioma since 19/11/2014. Austria: National approval since 19/10/1959, indicated for prevention and treatment of malaria due to *P. vivax*, *P. malariae*, *P. ovale*, and susceptible strains of *P. falciparum*. Also indicated for treatment of (juvenile) chronic rheumatoid arthritis and systemic lupus. FDA: Approved since 09/07/1975: Chloroquine Phosphate is indicated for suppressive treatment and for acute attacks of malaria due to *P. vivax*, *P. malariae*, *P. ovale*, and susceptible strains of *P. falciparum*. It	EMA: Not approved. Orphan designation for the treatment of glioma since 19/11/2014. Austria: National approval since 19/10/1959, indicated for prevention and treatment of malaria due to *P. vivax*, *P. malariae*, *P. ovale*, and susceptible strains of *P. falciparum*. Also indicated for treatment of (juvenile) chronic rheumatoid arthritis and systemic lupus. FDA: Approved since 09/07/1975: Chloroquine Phosphate is indicated for suppressive treatment and for acute attacks of malaria due to *P. vivax*, *P. malariae*, *P. ovale*, and susceptible strains of *P. falciparum*. It is also indicated for the treatment of extraintestinal amebiasis. **Emergency use authorization for Covid-19.**

Active substance	**Chloroquine**	**Chloroquine Phosphate** vs. Lopinavir/ritonavir	**Chloroquine Phosphate** vs. Lopinavir/ritonavir	**Chloroquine Phosphate** vs. Hydroxychloroquine Sulfate
	is also indicated for the treatment of extraintestinal amebiasis. **Emergency use authorization for Covid-19.**	**Emergency use authorization for Covid-19.**	is also indicated for the treatment of extraintestinal amebiasis. **Emergency use authorization for Covid-19.**	
Trial Identifier	ChiCTR2000029542	ChiCTR2000029609	ChiCTR2000029741	ChiCTR2000029898
Phase & Intention	Phase IV on safety and efficacy of the active substance **Chloroquine Phosphate** in hospitalised patients with confirmed Covid-19	Phase IV on safety and efficacy of the active substance **Chloroquine Phosphate** vs. Lopinavir/ritonavir in hospitalised patients with mild/ moderate and severe confirmed Covid-19	Phase IV on safety and efficacy of the active substance **Chloroquine Phosphate** vs. Lopinavir/ritonavir in hospitalised patients with mild/ moderate confirmed Covid-19	Phase IV on safety and efficacy of the active substance **Chloroquine Phospahte** vs. Hydroxychloroquine Sulfate in patients with confirmed severe Covid-19
Study design	Not-randomised, open-label study	Not-randomised, open-label study	Randomised, parallell assigned, open-label study	Randomised, parallell assigned, open-label study
Status trial	Recruiting	Not yet recruiting	Recruiting	Recruiting
Duration/ End of Study	6 months/ Estimated July 30, 2020	11 months/ Estimated December 31, 2020	11 months/ Estimated December 31, 2020	2 months/ Estimated April 30, 2020
Study details	Pts: n = 20 Location: China Intervention: Chloroquine Phosphate *(0.5 g twice a day for 10-days)* Control: Standard of care Duration of observation: up to 30 days Primary outcome: - Viral negative-transforming time - 30-day cause-specific mortality	Pts:: n = 205 Location: China Intervention: - Mild/moderate symptoms: - Group1 (n = 59): Chloroquine Phosphate *(0.25 g per tablet)* - Group2 (n = 59): Lopinavir/ritonavir *(lopinavir 200 mg/ritonavir 100 mg per tablet)* - Group3 (n = 59): Chloroquine Phosphate *(0.25 g per tablet)* + Lopinavir/ritonavir *(lopinavir 200 mg/ritonavir 100 mg per tablet)* - Severe symptoms: - Group1 (n = 14): Chloroquine Phosphate *(0.25 g per tablet)* - Group2 (n = 14): Lopinavir/ritonavir *(lopinavir 200 mg/ritonavir 100 mg per tablet)* Control: none Duration of observation: up to 30 days Primary outcome: Virus nucleic acid negative-transforming time	Pts: n = 112 Location: China Intervention: Chloroquine Phosphate *(not specified)* Control: Lopinavir/ritonavir *(not specified)* Duration of observation: up to 28 days Primary outcome: - Length of stay - Length of severe - Oxygenation index during treatment - All-cause mortality in 28 days - Peripheral blood cell count (including white blood cells, lymphocytes, neutrophils, etc.) - Procalcitonin - C-reactive protein - Inflammatory factors (including IL-6, IL-10, TNF-α, etc.) - Lymphocyte subsets and complement - Coagulation indicators (prothrombin time, activated partial prothrombin time, fibrinogen, D-dimer, platelet count) - Virus nucleic acid	Pts:: n = 100 Location: China Intervention: - Group 1: Hydroxychloroquine Sulfate *(Day1: first dose: 6 tablets (0.1 g/tablet), second dose: 6 tablets (0.1 g/tablet) after 6h; Day2~5: 2 tablets (0.1 g/table), BID)* - Group 2: Chloroquine Phosphate *(Day 1-3: 500 mg BID; Day 4-5: 250 mg BID)* Control: none Duration of observation: up to 28 days Primary outcome: Time to Clinical Improvement

Active substance	**Chloroquine**	**Chloroquine Phosphate** vs. Lopinavir/ritonavir	**Chloroquine Phosphate** vs. Lopinavir/ritonavir	**Chloroquine Phosphate** vs. Hydroxychloroquine Sulfate
Results	Publication availabe: [8]	Publication availabe: Huang 2020	No publications available yet.	No publications available yet.

Table 3.5-1: Chloroquine in clinical trial registry (Continued)

Active substance	**Chloroquine Phosphate** vs. Hydroxychloroquine Sulfate	**Chloroquine Phosphate** vs. Hydroxychloroquine Sulfate	**Chloroquine Phosphate** vs. Hydroxychloroquine Sulfate
Sponsor	Zhongshan Hospital Affiliated to Xiamen University, China	Zhongshan Hospital Affiliated to Xiamen University, China	Peking University Third Hospital, China
Mechanism of operation	Antiviral cell-entry inhibitor: endocytosis inhibitor	Antiviral cell-entry inhibitor: endocytosis inhibitor	Antiviral cell-entry inhibitor: endocytosis inhibitor
Regulatory status	EMA: Not approved. Orphan designation for the treatment of glioma since 19/11/2014. Austria: National approval since 19/10/1959, indicated for prevention and treatment of malaria due to *P. vivax*, *P. malariae*, *P. ovale*, and susceptible strains of *P. falciparum*. Also indicated for treatment of (juvenile) chronic rheumatoid arthritis and systemic lupus. FDA: Approved since 09/07/1975: Chloroquine Phosphate is indicated for suppressive treatment and for acute attacks of malaria due to *P. vivax*, *P. malariae*, *P. ovale*, and susceptible strains of *P. falciparum*. It is also indicated for the treatment of extraintestinal amebiasis. **Emergency use authorization for Covid-19.**	EMA: Not approved. Orphan designation for the treatment of glioma since 19/11/2014. Austria: National approval since 19/10/1959, indicated for prevention and treatment of malaria due to *P. vivax*, *P. malariae*, *P. ovale*, and susceptible strains of *P. falciparum*. Also indicated for treatment of (juvenile) chronic rheumatoid arthritis and systemic lupus. FDA: Approved since 09/07/1975: Chloroquine Phosphate is indicated for suppressive treatment and for acute attacks of malaria due to *P. vivax*, *P. malariae*, *P. ovale*, and susceptible strains of *P. falciparum*. It is also indicated for the treatment of extraintestinal amebiasis. **Emergency use authorization for Covid-19.**	EMA: Not approved. Orphan designation for the treatment of glioma since 19/11/2014. Austria: National approval since 19/10/1959, indicated for prevention and treatment of malaria due to *P. vivax*, *P. malariae*, *P. ovale*, and susceptible strains of *P. falciparum*. Also indicated for treatment of (juvenile) chronic rheumatoid arthritis and systemic lupus. FDA: Approved since 09/07/1975: Chloroquine Phosphate is indicated for suppressive treatment and for acute attacks of malaria due to *P. vivax*, *P. malariae*, *P. ovale*, and susceptible strains of *P. falciparum*. It is also indicated for the treatment of extraintestinal amebiasis. **Emergency use authorization for Covid-19.**
Trial Identifier	ChiCTR2000030054	ChiCTR2000029992	ChiCTR2000029899
Phase & Intention	Phase 0 on clinical efficacy of the active substance **Chloroquine Phosphate** vs. Hydroxychloroquine Sulfate in patients with confirmed mild/common Covid-19	Phase IV on clinical efficacy of the active substance **Chloroquine Phosphate** vs. Hydroxychloroquine Sulfate in patients with confirmed severe Covid-19	Phase IV on safety and efficacy of the active substance **Chloroquine Phosphate** vs. Hydroxychloroquine Sulfate in patients with confirmed mild/common Covid-19
Study design	Randomised, parallell assigned, open-label, placebo-controlled study	Randomised, parallell assigned, open-label, placebo-controlled study	Randomised, parallell assigned, open-label study
Status trial	Not yet recruiting	Not yet recruiting	Recruiting
Duration/ End of Study	3 months/ Estimated May 21, 2020	3 months/ Estimated May 20, 2020	2 months/ Estimated April 30, 2020
Study details	Pts: n = 100 Location: China Intervention:	Pts: n = 100 Location: China Intervention:	Pts: n = 100 Location: China Intervention:

Active substance	**Chloroquine Phosphate** vs. Hydroxychloroquine Sulfate	**Chloroquine Phosphate** vs. Hydroxychloroquine Sulfate	**Chloroquine Phosphate** vs. Hydroxychloroquine Sulfate
	- Group 1: Hydroxychloroquine Sulfate *(0.2 g bid x14 days/day)* - Group 2: Chloroquine Phosphate *(first dose 1 g x2 days, third day 0.5 g x12 days)* Control: Placebo oral tablet Duration of observation: up to 28 days Primary outcome: Clinical recovery time	- Group 1: Chloroquine Phosphate *(first dose 1 g x2 days, third day 0.5 g x12 days)* - Group 2: Hydroxychloroquine Sulfate *(0.2 g bid x14 days/day)* Control: Placebo oral tablet Duration of observation: up to 28 days Primary outcome: Clinical recovery time	- Group 1: Hydroxychloroquine Sulfate *(Day1: first dose: 6 tablets (0.1 g/tablet), second dose: 6 tablets (0.1 g/tablet) after 6h; Day2~5: 2 tablets (0.1 g/table), BID)* - Group 2: Chloroquine Phosphate *(Day 1-3: 500 mg BID; Day 4-5: 250 mg BID)* Control: none Duration of observation: up to 28 days Primary outcome: Time to Clinical Improvement
Results	No publications available yet.	No publications available yet.	No publications available yet.

*Table 3.5-1: **Chloroquine** in clinical trial registry (Continued)*

Active substance	**Chloroquine**	**Chloroquine**	**Chloroquine**	**Chloroquine**	**Chloroquine**
Sponsor	Oxford University Clinical Research Unit, Vietnam	UMC Utrecht	Government of Punjab, Specialized Healthcare and Medical Education Department	Fundação de Medicina Tropical Dr. Heitor Vieira Dourado	Fundação de Medicina Tropical Dr. Heitor Vieira Dourado
Trial Identifier	NCT04328493	NCT04362332, ARCHAIC trial	NCT04351191	NCT04342650	NCT04323527
Phase & Intention	Phase 2, on the safety and efficacy of chloroquine for the treatment of hospitalized adults with laboratory confirmed SARS-CoV-2 infection in Vietnam	Phase 4, to evaluate if treatment with only supportive care or addition of one of two anti-COVID_19 agents (chloroquine or hydroxychloroquine) results in less disease progression in patients with moderate to severe COVID-19 who require hospital admission	Phase 4, to to reduce burden on institutional healthcare services by determining efficacy of different chloroquine and hydroxychloroquine dosing regimens in controlling SARS-CoV-2 infection	Phase 2, to evaluate the efficacy and safety of chloroquine diphosphate in the treatment of patients with comorbidities, without severe acute respiratory syndrome, under the new Coronavirus (SARS-CoV2)	Phase 2, to evaluate efficacy and safety of chloroquine diphosphate for the treatment of hospitalized patients with severe acute respiratory syndrome secondary to SARS-CoV2
Study design	RCT, open-label, standard care comparator, parallel asignment	RCT, open label, cluster randomized design, parallel assignment	RCT, quadruple blind, standard care comparator, parallel asignment	RCT, quadruple blind, placebo comparator, parallel asignment	RCT, quadruple blind, active comparator, parallel asignment
Status trial	Recruiting	Recruiting	Recruiting	Recruiting	Recruiting
Duration/ End of Study	Study start: April 7, 2020 Estimated Primary Completion Date: April 1, 2021 Estimated Study Completion Date: April 1, 2022	Study start: April 14, 2020 Estimated Primary Completion Date: April 14, 2021 Estimated Study Completion Date: May 14, 2021	Study start: April 15, 2020 Estimated Primary Completion Date: May 30, 2020 Estimated Study Completion Date: June 30, 2020	Study start: April 8, 2020 Estimated Primary Completion Date: September 2020 Estimated Study Completion Date: September 2020	Study start: March 23, 2020 Estimated Primary Completion Date: August 31, 2020 Estimated Study Completion Date: August 31, 2020
Study details	N of pts: 250 Location/ centres: Vietnam Intervention/control: Up to 56 days	N of pts: 950 Location/ centres: Netherlands Intervention/control: Supportive care + chloroquine base arm; Supportive care +	N of pts: 400 Location/ centres: Pakistan Intervention/control: Cholorquine 500 mg BID for 5 days plus standard of care;	N of pts: 210 Location/ centres: Brazil Intervention/control: CQ 450mg twice daily (3 tablets of 150mg, every 12 hours) on day	N of pts: 440 Location/ centres: Brazil Intervention/control: Low dose chloroquine diphosphate (5 days) /

Active substance	Chloroquine	Chloroquine	Chloroquine	Chloroquine	Chloroquine
	Chloroquine loading dose of 1200mg on the first 24 hours after randomization, then 300mg once daily for 9 days / standard of care therapy Duration of observation/follow-up: Up to 56 days Primary end point(s): Viral clearance time [Time frame: Up to 56 days post randomization] Secondary endpoints: 8 listed, among Lengh of hospital stay, Time to death, Ventilator free days, Oxygene free days, Development of ARDS	hydroxychloroquine arm / Supportive care only Duration of observation/follow-up: 28 days Primary end point(s): Composite endpoint with disease progression defined as a NEWS2score ≥ 7 within 14 days or resulting in admission to Intensive/Medium Care unit or resulting in death within 14 days [Time frame: 14 days] Secondary endpoints: Side effects [Time frame: 28 days]	Hydroxychloroquine Regular dose; Hydroxychloroquine Loading Dose / Standard of care plus placebo Duration of observation/follow-up: 30 days Primary end point(s): RT-PCR result [Time frame: 6th and 7th day] Secondary endpoints: Progression of symptoms, Mortality	1, followed by CQ 450mg once daily (3 tablets of 150mg) from D2 to D5/ Placebo oral tablet Duration of observation/follow-up: up to 120 days Primary end point(s): Proportion of patients with onset of severe acute respiratory syndrome (SARS) [Time frame: 7 days after randomization] Secondary endpoints: 9 listed, among Mortality rate, Number of participants in need of intensive care support, Cumulative incidence of serious adverse events and grade 3 and 4 AEs, Incidence of cardiac disfunctions	high dose chloroquine diphosphate (10 days) Duration of observation/follow-up: Up to 28 days Primary end point(s): Mortality rate reduction of 50% by day 28 [Time frame: 28 days after randomization] Secondary endpoints: 15 listed, among Absolute mortality on days 7 and 14, Duration of mechanical ventilation, Absolute duration of hospital stay in days Prevalence of grade 3 and 4 adverse events, Prevalence of serious adverse events
Results	N.A.	N.A.	N.A.	N.A.	Preliminary results related to safety issue [82]

*Table 3.5-1: **Chloroquine** in clinical trial registry (Continued)*

Active substance	Chloroquine	Chloroquine	Chloroquine	Chloroquine
Sponsor	Medical University of Vienna	Washington University School of Medicine	See Remdesivir Table 3.1-1	See Remdesivir Table 3.1-1
Trial Identifier	NCT04351724	NCT04341727	ISRCTN83971151, SOLIDARITY trial	EudraCT 2020-001366-11, Spain arm of SOLIDARITY trial
Phase & Intention	Phase 2/3, on the efficacy and safety of experimental therapeutics for patients with COVID-19	Phase 3, to evaluate hydroxychloroquine alone or hydroxychloroquine plus azithromycin or chloroquine alone or chloroquine plus azithromycin in the treatment of SARS CoV-2 infection	See Remdesivir Table 3.1-1	See Remdesivir Table 3.1-1
Study design	RCT, open-label, active comparator, parallel assignment; three main study arms (antiviral treatments) and three substudies (A, B, C) are planned	RCT, open-label, active comparator, parallel assignment	See Remdesivir Table 3.1-1	See Remdesivir Table 3.1-1
Status trial	Recruiting	Recruiting	See Remdesivir Table 3.1-1	See Remdesivir Table 3.1-1
Duration/ End of Study	Study start: April 16, 2020 Estimated Primary Completion Date: December 1, 2020	Study start: April 4, 2020 Estimated Primary Completion Date: April 1, 2021	See Remdesivir Table 3.1-1	See Remdesivir Table 3.1-1

Active substance	Chloroquine	Chloroquine	Chloroquine	Chloroquine
	Estimated Study Completion Date: December 31, 2020	Estimated Study Completion Date: August 1, 2021		
Study details	N of pts: 500 Location/ centres: Austria Intervention/control: Hydroxychloroquine 200mg 2-0-2 on day 1 followed by 200mg 1-0-1, or Chloroquine 250mg 2-0-2; Lopinavir/Ritonavir 200mg/50mg 2-0-2 / Best standard of care Duration of observation/follow-up: Primary end point(s): sustained improvement (>48h) of one point on the WHO Scale [Time frame: Inclusion to day 29, daily evaluation] Secondary endpoints: 19 listed, among Mortality, Ventilator free days until day 29, Duration of hospitalization…	N of pts: 500 Location/ centres: US Intervention/control: Hydroxychloroquine 400mg orally twice a day for one day, followed by 200mg twice a day for four consecutive days; Hydroxychloroquine plus azithromycin; Chloroquine alone; Chloroquine plus azithromycin Duration of observation/follow-up: 42 days Primary end point(s): Hours to recovery [Time frame: 42 days] Secondary endpoints: Time fever resolution	See Remdesivir Table 3.1-1	See Remdesivir Table 3.1-1
Results	N.A.	N.A.	See Remdesivir Table 3.1-1	See Remdesivir Table 3.1-1

*Table 3.5-2: Publications on clinical trials on product **Chloroquine***

Author, year	**Huang et al. 2020 [8]**
Country	China
Sponsor	Sun Yat sen Memorial Hospital of Sun Yat sen University, China; Natural Science Foundation of Guangdong Province (2018A030313652); National Mega Projecton Major Infectious Disease Prevention (2017ZX10103011)
Study design	Open-label, randomised controlled trial
Number of pts	22 (10 vs. 12)
Intervention/Product	Chloroquine (500 mg) twice per day for 10 days
Comparator	Lopinavir/Ritonavir (400 mg/100 mg) twice per day for 10 days
Inclusion criteria	- Aged 18 years old - Diagnosed with Covid-19 according to WHO interim guidance Clinicalbmanagement of severe acute respiratory infection when novel coronavirus (2019 nCoV) infection is suspected (Interim guidance, 28 January 2020)
Exclusion criteria	- pregnant woman patients; - Documented allergic history to C hloroquine; - Documented history of hematological system diseases; - Documented history of chronic liver and kidney diseases; - Documented history of cardiac arrhythmia or chronic heart diseases; - Documented his tory of retina or hearing dysfunction; - Documented history of mental illnesses; - Use of digitalis due to the previous disease.
Pts pretreated +previous treatment	NR
Mean age of patients, yrs (range)	Total: 44.0 (36.5-57.5): IG: 41.5 (33.8-50.0) CG: 53.0 (41.8-63.5)
Sex % male (% female)	Total: 59.1 (40.9): IG: 70.0 (30.0) CG: 50 (50.0)
Follow-up (days)	14 (daily examination)
Severe cases, n (%)	Total: 8 (36.4) IG: 3 (30.0) CG: 5 (41.6)
Loss to follow-up, n (%)	NR
Outcomes: efficacy	
Overall survival (OS), n (%)	NR
No. Pts with virological cure (proportion) by day: chloroquine vs. lopinavir/ritonavir; RT-PCR negative	Day 7: 7 (70.0) vs. 7 (58.33), RR= 1.20 (CI: 0.60, 2.40), p=NR Day 10: 9 (90.0) vs. 9 (75.0), RR= 1.20 (CI: 0.84, 2.00), p=NR Day 14: 10 (100.0) vs. 11 (91.67), RR= 1.09 (CI: 1.00, 1.33), p=NR
No. Pts with CT scan improvement at (proportion) by day: chloroquine vs. lopinavir/ritonavir;	Day 10: 2 (20.0) vs. 1 (8.33), RR=2.4 (CI: 0.14, 12.32), p=NR Day 14: 10 (100.0) vs. 9 (75.0), RR=1.33 (CI: 1.00, 2.00), p=NR
Clinical outcomes, n (%)	Clinical recovery at day 10: 8 (80.0) vs. 7 (58.33), RR= 1.37 (CI: 0.80, 2.80), p=NR Hospital discarge at day 14: 10 (100.0) vs. 6 (50.0), RR= 2.0 (CI: 1.33,4.00), p=NR
Outcomes: safety	
Serious adverse events (SAE), N	None observed

Author, year	Huang et al. 2020 [8]
Adverse events (AE), N	Total: 9 (90.0) vs. 10 (83.33) Gastrointestinal: Vomiting: 5 (50.0) vs. 1 (8.33) Abdominal pain: 1 (10.0) vs. 2 (16.67) Nausea: 4 (40.0) vs. 5 (41.67) Diarrhea: 5 (50.0) vs. 8 (66.67) Neurological: Dizziness: 0 (0) vs. 2 (16.67) Headache: 0 (0) vs. 1 (8.33) Psychosis: 0 (0) vs. 1 (8.33) Rash or itchy: 1 (10.0) vs. 0 (0) Respiratory: Cough: 4 (40.0) vs. 6 (50.0) Shortness of breath: 1 (10.0) vs. 4 (33.33)

CG – Comparator group, CI – Confidence intervall, CT – Computer Tomography, IG – Intervention group, N – Number of adverse events, NR – Not reported, Pts – Patients, RR – Risk ratio

3.6 Hydroxychloroquine (Plaquenil®)

About the drug under consideration

Hydroxychloroquine is a common anti-malarial drug with theraputic as well as prophylactic indication. Due to its anti-inflammatory and immunomodulating effects, it is also used as treatment of rheumatoid arthritis and lupus. In recent in-vitro studies it is indicated, that the drug has also anti-viral effects, e.g. on the cell-entry mechanism of coronavirus like SARS-CoV-2, which is causing Covid-19 [84]. Hydroxychloroquine is closely related to cloroquine and shares the same pharmacokinetics, but showing a higher safety level and fewer concerns in drug-drug interactions.

Hydroxychloroquine (Plaquenil®) has been approved by the American Food and Drug Administration (FDA) since 18/04/1955 as treatment of uncomplicated malaria due to *P. falciparum, P. malariae*, *P. ovale*, *and P. vivax*. It is indicated for the prophylaxis of malaria in geographic areas where chloroquine resistance is not reported. Further it has an **Emergency Use Authorization for Covid-19 (March 30, 2020).** By the European Medicines Agency (EMA) it is not approved (but has an orphan designation for the treatment of antiphospholipid syndrome), whereas in Germany it is approved as antimalarial treatment as well as indication for the tratment of immune-mediated conditions like rheumatoid arthritis, discoid and systemic lupus erythematosus.

Recently, EMA issued a reminder of the risk of serious side effects with chloroquine and hydroxychloroquine because recent studies have reported serious, in some cases fatal, heart rhythm problems with chloroquine or hydroxychloroquine, particularly when taken at high doses or in combination with the antibiotic azithromycin [85]. As EMA pointed, some clinical trials currently investigating the effectiveness of chloroquine or hydroxychloroquine in treating COVID-19 use higher doses than those recommended for the authorised indications. While serious side effects can occur with recommended doses, higher doses can increase the risk of these side effects, including abnormal electrical activity that affects the heart rhythm (QT-prolongation).

Also the FDA issued reminders on reports of serious heart rhythm problems in patients with COVID-19 treated with hydroxychloroquine or chloroquine, often in combination with azithromycin and other QT prolonging medicines. Both drugs can cause abnormal heart rhythms such as QT interval prolongation and a dangerously rapid heart rate called ventricular tachycardia. Patients who also have other health issues such as heart and kidney disease are likely to be at increased risk of these heart problems when receiving these medicines [82].

Drug used in Covid-19 patients: ongoing studies

Recently, hydroxychloroquine is also applied in patients with Covid-19 infection. The search in clinical trials (humans only) in April 2020 for the 1st version of this report yielded no completed study on the safety and efficacy hydroxychloroquine for Covid-19 patients. Eight ongoing phase IV controlled trials (NCT04316377, EudraCT: 2020-000982-18, ChiCTR2000029559, ChiCTR2000029992, ChiCTR2000029898, ChiCTR2000029899, ChiCTR2000029868, ChiCTR2000029740), 5 ongoing phase III controlled trials (NCT04315896, NCT04321278, NCT04308668, NCT04315948, EudraCT: 2020-000890-25), one ongoing phase II controlled trial (EudraCT: 2020-001224-33) and one additional ongoing Chinese controlled trial with phase 0 (ChiCTR2000030054) could be identified.

Six phase IV controlled trials are expected to be completed in spring/early summer 2020, but no results are availabe yet. One phase IV controlled trial will be finished in spring 2021 and ones ending is not further specified. The first phase III study is expected to be completed in April 2020, the next two in late summer/autumn 2020, another one in March 2023 and the last phase III controlled trial ending is not further specified. The phase II clinical study has no further details on when it will be completed. The Chinese controlled trial in phase 0 is expected to be completed in May 2020.

Until 07 May 2020, an additional 35 ongoing RCTs are registered; two are visible as completed (NCT04261517, ChiCTR2000029868). Table 3.6-1 presents more details of the identified ongoing studies.

Drug used in Covid-19 patients: results of publications

So far (status: 07/05/2020) seven publications ([86] [EudraCT: 2020-000890-25]; [87, 88] [ChiCTR2000029559]) [89] [90] [91] [92] on the effectiveness and/or safety of hydroxychloroquine in adults hospitalised with Covid-19 could be identified. Unfortunatly, [87] and [89] are not published in English and [88] [90] [91] [92] are availabe just as pre-print but not yet peer-reviewed, thus not included in the Table 3.6-2.

In a non-randomised study published by Gautret et al. 2020 [86], 36 hospitalised Covid-19 patients (per-protocol) were assigned to hydroxychloroquine (n=20) or standard therapies (n=16) including symptomatic treatment and antibiotics based on clinical judgment. Comparing the proportion of patients that had negative PCR results in nasopharyngeal samples showed a significantly difference between the intervention group and control group at days 3-4-5 and 6 post-inclusion (Day 6: 14 (70.0%) vs. 2 (12.5%), difference 57.5 percentage points, p=0.001). Some patients of the intervention group where treated with azithromycin (n=6) in addition to the single drug hydroxychloroquine (n=14). The proportion of patients with negative PCR results in nasopharyngeal samples that where treated with hydroxychloroquine in combination with azithromycin compared to the patient treated with hydroxychloroquine or the control group was significantly different at days 3-4-5 and 6 post-inclusion (Day 6: 8 (57.1%) vs. 6 (100%) vs. 2 (12.5%), p=<0.001). Any (severe) adverse events were not reported in this publication, but will be in the next ones. For Chen J et al. 2020 (NCT04261517) [89] only an abstract is provided in English language, so just a short information is provided below, as well as for a recently published observational controled study by Geleris J et al. [93], Tang et al. study [90], Mahevas M et al. study [91] and study related to serious adverse events [92].

Chen J et al. 2020 [89]presented results from a small RCT with only 30 patients included. Patients in hydroxychloroquine group were given 400 mg per day for 5 days plus conventional treatments, while those in the control group were given conventional treatment only. The primary endpoint was a negative conversion rate of COVID-19 nucleic acid in respiratory pharyngeal swab on days 7 after randomization. On day 7, COVID-19 nucleic acid of throat swabs was negative in 13 (86.7%) cases in the hydroxychloroquine group and 14 (93.3%) cases in the control group (P>0.05). Four cases (26.7%) of the hydroxychloroquine group and 3 cases (20%) of the control group had transient diarrhea and abnormal liver function (P>0.05).

Tang et al. study 2020 (ChiCTR2000029868) [90] assessed the efficacy and safety of hydroxychloroquine (HCQ) plus standard-of-care (SOC) compared with SOC alone in adult patients with COVID-19. This was multicenter, open-label, randomized controlled trial which included 150 patients hospitalized with laboratory-confirmed COVID-19 (75 patients were assigned to HCQ plus SOC and 75 to SOC alone). The primary outcome was whether participants had a negative conversion of SARS-CoV-2 by 28 days (analyzed according to the intention-to-treat principle). The negative

conversion probability by 28 days in SOC plus HCQ group was 85.4% (95% confidence interval (CI) 73.8% to 93.8%), similar to that in the SOC group 81.3% (95%CI 71.2% to 89.6%). Between-group difference was 4.1% (95%CI -10.3% to 18.5%). In the safety population, adverse events were recorded in 7 (8.8%) HCQ non-recipients (N=80) and in 21 (30%) HCQ recipients (N=70). The most common adverse event in the HCQ recipients was diarrhea, reported in 7 (10%) patients and two HCQ patients reported serious adverse events.

Mahevas M et al. 2020 [91] presented results from an emulated trial aimed at assessing the effectiveness of hydroxychloroquine at 600 mg/day. 181 adult patients from four French hospitals with documented SARS-CoV-2 pneumonia and requiring oxygen ≥ 2 L/min were included: 84 received hydroxychloroquine within 48 hours of admission and 97 did not. The composite primary endpoint was transfer to intensive care unit (ICU) within 7 days from inclusion and/or death from any cause. In the weighted analysis, 20.2% patients in the hydroxychloroquine group were transferred to the ICU or died within 7 days vs 22.1% in the non-hydroxychloroquine group (16 vs 21 events, relative risk [RR] 0.91, 95% CI 0.47–1.80). In the hydroxychloroquine group, 2.8% of the patients died within 7 days vs 4.6% in the no-hydroxychloroquine group (3 vs 4 events, RR 0.61, 95% CI 0.13–2.89). 27.4% and 24.1%, respectively, developed acute respiratory distress syndrome within 7 days (24 vs 23 events, RR 1.14, 95% CI 0.65–2.00). Eight patients receiving hydroxychloroquine (9.5%) experienced electrocardiogram modifications requiring HCQ discontinuation.

One recent study reported serious heart rhythm problems with hydroxychloroquine, in combination with the antibiotic azithromycin [92]. Lane at al. 2020 [92] presented safety results of hydroxychloroquine, alone and in combination with azithromycin, from a multinational, network cohort and self-controlled case series study. 956,374 and 310,350 users of hydroxychloroquine and sulfasalazine, and 323,122 and 351,956 users of hydroxychloroquine-azithromycin and hydroxychloroquine-amoxicillin were included. They found that no excess risk of SAEs was identified when 30-day hydroxychloroquine and sulfasalazine use were compared. When azithromycin was added to hydroxychloroquine, an increased risk of 30-day cardiovascular mortality (CalHR2.19 [1.22- 3.94]), chest pain/angina (CalHR 1.15 [95% CI 1.05-1.26]), and heart failure (CalHR 1.22 [95% CI 1.02- 1.45]) were observed.

Geleris J et al. 2020 [93] recently presented results from an observational controlled study conducted at a large medical center in New York City. The primary end point was a composite of intubation or death in a time-to-event analysis. Authors compared outcomes in patients who received hydroxychloroquine with those in patients who did not, using a multivariable Cox model with inverse probability weighting according to the propensity score. Out of 1376 included consecutive patients, 811 (58.9%) received hydroxychloroquine (600 mg twice on day 1, then 400 mg daily for a median of 5 days); 45.8% of the patients were treated within 24 hours after presentation to the emergency department, and 85.9% within 48 hours. There was no significant association between hydroxychloroquine use and intubation or death (hazard ratio, 1.04, 95% confidence interval, 0.82 to 1.32) in the primary multivariable analysis with inverse probability weighting according to the propensity score.

Detailed information about the study results published by Gautret et al. [86] are presented in Table 3.6-2.

*Table 3.6-1: **Hydroxychloroquine (Plaquenil®)** in clinical trial registry*

Active substance	**Hydroxychloroquine**	**Hydroxychloroquine Sulfate** (Plaquenil®)	**Hydroxychloroquine** + Azithromycin	**Hydroxychloroquine** (Plaquenil®)
Sponsor	National Institute of Respiratory Diseases, Mexico; Sanofi	University Hospital, Akershus, Norway	Hospital Israelita Albert Einstein, São Paulo, Brazil	University of Minnesota, USA
Mechanism of operation	Antiviral cell-entry inhibitor: endocytosis inhibitor	Antiviral cell-entry inhibitor: endocytosis inhibitor	Antiviral cell-entry inhibitor: endocytosis inhibitor	Antiviral cell-entry inhibitor: endocytosis inhibitor
Regulatory status	EMA: Not approved. Orphan designation for the treatment of antiphospholipid syndrome. Gremany: Approved as antimalarial treatment, also indicated for the tratment rheumatoid arthritis, discoid and systemic lupus erythematosus, and dermatological conditions caused or aggravated by sunlight. FDA: Approved since 18/04/1955: Plaquenil® is indicated for the treatment of uncomplicated malaria due to *P. falciparum*, *P. malariae*, *P. ovale*, and *P. vivax*. Plaquenil® is indicated for the prophylaxis of malaria in geographic areas where chloroquine resistance is not reported. **Emergency use authorization for Covid-19.** Multiple generics available (e.g. Quensyl®).	EMA: Not approved. Orphan designation for the treatment of antiphospholipid syndrome. Gremany: Approved as antimalarial treatment, also indicated for the tratment rheumatoid arthritis, discoid and systemic lupus erythematosus, and dermatological conditions caused or aggravated by sunlight. FDA: Approved since 18/04/1955: Plaquenil® is indicated for the treatment of uncomplicated malaria due to *P. falciparum*, *P. malariae*, *P. ovale*, and *P. vivax*. Plaquenil® is indicated for the prophylaxis of malaria in geographic areas where chloroquine resistance is not reported. **Emergency use authorization for Covid-19.** Multiple generics available (e.g. Quensyl®).	EMA: Not approved. Orphan designation for the treatment of antiphospholipid syndrome. Gremany: Approved as antimalarial treatment, also indicated for the tratment rheumatoid arthritis, discoid and systemic lupus erythematosus, and dermatological conditions caused or aggravated by sunlight. FDA: Approved since 18/04/1955: Plaquenil® is indicated for the treatment of uncomplicated malaria due to *P. falciparum*, *P. malariae*, *P. ovale*, and *P. vivax*. Plaquenil® is indicated for the prophylaxis of malaria in geographic areas where chloroquine resistance is not reported. **Emergency use authorization for Covid-19.** Multiple generics available (e.g. Quensyl®).	EMA: Not approved. Orphan designation for the treatment of antiphospholipid syndrome. Gremany: Approved as antimalarial treatment, also indicated for the tratment rheumatoid arthritis, discoid and systemic lupus erythematosus, and dermatological conditions caused or aggravated by sunlight. FDA: Approved since 18/04/1955: Plaquenil® is indicated for the treatment of uncomplicated malaria due to *P. falciparum*, *P. malariae*, *P. ovale*, and *P. vivax*. Plaquenil® is indicated for the prophylaxis of malaria in geographic areas where chloroquine resistance is not reported. **Emergency use authorization for Covid-19.** Multiple generics available (e.g. Quensyl®).
Trial Identifier	NCT04315896	NCT04316377	NCT04321278	NCT04308668
Phase & Intention	Phase III on safety and efficacy of oral administration of the active substance Hydroxychloroquine in patients with confirmed Covid-19	Phase IV on virological and clinical effects of oral administration of the active substance Hydroxychloroquine Sulfate in hospitalised confirmed Covid-19 patients	Phase III on safety and clinical efficacy of Hydroxychloroquine associated with Azithromycin in patients with confirmed Covid-19 and pneumonia	Phase III on safety and efficacy of oral administration of the active substance Hydroxychloroquine in patients exposed to a Covid-19 case within 3 days as either a healthcare worker or household contact; or patients with confirmed diagnose of Covid-19; prevention-/treatment
Study design	Randomised, parallell assigned, double-blinded, placebo-controlled study	Pragmatic, randomised, parallell assigned, open-label, placebo-controlled study	Randomised, parallell assigned, open-label study	Randomised, parallell assigned, quadruple-blinded, placebo-controlled study
Status trial	Not yet recruiting	Not yet recruiting	Recruiting	Recruiting

Active substance	**Hydroxychloroquine**	**Hydroxychloroquine Sulfate** (Plaquenil®)	**Hydroxychloroquine** + Azithromycin	**Hydroxychloroquine** (Plaquenil®)
Duration/ End of Study	7 months/ Estimated October 31, 2020	12 months/ Estimated April 1, 2021	5 months/ Estimated August 30, 2020	1 month/ Estimated April 21, 2020
Study details	Pts: n = 500 Location: Mexico Intervention: Hydroxychloroquine *(400 mg/day for 10 days)* Control: Placebo oral tablet Duration of observation: up to 120 days Primary outcome: Incidence of all-cause mortality	Pts: n = 202 Location: Norway Intervention: Hydroxychloroquine sulfate *(400 mg)* Control: Placebo oral tablet Duration of observation: up to 90 days Primary outcome: Rate of decline in SARS-CoV-2 viral load assessed by real time polymerase chain reaction in nasopharyngeal samples	Pts: n = 440 Location: Brazil Intervention: Hydroxychloroquine *(400 mg 2x/day, 12/12h for 10 days) + Azithromycin (500 mg 1x/day for 10 days)* Control: Hydroxychloroquine *(400 mg 2x/day, 12/12h for 10 days)* Duration of observation: up to 29 days Primary outome: Evaluation of the clinical status of patients on the 15th day after randomisation defined by the ordinal scale of 7 points (score ranges from 1 to 7, with 7 being the worst score)	Pts: n = 3,000 Location: USA Intervention: Hydroxychloroquine *(200 mg tablet; 800 mg orally once, followed in 6 to 8 hours by 600 mg, then 600 mg once a day for 4 consecutive days)* Control: Placebo oral tablet Duration of observation: up to 14 days Primary outcome: - Number of participants at 14 days post enrollment with active COVID-19 disease - Ordinal Scale of COVID-19 Disease Severity at 14 days among those who are symptomatic at trial entry: 1) no COVID-19 illness; 2) COVID-19 illness with no hospitalization; 3) COVID-19 illness with hospitalization or death
Results	No publications available yet.	No publications available yet.	No publications available yet.	No publications available yet.

Table 3.6-1: ***Hydroxychloroquine (Plaquenil®)*** *in clinical trial registry (Continued)*

Active substance	**Hydroxychloroquine** vs. Remdesivir vs. Lopinavir/Ritonavir vs. Lopinavir/Ritonavir + Interferon Beta-1A	**Hydroxychloroquine** (Plaquenil®)	**Hydroxychloroquine** (Quensyl®)	**Hydroxychloroquine** (Plaquenil®)
Sponsor	Institut National de la Santé Et de la Recherche Médicale, France	Oslo University Hospital, Norway	Universitätsklinikum Tübingen, Germany	Fondation Méditerranée Infection - IHU Méditerranée Infection, France
Mechanism of operation	Antiviral cell-entry inhibitor: endocytosis inhibitor	Antiviral cell-entry inhibitor: endocytosis inhibitor	Antiviral cell-entry inhibitor: endocytosis inhibitor	Antiviral cell-entry inhibitor: endocytosis inhibitor
Regulatory status	EMA: Not approved. Orphan designation for the treatment of antiphospholipid syndrome. Gremany: Approved as antimalarial treatment, also indicated for the tratment rheumatoid arthritis, discoid and systemic lupus erythematosus, and dermatological conditions caused or aggravated by sunlight. FDA: Approved since 18/04/1955: Plaquenil® is indicated for the treatment of uncomplicated	EMA: Not approved. Orphan designation for the treatment of antiphospholipid syndrome. Gremany: Approved as antimalarial treatment, also indicated for the tratment rheumatoid arthritis, discoid and systemic lupus erythematosus,	EMA: Not approved. Orphan designation for the treatment of antiphospholipid syndrome. Gremany: Approved as antimalarial treatment, also indicated for the tratment rheumatoid arthritis, discoid and systemic lupus erythematosus, and dermatological conditions caused or aggravated by sunlight.	EMA: Not approved. Orphan designation for the treatment of antiphospholipid syndrome. Gremany: Approved as antimalarial treatment, also indicated for the tratment rheumatoid arthritis, discoid and systemic lupus erythematosus, and

Active substance	**Hydroxychloroquine** vs. Remdesivir vs. Lopinavir/Ritonavir vs. Lopinavir/Ritonavir + Interferon Beta-1A	**Hydroxychloroquine** (Plaquenil®)	**Hydroxychloroquine** (Quensyl®)	**Hydroxychloroquine** (Plaquenil®)
	malaria due to *P. falciparum*, *P. malariae*, *P. ovale*, and *P. vivax*. Plaquenil® is indicated for the prophylaxis of malaria in geographic areas where chloroquine resistance is not reported. **Emergency use authorization for Covid-19.** Multiple generics available (e.g. Quensyl®).	and dermatological conditions caused or aggravated by sunlight. FDA: Approved since 18/04/1955: Plaquenil® is indicated for the treatment of uncomplicated malaria due to *P. falciparum*, *P. malariae*, *P. ovale*, and *P. vivax*. Plaquenil® is indicated for the prophylaxis of malaria in geographic areas where chloroquine resistance is not reported. **Emergency use authorization for Covid-19.** Multiple generics available (e.g. Quensyl®).	FDA: Approved since 18/04/1955: Plaquenil® is indicated for the treatment of uncomplicated malaria due to *P. falciparum*, *P. malariae*, *P. ovale*, and *P. vivax*. Plaquenil® is indicated for the prophylaxis of malaria in geographic areas where chloroquine resistance is not reported. **Emergency use authorization for Covid-19.** Multiple generics available (e.g. Quensyl®).	dermatological conditions caused or aggravated by sunlight. FDA: Approved since 18/04/1955: Plaquenil® is indicated for the treatment of uncomplicated malaria due to *P. falciparum*, *P. malariae*, *P. ovale*, and *P. vivax*. Plaquenil® is indicated for the prophylaxis of malaria in geographic areas where chloroquine resistance is not reported. **Emergency use authorization for Covid-19.** Multiple generics available (e.g. Quensyl®).
Trial Identifier	NCT04315948 (Part of global WHO SOLIDARTY trial)	EudraCT: 2020-000982-18 (Part of global WHO SOLIDARTY trial)	EudraCT: 2020-001224-33	EudraCT: 2020-000890-25
Phase & Intention	Phase III on safety and efficacy of the active substance **Hydroxychloroquine** vs. Remdesivir vs. Lopinavir/Ritonavir vs. Lopinavir/Ritonavir + Interferon Beta-1A in hospitalised patients with confirmed Covid-19	Phase III/IV on safety and efficacy of the active substance **Hydroxychloroquine Sulfate** in hospitalised patients with confirmed Covid-19	Phase II on safety and efficacy of oral administration of the active substance **Hydroxychloroquine** in adult/elderly patients with acute Covid-19	Phase III on clinical effectiveness of oral administration of the active substance **Hydroxychloroquine** in patients with confirmed respiratory Covid-19 infection
Study design	Multicenter, randomised, parallell assigned, open-label study	Multicenter, randomised, parallell assigned, open-label study	Randomised, parallell assigned, double-blinded, placebo-controlled study	Single-arm, not blinded study
Status trial	Recruiting	Ongoing	Ongoing	Ongoing
Duration/ End of Study	36 months/ Estimated March 2023	12 months/ not specified	18 months/ A interim analysis will be done when 40% of events have accrued. In case the interim analysis shows a HR > 1.93 (nominal p < 0.0018), efficacy is shown and the trial may be stopped. Final analysis upon completion of the trial and final database lock	12 months/ not specified
Study details	Pts: n = 3,100 Location: France Intervention: - Group 1: Remdesivir *(200 mg i.v. Day 1, followed by 100 mg once-daily i.v. for duration of hospitalization up to 10 days)*	Pts: n = 443 Location: Norway Intervention: Hydroxychloroquine *(not specified)*	Pts: n = 220 Location: Germany Intervention: Hydroxychloroquine *(not specified)* Control: Placebo oral tablet Duration of observation: not given	Pts: n = 25 Location: France Intervention: Hydroxychloroquine *(not specified)* Control: none

Active substance	**Hydroxychloroquine** vs. Remdesivir vs. Lopinavir/Ritonavir vs. Lopinavir/Ritonavir + Interferon Beta-1A	**Hydroxychloroquine** (Plaquenil®)	**Hydroxychloroquine** (Quensyl®)	**Hydroxychloroquine** (Plaquenil®)
	- Group 2: Lopinavir/ritonavir (*400 mg lopinavir/100 mg ritonavir every 12 h for 14 days tablet form. Patients who are unable to take medications by mouth, 400 mg lopinavir/100 mg ritonavir 5-ml suspension every 12 h for 14 days via nasogastric tube)* - Group 3: Lopinavir/ritonavir + Interferon ß-1a *400 mg lopinavir/100 mg ritonavir every 12 h for 14 days in tablet form. Patients who are unable to take medications by mouth 400 mg lopinavir/100 mg ritonavir 5-ml suspension every 12 h for 14 days nasogastric tube. Interferon ß-1a subcutaneously at the dose of 44 µg for a total of 3 doses in 6 days (day 1, day 3, day 6))* - Group 4: Hydroxychloroquine Sulfate *(400 mg twice day 1, followed by 400 mg once daily for 9 days. Through nasogastric tube: 600 mg twice day 1, followed by a maintenance dose of 400 mg)* Control: Standard of care Duration of observation: 15 days Primary outcome: Percentage of subjects reporting each severity rating on a 7-point ordinal scale: 1) Not hospitalized, no limitations on activities 2) Not hospitalized, limitation on activities; 3) Hospitalized, not requiring supplemental oxygen; 4) Hospitalized, requiring supplemental oxygen; 6) Hospitalized, on non-invasive ventilation or high flow oxygen devices; 7) Hospitalized, on invasive mechanical ventilation or ECMO; 8) Death	Control: Standard of care Duration of observation: not given Primary outcome: In-hospital mortality	Primary outcome: Viral clearance defined as time to sustained SARS-CoV-2-specific RNA copy number ≤100, measured by real time reverse-transcription polymerase chain reaction in throat swabs	Duration of observation: at timepoints day 1, day 4, day 7 and day 14 Primary outcome: Results of SARS-COV2 virus detection, not further specified
Results	No publications available yet.	No publications available yet.	No publications available yet.	Publication available: [86]

Table 3.6-1: Hydroxychloroquine (Plaquenil®) in clinical trial registry (Continued)

Active substance	**Hydroxychloroquine Sulfate** vs. Chloroquin Phosphate	**Hydroxychloroquine** (Plaquenil®)	Chloroquin Phosphate vs. **Hydroxychloroquine Sulfate**	**Hydroxychloroquine Sulfate** vs. Chloroquin Phosphate
Sponsor	Zhongshan Hospital Affiliated to Xiamen University, China	Renmin Hospital of Wuhan University, China	Zhongshan Hospital Affiliated to Xiamen University, China	Peking University Third Hospital, China
Mechanism of operation	Antiviral cell-entry inhibitor: endocytosis inhibitor	Antiviral cell-entry inhibitor: endocytosis inhibitor	Antiviral cell-entry inhibitor: endocytosis inhibitor	Antiviral cell-entry inhibitor: endocytosis inhibitor
Regulatory status	EMA: Not approved. Orphan designation for the treatment of antiphospholipid syndrome. Gremany: Approved as antimalarial treatment, also indicated for the tratment rheumatoid arthritis, discoid and systemic lupus erythematosus, and dermatological conditions caused or aggravated by sunlight. FDA: Approved since 18/04/1955: Plaquenil® is indicated for the treatment of uncomplicated malaria due to *P. falciparum*, *P. malariae*, *P. ovale*, and *P. vivax*. Plaquenil® is indicated for the prophylaxis of malaria in geographic areas where chloroquine resistance is not reported. **Emergency use authorization for Covid-19.** Multiple generics available (e.g. Quensyl®).	EMA: Not approved. Orphan designation for the treatment of antiphospholipid syndrome. Gremany: Approved as antimalarial treatment, also indicated for the tratment rheumatoid arthritis, discoid and systemic lupus erythematosus, and dermatological conditions caused or aggravated by sunlight. FDA: Approved since 18/04/1955: Plaquenil® is indicated for the treatment of uncomplicated malaria due to *P. falciparum*, *P. malariae*, *P. ovale*, and *P. vivax*. Plaquenil® is indicated for the prophylaxis of malaria in geographic areas where chloroquine resistance is not reported. **Emergency use authorization for Covid-19.** Multiple generics available (e.g. Quensyl®).	EMA: Not approved. Orphan designation for the treatment of antiphospholipid syndrome. Gremany: Approved as antimalarial treatment, also indicated for the tratment rheumatoid arthritis, discoid and systemic lupus erythematosus, and dermatological conditions caused or aggravated by sunlight. FDA: Approved since 18/04/1955: Plaquenil® is indicated for the treatment of uncomplicated malaria due to *P. falciparum*, *P. malariae*, *P. ovale*, and *P. vivax*. Plaquenil® is indicated for the prophylaxis of malaria in geographic areas where chloroquine resistance is not reported. **Emergency use authorization for Covid-19.** Multiple generics available (e.g. Quensyl®).	EMA: Not approved. Orphan designation for the treatment of antiphospholipid syndrome. Gremany: Approved as antimalarial treatment, also indicated for the tratment rheumatoid arthritis, discoid and systemic lupus erythematosus, and dermatological conditions caused or aggravated by sunlight. FDA: Approved since 18/04/1955: Plaquenil® is indicated for the treatment of uncomplicated malaria due to *P. falciparum*, *P. malariae*, *P. ovale*, and *P. vivax*. Plaquenil® is indicated for the prophylaxis of malaria in geographic areas where chloroquine resistance is not reported. **Emergency use authorization for Covid-19.** Multiple generics available (e.g. Quensyl®).
Trial Identifier	ChiCTR2000030054	ChiCTR2000029559	ChiCTR2000029992	ChiCTR2000029898
Phase & Intention	Phase 0 on clinical efficacy of the active substance **Hydroxychloroquine Sulfate** vs. Chloroquine Phosphate in patients with confirmed mild/common Covid-19	Phase IV on clinical efficacy of the active substance **Hydroxychloroquine** in patients with confirmed Covid-19	Phase IV on clinical efficacy of the active substance Chloroquine Phosphate vs. **Hydroxychloroquine Sulfate** in patients with confirmed severe Covid-19	Phase IV on safety and efficacy of the active substance **Hydroxychloroquine Sulfate** vs. Chloroquine Phosphate in patients with confirmed severe Covid-19
Study design	Randomised, parallell assigned, open-label, placebo-controlled study	Singlecentered, randomised, parallell assigned, double-blinded, placebo-controlled study	Randomised, parallell assigned, open-label, placebo-controlled study	Randomised, parallell assigned, open-label study
Status trial	Not yet recruiting	Recruiting	Not yet recruiting	Recruiting

Active substance	**Hydroxychloroquine Sulfate** vs. Chloroquin Phosphate	**Hydroxychloroquine** (Plaquenil®)	Chloroquin Phosphate vs. **Hydroxychloroquine Sulfate**	**Hydroxychloroquine Sulfate** vs. Chloroquin Phosphate
Duration/ End of Study	3 months/ Estimated May 21, 2020	1 month/ Estimated February 29, 2020	3 months/ Estimated May 20, 2020	2 months/ Estimated April 30, 2020
Study details	Pts: n = 100 Location: China Intervention: - Group 1: Hydroxychloroquine Sulfate *(0.2 g bid x14 days/day)* - Group 2: Chloroquine Phosphate *(first dose 1 g x2 days, third day 0.5 g x12 days)* Control: Placebo oral tablet Duration of observation: up to 28 days Primary outcome: - Clinical recovery time	Pts: n = 300 Location: China Intervention: - Group 1: Hydroxychloroquine *(0.1 oral 2/day)* - Group 2: Hydroxychloroquine *(0.2 oral 2/day)* Control: Placebo oral tablet Duration of observation: not given Primary outcome: - T cell recovery time - Time when the nucleic acid of the novel coronavirus turns negative	Pts:: n = 100 Location: China Intervention: - Group 1: Chloroquine Phosphate *(first dose 1 g x2 days, third day 0.5 g x12 days)* - Group 2: Hydroxychloroquine Sulfate *(0.2 g bid x14 days/day)* Control: Placebo oral tablet Duration of observation: up to 28 days Primary outcome: - Clinical recovery time	Pts:: n = 100 Location: China Intervention: - Group 1: Hydroxychloroquine Sulfate *(Day1: first dose: 6 tablets (0.1 g/tablet), second dose: 6 tablets (0.1 g/tablet) after 6h; Day2~5: 2 tablets (0.1 g/table), BID)* - Group 2: Chloroquine Phosphate *(Day 1-3: 500 mg BID; Day 4-5: 250 mg BID)* Control: none Duration of observation: up to 28 days Primary outcome: Time to Clinical Improvement
Results	No publications available yet.	Publication available: **[88]; pre-print not peer-reviewed**	No publications available yet.	No publications available yet.

*Table 3.6-1: **Hydroxychloroquine (Plaquenil®)** in clinical trial registry (Continued)*

Active substance	**Hydroxychloroquine Sulfate** vs. Chloroquin Phosphate	**Hydroxychloroquine Sulfate**	**Hydroxychloroquine Sulfate**
Sponsor	Peking University Third Hospital, China	Ruijin Hospital, Shanghai Jiaotong University School of Medicine, China	The First Hospital of Peking University, China
Mechanism of operation	Antiviral cell-entry inhibitor: endocytosis inhibitor	Antiviral cell-entry inhibitor: endocytosis inhibitor	Antiviral cell-entry inhibitor: endocytosis inhibitor
Regulatory status	EMA: Not approved. Orphan designation for the treatment of antiphospholipid syndrome. Gremany: Approved as antimalarial treatment, also indicated for the tratment rheumatoid arthritis, discoid and systemic lupus erythematosus, and dermatological conditions caused or aggravated by sunlight. FDA: Approved since 18/04/1955: Plaquenil® is indicated for the treatment of uncomplicated malaria due to *P. falciparum*, *P. malariae*, *P. ovale*, and *P. vivax*. Plaquenil® is indicated for the prophylaxis of malaria in geographic areas where chloroquine resistance is not reported. **Emergency use authorization for Covid-19.** Multiple generics available (e.g. Quensyl®).	EMA: Not approved. Orphan designation for the treatment of antiphospholipid syndrome. Gremany: Approved as antimalarial treatment, also indicated for the tratment rheumatoid arthritis, discoid and systemic lupus erythematosus, and dermatological conditions caused or aggravated by sunlight. FDA: Approved since 18/04/1955: Plaquenil® is indicated for the treatment of uncomplicated malaria due to *P. falciparum*, *P. malariae*, *P. ovale*, and *P. vivax*. Plaquenil® is indicated for the prophylaxis of malaria in geographic areas where chloroquine resistance is not reported. **Emergency use authorization for Covid-19.** Multiple generics available (e.g. Quensyl®).	EMA: Not approved. Orphan designation for the treatment of antiphospholipid syndrome. Gremany: Approved as antimalarial treatment, also indicated for the tratment rheumatoid arthritis, discoid and systemic lupus erythematosus, and dermatological conditions caused or aggravated by sunlight. FDA: Approved since 18/04/1955: Plaquenil® is indicated for the treatment of uncomplicated malaria due to *P. falciparum*, *P. malariae*, *P. ovale*, and *P. vivax*. Plaquenil® is indicated for the prophylaxis of malaria in geographic areas where chloroquine resistance is not reported. **Emergency use authorization for Covid-19.**

Active substance	**Hydroxychloroquine Sulfate** vs. Chloroquin Phosphate	**Hydroxychloroquine Sulfate**	**Hydroxychloroquine Sulfate**
	vivax. Plaquenil® is indicated for the prophylaxis of malaria in geographic areas where chloroquine resistance is not reported. **Emergency use authorization for Covid-19.** Multiple generics available (e.g. Quensyl®).		Multiple generics available (e.g. Quensyl®).
Trial Identifier	ChiCTR2000029899	ChiCTR2000029868	ChiCTR2000029740
Phase & Intention	Phase IV on safety and efficacy of the active substance **Hydroxychloroquine Sulfate** vs. Chloroquine Phosphate in patients with confirmed mild/common Covid-19	Phase IV on efficacy and safety of high dose **Hydroxychloroquine Sulfate** tablets in treatment of mild/normal/severe type novel Covid-19 pneumonia.	Phase IV on clinical efficacy of **Hydroxychloquine** in treatment of novel Covid-19 infection.
Study design	Randomised, parallell assigned, open-label study	Randomised controlled open-label, multicenter trial	Randomised open-label control clinical trial
Status trial	Recruiting	Completed	Recuriting
Duration/ End of Study	2 months/ Estimated April 30, 2020	6 months/ Estimated end of June 2020	1 month/ Estimated end of February 2020
Study details	Pts: n = 100 Location: China Intervention: - Group 1: Hydroxychloroquine Sulfate *(Day1: first dose: 6 tablets (0.1 g/tablet), second dose: 6 tablets (0.1 g/tablet) after 6h; Day2~5: 2 tablets (0.1 g/table), BID)* - Group 2: Chloroquine Phosphate *(Day 1-3: 500 mg BID; Day 4-5: 250 mg BID)* Control: none Duration of observation: up to 28 days Primary outcome: Time to Clinical Improvement	Pts:: n = 360 Group 1: n = 180 Group 2: n = 180 Location: China Intervention: Oral Hydroxychloroquine Sulfate tablets (group 1) Control: Conventional treatment (group 2) Duration of observation: Not reported Primary outcome: Viral nucleic acid test	Pts: n = 78 Group 1: n = 54 Group 2: n = 24 Location: China Intervention: Oral Hydroxychloroquine Sulfate tablets (group 1) Control: Conventional therapy (group 2) Duration of observation: 4 weeks Primary outcome: - Oxygen index - Max respiratory rate - Lung radiography - Count of lymphocyte - Temperature - Other infection - Time when the nuleic acid of the novel Covid-19 turns negative
Results	No publications available yet.	No publications available yet.	No publications available yet.

*Table 3.6-1: **Hydroxychloroquine (Plaquenil®)** in clinical trial registry (Continued)*

Active substance	**Hydroxychloroquine**	**Hydroxychloroquine**	**Hydroxychloroquine**	**Hydroxychloroquine**	**Hydroxychloroquine**
Sponsor	University Hospital, Akershus	Rambam Health Care Campus	Prof. Dr. Umar Farooq, Ayub Medical College, Abbottabad	Bassett Healthcare	University Hospital, Angers

Active substance	**Hydroxychloroquine**	**Hydroxychloroquine**	**Hydroxychloroquine**	**Hydroxychloroquine**	**Hydroxychloroquine**
Trial Identifier	NCT04316377 EudraCT 2020-001010-38	NCT04323631	NCT04328272	NCT04328012 COVID MED trial	NCT04325893 EudraCT 2020-001271-33
Phase & Intention	Phase 4, to assess the virological and clinical effect of chloroquine therapy in patients with established COVID-19	Phase 1, to evaluate the efficacy of HCQ in patients with newly diagnosed COVID-19 who have mild to moderate disease or at risk for complications	Phase 3, to find the effectiveness of hydroxychloroquine alone and adjuvant with azithromycin in mild to severe Covide-19 pneumonia patients admitted to Coronavirus cell/ward of Ayub Teaching hospital, Abbottabad Pakistan	Phase 2/3, Comparison Of Therapeutics for Hospitalized Patients Infected With SARS-CoV-2 In a Pragmatic aDaptive randoMizED Clinical Trial During the COVID-19 Pandemic (COVID MED Trial)	Phase 3, to explore whether treatment with hydroxychloroquine improves prognosis and reduces the risk of death or use for invasive ventilation in patients with COVID-19
Study design	RCT, pragmatic, open-label, standard of care comparator, parallel assignment	RCT, open-label, standard of care comparator, sequential assignment	RCT, single-blind, placebo comparator, parallel assignment	RCT, double blind, placebo controlled, parallel assignment	RCT, double-blind, placebo-controled, parallel assignment
Status trial	Recruiting	Not yet recruiting	Not yet recruiting	Recruiting	Recruiting
Duration/ End of Study	Study start: March 25, 2020 Estimated Primary Completion Date: April 1, 2021 Estimated Study Completion Date: March 3, 2025	Study start: March 2020 Estimated Primary Completion Date: December 2020 Estimated Study Completion Date: December 2020	Study start: March 28, 2020 Estimated Primary Completion Date: May 28, 2020 Estimated Study Completion Date: June 28, 2020	Study start: April 6, 2020 Estimated Primary Completion Date: January 2021Estimated Study Completion Date: April 1, 2021	Study start: April 2020 Estimated Primary Completion Date: September 2020 Estimated Study Completion Date: September 2020
Study details	N of pts: 202 Location/ centres: Norway Intervention/control: 400 mg hydroxychloroquine sulphate (equalling 310 mg base) twice daily for seven days/Standard of care Duration of observation/follow-up: 90 days Primary end point(s): Rate of decline in SARS-CoV-2 viral load [Time frame: Baseline (at randomization) and at 96	N of pts: 1116 Location/ centres: Not provided Intervention/control: Hydroxychloroquine first day 400 mg twice daily, followed by 200mg twice daily on days 2-10/without hydroxychloroquine Duration of observation/follow-up: 28 days Primary end point(s): Number patients	N of pts: 75 Location/ centres: Pakistan Intervention/control: Hydroxychloroquine vs azithromycin vs placebo Duration of observation/follow-up: 7 days Primary end point(s): National Early Warning Score equal to zero [Time frame: 3-5 days]	N of pts: 4000 Location/ centres: US Intervention/control: standard care and hydroxychloroquine; standard care and lopinavir/ritonavir; standard care and losartan / standard care and placebo Duration of observation/follow-up: 60 days Primary end point(s): NIAID COVID-19 Ordinal Severity	N of pts: 1300 Location/ centres: France, Monaco Intervention/control: Hydroxychloroquine/Placebo Duration of observation/follow-up: 28 days Primary end point(s): Number of death from any cause, or the need for intubation and mechanical ventilation during the 14 days following inclusion and start of treatment [Time frame: Day 14] Secondary endpoints: Number of death from any cause, or the need for intubation and mechanical ventilation during the 28 days following inclusion and start of treatment; Clinical evolution on the WHO Ordinal Scale for Clinical Improvement for COVID-19 between day 0 and day 14 and day 28; Number of all-cause mortality at day 14 and day 28; Rate of positive

Active substance	Hydroxychloroquine	Hydroxychloroquine	Hydroxychloroquine	Hydroxychloroquine	Hydroxychloroquine
	hours]. Secondary endpoints: Change in National Early Warning Score score; Admission to intensive care unit ; In-hospital mortality; Duration of hospital admission; Mortality at 30 and 90 days; Clinical status	developing severe infection or death [Time frame: within 28 days] Secondary endpoints: Not provided	Secondary endpoints: C-reactive proteins; Lymphocyte Count; d-dimers	Scale (NCOSS) [Time frame: 60 days] Secondary endpoints: Hospital length of stay; Intensive care unit level LOS; Mechanical ventilation; survival	SARS-CoV-2 RT-PCR on nasopharyngeal samples at day 5 and day 10; Rate of positive SARS-CoV-2 RT-PCR on nasopharyngeal samples at day 10; The rate of venous thromboembolic events at day 28; Number of all-cause mortality at day 28 in patients aged 75 and older; Clinical evolution on the WHO OSCI scale for COVID-19 between day 0 and day 28 for patients aged 75 or older; Rate of severe adverse events at day 28; Number of all-cause mortality at day 14 in patients aged 75 and older
Results	N.A.	N.A.	N.A.	N.A.	N.A.

*Table 3.6-1: **Hydroxychloroquine (Plaquenil®)** in clinical trial registry (Continued)*

Active substance	Hydroxychloroquine	Hydroxychloroquine	Hydroxychloroquine	Hydroxychloroquine	Hydroxychloroquine
Sponsor	Intermountain Health Care, Inc.	Hospital do Coracao	Queen's Medical Centre	Intermountain Health Care, Inc.	University Hospital Tuebingen
Trial Identifier	NCT04329832	NCT04322123	NCT04345692	NCT04334382	NCT04342221
Phase & Intention	Phase 2, to compare two drugs (hydroxychloroquine and azithromycin) to see if hydroxychloroquine is better than azithromycin in treating hospitalized patients with suspected or confirmed COVID-19	Phase 3, to compared standard of care, hydroxychloroquine plus azithromycin and hydroxychloroquine monotherapy for treatment of hospitalized patients with COVID-19	Phase 3, to evaluate the safety and efficacy of hydroxychloroquine (HCQ) plus usual care compared to usual care in approximately 350 hospitalized patients diagnosed with COVID-19	Phase 3, to see if hydroxychloroquine is better than azithromycin in treating outpatients with suspected or confirmed COVID-19	Phase 3, to conduct a placebo-controlled trial in COVID-19 patients with mild to moderate disease in Germany to assess virological efficacy, tolerability and safety of hydroxychloroquine in the treatment of COVID-19
Study design	RCT, open-label, active comparator, parallel assignement	RCT, open-label, standard treatment control, parallel assignment	RCT, open-label, usual care comparator, parallel assignement	RCT, open-label, active comparator, parallel assignement	RCT, placebo-controled, quadruple blind, parallel assignement
Status trial	Recruiting	Recruiting	Recruiting	Recruiting	Recruiting
Duration/ End of Study	Study start: March 30, 2020 Estimated Primary Completion Date: December 31, 2020 Estimated Study Completion Date: December 31, 2021	Study start: April 1, 2020 Estimated Primary Completion Date: August 30, 2020 Estimated Study Completion Date:	Study start: March 26, 2020 Estimated Primary Completion Date: December 31, 2021 Estimated Study Completion Date: December 31, 2021	Study start: April2, 2020 Estimated Primary Completion Date: December 31, 2020 Estimated Study Completion Date: December 31, 2021	Study start: March 29, 2020 Estimated Primary Completion Date: March 2021 Estimated Study Completion Date: February 2022
Study details	N of pts: 300 Location/ centres: US	N of pts: 630 Location/ centres: Brazil	N of pts: 350 Location/ centres: US	N of pts: 1550 Location/ centres: US	N of pts: 220 Location/ centres: Germany

Active substance	Hydroxychloroquine	Hydroxychloroquine	Hydroxychloroquine	Hydroxychloroquine	Hydroxychloroquine
	Intervention/control: hydroxychloroquine 400 mg by mouth twice daily for 1 day, then 200 mg by mouth twice daily for 4 days / azithromycin 500 mg on day 1 plus 250 mg daily on days 2-5 Duration of observation/follow-up: 28 days Primary end point(s): COVID Ordinal Outcomes Scale at 14 days Secondary endpoints: Hospital-free days at 28 days, Ventilator-free days at 28 days, ICU-free days at 28 days, Time to a 1-point decrease in the WHO ordinal recovery score	Intervention/control: Hydroxychloroquine [400mg 2x/day, 12/12h] for 07 days; Hydroxychloroquine [400mg 2x/day, 12/12h] + azithromycin [500mg 1x/day]) for 07 days / standard treatment protocol Duration of observation/follow-up: 28 days Primary end point(s): Evaluation of the clinical status [Time frame: 15 days after randomization] Secondary endpoints: Ordinal scale in 7 days; Need of intubation and mechanical ventilation; Use of mechanical ventilation during hospital stay; Use of non-invasive ventilation; Hospital Length of Stay; All-cause mortality; Thromboembolic complications; Acute renal disfunction; Presence of virus at day 10 in subset of 180 patients; Safety outcome on QTc	Intervention/control: Hydroxychloroquine 400 mg 2x day by mouth on day 1, followed by 200 mg 2x day by mouth days 2-5 / usual care Duration of observation/follow-up: 28 days Primary end point(s): Clinical status [Time frame: Clinical Status (on a 7-point ordinal scale) at day 15] Secondary endpoints: Oxygenation; Mechanical Ventilation; Duration of hospitalization (days); 28-day mortality	Intervention/control: hydroxychloroquine 400mg po BID x 1 day, then 200mg po BID x 4 days/ azithromycin 500mg PO on day 1 plus 250mg PO daily on days 2-5 Duration of observation/follow-up: 28 days Primary end point(s): Hospitalization within 14 days of enrollment [Time Frame: From enrollment to 14 days after enrollment] Secondary endpoints: Duration of COVID-19-attributable symptoms, Hospital-free days at 28 days, Ventilator-free days at 28 days, ICU-free days at 28 days	Intervention/control: Hydroxychloroquine Sulfate, first dose: 800 mg. From 2nd day on, each patient will get 600 mg (3 capsules) once a day until day 7 (6 more does of 600 mg)/ placebo capsules Duration of observation/follow-up: 6 months Primary end point(s): Effect of HCQ on in vivo viral clearance [Time frame: 6 months] Secondary endpoints: In-hospital mortality, All-cause mortality, Proportion requiring non-invasive or invasive ventilation, Proportion admitted to ICU, Duration of hospitalization, Reduction in viral RNA load in upper respiratory tract specimen as assessed by area under viral load curve, Reduction in viral RNA load in upper respiratory tract specimen defined as decline of RNA load by 2 log-levels or to below detection level
Results	N.A.	N.A.	N.A.	N.A.	N.A.

*Table 3.6-1: **Hydroxychloroquine (Plaquenil®)** in clinical trial registry (Continued)*

Active substance	Hydroxychloroquine	Hydroxychloroquine	Hydroxychloroquine	Hydroxychloroquine	Hydroxychloroquine
Sponsor	Asan Medical Center	Rutgers, The State University of New Jersey	UMC Utrecht	NYU Langone Health	Shanghai Public Health Clinical Center
Trial Identifier	NCT04307693	NCT04336332	NCT04362332, ARCHAIC trial	NCT04369742	NCT04261517

Active substance	**Hydroxychloroquine**	**Hydroxychloroquine**	**Hydroxychloroquine**	**Hydroxychloroquine**	**Hydroxychloroquine**
Phase & Intention	Phase 2, to compare lopinavir/ritonavir or hydroxychloroquine in patients with mild coronavirus disease (COVID-19)	Phase 2, comparing the efficacy of single agent hydroxychloroquine to the combination of hydroxychloroquine and azithromycin, and to a delayed hydroxychloroquine regimen, which will serve as a contemporaneous Day 1-6 supportive care control, in eliminating detectable SARS-CoV-2 on day 6 following the initiation of treatment in order to determine which regimen is more effective	Phase 4, to evaluate if treatment with only supportive care or addition of one of two anti-COVID_19 agents (chloroquine or hydroxychloroquine) results in less disease progression in patients with moderate to severe COVID-19 who require hospital admission	Phase 2, to determine if HCQ is effective as treatment in hospitalized non-ICU patients with COVID-19	Phase 3, to evaluate the efficacy and safety of hydroxychloroquine in the treatment of COVID-19 pneumonia
Study design	RCT, open-label, parallel assignment	RCT, open label, placebo comparator, parallel assignment	RCT, open label, cluster randomized design, parallel assignment	RCT, double-blind, placebo-controled, parallel assignment	RCT, open label, conventional treatment comparator, parallel assignment
Status trial	Recruiting	Recruiting	Recruiting	Recruiting	**Completed**
Duration/ End of Study	Study start: March 11, 2020 Estimated Primary Completion Date: May 2020 Estimated Study Completion Date: May 2020	Study start: April 1, 2020 Estimated Primary Completion Date: April 30, 2021 Estimated Study Completion Date: April 30, 2021	Study start: April 14, 2020 Estimated Primary Completion Date: April 14, 2021 Estimated Study Completion Date: May 14, 2021	Study start: April 15, 2020 Estimated Primary Completion Date: June 2020 Estimated Study Completion Date: June 2020	Study start: February 6, 2020 Estimated Primary Completion Date: February 25, 2020 Estimated Study Completion Date: February 25, 2020
Study details	N of pts: 150 Location/ centres: Korea Intervention/control: Lopinavir/ritonavir 200mg/100mg 2 tablets by mouth, every 12 hours for 7-10 days; Hydroxychloroquine 200mg 2 tablets by mouth, every 12 hours for 7-10 days / control without these drugs	N of pts: 160 Location/ centres: US Intervention/control: Hydroxychloroquine Sulfate + Azithromycin; Hydroxychloroquine Sulfate/ Placebo Duration of observation/follow-up: up to 6 months	N of pts: 950 Location/ centres: Netherlands Intervention/control: Supportive care + chloroquine base arm; Supportive care + hydroxychloroquine arm / Supportive care only	N of pts: 626 Location/ centres: Intervention/control: HCQ 400mg (2 tab) by mouth BID (day 1), 200mg (1 tab) by mouth BID (days 2-5) / Calcium citrate 2 tablets (400mg) BID on day 1, 1 tablet (200mg) on days 2-5 Duration of observation/follow-up:	N of pts: 30 Location/ centres: China Intervention/control: hydroxychloroquine 400mg per day for 5 days, also take conventional treatments/ onventional treatments Duration of observation/follow-up: 14 days Primary end point(s): The virological clearance rate of throat swabs, sputum, or lower respiratory tract secretions at day 3, 5, 7; The mortality rate of subjects at weeks 2 [Time frame: 14 days after randomization]

Active substance	**Hydroxychloroquine**	**Hydroxychloroquine**	**Hydroxychloroquine**	**Hydroxychloroquine**	**Hydroxychloroquine**
	Duration of observation/follow-up: 28 days Primary end point(s): Viral load [Time frame: hospital day 3, 5, 7, 10, 14, 18] Secondary endpoints: Viral load change, Time to clinical improvement, Percentage of progression to supplemental oxygen requirement by day 7, Time to NEWS2 (National Early Warning Score 2) of 3 or more maintained for 24 hours by day 7, Time to clinical failure, defined as the time to death, mechanical ventilation, or ICU admission, Rate of switch to Lopinavir/ritonavir or hydroxychloroquine by day 7, adverse effects, Concentration of Lopinavir/ritonavir and hydroxychloroquine	Primary end point(s): Changes in patients viral load [Time frame: Baseline, day 3 and day 6], Second evaluation of changes in patients viral load [Time frame: Day 6] Secondary endpoints: Symptom questionnaire, Fever assessment, Discharge, Recovery, Assessment of agent toxicity, Vital Signs - Body Temperature, Oropharynx swab sample collections, Viral shedding assessment - nasopharyngeal secretions, Viral shedding assessment – serology, Cytokines in blood	Duration of observation/follow-up: 28 days Primary end point(s): Composite endpoint with disease progression defined as a NEWS2score ≥ 7 within 14 days or resulting in admission to Intensive/Medium Care unit or resulting in death within 14 days [Time frame: 14 days] Secondary endpoints: Side effects [Time frame: 28 days]	Primary end point(s): Cumulative incidence of SAEs through day 30 [Time frame: 30 days], Cumulative incidence of grade 3 or 4 AEs through day 30 [Time frame: 30 days]; Incidence of discontinuation of therapy (for any reason) [Time frame: 30 days]; Severe disease progression composite outcome [Time frame: 14 days] Secondary endpoints: 30-day mortality, hospital length of stay, noninvasive ventilator support, and cytokine release syndrome (CRS) grading scale, SARS-CoV-2 viral eradication at the EOT, changes in COVID-19 putative prognostic markers and cytokine levels, and titers of anti-SARS-CoV-2 antibodies	Secondary endpoints: Number of participants with treatment-related adverse events as assessed by CTCAE v5.0, The critical illness rate of subjects at weeks 2
Results	N.A.	N.A.	N.A.	N.A.	Not provided in registry or journal

*Table 3.6-1: **Hydroxychloroquine (Plaquenil®)** in clinical trial registry (Continued)*

Active substance	**Hydroxychloroquine**	**Hydroxychloroquine**	**Hydroxychloroquine**	**Hydroxychloroquine**	**Hydroxychloroquine**
Sponsor	Duke University	Groupe Hospitalier Paris Saint-Joseph	University Hospital Tuebingen	Susanne Arnold, University of Kentucky	Massachusetts General Hospital
Trial Identifier	NCT04335552	EudraCT 2020-001333-13	NCT04351516	NCT04374019	NCT04332991
Phase & Intention	Phase 2, evaluating the efficacy and safety of two potential treatments for hospitalized patients with confirmed SARS-CoV-2 infection	Phase III, to assess, in patients with ARDS caused by COVID-19, the efficacy of dexamethasone (DXM) associated with	Phase 2/3, evaluating hydroxychloroquine versus placebo in early ambulatory diagnosis and treatment of	Phase 2, evaluating efficacy and toxicity assessment of multiple therapies immediately after COVID19 positive	Phase 3, to compare the effect of hydroxychloroquine versus placebo on clinical outcomes, measured using the COVID Ordinal Outcomes Scale at Day 15, among adults with COVID-19 requiring hospitalization

Active substance	**Hydroxychloroquine**	**Hydroxychloroquine**	**Hydroxychloroquine**	**Hydroxychloroquine**	**Hydroxychloroquine**
		hydroxychloroquine (HCQ) compared to HCQ alone on mortality at 28 days	elderly COVID19 patients	testing in high-risk individuals	
Study design	RCT, open label, factorial assignment	RCT, open label, active comparator, parallel assignment	RCT, quadruple blind, placebo-controled, parallel assignment	RCT, open label, active comparator, parallel assignment	RCT, quadruple blind, placebo-controled, parallel assignment
Status trial	Recruiting	Ongoing	Recruiting	Recruiting	Recruiting
Duration/ End of Study	Study start: April 17, 2020 Estimated Primary Completion Date: August 1, 2020 Estimated Study Completion Date: August 1, 2020	Study start: 09 April 2020 Estimated Primary Completion Date: NA Estimated Study Completion Date: NA	Study start: April 21, 2020 Estimated Primary Completion Date: December 31, 2020 Estimated Study Completion Date: May 1, 2021	Study start: May 1, 2020 Estimated Primary Completion Date: May 2021 Estimated Study Completion Date: May 2021	Study start: April 2, 2020 Estimated Primary Completion Date: April 2021 Estimated Study Completion Date: July 2021
Study details	N of pts: 500 Location/ centres: US Intervention/control: Standard of care plus hydroxychloroquine for 5 days; Standard of care plus azithromycin for 5 days; Standard of care plus hydroxychloroquine plus azithromycin for 5 days/ Standard of care Duration of observation/follow-up: up to 46 days Primary end point(s): World Health Organization (WHO) ordinal scale measured at 14 days after enrollment [Time frame: Day 14] Secondary endpoints: Rates of death during the index hospitalization, Number of days on mechanical ventilation for patients who were on mechanical ventilation at baseline,	N of pts: 122 Location/ centres: France Intervention/control: Dexamethasone associated with hydroxychloroquine will be compared to hydroxychloroquine alone Duration of observation/follow-up: 60 days Primary end point(s): Mortality on D28 Secondary endpoints: Ventilator-free days, Mortality in intensive care unit, Mortality on D60, Number of episodes of pneumonia and bacteremia	N of pts: 350 Location/ centres: Germany Intervention/control: Hydroxychloroquine 600mg on the first day followed with 400mg/day divided in 2x200mg for 6 more days / Placebo Duration of observation/follow-up: 60 days Primary end point(s): Rate of hospitalization or death at day 7 after study inclusion [Time frame: 7 days] Secondary endpoints: not provided, but adverse events planned to be collected	N of pts: 240 Location/ centres: US Intervention/control: Hydroxychloroquine; Hydroxychloroquine and Azithromycin; Hydroxychloroquine and Ivermectin; Camostat Mesilate Duration of observation/follow-up: 40 days Primary end point(s): Clinical Deterioration [Time Frame: 14 days] Secondary endpoints: 14 listed, among mortality, Rate of severe adverse events, Oxygen-free days, Ventilator-free days, ICU-free days	N of pts: 510 Location/ centres: US Intervention/control: /Duration of observation/follow-up: 29 days Primary end point(s): COVID Ordinal Outcomes Scale on Day 15 [Time frame: assessed on study day 15] Secondary endpoints: 11 listed, among all-cause mortality, Oxygen-free days, Ventilator-free days, ICU-free days

Active substance	Hydroxychloroquine	Hydroxychloroquine	Hydroxychloroquine	Hydroxychloroquine	Hydroxychloroquine
	Proportion of patients not receiving mechanical ventilation at baseline who progress to requiring mechanical ventilation during the index hospitalization, WHO ordinal scale measured at 28 days after enrollment, Hospital length of stay in days for the index hospitalization, Rates of all-cause study medication discontinuation, Rates of severe adverse events				
Results	N.A.	N.A.	N.A.	N.A.	N.A.

*Table 3.6-1: **Hydroxychloroquine (Plaquenil®)** in clinical trial registry (Continued)*

Active substance	**Hydroxychloroquine**	**Hydroxychloroquine**	**Hydroxychloroquine**	**Hydroxychloroquine**	**Hydroxychloroquine**
Sponsor	LCMC Health	Bassett Healthcare	University Hospital, Montpellier	Sanofi	University of Utah
Trial Identifier	NCT04344444	NCT04328012, COVID MED trial	NCT04345861, COVIDOC trial	NCT04333654	NCT04342169
Phase & Intention	Phase 3, to evaluate clinical outcomes in patients with suspected or confirmed COVID-19 with early moderate to severe disease in a randomized controlled trial	Phase 2/3, to compare therapeutics for hospitalized patients infected with SARS-CoV-2 in a Pragmatic aDaptive randoMizED Clinical Trial During the COVID-19 Pandemic (COVID MED Trial)	Phase 2/3, to evaluate the efficacy and safety of the use of hydroxychloroquine (10 days) combined with azithromycin (5 days) compared to hydroxychloroquine (10 days) in the the clinical evolution by the ordinal scale of 7 points in adults hospitalized outside Intensive care unit with pneumonia caused by infection by the SARS-CoV2 virus in France	Phase 1, to assess the effect of hydroxychloroquine versus placebo on nasopharyngeal SARS-CoV-2 viral load, clinical signs and symptoms and progression of disease in outpatient adults with COVID-19, including the safety and tolerability of hydroxychloroquine	Phase 2, to measure the efficacy and safety of hydroxychloroquine for reducing viral load and shedding in adult outpatients with confirmed COVID-19
Study design	RCT, open label, supportive care control, parallel assignment	RCT, quadruple blind, placebo controlled, parallel assignment	RCT, double blind, active comparator, parallel assignment	RCT, quadruple blind, placebo controlled, parallel assignment	RCT, open label, placebo controled, parallel assignment
Status trial	Recruiting	Recruiting	Recruiting	Recruiting	Recruiting
Duration/ End of Study	Study start: April 10, 2020 Estimated Primary Completion Date: April 10, 2021 Estimated Study Completion Date: December 10, 2021	Study start: April 6, 2020 Estimated Primary Completion Date: January 1, 2021 Estimated Study Completion Date: April 1, 2021	Study start: April 11, 2020 Estimated Primary Completion Date: September 6, 2020 Estimated Study Completion Date: April 6, 2021	Study start: April 12, 2020 Estimated Primary Completion Date: May 2020 Estimated Study Completion Date: May 2020	Study start: April 14, 2020 Estimated Primary Completion Date: April 2022 Estimated Study Completion Date: April 2023
Study details	N of pts: 600 Location/ centres: US Intervention/control: Hydroxychloroquine 400 mg po bid on Day 1 Hydroxychloroquine 200 mg po bid days 2 through 5; Hydroxychloroquine as in Arm B AND Azithromycin 500 mg po on day 1 Azithromycin 250 mg po days 2 through 5/ Supportive care only	N of pts: 4000 Location/ centres: US Intervention/control: hydroxychloroquine sulfate 400 mg BID on Day 0 200 mg BID Days 1-4, days 1-13; lopinavir/ritonavir 400mg/200mg mg po BID X 5-14 days; losartan 25 mg po QD X 5-14 days/ Placebo	N of pts: 150 Location/ centres: France Intervention/control: hydroxychloroquine : 800mg(Day1) then 600 mg (Day 2 to Day 11) / Combination hydroxychloroquine : 800mg(Day1) then 600 mg (Day 2 to Day 11) Azithromycin 500mg (day 1) then 250 mg (Day 2 to Day 5) Duration of observation/follow-up: 29 days	N of pts: 210 Location/ centres: France, Netherlands, United States Intervention/control: Hydroxychloroquine, loading dose on day 1 followed by a daily maintenance dose during 9 days / Placebo Duration of observation/follow-up: 14 days	N of pts: 400 Location/ centres: US Intervention/control: HCQ 400mg po BID x 1 day, then 200mg po BID x 4 days / Placebo oral tablet Duration of observation/follow-up: 28 days Primary end point(s): Duration of viral shedding [Time frame: Days 1-14] Secondary endpoints: Duration of COVID-19-attributable symptoms, Hospitalization, Duration of viral shedding, Adult household contact viral acquisition

Active substance	Hydroxychloroquine	Hydroxychloroquine	Hydroxychloroquine	Hydroxychloroquine	Hydroxychloroquine
	Duration of observation/follow-up: Primary end point(s): Most severe outcome [Time frame: 5 days] Secondary endpoints: not provided	Duration of observation/follow-up: 60 days Primary end point(s): NIAID COVID-19 Ordinal Severity Scale (NCOSS) [Time frame: 60 days] Secondary endpoints: Hospital length of stay, Intensive care unit level LOS, Mechanical ventilation, survival	Primary end point(s): Time to clinical improvement of at least 1 level on the ordinal scale between Day 1 (day of the first administration of study drug) to Day 11 (day after last day of treatment) [Time frame: up to day 11] Secondary endpoints: 8 listed, among mortality, AEs, need to mechanical ventilation, transfer to ICU	Primary end point(s): Change from baseline to Day 3 in nasopharyngeal SARS-CoV-2 viral load (if quantitative PCR is available) [Time frame: Baseline to day 3]; Number of participants by PCR result status (positive or negative) (if quantitative PCR is not available) [Time frame: Baseline to Day 3] Secondary endpoints: 8 listed, among number of participants with Adverse Events, Percentage of participants hospitalized, Time to resolution of COVID-19 symptoms	
Results	N.A.	N.A.	N.A.	N.A.	N.A.

*Table 3.6-1: **Hydroxychloroquine (Plaquenil®)** in clinical trial registry (Continued)*

Active substance	Hydroxychloroquine	Hydroxychloroquine	Hydroxychloroquine	Hydroxychloroquine	Hydroxychloroquine
Sponsor	Washington University School of Medicine	Medical University of Vienna	University of Oxford / Clinical Trials and Research Governance	University of Oxford	Institute of Tropical Medicine, Belgium
Trial Identifier	NCT04341727	NCT04351724	EudraCT 2020-001209-22 ISRCTN86534580 PRINCIPLE Trial	ISRCTN50189673 EudraCT 2020-001113-21, RECOVERY Trial	EudraCT 2020-001417-21
Phase & Intention	Phase 3, to evaluate hydroxychloroquine alone or hydroxychloroquine plus azithromycin or chloroquine alone or chloroquine plus azithromycin in the treatment of SARS CoV-2 infection	Phase 2/3, on the efficacy and safety of experimental therapeutics for patients with COVID-19	Phase III, to assess the effectiveness of trial treatments in reducing the need for hospital admission or death for patients aged ≥50 years with serious comorbidity, and aged ≥65 with or without comorbidity and suspected COVID-19 infection during time of prevalent COVID-19 infections	Phase II/III, to provide reliable estimates of the effect of study treatments on death within 28 days of randomisation (with subsidiary analyses of cause of death)	Phase II, to evaluate the effect of hydroxychloroquine on viral shedding in mild COVID-19

Active substance	**Hydroxychloroquine**	**Hydroxychloroquine**	**Hydroxychloroquine**	**Hydroxychloroquine**	**Hydroxychloroquine**
Study design	RCT, open-label, active comparator, parallel assignment	RCT, open-label, active comparator, parallel assignment; three main study arms (antiviral treatments) and three substudies (A, B, C) are planned	RCT, open-label, usual care comparator	RCT, open-label, standard of care comparator, parallel assignment	RCT, open-label, symptomatic care comparator
Status trial	Recruiting	Recruiting	Ongoing	Ongoing	Ongoing
Duration/ End of Study	Study start: April 4, 2020 Estimated Primary Completion Date: April 1, 2021 Estimated Study Completion Date: August 1, 2021	Study start: April 16, 2020 Estimated Primary Completion Date: December 1, 2020 Estimated Study Completion Date: December 31, 2020	Study start: 26 March 2020 Estimated Primary Completion Date: NA Estimated Study Completion Date: NA	Study start: 17 March 2020 Estimated Primary Completion Date: NA Estimated Study Completion Date: NA	Study start: 12 April 2020 Estimated Primary Completion Date: NA Estimated Study Completion Date: NA
Study details	N of pts: 500 Location/ centres: US Intervention/control: Hydroxychloroquine 400mg orally twice a day for one day, followed by 200mg twice a day for four consecutive days; Hydroxychloroquine plus azithromycin; Chloroquine alone; Chloroquine plus azithromycin Duration of observation/follow-up: 42 days Primary end point(s): Hours to recovery [Time frame: 42 days] Secondary endpoints: Time fever resolution	N of pts: 500 Location/ centres: Austria Intervention/control: Hydroxychloroquine 200mg 2-0-2 on day 1 followed by 200mg 1-0-1, or Chloroquine 250mg 2-0-2; Lopinavir/Ritonavir 200mg/50mg 2-0-2 / Best standard of care Duration of observation/follow-up: Primary end point(s): sustained improvement (>48h) of one point on the WHO Scale [Time frame: Inclusion to day 29, daily evaluation] Secondary endpoints: 19 listed, among Mortality, Ventilator free days until day 29, Duration of hospitalization…	N of pts: 300 Location/ centres: UK Intervention/control: Hydroxychloroquine/Placebo Duration of observation/follow-up: 28 days Primary end point(s): Hospital admission or mortality related to suspected COVID-19 Secondary endpoints: 10 listed, among Duration of severe symptoms, Intensive Care Unit admission, Mechanical ventilation, Duration of hospital admission	N of pts: 2000 Location/ centres: UK Intervention/control: Hydroxychloroquine; Lopinavir/ritonavir/Azithromycin; Prednisolone; Hydrocortisone; Tocilizumab/Standard of care Duration of observation/follow-up: until death, discharge from hospital or 28 days post-randomisation (whichever is sooner). Longer term follow-up will be sought through linkage to electronic healthcare records and medical databases. Primary end point(s): All-cause mortality within 28 days of randomisation Secondary endpoints: Duration of hospitalisation, Use of ventilation	N of pts: 206 Location/ centres: Belgium Intervention/control: Hydroxychloroquine /Standard of care Duration of observation/follow-up: 21 days Primary end point(s): proportion of participants with a negative nasopharyngeal sample* by day 7 post diagnosis Secondary endpoints: frequency and pattern of reported adverse events, adverse reactions, Serious Adverse Events, Serious adverse reactions, and SUSARs; pattern and duration of clinical symptoms, as reported by the patients; rate of hospital admission during follow-up; proportion of participants with a negative nasopharyngeal sample* by day 7 POS; roportion of participants with a negative nasal swab + saliva sample* by day 7 post diagnosis
Results	N.A.	N.A.	N.A.	N.A.	N.A.

*Table 3.6-1: **Hydroxychloroquine (Plaquenil®)** in clinical trial registry (Continued)*

Active substance	**Hydroxychloroquine**	**Hydroxychloroquine**	**Hydroxychloroquine**	**Hydroxychloroquine**	**Hydroxychloroquine**
Sponsor	See Remdesivir Table 3.1-1	See Remdesivir Table 3.1-1	See Remdesivir Table 3.1-1	See Remdesivir Table 3.1-1	Government of Punjab, Specialized Healthcare and Medical Education Department
Trial Identifier	NCT04330690 Canadian arm of SOLIDARITY trial	NCT04321616, EudraCT 2020-000982-18, Norwegian part of Solidarity trial	EudraCT 2020-001366-11 Spain arm of SOLIDARITY trial	ISRCTN83971151, SOLIDARITY trial	NCT04351191
Phase & Intention	See Remdesivir Table 3.1-1	See Remdesivir Table 3.1-1	See Remdesivir Table 3.1-1	See Remdesivir Table 3.1-1	Phase 4, to to reduce burden on institutional healthcare services by determining efficacy of different chloroquine and hydroxychloroquine dosing regimens in controlling SARS-CoV-2 infection
Study design	See Remdesivir Table 3.1-1	See Remdesivir Table 3.1-1	See Remdesivir Table 3.1-1	See Remdesivir Table 3.1-1	RCT, quadruple blind, standard care comparator, parallel asignment
Status trial	See Remdesivir Table 3.1-1	See Remdesivir Table 3.1-1	See Remdesivir Table 3.1-1	See Remdesivir Table 3.1-1	Recruiting
Duration/ End of Study	See Remdesivir Table 3.1-1	See Remdesivir Table 3.1-1	See Remdesivir Table 3.1-1	See Remdesivir Table 3.1-1	Study start: April 15, 2020 Estimated Primary Completion Date: May 30, 2020 Estimated Study Completion Date: June 30, 2020
Study details	See Remdesivir Table 3.1-1	See Remdesivir Table 3.1-1	See Remdesivir Table 3.1-1	See Remdesivir Table 3.1-1	N of pts: 400 Location/ centres: Pakistan Intervention/control: Cholorquine 500 mg BID for 5 days plus standard of care; Hydroxychloroquine Regular dose; Hydroxychloroquine Loading Dose / Standard of care plus placebo Duration of observation/follow-up: 30 days Primary end point(s): RT-PCR result [Time frame: 6th and 7th day] Secondary endpoints: Progression of symptoms, Mortality
Results	See Remdesivir Table 3.1-1	See Remdesivir Table 3.1-1	See Remdesivir Table 3.1-1	See Remdesivir Table 3.1-1	N.A.

*Table 3.6-2: Publications on clinical trials on product **Hydroxycloroquine (Plaquenil®)***

Author, year	**Gautret et al. 2020** [86]	**Chen et al. 2020** [88]
Country	France	China
Sponsor	Fondation Méditerranée Infection - IHU Méditerranée Infection, Marseille,France; French Government under the « Investissements d'avenir » (Investments for the Future) program managed by the Agence Nationale de la Recherche	
Study design	Open-label, controlled trial	
Number of pts	42 (26 vs. 16) per-protocol: 36 (20 vs. 16); (Subgroup: 36 (14 vs. 6 vs. 16))	
Intervention/Product	Hydroxychloroquine sulfate (200 mg) three times per day + standard care for 10 days (Subgroup: n=6; hydroxychloroquine sulfate (200 mg three times per day) + azithomycin (500 mg on day1, then 250mg per day for 4 days) + standard care for 10 days)	
Comparator	Standard care (as necessary): Symptomatic treatment and antibiotics based on clinical judgment	
Inclusion criteria	- Hospitalized patients with confirmed COVID-19 - age >12 years - PCR documented SARS-CoV-2 carriage in nasopharyngeal sample at admission whatever their clinical status	-
Exclusion criteria	- known allergy to hydroxychloroquine or chloroquine or had another known contraindication to treatment with the study drug, including retinopathy, G6PD deficiency and QT prolongation - Breastfeeding and pregnant patients were excluded based on their declaration and pregnancy test results when required	-
Pts pretreated +previous treatment	NR	
Mean age of patients, yrs (SD)	**Total: 45.1 (22.0):** IG: 51.2 (18.7) CG: 37.3 (24.0)	
Sex % male (% female)	**Total: 41.7 (58.3):** IG: 45.0 (55.0) CG: 37.5 (62.5)	
Follow-up (days)	14 (daily examination)	
Clinical status: asymptomatic/ URTI/ LRTI (proportion)	**Total: 6 (16.7)/ 22 (61.1)/ 8 (22.2)** IG: 2 (10.0)/ 12 (60.0)/ 6 (30.0) CG: 4 (25.0)/ 10 (62.5)/ 2 (12.5)	
Loss to follow-up, n (%)	6 vs. 0 - 3 were transferred to intensive care unit - 1 died on day 3 - 1 recovered on day 2 - 1 stopped because of nausea at day 3	
Outcomes: efficacy		
Overall survival (OS), n (%)	NR	
No. Pts with virological cure (proportion) by day: hydoxycloroquine vs. control; negative nasopharyngeal PCR	per-protocol: Day 3: 10 (50.0) vs. 1 (6.3), difference 43.7 percentage points, p=0.005 Day 4: 12 (60.0) vs. 4 (25.0), difference 35.0 percentage points, p=0.04 Day 5: 13 (65.0) vs. 3 (18.8), difference 46.2 percentage points, p=0.006 Day 6: 14 (70.0) vs. 2 (12.5), difference 57.5 percentage points, p=0.001	

Author, year	Gautret et al. 2020 [86]	Chen et al. 2020 [88]
No. Pts with virological cure (proportion) by day: hydoxycloroquine vs. hydoxycloroquine + azithomycin vs. control; negative nasopharyngeal PCR	per-protocol: Day 3: 5 (35.7) vs. 5 (83.3) vs. 1 (6.3), p=0.002 Day 4: 7 (50.0) vs. 5 (83.3) vs. 4 (25.0), p=0.05 Day 5: 7 (50.0) vs. 6 (100.0) vs. 3 (18.8), p=0.002 Day 6: 8 (57.1) vs. 6 (100) vs. 2 (12.5), p=<0.001	
Outcomes: safety		
Serious adverse events (SAE), n	NR (will be presented in next paper)	
Adverse events (AE), n	NR (will be presented in next paper)	

CG – Control group, IG – Intervention group, LRTI – Lower tract respiratory infection,
NR – Not reported, Pts – Patients, SD – Standard deviaton, URTI – Upper tract respiratory infection

3.7 Camostat Mesilate (Foipan®)

About the drug under consideration

Camistat Mesilate (Foipan®) is classified as a so-called serine protease inhibitor, blocking several pancreatic and plasmatic enzymes like trypsin, thrombin and plasmin [94]. It is licenced for pancreatitis and reflux esophagitis after gastrectomy in Japan (PMDA). Further, studies showed effects on the cell-entry mechanism of coronaviruses (e.g. SARS-CoV and SARS-CoV-2) in in-vitro human cells [95, 96] as well as in pathogenic mice-models [97] by inhibiting the enzyme Transmembrane protease, serine 2 (TMPRSS2). Camistat Mesilate (Foipan®) ist not approved for any anti-viral use (FDA, EMA).

Drug used in Covid-19 patients: ongoing studies

In the course of the current urgent search for treatments against the novel Covid-19 disease (caused by SARS-CoV-2), Camistat Mesilate (Foipan®) is being considered as a potential therapeutic agent. Although, only one randomised clinical trial (NCT04321096) is registered in April 2020. This trial (phase II) on the efficacy of Camistat Mesilate (Foipan®) is still ongoing and recruition of patients is pending. The presented study is expected to be completed within a total of 9 months at end of December 2020. Until May 12, 2020, two more ongoing RCTs are listed, NCT04353284 and NCT04374019. A randomised, placebo controlled trial number NCT04353284 aims to evaluate the effect of camostat mesylate on COVID-19 infection in 114 ambulatory patients. More information is listed in Table 3.7-1 Details related to RCT number NCT04374019 can be found in Table 3.7-1: Hydroxychloroquine (Plaquenil®). Two RCTs related to combination therapy of camostat mesilate and hydroxychloroquine in COVID-19 patients (NCT04338906 and NCT04355052) are not listed here.

Drug used in Covid-19 patients: results of publications

Until now no scientific publication on clinical trials of Camostat Mesilate (Foipan®) in Covid-19 patients could be identified (status: 12/05/2020).

Table 3.7-1 ***Camostat Mesilate (Foipan®)*** *in clinical trial registry*

Active substance	**Camostat Mesilate** (Foipan®)
Sponsor	University of Aarhus, Denmark
Mechanism of operation	Antiviral cell-entry inhibitor: serine protease inhibitor
Regulatory status	Approved for pancreatitis and reflux esophagitis after gastrectomy in Japan (PMDA) Not approved (EMA, FDA) for Covid-19
Trial Identifier	NCT04321096
Phase & Intention	Phase II on safety and efficacy of oral administration of the active substance Camostat Mesilate (Foipan®) in Covid-19 infection-confirmed patients
Study design	Multicenter, randomised, parallell assingned, quadruple-blinded, placebo-controlled study

Active substance	**Camostat Mesilate** (Foipan®)
Status trial	Not yet recruiting
Duration/ End of Study	9 months /Estimated December 31, 2020
Study details	Pts: n=180 Location: Denmark Intervention: Camostat Mesilate (Foipan®) *(2x100 mg pills 3 times daily for 5 days)* Control: Placebo oral tablet Duration of observation: 30 days Primary outcome: Clinical improvement defined as live hospital discharge OR a 2 point improvement (from time of enrolment) in disease severity rating on the 7-point ordinal scale 1) Death; 2) Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO); 3) Hospitalized, on non-invasive ventilation or high flow oxygen devices; 4) Hospitalized, requiring supplemental oxygen; 5) Hospitalized, not requiring supplemental oxygen; 6) Not hospitalized, limitation on activities; 7) Not hospitalized, no limitations on activities
Results	No publications available yet.

Table 3.7-2 ***Camostat Mesilate (Foipan®)*** *in clinical trial registry* (continued)

Active substance	**Camostat Mesilate**	**Camostat Mesilate**
Sponsor	Yale University	See Table 3.7-1: Hydroxychloroquine (Plaquenil®)
Trial Identifier	NCT04353284	NCT04374019
Phase & Intention	Phase 2, to evalate the effect of camostat mesylate on COVID-19 infection in ambulatory patients	See Table 3.7-1: Hydroxychloroquine (Plaquenil®)
Study design	RCT, quadruple blind, placebo controlled, parallel assignment	See Table 3.7-1: Hydroxychloroquine (Plaquenil®)
Status trial	Recruiting	See Table 3.7-1: Hydroxychloroquine (Plaquenil®)
Duration/ End of Study	Study start: April 30, 2020 Estimated Primary Completion Date: May 31, 2021 Estimated Study Completion Date: May 31, 2021	See Table 3.7-1: Hydroxychloroquine (Plaquenil®)
Study details	N of pts: 114 Location/ centres: not provided Intervention/control: Camostat mesylate 200mg taken 7 days/ Placebo Duration of observation/follow-up: up to 1 year Primary end point(s): Change in SARS-COV-2 viral load [Time Frame: 2 days] Secondary endpoints: Change in SARS-COV-2 viral load, in positive COVID-19 status, in symptom severity, in symptom frequency, in body temperature, Time to clinical improvement	See Table 3.7-1: Hydroxychloroquine (Plaquenil®)
Results	N.A.	See Table 3.7-1: Hydroxychloroquine (Plaquenil®)

3.8 APN01/ Recombinant Human Angiotensin-converting Enzyme 2 (rhACE2)

Drug under consideration

APN01 is a recombinant human Angiotensin Converting Enzyme 2 (rhACE2) developed by Apeiron Biologics under Phase 2 clinical development in ALI (Acute Lung Injury) and PAH (Pulmonal arterial hypertension) [98]. ACE2 was identified as the functional SARS-CoV receptor in vivo [99]. The receptor binding domain (RBD) of SARS-CoV-2 is similar to the SARS-CoV RBD, indicating a possible common host cell receptor. Recently, ACE2 has been shown to be the cellular entry receptor for the novel coronavirus SARS-CoV-2. The rhACE 2 docks at the spike proteins on the surface of the Covid-19 virus, and thus prevents the virus from attaching to the cells. Treatment with rHACE2 could be used to not only obstruct viremia but also protect lungs from injury [100].

The therapy with APN01 is currently not approved by the European Medicine Agency (EMA) and Food and Drug Administraion (FDA) for COVID-19.

Ongoing studies

The search in two clinical trial registers (humans only) yielded no completed study on the safety and efficacy of RVD in COVID-19 patients. One ongoing phase 2 randomised controlled trial (RCT) to assess clinical efficacy of rhACE2/APN01 using a composite outcome of all cause-death or need of invasive mechanical ventilationas was identfied (NCT04335136, 2020-001172-15). The estimated completion date of the trial is in November 2020. Table 3.8-1 displays more details of the identified ongoing trials.

Until May 12, 2020, one RCT number NCT04287686 is visible as withdrawn (without CDE Approval), and it is not listed here.

Results of publications

Until May 12, 2020, no relevant finished publications or finished trials assessing the efficacy and safety could be identified. First results can be expected on the 10th of November 2020 (NCT04335136).

Table 3.8-1: ***APN01*** *in clinical trial registry*

Active substance	APN01/Recombinant Human Angiotensin-converting Enzyme 2 (rhACE2)
Sponsor/Collaborator	Apeiron Biologics
Mechanism of operation	Antiviral entry inhibitor (recombinant human Angiotensin Converting Enzyme 2 – rhACE2)
Regulatory status EMA/FDA	**EMA:** Not approved for the use of COVID-19 **FDA**: Not approved for the use of COVID-19
Trial Identifier	NCT04335136 https://clinicaltrials.gov/ct2/show/NCT04335136?term=apeiron&draw=2&rank=1
Phase & Intention	Phase 2 study to assess clinical efficacy of rhACE2 /APN01 in COVID-19 patients using a composite outcome of all cause-death or need of invasive mechanical ventilationas
Study design	Randomised, double-blind, placebo-controlled, multicentre study (Parallel assignment)
Status trial	Not yet recruiting
Duration/End of Study	~7 months / Start: April 2020 Primary completion date: September, 2020 Study completion date: November, 2020
Study details	
Number of Patients	n = 200
Location/Centres	Austria, Denmark, Germany / 7 study locations (Multicentre)
Intervention	Patients will be treated with **rhACE2/APN01** intravenously twice daily (n = NR)
Controls	Patients will be treated with **placebo** intravenously twice daily (n = NR)
Duration of observation/Follow-up (Current Primary Outcome Measures)	28 days
Endpoints (Current Primary Outcome Measures)	Cause of death or invasive mechanical ventilation
Results/Publication	Not provided

NR = Not reported, rhACE2 = Recombinant Human Angiotensin-converting Enzyme 2

3.9 Tocilizumab (Roactemra®)

Drug under consideration

Tocilizumab (*RoActemra*) is a human monoclonal antibody that specifically binds to soluble and membrane-bound interleukin (IL)-6 receptors (IL-6Rα), and inhibits IL-6-mediated signalling [101]. It is licensed in the EU for treating:

- rheumatoid arthritis in adults
- giant cell arteritis in adults
- active systemic juvenile idiopathic arthritis in patients aged ≥2 years
- juvenile idiopathic polyarthritis in patients aged ≥2 years
- chimeric antigen receptor (CAR) T cell-induced severe or life-threatening cytokine release syndrome (CRS) in patients aged ≥2 years [101].

When used to treat CRS, it is given as a 60-minute intravenous (IV) infusion in a dose of 8mg/kg (in patients weighing ≥30kg) or 12mg/kg (in patients weighing <30kg), to a maximum of 800mg per infusion [101]. Up to three additional doses of *RoActemra* may be administered, 8 hourly. When treating other

conditions (stated above), *RoActemra* can be administered by subcutaneous (SC) injection or IV infusion [101].

Tocilizumab is being investigated as a possible treatment for patients with moderate to severe or critical COVID-19.

Most cases of COVID-19 are mild (81%), and patients' symptoms are usually self-limiting with recovery in two weeks [102]. However, some patients develop severe symptoms and progress rapidly, experiencing acute respiratory distress syndrome and septic shock, eventually ending in multiple organ failure [102]. It has been reported that most patients with COVID-19 have increased concentrations of IL-6, C-reactive protein (CRP) and erythrocyte sedimentation rate [103]. However, severely affected patients appear to have even higher plasma levels of pro-inflammatory cytokines and experience severe cytokine storm including features of CRS [103, 104]. It has previously been suggested that IL-6 might play a role in the pathogenesis of SARS and MERS, other diseases caused by coronaviruses [104]. It is thought that neutralisation of the inflammatory pathway induced by IL-6 may reduce mortality.

Ongoing studies

The search in two clinical trial registers (humans only) in April 2020 yielded no completed study on the safety and efficacy of tocilizumab in COVID-19 patients.

There are 16 studies on-going or planned.

One multicentre phase IV randomised controlled trial (RCT), to test the safety and effectiveness of individually or simultaneously blocking IL-6 and IL-1 versus standard of care on blood oxygenation and systemic CRS in patients with COVID-19 coronavirus infection and acute hypoxic respiratory failure and systemic CRS, is due to start recruiting in Belgium in April 2020 (NCT04330638; COV-AID). It will have five active treatment arms, including monotherapy with IV tocilizumab, SC anakinra (an IL-1 inhibitor) and SC siltuximab (an IL-6 inhibitor), and combination therapy with tocilizumab plus either anakinra or siltuximab. The estimated completion date is December 2020.

A double-blind phase III RCT (NCT04320615; COVACTA; 2020-001154-22) to evaluate the efficacy, safety, pharmacodynamics, and pharmacokinetics of IV tocilizumab versus placebo in combination with standard of care (SOC) in 330 adults hospitalised with severe COVID-19 pneumonia was due to start on the 3rd of April. It has an estimated completion date of September 2021.

There are nine phase II trials assessing the efficacy of one or two doses of IV or SC tocilizumab.

- A double-blind placebo-controlled RCT (NCT04335071; CORON-ACT), due to start in Switzerland in April 2020, has a completion date of October 2020.
- The open-label COPERNICO RCT (NCT04335305) will evaluate the efficacy of tocilizumab combined with pembrolizumab compared to standard care in 24 adults with COVID-19 pneumonia and bad prognostic factors who are nonresponsive to frontline therapy within 48 hours from treatment initiation. It has yet to start recruiting, and has an estimated completion date of May 15, 2020.
- Another open-label RCT (NCT04333914; IMMUNONCOVID) will compare the efficacy of a single IV infusion of tocilizumab with a chloroquine analog (GNS561), an anti PD-1 (nivolumab) versus standard of care in patients with advanced or metastatic cancer who have Sars-CoV-2 infection not eligible to a resuscitation unit. It is due to start in April 2020 in France, and complete in August 2020.
- An RCT (NCT04331808; CORIMUNO-TOC) is recruiting patients with moderate or severe pneumonia associated with COVID-19 requiring no mechanical ventilation or critical pneumonia requiring mechanical ventilation. The estimated completion date is December 2021.
- TOCIVID is an open-label RCT due to start on the 4th of April with an estimated completion date in June 2021 (NCT04322773). This study will compare the effect of single doses of either one of three IL-6 inhibitors (SC tocilizumab, IV tocilizumab and SC sarilumab) with standard of care,

on time to independence from supplementary oxygen therapy, measured in days from baseline to day 28, in patients with severe SARS-CoV-2 pneumonia.

- An open-label RCT, TOCOVID (NCT04332094), and are recruiting in Spain and Italy, respectively. The first is a randomised trial and will assess use of tocilizumab in combination with hydroxychloroquine and azithromycin; it is due to complete October 2020.
- Three single-arm studies are planned. The first, TOCIVID-19, is recruiting in Italy (NCT04317092; 2020-001110-38), with an estimated completion date of 19th December 2022. COVIDOSE is recruiting in the US (NCT04331795) and recruiting 50 hospitalised, non-critically ill patients with COVID-19 pneumonitis with clinical risk factors for clinical decompensation, intensive care utilisation, and death. It is due to start April 2020, and finish in December 2020. The third study (NCT04315480) has finished recruiting and is due to complete in May 2020.

In addition, there are three further trials for which the phase is not stated. TOSCA (NCT04332913) is a prospective open-label study assessing tocilizumab efficacy and safety in 30 adults with COVID-19 complicated by acute distress respiratory syndrome and CRS. A three-arm active-comparator RCT will compare tocilizumab plus favipiravir, favipiravir monotherapy and tocilizumab monotherapy in China (NCT04310228). The TACOS trial, a retrospective observational cohort trial, is recruiting in China and comparing the efficacy and safety of tocilizumab and continuous renal replacement therapy in management of CRS triggered by COVID-19 (NCT04306705). Their estimated completion dates are March 2021, May 2020 and June 2020, respectively.

Table 3.9-1 displays more details of these 14 identified on-going trials.

A further two studies were identified but they are not included in Table 3.9-1:

1. ChiCTR2000029765 – A multicenter, randomized controlled trial for the efficacy and safety of tocilizumab in the treatment of new coronavirus pneumonia (COVID-19)
2. 2020-001386-37 – Uno studio randomizzato multicentrico in aperto per valutare l'efficacia della somministrazione precoce del Tocilizumab (TCZ) in pazienti affetti da polmonite da COVID-19.

Until May 11, 2020, 11 new ongoing RCTs were found in ClinicalTrials.gov and EudraCT registers; nine from Europe, one from Israel and one from US, in patients with severe COVID-19 pneumonia or for the treatment of Cytokine Release Syndrome. Details could be found in Table 3.9-1.

Results of publications

Until May 10, 2020 no relevant publications or finished RCTs assessing the efficacy and safety could be identified, except for two retrospective reports describing the experience of using tocilizumab in severe or critical COVID-19 patients [105] (found through searching the reference list in paper 4) [106] and one prospective series on 100 patients [107].

A retrospective analysis of data from 20 patients who received one of two doses of IV tocilizumab 400mg showed 15 (75%) had lowered their oxygen intake and one patient need no oxygen therapy. CT scans showed lung lesion opacity absorbed in 19 patients (90.5%). The percentage of lymphocytes in peripheral blood, which decreased in 85.0% patients (17/20) before treatment (mean, 15.52 ± 8.89%), returned to normal in 52.6% patients (10/19) on the fifth day after treatment. Abnormally elevated CRP decreased significantly in 84.2% patients (16/19). No adverse reactions were observed [105].

Luo et al. 2020 [106]retrospectively assessed the demographic, treatment, laboratory parameters of C-reactive protein (CRP) and IL-6 before and after therapy and clinical outcome in the 15 COVID-19 patients treated with tocilizumab (in 8 patients in combination with methylprednisolone). Two of them were moderately ill, six were seriously ill and seven were critically ill. Out of four patients who failed treatment, three patients had lethal outcome. Serum IL-6 level tended to further spiked firstly and then decreased after tocilizumab therapy in 10 patients. Authors concluded that tocilizumab appears to be an effective treatment option in COVID-19 patients with a risk of cytokine storms.

Toniati et al. 2020 [107] presented results of a prospective series of 100 consecutive patients in Italy with confirmed COVID-19 pneumonia and ARDS requiring ventilatory support to determine whether intravenous administration of tocilizumab was associated with improved outcome. Overall at 10 days, the respiratory condition was improved or stabilized in 77 (77%) patients; 61 showed a significant clearing of diffuse bilateral opacities on chest x-ray. 15 patients were discharged from the hospital. Respiratory condition worsened in 23 (23%) patients, of whom 20 (20%) died. During the 10-day follow-up, three cases of severe adverse events were recorded: two patients developed septic shock and died, one had gastrointestinal perforation requiring urgent surgery and was alive at day 10. Authors concluded that response to tocilizumab was rapid, sustained, and associated with significant clinical improvement.

*Table 3.9-1: **Tocilizumab** in clinical trial registry*

Active substance	Tocilizumab IV Tocilizumab IV plus anakinra SC	Tocilizumab IV	Tocilizumab IV	Tocilizumab IV plus pembrolizumab IV	Tocilizumab IV
Sponsor/Collaborator	University Hospital, Ghent	Hoffmann-La Roche	University Hospital Inselspital, Berne	MedSIR	Centre Leon Berard
Mechanism of operation	IL-6 inhibitor +/- IL-1 inhibitor	IL-6 inhibitor	IL-6 inhibitor	IL-6 inhibitor + PD-1 monoclonal antibody	IL-6 inhibitor
Regulatory status EMA/FDA	**EMA:** RoActemra is approved for IV or SC administration for treating: • Severe, active and progressive RA in adults not previously treated with MTX • Moderate to severe active RA in adults who have responded inadequately to, or who were intolerant to, previous DMARDs or TNF antagonists. • Active systemic juvenile idiopathic arthritis in patients aged ≥2 years, who have responded inadequately to previous NSAIDs and systemic corticosteroids. • Juvenile idiopathic polyarthritis in patients aged ≥2 years, who have responded inadequately to previous MTX. • Chimeric antigen receptor T cell-	**EMA:** RoActemra is approved for IV or SC administration for treating: • Severe, active and progressive RA in adults not previously treated with MTX • Moderate to severe active RA in adults who have responded inadequately to, or who were intolerant to, previous DMARDs or TNF antagonists. • Active systemic juvenile idiopathic arthritis in patients aged ≥2 years, who have responded inadequately to previous NSAIDs and systemic corticosteroids. • Juvenile idiopathic polyarthritis in patients aged ≥2 years, who have responded inadequately to previous MTX. • Chimeric antigen receptor T cell-induced severe or life-threatening CRS in patients aged ≥2 years (initial 15/01/2009). **FDA:** Actemra is approved for IV or SC administration for treating: • Adult patients with moderately to severely active RA who have had an inadequate response to one or more DMARDs. • Adult patients with giant cell arteritis.	**EMA:** RoActemra is approved for IV or SC administration for treating: • Severe, active and progressive RA in adults not previously treated with MTX • Moderate to severe active RA in adults who have responded inadequately to, or who were intolerant to, previous DMARDs or TNF antagonists. • Active systemic juvenile idiopathic arthritis in patients aged ≥2 years, who have responded inadequately to previous NSAIDs and systemic corticosteroids. • Juvenile idiopathic polyarthritis in patients aged ≥2 years, who have responded inadequately to previous MTX. • Chimeric antigen receptor T cell-induced severe or life-threatening CRS in patients aged ≥2 years (initial 15/01/2009).	**EMA:** RoActemra is approved for IV or SC administration for treating: • Severe, active and progressive RA in adults not previously treated with MTX • Moderate to severe active RA in adults who have responded inadequately to, or who were intolerant to, previous DMARDs or TNF antagonists. • Active systemic juvenile idiopathic arthritis in patients aged ≥2 years, who have responded inadequately to previous NSAIDs and systemic corticosteroids. • Juvenile idiopathic polyarthritis in patients aged ≥2 years, who have responded inadequately to previous MTX. • Chimeric antigen receptor T cell-	**EMA:** RoActemra is approved for IV or SC administration for treating: • Severe, active and progressive RA in adults not previously treated with MTX • Moderate to severe active RA in adults who have responded inadequately to, or who were intolerant to, previous DMARDs or TNF antagonists. • Active systemic juvenile idiopathic arthritis in patients aged ≥2 years, who have responded inadequately to previous NSAIDs and systemic corticosteroids. • Juvenile idiopathic polyarthritis in patients aged ≥2 years, who have responded inadequately to previous MTX. • Chimeric antigen receptor T cell-induced severe or life-threatening CRS in patients aged ≥2 years (initial 15/01/2009). **FDA:** Actemra is approved for IV or SC administration for treating: • Adult patients with moderately to severely active RA who have had an inadequate response to one or more DMARDs. • Adult patients with giant cell arteritis.

Active substance	Tocilizumab IV Tocilizumab IV plus anakinra SC	Tocilizumab IV	Tocilizumab IV	Tocilizumab IV plus pembrolizumab IV	Tocilizumab IV
	induced severe or life-threatening CRS in patients aged ≥2 years (initial 15/01/2009). **FDA:** Actemra is approved for IV or SC administration for treating: • Adult patients with moderately to severely active RA who have had an inadequate response to one or more DMARDs. • Adult patients with giant cell arteritis. • Patients aged ≥2 years with active polyarticular juvenile idiopathic arthritis. Systemic Juvenile Idiopathic Arthritis. • Patients aged ≥2 years with active systemic juvenile idiopathic arthritis. • Adults and pediatric patients aged ≥2 years with chimeric antigen receptor T cell-induced severe or life-threatening CKS (initial 01/08/2010).	• Patients aged ≥2 years with active polyarticular juvenile idiopathic arthritis. Systemic Juvenile Idiopathic Arthritis. • Patients aged ≥2 years with active systemic juvenile idiopathic arthritis. • Adults and pediatric patients aged ≥2 years with chimeric antigen receptor T cell-induced severe or life-threatening CKS (initial 01/08/2010).	**FDA:** Actemra is approved for IV or SC administration for treating: • Adult patients with moderately to severely active RA who have had an inadequate response to one or more DMARDs. • Adult patients with giant cell arteritis. • Patients aged ≥2 years with active polyarticular juvenile idiopathic arthritis. Systemic Juvenile Idiopathic Arthritis. • Patients aged ≥2 years with active systemic juvenile idiopathic arthritis. • Adults and pediatric patients aged ≥2 years with chimeric antigen receptor T cell-induced severe or life-threatening CKS (initial 01/08/2010).	induced severe or life-threatening CRS in patients aged ≥2 years (initial 15/01/2009). **FDA:** Actemra is approved for IV or SC administration for treating: • Adult patients with moderately to severely active RA who have had an inadequate response to one or more DMARDs. • Adult patients with giant cell arteritis. • Patients aged ≥2 years with active polyarticular juvenile idiopathic arthritis. Systemic Juvenile Idiopathic Arthritis. • Patients aged ≥2 years with active systemic juvenile idiopathic arthritis. • Adults and pediatric patients aged ≥2 years with chimeric antigen receptor T cell-induced severe or life-threatening CKS (initial 01/08/2010).	• Patients aged ≥2 years with active polyarticular juvenile idiopathic arthritis. Systemic Juvenile Idiopathic Arthritis. • Patients aged ≥2 years with active systemic juvenile idiopathic arthritis. • Adults and pediatric patients aged ≥2 years with chimeric antigen receptor T cell-induced severe or life-threatening CKS (initial 01/08/2010).
Trial Identifier	NCT04330638 (COV-AID)	NCT04320615 (COVACTA) 2020-001154-22	NCT04335071 (CORON-ACT)	NCT04335305 (COPERNICO)	NCT04333914 (IMMUNONCOVID)
Phase & Intention	Phase IV study is to test the safety and effectiveness of individually or	Phase III study to evaluate the efficacy, safety, pharmacodynamics, and pharmacokinetics of tocilizumab compared with a matching placebo in	Phase II study to evaluate whether treatment with tocilizumab reduces the	Phase II study to evaluate the efficacy of tocilizumab combined with pembrolizumab (MK-	Phase II study to compare the efficacy of a chloroquine analog (GNS561), an anti PD-1 (nivolumab) and an anti-IL-6 receptor

Active substance	Tocilizumab IV Tocilizumab IV plus anakinra SC	Tocilizumab IV	Tocilizumab IV	Tocilizumab IV plus pembrolizumab IV	Tocilizumab IV
	simultaneously blocking IL-6 and IL-1 versus SOC on blood oxygenation and systemic CRS in patients with COVID-19 coronavirus infection and acute hypoxic respiratory failure and systemic CRS.	combination with SOC in hospitalised patients with severe COVID-19 pneumonia.	severity and mortality in patients with COVID-19.	3475) compared to SOC in adult patients with COVID-19 pneumonia and bad prognostic factors who are nonresponsive to frontline therapy within 48 hours from treatment initiation.	(tocilizumab) versus SOC in patients with advanced or metastatic cancer who have Sars-CoV-2 infection not eligible to a resuscitation unit. According to severity level at time of enrolment, eligible patients will be randomised into 2 cohorts: • COHORT 1 (mild symptoms or asymptomatic): GNS561 vs anti-PD1 vs SOC (ratio 1:1:1). • COHORT 2 (moderate/severe symptoms): GNS561 vs anti-IL6 vs SOC (ratio 1:1:1).
Study design	Open-label, six-arm active-comparator RCT.	Double-blind, randomised placebo-controlled trial.	Double-blind randomised placebo-controlled trial.	Open-label RCT trial.	Open-label, active-comparator RCT.
Status trial	Not yet recruiting..due to start April 2020	Not yet recruiting..due to start April 3, 2020.	Not yet recruiting..due to start April, 2020.	Not yet recruiting..due to start March 30, 2020.	Not yet recruiting..due to start April 2020.
Duration/End of Study	Estimated Primary Completion Date: September 2020 Estimated Study Completion Date: December 2020	Estimated Primary Completion Date: August 31, 2021 Estimated Study Completion Date: September 30, 2021	Estimated Primary Completion Date: October 2020 Estimated Study Completion Date: October 2020	Estimated Primary Completion Date: May 15, 2020 Estimated Study Completion Date: May 15, 2020	Estimated Primary Completion Date: June 2020 Estimated Study Completion Date: August 2020
Study details					
Number of Patients	n = 342 (Child, Adult, Older Adult; 8 Years to 80 Years)	n = 330 (Adult, Older Adult; 18 Years and older)	n = 100 (Adult, Older Adult; 30 Years to 80 Years)	n = 24 (Adult, Older Adult; 18 Years and older)	n = 273 (Adult, Older Adult; 18 Years and older)
Location/Centres	Belgium	Not yet stated	Switzerland	Not yet stated	France
Intervention	• Tocilizumab – single IV infusion at a dose of 8mg/kg with max infusion of 800mg/injection • Anakinra – daily SC injection of 100mg for 28 days or until hospital discharge, whichever is first	Tocilizumab – Participants will receive 1 dose of IV tocilizumab. 1 additional dose may be given if clinical symptoms worsen or show no improvement.	Tocilizumab – patients get one dose (= 8mg/kg bodyweight, max. single dose 800mg) IV in 100 mL NaCl 0.9% after confirmation of progressive dyspnoea. Infusion time: 60 min. The procedure is repeated once if no clinical improvement in the 8-point WHO scale is observed.	• Toclizumab IV infusion over 60 minutes; 8mg/kg (up tomax 800mg per dose); single dose. • Pembrolizumab IV infusion over 30 minutes, 200mg; single dose Patients showing no clinical improvement in respiratory function after	• Chloroquine analog (GNS651) ○ Cohort 1 (arm B): 200mg bid loading dose for 2 days then, 200 qd orally for 14 consecutive days. ○ Cohorte 2 (arm E): 200mg bid loading dose for 2 days then, 200 qd/day orally, per os, for 14 consecutive days. • Nivolumab ○ Cohorte 1 (arm C): 0.3mg/Kg IV, single infusion at Day 1. IV

Active substance	Tocilizumab IV Tocilizumab IV plus anakinra SC	Tocilizumab IV	Tocilizumab IV	Tocilizumab IV plus pembrolizumab IV	Tocilizumab IV
	• Siltuximab – single IV infusion at a dose of 11mg/kg • Tocilizumab – single IV infusion at a dose of 8mg/kg with max infusion of 800mg/injection PLUS anakinra – daily SC injection of 100mg for 28 days or until hospital discharge, whichever is first • Siltuximab – single IV infusion at a dose of 11 mg/kg PLUS anakinra – daily SC injection of 100 mg for 28 days or until hospital discharge, whichever is first			12 hours could receive an additional dose of tocilizumab at the same dose level of the first administration. Patients who are showing SpO2 ≤ 94% on room air could receive an additional administration of pembrolizumab at the same recommended dose after 3 weeks from treatment initiation and/or an additional dose of tocilizumab after 4 weeks from treatment initiation at physician's discretion.	infusion over 60 minutes; 8mg/kg (up to max 800mg per dose); single dose. • Tocilizumab ○ Cohorte 2 (arm F): 400mg flat dose IV, single infusion at Day 1.
Controls	Usual care	Placebo – Participants will receive 1 dose of IV placebo matched to tocilizumab. Up to 1 additional dose may be given if clinical symptoms worsen or show no improvement.	Placebo – The placebo-controlled intervention is one dose (100 mL) NaCl 0.9% IV administered after confirmation of progressive dyspnoea. Infusion time: 60 min. The procedure is repeated once if no clinical improvement in the 8-point WHO scale is observed.	SOC – as per local written policies or guidelines comprises, as necessary and at physician's discretion, supplemental oxygen, non-invasive and invasive ventilation, antibiotic agents, vasopressor support, renal-replacement therapy, glucocorticoid, tocilizumab, virally targeted agents, chloroquine or hydroxychloroquine.	SOC. In cohorts 1 and 2, patients in the SOC arms should receive best supportive care, as per investigator's discretion and local routine practices. With regards to respiratory symptoms and medical resoures at investigational site, the following should be given acc. to patient's condition: oxygen, invasive/non-invasive ventilation, antibiotherapy, vasopressor support, renal replacement therapy, or extracorporeal membrane oxygenation. Additional care and medications should be administered in the patient's best interest.
Duration of observation/Follow-up	Up to 15 days	Up to 28 days	Up to 28 days	Up to 14 days	Up to 28 days

Active substance	Tocilizumab IV Tocilizumab IV plus anakinra SC	Tocilizumab IV	Tocilizumab IV	Tocilizumab IV plus pembrolizumab IV	Tocilizumab IV
(Current Primary Outcome Measures)					
Endpoints (Current Primary Outcome Measures)	Time to Clinical Improvement at day 15	Clinical Status Assessed Using a 7-Category Ordinal Scale at day 28	1. Number of patients with ICU admission at 7 days. 2. Number of patients with intubation at 14 days. 3. Number of patients with death at 28 days.	Percentage of patients with normalization of SpO2 ≥96% through day 14	28-day survival rate
Results/Publication	Not provided	Not provided	Not provided	Not provided	Not provided

CRS = cytokine release syndrome; DMARD = disease modifying anti-rheumatic drug; IL = interleukin; IV = intravenous; MTX = methotrexate; RCT = randomised controlled trial; RA = rheumatoid arthritis; SC = subcutaneous; SOC = standard of care; TNF = tumour necrosis factor

*Table 3.9-1: **Tocilizumab** in clinical trial registry (Continued)*

Active substance	**Tocilizumab**	**Tocilizumab**	**Tocilizumab**	**Tocilizumab**
Sponsor	Azienda Unità Sanitaria Locale Reggio Emilia	Hadassah Medical Organization	Emory University	The Parker Institute, Bispebjerg and Frederiksberg Hospital, The Capital Region of Denmark
Trial Identifier	NCT04346355	NCT04377750	NCT04361552	2020-001275-32
Phase & Intention	Phase 2, assessing whether early administration of tocilizumab compared to late administration of tocilizumab can reduce the number of patients with COVID-19 pneumonia who require mechanical ventilation	Phase 4, to test the hypothesis that anti-IL6 treatment can be effective in reducing the virus-induced cytokine storm, blocking deterioration of lung function or even promoting a rapid improvement of clinical conditions, preventing tracheal intubation and/or death	Phase 3, for the treatment of Cytokine Release Syndrome in patients with COVID-19 (SARS-CoV-2 infection)	Phase II, to investigate the effect of different types of IL-6 inhibition versus no adjuvant treatment compared to standard of care in patients with severe SARS-CoV-2 pneumonia
Study design	RCT, open-label, active comparator, parallel assignment	RCT, open-label, placebo-controled, parallel assignment	RCT, open-label, standard of care controled, parallel assignment	RCT, open-label, multicenter, sequential trial
Status trial	Recruiting	Recruiting	Recruiting	Ongoing
Duration/ End of Study	Study start: March 31, 2020 Estimated Primary Completion Date: May 30, 2020 Estimated Study Completion Date: May 30, 2020	Study start: April 8, 2020 Estimated Primary Completion Date: April 29, 2020 Estimated Study Completion Date: May 8, 2021	Study start: May 30, 2020 Estimated Primary Completion Date: May 30, 2022 Estimated Study Completion Date: May 30, 2022	Study start: 03/04/2020 Estimated Primary Completion Date: NA Estimated Study Completion Date: NA
Study details	N of pts: 398 Location/ centres: Italy Intervention/control: tocilizumab within 8 hours from entering the study + standard of care; 8 mg/kg IV up to a maximum of 800 mg with repetition of the same dosage after 12 hours / Standard of care; In the event of aggravation of COVID-19 pneumonia, according to protocol criteria, participants will receive tocilizumab 8 mg/kg IV up to a maximum of 800 mg with repetition of the same dosage after 12 hours Duration of observation/follow-up: 2 weeks	N of pts: 500 Location/ centres: Israel Intervention/control: Tocilizumab 8 mg/kg up to total dose of 800 mg / 100 ml of normal saline Duration of observation/follow-up: 1 month Primary end point(s): Survival [Time frame: One-month] Secondary endpoints: Not provided	N of pts: 180 Location/ centres: US Intervention/control: tocilizumab IV every 12 hours for up to 3 doses in the absence of disease progression or unacceptable toxicity and standard of care / Standard of care Duration of observation/follow-up: Up to 2 years Primary end point(s): 7-day length of invasive mechanical ventilation (MV) [Time frame: Up to 7 days]; 30-day	N of pts: 200 Location/ centres: Denmark Intervention/control: Tocilizumab; Sarilumab/Usual care Duration of observation/follow-up: Up to 28 days Primary end point(s): Time to independence from supplementary oxygen therapy in days Secondary endpoints: Number of deaths; Days out of hospital and alive at 28-day follow-up; Time to critical illness rate of

Active substance	Tocilizumab	Tocilizumab	Tocilizumab	Tocilizumab
	Primary end point(s): Entry into Intensive Care with invasive mechanical ventilation or death from any cause or clinical aggravation [Time frame: two weeks from participants' allocation to study arm] Secondary endpoints: Death from any cause, Tocilizumab toxicity, Levels of interleukin-6 and C-reactive protein (CRP) and their correlation with the effectiveness of the treatment, Evaluate the progress of the PaO2 / FiO2 ratio, Evaluate the trend over time of the lymphocyte count		mortality rate [Time frame: Up to 30-day after randomization] Secondary endpoints: Rate of intensive care (ICU) transfer, Rate of invasive mechanical ventilation, Rate of tracheostomy, Length of ICU stay, Length of hospital stay	subjects defined as requiring mechanical respiratory support (time frame: during treatment, 14 days, 28 days); C-reactive protein (CRP) level (time frame: baseline, peak during treatment, 14 days, 28 days); number of participants with treatment-related side effects as assessed by Common Terminology Criteria for Adverse Event (CTCAE) (time frame: during treatment, 14 days, 28 days)
Results	N.A.	N.A.	N.A.	N.A.

*Table 3.9-1: **Tocilizumab** in clinical trial registry (Continued)*

Active substance	Tocilizumab	Tocilizumab	Tocilizumab	Tocilizumab	Tocilizumab
Sponsor	CHU AMBROISE PARE	Fundación para la Investigación Biomédica del Hospital Universitario Ramón y Cajal	Universitätsklinikum Freiburg	University Hospital Ghent	Fundació Hospital Universitari Vall d'Hebron - Institut de Recerca (VHIR)
Trial Identifier	2020-001770-30	2020-002032-69	2020-001408-41	2020-001500-41	2020-001437-12
Phase & Intention	Phase II, to evaluate the safety and efficacy of the tocilizumab (Roactemra®) in hospitalized adults diagnosed with COVID-19	Phase II, to assess the impact of administering two different tocilizumab regimens versus the standard of care on IL-12 levels in patients with non-severe COVID-19 pneumonia	Phase II, to evaluate the efficacy and safety of tocilizumab in patients with severe COVID-19 pneumonia	Phase III, to compare the safety and efficacy of combinations of blockade of interleukin-6 pathway and interleukin-1 pathway to best standard of care in improving oxygenation and short- and long-term outcome of COVID-19 patients with acute hypoxic respiratory failure and systemic cytokine release syndrome	Phase IV, to assess the mortality impact at 28 days of an immunomodulatory strategy with 2 treatment regimens stratified according to IL-6 plasma levels, administered in addition to standard treatment, in adult patients with severe COVID-19 pneumonia
Study design	RCT, open-label, standard pf care comparator	RCT, open-label, standard pf care comparator	RCT, double-blind, placebo controlled	RCT, active and standard of care comparator, factorial design	RCT, open-label, active comparator, parallel assignment
Status trial	Ongoing	Ongoing	Ongoing	Ongoing	Ongoing
Duration/ End of Study	Study start: 21/04/2020	Study start: 04/05/2020	Study start: 21/04/2020	Study start: 03/04/2020	Study start: 09/04/2020 Estimated Primary Completion Date: NA

Active substance	**Tocilizumab**	**Tocilizumab**	**Tocilizumab**	**Tocilizumab**	**Tocilizumab**
	Estimated Primary Completion Date: NA Estimated Study Completion Date: NA	Estimated Primary Completion Date: NA Estimated Study Completion Date: NA	Estimated Primary Completion Date: NA Estimated Study Completion Date: NA	Estimated Primary Completion Date: NA Estimated Study Completion Date: NA	Estimated Study Completion Date: NA
Study details	N of pts: 60 Location/ centres: Belgium Intervention/control: Tocilizumab/Standard of care Duration of observation/follow-up: Primary end point(s): Clinical status assessed using a 7-category ordinal scale at Day 28 Secondary endpoints: Time to clinical improvement (TTCI) defined as a National Early Warning Score 2 (NEWS2) of ≤ 2 maintained for 24 hours; Time to improvement of at least 2 categories relative to baseline on a 7-category ordinal scale of clinical status; Incidence of mechanical ventilation; Ventilator-free days to Day 28; Organ failure-free days to Day 28; Incidence of intensive care unit (ICU) stay; Duration of ICU stay; Mortality rate up to 90 days; Time to hospital discharge or "ready for	N of pts: 78 Location/ centres: Spain Intervention/control: Tocilizumab/Standard of care Duration of observation/follow-up: 28 days Primary end point(s): Mean increase in IL-12 levels in the 3 study groups from the start of treatment (D0) to days D+1 and D+3 Secondary endpoints: Percentage of patients per group with cure/improvement/progression of pneumonia at D+3, D+7, and D+28; Proportion of patients with PaO2/FiO2 <300 (or SatO2/FiO2 ≤315) at some point over their course; All-cause mortality throughout 28 days; Length of hospital stay; Percentage of patients requiring ICU admission; Length of ICU stay; IL-12 levels at D+7; IL-10, IL-1, IL-6, IL-17 and IFN-gamma levels at D0, D+1, D+3 and D+7; IL-6, procalcitonin (PCT), C-reactive protein (CRP), D-dimer y ferritin levels at D0, D+1, D+3 and D+7; Pharmacokinetic	N of pts: 200 Location/ centres: Germany Intervention/control: Tocilizumab/Placebo Duration of observation/follow-up: 28 days, up tp 12 months Primary end point(s): Ventilator free days (d) (VFD) in the first 28 days after randomisation Secondary endpoints: 19 listed, among Mortality, Admission to intensive care unit, Days on ICU, Overall survival, QOL, AEs, SAEs	N of pts: 342 Location/ centres: Belgium Intervention/control: Anakirna; Tocilizumab; Siltuximab/Standard of care Duration of observation/follow-up: Up to 20 weeks post inclusion Primary end point(s): Time to clinical improvement (defined as the time from randomization to either an improvement of two points on a six-category ordinal scale measured daily till day 28 or discharge from the hospital or death) 1. Death 2. Hospitalized, on invasive mechanical ventilation or ECMO; 3. Hospitalized, on non-invasive ventilation or high flow oxygen devices; 4. Hospitalized, requiring supplemental oxygen 5. Hospitalized, not requiring supplemental oxygen 6. Not hospitalized Secondary endpoints: 32 listed, among All cause mortality, Ventilator-free days over 28 days from inclusion date, Duration of mechanical ventilation in ventilated patients, Duration of ICU stay in patients that	N of pts: 290 Location/ centres: Spain Intervention/control: Ciclosporin; Tocilizumab Duration of observation/follow-up: 28 days Primary end point(s): Mortality at day 28 after treatment initiation (proportion of patient died that day) Secondary endpoints: - Mortality at 48 hours, 7 days, at Intensive Care Unit and at hospital - Days with mechanical ventilation, days at Intensive Care Unit and days at hospital - Viral clearance (viral clearance / viral shedding) - Time until normal Oxygen saturation - Time until defervescence - Inflamatory reaction improvement (IL1b, IL12, IL2, TNFα, IFNγ, IL2Rs, IL6, Il10, ferritine, D-dimer, triglycerides, lymphopenia, protein C reactive, VSG) - Frequency and severity of adverse events according to common scales, proportion of patients drop-out due adverse events. Secondary infections. - Plasmatic parameters, direct or indirect: IL1b, IL12, IL2, TNFα, IFNγ, IL2Rs, IL6, Il10, ferritine, D-dimer, triglycerides, lymphopenia, protein C reactive, VSG) - Clinic Oxygenation parameters (PaO2, pulse oximetry) - Viral Clearance (viral clearance / viral

Active substance	**Tocilizumab**	**Tocilizumab**	**Tocilizumab**	**Tocilizumab**	**Tocilizumab**
	discharge" (as evidenced by normal body temperature and respiratory rate, and stable oxygen saturation on ambient air); - Duration of supplemental oxygen; Fever regression at day 2; CRP regression at day 5; Imaging regression at 72 hours	endpoints: Cmin, Cmax, Cmedia, Tmax and AUC on days D0, D + 1, D + 3 and D + 7; Serious and non-serious adverse events; Adverse events leading to treatment discontinuation; Number of deaths; Abnormalities in laboratory findings unrelated to COVID-19 disease		enrolled in trial while already on invasive or non-invasive mechanical ventilation, Time to progression to ARDS in ventilated patients, Incidence of AEs/SAEs during 28 days, Duration of hospital stay, Duration of hospital stay in survivors	shedding): PCR SARS-CoV-2 control - Standard Intensive Care Unit parameters: SOFA and APACHE II at hospitalisation, intubation day, mechanical ventilation withdrawal day, Intensive Care Unit discharge, Hospital discharge
Results	N.A.	N.A.	N.A.	N.A.	N.A.

*Table 3.9-1: **Tocilizumab** in clinical trial registry (Continued)*

Active substance	**Tocilizumab**	**Tocilizumab**
Sponsor	Assistance Publique - Hôpitaux de Paris	See Table 3.2-1: Lopinavir plus ritonavir
Trial Identifier	2020-001246-18	2020-001113-21 RECOVERY trial
Phase & Intention	Phase II/III, to determine which treatments (e.g. immune modulator drugs) have the most favourable benefit-risk in adult patients hospitalized with COVID-19	See Table 3.2-1: Lopinavir plus ritonavir
Study design	RCT, open-label, standard of care comparator, parallel assignment	See Table 3.2-1: Lopinavir plus ritonavir
Status trial	Ongoing	See Table 3.2-1: Lopinavir plus ritonavir
Duration/ End of Study	Study start: 25/03/2020 Estimated Primary Completion Date: NA Estimated Study Completion Date: NA	See Table 3.2-1: Lopinavir plus ritonavir
Study details	N of pts: 1000 Location/ centres: France Intervention/control: Sarilumab; Tocilizumab; Anakirna; Eculizumab; Baricitinib; Secukinumab; Bevacizumab; Hydroxychloroquine; Azithromycin/Standard of care Duration of observation/follow-up: Up to 90 days Primary end point(s): Survival without needs of ventilator utilization (including Non invasive ventilation) at day 14; OMS progression scale < or = 5 at day 4; Secondary endpoints: OMS progression scale at 4, 7 and 14 days, overall survival at 14, 28 and 90 days, time to discharge, time to oxygen supply independency, time to negative viral excretion; the 28-day ventilator free-days, respiratory acidosis at day 4; duration of hospitalization, time to negative viral excretion, time to ICU, different biological parameters improvement	See Table 3.2-1: Lopinavir plus ritonavir
Results	N.A.	See Table 3.2-1: Lopinavir plus ritonavir

*Table 3.9-2: **Tocilizumab** in clinical trial registry (Continued)*

Active substance	Tocilizumab IV	Tocilizumab IV and SC	Tocilizumab SC plus hydroxychloroquine and azithromycin	Tocilizumab	Tocilizumab
Sponsor/Collaborator	Assistance Publique - Hôpitaux de Paris	Frederiksberg University Hospital	Fundació Institut de Recerca de l'Hospital de la Santa Creu i Sant Pau	National Cancer Institute, Naples	University of Chicago
Mechanism of operation	IL-6 inhibitor	IL-6 inhibitor	IL-6 inhibitor + an antimalarial and macrolide antibiotic	IL-6 inhibitor	IL-6 inhibitor
Regulatory status EMA/FDA	**EMA:** RoActemra is approved for IV or SC administration for treating: • Severe, active and progressive RA in adults not previously treated with MTX • Moderate to severe active RA in adults who have responded inadequately to, or who were intolerant to, previous DMARDs or TNF antagonists. • Active systemic juvenile idiopathic arthritis in patients aged ≥2 years, who have responded inadequately to previous NSAIDs and systemic corticosteroids. • Juvenile idiopathic polyarthritis in patients aged ≥2 years, who have responded inadequately to previous MTX. • Chimeric antigen receptor T cell-induced severe or life-threatening CRS in patients aged ≥2 years (initial 15/01/2009). **FDA:** Actemra is approved for IV or SC administration for treating: • Adult patients with moderately to severely active RA who have had an	**EMA:** RoActemra is approved for IV or SC administration for treating: • Severe, active and progressive RA in adults not previously treated with MTX • Moderate to severe active RA in adults who have responded inadequately to, or who were intolerant to, previous DMARDs or TNF antagonists. • Active systemic juvenile idiopathic arthritis in patients aged ≥2 years, who have responded inadequately to previous NSAIDs and systemic corticosteroids. • Juvenile idiopathic polyarthritis in patients aged ≥2 years, who have responded inadequately to previous MTX. • Chimeric antigen receptor T cell-induced severe or life-	**EMA:** RoActemra is approved for IV or SC administration for treating: • Severe, active and progressive RA in adults not previously treated with MTX • Moderate to severe active RA in adults who have responded inadequately to, or who were intolerant to, previous DMARDs or TNF antagonists. • Active systemic juvenile idiopathic arthritis in patients aged ≥2 years, who have responded inadequately to previous NSAIDs and systemic corticosteroids. • Juvenile idiopathic polyarthritis in patients aged ≥2 years, who have responded inadequately to previous MTX. • Chimeric antigen receptor T cell-induced severe or life-	**EMA:** RoActemra is approved for IV or SC administration for treating: • Severe, active and progressive RA in adults not previously treated with MTX • Moderate to severe active RA in adults who have responded inadequately to, or who were intolerant to, previous DMARDs or TNF antagonists. • Active systemic juvenile idiopathic arthritis in patients aged ≥2 years, who have responded inadequately to previous NSAIDs and systemic corticosteroids. • Juvenile idiopathic polyarthritis in patients aged ≥2 years, who have responded inadequately to previous MTX. • Chimeric antigen receptor T cell-induced severe or life-	**EMA:** RoActemra is approved for IV or SC administration for treating: • Severe, active and progressive RA in adults not previously treated with MTX • Moderate to severe active RA in adults who have responded inadequately to, or who were intolerant to, previous DMARDs or TNF antagonists. • Active systemic juvenile idiopathic arthritis in patients aged ≥2 years, who have responded inadequately to previous NSAIDs and systemic corticosteroids. • Juvenile idiopathic polyarthritis in patients aged ≥2 years, who have responded inadequately to previous MTX. • Chimeric antigen receptor T cell-induced severe or life-threatening CRS in patients aged ≥2 years (initial 15/01/2009). **FDA:** Actemra is approved for IV or SC administration for treating: • Adult patients with moderately to severely active RA who have had an inadequate response to one or more DMARDs.

Active substance	Tocilizumab IV	Tocilizumab IV and SC	Tocilizumab SC plus hydroxychloroquine and azithromycin	Tocilizumab	Tocilizumab
	inadequate response to one or more DMARDs. • Adult patients with giant cell arteritis. • Patients aged ≥2 years with active polyarticular juvenile idiopathic arthritis. Systemic Juvenile Idiopathic Arthritis. • Patients aged ≥2 years with active systemic juvenile idiopathic arthritis. • Adults and pediatric patients aged ≥2 years with chimeric antigen receptor T cell-induced severe or life-threatening CKS (initial 01/08/2010).	threatening CRS in patients aged ≥2 years (initial 15/01/2009). **FDA:** Actemra is approved for IV or SC administration for treating: • Adult patients with moderately to severely active RA who have had an inadequate response to one or more DMARDs. • Adult patients with giant cell arteritis. • Patients aged ≥2 years with active polyarticular juvenile idiopathic arthritis. Systemic Juvenile Idiopathic Arthritis. • Patients aged ≥2 years with active systemic juvenile idiopathic arthritis. • Adults and pediatric patients aged ≥2 years with chimeric antigen receptor T cell-induced severe or life-threatening CKS (initial 01/08/2010).	threatening CRS in patients aged ≥2 years (initial 15/01/2009). **FDA:** Actemra is approved for IV or SC administration for treating: • Adult patients with moderately to severely active RA who have had an inadequate response to one or more DMARDs. • Adult patients with giant cell arteritis. • Patients aged ≥2 years with active polyarticular juvenile idiopathic arthritis. Systemic Juvenile Idiopathic Arthritis. • Patients aged ≥2 years with active systemic juvenile idiopathic arthritis. • Adults and pediatric patients aged ≥2 years with chimeric antigen receptor T cell-induced severe or life-threatening CKS (initial 01/08/2010).	threatening CRS in patients aged ≥2 years (initial 15/01/2009). **FDA:** Actemra is approved for IV or SC administration for treating: • Adult patients with moderately to severely active RA who have had an inadequate response to one or more DMARDs. • Adult patients with giant cell arteritis. • Patients aged ≥2 years with active polyarticular juvenile idiopathic arthritis. Systemic Juvenile Idiopathic Arthritis. • Patients aged ≥2 years with active systemic juvenile idiopathic arthritis. • Adults and pediatric patients aged ≥2 years with chimeric antigen receptor T cell-induced severe or life-threatening CKS (initial 01/08/2010).	• Adult patients with giant cell arteritis. • Patients aged ≥2 years with active polyarticular juvenile idiopathic arthritis. Systemic Juvenile Idiopathic Arthritis. • Patients aged ≥2 years with active systemic juvenile idiopathic arthritis. • Adults and pediatric patients aged ≥2 years with chimeric antigen receptor T cell-induced severe or life-threatening CKS (initial 01/08/2010).
Trial Identifier	NCT04331808 (CORIMUNO-TOC)	NCT04322773 (TOCIVID)	NCT04332094 (TOCOVID)	NCT04317092 (TOCIVID-19) 2020-001110-38	NCT04331795 (COVIDOSE)
Phase & Intention	Phase II study to determine the therapeutic effect and tolerance of tocizilumab in patients with moderate, severe pneumonia or critical pneumonia associated with	Phase II study to compare the effect of either one of three IL-6 inhibitor administrations, relative to SOC, on time to independence from	Phase II study to evaluate the use of tocilizumab in combination with hydroxychloroquine and azithromycin for the treatment of hospitalized	Phase II study to evaluate the effect of tocilizumab on mortality rate in patients with COVID-19 pneumonia.	Phase II study to establish proof of concept that tocilizumab is effective in decreasing signs, symptoms, and laboratory evidence of COVID-19 pneumonitis in hospitalised, non-critically ill patients with clinical risk

Active substance	Tocilizumab IV	Tocilizumab IV and SC	Tocilizumab SC plus hydroxychloroquine and azithromycin	Tocilizumab	Tocilizumab
	Coronavirus disease 2019 (COVID-19).	supplementary oxygen therapy, measured in days from baseline to day 28, in patients with severe SARS-CoV-2 pneumonia.	adult patients with COVID-19.		factors for clinical decompensation, intensive care utilisation, and death, as determined by the clinical outcome of resolution of fever and the biochemical outcome measures of time to CRP normalisation for the individual patient and the rate of patients whose CRP normalise.
Study design	Open-label RCT.	Open-label, four-arm active-comparator RCT.	Open-label randomised trial.	Open-label single-arm trial.	Open-label single-arm trial.
Status trial	Not yet recruiting..due to start March 31, 2020.	Not yet recruiting..due to start April 4, 2020	Recruiting..started April 2, 2020.	Recruiting..started March 19, 2020.	Not yet recruiting..due to start April 3, 2020.
Duration/End of Study	Estimated Primary Completion Date: March 31, 2021 Estimated Study Completion Date: December 31, 2021	Estimated Primary Completion Date: June 1, 2021 Estimated Study Completion Date: June 1, 2021	Estimated Primary Completion Date: September 2020 Estimated Study Completion Date: October 2020	Estimated Primary Completion Date: December 19, 2020 Estimated Study Completion Date: December 19, 2022	Estimated Primary Completion Date: July 1, 2020 Estimated Study Completion Date: December 1, 2020
Study details					
Number of Patients	n = 240 (Adult, Older Adult; 18 Years and older)	n = 200 (Adult, Older Adult, 18 Years and older)	n = 276 (Adult, Older Adult; 18 Years and older)	n = 330 (Child, Adult, Older Adult)	n = 50 (Adult, Older Adult; 18 Years and older)
Location/Centres	Not yet stated	Denmark	Spain	Italy	US

Active substance	Tocilizumab IV	Tocilizumab IV and SC	Tocilizumab SC plus hydroxychloroquine and azithromycin	Tocilizumab	Tocilizumab
Intervention	Tocilizumab 8mg/kg D1 and if no response (no decrease of oxygen requirement) a second injection at D3.	• Tocilizumab iv – single dose treatment with 400mg tocilizumab IV • Tocilizumab sc – single dose treatment with 2 x 162mg tocilizumab SC Sarilumab sc – single dose treatment with 1 x 200mg sarilumab SC	• Tocilizumab – 162mg sc x 2 doses + tocilizumab 162mg sc x 2 doses at 12 hours (day 1) • Hydroxychloroquine – 400mg/12h oral day 1 followed by 200mg/12h oral for 6 days (7 days in total) • Azithromycin – 500mg/day oral for 3 days	Tocilizumab 8mg/kg (up to a max 800mg per dose), with an interval of 12 hours.	• Tocilizumab (beginning single dose 200mg) Patient is eligible to receive up to 2 doses, with re-evaluation of clinical and biochemical responses performed every 24 hours. Second dose if evidence of clinical worsening or lack of C-reactive protein (CRP) response. • Low-dose tocilizumab (beginning single dose 80mg). Patient is eligible to receive up to 2 doses, with re-evaluation of clinical and biochemical responses performed every 24 hours. Second dose if evidence of clinical worsening or lack of CRP response.
Controls	SOC	SOC – management as usual	• Hydroxychloroquine oral – 400mg/12h on day 1 followed by 200mg/12h for 6 days (7 days in total) • Azithromycin oral – 500mg/day for 3 days	None	None
Duration of observation/Follow-up (Current Primary Outcome Measures)	Up to 14 days	Up to 28 days	Up to 14 days	Up to 1 month	Up to 4 weeks
Endpoints (Current Primary Outcome Measures)	1. Survival without needs of ventilator utilisation at day 14 2. WHO progression scale <=5 at day 4 3. Cumulative incidence of successful tracheal extubation at day 14 4. WHO progression scale <=7 at day 4	Time to independence from supplementary oxygen therapy up to 28 days.	1. In-hospital mortality at 2 weeks 2. Need for mechanical ventilation in the Intensive Care Unit through 2 weeks	One-month mortality rate	1. Clinical response over 24 hours 2. Biochemical response every 24 hours for up to 4 weeks

Active substance	Tocilizumab IV	Tocilizumab IV and SC	Tocilizumab SC plus hydroxychloroquine and azithromycin	Tocilizumab	Tocilizumab
Results/Publication	Not provided	Not provided	Not provided	Not provided	Not provided

CRS = cytokine release syndrome; DMARD = disease modifying anti-rheumatic drug; IL = interleukin; IV = intravenous; MTX = methotrexate; RCT = randomised controlled trial; RA = rheumatoid arthritis; SC = subcutaneous; SOC = standard of care; TNF = tumour necrosis factor

*Table 3.9-3: **Tocilizumab** in clinical trial registry (Continued)*

Active substance	Tocilizumab IV	Tocilizumab	Tocilizumab IV plus favipravir	Tocilizumab IV
Sponsor/Collaborator	Università Politecnica delle Marche	University of L'Aquila	Peking University First Hospital	Tongji Hospital
Mechanism of operation	IL-6 inhibitor	IL-6 inhibitor	IL-6 inhibitor + anti-viral agent	IL-6 inhibitor
Regulatory status EMA/FDA	**EMA:** RoActemra is approved for IV or SC administration for treating: • Severe, active and progressive RA in adults not previously treated with MTX • Moderate to severe active RA in adults who have responded inadequately to, or who were intolerant to, previous DMARDs or TNF antagonists. • Active systemic juvenile idiopathic arthritis in patients aged ≥2 years, who have responded inadequately to previous NSAIDs and systemic corticosteroids. • Juvenile idiopathic polyarthritis in patients aged ≥2 years, who have responded inadequately to previous MTX. • Chimeric antigen receptor T cell-induced severe or life-threatening CRS in patients aged ≥2 years (initial 15/01/2009). **FDA:** Actemra is approved for IV or SC administration for treating: • Adult patients with moderately to severely active RA who have had an inadequate response to one or more DMARDs. • Adult patients with giant cell arteritis.	**EMA:** RoActemra is approved for IV or SC administration for treating: • Severe, active and progressive RA in adults not previously treated with MTX • Moderate to severe active RA in adults who have responded inadequately to, or who were intolerant to, previous DMARDs or TNF antagonists. • Active systemic juvenile idiopathic arthritis in patients aged ≥2 years, who have responded inadequately to previous NSAIDs and systemic corticosteroids. • Juvenile idiopathic polyarthritis in patients aged ≥2 years, who have responded inadequately to previous MTX. • Chimeric antigen receptor T cell-induced severe or life-threatening CRS in patients aged ≥2 years (initial 15/01/2009). **FDA:** Actemra is approved for IV or SC administration for treating: • Adult patients with moderately to severely active RA who have	**EMA:** RoActemra is approved for IV or SC administration for treating: • Severe, active and progressive RA in adults not previously treated with MTX • Moderate to severe active RA in adults who have responded inadequately to, or who were intolerant to, previous DMARDs or TNF antagonists. • Active systemic juvenile idiopathic arthritis in patients aged ≥2 years, who have responded inadequately to previous NSAIDs and systemic corticosteroids. • Juvenile idiopathic polyarthritis in patients aged ≥2 years, who have responded inadequately to previous MTX. • Chimeric antigen receptor T cell-induced severe or life-threatening CRS in patients aged ≥2 years (initial 15/01/2009). **FDA:** Actemra is approved for IV or SC administration for treating: • Adult patients with moderately to severely active RA who have	**EMA:** RoActemra is approved for IV or SC administration for treating: • Severe, active and progressive RA in adults not previously treated with MTX • Moderate to severe active RA in adults who have responded inadequately to, or who were intolerant to, previous DMARDs or TNF antagonists. • Active systemic juvenile idiopathic arthritis in patients aged ≥2 years, who have responded inadequately to previous NSAIDs and systemic corticosteroids. • Juvenile idiopathic polyarthritis in patients aged ≥2 years, who have responded inadequately to previous MTX. • Chimeric antigen receptor T cell-induced severe or life-threatening CRS in patients aged ≥2 years (initial 15/01/2009). **FDA:** Actemra is approved for IV or SC administration for treating: • Adult patients with moderately to severely active RA who have had an inadequate response to one or more DMARDs. • Adult patients with giant cell arteritis.

Active substance	Tocilizumab IV	Tocilizumab	Tocilizumab IV plus favipravir	Tocilizumab IV
	• Patients aged ≥2 years with active polyarticular juvenile idiopathic arthritis. Systemic Juvenile Idiopathic Arthritis. • Patients aged ≥2 years with active systemic juvenile idiopathic arthritis. • Adults and pediatric patients aged ≥2 years with chimeric antigen receptor T cell-induced severe or life-threatening CKS (initial 01/08/2010).	had an inadequate response to one or more DMARDs. • Adult patients with giant cell arteritis. • Patients aged ≥2 years with active polyarticular juvenile idiopathic arthritis. Systemic Juvenile Idiopathic Arthritis. • Patients aged ≥2 years with active systemic juvenile idiopathic arthritis. • Adults and pediatric patients aged ≥2 years with chimeric antigen receptor T cell-induced severe or life-threatening CKS (initial 01/08/2010).	had an inadequate response to one or more DMARDs. • Adult patients with giant cell arteritis. • Patients aged ≥2 years with active polyarticular juvenile idiopathic arthritis. Systemic Juvenile Idiopathic Arthritis. • Patients aged ≥2 years with active systemic juvenile idiopathic arthritis. • Adults and pediatric patients aged ≥2 years with chimeric antigen receptor T cell-induced severe or life-threatening CKS (initial 01/08/2010).	• Patients aged ≥2 years with active polyarticular juvenile idiopathic arthritis. Systemic Juvenile Idiopathic Arthritis. • Patients aged ≥2 years with active systemic juvenile idiopathic arthritis. • Adults and pediatric patients aged ≥2 years with chimeric antigen receptor T cell-induced severe or life-threatening CKS (initial 01/08/2010).
Trial Identifier	NCT04315480	NCT04332913 (TOSCA)	NCT04310228	NCT04306705 (TACOS)
Phase & Intention	Phase II study to test the hypothesis that an anti-IL6 treatment can be effective in calming the virus-induced cytokine storm, blocking deterioration of lung function or even promoting a rapid improvement of clinical conditions, preventing naso-tracheal intubation and/or death.	Study (phase unknown) to verifying tocilizumab efficacy and safety in patients with COVID-19 complicated by acute distress respiratory syndrome (ARDS) and CRS.	Study (phase unkown) to evaluate the efficacy and safety of favipiravir combined with tocilizumab in the treatment of corona virus disease 2019	Study (phase unknown) to compare the efficacy and safety of tocilizumab and continuous renal replacement therapy (CRRT) in management of CRS triggered by COVID-19.
Study design	Open-label single-arm trial.	Open-label, prospective observational trial.	Open-label, three-arm active-comparator RCT. Cases allocated acc. to ratio of 3 (favipiravir +tocilizumab group): 1(favipiravir group): 1(tocilizumab group).	Retrospective observational cohort trial.
Status trial	Active, not recruiting.. started March 12, 2020.	Not yet recruiting..due to start April 1, 2020	Recruiting, started March 8, 2020	Recruiting..started February 20, 2020
Duration/End of Study	Estimated Primary Completion Date: April 9, 2020 Estimated Study Completion Date: May 2020	Estimated Primary Completion Date: December 31, 2020 Estimated Study Completion Date: March 31, 2021	Estimated Primary Completion Date: May 2020 Estimated Study Completion Date: May 2020	Estimated Primary Completion Date: May 30, 2020 Estimated Study Completion Date: June 20, 2020
Study details				
Number of Patients	n = 38 (Adult, Older Adult; 18 Years to 90 Years)	n = 30 (Adult, Older Adult; 18 Years and older)	n = 150 (Adult, Older Adult; 18 Years to 65)	n = 120 (Adult, Older Adult; 18 Years to 80 Years)
Location/Centres	Italy	Not yet stated	China	China
Intervention	Tocilizumab – single IV administration 8mg/Kg	Tocilizumab – no further details provided	*Arm 1 Drug: Favipiravir Combined With Tocilizumab*	• Tocilizumab – Subjects received 8 mg/kg (body weight) tocilizumab

Active substance	Tocilizumab IV	Tocilizumab	Tocilizumab IV plus favipravir	Tocilizumab IV
			Favipiravir: On the 1st day, 1600mg each time, twice a day; from the 2nd to the 7th day, 600mg each time, twice a day. Oral administration, max number of days taken is not more than 7 days. Tocilizumab:The first dose is 4 ~ 8mg/kg and the recommended dose is 400mg. For fever patients, an additional application (the same dose as before) is given if there is still fever within 24 hours after the first dose and the interval between two medications ≥ 12 hours.IV infusion, max cumulative number is two, and max single dose does not exceed 800mg. *Arm 2 Drug: Tocilizumab* The first dose is 4 ~ 8mg/kg and the recommended dose is 400mg. For fever patients, an additional application (the same dose as before) is given if there is still fever within 24 hours after the first dose and the interval between two medications ≥ 12 hours. IV infusion. The max cumulative number is two, and the max single dose does not exceed 800mg.	once in 100 ml 0.9% saline solution and administered IV within no less than 60 minutes. Tocilizumab was administered according to the local label. • Femoral vein catheterization was performed to complete continuous renal replacement therapy for consecutive 3 times or more. • SOC therapy per local written policies or guidelines and includes balancing of electrolytes and acid-base, the provision of enteral or parenteral nutrients support, antibiotics therapy, oxygen therapy and noninvasive ventilation.
Controls	None	None	*Arm 3 Drug: Favipiravir* On the 1st day, 1600mg each time, twice a day; from the 2nd to the 7th day, 600mg each time, twice a day. Oral administration, max number of days taken is not more than 7 days.	None
Duration of observation/Follow-up (Current Primary Outcome Measures)	Up to 7 days	Up to 14 days	Up to 3 months	Up to 14 days
Endpoints (Current Primary Outcome Measures)	1. arrest in deterioration of pulmonary function at 7 days 2. improving in pulmonary function at 7 days	Percentage of patients with complete recovery defined as fever disappearance and return to normal peripheral oxygen saturation values	Clinical cure rate at 3 months	Proportion of participants with normalisation of fever and oxygen saturation through day 14

Active substance	Tocilizumab IV	Tocilizumab	Tocilizumab IV plus favipravir	Tocilizumab IV
		(SpO2) after 14 days from the end of treatment with tocilizumab.		
Results/Publication	Not provided	Not provided	Not provided	Not provided

CRS = cytokine release syndrome; DMARD = disease modifying anti-rheumatic drug; IL = interleukin; IV = intravenous; MTX = methotrexate; RCT = randomised controlled trial; RA = rheumatoid arthritis; SC = subcutaneous; SOC = standard of care; TNF = tumour necrosis factor

3.10 Sarilumab (Keyzara®)

Drug under consideration

Sarilumab (*Kevzara*) is a human monoclonal antibody that specifically binds to soluble and membrane-bound interleukin (IL)-6 receptors (IL-6Rα), and inhibits IL-6-mediated signalling [108]. It is licensed in the EU for treating adults with rheumatoid arthritis, given by subcutaneous (SC) injection [108]. It is being investigated as a possible treatment for patients with moderate to severe or critical COVID-19.

Most cases of COVID-19 are mild (81%), and patients' symptoms are usually self-limiting with recovery in two weeks [102]. However, some patients develop severe symptoms and progress rapidly, experiencing acute respiratory distress syndrome and septic shock, eventually ending in multiple organ failure [102]. It has been reported that most patients with COVID-19 have increased concentrations of IL-6, C-reactive protein (CRP) and erythrocyte sedimentation rate [103]. However, severely affected patients appear to have even higher plasma levels of pro-inflammatory cytokines and experience severe cytokine storm including features of cytokine release syndrome (CRS) [103, 104]. It has previously been suggested that IL-6 might play a role in the pathogenesis of SARS and MERS, other diseases caused by coronaviruses [104]. It is thought that neutralisation of the inflammatory pathway induced by IL-6 may reduce mortality.

Experience of using tocilizumab, another IL-6 inhibitor, in severe or critical COVID-19 patients has been reported [105]. Retrospective analysis of data from 20 patients who received one of two doses of intravenous (IV) tocilizumab 400mg showed 15 (75%) had lowered their oxygen intake and one patient need no oxygen therapy. CT scans showed lung lesion opacity absorbed in 19 patients (90.5%). The percentage of lymphocytes in peripheral blood, which decreased in 85.0% patients (17/20) before treatment (mean, 15.52 ± 8.89%), returned to normal in 52.6% patients (10/19) on the fifth day after treatment. Abnormally elevated CRP decreased significantly in 84.2% patients (16/19). No obvious adverse reactions were observed.

Ongoing studies

The search in two clinical trial registers (humans only) in April 2020 yielded no completed study on the safety and efficacy of sarilumab in COVID-19 patients.

Three on-going phase II / III randomised controlled trials (RCT) to evaluate intravenous (IV) sarilumab in patients with COVID-19 have been recruiting patients since March 2020 – two trials in France (NCT04324073; CORIMUNO-SARI and NCT04327388; 2020-001162-12) and one in the US (NCT04315298). The estimated completion dates are December 2021, June 2021 and April 2021, respectively.

An open-label phase II RCT was due to start on the 4th of April with an estimated completion date of June 2021 (NCT04322773; TOCIVID). This study will compare the effect of single doses of one of three IL-6 inhibitors (SC sarilumab, SC tocilizumab and IV tocilizumab) with standard of care, on time to independence from supplementary oxygen therapy, measured in days from baseline to day 28, in patients with severe SARS-CoV-2 pneumonia. A further open-label phase II non-randomised controlled study is planned to evaluate the safety and effectiveness of potential anti-COVID-19 treatments, as an adjunct to clinical standard of care treatment, in hospitalised persons with moderate to severe COVID-19 disease (NCT04321993). Recruitment of 1,000 adults is due to start in April 2020, presumably in Canada as the trial is sponsored by Nova Scotia Health Authority (although not stated). Patients will be given either SC sarilumab, oral lopinavir + ritonavir (*Kaletra*), oral hydroxychloroquine sulphate, oral baricitinib (*Olumiant*) or clinical standard of care. The estimated completion date is July 2021.

Until May 11, 2020 eight further RCTs are found; seven as ongoing, and one as suspended, NCT04341870 - CORIMUNO-VIRO Trial (DSMB recommendation (futility)). The majority are placed in Europe, and in patients with moderate-to-severe COVID-19 pneumonia.

Table 3.10-1 displays more details of the identified on-going trials.

Results of publications

Until May 10, 2020 no relevant publications related to RCTs assessing the efficacy and safety of sarilumab could be identified.

*Table 3.10-1: **Sarilumab** in clinical trial registry*

Active substance	Sarilumab IV	Sarilumab IV	Sarilumab IV	Sarilumab SC	Sarilumab SC
Sponsor/Collaborator	Assistance Publique - Hôpitaux de Paris	Sanofi	Regeneron Pharmaceuticals	Frederiksberg University Hospital	Nova Scotia Health Authority
Mechanism of operation	IL-6 inhibitor	IL-6 inhibitor	IL-6 inhibitor	IL-6 inhibitor	IL-6 inhibitor
Regulatory status EMA/FDA	**EMA:** Kevzara for subcutaneous administration is approved for the treatment of moderately to severely active rheumatoid arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more disease modifying anti rheumatic drugs (23/06/2017). **FDA:** Kevzara for subcutaneous administration is approved for treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to one or more disease-modifying antirheumatic drugs (22/05/2017).	**EMA:** Kevzara for subcutaneous administration is approved for the treatment of moderately to severely active rheumatoid arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more disease modifying anti rheumatic drugs (23/06/2017). **FDA:** Kevzara for subcutaneous administration is approved for treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to one or more disease-modifying antirheumatic drugs (22/05/2017).	**EMA:** Kevzara for subcutaneous administration is approved for the treatment of moderately to severely active rheumatoid arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more disease modifying anti rheumatic drugs (23/06/2017). **FDA:** Kevzara for subcutaneous administration is approved for treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to one or more disease-modifying antirheumatic drugs (22/05/2017).	**EMA:** Kevzara for subcutaneous administration is approved for the treatment of moderately to severely active rheumatoid arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more disease modifying anti rheumatic drugs (23/06/2017). **FDA:** Kevzara for subcutaneous administration is approved for treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to one or more disease-modifying antirheumatic drugs (22/05/2017).	**EMA:** Kevzara for subcutaneous administration is approved for the treatment of moderately to severely active rheumatoid arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more disease modifying anti rheumatic drugs (23/06/2017). **FDA:** Kevzara for subcutaneous administration is approved for treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to one or more disease-modifying antirheumatic drugs (22/05/2017).
Trial Identifier	NCT04324073 (CORIMUNO-SARI)	NCT04327388 2020-001162-12	NCT04315298	NCT04322773 (TOCIVID)	NCT04321993
Phase & Intention	Phase II / III study to determine the therapeutic effect and tolerance of sarilumab in patients with moderate, severe pneumonia or critical pneumonia associated with Coronavirus disease 2019 (COVID-19).	Phase II / III study to evaluate the clinical efficacy of sarilumab relative to the control arm in adult patients hospitalized with severe or critical COVID-19.	Phase II / III study to determine the therapeutic effect and tolerance of sarilumab in patients with moderate, severe pneumonia or critical pneumonia associated with Coronavirus disease 2019 (COVID-19).	Phase II study to compare the effect of either one of three IL-6 inhibitor administrations, relative to the standard of care, on time to independence from supplementary oxygen therapy, measured in days from baseline to day 28, in patients with severe SARS-CoV-2 pneumonia.	Phase II study to evaluate safety and effectiveness of potential anti-COVID-19 treatments, as an adjunct to clinical standard of care treatment, in hospitalised persons with moderate to severe COVID-19 disease.

Active substance	Sarilumab IV	Sarilumab IV	Sarilumab IV	Sarilumab SC	Sarilumab SC
Study design	Open-label, active-comparator randomised controlled trial.	Adaptive, double-blind, randomised placebo-controlled trial.	Adaptive, double-blind, randomised placebo-controlled trial.	Open-label, four-arm active-comparator randomised controlled trial.	Open-label non-randomised (parallel assignment) controlled trial.
Status trial	Recruiting, started March 27, 2020.	Recruiting, started March 28, 2020	Recruiting, started March 18, 2020.	Not yet recruiting..due to start April 4, 2020	Not yet recruiting..due to start April 2020.
Duration/End of Study	Estimated Primary Completion Date: March 27, 2021 Estimated Study Completion Date: December 31, 2021	Estimated Primary Completion Date: July 30, 2020 Estimated Study Completion Date: June 2021	Estimated Primary Completion Date: March 9, 2021 Estimated Study Completion Date: April 1, 2021	Estimated Primary Completion Date: June 1, 2021 Estimated Study Completion Date: June 1, 2021	Estimated Primary Completion Date: February 2021 Estimated Study Completion Date: July 2021
Study details					
Number of Patients	n = 240 (Adult, Older Adult, 18 Years and older)	n = 300 (Adult, Older Adult, 18 Years and older)	n = 400 (Adult, Older Adult; 18 Years and older)	n = 200 (Adult, Older Adult, 18 Years and older)	n = 1,000 (Adult, Older Adult, 18 Years and older)
Location/Centres	France	France	US	Denmark	Not yet stated
Intervention	Sarilumab in an IV dose of 400 mg in a 1 hour-infusion at D1	• Sarilumab Dose 1 given intravenously one time on Day 1 • Sarilumab Dose 2 given intravenously one time on Day 1	• Single IV high-dose of sarilumab • Single IV low-dose of sarilumab	• Sarilumab sc – single dose treatment with 1 x 200 mg sarilumab subcutaneously • Tocilizumab iv – single dose treatment with 400 mg tocilizumab intravenously • Tocilizumab sc – single dose treatment with 2 x 162 mg tocilizumab subcutaneously	• Sarilumab 200mg subcutaneous injection once • Lopinavir/ritonavir tablet 200mg/50mg 2 tables by mouth, every 12 hours for 10 days • Hydroxychloroquine sulfate sulfate tablet 200 mg 2 tablets by mouth, every 12 hours for 10 days • Baricitinib 2 mg po daily for 10 days
Controls	Best standard of care	Matching placebo given intravenously one time on Day 1	Single IV dose of placebo to match sarilumab administration	Standard care – management as usual	No intervention – clinical standard of care
Duration of observation/Follow-up (Current Primary Outcome Measures)	Up to 14 days	Up to 29 days	Up to 29 days	Up to 28 days	Up to 15 days
Endpoints (Current Primary Outcome Measures)	1. Survival without needs of ventilator utilization at day 14. 2. WHO progression scale <=5 at day 4. 3. Cumulative incidence of successful tracheal extubation (defined as	Phase 2: Time to resolution of fever for at least 48 hours without antipyretics or until discharge, whichever is sooner until day 29. Phase 3: The percentage of patients reporting each severity rating on the 7-point ordinal scale at day 15.	Phase 2: Percent change in C-reactive protein (CRP) levels at day 4. Phase 3: Time to improvement (2 points) in clinical status assessment using the 7-point ordinal scale in patients with serum IL-6 levels greater than the	Time to independence from supplementary oxygen therapy up to 28 days.	Clinical status of subject at day 15

Active substance	Sarilumab IV	Sarilumab IV	Sarilumab IV	Sarilumab SC	Sarilumab SC
	duration extubation > 48h) at day 14. 4. WHO progression scale <=7 at day 4.		upper limit of normal up to day 29.		
Results/Publication	Not provided	Not provided	Not provided	Not provided	Not provided

*Table 3.10-2: **Sarilumab** in clinical trial registry (Continued)*

Active substance	**Sarilumab**	**Sarilumab**	**Sarilumab**	**Sarilumab**
Sponsor	Assistance Publique - Hôpitaux de Paris	Westyn Branch-Elliman	Rosario García de Vicuña	Department of Infectious diseases
Trial Identifier	NCT04341870, CORIMUNO-VIRO Trial	NCT04359901	2020-001634-36, NCT04357808 SARCOVID	2020-001367-88
Phase & Intention	Phase 2/3, to determine the therapeutic effect and tolerance of Sarilumab in combination with Azithromycin and Hydroxychloroquine, compared to Sarilumab only, patients with moderate, severe pneumonia associated with Coronavirus disease 2019 (COVID-19)	Phase 2, to determine whether blockade of IL-6R is beneficial in patients with COVID-19 infection of moderate severity	Phase II, to evaluate the efficacy of subcutaneous sarilumab in patients with moderate-severe COVID-19 infection	Phase III, to evaluate the efficacy and safety of convalescent anti-SARS-CoV-2 plasma, hydroxychloroquine, sarilumab and baricitinib compared with placebo in combination with standard of care (SOC) for the treatment of moderate-to-severe COVID-19 pneumonia on the basis of the composite endpoint: All-cause mortality or need of invasive mechanical ventilation up to 28 days
Study design	RCT, open-label, active comparator, parallel assignment	RCT, open-label, standard treatment comparator, parallel assignment	RCT, open-label, standard treatment comparator, parallel assignment	RCT, double-blind, multi-stage, 6-armed placebo-controlled trial in the framework of an adaptive trial platform
Status trial	**Suspended (DSMB recommendation (futility))**	Recruiting	Ongoing	Ongoing
Duration/ End of Study	Study start: April 11, 2020 Estimated Primary Completion Date: May 8, 2020 Estimated Study Completion Date: August 2020	Study start: April 10, 2020 Estimated Primary Completion Date: April 10, 2022 Estimated Study Completion Date: April 10, 2023	Study start: 09/04/2020 Estimated Primary Completion Date: NA Estimated Study Completion Date: NA	Study start: 14/04/2020 Estimated Primary Completion Date:NA Estimated Study Completion Date: NA
Study details	N of pts: 60 Location/ centres: France	N of pts: 120 Location/ centres: US	N of pts: 30 Location/ centres: Spain Intervention/control: Sarilumab/Current treatment standard	N of pts: 1500 Location/ centres: Denmark Intervention/control: Hydroxychloroquine; Baricitinib; Sarilumab; /Placebo

Active substance	**Sarilumab**	**Sarilumab**	**Sarilumab**	**Sarilumab**
	Intervention/control: Sarilumab + Azithromycin + Hydroxychloroquine/Sarilumab Duration of observation/follow-up: Up to 90 days Primary end point(s): Need for ventilation (including invasive and non invasive ventilation), intensive care or death [Time frame: 14 days] Secondary endpoints: Early improvement: OMS progression scale <= 5, Survival, ICU-free days alive, Ventilation-free days alive, Hospital-free days alive, Oxygen therapy-free days alive, Time to negative viral excretion, Immunophenotyping and multiplex cytokines	Intervention/control: Sarilumab plus standard care / Standard care Duration of observation/follow-up: 14 days Primary end point(s): Intubation or death [Time frame: within 14 days of enrollment] Secondary endpoints: ime to hospital discharge if alive, time to clinical recovery, ICU length of stay, time to return to normal or baseline oxygen saturation, and changes in laboratory biomarkers	Duration of observation/follow-up: Up to 2 months Primary end point(s): Time to become afebrile for a minimum period of 48 hours, without antipyretics; Average change in the ordinal scale of 7 points from the inclusion in the study until day 7; Secondary endpoints: Time to become afebrile for a minimum period of 48 hours, without antipyretics; Time to non-invasive mechanical ventilation (days); Time to invasive mechanical ventilation (days); Time to withdraw oxygen therapy (days); Average change in the ordinal scale of 7 points from the inclusion in the study until day 14	Duration of observation/follow-up: Up to 90 days Primary end point(s): All-cause mortality or need of invasive mechanical ventilation up to 28 days. Secondary endpoints: Frequency of adverse events; Frequency of severe adverse events; Time to improvement of at least 2 categories relative to baseline on a 7-category ordinal scale of clinical status; Ventilator-free days to day 28; Organ failure-free days to day 28; Duration of ICU stay; Mortality rate at days 7, 14, 21, 28, and 90; Length of hospital stay; Duration of supplemental oxygen
Results	N.A.	N.A.	N.A.	N.A.

*Table 3.10-3: **Sarilumab** in clinical trial registry (Continued)*

Active substance	**Sarilumab**	**Sarilumab**	**Sarilumab**	**Sarilumab**
Sponsor	Fundación para la Investigación Biomédica de Córdoba	Consorci Parc de Salut Mar (PSMAR)	See Table 3.10-1: Tocilizumab	See Table 3.10-1: Tocilizumab
Trial Identifier	2020-001531-27	2020-001290-74	2020-001275-32	2020-001246-18
Phase & Intention	Phase II, to decrease cases of ARDS in adults requiring HFNO or either non-invasive or invasive mechanical ventilation	Phase III, to assess the efficacy and safety of early treatment of sarilumab, added to standard treatment, in patients hospitalized for mild-moderate COVID-19 pneumonia, with criteria of a CURB 65 less than or equal to 1, oxygen saturation equal to or greater than 90%, MEWS less than 3 and with IL6 greater than 20 pg / mL	See Table 3.10-1: Tocilizumab	See Table 3.10-1: Tocilizumab
Study design	RCT, open-label, best available therapy comparator, parallel assignment	RCT, open-label, active comparator	See Table 3.10-1: Tocilizumab	See Table 3.10-1: Tocilizumab
Status trial	Ongoing	Ongoing	See Table 3.10-1: Tocilizumab	See Table 3.10-1: Tocilizumab
Duration/ End of Study	Study start: 18/04/2020 Estimated Primary Completion Date: NA Estimated Study Completion Date: NA	Study start: 11/04/2020 Estimated Primary Completion Date: NA Estimated Study Completion Date: NA	See Table 3.10-1: Tocilizumab	See Table 3.10-1: Tocilizumab
Study details	N of pts: 120 Location/ centres: Spain Intervention/control: Sarilumab/ Best available therapy Duration of observation/follow-up: 30 days Primary end point(s): Proportion of patients requiring or time (in days) until required: - High flow nasal oxygenation (HFNO) - Non-invasive mechanical ventilation type BiPAP - Non-invasive mechanical ventilation type CPAP - Invasive mechanical ventilation Secondary endpoints: Crude mortality at 28 days; Time to clinical improvement; Time (in days) until improvement in oxygenation for at least 48 hours; Proportion of patients requiring invasive mechanical ventilation; Proportion of	N of pts: 216 Location/ centres: Spain Intervention/control: Sarilumab / azithromycin; hydroxychloroquine Duration of observation/follow-up: Up to 28 days Primary end point(s): Time to clinical improvement Secondary endpoints: Clinical status evaluated with the ordinal scale of seven categories on days 7 and 14; 28-day mortality; Mechanical ventilation; Duration of mechanical ventilation; Duration of hospitalization of those who survive; time (in days) from the start of treatment until death; medication during the study period: vasopressors, renal replacement therapy, non-invasive mechanical ventilation, invasive mechanical ventilation, ECMO, antibiotics, glucocorticoids, others; Days from the beginning of the disease to the start of corticosteroid use; Days of corticosteroid treatment; - Interleukin 6 basal, at 12 hours, 24 hours, 48 hours, at 72 and at 7 days	See Table 3.10-1: Tocilizumab	See Table 3.10-1: Tocilizumab

	patients having negative COVID-19 CRP at each visit; Mean of serum cytokine levels; Incidence of adverse events…	- Baseline D-dimer, at 12 hours, 24 hours, 48 hours, at 72 and 7 days		
Results	N.A.	N.A.	See Table 3.10-1: Tocilizumab	See Table 3.10-1: Tocilizumab

3.11 Interferon beta 1a (SNG001)

About the drug under consideration

Interferon beta-1a (INFb) is a cytokine in the interferon family used to treat relapsing multiple sclerosis (MS). Interferon beta balances the expression of pro- and anti-inflammatory agents in the brain, leading to a reduction of neuron inflammation [109]. Clinical observations in mammals infected with the Middle East respiratory syndrome coronavirus (MERS-CoV) have shown clinical improvements with the use of INFb; and human trials are also underway to evaluate the effect of lopinavir/ritonavir in combination with INFb in patients with MERS-CoV. Finding of these studies have led to exploration of treatment with INFb in COVID-19 [110].

Two pharmaceuticals which the active substance INFb are commercially available: Rebif® and Avonex®. They are used to slow the progression of disability and reduce the number of relapses in MS. Rebif is approved by the European Medicines Agency (EMA) since 1998 and by the American Food and Drug Administration (FDA) since 2002. Avonex is approved by EMA since 1997 and by the FDA since 1996. Both drugs are approved for the treatment of relapsing forms of multiple sclerosis (MS), in cases of clinically isolated syndromes, as well as relapsing remitting disease, and active secondary progressive disease in adults.

Drug used in Covid-19 patients: ongoing studies

The search in clinical trials (humans only) in April 2020 yielded no completed studies on the safety and effectiveness of Interferon beta-1a for Covid-19 patients. Four ongoing trials could be identified: one phase II randomised controlled trial (RCT) (EudraCT 2020-001023-14), one phase III randomised trial (NCT04315948), one phase IV randomised, embedded, multifactorial adaptive platform trial (NCT02735707) and one observational study with unknown study phase (NCT04314817). The phase IV trial started in 2016 with the indications community-acquired pneumonia and influenza; and added COVID-19 just recently. The other three trials all started in March 2020. Results are expected in May 2021, January 2022 and January/March 2023. Three of the studies assess multiple interventions at the same time, including interferon beta-1a. One of the studies assesses interferon beta-1a in combination with Lopinavir/Ritonavir. Table 3.11-1 presents more details of the identified ongoing studies.

Until May 12, 2020, four ongoing RCTs are found in ClinicalTrial.gov and EudraCT registers, and one completed related to Interferon beta 1b. The completed RCT (NCT04276688) was conducted in Hong Kong, and its results are written in Section 3.13, related to Combination therapy (triple combination of interferon beta-1b, lopinavir–ritonavir, and ribavirin, compared with lopinavir–ritonavir alone). RCT number NCT04385095 is a phase 2, placebo-controlled trial, with the aim to determine the safety and efficacy of inhaled SNG001 (IFN-β1a for nebulisation) for the treatment of patients with confirmed SARS-CoV-2 infection in UK. In other RCTs, interferon beta-1a is used in combination with lopinavir/ritonavir. Details of these RCTs are shown in Table 3.11-1. Two RCTs are not listed here (NCT04350671 and NCT04343768, where interferon-β 1a is applied in combination with lopinavir/ritonavir and hydroxychloroquine).

Drug used in Covid-19 patients: results of publications

As mentioned above, the results from the first randomised controlled trail on triple combination of interferon beta-1b, lopinavir–ritonavir and ribavirin, in comparison with lopinavir–ritonavir (NCT04276688) are presented in Section 3.13 of this report [111].

*Table 3.11-1: **Interferon beta-1a** in clinical trial registry*

Active substance	Interferon beta-1a	Interferon beta-1a	Interferon beta-1a (SNG001)	Interferon beta-1a
Sponsor	MJM Bonten	Groupe Hospitalier Pitie-Salpetriere	Synairgen Research Limited	Institut National de la Santé Et de la Recherche Médicale
Mechanism of operation	Interferon	Interferon	Interferon	Interferon
Regulatory status	Rebif: EMA approval since 03/05/1998 and FDA approval since 07/03/2002 for the treatment of patients with relapsing multiple sclerosis (MS). Avonex: EMA approval since 13/03/1997 and FDA approval since 17/05/1996 for the treatment of patients with relapsing multiple sclerosis (MS).	Rebif: EMA approval since 03/05/1998 and FDA approval since 07/03/2002 for the treatment of patients with relapsing multiple sclerosis (MS). Avonex: EMA approval since 13/03/1997 and FDA approval since 17/05/1996 for the treatment of patients with relapsing multiple sclerosis (MS).	Rebif: EMA approval since 03/05/1998 and FDA approval since 07/03/2002 for the treatment of patients with relapsing multiple sclerosis (MS). Avonex: EMA approval since 13/03/1997 and FDA approval since 17/05/1996 for the treatment of patients with relapsing multiple sclerosis (MS).	Rebif: EMA approval since 03/05/1998 and FDA approval since 07/03/2002 for the treatment of patients with relapsing multiple sclerosis (MS). Avonex: EMA approval since 13/03/1997 and FDA approval since 17/05/1996 for the treatment of patients with relapsing multiple sclerosis (MS).
Trial Identifier	NCT02735707	NCT04314817	EudraCT 2020-001023-14	NCT04315948
Phase & Intention	Phase IV trial to evaluate the effect of a range of interventions to improve outcome in patients admitted to intensive care with community-acquired pneumonia.	Phase unknown This study investigates reports of adverse events.	Phase II 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 (COVID-19).	Phase III trial to evaluate the clinical efficacy and safety of different investigational therapeutics relative to the control arm in patients hospitalized with COVID-19.
Study design	Randomized, Embedded, Multifactorial Adaptive Platform Trial	Observational	Randomised, double-blind, placebo-controlled trial	Multi-centre, Adaptive, Randomized Trial
Status trial	Recruiting	Recruiting	Recruiting	Recruiting
Duration/ End of Study	Original study start date: April 2016. Study protocol amended (COVID-19 added) in March 2020. 2 years 4 months/ Estimated June 2022	2 years 10 months/ Estimated January 2023	1 year 2 months/ Estimated May 2021	3 years/ Estimated March 2023
Study details	Pts: n= 6800 Locations: Australia, Belgium, Canada, Croatia, Germany, Hungary, Ireland, Netherlands, New Zealand, Portugal, Romania, Spain, United Kingdom Interventions: - Interferon-β1a *(10 µg once daily for six days or until ICU discharge)* - fixed-duration Hydrocortisone	Pts: n= 1000 Locations: France Interventions: - Interferon-β1a - Lopinavir/ritonavir - Remdesivir - Chloroquine - Azithromycin	Pts: n= 400 Locations: United Kingdom + 20 sites in EEA member states Intervention: Interferon beta-1a Control: placebo Duration of observation/ follow-up: 14 days Primary outcome: change in condition measured using the	Pts: n = 3100 5 groups each n = 620 Location: France Interventions: - Group 1: Remdesivir - Group 2: Lopinavir / ritonavir - Group 3: Lopinavir / ritonavir plus interferon beta-1a (*44 µg for a total of 3 doses in 6 days)* - Group 4: Hydroxychloroquine

Active substance	Interferon beta-1a	Interferon beta-1a	Interferon beta-1a (SNG001)	Interferon beta-1a
	- shock-dependent Hydrocortisone - Ceftriaxone - Moxifloxacin or Levofloxacin; - Piperacillin-tazobactam - Ceftaroline - Amoxicillin-clavulanate - Macrolide (administered for 3-5 days or for up to 14 days) - Oseltamivir (administered for 5 days or 10 days) - Lopinavir/ritonavir - Hydroxychloroquine - Hydroxychloroquine+lopinavir/ritonavir - Anakinra Duration of observation/ follow-up: 90 days Primary outcomes: - all-cause mortality - days alive and outside of ICU	Duration of observation/ follow-up: NA Primary outcome: renal failure	Ordinal Scale for Clinical Improvement (WHO recommended scale) during the dosing period.	Control: Standard of care (group 5) Duration of observation/ follow-up: 28 days Primary outcomes: Percentage of subjects reporting each severity rating on a 7-point ordinal scale: 1) Not hospitalized, no limitations on activities; 2) Not hospitalized, limitation on activities; 3) Hospitalized, not requiring supplemental oxygen; 4) Hospitalized, requiring supplemental oxygen; 5) Hospitalized, on non-invasive ventilation or high flow oxygen devices; 6) Hospitalized, on invasive mechanical ventilation or ECMO (extracorporeal membrance oxygenation); 7) Death.
Results	No publications available yet.	No publications available yet.	No publications available yet.	No publications available yet.

*Table 3.11-2: **Interferon beta-1a** in clinical trial registry (continued)*

Active substance	Interferon beta-1a	Interferon beta-1a (in combination with lopinavir/ritonavir)	Interferon beta-1a (in combination with lopinavir/ritonavir)	Interferon beta-1a (in combination with lopinavir/ritonavir)	**Interferon beta-1b** (combination of lopinavir/ ritonavir, ribavirin and interferon beta-1b)
Sponsor	Synairgen Research Ltd.	See Remdesivir Table 3.1-1	See Remdesivir Table 3.1-1	See Remdesivir Table 3.1-1	See table Table 3.2-1: Lopinavir plus ritonavir (Kaletra®)
Trial Identifier	NCT04385095	NCT04315948, EudraCT 2020-000936-23, DisCoVeRy trial	ISRCTN83971151, SOLIDARITY trial	EudraCT 2020-001366-11, Spain arm of SOLIDARITY trial	NCT04276688
Phase & Intention	Phase 2, to determine the safety and efficacy of inhaled SNG001 (IFN-β1a for nebulisation) for the treatment of patients with confirmed SARS-CoV-2 infection	See Remdesivir Table 3.1-1	See Remdesivir Table 3.1-1	See Remdesivir Table 3.1-1	See table Table 3.2-1: Lopinavir plus ritonavir (Kaletra®)
Study design	RCT, quadruple-blind, placebo-controlled, parallel assignment	See Remdesivir Table 3.1-1	See Remdesivir Table 3.1-1	See Remdesivir Table 3.1-1	See table Table 3.2-1: Lopinavir plus ritonavir (Kaletra®)
Status trial	Recruiting	See Remdesivir Table 3.1-1	See Remdesivir Table 3.1-1	See Remdesivir Table 3.1-1	See table Table 3.2-1: Lopinavir plus ritonavir (Kaletra®)
Duration/ End of Study	Study start: March 16, 2020 Estimated Primary Completion Date: August 31, 2020 Estimated Study Completion Date: May 31, 2021	See Remdesivir Table 3.1-1	See Remdesivir Table 3.1-1	See Remdesivir Table 3.1-1	See table Table 3.2-1: Lopinavir plus ritonavir (Kaletra®)
Study details	N of pts: 400 Location/ centres: UK Intervention/control: Interferon Beta-1A via inhalation/ Placebo via inhalation Duration of observation/follow-up: Primary end point(s): Ordinal Scale for Clinical Improvement [Time frame: Day 1 to day 28] Secondary endpoints: Safety and tolerability, Progression to pneumonia, Time to clinical improvement, National Early Warning Score 2 (NEWS2) assessment of acute-illness severity	See Remdesivir Table 3.1-1	See Remdesivir Table 3.1-1	See Remdesivir Table 3.1-1	See table Table 3.2-1: Lopinavir plus ritonavir (Kaletra®)
Results	N.A.	See Remdesivir Table 3.1-1	See Remdesivir Table 3.1-1	See Remdesivir Table 3.1-1	Please see Section 3.13

3.12 Convalescent plasma transfusion and immune globulin concentrates (plasma derived medicinal products)

About the treatment under consideration

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, transfusion-related acute lung injury (TRALI) and circulatory overload [112-114]. Both, clinical trials and observational studies are under way by academic and industry to investigare efficacy and safety of passive antibody therapies for COVID-19 infection. Convalescent plasma was previously used for treatment of severe acute respiratory syndrome (SARS), pandemic 2009 influenza A (H1N1), avian influenza A (H5N1), several hemorrhagic fevers such as Ebola, and other viral infections with positive results related to different clinical outcomes. Currently it is used as one of unproved treatment of critically ill hospitalised COVID-19 patients to reduce their symptoms and mortality, because effective pharmaceutical therapy or vaccines are lacking and are undear clinical trial investigation process [112]. It is not known what doses would be effective therapeutically for COVID-19. As Casadevall and Pirofski published in March 2020 [112], six conditions must be met to deploy convalescent plasma treatment for COVID-19: availability of a population of donors who have recovered from the disease and can donate convalescent serum; blood banking facilities to process the serum donations; availability of assays, including serological assays, to detect SARS-CoV-2 in serum and virological assays to measure viral neutralization; virology laboratory support to perform these assays; prophylaxis and therapeutic protocols, which should ideally include randomized clinical trials to assess the efficacy of any intervention and measure immune responses; and regulatory compliance, including institutional review board approval, which may vary depending on location.

COVID-19 convalescent plasma therapy is not approved by the European Medicine Agency (EMA) and the Food and Drug Administration (FDA) for COVID-19. The European Commission (EC) and US Food and Drug Administration (FDA) recently published guidance on convalescent plasma collected from individuals who have recovered from COVID-19 and which may potentially be used as a treatment for COVID-19 [115, 116]. The EC guidance aims to facilitate a common approach across EU Member States to the donation, collection, testing, processing, storage, distribution and monitoring of convalescent plasma for the treatment of Covid-19 [115]. The FDA guidance provides recommendations on the pathways for use of investigational COVID-19 convalescent plasma; patient eligibility; collection of COVID-19 convalescent plasma, including donor eligibility and donor qualifications; labeling and record keeping. As COVID-19 convalescent plasma is regulated as an investigational product, three patways for use are available in US: 1. Clinical Trials; 2. Expanded Access; 3. Single Patient Emergency IND [116, 117].

Current US NIH COVID-19 Treatment Guidelines stated that there are insufficient clinical data to recommend either for or against the use of convalescent plasma or hyperimmune immunoglobulin for the treatment of COVID-19 (AIII) [118]. Randomised clinical trials are needed to provide the highest quality evidence on safety and efficacy of convalescent plasma in the treatment of COVID-19 patients. Monitored use in observational studies are proceed in parallel.

Ongoing studies

There are no completed clinical trials on the safety and efficacy of convalescent plasma in COVID-19 patients. The search in different clinical trials registries showed that both clinical trials and

observational studies are under way to investigare efficacy and safety of passive antibody therapies for COVID-19 infection.

Until 30 April 2020, out of 43 registered clinical trials, 26 are randomized control trials. Majority of registered clinical trials are in recruiting status or not yet recruiting status; one from European register (phase 2) is ongoing RCT (2020-001310-38), in Germany, and one (phase 2) is withdrawn in US (NCT04325672) due to opening of Expanded Access Protocol. The majority are located in China and US; the rest of studies are placed in Denmark, Hungary, Italy, Netherlands, Spain, Iran, Colombia, Mexico, India, Saudi Arabia, Canada, Egypt, Pakistan and Bahrein. The majority is planned to have primary completion date in 2020. Details of those 26 RCTs are written in Table 3.12-1.

*Table 3.12-1: RCTs related to **Convalescent plasma** therapy in clinical trial registry*

Active substance	**Convalescent plasma**	**Convalescent plasma**	**Convalescent plasma**	**Convalescent plasma**	**Convalescent plasma**
Sponsor/Collaborator	Hamilton Health Sciences Corporation/ Canadian Blood Services; Héma-Québec; University of Toronto; Université de Montréal	Institute of Liver and Biliary Sciences, India	Stony Brook University	Assistance Publique - Hôpitaux de Paris/ Etablissement Français du Sang	DRK-Bluspendedienst Baden-Württemberg - Hessen gGmbH
Mechanism of operation	Passive immunization (transfusion of apheresis frozen plasma (AFP) from COVID-19 convalescent patients allows the transfer of donor neutralizing antibodies directed against SARS-CoV2 antigens to the recipient, thus allowing the generation of passive immunization)	Passive immunization (transfusion of apheresis frozen plasma (AFP) from COVID-19 convalescent patients allows the transfer of donor neutralizing antibodies directed against SARS-CoV2 antigens to the recipient, thus allowing the generation of passive immunization)	Passive immunization (transfusion of apheresis frozen plasma (AFP) from COVID-19 convalescent patients allows the transfer of donor neutralizing antibodies directed against SARS-CoV2 antigens to the recipient, thus allowing the generation of passive immunization)	Passive immunization (transfusion of apheresis frozen plasma (AFP) from COVID-19 convalescent patients allows the transfer of donor neutralizing antibodies directed against SARS-CoV2 antigens to the recipient, thus allowing the generation of passive immunization)	Passive immunization (transfusion of apheresis frozen plasma (AFP) from COVID-19 convalescent patients allows the transfer of donor neutralizing antibodies directed against SARS-CoV2 antigens to the recipient, thus allowing the generation of passive immunization)
Regulatory status EMA/FDA	**EMA:** no marketing authorisation **FDA:** On March 25th, 2020, the FDA approved the use of convalescent plasma under the emergency investigational new drug (eIND) category	**EMA:** no marketing authorisation **FDA:** On March 25th, 2020, the FDA approved the use of convalescent plasma under the emergency investigational new drug (eIND) category	**EMA:** no marketing authorisation **FDA:** On March 25th, 2020, the FDA approved the use of convalescent plasma under the emergency investigational new drug (eIND) category	**EMA:** no marketing authorisation **FDA:** On March 25th, 2020, the FDA approved the use of convalescent plasma under the emergency investigational new drug (eIND) category	**EMA:** no marketing authorisation **FDA:** On March 25th, 2020, the FDA approved the use of convalescent plasma under the emergency investigational new drug (eIND) category
Trial Identifier	NCT04348656 (CONCOR-1)	NCT04346446	NCT04344535	NCT04345991 (COVIPLASM trial, a nested trial in the CORIMUNO-19 COHORT)	EudraCT 2020-001310-38 (CAPSID trial)
Phase & Intention	Phase III study to determine the efficacy of transfusion of COVID-19 convalescent plasma to adult patients admitted to hospital with COVID-19	Phase II study to evaluate the efficacy of this therapy in COVID-19 infected sick patients	Phase I / II study to find out if transfusion of blood plasma containing antibodies against COVID-19 (anti-SARS-CoV-2), which were donated from	Phase II study to evaluate the efficacy of convalescent plasma to treat SARS-COV2 infected patients	Phase II study to assess positive value of blood plasma from donors having built immunity against the new corona virus (SARS-CoV-2) transfused to patients suffering from SARS-CoV-2 infection

Active substance	Convalescent plasma	Convalescent plasma	Convalescent plasma	Convalescent plasma	Convalescent plasma
	infection at decreasing the frequency of in-hospital mortality in patients hospitalized for COVID-19		a patient who recovered from COVID-19 infection, is safe and can treat COVID-19 in hospitalized patients		To improve survival and remove criteria of severe COVID-19 (CoV-2 infection) within 21 days after randomization
Study design	**RCT**, open-label, standard of care-comparator, parallel assignment	**RCT**, open-label, active comparator, parallel assignment	**RCT**, Quadruple-blind, active comparator, parallel assignment	**RCT**, open-label, best standard of care-comparator, parallel assignment	**RCT**, open-label, best standard of care-comparator
Status trial	Not yet recruiting, started April 27, 2020	Recruiting, started April 21, 2020	Enrolling by invitation, started April 8, 2020	Not yet recruiting	Ongoing
Duration/End of Study	Estimated Primary Completion Date: October 31, 2020 Estimated Study Completion Date: December 31, 2020	Estimated Primary Completion Date: June 30, 2020 Estimated Study Completion Date: June 30, 2020	Estimated Primary Completion Date: April 30, 2021 Estimated Study Completion Date: August 31, 2021	Estimated Primary Completion Date: May 15, 2020 Estimated Study Completion Date: June 1, 2020	Estimated Primary Completion Date: NA Estimated Study Completion Date: NA
Study details					
Number of Patients	n = 1200 (16 Years and older - Child, Adult, Older Adult)	n = 20 (Adult, Older Adult, 18 Years to 65 years)	n = 500 (Adult, Older Adult; 18 Years and older)	n = 120 (Adult, Older Adult, 18 Years and older)	n = 120 (age ≥ 18 years and ≤ 75 years)
Location/Centres	Canada	India	US	France	Germany
Intervention	500 mL of ABO compatible convalescent apheresis plasma (from one single-donor unit of 500 mL or 2 units of 250 mL from 1-2 donations) collected by apheresis from donors who have recovered from COVID-19 and frozen (1 year expiration date from date of collection)	Convalescent Plasma+Supportive Care	Convalescent Plasma (450-550 mL of plasma containing anti-SARS-CoV-2 antibody titer ideally > 1:320, but meeting minimum titer per FDA Guidelines for convalescent plasma)	Transfusion of COVID-19 convalescent plasma (Two convalescent plasma units of 200 to 220 ml each will be transfused i.v. as early as possible and no later than 10 days after onset of clinical symptoms. In the absence of acute unforeseen adverse events in the first 3 patients, an additional 2 plasma units of 200/220 ml each will be transfused 24 hours after first 2 units: a total of 4 units / patient)	Convalescent Plasma against COVID-19 (Fresh frozen plasma (FFP) with marketing authorisation in Germany issued by PEI)
Controls	Standard of care	Random Donor Plasma+Supportive Care	Standard Donor Plasma	Standard of care	Best supportive care
Duration of observation/Follow-up	Until hospital discharge or death, up to 90 days (for an individual subject, the	Up to 28 days	Up to 90 days	Up to 28 days	Up to 60 days

Active substance	Convalescent plasma	Convalescent plasma	Convalescent plasma	Convalescent plasma	Convalescent plasma
(Current Primary Outcome Measures)	study ends 90 days after randomization)				
Endpoints (Current Primary Outcome Measures)	Intubation or death in hospital (Time Frame: Day 30) Endpoint of the need for intubation or patient death in hospital	Proportion of patients remaining free of mechanical ventilation in both groups (Time Frame: Day 7)	28 day ventilator free days (Time Frame: 28 days post randomization)	Survival without needs of ventilator utilization or use of immunomodulatory drugs [Time Frame: At day 14 after randomization] WHO progression scale ≥6 [Time Frame: at day 4 of randomization]	Composite endpoint of survival and no longer fulfilling criteria of severe COVID-19 within 21 days after randomization
Results/Publication	Not provided	Not provided	Not provided	Not provided	Not provided

*Table 3.12-1: RCTs related to **Convalescent plasma** therapy in clinical trial registry (Continued)*

Active substance	Convalescent plasma	Convalescent plasma	Convalescent plasma	Convalescent plasma	Convalescent plasma
Sponsor/Collaborator	Erasmus Medical Center/Maasstad Hospital	Artesh University of Medical Sciences	Birjand University of Medical Sciences	Ahvaz University of Medical Sciences	China-Japan friendship hospital / Union Hospital, Tongji Medical College, Huazhong university of Science and Technology /Red Cross Hospital in Wuhan of Hubei Province / Wuhan Asia Heart Hospital / Wuhan Maternal and Child Health Hospital
Mechanism of operation	Passive immunization (transfusion of apheresis frozen plasma (AFP) from COVID-19 convalescent patients allows the transfer of donor neutralizing antibodies directed against SARS-CoV2 antigens to the recipient, thus allowing the generation of passive immunization)	Passive immunization (transfusion of apheresis frozen plasma (AFP) from COVID-19 convalescent patients allows the transfer of donor neutralizing antibodies directed against SARS-CoV2 antigens to the recipient, thus allowing the generation of passive immunization)	Passive immunization (transfusion of apheresis frozen plasma (AFP) from COVID-19 convalescent patients allows the transfer of donor neutralizing antibodies directed against SARS-CoV2 antigens to the recipient, thus allowing the generation of passive immunization)	Passive immunization (transfusion of apheresis frozen plasma (AFP) from COVID-19 convalescent patients allows the transfer of donor neutralizing antibodies directed against SARS-CoV2 antigens to the recipient, thus allowing the generation of passive immunization)	Passive immunization (transfusion of apheresis frozen plasma (AFP) from COVID-19 convalescent patients allows the transfer of donor neutralizing antibodies directed against SARS-CoV2 antigens to the recipient, thus allowing the generation of passive immunization)
Regulatory status EMA/FDA	**EMA:** no marketing authorisation	**EMA:** no marketing authorisation	**EMA:** no marketing authorisation	**EMA:** no marketing authorisation	**EMA:** no marketing authorisation **FDA:** On March 25th, 2020, the FDA approved the use of convalescent

Active substance	Convalescent plasma	Convalescent plasma	Convalescent plasma	Convalescent plasma	Convalescent plasma
	FDA: On March 25th, 2020, the FDA approved the use of convalescent plasma under the emergency investigational new drug (eIND) category	**FDA:** On March 25th, 2020, the FDA approved the use of convalescent plasma under the emergency investigational new drug (eIND) category	**FDA:** On March 25th, 2020, the FDA approved the use of convalescent plasma under the emergency investigational new drug (eIND) category	**FDA:** On March 25th, 2020, the FDA approved the use of convalescent plasma under the emergency investigational new drug (eIND) category	plasma under the emergency investigational new drug (eIND) category
Trial Identifier	NCT04342182 (CONCOVID Study)	IRCT20200404046948N1	IRCT20200413047056N1	IRCT20200310046736N1	ChiCTR2000030702
Phase & Intention	Phase II/III study to decrease overall mortality in patients within COVID disease	Phase III study to evaluate the efficacy and safety of convalescent plasma in the treatment of patients with severe SARS-CoV-2 infection (COVID-19)	Phase III study to evaluate the efficacy of intravenous immunoglobulin and convalescent plasma in improving the condition of patients with COVID-19	Phase II/III study evaluating the therapeutic effect of Convalescent Plasma and Plasma-derived Immunoglobulin-enriched solution on COVID-19 Patients	Phase 0 study to evaluate efficacy and safety indicators of received convalescent plasma therapy
Study design	**RCT**, single-blind, standard of care-comparator, parallel assignment	**RCT**, open-label, conventional therapy comparator, parallel assignment	**RCT**, open-label, intravenous immunoglobulin and common national protocol comparator, three arms, parallel assignment	**RCT**, single-blind, Plasma-derived Immunoglobulin-enriched solution and - routine care comparator, three arms, parallel assignment	**RCT**, open-label, conventional treatment comparator, parallel assignment
Status trial	Recruiting, started April 8, 2020	Recruiting, started April 13, 2020	Recruiting, started April 18, 2020	Not yet recruiting	Recruiting
Duration/End of Study	Estimated Primary Completion Date: July 1, 2020 Estimated Study Completion Date: July 1, 2020	Estimated Primary Completion Date: NA Estimated Study Completion Date: NA	NA	NA	From 2020-02-15 to 2020-08-15
Study details					
Number of Patients	n = 426 (Adult, Older Adult; 18 Years and older)	n = 60 (Adult, Older Adult, 18 Years to 70 years)	15 (From 18 years old to 50 years old)	45 (From 20 years old to 45 years old)	n = 50 (age ≥ 18 years)
Location/Centres	Netherlands	Teheran	Iran	Iran	China

Active substance	Convalescent plasma	Convalescent plasma	Convalescent plasma	Convalescent plasma	Convalescent plasma
Intervention	Convalescent plasma (300mL of convalescent plasma from COVID-19 recovered donors)	Convalescent plasma	Intravenous immunoglobulin therapy+ common national protocol treatments convalescent plasma therapy+ common national protocol treatments	Convalescent plasma Plasma-derived Immunoglobulin-enriched solution	Conventional treatment combined with convalescent plasma treatment
Controls	Standard of care	Conventional therapy	Common national protocol treatments	Routine care	Conventional treatment
Duration of observation/Follow-up (Current Primary Outcome Measures)	Until hospital discharge or a maximum of 60 days whichever comes first	Up to 14 days	Up to 12 days	Up to 14 days	Up to 28 days
Endpoints (Current Primary Outcome Measures)	Overall mortality until discharge from the hospital or a maximum of 60 days after admission whichever comes first [Time Frame: until hospital discharge or a maximum of 60 days whichever comes first] the mortality in the 300ml convP group will be compared with the control arm	Clinical improvement within 14 days of admission	Lung involvement in X-ray and CT-scan, SPO2, LDH enzyme, viral load, acute phase protein, white blood cell count, ESR, length of hospital stay, duration of mechanical ventilation (from the start of the intervention for 12 days)	complete remission of clinical signs of disease; Negative result for COVID-19 RT-PCR test; Normal CT Scan	Time to clinical recovery after randomization
Results/Publication	Not provided	Not provided	Not provided	Not provided	Not provided

*Table 3.12-1: RCTs related to **Convalescent plasma** therapy in clinical trial registry (Continued)*

Active substance	Convalescent plasma	Convalescent plasma	Convalescent plasma	Convalescent plasma	Convalescent plasma
Sponsor/Collaborator	The First Affiliated Hospital of Zhengzhou University	China-Japan friendship hospital	Wuhan Jinyintan Hospital (Wuhan Infectious Diseases Hospital)	Renmin Hospital of Wuhan University	Johns Hopkins University
Mechanism of operation	Passive immunization (transfusion of apheresis frozen plasma (AFP) from COVID-19 convalescent	Passive immunization (transfusion of apheresis frozen plasma (AFP) from COVID-19 convalescent	Passive immunization (transfusion of apheresis frozen plasma (AFP) from COVID-19 convalescent	Passive immunization (transfusion of apheresis frozen plasma (AFP) from COVID-19 convalescent	Passive immunization (transfusion of apheresis frozen plasma (AFP) from COVID-19 convalescent patients allows the transfer of donor neutralizing

Active substance	Convalescent plasma	Convalescent plasma	Convalescent plasma	Convalescent plasma	Convalescent plasma
	patients allows the transfer of donor neutralizing antibodies directed against SARS-CoV2 antigens to the recipient, thus allowing the generation of passive immunization)	patients allows the transfer of donor neutralizing antibodies directed against SARS-CoV2 antigens to the recipient, thus allowing the generation of passive immunization)	patients allows the transfer of donor neutralizing antibodies directed against SARS-CoV2 antigens to the recipient, thus allowing the generation of passive immunization)	patients allows the transfer of donor neutralizing antibodies directed against SARS-CoV2 antigens to the recipient, thus allowing the generation of passive immunization)	antibodies directed against SARS-CoV2 antigens to the recipient, thus allowing the generation of passive immunization)
Regulatory status EMA/FDA	**EMA:** no marketing authorisation **FDA:** On March 25th, 2020, the FDA approved the use of convalescent plasma under the emergency investigational new drug (eIND) category.	**EMA:** no marketing authorisation **FDA:** On March 25th, 2020, the FDA approved the use of convalescent plasma under the emergency investigational new drug (eIND) category	**EMA:** no marketing authorisation **FDA:** On March 25th, 2020, the FDA approved the use of convalescent plasma under the emergency investigational new drug (eIND) category	**EMA:** no marketing authorisation **FDA:** On March 25th, 2020, the FDA approved the use of convalescent plasma under the emergency investigational new drug (eIND) category	**EMA:** no marketing authorisation **FDA:** On March 25th, 2020, the FDA approved the use of convalescent plasma under the emergency investigational new drug (eIND) category
Trial Identifier	ChiCTR2000030627	ChiCTR2000029757	ChiCTR2000030010	ChiCTR2000030929	NCT04323800
Phase & Intention	Phase 0 study to evaluate the effect of convalescent plasma therapy on the efficacy, safety and prognosis of severe COVID-19 patients, in order to find an effective treatment plan for COVID-19.	Phase 0 study to evaluate the efficacy of this therapy for the treatment of severe and critical novel coronavirus pneumonia (COVID-19)	Phase NA, to evaluate the efficacy and safety of anti-SARS-CoV-2 virus inactivated plasma in the treatment of severe novel coronavirus pneumonia patients (COVID-19)	Phase NA, to evaluate the efficacy and safety of anti-SARS-CoV-2 virus inactivated plasma in the treatment of severe novel coronavirus pneumonia (COVID-19)	Phase 2 Comparing the Efficacy and Safety Human Coronavirus Immune Plasma (HCIP) vs. Control (SARS-CoV-2 Non-immune Plasma) Among Adults Exposed to COVID-19
Study design	**RCT**, routine treatment-comparator, parallel assignment	**RCT**, open-label, Conventional treatment comparator, parallel assignment	**RCT**, double-blind, ordinary plasma comparator, parallel assignment	**RCT**, double-blind, ordinary plasma comparator, parallel assignment	**RCT**, triple-blind, standard plasma comparator, parallel assignment
Status trial	Recruiting, started	Recruiting, started	Not yet recruiting	Not yet recruiting	Not yet recruiting
Duration/End of Study	From 2020-02-01 to 2020-05-30	From 2020-02-14 to 2021-02-05	From 2020-02-19 to 2020-05-31	From 2020-03-17 to 2020-06-16	Estimated Primary Completion Date: December 31, 2022 Estimated Study Completion Date: January, 2023
Study details					
Number of Patients	n = 30	n = 200 (18 or more years old)	n = 100 (18 to 70 years old)	n = 60 (18 to 70 years old)	n = 150 (18 years and older)
Location/Centres	China	China	China	China	US

Active substance	Convalescent plasma	Convalescent plasma	Convalescent plasma	Convalescent plasma	Convalescent plasma
Intervention	Convalescent plasma therapy + routine treatment	Conventional treatment and convalescent plasma therapy	Anti-SARS-CoV-2 virus inactivated plasma	Anti-SARS-CoV-2 virus inactivated plasma	SARS-CoV-2 convalescent plasma
Controls	Routine treatment	Conventional treatment	Ordinary plasma	Ordinary plasma	SARS-CoV-2 non-immune Plasma (Standard plasma collected prior to December 2019)
Duration of observation/Follow-up (Current Primary Outcome Measures)	NA	Up to 28 days	Up to 28 days	Up to 28 days	28 (up to 90)
Endpoints (Current Primary Outcome Measures)	Temperature, Virus nucleic acid detection	The number of days between randomised grouping and clinical improvement (Time Frame: within 28 days admission)	Improvement of clinical symptoms (Clinical improvement is defined as a reduction of 2 points on the 6-point scale of the patient's admission status or discharge from the hospital)	Improvement of clinical symptoms (Clinical improvement is defined as a reduction of 2 points on the 6-point scale of the patient's admission status or discharge from the hospital)	Cumulative incidence of composite outcome of disease severity [Time Frame: Day 28]: the presence or occurrence of at least one of the following: Death; Requiring mechanical ventilation and/or in ICU; non-ICU hospitalization, requiring supplemental oxygen;non-ICU hospitalization, not requiring supplemental oxygen;Not hospitalized, but with clinical and laboratory evidence of COVID-19 infectionNot hospitalized, no clinical evidence of COVID-19 infection, but with positive PCR for SARS-CoV-2
Results/Publication	Not provided	Not provided	Not provided	Not provided	Not provided

*Table 3.12-1: RCTs related to **Convalescent plasma** therapy in clinical trial registry (Continued)*

Active substance	Convalescent plasma	Convalescent plasma	Convalescent plasma	Convalescent plasma	Convalescent plasma
Sponsor/Collaborator	Universidad del Rosario/ undación Universitaria de	Baylor Research Institute	Thomas Benfield, Hvidovre University Hospital	Cristina Avendaño Solá, Puerta de Hierro University Hospital	Stanford University

Active substance	**Convalescent plasma**	**Convalescent plasma**	**Convalescent plasma**	**Convalescent plasma**	**Convalescent plasma**
	Ciencias de la Salud;CES University;Instituto Distrital de Ciencia Biotecnología e Innovacion en Salud				
Mechanism of operation	Passive immunization (transfusion of apheresis frozen plasma (AFP) from COVID-19 convalescent patients allows the transfer of donor neutralizing antibodies directed against SARS-CoV2 antigens to the recipient, thus allowing the generation of passive immunization)	Passive immunization (transfusion of apheresis frozen plasma (AFP) from COVID-19 convalescent patients allows the transfer of donor neutralizing antibodies directed against SARS-CoV2 antigens to the recipient, thus allowing the generation of passive immunization)	Passive immunization (transfusion of apheresis frozen plasma (AFP) from COVID-19 convalescent patients allows the transfer of donor neutralizing antibodies directed against SARS-CoV2 antigens to the recipient, thus allowing the generation of passive immunization)	Passive immunization (transfusion of apheresis frozen plasma (AFP) from COVID-19 convalescent patients allows the transfer of donor neutralizing antibodies directed against SARS-CoV2 antigens to the recipient, thus allowing the generation of passive immunization)	Passive immunization (transfusion of apheresis frozen plasma (AFP) from COVID-19 convalescent patients allows the transfer of donor neutralizing antibodies directed against SARS-CoV2 antigens to the recipient, thus allowing the generation of passive immunization)
Regulatory status EMA/FDA	**EMA:** no marketing authorisation **FDA:** On March 25th, 2020, the FDA approved the use of convalescent plasma under the emergency investigational new drug (eIND) category.	**EMA:** no marketing authorisation **FDA:** On March 25th, 2020, the FDA approved the use of convalescent plasma under the emergency investigational new drug (eIND) category	**EMA:** no marketing authorisation **FDA:** On March 25th, 2020, the FDA approved the use of convalescent plasma under the emergency investigational new drug (eIND) category	**EMA:** no marketing authorisation **FDA:** On March 25th, 2020, the FDA approved the use of convalescent plasma under the emergency investigational new drug (eIND) category	**EMA:** no marketing authorisation **FDA:** On March 25th, 2020, the FDA approved the use of convalescent plasma under the emergency investigational new drug (eIND) category
Trial Identifier	NCT04332835	NCT04333251	NCT04345289	NCT04345523	NCT04355767
Phase & Intention	Phase 2/3 study to evaluate the effect of Convalescent Plasma for Patients With COVID-19	Phase 1 study Evaluating Efficacy and Safety of High-titer Anti-Sars-CoV-2 Plasma vs Best Supportive Care in Hospitalized Patients With Interstitial Pneumonia Due to COVID-19	Phase 3, to assess the safety and efficacy of novel treatment option of moderate-severe COVID-19	Phase 2, to study the efficacy and safety of passive immunotherapy with CP compared to a control of standard of care (SOC)	Phase 2, to evaluate the efficacy of treatment with high-titer Anti- SARS-CoV-2 plasma (convalescent plasma) versus control (standard plasma) in patients with COVID-19 respiratory symptoms
Study design	**RCT**, open-label, active comparator, parallel assignment	**RCT**, open-label, best supportive care comparator, parallel assignment	**RCT**, Quadruple blinded, placebo-controlled, multicenter, multi-stage study with six parallel treatment arms consisting	**RCT**, open-label, standard of care comparator, parallel assignment	**RCT**, double-blind, standard plasma comparator, parallel assignment

Active substance	Convalescent plasma	Convalescent plasma	Convalescent plasma	Convalescent plasma	Convalescent plasma
			of either convalescent plasma, sarilumab, hydroxychloroquine, baricitinib, intravenous and subcutaneous placebo, or oral placebo		
Status trial	Not yet recruiting	Not yet recruiting	Recruiting	Recruiting	Not yet recruiting
Duration/End of Study	Estimated Primary Completion Date: August 31, 2020 Estimated Study Completion DateDecember 31, 2020	Estimated Primary Completion Date: December 31, 2022 Estimated Study Completion Date: December 31, 2022	Estimated Primary Completion Date: June 15, 2021 Estimated Study Completion Date: June 15, 2021	Estimated Primary Completion Date: July, 2020 Estimated Study Completion Date: July, 2020	Estimated Primary Completion Date: December, 2022 Estimated Study Completion Date: December, 2022
Study details					
Number of Patients	n = 80 (18 to 60 years old)	n = 115 (18 years and older)	n = 1500 (18 years and older)	n = 278 (18 years and older)	n = 206 (18 years and older)
Location/Centres	Colombia	NA	Denmark	Spain	US
Intervention	Convalescent Plasma COVID-19 + Hydroxychloroquine	Convalescent plasma	Convalescent anti-SARS-CoV-2 plasma; Sarilumab; Baricitinib; Hydroxychloroquine	Fresh plasma from donor immunized against COVID-19	SARS-CoV-2 convalescent plasma
Controls	Hydroxychloroquine	Best supportive care	Injective placebo; Oral placebo	Standard of care	Standard Plasma
Duration of observation/Follow-up (Current Primary Outcome Measures)	Up to 28 days	An average 28 days	28 days, up to 90 days	15 days, Up to 3 months	15 days
Endpoints (Current Primary Outcome Measures)	Change in Viral Load; Change in Immunoglobulin M COVID-19 Titers; Change in Immunoglobulin G COVID-19 Titers	reduction in oxygen and ventilation support [Time frame: through study completion, an average of 4 weeks]	All-cause mortality or need of invasive mechanical ventilation [Time frame: 28 days]	Category Changes in Ordinal Scale [Time frame: 15 days]	Time to disease progression [TimefFrame: 15 days]
Results/Publication	Not provided	Not provided	Not provided	Not provided	Not provided

*Table 3.12-1: RCTs related to **Convalescent plasma** therapy in clinical trial registry (Continued)*

Active substance	**Convalescent plasma**	**Convalescent plasma**	**Convalescent plasma**	**Convalescent plasma**	**Convalescent plasma**
Sponsor/Collaborator	Royal College of Surgeons in Ireland - Medical University of Bahrain/ Salmaniya Medical Complex; Bahrain Defence Force Royal Medical Services, Military Hospital; Mohammed Bin Khalifa Bin Sulman Al Khalifa Cardiac Centre, Awali	Hospital Universitario Dr. Jose E. Gonzalez	Max R. O'Donnell, Columbia University/ New York Blood Center	Brigham and Women's Hospital	Vanderbilt University Medical Center
Mechanism of operation	Passive immunization (transfusion of apheresis frozen plasma (AFP) from COVID-19 convalescent patients allows the transfer of donor neutralizing antibodies directed against SARS-CoV2 antigens to the recipient, thus allowing the generation of passive immunization)	Passive immunization (transfusion of apheresis frozen plasma (AFP) from COVID-19 convalescent patients allows the transfer of donor neutralizing antibodies directed against SARS-CoV2 antigens to the recipient, thus allowing the generation of passive immunization)	Passive immunization (transfusion of apheresis frozen plasma (AFP) from COVID-19 convalescent patients allows the transfer of donor neutralizing antibodies directed against SARS-CoV2 antigens to the recipient, thus allowing the generation of passive immunization)	Passive immunization (transfusion of apheresis frozen plasma (AFP) from COVID-19 convalescent patients allows the transfer of donor neutralizing antibodies directed against SARS-CoV2 antigens to the recipient, thus allowing the generation of passive immunization)	Passive immunization (transfusion of apheresis frozen plasma (AFP) from COVID-19 convalescent patients allows the transfer of donor neutralizing antibodies directed against SARS-CoV2 antigens to the recipient, thus allowing the generation of passive immunization)
Regulatory status EMA/FDA	**EMA:** no marketing authorisation **FDA:** On March 25th, 2020, the FDA approved the use of convalescent plasma under the emergency investigational new drug (eIND) category	**EMA:** no marketing authorisation **FDA:** On March 25th, 2020, the FDA approved the use of convalescent plasma under the emergency investigational new drug (eIND) category	**EMA:** no marketing authorisation **FDA:** On March 25th, 2020, the FDA approved the use of convalescent plasma under the emergency investigational new drug (eIND) category	**EMA:** no marketing authorisation **FDA:** On March 25th, 2020, the FDA approved the use of convalescent plasma under the emergency investigational new drug (eIND) category	**EMA:** no marketing authorisation **FDA:** On March 25th, 2020, the FDA approved the use of convalescent plasma under the emergency investigational new drug (eIND) category
Trial Identifier	NCT04356534	NCT04358783	NCT04359810	NCT04361253	NCT04362176
Phase & Intention	Phase NA, study to to compare plasma therapy using convalescent plasma with antibody against SARS-CoV-2 to usual supportive therapy in COVID-19 patients with pneumonia and	Phase II study Evaluating the Efficacy and Safety of Plasma From Patients Cured of COVID-19 Compared to the Best Available Therapy in Subjects With SARS-CoV-2 Pneumonia	Phase 2, to Evaluate the Efficacy and Safety of Human Anti-SARS-CoV-2 Convalescent Plasma in Severely Ill Adults With COVID-19	Phase 3, to determine whether the early addition of HT-CCP to standard treatment improves the clinical outcome (as assessed by the Modified WHO Ordinal Scale) of patients with COVID-19 who are hospitalized	Phase 3, to Test the Safety and Efficacy of Convalescent Donor Plasma to Treat COVID-19 in Hospitalized Adults

Active substance	Convalescent plasma	Convalescent plasma	Convalescent plasma	Convalescent plasma	Convalescent plasma
	hypoxia, and to determine if the clinical course is improved			but not yet in moderate or severe ARDS	
Study design	**RCT**, open-label, routine care comparator, parallel assignment	**RCT**, Quadruple-blind, best available therapy comparator, parallel assignment	**RCT**, double-blind, non-convalescent plasma comparator, parallel assignment	**RCT**, double-blind, standard plasma comparator, parallel assignment	**RCT**, triple-blind, placebo comparator, parallel assignment
Status trial	Not yet recruiting	Not yet recruiting	Not yet recruiting	Not yet recruiting	Not yet recruiting
Duration/End of Study	Estimated Primary Completion Date: May 3, 2020 Estimated Study Completion Date: June 30, 2020	Estimated Primary Completion Date: Estimated Study Completion Date: February 1, 2021 May 30, 2021	Estimated Primary Completion Date: December 31, 2022 Estimated Study Completion Date: April, 2021	Estimated Primary Completion Date: June, 2021 Estimated Study Completion Date: December, 2021	Estimated Primary Completion Date: April, 2021 Estimated Study Completion Date: April, 2021
Study details					
Number of Patients	n = 40 (18 or more years old)	n = 30 (18 or more years old)	n = 105 (18 or more years old)	n = 220 (12 months and older)	n = 500 (18 years and older)
Location/Centres	Bahrain	Mexico	US	NA	US
Intervention	convalescent patient plasma plus routine local standard of care	Convalescent plasma from cured COVID-19 patients and Supportive management depending on individual needs	Convalescent Plasma (anti-SARS-CoV-2 plasma	High-Titer COVID-19 Convalescent Plasma (HT-CCP	SARS-CoV-2 convalescent plasma
Controls	Routine care for COVID-19 patients	Best available therapy	Non-convalescent plasma	Standard plasma (FFP)	Placebo
Duration of observation/Follow-up (Current Primary Outcome Measures)	10 day or until discharge	14 days, up to 90 days	Up to 28 days	14 days	15 days, up to 29 days
Endpoints (Current Primary Outcome Measures)	Requirement for invasive ventilation [Time frame: 10 day or until discharge]	Early all-cause mortality [Time frame: 14 days]	Time to Improvement [Time frame: Up to 28 days]	Modified WHO Ordinal Scale (MOS) score [Time frame: Day 14]	COVID Ordinal Outcomes Scale: Day 15 [Time frame: Study Day 15]
Results/Publication	Not provided	Not provided	Not provided	Not provided	Not provided

*Table 3.12-1: RCTs related to **Convalescent plasma** therapy in clinical trial registry (Continued)*

Active substance	Convalescent plasma
Sponsor/Collaborator	The First Affiliated Hospital of Nanchang University

Mechanism of operation	Passive immunization (transfusion of apheresis frozen plasma (AFP) from COVID-19 convalescent patients allows the transfer of donor neutralizing antibodies directed against SARS-CoV2 antigens to the recipient, thus allowing the generation of passive immunization)
Regulatory status EMA/FDA	**EMA:** no marketing authorisation **FDA:** On March 25th, 2020, the FDA approved the use of convalescent plasma under the emergency investigational new drug (eIND) category.
Trial Identifier	ChiCTR2000030179
Phase & Intention	Phase NA study to evaluate the effects of novel coronavirus pneumonia rehabilitation plasma in teatment of severe novel coronavirus pneumonia infection
Study design	**RCT**, routine treatment-comparator, parallel assignment
Status trial	Recruiting
Duration/End of Study	From 2020-02-24 to 2020-04-24
Study details	
Number of Patients	n = 100 (18 to 65 years)
Location/Centres	China
Intervention	Convalescent plasma therapy + routine treatment
Controls	Routine treatment
Duration of observation/Follow-up (Current Primary Outcome Measures)	NA
Endpoints (Current Primary Outcome Measures)	Cure rate; Mortality
Results/Publication	Not provided

Results of publications

A hand search on the 4 of May 2020 in PubMed was conducted and showed that there are still no results from clinical trials on the safety and efficacy of convalescent plasma in COVID-19 patients.

Results from case series, which involved from two to ten critically ill patients in China and Korea are published only [119-124]. The results from 10 severe adults cases with COVID-19, published by Duan et al. [119], showed that 200 ml of convalescent plasma transfusion with a high concentration of neutralizing antibodies can rapidly reduce the viral load and tends to improve clinical outcomes. Shen et al. [120] reported that administration of convalescent plasma containing neutralizing antibody in treatment of 5 critically ill patients with COVID-19 and ARDS in China was followed by improvement in their clinical status. Ye et al. [121], Ahn et al. [122], and Zhang et al. [123] also presented the positive results on clinical outcomes. Zeng et al. [124] presented results from case series of 6 COVID-19 subjects with respiratory failure who received convalescent plasma at a median of 21.5 days after first detection of viral shedding, all tested negative for SARS-CoV-2 RNA by 3 days after infusion, and 5 died eventually. They concluded that convalescent plasma treatment can discontinue SARS-CoV-2 shedding but cannot reduce mortality in critically end-stage COVID-19 patients, and treatment should be initiated earlier.

3.13 Combination therapy – triple combination of interferon beta-1b, lopinavir–ritonavir and ribavirin vs. lopinavir–ritonavir

Hung et al. 2020 [111] present the results of the first randomised controlled trial (NCT04276688) on the triple combination of interferon beta-1b, lopinavir–ritonavir, and ribavirin, compared with lopinavir–ritonavir alone, in the treatment of patients admitted to hospital with mild to moderate COVID-19 in Hong-Kong. In this multicentre, prospective, open-label, randomised, phase 2 trial, 127 patients were randomly assigned (2:1) to a 14-day combination of lopinavir 400 mg and ritonavir 100 mg every 12 h, ribavirin 400 mg every 12 h, and three doses of 8 million international units of interferon beta-1b on alternate days (combination group) or to 14 days of lopinavir 400 mg and ritonavir 100 mg every 12 h (control group). The primary endpoint was time to negative nasopharyngeal swab for SARS-CoV-2 RT-PCR. Secondary endpoints included time to symptom resolution by achieving a national early warning score 2 (NEWS2) of 0, a sequential organ failure assessment (SOFA) score of 0, 30-day mortality, and duration of hospital stay. Triple therapy was associated with a significant reduction in the duration of viral shedding (time to negative nasopharyngeal swab 7 days [IQR 5–11] in the combination group **vs** 12 days [8–15] in the control group; hazard ratio [HR] 4·37 [95% CI 1·86–10·24], p=0.0010), symptom alleviation (time to NEWS2 0 of 4 days [IQR 3–8] **vs** 8 days [7–9]; HR 3·92 [1·66–9·23], p<0.0001), and duration of hospital stay (9·0 days [7·0–13·0] **vs** 14·5 days [9·3–16·0]; HR 2·72 [1·2–6·13], p=0.016). There was no mortality in either group. The triple combination also suppressed IL-6 levels. Adverse events included self-limited nausea and diarrhoea with no difference between the two groups. No serious adverse events were reported in the combination group. One patient in the control group had a serious adverse event of impaired hepatic enzymes requiring discontinuation of treatment.

Table 3.13-1: Publications on clinical trials on triple combination of interferon beta-1b, lopinavir–ritonavir and ribavirin (NCT04276688)

Author, year [Reference]	**Hung et al. 2020 [111]**
Country	Hong-Kong
Sponsor/Funding	The Shaw-Foundation, Richard and Carol Yu, May Tam Mak Mei Yin, and Sanming Project of Medicine
Study design	Multicentre, prospective, open-label, randomised, phase 2 trial
Number of pts	127 patients were recruited; 86 were randomly assigned to the combination group and 41 were assigned to the control group
Intervention/Product	lopinavir 400 mg and ritonavir 100 mg every 12 h, ribavirin 400 mg every 12 h, and three doses of 8 million international units of interferon beta-1b on alternate days (combination group)
Comparator	lopinavir 400 mg and ritonavir 100 mg every 12 h (control group)
Inclusion criteria	Age at least 18 years, a national early warning score 2 (NEWS2) of at least 1, and symptom duration of 14 days or less upon recruitment
Exclusion criteria	Inability to comprehend and to follow all required study procedures; allergy or severe reactions to the study drugs; patients with known prolonged QT or PR interval, second- or third-degree heart block, or ventricular cardiac arrhythmias, including torsade de pointes; patients taking medication that will potentially interact with lopinavir/ritonavir, ribavirin or interferon-beta1b; patients with known history of severe depression; pregnant or lactation women; inability to comprehend and to follow all required study procedures; received an experimental agent (vaccine, drug, biologic, device, blood product, or medication) within 1 month prior to recruitment in this study or expect to receive an experimental agent during this study; unwilling to refuse participation in another clinical study through the end of this study; have a history of alcohol or drug abuse in the last 5 years; have any condition that the investigator believes may interfere with successful completion of the study
Pts pretreated + previous treatment	N.A
Mean age of patients, yrs (SD)	52 years (IQR 32–62)
Sex % male (% female)	68 (54%) men vs 59 (46%) women
Follow-up (days)	30 days
Clinical status	Mild to moderate COVID-19
Loss to follow-up, n (%)	1 patient in control group due to AE
Efficacy outcomes	
Overall survival (OS), n (%)	No patients died during the study
Time to negative nasopharyngeal swab	7 days [IQR 5–11] in the combination group vs 12 days [8–15] in the control group; hazard ratio [HR] 4·37 [95% CI 1·86–10·24], p=0.0010
Time to clinical improvement	Time to NEWS2 0 of 4 days [IQR 3–8] in the combination group vs 8 days [7–9] in the control group; HR 3·92 [1·66–9·23], p<0.0001
Length of hospitalisation	Duration of hospital stay (9·0 days [7·0–13·0] in the combination group **vs** 14·5 days [9·3–16·0] in the control group; HR 2·72 [1·2–6·13], p=0.016
Safety outcomes	
Adverse events (AEs)	41 (48%) of 86 patients in the combination group vs 20 (49%) of 41 patients in the control group most common: diarrhoea (52 [41%] of 127 patients), fever (48 [38%] patients), nausea (43 [34%]) and raised alanine transaminase level (18 [14%], p=ns
Serious adverse events (SAEs)	0 in combination group vs 1 in control group (impaired hepatic enzymes requiring discontinuation of treatment), p=0.15
Discontinuation of study drug due to AEs or SAEs	1 in the control group

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