



HTA Austria
Austrian Institute for
Health Technology Assessment
GmbH

Covid-19



HSS/ Horizon Scanning
Living Document V05 August 2020
Part 1



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Dieser Bericht soll folgendermaßen zitiert werden/This report should be referenced as follows:

AIHTA Policy Brief Nr.: 002_V5 2020: Covid-19, HSS/ Horizon Scanning, Living Document August 2020.

Wien: HTA Austria – Austrian Institute for Health Technology Assessment GmbH.

Interessenskonflikt

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IMPRESSUM

Medieninhaber und Herausgeber:

HTA Austria - Austrian Institute for Health Technology Assessment GmbH

Garnisongasse 7/Top20 | 1090 Wien – Österreich

www.aihta.ac.at

Für den Inhalt verantwortlich:

Priv.-Doz. Dr. phil. Claudia Wild, Geschäftsführung

Die **AIHTA Policy Briefs** erscheinen unregelmäßig und dienen der Veröffentlichung der Forschungsergebnisse des Austrian Institute for Health Technology Assessment.

Die **AIHTA Policy Briefs** erscheinen in geringer Auflage im Druck und werden über den Dokumentenserver „<https://eprints.aihta.at/view/types/policy=5Fbrief.htm>“ der Öffentlichkeit zur Verfügung gestellt.

AIHTA Policy Brief Nr.: 002

ISSN 2710-3234

ISSN online 2710-3242

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History of Changes	V05 August
August 10, 2020	Addition chapters on Colchicine (chapter 3.19)
August 11, 2020	Update Methodology (1.2)
August 14, 2020	Update Vaccine (chapter 2) Addition vignettes on Sinovac and SinoPharm vaccine
August 11, 2020	Update Remdesivir (chapter 3.1)
August 11, 2020	Update Lopinavir + Ritonavir (chapter 3.2)
August 12, 2020	Update Favipiravir (chapter 3.3)
August 12, 2020	Update Darunavir (chapter 3.4)
August 11, 2020	Update Chloroquine (chapter 3.5)
August 11, 2020	Update Hydroxychloroquine (chapter 3.6)
August 13, 2020	Update Camostat Mesilate (chapter 3.7)
August 13, 2020	Update APN01/rhACE2 (chapter 3.8)
August 14, 2020	Update Tocilizumab (chapter 3.9)
August 14, 2020	Update Sarilumab (chapter 3.10)
August 16, 2020	Update Interferon beta (chapter 3.11)
August 15, 2020	Update Concalescent plasma (chapter 3.12)
August 15, 2020	Plasma derived medicinal products (Update chapter 3.13)
August 16, 2020	Update Combination therapy (chapter 3.14)
August 14, 2020	Update Solnatide (chapter 3.15)
August 15, 2020	Update Umifenovir (chapter 3.16)
August 14, 2020	Update Dexamethasone (chapter 3.17)
August 14, 2020	Update Anakinra (chapter 3.18)

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), the Health Funds of the Regions and the Federation of Social Insurances to set up a Horizon Scanning system (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.

1.2 Methodology

To respond to this request,

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

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

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

Ongoing trials are reported in V1, April 2020 - V3, June 2020 of this Document and in the living documents - EUnetHTA (Covid-19 Rolling Collaborative Reviews: <https://eunetha.eu/rcr01-rcrxx/>).

From V4 July, 2020 of this HSS/ Horizon Scanning Document, only completed, terminated, withdrawn and suspended interventional clinical trials from ClinicalTrials.gov and EudraCT registers are reported.

From V5, August 2020 of this HSS/ Horizon Scanning Document only the best available evidence will be presented in.

**März 2020:
Österr. Politik empfiehlt
Aufbau von HSS
zu Covid-19**

**Information zu
* Status F&E
* Evidenz-basierter
Einkauf**

mehrstufige Methodik

**Bestandsaufnahme
selektive Suche
Vignetten
Monitoring**

**internationale/
europ. Zusammenarbeit**

**V1-V3: auch laufende
Studien - Verweis auf
EUnetHTA
V4: nur abgeschlossene
(oder beendete)
Interventionsstudien aus
2 Studienregistern
V5: nur mehr best
verfügbare Evidenz**

Table 1.2-1: International Sources

Primary sources	Link
WHO Drugs: Vaccines:	https://www.who.int/teams/blueprint/covid-19 https://www.who.int/blueprint/priority-diseases/key-action/Table_of_therapeutics_Appendix_17022020.pdf?ua=1 https://www.who.int/who-documents-detail/covid-19-candidate-treatments https://www.who.int/who-documents-detail/draft-landscape-of-covid-19-candidate-vaccines
Danish Medicine Agency Drugs: Vaccines:	https://laegemiddelstyrelsen.dk/da/nyheder/temaer/ny-coronavirus-covid-19/~/_media/5B83D25935DF43A38FF823E24604AC36.ashx https://laegemiddelstyrelsen.dk/da/nyheder/temaer/ny-coronavirus-covid-19/~/_media/3A4B7F16D0924DD8BD157BBE17BFED49.ashx
Pang et al. 2020 [1] Drugs: Vaccines:	https://www.mdpi.com/2077-0383/9/3/623 Table 5+6, Table 3+4
SPS HS-report (UK)	unpublished
Secondary sources	
VfA/ Verband Forschender Arzneimittelhersteller Drugs: Vaccines:	https://www.vfa.de/de/arzneimittel-forschung/woran-wir-forschen/therapeutische-medikamente-gegen-die-coronavirusinfektion-covid-19 https://www.vfa.de/de/arzneimittel-forschung/woran-wir-forschen/impfstoffe-zum-schutz-vor-coronavirus-2019-ncov
EMA/ European Medicines Agency Medicines:	https://www.ema.europa.eu/ https://www.ema.europa.eu/en/medicines/medicines-under-evaluation
FDA/US Food and Drug Administration	https://www.fda.gov/emergency-preparedness-and-response/counterterrorism-and-emerging-threats/coronavirus-disease-2019-covid-19
Trial Registries	
US National Library of Medicine European Union Drug Regulating Authorities Clinical Trials Database WHO International Clinical Trials Registry Platform TrialsTracker	https://clinicaltrials.gov/ https://eudract.ema.europa.eu/ https://www.who.int/ictrp/en/ http://Covid-19.trialstracker.net/
Up-to-date information on clinical trials and literature searching resources relating to COVID-19	
Cochrane COVID-19 Study Register 21/04.20	https://covid-19.cochrane.org/
Living mapping of research and a living systematic review	https://covid-nma.com/ https://covid-nma.com/dataviz/
Dynamic meta-analysis of evidences about drug efficacy and safety for COVID19 - meta/Evidence – COVID-19	http://metaevidence.org/COVID19.aspx
CORDITE (CORona Drug InTEractions database)	https://cordite.mathematik.uni-marburg.de/#/
Living listing of interventional clinical trials in Covid-19/2019-nCoV produced by the Anticancer Fund	http://www.redo-project.org/covid19db/ ; http://www.redo-project.org/covid19_db-summaries/
Global Coronavirus COVID-19 Clinical Trial Tracker	https://www.covid-trials.org/
LitCovid	https://www.ncbi.nlm.nih.gov/research/coronavirus/
UK NIHR Innovation Observatory NIHR COVID-19 Studies COVID-19 Therapeutics Dashboard COVID-19: a living systematic map of the evidence	https://www.nihr.ac.uk/covid-studies/ http://www.io.nihr.ac.uk/report/covid-19-therapeutics/ http://eppi.ioe.ac.uk/cms/Default.aspx?tabid=3765
WHO COVID-19 Database new search interface	https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov
COVID-evidence Database	https://covid-evidence.org/database

Medical Library Association – COVID-19 Literature search strategies	https://www.mlanet.org/page/covid-19-literature-searching
Centre of Evidence Based Dermatology (CEBD) - Coronavirus Dermatology Online Resource	https://www.nottingham.ac.uk/research/groups/cebd/resources/Coronavirus-resource/Coronavirushom
Ovid Expert Searches for COVID-19	http://tools.ovid.com/coronavirus/
EBSCO Covid-19 Portal Literature searching section of portal Information portal	https://covid-19.ebscomedical.com/research https://covid-19.ebscomedical.com/
NIH COVID-19 Treatment Guidelines. 2020.	https://covid19treatmentguidelines.nih.gov/introduction/
Tertiary sources	
NIPHNO	https://www.fhi.no/en/qk/systematic-reviews-hta/map/
INAHTA	http://www.inahta.org/covid-19-inahta-response/
EUnethTA Covid-19 Rolling Collaborative Reviews (RCR)	https://eunethta.eu/rcr01-rcrx/

Several organisations and international teams of researchers are providing up-to-date information through living listing of interventional clinical trials in Covid-19/2019-nCoV and literature resources (Table 1.2 2) [2-4] [2]. A short description of two of such databases is presented below.

“lebende” Dokumente mit up-to-date Informationen

Boutron et al., 2020 [3] are performing a living mapping of ongoing randomized trials, followed by living systematic reviews with pairwise meta-analyses and when possible, network meta-analyses focusing on two main questions: the effectiveness of preventive interventions for COVID-19 and the effectiveness of treatment interventions for COVID-19 (Figure 1.2-1).

Kartierung von aufenden RCTs

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

COVID-19 NMA

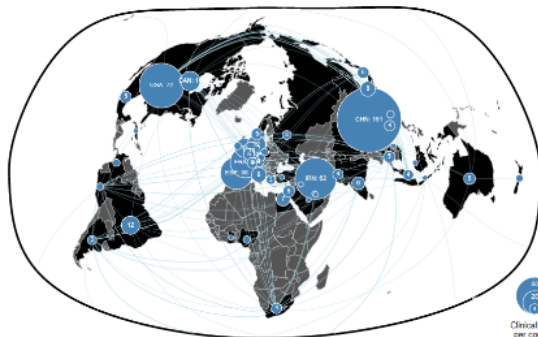
a living mapping of ongoing research.

▼ As of April 24, 2020...

The Covid-19 - living NMA initiative collected a number of 506 studies of treatments from the ICTRP. 278 of these trials are recruiting patients. Most of the studies are being conducted in Asia (264 trials) with the majority from China (151 trials). Other countries in Europe (160 trials) and North America (92 trials) are rapidly setting up new trials with the majority being conducted in multiple centers (194 trials).

Search:
Ex: Italy;Spain; australia; Spain; Assistance Publique - Hôpital de Paris...

▼ Map



▼ HELP 🗨

- Make your browser window as wide as possible for a 2-column display.
- Click on the map or any of the graphs to create filters on the data.
- All the filters are applied jointly, refining your selection.
- To select a Registration date, click and drag to create a range.
- At any moment you can click **Reset All** below to remove the filters.
- Click on the black arrows to open or close any section.
- For any questions or remarks, please contact us.

All trials selected (506) | [Reset All](#)

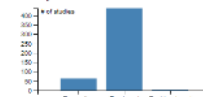
▼ Recruitment status

- Recruiting (278)
- Not recruiting (219)
- Completed (9)

▼ Registration date



▼ Study aim



▼ Disease severity



Thorlund et al., 2020 [4] developed a COVID-19 clinical trials registry to collate all trials related to COVID-19: Global Coronavirus COVID-19 Clinical Trial Tracker. Data is pulled from the International Clinical Trials Registry Platform, including those from the Chinese Clinical Trial Registry, ClinicalTrials.gov, Clinical Research Information Service - Republic of Korea, EU Clinical Trials Register, ISRCTN, Iranian Registry of Clinical Trials, Japan Primary Registries Network, and German Clinical Trials Register (Figure 1.2-2). They also use content aggregator services, such as LitCovid, to ensure that their data acquisition strategy is complete [5].

**COVID-19:
Clinical Trial Tracker**



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

1.3 Selection of Products for “Vignettes”

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 in 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.

**Vignetten zu Produkte, in
"fortgeschrittenen"
Stadien oder**

**häufig diskutiert/
publiziert**

2 Results: Vaccines

Table 2-1: Most advanced vaccines in the R&D pipeline (Phase 1 - Phase 3 clinical trials)

Company/Institution/Registry number	Technology		Stage/Sponsor	Source
	Platform	Type of candidate vaccine		
Moderna Therapeutics—US National Institute of Allergy NCT04283461 NCT04405076 NCT04470427	RNA	LNP-encapsulated mRNA vaccine encoding S protein	Phase 1 Phase 2 Phase 3 National Institute of Allergy and Infectious Diseases (NIAID)	[6-10]
CanSino Biological Inc. and Beijing Institute of Biotechnology ChiCTR2000030906/ NCT04313127 ChiCTR2000031781/ NCT04398147	Non-Replicating Viral Vector	adenovirus Type 5 Vector that expresses S protein	Phase 1 CanSino Biologics Inc.	[6-11]
			Phase 2 Jiangsu Provincial Center for Disease Control and Prevention/ Institute of Biotechnology, Academy of Military Medical Sciences, PLA of China/ CanSino Biologics Inc.	[6-8, 10, 11]
Inovio Pharmaceuticals NCT04336410 NCT04447781	DNA	DNA plasmid vaccine encoding S protein delivered by electroporation	Phase 1 Phase 1/2a Inovio Pharmaceuticals	[6-10]
Novavax NCT04368988	Protein Subunit	VLP-recombinant protein nanoparticle vaccine + Matrix M	Phase 1/2 Novavax	[6-9]
University of Queensland/GSK/Dynavax ACTRN12620000674932/NCT04495933	Protein Subunit	Molecular clamp stabilized Spike protein with MF59 adjuvant	Phase 1 The University of Queensland/Syneos Health, CEPI	[1, 2]
CureVac NCT04449276	RNA	mRNA	Phase 1 CureVac	[1, 2] [8,9]
University of Oxford/AstraZeneca ISRCTN 15281137/NCT04324606/	Non-Replicating Viral Vector	ChAdOx1 (AZD1222)	Phase 1/2 Phase 2b/3	[6-9] [10, 12]

Results: Vaccines

EudraCT 2020-001072-15 NCT04400838/EudraCT 2020-001228-32 ISRCTN89951424			Phase 3 University of Oxford/AstraZeneca	
BioNTech/Fosun Pharma/Pfizer ChiCTR2000034825 EudraCT 2020-001038-36/ NCT04380701 NCT04368728/EudraCT 2020-002641-42	RNA	3 LNP-mRNAs	Phase 1 Phase 1/2 Phase 2/3 BioNTech SE	[6-9] [10, 12]
Shenzhen Geno-Immune Medical Institute NCT04299724 NCT04276896	Synthetic mini-gene -based product	Pathogen-specific aAPC	Phase 1	[9]
		LV-SMENP-DC	Phase 1/2 Shenzhen Geno-Immune Medical Institute	[9]
Insitute of Biotechnology, Academy of Military Medical Sciences, PLA of China NCT04341389	Non-Replicating Viral Vector	adenovirus Type 5 Vector that expresses S protein	Phase 2 Insitute of Biotechnology, Academy of Military Medical Sciences, PLA of China	[6-9]
Symvivo Corporation NCT04334980	DNA bacTRL platform	bacTRL-Spike	Phase 1 Symvivo Corporation	[6-9]
Sinovac Biotech NCT04352608 NCT04383574 NCT04456595	Inactivated	inactivated + alum	Phase 1/2 Phase 3 Sinovac Research and Development Co, Ltd.	[6-10]
Wuhan Institute of Biological Products/Sinopharm ChiCTR2000031809 Beijing Institute of Biological Products/ Wuhan Institute of Biological Products/Sinopharm ChiCTR2000032459 ChiCTR2000034780/NCT04510207	Inactivated	Vero cells derived (cell culture-derived inactivated vaccines)	Phase 1/2 Wuhan Institute of Biological Products/Sinopharm	[6-8, 10, 11]
Phase 1/2 Phase 3 China National Biotec Group Company Limited			[10]	
Institute of Medical Biology, Chinese Academy of Medical Sciences NCT04412538	Inactivated	Inactivated	Phase 1 Phase 1/2	[10] [6]

Results: Vaccines

NCT04470609			Institute of Medical Biology, Chinese Academy of Medical Sciences	
Clover Biopharmaceuticals AUS Pty Ltd NCT04405908	Trimer-Tag© vaccine technology platform	spike proteins of the COVID-19 virus in a native trimeric form S-Trimer vaccine - a trimeric SARS-CoV-2 spike (S)-protein subunit	Phase 1 Clover Biopharmaceuticals AUS Pty Ltd	[6]
Aivita Biomedical, Inc. NCT04386252	Dendritic cell	Dendritic cell vaccine (autologous dendritic cells loaded with antigens from SARS-CoV-2, with or without GM-CFS)	Phase 1b/2 Aivita Biomedical, Inc.	[6]
Cadila Healthcare Limited CTRI/2020/07/026352	DNA	DNA plasmid vaccine	Phase 1/2 Cadila Healthcare Limited	[9]
Genexine Consortium NCT04445389	DNA	DNA Vaccine (GX-19)	Phase 1 Genexine Consortium	[9]
Osaka University/ AnGes/ Takara Bio JapicCTI-205328/ NCT04463472	DNA	DNA plasmid vaccine + Adjuvant	Phase 1/2 Osaka University/ AnGes/ Takara Bio	[9]
Gamaleya Research Institute NCT04436471 - Completed NCT04437875 - Completed	NonReplicating Viral Vector	Adeno-based (rAd5, rAd26)	Phase 1/2 Gamaleya Research Institute	[9]
Anhui Zhifei Longcom Biopharmaceutical/ Institute of Microbiology, Chinese Academy of Sciences NCT04445194 NCT04466085	Protein Subunit	Adjuvanted recombinant protein (RBDDimer)	Phase 1 Phase 2 Anhui Zhifei Longcom Biopharmaceutical/ Institute of Microbiology, Chinese Academy of Sciences	[9]
Vaxine Pty Ltd/Medytox NCT04453852	Protein Subunit	Recombinant spike protein with Advax™ adjuvant	Phase 1 Vaxine Pty Ltd	[9]
Imperial College London ISRCTN17072692	RNA	LNP-nCoVsaRNA	Phase 1 Imperial College London	[9]
People's Liberation Army (PLA) Academy of Military Sciences/Walvax Biotech ChiCTR2000034112	RNA	mRNA	Phase 1 People's Liberation Army (PLA) Academy of Military Sciences/Walvax Biotech	[9]
Medicago Inc./ Université Laval NCT04450004	VLP	Plant-derived VLP adjuvanted with GSK or Dynavax adjs.	Phase 1 Medicago Inc.	[9]
Bharat Biotech NCT044571519	Inactivated	Whole-Virion Inactivated	Phase 1/2 Bharat Biotech	[9, 10]

Results: Vaccines

Janssen Pharmaceutical Companies NCT04436276	NonReplicating Viral Vector	Ad26COVS1	Phase 1/2 Janssen Pharmaceutical Companies	[9, 10]
Kentucky Bioprocessing, Inc NCT04473690	Protein Subunit	RBD-based	Phase 1/2 Kentucky Bioprocessing, Inc	[9, 10]
Arcturus/Duke-NUS NCT04480957	RNA	mRNA	Phase 1/2 Arcturus/Duke-NUS	[9, 10]
Institute Pasteur/Themis/Univ. of Pittsburg CVR/Merck Sharp & Dohme NCT04497298	Replicating Viral Vector	Measles-vector based	Phase 1 Institute Pasteur/Themis/Univ. of Pittsburg CVR/Merck Sharp & Dohme	[9, 10]
Medigen Vaccine Biologics Corporation/NIAID/Dynavax NCT04487210	Protein Subunit	S-2P protein + CpG 1018	Phase 1 Medigen Vaccine Biologics Corporation/NIAID/Dynavax	[9, 10]

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 [13]. An mRNA-based virus has not been approved for use in humans yet [14].

**mRNA-1273
collab mit NIAID/CEPI**

Estimated timeline for approval

Currently, this is the first ongoing **phase 1** trial with 45 healthy participants (NCT04283461). 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 [15]. Safety reviews are in place before dose escalation [15]. The primary endpoint of the study is frequency and grade of adverse reactions at 7/28/394 days post injection [13]. The secondary endpoints measure the level of antibodies at 57 days post injection. The Phase I safety study should be completed by June 2021.

**Phase 1:
45 gesunde Erwachsene
Juni 2021**

A **phase 2a**, randomized, observer-blind, placebo controlled, dose-confirmation study to evaluate the safety, reactogenicity, and immunogenicity of mRNA-1273 vaccine in adults aged 18 years and older (NCT04405076) is underway. This Phase 2 study should be completed by August 2021.

**Phase 2a:
wird derzeit aufgesetzt
bis August 2021**

Moderna finalized the **phase 3** study protocol based on feedback from the U.S. Food and Drug Administration (FDA); the trial is currently ongoing (NCT04470427). The randomized, 1:1 placebo-controlled trial is expected to include approximately 30,000 participants enrolled in the U.S. It is expected to be conducted in collaboration with the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health (NIH). The 100 µg dose level was chosen as the optimal dose level to maximize the immune response while minimizing adverse reactions, based on the results of the Phase 1 study, <https://investors.modernatx.com/news-releases/news-release-details/moderna-advances-late-stage-development-its-vaccine-mrna-1273>. As NIAID established a new clinical trials network - The COVID-19 Prevention Trials Network (COVPN), that aims to enroll thousands of volunteers in large-scale clinical trials testing a variety of investigational vaccines and monoclonal antibodies intended to protect people from COVID-19, the first Phase 3 clinical trial that the COVPN is expected to conduct with the investigational mRNA-1273 vaccine, developed by NIAID scientists and their collaborators at Moderna, Inc., based in Cambridge, Massachusetts, <https://www.nih.gov/news-events/news-releases/nih-launches-clinical-trials-network-test-covid-19-vaccines-other-prevention-tools>.

**Phase 3 Studienprotokoll
veröffentlicht**

**RCT mit ca 30.000
Teilnehmer*innen**

**Zusammenarbeit mit
NIAID (NIH)**

As of August 17, 2020 a preliminary report with the results from the above mentioned phase 1 study was published [16]. After the first vaccination, antibody responses were higher with higher dose (day 29 enzyme-linked immunosorbent assay anti-S-2P antibody geometric mean titer [GMT], 40,227 in the 25-µg group, 109,209 in the 100-µg group, and 213,526 in the 250-µg group). After the second vaccination, the titers increased (day 57 GMT, 299,751, 782,719, and 1,192,154, respectively).

**vorläufige Publikation der
Phase 1 Studie**

**nach 2 Teilimpfungen:
Antikörper bei 100% der
Teilnehmer*innen**

After the second vaccination, serum neutralizing activity was detected by two methods in all participants evaluated, with values generally similar to those in the upper half of the distribution of a panel of control convalescent serum specimens. Solicited adverse events that occurred in more than half the participants included fatigue, chills, headache, myalgia, and pain at the injection site. Systemic adverse events were more common after the second vaccination, particularly with the highest dose, and three participants (21%) in the 250-µg dose group reported one or more severe adverse events. Authors concluded that the mRNA-1273 vaccine induced anti-SARS-CoV-2 immune responses in all participants, and no trial-limiting safety concerns were identified.

höhere Dosis, höhere Titer

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 [17-19]. The platform (non-replicating viral vector) of AD5-nCoV was originally used for an Ebola vaccine (AD5-EBOV) [19, 20].

AD5-nCoV

Estimated timeline for approval

The first clinical, **phase 1** trial (ChiCTR2000030906/NCT04313127) with 108 healthy adults 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 [21]. New RCT, **phase 2**, started also (ChiCTR2000031781/NCT04398147). This randomised, double-blinded, placebo-controlled, parallel, three groups trial aims to evaluate safety and immunogenicity for recombinant novel coronavirus disease vaccine (adenovirus vector) in healthy adults aged above 18 years. Two intervention groups are using middle or low dose of novel vaccine, and the third group is using placebo. The primary endpoints of the trial are adverse reactions 0-14 days post vaccination; anti-S antibody IgG titer on day 28 post vaccination and anti-SARS-CoV-2 neutralizing antibody titer on day 28 post vaccination. Six further safety-related and immunogenetic are registered as secondary endpoints [10, 11]. This RCT will be conducted from 2020-04-12 to 2021-01-31.

Phase 1:
108 gesunde Erwachsene
Dezember 2020

Phase 2:
Jänner 2021

As of 12 June, 2020 the results from above mentioned dose-escalation, open-label, non-randomised, first-in-human trial for adenovirus type-5 vectored COVID-19 vaccine were published (ChiCTR2000030906/NCT04313127) [22]. 108 participants (51% male, 49% female; mean age 36.3 years) were recruited and received the low dose (n=36), middle dose (n=36), or high dose (n=36) of the vaccine (all were included in the analysis). At least one adverse reaction within the first 7 days after the vaccination was reported in 30 (83%) participants in the low dose group, 30 (83%) participants in the middle dose group, and 27 (75%) participants in the high dose group. The most common

1 veröffentlichte klinische Studie:

108 Studienteilnehmer*innen erhalten unterschiedliche Dosierungen

injection site adverse reaction was pain, which was reported in 58 (54%) vaccine recipients, and the most commonly reported systematic adverse reactions were fever (50 [46%]), fatigue (47 [44%]), headache (42 [39%]), and muscle pain (18 [17%]). Most adverse reactions that were reported in all dose groups were mild or moderate in severity. No serious adverse event was noted within 28 days post-vaccination. ELISA antibodies and neutralising antibodies increased significantly at day 14, and peaked 28 days post-vaccination. Specific T-cell response peaked at day 14 post-vaccination.

As of 17 August, 2020 the results from the above mentioned phase 2 RCT were published [23]. 508 eligible participants (50% male; mean age 39.7 years, SD 12.5) consented to participate in the trial and were randomly assigned to receive the vaccine (1×10^{11} viral particles $n=253$; 5×10^{10} viral particles $n=129$) or placebo ($n=126$). In the 1×10^{11} and 5×10^{10} viral particles dose groups, the RBD-specific ELISA antibodies peaked at 656.5 (95% CI 575.2–749.2) and 571.0 (467.6–697.3), with seroconversion rates at 96% (95% CI 93–98) and 97% (92–99), respectively, at day 28. Both doses of the vaccine induced significant neutralising antibody responses to live SARS-CoV-2, with GMTs of 19.5 (95% CI 16.8–22.7) and 18.3 (14.4–23.3) in participants receiving 1×10^{11} and 5×10^{10} viral particles, respectively. Specific interferon γ enzyme-linked immunospot assay responses post vaccination were observed in 227 (90%, 95% CI 85–93) of 253 and 113 (88%, 81–92) of 129 participants in the 1×10^{11} and 5×10^{10} viral particles dose groups, respectively. Solicited adverse reactions were reported by 183 (72%) of 253 and 96 (74%) of 129 participants in the 1×10^{11} and 5×10^{10} viral particles dose groups, respectively. Severe adverse reactions were reported by 24 (9%) participants in the 1×10^{11} viral particles dose group and one (1%) participant in the 5×10^{10} viral particles dose group. No serious adverse reactions were documented. Authors concluded that the Ad5-vectored COVID-19 vaccine at 5×10^{10} viral particles is safe, and induced significant immune responses in the majority of recipients after a single immunisation.

**Publikation der
Phase 2 Studie (RCT)**

508 Teilnehmer*innen

96%/ 97%

**Serokonversionsrate bei
2 unterschiedlichen
Dosierungen**

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 [20, 24]. The company's DNA platform was previously utilised for a MERS-CoV vaccine (INO-4700) tested in a phase I trial [25].

INO-4800

Estimated timeline for approval

According to press releases from the manufacturer [25, 26], and ClinicalTrials.gov register, human testing (a **phase 1** clinical trial) started in April 2020. The results are aimed to be presented and published thereafter (April 2021). The phase 1, non-randomized, open-label, sequential assignment clinical trial (NCT04336410) in 40 healthy adult volunteers aims to evaluate the safety, tolerability and immunological profile of INO-4800 administered by intradermal (ID) injection followed by electroporation (EP) using CELLECTRA® 2000 device. The primary endpoints of the trial are as following: percentage of participants with adverse events (AEs); percentage of participants with administration (injection) site reactions; percentage of

**Phase 1:
40 gesunde Erwachsene**

April 2021

participants with adverse events of special interest (AESIs); change from baseline in Antigen-Specific Binding Antibody Titers; change from baseline in Antigen-Specific Interferon-Gamma (IFN- γ) Cellular Immune Response. Secondary endpoints are not provided [6-10]. This RCT will be conducted from April 2020 to April 2021. Estimated Primary Completion Date is April 2021.

Phase 1/2 trial (NCT04447781) aims to evaluate the safety, tolerability and immunological profile of INO-4800 administered by intradermal (ID) injection followed by electroporation (EP) using the CELLECTRA® 2000 device in 160 healthy adults aged 19 to 64 years in Republic of Korea. INO-4800 contains the plasmid pGX9501, which encodes for the full length of the Spike glycoprotein of SARS-CoV-2 [9].

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

**Phase 1/2:
160 gesunde Erwachsene
in Korea**

**keine veröffentlichten
klinischen Studien**

2.4 Novavax

About the vaccine

The Novavax COVID-19 vaccine being developed by Novavax and co-sponsored by CEPI [27] is a recombinant protein nanoparticle technology platform that is to generate antigens derived from the coronavirus spike (S) protein [28]. 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 [29, 30].

Estimated timeline for approval

Novavax has been assessing recombinant nanoparticle vaccine candidates in animal models and they initiated Phase 1 clinical trial in May/June 2020 [27]. Novavax has previous experience with both MERS and SARS [29]. The **phase 1/2**, randomized, placebo-controlled, triple-blind, parallel assignment clinical trial (NCT04368988) in 131 healthy adults aims to evaluate the immunogenicity and safety of SARS-CoV-2 rS nanoparticle vaccine with or without Matrix-M adjuvant in healthy participants ≥ 18 to 59 years of age. The study will be conducted in 2 parts. In Part 1, at least 1 and up to two SARS-CoV-2 rS constructs will be evaluated in up to 2 cohorts, which may be enrolled in parallel. An interim analysis of Part 1 safety and immunogenicity data will be performed prior to an optional expansion to Part 2. The primary endpoints of the trial are as following: subjects with solicited AEs - Phase 1; safety Laboratory Values (serum chemistry, hematology) - Phase 1 and serum IgG antibody levels specific for the SARS-CoV-2 rS protein antigen(s) - Phase 1. Secondary endpoints are not provided [6-9]. This RCT will be conducted from May 15, 2020 to July 31, 2021. Estimated Primary Completion Date is December 31, 2020.

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

**CEPI
Matrix-M™**

**Phase 1:
131 gesunde Erwachsene**

Juli 2021

**keine veröffentlichten
klinischen Studien**

2.5 University of Queensland/GSK/Dynavax

About the vaccine

Together with DynaVax and GlaxoSmithKline (GSK)¹, The University of Queensland currently investigates on a potential vaccine using molecular clamp stabilized Spike proteins [14, 20]. 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 [31].

Initially, this technology was designed to be a platform for generating vaccines against different viruses such as influenza, Ebola, and the MERS coronavirus [32].

Estimated timeline for approval

Phase 1 randomised, double blind, placebo-controlled, dosage-escalation trial has started on July 13, 2020 (ACTRN12620000674932/NCT04495933) with aim to evaluate the safety and immunogenicity of an adjuvanted SARS-CoV-2 sclamp protein subunit vaccine in healthy adults. The estimated study completion date is September 2021 [9].

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

DynaVax & GSK

**Beginn klinische Studie:
September 2021**

**keine veröffentlichten
klinischen Studien**

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) [14]. 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 [34]. 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 [35]

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 [36]. 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

mRNA

**Interimanalyse
von Phase 1**

¹ Both DynaVax and GSK will provide adjuvants.

To date (09/07/2020), one ongoing **Phase 1** (NCT04449276) study and no completed studies in humans are available for the vaccine candidates. **Phase 1** (NCT04449276) study aims to evaluate the safety and reactogenicity profile after 1 and 2 dose administrations of CVnCoV at different dose levels. It is funded by Coalition for Epidemic Preparedness Innovations (CEPI), and located in Belgium and Germany. 168 participants are planned to be enrolled in the trial [9].

Phase 1:
Beginn klinische Studie:
Sommer 2020
168 Teilnehmer*innen
keine veröffentlichten klinischen Studien

2.7 University of Oxford

About the vaccine

The **ChAdOx1 nCoV-19** (AZD1222, AstraZeneca licensed from Oxford University) 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 [17, 37].

ChAdOx1 nCoV-19

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 [37].

Estimated timeline for approval

Currently, the first clinical **phase 1/2** trial in 510 healthy adults is ongoing (ISRCTN 15281137/NCT04324606/EudraCT 2020-001072-15). 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 [38].

Phase 1/2:
510 gesunde Erwachsene
bis Mai 2021

Phase 2b/3 study (EudraCT 2020-001228-32/NCT04400838) is ongoing, with aim to determine the efficacy, safety and immunogenicity of the candidate Coronavirus Disease (COVID-19) vaccine ChAdOx1 nCoV-19. The primary endpoint is virologically confirmed (PCR positive) symptomatic COVID-19 infection.

Phase 2b/3 :
laufend

Phase 3 RCT (ISRCTN89951424) started in Brazil and South Africa, with another country in Africa set to follow, as well as a trial in the US [39]. Participants are randomly allocated to receive the investigational vaccine or a well-established meningitis vaccine. Volunteers will be followed for 12 months, and they will be tested for COVID-19 if they develop any symptoms which may represent COVID-19 disease [40]. The study is estimated to be completed in July 2021.

Phase 3 RCT
Brazilien, Südafrika, USA
12-Monate Follow-Up
Ende Juli 2021

As of 17 August, 2020, a preliminary report with the results from phase 1/2 single-blind, RCT (ISRCTN 15281137/NCT04324606/EudraCT 2020-001072-15) was published [41]. 1077 participants were enrolled and assigned to receive either ChAdOx1 nCoV-19 (n=543) or MenACWY (n=534), ten of whom were enrolled in the non-randomised ChAdOx1 nCoV-19 prime-boost group. Local and systemic reactions were more common in the ChAdOx1 nCoV-19 group and many were reduced by use of prophylactic paracetamol, including pain, feeling feverish, chills, muscle ache, headache, and malaise (all $p < 0.05$). There were no serious adverse events related to ChAdOx1 nCoV-19. In the ChAdOx1 nCoV-19 group, spike-specific T-cell responses peaked on day 14 (median 856 spot-forming cells per million peripheral blood mononuclear cells, IQR 493–1802; $n=43$). Anti-spike IgG responses rose by day 28 (median 157 ELISA units [EU], 96–317; $n=127$), and were boosted following a second dose (639 EU, 360–792; $n=10$). Neutralising antibody responses against SARS-CoV-2 were detected in 32 (91%) of 35 participants after a single dose when measured in MNA80 and in 35 (100%) participants when measured in PRNT50. After a booster dose, all participants had neutralising activity (nine of nine in MNA 80 at day 42 and ten of ten in Marburg VN on day 56). Neutralising antibody responses correlated strongly with antibody levels measured by ELISA ($R^2=0.67$ by Marburg VN; $p < 0.001$). Authors concluded that ChAdOx1 nCoV-19 showed an acceptable safety profile, and homologous boosting increased antibody responses and together with the induction of both humoral and cellular immune responses, support largescale evaluation of this candidate vaccine in an ongoing phase 3 programme.

vorläufige Publikation der Ergebnisse Phase 1/2:

Antikörper-Response bei 91% bis 100% der Teilnehmer*innen

2.8 BioNTech/Fosun Pharma/Pfizer

About the vaccine

The **BNT-162** vaccine candidate developed by BioNTech in collaboration with Fosun Pharma and Pfizer is an mRNA platform-based vaccine expressing codon-optimized undisclosed SARS-CoV-2 protein(s) encapsulated in 80-nm ionizable cationic lipid/ phosphatidylcholine/ cholesterol/ polyethylene glycol–lipid nanoparticles [14]. In 2018, Pfizer and BioNTech collaborated on mRNA-based vaccines for the prevention of influenza and their partnership applies outside of China [42]. BioNTech's partnership with Fosun Pharma applies for China only [42, 43].

BNT-162

Estimated timeline for approval

Currently, BNT-162 enters clinical testing by the end of April 2020 [44] and R&D is supposed to be carried out both in the US as well as in Germany [42]. This is a **phase 1/2**, randomized, placebo-controlled, triple-blind, dose-finding, and vaccine candidate-selection study in healthy adults (NCT04368728/EudraCT 2020-001038-36). The study will evaluate the safety, tolerability, immunogenicity, and potential efficacy of up to 4 different SARS-CoV-2 RNA vaccine candidates against COVID-19: as a 2-dose or single-dose schedule; at up to 3 different dose levels; in 3 age groups (18 to 55 years of age, 65 to 85 years of age, and 18 to 85 years of age). The study consists of 3 stages: Stage 1: to identify preferred vaccine candidate(s), dose level(s), number of doses, and schedule of administration (with the first 15 participants at each dose level of each vaccine candidate comprising a sentinel cohort); Stage 2: an expanded-cohort stage; and Stage 3; a final candidate/dose large-scale stage.

**Phase 1/2
mehrstufiges
Studiendesign**

Study NCT04380701 is located in Germany. **Phase 2/3 RCT** has started also (NCT04368728/EudraCT 2020-002641-42) with aim to describe the safety, tolerability, immunogenicity and efficacy of RNA vaccine candidate against COVID-19 in healthy adults. Estimated number of participants is 29481, and completion study date November 2022 [9].

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

**Phase 1/2
(Deutschland) hat
begonnen**

November 2022

**keine veröffentlichten
klinischen Studien**

2.9 Sinovac Biotech Ltd.

About the vaccine

The private Chinese biopharmaceutical company Sinovac Biotech Ltd. focuses on the research, development, manufacturing and commercialization of vaccines that protect against human infectious diseases. Sinovac Life Sciences Co., Ltd. is the developer of CoronaVac, an inactivated COVID-19 vaccine candidate, and will be the marketing authorization holder of CoronaVac in China with a vaccine production license from China National Medical Products Administration (NMPA).

CoronaVac

Estimated timeline for approval

The **phase 1 and 2** trials started on April 16, 2020 in Jiangsu Province, China: a group of healthy adults aged 18-59 years old were vaccinated with a 0, 14 day schedule. According to Sinovac announcement, preliminary phase I/II results showed that there was no serious adverse event after vaccinating a total of 743 volunteers in the trials, demonstrating a good safety profile for the vaccine candidate. Over 90% seroconversion was observed in the phase II clinical trial 14 days after completion of a two-dose vaccination at day 0 and day 14. A Phase II study on elderly adults is being conducted which will be followed by child and adolescent groups. The phase II trial is expected to be completed at the end of 2020 [45].

**Phase 1/2 :
743 Teilnehmer*innen**

Sinovac registered a new **Phase 3 RCT** (NCT04456595), with aim to assess efficacy and safety of the Adsorbed COVID-19 (inactivated) vaccine in health care professionals in Brazil. Estimated number of participants is 8870. The study is double-blind placebo-controlled trial with participants randomly allocated 1:1 to placebo and vaccine arms. The immunization schedule is two doses intramuscular injections (deltoid) with a 14-days interval. For efficacy, the study aims to detect COVID-19 cases, defined as symptomatic SARS-CoV-2 infections, after the second week post-immunization schedule. For safety and immunogenicity, participants are categorized in two age groups, Adults (18-59 years) and Elderly (60 years and above). Safety database aims to detect adverse reactions with frequency of 1:1000 or higher in adults and 1:500 in elderly. All participants will be followed up to 12 months. Interim preliminary efficacy analysis can be triggered by reaching the target number of 150 cases [9]. The study is estimated to be completed in October 2021.

**Sinovac: Phase 3
RCT in Brasilien
8.870, nur
Gesundheitspersonal**

**12-Monate Follow.Up
Oktober 2021**

2.10 China National Pharmaceutical Group Corporation (SINOPHARM)

About the vaccine

The China National Pharmaceutical Group Corporation (SINOPHARM), the state-owned Chinese company, developed a β -propiolactone-inactivated whole-virus vaccine against COVID-19 jointly by the Beijing Institute of Biological Products and the Wuhan Institute of Biological Products under SINOPHARM [46].

Estimated timeline for approval

In interim analysis related to safety and immunogenicity of an investigational inactivated whole-virus COVID-19 vaccine in China (Chinese Clinical Trial Registry Identifier: ChiCTR2000031809, Xia et al. 2020 [46, 47]) reported results from two double-blind RCTs, phase 1 and phase 2. The experimental group received a β -propiolactone-inactivated whole-virus vaccine against COVID-19. The placebo group contained only sterile phosphatebuffered saline and alum adjuvant.

In the phase 1 RCT, 96 participants were assigned to 1 of the 3 dose groups (2.5, 5, and 10 μ g/dose) and an aluminum hydroxide (alum) adjuvant-only group (n = 24 in each group), and received 3 intramuscular injections at days 0, 28, and 56. In the phase 2 RCT trial, 224 adults were randomized to 5 μ g/dose in 2 schedule groups (injections on days 0 and 14 [n = 84] vs alum only [n = 28], and days 0 and 21 [n = 84] vs alum only [n = 28]). The primary safety outcome was the combined adverse reactions 7 days after each injection, and the primary immunogenicity outcome was neutralizing antibody response 14 days after the whole-course vaccination, which was measured by a 50% plaque reduction neutralization test against live severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

Among 320 patients who were randomized, all completed the trial up to 28 days after the whole-course vaccination. The 7-day adverse reactions occurred in 3 (12.5%), 5 (20.8%), 4 (16.7%), and 6 (25.0%) patients in the alum only, low-dose, medium-dose, and high-dose groups, respectively, in the phase 1 trial; and in 5 (6.0%) and 4 (14.3%) patients who received injections on days 0 and 14 for vaccine and alum only, and 16 (19.0%) and 5 (17.9%) patients who received injections on days 0 and 21 for vaccine and alum only, respectively, in the phase 2 trial. The most common adverse reaction was injection site pain, followed by fever, which were mild and self-limiting; no serious adverse reactions were noted. The geometric mean titers of neutralizing antibodies in the low-, medium-, and high-dose groups at day 14 after 3 injections were 316 (95% CI, 218-457), 206 (95% CI, 123-343), and 297 (95% CI, 208-424), respectively, in the phase 1 trial, and were 121 (95% CI, 95-154) and 247 (95% CI, 176-345) at day 14 after 2 injections in participants receiving vaccine on days 0 and 14 and on days 0 and 21, respectively, in the phase 2 trial. Authors concluded that in this interim report of the phase 1 and phase 2 trials of an inactivated COVID-19 vaccine, patients had a low rate of adverse reactions and demonstrated immunogenicity; the study is ongoing. Efficacy and longer-term adverse event assessment will require phase 3 trials [46].

inactivated

**Phase 1 und
Phase 2 RCTs**

**Phase 1:
96 Teilnehmer*innen –
3 unterschiedliche
Dosierungen**

**Phase 2:
224 Teilnehmer*innen – 2
unterschiedliche
Zeitpläne**

**Endpunkte: Antikörper
Response**

Nebenwirkungen

A phase 3 double-blind, placebo controlled RCT has been initiated (ChiCTR2000034780), to evaluate the protective efficacy of inactivated SARS-CoV-2 Vaccine (Vero Cell) after full course of immunization in preventing diseases caused by the SARS-CoV-2 in healthy subjects aged 18 years old and above. The study is estimated to be completed in July 2021.

Phase 3 initiiert

Juli 2021

2.11 New vaccines entered in clinical investigation in healthy volunteers

As at 05 May 2020, **6 new vaccine trials** are registered in phase 1, phase 1/2 and phase 2, by Shenzhen Geno-Immune Medical Institute (NCT04299724 and NCT04276896); Insitute of Biotechnology, Academy of Military Medical Sciences, PLA of China (NCT04341389); Symvivo Corporation (NCT04334980); Sinovac (NCT04352608) and Wuhan Institute of Biological Products/Sinopharm (ChiCTR2000031809) (Table 2-1). NCT04299724 is phase 1 study related to pathogen-specific aAPC (aAPCs modified with lentiviral vector expressing synthetic minigene based on domains of selected viral proteins) and NCT04276896 is phase 1/2 study related to LV-SMENP-DC vaccine (DCs modified with lentiviral vector expressing synthetic minigene based on domains of selected viral proteins; administered with antigen-specific CTLs). NCT04341389 is phase 2 trial related to adenovirus Type 5 Vector expressing S protein. NCT04334980 is phase 1 study, the first-in-human study of bacTRL-Spike, and the first-in-human use of orally delivered bacTRL. Two clinical trials in phase 1/2 are related to inactivated vaccine: NCT04352608 is related to inactivated SARS-CoV-2 virus and ChiCTR2000031809 to Vero cells derived (cell culture-derived inactivated) vaccine [6-11].

Mai 2020:
6 neue Impfstoff-
Kandidaten in Phase 1-2
registriert

As at 13 June 2020, **four new vaccine trials** are registered: two new inactivated vaccines in phase 1 and phase 1/2, by Beijing Institute of Biological Products/Sinopharm (ChiCTR2000032459) and Institute of Medical Biology, Chinese Academy of Medical Sciences (NCT04412538) [10]; one S-Trimer vaccine - a trimeric SARS-CoV-2 spike (S)-protein subunit, through Trimer-Tag© vaccine technology platform, by Clover Biopharmaceuticals AUS Pty Ltd (NCT04405908), <https://www.pharmaadvancement.com/manufacturing/cepi-announces-covid-19-vaccine-development-partnership-with-clover-biopharmaceuticals-australian-subsiidiary/>, and one Dendritic cell vaccine (autologous dendritic cells loaded with antigens from SARS-CoV-2, with or without GM-CFS, by Aivita Biomedical, Inc. (NCT04386252) (Table 2-1).

Juni 2020:
weitere 4 neue Impfstoff-
Kandidaten in Phase 1-2
registriert

As at July 07, 2020, **nine Phase 1 new vaccines trials** are registered: three DNA vaccine, from Cadila Healthcare Limited (CTRI/2020/07/026352), Genexine Consortium (NCT04445389) and Osaka University/AnGes/Takara Bio (JapicCTI-205328); two NonReplicating Viral Vector vaccine from Gamaleya Research Institute (NCT04436471, NCT04437875); two Protein Subunit vaccines from Anhui Zhifei Longcom Biopharmaceutical/Institute of Microbiology, Chinese Academy of Sciences (NCT04445194) and Vaxine Pty Ltd/Medytox (NCT04453852); two RNA vaccines, Imperial College London (ISRCTN17072692) and People's Liberation Army (PLA) Academy of Military Sciences/Walvax Biotech (ChiCTR2000034112), and one VLP vaccine from Medicago Inc./Université Laval (NCT04450004) (Table 2-1) [10].

Juli 2020:
weitere 9 Impfstoff-
Kandidaten in Phase 1
registriert

As at August 14, 2020, **six new vaccines trials** (Phase 1 or Phase 1/ 2) are registered in ClinicalTrials.gov register: Bharat Biotech (NCT044571519, Inactivated); Janssen Pharmaceutical Companies (NCT04436276, NonReplicating Viral Vector, Ad26COVS1); Kentucky Bioprocessing, Inc (NCT04473690, Protein Subunit, RBD-based); Arcturus/Duke-NUS (NCT04480957, RNA, mRNA); Institute Pasteur/Themis/Univ. of Pittsburg CVR/Merck Sharp & Dohme (NCT04497298, Replicating Viral Vector, Measles-vector based) and Medigen Vaccine Biologics Corporation/NIAID/Dynavax (NCT04487210, Protein Subunit, S-2P protein + CpG 1018) (Table 2-1) [10].

Two studies are reported as completed [9], without published results. An open two stage non-randomized Phase 1/2 study (NCT04436471) with the participation of 38 healthy volunteers sponsored by Gamaleya Research Institute of Epidemiology and Microbiology, Health Ministry of the Russian Federation in collaboration with Acellena Contract Drug Research and Development aimed to evaluate the safety, tolerability and immunogenicity of the vaccine Gam-COVID-Vac, adenoviral-based vaccine against SARS-CoV-2, a solution for intramuscular injection.

According to recent press release, Russian COVID-19 vaccine, called Sputnik V, is the first in the world received national regulatory approval, and was approved for public use even ahead of its Phase III trial. No trial data are published.

Several clinical studies assessing Bacillus Calmette–Guérin (BCG) vaccine in prevention of COVID-19 are underway also. For example, RCTs in Netherlands (BCG-CORONA phase 3 trial, NCT04328441) and Australia (BRACE phase 3 trial, NCT04327206) aim to assess whether BCG-Danish reduces the incidence and severity of COVID-19 in health-care workers, and the effect this has on time away from work [48]. The same is true for US RCT (NCT04348370) [9]. The same is planned in Egypt (NCT04350931) and in Denmark (NCT04373291) (RCTs, not yet recruiting healthy volunteers) [9].

Utrecht scientists (in close collaboration with RIVM, Netherlands Pharmacovigilance center LAREB and the PHARMO Institute in the Netherlands) will lead a European project called ACCESS (**vACCine Covid-19 monitoring ReadinESS**) with aim to activate the infrastructure and prepare European organizations to collaboratively monitor the benefits, coverage and risks of the novel COVID-19 vaccines in their post-licensure phase. The project is funded by the European Medicines Agency (EMA), <https://www.uu.nl/en/news/monitoring-the-benefits-and-safety-of-the-new-corona-vaccines>.

On 09/07/2020, Medicines Regulatory Authorities published the report related to phase 3 COVID-19 vaccine trials [49]. They stressed the need for large phase 3 clinical trials that enroll many thousands of people, including those with underlying medical conditions, to generate relevant data for the key target populations. Also broad agreement was achieved that clinical studies should be designed with stringent success criteria that would allow a convincing demonstration of the efficacy of COVID-19 vaccines.

**August 2020:
weitere 6 Impfstoff-
Kandidaten in Phase 1/2
registriert**

**2 Studien ohne
Veröffentlichungen:
Gamaleya Research
Institute of Epidemiology
and Microbiology Health
Ministry of the Russian
Federation**

Sputnik zugelassen

**mehrere klinische Studien
mit BCG Vazzenen in
Phase 3 oder geplant**

**Impfkandidaten-
Infrastruktur und
Monitoring Projekt**

**Positionspapier der
Internationalen
Regulatoren**

**stringente klinische
Studien vonnöten !**

3 Results: Therapeutics

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

Drug	Mechanism of operation	Studies in ClinicalTrials.gov & EU CTR listed as completed, suspended, terminated or withdrawn, with trial identifier ²
Remdesivir (Veklury®)	Antiviral agent	NCT04252664 - Suspended NCT04257656 - Terminated NCT04292899, EudraCT 2020-000841-15 – Completed NCT04292730, EudraCT 2020-000842-32 – Completed NCT04280705 - Completed
Lopinavir + Ritonavir (Kaletra®)	Antiviral agent	NCT04276688 – Completed NCT04307693 – Terminated NCT04409483 - Withdrawn
Favipiravir (Avigan, T-705)	Antiviral agent	ChiCTR2000030254 – Completed NCT04349241- Completed
Darunavir (Prezista®)	Antiviral agent	No completed, withdrawn, suspended or terminated studies found
Camostat Mesilate (Foiipan®)	Antiviral cell-entry inhibitor	No completed, withdrawn, suspended or terminated studies found
APN01 (rhACE2)	Antiviral cell-entry inhibitor	NCT04287686 - Withdrawn
Tocilizumab (RoActemra®)	Monoclonal antibody	NCT04331795 - Completed NCT04346355 - Terminated NCT04361552 - Withdrawn NCT04320615, EudraCT 2020-001154-22 - Completed NCT04492501 - Completed
Sarilumab (Kevzara®)	Monoclonal antibody	NCT04341870 - Suspended
Interferon beta 1a (SNG001) and 1b	Interferon	NCT04276688 Interferon beta 1b – Completed NCT04343768 - Completed
Convalescent Plasma	Convalescent Plasma	NCT04325672 - Withdrawn NCT04346446 – Completed NCT04407208 - Completed NCT04441424 - Completed NCT04442958 – Completed NCT04389944 – Completed NCT04356534 – Completed
Plasma derived medicinal products	Plasma derived medicinal products	No completed, withdrawn, suspended or terminated studies found
Solnatide	Synthetic peptide	No completed, withdrawn, suspended or terminated studies found
Umifenovir (Arbidol®)	Antiviral agent	No completed, withdrawn, suspended or terminated studies found
Dexamethasone (and other corticosteroids)	Glucocorticoid	NCT04445506 – Completed NCT04327401 - Terminated Other corticosteroids: NCT04273321 - Completed

² Ongoing studies can be found in V1 and V2.

Anakinra (Kyneret®)	Interleukin 1 receptor antagonist	No completed, withdrawn, suspended or terminated studies found
Colchicine	An alkaloid, with anti-gout and anti-inflammatory activities	No completed, withdrawn, suspended or terminated studies found

3.1 Remdesivir (Veklury)

About the drug under consideration

Remdesivir (Veklury) is an antiviral medicine for systemic use which received a **conditional marketing authorisation** in EU in July, 2020. It is an adenosine nucleotide prodrug, metabolized within host cells to form the pharmacologically active nucleoside triphosphate metabolite. Remdesivir triphosphate acts as an analog of adenosine triphosphate (ATP) and competes with the natural ATP substrate for incorporation into nascent RNA chains by the SARS-CoV-2 RNA-dependent RNA polymerase. This results in delayed chain termination during replication of the viral RNA.

After the “rolling review” of data on the use of remdesivir to treat COVID-19 was concluded on 15 May 2020 [50] and after received application for conditional marketing authorisation (CMA) (08 June 2020), **European Medicine Agency’s (EMA)** Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion on June 25, 2020, recommending the granting of a **conditional marketing authorisation** [51]. This conditional marketing authorisation has been granted by the **European Commission** on **July 3, 2020**, https://ec.europa.eu/commission/presscorner/detail/en/mex_20_1266. The EMA’s positive recommendation is mainly based on preliminary data published by Beigel et al. [52], described in section below - Results of publications.

Remdesivir (Veklury) is subject to **additional monitoring for safety**. Due to a conditional marketing authorisation, Marketing Authorisation Holder (MAH) should complete some **measures to confirm the efficacy and safety within different timeframe**. Till August 2020, the MAH should submit the published final D28 mortality data by ordinal scale categories of Study CO-US-540-5776 (NIAID-ACTT1) and in addition, the MAH should discuss potential imbalance in the use of corticosteroids and effect modification in Study CO-US-540-5776. Till December 2020, MAH should submit the final clinical study report (CSR) of Study CO-US-540-5776 (NIAID-ACTT1); the final CSR for Part A (Day 28) of Study GS-US-540-5773; the final CSR for Part A (Day 28) of Study GS-US-540-5774, as well as analysis of all available safety data from clinical trials CO-US-540-5776, GS-US-540-5773, GS-US-540-5774 and CO-US-540-5758 when completed, including case narratives, detailed information about adverse reaction and exposure data as well as an analysis of occurrence and aggravation of AEs, SAEs and ADRs are associated with increasing exposure [53].

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

**erstes zugelassenes
antivirales Medikament
gegen Coronavirus**

**conditional marketing
authorisation**

**Zulassung basiert auf
vorläufigen Daten**

**Beigel et al. Studie
(NIAID-ACTT1)**

**bis August sollen “Safety”
Daten vorgelegt werden
(u.a. Mortalität)**

**indiziert für Patient*innen
≥ 12 Jahre mit
Lungenentzündung,
Sauerstoff-unterstützt
Verabreichung iv
5-10 Tage**

mg given by intravenous infusion, Day 2 onwards – 100 mg given once daily by intravenous infusion. The total **duration of treatment** should be at least 5 days and not more than 10 days. **Concomitant use** of remdesivir **with chloroquine phosphate or hydroxychloroquine sulphate** is **not recommended** due to antagonism observed in vitro.

The **most common adverse reaction** in healthy volunteers is increased transaminases (14%). The most common adverse reaction in patients with COVID-19 is nausea (4%) [53].

The use of RDV for COVID-19 was granted by the Food and Drug Administration (FDA) on the 19th of March in the course of the expanded access program to allow the emergency use, and in addition it has an orphan designation for Ebola since September 2015 [54]. On May 1, 2020 the **U.S. Food and Drug Administration (FDA)** has issued an **Emergency Use Authorization (EUA)** to permit the emergency use of the unapproved product remdesivir for treatment of suspected or laboratory confirmed coronavirus disease 2019 (COVID-19) in adults and children hospitalized with severe disease. Severe disease is defined as patients with an oxygen saturation (SpO₂) ≤ 94% on room air or requiring supplemental oxygen or requiring mechanical ventilation or requiring extracorporeal membrane oxygenation (ECMO). EUA was based on available data from two randomized clinical trials (NIAID ACTT-1 Study, NCT04280705 and Study GS-US-540-5773, NCT04292899); a compassionate use program in patients with COVID-19; from clinical trials in healthy volunteers and subjects with Ebola virus disease [55, 56]. On June 15, 2020 FDA issued the **warning about co-administration** of remdesivir and **chloroquine phosphate or hydroxychloroquine sulphate** which may result in reduced antiviral activity of remdesivir [57].

US COVID-19 Treatment Guidelines Panel issued recommendations on remdesivir treatment for patients with COVID-19 (as of July 24, 2020) [58]:

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

Nebenwirkungen

FDA: "expanded access program" (März)

Emergency Use Authorization (EUA) (Mai)

basierend auf 2 Studien:

**ACTT-1 (NIAID)
GS-US-540-5773**

FDA Warnung vor Komedikation Chloroquin phosphate, Hydroxychloroquin sulphate

Empfehlungen des US COVID-19 Treatment Guidelines Panel

RDV bei schwerer COVID-19 Erkrankung mit künstlicher Beatmung

insuffiziente Datenlage bei moderater/ milder Erkrankung

5-Tagestherapie

keine Aussagen zu Subgruppen möglich

difference between the remdesivir and placebo groups in time to recovery or mortality rate in these subgroups. However, because the trial was not powered to detect differences in outcomes in these subgroups, there is uncertainty as to the effect of remdesivir on the course of COVID-19 in these patients.

5. **Duration of Therapy for Patients Who Have Not Shown Clinical Improvement After 5 Days of Therapy:** There are insufficient data on the optimal duration of remdesivir therapy for patients with COVID-19 who have not shown clinical improvement after 5 days of therapy. In this group, some experts extend the total remdesivir treatment duration to up to 10 days (CIII).

**bei Nicht-Ansprechen ev.
Verlängerung auf 10-
Tagestherapie**

Rochwer et al. [59] published a **clinical practice guideline** in which the guideline panel makes a weak recommendation for the use of remdesivir in severe covid-19 while recommending continuation of active enrolment of patients into ongoing randomised controlled trials examining remdesivir. This was based on the linked systematic review (published 31 Jul 2020) which identified two randomised trials with 1300 participants, showing low certainty evidence that remdesivir may be effective in reducing time to clinical improvement and may decrease mortality in patients with severe covid-19. Remdesivir probably has no important effect on need for invasive mechanical ventilation. Remdesivir may have little or no effect on hospital length of stay.

**niedrige Evidenz der
Datenlage, weitere
klinische Studien zum
Nutzen notwendig**

Gilead Sciences Inc. said it plans to start human trials of an inhaled version of its anti-Covid-19 drug remdesivir. An inhaled version, through a nebulizer, could allow Gilead to give the drug to a broader group of patients, including those with milder symptomatic cases who don't need to be hospitalized, <https://www.pharmacist.com/article/gilead-begin-human-testing-inhaled-version-covid-19-drug-remdesivir>.

**Vorhaben von Gilead:
Darreichungsform mittels
Inhalator**

Completed, withdrawn, suspended or terminated studies

The search in two clinical trial registers (ClinicalTrials.gov and EUdraCT) on 06/07/2020 yielded no completed study on the safety and efficacy of RVD in COVID-19 patients. No suspended or terminated studies were found in addition to the two phase 3 randomised controlled trials (RCT) to evaluate intravenous RVD in patients with 2019-nCoV, initiated in the beginning of February in China, which are suspended (NCT04252664) or terminated (NCT04257656) (the epidemic of COVID-19 has been controlled well in China, and no eligible patients can be enrolled further).

**in ClinicalTrials.gov &
EUdraCT**

**keine weiteren beendeten
Studien
2 Phase 3 Studien
suspendiert/beendet**

The search in two clinical trial registers (ClinicalTrials.gov and EUdraCT) on 15/08/2020 yielded three completed studies on the safety and efficacy of RVD in COVID-19 patients: a phase 3 RCT (NCT04292899, EUdraCT 2020-000841-15) conducted in 4891 severe COVID-19 patients, with publication [60]; a phase 3 RCT conducted in 1113 moderate COVID-19 patients (NCT04292730, EudraCT 2020-000842-32), and phase 3 RCT, Adaptive COVID-19 Treatment Trial (ACTT) on 1062 COVID-19 patients (NCT04280705), with preliminary report [49].

Results of publications

At 6th of May 2020, Wang Y et al. [61] published results of the first randomised, double-blind, placebo-controlled, multicentre trial, conducted at ten hospitals in Hubei, China (NCT04257656), assessing the effect of intravenous remdesivir in adults admitted to hospital with severe COVID-19. The study was terminated before attaining the prespecified sample size (237 of the intended 453 patients were enrolled) because the outbreak of COVID-19 was brought under control in China. Patients were randomly assigned in a 2:1 ratio to intravenous remdesivir (200 mg on day 1 followed by 100 mg on days 2–10 in single daily infusions) or the same volume of placebo infusions for 10 days. Patients were permitted concomitant use of lopinavir–ritonavir, interferons, and corticosteroids.

The primary endpoint was time to clinical improvement up to day 28, defined as the time (in days) from randomisation to the point of a decline of two levels on a six-point ordinal scale of clinical status (from 1=discharged to 6=death) or discharged alive from hospital, whichever came first. Primary analysis was done in the intention-to-treat (ITT) population and safety analysis was done in all patients who started their assigned treatment. Remdesivir treatment was not associated with a statistically significant difference in time to clinical improvement (hazard ratio 1.23 [95% CI 0.87–1.75]).

Patients receiving remdesivir had a numerically faster time to clinical improvement than those receiving placebo among patients with symptom duration of 10 days or less, but this was not statistically significant also (hazard ratio 1.52 [0.95–2.43]). The duration of invasive mechanical ventilation was not significantly different between groups (numerically shorter in remdesivir recipients than placebo recipients). 22 (14%) of 158 patients on remdesivir died versus ten (13%) of 78 on placebo. There was no signal that viral load decreased differentially over time between remdesivir and placebo groups. Adverse events were reported in 102 (66%) of 155 remdesivir recipients versus 50 (64%) of 78 placebo recipients. Remdesivir was stopped early because of adverse events in 18 (12%) patients versus four (5%) patients who stopped placebo early (Table 3.1 1).

At May 22, 2020 Beigel et al. [52] published the preliminary report, on which the data and safety monitoring board recommended early unblinding of the results on the basis of findings from an analysis that showed shortened time to recovery in the remdesivir group. It is an ongoing double-blind, randomized, placebo-controlled trial of intravenous remdesivir in adults hospitalized with Covid-19 with evidence of lower respiratory tract involvement (NCT04280705). 1059 patients were randomly assigned to receive either remdesivir (200 mg loading dose on day 1, followed by 100 mg daily for up to 9 additional days) or placebo for up to 10 days. The primary outcome was the time to recovery, defined by either discharge from the hospital or hospitalization for infection-control purposes only. Those patients who received remdesivir had a median recovery time of 11 days (95% confidence interval [CI], 9 to 12), as compared with 15 days (95% CI, 13 to 19) in those who received placebo (rate ratio for recovery, 1.32; 95% CI, 1.12 to 1.55; $P < 0.001$). As authors stated, the primary outcome of the current trial was changed with protocol version 3 on April 2, 2020, from a comparison of the eight-category ordinal scale scores on day 15 to a comparison of time to recovery up to day 29 (as emerging data suggested that Covid-19 had a more

Ergebnisse der Studien:

**Wang (Hubei/ China):
frühzeitig beendet wegen
Mangel an Pts.**

**237 (statt 453) Pts.
ITT-Analyse
RDV iv 10 Tage**

**primärer Endpunkt:
klinische Verbesserung
innerhalb von 28 Tagen:**

**kein stat. signifikanter
Unterschied**

**keine Hinweise auf
Reduktion der Viruslast**

**AE 66%
frühzeitige Beendigung
wegen AE 12%**

Beigel (USA, UK, DK...):

**1.059 Pts
RDV iv 10 Tage**

**frühzeitige Entblindung
wegen verkürzter Zeit zu
Verbesserung (primärer
Endpunkt)**

**11 vs. 15 Tage
(Daten von 844 Pts.)**

protracted course than was previously known, which aroused concern that a difference in outcome after day 15 would have been missed by a single assessment at day 15), proposed by statisticians who had no knowledge of outcome data. The original primary outcome became the key secondary end point. The odds of improvement in the ordinal scale score were statistically significant higher in the remdesivir group, as determined by a proportional odds model at the day 15 visit, than in the placebo group (odds ratio for improvement, 1.50; 95% CI, 1.18 to 1.91; P=0.001; 844 patients).

The difference between the groups related to mortality was not statistically significant; the Kaplan-Meier estimates of mortality by 14 days were 7.1% with remdesivir and 11.9% with placebo (hazard ratio for death, 0.70; 95% CI, 0.47 to 1.04).

Serious adverse events (SAE) were reported for 114 of the 541 patients in the remdesivir group who underwent randomization (21.1%) and 141 of the 522 patients in the placebo group who underwent randomization (27.0%). Grade 3 or 4 adverse events occurred in 156 patients (28.8%) in the remdesivir group and in 172 in the placebo group (33.0%) (Table 3.1 1 continued).

The Living Systematic Review with Meta-Analysis (MA), related to these two RCTs, with the Summary of findings table (https://covid-nma.com/living_data/index.php) is provided in table 3.1-3. In the MA, there was a statistically significant reduction in the incidence of WHO progression score level 6 or above at days 14 to 28 with remdesivir compared with placebo (2 RCTs, n=1299: RR 0.76, 95% CI 0.62 to 0.93, I 2 0%; high certainty), and the incidence of WHO progression score level 7 or above at days 14 to 28 (2 RCTs, n=1299: RR 0.73, 95% CI 0.58 to 0.91, I 2 0%; high certainty). Also, there were statistically significantly fewer serious adverse events (not clearly defined in the studies) with remdesivir compared with placebo (2 RCTs, n=1296: RR 0.77, 95% CI 0.63 to 0.94, I 2 0%; moderate certainty).

**kein stat. signifikant
Unterschied bei Mortalität**

**kein Unterschied
bei SAE**

**Metaanalyse:
stat. signifikante
Reduktion in WHO
progression score mit RDV

stat. significant weniger
SAE mit RDV**

Table 3.1-1: Publications on clinical trials on product remdesivir

Author, year [Reference]	*Wang et al. 2020 [61]
Country	China
Sponsor/Funding	Chinese Academy of Medical Sciences Emergency Project of COVID-19, National Key Research and Development Program of China, the Beijing Science and Technology Project
Study design	Randomised, double-blind, placebo-controlled, multicentre trial NCT04257656
Number of pts	237 (RDV n=158, Placebo n=79)
Intervention/Product	Remdesivir (200 mg on day 1 followed by 100 mg on days 2–10 in single daily infusions)
Comparator	Placebo (same volume of placebo infusions for a total of 10 days)
Inclusion criteria	Men and non-pregnant women with COVID-19 who were aged at least 18 years and were RT-PCR positive for SARS-CoV-2, had pneumonia confirmed by chest imaging, had oxygen saturation of 94% or lower on room air or a ratio of arterial oxygen partial pressure to fractional inspired oxygen of 300 mm Hg or less, and were within 12 days of symptom onset
Exclusion criteria	Pregnancy or breast feeding; hepatic cirrhosis; alanine aminotransferase or aspartate aminotransferase more than five times the upper limit of normal; known severe renal impairment (estimated glomerular filtration rate <30 mL/min per 1.73 m ²) or receipt of continuous renal replacement therapy, haemodialysis, or peritoneal dialysis; possibility of transfer to a non-study hospital within 72 h; and enrolment into an investigational treatment study for COVID-19 in the 30 days before screening
Pts pretreated + previous treatment	Use of other treatments, including lopinavir–ritonavir, was permitted

Author, year [Reference]	*Wang et al. 2020 [61]
Mean age of patients, yrs (SD)	RDV group (66.0); Placebo (64.0)
Sex % male (% female)	RDV group (56.0 m vs 44 f); Placebo (65.0 m vs 35 f)
Follow-up (days)	Up to 28 days
Clinical status	Most patients were in category 3 of the six-point ordinal scale of clinical status at baseline
Loss to follow-up, n (%)	One patient in the placebo group withdrew their previously written informed consent after randomisation (158 and 78 patients were included in the ITT population)
Efficacy outcomes	
Overall survival (OS), n (%)	28-day mortality: 22 [14%] died in the remdesivir group vs 10 (13%) in the placebo group; difference 1.1% [95% CI -8.1 to 10.3]
Time to clinical improvement	RDV group: median 21.0 days [IQR 13.0–28.0] vs 23.0 days [15.0–28.0] in placebo group; HR 1.23 [95% CI 0.87–1.75]
Other efficacy outcomes	No statistically significant differences were observed between the two groups in length of oxygen support, hospital length of stay, days from randomisation to discharge, days from randomisation to death and distribution of six-category scale at day 7, day 14, and day 28, and viral load decrease over time
Safety outcomes	
Adverse events (AEs)	RDV group 102 (66%) of 155 patients vs 50 (64%) of 78 in the control group
Serious adverse events (SAEs)	28 (18%) in the remdesivir group vs 20 (26%) in the control group
Discontinuation of study drug due to AEs or SAEs	18 [12%] in the remdesivir group vs four [5%] in the placebo group), among whom seven (5%) were due to respiratory failure or acute respiratory distress syndrome in the remdesivir group

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

Table 3.1-2: Publications on clinical trials on product remdesivir continued

Author, year [Reference]	**Beigel et al. 2020 [52]
Country	United States, Denmark, United Kingdom, Greece, Germany, Korea, Mexico, Spain, Japan, Singapore
Sponsor/Funding	National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH), Bethesda, MD. Trial has been funded in part with federal funds from the NIAID and the National Cancer Institute, NIH, under contract HHSN261200800001E 75N910D00024, task order number 75N91019F00130/75N91020F00010, and by the Department of Defense, Defense Health Program. Trial has been supported in part by the NIAID of the NIH under award numbers UM1AI148684, UM1AI148576, UM1AI148573, UM1AI148575, UM1AI148452, UM1AI148685, UM1AI148450, and UM1AI148689; has also been funded in part by the governments of Japan, Mexico, Denmark, and Singapore; in South Korea received funding from the Seoul National University Hospital; support for the London International Coordinating Centre was also provided by the United Kingdom Medical Research Council (MRC_UU_12023/23).
Study design	Randomised, double-blind, placebo-controlled, multicentre trial NCT04280705
Number of pts	1063 (RDV n=541, Placebo n=522)
Intervention/Product	Remdesivir (200 mg on day 1 followed by 100 mg daily for up to 9 additional days intravenously)
Comparator	Placebo (same volume of placebo for a total of 10 days)

Author, year [Reference]	**Beigel et al. 2020 [52]
Inclusion criteria	To meet one of the following criteria suggestive of lower respiratory tract infection at the time of enrollment: radiographic infiltrates by imaging study, peripheral oxygen saturation (SpO2) \leq 94% on room air, or requiring supplemental oxygen, mechanical ventilation, or extracorporeal membrane oxygenation (ECMO); a laboratory-confirmed SARS-CoV-2 infection as determined by a positive reverse transcription, polymerase-chain-reaction (RT-PCR) assay result from any respiratory specimen collected <72 hours prior to randomization (during the study, this criterion was modified due to limitations in testing capacity to also allow a RT-PCR positive specimen that was collected <72 hours prior to randomization if the site was unable to obtain a repeat sample and if the participant had progressive disease consistent with ongoing SARS-CoV-2 infection); agreeing not to participate in another COVID-19 treatment clinical trial through Day 29 and practicing heterosexual abstinence or using study-specified contraception through Day 29 for women of childbearing potential
Exclusion criteria	Having either an alanine aminotransferase (ALT) or an aspartate aminotransferase (AST) > 5 times the upper limit of the normal range; impaired renal function as determined by calculating an estimated glomerular filtration rate (eGFR), or need for hemodialysis or hemofiltration; allergy to study product; pregnancy or breast-feeding; and anticipated discharge from the hospital or transfer to another hospital within 72 hours of enrollment
Pts pretreated + previous treatment	Use of other treatments, including lopinavir–ritonavir or other therapeutic agents (e.g. corticosteroids) was permitted, and should be discontinued on enrollment
Mean age of patients, yrs (SD)	RDV group (58.6); Placebo (59.2)
Sex % male (% female)	RDV group (65.1 m vs 34.9 f); Placebo (63.6 m vs 36.4 f)
Follow-up (days)	29 days
Clinical status	Most patients had severe disease; 25.6% were in category 7 of the ordinal scale; 18.5 in category 6; 39.6 in category 5; 11.9 in category 4
Loss to follow-up, n (%)	The results are preliminary; at D14 all patients did complete their 14 days follow-up and only 391/541 remdesivir patients and 340/522 of the placebo group had completed the trial through day 29.
Efficacy outcomes	
Overall survival (OS), n (%)	14-day mortality: 32 [7.1%] died in the remdesivir group vs 54 (11.9%) in the placebo group; HR 0.70 [95% CI 0.47 to 1.04]
Days to Recovery	RDV group: median 11 days [95% CI 9–12] vs 15 days [13–19] in placebo group; Recovery Rate Ratio 1.32 [95% CI 1.12–1.55]
Ordinal score at day 15 (\pm2 days)	The odds of improvement in the ordinal scale score were statistically significant higher in the remdesivir group, as determined by a proportional odds model at the day 15 visit, than in the placebo group (odds ratio for improvement, 1.50; 95% CI, 1.18 to 1.91; P=0.001; 844 patients)
Safety outcomes	
Grade 3 or 4 Adverse events (AEs)	RDV group 156 (28.8%) vs 172 (33.0%) in the control group
Serious adverse events (SAEs)	114 (21.1%) in the remdesivir group vs 141 (27%) in the control group
Discontinuation of study drug due to AEs or SAEs	38 in the remdesivir group vs 37 in the placebo group

**Preliminary report from the 1059 patients (538 assigned to remdesivir and 521 to placebo)

Table 3.1-3: Summary of findings table on remdesivir (2 RCTs: Wang, Beigel) - https://covid-nma.com/living_data/index.php

Summary of findings:						
Remdesivir compared to Placebo for Moderate/Severe COVID-19						
Patient or population: Moderate/Severe COVID-19						
Setting: Worldwide						
Intervention: Remdesivir						
Comparison: Placebo						
Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Placebo	Risk with Remdesivir				
Incidence of viral negative conversion D7	385 per 1.000	404 per 1.000 (281 to 585)	RR 1.05 (0.73 to 1.52)	196 (1 RCT)	⊕○○○ VERY LOW a,b,c	
Incidence of clinical improvement D7	26 per 1.000	25 per 1.000 (5 to 135)	RR 0.99 (0.18 to 5.27)	236 (1 RCT)	⊕○○○ VERY LOW b,d	
Incidence of clinical improvement D14-D28	577 per 1.000	652 per 1.000 (525 to 813)	RR 1.13 (0.91 to 1.41)	236 (1 RCT)	⊕⊕○○ LOW b,c	
Incidence of WHO progression score (level 6 or above D7)	205 per 1.000	267 per 1.000 (160 to 441)	RR 1.30 (0.78 to 2.15)	236 (1 RCT)	⊕⊕○○ LOW b,c	
Incidence of WHO progression score (level 6 or above D14-D28)	260 per 1.000	198 per 1.000 (161 to 242)	RR 0.76 (0.62 to 0.93)	1299 (2 RCTs)	⊕⊕⊕⊕ HIGH	
Incidence of WHO progression score (level 7 or above D7)	103 per 1.000	102 per 1.000 (45 to 227)	RR 0.99 (0.44 to 2.21)	236 (1 RCT)	⊕⊕○○ LOW b,c	
Incidence of WHO progression score (level 7 or above D14-D28)	233 per 1.000	170 per 1.000 (135 to 212)	RR 0.73 (0.58 to 0.91)	1299 (2 RCTs)	⊕⊕⊕⊕ HIGH	

All-cause mortality D7	51 per 1.000	63 per 1.000 (21 to 195)	RR 1.23 (0.40 to 3.81)	236 (1 RCT)	⊕⊕○○ LOW ^{b,c}
All-cause mortality D14-D28	107 per 1.000	79 per 1.000 (43 to 146)	RR 0.74 (0.40 to 1.37)	1299 (2 RCTs)	⊕⊕○○ LOW ^{e,f}
Adverse events D14-D28	641 per 1.000	660 per 1.000 (538 to 808)	RR 1.03 (0.84 to 1.26)	233 (1 RCT)	⊕⊕⊕○ MODERATE ^{g,h}
Serious adverse events D14-D28	268 per 1.000	207 per 1.000 (169 to 252)	RR 0.77 (0.63 to 0.94)	1296 (2 RCTs)	⊕⊕⊕○ MODERATE ^a

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

- a. Risk of bias downgraded by 1 level: some concerns regarding deviations from intended interventions and missing outcome data
- b. Indirectness downgraded by 1 level: single study from a single country, therefore results in this population might not be generalizable to other settings
- c. Imprecision downgraded by 1 level: due to wide confidence interval consistent with the possibility for benefit and the possibility for harm and low number of participants
- d. Imprecision downgraded by 2 levels: due to very wide confidence interval consistent with the possibility for benefit and the possibility for harm and low number of participants
- e. Inconsistency downgraded by 1 level: I²=58.14%
- f. Imprecision downgraded by 1 level: due to wide confidence interval consistent with the possibility for benefit and the possibility for harm
- g. Indirectness not downgraded: we presume that adverse event rate is not specific to a certain setting
- h. Imprecision downgraded by 1 level: low number of participants

On May 27, 2020 Goldman et al. [60] published the results from the randomized, open-label, phase 3 trial involving hospitalized patients with confirmed SARS-CoV-2 infection, oxygen saturation of 94% or less while they were breathing ambient air, and radiologic evidence of pneumonia (NCT04292899). 397 patients were randomly assigned in a 1:1 ratio to receive intravenous remdesivir for either 5 days or 10 days. All patients received 200 mg of remdesivir on day 1 and 100 mg once daily on subsequent days. The primary end point was clinical status on day 14, assessed on a 7-point ordinal scale. Trial did not show a significant difference between a 5-day course and a 10-day course of remdesivir. After adjustment for baseline clinical status, patients in the 10-day group had a distribution in clinical status at day 14 that was similar to that among patients in the 5-day group (P=0.14). The most common adverse events were nausea (9% of patients), worsening respiratory failure (8%), elevated alanine aminotransferase level (7%), and constipation (7%). The absence of a control group in this study did not permit an overall assessment of the efficacy of remdesivir (Table 3.1 1 continued).

**Goldman (USA, IT, SP...)
RCT, open-label
397 Pts.**

**Vergleich von 5 vs. 10
Tagen RDV**

**primärer Endpunkt:
klinischer Status
am Tag 14**

**kein stat. signifikanter
Unterschied**

No new RCT peer-reviewed articles have been published as of August 15, 2020.

Table 3.1-4: Publications on clinical trials on product remdesivir continued

Author, year [Reference]	Goldman et al. 2020 [60]
Country	United States, Italy, Spain, Germany, Hong Kong, Singapore, South Korea, and Taiwan
Sponsor/Funding	Chinese Academy of Medical Sciences Emergency Project of COVID-19, National Key Research and Development Program of China, the Beijing Science and Technology Project
Study design	Randomised, open-label, phase 3, multicentre trial (RDV 5-Day and 10-Day groups) NCT04292899
Number of pts	402 (RDV n=158, Placebo n=79) RDV group 5-Day (n=202); RDV group 10-Day (n=200)
Intervention/Product	200 mg of remdesivir on day 1, followed by 100 mg of remdesivir once daily for the subsequent 4 or 9 days
Comparator	No control group
Inclusion criteria	At least 12 years of age who had SARS-CoV-2 infection confirmed by polymerase-chain-reaction assay within 4 days before randomization; had radiographic evidence of pulmonary infiltrates and either had oxygen saturation of 94% or less while they were breathing ambient air or were receiving supplemental oxygen
Exclusion criteria	Patients who were receiving mechanical ventilation and extracorporeal membrane oxygenation (ECMO) at screening were excluded, as were patients with signs of multiorgan failure; alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels greater than 5 times the upper limit of the normal range or estimated creatinine clearance of less than 50 ml per minute (by the Cockcroft–Gault formula; Patients receiving concurrent treatment (within 24 hours before the start of trial treatment) with other agents with putative activity against Covid-19
Pts pretreated + previous treatment	Not permitted
Mean age of patients, yrs (SD)	RDV group 5-Day (61.0); RDV group 10-Day (62.0)
Sex % male (% female)	RDV group 5-Day (60.0 m vs 40 f); RDV group 10-Day (68.0 m vs 32 f)
Follow-up (days)	Up to 14 days
Clinical status	Greater proportions of patients in the 10-day group were in the two highest disease severity groups (patients in the 10-day group had significantly worse clinical status than those in the 5-day group (p=0.02)

Author, year [Reference]	Goldman et al. 2020 [60]
Loss to follow-up, n (%)	Of the 200 patients in the 5-day group, 172 (86%) completed the course of trial treatment; of the 197 patients in the 10-day group, 86 (44%) completed the course of treatment
Efficacy outcomes	
Overall survival (OS), n (%)	No patient in the 5-day group stopped treatment because of death; in 10-day group: death (12 [6%])
Clinical status assessed on day 14 on a 7-point ordinal scale	RDV 5-day group vs RDV 10-day group, p=0.14
Other efficacy outcomes	No statistically significant differences were observed between the two groups in Time to clinical improvement, Clinical improvement, Time to recovery, Recovery, Time to modified recovery, Modified recovery
Safety outcomes	
Adverse events (AEs)	RDV 5-day group 70% vs RDV 10-day group 74%
Serious adverse events (SAEs)	RDV 5-day group 21% vs RDV 10-day group 35%
AEs grade 3 or higher	Patients experiencing any adverse event of grade 3 or higher: 30% in the 5-day group and 43% in the 10-day group
Discontinuation of study drug due to AEs or SAEs	RDV 5-day group 4% vs RDV 10-day group 10%

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 [17, 62]. 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.

On July 4, 2020 WHO accepted the recommendation from the Solidarity Trial's International Steering Committee to discontinue the trial's lopinavir/ritonavir arms, <https://www.who.int/news-room/detail/04-07-2020-who-discontinues-hydroxychloroquine-and-lopinavir-ritonavir-treatment-arms-for-covid-19>. The Solidarity Trial was established by WHO to find an effective COVID-19 treatment for hospitalized patients. The International Steering Committee formulated the recommendation in light of the evidence for lopinavir/ritonavir vs standard-of-care from the Solidarity trial interim results, and from a review of the evidence from all trials presented at the 1-2 July WHO Summit on COVID-19 research and innovation. Interim trial results show that lopinavir/ritonavir produce little or no reduction in the mortality of hospitalized COVID-19 patients when compared to standard of care. This decision applies only to the conduct of the Solidarity trial in hospitalized patients and does not affect the possible evaluation in other studies of lopinavir/ritonavir in non-hospitalized patients or as pre- or post-exposure prophylaxis for COVID-19.

Kombinationstherapie für HIV zugelassen

Juli 2020: Zwischenergebnisse im Solidarity Trial zeigen keine Wirksamkeit bei hospitalisierten Patient*innen:

Abbruch des Therapiearms in Solidarity betrifft NICHT: nicht-hospitalisierte Patient*innen

The US COVID-19 Treatment Guidelines Panel **recommends against** using the Lopinavir/ritonavir (**AI**) or other HIV protease inhibitors (**AIII**), except in a clinical trial, because of unfavorable pharmacodynamics and because clinical trials have not demonstrated a clinical benefit in patients with COVID-19 [58].

Completed, withdrawn, suspended or terminated studies

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

The search in two clinical trial registers (ClinicalTrials.gov and EudraCT) on 08/06/2020 yielded no additional completed study on the safety and efficacy of RVD in COVID-19 patients. No suspended, but one terminated RCT were found (NCT04307693), comparing lopinavir/ritonavir with active comparator hydroxychloroquine, and no such intervention in control group. The reason of earlier termination is no patients were further enrolled since mid-Apr 2020.

The search in two clinical trial registers (ClinicalTrials.gov and EudraCT) on 06/07/2020 yielded no additional completed study on the safety and efficacy of RVD in COVID-19 patients. No suspended or terminated, but one withdrawn RCT (NCT04409483, TRASCOV) in Niger (comparing lopinavir/ritonavir with standard of care) was found; the reasons were epidemic dynamics. No additional completed, withdrawn, suspended and terminated studies were found until August 16, 2020.

Results of publications

So far (status: June 08, 2020) only two RCT publications [63] [64] on the effectiveness and safety of lopinavir in combination with ritonavir could be identified, in adults hospitalised with severe Covid-19 (clinical trial ChiCTR2000029308) and with mild-moderate Covid-19 (NCT04252885). In the study with severe Covid-19 (ChiCTR2000029308), 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 3.2-1. Details related to RCT number NCT04276688 are written in Section 3.14, related to Combination therapy.

Empfehlungen des US COVID-19 Treatment Guidelines Panel GEGEN Lopinavir/ritonavir

1 abgeschlossener RCT (China)

1 abgebrochener RCT (Südkorea) wegen Mangel an Pts

keine weiteren Studien

2 Publikationen zu RCTs: Pts mit schwerer und mit mild-moderater Erkrankung

Cao (China):

schwere Erkrankung: kein stat. signifikanter Unterschied in klinischer Verbesserung und Mortalität

SAE häufiger in Kontrollgruppe

Another published RCT by Yueping et al. 2020 (NCT04252885) [64] was an exploratory randomised (2:2:1) controlled trial, conducted in China, with aim to assess the efficacy and safety of lopinavir/ritonavir or arbidol monotherapy in 86 patients with mild/moderate COVID-19. 34 of them assigned to lopinavir/ritonavir; 35 to arbidol and 17 with no antiviral medication as control, with follow-up of 21 days. The rate of positive-to-negative conversion of SARS-CoV-2 nucleic acid, as the primary endpoint, was similar between groups (all $p > 0.05$) and there were no differences between groups in the secondary endpoints, the rates of antipyresis, cough alleviation, or improvement of chest CT at days 7 or 14 (all $p > 0.05$). At day 7, eight (23.5%) patients in the LPV/r group, 3 (8.6%) in the arbidol group and 2 (11.8%) in the control group showed a deterioration in clinical status from moderate to severe/critical ($p = 0.206$). Related to adverse events, 12 (35.3%) patients in the lopinavir/ritonavir group and 5 (14.3%) in the arbidol group experienced adverse events during the follow-up period, and no AE occurred in the control group.

The Living Systematic Review, related to these two RCTs mentioned above, Cao et al. 2020 and Yueping et al. 2020, with Summary of finding table (https://covid-nma.com/living_data/index.php) is provided in table 3.2-2.

No new RCT peer-reviewed articles have been published as of August 15, 2020.

On 29/06/2020 news related to the preliminary results related to lopinavir/ritonavir arm from the RECOVERY Trial were found, <https://www.recoverytrial.net/news/no-clinical-benefit-from-use-of-lopinavir-ritonavir-in-hospitalised-covid-19-patients-studied-in-recovery>. The independent Data Monitoring Committee conducted a routine review of the emerging data and recommended that the chief investigators be unblinded to the results for the lopinavir-ritonavir arm; the trial Steering Committee concluded that there is no beneficial effect of lopinavir-ritonavir in patients hospitalised with COVID-19 and closed randomisation to that treatment arm.

A total of 1596 patients were randomised to lopinavir-ritonavir vs 3376 patients randomised to usual care alone (4% patients required invasive mechanical ventilation when they entered the trial, 70% required oxygen alone, and 26% did not require any respiratory intervention). No significant difference was found in the primary endpoint of 28-day mortality (22.1% lopinavir-ritonavir vs. 21.3% usual care; relative risk 1.04 [95% confidence interval 0.91-1.18]; $p = 0.58$); the results were consistent in different subgroups of patients. No evidence of beneficial effects was found also on the risk of progression to mechanical ventilation or length of hospital stay. Investigators could not make conclusions about the effectiveness in mechanically ventilated patients as they were unable to study a large number of patients on invasive mechanical ventilation due to difficulty administering the drug to patients on ventilators.

The University of Oxford, the WHO and INSERM publicly announced that the lopinavir-ritonavir (Kaletra) arms of the RECOVERY, SOLIDARITY and DISCOVERY studies in adults hospitalized with severe COVID-19 will be stopped given the data showed no beneficial effect [65].

Yueping (China):

**mild/moderate
Erkrankung:**

**keine Unterschiede
zwischen den Gruppen**

**AE häufiger in
Interventionsgruppe**

**keine weiteren
Publikation**

**Ende Juni 2020: vorläufige
Ergebnisse im Recovery
Trial zeigen keine
Wirksamkeit bei
hospitalisierten
Patient*innen**

Therapiearm beendet

**kein Unterschied bei
Mortalität sowie bei
Progression zur
künstlichen Beatmung
oder bei Dauer des
Spitalsaufenthalts**

**Studienarme von
Recovery, Solidarity,
Discovery abgebrochen**

Table 3.2-1: Publication on clinical trial on lopinavir plus ritonavir (Kaletra®)

Author, year [Reference]	Cao et al. 2020 [63]
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	<ul style="list-style-type: none"> - 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 <ul style="list-style-type: none"> - Pneumonia confirmed by chest imaging - Oxygen saturation (Sao₂) of 94% or less while breathing ambient air or a ratio of the partial pressure of oxygen (Pao₂) to the fraction of inspired oxygen (Fio₂) (Pao₂:Fio₂) at or below 300 mg Hg
Exclusion criteria	<ul style="list-style-type: none"> - 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 <ul style="list-style-type: none"> - 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 be replaced or stopped during the trial period <ul style="list-style-type: none"> - 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 <ul style="list-style-type: none"> - 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 [63]
Clinical improvement, n (%) <i>Improvement of two points (from the status at randomisation) on a 7-category ordinal scale (NEWS2 score)</i>	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 (%) <i>5 most common AEs</i>	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 – Intention-to-treat, NR – Not reported

Table 3.2-2: Summary of findings table on lopinavir plus ritonavir (2 RCTs: Cao, Yueping) - https://covid-nma.com/living_data/index.php

Mild to Moderate patients

Summary of findings:						
Lopinavir + Ritonavir compared to Standard Care for Mild/Moderate COVID-19						
Patient or population: Mild/Moderate COVID-19						
Setting: Worldwide						
Intervention: Lopinavir + Ritonavir						
Comparison: Standard Care						
Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Standard Care	Risk with Lopinavir + Ritonavir				
Incidence of viral negative conversion D7	412 per 1.000	354 per 1.000 (169 to 733)	RR 0.86 (0.41 to 1.78)	51 (1 RCT)	⊕○○○ VERY LOW ^{a,b}	
WHO Clinical Progression Score (increase in 1 point) - not reported	-	-	-	-	-	outcome not yet measured or reported
Admission in ICU or death - not reported	-	-	-	-	-	outcome not yet measured or reported
Incidence of WHO progression score (level 6 or above) - not reported	-	-	-	-	-	outcome not yet measured or reported
Incidence of WHO progression score (level 7 or above D7)	0 per 1.000	0 per 1.000 (0 to 0)	RR 2.57 (0.13 to 50.76)	51 (1 RCT)	⊕○○○ VERY LOW ^{a,b}	zero events in control group
All-cause mortality D14-D28				51 (1 RCT)	⊕○○○ VERY LOW ^{a,c}	zero events in both groups
Adverse events D14-D28	0 per 1.000	0 per 1.000 (0 to 0)	RR 12.86 (0.81 to 204.97)	51 (1 RCT)	⊕○○○ LOW ^{b,d}	zero events in control group
Serious adverse events D14-D28	0 per 1.000	0 per 1.000 (0 to 0)	RR 1.54 (0.07 to 35.99)	51 (1 RCT)	⊕○○○ LOW ^{b,d}	zero events in control group

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Severe patients

Summary of findings:						
Lopinavir + Ritonavir compared to Standard Care for Moderate/Severe COVID-19						
Patient or population: Moderate/Severe COVID-19						
Setting: Worldwide						
Intervention: Lopinavir + Ritonavir						
Comparison: Standard Care						
Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Standard Care	Risk with Lopinavir + Ritonavir				
WHO Clinical Progression Score (increase in 1 point) - not reported	-	-	-	-	-	outcome not yet measured or reported
Incidence of WHO progression score (level 6 or above D7)	320 per 1.000	253 per 1.000 (163 to 394)	RR 0.79 (0.51 to 1.23)	199 (1 RCT)	⊕⊕○○ LOW ^{a,b}	
Incidence of WHO progression score (level 6 or above D14-D28)	280 per 1.000	232 per 1.000 (146 to 375)	RR 0.83 (0.52 to 1.34)	199 (1 RCT)	⊕⊕○○ LOW ^{a,b}	
Incidence of WHO progression score (level 7 or above D7)	110 per 1.000	111 per 1.000 (51 to 244)	RR 1.01 (0.46 to 2.22)	199 (1 RCT)	⊕⊕○○ LOW ^{a,b}	
Incidence of WHO progression score (level 7 or above D14-D28)	220 per 1.000	183 per 1.000 (103 to 317)	RR 0.83 (0.47 to 1.44)	199 (1 RCT)	⊕⊕○○ LOW ^{a,b}	
All-cause mortality D14-D28	250 per 1.000	193 per 1.000 (113 to 325)	RR 0.77 (0.45 to 1.30)	199 (1 RCT)	⊕⊕○○ LOW ^{a,b}	
Adverse events D14-D28	490 per 1.000	465 per 1.000 (348 to 622)	RR 0.95 (0.71 to 1.27)	199 (1 RCT)	⊕⊕⊕○ MODERATE ^{b,c}	
Serious adverse events D14-D28	320 per 1.000	192 per 1.000 (118 to 314)	RR 0.60 (0.37 to 0.98)	199 (1 RCT)	⊕⊕⊕○ MODERATE ^{c,d}	

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

- a. Indirectness downgraded by 1 level: single study from a single institution, therefore results in this population might not be generalizable to other settings
- b. Imprecision downgraded by 1 level: due to wide confidence interval consistent with the possibility for benefit and the possibility for harm and low number of participants
- c. We presume that the adverse event rates, and the corresponding relative risks, is similar across diverse settings; therefore not downgraded for indirectness
- d. Imprecision downgraded by 1 level: due to low number of participants

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) [66, 67].

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 [66]. Favipiravir (Avigan®) has not been approved by the European Medicines Agency (EMA) or the American Food and Drug Administration (FDA).

The US COVID-19 Treatment Guidelines Panel **recommends against** using the **Lopinavir/ritonavir (AI) or other HIV protease inhibitors (AIII)**, except in a clinical trial, because of unfavorable pharmacodynamics and because clinical trials have not demonstrated a clinical benefit in patients with COVID-19 [58].

Completed, withdrawn, suspended or terminated studies

The search in clinical trials (humans only) in April 2020 yielded one completed multicenter, randomised, open, positive, parallel-controlled clinical study (ChiCTR2000030254).

The search in two clinical trial registers (ClinicalTrials.gov and EUdraCT) on 08/06/2020 yielded no additional completed study on the safety and efficacy of favipiravir in COVID-19 patients. No suspended or terminated RCTs were found either.

The search in two clinical trial registers (ClinicalTrials.gov and EUdraCT) on 06/07/2020 found one completed RCT (NCT04349241) in Egypt, which assessed the safety and efficacy of favipiravir versus standard of care. No

antivirales Medikament

japanisches Influenza-Medikament (seit 2014),

von EMA / FDA nicht zugelassen

Empfehlungen des US COVID-19 Treatment Guidelines Panel GEGEN jegliche HIV Protease Inhibitoren

1 RCT abgeschlossen

Juni 2020: keine weiteren Studien abgeschlossen oder beendet registriert

Juli 2020: 1 RCT aus Ägypten

suspended or terminated RCTs were found on the safety and efficacy of favipiravir in COVID-19 patients. No additional completed, nor suspended or terminated RCTs were found until August 15, 2020.

Results of publications

As of 12/05/2020, only one publication [68] on the completed RCT (ChiCTR2000030254) about the efficacy and safety of favipiravir, **in comparison with umifenovir**, to treat Covid-19 patients was identified; however, as the publication was available just as pre-print but not yet peer-reviewed, it has not been extracted. Summary of findings table on favipiravir compared to umifenovir (1 RCT: Chen) is presented in Table 3.3-1.

**1 Publikation zu RCT
Vergleich mit Umifenovir**

As of 08/06/2020 one new publication about the efficacy and safety of favipiravir to treat Covid-19 patients could be identified, **in comparison with baloxavir marboxil**, Lou Y, medRxiv, 2020, ChiCTR2000029544 [69]: however, currently the publication is available just as pre-print but not yet peer-reviewed, thus it has not been extracted.

**1 weitere Publikation
Vergleich mit
Baloxavir marboxil**

Until August 15, 2020 interim results from an adaptive, multicenter, open label, randomized, phase 2/3 clinical trial (NCT04434248) of AVIFAVIR versus standard of care (SOC) in hospitalized patients with moderate COVID-19 pneumonia were published. 60 patients hospitalized with COVID-19 pneumonia were randomized into three treatment groups: AVIFAVIR 1600/600 mg, AVIFAVIR 1800/800 mg, or SOC. Each group comprised 20 patients and all randomized patients constituted safety and intent-to-treat (ITT) analysis sets. AVIFAVIR enabled SARS-CoV-2 viral clearance in 62.5% of patients within 4 days, and was safe and well-tolerated. Based on these interim results, the Russian Ministry of Health granted a conditional marketing authorization to AVIFAVIR, which makes it the only approved oral drug for treatment of moderate COVID-19 to date [70].

**AVIFAVIR
Phase 2/3 RCT bei
moderater Covid-19
Erkrankung

interim Auswertung
orale Verabreichung in
Russland „conditional“
zugelassen**

Table 3.3-1: Summary of findings table on favipiravir compared to umifenovir (1 RCT: Chen) - https://covid-nma.com/living_data/index.php

Summary of findings:						
Favipiravir compared to Umifenovir for COVID-19						
Patient or population: COVID-19						
Setting: Worldwide						
Intervention: Favipiravir						
Comparison: Umifenovir						
Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	N _e of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Umifenovir	Risk with Favipiravir				
Incidence viral negative conversion D7 - not reported	-	-	-	-	-	outcome not yet measured or reported
Clinical improvement - not reported	-	-	-	-	-	outcome not yet measured or reported
Incidence of clinical recovery D7	517 per 1.000	594 per 1.000 (470 to 744)	RR 1.15 (0.91 to 1.44)	240 (1 RCT)	⊕○○○ VERY LOW ^{a,b,c}	
Incidence of WHO progression score (level 6 or above) - not reported	-	-	-	-	-	outcome not yet measured or reported
Incidence of WHO progression score (level 7 or above) - not reported	-	-	-	-	-	outcome not yet measured or reported
All-cause mortality D7				240 (1 RCT)	⊕○○○ VERY LOW ^{b,d,e}	zero events in both groups
Adverse events D7	275 per 1.000	358 per 1.000 (245 to 523)	RR 1.30 (0.89 to 1.90)	240 (1 RCT)	⊕⊕○○ LOW ^{a,c,f}	

Serious adverse events D7

240 ⊕○○○ zero events in both
(1 RCT) VERY groups
LOW ^{a,d,f}

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

- a. Risk of bias downgraded by 1 level: some concerns or high risk regarding adequate randomization, deviations from intended interventions and outcome measurement
- b. Indirectness downgraded by 1 level: single study from a single country, therefore results in this population might not be generalizable to other settings
- c. Imprecision downgraded by 1 level: due to wide confidence interval consistent with the possibility for benefit and the possibility for harm and low number of participants
- d. Imprecision downgraded by 2 levels: no events in both groups and low number of participants
- e. Risk of bias downgraded by 1 level: some concerns regarding adequate randomization and deviations from intended interventions
- f. We presume that the adverse event rates, and the corresponding relative risks, is similar across diverse settings; therefore not downgraded for indirectness

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 [71].

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.

The US COVID-19 Treatment Guidelines Panel recommends **against** using the **Lopinavir/ritonavir (AI) or other HIV protease inhibitors (AIII)**, except in a clinical trial, because of unfavorable pharmacodynamics and because clinical trials have not demonstrated a clinical benefit in patients with COVID-19 [58].

Completed, withdrawn, suspended or terminated studies

The search in two clinical trial registers (ClinicalTrials.gov and EudraCT) on August 14, 2020 yielded no completed study on the safety and efficacy of darunavir in COVID-19 patients. No suspended or terminated RCTs were found either.

Results of publications

Until now (status: 14/08/2020) one scientific publication on RCTs of darunavir (Prezista®) in Covid-19 patients could be identified. Chen J et al. 2020 [72] published results from single-center, randomized, open-label trial (NCT04252274) which aimed to evaluate the antiviral activity and safety of darunavir/cobicistat (DRV/c) in treating mild COVID-19 patients. Participants were randomized to receive DRV/c for 5 days on the top of interferon alpha 2b inhaling or interferon alpha 2b inhaling alone. The proportion of negative PCR results at day 7 was 46.7% (7/15) and 60.0% (9/15) in the DRV/c and control groups ($p = 0.72$), respectively. The viral clearance rate at day 3 was 20% (3/15) in both study groups, while the number increased to 26.7% (4/15) in the DRV/c group and remained 20% (3/15) in the control group at day 5. Fourteen days after randomization, 1 participant in the DRV/c group progressed to critical illness and discontinued DRV/c, while all the patients in the control group were stable ($p = 1.0$). The frequencies of adverse events in the two groups were comparable. The authors concluded that five days of DRV/c did not increase the proportion of negative conversion vs standard of care alone, although it was well tolerated.

antivirales Medikament

**als HIV Medikament
zugelassen
EMA 2007**

**Empfehlungen des US
COVID-19 Treatment
Guidelines Panel GEGEN
jegliche HIV Protease
Inhibitoren**

**keine weiteren Studien in
ClinicalTrials.gov and
EudraCT als
abgeschlossen oder
beendet registriert**

Publikation zu RCT

**bei milder Covid-19
Erkrankung
DRV+IFN vs. IFN
kein Unterschied**

Table 3.4-1: Publication on clinical trial on *Darunavir/cobicistat (Prezista®)*

Author, year [Reference]	Chen J et al. 2020 [72]
Country	China
Sponsor/Funding	Ministry of Science and Technology of China (2017ZX09304027); the Shanghai Science and Technology Committee (20411950200); Shanghai Major Projects on Infectious Diseases (shslczdk01102); and the Shanghai "Rising Stars of Medical Talent" Youth Development Program, Specialist Program (No. 2019-72)
Study design	NCT04252274
Number of pts	30 participants (n ₁ =15 / n ₂ = 15)
Intervention/Product	Darunavir/cobicistat (800mg/150mg), 5 days (plus interferon alpha 2b and standard of care as per guideline recommendation in China)
Comparator	Standard care, 5 days (plus interferon alpha 2b; standard of care as per guideline recommendation in China)
Inclusion criteria	Laboratory-confirmed SARS-CoV-2 infection; willing to participate the study, as evidenced by signing an informed consent
Exclusion criteria	If they met any of the following criteria: hypersensitivity to darunavir, cobicistat, or any excipients; patients with severe liver injury (Child-Pugh Class C); patients receiving concomitant medications that are highly dependent on cytochrome P450 3A clearance, and for which the elevated plasma concentrations are associated with serious or life-threatening events; subjects considered to be unable to complete the study (eg, severely and critically ill patients) or not suitable for the study by researchers. Patients who met any of the following criteria were classified as severe cases: respiratory rate ≥ 30 times/min, pulse oxygen saturation $\leq 93\%$ at resting, or ratio between partial pressure of oxygen in arterial blood and fraction of inspired oxygen (PaO ₂ / FiO ₂) ≤ 300 mmHg. Critical illness was defined as respiratory failure that needed mechanical ventilation or shock or exacerbation of any comorbidity that required transfer to the intensive care unit.
Pts pretreated + previous treatment	Not reported
Mean age of patients, yrs (SD)	47.2 \pm 2.8 years
Sex % male (% female)	18 (60%) male
Follow-up (days)	14 days
Clinical status	Mild COVID-19
Loss to follow-up, n (%)	None
Efficacy outcomes	
Overall survival (OS), n (%)	All patients alive at day 14
Time to clinical improvement	The 11 patients with fever in the DRV/c group defervesced at a median (IQR) of 4 (2–6) days vs 8 patients in the control groups defervesced (IQR) at 5 (2–6.8) days after randomization (p = 0.72)
Other efficacy outcomes	
Viral clearance rate at day 7 after randomization	46.7% (7/15) and 60.0% (9/15) in the DRV/c and control groups (p = 0.72)
Viral clearance at day 3 and day 5	Day 3: 20% (3/15) in both study groups Day 5: 26.7% (4/15) in the DRV/c group and 20% (3/15) in the control group
Critical illness rate of subjects during the 14 days after randomization	1 participant in the DRV/r group progressed to critical illness (acute respiratory distress syndrome [ARDS]), none in the control group were stable (p = 1.0)
Safety outcomes	
Adverse events (AEs)	The frequencies of adverse events in the 2 groups were comparable

Author, year [Reference]	Chen J et al. 2020 [72]
Serious adverse events (SAEs)	<p>Anemia (hemoglobin levels dropped from 11.3 g/dL to 9.9 g/dL) 1 patient in the DRV/c group</p> <p>Elevated transaminase levels, defined as >2-fold of the upper limit of the normal range 13.3% (2/30 in the DRV/c group vs 26.7% (4/30) in the control group</p> <p>Renal dysfunction (defined as estimated glomerular filtration rate <90 mL/min/1.73 m² in patients without chronic kidney diseases) 13.3% (2/30) in the DRV/c group vs 6.7% (1/30) in the control group</p>
Discontinuation of study drug due to AEs or SAEs	No participants discontinued DRV/c due to these adverse events

3.5 Chloroquine (Resochin®) and

3.6 Hydroxychloroquine (Plaquenil®)

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

Last reporting V4/ July:

https://eprints.aihta.at/1234/10/Policy_Brief_002_Update_07.2020.pdf

3.7 Camostat Mesilate (Foipan®)

About the drug under consideration

Camostat Mesilate (Foipan®) is classified as a so-called serine protease inhibitor, blocking several pancreatic and plasmatic enzymes like trypsin, thrombin and plasmin [91]. 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 [92, 93] as well as in pathogenic mice-models [94] by inhibiting the enzyme Transmembrane protease, serine 2 (TMPRSS2). Camostat Mesilate (Foipan®) ist not approved for any anti-viral use (FDA, EMA).

Foipan (camostat) is one of the drugs for which the German Federal Ministry of Health initiated centralized procurement in April 2020 for the treatment of infected and seriously ill COVID-19 patients in Germany (<https://www.abda.de>). Up to August 1, 2020, 35 to 60 Covid-19 patients have been treated with the centrally procured medicinal product Foipan (Camostat) as part of an individual medical treatment. There was no obligation for the treating physicians to collect data in a registry [95].

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

**vom dt. BMG für schwere
Erkrankungen zentral
eingekauft**

Completed, withdrawn, suspended or terminated studies

As of August 15, 2020 no completed, withdrawn, suspended or terminated studies were found in ClinicalTrials.gov and EUdraCT registers.

in ClinicalTrials.gov and EUdraCT keine klinischen Studien registriert

Results of publications

Until now no scientific publication on a RCT of Camostat Mesilate (Foipan®) in Covid-19 patients could be identified (status: August 15, 2020).

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) [96]. ACE2 was identified as the functional SARS-CoV receptor in vivo [97]. 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 [98].

aus SARS-Forschung hervorgegangen

**keine Zulassung
1 Studie (Phase 2 RCT), vor
Rekrutierung**

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

Completed, withdrawn, suspended or terminated 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. Until May 12, 2020, one RCT number NCT04287686 is visible as withdrawn (without CDE Approval), and it is not listed here. As of August 15, 2020 no additional studies are found as withdrawn nor suspended or terminated.

in ClinicalTrials.gov and EUdraCT keine abgeschlossene, aber eine zurückgezogene Studie registriert

Results of publications

Until August 15, 2020, no relevant finished publications or finished trials assessing the efficacy and safety could be identified. First results can be expected on the 10th of November 2020 (NCT04335136) [99].

keine Publikationen zu klinischen Studien

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-6R α), and inhibits IL-6-mediated signalling [100]. 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 [100].

When used to treat CRS, it is given as a 60-minute intravenous (IV) infusion in a dose of 8mg/kg (in patients weighing ≥ 30 kg) or 12mg/kg (in patients weighing < 30 kg), to a maximum of 800mg per infusion [100]. 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 [100].

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 [101]. However, some patients develop severe symptoms and progress rapidly, experiencing acute respiratory distress syndrome and septic shock, eventually ending in multiple organ failure [101]. It has been reported that most patients with COVID-19 have increased concentrations of IL-6, C-reactive protein (CRP) and erythrocyte sedimentation rate [102]. However, severely affected patients appear to have even higher plasma levels of pro-inflammatory cytokines and experience severe cytokine storm including features of CRS [102, 103]. It has previously been suggested that IL-6 might play a role in the pathogenesis of SARS and MERS, other diseases caused by coronaviruses [103]. It is thought that neutralisation of the inflammatory pathway induced by IL-6 may reduce mortality.

The US COVID-19 Treatment Guidelines Panel stated that there are **insufficient data to recommend either for or against** the use of **interleukin-6 (IL-6) inhibitors** (e.g., **sarilumab, siltuximab, tocilizumab**) for the treatment of COVID-19 [58].

Completed, withdrawn, suspended or terminated studies

Until 08 July, 2020, one completed interventional single arm study (NCT04331795, COVIDOSE), one withdrawn RCT (NCT04361552, in US, abandoned due to drug billing issues) and one terminated RCT (NCT04346355, in Italy, based on interim analysis for futility and given an enrolment rate almost nil) on the safety and efficacy of tocilizumab in COVID-19 patients were found in ClinicalTrials.gov and EudraCT registers.

Until 15 August, 2020 two additional completed trials were found in ClinicalTrials.gov and EudraCT registers: NCT04320615, EudraCT 2020-001154-22, COVACTA RCT with 450 severe COVID-19 pneumonia patients enrolled and NCT04492501, interventional nRCT on severe and critical COVID-19 patients in Pakistan.

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

Covid-10: bei erhöhten IL-6-Spiegeln in schweren Erkrankungen

bei lebensbedrohlichem Zytokin-Freisetzungssyndrom

Verabreichung iv oder sc

in ClinicalTrials.gov & EudraCT keine abgeschlossenen, abgebrochenen oder zurückgezogenen Studien

Empfehlungen des US COVID-19 Treatment Guidelines Panel: insuffiziente Datenlage

1 beendeter RCT, 1 zurückgezogener (admin Gründe), 1 abgebrochener (Mangel an Rekrutierung)

**2 weitere beendete Studien
1 RCT COVACTA 450 Pts
1 nRCT**

Results of publications

Until June 9, 2020 no relevant publications or finished RCTs assessing the efficacy and safety could be identified, except for two retrospective reports describing the experience of using tocilizumab in severe or critical COVID-19 patients [104] (found through searching the reference list in paper 4) [105]; one prospective series on 100 patients [106] and two quasi-experimental study comparing tocilizumab with standard care in 154 critically ill COVID-19 patients admitted to centers in USA [107] and 168 severe COVID-19 patients in France (NCT04366206) [108].

In an inverse probability weighting (IPTW)-adjusted models, tocilizumab was associated with a 45% reduction in hazard of death [hazard ratio 0.55 (95% CI 0.33, 0.90)] and improved status on the ordinal outcome scale [odds ratio per 1-level increase: 0.59 (0.36, 0.95)]. Tocilizumab was associated with an increased proportion of patients with superinfections (54% vs. 26%; $p < 0.001$); there was no difference in 28-day case fatality rate among tocilizumab-treated patients with versus without superinfection [22% vs. 15%; $p = 0.42$] [107].

In the matched cohort ($n = 168$), tocilizumab 400 mg, single-dose, was associated with fewer primary outcomes: a composite of mortality and ventilation, with a maximum follow-up of 28 days (hazard ratio (HR) = 0.49 (95% confidence interval (95CI) = 0.3-0.81), p -value = 0.005). These results were similar in the overall cohort ($n = 246$), with Cox multivariable analysis yielding a protective association between tocilizumab and primary outcome (adjusted HR = 0.26 (95CI = 0.135-0.51), $p = 0.0001$). Analyses on mortality with 28-days follow-up yielded similar results [108].

A retrospective analysis of data from 20 patients who received one of two doses of IV tocilizumab 400mg showed 15 (75%) had lowered their oxygen intake and one patient need no oxygen therapy. CT scans showed lung lesion opacity absorbed in 19 patients (90.5%). The percentage of lymphocytes in peripheral blood, which decreased in 85.0% patients (17/20) before treatment (mean, $15.52 \pm 8.89\%$), returned to normal in 52.6% patients (10/19) on the fifth day after treatment. Abnormally elevated CRP decreased significantly in 84.2% patients (16/19). No adverse reactions were observed [104].

Luo et al. 2020 [105] retrospectively assessed the demographic, treatment, laboratory parameters of C-reactive protein (CRP) and IL-6 before and after therapy and clinical outcome in the 15 COVID-19 patients treated with tocilizumab (in 8 patients in combination with methylprednisolone). Two of them were moderately ill, six were seriously ill and seven were critically ill. Out of four patients who failed treatment, three patients had lethal outcome. Serum IL-6 level tended to further spiked firstly and then decreased after tocilizumab therapy in 10 patients. Authors concluded that tocilizumab appears to be an effective treatment option in COVID-19 patients with a risk of cytokine storms.

Toniati et al. 2020 [106] presented results of a prospective series of 100 consecutive patients in Italy with confirmed COVID-19 pneumonia and ARDS requiring ventilatory support to determine whether intravenous administration of tocilizumab was associated with improved outcome. Overall at 10 days, the respiratory condition was improved or stabilized in 77 (77%) patients; 61 showed a significant clearing of diffuse bilateral opacities on chest x-ray. 15 patients were discharged from the hospital. Respiratory condition worsened in 23 (23%) patients, of whom 20 (20%) died. During the 10-day

Juni 2020: bislang keine publizierten Ergebnisse aus RCTs

1 prospektive Fallserie mit 100 Pts
2 quasi-experimentelle Studien

Somers (USA)
154 Pts

ev. Reduktion der Mortalität trotz erhöhter Anzahl an Superinfektionen

Rossi (Frankreich)
retrospektive Fall-Kontroll Studie
246 Pts
in kombiniertem Endpunkt (Beatmung und Mortalität) ev. Verbesserung

retrospektive Fallserien: ev. Vorteile

Xu (China)
20 Pts

Luo (China)
15 Pts.

Toniati (Italien)
100 Pts.

follow-up, three cases of severe adverse events were recorded: two patients developed septic shock and died, one had gastrointestinal perforation requiring urgent surgery and was alive at day 10. Authors concluded that response to tocilizumab was rapid, sustained, and associated with significant clinical improvement [108].

No RCT peer-reviewed articles have been published as of July 8, 2020. Results from additional observational studies are presented below.

Guaraldi et al. 2020 [109] conducted a large retrospective, observational cohort study, which included adults with severe COVID-19 pneumonia admitted to tertiary care centres in Italy. All patients were treated with the standard of care (ie, supplemental oxygen, hydroxychloroquine, azithromycin, antiretrovirals, and low molecular weight heparin). A non-randomly selected subset of patients also received tocilizumab. Tocilizumab was given either intravenously at 8 mg/kg bodyweight (up to a maximum of 800 mg) in two infusions, 12 h apart, or subcutaneously at 162 mg administered in two simultaneous doses, one in each thigh (ie, 324 mg in total), when the intravenous formulation was unavailable. The primary endpoint was a composite of invasive mechanical ventilation or death. Of 1351 patients admitted, 544 (40%) had severe COVID-19 pneumonia and were included in the study. 57 (16%) of 365 patients in the standard care group needed mechanical ventilation, compared with 33 (18%) of 179 patients treated with tocilizumab ($p=0.41$; 16 [18%] of 88 patients treated intravenously and 17 [19%] of 91 patients treated subcutaneously). 73 (20%) patients in the standard care group died, compared with 13 (7%; $p<0.0001$) patients treated with tocilizumab (six [7%] treated intravenously and seven [8%] treated subcutaneously). After adjustment for sex, age, recruiting centre, duration of symptoms, and SOFA score, tocilizumab treatment was associated with a statistically significant reduced risk of invasive mechanical ventilation or death (adjusted hazard ratio 0.61, 95% CI 0.40–0.92; $p=0.020$). Twenty-four (13%) of 179 patients treated with tocilizumab were diagnosed with new infections, versus 14 (4%) of 365 patients treated with standard of care alone ($p<0.0001$). The authors concluded that treatment with tocilizumab, whether administered intravenously or subcutaneously, might reduce the risk of invasive mechanical ventilation or death in patients with severe COVID-19 pneumonia.

In Martínez-Sans et al. 2020 preprint article [110], results from large cohort study of patients hospitalized with COVID-19 in Spain were presented, based on the analysis from 1,229 subjects, with primary end point - the time from study baseline to death. The secondary outcome was a composite event including admission to the ICU or death. Of the 1,229 patients, 260 (21%) received a median total dose of 600 mg (IQR 600–800 mg) of tocilizumab. The control group ($n=969$) received standard care defined as specific treatment against SARS-CoV-2 (corticosteroids $n=582$, hydroxychloroquine $n=1134$, azithromycin $n=812$, lopinavir/ritonavir $n=753$). In the adjusted analyses a significant interaction was found between tocilizumab use and CRP values ($p=0.023$ and $p=0.012$ for primary and secondary endpoints, respectively). Subjects who received tocilizumab and had baseline CRP levels above 150 mg/L experienced lower rates of death (aHR 0.34, 95% CI 0.17 - 0.71, $p=0.005$) and ICU admission/death (aHR 0.39, 95% CI 0.19 - 0.80, $p=0.011$) than those who did not receive tocilizumab. This effect was not observed among patients with baseline CRP levels ≤ 150 mg/dL.

Juli 2020: keine publizierten RCTs

Guaraldi (Italien): Beobachtungsstudie, retrospektiv 1.352 Pts

schwere Covid-19 Erkrankungen

stat. signifikant Reduktion der künstlichen Beatmung oder Tod

Martínez-Sans (Spanien): Kohortenstudie 1.229 Pts schwere Covid-19 Erkrankungen

geringere Mortalität und ICU-Aufnahmen

Rojas-Marte et al. 2020 [111] conducted a retrospective, case-control, single-center study in US, in patients with severe to critical COVID-19 disease treated with tocilizumab. The primary endpoint was the overall mortality. Secondary endpoints were mortality in non-intubated patients and mortality in intubated patients. A total of 193 patients were included in the study: ninety-six patients received tocilizumab, and 97 served as the control group. There was a non-statistically significant lower mortality in the treatment group (52% vs. 62.1%, $P = 0.09$). There was statistically significant lower mortality in patients treated with tocilizumab (6% vs. 27%, $P = 0.024$) when intubated patients excluded. Bacteremia was more common in the control group (24% vs. 13%, $P = 0.43$), and fungemia was similar for both (3% vs. 4%, $P = 0.72$).

**Rojas-Marte (USA):
Fall-Kontrollstudie
193 Pts**

**geringere Mortalität
(wenn intubierte Pts
ausgenommen wurden)**

Kewan et al. 2020 [112] conducted a small retrospective cohort study in US, on 51 severe COVID-19 patients (tocilizumab cohort $n=28$, control cohort $n=23$). Shorter time to clinical improvement and shorter duration of invasive ventilation were observed, but were not statistically significant different between two cohorts. Statistically significant shorter was duration of vasopressor support compared to a control group (2 days vs 5 days, $p=0.039$). Similar rates of hospital-acquired infections occurred in both cohorts (18% in tocilizumab and 22% in control cohort).

**Kewan (USA):
Kohortenstudie
51 Pts**

**kürzere invasive
Beatmung, kürzere
Zeitspanne zu einer
Verbesserung**

The phase 3, RCT - COVACTA (NCT04320615, EUdraCT 2020-001154-22) study of tocilizumab with aim to evaluate the safety and efficacy of tocilizumab in 450 patients with severe COVID-19 pneumonia did not meet its primary endpoint of improved clinical status in hospitalised adult patients with severe COVID-19 associated pneumonia. In addition, the key secondary endpoints, which included the difference in patient mortality at week four, were not met; however, there was a positive trend in time to hospital discharge in patients treated with tocilizumab. The COVACTA study did not identify any new safety signals for tocilizumab [113].

**COVACTA: 450 Pts mit
schwerer
Lungenentzündung**

**kein Unterschied bei
klinischer Verbesserung
und Mortalität**

Summary of findings table on tocilizumab compared to standard of care (related to 1 RCT: Salvarani) is presented below (Table 3.9-2).

**positiver Trend bei
früherer Entlassung aus
Spital**

Table 3.9-2: Summary of findings table on tocilizumab compared to standard of care (1 RCT: Salvarani) [114] [115]

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of evidence	Comments
	Risk with standard of care	Risk with tocilizumab				
All-cause mortality at 30 days	32 per 1000	33 per 1000	RR1.05 (0.15 to 7.22)	123	low	Compared to SoC there is no effect on 30-day all cause mortality

Abbreviations: CI: Confidence interval; RR: Risk ratio
Source: [9]

Certainty assessment							Nº of patients		Effect		Certainty
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tocilizumab	Trattamento standard	Relative (95% CI)	Absolute (95% CI)	
Mortality, any cause, at 30 days											
1 ¹	randomised trials	serious ^a	not serious	not serious	serious ^b	none	2/60 (3.3%)	2/63 (3.2%)	RR 1.05 (0.15 to 7.22)	2 more per 1.000 (from 27 fewer to 197 more)	⊕⊕○○ LOW

CI: Confidence interval; RR: Risk ratio; Explanations a. Downgraded of one level for high risk of detection bias and unclear risk of selection bias b. Downgraded of one level for small sample size

3.10 Sarilumab (Kevzara®)

Drug under consideration

Sarilumab (*Kevzara*) is a human monoclonal antibody that specifically binds to soluble and membrane-bound interleukin (IL)-6 receptors (IL-6R α), and inhibits IL-6-mediated signalling [116]. It is licensed in the EU for treating adults with rheumatoid arthritis, given by subcutaneous (SC) injection [116]. It is being investigated as a possible treatment for patients with moderate to severe or critical COVID-19.

The US COVID-19 Treatment Guidelines Panel stated that there **are insufficient data to recommend either for or against** the use of interleukin-6 (IL-6) inhibitors (e.g., sarilumab, siltuximab, tocilizumab) for the treatment of COVID-19 [58].

Completed, withdrawn, suspended or terminated studies

The search in two clinical trial registers (humans only) in April 2020 yielded no completed study on the safety and efficacy of sarilumab in COVID-19 patients. Until May 11, 2020 one RCT found as suspended, NCT04341870 - CORIMUNO-VIRO Trial (DSMB recommendation (futility)). As of 08 July, 2020, no completed, withdrawn, additional suspended or terminated studies were found in ClinicalTrials.gov and EUdraCT registers. The same is true until August 15, 2020.

Results of publications

Until May 10, 2020 no relevant publications related to RCTs assessing the efficacy and safety of sarilumab could be identified. As of 09 June, 2020, unpublished interim analysis data from RCT comparing sarilumab high dose (400 mg) and sarilumab low dose (200 mg) with placebo could be found on meta/ Evidence web site

(<http://metaevidence.org/viewPathology2.aspx?exposition=553&comparator=0&pathology=87&domain=12>). After peer-reviewed publication appears, results will be extracted in tabular format.

No new RCT peer-reviewed articles have been published as of August 15, 2020 [117].

Della-Torre et al. 2020 [118] published results from an prospective open-label cohort study of sarilumab in 28 severe COVID-19 pneumonia (PaO₂/FiO₂ <300 mm Hg) patients with hyperinflammation (elevated inflammatory markers and serum IL-6 levels), in Italy. Sarilumab 400 mg was administered intravenously in addition to standard of care. Results were compared with contemporary matched patients treated with standard of care alone. Clinical improvement, mortality, safety and predictors of response were assessed at 28 days. Twenty-eight patients were treated with sarilumab and 28 contemporary patients receiving standard of care alone were used as controls. At day 28 of follow-up, 61% of patients treated with sarilumab experienced clinical improvement and 7% died, not significantly different from the comparison group (clinical improvement 64%, mortality 18%; p=NS). Baseline PaO₂/FiO₂ ratio >100 mm Hg and lung consolidation <17% at CT scan predicted clinical improvement in patients treated with sarilumab. Median time to clinical improvement in patients with lung consolidation <17% was shorter after

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

Covid-10: bei erhöhten IL-6-Spiegeln

Empfehlung des US COVID-19 Treatment Guidelines Panel: insuffiziente Datenlage

ClinicalTrials.gov & EUdraCT

April: keine Studien registriert

Mai: 1 RCT abgebrochen

Juni: keine weiteren Studien

keine Publikation zu einer klinischen Studie

eine Interimauswertung

keine publizierten RCTs

Della-Torre (Italien): prospektive open-label Kohortenstudie 56 Pts

kein Unterschied zur Standardbehandlung

sarilumab (10 days) than after standard treatment (24 days; $p=0.01$). The rate of infection and pulmonary thrombosis was similar between the two groups. Authors concluded that at day 28, overall clinical improvement and mortality in patients with severe COVID-19 were not significantly different between sarilumab and standard of care. Sarilumab was associated with faster recovery in a subset of patients showing minor lung consolidation at baseline.

On July 03, 2020 in press release related to sarilumab RCT conducted in US, <https://www.clinicaltrialsarena.com/news/kevzara-us-covid19-trial-data/>, Sanofi and Regeneron Pharmaceuticals have reported that this phase III clinical trial of sarilumab, compared 400mg dose of the drug plus best supportive care to best supportive care alone, failed to meet its primary and key secondary endpoints in Covid-19 patients who required mechanical ventilation in the US. The primary analysis involved 194 patients who were critically ill and were on mechanical ventilation at the time of enrolment. Minor positive trends were demonstrated in the primary pre-specified analysis group but did not achieve statistical significance. These trends were countered by negative trends in a subgroup of critical patients who were not on mechanical ventilation at baseline. In the primary analysis arm, adverse events were reported in 80% of patients treated with sarilumab and 77% of those on placebo. Serious adverse events in at least 3% of patients, more frequent among sarilumab patients, were multi-organ dysfunction syndrome and hypotension. Based on the data, the companies have halted this US-based trial, including a second cohort of patients who were on a higher 800mg dose of the drug. The trial being conducted outside of the US is continuing, in hospitalised patients with severe and critical Covid-19 using a different dosing regimen.

Juli 2020: Pressemeldung zu RCT mit 194 Pts

kein Unterschied mehr SAE in Sarilumab Gruppe

3.11 Interferon beta 1a (SNG001) (Rebif®, Avonex®) and Interferon beta 1b (Betaferon®, Extavia®)

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 [119]. 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 [120].

Two pharmaceuticals which the active substance Interferon beta-1a 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.

INFb Präparate bei Multipler Sklerose zugelassen (EMA)

Interferon beta-1a: Rebif® Avonex® seit 1997/1998 zugelassen

nicht für Covid-19

Two pharmaceuticals, with the active substance Interferon beta-1b, are commercially available in EU: Betaferon® and Extavia® to treat adults with multiple sclerosis (MS) [121, 122]. Betaferon® is approved by the European Medicines Agency (EMA) since 1995. Extavia® is approved by EMA since 2008. Interferon beta-1a and beta-1b are not approved for COVID-19 patients treatment.

The US COVID-19 Treatment Guidelines Panel [58] **recommends against** use of the interferons (alfa or beta) for the treatment of severely or critically ill patients with COVID-19, except in the context of a clinical trial (AIII).

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

Completed, withdrawn, suspended or terminated studies

The search in clinical trials (humans only) in April 2020 yielded no completed studies on the safety and effectiveness of Interferon beta-1a for Covid-19 patients. Until May 12, 2020, one completed RCT was found related to Interferon beta 1b. The completed RCT (NCT04276688) was conducted in Hong Kong, and its results are written in Section 3.13, related to Combination therapy (triple combination of interferon beta-1b, lopinavir–ritonavir, and ribavirin, compared with lopinavir–ritonavir alone).

As of June 12, 2020, one additional completed RCT in Iran was found in ClinicalTrials.gov register (COVIFERON, NCT04343768), related to the combination therapy of Interferon beta 1a and Interferon beta 1b with hydroxychloroquine and lopinavir/ritonavir in comparison with controlled group treated with hydroxychloroquine and lopinavir/ritonavir (three study arms: Interferon beta 1a + hydroxychloroquine + lopinavir/ritonavir; Interferon beta 1b + hydroxychloroquine + lopinavir/ritonavir; hydroxychloroquine +lopinavir/ritonavir). Results are not yet published in peer-review journal.

As of July 7, 2020 no additional studies are found as completed, nor withdrawn or suspended or terminated. The same is true until August 15, 2020.

Results of publications

As mentioned above, the results from the first randomised controlled trail on triple combination of interferon beta-1b, lopinavir–ritonavir and ribavirin, in comparison with lopinavir–ritonavir (NCT04276688) are presented in Section 3.14 of this report [123]. On May 30, 2020, preprint was identified (medRxiv platform) related to the results from RCT on Interferon beta-1a treatment (n=46) vs the standard of care (n=46), in 92 patients with severe COVID-19 in Iran [124]. Finally 81 patients (42 in the IFN and 39 in the control group) completed the study. Time to the clinical response was not significantly different between the IFN and the control (IRCT20100228003449N28) groups (9.7 +/- 5.8 vs. 8.3 +/- 4.9 days respectively, P=0.95). On day 14, 66.7% vs. 43.6% of patients in the IFN group and the control group were discharged, respectively (OR= 2.5; 95% CI: 1.05- 6.37). The 28-day overall mortality was significantly lower in the IFN then the control group (19% vs. 43.6% respectively, p= 0.015). Early administration significantly reduced mortality (OR=13.5; 95% CI: 1.5-118). After the peer-reviewed publication appears, results will be extracted in tabular format.

**Interferon beta-1b:
Betaferon® and Extavia®
seit 1995/2008 zugelassen
nicht für Covid-19**

**Empfehlung des US
COVID-19 Treatment
Guidelines Panel: nur in
klinischen Studien**

**ClinicalTrials.gov &
EUdraCT
April: keine Studien
registriert
Mai: 1 RCT
(Kombinationstherapie,
vgl. 3.13)**

**Juni 2020:
1 weiterer RCT (Iran)**

**(Kombinationstherapie)
Ergebnisse liegen noch
nicht vor**

**Juli/ August 2020: keine
weiteren Studien**

**Preprint RCT (Iran)
92 Pts**

**Reduktion der 28-Tages
Mortalität insb. bei früher
Verabreichung
von IFN**

As of August 16, 2020, two new published RCTs were identified: results from Huang et al. 2020 (ChiCTR2000029387) [125] related to Ribavirin Plus Interferon-Alpha, Lopinavir/Ritonavir Plus Interferon-Alpha, and Ribavirin Plus Lopinavir/Ritonavir Plus Interferon-Alpha in Patients With Mild to Moderate COVID-19 were presented in Section 3.14 of this report.

in Esquivel-Moynelo et al. 2020 [126] presented the results from a RCT for efficacy and safety evaluation of subcutaneous IFN- α 2b and IFN γ administration in patients positive to SARS-CoV-2. Patients were randomly assigned in a 1:1 ratio to receive either, subcutaneous treatment with a combination of 3.0 MIU IFN- α 2b and 0.5 MIU IFN- γ , twice a week for two weeks, or thrice a week intramuscular injection of 3.0 MIU IFN- α 2b. Additionally, all patients received lopinavir-ritonavir 200/50 mg every 12 h and chloroquine 250 mg every 12 h (standard of care). The primary endpoints were the time to negativization of viral RNA and the time to progression to severe COVID-19, from the start of treatment. A total of 79 patients with laboratory-confirmed SARS-CoV-2 infection, including symptomatic or asymptomatic conditions, fulfilled the inclusion criteria and underwent randomization. None of the subjects transit to severe COVID-19 during the study or the epidemiological follow-up for 21 more days. None of the patients developed severe COVID-19.

**August 2020:
2 RCTs publiziert
1 RCT zu Kombinations-
therapie in 3.14**

**1 RCT zu
Kombinationstherapie IFN
(unterscheidliche
Dosierungen) + Kaletra**

**79 symptomatische/
asymptomatische Pts.**

3.12 Convalescent plasma transfusion

About the treatment under consideration

Convalescent plasma is plasma collected from patients that have recovered from an infectious disease and can be transfused to patients fighting an infection or can be used to manufacture immune globulin concentrates (plasma derived medicinal products). Possible explanations for the efficacy are that the antibodies from convalescent plasma might suppress viraemia and activate the complement system, thus promoting viral elimination. Antibody is most effective when administered shortly after the onset of symptoms, and a sufficient amount of antibody must be administered. Plasma transfusions may be associated with transfusion reactions such as allergic reactions, antibody-mediated enhancement of infection, transfusion-related acute lung injury (TRALI) and circulatory overload [127-129]. Rare complications include the transmission of infectious pathogens and red cell alloimmunization.

Convalescent plasma was previously used for treatment of severe acute respiratory syndrome (SARS), pandemic 2009 influenza A (H1N1), avian influenza A (H5N1), several hemorrhagic fevers such as Ebola, and other viral infections with positive results related to different clinical outcomes [127]. Six conditions must be met to deploy convalescent plasma treatment for COVID-19: availability of a population of donors who have recovered from the disease and can donate convalescent serum; blood banking facilities to process the serum donations; availability of assays, including serological assays, to detect SARS-CoV-2 in serum and virological assays to measure viral neutralization; virology laboratory support to perform these assays; prophylaxis and therapeutic protocols, which should ideally include randomized clinical trials to assess the efficacy of any intervention and measure immune responses; and regulatory compliance, including institutional review board approval, which may vary depending on location.

**(Re-) Konvaleszenzplasma
von covid-19
Patient*innen,
die sich von der
Erkrankung bereits erholt
haben**

**auch zur Herstellung von
Immunglobulin-
konzentraten verwendet**

**erprobt bei influenza
H1N1, H5N1, Ebola sowie
weiteren viralen
Infektionserkrankungen**

**Bedingungen:
Vefügbarkheit
Blutbank
serologische Testung**

COVID-19 convalescent plasma therapy and immune globulin concentrates are not approved by the European Medicine Agency (EMA) and the Food and Drug Administration (FDA) for COVID-19. The European Commission (EC) and US Food and Drug Administration (FDA) recently published guidance on convalescent plasma collected from individuals who have recovered from COVID-19 and which may potentially be used as a treatment for COVID-19 [130, 131]. The EC guidance aims to facilitate a common approach across EU Member States to the donation, collection, testing, processing, storage, distribution and monitoring of convalescent plasma for the treatment of Covid-19 [130]. The FDA guidance provides recommendations on the pathways for use of investigational COVID-19 convalescent plasma; patient eligibility; collection of COVID-19 convalescent plasma, including donor eligibility and donor qualifications; labeling and record keeping. As COVID-19 convalescent plasma is regulated as an investigational product, three pathways for use are available in US: 1. Clinical Trials; 2. Expanded Access; 3. Single Patient Emergency IND [131, 132].

On July 31, 2020 European Commission strengthens support for treatment through convalescent plasma. This action is part of the Emergency Support Instrument (ESI) and grants will be provided to public and NGO blood-collection services authorised to collect plasma [133].

Current US NIH COVID-19 Treatment Guidelines stated that there are insufficient clinical data to recommend either for or against the use of convalescent plasma for the treatment of COVID-19 [134].

Completed, withdrawn, suspended or terminated studies

As of June 12, 2020 one RCT (NCT04346446) conducted in India, comparing convalescent plasma+supportive care with random donor plasma+supportive care in severely sick COVID-19 patients, is listed as completed (May 30, 2020) in ClinicalTrials.gov register. Nor results posted nor publication is provided yet. One interventional single group study (NCT04325672) was withdrawn due to opening Expanded Access Protocol. As of July 09, 2020 one interventional single group assignment study in Indonesia on 10 patients is completed (NCT04407208). Two RCTs were completed as well: one performed on 49 patients in Iraq (NCT04441424) and one with 60 patients in Turkey (NCT04407208). Nor results posted nor publication is provided yet. As of August 15, 2020 one single-arm interventional study in Switzerland, on 15 adult patients with moderate to severe COVID-19 (NCT04389944), and one RCT on 40 COVID-19 patient with hypoxia in Bahrain were completed (NCT04356534). No results are posted yet.

Results of publications

Results from case series, which involved from two to ten critically ill patients in China and Korea are published only [135-140]. The results from 10 severe adults cases with COVID-19, published by Duan et al. [135], showed that 200 ml of convalescent plasma transfusion with a high concentration of neutralizing antibodies can rapidly reduce the viral load and tends to improve clinical outcomes. Shen et al. [136] reported that administration of convalescent plasma containing neutralizing antibody in treatment of 5 critically ill patients with COVID-19 and ARDS in China was followed by improvement in their clinical status. Ye et al. [137], Ahn et al. [138], and Zhang et al. [139] also presented the positive results on clinical outcomes. Zeng et al. [140] presented results from case series of 6 COVID-19 subjects

Blutprodukte für covid-19 nicht zugelassen

EMA (& EC) Guidance zur Verwendung

US NIH COVID-19 Treatment Guidelines: insuffiziente Datenlage

in ClinicalTrials.gov: 1 abgeschlossener RCT (Indien), aber keine Ergebnisse

3 abgeschlossene Studien: Indien, Irak, Türkei

August: 2 weitere Studien wurden abgeschlossen: ohne Ergebnispräsentation

keine Ergebnisse aus RCTs publiziert

Fallserien: rasche Reduktion der Viruslast, aber keine Reduktion von Mortalität

frühe Verabreichung

with respiratory failure who received convalescent plasma at a median of 21.5 days after first detection of viral shedding, all tested negative for SARS-CoV-2 RNA by 3 days after infusion, and 5 died eventually. They concluded that convalescent plasma treatment can discontinue SARS-CoV-2 shedding but cannot reduce mortality in critically end-stage COVID-19 patients, and treatment should be initiated earlier.

The aim of the published **Cochrane Systematic Review** (observational studies) in May 2020 was to assess whether convalescent plasma or hyperimmune immunoglobulin transfusion is effective and safe in the treatment of people with COVID-19 [141]. Authors included eight studies (seven case-series, one prospectively planned, single-arm intervention study) with 32 participants (they identified a further 48 ongoing studies evaluating convalescent plasma, 47 studies or hyperimmune immunoglobulin, one study, of which 22 are randomised). Overall risk of bias of the eight included studies was high and all outcomes were rated as very low certainty. Authors were unable to summarise numerical data in any meaningful way and results were reported narratively. They identified very low-certainty evidence on the effectiveness and safety of convalescent plasma therapy for people with COVID-19.

As of June 12, 2020 results from one quasi-experimental study in 195 patients with COVID-19 (severe to critical) admitted to single center in USA, comparing convalescent plasma with standard care, were published, but not yet peer-reviewed, so data were not extracted here [142].

As of July 09, 2020 additional observational studies were published related to safety and efficacy of COVID-19 convalescent plasma. Joyner et al. 2020 [143] provided results from the convenience sample of 20,000 hospitalized patients with severe or life-threatening COVID-19, treated with COVID-19 convalescent plasma through the US FDA Expanded Access Program for COVID-19 convalescent plasma. Approximately 200–500 mL of convalescent plasma was administered intravenously according to institutional transfusion guidelines. The incidence of all serious adverse events was low (transfusion reactions (n=89; <1%); thromboembolic or thrombotic events (n=87; <1%), and cardiac events (n=680, ~3%). The majority of the thromboembolic or thrombotic events (n=55) and cardiac events (n=562) were judged to be unrelated to the plasma transfusion per se. The seven-day mortality rate was 8.6% (8.2%, 9.0%). It was higher among more critically-ill patients relative to less ill counterparts, including patients admitted to the intensive care unit vs. not admitted (10.5% vs. 6.0%), mechanically ventilated vs. not ventilated (12.1% vs. 6.2%), and with septic shock or multiple organ dysfunction/failure vs. those without dysfunction/failure (14.0% vs. 7.6%). The authors concluded that transfusion of convalescent plasma is safe in hospitalized patients with COVID-19. Earlier administration of plasma within the clinical course of COVID-19 is more likely to reduce mortality.

Erkurt M et al. 2020 [144] reported the results on 26 severe Covid-19 patients in intensive care unit, who had quantitative reverse transcriptase–polymerase chain reaction positive Sars-Cov-2 infection, treated with convalescent plasma (200cc). There were no statistically significant differences in leukocyte, neutrophil, lymphocyte, platelet, CRP, ferritin, LDH, ALT, AST, sO₂ and total bilirubin values just before and after 1 week of convalescent plasma. A statistically significant difference was found between age and lymphocyte values of living and dying patients. The patients who died were determined to have older age (74.6 vs 61.85, p = 0.018) and more severe

Cochrane Review zu Beobachtungsstudien

8 Studien inkludiert, hoher RoB, niedrige Sicherheit

keine sicheren Aussagen möglich

Juni: 1 quasi-experimentelle Studie 195 Pts, noch keine Ergebnisse

Juli 2020: Joyner (USA): FDA Expanded Access Program for COVID-19 convalescent plasma

20,000 hospitalisierte Pts. niedrige AE/ SAE Raten

frühe Verabreichung reduziert möglicherweise Mortalität mehr als spätere

Erkurt (Türkei): 26 Pts

in frühem Stadium, bei Pts ohne Bedarf nach künstlicher Beatmung ev. kurative Therapie

lymphopenia (0.47 vs 1.18, $p = 0.001$). The authors concluded that in early stage Covid-19 patients who do not need mechanical ventilation, convalescent plasma treatment may be a curative treatment option.

Hegerova et al. 2020 [145] reported the early clinical experience of 20 hospitalized patients treated with convalescent plasma compared to 20 matched controls with severe or life-threatening Covid-19 infection. Laboratory and respiratory parameters were improved in patients following convalescent plasma infusion, their status was similar to that seen in controls. A similar proportion of patients in each group were discharged, while the 7 and 14- day case fatality rate in convalescent plasma patients compared favorably to that in controls. Convalescent plasma infusion was safe without adverse events. There was no evidence of clinical worsening to suggest a hyperimmune response. An increased risk of VTE in convalescent plasma patients was not seen, although the incidence was high in both groups despite heparin prophylaxis, as seen in Covid-19.

**Hegerova (Schweden, USA):
20 Pts.
ev. Vorteile bei Mortalität**

Xia et al. 2020 [146] reported the results of 1,568 severe or critical COVID-19 patients, including 1,430 patients who only received standard treatment and 138 patients who also received 200-1200 mL ABO-compatible COVID-19 convalescent plasma (CCP group), in Wuhan, China. Three patients (2.2%) died in the CCP group up to April 20, reducing approximately 50% of the mortality rate when compared to that in the standard-treatment group (4.1%). For the 126 non-ICU patients before CCP therapy, 3 patients (2.4%) were admitted to ICU, as compared to 72 out of 1,403 (5.1%) ICU admissions in the standard-treatment group. Within 14 days after CCP therapy, 20 out of the 25 (80%) patients who were SARS-CoV-2 positive became virus-free. 77.9% of cases represented lung lesion absorption within 14 days after CCP therapy. Three patients had minor allergic reactions (pruritus or erythema) during the transfusion, but no severe transfusion reactions such as transfusion-associated circulatory overload (TACO), transfusion-related acute lung injury (TRALI), or severe allergic reactions were observed. Patients whose SCSS was 5 before therapy showed no improvements after CCP therapy. Within 7 days after CCP therapy, 66.7% and 83.4% of patients showed various degrees of clinical improvements in patients whose SCSS was 4 or 3, respectively. The authors concluded that CCP, transfused even after two weeks (median of 45 days in our cohort) of symptom onset, could improve the symptoms and mortality in severe or critical COVID-19 patients.

**Xia (China):
138 Pts.**

Verbesserung der Symptomatik und Reduktion der Mortalität

On July 10, 2020 Piechotta et al. [147] published the **first living update of Cochrane Systematic Review**, with results from four controlled studies (1 RCT (stopped early) with 103 participants, of whom 52 received convalescent plasma; and 3 controlled NRSIs with 236 participants, of whom 55 received convalescent plasma) to assess effectiveness of convalescent plasma. Control groups received standard care at time of treatment without convalescent plasma. Related to the outcome - All- cause mortality at hospital discharge (1 controlled NRSI, 21 participants) - authors are very uncertain whether convalescent plasma has any effect on all-cause mortality at hospital discharge (risk ratio (RR) 0.89, 95% confidence interval (CI) 0.61 to 1.31; very low-certainty evidence). On outcome - Time to death (1 RCT, 103 participants; 1 controlled NRSI, 195 participants) - authors are also very uncertain whether convalescent plasma prolongs time to death (RCT: hazard ratio (HR) 0.74, 95% CI 0.30 to 1.82; controlled NRSI: HR 0.46, 95% CI 0.22 to 0.96; very low-certainty evidence). The same is true for outcome

Cochrane Systematic Review:

**4 CT (1 RCT): 104 Pts
3 NRSI: 236 Pts.**

**Mortalität: unsichere Evidenz
Zeit zum Tod: sehr unsichere Evidenz
Verbesserung der klinischen Symptome: sehr unsichere Evidenz**

Improvement of clinical symptoms, assessed by need for respiratory support (1 RCT, 103 participants; 1 controlled NRSI, 195 participants): at seven days - RCT: RR 0.98 (95% CI 0.30 to 3.19), 14 days - RCT: RR 1.85 (95% CI 0.91 to 3.77); controlled NRSI: RR 1.08 (95% CI 0.91 to 1.29), and 28 days - RCT: RR 1.20 (95% CI 0.80 to 1.81; very low- certainty evidence). No studies reported outcome Quality of life. For safety outcomes authors also included non- controlled NRIS: there was limited information regarding adverse events. Of the controlled studies, none reported on this outcome in the control group. There is only very low- certainty evidence for safety of convalescent plasma for COVID- 19.

As of August 15, 2020 one additional observational study was published by Joyner et al. 2020 [133]. In their preprint, they reported results from open-label, Expanded Access Program (EAP) for the treatment of COVID-19 patients with human convalescent plasma (NCT04338360). They evaluated seven and 30-day mortality in 35,322 hospitalized adults transfused with COVID-19 convalescent plasma. This cohort included a high proportion of critically-ill patients, with 52.3% in the intensive care unit (ICU) and 27.5% receiving mechanical ventilation at the time of plasma transfusion. The seven-day mortality rate was 8.7% [95% CI 8.3%-9.2%] in patients transfused within 3 days of COVID-19 diagnosis but 11.9% [11.4%-12.2%] in patients transfused 4 or more days after diagnosis ($p < 0.001$). Similar findings were observed in 30-day mortality (21.6% vs. 26.7%, $p < 0.0001$). Importantly, a gradient of mortality was seen in relation to IgG antibody levels in the transfused plasma. For patients who received high IgG plasma (> 18.45 S/Co), seven-day mortality was 8.9% (6.8%, 11.7%); for recipients of medium IgG plasma (4.62 to 18.45 S/Co) mortality was 11.6% (10.3%, 13.1%); and for recipients of low IgG plasma (< 4.62 S/Co) mortality was 13.7% (11.1%, 16.8%) ($p = 0.048$). This unadjusted dose-response relationship with IgG was also observed in thirty-day mortality ($p = 0.021$). The pooled relative risk of mortality among patients transfused with high antibody level plasma units was 0.65 [0.47-0.92] for 7 days and 0.77 [0.63-0.94] for 30 days compared to low antibody level plasma units. Authors concluded that the relationships between reduced mortality and both earlier time to transfusion and higher antibody levels provide signatures of efficacy for convalescent plasma in the treatment of hospitalized COVID-19 patients, which may be informative for the treatment of COVID-19 and design of randomized clinical trials involving convalescent plasma.

Results from the **first RCT** (ChiCTR200029757) conducted in 103 patients with COVID-19 (severe to critical) admitted to 7 centers in China, with aim to evaluate the efficacy and adverse effects of convalescent plasma therapy with a high titer of antibody to SARS-CoV-2, is published in JAMA [148]. Patients were randomised to Convalescent plasma in addition to standard treatment ($n = 52$) vs standard treatment alone (control) ($n = 51$), stratified by disease severity. Primary outcome was time to clinical improvement within 28 days, defined as patient discharged alive or reduction of 2 points on a 6-point disease severity scale (ranging from 1 [discharge] to 6 [death]). Secondary outcomes included 28-day mortality, time to discharge, and the rate of viral polymerase chain reaction (PCR) results turned from positive at baseline to negative at up to 72 hours.

**August 2020: 1
Beobachtungsstudie mit
35.322 Pts (52,3% in ICU,
27,5% Beatmung)**

**frühere Verabreichung
von CVPlasma,
höhere IgG Titer – bessere
Ergebnisse**

**Li (China)
RCT, 103 Pts (statt 200,
wegen Mangel an Pts)**

**mit Rekonvaleszenten-
Plasma mit hohem
IgG-Titer
Endpunkte:
Zeit bis zur klinischen
Verbesserung
28 Tages Mortalität**

Convalescent plasma therapy added to standard treatment, compared with standard treatment alone, did not result in a statistically significant improvement in time to clinical improvement within 28 days (51.9% (27/52) of the convalescent plasma group vs 43.1% (22/51) in the control group (difference, 8.8% [95% CI, -10.4% to 28.0%]; hazard ratio [HR], 1.40 [95% CI, 0.79-2.49]; $p = 0.26$). Among those with severe disease, the primary outcome was statistically significant in favour of convalescent plasma (91.3% (21/23) vs 68.2% (15/22) of the control group (HR, 2.15 [95% CI, 1.07-4.32]; $p = 0.03$); among those with life-threatening disease the primary outcome occurred in 20.7% (6/29) of the convalescent plasma group vs 24.1% (7/29) of the control group (HR, 0.88 [95% CI, 0.30-2.63]; $p = 0.83$) (P for interaction = 0.17). There was no significant difference in 28-day mortality (15.7% vs 24.0%; OR, 0.65 [95% CI, 0.29-1.46]; $p = 0.30$) or time from randomization to discharge (51.0% vs 36.0% discharged by day 28; HR, 1.61 [95% CI, 0.88-2.93]; $p = 0.12$). Two patients in the convalescent plasma group experienced adverse events within hours after transfusion that improved with supportive care. Interpretation of results is limited by early termination of the trial, which may have been underpowered to detect a clinically important difference. The trial was terminated before it reached its targeted original sample size of 200 patients (103 were enrolled, for whom randomization was stratified by disease severity) because the COVID-19 outbreak in China was being contained while the trial was ongoing and new cases were unavailable for enrollment (Table 3.12-1).

keine stat. signifikanten Unterschiede bei

Transfusions-bedingte AE

frühzeitiger Abbruch der Studie und daher „underpowering“

One RCT appeared as **preprint** (NCT04342182), performed on 86 patients with COVID-19 (moderate-critical) admitted to 14 centers in the Netherlands, but halted prematurely [149]. The Convalescent-plasma-for-COVID (ConCOVID) study was a randomized trial comparing convalescent plasma with standard of care therapy in Dutch patients hospitalized for COVID-19. Patients were randomized 1:1 and received 300ml of plasma with anti-SARSCoV-2 neutralizing antibody titers of at least 1:80. The primary endpoint was day-60 mortality and key secondary endpoints were hospital stay and WHO 8-point disease severity scale improvement on day 15. The trial was halted prematurely after 86 patients were enrolled. Although symptomatic for only 10 days (IQR 6-15) at the time of inclusion, 53 of 66 patients tested had anti-SARS-CoV-2 antibodies at baseline. A SARS-CoV-2 plaque reduction neutralization test showed neutralizing antibodies in 44 of the 56 (79%) patients tested with median titers comparable to the 115 donors (1:160 vs 1:160, $p=0.40$).

RCT als preprint (Niederlande): 86 Pts.

Because these observations caused concerns about the potential benefit of convalescent plasma in the study population, after discussion with the data safety monitoring board, the study was discontinued. No difference in mortality ($p=0.95$), hospital stay ($p=0.68$) or day-15 disease severity ($p=0.58$) was observed between plasma treated patients and patients on standard of care. The authors concluded that most COVID-19 patients already have high neutralizing antibody titers at hospital admission. Screening for antibodies and prioritizing convalescent plasma to risk groups with recent symptom onset will be key to identify patients that may benefit from convalescent plasma.

Studie wurde abgebrochen wegen Zweifel an Wirksamkeit bei Mortalität, Krankenhausaufenthalt, Schwere der Erkrankung

kein Unterschied

The Living Systematic Review, related to these two RCTs mentioned above, Li et al. 2020 [148], and Gharbharan et al. 2020 [149], with Summary of findings table is provided in Table 3.12-2 [150, 151].

Antikörper Titer sind essentiell

No new RCT peer-reviewed articles have been published as of August 15, 2020.

August: keine weiteren RCTs

Table 3.12-1: Publications on clinical trials on Convalescent plasma [148]

Author, year [Reference]	*Li et al. 2020 [148]
Country	China
Study design	RCT, open-label, multicenter
Number of pts	103 patients were recruited; 52 were randomly assigned to the convalescent plasma+standard treatment group and 51 to the control group
Intervention/Product	Convalescent plasma+standard treatment
Comparator	Standard treatment
Mean age of patients, yrs (SD)	Median age, 70 years
Sex % male (% female)	60 (58.3%) men
Follow-up (days)	28 days
Clinical status	Severe of life-treatening COVID-19
Loss to follow-up, n (%)	2 patients
Efficacy outcomes	
Overall survival (OS), n (%)	28-day mortality (15.7% vs 24.0%; OR, 0.65 [95% CI, 0.29-1.46]; p =0.30)
Time to clinical improvement within 28 days	(51.9% (27/52) of the convalescent plasma group vs 43.1% (22/51) in the control group (difference, 8.8% [95% CI, -10.4% to 28.0%]; hazard ratio [HR], 1.40 [95% CI, 0.79-2.49]; p =0.26)
Time from randomization to discharge	(51.0% vs 36.0% discharged by day 28; HR, 1.61 [95% CI, 0.88-2.93]; p = 0.12)
Time to negative conversion rate of viral PCR at 72 hours	(87.2% of the convalescent plasma group vs 37.5% of the control group (OR, 11.39 [95% CI, 3.91-33.18]; p < 0.001)
Safety outcomes	
Adverse events (AEs)	2 patients in the convalescent plasma group

*The trial was terminated early after 103 of a planned 200 patients were enrolled.

Table 3.12-2: Summary of findings table on Convalescent plasma (2 RCTs: Li and Gharbharan) [148],[149],[150, 151]

Outcome	No. of patients		Effect		Number of studies	Certainty of evidence
	CPT	Standard Treatment	Relative (95% CI)	Absolute (95% CI)		
All-cause mortality	14/95 (14.7%)	23/94 (24.5%)	RR 0.60 (0.33 to 1.10)	98 fewer per 1,000 (from 164 fewer to 24 more)	1 ^{1,2}	Low
All-cause mortality – serious patients	8/23 (34.8%)	10/22 (45.5%)	RR 0.77 (0.37 to 1.58)	105 fewer per 1,000 (from 286 fewer to 264 more)	1 ²	Low
All-cause mortality – critically ill patients	0/29 (0.0%)	2/29 (6.9%)	RR 0.20 (0.01 to 3.99)	55 fewer per 1,000 (from 68 fewer to 206 more)	1 ²	Low
SARS-CoV-2 clearance	41/52 (78.8%)	15/51 (29.4%)	RR 2.67 (1.71 to 4.18)	491 more per 1,000 (from 209 more to 935 more)	1 ²	Very low
SARS-CoV-2 clearance – serious patients	19/23 (82.6%)	7/22 (31.8%)	RR 2.60 (1.37 to 4.92)	509 more per 1,000 (from 118 more to 1,000 more)	1 ²	Very low
SARS-CoV-2 clearance – critically ill patients	22/29 (75.9%)	8/29 (27.6%)	RR 2.75 (1.47 to 5.13)	483 more per 1,000 (from 130 more to 1,000 more)	1 ²	Very low
Number of patients discharged	26/52 (50.0%)	18/51 (35.3%)	RR 1.35 (1.00 to 1.84)	124 more per 1,000 (from 0 fewer to 296 more)	1 ²	Very low
Number of patients discharged – serious patients	21/23 (91.3%)	15/22 (68.2%)	RR 1.34 (0.98 to 1.83)	232 more per 1,000 (from 14 fewer to 566 more)	1 ²	Very low
Number of patients discharged – critically ill patients	5/29 (17.2%)	3/29 (10.3%)	RR 1.67 (0.44 to 6.34)	69 more per 1,000 (from 58 fewer to 552 more)	1 ²	Very low
Duration of hospitalisation (follow up range 28-60 days)	NA	NA	HR 1.21 (0.64 to 2.28)	NA	1 ^{1,2}	Very low
Duration of hospitalisation – serious patients	NA	NA	HR 1.97 (1.00 to 3.88)	NA	1 ²	Low
Duration of hospitalisation – critically ill patients	NA	NA	HR 1.90 (0.45 to 8.04)	NA	1 ²	Low
Number of patients with adverse events	2/51 (3.9%)	0/50 (0.0%)	RR 2.94 (0.32 to 27.32)	0 fewer per 1,000 (from 0 fewer to 0 more)	1 ²	Low
Number of patients with adverse events – serious patients	1/23 (4.3%)	0/22 (0.0%)	RR 2.88 (0.12 to 67.03)	0 fewer per 1,000 (from 0 fewer to 0 more)	1 ²	Low

Serious adverse events D14-D28	0 per 1,000	0 per 1,000 (0 to 0)	RR 2.94 (0.12 to 70.56)	101 (1 RCT)	⊕○○○ VERY LOW ^{c,f,g}	zero events in control group
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*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

- Risk of bias downgraded by 1 level: some concerns or high risk of bias regarding adequate randomization, deviation from intended intervention and outcome measurement
- Indirectness downgraded by 1 level: single study from a single country, therefore results in this population might not be generalizable to other settings
- Imprecision downgraded by 2 level: due to very wide confidence interval consistent with the possibility for benefit and the possibility for harm and low number of participants
- Imprecision downgraded by 1 level: due to wide confidence interval consistent with the possibility for benefit and the possibility for harm and low number of participants
- Risk of bias downgraded by 1 level: some concerns or high risk of bias regarding adequate randomization and deviation from intended intervention
- Risk of bias downgraded by 1 level: some concerns or high risk of bias regarding adequate randomization, deviation from intended intervention and outcome measurement
- We presume that the adverse event rates, and the corresponding relative risks, is similar across diverse settings; therefore not downgraded for indirectness

3.13 Plasma derived medicinal products

As Marovich et al. 2020 [152] stated, neutralizing monoclonal antibodies to SARS-CoV-2 have the potential to be used for both prevention and treatment of infection. They can help to guide vaccine design and development as well. The main target of SARS-CoV-2 neutralizing monoclonal antibodies is the surface spike glycoprotein that mediates viral entry into host cells. Some products will include of a combination of 2 monoclonal antibodies targeting different sites on the spike protein. Due to long half-life of most monoclonal antibodies (approximately 3 weeks for IgG1), a single infusion should be sufficient. A potential limitation of monoclonal antibodies for treatment of COVID-19 is the unknown bioavailability of passively infused IgG in tissues affected by the disease, especially the lungs, which serve as a key target of SARS-CoV-2 infection. Due to the effect of viral diversity it will be important to monitor for the emergence of resistant viral mutations under selective pressure of monoclonal antibody treatment.

Several clinical trials are already registered in ClinicalTrials.gov with several SARS-CoV-2 monoclonal antibodies, and are underway (for example: NCT04425629; NCT04346277; NCT04391309; NCT04268537; NCT04441918; NCT04426695; NCT04429529; NCT04454398; NCT04453384) [9].

To block disease progression, therapeutic trials will include treatment of patients with varying degrees of illness. In the prevention of COVID-19, passive infusion of monoclonal antibodies as preexposure or postexposure prophylaxis might offer immediate protection from infection that could last weeks or months [152]. Newer technologies that modify the Fc region of the antibody to extend the half-life of monoclonal antibodies can provide potentially protective levels for months, depending on the monoclonal antibody concentrations required. Possible disease enhancement include antibody-mediated enhancement of viral entry and replication in target cells (Fc-bearing monocytes or macrophages) and virus-antibody immune complexes and the associated cytokine release [152].

As stated in Press release on July 06, 2020, <https://investor.regeneron.com/news-releases/news-release-details/regeneron-announces-start-regn-cov2-phase-3-covid-19-prevention>, Regeneron Pharmaceuticals, Inc. (NASDAQ: REGN) announced the initiation of late-stage clinical trials evaluating REGN-COV2, Regeneron's investigational double antibody cocktail for the treatment and prevention of COVID-19. REGN-COV2's two antibodies bind non-competitively to the critical receptor binding domain of the virus's spike protein, which diminishes the ability of mutant viruses to escape treatment and protects against spike variants that have arisen in the human population. All trials are adaptively-designed, and the ultimate numbers of patients enrolled will depend on trial progress and insights from Phase 2 studies.

A Phase 3 prevention trial will evaluate REGNCOV2's ability to prevent infection among uninfected people who have had close exposure to a COVID-19 patient (such as the patient's housemate). It is being run jointly with the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health (NIH). The Phase 3 prevention trial is being conducted at approximately 100 sites and is

**neutralisierende
monoklonale Antikörper:
Prävention und
Behandlung**

**Halbwertszeit bis
3 Wochen von Vorteil**

**Nachteil: unbekannte
Bioverfügbarkeit der
infundierten Antikörper**

**zahlreiche klinische
Studien registriert**

**Prä- und post
Expositionsprophylaxe**

**kombinierte Antikörper-
"Cocktails" zur
Prävention**

**Phase 3
REGNCOV2 Studie
NIAID (NIH) Studie mit
2.000 Teilnehmer*innen**

expected to enroll 2,000 patients in the U.S.; the trial will assess SARS-CoV-2 infection status.

REGN-COV2 has also moved into the Phase 2/3 portion of two adaptive Phase 1/2/3 trials testing the cocktail's ability to treat hospitalized and non-hospitalized (or "ambulatory") patients with COVID-19. The two Phase 2/3 treatment trials in hospitalized (estimated enrollment =1,850) and non-hospitalized (estimated enrollment =1,050) patients are planned to be conducted at approximately 150 sites in the U.S., Brazil, Mexico and Chile, and will evaluate virologic and clinical endpoints, with preliminary data expected later this summer.

As of August 15, 2020 no studies are found as completed, nor withdrawn or suspended or terminated.

Current US NIH COVID-19 Treatment Guidelines stated that there are insufficient clinical data to recommend either for or against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) immunoglobulins for the treatment of COVID-19 [134].

No RCT peer-reviewed articles have been published as of August 15, 2020.

3.14 Combination therapy – triple combination of interferon beta-1b, lopinavir–ritonavir and ribavirin vs. lopinavir–ritonavir or other triple combination of interferons

Hung et al. 2020 [123] present the results of the first randomised controlled trial (NCT04276688) on the triple combination of interferon beta-1b, lopinavir–ritonavir, and ribavirin, compared with lopinavir–ritonavir alone, in the treatment of patients admitted to hospital with mild to moderate COVID-19 in Hong-Kong. In this multicentre, prospective, open-label, randomised, phase 2 trial, 127 patients were randomly assigned (2:1) to a 14-day combination of lopinavir 400 mg and ritonavir 100 mg every 12 h, ribavirin 400 mg every 12 h, and three doses of 8 million international units of interferon beta-1b on alternate days (combination group) or to 14 days of lopinavir 400 mg and ritonavir 100 mg every 12 h (control group). The primary endpoint was time to negative nasopharyngeal swab for SARS-CoV-2 RT-PCR. Secondary endpoints included time to symptom resolution by achieving a national early warning score 2 (NEWS2) of 0, a sequential organ failure assessment (SOFA) score of 0, 30-day mortality, and duration of hospital stay. Triple therapy was associated with a significant reduction in the duration of viral shedding (time to negative nasopharyngeal swab 7 days [IQR 5–11] in the combination group vs 12 days [8–15] in the control group; hazard ratio [HR] 4.37 [95% CI 1.86–10.24], $p=0.0010$), symptom alleviation (time to NEWS2 0 of 4 days [IQR 3–8] vs 8 days [7–9]; HR 3.92 [1.66–9.23], $p<0.0001$), and duration of hospital stay (9.0 days [7.0–13.0] vs 14.5 days [9.3–16.0]; HR 2.72 [1.2–6.13], $p=0.016$). There was no mortality in either group. The triple combination also suppressed IL-6 levels. Adverse events included self-limited nausea and diarrhoea with no difference between the two groups. No serious adverse events were reported in the combination group. One

Behandlung von hospitalisierten und ambulanten Patient*innen

erste Ergebnisse: Spätsommer 2020

August 2020: keine weiteren Studien

NIH Behandlungsguideline: insuffiziente Datenlage

Reduktion der Dauer der Virusausscheidung, Symptomverbesserung, Dauer des Krankenhausaufenthalts

kein Unterschied bei AE keine Todesfälle in beiden Gruppen

patient in the control group had a serious adverse event of impaired hepatic enzymes requiring discontinuation of treatment.

The Living Systematic Review, related to this RCT mentioned above, with Summary of finding table (https://covid-nma.com/living_data/index.php) is provided in table 3.14-2.

One new RCT peer-reviewed articles have been published as of August 16, 2020.

Huang et al. 2020 [125] reported the results from a single-center, randomized, open-labeled, prospective clinical trial (ChiCTR2000029387). 101 eligible patients with mild to moderate COVID-19 were randomized into three groups: ribavirin (RBV) plus interferon- α (IFN- α), lopinavir/ritonavir (LPV/r) plus IFN- α , and RBV plus LPV/r plus IFN- α at a 1:1:1 ratio, with a 28-d follow-up. The outcomes include the difference in median interval to SARS-CoV-2 nucleic acid negativity, the proportion of patients with SARS-CoV-2 nucleic acid negativity at day 14, the mortality at day 28, the proportion of patients re-classified as severe cases, and adverse events during the study period. The median interval from baseline to SARS-CoV-2 nucleic acid negativity was 12 d in the LPV/r+IFN- α -treated group, as compared with 13 and 15 d in the RBV+IFN- α -treated group and in the RBV+LPV/r+ IFN- α -treated group, respectively ($p=0.23$). The proportion of patients with SARS-CoV-2 nucleic acid negativity in the LPV/r+IFN- α -treated group (61.1%) was higher than the RBV+ IFN- α -treated group (51.5%) and the RBV+LPV/r+IFN- α -treated group (46.9%) at day 14; however, the difference between these groups was calculated to be statistically insignificant. The RBV+LPV/r+IFN- α -treated group developed a significantly higher incidence of gastrointestinal adverse events than the LPV/r+ IFN- α -treated group and the RBV+ IFN- α -treated group. Authors concluded that there are no significant differences among the three regimens in terms of antiviral effectiveness in patients with mild to moderate COVID19. The combination of RBV and LPV/r is associated with a significant increase in gastrointestinal adverse events, suggesting that RBV and LPV/r should not be co-administered to COVID-19 patients simultaneously.

**keine weiteren RCTs
publiziert**

**August 2020:
ein weiterer RCT**

RCT: 101 Pts

**3 Gruppen:
RBV+IFN
LPV+IFN
RBV+LPV**

kein Unterschied

Table 3.14-1: Publications on clinical trials on triple combination of interferon beta-1b, lopinavir–ritonavir and ribavirin

Author, year [Reference]	Hung et al. 2020 [123]
Country	Hong-Kong
Sponsor/Funding	The Shaw-Foundation, Richard and Carol Yu, May Tam Mak Mei Yin, and Sanming Project of Medicine
Study design	Multicentre, prospective, open-label, randomised, phase 2 trial
Number of pts	127 patients were recruited; 86 were randomly assigned to the combination group and 41 were assigned to the control group
Intervention/Product	lopinavir 400 mg and ritonavir 100 mg every 12 h, ribavirin 400 mg every 12 h, and three doses of 8 million international units of interferon beta-1b on alternate days (combination group)
Comparator	lopinavir 400 mg and ritonavir 100 mg every 12 h (control group)
Inclusion criteria	Age at least 18 years, a national early warning score 2 (NEWS2) of at least 1, and symptom duration of 14 days or less upon recruitment
Exclusion criteria	Inability to comprehend and to follow all required study procedures; allergy or severe reactions to the study drugs; patients with known prolonged QT or PR interval, second- or third-degree heart block, or ventricular cardiac arrhythmias, including torsade de pointes; patients taking medication that will potentially interact with lopinavir/ritonavir, ribavirin or interferon-beta 1b; patients with known history of severe depression; pregnant or lactation women; inability to comprehend and to follow all required study procedures; received an experimental agent (vaccine, drug, biologic, device, blood product, or medication) within 1 month prior to recruitment in this study or expect to receive an experimental agent during this study; unwilling to refuse participation in another clinical study through the end of this study; have a history of alcohol or drug abuse in the last 5 years; have any condition that the investigator believes may interfere with successful completion of the study
Pts pretreated + previous treatment	N.A
Mean age of patients, yrs (SD)	52 years (IQR 32–62)
Sex % male (% female)	68 (54%) men vs 59 (46%) women
Follow-up (days)	30 days
Clinical status	Mild to moderate COVID-19
Loss to follow-up, n (%)	1 patient in control group due to AE
Efficacy outcomes	
Overall survival (OS), n (%)	No patients died during the study
Time to negative nasopharyngeal swab	7 days [IQR 5–11] in the combination group vs 12 days [8–15] in the control group; hazard ratio [HR] 4.37 [95% CI 1.86–10.24], p=0.0010
Time to clinical improvement	Time to NEWS2 0 of 4 days [IQR 3–8] in the combination group vs 8 days [7–9] in the control group; HR 3.92 [1.66–9.23], p<0.0001
Length of hospitalisation	Duration of hospital stay (9.0 days [7.0–13.0] in the combination group vs 14.5 days [9.3–16.0] in the control group; HR 2.72 [1.2–6.13], p=0.016
Safety outcomes	
Adverse events (AEs)	41 (48%) of 86 patients in the combination group vs 20 (49%) of 41 patients in the control group most common: diarrhoea (52 [41%] of 127 patients), fever (48 [38%] patients), nausea (43 [34%]) and raised alanine transaminase level (18 [14%], p=ns
Serious adverse events (SAEs)	0 in combination group vs 1 in control group (impaired hepatic enzymes requiring discontinuation of treatment), p=0.15
Discontinuation of study drug due to AEs or SAEs	1 in the control group

Table 3.14-2: Summary of findings table on triple combination of interferon beta-1b, lopinavir–ritonavir and ribavirin (1 RCT: Hung) - https://covid-nma.com/living_data/index.php

Summary of findings:						
Lopinavir + Ritonavir + Ribavirin + Interferon-b-1b compared to Lopinavir + Ritonavir for Mild/Moderate COVID-19						
Patient or population: Mild/Moderate COVID-19						
Setting: Worldwide						
Intervention: Lopinavir + Ritonavir + Ribavirin + Interferon-b-1b						
Comparison: Lopinavir + Ritonavir						
Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Lopinavir + Ritonavir	Risk with Lopinavir + Ritonavir + Ribavirin + Interferon-b-1b				
Incidence of viral negative conversion D7	902 per 1.000	875 per 1.000 (767 to 993)	RR 0.97 (0.85 to 1.10)	127 (1 RCT)	⊕⊕○○ LOW ^{a,b}	
WHO Clinical Progression Score (decrease in 1 point) (i.e., improvement) - not reported	-	-	-	-	-	outcome not yet measured or reported
Admission in ICU or death - not reported	-	-	-	-	-	outcome not yet measured or reported
Incidence of WHO progression score (level 6 or above) - not reported	-	-	-	-	-	outcome not yet measured or reported
Incidence of WHO progression score (level 7 or above) - not reported	-	-	-	-	-	outcome not yet measured or reported
All-cause mortality D7				127 (1 RCT)	⊕○○○ VERY LOW ^{a,c}	zero events in both groups

All-cause mortality D14-D28				127 (1 RCT)	⊕○○○ VERY LOW a,c	zero events in both groups
Adverse events D14-D28	488 per 1.000	478 per 1.000 (327 to 698)	RR 0.98 (0.67 to 1.43)	127 (1 RCT)	⊕⊕⊕○ MODERATE d,e	
Serious adverse events D14-D28	24 per 1.000	4 per 1.000 (0 to 94)	RR 0.16 (0.01 to 3.87)	127 (1 RCT)	⊕⊕○○ LOW ^{d,f}	

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

- a. Indirectness downgraded by 1 level: single study from a single country, therefore results in this population might not be generalizable to other settings
- b. Imprecision downgraded by 1 level: low number of participants
- c. Imprecision downgraded by 2 levels: no events in both groups and low number of participants
- d. Indirectness not downgraded: we presume that adverse event rate is not specific to a certain setting
- e. Imprecision downgraded by 1 level: due to wide confidence interval consistent with the possibility for benefit and the possibility for harm and low number of participants
- f. Imprecision downgraded by 2 levels: due to very wide confidence interval consistent with the possibility for benefit and the possibility for harm and low number of participants

3.15 Solnatide

About the treatment under consideration

The therapeutic molecule solnatide (INN) has been designed by APEPTICO (a privately-held biotechnology company from Vienna/Austria) for the therapeutic treatment of patients with Acute Respiratory Distress Syndrome (ARDS) and various forms of life-threatening Pulmonary Oedema (PPO). Solnatide is a synthetic peptide of less than 20 amino acids applied directly in the lower airways in the form of a liquid aerosol, aims to accelerate the dissolution of alveolar oedema and reduce barrier damage caused by Covid-19 in the lungs. In 2013, APEPTICO successfully completed a phase I clinical study in healthy subjects, proving the safety of solnatide, as well as two phase II clinical studies (a randomized, double-blinded placebo-controlled trial using inhaled solnatide in mechanically-ventilated ARDS patients with lung

**Medikament gegen
akutes Atemnotsyndrom**

Verabreichung: Inhalation

**2013: Phase 1 Studie
abgeschlossen +
2 Phase 2 Studien an
beatmeten Pts.**

oedema; a randomized, placebo-controlled pilot study in patients suffering from primary graft dysfunction (PGD) following lung transplantation).

Currently, solnatide is investigated in a Phase IIB trial (EUDRACT No. 2017-003855-47) for the “treatment of pulmonary permeability oedema in patients with ARDS”. The Phase IIB clinical trial has been approved by the German and the Austrian Competent Authorities, as well by Ethic Committees of leading Medical University Hospitals in Germany as well Austria.

In April 2020, solnatide has been approved for Compassionate Use by the Austrian Federal Office for Safety in Health Care (BASG) for the treatment of patients infected by the novel coronavirus SARS-CoV-2 and subsequently developing severe pulmonary dysfunction (severe COVID-19), as well as by the Italian Medicines Agency and the Ethics Committee of the National Institute for Infectious Diseases (Lazzaro Spallanzani-Rome), within the compassionate use program of drugs undergoing clinical trials for the treatment of COVID-19 patients suffering from pulmonary oedema and acute respiratory distress syndrome.

APEPTICO Forschung und Entwicklung GmbH has signed, together with the “solnatide consortium”, the Grant Agreement ID: 101003595 with the European Commission to accelerate the process of making APEPTICO’s proprietary investigational medicinal product (IMP) solnatide available for medical treatment of patients severely affected by the novel coronavirus 2019 (SARS-CoV-2) disease, COVID-19; the Grant Agreement was made available via the Horizon2020 programme “Advancing knowledge for the clinical and public health response to the 2019-nCoV epidemic” (https://ec.europa.eu/commission/presscorner/detail/en/ip_20_386). Project started on 1 April 2020 and will end on 31 December 2021.

One ongoing randomised, double-blind, placebo controlled, parallel assignment trial with aim to assess efficacy and safety of 7 days orally inhaled 100 mg solnatide to treat pulmonary permeability oedema of 40 SARS-Cov-2 positive patients with moderate-to-severe ARDS is registered in EUdraCT register (EudraCT number 2020-001244-26), <https://www.clinicaltrialsregister.eu/ctr-search/trial/2020-001244-26/AT> [153].

Completed, withdrawn, suspended or terminated studies

As of August 15, 2020 no completed, withdrawn, suspended or terminated studies related to solnatide in COVID-19 patients were found in ClinicalTrials.gov and EUdraCT registers [153].

Results of publications

As of August 15, 2020 no publications related to the RCTs of solnatide in COVID-19 patients were found [153].

**derzeit laufende Studie:
Phase 2B**

**April: BASG, AIFA lassen
Solnatide für
“Compassionate Use” zu**

**EC-Grant seit April für
covid-19**

**1 laufender RCT mit 40
moderat bis schwer Covid-
19 Erkrankten**

**ClinicalTrials.gov &
EUdraCT: keine klinischen
Studien registriert,**

keine Publikation von RCT

3.16 Umifenovir (Arbidol®)

About the treatment under consideration

Umifenovir (Arbidol), an indole-derivative is a broad-spectrum drug against a wide range of enveloped and non-enveloped viruses: it interacts preferentially with aromatic amino acids, and it affects multiple stages of the virus life cycle, either by direct targeting viral proteins or virus-associated host factors. Umifenovir's ability to exert antiviral effects through multiple pathways has resulted in considerable investigation into its use for a variety of enveloped and non-enveloped RNA and DNA viruses, including Flavivirus, Zika virus, foot-and-mouth disease, Lassa virus, Ebola virus, herpes simplex, hepatitis B and C viruses, chikungunya virus, reovirus, Hantaan virus, and coxsackie virus B5. This dual activity may also confer additional protection against viral resistance, as the development of resistance to umifenovir does not appear to be significant. Umifenovir is currently being investigated as a potential treatment and prophylactic agent for COVID-19 caused by SARS-CoV2 infections in combination with both currently available and investigational HIV therapies (<https://pubchem.ncbi.nlm.nih.gov/compound/Arbidol>). Its use is only in China and Russia, since not approved by neither the FDA nor the EMA.

As Wang et al. 2020 recently published, arbidol efficiently inhibited SARS-CoV-2 infection in vitro (it appears to block virus entry by impeding viral attachment and release from the EIs) [154].

One small retrospective observational study published by Zhu et al. 2020 [155] evaluated the antiviral effect and safety of lopinavir/ritonavir (2x 400 mg/100 mg, n=34) and umifenovir (3x0.2 g, n=16) patients with COVID-19, treated for one week. No difference in fever duration was found between the two groups (p=0.61), but patients in umifenovir group had a shorter duration of positive RNA test (p<0.01).

Completed, withdrawn, suspended or terminated studies

As of August 15, 2020 no completed, withdrawn, suspended or terminated studies related to umifenovir were found in ClinicalTrials.gov and EudraCT registers.

Results of publications

As already mentioned above, in section related to of lopinavir/ritonavir, RCT published by Yueping et al. 2020 (NCT04252885) [64] was an exploratory randomised (2:2:1) controlled trial, conducted in China, with the aim to assess the efficacy and safety of lopinavir/ritonavir or arbidol monotherapy in 86 patients with mild/moderate COVID-19. 34 of them assigned to lopinavir/ritonavir; 35 to arbidol and 17 with no antiviral medication as control, with follow-up of 21 days. The rate of positive-to-negative conversion of SARS-CoV-2 nucleic acid, as the primary endpoint, was similar between groups (all P>0.05) and there were no differences between groups in the secondary endpoints, the rates of antipyresis, cough alleviation, or improvement of chest CT at days 7 or 14 (all p>0.05). At day 7, eight (23.5%) patients in the LPV/r group, 3 (8.6%) in the arbidol group and 2 (11.8%) in the control group showed a deterioration in clinical status from moderate to severe/critical (p=0.206). Related to adverse events, 12 (35.3%) patients in the lopinavir/ritonavir group and 5 (14.3%) in the arbidol group experienced adverse events during the follow-up period, and no AE occurred in the control group [64].

**antivirales Medikament
zugelassen in China,
Russland, aber nicht EMA/
FDA**

**Erprobung bei
verschiedenen Viren:**

**Flavi-, Zika-,
Lassa-, Ebola Virus,
Herpes simplex, Hepatitis
B & C**

1 in vitro Publikation

**Zhu (China):
retrospektive Studie
34 Pts.**

**ClinicalTrials.gov &
EudraCT: keine Studien
registriert**

**Yueping (China)
RCT, 86 Pts.
leichte/ moderate
Erkrankung**

**kein Unterschied
zwischen den Gruppen in
einigen
Surrogatendpunkten**

mehr AE

The Living Systematic Review, related to this RCT mentioned above, with Summary of findings table (https://covid-nma.com/living_data/index.php) is provided in table 3.16-1.

One publication [68] on the completed RCT (ChiCTR2000030254) about the efficacy and safety of favipiravir, in comparison with umifenovir, to treat Covid-19 patients was identified; however, as the publication was available just as pre-print but not yet peer-reviewed, it has not been extracted.

**1 RCT nur im preprint
(nicht peer-reviewed)**

No new RCT peer-reviewed articles have been published as of August 15, 2020.

Table 3.16-1: Summary of findings table, on umifenovir (1 RCT: Yueping) - https://covid-nma.com/living_data/index.php

Summary of findings:						
Umifenovir compared to Standard Care for Mild/Moderate COVID-19						
Patient or population: Mild/Moderate COVID-19						
Setting: Worldwide						
Intervention: Umifenovir						
Comparison: Standard Care						
Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	N _o of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Standard Care	Risk with Umifenovir				
Incidence of viral negative conversion (D7)	412 per 1.000	371 per 1.000 (181 to 758)	RR 0.90 (0.44 to 1.84)	52 (1 RCT)	⊕○○○ VERY LOW ^{a,b}	
WHO Clinical Progression Score (increase in 1 point) - not reported	-	-	-	-	-	outcome not yet measured or reported
Admission in ICU - not reported	-	-	-	-	-	outcome not yet measured or reported
Incidence of WHO progression score (level 6 or above) - not reported	-	-	-	-	-	outcome not yet measured or reported
Incidence of WHO progression score (level 7 or above D7)				52 (1 RCT)	⊕○○○ VERY LOW ^{a,c}	zero events in both groups
All-cause mortality D14-D28				52 (1 RCT)	⊕○○○ VERY LOW ^{a,c}	zero events in both groups

Adverse events D14-D28	0 per 1.000	0 per 1.000 (0 to 0)	RR 5.50 (0.32 to 94.06)	52 (1 RCT)	⊕⊕○○ LOW ^{b,d}	zero events in control group
Serious adverse events D14-D28				52 (1 RCT)	⊕⊕○○ LOW ^{c,d}	zero events in both groups

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

3.17 Dexamethasone and other corticosteroids

About the drug under consideration

Dexamethasone (Dexamethasone Mylan), manufactured by Mylan, is a long-acting glucocorticoid which is used principally as an anti-inflammatory or immunosuppressant agent. During a short-term therapy, in compliance with the dosage recommendations and close monitoring of patients, the risk of side effects is low. The usual side effects of short-term dexamethasone treatment (days/weeks) include weight gain, psychological disorders, glucose intolerance and transitory adrenocortical insufficiency. Long-term dexamethasone treatment (months/years) usually causes central obesity, skin fragility, muscle atrophy, osteoporosis, growth retardation and longterm suprarenal insufficiency [156-158].

The proposed mechanism of glucocorticoids in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) involves the mitigation of an excessive immune response that can lead to acute respiratory distress syndrome (ARDS) and multi-organ failure. ARDS develops in approximately 20% of COVID-19 patients and is linked to multi-organ failure through cytokine release syndrome [159, 160].

Dexamethasone is authorised at national level in the EU and is used in a wide range of conditions, including rheumatic problems, skin diseases, severe allergies, asthma and chronic obstructive lung disease. On 24 July 2020, EMA's human medicines committee (CHMP) started a review under Article 5(3) of Regulation 726/2004 of the results from the RECOVERY study arm and will provide an opinion on the results of this study and on the potential use of dexamethasone to treat adults with COVID-19 [161]. The UK has approved dexamethasone for the treatment of Covid-19 on June 16, 2020 [162].

**Glukokortikoide:
entzündungshemmend**

**EMA keine Zulassung, UK:
Zulassung im Juni für
Covid-19**

There are several registered ongoing clinical trials in Covid-19 patients in ClinicalTrials.gov and EUdraCT registers. Results from published small case series and retrospective cohort studies with short courses of corticosteroids in patients with COVID-19 reported conflicting results, both beneficial and harmful effects [163-168]. Cruz et al. 2020 (EUPAS34753) [169] published a non-randomised retrospective cohort study on 463 patients with COVID-19 pneumonia (moderate, severe, critical) and complicated with ARDS and/or an hyperinflammatory syndrome admitted to a single center in Spain, treated with corticosteroids (n=396) in comparisons with standard of care (n=67). Global mortality was 15.1%. In-hospital mortality was lower in patients treated with steroids than in controls (13.9% [55/396] versus 23.9% [16/67], HR 0.51 [0.27-0.96], p= 0.044). Steroid treatment reduced mortality by 41.8% relative to no steroid treatment (RRR 0,42 [0.048- 0.65]). Initial treatment with 1 mg/kg/day of methylprednisolone versus steroid pulses was not associated with in-hospital mortality (13.5% [42/310] versus 15.1% [13/86], OR 0.880 [0.449-1.726], p=0.710).

**mehrere Studien sind registriert
Cruz (Spanien):
retrospektive Studie
463 Pts**

geringere Mortalität

Salton et al. 2020 [170] conducted a non-randomised, longitudinal study on 173 patients with confirmed COVID-19 (severe) pneumonia admitted to fourteen centers in Italy (NCT04323592) to explore the association between exposure to prolonged, low-dose, methylprednisolone (MP) treatment and need for ICU referral, intubation or death within 28 days (composite primary endpoint). 83 patients received methylprednisolone (80 mg iv for at least eight days, followed by 16 orally or 20 mg iv, twice daily) and 90 patients received control treatment. Unexposed patients (controls) were selected from concurrent consecutive COVID-19 patients with the same inclusion and exclusion criteria. Patients in both study groups received standard of care, comprising noninvasive respiratory support, antibiotics, antivirals, vasopressors, and renal replacement therapy as deemed suitable by the healthcare team. The composite primary endpoint was met by 19 vs. 40 [adjusted hazard ratio (HR) 0.41; 95% confidence interval (CI): 0.24-0.72]. Transfer to ICU and need for invasive MV was necessary in 15 vs. 27 (p=0.07) and 14 vs. 26 (p=0.10), respectively. By day 28, the MP group had fewer deaths (6 vs. 21, adjusted HR=0.29; 95% CI: 0.12-0.73) and more days off invasive MV (24.0 ± 9.0 vs. 17.5 ± 12.8; p=0.001). Study treatment was associated with rapid improvement in PaO₂:FiO₂ and CRP levels. The complication rate was similar for the two groups (p=0.84).

**Salton (Italien):
Longitudinal Studie
173Pts.**

**geringere Mortalität,
weniger ICU-Transfers
weniger künstliche
Beatmung**

Wu et al. 2020 [171] conducted a non-randomised, retrospective cohort study on 720 patients with COVID-19 (severe-critical) admitted to two centers in China with aim to compare use of any intravenous corticosteroid (for 5 or 6 days) in hospital, against no corticosteroid use. Corticosteroids were administered in 531 (35.1%) severe and 159 (63.9%) critical patients. Compared to no corticosteroid use group, systemic corticosteroid use showed no benefit in reducing in-hospital mortality in both severe cases (HR=1.77, 95% CI: 1.08-2.89, p=0.023), and critical cases (HR=2.07, 95% CI: 1.08-3.98, p=0.028).

**Wu (China):
retrospektive
Kohortenstudie
720 Pts.**

kein Unterschied

Bani-Sadr et al. 2020 [172] published results from a before–after study which was performed to evaluate the effect of addition of corticosteroids to our institution’s COVID-19 treatment protocol on hospital mortality. A total of 257 patients with a COVID-19 diagnosis were included in this study between 3 March 2020 and 14 April 2020. As corticosteroids were widely used after 27 March 2020, two periods were considered for the purposes of this study: the ‘before’ period from 3–20 March 2020 (n = 85); and the ‘after’ period from 26 March–14 April 2020 (n = 172). The ‘after’ period was associated with a lower

**Bani-Sadr
Vorher-Nachher Studie
257 Pts.**

Reduktion der Mortalität

risk of death [adjusted hazard ratio (aHR) = 0.47, 95% confidence interval (CI) 0.23–0.97; p = 0.04] and a lower risk of ICU admission or of death before ICU admission (aHR = 0.37, 95% CI 0.21–0.64; p = 0.0005) by multivariate analysis adjusted for age, National Early Warning score and institutionalisation status. Authors concluded that addition of corticosteroids to their institution’s COVID-19 treatment protocol was associated with a significant reduction in hospital mortality in the ‘after’ period.

Based on results of the RECOVERY Trial described below, the US COVID-19 Treatment Guidelines Panel **recommends using dexamethasone** (at a dose of 6 mg per day for up to 10 days) in patients with COVID-19 who are mechanically ventilated (**AI**) and in patients with COVID-19 who require supplemental oxygen but who are not mechanically ventilated (**BI**). The Panel **recommends against** using dexamethasone in patients with COVID-19 who do not require supplemental oxygen (**AI**) [58]. If dexamethasone is not available, the Panel **recommends using** alternative glucocorticoids such as **prednisone, methylprednisolone, or hydrocortisone (AIII)** [61].

Empfehlungen des US COVID-19 Treatment Guidelines Panel: bei künstlich beatmeten Patient*innen, nicht jedoch bei nicht beatmeten Pts.

Completed, withdrawn, suspended or terminated studies

As of July 07, 2020 two completed (NCT04445506, related to dexamethasone, and NCT04273321, related to methylprednisolone) were found.

2 abgeschlossene RCTs

As of August 10, 2020 one terminated RCT - NCT04327401 (CoDEX), related to dexamethasone was found; none additional completed, nor withdrawn or suspended interventional studies were found in ClinicalTrials.gov and EUdraCT registers. In this terminated RCT conducted in 299 COVID-19 patients with moderate and severe ARDS in Brazil, the Data Monitoring Committee recommended to stop the trial based on the Recovery Trial results, which was accepted by the CoDEX Steering Committee. The results of this RCT are not yet published [9].

1 abgebrochener RCT wegen (besseren Ergebnissen in) Recovery Trial in Brasilien

Results of publications

One peer-reviewed scientific publication on RCTs of dexamethasone arm of the RECOVERY trial in Covid-19 patients could be identified (status: 14/08/2020) [173]. The RECOVERY trial was designed to evaluate the effects of potential treatments in patients hospitalized with Covid-19 at 176 NHS organizations in the UK and was supported by the National Institute for Health Research Clinical Research Network. The primary outcome was all-cause mortality within 28 days after randomization; further analyses were specified at 6 months. Secondary outcomes were the time until discharge from the hospital and, among patients not receiving invasive mechanical ventilation at the time of randomization, subsequent receipt of invasive mechanical ventilation (including extracorporeal membrane oxygenation) or death. Other prespecified clinical outcomes included cause-specific mortality, receipt of renal hemodialysis or hemofiltration, major cardiac arrhythmia (recorded in a subgroup), and receipt and duration of ventilation. The randomization of patients to receive dexamethasone, hydroxychloroquine, or lopinavir-ritonavir has now been stopped, the trial continues randomization to groups receiving azithromycin, tocilizumab, or convalescent plasma.

**1 RCT (Recovery) –UK
2.104 Pts**

Results from preliminary report of the RECOVERY trial are related to the comparison of oral or intravenous dexamethasone 6 mg given once daily for up to ten days (2104 patients) plus the usual standard of care vs. usual care alone (4321 patients). Authors showed that overall, 482 (22.9%) patients allocated dexamethasone and 1110 (25.7%) patients allocated usual care died within 28 days (age adjusted rate ratio [RR] 0.83; 95% confidence interval [CI] 0.75 to 0.93; $P < 0.001$). The proportional and absolute mortality rate reductions varied significantly depending on level of respiratory support at randomization (test for trend $p < 0.001$): dexamethasone reduced deaths by one-third in patients receiving invasive mechanical ventilation (29.3% vs. 41.4%, RR 0.64 [95% CI 0.51 to 0.81]), by one-fifth in patients receiving oxygen without invasive mechanical ventilation (23.3% vs. 26.2%, RR 0.82 [95% CI 0.72 to 0.94]), but did not reduce mortality in patients not receiving respiratory support at randomization (17.8% vs. 14.0%, RR 1.19 [95% CI 0.91 to 1.55]). Allocation to dexamethasone was associated with a shorter duration of hospitalization than usual care (median 12 days vs. 13 days) and a greater probability of discharge within 28 days (rate ratio 1.10 [95% CI 1.03 to 1.17]) with the greatest effect seen among those receiving invasive mechanical ventilation at baseline (11.5 by chi-square test for trend). The risk of progression to invasive mechanical ventilation was lower among those allocated dexamethasone vs. usual care (risk ratio 0.92 [95% CI 0.84 to 1.01]). Analyses are ongoing regarding cause-specific mortality, the need for renal dialysis or hemofiltration, and the duration of ventilation [173, 174].

The summary of findings table, with moderate certainty of evidence related to effectiveness and safety of dexamethasone reported in RECOVERY trial, prepared by Cruciani et al. 2020 [175] can be found in Table 3.17-1.

**Reduktion der Mortalität
RR -30% bei Pts. mit
künstlicher Beatmung**

**RR -20% bei Pts. mit
Sauerstoff ohne invasive
Beatmung**

**ohne Effekt auf Mortalität
bei Pts ohne Untestützung
bei Beatmung**

**zusätzlich: kürzere
Hospitalisierung**

**Zusammenfassung der
Evidenz für
unterschiedliche Pts-
Populationen**

Table 3.17-1: Summary of findings table, on dexamethasone (1 RCT: Horbey) [175]

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Absolute effect (95% CI)	Number of participants (studies)	Certainty of evidence (GRADE)	Comments
	Risk with Standard Treatment	Risk with Dexamethasone					
All-cause Mortality	257 per 1000	229 per 1000	RR 0.88 (0.79 to 0.96)	28 fewer per 1.000 (from 49 fewer to 5 fewer)	6425 (1 RCT)	Moderate ⊕⊕⊕○	Downgraded of one level for high risk of detection bias
All-cause Mortality – mild/moderate patients	140 per 1000	178 for 1000	RR 1.27 (1.00 to 1.61)	38 more per 1.000 (from 0 fewer to 86 more)	1535 (1 RCT)	Moderate ⊕⊕⊕○	Downgraded of one level for high risk of detection bias
Mortality by all causes - severe patients	262 per 1000	233 for 1000	RR 0.89 (0.79 to 1.00)	29 fewer per 1.000 (from 55 fewer to 0 fewer)	3883 (1 RCT)	Moderate ⊕⊕⊕○	Downgraded of one level for high risk of detection bias
Mortality by all causes – critically ill patients	414 per 1000	293 per 1000	RR 0.72 (0.58 to 0.86)	120 fewer per 1.000 (from 174 fewer to 58 fewer)	1007 (1 RCT)	Moderate ⊕⊕⊕○	Downgraded of one level for high risk of detection bias
Number of patients discharged within 28 days	635 per 1000	672 per 1000	RR 1.06 (1.02 to 1.10)	38 more per 1.000 (from 13 more to 64 more)	6425 (1 RCT)	Moderate ⊕⊕⊕○	Downgraded of one level for high risk of detection bias
Number of patients discharged within 28 days - mild/moderate patients	804 per 1000	768 per 1000	RR 0.96 (0.90 to 1.01)	32 fewer per 1.000 (from 80 fewer to 8 more)	1535 (1 RCT)	Moderate ⊕⊕⊕○	Downgraded of one level for high risk of detection bias

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Absolute effect (95% CI)	Number of participants (studies)	Certainty of evidence (GRADE)	Comments
	Risk with Standard Treatment	Risk with Dexamethasone					
Number of patients discharged within 28 days - severe patients	675 per 1000	720 per 1000	RR 1.07 (1.02 to 1.12)	47 more per 1.000 (from 13 more to 81 more)	3883 (1 RCT)	Moderate ⊕⊕⊕○	Downgraded of one level for high risk of detection bias
Number of patients discharged within 28 days - critically ill patients	233 per 1000	330 per 1000	RR 1.42 (1.15 to 1.74)	98 more per 1.000 (from 35 more to 172 more)	1007 (1 RCT)	Moderate ⊕⊕⊕○	Downgraded of one level for high risk of detection bias

CI: Confidence interval; RR: Risk ratio

Evaluation of the quality of the tests according to the GRADE Working Group

High Quality: We are very confident that the real effect is close to that of the estimated effect

Moderate Quality: We are moderately confident in the effect estimation: the real effect may be close to the estimated effect, but there is a possibility that it is substantially different

Low Quality: Our confidence in the effect estimation is limited: the real effect may be substantially different from the estimated effect

Very Low Quality : We have very little confidence in estimating the effect: the actual effect is likely to be substantially different from the estimated one.

Explanations: Serious Risk of Bias - Lowered by one level for high for high risk of detection bias

3.18 Anakinra (Kineret®)

About the drug under consideration

Anakinra (Kineret®) is an immunosuppressive medicine, a copy of a natural human protein - 'human interleukin 1 receptor antagonist' (r-metHuIL-1ra, produced in *Escherichia coli* cells by recombinant DNA technology). Anakinra neutralises the biologic activity of interleukin-1 α (IL-1 α) and interleukin-1 β (IL-1 β) by competitively inhibiting their binding to interleukin-1 type I receptor (IL-1RI). Interleukin-1 (IL-1) is a pivotal pro-inflammatory cytokine mediating many cellular responses including those important in synovial inflammation. Anakinra is authorised in the EU for Rheumatoid Arthritis (RA), Cryopyrin-Associated Periodic Syndromes (CAPS), Familial Mediterranean Fever (FMF) and Still's Disease [177]. Boehringer Ingelheim RCV GmbH & Co KG, Austria and Pfizer Health AB, Sweden, are listed as manufacturer of the biological active substance, and Swedish Orphan Biovitrum AB, Sweden, as Marketing Authorisation Holder, responsible for batch release. Kineret received a marketing authorisation valid throughout the European Union on 8 March 2002; Anakinra received the FDA approval in November 2001. It is available as a solution for injection under the skin. Anakinra is not authorised in Covid-19 patients (EMA, FDA).

There are several ongoing clinical trials in Covid-19 [178]; it has been used already in several small case-series [179-181] and retrospective cohort study in Covid-19 patients [182]. Cavalli et al. 2020 [182] presented results of the retrospective cohort study in patients with COVID-19 and moderate-to-severe ARDS, managed with non-invasive ventilation outside of the ICU, and treated with high-dose anakinra, 5 mg/kg twice daily, infused over 1 h (n=29), in comparison with standard treatment group (n=16, 200 mg hydroxychloroquine twice a day orally and 400 mg lopinavir with 100 mg ritonavir twice a day orally). Treatment with anakinra was safe and associated with clinical improvement in 72% of patients. At 21 days, survival was statistically significant different in favour of anakinra: 90% in the high-dose anakinra group vs 56% in the standard treatment group (p=0.009). Mechanical ventilation-free survival did not statistically significant differ between treatment groups: 72% in the anakinra group versus 50% in the standard treatment group (p=0.15). This was a part of the COVID-19 Biobank study, which is registered with ClinicalTrials.gov, NCT04318366.

The US COVID-19 Treatment Guidelines Panel stated that there are insufficient data to recommend either for or against Interleukin-1 inhibitors (e.g., anakinra) therapy in patients with COVID-19 disease [58].

Completed, withdrawn, suspended or terminated studies

As of August 14, 2020, no completed, withdrawn, suspended or terminated interventional studies were found on Anakinra in ClinicalTrials.gov and EUdRACT registers.

Results of publications

**Immunsuppressivum,
humaner Interleukin-1
Rezeptorantagonist**

**EMA-Zulassung für
Rheumatoide Arthritis seit
2002**

nicht jedoch für Covid-19

**mehrere laufende
Studien,
veröffentlicht nur kleine
Fallserien und
Kohortenstudien**

**Cavalli (Italien)
29 Pts.
Mortalität besser
künstliche Beatmungs-
freie Tage aber gleich**

**Empfehlung des US
COVID-19 Treatment
Guidelines Panel:
insuffiziente Datenlage**

keine weiteren Studien

Until now no scientific publication on RCTs of Anakinra (Kineret®) in Covid-19 patients could be identified (status: 14/08/2020).

**keine Publikation
eines RCTs**

One prospective cohort study, Ana-COVID study, with 52 consecutive severe Covid-19 patients who received subcutaneous anakinra at dose of 100 mg twice daily for 72 h, followed by 100 mg daily for 7 days, in addition to the standard treatment and supportive care (with a historical comparison group, n=44 patients, who received standard care) published by Huet et al. 2020 [183], found statistically significant difference in favour of anakinra for need of invasive mechanical ventilation in the ICU and mortality. Admission to the ICU for mechanical ventilation or death occurred in 13 (25%) patients in the anakinra group vs 32 (73%) patients in the historical group (hazard ratio [HR] 0.22 [95% CI 0.11–0.41; p<0.0001). The treatment effect of anakinra remained significant in the multivariate analysis (HR 0.22 [95% CI 0.10–0.49]; p=0.0002). Similar results were observed for death alone (HR 0.30 [95% CI 0.12–0.71; p=0.0063) and need for invasive mechanical ventilation alone (0.22 [0.09–0.56]; p=0.0015). Among the 39 patients in the anakinra group who were alive and did not require mechanical ventilation, the mean need for oxygen decreased from a median of 7 L/min (IQR 6–9) at day 0 to a median of 2 L/min (0–4) at day 7 (two missing values); the median difference was –4 L/min (IQR 0–4; p<0.0001, signed-rank test). An increase in liver aminotransferases occurred in seven (13%) patients in the anakinra group and four (9%) patients in the historical group. Ten (19%) patients in the anakinra group and five (11%) in the historical group developed a thromboembolic event during the hospital stay. Among the anakinra group, seven (13%) had a pulmonary embolism, three (6%) had deep vein thrombosis of the lower limbs, and one (2%) had arterial thrombosis. Authors concluded that in severe forms of COVID-19-related pneumonia requiring oxygen therapy, a 10-day treatment with subcutaneous anakinra was associated with the reduction of both need of mechanical ventilation and mortality, as compared with a historical group with similar characteristics.

**1 prospektive
Kohortenstudie,
52 Pts.**

**geringere Mortalität,
ICU-Aufnahmen,
künstliche Beatmung**

3.19 Colchicine

About the drug under consideration

Colchicine is an alkaloid isolated from the autumn crocus, Colchicum autumnale, with anti-gout and anti-inflammatory activities. In July 2009, the FDA approved colchicine tablets for the treatment of acute gout flares, and Familial Mediterranean fever, Colcrys (a branded colchicine) in the US. Colchicine is available throughout the world in a generic form [184].

**toxisches Alkaloid
wirkt als Zellgift
(Mitosehemmung)**

According the FDA label document (revised 2020) Colcrys (colchicine, USP, tablets for oral use) is indicated for prophylaxis and treatment of gout flares in adults and for Familial Mediterranean fever (FMF) in adults and children 4 years or older. The mechanism by which COLCRYS (Takeda Pharmaceuticals USA) exerts its beneficial effect in patients with FMF has not been fully elucidated; however, evidence suggests that colchicine may interfere with the intracellular assembly of the inflammasome complex present in neutrophils and monocytes that mediates activation of interleukin-1 β . Additionally, colchicine disrupts

generisch

cytoskeletal functions through inhibition of β -tubulin polymerization into microtubules and consequently prevents the activation, degranulation and migration of neutrophils thought to mediate some gout symptoms [185].

Completed, withdrawn, suspended or terminated studies

As of August 14, 2020, no completed, withdrawn, suspended or terminated interventional studies were found on colchicine in ClinicalTrials.gov and EUdraCT registers.

keine Studien

Results of publications

Deftereos et al. 2020 [186] reported results from open-label, randomized controlled trial (NCT04326790) on 105 patients hospitalized with COVID-19 in 16 tertiary hospitals in Greece (randomization in a 1:1 allocation to either standard medical treatment or colchicine with standard medical treatment). Patient recruitment started on April 3, 2020, and was terminated on April 27, 2020, because of slow enrollment as a result of the rapid flattening of the curve of COVID-19 cases in Greece. Primary end points were (1) maximum high-sensitivity cardiac troponin level; (2) time for C-reactive protein to reach more than 3 times the upper reference limit; and (3) time to deterioration by 2 points on a 7-grade clinical status scale, ranging from able to resume normal activities to death. Secondary end points were (1) the percentage of participants requiring mechanical ventilation, (2) all-cause mortality, and (3) number, type, severity, and seriousness of adverse events. The clinical primary end point rate was 14.0% in the control group (7 of 50 patients) and 1.8% in the colchicine group (1 of 55 patients) (odds ratio, 0.11; 95% CI, 0.01-0.96; $P = 0.02$). Mean (SD) event-free survival time was 18.6 (0.83) days in the control group vs 20.7 (0.31) in the colchicine group (log rank $P = 0.03$). Adverse events were similar in the 2 groups, except for diarrhea, which was more frequent with colchicine group than the control group (25 patients [45.5%] vs 9 patients [18.0%]; $P = 0.003$). Authors concluded that, participants who received colchicine had statistically significant improved time to clinical deterioration compared with a control group that did not receive colchicine. However, the observed difference was based on a narrow margin of clinical significance; therefore, these observations should be considered hypothesis generating. There were no differences in hs cTn or C-reactive protein levels between the groups.

**1 publizierter RCT
(Griechenland):
105 Pts.**

**klinisch gering-relevanter
Unterschied bei
Verbesserung der
Erkrankung**

**viele Surrogatendpunkte
niedrige Evidenz**

Summary of Finding table related to colchicine compared to standard care for moderate/severe COVID-19 patients is presented in Table 3.19-1 below.

Table 3.19-1: Summary of findings table on colchicine compared to standard care (1 RCT: Deftereos) - https://covid-nma.com/living_data/index.php

Summary of findings:						
Colchicine compared to Standard Care for Moderate/Severe COVID-19						
Patient or population: Moderate/Severe COVID-19						
Setting: Worldwide						
Intervention: Colchicine						
Comparison: Standard Care						
Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Standard Care	Risk with Colchicine				
Incidence viral negative conversion D7 - not reported	-	-	-	-	-	outcome not yet measured or reported
Clinical improvement - not reported	-	-	-	-	-	outcome not yet measured or reported
Incidence of WHO progression score (level 6 or above D14-D28)	130 per 1.000	18 per 1.000 (3 to 140)	RR 0.14 (0.02 to 1.08)	110 (1 RCT)	⊕○○○ VERY LOW ^{a,b,c}	
Incidence of WHO progression score (level 7 or above D14-D28)	111 per 1.000	18 per 1.000 (2 to 143)	RR 0.16 (0.02 to 1.29)	110 (1 RCT)	⊕○○○ VERY LOW ^{b,c}	
All-cause mortality D14-D28	74 per 1.000	18 per 1.000 (2 to 155)	RR 0.24 (0.03 to 2.09)	110 (RCTs)	⊕○○○ VERY LOW ^{b,c}	
Adverse events - not reported	-	-	-	-	-	outcome not yet measured or reported
Serious adverse events D14-D28				105 (1 RCT)	⊕○○○ VERY LOW ^{a,d,e}	zero events in both groups

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

- a. Risk of bias downgraded by 1 level: some concerns regarding deviation from intended intervention and outcome measurement
- b. Indirectness downgraded by 1 level: single study from a single country, therefore results in this population might not be generalizable to other settings
- c. Imprecision downgraded by 2 levels: due to very wide confidence interval consistent with the possibility for benefit and the possibility for harm and low number of participants
- d. We presume that the adverse event rates, and the corresponding relative risks, is similar across diverse settings; therefore not downgraded for indirectness
- e. Imprecision downgraded by 2 levels: no events in both groups

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