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Covid-19

HSS/ Horizon Scanning
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Inhalt

Tabellenverzeichnis

Deutsche Zusammenfassung

Hintergrund

Policy-Frage

Am 30. März 2020 wurde vom österreichischen Gesundheitsministerium (BMSGPK) und weiteren gesundheitspolitischen Akteur*innen der Wunsch geäußert, ein Horizon Scanning System (HSS) für Covid-19 Medikamente und Impfstoffe einzurichten. Die Etablierung eines solchen HSS für Covid-19 Interventionen hat die folgenden Absichten:

30. März 2020: Etablierung von Covid-19 HSS (Medikamente + Impfstoffe)

a. Frühzeitige Informationen für gesundheitspolitische Entscheidungsträger darüber, welche Interventionen (Impfungen und Medikamente) derzeit in klinischen Studien erprobt werden und
b. Monitoring dieser in den nächsten Monaten, um gegebenenfalls einen evidenzbasierten Einkauf zu unterstützen.

Informationen über *Status von F&E *evidenzbasierter Einkauf

Methodik

Um diese Aufgabe zu erfüllen,

mehrstufiger Ansatz:

1. wird in einem ersten Schritt eine auf internationalen Quellen basierende Bestandsaufnahme zu Covid-19 Medikamente und Impfstoffe erstellt.
2. In einem zweiten Schritt wird eine selektive Recherche mittels Handsuche in Studienregistern nach Informationen über klinische Studien am Menschen und den Stand der Forschung durchgeführt.
3. Diese Informationen bilden die Grundlage für sogenannte "Vignetten" (Kurzbeschreibungen) für jene Produkte, die sich bereits in einem "fortgeschrittenen" Stadium befinden.
4. Anschließend werden die Produkte hinsichtlich des Status der klinischen Studien bis zur Zulassung beobachtet und schließlich auf Nutzen und Schaden bewertet.

Bestandsaufnahme selektive Suche Vignetten Monitoring

Alle Arbeitsschritte werden in enger internationaler (europäischer) Zusammenarbeit durchgeführt.

internationale/ europ. Zusammenarbeit

Zusätzlich werden Informationen über öffentliche Mittel für die Entwicklung von Medikamenten und Impfstoffen gesammelt.

zusätzlich: öffentliche Finanzierung von F&E

Folglich wird der vorliegende Bericht mehreren Versionen verfügbar sein:

- Version 1 (V1, April 2020): Bestandsaufnahme + Vignetten für die bis dato fortgeschrittensten Produkte
- Version 2+ (V2, V3…): monatliches Monitoring und Update

V1: Bestandsaufnahme + Vignetten
V2: monatliches Monitoring

Table 0-1.1: Internationale Quellen

Primäre Quellen	**Link**
WHO Medikamente: Impfungen:	 https://www.who.int/blueprint/priority-diseases/key-action/Table_of_therapeutics_Appendix_17022020.pdf?ua=1 https://www.who.int/blueprint/priority-diseases/key-action/Novel_Coronavirus_Landscape_nCoV_Mar26.PDF?ua=1
Danish Medicine Agency Medikamente: Impfungen:	 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] Medikamente: Impfungen:	https://www.mdpi.com/2077-0383/9/3/623 Tabelle 5+6, Tabelle 3+4
SPS HS-report (UK)	unveröffentlicht
Sekundäre Quellen	
VfA/ Verband Forschender Arzneimittelhersteller Medikamente: Impfungen:	 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 Medikamente:	https://www.ema.europa.eu/ https://www.ema.europa.eu/en/medicines/medicines-under-evaluation
Register	
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://covid19.trialstracker.net/
Systematische Reviews & HTAs	
HTAs und SR: NIPHNO	https://www.fhi.no/en/qk/systematic-reviews-hta/map/
INAHTA	http://www.inahta.org/covid-19-inahta-response/

Auswahl der Produkte für „Vignetten“

Produkte, in "fortgeschrittenen" Stadien

häufig genannte potentielle Kandidaten

Die folgenden Produkte wurden aus folgenden Gründen zur weiteren Betrachtung (1. Suche in Registerdatenbanken und 2. Beschreibung in Form von „Vignetten") ausgewählt:

- Produkte, die sich bereits in einem „fortgeschrittenen" Stadium befinden,
- Produkte, die am häufigsten in klinischen Fachzeitschriften als potenzielle Kandidaten diskutiert werden.

Teil 2 (Appendix): vollständige Listen

Die vollständige Liste aller Produkte findet sich in Teil 2/ Part 2 Tabelle A-1: Impfstoffe, Tabelle A-2: Therapeutika, Tabelle A-3:EudraCT registry studies.

Stand der Entwicklungen von Therapeutika (Repurposing)

keine zugelassenen Medikamente für Covid-19

Repurposing Produktgruppen

Aktuell stehen keine zugelassenen Medikamente für Covid--19 zur Verfügung. Eine große Bandbreite an **antiviralen Wirkstoffen** wird derzeit auf die Wirksamkeit gegen SARS-CoV-2/Covid-19 getestet. Bei einem Großteil der Wirkstoffe, die derzeit getestet werden, handelt es sich um „Repurposing“, also Medikamente, die bereits für andere Indikationen (vorrangig andere virale Infektionen) **zugelassen** sind.

Internationale Regulatoren betonen allerdings deutlich, dass robuste Evidenz für Zulassungssudien voliegen muss [2]. Die European Medicines Agency (EMA) begründete am 9. April eine eigene Covid-19 Task Force [3].

Antivirale Medikamente, Immunmodulatoren, Antikörper….

Fokus auf zielgerichtete Therapien

Pathogen-gerichtete (zielgerichtete) vs. immunmodulatorische Ansätze

Immunmodulatoren gegen schwere Komplikationen bei SARS-CoV-2 „Zytokinsturm“

Bei den Therapien für Patient*innen mit Covid--19 ist zwischen **zielgerichteten Therapeutika** (antivirale Medikamente) und **intensivmedizinischen** Therapieansätzen (supportive care) zu unterscheiden. Zielgerichtete Therapeutika richten sich gegen virale oder auch humane Proteine oder zelluläre Prozesse, mit dem Ziel, den Vermehrungszyklus des Virus (Eindringen in die Zellen, Replikation in den Zellen, Freisetzung aus den Zellen) zu blockieren.

Immunreaktionen sind bei Infizierten grundsätzlich erwünscht; sie dürfen nur nicht so exzessiv ausfallen, dass sie in der Lunge mehr Schaden anrichten als helfen. Deshalb sollen in mehreren Projekten überschießende Immunreaktionen bei schwer Erkrankten gedämpft werden [4]. Schwere Komplikationen bei SARS-CoV-2 Infektionen entstehen durch eine zu starke Immunantwort des Körpers, einem sogenannten „**Zytokinsturm**“ oder „cytokine release syndrome (CRS)“. Eine Blockierung dieser Immunreaktion durch **Immunmodulatoren** ist daher eine Therapieoption für Patient*innen mit schweren Covid-19-bedingten Krankheitsverläufen. Immunmodulatoren sind keine zielgerichteten (Pathogen-gerichteten) Therapeutika. Allerdings wirken einige der derzeit getesteten Wirkstoffe gleichzeitig Pathogen-gerichtet und immunmodulatorisch (z.B. Chloroquin).

Chloroquin Pathogen-gerichtet und immunmodulatorisch

Ein stark im Fokus der klinischen Forschung stehender Wirkstoff ist **Chloroquin**, das zur Therapie und Prophylaxe von Malaria sowie zu Behandlung von Autoimmunerkrankungen zugelassen ist. In Zellkulturexperimenten erzielte Chloroquin eine Unterdrückung der Reproduktion von SARS-CoV-2. **Hydroxychloroquin** ist ein Derivat von Chloroquin mit ähnlichen Wirkweisen und Anwendungen.

Interferone zur Immunabwehr viraler Infektionen

Interferone sind ein wesentlicher Bestandteil der natürlichen Immunabwehr gegen virale Infektionen. Die therapeutische Verabreichung zusätzlicher Interferone wird in vielen klinischen Studien getestet, meist als Kombinationstherapie mit antiviralen Wirkstoffen.

monoklonale Antikörper bei schwer infizierten Patient*innen

Monoklonale Antikörper sollen gegen die Komplikationen "Zytokinsturm" bei schwerer Covid-19 Erkrankung eingesetzt werden. Die Antikörper haben das Ziel, den Coronavirus zu neutralisieren und als vorbeugende Behandlung eingesetzt zu werden.

Tabelle 0-2: Produktübersicht zu Covid-19 Medikamenten (fortgeschrittene Entwicklungsstadien) (n=11)

Produkt	Hersteller	Phase der klinischen Prüfung/ Studienende	Studien-Status: Recruiting, laufend, preclinical
Remdesivir (GS-5734)	Gilead	Phase III zu Wirksamkeit & Sicherheit; 04/2020 Phase III zu Wirksamkeit & Sicherheit; 05/2020 Phase III zu Wirksamkeit & Sicherheit; 05/2020 Phase III zu Wirksamkeit & Sicherheit; 04/2023 Phase III zu Wirksamkeit & Sicherheit; 03/2023 Phase III zu Sicherheit; 05/2020 Phase II/III zu Wirksamkeit; 11/2020	7 laufende Studien: 6: recruiting 1: vor recruiting
Lopinavir + Ritonavir (Kaletra®)	Abbott-AbbVie + Generika	Phase IV zu Wirksamkeit; 06/2020 Phase IV zu Wirksamkeit; 07/2020 Phase III zu Wirksamkeit & Sicherheit; 03/2023 Phase III zu Wirksamkeit; 03/2021 Phase II zu Wirksamkeit; 05/2020 Phase NA zu Wirksamkeit & Sicherheit: 01/2021 Phase NA zu Wirksamkeit & Sicherheit: 02/2021 Phase NA zu Wirksamkeit & Sicherheit: 02/2021 Phase NA zu Wirksamkeit & Sicherheit: 03/2020 Phase NA zu Wirksamkeit & Sicherheit: 12/2020 Phase NA zu Wirksamkeit & Sicherheit: 04/2020	1 publizierter RCT 11 laufende Studien: 9: recruiting 2: vor recuriting
Favipirvir (Avigan®)	Fujifilm	Phase NA zu Wirksamkeit & Sicherheit: 03/2020 Phase NA zu Wirksamkeit & Sicherheit: 06/2020 Phase NA zu Wirksamkeit & Sicherheit: 05/2020 Phase NA zu Wirksamkeit & Sicherheit: 05/2020 Phase NA zu Wirksamkeit & Sicherheit: 04/2020	1 (un-)publizierter RCT 4 laufende Studien: 2: recuriting 2: vor recuriting
Darunavir (Prezista®)	Janssen-Cilag	Phase III zu Wirksamkeit & Sicherheit: 12/2020 Phase NA zu Wirksamkeit & Sicherheit: 12/2020	2 laufende Studien: 1: recruiting 1: vor recruiting
Chloroquine Phosphate (Resochin®)	Bayer Vital + Generika	Phase IV zu Wirksamkeit & Sicherheit: 06/2020 Phase IV zu Wirksamkeit & Sicherheit: 06/2020 Phase IV zu Wirksamkeit & Sicherheit: 07/2020 Phase IV zu Wirksamkeit & Sicherheit: 12/2020 Phase IV zu Wirksamkeit & Sicherheit: 12/2020 Phase IV zu Wirksamkeit & Sicherheit: 04/2020 Phase IV zu Wirksamkeit: 05/2020 Phase IV zu Wirksamkeit & Sicherheit: 04/2020 Phase NA zu Wirksamkeit: 05/2020 Phase NA zu Wirksamkeit: 02/2021 Phase NA zu Wirksamkeit: 02/2021	1 publizierter RCT 11 laufende Studien: 7: recruiting 4: vor recruiting
Hydroxychloroquine (Plaquenil®)	Sanofi Aventis + Generika	Phase IV zu Wirksamkeit: 04/2021 Phase IV zu Wirksamkeit: 02/2020 Phase IV zu Wirksamkeit: 05/2020 Phase IV zu Wirksamkeit: 02/2020 Phase IV zu Wirksamkeit & Sicherheit: 04/2020 Phase IV zu Wirksamkeit & Sicherheit: 04/2020 Phase IV zu Wirksamkeit & Sicherheit: 06/2020 Phase III/IV zu Wirksamkeit & Sicherheit: NR Phase III zu Wirksamkeit & Sicherheit: 10/2020 Phase III zu Wirksamkeit & Sicherheit: 08/2020 Phase III zu Wirksamkeit & Sicherheit: 04/2020 Phase III zu Wirksamkeit & Sicherheit: 03/2023 Phase III zu Wirksamkeit: NR Phase II zu Wirksamkeit & Sicherheit: NR Phase NA zu Wirksamkeit: 05/2020	1 publizierte CT 1 (un-)publizierter RCT 13 laufende Studien: 7: recruiting 4: vor recuriting 2: keine Information
Camostat Mesilate (Foipan®)	Ono Pharmaceutical (Japan)	Phase II zu Wirksamkeit & Sicherheit: 12/2020	1 laufende Studie: vor recruiting
APN01 (rhACE2)	Apeiron Biologics	Phase II zu Wirksamkeit: 11/2020	1 laufende Studie: vor recruiting
Tocilizumab (Roactemra®)	Hoffmann-La Roche	Phase IV zu Wirksamkeit & Sicherheit: 12/2020 Phase III zu Wirksamkeit & Sicherheit: 09/2021	14 laufende Studien: 4: recruiting

		Phase II zu Sicherheit: 10/2020 Phase II zu Wirksamkeit: 05/2020 Phase II zu Wirksamkeit: 08/2020 Phase II zu Wirksamkeit: 06/2021 Phase II zu Wirksamkeit: 10/2020 Phase II zu Wirksamkeit: 12/2020 Phase II zu Wirksamkeit: 05/2020 Phase II zu Wirksamkeit & Sicherheit: 12/2021 Phase II zu Wirksamkeit & Sicherheit: 12/2022 Phase NA zu Wirksamkeit & Sicherheit: 05/2021 Phase NA zu Wirksamkeit & Sicherheit: 05/2020 Phase NA zu Wirksamkeit & Sicherheit: 06/2020	10: vor recruiting
Sarilumab (Kevzara®)	Sanofi Aventis	Phase II/III zu Wirksamkeit & Sicherheit: 12/2021 Phase II/III zu Wirksamkeit: 06/2021 Phase II/III zu Wirksamkeit & Sicherheit: 03/2021 Phase II zu Wirksamkeit: 06/2021 Phase II zu Wirksamkeit & Sicherheit: 02/2021	5 laufende Studien: 3: recruiting 2: vor recruiting
Interferon beta 1a (SNG001)	Synairgen	Phase IV zu Wirksamkeit: 06/2022 Phase III zu Wirksamkeit & Sicherheit: 03/2023 Phase II zu Wirksamkeit & Sicherheit: 05/2021 Phase NA zu Sicherheit: 01/2023	4 laufende Studien: recruiting

Remdesivir

Remdesivir ist ein kürzlich entwickeltes Medikament mit einem breiten antiviralen Spektrum. Es ist bislang für keine Indikation zugelassen. Remdesivir hält „orphan drug designation“ (EMA, FDA) für die Indikation Ebola. In vitro zeigt es Wirkung gegen verschiedene Viren, inklusive SARS-CoV, MERS-CoV und andere humane und zoonotische Coronaviren. In Zellkulturexperimenten erzielte Remdesivir eine Unterdrückung der Reproduktion von SARS-CoV-2.

Remdesivir wird derzeit in mehreren klinischen Studien (7 Studien, davon 6 Phase III randomisierte kontrollierte Studien [RCTs]) untersucht, von denen zwei Studien Firmenstudien von Gilead sind und weitere fünf Studien von öffentlichen Institutionen durchgeführt werden. Alle Studien befinden sich im Stadium der Rekrutierung. Die Gilead (Zulassungs-) Studien untersuchen Remdesivir sowohl bei „moderat“ Erkrankten wie bei schwer an Covid-19 Erkrankten. Erste Ergebnisse können im Mai 2020 erwartet werden. Ergebnisse aus den öffentlich-finanzierten Studien könnten ev. auch bereits im April 2020 zu erwarten sein.

derzeit 7 Studien im Laufen (6 RCTs)
alle im „Recruiting“

davon 2 Gilead,
5 öffentlich-finanzierte Studien

erste Ergebnisse:
Mai 2020

Lopinavir + Ritonavir Kombinationstherapie (Kaletra®)

Kombinationstherapie für HIV zugelassen

1 RCT (China, publiziert): kein Unterschied zur Kontrollgruppe

11 laufende Studien (10 RCTs): alle im/vor „Recruiting"

erste Ergebnisse: Sommer 2020

Lopinavir in Kombination mit Ritonavir ist seit 2000 (FDA), resp. 2001 (EMA) für die Therapie von HIV zugelassen, nicht jedoch für Covid-19. Die ersten Ergebnisse einem RCT mit Patient*innen mit Covid-19 wurden am 18.03.2020 publiziert [5]. Die Behandlung von Patient*innen mit der Kombination zweier anti-HIV Medikamente Lopinavir + Ritonavir (zusätzlich zur Standardbehandlung) erzielte keine Verbesserung in Bezug auf die Dauer bis zur Genesung im Vergleich zur Standardbehandlung. Die Rate an Patient*nnen mit detektierbarer viraler RNA unterschied sich *nicht* zwischen den beiden Gruppen, woraus die Autor*innen schließen, dass der grundlegende erwünschte Effekt der Kombinationstherapie – Inhibierung der viralen Reproduktion – nicht erzielt wurde [5]. Elf weitere Studien laufen zur Zeit (10 RCTs, 9 davon in China, 1 in Frankreich, 1 in Kanada, alle öffentlich finanziert). Die frühsten Ergebnisse von zwei Studien sind im Sommer 2020 zu erwarten.

Favipiravir *(Avigan®)*

japanisches Influenza-Medikament, von EMA nicht zugelassen

1 RCT abgeschlossen (noch unpubliziert)
4 klinische Studien: 3 RCTs+1 nRCT laufend
erste Ergebnisse: Mai 2020

Favipiravir wurde 1999 von einer japanischen Pharmafirma als Grippemedikament (Handelsname: Avigan) entwickelt. Es hält keine EMA-Zulassung. Favipiravir wurde in Einzelfälle gegen Ebola eingesetzt. Im Februar 2020 wurde Favipiravir in China in einer ersten nicht randomisierten Doppelblindstudie (nRCT) an 80 Patient*innen als antivirale Therapie gegen das Coronavirus SARS-CoV-2 getestet. Favipiravir wird derzeit in mehreren klinischen Studien (1 abgeschlossene kontrollierte Studie, 3 laufende RCTs und 1 laufender nRCT) untersucht, von denen alle Studien von öffentlichen Institutionen (nur China) durchgeführt werden. Vier Studien befinden sich im Stadium der Rekrutierung oder noch davor. Die abgeschlossene Studie wird demnächst (nach peer-review) veröffentlicht. Erste Ergebnisse können im April/Mai 2020 erwartet werden.

Darunavir (Prezista®)

als HIV Medikament zugelassen
2 laufende RCTs (China)

Darunavir ist seit 2006 (FDA), resp. 2007 (EMA) für die Therapie von HIV zugelassen, nicht jedoch für Covid-19. Derzeit laufen zwei RCTs (in China), eine Studie rekrutiert, die andere noch nicht. Ergebnisse sind erst ab Dezember 2020 zu erwarten.

Chloroquin (Resochin®) und Hydroxychloroquin (Plaquenil®)

bei Malaria und Autoimmunerkrankungen
FDA: emergency Zulassung für Covid-19, NICHT EMA

Chloroquin Phosphate und Hydroxychloroquin sind seit den 70er Jahren als Arzneistoffe zur Therapie und Chemoprophylaxe von Malaria sowie zu Behandlung von Autoimmunerkrankungen zugelassen. Die FDA verfügte jüngst eine „emergency use authorization for Covid-19", nicht jedoch die EMA. Chloroquin Phosphate und Hydroxychloroquin (als Kombinatinstherapie mit Azithromycin) wird jedoch – aufgrund der Nebenwirkungen - ausschließlich bei schweren Krankheitsverläufen empfohlen, nicht als Prophylaxe bis valide Evidenz vorliegt [6, 7].

Für **Chloroquin Phosphate** (als Monotherapie oder als Kombinationstherapie mit Lopinavir + Ritonavir) sind 11 klinische Studien (alle in China, alle öffentlich finanziert, 8 davon kontrolliert Phase VI, rekrutierend) zur Effektivität von Chloroquin mit hospitalisierten Patient*innen mit schwerer Covid-19 Erkrankung registriert. In der einzigen veröffentlichten Studie [8] an 22 Patient*innen wird von einem kleinen Nutzen berichtet. Erste Ergebnisse von größeren Studien sind ab Frühsommer und Herbst 2020 zu erwarten.

11 Studien (China): zumeist Phase IV

kleine Studie publiziert: marginaler Effekt
weitere Ergebnisse 2020

Derzeit laufen 15 klinische Studien (8 kontrollierte Phase IV in China, 5 Phase III RCTs, alle öffentlich finanziert) zu **Hydroxychloroquin** (als Monotherapie oder als Kombinationstherapie mit Lopinavir + Ritonavir) zu Patient*innen mit verschiedenen Schweregraden der Covid-19 Erkrankung. Die in China registrierten Studien zur Effektivität von Hydroxychloroquin mit Patient*innen mit Covid-19 registriert überschneiden sich teilweise mit den Studien zu Chloroquin.

15 Studien (China), 2 abgeschlossen (FR, China) und 13 laufende

In einer nRCT in Frankreich wurden 70 % der Patient*nnen mit Covid-19, die mit Hydroxychloroquin behandelt wurden (n=20) nach sechs Tagen virus-frei getestet. Im Vergleich dazu wurden nur 12,5 % der Covid-19 Patient*innen in einer nicht näher definierten Kontrollgruppe nach sechs Tagen virus-frei getestet. Die Studie weist allerdings mehrere schwerwiegende methodische Mängel auf. In China sind 12 klinische Studien zur Effektivität von Hydroxychloroquin mit Patient*innen mit Covid-19 registriert (diese überschneiden sich teilweise mit den Studien zu Chloroquin). Weitere Ergebnisse sind ab Mai 2020 zu erwarten.

Studie aus FR mit schweren methodischen Mängeln: Behandlung erfolgreich

weitere Ergebnisse: ab Mai 2020

Camostat Mesilate (Foipan®)

Camostat ist ein Wirkstoff aus der Gruppe der Protease-Inhibitoren, der unter anderem bei einer Entzündung der Bauchspeicheldrüse und einer postoperativen Refluxösophagitis eingesetzt wird (Zulassung nur in Japan, nicht von EMA, FDA). Weil Camostat die Protease TMPRSS2 hemmt, welche für das Eindringen von SARS-CoV-2 in die Wirtszellen wichtig ist, wurde das Arzneimittel im Jahr 2020 für die Behandlung von Covid-19 untersucht.

Protease-Inhibitor bei Entzündung der Bauchspeicheldrüse
Zulassung: Japan, nicht EMA, FDA

Derzeit ist nur ein RCT (Dänemark, öffentliche Finanzierung) registriert. Ein Ergebnis ist mit Dezember 2020 zu erwarten.

1 Studie (RCT) in DK

APN01 (rhACE2)

Das Medikament **APN01** ist aus der SARS-Forschung hervorgegangen und wurde zwischenzeitlich auch schon in Patient*innenstudien gegen andere Lungenerkrankungen erprobt. APN01 hat derzeit keine Zulassung, weder von EMA, noch von FDA. Es blockiert ein Molekül auf Viren, das diese zum Eindringen in Lungenzellen benötigen und hilft zusätzlich dabei, Lungenschäden durch Entzündungsreaktionen zu vermeiden.

aus SARS-Forschung hervorgegangen

keine Zulassung
1 Studie (Phase II RCT), vor Rekrutirung

APN01 wird derzeit in einem Phase II RCT klinisch untersucht; die Rekrutierung hat aber noch nicht begonnen. Erste Ergebnisse sind im November 2020 zu erwarten.

Ergebnisse frühestens November 2020

Tocilizumab (Roactemra®)

Tocilizumab ist ein monoklonaler Antikörper, der auf den Interleukin-6-Rezeptor abzielt. Er ist u.a. für die rheumatoide Arthritis zugelassen (EMA-Zulassung: 2009), nicht aber bei Covid-19. Derzeit existieren vorläufige Ergebnisse einer unkontrollierten, retrospektiven Studie bei 20 Patient*innen mit schwerer Covid-19-Erkrankung und erhöhten IL-6-Spiegeln.

Tocilizumab wird derzeit in 16 klinischen Studien (9 Phase II zum Teil RCTs, aber auch einarmigen Studien, weiter Phase IV Studien, zumeist öffentlich finanziert, Europa und USA) erprobt, die meisten Studien sind allerdings noch im Stadium der Rekrutierung. In Italien ist eine Studie mit Patient*innen mit Covid-19 und erhöhten IL-6-Spiegeln angelaufen. Erste Ergebnisse sind Mitte 2020 zu erwarten.

Interleukin-6-Rezeptor für rheumatoide Arthritis zugelassen (EMA)

Covid-10: bei erhöhten IL-6-Spiegeln, schwere Erkrankungen

16 Studien (häufig RCTs, aber auch einarmige)

Sarilumab (Kevzara®)

Sarilumab ist ebenfalls ein humaner monoklonaler Antikörper gegen den Interleukin-6-Rezeptor, der zur Behandlung von rheumatoider Arthritis entwickelt wurde (EMA-Zulassung 2017).

Sarilumab wird derzeit in fünf klinischen Studien (Europa, USA und Kanada, 3 Phase II/ III RCTs, 2 Phase II RCTs, 2 davon von Sanofi/ Regeneron Pharmaceuticals finanziert) erprobt, die meisten Studien sind allerdings noch im Stadium der Rekrutierung. Erste Ergebnisse sind erst 2021 zu erwarten.

Interleukin-6-Rezeptor für rheumatoide Arthritis zugelassen (EMA)

5 Studien (Phase II+III RCTs)
frühestens 2021

Interferon beta 1a (SNG001)

Interferone sind Varianten körpereigener Botenstoffe, die gentechnisch hergestellt werden. Sie bekämpfen nicht die Viren, sondern fördern die körpereigene Virenabwehr. Zwei INFb Präparate (Rebif® und Avonex®, EMA-Zulassung 90er Jahre) sind bei Multipler Sklerose zugelassen.

INFb wird derzeit in vier klinischen Studien (Phase II, III und IV, 3 RCTs und 1 Beobachtungsstudie, 1 firmenfinanzierte Studie/Synairgen) erprobt. Die meisten Studien sind noch im Stadium der Rekrutierung. Erste Ergebnisse sind erst 2021 zu erwarten.

INFb Präparate bei Multipler Sklerose zugelassen (EMA)

4 Studien (Phase II-IV)
frühestens 2021

Stand der Impfstoffentwicklung

derzeit kein Impfstoff

Aktuell steht kein Impfstoff zum Schutz vor Covid-19 zur Verfügung.

zwischen 48 und 54 Impfstoffprojekte genannt

Es gibt allerdings eine Vielzahl von Projekten in der Entwicklungsphase. Es werden zwischen 48 [4], 50 [9], 54 (Vorarbeiten der Gesundheit Österreich GmbH [GÖG]) und 79 (Teil 2 dieses Berichts) **Impfstoffprojekte** genannt, die auf unterschiedlichen Plattformen aufbauen z. B. DNA, RNA, Proteinen oder Vektor-Impfstoffe. Die Unternehmen und Forschungsinstitute arbeiten auf unterschiedliche Impfstoffe hin. Die meisten ihrer Projekte zielen dabei auf eine der folgenden drei Impfstoffarten ab:

unterschiedliche Arten von Impfstoffen

Lebendimpfstoffe

Lebendimpfstoffe mit Vektorviren: Bei mehreren Projekten dienen gut bekannte, harmlose Viren als Ausgangspunkt. Vektorviren sind intakte Viren, die allerdings keine Krankheit hervorrufen können. Diese harmlosen Viren werden „verkleidet", im aktuellen Fall als SARS-Cov-2. Dazu werden mittels Genschere Oberflächenproteine des neuen Coronavirus eingefügt, damit das menschliche Immunsystem einen Schutz dagegen aufbaut [10]. Aufbauend auf einem Vektorvirus sind auch der erste zugelassene Ebola-Impfstoff, ein weiterer Ebola-Impfstoff (dessen Zulassung beantragt ist) und weitere experimentelle Impfstoffe entwickelt worden. Diese Strategie kommt nun beispielsweise in den Covid-19-Projekten von *Janssen*, dem *Deutschen Zentrum für Infektionsforschung* (*DZIF)* und der *University of Oxford* zur Anwendung [4].

Totimpfstoffe

Totimpfstoffe mit Virusproteinen: Mehrere Projekte, die auf Impfstoffe mit Virusproteinen abzielen (wie etwa die von *Novavax*, *Greffex* und der *University of Queensland*), beruhen auf lang bewährter Technologie: Sehr viele zugelassene Impfstoffe sind zusammengesetzt; beispielsweise solche gegen Tetanus, Hepatitis B oder Grippe. Totimpfstoffe enthalten Virusproteine (nicht-replizierender viraler Vektor), die eine Immunantwort auslösen, ohne dass dabei durch das Virus ein Krankheitsgeschehen bei einem Menschen ausgelöst wird [4].

Genbasierte Impfstoffe

Genbasierte Impfstoffe: Zum anderen gibt es auch neue Ideen für Impfstoffe, die auf DNA oder mRNA basieren. Diese Impfstoffe enthalten ausgewählte Gene des Virus in Form von mRNA[1] bzw. DNA, sodass im menschlichen Körper Virusproteine gebildet werden, die dann wiederum zur Immunität führen. Zu den Unternehmen, die solche Impfstoffe gegen Covid-19 entwickeln, gehören *CureVac*, *BioNTech*, *Moderna*, *Inovio*, *Arcturus* und *LineaRx/Takis*; auch das *OpenCorona Konsortium* entwickelt einen DNA-basierten Impfstoff [4].

[1] Als mRNA (messenger RNA), auch Boten-RNA genannt, wird das einzelsträngige RNA-Transkript eines zu einem Gen gehörigen Teilabschnitts der DNA bezeichnet.

Fortgeschrittene Impfstoffprojekte

Impfstoffprojekte teilweise schon weit fortgeschritten (Erprobung mit Freiwilligen)

Neue Technologien und Vorerfahrungen mit Impfstoffprojekten gegen verwandte Viren (siehe zuvor) machen eine enorme Beschleunigung möglich. Das belegen die Zwischenstände, die einige Unternehmen und Forschungsgruppen für ihre Projekte gemeldet haben. Die Projekte, die schon am weitesten vorangekommen sind, sind bereits in Etappe 4 bzw. Phase 1 eingetreten - der Erprobung mit Freiwilligen - oder sie planen, das in den kommenden Monaten zu tun.

Tabelle 0-3: Produktübersicht zu fortgeschrittenen Impfstoffprojekten

Produkt	Hersteller	Wirkmechanismus	Phase der klinischen Prüfung; Studienende (MM/JJJJ)	Studien-Status
mRNA-1273	ModernaTX	mRNA-genbasierter Impfstoff	Phase I zu Sicherheit; 06/2022	laufend
AD5-nCoV	CanSino Biological	Lebendimpfstoffe mit Vektorviren	Phase I zu Sicherheit; 12/2022	laufend
ChAdOx1 nCoV-19	University of Oxford	Lebendimpfstoffe mit Vektorviren	Phase I/II zu Wirksamkeit und Sicherheit; 05/2021	laufend
INO-4800	Inovio Pharmaceuticals	DNA-genbasierter Impfstoff	Klinische Testung (Phase I) startet voraussichtlich in 04/2020	präklinisch
Novavax COVID-19 Vaccine	Novavax	Virusprotein-Totimpfstoff	Klinische Testung (Phase I) startet frühestens in 06/2020	präklinisch
N.A.	University of Queensland/ GSK / Dynavax	Virusprotein-Totimpfstoff	Klinische Testung (Phase I) startet voraussichtlich in 06/2020	präklinisch
COVID-19 mRNA mobile unit	CureVac	mRNA-genbasierter Impfstoff	Klinische Testung (Phase I) startet frühestens in 06/2020	präklinisch
BNT-162	BioNTech/Fosun Pharma/Pfizer	mRNA-genbasierter Impfstoff	Klinische Testung (Phase I) startet voraussichtlich in 04/2020	präklinisch

mRNA-1273 von Moderna

in klinischer Erprobung an 45 gesunden Proband*innen

Eine erste klinische Studie mit einem **mRNA-Impfstoff** gegen SARS-CoV-2 ist am 16.03.2020 in Seattle angelaufen. Die von der US-Firma *Moderna* mit *dem U.S. National Institute of Allergy and Infectious Diseases* entwickelte Vakzine **mRNA-1273** enthält die Bauanleitung für die Konfiguration des viralen Spike-Proteins, die vor Andocken des Virus an die Zelle vorliegt. Das *Kaiser Permanente Institute* verabreicht seit 16.03.2020 45 gesunden Proband*innen Spritzen in zwei 28 Tage auseinanderliegenden Dosen. Diese **Phase-1-Studie** (NCT04283461) soll zunächst testen, ob die Vakzine verträglich und sicher sind [11].

Ad5-nCoV von CanSinoBIO

chinesiche Phase 1 Studie: 108 Testpersonen

Laut Medienberichten erlaubte China dem chinesischen Unternehmen CanSinoBIO die klinischen Tests ihres Mittels Ad5-nCoV, die mit 108 Testpersonen am Tongji Hospital in Wuhan durchgeführt werden. Der Impfstoffkandidat von CanSinoBIO ist damit der erste neuartige Coronavirus-Impfstoff gegen Covid-19 in einer klinischen **Phase-1-Studie in China** (ChiCTR2000030906) und basiert auf CanSinoBIOs Adenovirus-basierter Technologieplattform für virale Vektorimpfstoffe. Ad5-nCoV ist ein gentechnisch veränderter Impfstoffkandidat mit dem replikationsdefekten Adenovirus Typ 5 als Vektor zur Expression des SARS-CoV-2-Spike-Proteins. Ergebnisse aus präklinischen Tierstudien mit Ad5-nCoV zeigen, dass der Impfstoffkandidat in Tiermodellen eine starke Immunantwort auslösen kann. Präklinische Tiersicherheitsstudien zeigten ebenfalls ein gutes Sicherheitsprofil [12].

ChAdOx1 der Oxford University

April 2020: erste klinische Tests am Menschen

Auch ein Forschungsteam am *Jenner Institute der Universität Oxford* (UK) arbeitet gemeinsam mit dem italienischen Hersteller *Advent Srl* an der Entwicklung eines Coronavirus-Impfstoffs. Noch im **April 2020** soll mit klinischen Tests des **Impfstoffkandidaten ChAdOx1** am Menschen begonnen werden. Der Impfstoff wird unter Verwendung einer sicheren Version eines **Adenovirus** hergestellt. Das Adenovirus wurde so modifiziert, dass es sich nicht im Körper vermehren kann, und der genetische Code zur Bereitstellung von Anweisungen für die Herstellung des Coronavirus-Spike-Proteins wurde hinzugefügt, damit das Adenovirus dieses Protein nach der Impfung produzieren kann. Dies führt zur Bildung von Antikörpern gegen das Spike-Protein (S-Protein), das sich auf der Oberfläche von Coronaviren befindet [13].

INO-4800 von Inovio

April 2020: klinische Studie an 30 Freiwilligen beginnt

Laut eine Presseaussendung plant *Inovio* (USA) mit dem *Wistar Institute* (USA) und *Beijing Advaccine Biotechnology* (CHN) im **April 2020** mit klinischen Studien für ihren **DNA-Impfstoffkandidaten INO-4800** an 30 gesunden Freiwilligen in den USA und bald darauf in China und Südkorea zu beginnen. Der veröffentlichte Zeitplan sieht vor, die Ergebnisse der Clinical Trials im Herbst 2020 zu veröffentlichen [14, 15]. Die Plattform von *Inovio* liefert die optimierte DNA in Zellen, wo sie in Proteine übersetzt wird, die das Immunsystem eines Individuums aktivieren, um eine robuste gezielte T-Zell- und Antikörperantwort zu erzeugen. *Inovio* zielt darauf ab, das therapeutische Spektrum monoklonaler Antikörper mit seiner DNA-kodierten monoklonalen Antikörpertechnologie signifikant zu erweitern [16].

Novavax (USA)

Mai/ Juni 2020: Erprobung am Menschen beginnt

Das amerikanische Unternehmen *Novavax* testet derzeit mehrere Impfstoffkandidaten in präklinischen Studien und plant ab Mai oder Juni 2020 mit der Erprobung am Menschen zu beginnen. Die Impfstoffkandidaten von *Novavax* wurden mit der hauseigenen Plattform für rekombinante Protein-Nanopartikel-Technologie entwickelt, um Antigene zu erzeugen, die vom Coronavirus-Spike (S) -Protein abgeleitet sind. *Novavax* wird

voraussichtlich auch seine Matrix-M™-Adjuvantien[2] verwenden, um die Immunantwort des Impfstoffkandidaten zu verbessern (Novavax 2020). *Novavax* erhält von der *Coalition for Epidemic Preparedness Innovations (CEPI)* (siehe 0) eine Anfangsfinanzierung in Höhe von 4 Mio. USD, um die Entwicklung eines Covid-19-Impfstoffs zu unterstützen. Es wurde (noch) kein Name für den Impfstoffkandidaten von *Novavax* veröffentlicht.

University of Queensland (AUS)

Juni 2020: erste Erprobung an Menschen

In Australien untersucht die *Universität Queensland* mit dem Unternehmen *Dynavax* und *GSK*, die Adjuvantien beisteuern, das Potenzial eines Impfstoffs mit genetisch veränderten Virusproteinen, wodurch eine Immunreaktion verstärkt werden soll (The Guardian 2020). Die Erprobung am Menschen soll laut Medienberichten im **Juni 2020** beginnen. Auch die *Universität Queensland* wird von der *Coalition for Epidemic Preparedness Innovations (CEPI)* finanziell unterstützt. Es wurde (noch) kein Name für den Impfstoffkandidaten der *Universität Queensland* veröffentlicht.

CureVac (DE)

Juni/ Juli 2020: Beginn Phase 1 Studie

Das deutsche Biotechnologie-Unternehmen *CureVac* forscht ebenfalls an einem Protamin-komplexgebundenen **mRNA-basierten Impfstoffkandidaten** [17]. Nach eigenen Angaben habe das Unternehmen zwei Varianten eines Impfstoffs ausgewählt, die sich in Produktion befänden. Phase-1-Studien sollen laut Berichten im **Juni oder Juli 2020** starten, um die Variante mit der besten Wirkung zu finden. Ende Januar 2020 erhielt Curevac von CEPI eine Förderung in Höhe von bis zu 8,3 Mio. Euro für die beschleunigte Impfstoffentwicklung und -herstellung sowie für klinische Studien [18]. Die Europäischen Kommision investiert 80 Mio. Euro für Forschung & Entwicklung für das Unternehmen sowie die Produktion eines Impfstoffs. Die Finanzierung wird als Darlehen der Europäischen Investitionsbank (EIB) zur Verfügung gestellt [19, 20].

BNT162 von BioNTech, Pfizer und Fosun Pharma

Ende April 2020 (China): Beginn klinische Studie

Das Mainzer Unternehmen *BioNTech* entwickelt gemeinsam mit dem chinesischen Partner *Fosun Pharma* sowie *Pfizer* in den USA den mRNA-basierten Impfstoffkandidaten **BNT162**. BioNTech beabsichtigt, vorbehaltlich der behördlichen Genehmigung, die klinische Studie des Produktkandidaten BNT162 **Ende April 2020 in China** zu beginnen. BNT162 ist auch der erste Produktkandidat des Projekts *Lightspeed*, *BioNTechs* beschleunigtes Entwicklungsprogramm, das die Prävention und Behandlung von Covid-19-Infektionen umfasst. Für das Programm nutzt *BioNTech* gemeinsam mit dem Partner *Polymun* die **eigenen mRNA-Plattformen** für Infektionskrankheiten sowie die unternehmenseigene GMP-zertifizierte Infrastruktur für die mRNA-Impfstoffherstellung in Europa [21].

[2] Adjuvantien sind "Wirkverstärker" für Impfstoffe, die es unter anderem ermöglichen können, dass wesentlich weniger Virusprotein pro Impfinjektion für eine Immunisierung ausreichen bzw. mit einer gegebenen Menge produziertem Virusprotein mehr Injektionsdosen hergestellt werden können.

Product Development Partnerships (PDP) und Finanzielle Unterstützung

Europäische Kommission: Forschungsförderung: SC1-PHE-CORONAVIRUS-2020

17 Forschungsprojekte

Bereits am 30. Januar 2020 veröffentlichte die Europäische Kommission einen Aufruf zur Interessenbekundung im Rahmen des Horizon 2020 EU-Forschungsrahmenprogramms mit dem Titel „SC1-PHE-CORONAVIRUS-2020: Fortschrittliche Erkenntnisse für die klinische und gesundheitliche Reaktion auf die COVID-19-Epidemie“, mit einem Budget von 10 Mio. Euro, das in der Folge auf 47,5 Mio. Euro aufgestockt wurde. 17 Forschungsprojekte mit 136 Forschungsteams aus EU-Mitgliedstaaten und anderen europäischen Ländern kamen in die engere Auswahl für eine Finanzierung und arbeiten innerhalb der Teilbereiche Epidemiology (inkl. Pandemic Modelling), Diagnostics, Treatment sowie Vaccines, um Kenntnisse zum Coronavirus (SARS-CoV-2) zu verbessern und um das klinische Management von Patient*innen, die mit dem Virus infiziert sind, effizienter zu gestalten. Für den Teilbereich Vaccines wurden folgende Projekte ausgewählt [20]:

OpenCorona

PREVENT-nCoV

- **OpenCorona** mit dem Titel „Rapid therapy development through Open Coronavirus Vaccine Platform“; geführt vom schwedischen *Karolinska Institutet* in Kooperation mit siebenPartnern aus DE, IT und SE (5).
- **PREVENT-nCoV** mit dem Titel „Prevention of 2019 nCoV infection through development and clinical testing of a novel Virus Like Particle (VLP) vaccine”; geführt vom dänischen *AdaptVac* in Kooperation mit sechs Partnern aus DE, DK (3) und NL(2).

Zudem werden mehrere Impfstoffprojekte von der **Coalition for Epidemic Preparedness Innovations (CEPI)** finanziell unterstützt.

Coalition for Epidemic Preparedness Innovations (CEPI)

CEPI 2017 als Reaktion auf Ebola gegründet

Forschungsförderung von 8 Impfprojekten

Die **Coalition for Epidemic Preparedness Innovations (CEPI)** wurde 2017 von mehreren staatlichen und nicht-staatlichen Geldgebern als Reaktion auf die Ebola-Krise 2014 gegründet. Die weltweite Allianz in öffentlich-privater Partnerschaft zwischen Staaten[3], Stiftungen (u.a. die Bill & Melinda Gates Foundation und der Wellcome Trust), Forschungseinrichtungen, Pharmaunternehmen, der WHO sowie der EU-Kommission, hat den Aufbau eines Forschungsnetzwerks zur Erforschung und Entwicklung neuer Impfstoffe zur besseren und direkteren Reaktion auf eventuell bevorstehende Ausbrüche neuer viraler Infekte zum Ziel. Mit Stand 23.03.2020 co-finanziert CEPI **acht Forschungsprojekte** zur Entwicklung von Impfstoffen gegen Covid-19 [22, 23]:

1. Konsortium geführt von *Institut Pasteur* (FR) gemeinsam mit *Themis Bioscience* (AT) und der *University of Pittsburgh* (USA), 4,9 Mio. USD, präklinische Phase,
2. *Moderna* (USA) mit dem U.S. National Institute of Allergy and Infectious Diseases, Phase I,

[3] Norwegen, UK, Deutschland, Japan, Kanada, Äthiopien, Australien, Belgien, Dänemark, Finnland

3. Inovio *Pharmaceuticals* (USA) mit dem *Wistar Institute* (USA) und *Beijing Advaccine Biotechnology* (CHN), 65 Mio. USD, präklinische Phase,
4. *NovaVax* (USA), präklinische Phase,
5. *CureVac* (DE), 42,3 Mio. USD, präklinische Phase,
6. *University of Hong Kong* (CHN), 0,6 Mio. USD, präklinische Phase,
7. *University of Oxford* (UK), präklinische Phase,
8. *University of Queensland* (AUT) mit dem Unternehmen *Dynavax* und *GSK*, die Adjuvantien beisteuern, 10,6 Mio. USD, präklinische Phase.

OpenCorona Konsortium

Konsortium geführt von schwedischem Karolinska Institutet

Beginn mit Test an Tests an Tiermodellen 2020

Versuche an Menschen 2021

Das *OpenCorona* Konsortium, das von dem schwedischen *Karolinska Institutet* geführt wird, hat als Erstes den Horizon 2020 EU-Zuschuss für ihr Impfstoffprojekt im Gesamtwert von 3 Mio. Euro erhalten. Die Mitglieder des Konsortiums sind das *Universitätsklinikum Karolinska, Cobra Biologics, Adlego AB, FoHM* (The Public Health Agency of Sweden), *IGEA Clinicla Biophysics, Svenska Vaccinfabriken Produktion AB* and *Universität Giessen*. Mit diesem Zuschuss hat die Forschungsgruppe des Impfstoffprojekts einen großen Teil der Finanzierung für die Entwicklung eines Impfstoffkandidaten gegen das Coronavirus und die Durchführung einer klinischen Phase-I-Studie erhalten. Der Professor und Leiter der Abteilung für Labormedizin des *Karolinska Institutet* Matti Sällberg vermutet, dass sie höchstwahrscheinlich einen **DNA–Impfstoff** entwickeln werden, da man aus Erfahrung wisse, dass diese stabil sind und die Infrastruktur bereits vorhanden ist, um Millionen Dosen dieses Impfstofftyps herzustellen [24]. Als DNA-Impfstoff wird das Plasmid an den Muskel des Patienten/der Patientin abgegeben, der dann ein virales Antigen produziert, gegen das das Immunsystem reagiert. Derzeit stehen aber noch mehrere Impfstoffkandidaten in den Gefrierschränken der Abteilung für Labormedizin zur Verfügung. Die Forscher/-innen planen, Ende März 2020 mit parallelen Tests an Tiermodellen zu beginnen. Die ersten Versuche am Menschen werden voraussichtlich im Jahr 2021 beginnen und am *Universitätsklinikum Karolinska* stattfinden [25].

PREVENT-nCoV Konsortium

Konsortium geführt von AdaptVac (DNK)

Ziel: erste klinische Prüfungen in ca 12 Monaten

Das *PREVENT-nCoV* Konsortium hat ebenfalls den Horizon 2020 EU-Zuschuss mit einem Gesamtwert von 2,7 Mio. Euro erhalten und setzt die von *AdaptVac (DNK)* entwickelte **universal viral Capsid-like Particle (CLP) Technologie** sowie **ExpreS2ion's non-viral Drosophila S2 cells expression system** ein, um einen optimalen Impfstoff gegen das SARS-CoV-2-Virus zu liefern. Die Mitglieder des Konsortiums sind *AdaptVac* (Lead); *Institut für Tropenmedizin* (ITM) der Universität Tübingen; Abteilung für Medizinische Mikrobiologie des *Universitätsklinikums Leiden (LUMC);* Abteilung für Immunologie und Mikrobiologie der *Universität Kopenhagen; ExpreS2ion Biotechnologies;* und das Labor für Virologie der Wageningen Universität. Das Ziel besteht darin, dass der Impfstoff die ersten klinischen Tests am Menschen abschließt, um die Sicherheit und Wirksamkeit innerhalb von 12 Monaten nachzuweisen [26].

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,

9. As a first step an inventory, based on international sources, is built.
10. 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.
11. This information forms the basis for “vignettes” (short descriptions) for those products that are already in an "advanced" stage.
12. 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/blueprint/priority-diseases/key-action/Table_of_therapeutics_Appendix_17022020.pdf?ua=1 https://www.who.int/blueprint/priority-diseases/key-action/Novel_Coronavirus_Landscape_nCoV_Mar26.PDF?ua=1
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
Sekundäre Quellen	
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 Medikamente:	https://www.ema.europa.eu/ https://www.ema.europa.eu/en/medicines/medicines-under-evaluation
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/
Tertiary sources	
NIPHNO	https://www.fhi.no/en/qk/systematic-reviews-hta/map/
INAHTA	http://www.inahta.org/covid-19-inahta-response/

1.3 Selection of Products for "Vignettes"

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	Estimated Timeline	Technology		Stage/Funding	Source
		Platform	Type of candidate vaccine		
Moderna Therapeutics—US National Institute of Allergy	Early stage (phase 1), clinical trial in US	RNA	LNP-encapsulated mRNA	Phase1 (NCT04283461) Funding by CEPI	[1, 2] SPS Coronavirus HS report (UK), GÖG
CanSino Biological Inc. and Beijing Institute of Biotechnology	Clinical evaluation ongoing	Non-Replicating Viral Vector	adenovirus Type 5 Vector	Phase 1 ChiCTR2000030906/ NCT04313127	[2, 3], GÖG
Inovio Pharmaceuticals	Human testing in the next few months	DNA	DNA plasmid vaccine Electroporation device	Preclinical Funding by CEPI, up to $9 million	[1, 2], GÖG
Novavax	3 months	Protein Subunit	VLP-recombinant protein nanoparticle vaccine + Matrix M	Preclinical	[1, 2], GÖG
University of Queensland/GSK/Dynavax	6 months	Protein Subunit	Molecular clamp stabilized Spike protein	Preclinical Funding by CEPI	[1, 2], GÖG
CureVac	Not available	RNA	mRNA	Preclinical; Phase 1 studie will start in June/July 2020	[1, 2] GÖG
University of Oxford	Not available	Non-Replicating Viral Vector	ChAdOx1	Preclinical (Phase I/II study planned: NCT04324606; estimated completion: May 2021)	[2, 3] SPS Coronavirus HS report (UK), GÖG
BioNTech/Fosun Pharma/Pfizer	Not available	RNA	mRNA	Preclinical; Mar 20: Clinical testing of this m-RNA vaccine to start in April 2020	[2] SPS Coronavirus HS report (UK), GÖG

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 [27]. An mRNA-based virus has not been approved for use in humans yet [28].

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 [29]. Safety reviews are in place before dose escalation [29]. The primary endpoint of the study is frequency and grade of adverse reactions at 7/28/394 days post injection [27]. 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 [27], 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 [30-32]. The platform (non-replicating viral vector) of AD5-nCoV was originally used for an Ebola vaccine (AD5-EBOV) [32, 33].

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 [34].

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
Sponsor	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
Regulatory status	Not approved
Trial Identifier	ChiCTR2000030906 NCT04313127
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
Study design	Non-randomized, single-centre, sequentially assigned, dose-escalating, phase I clinical trial
Status trial	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
Study details	N of pts: 108 Location/ centres: China, Hubei 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.
Results	N.A.

Sources: [30-34], 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 [33, 35]. 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

At this moment in time, INO-4800 is still in the preclinical phase. According to press releases from the manufacturer [14, 15], human testing (a phase I clinical trial) may start in April 2020. The results are aimed to be presented and published thereafter (fall 2020).

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	N.A.
Phase & Intention	Preclinical phase; human testing in 30 healthy volunteers planned to start in April 2020
Study design	N.A.
Status trial	N.A.
Duration/ End of Study	N.A.
Study details	N.A.
Results	N.A.

Sources: [14, 15, 33, 35]. 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 [36] is a recombinant protein nanoparticle technology platform that is to generate antigens derived from the coronavirus spike (S) protein [37]. 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 [38, 39].

Estimated timeline for approval

Currently, Novavax has been assessing recombinant nanoparticle vaccine candidates in animal models and they aim to initiate Phase I clinical trial in May/June 2020 [36]. Novavax has previous experience with both MERS and SARS [38].

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 Vaccin**
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	N.A.
Phase & Intention	Preclinical phase; phase 1 study will start in June/July 2020
Study design	N.A.
Status trial	N.A.
Duration/ End of Study	N.A
Study details	N.A.
Results	N.A.

Sources: [36, 37] 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)[4], The University of Queensland currently investigates on a potential vaccine using molecular clamp stabilized Spike proteins [28, 33]. 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 [40].

Initially, this technology was designed to be a platform for generating vaccines against different viruses such as influenza, Ebola, and the MERS coronavirus [41].

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 [42].

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

[4] Both DynaVax and GSK will provide adjuvants.

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: [28, 33, 41-43]. 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) [28]. 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 [44]. 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 [45].

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 [46]. 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 [47]. 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 [48].

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, 28, 47, 49] 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, 30].

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 [50].

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	Not yet 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, 30, 33, 50]. 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 Focun 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 [28]. In 2018, Pfizer and BioNTech collaborated on mRNA-based vaccines for the prevention of influenza and their partnership applies outside of China [51]. BioNTech's partnership with Fosun Pharma applies for China only [51, 52].

Estimated timeline for approval

Currently, BNT-162 is expected to enter clinical testing by the end of April 2020 [53] and R&D is supposed to be carried out both in the US as well as in Germany [51].

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	N.A.
Phase & Intention	Preclinical phase, phase I study will start in the end of April 2020
Study design	N.A.
Status trial	N.A.
Duration/ End of Study	N.A.
Study details	N.A.
Results	N.A.

Sources: [28, 53]. Abbreviations: N.A. – not applicable.

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) Phase III (NCT04257656) 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) Phase II / III (NCT04321616)
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)
Favipiravir (Avigan, T-705)	Antiviral agent	Phase NA (ChiCTR2000029548) Phase NA (ChiCTR2000029544) Phase NA (ChiCTR2000029600) Phase NA (ChiCTR2000030113) Phase NA (ChiCTR2000030254)
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)
Hydroxychloroquine (Plaquenil®)	Antiviral cell-entry inhibitor	Phase IV (NCT04316377) Phase IV (ChiCTR2000029559) Phase IV (ChiCTR2000029992) Phase IV (ChiCTR2000029898) Phase IV (ChiCTR2000029899) Phase IV (ChiCTR2000029868) Phase IV (ChiCTR2000029740) Phase III / IV (EudraCT: 2020-000982-18) Phase III (NCT04315896) Phase III (NCT04321278) Phase III (NCT04308668) Phase III (NCT04315948) Phase III (EudraCT: 2020-000890-25) Phase II (EudraCT: 2020-001224-33) Phase 0 (ChiCTR2000030054)
Camostat Mesilate (Foipan®)	Antiviral cell-entry inhibitor	Phase II (NCT04321096)
APN01 (rhACE2)	Antiviral cell-entry inhibitor	Phase II (NCT04335136)
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)
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)
Interferon beta 1a (SNG001)	Interferon	Phase IV (NCT02735707) Phase III (NCT04315948) Phase II (EudraCT: 2020-001023-14) Phase NA (NCT04314817)

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 [54].

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 [55]. 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 [56].

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 [57]. Furthermore, it has orphan designation for the treatment of Ebola virus disease since February 2016. RVD is not approved by the Food and Drug Administration (FDA), but the use of RDV for COVID-19 was granted 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 [58].

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. Two ongoing phase 3 randomised controlled trials (RCT) to evaluate intravenous RVD in patients with 2019-nCoV were initiated in the beginning of February in

China (NCT04252664 and NCT04257656). The estimated completion date of both trials is in April 2020. 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, and one is a multicentre trial conducted in 3 centres in France (NCT04315948) with the estimated completion date in March 2023. Table 3.1-1 displays more details of the identified ongoing trials.

Results of publications

A hand search on the 3rd of April 2020 in PubMed was conducted and gave 27 hits. So far no relevant finished publications or finished trials assessing the efficacy and safety could be identified. First results can be expected on the 10th of April 2020 (NCT04252664).

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	Remdesivir/GS-5743
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	Oslo University Hospital
Mechanism of operation	Antiviral agent	Antiviral agent	Antiviral agent	Antiviral agent	Antiviral agent	Antiviral agent	Antiviral agent
Regulatory status EMA/FDA	**EMA:** Not approved[5], but orphan designation for the treatment of Ebola virus disease (17/02/2016) **FDA:** not approved[6], but orphan designation for Ebola (18/09/2015)	**EMA:** Not approved[5], but orphan designation for the treatment of Ebola virus disease (17/02/2016) **FDA:** not approved[6], but orphan designation for Ebola (18/09/2015)	**EMA:** Not approved[5], but orphan designation for the treatment of Ebola virus disease (17/02/2016) **FDA:** not approved[6], but orphan designation for Ebola (18/09/2015)	**EMA:** Not approved[5], but orphan designation for the treatment of Ebola virus disease (17/02/2016) **FDA:** not approved[6], but orphan designation for Ebola (18/09/2015)	**EMA:** Not approved[5], but orphan designation for the treatment of Ebola virus disease (17/02/2016) **FDA:** not approved[6], but orphan designation for Ebola (18/09/2015)	**EMA:** Not approved[5], but orphan designation for the treatment of Ebola virus disease (17/02/2016) **FDA:** not approved[6], but orphan designation for Ebola (18/09/2015)	**EMA:** Not approved[5], but orphan designation for the treatment of Ebola virus disease (17/02/2016) **FDA:** not approved[6], but 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 https://clinicaltrials.gov/ct2/show/NCT04280705	NCT04315948 https://clinicaltrials.gov/ct2/show/NCT04315948	NCT04321616 https://clinicaltrials.gov/ct2/show/NCT04321616?term=remdesivir&draw=4&rank=8

5 RDV was recommended on compassionate use for COVID-19 (03/04/2020) by the EMA 57. European Medicines Agency (EMA). EMA provides recommendations on compassionate use of remdesivir for COVID-19. 2020 [cited 2020 03.04.2020]; Available from: https://www.ema.europa.eu/en/news/ema-provides-recommendations-compassionate-use-remdesivir-covid-19..

6 The use of RDV for COVID-19 was granted in the course of the expanded access program to allow the emergency use (19/03/2020) by the FDA 58. Food and Drug Administration (FDA). Coronavirus (COVID-19) Update: FDA Continues to Facilitate Development of Treatments. 2020 [cited 2020 03.04.2020]; Available from: https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-continues-facilitate-development-treatments..

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	Phase 2/3[7] study to evaluate the efficacy of different antiviral drugs in SARS-CoV-2 infected patients
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 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)	Open randomised adaptive controlled multicentre trial (Parallel Assignment)
Status trial	Recruiting	Recruiting	Recruiting	Recruiting	Recruiting	Recruiting	Not yet 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	~7 months / Start: March 26, 2020 Primary completion date: August 2020 Study completion date: November 2020
Study details							
Number of Patients	n = 308	n = 453	n = 600	n = 400	n = 440	n = 3100	n = 700

[7] The entry in the clinical trial register indicates that this trial has a phase 2, as well as a phase 3 status.

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)	NR[8]
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 2, 3, 4, 5, 6, 7, 8, 9, and 10 (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 standard of care therapy together with RDV 200 mg on day 1 followed by RDV 100 mg on days 2, 3, 4, 5, 6, 7, 8, 9, and 10 (n = NR)	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) **Lopinavir/ritonavir** (400 lopinavir mg/100 mg ritonavir) will be administered every 12 h	**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)[9] **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)

[8] The official trial name is (Norwegian) NOR Solidarity Multicenter Trial, but the definite location is not reported.

[9] The trial has three study arms, each having either Hydroxychloroquine, Remdesivir or Standard of Care as active comparator and the other two as interventions.

						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. 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	SOC (n = 620)	SOC (n = NA)

					hospitalization up to a 10 days total course (n=220)		
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	3 weeks
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	All cause in-hospital mortality
Results/Publication	Not provided	Not provided	Not provided	Not provided	Not provided	Not provided	Not provided

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

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 [30, 59].

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) 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.

Drug used in Covid-19 patients: results of publications

So far (status: 03.04.2020) 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

*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:

	- 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	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	Study (phase not reported) on safety and efficacy of **lopinavir/ ritonavir** plus alpha-interferon atomisation in the treatment of novel Covid-19.

			and ribavirin plus **lopinavir/ritonavir** plus interferon-alpha in in patients with mild to moderate novel Covid-19 pneumonia.		thymosin a1 in the treatment of Covid-19.	
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; 6) Admission to ECMO (extracorporeal	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

	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 3.2-2: 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) [60, 61].

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 [60]. 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) 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.

Drug used in Covid-19 patients: results of publications

So far (status: 06/04/2020), only one publication [62] on the completed clinical trial (ChiCTR2000030254) about the efficacy and safety of favipiravir 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.

*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

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: [62]; 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: Publications on clinical trials on product **favipiravir (Avigan®)** – publication forthcoming*

Author, year [Reference]	**Chen et al. 2020 [62]**
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 [63].

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 11th 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 [30]. 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.

Drug used in Covid-19 patients: results of publications

Until now (status: 07/04/2020) no scientific publication on clinical trials 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 [64]. 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.

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) 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.

Drug used in Covid-19 patients: results of publications

So far (status: 07/04/2020) one publication [8] [ChiCTR2000029542]) on the effectiveness and safety of chloroquine in adults hospitalised with Covid-19 could be identified. 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.

*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
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	Pts: n = 100 Location: China	Pts: n = 80 Location: China	Pts: n = 10 Location: China

	Intervention: Chloroquine Phosphate *(not specified)* Control: Standard of care Duration of observation: up to 30 days Primary outcome: Length of hospital stay	Intervention: Chloroquine Phosphate *(not specified)* Control: none Duration of observation: up to 30 days Primary outcome: Length of hospital stay	Intervention: Chloroquine Phosphate *(not specified)* Control: no treatment Duration of observation: not given Primary outome: Time to clinical recovery	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	**Chloroquin 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 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	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
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	**Chloroquin Phosphate** vs. Hydroxychloroquine Sulfate	**Chloroquin Phosphate** vs. Hydroxychloroquine Sulfate	**Chloroquin 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: - 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)*	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)*	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: Placebo oral tablet Duration of observation: up to 28 days Primary outcome: Clinical recovery time	Control: Placebo oral tablet Duration of observation: up to 28 days Primary outcome: Clinical recovery time	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 3.5-2: 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 [65]. 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**. 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.

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) 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. Table 3.6-1 presents more details of the identified ongoing studies.

Drug used in Covid-19 patients: results of publications

So far (status: 06/04/2020) three publications ([66] [EudraCT: 2020-000890-25]; [67, 68] [ChiCTR2000029559]) on the effectiveness and/or safety of hydroxychloroquine in adults hospitalised with Covid-19 could be identified. Unfortunatly, [67] is not published in English and [68] is currently availabe just as pre-print but not yet peer-reviewed, thus not included. In [66] 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. Detailed information about the study results are presented in Table 3.6-2.

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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
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 malaria due to *P.*	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.*	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.*	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®).	*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®).	*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®).	*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)* - 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*	Pts::n = 443 Location: Norway Intervention: Hydroxychloroquine *(not specified)* Control: Standard of care Duration of observation: not given Primary outcome: In-hospital mortality	Pts: n = 220 Location: Germany Intervention: Hydroxychloroquine *(not specified)* Control: Placebo oral tablet Duration of observation: not given 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	Pts::n = 25 Location: France Intervention: Hydroxychloroquine *(not specified)* Control: none 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

	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			
Results	No publications available yet.	No publications available yet.	No publications available yet.	Publication available: [66]

*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
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: **[68]; 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.** 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 3.6-2: Publications on clinical trials on product **Hydroxycloroquine (Plaquenil®)***

Author, year	**Gautret et al. 2020** [66]	**Chen et al. 2020** [68]
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 [66]	Chen et al. 2020 [68]
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 [69]. 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 [70, 71] as well as in pathogenic mice-models [72] 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. 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. More information is listed in Table 3.7-1

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: 03/04/2020).

*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
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.

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) [73]. ACE2 was identified as the functional SARS-CoV receptor in vivo [74]. 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 [75].

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. The estimated completion date of the trial is in November 2020.

Table 3.8-1 displays more details of the identified ongoing trials.

Results of publications

A hand search on the 7th of April 2020 in PubMed was conducted and gave 0 hits. So far 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 [76]. 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 [76].

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 [76]. 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 [76].

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 [77]. However, some patients develop severe symptoms and progress rapidly, experiencing acute respiratory distress syndrome and septic shock, eventually ending in multiple organ failure [77]. It has been reported that most patients with COVID-19 have increased concentrations of IL-6, C-reactive protein (CRP) and erythrocyte sedimentation rate [78]. However, severely affected patients appear to have even higher plasma levels of pro-inflammatory cytokines and experience severe cytokine storm including features of CRS [78, 79]. It has previously been suggested that IL-6 might play a role in the pathogenesis of SARS and MERS, other diseases caused by coronaviruses [79]. 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) yielded no completed study on the safety and efficacy of tocilizumab in COVID-19 patients.

There are currently 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.

Results of publications

A search on the 7th of April 2020 in PubMed was conducted and gave 11 hits. So far no relevant finished publications or finished trials assessing the efficacy and safety could be identified, except for one retrospective report describing the experience of using tocilizumab in severe or critical COVID-19 patients [80] (found through searching the reference list in paper 4) .

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 obvious adverse reactions were observed.

*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.	**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.

	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).	• 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).	**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).	• 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	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 simultaneously blocking IL-6 and IL-1 versus SOC on blood oxygenation and	Phase III study to evaluate the efficacy, safety, pharmacodynamics, and pharmacokinetics of tocilizumab compared with a matching placebo in combination with SOC in hospitalised patients with severe COVID-19 pneumonia.	Phase II study to evaluate whether treatment with tocilizumab reduces the severity and mortality in patients with COVID-19.	Phase II study to evaluate the efficacy of tocilizumab combined with pembrolizumab (MK-3475) compared to SOC in adult patients with COVID-19 pneumonia and bad	Phase II study to compare the efficacy of a chloroquine analog (GNS561), an anti PD-1 (nivolumab) and an anti-IL-6 receptor (tocilizumab) versus SOC in patients with advanced or metastatic cancer

	systemic CRS in patients with COVID-19 coronavirus infection and acute hypoxic respiratory failure and systemic CRS.			prognostic factors who are nonresponsive to frontline therapy within 48 hours from treatment initiation.	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 • Siltuximab – single IV infusion at a dose of 11mg/kg • Tocilizumab – single IV infusion at a dose of 8mg/kg with max infusion of	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 12 hours could receive an additional dose of tocilizumab at the same dose level of the first administration. Patients	• 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 infusion over 60 minutes; 8mg/kg (up to max 800mg per dose); single dose. • Tocilizumab

	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			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.	○ 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 (Current Primary Outcome Measures)	Up to 15 days	Up to 28 days	Up to 28 days	Up to 14 days	Up to 28 days
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 3.9-2: **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-	**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

	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).	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).	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).
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 Coronavirus disease 2019 (COVID-19).	Phase II study to compare the effect of either one of three IL-6 inhibitor administrations, relative to SOC, on time to independence from supplementary oxygen therapy, measured in days from baseline to day 28, in	Phase II study to evaluate the use of tocilizumab in combination with hydroxychloroquine and azithromycin for the treatment of hospitalized adult patients with COVID-19.	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 factors for clinical decompensation, intensive care utilisation, and death, as determined by the clinical

		patients with severe SARS-CoV-2 pneumonia.			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
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
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.	**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.	**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.	**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

	• 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. • 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).	• 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. • 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).	• 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. • 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).	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. • 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,	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.

	preventing naso-tracheal intubation and/or death.			
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* 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)	• Tocilizumab – Subjects received 8 mg/kg (body weight) tocilizumab 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.

			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.	
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 (SpO2) after 14 days from the end of treatment with tocilizumab.	Clinical cure rate at 3 months	Proportion of participants with normalisation of fever and oxygen saturation through day 14
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 [81]. It is licensed in the EU for treating adults with rheumatoid arthritis, given by subcutaneous (SC) injection [81]. 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 [77]. However, some patients develop severe symptoms and progress rapidly, experiencing acute respiratory distress syndrome and septic shock, eventually ending in multiple organ failure [77]. It has been reported that most patients with COVID-19 have increased concentrations of IL-6, C-reactive protein (CRP) and erythrocyte sedimentation rate [78]. 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) [78, 79]. It has previously been suggested that IL-6 might play a role in the pathogenesis of SARS and MERS, other diseases caused by coronaviruses [79]. 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 [80]. 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) 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.

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

Results of publications

A search on the 7th of April 2020 in PubMed was conducted and gave 1 hit. So far no relevant finished trials 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.

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 duration extubation > 48h) at day 14.	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

	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

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 [82]. 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 [83].

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) 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.

Drug used in Covid-19 patients: results of publications

Currently there are no completed studies. First results are expected in May 2021.

*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)*	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

	- fixed-duration Hydrocortisone - 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.

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