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Austrian Institute for
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GmbH

Covid-19

HSS/ Horizon Scanning

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June 12, 2020	Addition chapters on Solnatide (chapter 3.14) and Umifenovir (chapter 3.15)
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June 13, 2020	Update Vaccine (chapter 2)
June 08,2020	Update Remdesivir (chapter 3.1)
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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 ystem (HSS) for medicines and vaccines. The establishment of a HSS/ Horizon Scanning System for Covid-19 interventions has the intentions of

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

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

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,

mehrstufige Methodik

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.

Bestandsaufnahme
selektive Suche
Vignetten
Monitoring

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

internationale/ europ. Zusammenarbeit

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

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

V1: Bestandsaufnahme + Vignetten
V2, V3, ...: monatliches Monitoring

Table 1.2-1: International Sources

Primary sources	Link
WHO Drugs: Vaccines:	https://www.who.int/teams/blueprint/covid-19 https://www.who.int/blueprint/priority-diseases/key-action/Table_of_therapeutics_Appendix_17022020.pdf?ua=1 https://www.who.int/who-documents-detail/covid-19-candidate-treatments https://www.who.int/who-documents-detail/draft-landscape-of-covid-19-candidate-vaccines
Danish Medicine Agency Drugs: Vaccines:	https://laegemiddelstyrelsen.dk/da/nyheder/temaer/ny-coronavirus-covid-19/~/media/5B83D25935DF43A38FF823E24604AC36.ashx https://laegemiddelstyrelsen.dk/da/nyheder/temaer/ny-coronavirus-covid-19/~/media/3A4B7F16D0924DD8BD157BBE17BFED49.ashx
Pang et al. 2020 [1]	https://www.mdpi.com/2077-0383/9/3/623 Table 5+6,

Drugs: Vaccines:	Table 3+4
SPS HS-report (UK)	unpublished
Secondary sources	
VfA/ Verband Forschender Arzneimittelhersteller Drugs: Vaccines:	https://www.vfa.de/de/arzneimittel-forschung/woran-wir-forschen/therapeutische-medikamente-gegen-die-coronavirusinfektion-covid-19 https://www.vfa.de/de/arzneimittel-forschung/woran-wir-forschen/impfstoffe-zum-schutz-vor-coronavirus-2019-ncov
EMA/ Europen Medicines Agency Medicines:	https://www.ema.europa.eu/ https://www.ema.europa.eu/en/medicines/medicines-under-evaluation
FDA/US Food and Drug Administration	https://www.fda.gov/emergency-preparedness-and-response/counterterrorism-and-emerging-threats/coronavirus-disease-2019-covid-19
Trial Registries	
US National Library of Medicine European Union Drug Regulating Authorities Clinical Trials Database WHO International Clinical Trials Registry Platform TrialsTracker	https://clinicaltrials.gov/ https://eudract.ema.europa.eu/ https://www.who.int/ictrp/en/ http://Covid-19.trialstracker.net/
Up-to-date information on clinical trials and literature searching resources relating to COVID-19	
Cochrane COVID-19 Study Register 21/04.20	https://covid-19.cochrane.org/
Living mapping of research and a living systematic review	https://covid-nma.com/ https://covid-nma.com/dataviz/
Dynamic meta-analysis of evidences about drug efficacy and safety for COVID19 - meta/Evidence – COVID-19	http://metaevidence.org/COVID19.aspx
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/

Several organisations and international teams of researchers are providing up-to-date information through living listing of interventional clinical trials

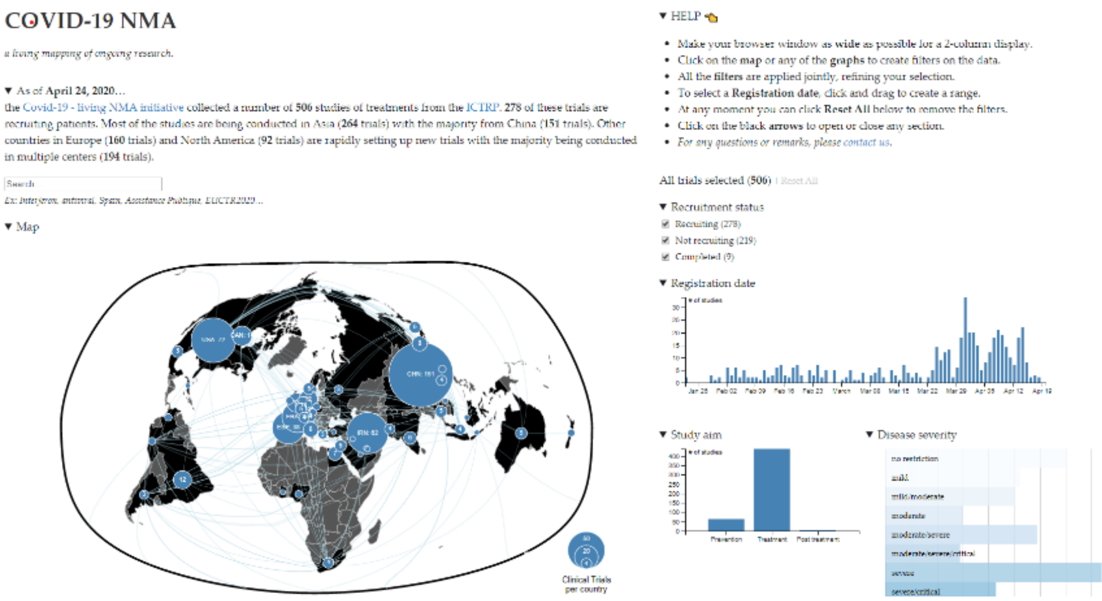
"lebende" Dokumente mit up-to-date Informationen

in Covid-19/2019-nCoV and literature resources (Table 1.2 2) [2-4]. A short description of two of such databases is presented below.

Kartierung von aufenden RCTs

Boutron et al., 2020 [2] are performing a living mapping of ongoing randomized trials, followed by living systematic reviews with pairwise meta-analyses and when possible, network meta-analyses focusing on two main questions: the effectiveness of preventive interventions for COVID-19 and the effectiveness of treatment interventions for COVID-19 (Figure 1.2-1).

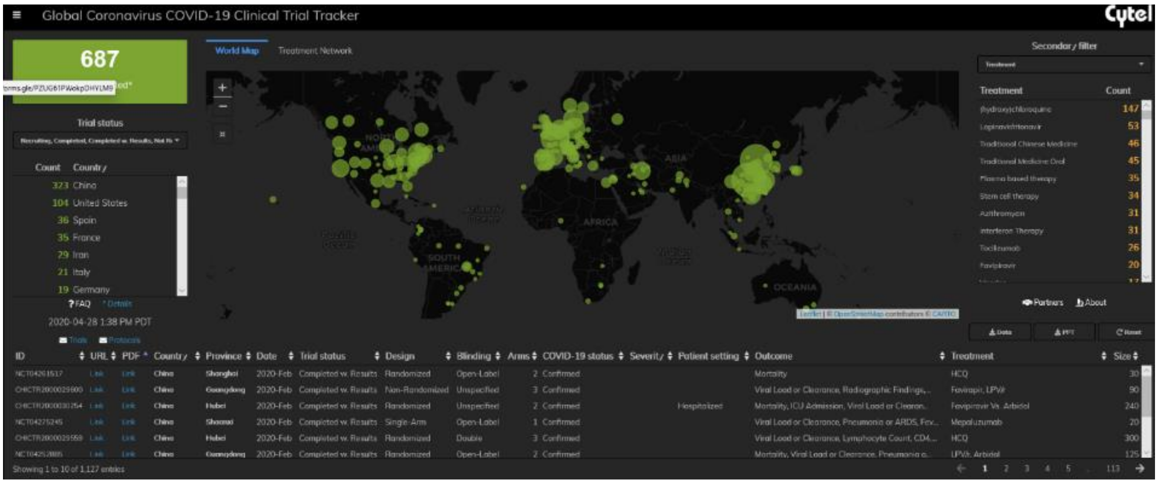
Figure 1.2-1: A living mapping of ongoing randomized trials, living systematic reviews with pairwise meta-analyses and network meta-analyses



COVID-19: Clinical Trial Tracker

Thorlund et al., 2020 [3] 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 [4].

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

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

Vignetten zu Produkte, in "fortgeschrittenen" Stadien oder

häufig diskutiert

2 Results: Vaccines

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

Company/Institution/Registry number	Technology		Stage/Sponsor	Source
	Platform	Type of candidate vaccine		
Moderna Therapeutics—US National Institute of Allergy **NCT04283461** **NCT04405076**	RNA	LNP-encapsulated mRNA vaccine encoding S protein	**Phase 1** **Phase 2** National Institute of Allergy and Infectious Diseases (NIAID)	[5-9]
CanSino Biological Inc. and Beijing Institute of Biotechnology **ChiCTR2000030906/ NCT04313127**	Non-Replicating Viral Vector	adenovirus Type 5 Vector that expresses S protein	**Phase 1** CanSino Biologics Inc.	[5-10]
CanSino Biological Inc. and Beijing Institute of Biotechnology **ChiCTR2000031781/ NCT04398147**	Non-Replicating Viral Vector	adenovirus Type 5 Vector that expresses S protein	**Phase 2** Jiangsu Provincial Center for Disease Control and Prevention/ Institute of Biotechnology, Academy of Military Medical Sciences, PLA of China/ CanSino Biologics Inc.	[5-7, 9, 10]
Inovio Pharmaceuticals **NCT04336410**	DNA	DNA plasmid vaccine encoding S protein delivered by electroporation	**Phase 1** Inovio Pharmaceuticals	[5-9]
Novavax **NCT04368988**	Protein Subunit	VLP-recombinant protein nanoparticle vaccine + Matrix M	**Phase 1/2** Novavax	[5-8]
University of Queensland/GSK/Dynavax	Protein Subunit	Molecular clamp stabilized Spike protein	Preclinical Funding by CEPI	[1, 2]
CureVac	RNA	mRNA	Preclinical; Phase 1 study will start in June/July 2020	[1, 2]
University of Oxford **NCT04324606/** **EudraCT 2020-001072-15** **NCT04400838/EUdraCT 2020-001228-32**	Non-Replicating Viral Vector	ChAdOx1	**Phase 1/2** **Phase 2b/3** University of Oxford/AstraZeneca	[5-8] [9, 11]
BioNTech/Fosun Pharma/Pfizer **EudraCT 2020-001038-36/**	RNA	mRNA	**Phase 1/2** BioNTech RNA Pharmaceuticals GmbH	[5-8] [9, 11]

NCT04368728 **NCT04380701**				
Shenzhen Geno-Immune Medical Institute **NCT04299724**	Synthetic mini-gene -based product	Pathogen-specific aAPC	**Phase 1** Shenzhen Geno-Immune Medical Institute	[8]
Shenzhen Geno-Immune Medical Institute **NCT04276896**	Synthetic mini-gene -based product	LV-SMENP-DC	**Phase 1/2** Shenzhen Geno-Immune Medical Institute	[8]
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	[5-8]
Symvivo Corporation **NCT04334980**	DNA bacTRL platform	bacTRL-Spike	**Phase 1** Symvivo Corporation	[5-8]
Sinovac **NCT04352608** **NCT04383574**	Inactivated	inactivated + alum	**Phase 1/2** Sinovac Research and Development Co., Ltd.	[5-9]
Wuhan Institute of Biological Products/Sinopharm **ChiCTR2000031809**	Inactivated	Vero cells derived (cell culture-derived inactivated vaccines)	**Phase 1/2** Wuhan Institute of Biological Products/Sinopharm	[5-7, 9, 10]
Beijing Institute of Biological Products/Sinopharm **ChiCTR2000032459**	Inactivated	Inactivated	**Phase 1/2** Beijing Institute of Biological Products/Sinopharm	[9]
Institute of Medical Biology, Chinese Academy of Medical Sciences **NCT04412538**	Inactivated	Inactivated	**Phase 1** Institute of Medical Biology, Chinese Academy of Medical Sciences	[9] [5]
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	[5]
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.	[5]

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

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 [14]. Safety reviews are in place before dose escalation [14]. The primary endpoint of the study is frequency and grade of adverse reactions at 7/28/394 days post injection [12]. 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
August 2021

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

keine veröffentlichten klinischen Studien

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 [15-17]. The platform (non-replicating viral vector) of AD5-nCoV was originally used for an Ebola vaccine (AD5-EBOV) [17, 18].

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 [19]. New RCT, **phase 2**, started also (ChiCTR2000031781/NCT04398147). This randomised, double-blinded, placebo-controlled, parallel, three groups trial

Phase 1:
108 gesunde Erwachsene
Dezember 2020

Phase 2:
Jänner 2021

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 [9, 10]. This RCT will be conducted from 2020-04-12 to 2021-01-31.

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) [20]. 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 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.

1 veröffentlichte klinische Studie:

108 Studienteil-nehmer*innen erhalten unterschiedliche 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 [18, 21]. The company's DNA platform was previously utilised for a MERS-CoV vaccine (INO-4700) tested in a phase I trial [22].

INO-4800

Estimated timeline for approval

According to press releases from the manufacturer [22, 23], 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 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 [5-9]. This RCT will be conducted from April 2020 to April 2021. Estimated Primary Completion Date is April 2021.

Phase 1:
40 gesunde Erwachsene

April 2021

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

keine veröffentlichten klinischen Studien

2.4 Novavax

About the vaccine

The Novavax COVID-19 vaccine being developed by Novavax and co-sponsored by CEPI [24] is a recombinant protein nanoparticle technology platform that is to generate antigens derived from the coronavirus spike (S) protein [25]. 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 [26, 27].

CEPI
Matrix-M™

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 [24]. Novavax has previous experience with both MERS and SARS [26]. The **phase 1**, randomized, placebo-controled, triple-blind, parallel assignment clinical trial (NCT04368988) in 131 healthy adults aims to evaluate the immunogenicity and safety of SARS-CoV-2 rS nanoparticle vaccine with or without Matrix-M adjuvant in healthy participants ≥ 18 to 59 years of age. The study will be conducted in 2 parts. In Part 1, at least 1 and up to two SARS-CoV-2 rS constructs will be evaluated in up to 2 cohorts, which may be enrolled in parallel. An interim analysis of Part 1 safety and immunogenicity data will be performed prior to an optional expansion to Part 2. The primary endpoints of the trial are as following: subjects with solicited AEs - Phase 1; safety Laboratory Values (serum chemistry, hematology) - Phase 1 and serum IgG antibody levels specific for the SARS-CoV-2 rS protein antigen(s) - Phase 1. Secondary endpoints are not provided [5-8]. This RCT will be conducted from May 15, 2020 to July 31, 2021. Estimated Primary Completion Date is December 31, 2020.

Phase 1:
131 gesunde Erwachsene

Juli 2021

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

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 [13, 18]. 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

DynaVax & GSK

[1] Both DynaVax and GSK will provide adjuvants.

system may induce a response, by recognising them as the correct antigen on the surface of the virus, more easily [28].

Initially, this technology was designed to be a platform for generating vaccines against different viruses such as influenza, Ebola, and the MERS coronavirus [29].

Estimated timeline for approval

At this moment in time, the vaccine candidate developed by the University of Queensland is still in the preclinical phase. According to press releases, human clinical trials may start in June 2020 [30].

präklinische Phase
Beginn klinische Studie: Juni 2020

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

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) [13]. 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 [31]. 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 [32].

mRNA

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 [33]. 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.

präklinische Phase

Estimated timeline for approval

During a press conference call on March 17, 2020, CureVac explained that they are currently encoding 1 specific protein, which is present on the surface of the new coronavirus and which is sufficient to activiate the immune system. They are currently waiting for the animal data and already started with the production of 2 vaccine candidates for use in humans [34]. Those suitable vaccine canditates were selected from several constructs. The selection criteria applied were based on quality and biological activity. CureVac is also collaborating with the German Paul Ehrlich Institute (PEI) and European health authorities. The start of the clinical trials is planned for early summer 2020 and it was reported that two primary study centers have already been determined [35].

Collab mit PEI
Beginn klinische Studie: Sommer 2020

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

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 [15, 36].

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 [36].

Estimated timeline for approval

Currently, the first clinical **phase 1/2** trial in 510 healthy adults is ongoing (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 [37].

Phase ½:
510 gesunde Erwachsene

Mai 2021

Phase 2b/3 study (EUdraCT 2020-001228-32/NCT04400838) is currently 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 :
Am Beginn

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

keine veröffentlichten klinischen Studien

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 [13]. In 2018, Pfizer and BioNTech collaborated on mRNA-based vaccines for the prevention of influenza and their partnership applies outside of China [38]. BioNTech's partnership with Fosun Pharma applies for China only [38, 39].

BNT-162

Estimated timeline for approval

Currently, BNT-162 enters clinical testing by the end of April 2020 [40] and R&D is supposed to be carried out both in the US as well as in Germany [38]. This is a **phase 1/2**, randomized, placebo-controlled, triple-blind, dose-finding, and vaccine candidate-selection study in healthy adults (NCT04368728/EudraCT 2020-001038-36). The study will evaluate the safety, tolerability, immunogenicity, and potential efficacy of up to 4 different SARS-CoV-2 RNA vaccine candidates against COVID-19: as a 2-dose or single-dose schedule; at up to 3 different dose levels; in 3 age groups (18 to 55 years of age, 65 to 85 years of age, and 18 to 85 years of age. The study consists of 3 stages: Stage 1: to identify preferred vaccine candidate(s), dose level(s), number of doses, and schedule of administration (with the first 15 participants at each dose level of each vaccine candidate comprising a sentinel cohort); Stage 2: an expanded-cohort stage; and Stage 3; a final candidate/dose large-scale stage. Estimated Primary Completion Date and Study Completion Date is January 27, 2023.

Phase 1/2 mehrstufiges Studiendesign

Jänner 2023

Study NCT04380701 is located in Germany.

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

keine veröffentlichten klinischen Studien

2.9 New vaccines entered in clinical investigation in healthy volunteers

As at 05 May 2020, **6 new vaccines** are registered in phase 1, phase 1/2 and phase 2, by Shenzhen Geno-Immune Medical Institute (NCT04299724 and NCT04276896); Insitute of Biotechnology, Academy of Military Medical Sciences, PLA of China (NCT04341389); Symvivo Corporation (NCT04334980); Sinovac (NCT04352608) and Wuhan Institute of Biological Products/Sinopharm (ChiCTR2000031809) (Table 2-1). NCT04299724 is phase 1 study related to pathogen-specific aAPC (aAPCs modified with lentiviral vector expressing synthetic minigene based on domains of selected viral proteins) and NCT04276896 is phase 1/2 study related to LV-SMENP-DC vaccine (DCs modified with lentiviral vector expressing synthetic minigene based on domains of selected viral proteins; administered with antigen-specific CTLs). NCT04341389 is phase 2 trial related to adenovirus Type 5 Vector expressing S protein. NCT04334980 is phase 1 study, the first-in-human study of bacTRL-Spike, and the first-in-human use of orally delivered bacTRL. Two clinical trials in phase 1/2 are related to inactivated vaccine: NCT04352608 is related to inactivated SARS-CoV-2 virus and ChiCTR2000031809 to Vero cells derived (cell culture-derived inactivated) vaccine [5-10].

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

As at 13 June 2020, **four new vaccines** 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) [9]; 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-

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

australian-subsidiary/, 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).

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 [41]. The same is true for US RCT (NCT04348370) [8]. The same is planned in Egypt (NCT04350931) and in Denmark (NCT04373291) (RCTs, not yet recruiting healthy volunteers) [8].

mehrere klinische Studien mit BCG Vazzinen in Phase 3 oder geplant

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.

Impfkandidaten-Infrastruktur und Monitoring Projekt

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 (GS-5734)	Antiviral agent	NCT04252664 - **Suspended** NCT04257656 - **Terminated**
Lopinavir + Ritonavir (Kaletra®)	Antiviral agent	NCT04276688 – **Completed** NCT04307693 - **Terminated**
Favipiravir (Avigan, T-705)	Antiviral agent	ChiCTR2000030254 - **Completed**
Darunavir (Prezista®)	Antiviral agent	No studies found
Chloroquine Phosphate (Resochin®)	Antiviral cell-entry inhibitor	NCT04420247 - **Suspended** NCT04341727 - **Suspended**
Hydroxychloroquine (Plaquenil®)	Antiviral cell-entry inhibitor	ChiCTR2000029868 - **Completed** NCT04261517 - **Completed** NCT04420247- **Suspended** NCT04341727- **Suspended** NCT04334967 - **Suspended** NCT04333654 - **Suspended** NCT04347512 - **Withdrawn**
Camostat Mesilate (Foipan®)	Antiviral cell-entry inhibitor	No studies found
APN01 (rhACE2)	Antiviral cell-entry inhibitor	NCT04287686 - **Withdrawn**
Tocilizumab (RoActemra®)	Monoclonal antibody	No studies found
Sarilumab (Kevzara)	Monoclonal antibody	NCT04341870 - **Suspended**
Interferon beta 1a (SNG001) **and 1b**	Interferon	NCT04276688 Interferon beta 1b – **Completed** NCT04343768 - **Completed**
Convalescent Plasma (interventional studies n =43, RCTs=26)	Convalescent Plasma	NCT04325672 - **Withdrawn** NCT04346446 - **Completed**
Solnatide	**Solnatide**	No studies found
Umifenovir	**Umifenovir**	No studies found

[2] Ongoing studies can be found in V1 and V2.

3.1 Remdesivir/GS-5734

About the drug under consideration

Remdesivir (RDV)/GS-5734 constitutes another potential therapeutic treatment of the 2019 novel coronavirus shortly called COVID-19 or 2019-nCoV. RDV has a broad spectrum of antiviral activities against RNA viruses. RDV is a nucleotide analogue inhibitor of RNA-dependent RNA polymerases (RdRps). Originally it was utilised against the severe acute respiratory syndrome-CoV (SARS-COV) and the Middle East respiratory syndrome (MERS-COV). Research has shown that RDV could effectively inhibit MERS-COV replication in vitro, and showed efficacy against SARS-COV in animal trials. Furthermore, phase 3 clinical trials of RVD examining pharmacokinetics and safety had been completed for the treatment of Ebola [42].

antivirales Medikament virostatisch (virushemmend) : RDV

MERS/ SARS erprobt

In 2020 RDV has been utilised in hundreds of COVID-19 patients in the US and Europe outside of a clinical trial in what is called compassionate use [43]. One case study published in the New England Journal of Medicine (NEJM) reports the use of RDV in a patient with COVID-19. In this case report, the treatment with intravenous RVD was initiated on the evening of day 7, without observation of apparent adverse events in association with the infusion. On the 8th day after hospitalisation (the 12th day after onset) the clinical symptoms improved on the 8th day after hospitalisation [44].

Covid-19 in "compassionate use"

intravenöse Verabreichung

The therapy with RVD is not approved by the **European Medicine Agency (EMA)** for COVID-19, but was recommended on compassionate use for on the 3rd of April 2020 [45]. On May 11, 2020 EMA's human medicines committee (CHMP) has recommended **expanding the compassionate use** of the investigational medicine remdesivir. In addition to patients undergoing invasive mechanical ventilation, the compassionate use recommendations now cover the treatment of hospitalised patients requiring supplemental oxygen, non-invasive ventilation, high-flow oxygen devices or ECMO (extracorporeal membrane oxygenation). More information is available in the summary on compassionate use and the conditions of use of remdesivir [46]. Furthermore, it has orphan designation for the treatment of Ebola virus disease since February 2016.

EMA Empfehlung "compassionate use" (April)

„expanding the compassionate use" (Mai)

On April 30, 2020 EMA's human medicines committee (CHMP) has started a 'rolling review' of data on the use of the investigational antiviral medicine remdesivir for the treatment of coronavirus disease (COVID-19), based on preliminary results from the ACTT-1 study, which suggest a beneficial effect of remdesivir in the treatment of hospitalised patients with mild-to-moderate or severe COVID-19. As stated, EMA has not yet evaluated the full study and it is too early to draw any conclusions regarding the benefit-risk balance of the medicine. A rolling review is one of the regulatory tools available to the Agency to speed up the assessment of a promising investigational medicine during a public health emergency, such as the ongoing pandemic. The CHMP will evaluate all data on remdesivir, including evidence from a recently published study from China and other clinical trials and conclude on the medicine's benefits and risks as soon as possible [47].

"rolling review" (Zulassungsbeginn) basierend auf ACTT-1 Studie

weitere Daten werden evaluiert für Zulassung

This "rolling review" of data on the use of remdesevir to treat COVID-19 is concluded on 15 May 2020 [48]. According to the press release (08 June 2020), EMA received an application for conditional marketing authorisation (CMA) of the remdesivir for the treatment of COVID-19 and has formally started its evaluation. Opinion could be issued within the weeks, because some data are already assessed during the roling review (data on quality and manufacturing, preliminary data from several clinical studies and supporting data from compassionate use programmes; in parallel safety committee (PRAC) completed the initial assessment of the preliminary risk management planand, and EMA's committee for medicines for children issued opinion on the company's paediatric investigation plan) [49].

15. Mai: EMA erhält Zulassungsantrag von Gilead für „conditional marketing authorisation (CMA)"

= formaler Beginn des Zulassungsverfahrens

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 [50]. 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 [51, 52].

FDA: "expanded access program" (März)

Emergency Use Authorization (EUA) (Mai)

basierend auf 2 Studien:

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

Completed, withdrawn, suspended or terminated studies

The search in two clinical trial registers (ClinicalTrials.gov and EUdraCT) on 08/06/2020 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 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/beendigt

Results of publications

At 6th of May 2020, Wang Y et al. [53] 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.

Ergebnisse der Studien:

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

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

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]).

primärer Endpunkt: klinische Verbesserung innerhalb von 28 Tagen:

kein stat. signifikanter Unterschied

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).

keine Hinweise auf Reduktion der Viruslast

AE 66%
frühzeitige Beendigung wegen AE 12%

At May 22, 2020 Beigel et al. [54] 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 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).

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.)

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).

kein stat. signifikant Unterschied bei Mortalität

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).

kein Unterschied bei SAE

The Living Systematic Review with Meta-Analysis (MA), related to these two RCTs, with the Summary of finding 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).

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** [53]*
Country	China
Sponsor/Funding	Chinese Academy of Medical Sciences Emergency Project of COVID-19, National Key Research and Development Program of China, the Beijing Science and Technology Project
Study design	Randomised, double-blind, placebo-controlled, multicentre trial **NCT04257656**
Number of pts	237 (RDV n=158, Placebo n=79)
Intervention/Product	Remdesivir (200 mg on day 1 followed by 100 mg on days 2–10 in single daily infusions)
Comparator	Placebo (same volume of placebo infusions for a total of 10 days)
Inclusion criteria	Men and non-pregnant women with COVID-19 who were aged at least 18 years and were RT-PCR positive for SARS-CoV-2, had pneumonia confirmed by chest imaging, had oxygen saturation of 94% or lower on room air or a ratio of arterial oxygen partial pressure to fractional inspired oxygen of 300 mm Hg or less, and were within 12 days of symptom onset
Exclusion criteria	Pregnancy or breast feeding; hepatic cirrhosis; alanine aminotransferase or aspartate aminotransferase more than five times the upper limit of normal; known severe renal impairment (estimated glomerular filtration rate <30 mL/min per 1·73 m^2) or receipt of continuous renal replacement therapy, haemodialysis, or peritoneal dialysis; possibility of transfer to a non-study hospital within 72 h; and enrolment into an investigational treatment study for COVID-19 in the 30 days before screening
Pts pretreated + previous treatment	Use of other treatments, including lopinavir–ritonavir, was permitted
Mean age of patients, yrs (SD)	RDV group (66.0); Placebo (64.0)
Sex % male (% female)	RDV group (56.0 m vs 44 f); Placebo (65.0 m vs 35 f)
Follow-up (days)	Up to 28 days
Clinical status	Most patients were in category 3 of the six-point ordinal scale of clinical status at baseline
Loss to follow-up, n (%)	One patient in the placebo group withdrew their previously written informed consent after randomisation (158 and 78 patients were included in the ITT population)
Efficacy outcomes	
Overall survival (OS), n (%)	28-day mortality: 22 [14%] died in the remdesivir group vs 10 (13%) in the placebo group; difference 1·1% [95% CI –8·1 to 10·3]
Time to clinical improvement	RDV group: median 21·0 days [IQR 13·0–28·0] vs 23·0 days [15·0–28·0] in placebo group; HR 1·23 [95% CI 0·87–1·75]
Other efficacy outcomes	No statisticaly significant differences were observed between the two groups in length of oxygen support, hospital length of stay, days from randomisation to discharge, days from randomisation to death and distribution of six-category scale at day 7, day 14, and day 28, and viral load decrease over time
Safety outcomes	
Adverse events (AEs)	RDV group 102 (66%) of 155 patients vs 50 (64%) of 78 in the control group
Serious adverse events (SAEs)	28 (18%) in the remdesivir group vs 20 (26%) in the control group
Discontinuation of study drug due to AEs or SAEs	18 [12%] in the remdesivir group *vs* four [5%] in the placebo group), among whom seven (5%) were due to respiratory failure or acute respiratory distress syndrome in the remdesivir group

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

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

Author, year [Reference]	****Beigel et al. 2020** [54]
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)
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) ≤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 [13·0–19·0] in placebo group; Recovery Rate Ratio 1·32 [95% CI 1·12–1·55]

Author, year [Reference]	**Beigel et al. 2020** [54]
Ordinal score at day 15 (±2 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:** Wordwide **Intervention:** Remdesivir **Comparison:** Placebo						
Outcomes	**Anticipated absolute effects* (95% CI)**		**Relative effect (95% CI)**	**№ 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: I^2=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. [55] 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

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

Author, year [Reference]	**Goldman et al. 2020** [55]
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)
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	

Author, year [Reference]	**Goldman et al. 2020** [55]
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 statisticaly 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 [15, 56].

Kombinationstherapie für HIV zugelassen

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.

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 it results are written in part 3.13 (Combination therapy), since this is triple combination of interferon beta-1b, lopinavir–ritonavir, and ribavirin, compared with lopinavir–ritonavir alone.

1 abgeschlossener RCT (China)

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.

1 abgebrochener RCT (Südkorea) wegen Mangel an Pts

Results of publications

So far (status: June 08, 2020) only two publication [57] [58] 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-. Details related to RCT number NCT04276688 are written in Section 3.13, related to Combination therapy.

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) [58] 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 occured in the control group.

Yueping (China):

mild/moderate Erkrankung:

keine Unterschiede zwischen den Gruppen

AE häufiger in Interventionsgruppe

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.

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

Author, year [Reference]	**Cao et al. 2020 [57]**
Country	China
Sponsor	Major Projects of National Science and Technology on New Drug Creation and Development, the Chinese Academy of Medical Sciences (CAMS) Emergency Project of Covid-19 and a National Science Grant for Distinguished Young Scholars
Study design	Open-label, individually randomised, controlled trial
Number of pts	199 (99 vs. 100)
Intervention/Product	Lopinavir (400mg) + ritonavir (100mg) twice daily + standard care for 14 days
Comparator	Standard care (as necessary): supplemental oxygen, noninvasive and invasive ventilation, antibiotic agents, vasopressor support, renal-replacement therapy, and extracorporeal membrane oxygenation (ECMO)
Inclusion criteria	- Male and nonpregnant woman ≥18 years of age - Positive reverse-transcriptase–polymerase chain-reaction (RT-PCR) assay (Shanghai ZJ Bio-Tec or Sansre Biotech) for SARS-CoV-2 S-CoV-2 - Pneumonia confirmed by chest imaging - Oxygen saturation (Sao_2) of 94% or less while breathing ambient air or a ratio of the partial pressure of oxygen (Pao_2) to the fraction of inspired oxygen (Fio_2) (Pao_2:Fio_2) at or below 300 mg Hg
Exclusion criteria	- Physician decision that involvement in the trial was not in the patient's best interest - Presence of any condition that would not allow the protocol to be followed safely - Known allergy or hypersensitivity to lopinavi/ ritonavir - Known severe liver disease - Use of medications that are contra indicated with lopinavir/ ritonavir and that could not b replaced or stopped during the trial period - Pregnancy or breast-feeding - Known HIV infection, because of concerns about the development of resistance to lopinavir/ ritonavir if used without combining with other antiretrovirals
Pts pretreated +previous treatment	NR
Median age of patients, yrs (range)	Total: 58.0 (49.0-68.0): IG: 58.0 (50.0-68.0) CG: 58.0 (48.0-68.0)
Sex % male (% female)	Total: 60.3 (39.7): IG: 61.6 (38.4) CG: 59.0 (61.0)
Follow-up (days)	7, 14, 28
Loss to follow-up, n (%)	5 vs. 0 - 3 died within 24 hours after randomisation. - 2 did not receive lopinavir/ ritonavir because the attending physician refused to describe it.
Outcomes: efficacy	
Overall survival (OS), n (%)	NR
Median time to clinical improvement (days): *Time from randomisation to an improvement of two points (from the status at randomisation) on a 7-category ordinal scale (NEWS2 score) OR live discharge from the hospital, whichever came first*	ITT population: 16 v. 16, HR 1.31; 95% CI 0.95-1.85, p=0.09 Modified ITT population: 15 vs. 16, HR 1.39, 95% CI 1.00-1.91, p=NR No significant differences were observed when the time to clinical improvement was assessed by NEWS2 score at entry in the ITT population.

Author, year [Reference]	Cao et al. 2020 [57]
Clinical improvement, n (%) *Improvement of two points (from the status at randomisation) on a 7-category ordinal scale (NEWS2 score)*	ITT population: Day 7: 6 (6.1) vs. 2 (2.0), difference 4.1 percentage points, 95% CI -1.4-9.5, p=NR Day 14: 45 (45.5) vs. 30 (30.0), difference 15.5 percentage points, 95% CI 2.2-28.8, p=NR Day 28: 78 (78.8) vs. 70 (70.0), difference 8.8 percentage points, 95% CI -3.3-20.9, p=NR
Mortality at day 28 (%)	ITT population: 19.2 vs. 25.0, difference −5.8 percentage points; 95% CI −17.3 to 5.7, p=NR Modified ITT population: 16.7 vs. 25.0, difference -8.3 percentage points; 95% CI -19.6 to 3.0, p=NR
Median duration of invasive mechanical ventilation (days)	ITT population: 4 vs. 5, difference -1; 95% CI -4-2, p=NR
Median duration of hospitalisation (days)	ITT population: 14 vs. 16, difference 1; 95% CI 0-2, p=NR
Median time from treatment initiation to death (days)	ITT population: 9 vs. 12, difference -3, 95% -6-2, p=NR
Proportions with viral RNA detection over time (%)	Day 5: 34.5 vs. 32.9 Day 10: 50.0 vs. 48.6 Day 14: 55.2 vs. 57.1 Day 21: 58.6 vs. 58.6 Day 28, 60.3 vs. 58.6
Outcomes: safety	
Serious adverse events (SAE), n	Total: 19 (20.0) vs. 32 (32.3) Respiratory failure or ARDS: 12 (12.6) vs. 27 (27.3) Acute kidney injury: 3 (3.2) vs. 6 (6.1) Secondary infection: 1 (1.1) vs. 6 (6.1) Shock: 2 (2.1) vs. 2 (2.0) Severe anemia: 3 (3.2) vs. 0 (0.0) Acute gastritis: 2 (2.1) vs. 0 (0.0) Hemorrhage of lower digestive tract: 2 (2.1) vs. 0 (0.0) Pneumothorax: 0 (0.0) vs. 2 (2.0) Unconsciousness: 1 (1.1) vs. 0 (0.0) Disseminated intravascular coagulation: 1 (1.1) vs. 1 (1.0) Sepsis: 0 (0.0) vs. 1 (1.0) Acute heart failure: 0 (0.0) vs. 1 (1.0)
Adverse events (AE) that occurred during treatment, n (%) *5 most common AEs*	Total: 46 (48.4) vs. 49 (49.5) Lymphopenia: 16 (16.8) vs. 12 (12.1) Nausea: 9 (9.5) vs. 0 (0.0) Thrombocytopenia: 6 (6.3) vs. 10 (10.1) Leukopenia: 7 (7.4) vs. 13 (13.1) Vomiting: 6 (6.3) vs. 0 (0.0)
Premature discontinuation of treatment due to AEs, n (%)	13 (13.8)

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

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)**	**№ 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)	№ 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) [59, 60].

antivirales Medikament

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

japanisches Influenza-Medikament (seit 2014),

von EMA / FDA nicht zugelassen

treating Ebola; however, evidence on the effectiveness was lacking [59]. Favipiravir (Avigan®) has not been approved by the European Medicines Agency (EMA) or the American Food and Drug Administration (FDA).

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).

1 RCT abgeschlossen

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 RCT were found either.

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

Results of publications

As of 12/05/2020, only one publication [61] 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 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 [62]: 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

3.4 Darunavir

About the drug under consideration

Darunavir is an antiviral agent from the group of human immunodeficiency virus (HIV) protease inhibitors for the treatment of HIV-1 infections. The effects are based on the inhibition of the HIV protease, which plays a central role in the maturation of the virus and virus replication. Darunavir is combined with a pharmacokinetic booster such as ritonavir or cobicistat [63].

antivirales Medikament

als HIV Medikament zugelassen EMA 2007

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.

Completed, withdrawn, suspended or terminated studies

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

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

Results of publications

Until now (status: 08/06/2020) no scientific publication on RCTs of darunavir (Prezista®) in Covid-19 patients could be identified.

keine Publikation einer klinischn Studie

3.5 Chloroquine (Resochin®)

About the drug under consideration

Chloroquine is a anti-malarial drug with theraputic as well as prophylactic indication. It has due to its anti-inflammatory and immunomodulating effects, further therapeutic indications for rheumatoid arthritis and lupus. In recent in-vitro studies it is indicated, that the drug has also anti-viral effects, e.g. on the cell-entry mechanism of coronavirus like SARS-CoV-2, which is causing Covid-19 [64]. Chloroquine is closely related to hydroxychloroquine and shares the same pharmacokinetics, but showing a lower safety level and more concerns in drug-drug interactions.

Medikament bei Malaria & Autoimmun-erkrankungen

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

FDA: emergency Zulassung für Covid-19

NICHT EMA

Recently, EMA issued a reminder on the risk of serious side effects with chloroquine and hydroxychloroquine because recent studies have reported serious, in some cases fatal, heart rhythm problems with chloroquine or hydroxychloroquine, particularly when taken at high doses or in combination with the antibiotic azithromycin [65]. As EMA pointed out, some clinical trials currently investigating the effectiveness of chloroquine or hydroxychloroquine in treating COVID-19 use higher doses than those recommended for the authorised indications. While serious side effects can occur with recommended doses, higher doses can increase the risk of these side effects, including abnormal electrical activity that affects the heart rhythm (QT-prolongation).

EMA & FDA Warnungen:

schwerwiegende Nebenwirkungen

Also the FDA issued reminders on reports of serious heart rhythm problems in patients with COVID-19 treated with hydroxychloroquine or chloroquine, often in combination with azithromycin and other QT prolonging medicines. Both drugs can cause abnormal heart rhythms such as QT interval prolongation and a dangerously rapid heart rate called ventricular tachycardia. Patients who also have other health issues such as heart and kidney disease are likely to be at increased risk of these heart problems when receiving these medicines [66].

Verlängeung des QT-Intervall: gefährliche Herzrhythmus-störungen

Completed, withdrawn, suspended or terminated studies

The search in two clinical trial registers (ClinicalTrials.gov and EUdraCT) on 08/06/2020 yielded no completed study on the safety and efficacy of chloroquine in COVID-19 patients. Two suspended RCTs were found: NCT04420247 (because WHO has recommended chloroquine studies to be suspended for lack of efficacy), and NCT04341727 (DSMB recommended study suspension slow accrual).

keine weiteren Studien in ClinicalTrials.gov & EudraCT abgeschlossen
2 RCTs wurden abgebrochen

Results of publications

So far (status: 09/05/2020) one publication [67] [ChiCTR2000029542]) on the effectiveness and safety of chloroquine in adults hospitalised with Covid-19 could be identified. Also, authors of a RCT with registry number NCT04323527 published preliminary results on safety issues [66]. In [67] 22 hospitalised Covid-19 patients were assigned to chloroquine (n=10) or comparator treatment lopinavir/ritonavir (n=12). Comparing the virological cure (RT-PCR negative) of the chloroquine intervention group to the lopinavir/ritonavir comparator group, the percentages of patients who became SARS-CoV-2 negative were slightly higher at day 7 (70.0% vs. 58.33%, RR= 1.20 [CI: 0.60, 2.40]), day 10 (90.0% vs. 75.0%, RR= 1.20 [CI: 0.84, 2.00]), and day 14 (100.0% vs. 91.67%, RR= 1.09 [CI: 1.00, 1.33]). Also the proportion of CT-scan improvement of the chloroquine intervention group compared to the lopinavir/ritonavir comparator group, was higher at day 10 (20.0% vs. 8.33%, RR=2.4 (CI: 0.14, 12.32) and day 14 (100.0% vs. 75.0%, RR=1.33 [CI: 1.00, 2.00]). In addition, patients treated with chloroquine were discharged from hospital much earlier than patients treated with lopinavir/ritonavir (clinical recovery at day 10: 80.0% vs. 58.33%, RR= 1.37 [CI: 0.80, 2.80]; hospital discarge at day 14: 100.0% vs. 50.0%, RR= 2.0 [CI: 1.33,4.00]). Concerning all adverse events that occured during the follow-up of 14 days, the intervention group showed 9 different adverse events, the comparator group 10. Neurological events were more common in the lopinavir/ ritonavir comparator group. Severe adverse events were not reported. Overall, a slight clinical benefit could be observed with chloroquine treatment beyond lopinavir/ ritonavir treatment in hospitalised adult patients with Covid-19. Detailed information about the study results are presented in Table 3.5-2.

1 Publikation Huang (China):

22 Pts. Im Vergleich mit lopinavir/ritonavir

gewisse bessere Ergebnisse in Interventionsgruppe

Borba et al. 2020 (NCT04323527) [66] [68] presented preliminary safety results of a randomised, double-blind, phase IIb clinical trial with 81 adult patients who were hospitalized with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection at a tertiary care facility in Manaus, Brazilian Amazon. Patients were allocated to receive high-dosage CQ (ie, 600 mg CQ twice daily for 10 days) or low-dosage CQ (ie, 450 mg twice daily on day 1 and once daily for 4 days). Primary outcome was reduction in lethality by at least 50% in the high-dosage group compared with the low-dosage group. Out of a predefined sample size of 440 patients, 81 were enrolled (41 [50.6%] to high-dosage group and 40 [49.4%] to low-dosage group). Enrolled patients had a mean (SD) age of 51.1 (13.9) years, and most (60 [75.3%]) were men. Older age (mean [SD] age, 54.7 [13.7] years vs 47.4 [13.3] years) and more heart disease (5 of 28 [17.9%] vs 0) were seen in the high-dose group. Lethality until day 13 was 39.0% in the high-dosage group (16 of 41) and 15.0% in the low-dosage group (6 of 40). The high-dosage group presented more instances of QTc interval greater than 500 milliseconds (7 of 37 [18.9%]) compared with the low-dosage group (4 of 36 [11.1%]). Respiratory secretion at day 4 was negative in only 6 of 27 patients (22.2%). The authors concluded that the preliminary findings of their study suggest that the higher CQ dosage should not be recommended for critically ill patients with COVID-19 because of its potential safety hazards, especially when taken concurrently with azithromycin and oseltamivir. The authors pointed out that these findings cannot be extrapolated to patients with nonsevere COVID-19.

Borba (Brasilien) RCT, 440 Pts

Analyse von Sicherheitsendpunkten:

höhere CQ Dosierung kann nicht empfohlen werden, wegen Nebenwirkungen

No new RCT peer-reviewed articles have been found as of June 08, 2020.

keine weiteren Publikationen zu RCTs

Table 3.5-1: Publications on clinical trials on product Chloroquine

Author, year	**Huang et al. 2020 [67]**
Country	China
Sponsor	Sun Yat sen Memorial Hospital of Sun Yat sen University, China; Natural Science Foundation of Guangdong Province (2018A030313652); National Mega Projecton Major Infectious Disease Prevention (2017ZX10103011)
Study design	Open-label, randomised controlled trial
Number of pts	22 (10 vs. 12)
Intervention/Product	Chloroquine (500 mg) twice per day for 10 days
Comparator	Lopinavir/Ritonavir (400 mg/100 mg) twice per day for 10 days
Inclusion criteria	- Aged 18 years old - Diagnosed with Covid-19 according to WHO interim guidance Clinicalbmanagement of severe acute respiratory infection when novel coronavirus (2019 nCoV) infection is suspected (Interim guidance, 28 January 2020)
Exclusion criteria	- pregnant woman patients; - Documented allergic history to C hloroquine; - Documented history of hematological system diseases; - Documented history of chronic liver and kidney diseases; - Documented history of cardiac arrhythmia or chronic heart diseases; - Documented his tory of retina or hearing dysfunction; - Documented history of mental illnesses; - Use of digitalis due to the previous disease.
Pts pretreated +previous treatment	NR
Mean age of patients, yrs (range)	Total: 44.0 (36.5-57.5): IG: 41.5 (33.8-50.0) CG: 53.0 (41.8-63.5)
Sex % male (% female)	Total: 59.1 (40.9): IG: 70.0 (30.0) CG: 50 (50.0)
Follow-up (days)	14 (daily examination)
Severe cases, n (%)	Total: 8 (36.4) IG: 3 (30.0) CG: 5 (41.6)
Loss to follow-up, n (%)	NR
Outcomes: efficacy	
Overall survival (OS), n (%)	NR
No. Pts with virological cure (proportion) by day: chloroquine vs. lopinavir/ritonavir; RT-PCR negative	Day 7: 7 (70.0) vs. 7 (58.33), RR= 1.20 (CI: 0.60, 2.40), p=NR Day 10: 9 (90.0) vs. 9 (75.0), RR= 1.20 (CI: 0.84, 2.00), p=NR Day 14: 10 (100.0) vs. 11 (91.67), RR= 1.09 (CI: 1.00, 1.33), p=NR
No. Pts with CT scan improvement at (proportion) by day: chloroquine vs. lopinavir/ritonavir;	Day 10: 2 (20.0) vs. 1 (8.33), RR=2.4 (CI: 0.14, 12.32), p=NR Day 14: 10 (100.0) vs. 9 (75.0), RR=1.33 (CI: 1.00, 2.00), p=NR
Clinical outcomes, n (%)	Clinical recovery at day 10: 8 (80.0) vs. 7 (58.33), RR= 1.37 (CI: 0.80, 2.80), p=NR Hospital discarge at day 14: 10 (100.0) vs. 6 (50.0), RR= 2.0 (CI: 1.33,4.00), p=NR
Outcomes: safety	
Serious adverse events (SAE), N	None observed

Author, year	**Huang et al. 2020 [67]**
Adverse events (AE), N	Total: 9 (90.0) vs. 10 (83.33) Gastrointestinal: Vomiting: 5 (50.0) vs. 1 (8.33) Abdominal pain: 1 (10.0) vs. 2 (16.67) Nausea: 4 (40.0) vs. 5 (41.67) Diarrhea: 5 (50.0) vs. 8 (66.67) Neurological: Dizziness: 0 (0) vs. 2 (16.67) Headache: 0 (0) vs. 1 (8.33) Psychosis: 0 (0) vs. 1 (8.33) Rash or itchy: 1 (10.0) vs. 0 (0) Respiratory: Cough: 4 (40.0) vs. 6 (50.0) Shortness of breath: 1 (10.0) vs. 4 (33.33)

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

3.6 Hydroxychloroquine (Plaquenil®)

About the drug under consideration

droxychloroquine is a common anti-malarial drug with theraputic as well as prophylactic indication. Due to its anti-inflammatory and immunomodulating effects, it is also used as treatment of rheumatoid arthritis and lupus. In recent in-vitro studies it is indicated, that the drug has also anti-viral effects, e.g. on the cell-entry mechanism of coronavirus like SARS-CoV-2, which is causing Covid-19 [69]. Hydroxychloroquine is closely related to cloroquine and shares the same pharmacokinetics, but showing a higher safety level and fewer concerns in drug-drug interactions.

prophylaktisches Anti-Malariamedikament

mit CQ „verwandt"

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

seit 1955 von FDA zugelassen

Emergency Use Authorization f(EUA) (März)

nicht von EMA

Recently, EMA issued a reminder of the risk of serious side effects with chloroquine and hydroxychloroquine because recent studies have reported serious, in some cases fatal, heart rhythm problems with chloroquine or hydroxychloroquine, particularly when taken at high doses or in combination with the antibiotic azithromycin [70]. As EMA pointed, some clinical trials currently investigating the effectiveness of chloroquine or hydroxychloroquine in treating COVID-19 use higher doses than those recommended for the authorised indications. While serious side effects can occur with recommended doses, higher doses can increase the risk of these side effects, including abnormal electrical activity that affects the heart rhythm (QT-prolongation).

EMA & FDA Warnungen:

schwerwiegende Nebenwirkungen

Also the FDA issued reminders on reports of serious heart rhythm problems in patients with COVID-19 treated with hydroxychloroquine or chloroquine, often in combination with azithromycin and other QT prolonging medicines. Both drugs can cause abnormal heart rhythms such as QT interval prolongation and a dangerously rapid heart rate called ventricular tachycardia. Patients who also have other health issues such as heart and kidney disease are likely to be at increased risk of these heart problems when receiving these medicines [66].

Verlängeung des QT-Intervall: gefährliche Herzrhythmus-störungen

Completed, withdrawn, suspended or terminated studies

Four suspended RCTs were found: NCT04420247 (because WHO has recommended chloroquine studies to be suspended for lack of efficacy); NCT04341727 (DSMB recommended study suspension slow accrual); NCT04334967 (due to suspected unfavorable risk/benefit assessment); NCT04333654 (Sponsor decision pending further evaluation of information related to benefit-risk). One withdrawn RCT was found, NCT04347512 (in view of the notices concerning hydroxichloroquine issued by the regulatory authorities).

4 RCTs abgebrochen: 1 x Mangel an Wirksamkeit, 1 x langsame Rekrutierung, 2 x wegen Nebenwirkungen

Results of publications

So far (status: 07/05/2020) seven publications ([71] [EudraCT: 2020-000890-25]; [72, 73] [ChiCTR2000029559]) [74] [75] [76] [77] on the effectiveness and/or safety of hydroxychloroquine in adults hospitalised with Covid-19 could be identified. Unfortunatly, [72] and [74] are not published in English and [73] [75] [76] [77] are availabe just as pre-print but not yet peer-reviewed, thus not included in the Table 3.6-1.

bislang 7 Publikationen, davon 2 nicht in English, 4 nur als pre-print (nicht peer-reviewed)

In a non-randomised study published by Gautret et al. 2020 [71], 36 hospitalised Covid-19 patients (per-protocol) were assigned to hydroxychloroquine (n=20) or standard therapies (n=16) including symptomatic treatment and antibiotics based on clinical judgment. Comparing the proportion of patients that had negative PCR results in nasopharyngeal samples showed a significantly difference between the intervention group and control group at days 3-4-5 and 6 post-inclusion (Day 6: 14 (70.0%) vs. 2 (12.5%), difference 57.5 percentage points, p=0.001). Some patients of the intervention group where treated with azithromycin (n=6) in addition to the single drug hydroxychloroquine (n=14). The proportion of patients with negative PCR results in nasopharyngeal samples that where treated with hydroxychloroquine in combination with azithromycin compared to the patient treated with hydroxychloroquine or the control group was significantly different at days 3-4-5 and 6 post-inclusion (Day 6: 8 (57.1%) vs. 6 (100%) vs. 2 (12.5%), p=<0.001). Any (severe) adverse events were not reported in this publication, but will be in the next ones. For Chen J et al. 2020 (NCT04261517) [74] only an abstract is provided in English language, so just a short information is provided below, as well as for a recently published observational controled study by Geleris J et al. [78], Tang et al. study [75], Mahevas M et al. study [76] and study related to serious adverse events [77].

Gautret (Frankreich) RCT, 36 Pts

bessere Ergebnisse in Interventinsgruppe, AE/ SAE nicht berichtet

Chen J et al. 2020 [74] presented results from a small RCT with only 30 patients included. Patients in hydroxychloroquine group were given 400 mg per day for 5 days plus conventional treatments, while those in the control group were given conventional treatment only. The primary endpoint was a negative conversion rate of COVID-19 nucleic acid in respiratory pharyngeal swab on days 7 after randomization. On day 7, COVID-19 nucleic acid of throat swabs was negative in 13 (86.7%) cases in the hydroxychloroquine group and 14 (93.3%) cases in the control group (P>0.05). Four cases (26.7%) of the hydroxychloroquine

Chen (China), RCT, 30Pts

schlechtere Ergebnisse in Interventionsgruppe

group and 3 cases (20%) of the control group had transient diarrhea and abnormal liver function (P>0.05).

Tang et al. study 2020 (ChiCTR2000029868) [75] [79] assessed the efficacy and safety of hydroxychloroquine (HCQ) plus standard-of-care (SOC) compared with SOC alone in adult patients with COVID-19. This was multicenter, open-label, randomized controlled trial which included 150 patients hospitalized with laboratory-confirmed COVID-19 (75 patients were assigned to HCQ plus SOC and 75 to SOC alone). The primary outcome was whether participants had a negative conversion of SARS-CoV-2 by 28 days (analyzed according to the intention-to-treat principle). The negative conversion probability by 28 days in SOC plus HCQ group was 85.4% (95% confidence interval (CI) 73.8% to 93.8%), similar to that in the SOC group 81.3% (95%CI 71.2% to 89.6%). Between-group difference was 4.1% (95%CI -10.3% to 18.5%). In the safety population, adverse events were recorded in 7 (8.8%) HCQ non-recipients (N=80) and in 21 (30%) HCQ recipients (N=70). The most common adverse event in the HCQ recipients was diarrhea, reported in 7 (10%) patients and two HCQ patients reported serious adverse events.

Tang (China)
RCT, 150 Pts.

kein Unterschied zwischen den Gruppen bei klinischer Verbesserung

höhere AE unter HCQ

Mahevas et al. 2020 [76] presented results from an emulated trial aimed at assessing the effectiveness of hydroxychloroquine at 600 mg/day. 181 adult patients from four French hospitals with documented SARS-CoV-2 pneumonia and requiring oxygen ≥ 2 L/min were included: 84 received hydroxychloroquine within 48 hours of admission and 97 did not. The composite primary endpoint was transfer to intensive care unit (ICU) within 7 days from inclusion and/or death from any cause. In the weighted analysis, 20.2% patients in the hydroxychloroquine group were transferred to the ICU or died within 7 days vs 22.1% in the non-hydroxychloroquine group (16 vs 21 events, relative risk [RR] 0.91, 95% CI 0.47–1.80). In the hydroxychloroquine group, 2.8% of the patients died within 7 days vs 4.6% in the no-hydroxychloroquine group (3 vs 4 events, RR 0.61, 95% CI 0.13–2.89). 27.4% and 24.1%, respectively, developed acute respiratory distress syndrome within 7 days (24 vs 23 events, RR 1.14, 95% CI 0.65–2.00). Eight patients receiving hydroxychloroquine (9.5%) experienced electrocardiogram modifications requiring HCQ discontinuation.

Mahevas (Frankreich)
Routinedaten, 181 Pts.

kein Unterschied bei ICU und Mortalität

One recent study reported serious heart rhythm problems with hydroxychloroquine, in combination with the antibiotic azithromycin [77]. Lane et al. 2020 [77] presented safety results of hydroxychloroquine, alone and in combination with azithromycin, from a multinational, network cohort and self-controlled case series study. 956,374 and 310,350 users of hydroxychloroquine and sulfasalazine, and 323,122 and 351,956 users of hydroxychloroquine-azithromycin and hydroxychloroquine-amoxicillin were included. They found that no excess risk of SAEs was identified when 30-day hydroxychloroquine and sulfasalazine use were compared. When azithromycin was added to hydroxychloroquine, an increased risk of 30-day cardiovascular mortality (CalHR2.19 [1.22- 3.94]), chest pain/angina (CalHR 1.15 [95% CI 1.05-1.26]), and heart failure (CalHR 1.22 [95% CI 1.02- 1.45]) were observed.

Lane (Europa)
Multinationale Network-Kohorte

SAE Risken nur HCQ in Kombination mit Azithromycin

Geleris et al. 2020 [78] recently presented results from an observational controlled study conducted at a large medical center in New York City. The primary end point was a composite of intubation or death in a time-to-event analysis. Authors compared outcomes in patients who received hydroxychloroquine with those in patients who did not, using a multivariable Cox model with inverse probability weighting according to the propensity score. Out of 1376 included consecutive patients, 811 (58.9%) received

Geleris (USA)
prospektive Beobactungstudie, 1.376 Pts.

kein Unterschied bei Intubation und Mortalität

hydroxychloroquine (600 mg twice on day 1, then 400 mg daily for a median of 5 days); 45.8% of the patients were treated within 24 hours after presentation to the emergency department, and 85.9% within 48 hours. There was no significant association between hydroxychloroquine use and intubation or death (hazard ratio, 1.04, 95% confidence interval, 0.82 to 1.32) in the primary multivariable analysis with inverse probability weighting according to the propensity score.

On 05/06/2020 news related to the preliminary results from the RECOVERY Trial were found; a total of 1542 patients were randomised to hydroxychloroquine and compared with 3132 patients randomised to usual care alone. No significant difference was found in the primary endpoint of 28-day mortality (25.7% hydroxychloroquine vs. 23.5% usual care; hazard ratio 1.11 [95% confidence interval 0.98-1.26]; p=0.10). Also no evidence was found of beneficial effects on hospital stay duration or other outcomes. Therefore decision was made to stop enrolling participants to the hydroxychloroquine arm of the RECOVERY Trial with immediate effect. These news are published also in BMJ on June 08, 2020 [80]. Detailed information about the study results will be provided after the peer-reviewed publication appears.

RECOVERY Studie TCT, 4.674 Pts.

kein Unterschied bei Mortalität und Dauer Spitalsaufenthalt

Rekrutierung wurde gestoppt

Detailed information about the study results published by Gautret et al. [71] and Tang et al. BMJ, 2020 [79] are presented in Table 3.6-1.

Table 3.6-1: Publications on clinical trials on product Hydroxycloroquine (Plaquenil®)

Author, year	**Gautret et al. 2020** [71]	**Tang et al.,2020** [79]
Country	France	China
Sponsor	Fondation Méditerranée Infection - IHU Méditerranée Infection, Marseille,France; French Government under the « Investissements d'avenir » (Investments for the Future) program managed by the Agence Nationale de la Recherche	Emergent Projects of National Science and Technology, National Natural Science Foundation of China, National Key Research and Development Program of China), Shanghai Municipal Key Clinical Specialty, National Innovative Research Team of High-level Local Universities in Shanghai, Shanghai Key Discipline for Respiratory Diseases, National Major Scientific and Technological Special Project for Significant New Drugs Development, Key Projects in the National Science and Technology Pillar Program during the Thirteenth Five-year Plan Period
Study design	Open-label, controlled trial	RCT, parallel, multicentre, open-label
Number of pts	42 (26 vs. 16) per-protocol: 36 (20 vs. 16); (Subgroup: 36 (14 vs. 6 vs. 16))	150 patients (75 were randomly assigned to HCQ plus standard care and 75 to the standard of care alone
Intervention/Product	HCQ (200 mg) three times per day + standard care for 10 days (Subgroup: n=6; HCQ (200 mg three times per day) + azithomycin (500 mg on day1, then 250mg per day for 4 days) + standard care for 10 days)	HCQ plus standard care
Comparator	Standard care (as necessary): Symptomatic treatment and antibiotics based on clinical judgment	Standard of care alone
Inclusion criteria	- Hospitalized patients with confirmed COVID-19 - age >12 years - PCR documented SARS-CoV-2 carriage in nasopharyngeal sample at admission whatever their clinical status	- Age 18 years or older, ongoing SARS-CoV-2 infection confirmed in upper or lower respiratory tract specimens with real time reverse transcriptase polymerase chain reaction (RT-PCR), willingness to participate, and consent not to be enrolled in other clinical trials during the study period
Exclusion criteria	- known allergy to hydroxychloroquine or chloroquine or had another known contraindication to treatment with the study drug, including retinopathy, G6PD deficiency and QT prolongation - Breastfeeding and pregnant patients were excluded based on their declaration and pregnancy test results when required	Age below 18 years; severe conditions incl. malignancies, heart, liver, or kidney disease or poorly controlled metabolic diseases; unsuitability for oral administration; pregnancy or lactation; allergy to hydroxy-chloroquine; inability to cooperate with investigators due to cognitive impairments or poor mental status; severe hepatic impairment (for example, Child Pugh grade C, alanine aminotransferase more than fivefold the upper limit); and severe renal impairment (estimated glomerular filtration rate ≤30 mL/min/1.73 m2) or receipt of continuous renal replace-ment therapy, haemodialysis, or peritoneal dialysis
Pts pretreated +previous treatment	NR	Diferent drug listed

Author, year	**Gautret et al. 2020** [71]	**Tang et al.,2020** [79]
Mean age of patients, yrs (SD)	**Total: 45.1 (22.0):** IG: 51.2 (18.7) CG: 37.3 (24.0)	46 years
Sex % male (% female)	**Total: 41.7 (58.3):** IG: 45.0 (55.0) CG: 37.5 (62.5)	82 (55%) men (45%) women
Follow-up (days)	14 (daily examination)	28 days
Clinical status: asymptomatic/ URTI/ LRTI (proportion)	**Total: 6 (16.7)/ 22 (61.1)/ 8 (22.2)** IG: 2 (10.0)/ 12 (60.0)/ 6 (30.0) CG: 4 (25.0)/ 10 (62.5)/ 2 (12.5)	Mild, moderate and severe COVID-19
Loss to follow-up, n (%)	6 vs. 0 - 3 were transferred to intensive care unit - 1 died on day 3 - 1 recovered on day 2 - 1 stopped because of nausea at day 3	6 patients in HCQ group, 1 in control group
Outcomes: efficacy		
Overall survival (OS), n (%)	NR	No patients died during the study
No. Pts with virological cure (proportion) by day: hydoxycloroquine vs. control; negative nasopharyngeal PCR	per-protocol: Day 3: 10 (50.0) vs. 1 (6.3), difference 43.7 percentage points, p=0.005 Day 4: 12 (60.0) vs. 4 (25.0), difference 35.0 percentage points, p=0.04 Day 5: 13 (65.0) vs. 3 (18.8), difference 46.2 percentage points, p=0.006 Day 6: 14 (70.0) vs. 2 (12.5), difference 57.5 percentage points, p=0.001	Negative conversion probability by 28 days in SOC plus HCQ group was 85.4% (95% confidence interval (CI) 73.8% to 93.8%), similar to that in the SOC group 81.3% (95%CI 71.2% to 89.6%); between-group difference was 4.1% (95%CI -10.3% to 18.5%)
No. Pts with virological cure (proportion) by day: hydoxycloroquine vs. hydoxycloroquine + azithomycin vs. control; negative nasopharyngeal PCR	per-protocol: Day 3: 5 (35.7) vs. 5 (83.3) vs. 1 (6.3), p=0.002 Day 4: 7 (50.0) vs. 5 (83.3) vs. 4 (25.0), p=0.05 Day 5: 7 (50.0) vs. 6 (100.0) vs. 3 (18.8), p=0.002 Day 6: 8 (57.1) vs. 6 (100) vs. 2 (12.5), p=<0.001	19 v 21 days; hazard ratio 1.01, 0.59 to 1.74; P=0.97 by log rank tes
Outcomes: safety		
Serious adverse events (SAE), n	NR (will be presented in next paper)	21 (30%) HCQ recipients (N=70) vs 7 (8.8%) HCQ non-recipients (N=80)
Adverse events (AE), n	NR (will be presented in next paper)	2 patients in HCQ group vs no in control group
Discontinuation of study drug due to AEs or SAEs		1 in the HCQ group

CG – Control group, IG – Intervention group, LRTI – Lower tract respiratory infection,

3.7 Mesilate (Foipan®)

About the drug under consideration

Camistat Mesilate (Foipan®) is classified as a so-called serine protease inhibitor, blocking several pancreatic and plasmatic enzymes like trypsin, thrombin and plasmin [81]. 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 [82, 83] as well as in pathogenic mice-models [84] by inhibiting the enzyme Transmembrane protease, serine 2 (TMPRSS2). Camistat Mesilate (Foipan®) ist not approved for any anti-viral use (FDA, EMA).

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

Completed, withdrawn, suspended or terminated studies

As of June 08, 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 clinical trials of Camostat Mesilate (Foipan®) in Covid-19 patients could be identified (status: 08/06/2020).

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) [85]. ACE2 was identified as the functional SARS-CoV receptor in vivo [86]. 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 [87].

aus SARS-Forschung hervorgegangen

keine Zulassung
1 Studie (Phase 2 RCT), vor Rekrutirung

The therapy with APN01 is currently not approved by the European Medicine Agency (EMA) and Food and Drug Administraion (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 08 June, 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 June 08, 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).

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-6Rα), and inhibits IL-6-mediated signalling [88]. It is licensed in the EU for treating:

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

Covid-10: bei erhöhten IL-6-Spiegeln

in schweren Erkrankungen

- 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 [88].

When used to treat CRS, it is given as a 60-minute intravenous (IV) infusion in a dose of 8mg/kg (in patients weighing ≥30kg) or 12mg/kg (in patients weighing <30kg), to a maximum of 800mg per infusion [88]. 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 [88].

bei lebensbedrohlichem Zytokin-Freisetzungssyndrom

Verabreichung iv oder sc

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 [89]. However, some patients develop severe symptoms and progress rapidly, experiencing acute respiratory distress syndrome and septic shock, eventually ending in multiple organ failure [89]. It has been reported that most patients with COVID-19 have increased concentrations of IL-6, C-reactive protein (CRP) and erythrocyte sedimentation rate [90]. However, severely affected patients appear to have even higher plasma levels of pro-inflammatory cytokines and experience severe cytokine storm including features of CRS [90, 91]. It has previously been suggested that IL-6 might play a role in the pathogenesis of SARS and MERS, other diseases caused by coronaviruses [91]. It is thought that neutralisation of the inflammatory pathway induced by IL-6 may reduce mortality.

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

Completed, withdrawn, suspended or terminated studies

Until 09 June, 2020, no completed, withdrawn, suspended or terminated RCTs on the safety and efficacy of tocilizumab in COVID-19 patients were found in ClinicalTrials.gov and EudraCT registers.

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 [92] (found through searching the reference list in paper 4) [93]; one prospective series on 100 patients [94] and two quasy-experimental study comparing tocilizumab with standard care in 154 critically ill COVID-19 patients admitted to centers in USA [95] and 168 severe COVID-19 patients in France (NCT04366206) [96].

bislang keine publizierten Ergebnisse aus RCTs

1 prospektive Fallserie mit 100 Pts
2 quasi-experimentelle Studien

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] [95].

Somers (USA)
154 Pts

ev. Reuktion der Mortalität trotz erhöhter Anzahl an Superinfektionen

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 [96].

Rossi (Frankreich)
retrospective case-control, 246 Pts

in kombiniertem Endpunkt (Beatmung und Mortalität) ev. Verbesserung

A retrospective analysis of data from 20 patients who received one of two doses of IV tocilizumab 400mg showed 15 (75%) had lowered their oxygen intake and one patient need no oxygen therapy. CT scans showed lung lesion opacity absorbed in 19 patients (90.5%). The percentage of lymphocytes in peripheral blood, which decreased in 85.0% patients (17/20) before treatment (mean, 15.52 ± 8.89%), returned to normal in 52.6% patients (10/19) on the fifth day after treatment. Abnormally elevated CRP decreased significantly in 84.2% patients (16/19). No adverse reactions were observed [92].

retrospektive Fallserien: ev. Vorteile

Xu (China)
20 Pts

Luo (China)
15 Pts.

Luo et al. 2020 [93] 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 [94] presented results of a prospective series of 100 consecutive patients in Italy with confirmed COVID-19 pneumonia and ARDS requiring ventilatory support to determine whether intravenous administration of tocilizumab was associated with improved outcome. Overall at 10 days, the respiratory condition was improved or stabilized in 77 (77%) patients; 61 showed a significant clearing of diffuse bilateral opacities on chest x-ray. 15 patients were discharged from the hospital. Respiratory condition worsened in 23 (23%) patients, of whom 20 (20%) died. During the 10-day follow-up, three cases of severe adverse events were recorded: two patients developed septic shock and died, one had gastrointestinal perforation requiring urgent surgery and was alive at day 10. Authors concluded that response to tocilizumab was rapid, sustained, and associated with significant clinical improvement [96].

Toniati (Italien)
100 Pts.

3.10 Sarilumab (Keyzara®)

Drug under consideration

Sarilumab (*Kevzara*) is a human monoclonal antibody that specifically binds to soluble and membrane-bound interleukin (IL)-6 receptors (IL-6Rα), and inhibits IL-6-mediated signalling [97]. It is licensed in the EU for treating adults with rheumatoid arthritis, given by subcutaneous (SC) injection [97]. It is being investigated as a possible treatment for patients with moderate to severe or critical COVID-19.

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

Covid-10: bei erhöhten IL-6-Spiegeln

Experience of using tocilizumab, another IL-6 inhibitor, in severe or critical COVID-19 patients has been reported [92].

Completed, withdrawn, suspended or terminated studies

April: 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 09 June 2020, no completed, withdrawn, additional suspended or terminated studies were found in ClinicalTrials.gov and EUdraCT registers.

ClinicalTrials.gov & EUdraCT
April: keine Studien registriert
Mai: 1 RCT abgebrochen
Juni: keine weiteren Studien

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

keine Publikation zu einer klinischen Studie

eine Interimauswertung

(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.

3.11 Interferon beta 1a (SNG001) (Rebif®, Avonex®)

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 [98]. 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 [99].

INFb Präparate bei Multipler Sklerose zugelassen (EMA)

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

Rebif®
Avonex®
seit 1997/1998 zugelassen

Completed, withdrawn, suspended or terminated studies

Mai: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).

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

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 hydroxychlorochine and lipinavir/ritonavir in comparison with controlled group treated with hydroxychlorochine and lipinavir/ritonavir (three study arms: Interferon beta 1a + hydroxychlorochine + lipinavir/ritonavir; Interferon beta 1b + hydroxychlorochine + lipinavir/ritonavir; hydroxychlorochine +lipinavir/ritonavir). Results are not yet published in peer-review journal.

Juni: 1 weiterer RCT (Iran)

(Kombinationstherapie) Ergebnisse liegen noch nicht vor

Results of publications

As mentioned above, the results from the first randomised controlled trail on triple combination of interferon beta-1b, lopinavir–ritonavir and ribavirin, in comparison with lopinavir–ritonavir (NCT04276688) are presented in Section 3.13 of this report [100]. On May 30, 2020, preprint was identified (medRxiv platform) related to the results from RCT on Interferon beta-1a treatment vs the standard of care, in 42 patients with severe COVID-19 in Iran [101]. 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.

Preprint RCT (Iran) 42 Pts

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

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

About the treatment under consideration

Convalescent plasma is plasma collected from patients that have recovered from an infectious disease and can be transfused to patients fighting an infection or can be used to manufacture immune globulin concentrates (plasma derived medicinal products). Possible explanations for the efficacy are that the antibodies from convalescent plasma might suppress viraemia and activate the complement system, thus promoting viral elimination. Antibody is most effective when administered shortly after the onset of symptoms, and a sufficient amount of antibody must be administered. Plasma transfusions may be associated with transfusion reactions such as allergic reactions, antibody-mediated enhancement of infection, transfusion-related acute lung injury (TRALI) and circulatory overload [102-104]. Rare complications include the transmission of infectious pathogens and red cell alloimmunization.

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

auch zur Herstellung von Immunglobulin-konzentraten verwendet

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 [102]. 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.

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

Bedingungen:
Vefügbarkeit
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 [105, 106]. 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 [105]. The FDA guidance provides recommendations on the pathways for use of investigational COVID-19 convalescent plasma; patient eligibility; collection of COVID-19 convalescent plasma, including donor eligibility and donor qualifications; labeling and record keeping. As COVID-19 convalescent plasma is regulated as an investigational product, three patways for use are available in US: 1. Clinical Trials; 2. Expanded Access; 3. Single Patient Emergency IND [106, 107].

Blutprodukte für covid-19 nicht zugelassen

EMA (& EC) Guidance zur Verwendung

Current US NIH COVID-19 Treatment Guidelines stated that there are insufficient clinical data to recommend either for or against the use of convalescent plasma or hyperimmune immunoglobulin for the treatment of COVID-19 (AIII) [108].

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.

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

Results of publications

Results from case series, which involved from two to ten critically ill patients in China and Korea are published only [109-114]. The results from 10 severe adults cases with COVID-19, published by Duan et al. [109], 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. [110] 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. [111], Ahn et al. [112], and Zhang et al. [113] also presented the positive results on clinical outcomes. Zeng et al. [114] presented results from case series of 6 COVID-19 subjects with respiratory failure who received convalescent plasma at a median of 21.5 days after first detection of viral shedding, all tested negative for SARS-CoV-2 RNA by 3 days after infusion, and 5 died eventually. They concluded that convalescent plasma treatment can discontinue SARS-CoV-2 shedding but cannot reduce mortality in critically end-stage COVID-19 patients, and treatment should be initiated earlier.

keine Ergebnisse aus RCTs publiziert

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

frühe Verabreichung

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 [115]. 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.

Cochrane Review zu Beobachtungstudien

8 Studien inkludiert, hoher RoB, niedrige Sicherheit

keine sicheren Aussagen möglich

As of June 12, 2020 results from one quasy-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 [116].

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

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 [117]. 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.

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 3.122.1).

keine stat. signifikanten Unterschiede bei

Transfusions-bedingte AE

frühzeitiger Abbruch der Studie und daher „underpowering“

Table 3.12-1: Publications on clinical trials on Convalescent plasma [117]

Author, year [Reference]	***Li et al. 2020 [117]**
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.

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

Hung (China)
RCT, 127 Pts.

Reduktion der Dauer der Virusausscheidung, Symtomverbesserung, Dauer des Krankenhausaufenthalts

kein Unterschied bei AE
keine Todesfälle in beiden Gruppen

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

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 3.13-2.

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

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

Table 3.13-2: 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)	№ 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

3.14 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.

derzeit laufende Studie: Phase 2B

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.

April: BASG, AIFA lassen Solnatide für "Compassionate Use" zu

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.

EC-Grant seit April für covid-19

Completed, withdrawn, suspended or terminated studies

As of June 12, 2020 no completed, withdrawn, suspended or terminated studies related to solnatide in COVID-19 patients were found in ClinicalTrials.gov and EUdraCT registers.

ClinicalTrials.gov & EUdraCT: keine klinischen Studien registriert, keine Publikation von RCT

Results of publications

As of June 12, 2020 no publications related to RCTs of solnatide in COVID-19 patients were found.

3.15 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

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

Erprobung bei verschiedenen Viren:

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

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 Els) [118].

1 in vitro publication

Completed, withdrawn, suspended or terminated studies

As of June 12, 2020 no completed, withdrawn, suspended or terminated studies related to umifenovir were found in ClinicalTrials.gov and EUdraCT registers.

ClinicalTrials.gov & EudraCT: keine Studien registriert

Results of publications

As already mentioned above, in section related to of lopinavir/ritonavir, RCT published by Yueping et al. 2020 (NCT04252885) [58] 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 occured in the control group [58].

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 finding table (https://covid-nma.com/living_data/index.php) is provided in table 3.15-1.

One publication [61] 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)

Table 3.15-1: 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)**	**№ 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
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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

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