HTA Austria
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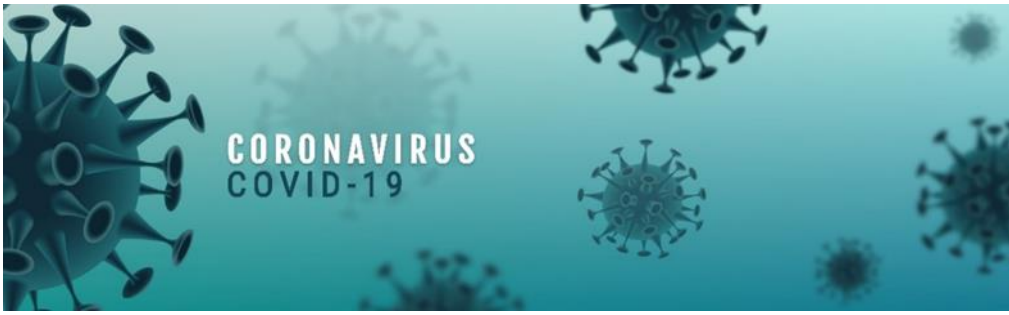
Covid-19



HSS/ Horizon Scanning
Living Document V07 October 2020
Part 1

AIHTA Policy Brief Nr.: 002
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Part 1

Vienna, October 2020

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October, 2020	Addition chapter on Lenzilumab (chapter 3.23)
October, 2020	Methodology (1.2) – no changes
October, 2020	Update Vaccine (chapter 2)
October, 2020	Update Remdesivir (chapter 3.1)
October, 2020	Lopinavir + Ritonavir (chapter 3.2) - Reporting finished
October, 2020	Update Favipiravir (chapter 3.3)
October, 2020	Darunavir (chapter 3.4) – no changes
October, 2020	Camostat Mesilate (chapter 3.7) – no changes
October, 2020	APN01/rhACE2 (chapter 3.8)
October, 2020	Update Tocilizumab (chapter 3.9)
October, 2020	Update Sarilumab (chapter 3.10)
October, 2020	Update Interferon beta (chapter 3.11)
October, 2020	Update Concalescent plasma (chapter 3.12)
October, 2020	Update Plasma derived medicinal products (chapter 3.13) – REGN-COV2; LY-CoV555 and LY-CoV016; AZD7422
October, 2020	Update Combination therapy (chapter 3.14)
October, 2020	Solnatide (chapter 3.15) – no changes
October, 2020	Update Umifenovir (chapter 3.16)
October, 2020	Update Dexamethasone and other corticosteroids (chapter 3.17)
October, 2020	Anakinra (chapter 3.18) – no changes
October, 2020	Colchicine (chapter 3.19)
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October, 2020	Gimsilumab (chapter 3.21) – no changes
October, 2020	Canakinumab (chapter 3.22) – no changes

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 Einkauf**

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

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

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

From V4 July, 2020 of this HSS/ Horizon Scanning Document, only completed, terminated, withdrawn and suspended interventional clinical trials from ClinicalTrials.gov and EUdraCT registers are reported.

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

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

Table 1.2-1: International Sources

Primary sources	Link
WHO Drugs: Vaccines:	https://www.who.int/teams/blueprint/covid-19 https://www.who.int/blueprint/priority-diseases/key-action/Table_of_therapeutics_Appendix_17022020.pdf?ua=1 https://www.who.int/who-documents-detail/covid-19-candidate-treatments https://www.who.int/who-documents-detail/draft-landscape-of-covid-19-candidate-vaccines
Danish Medicine Agency Drugs: Vaccines:	https://laegemiddelstyrelsen.dk/da/nyheder/temaer/ny-coronavirus-covid-19/~/media/5B83D25935DF43A38FF823E24604AC36.ashx https://laegemiddelstyrelsen.dk/da/nyheder/temaer/ny-coronavirus-covid-19/~/media/3A4B7F16D0924DD8BD157BBE17BFED49.ashx
Pang et al. 2020 [1] Drugs: Vaccines:	https://www.mdpi.com/2077-0383/9/3/623 Table 5+6, Table 3+4
SPS HS-report (UK)	unpublished
Secondary sources	
VfA/ Verband Forschender Arzneimittelhersteller Drugs: Vaccines:	https://www.vfa.de/de/arzneimittel-forschung/woran-wir-forschen/therapeutische-medikamente-gegen-die-coronavirusinfektion-covid-19 https://www.vfa.de/de/arzneimittel-forschung/woran-wir-forschen/impfstoffe-zum-schutz-vor-coronavirus-2019-ncov
EMA/ 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
CORDITE (CORona Drug InTEractions database)	https://cordite.mathematik.uni-marburg.de/#/
Living listing of interventional clinical trials in Covid-19/2019-nCoV produced by the Anticancer Fund	http://www.redo-project.org/covid19db/; http://www.redo-project.org/covid19_db-summaries/
Global Coronavirus COVID-19 Clinical Trial Tracker	https://www.covid-trials.org/
LitCovid	https://www.ncbi.nlm.nih.gov/research/coronavirus/
UK NIHR Innovation Observatory NIHR COVID-19 Studies COVID-19 Therapeutics Dashboard COVID-19: a living systematic map of the evidence	https://www.nihr.ac.uk/covid-studies/ http://www.io.nihr.ac.uk/report/covid-19-therapeutics/ http://eppi.ioe.ac.uk/cms/Default.aspx?tabid=3765
WHO COVID-19 Database new search interface	https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov
COVID-evidence Database	https://covid-evidence.org/database
Medical Library Association – COVID-19 Literature search strategies	https://www.mlanet.org/page/covid-19-literature-searching

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

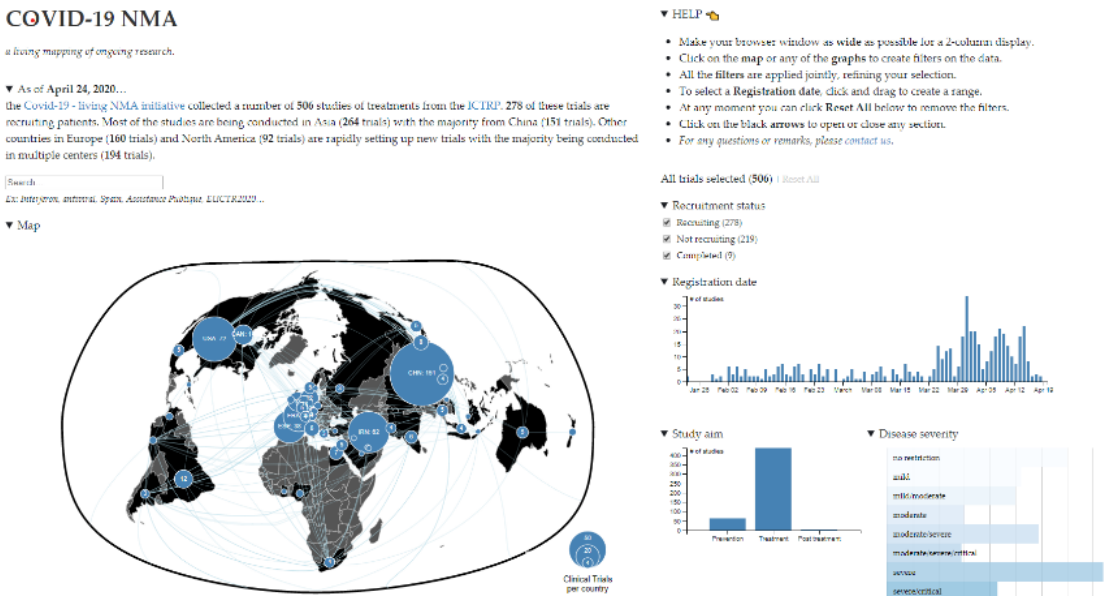
"lebende" Dokumente mit up-to-date Informationen

Several organisations and international teams of researchers are providing up-to-date information through living listing of interventional clinical trials in Covid-19/2019-nCoV and literature resources (Table 1.2 -1) [2-4] [2]. A short description of two of such databases is presented below.

Kartierung von aufenden RCTs

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

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



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

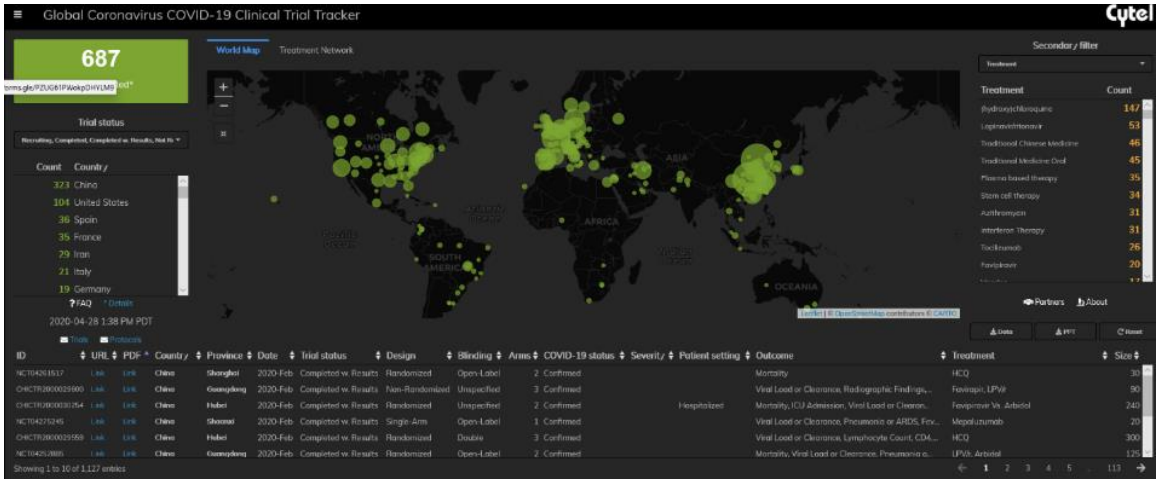


Figure 1.2-2: Global Coronavirus COVID-19 Clinical Trial Tracker - a real-time dashboard of clinical trials for COVID-19

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:

Vignetten zu Produkte, in "fortgeschrittenen" Stadien oder

- most advanced in clinical research in humans

häufig diskutiert/ publiziert

- most often discussed in clinical journals as potential candidates

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

2 Results: Vaccines

As of October 10, 2020 nine scientific articles were published with results related to early phases vaccine trials (phase 1, 1/2 or phase 2):

9 Publikationen zu Phase 1, 1/2 oder Phase 2 Impfstudien

1. a preliminary report with the results from the phase 1 study (NCT04283461) on Moderna Therapeutics vaccine [6];-and
2. the results from the expanded phase 1 study (NCT04283461) in older adults [7]
3. the results from the phase 1, dose-escalation, open-label, non-randomised, first-in-human trial for adenovirus type-5 vectored COVID-19 vaccine (ChiCTR2000030906/NCT04313127) [8],
4. as well as phase 2, randomised controlled trials (ChiCTR2000031781/NCT04398147) on CanSino Biological vaccine [9];
5. the results from the phase 1/2 RCT (NCT04368988) on Novavax vaccine [10];
6. a preliminary report with the results from phase 1/2 single-blind, RCT (ISRCTN 15281137/NCT04324606/EudraCT 2020-001072-15) on Oxford/Astra Zeneca [11];
7. results from two open, non-randomised phase 1/2 studies at two hospitals in Russia (NCT04436471 and NCT04437875) on Gamaleya vaccine [12].
8. Results from two phase 1/2 trials on BNT162b1 vaccine, one in US (NCT04368728/EudraCT 2020-001038-36) [13],
9. and one in Germany (NCT04380701, EudraCT 2020-001038-36) [14].

Due to an acceptable safety profile and induction of both humoral and cellular immune responses in participants, largescale evaluation of this candidate vaccines is ongoing in phase 3 programme.

As of October 10, 2020 effectivenes and safety of nine coronavirus vaccines are investigated in the final phase 3, randomised controlled trials:

Okt 2020: 9 Phase 3 RCTs laufen zu folgenden Produkten

Moderna
CanSino
Oxford/ AstraZeneca
BioNTech
Sinovac
Sinopharm
Gamaleya
Janssen Pharmaceuticals
Novavax

1. Moderna Therapeutics (RNA LNP-encapsulated mRNA vaccine encoding S protein);
2. CanSino Biological (Non-Replicating Viral Vector adenovirus Type 5 Vector vaccine that expresses S protein);
3. University of Oxford/AstraZeneca (Non-Replicating Viral Vector ChAdOx1 (AZD1222) vaccine);
4. BioNTech/Fosun Pharma/Pfizer (RNA 3 LNP-mRNAs vaccine);
5. Sinovac Biotech (inactivated vaccine);
6. Sinopharm (inactivated vaccine);
7. Gamaleya Research Institute (Non-Replicating Viral Vector Adeno-based - rAd5, rAd26) vaccine; and
8. Janssen Pharmaceuticals (Non-Replicating Viral Vector Ad26COVS1 vaccine); and

9. Novavax (Protein Subunit, VLP-recombinant protein nanoparticle vaccine + Matrix M) vaccine.

1 schwerwiegende Nebenwirkung bei AstraZeneca nach kurzer Pausierung Fortführung

1 Unterbrechung (Janssen/ J&J)

derzeit 2 Impfstoffe in „rolling review" bei EMA – Zulassung: Oxford/AstraZeneca BioNTech/ Pfizer

Because AstraZeneca reports suspected serious adverse event in a person who received the Oxford vaccine in the United Kingdom in September 2020, enrolment in global trials of this coronavirus-vaccine candidate are currently on hold. AstraZeneca voluntarily paused vaccination to allow review of safety data by an independent committee [15]. After few days pause, the trials restarted again. On October 01, 2020 EMA announced that EMA's human medicines committee (CHMP) has started the first 'rolling review' of University of Oxford/AstraZeneca vaccine [16].

On Oct 13th also Johnson & Johnson (Janssen) Covid-19 vaccine study was paused due to unexplained illness in participant.

On October 06, 2020 EMA's human medicines committee (CHMP) has started a 'rolling review' of data on a BNT162b2 vaccine, which is being developed by BioNTech in collaboration with Pfizer [17].

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

Company/Institution/Registry number	Technology		Stage/Sponsor	Source
	Platform	**Type of candidate vaccine**		
Moderna Therapeutics—US National Institute of Allergy **NCT04283461** **NCT04405076** **NCT04470427**	RNA	LNP-encapsulated mRNA vaccine encoding S protein	**Phase 1** **Phase 2** **Phase 3** National Institute of Allergy and Infectious Diseases (NIAID)	[18-22]
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.	[18-23]
ChiCTR2000031781/ **NCT04398147** **NCT04526990** **NCT04540419**			**Phase 2** Jiangsu Provincial Center for Disease Control and Prevention/ Institute of Biotechnology, Academy of Military Medical Sciences, PLA of China/ CanSino Biologics Inc. **Phase 3**	[18-20, 22, 23]
Inovio Pharmaceuticals **NCT04336410** **NCT04447781**	DNA	DNA plasmid vaccine encoding S protein delivered by electroporation	**Phase 1** **Phase 1/2a** Inovio Pharmaceuticals	[18-22]
Novavax **NCT04368988** **NCT04533399** **EUdraCT 2020-004123-16**	Protein Subunit	VLP-recombinant protein nanoparticle vaccine + Matrix M	**Phase 1/2** Novavax **Phase 2b** **Phase 3**	[18-21]
University of Queensland/ GSK/Dynavax **ACTRN12620000674932/NCT04495933**	Protein Subunit	Molecular clamp stabilized Spike protein with MF59 adjuvant	**Phase 1** The University of Queensland/Syneos Health, CEPI	[1, 2]
CureVac **NCT04449276** **NCT04515147**	RNA	mRNA	**Phase 1** CureVac **Phase 2**	[1, 2] [8,9]
University of Oxford/AstraZeneca **ISRCTN 15281137/NCT04324606/** **EudraCT 2020-001072-15**	Non-Replicating Viral Vector	ChAdOx1 (AZD1222)	**Phase 1/2** **Phase 2b/3** **Phase 3**	[18-21] [22, 24]

NCT04400838/EUdraCT 2020-001228-32 ISRCTN89951424, NCT04516746, NCT04540393			University of Oxford/AstraZeneca	
BioNTech/Fosun Pharma/Pfizer **ChiCTR2000034825 EudraCT 2020-001038-36/ NCT04380701 NCT04368728/EudraCT 2020-002641-42**	RNA	3 LNP-mRNAs	**Phase 1 Phase 1/2 Phase 2/3** BioNTech SE	[18-21] [22, 24]
Shenzhen Geno-Immune Medical Institute **NCT04299724**	Synthetic mini-gene -based product	Pathogen-specific aAPC	**Phase 1**	[21]
NCT04276896		LV-SMENP-DC	**Phase 1/2** Shenzhen Geno-Immune Medical Institute	[21]
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	[18-21]
Symvivo Corporation **NCT04334980**	DNA bacTRL platform	bacTRL-Spike	**Phase 1** Symvivo Corporation	[18-21]
Sinovac Biotech **NCT04352608 NCT04383574 NCT04551547 NCT04456595**	Inactivated	inactivated + alum	**Phase 1/2 Phase 3** Sinovac Research and Development Co, Ltd.	[18-22]
Wuhan Institute of Biological Products/Sinopharm **ChiCTR2000031809 ChiCTR2000034780**	Inactivated	Vero cells derived (cell culture-derived inactivated vaccines)	**Phase 1/2** Wuhan Institute of Biological Products/Sinopharm **Phase 3**	[18-20, 22, 23]
Beijing Institute of Biological Products/ Wuhan Institute of Biological Products/Sinopharm **ChiCTR2000032459 ChiCTR2000034780/NCT04510207 NCT04560881**			**Phase 1/2** **Phase 3** China National Biotec Group Company Limited	[22]
Institute of Medical Biology, Chinese Academy of Medical Sciences **NCT04412538**	Inactivated	Inactivated	**Phase 1 Phase 1/2**	[22] [18]

NCT04470609			Institute of Medical Biology, Chinese Academy of Medical Sciences	
Clover Biopharmaceuticals AUS Pty Ltd **NCT04405908**	Trimer-Tag© vaccine technology platform	spike proteins of the COVID-19 virus in a native trimeric form S-Trimer vaccine - a trimeric SARS-CoV-2 spike (S)-protein subunit	**Phase 1** Clover Biopharmaceuticals AUS Pty Ltd	[18]
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.	[18]
Cadila Healthcare Limited **CTRI/2020/07/026352**	DNA	DNA plasmid vaccine	**Phase 1/2** Cadila Healthcare Limited	[21]
Genexine Consortium **NCT04445389**	DNA	DNA Vaccine (GX-19)	**Phase 1/2** Genexine Consortium	[21]
Osaka University/ AnGes/ Takara Bio **JapicCTI-205328/ NCT04463472 NCT04527081**	DNA	DNA plasmid vaccine + Adjuvant	**Phase 1/2** Osaka University/ AnGes/ Takara Bio	[21]
Gamaleya Research Institute **NCT04436471 - Completed NCT04437875 – Completed NCT04530396 NCT04564716**	NonReplicating Viral Vector	Adeno-based (rAd5, rAd26)	**Phase 1/2** Gamaleya Research Institute **Phase 3**	[21]
Anhui Zhifei Longcom Biopharmaceutical/ Institute of Microbiology, Chinese Academy of Sciences **NCT04445194 NCT04537949 NCT04466085**	Protein Subunit	Adjuvanted recombinant protein (RBDDimer)	**Phase 1 Phase 1/2 Phase 2** Anhui Zhifei Longcom Biopharmaceutical/ Institute of Microbiology, Chinese Academy of Sciences	[21]
Vaxine Pty Ltd/Medytox **NCT04453852**	Protein Subunit	Recombinant spike protein with Advax™ adjuvant	**Phase 1** Vaxine Pty Ltd	[21]
Imperial College London **ISRCTN17072692**	RNA	LNP-nCoVsaRNA	**Phase 1** Imperial College London	[21]
People's Liberation Army (PLA) Academy of Military Sciences/Walvax Biotech **ChiCTR2000034112**	RNA	mRNA	**Phase 1** People's Liberation Army (PLA) Academy of Military Sciences/Walvax Biotech	[21]
Medicago Inc./ Université Laval **NCT04450004**	VLP	Plant-derived VLP adjuvanted with GSK or Dynavax adjs.	**Phase 1** Medicago Inc.	[21]

Bharat Biotech **NCT044571519** **CTRI/2020/09/027674**	Inactivated	Whole-Virion Inactivated	**Phase 1/2** Bharat Biotech	[21, 22]
Janssen Pharmaceutical Companies **NCT04436276** **NCT04505722**	NonReplicating Viral Vector	Ad26COVS1	**Phase 1/2** Janssen Pharmaceutical Companies **Phase 3**	[21, 22]
Kentucky Bioprocessing, Inc **NCT04473690**	Protein Subunit	RBD-based	**Phase 1/2** Kentucky Bioprocessing, Inc	[21, 22]
Arcturus/Duke-NUS **NCT04480957**	RNA	mRNA	**Phase 1/2** Arcturus/Duke-NUS	[21, 22]
Institute Pasteur/Themis/Univ. of Pittsburg CVR/Merck Sharp & Dohme **NCT04497298**	Replicating Viral Vector	Measles-vector based	**Phase 1** Institute Pasteur/Themis/Univ. of Pittsburg CVR/Merck Sharp & Dohme	[21, 22]
Medigen Vaccine Biologics Corporation/NIAID/Dynavax **NCT04487210**	Protein Subunit	S-2P protein + CpG 1018	**Phase 1** Medigen Vaccine Biologics Corporation/NIAID/Dynavax	[21, 22]
Research Institute for Biological Safety Problems, Rep of Kazakhstan **NCT04530357**	Inactivated	Inactivated	**Phase 1/2** Research Institute for Biological Safety Problems	[22] [21]
ReiThera/LEUKOCARE/Univercells **NCT04528641**	Non-Replicating Viral Vector	Replication defective Simian Adenovirus (GRAd) encoding S	**Phase 1** ReiThera	[22] [21]
Instituto Finlay de Vacunas, Cuba **IFV/COR/04**	Protein Subunit	RBD + Adjuvant	**Phase 1** Instituto Finlay de Vacunas	[22]
West China Hospital, Sichuan University **ChiCTR2000037518**	Protein Subunit	RBD (baculovirus production expressed in Sf9 cells)	**Phase 1** West China Hospital, Sichuan University	[22]
Beijing Wantai Biological Pharmacy/ Xiamen University **ChiCTR2000037782**	Replicating Viral Vector	Intranasal flu-based-RBD	**Phase 1** Beijing Wantai Biological Pharmacy/ Xiamen University	[22]
Sanofi Pasteur/GSK **NCT04537208**	Protein Subunit	S protein (baculovirus production)	**Phase 1/2** Sanofi Pasteur	[22] [21]
Federal Budgetary Research Institution State Research Center of Virology and Biotechnology "Vector" **NCT04527575**	Protein Subunit	Peptide	**Phase 1** Federal Budgetary Research Institution State Research Center of Virology and Biotechnology "Vector"	[22] [21]
SpyBiotech/Serum Institute of India **ACTRN12620000817943**	VLP	RBD-HBsAg VLPs	**Phase 1/2** Serum Institute of India	[22]
Beijing Minhai Biotechnology Co., Ltd ChiCTR2000038804	Inactivated	Inactivated	**Phase 1**	[22]

			Jiangsu Provincial Center for Disease Control and Prevention(Public Health Research Institute of Jiangsu Province)	
Vaxart **NCT04563702**	Non-Replicating Viral Vector	Ad5 adjuvanted Oral Vaccine platform	**Phase 1** Vaxarat	[22]
Ludwig-Maximilians - University of Munich **NCT04569383**	Non-Replicating Viral Vector	MVA-SARS-2-S	Phase 1 Universitätsklinikum Hamburg-Eppendorf	[22]
West China Hospital, Sichuan University **ChiCTR2000037518**	Protein Subunit	RBD (baculovirus production expressed in Sf9 cells)	**Phase 1** West China Hospital, Sichuan University	[22]
University Hospital Tuebingen **NCT04546841**	Protein Subunit	SARS-CoV-2 HLA-DR peptide	**Phase 1** University Hospital Tuebingen	[22]
COVAXX **NCT04545749**	Protein Subunit	S1-RBD-protein	**Phase 1** United Biomedical Inc., Asia	[22]

2.1 Moderna Therapeutics—US National Institute of Allergy

About the vaccine

mRNA-1273 collab mit NIAID/CEPI

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 [25]. An mRNA-based virus has not been approved for use in humans yet [26].

Estimated timeline for approval

Phase 1: 45 gesunde Erwachsene Juni 2021

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 [27]. Safety reviews are in place before dose escalation [27]. The primary endpoint of the study is frequency and grade of adverse reactions at 7/28/394 days post injection [25]. 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 2a: wird derzeit aufgesetzt bis August 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 3 Studienprotokoll veröffentlicht

RCT mt ca 30.000 Teilnehmer*innen

Zusammenarbeit mit NIAID (NIH)

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

vorläufige Publikation der Phase 1 Studie

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

As of August 17, 2020 a preliminary report with the results from the above mentioned phase 1 study was published [6]. After the first vaccination, antibody responses were higher with higher dose (day 29 enzyme-linked immunosorbent assay anti–S-2P antibody geometric mean titer [GMT], 40,227 in the 25-µg group, 109,209 in the 100-µg group, and 213,526 in the 250-µg group). After the second vaccination, the titers increased (day 57 GMT, 299,751, 782,719, and 1,192,154, respectively).

höhere Dosis, höhere Titer

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

Okt. 2020: Publikation der Phase 1 Studie

unterschiedliche Dosierung in verschiedenen Altersgruppen

As of October 10, 2020 Anderson et al 2020 [7] published results from the above mentioned phase 1, dose-escalation, open-label trial in healthy adults which was expanded to include 40 older adults, who were stratified according to age (56 to 70 years or ≥71 years). All the participants were assigned sequentially to receive two doses of either 25 µg or 100 µg of vaccine administered 28 days apart. Solicited adverse events were predominantly mild or moderate in severity and most frequently included fatigue, chills, headache, myalgia, and pain at the injection site. Such adverse events were dose-dependent and were more common after the second immunization. Binding-antibody responses increased rapidly after the first immunization. By day 57, among the participants who received the 25-µg dose, the anti–S-2P geometric mean titer (GMT) was 323,945 among those between the ages of 56 and 70 years and 1,128,391 among those who were 71 years of age or older; among the participants who received the 100-µg dose, the GMT in the two age subgroups was 1,183,066 and 3,638,522, respectively. After the second immunization, serum neutralizing activity was detected in all the participants by multiple methods. Binding and neutralizing-antibody responses appeared to be similar to those previously reported among vaccine recipients between the ages of 18 and 55 years and were above the median of a panel of controls who had donated convalescent serum. The vaccine elicited a strong CD4 cytokine response involving type 1 helper T cells. Authors concluded that in this small study involving older adults, adverse events associated with the mRNA-1273 vaccine were mainly mild or moderate. The 100-µg dose induced higher binding- and neutralizing-antibody titers than the 25-µg dose, which supports the use of the 100-µg dose in a phase 3 vaccine trial.

2.2 CanSino Biological Inc. and Beijing Institute of Biotechnology

About the vaccine

AD5-nCoV

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 [28-30]. The platform (non-replicating viral vector) of AD5-nCoV was originally used for an Ebola vaccine (AD5-EBOV) [30, 31].

Estimated timeline for approval

Phase 1:
108 gesunde Erwachsene
Dezember 2020

Phase 2:
Jänner 2021

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 [32]. New RCT, **phase 2**, started also (ChiCTR2000031781/NCT04398147). This randomised, double-blinded, placebo-controlled, parallel, three groups trial aims to evaluate safety and immunogenicity for recombinant novel coronavirus disease vaccine (adenovirus vector) in healthy adults aged above 18 years. Two intervention groups are using middle or low dose of novel vaccine, and the third group is using placebo. The primary endpoints of the trial are adverse reactions 0-14 days post vaccination; anti-S antibody IgG titer on day 28 post vaccination and anti-SARS-CoV-2 neutralizing antibody titer on day 28 post vaccination. Six further safety-related and immunogenetic are registered as secondary endpoints [22, 23]. This RCT will be conducted from 2020-04-12 to 2021-01-31.

1 veröffentlichte klinische Studie:

108 Studienteil-nehmer*innen erhalten unterschiedliche Dosierungen

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) [8]. 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.

As of 17 August, 2020 the results from the above mentioned phase 2 RCT were published [9]. 508 eligible participants (50% male; mean age 39·7 years, SD 12·5) consented to participate in the trial and were randomly assigned to receive the vaccine (1×10^{11} viral particles n=253; 5×10^{10} viral particles n=129) or placebo (n=126). In the 1×10^{11} and 5×10^{10} viral particles dose groups, the RBD-specific ELISA antibodies peaked at 656·5 (95% CI 575·2–749·2) and 571·0 (467·6–697·3), with seroconversion rates at 96% (95% CI 93–98) and 97% (92–99), respectively, at day 28. Both doses of the vaccine induced significant neutralising antibody responses to live SARS-CoV-2, with GMTs of 19·5 (95% CI 16·8–22·7) and 18·3 (14·4–23·3) in participants receiving 1×10^{11} and 5×10^{10} viral particles, respectively. Specific interferon γ enzyme-linked immunospot assay responses post vaccination were observed in 227 (90%, 95% CI 85–93) of 253 and 113 (88%, 81–92) of 129 participants in the 1×10^{11} and 5×10^{10} viral particles dose groups, respectively. Solicited adverse reactions were reported by 183 (72%) of 253 and 96 (74%) of 129 participants in the 1×10^{11} and 5×10^{10} viral particles dose groups, respectively. Severe adverse reactions were reported by 24 (9%) participants in the 1×10^{11} viral particles dose group and one (1%) participant in the 5×10^{10} viral particles dose group. No serious adverse reactions were documented. Authors concluded that the Ad5-vectored COVID-19 vaccine at 5×10^{10} viral particles is safe, and induced significant immune responses in the majority of recipients after a single immunisation.

Publikation der Phase 2 Studie (RCT)

508 Teilnehmer*innen

96%/ 97% Serokonversionsrate bei 2 unterschiedlichen Dosierungen

Two new **phase 3** RCTs are registered: a global multicenter, randomized, double-blind, placebo-controlled, adaptive designed clinical trial, to evaluate the efficacy, safety and immunogenicity of Recombinant Novel Coronavirus Vaccine (Adenovirus Type 5 Vector) in adults 18 years old and above, planned to enrol 40,000 partcipants in Pakistan (NCT04526990), and on 500 participants in Russian federation (NCT04540419). Estimated completion dates are December, 2021 and July, 2021, respectively [21].

2 neue Phase 3 RCTs registriert:
40.000 in Pakistan
500 Russland

bis 2021

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 [31, 33]. The company's DNA platform was previously utilised for a MERS-CoV vaccine (INO-4700) tested in a phase I trial [34].

INO-4800

Estimated timeline for approval

According to press releases from the manufacturer [34, 35], 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

Phase 1:
40 gesunde Erwachsene

April 2021

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 [18-22]. This RCT will be conducted from April 2020 to April 2021. Estimated Primary Completion Date is April 2021.

Phase 1/2: 160 gesunde Erwachsene in Korea

Phase 1/2 trial (NCT04447781) aims to evaluate the safety, tolerability and immunological profile of INO-4800 administered by intradermal (ID) injection followed by electroporation (EP) using the CELLECTRA® 2000 device in 160 healthy adults aged 19 to 64 years in Republic of Korea. INO-4800 contains the plasmid pGX9501, which encodes for the full length of the Spike glycoprotein of SARS-CoV-2 [21].

keine veröffentlichten klinischen Studien

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

2.4 Novavax

About the vaccine

CEPI
Matrix-M™

The Novavax COVID-19 vaccine being developed by Novavax and co-sponsored by CEPI [36] is a recombinant protein nanoparticle technology platform that is to generate antigens derived from the coronavirus spike (S) protein [37]. Novavax also expects to utilize its proprietary Matrix-M™ adjuvant in order to enhance immune responses. Matrix-M™ is Novavax patented saponin-based adjuvant that has the potential to boost the immune system by stimulating the entry of antigen-presenting cells into the injection site and enhancing antigen presentation in local lymph nodes, boosting immune responses [38, 39].

Estimated timeline for approval

Phase 1: 131 gesunde Erwachsene

Juli 2021

Novavax has been assessing recombinant nanoparticle vaccine candidates in animal models and they initiated Phase 1 clinical trial in May/June 2020 [36]. Novavax has previous experience with both MERS and SARS [38]. The phase 1/2, 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 [18-21]. This RCT will be conducted from May 15, 2020 to July 31, 2021. Estimated Primary Completion Date is December 31, 2020.

Phase 2b RCT 2.904 Südafrika bis 2021

A phase 2b RCT trial (NCT04533399) started also, to evaluate the effectiveness and safety in South Africans adults; 2904 participants are planned to enrolled, with estimated primary completion date in November 2021 [21].

A **phase 3** RCT (EUdraCT 2020-004123-16) is ongoing, in healthy adults in the UK. Main aim is to demonstrate the efficacy of SARS-CoV-2 rS with Matrix-M1 adjuvant in the prevention of virologically confirmed (by polymerase chain reaction [PCR]) to SARS-CoV-2, symptomatic COVID-19, when given as a 2-dose vaccination regimen, as compared to placebo, in serologically negative (to SARS-CoV-2) adult participants. 9000 participants are planned to enrolled.

Publikation der Phase 1/2

keine schwerwiegenden NW beobachtet

A randomized, placebo-controlled, phase 1–2 trial to evaluate the safety and immunogenicity of the rSARS-CoV-2 vaccine (in 5-µg and 25-µg doses, with or without Matrix-M1 adjuvant, and with observers unaware of trial-group assignments) in 131 healthy adults. In phase 1, vaccination comprised two intramuscular injections, 21 days apart. After randomization, 83 participants were assigned to receive the vaccine with adjuvant and 25 without adjuvant, and 23 participants were assigned to receive placebo. No serious adverse events were noted. Reactogenicity was absent or mild in the majority of participants, more common with adjuvant, and of short duration (mean, ≤2 days). One participant had mild fever that lasted 1 day. Unsolicited adverse events were mild in most participants; there were no severe adverse events. The addition of adjuvant resulted in enhanced immune responses, was antigen dose–sparing, and induced a T helper 1 (Th1) response. The two-dose 5-µg adjuvanted regimen induced geometric mean anti-spike IgG (63,160 ELISA units) and neutralization (3906) responses that exceeded geometric mean responses in convalescent serum from mostly symptomatic Covid-19 patients (8344 and 983, respectively). Authors concluded that at 35 days, NVX-CoV2373 appeared to be safe, and it elicited immune responses that exceeded levels in Covid-19 convalescent serum. The Matrix-M1 adjuvant induced CD4+ T-cell responses that were biased toward a Th1 phenotype [10].

2.5 University of Queensland/GSK/Dynavax

About the vaccine

DynaVax & GSK

Together with DynaVax and GlaxoSmithKline (GSK)[1], The University of Queensland currently investigates on a potential vaccine using molecular clamp stabilized Spike proteins [26, 31]. The so called 'molecular clamp' technology is hereby utilised: the intended prevention is through synthesising surface proteins and „clamping" them into shape. In so doing, the immune system may induce a response, by recognising them as the correct antigen on the surface of the virus, more easily [40].

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

Estimated timeline for approval

Beginn klinische Studie: September 2021

Phase 1 randomised, double blind, placebo-controled, dosage-escalaction trial has started on July 13, 2020 (ACTRN12620000674932/NCT04495933) with aim to evaluate the safety and immunogenicity of an adjuvanted SARS-

[1] Both DynaVax and GSK will provide adjuvants.

CoV-2 sclamp protein subunit vaccine in healthy adults. The estimated study completion date is September 2021 [9].

keine veröffentlichten klinischen Studien

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

2.6 CureVac

About the vaccine

mRNA

The vaccine candidates developed by CureVac are a protamine-complexed mRNA-based vaccine expressing undisclosed SARS-CoV-2 protein(s) [26]. 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 [42]. 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 [43].

Interimanalyse von Phase 1

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 [44]. The same concept and technology that was applied in the development of this vaccine will also be used for the vaccine against the the new coronavirus.

Estimated timeline for approval

Phase 1:
Beginn klinische Studie: Sommer 2020
168 Teinehmer*innen

To date (10/10/2020), one ongoing **Phase 1** (NCT04449276) study and no completed studies in humans are available for the vaccine candidates. Phase 1 (NCT04449276) study aims to evaluate the safety and reactogenicity profile after 1 and 2 dose administrations of CVnCoV at different dose levels. Is is funded by Coalition for Epidemic Preparedness Innovations (CEPI), and located in Belgium and Germany. 168 participants are planned to be enroll in the trial [21].

keine veröffentlichten klinischen Studien

Beginn Phase 2

Phase 2, RCT (NCT04515147) started also with aimto evaluate the safety and reactogenicity profile after 1 and 2 dose administrations of investigational SARS-CoV-2 mRNA vaccine (CVnCoV) at different dose levels and to evaluate the humoral immune response after 1 and 2 dose administrations of CVnCoV. 691 participants are planned to be enroll in the trial, with estimated study completion date in November 2021 [21].

2.7 University of Oxford

About the vaccine

ChAdOx1 nCoV-19

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 [28, 45].

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 [45].

Estimated timeline for approval

Phase 1/2:
510 gesunde Erwachsene

bis Mai 2021

Currently, the first clinical **phase 1/2** trial in 510 healthy adults is ongoing (ISRCTN 15281137/NCT04324606/EudraCT 2020-001072-15**)**. The study is a single-blinded, placebo-controlled, multi-centre randomised controlled trial to test efficacy, safety and immunogenicity of ChAdOx1 nCoV-19. The primary endpoints are number of virologically confirmed symptomatic cases/symptomatic cases of COVID-19 (efficacy) and occurrence of serious adverse events (safety). Primary endpoints are measured within six months and an optional follow-up visit is offered at day 364. The study is estimated to be completed in May 2021 [46].

Phase 2b/3 :
laufend

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

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

Ende Juli 2021

Phase 3 RCT (ISRCTN89951424) started in Brazil and South Africa, with another country in Africa set to follow, as well as a trial in the US (NCT04516746) [47]. Participants are randomly allocated to receive the investigational vaccine or a well-established meningitis vaccine. Volunteers will be followed for 12 months, and they will be tested for COVID-19 if they develop any symptoms which may represent COVID-19 disease[48]. The study is estimated to be completed in July 2021. In Russian Federation, phase 3 RCT (NCT04540393), planned to involve 100 adult healthy volunteers, with estimated study completion date in March 2021.

vorläufige Publikation der Ergebnisse Phase 1/2:

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

As of 17 August, 2020, a preliminary report with the results from phase 1/2 single-blind, RCT (ISRCTN 15281137/NCT04324606/EudraCT 2020-001072-15) was published [11]. 1077 participants were enrolled and assigned to receive either ChAdOx1 nCoV-19 (n=543) or MenACWY (n=534), ten of whom were enrolled in the non-randomised ChAdOx1 nCoV-19 prime-boost group. Local and systemic reactions were more common in the ChAdOx1 nCoV-19 group and many were reduced by use of prophylactic paracetamol, including pain, feeling feverish, chills, muscle ache, headache, and malaise (all $p<0{\cdot}05$). There were no serious adverse events related to ChAdOx1 nCoV-19. In the ChAdOx1 nCoV-19 group, spike-specific T-cell responses peaked on day 14 (median 856 spot-forming cells per million peripheral blood mononuclear cells, IQR 493–1802; n=43). Anti-spike IgG responses rose by day 28 (median 157 ELISA units [EU], 96–317; n=127), and were boosted following a second dose (639 EU, 360–792; n=10). Neutralising antibody responses against SARS-CoV-2 were detected in 32 (91%) of 35 participants after a single dose when measured in MNA80 and in 35 (100%) participants when measured in PRNT50. After a booster dose, all participants had neutralising activity (nine of nine in MNA 80 at day 42 and ten of ten in Marburg VN on day 56). Neutralising antibody responses correlated strongly with antibody levels measured by ELISA ($R^2=0{\cdot}67$ by Marburg VN; $p<0{\cdot}001$). Authors concluded that ChAdOx1 nCoV-19 showed an acceptable safety profile, and homologous boosting increased antibody responses and together

with the induction of both humoral and cellular immune responses, support largescale evaluation of this candidate vaccine in an ongoing phase 3 programme.

Sept 2020: RCT angehalten wegen schwerwiegender Nebenwirkungen

In September 2020, AstraZeneca reports suspected serious adverse event in a person who received the Oxford vaccine in the United Kingdom. Enrolment in global trials of a this coronavirus-vaccine candidate are on hold. AstraZeneca voluntarily paused vaccination to allow review of safety data by an independent committee [15].

Okt 2020: EMA Zulassungsbeginn in Form von "rolling review" basierend auf vorläufigen Daten

On October 01, 2020 EMA announced that EMA's human medicines committee (CHMP) has started the first 'rolling review' of this vaccine [16]. The decison to start the rolling review is based on preliminary results from non-clinical and early clinical studies suggesting that the vaccine triggers the production of antibodies and T cells (cells of the immune system, the body's natural defences) that target the virus. The rolling review will continue until enough evidence is available to support a formal marketing authorisation application.

2.8 BioNTech/Fosun Pharma/Pfizer

About the vaccine

BNT-162

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 [26]. In 2018, Pfizer and BioNTech collaborated on mRNA-based vaccines for the prevention of influenza and their partnership applies outside of China [49]. BioNTech's partnership with Fosun Pharma applies for China only [49, 50].

Estimated timeline for approval

Phase 1 / 2 mehrstufiges Studiendesign

Currently, BNT-162 enters clinical testing by the end of April 2020 [51] and R&D is supposed to be carried out both in the US as well as in Germany [49]. 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 BNT162a1, BNT162b1, BNT162b2, and BNT162c2): 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. Study NCT04380701 is located in Germany.

Phase 1/ 2 (Deutschland) hat begonnen

November 2022

Publikation der Phase 1/ 2

unterschiedliche Dosierungen

Mulligan et al 2020 [13] published results from above mentioned phase 1/ 2 ongoing study among 45 healthy adults (18–55 years of age) in US, who were randomized to receive 2 doses—separated by 21 days—of 10 μg, 30 μg or 100 μg of BNT162b1 (NCT04368728/EudraCT 2020-001038-36). BNT162b1 is a lipid-nanoparticle-formulated, nucleoside-modified mRNA vaccine that

encodes the trimerized receptor-binding domain (RBD) of the spike glycoprotein of SARS-CoV-2. Local reactions and systemic events were dose-dependent, generally mild to moderate, and transient. A second vaccination with 100 µg was not administered because of the increased reactogenicity and a lack of meaningfully increased immunogenicity after a single dose compared with the 30-µg dose. RBD-binding IgG concentrations and SARS-CoV-2 neutralizing titres in sera increased with dose level and after a second dose. Geometric mean neutralizing titres reached 1.9–4.6-fold that of a panel of COVID-19 convalescent human sera, which were obtained at least 14 days after a positive SARS-CoV-2 PCR. These results support further evaluation of this mRNA vaccine candidate.

weitere Phase 1 / 2 Studie publiziert

18-55 J

Sahin et al. 2020 published results from a second, non-randomised open-label phase 1/ 2 trial in healthy adults, 18-55 years of age in Germany (NCT04380701, EudraCT 2020-001038-36) [14] providing a detailed characterisation of antibody and T-cell immune responses elicited by BNT162b1 vaccination. Two doses of 1 to 50 μg of BNT162b1 elicited robust CD4+ and CD8+ T-cell responses and strong antibody responses, with RBD-binding IgG concentrations clearly above those in a COVID-19 human convalescent sample (HCS) panel. Day 43 SARS-CoV-2 serum neutralising geometric mean titers were 0.7-fold (1 μg) to 3.5-fold (50 μg) those of the HCS panel. Immune sera broadly neutralised pseudoviruses with diverse SARS-CoV-2 spike variants. Most participants had T helper type 1 (TH1) skewed T cell immune responses with RBD-specifc CD8+ and CD4+ T-cell expansion. Interferon (IFN)γ was produced by a high fraction of RBD-specifc CD8+ and CD4+ T cells. The robust RBD-specifc antibody, T-cell and favourable cytokine responses induced by the BNT162b1 mRNA vaccine suggest multiple benefcial mechanisms with potential to protect against COVID-19.

Publikation zu Sicherheitsdaten zur Auswahl von Kandidaten für Phase 2 / 3

Walsh et al 2020 [52, 53] recently reported, as preprint, additional safety and immunogenicity data from the US Phase 1 trial that supported selection of the vaccine candidate advanced to a pivotal phase 2/3 safety and efficacy evaluation: a direct comparison between BTN126b1 and BTN162b2 (NCT04368728) in healthy adults 18–55 and 65–85 years of age. BNT162b1 encodes a secreted trimerized SARS-CoV-2 receptor-binding domain, and BNT162b2 encodes a prefusion stabilized membrane-anchored SARS-CoV-2 full-length spike. Interim safety and immunogenicity data of BNT162b1 in younger adults have been reported previously from US and German trials. In both younger and older adults, the 2 vaccine candidates elicited similar dose dependent SARS-CoV-2–neutralizing geometric mean titers (GMTs), comparable to or higher than the GMT of a panel of SARS-CoV-2 convalescent sera. BNT162b2 was associated with less systemic reactogenicity, particularly in older adults. Authors concluded that results support selection of the BNT162b2 vaccine candidate for phase 2/3 large-scale safety and efficacy evaluation, currently underway.

Phase 2/3 RCT läuft derzeit

Phase 2/3 RCT is ongoing (NCT04368728/EudraCT 2020-002641-42) with aim to describe the safety, tolerability, immunogenicity and efficacy of RNA vaccine candidate against COVID-19 in healthy adults (Argentina, Brazil, South Africa, Turkey, US). The candidate selected for evaluation in Phase 2/3 is BNT162b2 (mid-dose). Estimated number of participants is 43998, and completion study date December 2022 [9].

On October 06, 2020 EMA announced that EMA's human medicines committee (CHMP) has started a 'rolling review' of BNT162b2 vaccine [17]. The decison to start the rolling review is based on preliminary results from non-clinical and early clinical studies suggesting that the vaccine triggers the production of antibodies and T cells (cells of the immune system, the body's natural defences) that target the virus. The rolling review will continue until enough evidence is available to support a formal marketing authorisation application.

Okt 2020: EMA Zulassungsbeginn in Form von "rolling review" mit vorläufigen Daten

2.9 Sinovac Biotech Ltd.

About the vaccine

CoronaVac

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

Estimated timeline for approval

Phase 1/2 : 743 Teilnehmer*innen

The **phase 1 and 2** trials started on April 16, 2020 in Jiangsu Province, China: a group of healthy adults aged 18-59 years old were vaccinated with a 0, 14 day schedule. According to Sinovac announcement, preliminary phase I/II results showed that there was no serious adverse event after vaccinating a total of 743 volunteers in the trials, demonstrating a good safety profile for the vaccine candidate. Over 90% seroconversion was observed in the phase II clinical trial 14 days after completion of a two-dose vaccination at day 0 and day 14. A Phase II study on elderly adults is being conducted which will be followed by child and adolescent groups. The phase II trial is expected to be completed at the end of 2020 [54].

A **phase 1/2** RCT on 552 healthy volunteers in China (NCT04551547) aims to evaluate the safety and immunogenicity of the experimental vaccine in healthy children and adolescents aged 3-17 years. Estimated study completion date is September 2021.

Sinovac: Phase 3 RCT in Brazilien 8.870, nur Gesundsheitspersonal

12-Monate Follow.Up Oktober 2021

Sinovac registered a new **Phase 3** RCT (NCT04456595), with aim to assess efficacy and safety of the Adsorbed COVID-19 (inactivated) vaccine in health care professionals in Brazil. Estimated number of participants is 8870. The study is double-blind placebo-controlled trial with participants randomly allocated 1:1 to placebo and vaccine arms. The immunization schedule is two doses intramuscular injections (deltoid) with a 14-days interval. For efficacy, the study aims to detect COVID-19 cases, defined as symptomatic SARS-CoV-2 infections, after the second week post-immunization schedule. For safety and immunogenicity, participants are categorized in two age groups, Adults (18-59 years) and Elderly (60 years and above). Safety database aims to detect adverse reactions with frequency of 1:1000 or higher in adults and 1:500 in elderly. All participants will be followed up to 12 months. Interim preliminary efficacy analysis can be triggered by reaching the target number of 150 cases [21]. The study is estimated to be completed in October 2021.

2.10 China National Pharmaceutical Group Corporation (SINOPHARM)

About the vaccine

inactivated

The China National Pharmaceutical Group Corporation (SINOPHARM), the state-owned Chinese company, developed a β-propiolactone–inactivated whole-virus vaccine against COVID-19 jointly by the Beijing Institute of Biological Products and the Wuhan Institute of Biological Products under SINOPHARM [55].

Estimated timeline for approval

Phase 1 und Phase 2 RCTs

In interim analysis related to safety and immunogenicity of an investigational inactivated whole-virus COVID-19 vaccine in China (Chinese Clinical Trial Registry Identifier: ChiCTR2000031809, Xia et al. 2020 [55, 56]) reported results from two double-blind RCTs, phase 1 and phase 2. The experimental group received a β-propiolactone–inactivated whole-virus vaccine against COVID-19. The placebo group contained only sterile phosphatebuffered saline and alum adjuvant.

Phase 1: 96 Teilnehmer*innen – 3 unterschiedliche Dosierungen

Phase 2: 224 Teilnehmer*innen – 2 unterschiedliche Zeitpläne

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

Endpunkte: Antikörper Response

Nebenwirkungen

Among 320 patients who were randomized, all completed the trial up to 28 days after the whole-course vaccination. The 7-day adverse reactions occurred in 3 (12.5%), 5 (20.8%), 4 (16.7%), and 6 (25.0%) patients in the alum only, low-dose, medium-dose, and high-dose groups, respectively, in the phase 1 trial; and in 5 (6.0%) and 4 (14.3%) patients who received injections on days 0 and 14 for vaccine and alum only, and 16 (19.0%) and 5 (17.9%) patients who received injections on days 0 and 21 for vaccine and alum only, respectively, in the phase 2 trial. The most common adverse reaction was injection site pain, followed by fever, which were mild and self-limiting; no serious adverse reactions were noted. The geometric mean titers of neutralizing antibodies in the low-, medium-, and high-dose groups at day 14 after 3 injections were 316 (95% CI, 218-457), 206 (95% CI, 123-343), and 297 (95% CI, 208-424), respectively, in the phase 1 trial, and were 121 (95% CI, 95-154) and 247 (95% CI, 176-345) at day 14 after 2 injections in participants receiving vaccine on days 0 and 14 and on days 0 and 21, respectively, in the phase 2 trial. Authors concluded that in this interim report of the phase 1 and phase 2 trials of an inactivated COVID-19 vaccine, patients had a low rate of adverse reactions and demonstrated immunogenicity; the study is ongoing. Efficacy and longer-term adverse event assessment will require phase 3 trials [55].

Phase 3 initiiert

Juli 2021

A **phase 3** double-blind, placebo controlled RCT has been initiated (ChiCTR2000034780), to evaluate the protective efficacy of inactivated SARS-CoV-2 Vaccine (Vero Cell) after full course of immunization in

preventing diseases caused by the SARS-CoV-2 in healthy subjects aged 18 years old and above. The study is estimated to be completed in July 2021.

A phase 3, randomized, double blind, placebo parallel-controlled clinical trial to evaluate the efficacy, immunogenicity and safety of the inactivated SARS-CoV-2 Vaccine (Vero cell) in Argentina, in 3000 healthy participants aged between 18 and 85 years old, is underway also (NCT04560881). The study is estimated to be completed in December 2021.

2.11 New vaccines entered in clinical investigation in healthy volunteers

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

As at 05 May 2020, **6 new vaccine trials** are registered in phase 1, phase 1/2 and phase 2, by Shenzhen Geno-Immune Medical Institute (NCT04299724 and NCT04276896); Insitute of Biotechnology, Academy of Military Medical Sciences, PLA of China (NCT04341389); Symvivo Corporation (NCT04334980); Sinovac (NCT04352608) and Wuhan Institute of Biological Products/Sinopharm (ChiCTR2000031809) (Table 2-1). NCT04299724 is phase 1 study related to pathogen-specific aAPC (aAPCs modified with lentiviral vector expressing synthetic minigene based on domains of selected viral proteins) and NCT04276896 is phase 1/2 study related to LV-SMENP-DC vaccine (DCs modified with lentiviral vector expressing synthetic minigene based on domains of selected viral proteins; administered with antigen-specific CTLs). NCT04341389 is phase 2 trial related to adenovirus Type 5 Vector expressing S protein. NCT04334980 is phase 1 study, the first-in-human study of bacTRL-Spike, and the first-in-human use of orally delivered bacTRL. Two clinical trials in phase 1/2 are related to inactivated vaccine: NCT04352608 is related to inactivated SARS-CoV-2 virus and ChiCTR2000031809 to Vero cells derived (cell culture-derived inactivated) vaccine [18-23].

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

As at 13 June 2020, **four new vaccine trials** are registered: two new inactivated vaccines in phase 1 and phase 1/2, by Beijing Institute of Biological Products/Sinopharm (ChiCTR2000032459) and Institute of Medical Biology, Chinese Academy of Medical Sciences (NCT04412538) [22]; one S-Trimer vaccine - a trimeric SARS-CoV-2 spike (S)-protein subunit, through Trimer-Tag© vaccine technology platform, by Clover Biopharmaceuticals AUS Pty Ltd (NCT04405908), https://www.pharmaadvancement.com/manufacturing/cepi-announces-covid-19-vaccine-development-partnership-with-clover-biopharmaceuticals-australian-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).

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

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

vaccine from Medicago Inc./Université Laval (NCT04450004) (Table 2-1) [22].

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

As at August 14, 2020, **six new vaccines trials** (Phase 1 or Phase 1/ 2) are registered in ClinicalTrials.gov register: Bharat Biotech (NCT044571519, Inactivated); Janssen Pharmaceutical Companies (NCT04436276, NonReplicating Viral Vector, Ad26COVS1); Kentucky Bioprocessing, Inc (NCT04473690, Protein Subunit, RBD-based); Arcturus/Duke-NUS (NCT04480957, RNA, mRNA); Institute Pasteur/Themis/Univ. of Pittsburg CVR/Merck Sharp & Dohme (NCT04497298, Replicating Viral Vector, Measles-vector based) and Medigen Vaccine Biologics Corporation/NIAID/Dynavax (NCT04487210, Protein Subunit, S-2P protein + CpG 1018) (Table 2-1) [22].

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

Two studies are reported as completed (NCT04436471 and NCT04437875) [21], sponsored by **Gamaleya Research Institute of Epidemiology and Microbiology, Health Ministry of the Russian Federation** in collaboration with Acellena Contract Drug Research and Development, aimed to evaluate the safety, tolerability and immunogenicity of the vaccine Gam-COVID-Vac, adenoviral-based vaccine against SARS-CoV-2, a solution for intramuscular injection, now with published results. A heterologous COVID-19 vaccine consisting of two components, a recombinant adenovirus type 26 (rAd26) vector and a recombinant adenovirus type 5 (rAd5) vector, both carrying the gene for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike glycoprotein (rAd26-S and rAd5-S). Trials aimed to assess the safety and immunogenicity of two formulations (frozen and lyophilised) of this vaccine.

Phase 1/ 2 Studien in Russland

Two open, non-randomised **phase 1/2** studies at two hospitals in Russia (NCT04436471 and NCT04437875) enrolled healthy adult volunteers (men and women) aged 18–60 years. In phase 1 of each study, administered intramuscularly on day 0 either one dose of rAd26-S or one dose of rAd5-S and assessed the safety of the two components for 28 days. In phase 2 of the study, which began no earlier than 5 days after phase 1 vaccination, administered intramuscularly a prime-boost vaccination, with rAd26-S given on day 0 and rAd5-S on day 21. Primary outcome measures were antigen-specific humoral immunity (SARS-CoV-2-specific antibodies measured by ELISA on days 0, 14, 21, 28, and 42) and safety (number of participants with adverse events monitored throughout the study). Secondary outcome measures were antigen-specific cellular immunity (T-cell responses and interferon-γ concentration) and change in neutralising antibodies (detected with a SARS-CoV-2 neutralisation assay).

insg. 76 Teilnehmer*innen (je 38) gute Verträglichkeit und Antikörperentwicklung

76 participants were enrolled to the two studies (38 in each study). In each study, nine volunteers received rAd26-S in phase 1, nine received rAd5-S in phase 1, and 20 received rAd26-S and rAd5-S in phase 2. Both vaccine formulations were safe and well tolerated. The most common adverse events were pain at injection site (44 [58%]), hyperthermia (38 [50%]), headache (32 [42%]), asthenia (21 [28%]), and muscle and joint pain (18 [24%]). Most adverse events were mild and no serious adverse events were detected. All participants produced antibodies to SARS-CoV-2 glycoprotein. At day 42, receptor binding domain-specific IgG titres were 14 703 with the frozen formulation and 11 143 with the lyophilised formulation, and neutralising antibodies were 49.25 with the frozen formulation and 45.95 with the lyophilised formulation, with a seroconversion rate of 100%. Cell-mediated responses were detected in all participants at day 28, with median cell proliferation of 2.5% CD4+ and 1.3% CD8+ with the frozen formulation, and a median cell proliferation of 1.3% CD4+ and 1·1% CD8+ with the lyophilised formulation. Authors concluded that the heterologous rAd26 and

rAd5 vector-based COVID-19 vaccine has a good safety profile and induced strong humoral and cellular immune responses in participants [12].

Sputnik zugelassen Phase 3 aber erst begonnen

Based on these results, according to recent press release, Russian COVID-19 vaccine, called Sputnik V, is the first in the world received national regulatory approval, and was approved for public use even ahead of its Phase III trial. **Phase 3** randomised controlled trial is now underway (NCT04530396). The trial will include 40000 volunteers, with estimated study completion date in May 2021. Phase 3 randomised controlled trial is underway (NCT04564716) in Belarus also, with estimated enrollment of 100 participants.

Janssen Pharmaceutical: Beginn Phase 3 60.000 Teilnehmer*innen Ende 2023

Janssen Pharmaceutical registered **phase 3**, randomised controlled trial (NCT04505722) to demonstrate the efficacy of Ad26.COV2.S in the prevention of molecularly confirmed moderate to severe/critical COVID-19, compared to placebo, in SARS-CoV-2 adult participants. Estimated enrollment is 60,000 participants, with study completion day in March 2023.

Publikation von Phase 1/ 2 Studie

56 Teilnehmer*innen unterschiedliche Dosierungen

Sadoff et al. 2020 [57] reported, as preprint, interim results of a a phase 1 / 2 a, double-blind, randomized, placebo-controlled, Janssen Pharmaceutical trial related to safety and immunogenicity of the Ad26.COV2.S COVID-19 vaccine candidate (NCT04436276) in healthy adults. Ad26.COV2.S was administered at a dose level of 5x1010 or 1x1011 viral particles (vp) per vaccination, either as a single dose or as a two-dose schedule spaced by 56 days in healthy adults (18-55 years old; cohort 1a & 1b; n= 402 and healthy elderly >65 years old; cohort 3; n=394). Vaccine elicited S specific antibody levels were measured by ELISA and neutralizing titers were measured in a wild-type virus neutralization assay (wtVNA). CD4+ T-helper (Th)1 and Th2, and CD8+ immune responses were assessed by intracellular cytokine staining (ICS).

vorläufige Ergebnisse:

milde oder moderate Nebenwirkungen

Interim analyses after the first dose of blinded safety data from cohorts 1a, 1b and 3 and group unblinded immunogenicity data from cohort 1a and 3 are presented in details. In cohorts 1 and 3 solicited local adverse events were observed in 58% and 27% of participants, respectively. Solicited systemic adverse events were reported in 64% and 36% of participants, respectively. Fevers occurred in both cohorts 1 and 3 in 19% (5% grade 3) and 4% (0% grade 3), respectively, were mostly mild or moderate, and resolved within 1 to 2 days after vaccination. The most frequent local adverse event (AE) was injection site pain and the most frequent solicited AEs were fatigue, headache and myalgia. Authors concluded that the safety profile and immunogenicity after only a single dose are supportive for further clinical development of Ad26.COV2.S at a dose level of 5x1010 vp, as a potentially protective vaccine against COVID-19.

Studienunterbrechung wegen NW

On Oct 13th also Johnson & Johnson (Janssen) Covid-19 vaccine study was paused due to unexplained illness in participant.

Sept 2020: 7 neue Impfstudien registriert

As at September 09, 2020, **seven new vaccine trials** (phase 1 or phase 1/ 2) are registered in ClinicalTrials.gov register: on inactivated vaccine from Research Institute for Biological Safety Problems, Rep of Kazakhstan (NCT04530357); four protein subunit vaccines from Instituto Finlay de Vacunas, Cuba (IFV/COR/04); West China Hospital, Sichuan University (ChiCTR2000037518); Sanofi Pasteur/GSK (NCT04537208), and Federal Budgetary Research Institution State Research Center of Virology and Biotechnology "Vector" (NCT04527575); one Non-Replicating Viral Vector vaccine from ReiThera/LEUKOCARE/Univercells (NCT04528641), and one

intranasal Replicating Viral Vector vaccine from Beijing Wantai Biological Pharmacy/ Xiamen University (ChiCTR2000037782) (Table 2-1) [22].

Okt 2020: 7 neue Impfstudien registriert

As of October 02, 2020, seven new vaccine trials (phase 1 or phase 1/ 2) are registered: one VLP (RBD-HBsAg VLPs) from SpyBiotech/Serum Institute of India (ACTRN12620000817943); one inactivated from Beijing Minhai Biotechnology Co., Ltd (ChiCTR2000038804); two Non-Replicating Viral Vector vaccine from Vaxart (NCT04563702) and Ludwig-Maximilians - University of Munich (NCT04569383); and three protein subunit from West China Hospital, Sichuan University (ChiCTR2000037518), University Hospital Tuebingen (NCT04546841) and COVAXX (NCT04545749) [22].

mehrere klinische Studien mit BCG Vazzinen in Phase 3 oder geplant

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 [58]. The same is true for US RCT (NCT04348370) [21]. The same is planned in Egypt (NCT04350931) and in Denmark (NCT04373291) (RCTs, not yet recruiting healthy volunteers) [21].

Impfkandidaten-Infrastruktur und Monitoring Projekt

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.

Positionspapier der Internationalen Regulatoren

stringente klinische Studien vonnöten !

On 09/07/2020, Medicines Regulatory Authorities published the report related to phase 3 COVID-19 vaccine trials [59]. They stressed the need for large phase 3 clinical trials that enroll many thousands of people, including those with underlying medical conditions, to generate relevant data for the key target populations. Also broad agreement was achieved that clinical studies should be designed with stringent success criteria that would allow a convincing demonstration of the efficacy of COVID-19 vaccines.

3 Results: Therapeutics

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

Drug	Mechanism of operation	Studies in ClinicalTrials.gov & EU CTR listed as completed, suspended, terminated or withdrawn, with trial identifier[2]
Remdesivir (Veklury®)	Antiviral agent	NCT04252664 – **Suspended** NCT04257656 – **Terminated** NCT04292899, EUdraCT 2020-000841-15 – **Completed** NCT04292730, EudraCT 2020-000842-32 – **Completed** NCT04280705 – **Completed**
Lopinavir + Ritonavir (Kaletra®)	Antiviral agent	NCT04276688 – **Completed** NCT04307693 – **Terminated** NCT04409483 – **Withdrawn**
Favipiravir (Avigan, T-705)	Antiviral agent	ChiCTR2000030254 – **Completed** NCT04349241– **Completed** NCT04542694 – **Completed** NCT04542694 – **Completed**
Darunavir (Prezista®)	Antiviral agent	No completed, withdrawn, suspended or terminated studies found
Camostat Mesilate (Foipan®)	Antiviral cell-entry inhibitor	No completed, withdrawn, suspended or terminated studies found
APN01 (rhACE2)	Antiviral cell-entry inhibitor	NCT04287686 – **Withdrawn**
Tocilizumab (RoActemra®)	Monoclonal antibody	NCT04331795 – **Completed** NCT04346355 – **Terminated** NCT04361552 – **Withdrawn** NCT04320615, EudraCT 2020-001154-22 – **Completed** NCT04492501 – **Completed** NCT04519385 – **Completed** NCT04363736 – **Completed** NCT04403685 – **Terminated** NCT04322773 – **Terminated**
Sarilumab (Kevzara®)	Monoclonal antibody	NCT04341870 – **Suspended** NCT04327388 – **Completed** NCT04315298 – **Completed**
Interferon beta 1a (SNG001) **and 1b**	Interferon	NCT04276688 Interferon beta 1b – **Completed** NCT04343768 – **Completed**
Convalescent Plasma	Convalescent Plasma	NCT04325672 – **Withdrawn** NCT04346446 – **Completed** NCT04407208 – **Completed** NCT04441424 – **Completed** NCT04442958 – **Completed** NCT04389944 – **Completed** NCT04356534 – **Completed** NCT04442958 – **Completed** NCT04569188 – **Completed** NCT04392414 – **Completed** NCT04375098 – **Completed**

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

		NCT04383535 – **Completed**
Plasma derived medicinal products	Plasma derived medicinal products	NCT04411628 - **Completed**
Solnatide	Synthetic peptide	No completed, withdrawn, suspended or terminated studies found
Umifenovir (Arbidol®)	Antiviral agent	No completed, withdrawn, suspended or terminated studies found
Dexamethasone and other corticosteroids	Glucocorticoid	NCT04445506 – **Completed** NCT04327401 – **Terminated** Other corticosteroids: NCT04273321 – **Completed**
Anakinra (Kyneret®)	Interleukin 1 receptor antagonist	No completed, withdrawn, suspended or terminated studies found
Colchicine	An alkaloid, with anti-gout and anti-inflammatory activities	No completed, withdrawn, suspended or terminated studies found
Nafamostat (Futhan©)	Trypsin-like serine protease inhibitor	No completed, withdrawn, suspended or terminated studies found
Gimsilumab	Human monoclonal antibody	No completed, withdrawn, suspended or terminated studies found
Canakinumab	Human monoclonal antibody	No completed, withdrawn, suspended or terminated studies found
Lenzilumab	Recombinant monoclonal antibody	No completed, withdrawn, suspended or terminated studies found

3.1 Remdesivir (Veklury®)

About the drug under consideration

erstes zugelassenes antivirales Medikament gegen Coronavirus

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

conditional marketing authorisation

Zulassung basiert auf vorläufigen Daten

Beigel et al.Studie (NIAID-ACTT1)

After the "rolling review" of data on the use of remdesevir to treat COVID-19 was concluded on 15 May 2020 [60] and after received application for conditional marketing authorisation (CMA) (08 June 2020), **European Medicine Agency's (EMA)** Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion on June 25, 2020, recommending the granting of a **conditional marketing authorisation** [61].This conditional marketing authorisation has been granted by the **European Commission** on **July 3, 2020,** https://ec.europa.eu/commission/presscorner/detail/en/mex_20_1266. The EMA's positive recommendation is mainly based on preliminary data published by Beigel et al. [62], described in section below - Results of publications.

bis August sollen "Safety" Daten vorgelegt werden (u.a. Mortalität)

Remdesivir (Veklury) is subject to **additional monitoring for safety**. Due to a conditional marketing authorisation, Marketing Authorisation Holder (MAH) should complete some **measures to confirm the efficacy and safety**

within different timeframe. Till August 2020, the MAH should submit the published final D28 mortality data by ordinal scale categories of Study CO-US-540-5776 (NIAID-ACTT1) and in addition, the MAH should discuss potential imbalance in the use of corticosteroids and effect modification in Study CO-US-540-5776. Till December 2020, MAH should submit the final clinical study report (CSR) of Study CO-US-540-5776 (NIAID-ACTT1); the final CSR for Part A (Day 28) of Study GS-US-540-5773; the final CSR for Part A (Day 28) of Study GS-US-540-5774, as well as analysis of all available safety data from clinical trials CO-US-540-5776, GS-US-540-5773, GS-US-540-5774 and CO-US-540- 5758 when completed, including case narratives, detailed information about adverse reaction and exposure data as well as an analysis of occurrence and aggravation of AEs, SAEs and ADRs are associated with increasing exposure [63].

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

Remdesivir (Veklury) is **indicated** for the treatment of coronavirus disease 2019 (COVID-19) in adults and adolescents (aged 12 years and older with body weight at least 40 kg) with pneumonia requiring supplemental oxygen. The drug is for administration by intravenous infusion after further dilution. The **recommended dosage** of remdesivir in patients 12 years of age and older and weighing at least 40 kg is: Day 1 – single loading dose of remdesivir 200 mg given by intravenous infusion, Day 2 onwards – 100 mg given once daily by intravenous infusion. The total **duration of treatment** should be at least 5 days and not more than 10 days. **Concomitant use** of remdesivir **with chloroquine phosphate or hydroxychloroquine sulphate** is **not recommended** due to antagonism observed in vitro.

Nebenwirkungen

The **most common adverse reaction** in healthy volunteers is increased transaminases (14%). The most common adverse reaction in patients with COVID-19 is nausea (4%) [63].

Okt 2020: EMA beginnt Sicherheitsanalyse wegen Inzidenzen zu aktutem Nierenversagen nach Remdesivir Therapie

On October 02, 2020 EMA announced that EMA's safety committee (PRAC) has started a review of a safety signal to assess reports of acute kidney injury in some patients with COVID-19 taking Veklury (remdesivir) [64]. The reports form a 'safety signal' - information on a new or incompletely documented adverse event that is potentially caused by a medicine and that warrants further investigation. The PRAC has started this review based on the results from continuous signal detection work undertaken in EudraVigilance. The PRAC is now carefully assessing all available data to evaluate if the medicine may have been responsible for the kidney problems and if there is a need to update the existing information for Veklury.

derzeit haben sich Anwendungs-Empfehlungen nicht geändert

Recommendations for the use of this medicine have not changed. The product information already advises doctors to monitor patients for renal impairment prior to and during treatment and not start treatment in patients with an important decrease in renal function. EMA is reviewing any new information that becomes available through monthly summary safety reports (a tool for enhanced safety monitoring), periodic safety update reports and signal detection. In cases where a causal relationship is confirmed or considered likely, regulatory action may be necessary and this usually takes the form of an update of the SmPC and the package leaflet. EMA will further communicate on the outcome of the PRAC's review.

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 [65]. 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 [66, 67]. On June 15, 2020 FDA issued the **warning about co-administration** of remdesivir and **chloroquine phosphate or hydroxychloroquine sulphate** which may result in reduced antiviral acitvity of remdesivir [68]. On August 28, 2020 FDA **broadens Emergency Use Authorization** for Veklury (remdesivir) to include **all hospitalized adult and pediatric patients with suspected or laboratory-confirmed COVID-19, irrespective of their severity of disease** [69].

FDA: "expanded access program" (März)

Emergency Use Authorization (EUA) (Mai)

basierend auf 2 Studien:

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

FDA Warnung vor Komedikation Chloroquin phosphate, Hydroxychloroquin sulphate

Aug 2020: FDA verbreitert Indikation auf alle hospitalisierten Pts.

US COVID-19 Treatment Guidelines Panel issued recommendations on remdesivir treatment for patients with COVID-19 (as of July 24, 2020) [70]:

Empfehlungen des US COVID-19 Treatment Guidelines Panel

1. **Recommendation for Prioritizing Limited Supplies of Remdesivir**: Because remdesivir supplies are limited, the Panel recommends that remdesivir be prioritized for use in hospitalized patients with COVID-19 who require supplemental oxygen but who are not on high-flow oxygen, noninvasive ventilation, mechanical ventilation, or extracorporeal membrane oxygenation (ECMO) **(BI).**

   RDV bei schwerer COVID-19 Erkrankung mit künstlicher Beatmung

2. **Recommendation for Patients with Mild or Moderate COVID-19:** There are insufficient data for the Panel to recommend either for or against the use of remdesivir in patients with mild or moderate COVID-19.

   insuffiziente Datenlage bei moderater/ milder Erkrankung

3. **Recommendation for Patients with COVID-19 Who Are on Supplemental Oxygen but Who Do Not Require High-Flow Oxygen, Noninvasive or Invasive Mechanical Ventilation, or ECMO:** The Panel recommends using remdesivir for 5 days or until hospital discharge, whichever comes first **(AI)**. If a patient who is on supplemental oxygen while receiving remdesivir progresses to requiring high-flow oxygen, noninvasive or invasive mechanical ventilation, or ECMO, the course of remdesivir should be completed.

   5-Tagestherapie

4. **Recommendation for Patients with COVID-19 Who Require High-Flow Oxygen, Noninvasive Ventilation, Mechanical Ventilation, or ECMO**: Because there is uncertainty regarding whether starting remdesivir confers clinical benefit in these groups of patients, the Panel cannot make a recommendation either for or against starting remdesivir. In a randomized clinical trial, there was no observed difference between the remdesivir and placebo groups in time to recovery or mortality rate in these subgroups. However, because the trial was not powered to detect differences in outcomes in these

   keine Aussagen zu Subgruppen möglich

subgroups, there is uncertainty as to the effect of remdesivir on the course of COVID-19 in these patients.

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

bei Nicht-Ansprechen ev. Verlängerung auf 10-Tagestherapie

Rochwer et al. [71] published a **clinical practice guideline** in which the guideline panel makes a weak recommendation for the use of remdesivir in severe covid-19 while recommending continuation of active enrolment of patients into ongoing randomised controlled trials examining remdesivir. This was based on the linked systematic review (published 31 Jul 2020) which identified two randomised trials with 1300 participants, showing low certainty evidence that remdesivir may be effective in reducing time to clinical improvement and may decrease mortality in patients with severe covid-19. Remdesivir probably has no important effect on need for invasive mechanical ventilation. Remdesivir may have little or no effect on hospital length of stay.

niedrige Evidenz der Datenlage, weitere klinsche Studien zum Nutzen notwendig

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

Vorhaben von Gilead: Darreichungsform mittels Inhalator

Completed, withdrawn, suspended or terminated studies

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

in ClinicalTrials.gov & EUdraCT

keine weiteren beendeten Studien

The search in two clinical trial registers (ClinicalTrials.gov and EUdraCT) on 15/08/2020 yielded three completed studies on the safety and efficacy of RVD in COVID-19 patients: a phase 3 RCT (NCT04292899, EUdraCT 2020-000841-15) conducted in 4891 severe COVID-19 patients, with publication [72]; a phase 3 RCT conducted in 1113 moderate COVID-19 patients (NCT04292730, EudraCT 2020-000842-32), and phase 3 RCT, Adaptive COVID-19 Treatment Trial (ACTT) on 1062 COVID-19 patients (NCT04280705), with preliminary report [49]. As of 10/10/2020 no new completed, withdrawn, suspended or terminated studies found.

Sept 2020: keine weiteren beendeten Studien

Results of publications

Ergebnisse der Studien:

At 6th of May 2020, Wang Y et al. [73] 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.

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. [62] 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. Details could be found in previous versions of this Report.

Beigel (USA, UK, DK....): 1.059 Pts
RDV iv 10 Tage

frühzeitige Entblindung wegen verkürzter Zeit zu Verbesserung (primärer Endpunkt)

On October 8, 2020 the final report of Beigel et al. [74] was published. It is an ongoing was double-blind, randomized, placebo-controlled trial of intravenous remdesivir in adults hospitalized with Covid-19 with evidence of lower respiratory tract involvement (NCT04280705). 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 by day 29, defined by either discharge from the hospital or hospitalization for infection-control purposes only. A total of 1062 patients underwent randomization (with 541 assigned to remdesivir and 521 to placebo). Those who received remdesivir had a median recovery time of 10 days (95% confidence interval [CI], 9 to 11), as compared with 15 days (95% CI, 13 to 18) among those who received placebo (rate ratio for recovery, 1.29; 95% CI, 1.12 to 1.49; $P<0.001$, by a log-rank test). The rate ratio for recovery was largest among patients with a baseline ordinal score of 5 (rate ratio for recovery, 1.45; 95% CI, 1.18 to 1.79). In an analysis that used

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

a proportional odds model with an eight-category ordinal scale, the patients who received remdesivir were found to be more likely than those who received placebo to have clinical improvement at day 15 (odds ratio, 1.5; 95% CI, 1.2 to 1.9, after adjustment for actual disease severity).

bei Mortalität: kein Unterschied

The Kaplan–Meier estimates of mortality were 6.7% with remdesivir and 11.9% with placebo by day 15 (hazard ratio, 0.55; 95% CI, 0.36 to 0.83) and 11.4% with remdesivir and 15.2% with placebo by day 29 (hazard ratio, 0.73; 95% CI, 0.52 to 1.03). The between group differences in mortality varied considerably according to baseline severity, with the statisticaly significant difference seen among patients with a baseline ordinal score of 5 (hazard ratio, 0.30; 95% CI, 0.14 to 0.64). Serious adverse events were reported in 131 of the 532 patients who received remdesivir (24.6%) and in 163 of the 516 patients who received placebo (31.6%) (Table 3.1-2 continued). There were 47 serious respiratory failure adverse events in the remdesivir group (8.8% of patients), including acute respiratory failure and the need for endotracheal intubation, and 80 in the placebo group (15.5% of patients). No deaths were considered by the investigators to be related to treatment assignment.

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

Author, year [Reference]	***Wang et al. 2020** [73]
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** [62]
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	1062 (RDV n=541, Placebo n=521)
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 (SpO_2) ≤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 (63.7 m vs 36.3 f)
Follow-up (days)	29 days
Clinical status	Most patients had severe disease (59.2%); 18.2 in category 6 - receiving non-invasive mechanical ventilation or high-flow oxygen devices and 41.0% in category 5 – requiring supplemental oxygen; 26.8%-were in category 7 of the ordinal scale – receiving invasive mechanical ventilation or ECMO; 13.0% in category 4 – not requiring supplemental oxygen, requiring ongoing medical care

Author, year [Reference]	**Beigel et al. 2020 [62]
Loss to follow-up, n (%)	531 patients (98.2%) received remdesivir as assigned; 52 patients had remdesivir treatment discontinued before day 10 because of an adverse event or a serious adverse event other than death and 10 withdrew consent. 517 patients (99.2%) received placebo as assigned. 70 patients discontinued placebo before day 10 because of an adverse event or a serious adverse event other than death and 14 withdrew consent. A total of 517 patients in the remdesivir group and 508 in the placebo group completed the trial through day 29, recovered, or died.
Efficacy outcomes	
All-cause Mortality, n (%)	Kaplan–Meier estimates of mortality **by day 15** were 6.7% in the remdesivir group and 11.9% in the placebo group (hazard ratio, 0.55; 95% CI, 0.36 to 0.83); the estimates **by day 29** were 11.4% and 15.2% in two groups, respectively (hazard ratio, 0.73; 95% CI, 0.52 to 1.03); The between group differences in mortality varied considerably according to baseline severity; the statisticaly significant difference among patients with a baseline ordinal score of 5 (hazard ratio, 0.30; 95% CI, 0.14 to 0.64)
Time to Recovery	RDV group: median 10 days vs 15 days in placebo group; Recovery Rate Ratio 1·29 [95% CI 1·12–1·49, p<0.001]
Improvement in Ordinal score at day 15 (±2 days)	The odds of improvement in the ordinal scale score: statistically significant higher in the remdesivir group (as determined by a proportional odds model at the day 15 visit) vs placebo group (odds ratio for improvement, 1.50; 95% CI, 1.2 to 1.9)
Time to Discharge	Remdesivir group: shorter time to discharge or to a National Early Warning Score of 2 or lower vs the placebo group (median, 8 days vs. 12 days; hazard ratio, 1.27; 95% CI, 1.10 to 1.46)
Duration of hospitalisation	Median duration of initial hospitalization (IQR) — days: 12 vs 17 in placebo group; difference (95% CI) -5.0 (-7.7 to -2.3)
Duration of Oxygen	Median days receiving oxygen if receiving oxygen at baseline (IQR): Remdesivir group 13 (5 to 28) vs 21 (8 to 28) placebo group; difference (95% CI) -8.0 (-11.8 to -4.2)
Duration of Noninvasive ventilation or high-flow oxygen	Median days of noninvasive ventilation or high-flow oxygen use during study if receiving these interventions at baseline (IQR): Remdesivir group 6 (3 to 18) vs 6 (3 to 16) placebo group; difference (95% CI) 0 (-2.6 to 2.6)
Duration of Mechanical ventilation or ECMO	Median days of mechanical ventilation or ECMO during study if receiving these interventions at baseline (IQR): Remdesivir group 17 (9 to 28) vs 20 (8 to 28) placebo group; difference (95% CI) -3.0 (-9.3 to 3.3)
Safety outcomes	
Grade 3 or 4 Adverse events (AEs)	RDV group 273 (51.3%) vs 295 (57.2%) in the control group
Serious adverse events (SAEs)	131 of 532 patients (24.6%) in the remdesivir group vs 163 of 516 patients (31.6%) in the control group; 47 serious respiratory failure adverse events in the remdesivir group (8.8% of patients), including acute respiratory failure and the need for endotracheal intubation, and 80 in the placebo group (15.5% of patients)
Discontinuation of study drug due to AEs or SAEs	52 in the remdesivir group *vs* 70 in the placebo group

**Final report from the 1062 patients (541 assigned to remdesivir and 521 to placebo)

On May 27, 2020 Goldman et al. [72] 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 3.1-3 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 3.1-3: Publications on clinical trials on product remdesivir continued

Author, year [Reference]	**Goldman et al. 2020** [72]
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	
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%

One new RCT peer-reviewed article has been published as of September 10 2020. Spinner et al. 2020 [75] published results from a randomised, open-label, phase 3 trial (NCT04292730) performed on hospitalised patients with moderate COVID-19 pneumonia (pulmonary infiltrates and room-air oxygen saturation >94%) enrolled from March 15 through April 18, 2020, at 105 hospitals in the United States, Europe, and Asia. The primary end point was clinical status on day 11 on a 7-point ordinal scale ranging from death (category 1) to discharged (category 7). Patients were randomized in a 1:1:1 ratio to receive a 10-day course of remdesivir (n = 197), a 5-day course of remdesivir (n = 199), or standard care (n = 200). Remdesivir was dosed intravenously at 200 mg on day 1 followed by 100 mg/d.

1 RCT veröffentlicht: USA, Europa, Asien

5-Tage vs 10-Tage vs. SOC

Among 596 patients who were randomized, 584 began the study and received remdesivir or continued standard care and 533 (91%) completed the trial. Median length of treatment was 5 days for patients in the 5-day remdesivir group and 6 days for patients in the 10-day remdesivir group. On day 11, patients in the 5-day remdesivir group had statistically significantly higher odds of a better clinical status distribution than those receiving standard care (odds ratio, 1.65; 95% CI, 1.09-2.48; p=0.02). The clinical status distribution on day 11 between the 10-day remdesivir and standard care groups was not significantly different (p=0.18 by Wilcoxon rank sum test).

596 Pts

There were no significant differences between the 5-day or 10-day remdesivir groups and standard care for any of the exploratory end points—time to 2-point or greater improvement in clinical status, time to 1-point or greater improvement in clinical status, time to recovery, time to modified recovery, and time to discontinuation of oxygen support. There were no significant differences between the remdesivir and standard care groups in duration of oxygen therapy or hospitalization. The KaplanMeier estimates of all-cause mortality at day 28 were 1% (95% CI, 0.0%-2.6%) for the 5-day remdesivir group (log-rank p=0.43 vs standard care), 2% (95% CI, 0.0%-3.6%) for the 10-day remdesivir group (log-rank p=0.72 vs standard care), and 2% (95% CI, 0.1%-4.1%) for the standard care group.

kein signifikanter Unterschied zwischen 5 vs. 10 Tage vs. SOC

Adverse events were experienced by 51% of patients in the 5-day remdesivir group, 59% in the 10-day remdesivir group, and 47% in the standard care group. The difference in proportions between the 5-day remdesivir group and standard care was not statistically significant (4.8%; 95% CI, –5.2% to 14.7%; p=0.36), but the difference between the 10-day remdesivir group and standard care was significant (12.0%; 95% CI, 1.6%-21.8%; p=0.02). Nausea (10% vs 3%), hypokalemia (6% vs 2%), and headache (5% vs 3%) were more frequent among remdesivir-treated patients compared with standard care.

AE signifikanter Unterschied zwischen 10 Tage vs. SOC zu Ungunsten von Remdesivir

Serious adverse events were less common in the remdesivir groups (5% in both) than in the standard care group (9%), differences of -4.3% (95% CI, -9.7% to 0.9%; p=0.11) for the 5-day remdesivir group vs standard care and -3.8% (95% CI, -9.3% to 1.4%; p=0.17) for the 10-day remdesivir group vs standard care. All 9 deaths through day 28 (2 [1%] in the 5-day remdesivir group, 3 [2%] in the 10-day remdesivir group, and 4 [2%] in the standard care group) occurred in patients aged 64 years or older, and none was attributed to remdesivir treatment.

SAE häufiger in SOC Gruppe

Authors concluded that among patients with moderate COVID-19, those randomized to a 10-day course of remdesivir did not have a statistically significant difference in clinical status compared with standard care at 11 days after initiation of treatment. Patients randomized to a 5-day course of remdesivir had a statistically significant difference in clinical status compared

Schlussfolgerungen der Autor*innen: 5-Tage Remdesivir besser als SOC, aber klinische Relevanz ist ungewiß

with standard care, but the difference was of uncertain clinical importance (Table 3.1-4 continued).

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

Author, year [Reference]	Spinner et al. 2020 [75]
Country	United States, Europe, and Asia
Sponsor/Funding	Gilead Sciences
Study design	NCT04292730
Number of pts	596 patients who were randomized, 584 began the study and received remdesivir or continued standard care and 533 (91%) completed the trial
Intervention/Product	10-day course of remdesivir (n = 197), a 5-day course of remdesivir (n = 199; Remdesivir was dosed intravenously at 200 mg on day 1 followed by 100 mg/d
Comparator	Standard care (n = 200)
Inclusion criteria	Hospitalized patients with SARS-CoV-2 infection confirmed by polymerase chain reaction assay within 4 days of randomization and moderate COVID-19 pneumonia (defined as any radiographic evidence of pulmonary infiltrates and oxygen saturation >94% on room air)
Exclusion criteria	Patients with alanine aminotransferase or aspartate aminotransferase greater than 5 times the upper limit of normal or creatinine clearance of less than 50 mL/min
Pts pretreated + previous treatment	Not reported
Mean age of patients, yrs (SD)	57 [interquartile range, 46-66] years
Sex % male (% female)	227 [39%] women
Follow-up (days)	28 days
Clinical status	Moderate COVID-19
Loss to follow-up, n (%)	12 randomized patients did not receive treatment: 8 withdrew consent, 3 had protocol violations, and 1 was withdrawn by investigator discretion; 533 (91%) completed the trial through day 28; Of 191 patients in the 5-day remdesivir group, 145 (76%) completed the assigned treatment duration (median, 5 doses; range, 1-5): reasons for discontinuing treatment included hospital discharge (35 patients [18%]), withdrawal of consent (5 [3%]), and adverse events (4 [2%]). Of the 193 patients in the 10-day remdesivir group, 73 (38%) completed the assigned treatment duration; the median number of doses for the group was 6 (range, 1-10): reasons for discontinuing treatment included hospital discharge (98 patients [51%]), adverse events (8 [4%]), and withdrawal of consent (6 [3%]).
Efficacy outcomes	
Overall survival (OS), n (%)	At day 28 were 1% (95% CI, 0.0%-2.6%) for the 5-day remdesivir group (log-rank p=0.43 vs standard care), 2% (95% CI, 0.0%-3.6%) for the 10-day remdesivir group (log-rank p=0.72 vs standard care), and 2% (95% CI, 0.1%-4.1%) for the standard care group
Clinical status on day 11 on a 7-point ordinal scale ranging from death (category 1) to discharged (category 7)	On day 11, patients in the 5-day remdesivir group: statistically significantly higher odds of a better clinical status distribution vs standard care (odds ratio, 1.65; 95% CI, 1.09-2.48; p=0.02). The clinical status distribution on day 11 between the 10-day remdesivir vs standard care groups: not significantly different (p=0.18 by Wilcoxon rank sum test).
Other efficacy outcomes	No significant differences between the 5-day or 10-day remdesivir groups and standard care for any of the exploratory end points—time to 2-point or greater improvement in clinical status, time to 1-point or greater improvement in clinical status, time to recovery, time to modified recovery, and time to discontinuation of oxygen support; no significant differences between the remdesivir and standard care groups in duration of oxygen therapy or hospitalization
Safety outcomes	

Author, year [Reference]	Spinner et al. 2020 [75]
Adverse events (AEs)	51% of patients in the 5-day remdesivir group, 59% in the 10-day remdesivir group, and 47% in the standard care group. The difference in proportions between the 5-day remdesivir group and standard care was not statistically significant (4.8%; 95% CI, −5.2% to 14.7%; p=0.36). The difference between the 10-day remdesivir group and standard care was significant (12.0%; 95% CI, 1.6%-21.8%; p=0.02). Nausea (10% vs 3%), hypokalemia (6% vs 2%), and headache (5% vs 3%) were more frequent among remdesivir-treated patients compared with standard care.
Serious adverse events (SAEs)	Less common in the remdesivir groups (5% in both) than in the standard care group (9%), differences of -4.3% (95% CI, -9.7% to 0.9%; p=0.11) for the 5-day remdesivir group vs standard care and -3.8% (95% CI, -9.3% to 1.4%; p=0.17) for the 10-day remdesivir group vs standard care. All 9 deaths through day 28 (2 [1%] in the 5-day remdesivir group, 3 [2%] in the 10-day remdesivir group, and 4 [2%] in the standard care group) occurred in patients aged 64 years or older, and none was attributed to remdesivir treatment.
Discontinuation of study drug due to AEs or SAEs	10-day remdesivir 8 (4%); 5-day remdesivir 4 (2%); standard care NA

Meta-Analyse von 3 RCTs

kein Unterschied: all-cause mortality

Unterschied bei klinischer Verbesserung und bei Nebenwirkungen

According to the currently published Forest Plot related to the outcome all-cause mortality, no statistically significant difference was found between remedesivir vs standard care/placebo at days 14-28 (3 RCTs; RR 0.71, 95% CI 0.44-1.14). 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 (3 RCTs, n=1299: RR 0.70, 95% CI 0.57 to 0.86), and the incidence of WHO progression score level 7 or above at days 14 to 28 (3 RCTs, RR 0.57, 95% CI 0.57 to 0.89). There were statistically significantly fewer serious adverse events with remdesivir compared with placebo (3 RCTs, RR 0.74, 95% CI 0.62 to 0.88). Also, the outcome Time to clinical improvement was statistically significantly better in remdesivir group (2 RCTs: Wang, Spinner; RR 1.17, 95% CI 1.02 to 1.34).

The Living Systematic Review with Meta-Analysis (MA), related to Remdesivir 5 days vs Remdesivir 10 days (2 RCTs, Spinner and Goldman) and Remdesivir 5 days vs Standard care (1 RCT, Spinner) with the Summary of findings tables (**https://covid-nma.com/living_data/index.php**) are presented in Table 3.1-5 and Table 3.1-6 below.

Table 3.1-5: Summary of findings table on remdesivir 5 days vs remdesivir 10 days (2 RCTs: Spinner, Goldman) - https://covid-nma.com/living_data/index.php

Author(s): C. Bollig, C. Schmucker, J.J. Meerpohl
Question: Remdesivir 5 days compared to Remdesivir 10 days for Mild/Moderate/Critical/Severe Covid-19 [a]
Setting: Worldwide
Bibliography: https://covid-nma.com

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Remdesivir 5 days	Remdesivir 10 days	Relative (95% CI)	Absolute (95% CI)		
Incidence of viral negative conversion D7 - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	
Incidence of clinical improvement D7												
2 [b]	randomised trials	serious [c]	not serious	not serious	serious [d]	none	177/401 (44.1%)	146/397 (36.8%)	**RR 1.19** (1.01 to 1.40)	**70 more per 1.000** (from 4 more to 147 more)	⨁⨁◯◯ LOW	
Incidence of clinical improvement D14-28												
2 [b]	randomised trials	serious [c]	serious [e]	not serious	serious [f]	none	300/401 (74.8%)	281/397 (70.8%)	**RR 1.06** (0.87 to 1.30)	**42 more per 1.000** (from 92 fewer to 212 more)	⨁◯◯◯ VERY LOW	
Incidence of WHO progression score (level 6 or above) D14-28												
2 [b]	randomised trials	serious [c]	not serious	not serious	serious [d]	none	44/401 (11.0%)	69/397 (17.4%)	**RR 0.63** (0.45 to 0.88)	**64 fewer per 1.000** (from 96 fewer to 21 fewer)	⨁⨁◯◯ LOW	
Incidence of WHO progression score (level 7 or above) D14-28												
2 [b]	randomised trials	serious [g]	not serious	not serious	serious [d]	none	34/401 (8.5%)	58/397 (14.6%)	**RR 0.58** (0.40 to 0.85)	**61 fewer per 1.000** (from 88 fewer to 22 fewer)	⨁⨁◯◯ LOW	
All-cause mortality D14-28												
2 [b]	randomised trials	serious [g]	not serious	not serious	serious [f]	none	18/401 (4.5%)	24/397 (6.0%)	**RR 0.74** (0.41 to 1.34)	**16 fewer per 1.000** (from 36 fewer to 21 more)	⨁⨁◯◯ LOW	
Adverse events												
2 [b]	randomised trials	serious [c]	not serious	not serious	not serious	none	239/401 (59.6%)	258/397 (65.0%)	**RR 0.93** (0.84 to 1.03)	**45 fewer per 1.000** (from 104 fewer to 19 more)	⨁⨁⨁◯ MODERATE	
Serious adverse events												
2 [b]	randomised trials	serious [c]	not serious	not serious	serious [d]	none	51/401 (12.7%)	78/397 (19.6%)	**RR 0.64** (0.47 to 0.87)	**71 fewer per 1.000** (from 104 fewer to 26 fewer)	⨁⨁◯◯ LOW	

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Last update: September 18, 2020
b. Spinner CD, 2020; Goldman JD, 2020
c. Risk of bias downgraded by 1 level: some concerns due to concerns during the randomization process, deviation from intended intervention and outcome measurement
d. Imprecision downgraded by 1 level: due to low number of events and/or participants
e. Inconsistency downgraded by 1 level: I²= 79.3%
f. Imprecision downgraded by 1 level: due to wide confidence interval consistent with the possibility for benefit and the possibility for harm
g. Risk of bias downgraded by 1 level: some concerns due to concerns during the randomization process and deviation from intended intervention

Table 3.1-6: Summary of findings table on remdesivir 5 days vs standard care (1 RCT: Spinner) - https://covid-nma.com/living_data/index.php

Summary of findings:

Remdesivir 5 days compared to Standard Care for Mild to Severe Covid-19

Patient or population: Mild to Severe Covid-19
Setting: Worldwide
Intervention: Remdesivir 5 days
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 Remdesivir 5 days				
Incidence of viral negative conversion D7 - not reported	-	-	-	-	-	outcome not yet measured or reported
Incidence of clinical improvement D7	470 per 1.000	**531 per 1.000** (437 to 649)	**RR 1.13** (0.93 to 1.38)	399 (1 RCT) [b]	⨁⨁◯◯ LOW [c,d]	
Incidence of clinical improvement D14-28	830 per 1.000	**863 per 1.000** (789 to 938)	**RR 1.04** (0.95 to 1.13)	399 (1 RCT) [b]	⨁⨁◯◯ LOW [c,e]	
Incidence of clinical recovery D7	505 per 1.000	**571 per 1.000** (480 to 687)	**RR 1.13** (0.95 to 1.36)	399 (1 RCT) [b]	⨁⨁◯◯ LOW [c,d]	
Incidence of clinical recovery D14-28	850 per 1.000	**876 per 1.000** (816 to 952)	**RR 1.03** (0.96 to 1.12)	399 (1 RCT) [b]	⨁⨁◯◯ LOW [c,e]	
WHO progression score (level 6 or above D14-28)	40 per 1.000	**15 per 1.000** (4 to 56)	**RR 0.38** (0.10 to 1.40)	399 (1 RCT) [b]	⨁◯◯◯ VERY LOW [c,f]	
WHO progression score (level 7 or above D14-28)	40 per 1.000	**10 per 1.000** (2 to 47)	**RR 0.25** (0.05 to 1.17)	399 (1 RCT) [b]	⨁⨁◯◯ LOW [f]	
All-cause mortality D14-D28	20 per 1.000	**10 per 1.000** (2 to 54)	**RR 0.50** (0.09 to 2.71)	399 (1 RCT) [b]	⨁⨁◯◯ LOW [f]	
Adverse events D14-28	465 per 1.000	**493 per 1.000** (400 to 605)	**RR 1.06** (0.86 to 1.30)	399 (1 RCT) [b]	⨁⨁◯◯ LOW [c,d]	
Serious adverse events D14-28	90 per 1.000	**45 per 1.000** (21 to 98)	**RR 0.50** (0.23 to 1.09)	399 (1 RCT) [b]	⨁⨁◯◯ LOW [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. Last update: September 18, 2020
b. Spinner CD, 2020
c. Risk of bias downgraded by 1 level: some concerns due to deviation from intended intervention and outcome measurement
d. 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
e. Imprecision downgraded by 1 level: due to low number of events and/or 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 very low number of events

3.2 Lopinavir + Ritonavir (Kaletra®)

wegen erwiesenem Mangel an Wirksamkeit wurde Beobachtung beendet

Due to the lack of effectiveness of lopinavir/ritonavir in treating adults hospitalized with COVID-19 patients and the decisions to stop enrolling participants to the lopinavir/ritonavir (Kaletra) arms of the RECOVERY, SOLIDARITY and DISCOVERY studies in adults hospitalized with COVID-19, our reporting related to lopinavir/ritonavir was stopped also.

Last reporting V6/September 2020:
https://eprints.aihta.at/1234/50/Policy_Brief_002_Update_09.2020.pdf

3.3 Favipiravir (Avigan®)

About the drug under consideration

antivirales Medikament

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) [82, 83].

japanisches Influenza-Medikament (seit 2014),

von EMA / FDA nicht zugelassen

In 2014, it was approved in Japan for the treatment of novel or re-emerging pandemic influenza virus infections. However, use has been limited to cases, in which other influenza antiviral drugs are not sufficiently effective because favipiravir was only investigated in non-clinical studies in avian influenza A (H5N1 and H7N9) and efficacy against seasonal influenza A or B has not been sufficiently demonstrated. Furthermore, favipiravir was also trialled for treating Ebola; however, evidence on the effectiveness was lacking [82]. Favipiravir (Avigan®) has not been approved by the European Medicines Agency (EMA) or the American Food and Drug Administration (FDA).

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

The US COVID-19 Treatment Guidelines Panel **recommends against** using the **Lopinavir/ritonavir (AI) or other HIV protease inhibitors (AIII),** except in a clinical trial, because of unfavorable pharmacodynamics and because clinical trials have not demonstrated a clinical benefit in patients with COVID-19 [70].

Completed, withdrawn, suspended or terminated studies

1 RCT abgeschlossen

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

Juni 2020: keine weiteren Studien abgeschlossen oder beendet registriert

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

Juli 2020: 1 RCT aus Ägypten

Sept 2020: 1 RCT aus Russland

The search in two clinical trial registers (ClinicalTrials.gov and EUdraCT) on 06/07/2020 found one completed RCT (NCT04349241) in Egypt, which assessed the safety and efficacy of favipiravir versus standard of care. No suspended or terminated RCTs were found on the safety and efficacy of favipiravir in COVID-19 patients. No additional completed, nor suspended or terminated RCTs were found until August 15, 2020. One RCT is registered as completed until September 12, 2020 (NCT04542694). It aimed to assess the efficacy and safety of favipiravir compared with the standard of care in

200 hospitalized patients with moderate COVID-19 pneumonia in Russian Federation [21]. Until October 10, 2020 one completed RCT was found (NCT04542694), comparing favipiravir vs standard of care in 200 hospitalised patients with moderate COVID-19 pneumonia in Russian Federation.

Results of publications

1 Publikation zu RCT Vergleich mit Umifenovir

As of 12/05/2020, only one publication [84] on the completed RCT (ChiCTR2000030254) about the efficacy and safety of favipiravir, **in comparison with umifenovir**, to treat Covid-19 patients was identified; however, as the publication was available just as pre-print but not yet peer-reviewed, it has not been extracted. Summary of findings table on favipiravir compared to umifenovir (1 RCT: Chen) is presented in Table 3.3-1.

1 weitere Publikation Vergleich mit Baloxavir marboxil

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**, and **lopinavir + ritonavir or darunavir/cobicistat + umifenovir + interferon-a,** Lou Y, medRxiv, 2020, ChiCTR2000029544 [85]: however, currently the publication is available just as pre-print but not yet peer-reviewed, thus it has not been extracted.

30 Pts

Ergebnisse: kein Zusatznutzen durch Baloxavir marboxil oder Favipiravir

This was an exploratory trial with 3 arms involving hospitalized adult patients with COVID-19. Patients were randomized assigned in a 1:1:1 ratio into baloxavir marboxil group, favipiravir group, and control group. The primary outcome was the percentage of subjects with viral negative by Day 14 and the time from randomization to clinical improvement. Virus load reduction, blood drug concentration and clinical presentation were also observed. The trial was registered with Chinese Clinical Trial Registry (ChiCTR 2000029544). Baloxavir showed antiviral activity in vitro with the half-maximal effective concentration (EC50) of 5.48 μM comparable to arbidol and lopinavir, but favipiravir did not demonstrate significant antiviral activity up to 100 μM. Thirty patients were enrolled. The percentage of patients who turned viral negative after 14-day treatment was 70%, 77%, and 100% in the baloxavir, favipiravir, and control group respectively, with the medians of time from randomization to clinical improvement was 14, 14 and 15 days, respectively. Authors concluded that findings do not support adding either baloxavir or favipiravir under the trial dosages to the existing standard treatment.

Summary of findings table on favipiravir compared to baloxavir marboxil and lopinavir + ritonavir or darunavir/cobicistat + umifenovir + interferon-a (1 RCT: Lou 2020) [69] is presented in Table 3.3-1.

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

interim Auswertung orale Verabreichung in Russland „conditional" zugelassen

Until August 15, 2020 interim results from an adaptive, multicenter, open label, randomized, phase 2/3 clinical trial (NCT04434248) of AVIFAVIR **versus standard of care** (SOC) in hospitalized patients with moderate COVID-19 pneumonia were published. 60 patients hospitalized with COVID-19 pneumonia were randomized into three treatment groups: AVIFAVIR 1600/600 mg, AVIFAVIR 1800/800 mg, or SOC. Each group comprised 20 patients and all randomized patients constituted safety and intent-to-treat (ITT) analysis sets. AVIFAVIR enabled SARS-CoV-2 viral clearance in 62.5% of patients within 4 days, and was safe and well-tolerated. Based on these interim results, the Russian Ministry of Health granted a conditional marketing authorization to AVIFAVIR, which makes it the only approved oral drug for treatment of moderate COVID-19 to date [86]. No new publications on the completed RCTs were found, as of September 12, 2020.

As on October 10, 2020 on new RCT was published (Japan Registry of Clinical Trials jRCTs041190120), related to early versus late favipiravir in hospitalised patients with COVID-19 [87]. Patients were randomly assigned at a 1:1 ratio to **early or late favipiravir therapy** (the same regimen starting on day 6 instead of day 1). Eighty-nine patients were enrolled, of whom 69 were virologically evaluable. Viral clearance occurred within 6 days in 66.7% and 56.1% of the early and late treatment groups (adjusted hazard ratio [aHR], 1.42; 95% confidence interval [95% CI], 0.76–2.62). Of 30 patients who had a fever (≥37.5°C) on day 1, time to defervescence was 2.1 days and 3.2 days in the early and late treatment groups (aHR, 1.88; 95%CI, 0.81–4.35). During therapy, 84.1% developed transient hyperuricemia. Favipiravir did not significantly improve viral clearance as measured by RT-PCR by day 6 but was associated with numerical reduction in time to defervescence. Neither disease progression nor death occurred to any of the patients in either treatment group during the 28-day participation.

Okt 2020:
RCT mit 89 Pts.
Japan
Vergleich von früher und später Favipiravir Therapie bei hospitalisierten Pts.

kein Unterschied

Table 3.3-1: Summary of findings table on favipiravir compared to baloxavir marboxil and lopinavir + ritonavir or darunavir/cobicistat + umifenovir + interferon-a (1 RCT: Lou 2020) [69] - https://covid-nma.com/living_data/index.php

Summary of findings:

Favipiravir compared to Lopinavir + Ritonavir or Darunavir/Cobicistat + Umifenovir + Interferon-a for Mild/COVID-19

Patient or population: Mild/COVID-19
Setting: Worldwide
Intervention: Favipiravir
Comparison: Lopinavir + Ritonavir or Darunavir/Cobicistat + Umifenovir + Interferon-a

Outcomes	Anticipated absolute effects* (95% CI) Risk with Lopinavir + Ritonavir or Darunavir/Cobicistat + Umifenovir + Interferon-a	Risk with Favipiravir	Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
Incidence viral negative conversion D7	500 per 1.000	**400 per 1.000** (150 to 1.000)	**RR 0.80** (0.30 to 2.13)	20 (1 RCT)	⊕◯◯◯ VERY LOW [a,b,c]	
Incidence clinical Improvement D7	100 per 1.000	**200 per 1.000** (21 to 1.000)	**RR 2.00** (0.21 to 18.69)	20 (1 RCT)	⊕◯◯◯ VERY LOW [b,c,d]	
Incidence clinical Improvement D14-D28	500 per 1.000	**500 per 1.000** (210 to 1.000)	**RR 1.00** (0.42 to 2.40)	20 (1 RCT)	⊕◯◯◯ VERY LOW [b,c,d]	
Incidence of WHO progression score (level 6 or above D14-D28)				20 (1 RCT)	⊕◯◯◯ VERY LOW [b,d,e]	zero events in both groups
Incidence of WHO progression score (level 7 or above D14-D28)				20 (1 RCT)	⊕◯◯◯ VERY LOW [a,b,e]	zero events in both groups
All-cause mortality D7				20 (1 RCT)	⊕◯◯◯ VERY LOW [a,b,e]	zero events in both groups
All-cause mortality D14-D28				20 (1 RCT)	⊕◯◯◯ VERY LOW [a,b,e]	zero events in both groups
Adverse events - not reported	-	-	-	-	-	outcome not yet measured or reported
Serious adverse events D14-D28	400 per 1.000	**400 per 1.000** (136 to 1.000)	**RR 1.00** (0.34 to 2.93)	20 (1 RCT)	⊕⊕◯◯ LOW [d,f,g]	

***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 adequate randomization, deviations from intended interventions and selection of the reported results
b. Indirectness downgraded by 1 level: single study from a single institution, therefore results in this population might not be generalizable to other settings
c. Imprecision downgraded by 2 levels: due to very wide confidence interval consistent with the possibility for benefit and the possibility for harm and very low number of participants
d. Risk of bias downgraded by 1 level: some concerns regarding adequate randomization, deviations from intended interventions, measurement of the outcome and selection of the reported results
e. Imprecision downgraded by 2 levels: no events in both groups and very low number of participants
f. Indirectness not downgraded: we presume that adverse event rate is not specific to a certain setting
g. Imprecision downgraded by 1 level: due to wide confidence interval consistent with the possibility for benefit and the possibility for harm and very low number of participants

Table 3.3-2: Summary of findings table on favipiravir compared to umifenovir (1 RCT: Chen) - https://covid-nma.com/living_data/index.php)

Summary of findings:						
Favipiravir compared to Umifenovir for COVID-19						
Patient or population: COVID-19 **Setting**: Worldwide **Intervention**: Favipiravir **Comparison**: Umifenovir						
Outcomes	**Anticipated absolute effects*** **(95% CI)**		**Relative effect (95% CI)**	**№ of participants (studies)**	**Certainty of the evidence (GRADE)**	**Comments**
	Risk with Umifenovir	**Risk with Favipiravir**				
Incidence viral negative conversion D7 - not reported	-	-	-	-	-	outcome not yet measured or reported
Clinical improvement - not reported	-	-	-	-	-	outcome not yet measured or reported
Incidence of clinical recovery D7	517 per 1.000	**594 per 1.000** (470 to 744)	**RR 1.15** (0.91 to 1.44)	240 (1 RCT)	⨁◯◯◯ VERY LOW [a,b,c]	
Incidence of WHO progression score (level 6 or above) - not reported	-	-	-	-	-	outcome not yet measured or reported
Incidence of WHO progression score (level 7 or above) - not reported	-	-	-	-	-	outcome not yet measured or reported
All-cause mortality D7				240 (1 RCT)	⨁◯◯◯ VERY LOW [b,d,e]	zero events in both groups
Adverse events D7	275 per 1.000	**358 per 1.000** (245 to 523)	**RR 1.30** (0.89 to 1.90)	240 (1 RCT)	⨁⨁◯◯ LOW [a,c,f]	

Serious adverse events D7		240 (1 RCT)	⊕◯◯◯ VERY LOW [a,d,f]	zero events in both groups

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence

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

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

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

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

Explanations

a. Risk of bias downgraded by 1 level: some concerns or high risk regarding adequate randomization, deviations from intended interventions and outcome measurement

b. Indirectness downgraded by 1 level: single study from a single country, therefore results in this population might not be generalizable to other settings

c. Imprecision downgraded by 1 level: due to wide confidence interval consistent with the possibility for benefit and the possibility for harm and low number of participants

d. Imprecision downgraded by 2 levels: no events in both groups and low number of participants

e. Risk of bias downgraded by 1 level: some concerns regarding adequate randomization and deviations from intended interventions

f. We presume that the adverse event rates, and the corresponding relative risks, is similar across diverse settings; therefore not downgraded for indirectness

3.4 Darunavir

About the drug under consideration

antivirales Medikament

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 [88].

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.

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

The US COVID-19 Treatment Guidelines Panel recommends **against** using the **Lopinavir/ritonavir (AI) or other HIV protease inhibitors (AIII),** except in a clinical trial, because of unfavorable pharmacodynamics and because clinical trials have not demonstrated a clinical benefit in patients with COVID-19 [70].

Completed, withdrawn, suspended or terminated studies

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

The search in two clinical trial registers (ClinicalTrials.gov and EUdraCT) on October 10 2020 yielded no completed study on the safety and efficacy of darunavir in COVID-19 patients. No suspended or terminated RCTs were found either.

Results of publications

Publikation zu RCT

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

Until now (status: 10/10/2020) one scientific publication on RCTs of darunavir (Prezista®) in Covid-19 patients could be identified. Chen J et al. 2020 [89] published results from single-center, randomized, open-label trial (NCT04252274) which aimed to evaluate the antiviral activity and safety of darunavir/cobicistat (DRV/c) in treating mild COVID-19 patients. Participants were randomized to receive DRV/c for 5 days on the top of interferon alpha 2b inhaling or interferon alpha 2b inhaling alone. The proportion of negative PCR results at day 7 was 46.7% (7/15) and 60.0% (9/15) in the DRV/c and control groups (p = 0.72), respectively. The viral clearance rate at day 3 was 20% (3/15) in both study groups, while the number increased to 26.7% (4/15) in the DRV/c group and remained 20% (3/15) in the control group at day 5. Fourteen days after randomization, 1 participant in the DRV/c group progressed to critical illness and discontinued DRV/c, while all the patients in the control group were stable (p=1.0). The frequencies of adverse events in the two groups were comparable. The authors concluded that five days of DRV/c did not increase the proportion of negative conversion vs standard of care alone, although it was well tolerated.

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

Author, year [Reference]	**Chen J et al. 2020 [89]**
Country	China
Sponsor/Funding	Ministry of Science and Technology of China (2017ZX09304027); the Shanghai Science and Technology Committee (20411950200); Shanghai Major Projects on Infectious Diseases (shslczdzk01102); and the Shanghai "Rising Stars of Medical Talent" Youth Development Program, Specialist Program (No. 2019–72)
Study design	NCT04252274
Number of pts	30 participants (n_1=15 / n_2= 15)
Intervention/Product	Darunavir/cobicistat (800mg/150mg), 5 days (plus interferon alpha 2b and standard of care as per guideline recommendation in China)
Comparator	Standard care, 5 days (plus interferon alpha 2b; standard of care as per guideline recommendation in China)
Inclusion criteria	Laboratory-confirmed SARS-CoV-2 infection; willing to participate the study, as evidenced by signing an informed consent
Exclusion criteria	If they met any of the following criteria: hypersensitivity to darunavir, cobicistat, or any excipients; patients with severe liver injury (Child-Pugh Class C); patients receiving concomitant medications that are highly dependent on cytochrome P450 3A clearance, and for which the elevated plasma concentrations are associated with serious or life-threatening events; subjects considered to be unable to complete the study (eg, severely and critically ill patients) or not suitable for the study by researchers. Patients who met any of the following criteria were classified as severe cases: respiratory rate ≥30 times/min, pulse oxygen saturation ≤93% at resting, or ratio between partial pressure of oxygen in arterial blood and fraction of inspired oxygen (PaO2/ FiO2) ≤300 mmHg. Critical illness was defined as respiratory failure that needed mechanical ventilation or shock or exacerbation of any comorbidity that required transfer to the intensive care unit.
Pts pretreated + previous treatment	Not reported
Mean age of patients, yrs (SD)	47.2 ± 2.8 years
Sex % male (% female)	18 (60%) male
Follow-up (days)	14 days
Clinical status	Mild COVID-19
Loss to follow-up, n (%)	None
Efficacy outcomes	
Overall survival (OS), n (%)	All patients alive at day 14
Time to clinical improvement	The 11 patients with fever in the DRV/c group defervesced at a median (IQR) of 4 (2–6) days vs 8 patients in the control groups defervesced (IQR) at 5 (2–6.8) days after randomization (p = 0.72)
Other efficacy outcomes	
Viral clearance rate at day 7 after randomization	46.7% (7/15) and 60.0% (9/15) in the DRV/c and control groups (p = 0.72)
Viral clearance at day 3 and day 5	Day 3: 20% (3/15) in both study groups Day 5: 26.7% (4/15) in the DRV/c group and 20% (3/15) in the control group
Critical illness rate of subjects during the 14 days after randomization	1 participant in the DRV/r group progressed to critical illness (acute respiratory distress syndrome [ARDS]), none in the control group were stable (p = 1.0)
Safety outcomes	
Adverse events (AEs)	The frequencies of adverse events in the 2 groups were comparable

Author, year [Reference]	Chen J et al. 2020 [89]
Serious adverse events (SAEs)	Anemia (hemoglobin levels dropped from 11.3 g/dL to 9.9 g/dL) 1 patient in the DRV/c group Elevated transaminase levels, defined as >2-fold of the upper limit of the normal range 13.3% (2/30 in the DRV/c group vs 26.7% (4/30) in the control group Renal dysfunction (defined as estimated glomerular filtration rate <90 mL/min/1.73 m^2 in patients without chronic kidney diseases) 13.3% (2/30) in the DRV/c group vs 6.7% (1/30) in the control group
Discontinuation of study drug due to AEs or SAEs	No participants discontinued DRV/c due to these adverse events

Table 3.4-2: Summary of findings table on darunavir/cobicistat compared to standard care (1 RCT: Chen J) - https://covid-nma.com/living_data/index.php [89]

Summary of findings:

Darunavir/cobicistat compared to Standard Care for Moderate COVID-19

Patient or population: Moderate COVID-19
Setting: Worldwide
Intervention: Darunavir/cobicistat
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 Darunavir/cobicistat				
Incidence of viral negative conversion D7	600 per 1.000	**468 per 1.000** (234 to 924)	**RR 0.78** (0.39 to 1.54)	30 (1 RCT)	⨁◯◯◯ VERY LOW [a,b,c]	
Clinical improvement - not reported	-	-	-	-	-	outcome not yet measured or reported
Clinical recovery - not reported	-	-	-	-	-	outcome not yet measured or reported
WHO progression score (level 6 or above) - not reported	-	-	-	-	-	outcome not yet measured or reported
WHO progression score (level 7 or above D7)	0 per 1.000	**0 per 1.000** (0 to 0)	**RR 3.00** (0.13 to 68.26)	30 (1 RCT)	⨁◯◯◯ VERY LOW [a,b,d]	zero events in control group
All-cause mortality D14-D28				30 (1 RCT)	⨁◯◯◯ VERY LOW [a,b,e]	zero events in both groups
Adverse events - not reported	-	-	-	-	-	outcome not yet measured or reported
Serious adverse events D14-D28				30 (1 RCT)	⨁◯◯◯ VERY LOW [e,f,g]	zero events in both groups

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

CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Risk of bias downgraded by 1 level: some concerns or high risk due to concerns during the randomization process, deviation from intended intervention and selection of reported results
b. Indirectness downgraded by 1 level: single study from a single institution, therefore results in this population might not be generalizable to other settings
c. Imprecision downgraded by 2 levels: due to wide confidence interval consistent with the possibility for benefit and the possibility for harm and very 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 very low number of participants
e. Imprecision downgraded by 2 levels: no events in both groups and very low number of participants
f. Risk of bias downgraded by 2 levels: some concerns or high risk due to concerns during the randomization process, deviation from intended intervention, missing data and selection of reported results
g. We presume that the adverse event rates, and the corresponding relative risks, is similar across diverse settings; therefore not downgraded for indirectness

3.5 Chloroquine (Resochin®) and

3.6 Hydroxychloroquine (Plaquenil®)

wegen erwiesenem Mangel an Wirksamkeit wurde Beobachtung beendet

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

Last reporting V4/ July:
https://eprints.aihta.at/1234/10/Policy_Brief_002_Update_07.2020.pdf

3.7 Camostat Mesilate (Foipan®)

About the drug under consideration

Protease-Inhibitor bei Entzündung der Bauchspeicheldrüse Zulassung: Japan, Süd-Korea

nicht EMA, FDA
FDA: Orphan Drug Designation seit 2011

Camostat Mesilate (Foipan®) is classified as a so-called serine protease inhibitor, blocking several pancreatic and plasmatic enzymes like trypsin, thrombin and plasmin [90]. 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 [91, 92] as well as in pathogenic mice-models [93] by inhibiting the enzyme Transmembrane protease, serine 2 (TMPRSS2). In South Korea, camostat is on the market since 1989 (e.g. Foistar®, Daewoong pharma). Currently, multiple companies market camostat as a generic drug in Japan and South Korea. Camostat has a known and acceptable safety profile. Orphan drug designation was received in May 2011 from the FDA for the treatment of chronic pancreatitis. (https://www.accessdata.fda.gov/scripts/opdlisting/oopd/).

Camostat Mesilate (Foipan®) ist not approved for any anti-viral use (FDA, EMA).

vom dt. BMG für schwere Erkrankungen zentral eingekauft

Foipan (camostat) is one of the drugs for which the German Federal Ministry of Health initiated centralized procurement in April 2020 for the treatment of infected and seriously ill COVID-19 patients in Germany (https://www.abda.de). Up to August 1, 2020, 35 to 60 Covid-19 patients have been treated with the centrally procured medicinal product Foipan (Camostat) as part of an individual medical treatment. There was no obligation for the treating physicians to collect data in a registry [94].

Completed, withdrawn, suspended or terminated studies

in ClinicalTrials.gov and EUdraCT keine klinischen Studien registriert

As of October 10, 2020 no completed, withdrawn, suspended or terminated studies were found in ClinicalTrials.gov and EUdraCT registers.

Results of publications

Until now no scientific publication on a RCT of Camostat Mesilate (Foipan®) in Covid-19 patients could be identified (status: October 11, 2020).

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

Drug under consideration

aus SARS-Forschung hervorgegangen

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

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

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

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

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 October 10, 2020 no additional studies are found as withdrawn nor suspended or terminated.

Results of publications

keine Publikationen zu klinischen Studien

Until October 11, 2020, no relevant finished publications or finished trials assessing the efficacy and safety could be identified. First results, related to a phase 2/3 study of hrsACE2 in 200 hospitalised patients with COVID-19, with primary composite outcome – All-cause mortality or invasive mechanical ventilation can be expected on the 10th of November 2020 (NCT04335136) [98].

3.9 Tocilizumab (Roactemra®)

Drug under consideration

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

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

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 [99]. It is licensed in the EU for treating: rheumatoid arthritis in adults; giant cell arteritis in adults; active systemic juvenile idiopathic arthritis in patients aged ≥2 years; juvenile idiopathic polyarthritis in patients aged ≥2 years; chimeric antigen receptor (CAR) T cell-induced severe or life-threatening cytokine release syndrome (CRS) in patients aged ≥2 years [99].

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 [99]. 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 [99].

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 [100]. However, some patients develop severe symptoms and progress rapidly, experiencing acute respiratory distress syndrome and septic shock, eventually ending in multiple organ failure [100]. It has been reported that most patients with COVID-19 have increased concentrations of IL-6, C-reactive protein (CRP) and erythrocyte sedimentation rate [101]. However, severely affected patients appear to have even higher plasma levels of pro-inflammatory cytokines and experience severe cytokine storm including features of CRS [101, 102]. It has previously been suggested that IL-6 might play a role in the pathogenesis of SARS and MERS, other diseases caused by coronaviruses [102]. 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

The US COVID-19 Treatment Guidelines Panel **recommend against** anti-IL-6 receptor monoclonal antibodies (e.g., sarilumab, tocilizumab) or anti-IL-6 monoclonal antibody (siltuximab) (BI) for the treatment of COVID-19 [70], except in a clinical trial.

Empfehlungen des US COVID-19 Treatment Guidelines Panel: insuffiziente Datenlage, nur in klinischen Studien

Completed, withdrawn, suspended or terminated studies

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

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

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

2 weitere beendete Studien
1 RCT COVACTA 450 Pts
1 nRCT

As of 11 September 2020, two additional RCTs are completed: a RCT comparing the survival benefit of tocilizumab therapy with dexamethasone in 69 patients with severe COVID 19 in Egypt (NCT04519385) and a RCT assess the pharmacodynamics, pharmacokinetics, safety and efficacy of two different doses of tocilizumab in combination with standard-of-care (SOC) in 100 hospitalized adult participants with moderate to severe COVID-19 pneumonia NCT04363736 (MARIPOSA). Results are not published yet [21].

Sept 2020: 2 RCTs beendet

Ergebnisse noch nicht veröffentlicht

One RCT is terminated due to safety issue; RCT on 129 patients in Brazil compared tocilizumab vs best supportive care NCT04403685 (TOCIBRAS).

1 RCT abgebrochen wegen NW/ Sicherheit

As of 11 October 2020, one additional RCT is terminated (NCT04322773, TOCIVID trial), due to changed clinical conditions and too few patients available.

Results of publications

Juni 2020: bislang keine publizierten Ergebnisse aus RCTs

1 prospektive Fallserie mit 100 Pts
2 quasi-experimentelle Studien

Toniati et al. 2020 [103] 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 [104].

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

geringere Mortalität und ICU-Aufnahmen

In Martínez-Sans et al. 2020 preprint article [105], results from large cohort study of patients hospitalized with COVID-19 in Spain were presented, based on the analysis from 1,229 subjects, with primary end point - the time from study baseline to death. The secondary outcome was a composite event including admission to the ICU or death. Of the 1,229 patients, 260 (21%) received a median total dose of 600 mg (IQR 600–800 mg) of tocilizumab. The control group (n=969) received standard care defined as specific treatment agains SARS-CoV-2 (corticosteroids n=582, hydroxychloroquine n=1134, azithromycin n=812, lopinavir/ritonavir n=753). In the adjusted analyses a significant interaction was found between tocilizumab use and CRP values (p=0.023 and p=0.012 for primary and secondary endpoints, respectively). Subjects who received tocilizumab and had baseline CRP levels above 150 mg/L experienced lower rates of death (aHR 0.34, 95% CI 0.17 - 0.71, p=0.005) and ICU admission/death (aHR 0.39, 95% CI 0.19 – 0.80, p=0.011) than those who did not receive tocilizumab. This effect was not observed among patients with baseline CRP levels ≤150 mg/dL.

COVACTA:
RCT mit 450 Pts
mit schwerer Lungenentzündung

kein Unterschied bei klinischer Verbesserung und Mortalität

positiver Trend bei früherer Entlassung aus Spital

The phase 3, RCT - COVACTA (NCT04320615, EUdraCT 2020-001154-22) study of tocilizumab with aim to evaluate the safety and efficacy of tocilizumab in 450 patients with severe COVID-19 pneumonia did not meet its primary endpoint of improved clinical status in hospitalised adult patients with severe COVID-19 associated pneumonia. In addition, the key secondary endpoints, which included the difference in patient mortality at week four, were not met; however, there was a positive trend in time to hospital discharge in patients treated with tocilizumab. The COVACTA study did not identify any new safety signals for tocilizumab [106]. Full results of the trial have not yet been published. Rosas et al. 2020 [107] reported these results as preprint: 452 patients were randomized; the modified-intention-to-treat population included 294 tocilizumab-treated and 144 placebo-treated patients. Clinical status at day 28 was not statistically significantly improved for tocilizumab versus placebo (P=0.36). Median (95% CI) ordinal scale values at day 28: 1.0 (1.0 to 1.0) for tocilizumab and 2.0 (1.0 to 4.0) for placebo (odds ratio, 1.19 [0.81 to 1.76]). There was no difference in mortality at day 28 between tocilizumab (19.7%) and placebo (19.4%) (difference, 0.3% [95% CI, –7.6 to 8.2]; nominal P=0.94). Median time to hospital discharge was 8 days shorter with tocilizumab than placebo (20.0 and 28.0, respectively; nominal P=0.037; hazard ratio 1.35 [95% CI 1.02 to 1.79]). Median duration of ICU stay was 5.8 days shorter with tocilizumab than placebo (9.8 and 15.5, respectively; nominal P=0.045). In the safety population, serious adverse events occurred

in 34.9% of 295 patients in the tocilizumab arm and 38.5% of 143 in the placebo arm.

RCT (China)
65 Pts

kleiner nicht-signifikanter Unterscheid bei Heilungsraten bei deutlich mehr Nebenwirkungen

Wang et al. 2020 [108] reported, as preprint, results from a small randomized, controlled, open-label, multicenter trial at 6 hospitals in Anhui and Hubei (ChiCTR2000029765). Patients were randomly assigned in a 1:1 ratio to receive either tocilizumab in addition to standard care, or standard care alone. The first dose of tocilizumab was 400 mg, diluted in 100 ml 0.9% saline, and intravenous dripped in more than 1 h. A second dose was given if a patient remained febrile for 24 hours after the first dose. The primary endpoint was the cure rate. Primary analysis was done in the intention -to -treat (ITT) population and safety analysis was done in all patients who started their assigned treatment. 65 patients were enrolled and randomly assigned to a treatment group (33 to tocilizumab and 32 to the controls). One patient in the control group, who aggravated severely 3 days after randomization, was transferred to the tocilizumab group. The cure rate in tocilizumab group was higher than that in the controls but not significant (94.12% vs 87.10%, P=0.4133). Adverse events were recorded in 20 (58.82%) of 34 tocilizumab recipients versus 4 (12.90%) of 31 in the controls. No serious adverse events were reported in tocilizumab group.

EMPACTA
389 Pts
RCT (US, SA,Kenya, Brasilien, Mexiko, Peru)

Vorteil bei Verhinderung im Fortschreiten der Erkrankung

bei weiteren Endpunkten: kein Unterschied

On September 18, 2020 Roche announced (https://www.roche.com/media/releases/med-cor-2020-09-18.htm) that the phase III EMPACTA study (389 patients in the United States, South Africa, Kenya, Brazil, Mexico and Peru) met its primary endpoint, showing that patients with COVID-19 associated pneumonia who received Actemra®/RoActemra® (tocilizumab) plus standard of care were 44% less likely to progress to mechanical ventilation or death compared to patients who received placebo plus standard of care (log-rank p-value = 0.0348; HR [95% CI] = 0.56 [0.32, 0.97]). The cumulative proportion of patients who progressed to mechanical ventilation or death by day 28 was 12.2% in the Actemra/RoActemra arm versus 19.3% in the placebo arm. The EMPACTA study did not identify any new safety signals for Actemra/RoActemra. Key secondary outcomes (difference in time to hospital discharge or "ready for discharge" to day 28; difference in time to improvement in ordinal clinical status to day 28; time to clinical failure to day 28 and mortality by day 28) were not statisticaly significant different between groups. At day 28, incidence of infections was 10% and 11% in the Actemra/RoActemra and placebo arms, respectively, and the incidence of serious infections was 5.0% and 6.3% in the Actemra/RoActemra and placebo arms, respectively. The most common adverse events in patients who received Actemra/RoActemra were constipation (5.6%), anxiety (5.2%), and headache (3.2%).

Tocilizumab auch in RECOVERY

Tocilizumab continues to be evaluated in the RECOVERY trial. Because over 850 patients randomised to tocilizumab versus standard of care (almost twice the size of the COVACTA trial) will provide critical data to confirm or refute the COVACTA results. [109]

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

Table 3.9-1: Summary of findings table on tocilizumab compared to standard of care (1 RCT: Salvarani) **[110]**

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

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

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

[111]

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

3.10 Sarilumab (Kevzara®)

Drug under consideration

Sarilumab (*Kevzara*) is a human monoclonal antibody that specifically binds to soluble and membrane-bound interleukin (IL)-6 receptors (IL-6Rα), and inhibits IL-6-mediated signalling [112]. It is licensed in the EU for treating adults with rheumatoid arthritis, given by subcutaneous (SC) injection [112]. 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

The US COVID-19 Treatment Guidelines Panel **recommend against** anti-IL-6 receptor monoclonal antibodies (e.g., sarilumab, tocilizumab) or anti-IL-6 monoclonal antibody (siltuximab) (BI) for the treatment of COVID-19 [70], except in a clinical trial.

Empfehlung des US COVID-19 Treatment Guidelines Panel: insuffiziente Datenlage, nur in klinischen Studien

Completed, withdrawn, suspended or terminated studies

The search in two clinical trial registers (humans only) in April 2020 yielded no completed study on the safety and efficacy of sarilumab in COVID-19 patients. Until May 11, 2020 one RCT found as suspended, NCT04341870 - CORIMUNO-VIRO Trial (DSMB recommendation (futility)). As of 08 July, 2020, no completed, withdrawn, additional suspended or terminated studies were found in ClinicalTrials.gov and EUdraCT registers. The same is true until August 15, 2020. As of September 11, 2020, one completed RCT was found: adaptive phase 3, double-blind, placebo-controlled study assessing efficacy and safety of sarilumab in 421 hospitalized patients with severe or critical COVID-19 (NCT04327388).

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

As of October 11, 2020 one additional completed RCT was found (NCT04315298), which included 1912 hospitalised COVID-19 patients in US.

Okt: 1 beendeter RCT

Results of publications

keine Publikation zu einer klinischen Studie

Until May 10, 2020 no relevant publications related to RCTs assessing the efficacy and safety of sarilumab could be identified. As of 09 June, 2020, unpublished interim analysis data from RCT comparing sarilumab high dose (400 mg) and sarilumab low dose (200 mg) with placebo could be found on meta/ Evidence web site http://metaevidence.org/viewPathology2.aspx?exposition=553&comparator=0&pathology=87&domain=12). After peer-reviewed publication appears, results will be extracted in tabular format.

eine Interimauswertung

keine publizierten RCTs

No new RCT peer-reviewed articles have been published as of September 11, 2020 [113].

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

kein Unterschied zur Standardbehandlung

Della-Torre et al. 2020 [114] published results from an prospective open-label cohort study of sarilumab in 28 severe COVID-19 pneumonia (PaO2/FiO2 <300 mm Hg) patients with hyperinflammation (elevated inflammatory markers and serum IL-6 levels), in Italy. Sarilumab 400 mg was administered intravenously in addition to standard of care. Results were compared with contemporary matched patients treated with standard of care alone. Clinical improvement, mortality, safety and predictors of response were assessed at 28 days. Twenty-eight patients were treated with sarilumab and 28 contemporary patients receiving standard of care alone were used as controls. At day 28 of follow-up, 61% of patients treated with sarilumab experienced clinical improvement and 7% died, not significantly different from the comparison group (clinical improvement 64%, mortality 18%; p=NS). Baseline PaO2/FiO2 ratio >100 mm Hg and lung consolidation <17% at CT scan predicted clinical improvement in patients treated with sarilumab. Median time to clinical improvement in patients with lung consolidation <17% was shorter after sarilumab (10 days) than after standard treatment (24 days; p=0.01). The rate of infection and pulmonary thrombosis was similar between the two groups. Authors concluded that at day 28, overall clinical improvement and mortality in patients with severe COVID-19 were not significantly different between sarilumab and standard of care. Sarilumab was associated with faster recovery in a subset of patients showing minor lung consolidation at baseline.

Juli 2020: Pressemeldung zu RCT mit 194 Pts

kein Unterschied mehr SAE in Sarilumab Gruppe

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

Gremese et al. 2020 [115] published results from observational cohort study of the off-label intravenous use of sarilumab in 53 patients with severe SARS-CoV-2-related pneumonia. Sarilumab 400 mg was administered intravenously on day 1, with eventual additional infusion based on clinical judgement, and patients were followed for at least 14 days, unless previously discharged or dead. 39 (73.6%) patients were treated in medical wards [66.7% with a single infusion; median PaO2/FiO2:146 (IQR:120–212)] while 14 (26.4%) in ICU [92.6% with a second infusion; median PaO2/FiO2: 112 (IQR:100–141.5)]. Within the medical wards, 7 (17.9%) required ICU admission, 4 of whom were re-admitted to the ward within 5–8 days. At 19 days median follow-up, 89.7% of medical inpatients significantly improved (46.1% after 24 h, 61.5% after 3 days), 70.6% were discharged from the hospital and 85.7% no longer needed oxygen therapy. Within patients receiving sarilumab in ICU, 64.2% were discharged from ICU to the ward and 35.8% were still alive at the last follow-up. Overall mortality rate was 5.7%.

Beobachtungsstudie
53 Pts
zu Pts mit schwerer Erkrankung (Lungenentzündung), teilweise ICU

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

About the drug under consideration

Interferon beta-1a (INFb) is a cytokine in the interferon family used to treat relapsing multiple sclerosis (MS). Interferon beta balances the expression of pro- and anti-inflammatory agents in the brain, leading to a reduction of neuron inflammation [116]. 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 [117].

INFb Präparate bei Multipler Sklerose zugelassen (EMA)

Two pharmaceuticals which the active substance Interferon beta-1a are commercially available: Rebif® and Avonex®. They are used to slow the progression of disability and reduce the number of relapses in MS. Rebif is approved by the European Medicines Agency (EMA) since 1998 and by the American Food and Drug Administration (FDA) since 2002. Avonex is approved by EMA since 1997 and by the FDA since 1996. Both drugs are approved for the treatment of relapsing forms of multiple sclerosis (MS), in cases of clinically isolated syndromes, as well as relapsing remitting disease, and active secondary progressive disease in adults.

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

nicht für Covid-19

Two pharmaceuticals, with the active substance Interferon beta-1b, are commercially available in EU: Betaferon® and Extavia® to treat adults with multiple sclerosis (MS) [118, 119]. Betaferon® is approved by the European Medicines Agency (EMA) since 1995. Extavia® is approved by EMA since 2008. Interferon beta-1a and beta-1b are not approved for COVID-19 patients treatment.

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

The US COVID-19 Treatment Guidelines Panel [70] **recommends against** use of the **interferons (alfa or beta)** for the treatment of **severely or critically ill** patients with COVID-19, except in the context of a clinical trial (AIII).

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

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

Completed, withdrawn, suspended or terminated studies

The search in clinical trials (humans only) in April 2020 yielded no completed studies on the safety and effectiveness of Interferon beta-1a for Covid-19 patients. Until May 12, 2020, one completed RCT was found related to Interferon beta 1b. The completed RCT (NCT04276688) was conducted in Hong Kong, and its results are written in Section 3.14, related to Combination therapy.

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

Juni 2020: 1 weiterer RCT (Iran)
(Kombinationstherapie)
Ergebnisse liegen noch nicht vor

As of July 7, 2020 no additional studies are found as completed, nor withdrawn or suspended or terminated. The same is true until August 15, 2020 and September 12, 2020. No additional studies are found until October 11, 2020.

Sept 2020: keine weiteren Studien

Results of publications

As mentioned above, the results from the first randomised controlled trial on triple combination of interferon beta-1b, lopinavir–ritonavir and ribavirin, in comparison with lopinavir–ritonavir (NCT04276688) are presented in Section 3.14 of this report [120].

Kombinationstherapie: Ergebnisse in 3.14

Davoudi-Monfared et al. 2020 published results related to the RCT on Interferon beta-1a treatment (n=46) vs the standard of care (n=46), in 92 patients with severe COVID-19 in Iran [121]. Finally 81 patients (42 in the IFN and 39 in the control group) completed the study. Time to the clinical response was not significantly different between the IFN and the control (IRCT20100228003449N28) groups (9.7 +/- 5.8 vs. 8.3 +/- 4.9 days respectively, P=0.95). On day 14, 66.7% vs. 43.6% of patients in the IFN group and the control group were discharged, respectively (OR= 2.5; 95% CI: 1.05-6.37). The 28-day overall mortality was significantly lower in the IFN then the control group (19% vs. 43.6% respectively, p= 0.015). Early administration significantly reduced mortality (OR=13.5; 95% CI: 1.5-118). After the peer-reviewed publication appears, results will be extracted in tabular format.

RCT (Iran)
92 Pts

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

As of August 16, 2020, two new published RCTs were identified: results from Huang et al. 2020 (ChiCTR2000029387) [122] related to Ribavirin Plus Interferon-Alpha, Lopinavir/Ritonavir Plus Interferon-Alpha, and Ribavirin Plus Lopinavir/Ritonavir Plus Interferon-Alpha in Patients With Mild to Moderate COVID-19 were presented in Section 3.14 of this report.

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

1 RCT zu Kombinationstherapie IFN (unterscheidliche Dosierungen) + Kaletra

79 symptomatische/ asymptomatische Pts.

Esquivel-Moynelo et al. 2020 [123] presented the results from a RCT for efficacy and safety evaluation of subcutaneous IFN -α2b and IFNγ administration in patients positive to SARS-CoV-2. Patients were randomly assigned in a 1:1 ratio to receive either, subcutaneous treatment with a combination of 3.0 MIU IFN-α2b and 0.5 MIU IFN-γ, twice a week for two weeks, or thrice a week intramuscular injection of 3.0 MIU IFN-α2b. Additionally, all patients received lopinavir-ritonavir 200/50 mg every 12 h and chloroquine 250 mg every 12 h (standard of care). The primary endpoints were the time to negativization of viral RNA and the time to progression to severe COVID-19, from the start of treatment. A total of 79 patients with laboratory-confirmed SARS-CoV-2 infection, including symptomatic or asymptomatic conditions, fulfilled the inclusion criteria and underwent randomization. None of the subjects transit to severe COVID-19 during the study or the epidemiological follow-up for 21 more days. None of the patients developed severe COVID-19

Rahmani et al. 2020
RCT (Iran)
80 Pts
(66 beendeten Studie)

As of September 12, 2020 a new published RCTs were ideintified. Rahmani et al. 2020 [124] published the results of RCT evaluated efficacy and safety of interferon (IFN) β-1b in the treatment of patients with severe COVID-19 (IRCT20100228003449N27). In the open-label, randomized clinical trial, adult patients (≥18 years old) with severe COVID-19 were randomly assigned (1:1) to the IFN group or the control group. Patients in the IFN group received IFN β-1b (250 mcg subcutaneously every other day for two consecutive weeks) along with the national protocol medications while in the control group, patients received only the national protocol medications (lopinavir/ritonavir or atazanavir/ritonavir plus hydroxychloroquine for 7–10 days). The primary outcome of the study was time to clinical improvement. Secondary outcomes were in-hospital complications and 28-day mortality.

Zeit zur klinischen Verbesserung signifikant kürzer mit IFN, weniger ICU Einweisungen

nicht aber Dauer der Hospitalisierung und in ICU

Between April 20 and May 20, 2020, 80 patients were enrolled and finally 33 patients in each group completed the study. Time to clinical improvment in the IFN group was significantly shorter than the control group ([9(6–10) vs. 11(9–15) days respectively, p = 0.002, HR = 2.30; 95% CI: 1.33–3.39]). At day 14, the percentage of discharged patients was 78.79% and 54.55% in the IFN and control groups respectively (OR = 3.09; 95% CI: 1.05–9.11, p = 0.03). ICU admission rate in the control group was significantly higher than the IFN group (66.66% vs. 42.42%, p = 0.04). The duration of hospitalization and ICU stay were not significantly different between the groups All-cause 28-day mortality was 6.06% and 18.18% in the IFN and control groups respectively (p = 0.12). IFN β-1b was effective in shortening the time to clinical improvement without serious adverse events in patients with severe COVID-19. Furthermore, admission in ICU and need for invasive mechanical ventilation decreased following administration of IFN β-1b.

sehr niedrige Evidenz: bei Mortalität signifikante Vorteile

Summary of Findings table related to results of 2 RCTs (Davoudi-Monfared, Rahmani), related to comparisons of interferon beta-1a vs standard of care in patients with moderate/severe/critical COVID-19 patients, is presented in Table 3.11-1. In summary, according to the very low certainty of evidence, WHO progression score level 6 or above D14-D28; WHO progression score level 7 or above D14-D28; All-cause mortality D7 and All-cause mortality D14-28 were statisticaly significant better in favour of interferon beta-1a.

Table 3.11-1: Summary of findings table on Interferon β-1a compared to Standard Care for Moderate/Severe/Critical COVID-19 (2 RCTs: Davoudi-Monfared, Rahmani) - https://covid-nma.com/living_data/index.php

Summary of findings:

Interferon β-1a compared to Standard Care for Moderate/Severe/Critical COVID-19

Patient or population: Moderate/Severe/Critical COVID-19
Setting: Worldwide
Intervention: Interferon β-1a
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 Interferon β-1a				
Incidence viral negative conversion D7 - not reported	-	-	-	-	-	outcome not yet measured or reported
Clinical improvement - not reported	-	-	-	-	-	outcome not yet measured or reported
WHO progression score level 6 or above D7	293 per 1.000	**149 per 1.000** (59 to 375)	**RR 0.51** (0.20 to 1.28)	165 (2 RCTs) [b]	⨁◯◯◯ VERY LOW [c,d,e]	
WHO progression score level 6 or above D14-D28	268 per 1.000	**123 per 1.000** (64 to 241)	**RR 0.46** (0.24 to 0.90)	165 (2 RCTs) [b]	⨁◯◯◯ VERY LOW [c,d,f]	
WHO progression score level 7 or above D7	256 per 1.000	**149 per 1.000** (79 to 277)	**RR 0.58** (0.31 to 1.08)	165 (2 RCTs) [b]	⨁◯◯◯ VERY LOW [d,e,g]	
WHO progression score level 7 or above D14-D28	268 per 1.000	**123 per 1.000** (64 to 241)	**RR 0.46** (0.24 to 0.90)	165 (2 RCTs) [b]	⨁◯◯◯ VERY LOW [d,f,g]	
All-cause mortality D7	134 per 1.000	**15 per 1.000** (1 to 122)	**RR 0.11** (0.01 to 0.91)	165 (2 RCTs) [b]	⨁◯◯◯ VERY LOW [d,f,g]	
All-cause mortality D14-D28	280 per 1.000	**123 per 1.000** (65 to 238)	**RR 0.44** (0.23 to 0.85)	165 (2 RCTs) [b]	⨁◯◯◯ VERY LOW [d,f,g]	
Adverse events - not reported	-	-	-	-	-	outcome not yet measured or reported
Serious adverse events - not reported	-	-	-	-	-	outcome not yet measured or reported

***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. Last update: September 18, 2020
b. Davoudi-Monfared E, 2020; Rahmani H, 2020
c. Risk of bias downgraded by 2 levels: some concerns or high risk due to concerns during the randomization process, deviation from intended intervention, missing data, outcome measurement and selection of reported results
d. Indirectness downgraded by 1 level: studies from a single country, therefore results in this population might not be generalizable to other settings
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 events
f. Imprecision downgraded by 1 level: due to low number of events and/or participants
g. Risk of bias downgraded by 2 levels: some concerns or high risk due to concerns during the randomization process, deviation from intended intervention, missing data and selection of the reported result

3.12 Convalescent plasma transfusion

About the treatment under consideration

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

auch zur Herstellung von Immunglobulin-konzentraten verwendet

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 [125-127]. Rare complications include the transmission of infectious pathogens and red cell alloimmunization.

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

Bedingungen: Vefügbarkeit Blutbank serologische Testung

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 [125]. 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.

Blutprodukte für covid-19 nicht zugelassen

EMA (& EC) Guidance zur Verwendung

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) 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 [128, 129]. 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 [128]. 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 [129, 130].

EC im Juli 2020: Emergency Support

On July 31, 2020 European Commission strengthens support for treatment through convalescent plasma. This action is part of the Emergency Support Instrument (ESI) and grants will be provided to public and NGO blood-collection services authorised to collect plasma [131].

FDA im August 2020: Emergency Authorization

On August 23, 2020 the FDA issued an **emergency use authorization (EUA)** for investigational convalescent plasma for the treatment of COVID-19 in hospitalized patients. Based on scientific evidence available, the FDA concluded, as outlined in its decision memorandum (https://www.fda.gov/media/141480/download), convalescent plasma may be effective in treating COVID-19 (in lessening the severity or shortening the length of COVID-19 illness in some hospitalized patients) and that the known and potential benefits of the product outweigh the known and potential risks of the product [132].

US NIH COVID-19 Treatment Guidelines: insuffiziente Datenlage weder für noch gegen CVP

Current US **NIH COVID-19 Treatment Guidelines** stated that there are insufficient clinical data to recommend either for or against the use of convalescent plasma for the treatment of COVID-19 [133]. As of September 01, 2020 the COVID-19 Treatment Guidelines Panel's Statement on the Emergency Use Authorization of Convalescent Plasma for the Treatment of COVID-19 is as the following: There are insufficient data to recommend either for or against the use of convalescent plasma for the treatment of COVID-19; Available data suggest that serious adverse reactions following the administration of COVID-19 convalescent plasma are infrequent and consistent with the risks associated with plasma infusions for other indications. The long-term risks of treatment with COVID-19 convalescent plasma and whether its use attenuates the immune response to SARS-CoV-2, making patients more susceptible to reinfection, have not been evaluated;

prosepektive RCTs notwendig

Convalescent plasma should not be considered standard of care for the treatment of patients with COVID-19; Prospective, well-controlled, adequately powered randomized trials are needed to determine whether convalescent plasma is effective and safe for the treatment of COVID-19. Members of the public and health care providers are encouraged to participate in these prospective clinical trials; The Panel will continue to evaluate emerging clinical data on the use of convalescent plasma for the treatment of COVID-19 and will update the Convalescent Plasma section of the Guidelines in the near future [133].

Completed, withdrawn, suspended or terminated studies

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

3 abgeschlossene Studien: Indien, Irak, Türkei

August/ Sept: weitere Studien wurden abgechlossen: ohne Ergebnispräsentation

As of June 12, 2020 one RCT (NCT04346446) conducted in India, comparing convalescent plasma+supportive care with random donor plasma+supportive care in severely sick COVID-19 patients, is listed as completed (May 30, 2020) in ClinicalTrials.gov register. Nor results posted nor publication is provided yet. One interventional single group study (NCT04325672) was withdrawn due to opening Expanded Access Protocol. As of July 09, 2020 one interventional single group assignment study in Indonesia on 10 patients is completed (NCT04407208). Two RCTs were completed as well: one performed on 49 patients in Iraq (NCT04441424) and one with 60 patients in Turkey (NCT04407208). Nor results posted nor publication is provided yet. As of August 15, 2020 one single-arm interventional study in Switzerland, on 15 adult patients with moderate to severe COVID-19 (NCT04389944), and one RCT on 40 COVID-19 patient with hypoxia in Bahrain were completed (NCT04356534). No results are posted yet. As of August 15, 2020 one RCT in Turkey (NCT04442958) was completed, on 60 severe Covid-19 patients followed up in critical care unit. As of October 11, 2020 one phase 2 trial was completed in Italy (NCT04569188), on 21 elderly Covid-19 patients; one phase 2 RCT in Russian Federation, on 60 patients with moderate and severe COVID-19 disease (NCT04392414); one

phase 2 RCT in 58 patients in Chile (NCT04375098) and one RCT in Argentina (NCT04383535), in 333 patients with COVID-19.

Results of publications

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

20,000 hospitalisierte Pts.
niedrige AE/ SAE Raten

frühe Verabreichung reduziert möglicherweise Mortalität mehr als spätere

As of July 09, 2020 prospective observational studis were published related to safety and efficacy of COVID-19 convalescent plasma. Joyner et al. 2020 [134] provided results from the convenience sample of 20,000 hospitalized patients with severe or life-threatening COVID-19, treated with COVID-19 convalescent plasma through the US FDA Expanded Access Program for COVID-19 convalescent plasma. Approximately 200 – 500 mL of convalescent plasma was administered intravenously according to institutional transfusion guidelines. The incidence of all serious adverse events was low (transfusion reactions (n=89; <1%); thromboembolic or thrombotic events (n=87; <1%), and cardiac events (n=680, ~3%). The majority of the thromboembolic or thrombotic events (n=55) and cardiac events (n=562) were judged to be unrelated to the plasma transfusion per se. The seven-day mortality rate was 8.6% (8.2%, 9.0%). It was higher among more critically-ill patients relative to less ill counterparts, including patients admitted to the intensive care unit vs. not admitted (10.5% vs. 6.0%), mechanically ventilated vs. not ventilated (12.1% vs. 6.2%), and with septic shock or multiple organ dysfunction/failure vs. those without dysfunction/failure (14.0% vs. 7.6%). The authors concluded that transfusion of convalescent plasma is safe in hospitalized patients with COVID-19. Earlier administration of plasma within the clinical course of COVID-19 is more likely to reduce mortality.

Xia (China):
138 Pts.

Verbesserung der Symptomatik und Reduktion der Mortalität

Xia et al. 2020 [135] reported the results of 1,568 severe or critical COVID-19 patients, including 1,430 patients who only received standard treatment and 138 patients who also received 200-1200 mL ABO-compatible COVID-19 convalescent plasma (CCP group), in Wuhan, China. Three patients (2.2%) died in the CCP group up to April 20, reducing approximately 50% of the mortality rate when compared to that in the standard-treatment group (4.1%). For the 126 non-ICU patients before CCP therapy, 3 patients (2.4%) were admitted to ICU, as compared to 72 out of 1,403 (5.1%) ICU admissions in the standard-treatment group. Within 14 days after CCP therapy, 20 out of the 25 (80%) patients who were SARS-CoV-2 positive became virus-free. 77.9% of cases represented lung lesion absorption within 14 days after CCP therapy. Three patients had minor allergic reactions (pruritus or erythema) during the transfusion, but no severe transfusion reactions such as transfusion-associated circulatory overload (TACO), transfusion-related acute lung injury (TRALI), or severe allergic reactions were observed. Patients whose SCSS was 5 before therapy showed no improvements after CCP therapy. Within 7 days after CCP therapy, 66.7% and 83.4% of patients showed various degrees of clinical improvements in patients whose SCSS was 4 or 3, respectively. The authors concluded that CCP, transfused even after two weeks (median of 45 days in our cohort) of symptom onset, could improve the symptoms and mortality in severe or critical COVID-19 patients.

Cochrane Systematic Review:

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

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

On July 10, 2020 Piechotta et al. [136] published the **first living update of Cochrane Systematic Review,** with results from four controlled studies (1 RCT (stopped early) with 103 participants, of whom 52 received convalescent plasma; and 3 controlled NRSIs with 236 participants, of whom 55 received convalescent plasma) to assess effectiveness of convalescent plasma. Control groups received standard care at time of treatment without convalescent plasma. Related to the outcome - All- cause mortality at hospital discharge (1 controlled NRSI, 21 participants) - authors are very uncertain whether convalescent plasma has any effect on all- cause mortality at hospital discharge (risk ratio (RR) 0.89, 95% confidence interval (CI) 0.61 to 1.31; very low- certainty evidence). On outcome - Time to death (1 RCT, 103 participants; 1 controlled NRSI, 195 participants) - authors are also very uncertain whether convalescent plasma prolongs time to death (RCT: hazard ratio (HR) 0.74, 95% CI 0.30 to 1.82; controlled NRSI: HR 0.46, 95% CI 0.22 to 0.96; very low- certainty evidence). The same is true for outcome Improvement of clinical symptoms, assessed by need for respiratory support (1 RCT, 103 participants; 1 controlled NRSI, 195 participants): at seven days - RCT: RR 0.98 (95% CI 0.30 to 3.19), 14 days - RCT: RR 1.85 (95% CI 0.91 to 3.77); controlled NRSI: RR 1.08 (95% CI 0.91 to 1.29), and 28 days - RCT: RR 1.20 (95% CI 0.80 to 1.81; very low- certainty evidence). No studies reported outcome Quality of life. For safety outcomes authors also included non- controlled NRSIs: there was limited information regarding adverse events. Of the controlled studies, none reported on this outcome in the control group. There is only very low- certainty evidence for safety of convalescent plasma for COVID- 19.

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

frühere Verabreichung von CVPlasma, höhere IgG Titer – bessere Ergebnisse

As of August 15, 2020 one additional observational study was published by Joyner et al. 2020 [131]. In their preprint, they reported results from open-label, Expanded Access Program (EAP) for the treatment of COVID-19 patients with human convalescent plasma (NCT04338360). They evaluated seven and 30-day mortality in 35,322 hospitalized adults transfused with COVID-19 convalescent plasma. This cohort included a high proportion of critically-ill patients, with 52.3% in the intensive care unit (ICU) and 27.5% receiving mechanical ventilation at the time of plasma transfusion. The seven-day mortality rate was 8.7% [95% CI 8.3%-9.2%] in patients transfused within 3 days of COVID-19 diagnosis but 11.9% [11.4%-12.2%] in patients transfused 4 or more days after diagnosis ($p<0.001$). Similar findings were observed in 30-day mortality (21.6% vs. 26.7%, $p<0.0001$). Importantly, a gradient of mortality was seen in relation to IgG antibody levels in the transfused plasma. For patients who received high IgG plasma (>18.45 S/Co), seven-day mortality was 8.9% (6.8%, 11.7%); for recipients of medium IgG plasma (4.62 to 18.45 S/Co) mortality was 11.6% (10.3%, 13.1%); and for recipients of low IgG plasma (<4.62 S/Co) mortality was 13.7% (11.1%, 16.8%) ($p=0.048$). This unadjusted dose-response relationship with IgG was also observed in thirty-day mortality ($p=0.021$). The pooled relative risk of mortality among patients transfused with high antibody level plasma units was 0.65 [0.47-0.92] for 7 days and 0.77 [0.63-0.94] for 30 days compared to low antibody level plasma units. Authors concluded that the relationships between reduced mortality and both earlier time to transfusion and higher antibody levels provide signatures of efficacy for convalescent plasma in the treatment of hospitalized COVID-19 patients, which may be informative for the treatment of COVID-19 and design of randomized clinical trials involving convalescent plasma.

Results from the **first RCT** (ChiCTR200029757) conducted in 103 patients with COVID-19 (severe to critical) admitted to 7 centers in China, with aim to evaluate the efficacy and adverse effects of convalescent plasma therapy with a high titer of antibody to SARS-CoV-2, is published in JAMA [137]. 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 3.12-1).

keine stat. signifikanten Unterschiede bei

Transfusions-bedingte AE

frühzeitiger Abbruch der Studie und daher „underpowering“

One **RCT** appeared as **preprint** (NCT04342182), performed on 86 patients with COVID-19 (moderate-critical) admitted to 14 centers in the Netherlands, but halted prematurely [138]. The Convalescent-plasma-for-COVID (ConCOVID) study was a randomized trial comparing convalescent plasma with standard of care therapy in Dutch patients hospitalized for COVID-19. Patients were randomized 1:1 and received 300ml of plasma with anti-SARSCoV-2 neutralizing antibody titers of at least 1:80. The primary endpoint was day-60 mortality and key secondary endpoints were hospital stay and WHO 8-point disease severity scale improvement on day 15. The trial was halted prematurely after 86 patients were enrolled. Although symptomatic for only 10 days (IQR 6-15) at the time of inclusion, 53 of 66 patients tested had anti-SARS-CoV-2 antibodies at baseline. A SARS-CoV-2 plaque reduction neutralization test showed neutralizing antibodies in 44 of the 56 (79%) patients tested with median titers comparable to the 115 donors (1:160 vs 1:160, p=0.40).

RCT als preprint (Niederlande): 86 Pts.

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

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

kein Unterschied

Antikörper Titer sind essentiell

The Living Systematic Review, related to these two RCTs mentioned above, Li et al. 2020 [137], and Gharbharan et al. 2020 [138], with Summary of findings table is provided in Table 3.12-2 [139, 140].

As of September 11, 2020, one new multi-center RCT (NCT04345523) article has been published as **preprint** [141]: All patients received standard of care treatment, including off-label use of marketed medicines, and were randomized 1:1 to receive one dose (250-300 mL) of CP from donors with IgG anti-SARS-CoV-2. The trial was stopped after first interim analysis due to the fall in recruitment related to pandemic control. With 81 patients randomized, there were no patients progressing to mechanical ventilation or death among the 38 patients assigned to receive plasma (0%) versus 6 out of 43 patients (14%) progressing in control arm. Mortality rates were 0% vs 9.3% at days 15 and 29 for the active and control groups, respectively. No significant differences were found in secondary endpoints. At inclusion, patients had a median time of 8 days (IQR, 6-9) of symptoms and 49,4% of them were positive for anti-SARS-CoV-2 IgG antibodies. Authors concluded that convalescent plasma could be superior to standard of care in avoiding progression to mechanical ventilation or death in hospitalized patients with COVID-19. The strong dependence of results on a limited number of events in the control group prevents drawing firm conclusions about CP efficacy from this trial.

Sept 2020: Publikation zu RCT CVP vs. SOC

frühzeitiger Abbruch wegen Mangel an Rekrutierung: Interim Analyse von 81 Pts

CVP besser bei Vermeidung von künstlicher Beatmung und Tod

Ergebnisse aber unzuverlässig

As of October 11, 2020, Agarwal et al. 2020 [142] reported, as preprint, results from open-label, parallel-arm, phase 2, multicentre, randomized controlled trial in India (CTRI/2020/04/024775) conducted on hospitalized, moderately ill confirmed COVID-19 patients (PaO2/FiO2: 200-300 or respiratory rate > 24/min and SpO2 ≤ 93% on room air). 464 participants were enrolled; 235 and 229 in intervention and control arm, respectively. Composite primary outcome was achieved in 44 (18.7%) participants in the intervention arm and 41 (17.9%) in the control arm [aOR: 1.09; 95% CI: 0.67, 1.77]. Mortality was documented in 34 (13.6%) and 31 (14.6%) participants in intervention and control arm, respectively [aOR) 1.06 95% CI: -0.61 to 1.83]. Authors concluded that convalescent plasma was not associated with reduction in mortality or progression to severe COVID-19.

Okt 2020
preprint RCT
(open-label)
Indien
464 Pts

kein Unterschied bei Mortalität oder Fortschreiten der Krankheit

Balcells et al. 2020 [143] reported, as preprint, results from open-label, single-center, randomized clinical trial performed in an academic center in Santiago, Chile (NCT04375098). Of 58 randomized patients (mean age, 65.8 years, 50% male), 57 (98.3%) completed the trial. A total of 13 (43.3%) participants from the deferred group received plasma based on clinical aggravation. No benefit was found in the primary outcome (32.1% vs 33.3%, OR 0.95, 95% CI 0.32-2.84, p>0.99) in the early versus deferred CP group. In-hospital mortality rate was 17.9% vs 6.7% (OR 3.04, 95% CI 0.54-17.2, p=0.25), mechanical ventilation 17.9% vs 6.7% (OR 3.04, 95% CI 0.54-17.2, p=0.25), and prolonged hospitalization 21.4% vs 30% (OR 0.64, 95%CI, 0.19-2.1, p=0.55) in early versus deferred CP group, respectively. Viral clearance rate on day 3 (26%

preprint RCT
(open-label)
Chile
58 Pts

kein Unterschied bei Mortalität, Dauer des Krankenhausaufenthalts und künstlicher Beatmung

vs 8%, p=0.20) and day 7(38% vs 19%, p=0.37) did not differ between groups. Two patients experienced serious adverse events within 6 or less hours after plasma transfusion. Authors concluded that immediate addition of CP therapy in early stages of COVID-19 -compared to its use only in case of patient deterioration- did not confer benefits in mortality, length of hospitalization or mechanical ventilation requirement.

Table 3.12-1: Publications on clinical trials on Convalescent plasma [137]

Author, year [Reference]	***Li et al. 2020 [137]**
Country	China
Study design	RCT, open-label, multicenter
Number of pts	103 patients were recruited; 52 were randomly assigned to the convalescent plasma+standard treatment group and 51 to the control group
Intervention/Product	Convalescent plasma+standard treatment
Comparator	Standard treatment
Mean age of patients, yrs (SD)	Median age, 70 years
Sex % male (% female)	60 (58.3%) men
Follow-up (days)	28 days
Clinical status	Severe of life-treatening COVID-19
Loss to follow-up, n (%)	2 patients
Efficacy outcomes	
Overall survival (OS), n (%)	28-day mortality (15.7% vs 24.0%; OR, 0.65 [95% CI, 0.29-1.46]; p =0.30)
Time to clinical improvement within 28 days	(51.9% (27/52) of the convalescent plasma group vs 43.1% (22/51) in the control group (difference, 8.8% [95% CI, −10.4% to 28.0%]; hazard ratio [HR], 1.40 [95% CI, 0.79-2.49]; p =0.26)
Time from randomization to discharge	(51.0% vs 36.0% discharged by day 28; HR, 1.61 [95% CI, 0.88-2.93]; p = 0.12)
Time to negative conversion rate of viral PCR at 72 hours	(87.2% of the convalescent plasma group vs 37.5% of the control group (OR, 11.39 [95% CI, 3.91-33.18]; p < 0.001)
Safety outcomes	
Adverse events (AEs)	2 patients in the convalescent plasma group

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

Table 3.12-2: Summary of findings table on Convalescent plasma (2 RCTs: Li and Gharbharan) [137],[149],[139, 140]

Outcome	No. of patients		Relative effect (95% CI)	Absolute effect (95% CI)	No. of studies	Certainty of evidence
	CPT	Standard Treatment				
All-cause mortality	14/95 (14.7%)	23/94 (24.5%)	RR 0.60 (0.33 to 1.10)	98 fewer per 1,000 (from 164 fewer to 24 more)	2	Low
serious patients	8/23 (34.8%)	10/22 (45.5%)	RR 0.77 (0.37 to 1.58)	105 fewer per 1,000 (from 286 fewer to 264 more)	1[144][144][143][144]	Low
critically ill patients	0/29 (0.0%)	2/29 (6.9%)	RR 0.20 (0.01 to 3.99)	55 fewer per 1,000 (from 68 fewer to 206 more)	1	Low
SARS-CoV-2 clearance	41/52 (78.8%)	15/51 (29.4%)	RR 2.67 (1.71 to 4.18)	491 more per 1,000 (from 209 more to 935 more)	1	Very low
serious patients	19/23 (82.6%)	7/22 (31.8%)	RR 2.60 (1.37 to 4.92)	509 more per 1,000 (from 118 more to 1,000 more)	1[144][144][143][144]	Very low
critically ill patients	22/29 (75.9%)	8/29 (27.6%)	RR 2.75 (1.47 to 5.13)	483 more per 1,000 (from 130 more to 1,000 more)	1	Very low
Number of patients discharged	26/52 (50.0%)	18/51 (35.3%)	RR 1.35 (1.00 to 1.84)	124 more per 1,000 (from 0 fewer to 296 more)	1	Very low
serious patients	21/23 (91.3%)	15/22 (68.2%)	RR 1.34 (0.98 to 1.83)	232 more per 1,000 (from 14 fewer to 566 more)	1	Very low
critically ill patients	5/29 (17.2%)	3/29 (10.3%)	RR 1.67 (0.44 to 6.34)	69 more per 1,000 (from 58 fewer to 552 more)	1	Very low
Duration of hospitalisation (follow up range 28-60 days)	NA	NA	HR 1.21 (0.64 to 2.28)	NA	2	Very low
serious patients	NA	NA	HR 1.97 (1.00 to 3.88)	NA	1[144][144][143][144]	Low
critically ill patients	NA	NA	HR 1.90 (0.45 to 8.04)	NA	1	Low
Number of patients with AE	2/51 (3.9%)	0/50 (0.0%)	RR 2.94 (0.32 to 27.32)	0 fewer per 1,000 (from 0 fewer to 0 more)	1	Low
serious patients	1/23 (4.3%)	0/22 (0.0%)	RR 2.88 (0.12 to 67.03)	0 fewer per 1,000 (from 0 fewer to 0 more)	1	Low
critically ill patients	1/28 (3.6%)	0/28 (0.0%)	RR 3.00 (0.13 to 70.64)	0 fewer per 1,000 (from 0 fewer to 0 more)	1	Low
Number of patients with SAE	None reported	None reported	NA	NA	1	Low

Source: [139] **Abbreviations:** AE=Adverse Events; SAE=Serious Adverse Events .

3.13 Plasma derived medicinal products

Neutralizing monoclonal antibodies

neutralisierende monoklonale Antikörper: Prävention und Behandlung

As Marovich et al. 2020 [145] stated, **neutralizing monoclonal antibodies** to SARS-CoV-2 have the potential to be used for both prevention and treatment of infection. They can help to guide vaccine design and development as well. The main target of SARS-CoV-2 neutralizing monoclonal antibodies is the surface spike glycoprotein that mediates viral entry into host cells. Some products will include of a combination of 2 monoclonal antibodies targeting different sites on the spike protein. Due to long half-life of most monoclonal antibodies (approximately 3 weeks for IgG1), a single infusion should be sufficient. A potential limitation of monoclonal antibodies for treatment of COVID-19 is the unknown bioavailability of passively infused IgG in tissues affected by the disease, especially the lungs, which serve as a key target of SARS-CoV-2 infection. Due to the effect of viral diversity it will be important to monitor for the emergence of resistant viral mutations under selective pressure of monoclonal antibody treatment.

Halbwertszeit bis 3 Wochen von Vorteil

Nachteil: unbekannte Bioverfügbarkeit der infundierten Antikörper

Several clinical trials are already registered in ClinicalTrials.gov with several SARS-CoV-2 monoclonal antibodies, and are underway (for example: NCT04425629; NCT04346277; NCT04391309; NCT04268537; NCT04441918; NCT04426695; NCT04429529; NCT04454398; NCT04453384) [21].

zahlreiche klinische Studien registriert

To block disease progression, therapeutic trials will include treatment of patients with varying degrees of illness. In the prevention of COVID-19, passive infusion of monoclonal antibodies as preexposure or postexposure prophylaxis might offer immediate protection from infection that could last weeks or months [145]. Newer technologies that modify the Fc region of the antibody to extend the half-life of monoclonal antibodies can provide potentially protective levels for months, depending on the monoclonal antibody concentrations required. Possible disease enhancement include antibody-mediated enhancement of viral entry and replication in target cells (Fc-bearing monocytes or macrophages) and virus-antibody immune complexes and the associated cytokine release [145].

Prä- und post Expositionsprophylaxe

Preliminary results from several trials have been reported in press release format. Publication of the complete results are necessary to evaluate the quality of the trials and the efficacy of monoclonal antibodies.

3.13.1 REGN-COV2 - combination of two monoclonal antibodies (REGN10933 and REGN10987)

kombinierte Antikörper-"Cocktails" zur Prävention

As stated in Press release on July 06, 2020, https://investor.regeneron.com/news-releases/news-release-details/regeneron-announces-start-regn-cov2-phase-3-covid-19-prevention, Regeneron Pharmaceuticals, Inc. (NASDAQ: REGN) announced the initiation of late-stage clinical trials evaluating REGN-COV2, Regeneron's investigational double antibody cocktail for the **treatment and prevention** of COVID-19.

REGN-COV2's two antibodies bind non-competitively to the critical receptor binding domain of the virus's spike protein, which diminishes the ability of mutant viruses to escape treatment and protects against spike variants that have arisen in the human population. All trials are adaptively-designed, and

the ultimate numbers of patients enrolled will depend on trial progress and insights from phase 2 studies.

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

A **phase 3** prevention trial will evaluate REGNCOV2's ability to prevent infection among uninfected people who have had close exposure to a COVID-19 patient (such as the patient's housemate). It is being run jointly with the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health (NIH). The Phase 3 prevention trial is being conducted at approximately 100 sites and is expected to enroll 2,000 patients in the U.S.; the trial will assess SARS-CoV-2 infection status.

Behandlung von hospitalisierten und ambulanten Patiente*innen
1.050 Pts.
In Planung

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

Sept 2020:
RECOVERY nimmt REGNCOV2 als Studienmedikament auf

On September 14, 2020 the University of Oxford and Regeneron Pharmaceuticals, Inc. announced that RECOVERY (Randomised Evaluation of COVid-19 thERapY), one of the world's largest randomised clinical trials of potential COVID-19 treatments, will evaluate Regeneron's investigational anti-viral antibody cocktail, REGNCOV2, https://www.recoverytrial.net/news/recovery-covid-19-phase-3-trial-to-evaluate-regeneron2019s-regn-cov2-investigational-antibody-cocktail-in-the-uk. The phase 3 open-label trial in patients hospitalised with COVID-19 will compare the effects of adding REGN-COV2 to the usual standard-of-care versus standard-of-care on its own. REGN-COV2 is the first specifically designed COVID-19 therapy being evaluated by RECOVERY. The open-label RECOVERY trial will assess the impact of adding REGN-COV2 to the usual standard-of-care on all-cause mortality 28 days after randomisation. Other endpoints include the impact on hospital stay and the need for ventilation. It is anticipated that at least 2,000 patients will be randomly allocated to receive REGN-COV2 plus usual standard-of-care, and results will be compared with at least 2,000 patients who receive standard-of-care on its own. Usual standard-of-care varies by local hospital.

Sept 2020:

erste Daten (275 Pts) zeigen Reduktion der Viruslast und von Krankheitssymptomen bei nicht-hospitalisierten Pts.

On September 29, 2020 Regeneron Pharmaceuticals, Inc. announced the first data from a descriptive analysis of a seamless phase 1/2/3 trial of its investigational antibody cocktail REGN-COV2 showing it reduced viral load and the time to alleviate symptoms in non-hospitalized patients with COVID-19. REGN-COV2 also showed positive trends in reducing medical visits. Infusion reactions were seen in 4 patients (2 on placebo and 2 on REGN-COV2). Serious adverse events occurred in 2 placebo patients, 1 low dose patient and no high dose patients. There were no deaths in the trial. The descriptive analysis included the first 275 patients enrolled in the trial and was designed to evaluate anti-viral activity with REGN-COV2 and identify patients most likely to benefit from treatment; the next cohort, which could be used to rapidly and prospectively confirm these results, has already been enrolled. Patients in the trial were randomized 1:1:1 to receive a one-time infusion of 8 grams of REGN-COV2 (high dose), 2.4 grams of REGN-COV2 (low dose) or placebo. All patients entering the trial had laboratory-confirmed COVID-19 that was being treated in the outpatient setting. Patients were prospectively characterized prior to treatment by serology tests to see if they had already generated antiviral antibodies on their own and were classified as

seronegative (no measurable antiviral antibodies) or seropositive (measurable antiviral antibodies). Approximately 45% of patients were seropositive, 41% were seronegative and 14% were categorized as "other" due to unclear or unknown serology status,

https://investor.regeneron.com/news-releases/news-release-details/regenerons-regn-cov2-antibody-cocktail-reduced-viral-levels-and.

3.13.2 LY-CoV555 - neutralizing IgG1 monoclonal antibody (bamlanivimab) and LY-CoV016 - recombinant fully human monoclonal neutralizing antibody (etesevimab)

2 weitere monoklonale Antikörper Medikamente:

LY-CoV555 is a neutralizing IgG1 monoclonal antibody (mAb) directed against the spike protein of SARS-CoV-2. It is designed to block viral attachment and entry into human cells, thus neutralizing the virus, potentially preventing and treating COVID-19. LY-CoV555 emerged from the collaboration between Lilly and AbCellera to create antibody therapies for the prevention and treatment of COVID-19. Lilly scientists rapidly developed the antibody in less than three months after it was discovered by AbCellera and tested by the scientists at the National Institute of Allergy and Infectious Diseases (NIAID) Vaccine Research Center. It was identified from a blood sample taken from one of the first US patients who recovered from COVID-19.

LY-CoV555 (Bamlanivimab)

LY-CoV016 (also known as JS016) is a recombinant fully human monoclonal neutralizing antibody, which specifically binds to the SARS-CoV-2 surface spike protein receptor binding domain with high affinity and can effectively block the binding of the virus to the ACE2 host cell surface receptor.

LY-CoV016 (Etesevimab)

LY-CoV555: Phase 1

Lilly has successfully completed enrollment and primary safety assessments of LY-CoV555 in a **phase 1** study of hospitalized patients with COVID-19 (NCT04411628) and long-term follow-up is ongoing.

BLAZE-1: RCT, Phase 2 800 Pts. LY-CoV555 & LY-CoV016

milde/ moderate Erkrankung symptomatische, nicht-hospitalisierte Pts.

Endpunkte: Reduktion der Viruslast, Hospitalisierung, Besuche in Notfallambulanz

BLAZE-1 (NCT04427501) is ongoing randomized, double-blind, placebo-controlled **phase 2** study designed to assess the efficacy and safety of LY-CoV555 and LY-CoV016 for the treatment of symptomatic COVID-19 in the outpatient setting. Across all treatment arms, the trial will enroll an estimated 800 participants. The monotherapy arms of the trial enrolled mild-to-moderate recently diagnosed COVID-19 patients across four groups (placebo, LY-CoV555 700 mg, LY-CoV555 2800 mg, and LY-CoV555 7000 mg). To be eligible, patients were required to have mild or moderate symptoms of COVID-19 as well as a positive SARS-CoV-2 test based on a sample collected no more than 3 days prior to drug infusion. The primary outcome measure for the BLAZE-1 monotherapy arms was change from baseline to Day 11 in SARS-CoV-2 viral load. Additional endpoints include the percentage of participants who experience COVID-related hospitalization, ER visit or death from baseline through Day 29, as well as safety. The study is ongoing with additional treatment arms.

BLAZE-2: RCT, Phase 3 initiiert

Lilly recently initiated a **phase 3** study for the prevention of COVID-19 in residents and staff at long-term care facilities (NCT04497987, BLAZE-2).

NIH-Studien: ACTIV-2 and ACTIV-3

In addition, LY-CoV555 is being tested in the National Institutes of Health-led ACTIV-2 and ACTIV-3 studies of ambulatory and hospitalized COVID-19 patients.

Sept 2020: erste Ergebnisse BLAZE-1

mit LY-CoV555 frühere Reduktion der Viruslast, weniger Hospitaliseirungen und Notfallambulanzbesuche

On September 16, 2020 Eli Lilly and Company announced proof of concept data from an interim analysis of the BLAZE-1 clinical trial, showing a reduced rate of hospitalization for patients treated with LY-CoV555. The trial enrolled mild-to-moderate recently diagnosed COVID-19 patients across four groups (placebo, 700 mg, 2800 mg, and 7000 mg). The prespecified primary endpoint, change from baseline in viral load at day 11, was met at the 2800 mg dose level, but not the others. Most patients, including those receiving placebo, demonstrated near complete viral clearance by day 11. Additional analyses of viral data demonstrated that LY-CoV555 improved viral clearance at an earlier time point (day 3) and reduced the proportion of patients with persistently high viral load at later time points. These biomarker data correlated with LY-CoV555's positive impact on the prespecified endpoint of COVID-19-related hospitalization or ER visit. This endpoint occurred in 1.7 percent (5/302) of LY-CoV555 patients, pooled across dose groups, as compared to 6 percent (9/150) of placebo patients, which corresponds to a 72 percent risk reduction in this limited population.

Hospitalisierungen (trotz LY-CoV555) wahrscheinlicher bei Pts. mit Risikofaktoren (Alter, BMI)

Most study hospitalizations occurred in patients with underlying risk factors (age or BMI), suggesting a more pronounced treatment effect for patients in these higher-risk groups. Ongoing studies will seek to confirm this finding. Across all treatment groups (including placebo), no patients progressed to mechanical ventilation or died. Exploratory analyses indicated a more rapid improvement in symptoms for patients treated with LY-CoV555 versus placebo, supporting the hospitalization effect. LY-CoV555 was well-tolerated, with no drug-related serious adverse events reported. Treatment emergent adverse events were similar across all dose groups and comparable to placebo. Viral RNA sequencing revealed putative LY-CoV555-resistance variants in placebo and all treatment arms. The rate of resistance variants was numerically higher in treated patients (8 percent) versus placebo (6 percent).

BLAZE-1 Studie läuft und rekrutiet auch Pts. mit höherem Risiko auf Hospitalisierungen

The BLAZE-1 clinical trial remains ongoing, testing LY-CoV555 in combination with a second Lilly antibody, LY-CoV016, which binds a different epitope in the SARS-CoV-2 spike region. The trial is currently enrolling a larger, confirmatory cohort of higher risk patients, testing the ability of the antibody combination to reduce the number of patients with persistently high viral load and reduce COVID-related hospitalizations. https://www.prnewswire.com/news-releases/lilly-announces-proof-of-concept-data-for-neutralizing-antibody-ly-cov555-in-the-covid-19-outpatient-setting-301131785.html

Okt 2020: weitere Auswertungen zu BLAZE-1 bestätigen erste Analysen

neue Kohorte mit Kombinationstherapie (CoV555 +LY-CoV016) 268 Pts

frühere Reduktion der Viruslast

On October 7, 2020 Eli Lilly and Company announced data from a new interim analysis of the BLAZE-1 clinical trial showed that combination therapy with two of Lilly's SARS-CoV-2 neutralizing antibodies reduced viral load, symptoms and COVID-related hospitalization and ER visits. The randomized, double-blind, placebo-controlled phase 2 study evaluated LY-CoV555 and LY-CoV016, which bind complementary regions of the SARS-CoV-2 spike protein, for the treatment of symptomatic COVID-19 in the outpatient setting. The combination cohort enrolled recently diagnosed patients with mild-to-moderate COVID-19, who were assigned to 2800 mg of each antibody (n=112) or placebo (n=156). The combination therapy significantly reduced viral load at day 11 ($p=0.011$), meeting the primary endpoint of the study. Most patients, including those receiving placebo, demonstrated near complete viral clearance by day 11. Further, combination treatment reduced viral levels at day 3 ($p=0.016$) and day 7 ($p<0.001$)—earlier time points during the course of infection when higher viral loads are typically seen. Combination therapy significantly reduced the time-weighted

average change from baseline from day 1 to 11. An exploratory analysis showed that the proportion of patients with persistent high viral load at day 7 for combination therapy was lower (3.0 percent) versus placebo (20.8 percent), corresponding to a nominal p value of $p<0.0001$ without multiplicity adjustment. No emergent putative resistance variants have been observed thus far in patients treated with combination therapy.

Ergebnisse in Kombinationstherapie gleich wie in Monotherapie LY-CoV555

Hospitalisierungen und Notfallambulanzbesuche seltener mit Kombinationstherapie

The combination therapy also met prespecified clinical endpoints, including the time-weighted average change from baseline in total symptom score from day 1 to 11 ($p=0.009$). The improvement in symptoms was observed as early as three days after dosing and was similar in magnitude and timing to improvements previously seen with LY-CoV555 monotherapy. The rate of COVID-related hospitalization and ER visits was lower for patients treated with combination therapy (0.9 percent) versus placebo (5.8 percent), a relative risk reduction of 84.5 percent ($p=0.049$). This was also similar to observations for LY-CoV555 monotherapy. Combination therapy has been generally well tolerated with no drug-related serious adverse events. In LY-CoV555 monotherapy studies there have been isolated drug-related infusion reactions or hypersensitivity that were generally mild (two reported as serious infusion reactions, all patients recovered). Treatment emergent adverse events were comparable to placebo for both LY-CoV555 monotherapy and combination therapy.

basierend auf Daten wurde Antrag auf FDA emergency use authorisation (EUA) gestellt

Regulatory update: Based on the combination therapy data, along with the previously disclosed findings for LY-CoV555 monotherapy, Lilly has engaged global regulators, including the FDA regarding potential emergency use authorisation (EUA). Lilly has now submitted an initial request for EUA for LY-CoV555 monotherapy in higher-risk patients who have been recently diagnosed with mild-to-moderate COVID-19.

pragmatic trial planned by Eli Lilly

To generate additional efficacy and safety data, Lilly plans to initiate a pragmatic, open-label study in October 2020, enrolling patients treated with either monotherapy or combination therapy, with a focus on collecting data regarding hospitalizations, deaths and safety.

3.13.3 AZD7442 - combination of two monoclonal antibodies (AZD8895 + AZD1061)

AZD7442 Kombination aus 2 monoklonalen Antikörpern Vanderbilt University/ AstraZeneca

AZD7442 is a combination of two mAbs (AZD8895 + AZD1061) derived from convalescent patients with SARS-CoV-2 infection. Discovered by Vanderbilt University Medical Center and licensed to AstraZeneca in June 2020, the mAbs were optimised by AstraZeneca with half-life extension and reduced Fc receptor binding. The half-life extended mAbs should afford at least six months of protection from COVID-19.

Phase 1
Ende Sept 2021

NCT04507256 is a **phase 1**, first time in human, randomised, double-blind, placebo-controlled, and dose escalation study that aims to evaluate the safety, tolerability and pharmacokinetics of AZD7442 in healthy participants. Estimated study completion date is September 2021.

Phase 2

Should AZD7442 prove to be tolerated and have a favourable safety profile in the trial, AstraZeneca will progress it into larger late-stage **phase 2** and phase 3 trials to evaluate ist efficacy as a potential preventative and treatment approach against COVID-19.

https://www.astrazeneca.com/media-centre/press-releases/2020/phase-1-clinical-trial-initiated-for-monoclonal-antibody-combination-for-the-prevention%E2%80%A6

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

Reduktion der Dauer der Virusausscheidung, Symtomverbesserung, Dauer des Krankenhausaufenthalts

kein Unterschied bei AE keine Todesfälle in beiden Gruppen

Hung et al. 2020 [120] 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.

keine weiteren RCTs publiziert

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

August 2020: ein weiterer RCT

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

RCT: 101 Pts

3 Gruppen: RBV+IFN LPV/r+IFN RBV+LPV/r

kein Unterschied

Huang et al. 2020 [122] reported the results from a single-center, randomized, open-labeled, prospective clinical trial (ChiCTR2000029387). 101 eligible patients with mild to moderate COVID-19 were randomized into three groups: ribavirin (RBV) plus interferon-a (IFN-a), lopinavir/ritonavir (LPV/r) plus IFN-a, and RBV plus LPV/r plus IFN-a at a 1:1:1 ratio, with a 28-d follow-up. The outcomes include the difference in median interval to SARS-CoV-2 nucleic acid negativity, the proportion of patients with SARS-CoV-2 nucleic acid negativity at day 14, the mortality at day 28, the proportion of patients re-classified as severe cases, and adverse events during the study period. The median interval from baseline to SARS-CoV-2 nucleic acid negativity was 12 d in the LPV/r+IFN-a-treated group, as compared with 13 and 15 d in the RBV+IFN-a-treated group and in the RBV+LPV/r+ IFN-a-treated group, respectively (p=0.23). The proportion of patients with SARS-CoV-2 nucleic acid negativity in the LPV/ r+IFN-a-treated group (61.1%) was higher than the RBV+ IFN-a-treated group (51.5%) and the

RBV+LPV/r+IFN-a-treated group (46.9%) at day 14; however, the difference between these groups was calculated to be statistically insignificant. The RBV+LPV/ r+IFN-a-treated group developed a significantly higher incidence of gastrointestinal adverse events than the LPV/r+ IFN-a-treated group and the RBV+ IFN-a-treated group. Authors concluded that there are no significant differences among the three regimens in terms of antiviral effectiveness in patients with mild to moderate COVID19. The combination of RBV and LPV/r is associated with a significant increase in gastrointestinal adverse events, suggesting that RBV and LPV/r should not be co-administered to COVID-19 patients simultaneously.

RCT (China)
89 Pts.

3 Gruppen
Novaferon (IFN-I)
LPV/r
Novaferon + LPV/r

bessere Ergebnisse in IFN Gruppen

One new RCT **preprint** article has been published as of September 12, 2020: Chinese RCT published by Zheng et al. 2020 [81, 146] with three arms including 89 patients has evaluated the effect of Novaferon (the pharmaceutical which has similar properties of IFN-I but its antiviral activities has been greatly improved being at least 10 times more potent than human interferon α -2b) (n=30), Lopinavir/Ritonavir (n=29) and Novaferon + Lopinavir/Ritonavir (n=30) in COVID-19 patients. The groups treated with Novaferon alone or in combination with Lopinavir/Ritonavir showed significantly higher clearance rates on day 6 than the group treated with Lopinavir/Ritonavir alone, but the certainty on the evidence is very low. No serious adverse events were reported.

The Living Systematic Review, related to this RCT mentioned above, with Summary of finding table is provided in Table 3.14-2 continued.

Okt 2020:
preprint RCT
China
94 Pts.

rSIFN vs. IFN-a
beide in Kombination mit Lopinavir oder Ritonavir oder Umifenovir

One new RCT peer-reviewed articles have been published as of October 10, 2020. Li C et al 2020 [147] reported, as preprint, results from a multicenter, randomized controlled trial (ChiCTR2000029638) with aim to evaluate the efficacy and safety of recombinant super-compound interferon versus traditional interferon alpha added to baseline antiviral agents (lopinavir rSIFN-co –ritonavir or umifenovir) for the treatment of moderate-to-severe COVID-19. Recombinant super-compound interferon (rSIFN-co) is a new genetically engineered interferon. Participants received rSIFN-co (12 million international units [IU], twice daily) or interferon alpha (5 million IU, twice daily) nebulization added to baseline antiviral agents for no more than 28 days. The primary outcome was the time to clinical improvement. Secondary outcomes included the overall rate of clinical improvement assessed on day 28the time to radiological improvement and virus nucleic acid negative conversion, and adverse events.

signifikanter Unterschied zugunsten von rSIFN-co bei klinischer Verbesserung und bei Nebenwirkungen

94 patients hospitalized with moderate-to-severe COVID-19 were included in the safety set (46 patients assigned to rSIFN-co group, 48 to interferon alpha group). Individuals in the rSIFN-co group showed shorter time to clinical improvement (11.5 days vs 14.0 days; p = 0.019) as compared to those in the interferon alpha group. The overall rate of clinical improvement on day 28 was much higher in the rSIFN-co group than that in the interferon alpha group (93.5% vs 77.1%; difference, 16.4%; 95% condence interval 3% to 30%). The time to radiological improvement and the time to virus nucleic acid negative conversion were also much shorter in the rSIFN-co group (8.0 days vs 10.0 days, p = 0.002; 7.0 days vs 10.0 days, p = 0.018, respectively). Adverse events were reported in 13 (28.3%) patients in the rSIFN-co group and 18 (37.5%) patients in the interferon alpha group. No patients died during the study. Authors concluded that rSIFN-co added to antiviral agents was safe and more ecient than interferon alpha plus antiviral agents in the treatment of moderate-to-severe COVID-19. Future clinical study of rSIFN-co therapy alone or combined with other antiviral therapy is warranted.

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

Author, year [Reference]	**Hung et al. 2020 [120]**
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 3.14-2: Summary of findings table on triple combination of interferon beta-1b, lopinavir–ritonavir and ribavirin (1 RCT: Hung) - https://covid-nma.com/living_data/index.php

Summary of findings:						
Lopinavir + Ritonavir + Ribavirin + Interferon-b-1b compared to Lopinavir + Ritonavir for Mild/Moderate COVID-19						
Patient or population: Mild/Moderate COVID-19 **Setting**: Worldwide **Intervention**: Lopinavir + Ritonavir + Ribavirin + Interferon-b-1b **Comparison**: Lopinavir + Ritonavir						
Outcomes	**Anticipated absolute effects* (95% CI)**		**Relative effect (95% CI)**	**№ 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

Table 3.14-2 continued: Summary of findings tables on Novaferon , Lopinavir/Ritonavir and Novaferon + Lopinavir/Ritonavir (1 RCT: Zheng 2020)

Novaferon versus Lopinavir/Ritonavir

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Absolute effect (95% CI)	Number of participants (studies)	Certainty of evidence
	Risk with Lopinavir/ Ritonavir	Risk with Novaferon				
SARS-CoV-2 clearance	517 per 1000	567 per 1000	RR 1.10 (0.68 to 1.75)	**52 more per 1000 (from 166 fewer to 388 more)**	59	Very low
Progression of COVID-19 severity	143 per 1000	0 per 1000	RR 0.11 (0.01 to 1.97)	**127 fewer per 1000 (from 141 fewer to 139 more)**	56	Very low
Number with adverse events	138 per 1000	0 per 1000	RR 0.11 (0.01 to 1.91)	**123 fewer per 1000 (from 137 fewer to 126 more)**	59	Very low

Explanations of GRADE: Level of certainty was downgraded of one level for high risk of performance bias and unclear risk of selection bias, and further downgraded of two levels for very few events and small sample size

Novaferon versus Novaferon + Lopinavir/Ritonavir

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Absolute effect (95% CI)	Number of participants (studies)	Certainty of evidence
	Risk with Novaferon + Lopinavir/ Ritonavir	Risk with Novaferon				
SARS-CoV-2 clearance	700 per 1000	567 per 1000	RR 1.24 (0.84 to 1.83)	**136 more per 1000 (from 91 fewer to 470 more)**	60	Very low
Number with adverse events	100 per 1000	0 per 1000	RR 7.00 (0.38 to 129.93)	**0 fewer per 1000 (from 0 fewer to 0 fewer)**	60	Very low
Number with severe adverse events	Serious adverse events were not reported in either group.					Low
Progression of COVID-19 severity	None of the patients, with a moderate disease severity, had worsened disease.					Low

Explanations of GRADE: For the outcomes "SARS-CoV-2 clearance" and "Number with adverse events", the level of certainty was downgraded of two levels for very few events and small sample size, and further downgraded of one level for small sample size. For the outcomes "Number with severe adverse events" and "Progression of COVID-19 severity", the level of certainty was downgraded of one level for high risk of performance bias and unclear risk of selection bias, and further downgraded of one level for small sample size

Novaferon + Lopinavir/Ritonavir versus Lopinavir/Ritonavir

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Absolute effect (95% CI)	Number of participants (studies)	Certainty of evidence
	Risk with Lopinavir/ Ritonavir	Risk with Novaferon + Lopinavir/ Ritonavir				
SARS-CoV-2 clearance	517 per 1000	700 per 1000	RR 1.35 (0.89 to 2.06)	**181 more per 1000 (from 57 fewer to 548 more)**	59	Very low
Progression of COVID-19 severity	143 per 1000	0 per 1000	RR 0.11 (0.18 to 2.96)	**127 fewer per 1000 (from 141 fewer to 139 more)**	56	Very low
Number with severe adverse events	138 per 1000	100 per 1000	RR 0.72 (0.18 to 2.96)	**39 fewer per 1000 (from 113 fewer to 270 more)**	59	Low

Explanations of GRADE: For the outcomes "SARS-CoV-2 clearance" and "Number with adverse events", the level of certainty was downgraded of two levels for very few events and small sample size, and further downgraded of one level for small sample size. For the outcomes "Number with severe adverse events" and "Progression of COVID-19 severity", the level of certainty was downgraded of one level for high risk of performance bias and unclear risk of selection bias, and further downgraded of one level for small sample size

Novaferon + Lopinavir/Ritonavir versus Lopinavir/Ritonavir

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Absolute effect (95% CI)	Number of participants (studies)	Certainty of evidence
	Risk with Lopinavir/ Ritonavir	Risk with Novaferon + Lopinavir/ Ritonavir				
SARS-CoV-2 clearance	517 per 1000	700 per 1000	RR 1.35 (0.89 to 2.06)	**181 more per 1000 (from 57 fewer to 548 more)**	59	Very low
Progression of COVID-19 severity	143 per 1000	0 per 1000	RR 0.11 (0.18 to 2.96)	**127 fewer per 1000 (from 141 fewer to 139 more)**	56	Very low
Number with severe adverse events	138 per 1000	100 per 1000	RR 0.72 (0.18 to 2.96)	**39 fewer per 1000 (from 113 fewer to 270 more)**	59	Low

Explanations of GRADE: For the outcomes "SARS-CoV-2 clearance" and "Progression of COVID-19 severity", the level of certainty was downgraded of two levels for very few events and small sample size, and further downgraded of one level for small sample size. For the outcome "Number with severe adverse events" the level of certainty was downgraded of one level for high risk of performance bias and unclear risk of selection bias, and further downgraded of one level for small sample size.

3.15 Solnatide

About the treatment under consideration

Medikament gegen akutes Atemnotsyndrom

Verabreichung: Inhalation

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

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

derzeit laufende Studie: Phase 2B

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.

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

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.

EC-Grant seit April für covid-19

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.

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

One ongoing randomised, double-blind, placebo controlled, parallel assignment trial with aim to assess efficacy and safety of 7 days orally inhaled 100 mg solnatide to treat pulmonary permeability oedema of 40 SARS-Cov-2 positive patients with moderate-to-severe ARDS is registered in EUdraCT register (EudraCT number 2020-001244-26), https://www.clinicaltrialsregister.eu/ctr-search/trial/2020-001244- 26/AT [148].

Completed, withdrawn, suspended or terminated studies

As of October 10, 2020 no completed, withdrawn, suspended or terminated studies related to solnatide in COVID-19 patients were found in ClinicalTrials.gov and EUdraCT registers [148].

ClinicalTrials.gov & EUdraCT: keine klinischen Studien registriert,

Results of publications

keine Publikation von RCT

As of October 10, 2020 no publications related to the RCTs of solnatide in COVID-19 patients were found [148].

3.16 Umifenovir (Arbidol®)

About the treatment under consideration

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

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

Erprobung bei verschiedenen Viren:

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

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) [149].

1 in vitro Publikation

One small retrospective observational study published by Zhu et al. 2020 [150] evaluated the antiviral effect and safety of lopinavir/ritonavir (2x 400 mg/100 mg, n=34) and umifenovir (3x0.2 g, n=16) patients with COVID-19, treated for one week. No difference in fever duration was found between the two groups (p=0.61), but patients in umifenovir group had a shorter duration of positive RNA test (p<0.01).

Zhu (China): retrospektive Studie 34 Pts.

Completed, withdrawn, suspended or terminated studies

As of October 10, 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

RCT published by Yueping et al. 2020 (NCT04252885) [78] 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 [78].

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

kein Unterschied zwischen den Gruppen in einigen Surrogatendpunkten

mehr AE

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

One publication [84] on the completed RCT (ChiCTR2000030254) about the efficacy and safety of favipiravir, in comparison with umifenovir, to treat Covid-19 patients was identified; however, as the publication was available just as pre-print but not yet peer-reviewed, it has not been extracted. Summary of findings table can be found in Section related to favipiravir.

1 RCT nur im preprint (nicht peer-reviewed)

No new RCT peer-reviewed articles have been published as of September 07, 2020. As of October 10, 2020 one new RCT (IRCT20180725040596N2), has been published by Nojomi et al. 2020, as preliminary report in the format of preprints [151]. This was an open label randomized controlled trial, effectiveness of umifenovir on COVID-19 disease was conducted in a teaching hospital. One hundred eligible patients with diagnosis of Covid-19 recruited in the study and assigned randomly to two groups of either hydroxychloroquine just on the 1st day followed by Kaletra (lopinavir-ritonavir) or hydroxychloroquine just on the 1st day followed by umifenovir 7-14 days based on severity of disease. The primary outcome was hospitalization duration and clinical improvement 7 days after admission. The criteria of improvement were relief of cough, dyspnea and fever. Time to relieving fever was assessed across two groups too. Without any drop-out, 100 patients were entered to final analysis. The mean age of the patients was 56.6 (17.8) and 56.2 (14.8) in umifenovir and lopinavir-ritonavir groups respectively. Majority of patients were male across two groups (66% and 54%). The duration of hospitalization in umifenovir group was less than lopinavir-ritonavir arm significantly (7.2 versus 9.6 days; p=0.02). Time to relief fever was almost similar across two groups (2.7 versus 3.1 days in umifenovir and lopinavir-ritonavir arms respectively). Peripheral oxygen saturation rate was different after seven days of admission across two groups significantly (94% versus 92% in umifenovir and lopinavir-ritonavir groups respectively) (p=0.02). Based on multiple linear regression analysis, IHD, Na level and oxygen saturation at the time of admission and type of therapy were the independent adjusted variables that determined the duration of hospitalization in patients with COVID-19. No severe side effects were found for both drugs. Authors concluded that umifenovir, compared to lopinavir-ritonavir, significantly contributes to clinical and laboratory improvements, including peripheral oxygen saturation, requiring ICU

Okt 2020:
RCT (Iran)
100 Pts.

in Kombinationstherapie kleine Vorteile

admissions, duration of hospitalization, chest CT involvements, WBC, and ESR, so suggest further studies on umifenovir using larger sample size and multicenter design.

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

Summary of findings:						
Umifenovir compared to Standard Care for Mild/Moderate COVID-19						
Patient or population: Mild/Moderate COVID-19 **Setting**: Worldwide **Intervention**: Umifenovir **Comparison**: Standard Care						
Outcomes	**Anticipated absolute effects*** **(95% CI)**		**Relative effect (95% CI)**	**№ of participants (studies)**	**Certainty of the evidence (GRADE)**	**Comments**
	Risk with Standard Care	**Risk with Umifenovir**				
Incidence of viral negative conversion (D7)	412 per 1.000	**371 per 1.000** (181 to 758)	**RR 0.90** (0.44 to 1.84)	52 (1 RCT)	⨁◯◯◯ VERY LOW [a,b]	
WHO Clinical Progression Score (increase in 1 point) - not reported	-	-	-	-	-	outcome not yet measured or reported
Admission in ICU - not reported	-	-	-	-	-	outcome not yet measured or reported
Incidence of WHO progression score (level 6 or above) - not reported	-	-	-	-	-	outcome not yet measured or reported
Incidence of WHO progression score (level 7 or above D7)				52 (1 RCT)	⨁◯◯◯ VERY LOW [a,c]	zero events in both groups
All-cause mortality D14-D28				52 (1 RCT)	⨁◯◯◯ VERY LOW [a,c]	zero events in both groups
Adverse events D14-D28	0 per 1.000	**0 per 1.000** (0 to 0)	**RR 5.50** (0.32 to 94.06)	52 (1 RCT)	⨁⨁◯◯ LOW [b,d]	zero events in control group
Serious adverse events D14-D28				52 (1 RCT)	⨁⨁◯◯ LOW [c,d]	zero events in both groups

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

CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence

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

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

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

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

3.17 Dexamethasone and other corticosteroids

About the drug under consideration

Glukokortikoide: entzündungshemmend

Dexamethasone (Dexamethasone Mylan), manufactured by Mylan, is a long-acting glucocorticoid which is used principally as an anti-inflammatory or immunosuppressant agent. During a short-term therapy, in compliance with the dosage recommendations and close monitoring of patients, the risk of side effects is low. The usual side effects of short-term dexamethasone treatment (days/weeks) include weight gain, psychological disorders, glucose intolerance and transitory adrenocortical insufficiency. Long-term dexamethasone treatment (months/years) usually causes central obesity, skin fragility, muscle atrophy, osteoporosis, growth retardation and longterm suprarenal insufficiency [152-154]. Daily regimen of dexamethasone 6 mg once daily is equivalent to 160 mg of hydrocortisone, 40 mg of prednisone, and 32 mg of methylprednisolone.

The proposed mechanism of glucocorticoids in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) involves the mitigation of an excessive immune response that can lead to acute respiratory distress syndrome (ARDS) and multi-organ failure. ARDS develops in approximately 20% of COVID-19 patients and is linked to multi-organ failure through cytokine release syndrome [155, 156].

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

Dexamethasone is authorised at national level in the EU and is used in a wide range of conditions, including rheumatic problems, skin diseases, severe allergies, asthma and chronic obstructive lung disease. On 24 July 2020, EMA's human medicines committee (CHMP) started a review under Article 5(3) of Regulation 726/2004 of the results from the RECOVERY study arm and will provide an opinion on the results of this study and on the potential use of dexamethasone to treat adults with COVID-19 [157]. The UK has approved dexamethasone for the treatment of Covid-19 on June 16, 2020 [158].

EMA- CHMP: Zulassungsantrag von Taw Pharma (Sept 2020)

CHMP is currently evaluating Dexamethasone Taw for a marketing authorisation for the treatment of hospitalised adult patients with COVID-19. The applicant, Taw Pharma, is developing Dexamethasone Taw as a hybrid medicine; like its "reference medicine", Fortecortin Inject, Dexamethasone Taw is injectable. The evaluation of Dexamethasone Taw began on 31 August 2020. It has no impact on the use of other dexamethasone medicines [159]. As part of its evaluation, the CHMP will consider the outcome of its ongoing review of the use of dexamethasone to treat COVID-19, mentioned above.

Sept 2020: Basierend auf Ergebnissen aus RECOVERY

EMA (Rasch-)Zulassung für Pts mit (künstlicher) Beatmung oder Sauerstoff Supplementierung

On September 18, 2020 EMA announced that CHMP has completed its review of results from the RECOVERY study arm that involved the use of the dexamethasone in the treatment of patients with COVID-19 admitted to hospital, and has concluded that dexamethasone can be considered a treatment option for patients who require oxygen therapy (from supplemental oxygen to mechanical ventilation). Based on the review of available data, EMA is endorsing the use of dexamethasone in adults and adolescents (from 12 years of age and weighing at least 40 kg) who require supplemental oxygen therapy. Dexamethasone can be taken by mouth or given as an injection or infusion (drip) into a vein. In all cases, the recommended dose in adults and adolescents is 6 milligrams once a day for up to 10 days. Companies that market dexamethasone medicines can request this new use to be added to

their product's license by submitting an application to national medicines agencies or to EMA [160].

There are several registered ongoing clinical trials on corticosteroid treatment in Covid-19 patients in ClinicalTrials.gov and EUdraCT registers. Results from published small case series and retrospective cohort studies with short courses of corticosteroids in patients with COVID-19 reported conflicting results, both beneficial and harmful effects.

mehrere Studien sind registriert, Ergebnisse aus kleinen Studien zeigen widersprüchliche Resultate

Based on results of the RECOVERY Trial described below, the US COVID-19 Treatment Guidelines Panel **recommends using dexamethasone** (at a dose of 6 mg per day for up to 10 days) in patients with COVID-19 who are mechanically ventilated **(AI)** and in patients with COVID-19 who require supplemental oxygen but who are not mechanically ventilated **(BI)**. The Panel **recommends against** using dexamethasone in patients with COVID-19 who do not require supplemental oxygen **(AI)** [70]. If dexamethasone is not available, the Panel **recommends using** alternative glucocorticoids such as **prednisone**, **methylprednisolone**, or **hydrocortisone (AIII)** [61].

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

Recently, a prospective meta-analysis from the WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group with pooled data from 7 trials, evaluating systemic corticosteroids versus usual care in COVID-19 critically ill patients [161], and the new WHO living guidance on corticosteroids for COVID-19 were published [162, 163]. The resulting evidence summary suggested that systemic corticosteroids probably reduce 28-day mortality in patients with critical COVID-19 (moderate certainty evidence; seven studies,1703 patients; relative risk [RR] 0.80, 95% CI 0.70–0.91; absolute effect estimate 87 fewer deaths per 1000 patients, 95% CI 124 fewer to 41 fewer), and also in those with severe disease (moderate certainty evidence; one study, 3883 patients; RR 0.80, 95% CI 0.70–0.92; absolute effect estimate 67 fewer deaths per 1000 patients, 95% CI 100 fewer to 27 fewer). Systemic corticosteroids may increase the risk of death when administered to patients with non-severe COVID-19 (low certainty evidence; one study, 1535 patients; RR 1.22, 95% CI 0.93–1.61; absolute effect estimate 39 more per 1000 patients, 95% CI 12 fewer to 107 more). Systemic corticosteroids probably reduce the need for invasive mechanical ventilation (moderate certainty of evidence; two studies, 5481 patients; RR 0.74, 95% CI 0.59–0.93). Harms, in the context of the mortality reduction in severe disease, are minor.

Metaanalyse von 7 Studien, 1.703 Pts.

systemische Kortikosteroide verringern wahrscheinlich die 28-Tage Mortalität in Schwererkrankten

erhöhen aber das Risiko zu Versterben in nicht-schweren Erkrankungen

The WHO panel made two recommendations: a **strong recommendation** (based on moderate certainty evidence) **for systemic** (i.e. intravenous or oral) **corticosteroid therapy** (e.g. 6 mg of dexamethasone orally or intravenously daily or 50 mg of hydrocortisone intravenously every 8 hours) for 7 to 10 days in **patients with severe and critical COVID-19**, and a **conditional recommendation** (based on low certainty evidence) **not to use corticosteroid therapy** in **patients with non-severe COVID-19** [162, 163].

WHO Empfehlung: Starke Empfehlung bei kritischen und schwer Erkrankte
Bedingte Empfehlung, NICHT zu verwenden bei nicht-schwer Erkrankten

Completed, withdrawn, suspended or terminated studies

As of September 11, 2020 two completed (NCT04445506, related to dexamethasone, and NCT04273321, related to methylprednisolone) and one terminated RCT - NCT04327401 (CoDEX), related to dexamethasone were found in ClinicalTrials.gov and EUdraCT registers. In the terminated RCT conducted in 299 COVID-19 patients with moderate and severe ARDS in Brazil, the Data Monitoring Committee recommended to stop the trial based on the Recovery Trial results, which was accepted by the CoDEX Steering Committee. The results of this RCT have been published recently [164]. DEXA-COVID trial (NCT04325061, EudraCT 2020-001278-31) on dexamethasone, is written as suspended (lack of enrollment) in ClinicalTrials.gov, but as ongoing in EUdraCT register. The results of this RCT are not yet published [21]. No additional completed, suspended, withdrawn or terminated trials were found until October 11, 2020.

2 abgeschlossene RCTs
1 abgebrochener RCT wegen (besseren Ergebnissen in) Rovery Trial in Brazilien

1 eingestellter RCT – wegen Magel an Rekrutierung

Results of publications

As of 11/09/2020, five new RCTs were published and included in meta-analysis provided by EUnetHTA RCR Team [165] in addition to the RECOVERY trail. Meta-analysis included six RCTs: two related to dexamethasone treatment – the largest, **RECOVERY trial** (**NCT04381936, EudraCT 2020-001113-21**) [166]; and **CoDEX trial** (**NCT04327401**) [164]; two related to hydrocortisone treatment - **CAPE-COVID trial** (**NCT02517489**) [167] and **REMAPCAP trial** (**NCT02735707**) [168], and two RCTs related to methylprednisolone - **MetCOVID trial** (**NCT04343729**) [169] and **GLUCOCOVID trial** (**EudraCT 2020-001934-37**) [170]. Corticosteroid regimens included: **dexamethasone** 6 mg daily up to 10 days in RECOVERY trial and 20 mg daily for 5 days followed by 10 mg daily for 5 days in CoDEX trial [166] [164]; **hydrocortisone** 200 mg daily for 4 to 7 days followed by 100 mg daily for 2 to 4 days and then 50 mg daily for 2 to 3 days in CAPE-COVID trial [167] and **hydrocortisone** 200 mg daily for 7 days in REMAPCAP trial [168]; and **methylprednisolone** 0.5 mg/kg twice daily, for 5 days in MetCOVID trial [169]and 40 mg every 12 hours for 3 days and then 20 mg every 12 hours for 3 days in GLUCOCOVID trial [170]. According to the classification as low or high corticosteroids dose, three RCTs are classified as low dose (RECOVERY, CAPE-COVID, REMAPCAP) [166-168], and the rest as high dose[164, 169, 170]. REMAPCAP was an international study (recruiting in 14 European countries, Australia, Canada, New Zealand, Saudi Arabia and the United Kingdom) [168]; the rest were conducted in individual countries [164, 166, 167, 169, 170].

6 RCTs veröffentlicht:

RECOVERY
CoDEX
CAPE-COVID
REMAPCAP
MetCOVID
GLUCOCOVID

unterschiedliche Dosierungen

The RCT with the largest number of included COVID-19 patients is RCTs of dexamethasone arm of the RECOVERY trail in Covid-19 patients [166]. The RECOVERY trial was designed to evaluate the effects of potential treatments in patients hospitalized with Covid-19 at 176 NHS organizations in the UK and was supported by the National Institute for Health Research Clinical Research Network. The primary outcome was all-cause mortality within 28 days after randomization; further analyses were specified at 6 months. Secondary outcomes were the time until discharge from the hospital and, among patients not receiving invasive mechanical ventilation at the time of randomization, subsequent receipt of invasive mechanical ventilation (including extracorporeal membrane oxygenation) or death. Other prespecified clinical outcomes included cause-specific mortality, receipt of renal hemodialysis or hemofiltration, major cardiac arrhythmia (recorded in a subgroup), and receipt and duration of ventilation. The randomization of patients to receive dexamethasone, hydroxychloroquine, or lopinavir–

größter RCT: RECOVERY

2.104 Pts

ritonavir has now been stopped, the trial continues randomization to groups receiving azithromycin, tocilizumab, or convalescent plasma.

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

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

ohne Effekt auf Mortalität bei Pts ohne Untestützun bei Beatmung

zusätzlich: kürzere Hospitalisierung

Results from preliminary report of the RECOVERY trial are related to the comparison of oral or intravenous dexamethasone 6 mg given once daily for up to ten days (2104 patients) plus the usual standard of care vs. usual care alone (4321 patients). Authors showed that overall, 482 (22.9%) patients allocated dexamethasone and 1110 (25.7%) patients allocated usual care died within 28 days (age adjusted rate ratio [RR] 0.83; 95% confidence interval [CI] 0.75 to 0.93; P<0.001). The proportional and absolute mortality rate reductions varied significantly depending on level of respiratory support at randomization (test for trend p<0.001): dexamethasone reduced deaths by one-third in patients receiving invasive mechanical ventilation (29.3% vs. 41.4%, RR 0.64 [95% CI 0.51 to 0.81]), by one-fifth in patients receiving oxygen without invasive mechanical ventilation (23.3% vs. 26.2%, RR 0.82 [95% CI 0.72 to 0.94], but did not reduce mortality in patients not receiving respiratory support at randomization (17.8% vs. 14.0%, RR 1.19 [95% CI 0.91 to 1.55]. Allocation to dexamethasone was associated with a shorter duration of hospitalization than usual care (median 12 days vs. 13 days) and a greater probability of discharge within 28 days (rate ratio 1.10 [95% CI 1.03 to 1.17]) with the greatest effect seen among those receiving invasive mechanical ventilation at baseline (11.5 by chi-square test for trend). The risk of progression to invasive mechanical ventilation was lower among those allocated dexamethasone vs. usual care (risk ratio 0.92 [95% CI 0.84 to 1.01). Analyses are ongoing regarding cause-specific mortality, the need for renal dialysis or hemofiltration, and the duration of ventilation [165, 166].

CoDEX
299 Pt (Brasilien)

kein signifikanter Unterschied, aber wegen Abbruch "underpowered" für valide Ergebnisse

The **CoDEX trial** randomized 299 patients in 41 ICUs in Brazil with moderate or severe ARDS and COVID-19 to open-label high-dose dexamethasone (20 mg/d for 5 days, then 10 mg/d for 5 days) vs usual care alone, with the primary outcome ventilator-free days through day 28, which were greater in patients randomized to dexamethasone (6.6 vs 4.0, p=0.04). 28-day mortality was not significantly different between patients randomized to corticosteroids vs usual care (56.3% vs 61.5%, p=0.83); stopping the study early when RECOVERY results were announced resulted in a sample size that was underpowered to adequately evaluate the effect of corticosteroids on mortality [164, 171].

CAPE COVID
149 Pts (Frankreich)
bessere Ergebnisse mit hydrocortisone

The **CAPE COVID trial** was blinded, placebo-controlled trial randomized 149 patients in 9 ICUs in France with severe respiratory disease from COVID-19 to low-dose hydrocortisone (200 mg/d infusion, tapered per protocol) vs placebo. The primary outcome of 21-day treatment failure, defined as death or ongoing respiratory support with mechanical ventilation or high-flow oxygen, occurred in 42.1% of patients randomized to hydrocortisone vs 50.7% of those randomized to placebo (p=0.29) [167, 171].

REMAP-CAP
403 Pts (UK, CA, USA)
bessere Ergebnisse mit hydrocortisone

The **REMAP-CAP trial**, an existing multicenter, multinational adaptive platform trial for pneumonia, randomized 403 patients with severe COVID-19 (in the intensive care unit and receiving respiratory or cardiovascular organ support) to 1 of 3 open-label groups: fixed low-dose hydrocortisone, shock-dependent hydrocortisone, or no hydrocortisone. The primary study outcome was days patients remained alive and free of organ support to day 21. The Bayesian model found that fixed-dose hydrocortisone (93% probability), as well as shock-dependent hydrocortisone (80% probability), were both likely superior to no hydrocortisone, but data were insufficient to confirm a single optimal regimen. In addition, the probabilities did not meet the prespecified probabilities to define success [168, 171].

MetCOVID trial was parallel, double-blind, placebo-controlled, randomized, phase IIb clinical trial, performed with hospitalized patients aged ≥ 18 years with clinical, epidemiological and/or radiological suspected COVID-19, at a tertiary care facility in Brazil. Patients were randomly allocated (1:1 ratio) to receive either intravenous methylprednisolone (0.5 mg/kg) or placebo (saline solution), twice daily, for 5 days. The primary outcome was 28-day mortality. 416 patients were randomized, and 393 analysed as mITT, methylprednisolone in 194 and placebo in 199 individuals. SARS-CoV-2 infection was confirmed by RT-PCR in 81.3%. Mortality at day 28 was not different between groups. A subgroup analysis showed that patients over 60 years in the methylprednisolone group had a lower mortality rate at day 28. Patients in the methylprednisolone arm tended to need more insulin therapy, and no difference was seen in virus clearance in respiratory secretion until day 7 [169].

MetCOVID
418 Pts (Brasilien)
methylprednisolone

kein Unterschied zwischen Gruppen bei Mortalität methylprednisolone

Subgruppenanalyse: >60 Jahre bessere Ergebnisse

GLUCOCOVID trial was multicentric, partially randomized, preference, open-label trial, including adults with COVID-19 pneumonia, impaired gas exchange and biochemical evidence of hyper-inflammation, aimed to determine whether a 6-day course of intravenous methylprednisolone improves outcome in patients with SARS CoV-2 infection at risk of developing Acute Respiratory Distress Syndrome (ARDS). Patients were assigned to standard of care (SOC), or SOC plus intravenous methylprednisolone (40mg/12h 3 days, then 20mg/12h 3 days). The primary endpoint was a composite of death, admission to the intensive care unit (ICU) or requirement of non-invasive ventilation (NIV). 85 patients (34, randomized to MP; 22, assigned to MP by clinician's preference; 29, control group) were analysed. Patients' age (mean 68±12 yr) was related to outcome. The use of methylprednisolone was associated with a reduced risk of the composite endpoint in the intention-to-treat, age-stratified analysis (combined risk ratio -RR- 0.55 [95% CI 0.33-0.91]; p=0.024). In the per-protocol analysis, RR was 0.11 (0.01-0.83) in patients aged 72 yr or less, 0.61 (0.32-1.17) in those over 72 yr, and 0.37 (0.19-0.74, p=0.0037) in the whole group after age-adjustment by stratification. The decrease in C-reactive protein levels was more pronounced in the methylprednisolone group (p=0.0003). Hyperglycaemia was more frequent in the methylprednisolone group [169].

GLUCOCOVID
85 Pts (Spanien)
Methylprednisolone

Bessere Ergebnisse bei „composite"Endpunkten

Ergebnisse sind ebenfalls alters-abhängig

Data on moderate, low and very low certainty of evidence, related to effectiveness and safety of dexamethasone and other corticosteroids reported in these 6 RCTs, prepared by Cruciani et al. [172, 173], can be found in the Summary of Findings Table 3.17-1. In summary, according to the results of six RCTs [164, 167-170, 174] with moderate certainty of evidence, corticosteroids probably reduce the risk of mortality for all causes in COVID-19 patients /RR 0.90 (95% CI 0.83 to 0.97); absolute effect estimate 27 fewer per 1000 (95% CI from 47 fewer to 8 fewer). The same is true for severe COVID-19 patients (three RCTs [168, 170, 174]) /RR 0.89 (95% CI 0.80 to 1.00); absolute effect estimate 29 fewer per 1000 (95% CI from 53 fewer to 0 fewer)/ and critically ill COVID-19 patients (two RCTs, [167, 174]) /RR 0.69 (95% CI 0.58 to 0.83); absolute effect estimate 124 fewer per 1000 (95% CI from 168 fewer to 68 fewer)/.

Zusammenfassung der Ergebnisse:

moderate Evidenz zu Gunsten von Reduktion der Gesamtmortalität bei schweren und kritisch Erkrankten

In patients with mild/moderate COVID-19 disease, systemic corticosteroids probably increase the risk of death (moderate certainty of evidence, one RCT [174] /RR 1.27 (95% CI 1.00 to 1.61); absolute effect estimate 38 more per 1000 (95% CI from 0 fewer to 86 more).

moderate Evidenz (Mortalität) zu Ungunsten bei mild/ moderat Erkrankten

niedrige Sicherheit der Evidenz bei weiteren Endpunkten (Dauer der Hospitalisierung, SAE)

According to the results of two RCTs [164, 174] with very low certainty of evidence, whether or not corticosteroids impact on the increase number of patients discharged to 28 days is uncertain /RR 1.25 (95% CI 0.82 to 1.91); absolute effect estimate 155 more per 1000 (95% CI from 112 fewer to 564 more). According to the results of 3 RCTs [164, 167, 168] with low certainty of evidence, corticosteroids may not increase the number of patients with serious adverse events /RR 1.47 (95% CI 0.31 to 7.04); absolute effect estimate 15 more per 1000 (95% CI from 21 fewer to 188 more).

Okt 2020:
RCT (Iran)
68 Pts.

schwere Erkrankung

signifikante Ergebnisse bei klinischer Verbesserung und bei Mortalität

As of October 11, 2020 Edalatifard et al. 2020 [175] published results of a single-blind, randomized, controlled, clinical trial involving severe hospitalized patients with confirmed COVID-19 at the early pulmonary phase of the illness in Iran (IRCT20200404046947N1). Patients were randomly allocated in a 1:1 ratio by block randomization method to receive standard care with methylprednisolone pulse (intravenous injection, 250mg/day for 3 days) or standard care alone. The study endpoint was the time of clinical improvement or death, whichever came first. Primary and safety analysis was done in the intention-to-treat (ITT) population. Sixty-eight eligible patients underwent randomization (34 patients in each group) The percentage of improved patients was significantly higher in the methylprednisolone group than in the standard care group (32 (94.1%) vs 16 (57.1%); P =0.001) and the mortality rate was significantly lower in the methylprednisolone group (2 (5.9%) vs 12 (42.9%); P <0.001). Patients in the methylprednisolone intervention group had a significantly increased survival time compared with the patients in the standard care group [Log rank test: P<0.001; Hazard ratio: 0.293; 95% CI: 0.154-0.555]. A total of two patients in each group (5.8% and 7.1% respectively) showed severe adverse events between initiation of treatment and the end of the study. There were one infection and one edema adverse event in the methylprednisolone group and two shock adverse events in the standard care group. Following the use of high dose of corticosteroids, most of the patients required insulin due to their known or hidden diabetes, and the insulin requirement was increased in the intervention group especially in diabetic and overweight patients.

Phase 2 RCT
(Iran)
29 Pts.

signifikante Vorteile bei Mortalität

Farahani et al. 2020 [176] reported, as preprint, results from phase 2, double-blind, randomized, clinical trial in 29 adults with intermediate or severe COVID-19 with PaO2/FiO2 less than 300 and progressive disease unresponsive to standard treatments admitted to the intensive care unit (ICU) (IRCT20200406046963N1). Patients were randomly allocated in either control or investigation group. The control group received recommended regimen for COVID-19. The investigation group received the recommended regimen plus methylprednisolone (1000mg/day for three days) and oral prednisolone 1mg/kg with tapering of dose within ten days. The primary objective of this study was to investigate the efficacy of methylprednisolone pulse on mortality rate, blood O2 saturation, and need for further oxygen therapy. Fourteen patients allocated in the investigation group, and 15 patients assigned to the control group. There was no mortality among the patients receiving the methylprednisolone treatment, but the mortality was high in patients without methylprednisolone therapy. In addition to improvement of respiratory outcome, Glasgow Coma Scale (GCS) of methylprednisolone group significantly ($p < 0.001$) improved also.

Table 3.17-1: Summary of findings table, on dexamethasone and other corticosteroids (6 RCTs: Horbey, Tomazini, Dequin, REMAP-CAP Investigators, Jeronimo, Corral) [164, 167-170, 173]

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Absolute effect difference (95% CI)	Number of participants (studies)	Certainty of evidence (GRADE)	Comments
	Risk with no corticosteroids	Risk with corticosteroids					
All-cause Mortality	274 per 1000	247 per 1000	**RR 0.90** (0.83 to 0.97)	**27 fewer per 1.000** (from 47 fewer to 8 fewer)	7590 (6 RCTs)	MODERATE ⊕⊕⊕◯	Downgraded of one level for performance bias; high risk in 4 studies and unclear in one study; selection bias: high risk in 1 study and unclear in another study
Mortality in patients with mild/moderate severity	140 per 1000	178 per 1000	**RR 1.27** (1.00 to 1.61)	**38 more per 1.000** (from 0 fewer to 86 more)	1535 (1 RCT)	MODERATE ⊕⊕⊕◯	Downgraded of one level for high risk of performance bias
Mortality - severe patients	263 per 1000	234 per 1000	**RR 0.89** (0.80 to 1.00)	**29 fewer per 1.000** (from 53 fewer to 0 fewer)	4184 (3 RCTs)	MODERATE ⊕⊕⊕◯	Downgraded of one level for high risk of performance bias in all 3 studies
Mortality – critical patients	401 per 1000	277 per 1000	**RR 0.69** (0.58 to 0.83)	**124 fewer per 1.000** (from 168 fewer to 68 fewer)	1156 (2 RCTs)	MODERATE ⊕⊕⊕◯	Downgraded of one level for high risk of performance bias in 1 study
Number of patients discharged within 28 days	620 per 1000	645 per 1000	**RR 1.25** (0.82 to 1.91)	**155 more per 1.000** (from 112 fewer to 564 more)	6724 (2 RCTs)	VERY LOW ⊕◯◯◯	Downgraded of one level for high risk of performance bias in both studies and of two levels for heterogeneity. I^2=75%
Number of patients with serious adverse events	31 per 1000	33 per 1000	**RR 1.47** (0.31 to 7.04)	**15 more per 1.000** (from 21 fewer to 188 more)	686 (3 RCsT)	LOW ⊕⊕◯◯	Downgraded of one level for high risk of performance bias in 2 studies and of one level for heterogeneity. I^2=49%

CI: Confidence interval; **RR**: Risk ratio

GRADE Working Group grades of evidence

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

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

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

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

Source: [111]

3.18 Anakinra (Kineret®)

About the drug under consideration

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

Immunsuppressivum, humaner Interleukin-1 Rezeptorantagonist

EMA-Zulassung für Rheumatoide Arthritis seit 2002

nicht jedoch für Covid-19

There are several ongoing clinical trials in Covid-19 [178]; it has been used already in several small case-series [179-181] and retrospective cohort study in Covid-19 patients [182].

mehrere laufende Studien,

The US COVID-19 Treatment Guidelines Panel stated that there are insufficient data to recommend either for or against Interleukin-1 inhibitors (e.g., anakinra) therapy in patients with COVID-19 disease [70].

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

Completed, withdrawn, suspended or terminated studies

As of October 11, 2020, no completed, withdrawn, suspended or terminated interventional studies were found on anakinra in ClinicalTrials.gov and EUdraCT registers.

keine weiteren Studien

Results of publications

Until now no scientific publication on RCTs of anakinra (Kineret®) in Covid-19 patients could be identified (status: 11/10/2020).

keine Publikation eines RCTs

One prospective cohort study, Ana-COVID study, with 52 consecutive severe Covid-19 patients who received subcutaneous anakinra at dose of 100 mg twice daily for 72 h, followed by 100 mg daily for 7 days, in addition to the standard treatment and supportive care (with a historical comparison group, n=44 patients, who received standard care) published by Huet et al. 2020 [183], found statistically significant difference in favour of anakinra for need of invasive mechanical ventilation in the ICU and mortality. Admission to the ICU for mechanical ventilation or death occurred in 13 (25%) patients in the anakinra group vs 32 (73%) patients in the historical group (hazard ratio [HR] 0.22 [95% CI 0.11–0.41; p<0.0001). The treatment effect of anakinra remained significant in the multivariate analysis (HR 0.22 [95% CI 0.10–0.49]; p=0.0002). Similar results were observed for death alone (HR 0.30 [95% CI 0.12–0.71; p=0.0063) and need for invasive mechanical ventilation alone (0.22 [0.09–0.56]; p=0.0015). Among the 39 patients in the anakinra group

1 prospektive Kohortenstudie, 52 Pts.

geringere Mortalität, ICU-Aufnahmen, künstliche Beatmung

who were alive and did not require mechanical ventilation, the mean need for oxygen decreased from a median of 7 L/min (IQR 6–9) at day 0 to a median of 2 L/min (0–4) at day 7 (two missing values); the median difference was –4 L/min (IQR 0–4; $p<0.0001$, signed-rank test). An increase in liver aminotransferases occurred in seven (13%) patients in the anakinra group and four (9%) patients in the historical group. Ten (19%) patients in the anakinra group and five (11%) in the historical group developed a thromboembolic event during the hospital stay. Among the anakinra group, seven (13%) had a pulmonary embolism, three (6%) had deep vein thrombosis of the lower limbs, and one (2%) had arterial thrombosis. Authors concluded that in severe forms of COVID-19-related pneumonia requiring oxygen therapy, a 10-day treatment with subcutaneous anakinra was associated with the reduction of both need of mechanical ventilation and mortality, as compared with a historical group with similar characteristics.

3.19 Colchicine

About the drug under consideration

toxisches Alkaloid wirkt als Zellgift (Mitosehemmung)

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

generisch

According the FDA label document (revised 2020) Colcrys (colchicine, USP, tables for oral use) is indicated for prophylaxis and treatment of gout flares in adults and for Familial Mediterranean fever (FMF) in adults and children 4 years or older. The mechanism by which COLCRYS (Takeda Pharmaceuticals USA) exerts its beneficial effect in patients with FMF has not been fully elucidated; however, evidence suggests that colchicine may interfere with the intracellular assembly of the inflammasome complex present in neutrophils and monocytes that mediates activation of interleukin-1β. Additionally, colchicine disrupts cytoskeletal functions through inhibition of β-tubulin polymerization into microtubules and consequently prevents the activation, degranulation and migration of neutrophils thought to mediate some gout symptoms [185]. Colchicine is not authorised in Covid-19 patients (EMA, FDA).

Completed, withdrawn, suspended or terminated studies

keine Studien

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

Results of publications

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

1 publizierter RCT (Griechenland): 105 Pts.

klinisch gering-relevanter Unterschied bei Verbesserung der Erkrankung

viele Surrogatendpunkte niedrige Evidenz

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

Salehzadeh et al. 2020 [187] reported results (as preprint) from prospective, open-label, randomized and double blind clinical trial, in 100 patients hospitalized with COVID-19 in Iran (IRCT20200418047126N1). Patients were randomized in a 1:1 allocation, to either standard medical treatment (hydroxychloroquine) or colchicine with standard medical treatment. Colchicine group were received 1 mg tablet of colchicine daily alongside the hydroxychloroquine for 6 days. Primary end points were length of hospitalization; symptoms and co-existed disease. Secondary end points were examined 2 weeks after discharge and included mortality and morbidity; re-admission and symptoms. Duration of hospitalisation and duration of fever were significantly different between patients groups, in favour of colchicine ($p<0.05$). Although in colchicine group dyspnea was improved more rapid than the placebo group, difference was not statistically significant. None of the patients died or were readmitted.

RCT preprint (Iran) 100 Pts.

kein Unterschied

Lopes et al. 2020 [188], reported (as preprint) interim results of a single-center, randomized, double-blinded, placebo controlled clinical trial of colchicine for the treatment of 38 moderate to severe COVID-19 patients in Brazil. Colchicine regimen was 0.5 mg thrice daily for 5 days, then 0.5 mg twice daily for 5 days. The first dose was 1.0 mg whether body weight was ≥ 80 kg. The primary endpoints were the need for supplemental oxygen; time of hospitalization; need for admission and length of stay in intensive care unit; and death rate and causes of mortality. As secondary endpoints, serum C-reactive protein, serum lactate dehydrogenase and relation neutrophil to

RCT preprint (Brasilien) 38 Pt.

Reduktion von Sauerstoff Supplementierung und von Hospitalisierung

lymphocyte of peripheral blood samples from day zero to day 7; the number, type, and severity of adverse events; frequency of interruption of the study protocol due to adverse events; and frequency of QT interval above 450 ms were assessed. Thirty-five patients (18 for placebo and 17 for colchicine) completed the study. Median (and interquartile range) time of need for supplemental oxygen was 3.0 (1.5- 6.5) days for the colchicine group and 7.0 (3.0-8.5) days for placebo group ($p=0.02$). Median (IQR) time of hospitalization was 6.0 (4.0-8.5) days for the colchicine group and 8.5 (5.5-11.0) days for placebo group ($p=0.03$). At day 2, 53% vs 83% of patients maintained the need for supplemental oxygen, while at day 7 the values were 6% vs 39%, in the colchicine and placebo groups, respectively (log rank; $p=0.01$). Hospitalization was maintained for 53% vs 78% of patients at day 5 and 6% vs 17% at day 10, for the colchicine and placebo groups, respectively (log rank; $p=0.01$). One patient per group needed admission to ICU. No recruited patient died. At day 4, patients of colchicine group presented significant reduction of serum C-reactive protein compared to baseline ($p<0.001$). The majority of adverse events were mild and did not lead to patient withdrawal. Diarrhea was more frequent in the colchicine group ($p=0.17$). Cardiac adverse events were absent. Authors concluded that the use of colchicine reduced the length of both, supplemental oxygen therapy and hospitalization. Clinical trials with larger numbers of patients should be conducted to further evaluate the efficacy and safety of colchicine as an adjunctive therapy for hospitalized patients with moderate to severe COVID-19.

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

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

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

CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence

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

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

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

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

Explanations

a. Risk of bias downgraded by 1 level: some concerns regarding deviation from inteded intervention and outcome measurement

b. Indirectness downgraded by 1 level: single study from a single country, therefore results in this population might not be generalizable to other settings

c. Imprecision downgraded by 2 levels: due to very wide confidence interval consistent with the possibility for benefit and the possibility for harm and low number of participants

d. We presume that the adverse event rates, and the corresponding relative risks, is similar across diverse settings; therefore not downgraded for indirectness

e. Imprecision downgraded by 2 levels: no events in both groups

3.20 Nafamostat (Futhan©)

About the drug under consideration

Proteaseinhibitor

Camostat, its active metabolite GBPA/FOY 251 [174, 189-191], and nafamostat [189, 191] directly inhibit TMPRSS2 enzymatic activity. This has been confirmed in a molecular dynamics and Markov model study, in preprint [192, 193]. All three molecules were also shown to inhibit the activation and cellular entry of SARS-CoV-2 [192, 194-196].

Zulassung in Japan seit 1986
als Generikum verfügbar

verschiedene Anbiete in Asien arbeite an oraler Verabreichung

Nafamostat mesilate (FUT-175, Futhan®, Nichi-Iko Pharmaceutical) is, like camostat, a trypsin-like serine protease inhibitor. Nafamostat 10mg for injection is on the market in Japan since 1986 for acute symptoms of pancreatitis; 50mg for injection is marketed since 1989 for disseminated intravascular coagulation and prevention of coagulation of perfused blood during extravascular circulation of patients with bleeding lesions or bleeding tendencies. Nafamostat is a serine protease inhibitor (with implications on coagulation, fibrinolysis, complement system, inflammatory cytokine release) and is quickly hydrolysed, the reason why it is typically administered as an intravenous drip. Meanwhile, multiple companies market nafamostat generics in Japan and South Korea (e.g. Futhan, SK Chemicals). Nafamostat is not approved for any use by EMA or FDA. Sun Pharma in India has initiated manufacturing both the API and the finished product of nafamostat in India using technology from its subsidiary, Pola Pharma Japan [192, 197]. Different initiatives are ongoing to prepare an oral formulation with or without slow release characteristics. For example, Ensysce in the US is developing different routes of administration of nafamostat through its subsidiary Covistat, including the oral and inhaled route (www.covistat.com). Nafamostat is also being developed for inhaled use in Japan by University of Tokyo, RIKEN, Nichi-Iko and Daiichi Sankyo [192, 198], and in Germany, funded by BMBF [192, 199].

Completed, withdrawn, suspended or terminated studies

As of October 11, 2020, no completed, withdrawn, suspended or terminated interventional studies were found on nafamostat in ClinicalTrials.gov and EUdraCT registers.

keine abgeschlossenen, abgebrochenen Studien

Results of publications

Until now, no scientific publication on randomized clinical trials of nafamostat in Covid-19 patients could be identified.

keine veröffentlichten Studien

3.21 Gimsilumab

About the drug under consideration

Gimsilumab is a fully human monoclonal antibody that acts on granulocyte-macrophage colony-stimulating factor (GM-CSF) [1]; it is manufactured by Roivant Sciences Ltd. /Altasciences. Gimsilumab – ATC-code not assigned yet. Gimsilumab belongs to anti-inflammatories, antirheumatics, monoclonal antibodies drug class and has no approvement for any indication by EMA or FDA yet. It is known that studies are currently underway for these indications (excluding Covid-19): adult respiratory distress syndrome (Phase IIA) and ankylosing spondylitis (Phase IA) [200-202].

Monoklonaler Antkörper in Entwicklung

EMA/ FDA: keine Zulassung

Completed, withdrawn, suspended or terminated studies

As of October 11, 2020, no completed, withdrawn, suspended or terminated interventional studies were found on gimsilumab in ClinicalTrials.gov and EUdraCT registers.

keine abgeschlossenen, abgebrochenen Studien

Results of publications

There are no published results from RCTs related to effectiveness and safety of gimsilumab for Covid-19 treatment. There are no published results from observational studies related to effectiveness and safety of gimsilumab for Covid-19 treatment. There is one Phase II study of Gimsilumab, estimated study completion date is March 2021 [202, 203].

keine veröffentlichten Studien

1 Phase 2 Studie läuft

3.22 Canakinumab

About the drug under consideration

Canakinumab is a human monoclonal anti-human interleukin-1 beta (IL-1 beta) antibody of the IgG1/κ isotype manufactured by Novartis Pharma AG. Canakinumab binds with high affinity specifically to human IL-1 beta and neutralises the biological activity of human IL-1 beta by blocking its interaction with IL-1 receptors, thereby preventing IL-1 beta-induced gene activation and the production of inflammatory mediators [204]. Canakinumab – ATC-code L04AC08. Has orphan designation for familial mediterranean fever; cryopyrin-associated periodic syndromes; juvenile rheumatoid arthritis; inflammation; peroxisomal disorders; familial autosomal dominant periodic fever [204, 205].

Monoklonaler Antkörper

EMA Orphan Drug Zulassung für diverse Indikationen

Canakinumab has EMA approved indications for: Periodic fever syndromes; Cryopyrin-associated periodic syndromes; Cryopyrin-associated periodic syndromes Tumour necrosis factor receptor associated periodic syndrome (TRAPS); Hyperimmunoglobulin D syndrome (HIDS)/mevalonate kinase deficiency (MKD); Familial Mediterranean fever (FMF); Still's disease; Gouty arthritis [204, 206]. Canakinumab is not authorised in Covid-19 patients (EMA, FDA).

Completed, withdrawn, suspended or terminated studies

As of October 11, 2020, no completed, withdrawn, suspended or terminated interventional studies were found on canakinumab in ClinicalTrials.gov and EUdraCT registers.

keine abgeschlossenen, abgebrochenen Studien

Results of publications

keine veröffentlichten Studien
1 Phase 2 Studie läuft

There are no published RCTs related to effectiveness and safety of canakinumab for Covid-19. Two studies of canakinumab are still ongoing: one Phase III study, estimated study completion date on December 2020 and one Phase II study, estimated completion date on December 2020 [206-208]. There are no current published results from observational studies of canakinumab for Covid-19 treatment.

3.23 Lenzilumab

About the drug under consideration

Monoklonaler Antikörper

für keine Indikation bislang zugelassen

FDA: für Einzelanwendungen im Notfall – compassionate use zur Verhinderung von akutem Lungenversagen

Lenzilumab is a first-in-class Humaneered® recombinant monoclonal antibody targeting human GM-CSF, with potential immunomodulatory activity, high binding affinity in the picomolar range, 94% homology to human germline, and has low immunogenicity. Following intravenous administration, lenzilumab binds to and neutralizes GM-CSF, preventing GM-CSF binding to its receptor, thereby preventing GM-CSF-mediated signaling to myeloid progenitor cells. The inhibition of GM-CSF signaling may be beneficial in improving the hyperinflammation-related lung damage in the most severe cases of COVID-19. This blockade can be achieved through antagonism of the GM-CSF receptor or the direct binding of circulating GM-CSF [209, 210].

Lenzilumab is not authorised in Covid-19 patients (EMA, FDA). FDA has approved the administration of lenzilumab for COVID-19 patients under individual patient emergency IND applications to patients under the company's compassionate use program.

Completed, withdrawn, suspended or terminated studies

Okt 2020: keine weiteren Studien

As of October 11, 2020, no completed, withdrawn, suspended or terminated interventional studies were found on lenzilumab in ClinicalTrials.gov and EUdraCT registers.

Results of publications

There are no published RCTs related to effectiveness and safety of lenzilumab for Covid-19.

Fall-Kontroll Studie 27 Pts.

raschere klinische Verbesserung

Temesgen et al. 2020 [211] published results from case-control study in US. Twelve patients were treated with lenzilumab; 27 patients comprised the matched control cohort (untreated). Clinical improvement, defined as improvement of at least 2 points on the 8-point ordinal clinical endpoints scale, was observed in 11 out of 12 (92%) lenzilumab treated patients and 22 out of 27 (81%) untreated patients. The time to clinical improvement was significantly shorter for lenzilumab-treated group compared to the untreated cohort: median 5 days vs. 11 days ($p=0.006$). Similarly, the proportion of patients with acute respiratory distress syndrome (ARDS) ($SpO2/FiO2 < 315$) was significantly reduced over time when treated with lenzilumab compared to untreated ($p< 0.001$). Significant improvement in inflammatory markers (C-Reactive Protein, interleukin 6) and markers of disease severity (absolute lymphocyte count) were observed in patients who received lenzilumab, but not in untreated patients. Cytokine analysis showed a reduction in inflammatory myeloid cells two days after lenzilumab treatment. There were no treatment-emergent adverse events attributable to lenzilumab. Authors concluded that in high-risk COVID-19 patients with severe pneumonia, GM-CSF neutralization with lenzilumab was safe and associated with faster improvement in clinical outcomes, including oxygenation, and greater reductions in inflammatory markers compared to a matched control cohort of patients hospitalized with severe COVID-19 pneumonia.

Phase 3 RCT an hospitalisierten Pts mit Lungenentzündung 300 Pts.

A multicenter, phase 3, randomized, double-blinded, controlled, clinical trial with lenzilumab for the prevention of ARDS and/or death in hospitalized patients with pneumonia associated with coronavirus 2 (SARS-CoV-2) infection in COVID-19 patients is ongoing in US (NCT04351152). The primary objective of this study is to assess whether the use of lenzilumab in addition to current standard of care can alleviate the immune-mediated cytokine release syndrome (CRS) and reduce the time to recovery in 300 hospitalized patients with severe or critical COVID-19 pneumonia, with estimated completion date on September 2020 [21].

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