HTA Austria
Austrian Institute for
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GmbH

Covid-19

HSS/ Horizon Scanning

Living Document **V08 November** 2020

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05/11/2020	Addition chapter on Vitamin D (chapter 3.24)
09/11/2020	Methodology (1.2) – no changes
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10/11/2020	Update Remdesivir (chapter 3.1)
10/11/2020	Update Favipiravir (chapter 3.3)
10/11/2020	Darunavir (chapter 3.4) – no changes
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12/11/2020	Solnatide (chapter 3.15) – no changes
13/11/2020	Update Umifenovir (chapter 3.16)
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13/11/2020	Lenzilumab (chapter 3.23) – 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

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.

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

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.

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

internationale/ europ. Zusammenarbeit

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 Version 8 November, 2020 only terminated, withdrawn and suspended interventional clinical trials 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).

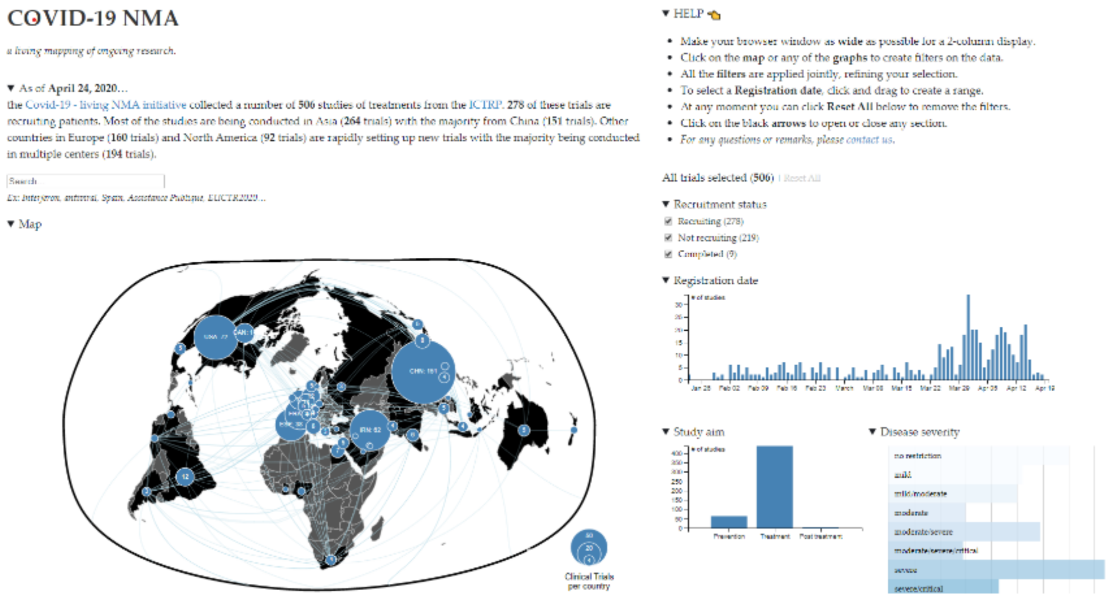

Figure 1.2-1: A living mapping of ongoing randomized trials, living systematic reviews with pairwise meta-analyses and network meta-analyses

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].

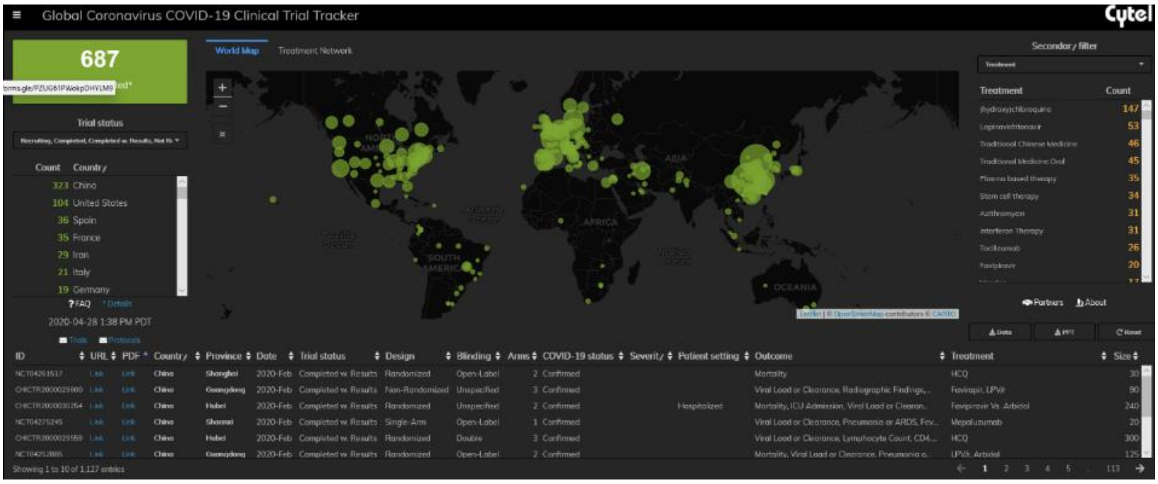

Figure 1.2-2: Global Coronavirus COVID-19 Clinical Trial Tracker - a real-time dashboard of clinical trials for COVID-19

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:

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

Vignetten zu Produkte, in "fortgeschrittenen" Stadien oder

häufig diskutiert/ publiziert

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 November 12 2020, ten COVID-19 candidate vaccines are investigated in phase 3 RCTs:

10 Impfstoffe in Phase 3

1. Moderna Therapeutics/NIAID (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/Wuhan Institute of Biological Products (inactivated vaccine);
7. Sinopharm/Beijing Institute of Biological Products (inactivated vaccine)
8. Gamaleya Research Institute (Non-Replicating Viral Vector Adeno-based - rAd5, rAd26) vaccine; and
9. Janssen Pharmaceuticals (Non-Replicating Viral Vector Ad26COVS1 vaccine); and
10. Novavax (Protein Subunit, VLP-recombinant protein nanoparticle vaccine + Matrix M) vaccine.

For these ten coronavirus vaccines are investigated in the phase 3 RCTs, the following articles were published with results related to early phases vaccine trials (phase 1, 1/2 or phase 2):

12 Publikationen zu

Phase 1,
1/2 oder
Phase 2

Impfstudien

1. Two on Moderna Therapeutics/NIAID vaccine: a preliminary report with the results from the phase 1 study (NCT04283461) [6] and
2. the results from the expanded phase 1 study (NCT04283461) in older adults [7];
3. Two on CanSino Biological vaccine: 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], as well as
4. phase 2, randomised controlled trials (ChiCTR2000031781/NCT04398147) [9];
5. One on Novavax vaccine: the results from the phase 1/2 RCT (NCT04368988) [10];
6. One on Oxford/Astra Zeneca vaccine: a preliminary report with the results from phase 1/2 single-blind, RCT (ISRCTN 15281137/NCT04324606/EudraCT 2020-001072-15) [11];
7. One with results on Gamaleya vaccine, from two open, non-randomised phase 1/2 studies at two hospitals in Russia (NCT04436471 and NCT04437875) [12];

8. Three on **BioNTech/Fosun Fharma/Pfizer** vaccine**:** results from two phase 1/2 trials on **BNT**162b1 vaccine, one in US (NCT04368728/EudraCT 2020-001038-36) [13],
9. and one in Germany (NCT04380701, EudraCT 2020-001038-36) [14] as well as
10. additional safety and immunogenicity results from the US phase 1 trial (NCT04368728/EudraCT 2020-001038-36) [52, 53].
11. Two related to **Sinopharm vaccine**: results from two double-blind RCTs, phase 1 and phase 2 (ChiCTR2000031809) [15, 16] on Sinopharm/**Wuhan Institute of Biological Products** vaccine and
12. results from phase 1/2 clinical trials (ChiCTR2000032459) [17] on Sinopharm/**Beijing Institute of Biological Products**, BBIBP-CorV vaccine.

Safety concern:

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 was on hold. AstraZeneca voluntarily paused vaccination to allow review of safety data by an independent committee [18]. One death occurred in Brazil on 19 October 2020. After pause, the trials restarted again. On Oct 13th also Johnson & Johnson (Janssen) Covid-19 vaccine clinical trials were temporarily paused due to unexplained illness in the ENSEMBLE study participant.

1 schwerwiegende Nebenwirkung bei AstraZeneca nach kurzer Pausierung Fortführung

1 Unterbrechung (Janssen/ J&J)

Approval status:

On 09/07/2020, Medicines Regulatory Authorities published the report related to phase 3 COVID-19 vaccine trials [20]. 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. 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.

Positionspapier der Internationalen Regulatoren

On November 11, 2020 EMA publishes safety monitoring plan and guidance on risk management planning for COVID-19 vaccines, https://www.ema.europa.eu/en/news/ema-publishes-safety-monitoring-plan-guidance-risk-management-planning-covid-19-vaccines.

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 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 [21]. On November 16, 2020 EMA announced that EMA's human medicines committee (CHMP) has started a 'rolling review' of data on a mRNA-1273 COVID-19 vaccine, developed by **Moderna Biotech** Spain, S.L. (a subsidiary of Moderna, Inc.), based on preliminary results from non-clinical studies and early clinical studies in adults which suggest 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.

derzeit 3 Impfstoffe in „rolling review" bei EMA – Zulassung:

Oxford/AstraZeneca
BioNTech/ Pfizer
Moderna

Table 2-1: Vaccines in the R&D pipeline (Phase 1 - Phase 3 clinical trials, not preclinical stages), Nov 12, 2020

Source: DRAFT landscape of COVID-19 candidate vaccines –
12 November 2020 - 48 candidate vaccines in clinical evaluation, https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines

COVID-19 Vaccine developer/ manufacturer	Vaccine platform	Type of candidate vaccine	Number of doses	Timing of doses	Route of Administration	Clinical Stage			
						Phase 1	Phase 1/2	Phase 2	Phase 3
Sinovac	Inactivated	Inactivated	2	0,14 days	IM		NCT04383574 NCT04352608 NCT04551547		NCT04456595 669/UN6.KEP/EC/2020 NCT04582344 NCT04617483
Wuhan Institute of Biological Products/Sinopharm	Inactivated	Inactivated	2	0,21 days	IM		ChiCTR2000031809 Interim Report		ChiCTR2000034780 ChiCTR2000039000 NCT04612972
Beijing Institute of Biological Products/Sinopharm	Inactivated	Inactivated	2	0,21 days	IM		ChiCTR2000032459 Study Report		ChiCTR2000034780 NCT04560881
Bharat Biotech	Inactivated	Whole-Virion Inactivated	2	0, 28 days	IM		CTRI/2020/07/026300 CTRI/2020/09/027674		CTRI/2020/11/028976
University of Oxford/AstraZeneca	Non-Replicating Viral Vector	ChAdOx1-S	2	0,28 days	IM		PACTR202006922165132 2020-001072-15 NCT04568031 Interim Report	2020-001228-32	ISRCTN89951424 NCT04516746 NCT04540393 CTRI/2020/08/027170
CanSino Biological Inc./Beijing Institute of Biotechnology	Non-Replicating Viral Vector	Adenovirus Type 5 Vector	1		IM	ChiCTR2000030906 NCT04568811 Study Report		ChiCTR2000031781 NCT04566770 Study Report	NCT04526990 NCT04540419
Gamaleya Research Institute	Non-Replicating Viral Vector	Adeno-based (rAd26-S+rAd5-S)	2	0,21 days	IM		NCT04436471 NCT04437875 Study Report	NCT04587219	NCT04530396 NCT04564716
Janssen Pharmaceutical Companies	Non-Replicating Viral Vector	Adenovirus Type 26 vector	1 2	0 0, 56 days	IM		NCT04436276 NCT04509947	NCT04535453	NCT04505722 NCT04614948
Novavax	Protein Subunit	Full length recombinant SARS CoV-2 glycoprotein nanoparticle	2	0,21 days	IM		NCT04368988 Study Report	NCT04533399 (phase 2b)	2020-004123-16 NCT04611802

		vaccine adjuvanted with Matrix M							
Moderna/NIAID	RNA	LNP-encapsulated mRNA	2	0,28 days	IM	NCT04283461 Interim Report Final Report		NCT04405076	NCT04470427
BioNTech/Fosun Pharma/Pfizer	RNA	3 LNP-mRNAs	2	0,28 days	IM	NCT04368728 Study Report	2020-001038-36 ChiCTR2000034825 NCT04537949 NCT04588480 Study Report1 Study Report2		NCT04368728
Beijing Wantai Biological Pharmacy/ Xiamen University	Replicating Viral Vector	Intranasal flu-based-RBD	1		IN	ChiCTR2000037782		ChiCTR2000039715	
Anhui Zhifei Longcom Biopharmaceutical/Institute of Microbiology, Chinese Academy of Sciences	Protein Subunit	Adjuvanted recombinant protein (RBD-Dimer)	2 or 3	0,28 or 0,28,56 days	IM	NCT04445194	NCT04550351	NCT04466085	
Curevac	RNA	mRNA	2	0, 28 days	IM	NCT04449276		NCT04515147	
Institute of Medical Biology, Chinese Academy of Medical Sciences	Inactivated	Inactivated	2	0, 28 days	IM	NCT04412538	NCT04470609		
Research Institute for Biological Safety Problems, Rep of Kazakhstan	Inactivated	Inactivated	2	0, 21 days	IM		NCT04530357		
Beijing Minhai Biotechnology Co., Ltd.	Inactivated	Inactivated	2		IM	ChiCTR2000038804	ChiCTR2000039462		

Inovio Pharmaceuticals/ International Vaccine Institute	DNA	DNA plasmid vaccine with electroporation	2	0, 28 days	ID		NCT04447781 NCT04336410		
Osaka University/ AnGes/ Takara Bio	DNA	DNA plasmid vaccine + Adjuvant	2	0, 14 days	IM		NCT04463472 NCT04527081		
Cadila Healthcare Limited	DNA	DNA plasmid vaccine	3	0, 28, 56 days	ID		CTRI/2020/07/026352		
Genexine Consortium	DNA	DNA Vaccine (GX-19)	2	0, 28 days	IM		NCT04445389		
Kentucky Bioprocessing, Inc	Protein Subunit	RBD-based	2	0, 21 days	IM		NCT04473690		
Sanofi Pasteur/GSK	Protein Subunit	S protein (baculovirus production)	2	0, 21 days	IM		NCT04537208		
Biological E Ltd	Protein Subunit	Adjuvanted protein subunit (RBD)	2	0, 28 days	IM		CTRI/2020/11/029032		
Israel Institute for Biological Research	Replicating Viral Vector	VSV-S	1		IM		NCT04608305		
Arcturus/Duke-NUS	RNA	mRNA			IM		NCT04480957		
SpyBiotech/Serum Institute of India	VLP	RBD-HBsAg VLPs	2	0, 28 days	IM		ACTRN12620000817943		
Symvivo	DNA	bacTRL-Spike	1		Oral	NCT04334980			
ImmunityBio, Inc. & NantKwest Inc.	Non-Replicating Viral Vector	hAd5 S+N 2nd Generation Human Adenovirus Type 5 Vector (hAd5) Spike (S) + Nucleocapsid (N)	2	0, 21 days	SC	NCT04591717			
ReiThera/LEUKOCARE/Univercells	Non-Replicating Viral Vector	Replication defective Simian Adenovirus (GRAd) encoding S	1		IM	NCT04528641			

CanSino Biological Inc/Institute of Biotechnology, Academy of Military Medical Sciences, PLA of China	Non-Replicating Viral Vector	Ad5-nCoV	2	0, 28 days	IM/mucosal	NCT04552366			
Vaxart	Non-Replicating Viral Vector	Ad5 adjuvanted Oral Vaccine platform	2	0, 28 days	Oral	NCT04563702			
Ludwig-Maximilians - University of Munich	Non-Replicating Viral Vector	MVA-SARS-2-S	2	0, 28 days	IM	NCT04569383			
Clover Biopharmaceuticals Inc./GSK/Dynavax	Protein Subunit	Native like Trimeric subunit Spike Protein vaccine	2	0, 21 days	IM	NCT04405908			
Vaxine Pty Ltd/Medytox	Protein Subunit	Recombinant spike protein with Advax™ adjuvant	1		IM	NCT04453852			
University of Queensland/CSL/Seqirus	Protein Subunit	Molecular clamp stabilized Spike protein with MF59 adjuvant	2	0, 28 days	IM	ACTRN12620000674932p ISRCTN51232965			
Medigen Vaccine Biologics Corporation/NIAID/Dynavax	Protein Subunit	S-2P protein + CpG 1018	2	0, 28 days	IM	NCT04487210			
Instituto Finlay de Vacunas, Cuba	Protein Subunit	rRBD produced in CHO-cell chemically conjugate to tetanus toxoid	2	0, 28 days	IM	IFV/COR/06			
Instituto Finlay de Vacunas, Cuba	Protein Subunit	RBD + Adjuvant	2	0, 28 days	IM	IFV/COR/04 IFV/COR/05			
FBRI SRC VB VECTOR, Rospotrebnadzor, Koltsovo	Protein Subunit	Peptide	2	0, 21 days	IM	NCT04527575			

West China Hospital, Sichuan University	Protein Subunit	RBD (baculovirus production expressed in Sf9 cells)	2	0, 28 days	IM	ChiCTR2000037518			
University Hospital Tuebingen	Protein Subunit	SARS-CoV-2 HLA-DR peptides	1		SC	NCT04546841			
COVAXX / United Biomedical Inc. Asia	Protein Subunit	Multitope peptide-based S1-RBD-protein vaccine	2	0, 28 days	IM	NCT04545749			
Merck Sharp & Dohme/IAVI	Replicating Viral Vector	Replication-competent VSV delivering the SARS-CoV-2 Spike	1		IM	NCT04569786			
Institute Pasteur/Themis/Univ. of Pittsburg CVR/Merck Sharp & Dohme	Replicating Viral Vector	Measles-vector based	1 or 2	0, 28 days	IM	NCT04497298			
Imperial College London	RNA	LNP-nCoVsaRNA	2		IM	ISRCTN17072692			
People's Liberation Army (PLA) Academy of Military Sciences/Walvax Biotech.	RNA	mRNA	2	0, 14 or 0, 28 days	IM	ChiCTR2000034112 ChiCTR2000039212			
Medicago Inc.	VLP	Plant-derived VLP adjuvanted with GSK or Dynavax adjs.	2	0, 21 days	IM	NCT04450004			

2.1 Moderna Therapeutics—US National Institute of Allergy

About the vaccine

The **mRNA-1273** vaccine candidate developed by ModernaTX, Inc. in collaboration with NIAID and sponsored by NIAID/CEPI is an LNP-encapsulated mRNA-based vaccine (mRNA-1273) intended for prevention through full-length, perfusion stabilized spike (S) protein of SARS-CoV-2 that is the key into the human cell [22].

mRNA-1273
collab mit NIAID/CEPI

Estimated timeline for approval

Phase 1 trial with 45 healthy participants (NCT04283461) is ongoing. 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 [24]. The Phase I safety study should be completed by June 2021.

Phase 1:
45 gesunde Erwachsene
Juni 2021

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

Phase 2a:
bis August 2021

The randomized, **phase 3,** 1:1 placebo-controlled trial is currently ongoing (NCT04470427). It is expected to include approximately 30,000 participants enrolled in the U.S.

Phase 3 Studienprotokoll
RCT mt ca 30.000
Teilnehmer*innen

Results of publications

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). 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.

vorläufige Publikation der
Phase 1 Studie

höhere Dosis,
höhere Titer

Anderson et al. 2020 [7] published results from the above mentioned phase 1 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. Binding-antibody responses increased rapidly after the first immunization. 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.

Okt. 2020:
Publikation der
Phase 1 Studie

unterschiedliche
Dosierung in
verschiedenen
Altersgruppen

On November 16, Moderna, Inc. announced that the independent, NIH-appointed Data Safety Monitoring Board (DSMB) has informed Moderna that their phase 3 study of mRNA-1273 vaccine candidate, enrolled more than 30,000 participants in the U.S., has met the statistical criteria pre-specified in the study protocol for efficacy, with a vaccine efficacy of 94.5%. A review of solicited adverse events indicated that the vaccine was generally well tolerated, https://investors.modernatx.com/news-releases/news-release-details/modernas-covid-19-vaccine-candidate-meets-its-primary-efficacy.

2.2 CanSino Biological Inc. and Beijing Institute of Biotechnology

About the vaccine

The **AD5-nCoV** vaccine candidate developed by CanSino Biologics Inc. and the Beijing Institute of Biotechnology is a replication-defective adenovirus type 5 that expresses SARS-CoV-2 spike proteins. The platform (non-replicating viral vector) of AD5-nCoV was originally used for an Ebola vaccine (AD5-EBOV) [27, 28].

AD5-nCoV

Estimated timeline for approval

The first clinical, **phase 1** trial (ChiCTR2000030906/ NCT04313127) with 108 healthy adults is a single-centre dose-escalation study to test both the safety and tolerability of AD5-nCoV injections in three intervention groups using different dosages (low, medium and high). The primary endpoint of the trial is adverse reactions up to seven days post-vaccination. The study is estimated to be completed in December 2022 [29]. A RCT, **phase 2**, double-blinded, placebo-controlled, parallel, three groups trial (ChiCTR2000031781/NCT04398147), aims to evaluate vaccine safety and immunogenicity 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. This RCT will be conducted from 2020-04-12 to 2021-01-31.

Phase 1:
108 gesunde Erwachsene
Dezember 2020

Phase 2:
Jänner 2021

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 [32].

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

bis 2021

Results of publications

The results from phase 1 study were published (ChiCTR2000030906/NCT04313127) [8]. 108 participants 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.

1 veröffentlichte Phase 1 Studie:

108 Studienteil-nehmer*innen erhalten unterschiedliche Dosierungen

The results from the above mentioned phase 2 RCT were published also [9]; 508 eligible participants 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. 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.

Publikation der Phase 2 Studie (RCT)

508 Teilnehmer*innen

96%/ 97% Serokonversionsrate bei 2 unterschiedlichen Dosierungen

2.3 University of Oxford/ Astra Zeneca

About the vaccine

The **ChAdOx1 nCoV-19** (AZD1222, AstraZeneca licensed from Oxford University) vaccine candidate developed by the Jenner Institute at Oxford University is based on a non-replicating viral vector. A chimpanzee adenovirus platform is hereby used [25, 33]. 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 [33].

ChAdOx1 nCoV-19

Estimated timeline for approval

Currently, the first clinical **phase 1/2** single-blinded, placebo-controlled, multi-centre randomised controlled trial to test efficacy, safety and immunogenicity of ChAdOx1 nCoV-19 in 510 healthy adults is ongoing (ISRCTN 15281137/NCT04324606/EudraCT 2020-001072-15). The primary endpoints are number of virologically confirmed symptomatic cases/symptomatic cases of COVID-19 (efficacy) and occurrence of serious adverse events (safety), 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 [34].

Phase 1/2: 510 gesunde Erwachsene

bis Mai 2021

Phase 2b/3 study (EUdraCT 2020-001228-32/NCT04400838) is ongoing; the primary endpoint is virologically confirmed (PCR positive) symptomatic COVID-19 infection.

Phase 2b/3 : laufend

Phase 3 RCT (ISRCTN89951424) started in Brazil and South Africa, with another country in Africa set to follow, as well as a trial in the US (NCT04516746) [35]. 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[36]. The study is estimated to be completed in July 2021.

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

Ende Juli 2021

Results of publications

A preliminary report with the results from **phase 1/2** 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 (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; $p<0{\cdot}001$).

vorläufige Publikation Phase 1/2: 1.077 Teilnehmer*innen

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

2.4 BioNTech/Fosun Pharma/Pfizer

About the vaccine

The **BNT-162** vaccine candidate developed by BioNTech in collaboration with Fosun Pharma and Pfizer is an mRNA platform-based vaccine expressing codon-optimized undisclosed SARS-CoV-2 protein(s) encapsulated in 80-nm ionizable cationic lipid/ phosphatidylcholine/ cholesterol/ polyethylene glycol–lipid nanoparticles [23].

BNT-162

Estimated timeline for approval

A **phase 1/2**, randomized, placebo-controlled, triple-blind, dose-finding, and vaccine candidate-selection study in healthy adults in the US as well as in Germany [37] (NCT04368728/EudraCT 2020-001038-36). The study evaluates 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 mehrstufiges Studiendesign

Phase 1/ 2 (Deutschland)

November 2022

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].

Phase 2/3 RCT läuft derzeit

Results of publications

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). 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.

Publikation der Phase 1/ 2

unterschiedliche Dosierungen

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.

weitere Phase 1 / 2 Studie publiziert

18-55 J

Walsh et al. 2020 [40, 41] 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. 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.

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

2.5 Sinovac Biotech Ltd.

About the vaccine

Sinovac Life Sciences Co., Ltd. is the developer of CoronaVac, an inactivated COVID-19 vaccine candidate, and will be the marketing authorization holder of CoronaVac in China with a vaccine production license from China National Medical Products Administration (NMPA).

CoronaVac

Estimated timeline for approval

The **phase 1 and 2** trials started on April 16, 2020 in Jiangsu Province, China: a group of healthy adults aged 18-59 years old were vaccinated with a 0, 14 day schedule. According to Sinovac announcement, preliminary phase I/II results showed that there was no serious adverse event after vaccinating a total of 743 volunteers in the trials, demonstrating a good safety profile for the

Phase 1/2 : 743 Teilnehmer*innen

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 [42].

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

Phase 3 RCT (NCT04456595) aims 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. All participants will be followed up to 12 months. Interim preliminary efficacy analysis can be triggered by reaching the target number of 150 cases [32]. The study is estimated to be completed in October 2021.

2.6 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 [15].

Estimated timeline for approval

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. It is currently underway in Abu Dhabi and United Arab Emirates. The study is estimated to be completed in July 2021.

Dezember 2021

A **phase 3**, randomized, double blind, placebo parallel-controlled clinical trial to evaluate the efficacy, immunogenicity and safety of this vaccine 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.

Results of publications

Phase 1 und Phase 2 RCTs

In interim analysis of Xia et al. 2020 [55, 56], related to safety and immunogenicity of an investigational inactivated whole-virus COVID-19 vaccine in China reported results from two double-blind RCTs, **phase 1 and phase 2** (ChiCTR2000031809). The experimental group received a β-propiolactone–inactivated whole-virus vaccine against COVID-19, developed by **Wuhan Institute of Biological Products**. The placebo group contained only sterile phosphate buffered saline and alum adjuvant.

In the **phase 1 RCT**, 96 participants were assigned to 1 of the 3 dose groups (2.5, 5, and 10 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]). Xia et al. 2020 [17] recently published evidence for the safety and immunogenicity of a SARS-CoV-2 vaccine candidate developed by **China National Biotec Group** and the **Beijing Institute of Biological Products** (BBIBP-CorV), which was tested in randomised, double-blind, placebo controlled **phase 1/2** clinical trials in healthy individuals aged 18 years and older (ChiCTR2000032459). In the phase 1 dose-escalating trial, the vaccine was given at a two-dose schedule at three different concentrations (2 µg, 4 µg, and 8 µg per dose) and was well tolerated in both age groups (18–59 years and ≥60 years). The early **phase 2** trial of the BBIBP-CorV vaccine in healthy adults aged 18–59 years assessed the effect of shortening the interval between two doses from 28 days to 14 days or 21 days on the vaccine's immunogenicity. The 4 µg dose of the vaccine was the most immunogenic when given at the 21-day interval (neutralising antibody titre 283), but its immunogenicity significantly decreased when the interval was reduced to 14 days (neutralising antibody titre 170), suggesting that the interval cannot be shorter than 3 weeks [17, 43]].

Phase 1: 96 Teilnehmer*innen – 3 unterschiedliche Dosierungen

Phase 2: 224 Teilnehmer*innen – 2 unterschiedliche Zeitpläne

Endpunkte: Antikörper Response

weitere Intervalle – bessere Immunantwort

2.7 Gamaleya Research Institute

About the vaccine

Vaccine Gam-COVID-Vac, adenoviral-based vaccine against SARS-CoV-2, a solution for intramuscular injection, is 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). The trials are sponsored by **Gamaleya Research Institute of Epidemiology and Microbiology, Health Ministry of the Russian Federation** in collaboration with Acellena Contract Drug Research and Development.

Gam-COVID-Vac

Estimated timeline for approval

Based on results of two open, non-randomised **phase 1/2** studies, presented below, 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 1/ 2 als Sputnik zugelassen ohne RCT

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.

Phase 3 RCT_ läuft bis Mai 2021

Results of publications

Two **phase 1/2** studies on healthy adult volunteers (men and women) aged 18–60 years are reported as completed (NCT04436471 and NCT04437875) [32]. 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

Phase 1/ 2 Studien in Russland

76 Teilnehmer*innen

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.

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. 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% [12].

wenig Nebenwirkungen, Antikörper

2.8 Janssen Pharmaceutical

About the vaccine

The Janssen Pharmaceutical Companies of Johnson & Johnson developed the investigational vaccine (also known as Ad.26.COV2.S), a recombinant vector vaccine that uses a human adenovirus to express the SARS-CoV-2 spike protein in cells.

Ad.26.COV2.S

Estimated timeline for approval

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.

Phase 3 RCT mit 60.000 Teilnehmer*innen

März 2023

Results of publications

Sadoff et al. 2020 [44] reported, as preprint, interim results of a **phase 1/2**, double-blind, randomized, placebo-controlled 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). 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.

Phase 1/2
2 Dosierungen
2 Intervalle
3 Kohorten

2.9 Novavax

About the vaccine

The Novavax COVID-19 vaccine being developed by Novavax and co-sponsored by CEPI [45] is a recombinant protein nanoparticle technology platform that is to generate antigens derived from the coronavirus spike (S) protein [46]. Matrix-M™ is Novavax patented saponin-based adjuvant that

CEPI
Matrix-M™

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 [47, 48].

Estimated timeline for approval

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 [32, 49-51]. This RCT will be conducted from May 15, 2020 to July 31, 2021. Estimated Primary Completion Date is December 31, 2020.

Phase 1:
131 gesunde Erwachsene

Juli 2021

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 [32].

Phase 2b RCT
2.904 Südafrika
bis 2021

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.

Phase 3
9.000 Teilnehmer*innen
in UK

Results of publications

A results from above mentioned 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 were published [10]. 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. Unsolicited adverse events were mild in most participants; there were no severe adverse events. 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).

Publikation der Phase 1/2

keine schwerwiegenden NW beobachtet

3 Results: Therapeutics

EMA scientific advice für viele unterschiedliche Medikamente

EMA is providing guidance to assist developers of potential COVID-19 medicines, to prepare for eventual applications for marketing authorisation. This includes scientific advice, as well as informal consultation with the COVID-19 EMA pandemic Task Force (COVID-ETF). The outcome of any consultation or advice from EMA is not binding on developers. COVID-19 medicines that have received EMA advice can be found in Table 3-1 below, https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/treatments-vaccines-covid-19.

Table 3-1: COVID-19 medicines that have received EMA advice

Product	Developer	Therapeutic class/drug type	Development stage at time of guidance
VIR-7831, VIR-7832	Vir Biotechnology/GSK	Antiviral (monoclonal antibody)	Clinical phase
UNI911	Union Therapeutics	Antiviral	Clinical phase
Tocilizumab	Roche	Immunomodulator	Clinical phase
SNG-001	Synargein	Immunomodulator	Clinical phase
Siltuximab	EUSApharma	Immunomodulator	Clinical phase
Sarilumab	Sanofi Aventis	Immunomodulator	Clinical phase
Remdesivir	Gilead	Antiviral	Clinical phase
RBT-9	Renibus Therapeutics Inc	Antiviral	Clinical phase
Ravulizumab	Alexion	Other therapeutics	Clinical phase
Otilimab	GSK	Immunomodulator	Clinical phase
Meplazumab	Jiangsu Pacific Meinuoke Biophar.	Antiviral (mAb)	Clinical phase
Mavrilimumab	Kiniksa Pharmaceuticals	Immunomodulator	Clinical phase
Gimsilumab	Roivant	Immunomodulator	Clinical phase
Favipiravir	Glenmark Pharmaceuticals Ltd	Antiviral	Clinical phase
Emapalumab and anakinra	Swedish Orphan Biovitrum AB	Immunomodulator	Clinical phase
Eculizumab	Alexion	Immunomodulator	Clinical phase
Danoprevir	Ascletis Pharmaceuticals Co Ltd	Antiviral	Clinical phase
Copper chloride	ACOM srl	Antiviral	Clinical phase
Chloroquine and hydroxychloroquine cyclops DPI	PureIMS	Other therapeutics	Clinical phase
Chloroquine	Oxford University	Other therapeutics	Clinical phase
CD24Fc	Oncoimmune Inc	Immunomodulator	Clinical phase
Baricitinib	Eli Lilly	Immunomodulator	Clinical phase
Apremilast	Amgen Europe BV	Immunomodulator	Clinical phase
APN01	Apeiron Biologics	Immunomodulator	Clinical phase
Anti-SARS-CoV-2 polyclonal hyperimmune immunoglobulin	Alliance hyperimmune project (Biotest AG, Bio Products Laboratory, LFB, Octapharma, CSL Behring and Takeda)	Antiviral	Clinical phase
Acalabrutinib	Acerta Pharma BV	Immunomodulator	Clinical phase

In this document we present information for some therapies in development

Table 3 -2: Most advanced therapeutics in the R&D pipeline

Drug	Mechanism of operation	Approval Status Withdrawn, suspended or terminated
Remdesivir (Veklury®)	Antiviral agent	Approved by EMA (conditional marketing authorisation) and FDA (marketing authorisation) 2 RCTs (suspended and terminated)
Favipiravir (Avigan, T-705)	Antiviral agent	No withdrawn, suspended or terminated studies found
Darunavir (Prezista®)	Antiviral agent	No withdrawn, suspended or terminated studies found
Camostat Mesilate (Foipan®)	Antiviral cell-entry inhibitor	No withdrawn, suspended or terminated studies found
APN01 (rhACE2)	Antiviral cell-entry inhibitor	1 RCT – Withdrawn
Tocilizumab (RoActemra®)	Monoclonal antibody	1 RCT withdrawn, 4 RCTs terminated
Sarilumab (Kevzara®)	Monoclonal antibody	1 RCT suspended, 1 RCTs terminated
Interferon beta 1a (SNG001) **and 1b**	Interferon	1 RCT suspended
Convalescent Plasma	Convalescent Plasma	1 RCT terminated, 1 RCT withdrawn
Plasma derived medicinal products: REGN-COV2; LY-CoV555 (bamlanivimab); LY-CoV016 (etesevimab); AZD7442	Neutralizing monoclonal antibodies	No withdrawn, suspended or terminated studies found
Solnatide	Synthetic peptide	No withdrawn, suspended or terminated studies found
Umifenovir (Arbidol®)	Antiviral agent	No withdrawn, suspended or terminated studies found
Dexamethasone and other corticosteroids	Glucocorticoid	EMA CHMP positive opinion on dexamethasone 2 RCTs terminated, 1 RCT suspended, 1 RCT withdrawn
Anakinra (Kyneret®)	Interleukin 1 receptor antagonist	1 RCT suspended, 1 RCT terminated
Colchicine	An alkaloid, with anti-gout and anti-inflammatory activities	No withdrawn, suspended or terminated studies found
Nafamostat (Futhan©)	Trypsin-like serine protease inhibitor	No withdrawn, suspended or terminated studies found
Gimsilumab	Human monoclonal antibody	No withdrawn, suspended or terminated studies found
Canakinumab	Human monoclonal antibody	No withdrawn, suspended or terminated studies found
Lenzilumab	Recombinant monoclonal antibody	No withdrawn, suspended or terminated studies found
Vitamin D	Vitamin	No withdrawn, suspended or terminated studies found

3.1 Remdesivir (Veklury®)

About the drug under consideration

Remdesivir (Veklury) is an antiviral medicine for systemic use which received a **conditional marketing authorisation** in **EU** in July, 2020 [52][53][54], https://ec.europa.eu/commission/presscorner/detail/en/mex_20_1266..

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.

erstes zugelassenes antivirales Medikament gegen Coronavirus: conditional marketing authorisation
indiziert für Patient*nnen ≥ 12 Jahre mit Lungenentzündung, Sauerstoff-unterstützt
Verabreichung iv
5-10 Tage

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%) [55].

Nebenwirkungen

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** [63].

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) [56].

Okt 2020:
EMA Sicherheitsanalyse

On October 22, 2020 the **U.S. Food and Drug Administration approved** remdesivir for use in adult and pediatric patients 12 years of age and older and weighing at least 40 kilograms (about 88 pounds) for the treatment of **COVID-19 requiring hospitalization**.

FDA Zulassung im Okt 2020

US COVID-19 Treatment Guidelines Panel issued recommendations on remdesivir treatment for patients with COVID-19 (as of October 9, 2020) [62]:

US COVID-19 Treatment Guidelines

For patients with COVID-19 who are not hospitalised or who are hospitalised with moderate disease but do not require supplemental oxygen

niedrige Evidenz der Datenlage,

Recommendations:

weitere klinsche Studien zum Nutzen notwendig

The Panel does not recommend any specific antiviral or immunomodulatory therapy for the treatment of COVID-19 in these patients. Patients are considered to have moderate disease if they have clinical or radiographic evidence of lower respiratory tract infection and a saturation of oxygen (SpO2) ≥94% on room air at sea level.; There are insufficient data for the Panel to recommend either for or against the use of remdesivir for the treatment of COVID-19.; The Panel recommends against the use of dexamethasone (AI) or other corticosteroids for the treatment of COVID-19 (AIII) unless a patient has another clinical indication for corticosteroid therapy.

For hospitalised patients with COVID-19 who require supplemental oxygen but who do not require delivery of oxygen through a high-flow device, noninvasive ventilation, invasive mechanical ventilation, or extracorporeal membrane oxygenation

Recommendations (the options below are listed in order of preference; however, all these options are considered acceptable):

Remdesivir 200 mg intravenously (IV) for 1 day, followed by remdesivir 100 mg IV for 4 days or until hospital discharge, whichever comes first (AI); *or* A combination of remdesivir (dose and duration as above) plus dexamethasone 6 mg IV or orally for up to 10 days or until hospital discharge (BIII); *or* If remdesivir cannot be used, dexamethasone may be used instead (BIII).

For hospitalised patients with COVID-19 who require delivery of oxygen through a high-flow device or noninvasive ventilation but not invasive mechanical ventilation or extracorporeal membrane oxygenation

Recommendations (the options below are listed in order of preference; however, both options are considered acceptable):

A combination of dexamethasone plus remdesivir at the doses and durations discussed above (AIII); or Dexamethasone alone at the dose and duration discussed above (AI).

For hospitalised patients with COVID-19 who require invasive mechanical ventilation or extracorporeal membrane oxygenation

Recommendations (the options below are listed in order of preference; however, both options are considered acceptable):
Dexamethasone at the dose and duration discussed above **(AI)**; **or** **Dexamethasone** plus **remdesivir** for patients who have recently been intubated at the doses and durations discussed above **(CIII)**.

Vorhaben von Gilead: Darreichungsform mittels Inhalator

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.

Withdrawn, suspended or terminated studies

in ClinicalTrials.gov & EUdraCT keine weiteren beendeten Studien

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, 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).

Results of publications

Wang Y et al. 2020 [65] published results of the first randomised, double-blind, placebo-controlled, multicentre trial, conducted in China (**NCT04257656**), on 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. 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]); duration of invasive mechanical ventilation; viral load; adverse events.

Ergebnisse der Studien:

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

keine Unterschiede bei klinischer Verbesserung, invasiver Beatmung

Beigel et al. 2020 [66] reported results from double-blind, randomized, placebo-controlled trial of intravenous remdesivir in 1062 adults hospitalized with Covid-19 (541 assigned to remdesivir and 521 to placebo) (**NCT04280705**). Remdesivir group had a median recovery time of 10 days (95% confidence interval [CI], 9 to 11) vs 15 days (95% CI, 13 to 18) among placebo group (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). The Kaplan–Meier estimates of mortality were 6.7% with remdesivir vs 11.9% in placebo group by day 15 (hazard ratio, 0.55; 95% CI, 0.36 to 0.83); 11.4% with remdesivir vs 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%). 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.

Beigel (USA)
1.062 Pts.
kürzere Dauer zur Erholung

Unterschiede bei Baseline-Schwergrad erschweren die Interpretation der Mortalitätsdaten

Goldman et al. 2020 [64] published the results from the randomized, open-label, phase 3 trial involving 397 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**), to receive intravenous remdesivir for either 5 days or 10 days. Trial did not show a significant difference between a 5-day course and a 10-day course of remdesivir. -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.

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

Vergleich von 5 vs. 10 Tagen RDV

primärer Endpunkt: klinischer Status am Tag 14

Spinner et al. 2020 [67] published results from a randomised, open-label, phase 3 trial (**NCT04292730**) performed on 596 hospitalised patients with moderate COVID-19 pneumonia (pulmonary infiltrates and room-air oxygen saturation >94%). 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). On day 11, patients in the 5-day remdesivir group had statistically significantly higher odds of a better clinical status distribution vs standard care (odds ratio, 1.65; 95% CI, 1.09-2.48; $p=0.02$), but the difference was of uncertain clinical importance. 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).

Spinner (USA, Europa, Asien)

5-Tage vs
10-Tage vs.
SOC

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, duration of oxygen therapy or hospitalization and all-cause mortality at day 28. The difference in AEs 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. Serious adverse events were less common in the remdesivir groups, but the difference was not statisticaly significant.

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

AE signifikanter Unterschied zwischen 10 Tage vs. SOC zu Ungunsten von Remdesivir
SAE häufiger in SOC Gruppe

Interim results from the **WHO SOLIDARITY trial** (**ISRCTN83971151, NCT04315948**), large, international, adaptive, open-label, randomized controlled trial to evaluate remdesivir, lopinavir/ritonavir, interferon beta-1a and hydroxychloroquine treatment for COVID-19, were published as as preprint, with 2750 patients allocated to remdesivir [68]. Death rate ratio was not statisticaly significant different between remdesivir and standard care; RR=0.95 (0.81-1.11, p=0.50; 301/2743 active vs 303/2708 control). The same was true for the outocmes: initiation of ventilation and hospitalisation duration, and other three investigation treatment.

WHO SOLIDARITY

kein Unterschied bei Mortalität
kein Unterschied bei anderen Endpunkten

According to the current **Living Systematic Review with Meta-Analysis (MA)** including **4 RCTs** (Wang, Beigel, Spinner and SOLIDARITY-Remdesivir) (https://covid-nma.com/living_data/index.php), on remdesivir compared with standard care/placebo, related to the outcome All-cause mortality at days 14-28 (4 RCTs): RR 0.90, 95% CI 0.73 to 1.11) (moderate certainty of evidence). Outcome: incidence of WHO progression score level 7 or above at days 7 (2 RCTs): RR 0.70, 95% CI 0.59 to 0.82) (moderate certainty of evidence). Outcome: Serious adverse events (3 RCTs): RR 0.74, 95% CI 0.62 to 0.88 (high certainty of evidence). Details on other outcomes can be found in the Summary of findings Table 3.1-1.

kein Unterschied: all-cause mortality

Unterschied bei klinischer Verbesserung und bei Nebenwirkungen

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

Table 3.1-1: Summary of findings table on ***Remdesivir vs Standard care / Placebo*** *(4 RCTs: Wang, Beigel, Spinner, SOLIDARITY-Remdesivir) - https://covid-nma.com/living_data/index.php*

Remdesivir compared to Standard Care/Placebo for Mild/Moderate/Severe/Critical COVID-19

Patient or population: Mild/Moderate/Severe/Critical COVID-19
Setting: Wordwide
Intervention: Remdesivir
Comparison: Standard Care/Placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Standard Care/Placebo	Risk with Remdesivir				
Viral negative conversion D3	292 per 1.000	**284 per 1.000** (178 to 450)	**RR 0.97** (0.61 to 1.54)	196 (1 RCT) [b]	⊕◯◯◯ VERY LOW [c,d,e]	
Viral negative conversion D7	492 per 1.000	**502 per 1.000** (374 to 679)	**RR 1.02** (0.76 to 1.38)	196 (1 RCT) [b]	⊕◯◯◯ VERY LOW [c,d,f]	
Clinical improvement D7	345 per 1.000	**366 per 1.000** (307 to 439)	**RR 1.06** (0.89 to 1.27)	832 (2 RCTs) [g]	⊕⊕⊕◯ MODERATE [f]	
Clinical improvement D14-D28	759 per 1.000	**805 per 1.000** (751 to 858)	**RR 1.06** (0.99 to 1.13)	832 (2 RCTs) [g]	⊕⊕⊕◯ MODERATE [h]	
WHO progression score (level 6 or above) D7	451 per 1.000	**419 per 1.000** (243 to 717)	**RR 0.93** (0.54 to 1.59)	1298 (2 RCTs) [i]	⊕⊕◯◯ LOW [f,j]	
WHO progression score (level 6 or above) D14-D28 - not reported	-	-	-	-	-	outcome not yet measured or reported
WHO progression score (level 7 or above) D7	359 per 1.000	**251 per 1.000** (212 to 294)	**RR 0.70** (0.59 to 0.82)	1298 (2 RCTs) [i]	⊕⊕⊕◯ MODERATE [h]	
WHO progression score level 7 or above D14-28 - not reported	-	-	-	-	-	outcome not yet measured or reported
All-cause mortality D7	63 per 1.000	**43 per 1.000** (18 to 104)	**RR 0.68** (0.28 to 1.64)	1298 (2 RCTs) [i]	⊕◯◯◯ VERY LOW [e,l]	
All-cause mortality D14-D28	112 per 1.000	**101 per 1.000** (82 to 125)	**RR 0.90** (0.73 to 1.11)	7345 (4 RCTs) [m]	⊕⊕⊕◯ MODERATE [f]	
Adverse events	583 per 1.000	**583 per 1.000** (507 to 671)	**RR 1.00** (0.87 to 1.15)	1894 (3 RCTs) [k]	⊕⊕⊕◯ MODERATE [n,o]	
Serious adverse events	252 per 1.000	**186 per 1.000** (156 to 221)	**RR 0.74** (0.62 to 0.88)	1894 (3 RCTs) [k]	⊕⊕⊕⊕ HIGH [o]	

***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: November 6, 2020
b. Wang Y, 2020
c. Risk of bias downgraded by 1 level: some concerns with missing data
d. Indirectness downgraded by 1 level: despite a multicenter design this is a single study from a single country, therefore results in this population might not be generalizable to other settings
e. 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 events
f. 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
g. Spinner CD, 2020; Wang Y, 2020
h. Imprecision downgraded by 1 level: due to low number of events and/or participants
i. Wang Y, 2020; Beigel JH, 2020
j. Inconsistency downgraded by 1 level: $I^2=77\%$
k. Beigel JH, 2020; Spinner CD, 2020; Wang Y, 2020
l. Inconsistency downgraded by 1 level: $I^2=53.1\%$
m. Spinner CD, 2020; SOLIDARITY (Remdesivir), 2020; Beigel JH, 2020; Wang Y, 2020
n. Inconsistency downgraded by 1 level: $I^2=60.2\%$
o. We presume that the adverse event rates, and the corresponding relative risks, are similar across diverse settings; therefore not downgraded for indirectness

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

Remdesivir 5 days compared to Remdesivir 10 days for Mild/Moderate/Critical/Severe Covid-19

Patient or population: Mild/Moderate/Critical/Severe Covid-19
Setting: Worldwide
Intervention: Remdesivir 5 days
Comparison: Remdesivir 10 days

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Remdesivir 10 days	Risk with Remdesivir 5 days				
Incidence of viral negative conversion D7 - not reported	-	-	-	-	-	outcome not yet measured or reported
Incidence of clinical improvement D7	368 per 1.000	**438 per 1.000** (371 to 515)	**RR 1.19** (1.01 to 1.40)	798 (2 RCTs) [b]	⊕⊕◯◯ LOW [c,d]	
Incidence of clinical improvement D14-28	708 per 1.000	**750 per 1.000** (616 to 920)	**RR 1.06** (0.87 to 1.30)	798 (2 RCTs) [b]	⊕◯◯◯ VERY LOW [c,e,f]	
Incidence of WHO progression score (level 6 or above) D14-28	174 per 1.000	**109 per 1.000** (78 to 153)	**RR 0.63** (0.45 to 0.88)	798 (2 RCTs) [b]	⊕⊕◯◯ LOW [c,d]	
Incidence of WHO progression score (level 7 or above) D14-28	146 per 1.000	**85 per 1.000** (58 to 124)	**RR 0.58** (0.40 to 0.85)	798 (2 RCTs) [b]	⊕⊕◯◯ LOW [d,g]	
All-cause mortality D14-28	60 per 1.000	**45 per 1.000** (25 to 81)	**RR 0.74** (0.41 to 1.34)	798 (2 RCTs) [b]	⊕⊕◯◯ LOW [f,g]	
Adverse events	650 per 1.000	**604 per 1.000** (546 to 669)	**RR 0.93** (0.84 to 1.03)	798 (2 RCTs) [b]	⊕⊕⊕◯ MODERATE [c]	
Serious adverse events	196 per 1.000	**126 per 1.000** (92 to 171)	**RR 0.64** (0.47 to 0.87)	798 (2 RCTs) [b]	⊕⊕◯◯ LOW [c,d]	

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

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

GRADE Working Group grades of evidence

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

Explanations

a. 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: $I^2 = 79.3\%$
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

3.2 Lopinavir + Ritonavir (Kaletra®)

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.

wegen erwiesenem Mangel an Wirksamkeit wurde Beobachtung beendet

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

Favipiravir (Avigan®), an antiviral drug, is a new type of RNA-dependent RNA polymerase (RdRp) inhibitor [69, 70].

antivirales Medikament

Favipiravir (Avigan®) has not been approved by the European Medicines Agency (EMA) or the American Food and Drug Administration (FDA) for COVID-19.

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 [62].

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

Withdrawn, suspended or terminated studies

No withdrawn, suspended or terminated RCTs were found in two clinical trial registers (ClinicalTrials.gov and EUdraCT).

Results of publications

Chen C et al. 2020 [71] published results (as preprint) on a RCT (**ChiCTR2000030254**) related to efficacy and safety of favipiravir, **in comparison with umifenovir.** Summary of findings table on favipiravir compared to umifenovir (1 RCT: Chen) is presented in Table 3.3-1.

1 Publikation zu RCT Vergleich mit Umifenovir

Lou Y et al. 2020, published as preprint results of exploratory RCT with 3 arms (**ChiCTR2000029544**) [72] related to the efficacy and safety of favipiravir **in comparison with baloxavir marboxil**, and **lopinavir + ritonavir or darunavir/cobicistat + umifenovir + interferon-a** in hospitalized adult patients with COVID-19. 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.

1 weitere Publikation Vergleich mit Baloxavir marboxil

Summary of findings table on favipiravir compared to baloxavir marboxil is presented in Table 3.3-2 and favipiravir compared to lopinavir + ritonavir or darunavir/cobicistat + umifenovir + interferon-a (1 RCT: Lou 2020) [69] is presented in Table 3.3-3.

Interim results from an adaptive, multicenter, open label, randomized, phase 2/3 clinical trial (**NCT04434248**) of favipiravir (AVIFAVIR) **versus standard of care** (SOC) in 60 hospitalized patients with moderate COVID-19 pneumonia were published (three treatment groups: AVIFAVIR 1600/600 mg, AVIFAVIR 1800/800 mg, or SOC). 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 [73].

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

interim Auswertung orale Verabreichung in Russland „conditional" zugelassen

Dabbous HM et al. 2020 published results, as preprint, from open-label, phase 3 RCT, comparing **favipiravir vs standard care** (hydroxychloroquine plus oseltamivir) in 100 patients with mild to moderate COVID-19 in Egypt (**NCT04349241**) [74]. No statistically significant difference was found related to time to PCR negativity (p=0.7). Four patients in favipiravir group had increase in liver transaminase, and 20 patients in standard care group (hydroxychloroquine plus oseltamivir) developed heartburn and nausea. One patient died in hydroxychloroquine plus oseltamivir group after acute myocarditis resulted in acute heart failure.

Phase 3 RCT (Ägypten) kein Unterschied

Doi et al. 2020 published results from RCT (Japan Registry of Clinical Trials **jRCTs041190120**), related to early versus late favipiravir in hospitalised patients with COVID-19 [75]. 88 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). 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. 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

Zhao H et al. 2020, published results from RCT in moderate to critical COVID-19 patients in China, comparing **favipiravir to tocilizumab and favipiravir plus tocilizumab (ChiCTR2000030096, NCT04310228)** [76]. Patients were randomly assigned (3:1:1) to a 14-day combination of favipiravir combined with tocilizumab (combination group), favipiravir, and tocilizumab. The cumulative lung lesion remission rate at day 14 was significantly higher in combination group as compared with favipiravir group (p = 0.019, HR 2.66 95% CI [1.08 to 6.53]); a significant difference between tocilizumab and favipiravir found also (p = 0.034, HR 3.16, 95% CI 0.62 to 16.10). There was no significant difference between the combination group and the tocilizumab group (p = 0.575, HR 1.28 95%CI 0.39 to 4.23). Combined therapy can also significantly relieve clinical symptoms and help blood routine to return to normal. No serious adverse events were reported.

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

Summary of findings:						
Favipiravir compared to Umifenovir for COVID-19						
Patient or population: COVID-19 **Setting**: Worldwide **Intervention**: Favipiravir **Comparison**: Umifenovir						
Outcomes	**Anticipated absolute effects*** **(95% CI)**		**Relative effect (95% CI)**	**№ 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

Table 3.3-2: Summary of findings table on ***favipiravir compared to baloxavir marboxil*** *(1 RCT: Lou 2020) [69] - https://covid-nma.com/living_data/index.php*

Favipiravir compared to Baloxavir marboxil for Mild/COVID-19

Patient or population: Mild/COVID-19
Setting: Worldwide
Intervention: Favipiravir
Comparison: Baloxavir marboxil

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Baloxavir marboxil	Risk with Favipiravir				
Incidence viral negative conversion D7	600 per 1.000	**402 per 1.000** (162 to 996)	**RR 0.67** (0.27 to 1.66)	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	600 per 1.000	**498 per 1.000** (222 to 1.000)	**RR 0.83** (0.37 to 1.85)	20 (1 RCT)	⊕◯◯◯ VERY LOW [b,c,d]	
Incidence of WHO progression score (level 6 or above D14-D28)	100 per 1.000	**33 per 1.000** (2 to 732)	**RR 0.33** (0.02 to 7.32)	20 (1 RCT)	⊕◯◯◯ VERY LOW [b,c,d]	
Incidence of WHO progression score (level 7 or above D14-D28)	100 per 1.000	**33 per 1.000** (2 to 732)	**RR 0.33** (0.02 to 7.32)	20 (1 RCT)	⊕◯◯◯ VERY LOW [a,b,c]	
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	600 per 1.000	**402 per 1.000** (162 to 996)	**RR 0.67** (0.27 to 1.66)	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 3.3-3: Summary of findings table on favipiravir ***compared to lopinavir + ritonavir or darunavir/cobicistat + umifenovir + interferon-a*** *(1 RCT: Lou 2020) [69] - https://covid-nma.com/living_data/index.php*

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

3.4 Darunavir

About the drug under consideration

Darunavir is an antiviral agent from the group of human immunodeficiency virus (HIV) protease inhibitors for the treatment of HIV-1 infections. Darunavir is combined with a pharmacokinetic booster such as ritonavir or cobicistat [77].

antivirales Medikament

Darunavir (Prezista®) has not been approved by the European Medicines Agency (EMA) or the American Food and Drug Administration (FDA) for COVID-19.

als HIV Medikament zugelassen EMA 2007

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 [62].

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

Withdrawn, suspended or terminated studies

The search in two clinical trial registers (ClinicalTrials.gov and EUdraCT) yielded no suspended, withdrawn or terminated RCTs in COVID-19.

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

Results of publications

Chen J et al. 2020 [78] 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. DRV/c did not increase the proportion of negative conversion vs standard of care 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 findings are presented in Table 3.4-1.

Publikation zu RCT

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

*Table 3.4-1: Summary of findings table on **darunavir/cobicistat compared to standard care** (1 RCT: Chen J) - https://covid-nma.com/living_data/index.php [78]*

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

Patient or population: Moderate COVID-19
Setting: Worldwide
Intervention: Darunavir/cobistat
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, 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. 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®)

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.

wegen erwiesenem Mangel an Wirksamkeit wurde Beobachtung beendet

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

3.7 Camostat Mesilate (Foipan®)

About the drug under consideration

Camostat Mesilate (Foipan®) is classified as a so-called serine protease inhibitor, blocking several pancreatic and plasmatic enzymes like trypsin, thrombin and plasmin [79]. Studies showed effects on the cell-entry mechanism of coronaviruses (e.g. SARS-CoV and SARS-CoV-2) in in-vitro human cells [80, 81] as well as in pathogenic mice-models [82] by inhibiting the enzyme Transmembrane protease, serine 2 (TMPRSS2).

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

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

nicht EMA, FDA
FDA: Orphan Drug Designation seit 2011
vom dt. BMG für schwere Erkrankungen zentral eingekauft

It 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 [83].

Withdrawn, suspended or terminated studies

No withdrawn, suspended or terminated studies were found in ClinicalTrials.gov and EUdraCT registers.

in ClinicalTrials.gov and EUdraCT keine klinischen Studien registriert

Results of publications

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

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

Drug under consideration

APN01 is a recombinant human Angiotensin Converting Enzyme 2 (rhACE2) developed by Apeiron Biologics under Phase 2 clinical development in ALI (Acute Lung Injury) and PAH (Pulmonal arterial hypertension) [84], [85], [86].

aus SARS-Forschung hervorgegangen

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

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

Withdrawn, suspended or terminated studies

One RCT number NCT04287686 is visible as withdrawn (without CDE Approval).

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

Results of publications

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) [87].

keine Publikationen zu klinischen Studien

3.9 Tocilizumab (Roactemra®)

Drug under consideration

Tocilizumab (*RoActemra*) is a human monoclonal antibody that specifically binds to soluble and membrane-bound interleukin (IL)-6 receptors (IL-6Rα), and inhibits IL-6-mediated signalling [88].

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

Tocilizumab is being investigated as a possible treatment for patients with moderate to severe or critical COVID-19. The therapy is currently not approved by the European Medicine Agency (EMA) and Food and Drug Administraion (FDA) for COVID-19.

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 [62], except in a clinical trial.

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

Withdrawn, suspended or terminated studies

One withdrawn RCT (NCT04361552, in US, abandoned due to drug billing issues) and four terminated RCTs were found in ClinicalTrials.gov and EudraCT registers: NCT04346355, in Italy, based on interim analysis for futility and given an enrolment rate almost nil; RCT on 129 patients in Brazil compared tocilizumab vs best supportive care NCT04403685 (TOCIBRAS) due to safety issue; RCT NCT04322773, TOCIVID trial, due to changed clinical conditions and too few patients available; RCT NCT04335071 (CORON-ACT) in Switzerland because dexamethasone was included in the standard care and planned number of patients was not possible to recruit in the planned study period) .

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

Results of publications

Rosas et al. 2020 [96] reported results from the phase 3, RCT - **COVACTA** (**NCT04320615, EUdraCT 2020-001154-22**) as preprint: 452 patients with severe COVID-19 pneumonia 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.

COVACTA
4RCT, 52 Pts
schwere Erkrankung

kein Unterschied bei Mortalität, aber kürzer Zeit zur Erholung

Wang et al. 2020 [97] reported, as preprint, results from a small randomized, controlled, open-label, multicenter trial at 6 hospitals in Anhui and Hubei (**ChiCTR2000029765**). 65 moderate to severe patients were enrolled and randomly assigned to a treatment group (33 to tocilizumab and 32 to the controls). 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.

Wang (China)
65 Pts
schwere Erkrankung

Salama et al. 2020 [98], reported as preprint, results from the phase III **EMPACTA** study (**NCT04372186**) (389 patients in the United States, South Africa, Kenya, Brazil, Mexico and Peru), showing that patients with COVID-19 associated pneumonia who received 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 tocilizumab arm versus 19.3% in the placebo arm. 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 tocilizumab and placebo arms, respectively, and the incidence of serious infections was 5.0% and 6.3% in tocilizumab and placebo arms, respectively. The most common adverse events in patients who received tocilizumab were constipation (5.6%), anxiety (5.2%), and headache (3.2%).

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

Vorteil bei Verhinderung im Fortschreiten der Erkrankung

bei weiteren Endpunkten: kein Unterschied

Hermine et al. 2020 [99] published the results from multicentre **CORIMUNO-TOCI-1** RCT (**NCT04331808**), which included 131 moderate to severe COVID-19 patients (63 treated with tocilizumab, others in usual care group) in France, with follow-up through 28 days. In the TCZ group, 12 patients had a WHO-CPS score greater than 5 at day 4 vs 19 in the UC group (median posterior absolute risk difference [ARD] -9.0%; 90% credible interval [CrI], -21.0 to 3.1), with a posterior probability of negative ARD of 89.0% not achieving the 95% predefined efficacy threshold. At day 14, 12% (95% CI -28% to 4%) fewer patients needed noninvasive ventilation (NIV) or mechanical ventilation (MV) or died in the TCZ group than in the UC group (24% vs 36%, median posterior hazard ratio [HR] 0.58; 90% CrI, 0.33-1.00), with a posterior probability of HR less than 1 of 95.0%, achieving the predefined efficacy threshold. The HR for MV or death was 0.58 (90% CrI, 0.30 to 1.09). At day 28, 7 patients had died in the TCZ group and 8 in the UC group (adjusted HR, 0.92; 95% CI 0.33-2.53). Serious adverse events occurred in 20 (32%) patients in the TCZ group and 29 (43%) in the UC group (p=0.21).

CORIMUNO-TOCI-1
131 Pts.
moderate bis schwere Erkrankung

Vorteil bei Bedarf nach Beatmung
kein Unterschied bei Mortalität

Salvarani et al. 2020 [100] published results from multicentre RCT (**RCT-TCZ-COVID-19**) (**NCT04346355**) conducted on 126 severe COVID-19 patients in Italy (60 received tocilizumab). Seventeen patients of 60 (28.3%) in the tocilizumab arm and 17 of 63 (27.0%) in the standard care group showed clinical worsening within 14 days since randomization (rate ratio, 1.05; 95% CI, 0.59-1.86). Two patients in the experimental group and 1 in the control group died before 30 days from randomization, and 6 and 5 patients were intubated in the 2 groups, respectively. The trial was prematurely interrupted after an interim analysis for futility.

RCT-TCZ-COVID-19
126 Pts
schwere Erkrankung

kein Unterscheid, frühzeitiger Studienabbruch

Stone et al. 2020 [101] published results from multicentre RCT (**NCT04356937**) conducted on 243 moderate to severe COVID-19 patients in US (161 received tocilizumab). The hazard ratio for intubation or death in the tocilizumab group vs placebo group was 0.83 (95% confidence interval [CI], 0.38 to 1.81; p=0.64), and the hazard ratio for disease worsening was 1.11 (95% CI, 0.59 to 2.10; p=0.73). At 14 days, 18.0% of the patients in the tocilizumab group and 14.9% of the patients in the placebo group had worsening of disease. The median time to discontinuation of supplemental oxygen was 5.0 days (95% CI, 3.8 to 7.6) in the tocilizumab group vs 4.9 days (95% CI, 3.8 to 7.8) in the placebo group (p=0.69). At 14 days, 24.6% of the patients in the tocilizumab group and 21.2% of the patients in the placebo group were still receiving supplemental oxygen. Patients who received tocilizumab had fewer serious infections than patients who received placebo.

RCT 243
moderate bis schwere Erkrankung

keine oder klaum Unterschiede in einigen Endpunkten

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 [102].

Tocilizumab auch in RECOVERY
850 Pts

Meta-analysis with Summary of findings table on tocilizumab compared to standard of care (related to **6 RCTs**) is presented in Table 3.9-1. In all outcomes presented, including All-cause mortality, there was no statistically significant diference in risk ratio between tocilizumab and standard care/placebo group.

Table 3.9-1: Summary of findings table on ***tocilizumab compared standard care/placebo*** *(6 RCTs: Rosas, Wang, Hermine, Salvarani, Stone, Salama)*

Tocilizumab compared to Standard care/Placebo for Mild/Moderate/Severe/Critical COVID-19

Patient or population: Mild/Moderate/Severe/Critical COVID-19
Setting: Worldwide
Intervention: Tocilizumab
Comparison: Standard care/Placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Standard care/Placebo	Risk with Tocilizumab				
Incidence of viral negative conversion D7 - not reported	-	-	-	-	-	outcome not yet measured or reported
Clinical improvement D7 - not measured	-	-	-	-	-	outcome not yet measured or reported
Clinical improvement D14-28	897 per 1.000	**906 per 1.000** (843 to 977)	**RR 1.01** (0.94 to 1.09)	366 (2 RCTs) [b]	⊕⊕◯◯ LOW [c,d]	
Incidence of WHO progression score (level 6 or above) D7	537 per 1.000	**483 per 1.000** (419 to 564)	**RR 0.90** (0.78 to 1.05)	582 (2 RCTs) [e]	⊕⊕⊕◯ MODERATE [d]	
Incidence of WHO progression score (level 6 or above) D14-D28	381 per 1.000	**308 per 1.000** (247 to 392)	**RR 0.81** (0.65 to 1.03)	582 (2 RCTs) [e]	⊕⊕⊕◯ MODERATE [d]	
Incidence of WHO progression score (level 7 or above) D7	399 per 1.000	**347 per 1.000** (247 to 487)	**RR 0.87** (0.62 to 1.22)	582 (2 RCTs) [e]	⊕⊕⊕◯ MODERATE [d]	
Incidence of WHO progression score (level 7 or above) D14-D28	312 per 1.000	**278 per 1.000** (209 to 371)	**RR 0.89** (0.67 to 1.19)	582 (2 RCTs) [e]	⊕⊕⊕◯ MODERATE [d]	
All-cause mortality D7	73 per 1.000	**83 per 1.000** (42 to 164)	**RR 1.14** (0.58 to 2.25)	452 (1 RCT) [f]	⊕⊕◯◯ LOW [g]	
All-cause mortality D14-D28	104 per 1.000	**114 per 1.000** (83 to 156)	**RR 1.1** (0.8 to 1.5)	1327 (5 RCTs) [h]	⊕⊕◯◯ LOW [d,i]	
Adverse events	124 per 1.000	**241 per 1.000** (71 to 825)	**RR 1.94** (0.57 to 6.64)	431 (3 RCTs) [j]	⊕◯◯◯ VERY LOW [c,g,k,l]	
Serious adverse events	442 per 1.000	**384 per 1.000** (322 to 464)	**RR 0.87** (0.73 to 1.05)	1392 (6 RCTs) [m]	⊕⊕◯◯ LOW [c,d,i]	

***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: November 6, 2020
b. Stone JH, 2020; Salvarani C, 2020
c. Risk of bias downgraded by 1 level: some concerns or high risk regarding deviations from intended interventions, randomization, and outcome measurement
d. Imprecision downgraded by 1 level: due to low number of events and participants
e. Hermine O, 2020; Rosas I, 2020
f. Rosas I, 2020
g. Imprecision downgraded by 2 levels: due to low number of events and a wide confidence interval consistent with the possibility for benefit and the possibility for harm
h. Stone JH, 2020; Hermine O, 2020; Rosas I, 2020; Salama C, 2020; Salvarani C, 2020
i. Risk of bias downgraded by 1 level: some concerns or high risk regarding deviations from intended interventions and randomization
j. Stone JH, 2020; Wang D, 2020; Salvarani C, 2020
k. Inconsistency downgraded by 1 level: unexplained statistical heterogeneity (I-sq = 83.5%)
l. We presume that the adverse event rates, and the corresponding relative risks, are similar across diverse setting

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 [105]. It is being investigated as a possible treatment for patients with moderate to severe or critical COVID-19. The therapy is currently not approved by the European Medicine Agency (EMA) and Food and Drug Administraion (FDA) for 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 [62], except in a clinical trial.

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

Withdrawn, suspended or terminated studies

One RCT found as suspended, NCT04341870 - CORIMUNO-VIRO Trial (DSMB recommendation (futility)). One RCT found as terminated, NCT04322773 (TOCIVID) in Denmark, due to changed clinical conditions and too few patients available).

Results of publications

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 194 critically ill Covid-19 patients who required mechanical ventilation in the US. In the primary analysis arm, adverse events were reported in 80% of patients treated with sarilumab and 77% of those on placebo. Serious adverse events in at least 3% of patients, more frequent among sarilumab patients, were multi-organ dysfunction syndrome and hypotension. Based on the data, the companies have halted this US-based trial, including a second cohort of patients who were on a higher 800mg dose of the drug. The trial being conducted outside of the US is continuing, in hospitalised patients with severe and critical Covid-19 using a different dosing regimen.

Juli 2020: Pressemeldung zu RCT mit 194 Pts

kein Unterschied
mehr SAE in Sarilumab Gruppe

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

About the drug under consideration

Interferon beta-1a (INFb) is a cytokine in the interferon family used to treat relapsing multiple sclerosis (MS). Finding of studies in patients with MERS-CoV have led to exploration of treatment with INFb in COVID-19 [110].

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) [111, 112]. 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 [62] **recommends against** use of the **interferons (alfa or beta)** for the treatment of **severely or critically ill** patients with COVID-19, except in the context of a clinical trial (AIII).

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

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

Withdrawn, suspended or terminated studies

One RCT was found as suspended, NCT04469491 (COV-NI), on interferon beta 1b by nebulization in France (in anticipation for Data and Safety Monitoring Board).

Results of publications

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 [113].

Kombinationstherapie: Ergebnisse in 3.14

Results from **Huang et al. 2020** (**ChiCTR2000029387**) [114] 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

Esquivel-Moynelo et al. 2020 [116] presented the results from a RCT for efficacy and safety evaluation of subcutaneous IFN -α2b and IFNγ administration in 79 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). None of the patients developed severe COVID-19 during the study or the epidemiological follow-up for 21 more days.

1 RCT
79 Pts.
Kombinationstherapie IFN (unterscheidliche Dosierungen) + Kaletra

79 symptomatische/ asymptomatische Pts.

Monk et al. 2020 published results from randomised, double-blind, placebo-controlled, phase 2 pilot trial at nine UK sites (NCT04385095) [117]. 101 COVId-19 hospitalized adult patients were randomly assigned (1:1) to receive **inhaled nebulised interferon beta-1a** (SNG001) (6 MIU) or placebo by

1 RCT
101 Pts
inhaltiertes INF

inhalation via a mouthpiece daily for 14 days. 66 (67%) patients required oxygen supplementation at baseline: 29 in the placebo group and 37 in the SNG001 group. Patients receiving SNG001 had greater odds of improvement on the OSCI scale (odds ratio 2·32 [95% CI 1·07–5·04]; p=0·033) on day 15 or 16 and were more likely than those receiving placebo to recover to an OSCI score of 1 (no limitation of activities) during treatment (hazard ratio 2·19 [95% CI 1·03–4·69]; p=0·043). No significant difference was found between treatment groups in the odds of hospital discharge by day 28: 39 (81%) of 48 patients had been discharged in the nebulised interferon beta-1a group compared with 36 (75%) of 48 in the placebo group (OR 1·84 [95% CI 0·64–5·29]; p=0·26). There was no significant difference between treatment groups in the odds of intubation or the time to intubation or death. SNG001 was well tolerated: the most frequently reported treatment-emergent adverse event was headache (seven [15%] patients in the SNG001 group and five [10%] in the placebo group). There were three deaths in the placebo group and none in the SNG001 group.

Vorteil bei klinischen Verbesserungen, nicht aber bei Dauer des Spitalsaufenthalts

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 (IRCT20100228003449N28) [115]. 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 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).

RCT (Iran)
92 Pts

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

Rahmani et al. 2020 [118] published the results of RCT evaluated efficacy and safety of interferon (IFN) β-1b in the treatment of 80 patients with severe COVID-19 (IRCT20100228003449N27). 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). 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).

RCT (Iran)
80 Pts
Zeit zur klinischen Verbesserung signifikant kürzer mit IFN, weniger ICU Einweisungen

nicht aber Dauer der Hospitalisierung und in ICU

In SOLIDARITY (INF) RCT (ISRCTN83971151) results on comparisons of subcutaneous interferon beta-1a vs standard care in patients with mild to critical COVID-19 admitted to 405 centers in 30 countries were published as preprint [68]. In 11,266 adults were randomized, with 2750 allocated remdesivir, 954 hydroxychloroquine, 1411 lopinavir, 651 interferon plus lopinavir, 1412 only interferon, and 4088 no study drug. Death rate ratio for interferon was not statistically significant different in comparision with control group: RR=1.16 (0.96-1.39, p=0.11; 243/2050 vs 216/2050) (or 1.12, 0.83-1.51, without lopinavir co-administration). The same is true for outcomes Initiation of ventilation or Hospitalisation duration.

SOLIDARITY
651 Pts INF + lopinavir, 1.412 Pts. nur INF

keine Unterscheide bei den Endpunkten

Summary of Findings table related to **meta-analysis** on results of **3 RCTs** (Davoudi-Monfared, Rahmani, SOLIDARITY-INF), on 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 were all statisticaly significant better in favour of interferon beta-1a, but not outcome All-cause mortality D14-28: RR 0.68 (95%CI 0.32 to 1.45).

sehr niedrige Evidenz: bei Mortalität signifikante Vorteile

Table 3.11-1: Summary of findings table on ***Interferon β-1a compared to Standard Care for Moderate/Severe/Critical COVID-19*** *(3 RCTs: Davoudi-Monfared, Rahmani, SOLIDARITY-INF) – https://covid-nma.com/living_data/index.php*

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

Patient or population: Moderate/Severe/Critical COVID-19
Setting: Worldwide
Intervention: Interferon β
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				
Viral negative conversion - 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 [c,d,e]	
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 [e,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 [e,f,g]	
All-cause mortality D14-D28	112 per 1,000	**76 per 1,000** (36 to 163)	**RR 0.68** (0.32 to 1.45)	4265 (3 RCTs) [i]	⨁◯◯◯ VERY LOW [g,j,k]	
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: November 10, 2020
b. Davoudi-Monfared E, 2020; Rahmani H, 2020
c. Risk of bias downgraded by 2 levels: some concerns regarding adequate randomization, outcome measurement and selection of reported results, and high risk regarding deviations from intended interventions and missing data
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 2 levels: due to wide confidence interval consistent with the possibility for benefit and the possibility for harm and low number of participants and 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 regarding adequate randomization and selection of reported results, and high risk regarding deviations from intended interventions and missing data
h. Imprecision downgraded by 1 level: due to wide confidence interval consistent with the possibility for benefit and the possibility for no effect and low number of participants and events
i. Davoudi-Monfared E, 2020; Rahmani H, 2020; SOLIDARITY, 2020
j. Inconsistency downgraded by 1 level: $I^2=71.2\%$
k. Imprecision downgraded by 2 levels: due to wide confidence interval consistent with the possibility for benefit and the possibility for harm

3.12 Convalescent plasma transfusion

About the treatment under consideration

Convalescent plasma is plasma collected from patients that have recovered from an infectious disease and can be transfused to patients fighting an infection or can be used to manufacture immune globulin concentrates (plasma derived medicinal products). Possible explanations for the efficacy are that the antibodies from convalescent plasma might suppress viraemia and activate the complement system, thus promoting viral elimination. Antibody is most effective when administered shortly after the onset of symptoms, and a sufficient amount of antibody must be administered. Plasma transfusions may be associated with transfusion reactions such as allergic reactions, antibody-mediated enhancement of infection, transfusion-related acute lung injury (TRALI) and circulatory overload [119-121]. Rare complications include the transmission of infectious pathogens and red cell alloimmunization.

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

auch zur Herstellung von Immunglobulin-konzentraten verwendet

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 [122, 123]. 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 [122]. 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 [123, 124].

EMA & FDA Guidance zu CVP

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 [126].

FDA im August 2020: Emergency Authorization

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 (last update October 9, 2020) [127].

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

Withdrawn, suspended or terminated studies

1 RCT was found as withdrawn in US, NCT04467151 (did not obtain funding to proceed) and 1 RCT found as terminated in Italy, NCT04393727, the Promoter was changed and a new study promoted by AIFA started).

Results of publications

Li et al. 2020 published results from RCT (**ChiCTR200029757**) [131] conducted in 103 patients with COVID-19 (severe to critical) admitted to 7 centers in China. 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,

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

keine Unterschiede bei Endpunkten

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.

Gharbharan et al. 2020 [132], published results as **preprint,** from prematurely **halted RCT** (**NCT04342182**), performed on 86 patients with COVID-19 (moderate-critical) admitted to 14 centers in the Netherlands [132].

RCT (Niederlande): 86 Pts.,

Avendano-Sola et al. 2020 published as **preprint,** results of multi-center RCT (**NCT04345523**) [135]: 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.

Sept 2020: Publikation zu RCT CVP vs. SOC

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

Agarwal et al. 2020 [136] [137] reported 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 (progression to severe disease or all cause mortality at 28 days) was achieved in 44 (19%) participants in the intervention arm and 41 (18%) in the control arm (risk difference 0.008 (95% confidence interval -0.062 to 0.078); risk ratio 1.04, 95% confidence interval 0.71 to 1.54

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

kein Unterschied bei Mortalität oder Fortschreiten der Krankheit

The **Living Systematic Review with meta-analysis**, related to these **four RCTs** mentioned above, Li et al. 2020 [131], Gharbharan et al. 2020 [132], Avendano-Sola et al. 2020 [141] and Agarwal et al. 2020 [136] with **Summary of findings table** is provided in Table 3.12-2.

In summary, risk ration related to all outcomes listed was not statisticaly significant different between convalescent plasma and standard care.

Balcells et al. 2020 [138] reported, as preprint, results from open-label, single-center, randomized clinical trial performed in an academic center in Santiago, Chile, including 58 patients (NCT04375098). 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% 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.

preprint RCT (open-label) Chile 58 Pts

kein Unterschied bei Mortalität, Dauer des Krankenhausaufenthalts und künstlicher Beatmung

Table 3.12-1: Summary of findings table on ***Convalescent plasma compared to Standard Care for Mild/Moderate/Severe/Critical COVID-19*** *(4 RCTs: Li, Gharbharan, Avendano-Sola, Agarwal) [131],[149], [141], [136]*

Convalescent plasma compared to Standard Care for Mild/Moderate/Severe/Critical COVID-19

Patient or population: Mild/Moderate/Severe/Critical COVID-19
Setting: Worldwide
Intervention: Convalescent plasma
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 Convalescent plasma				
Incidence of viral negative conversion D7	448 per 1.000	**569 per 1.000** (484 to 672)	**RR 1.27** (1.08 to 1.50)	536 (2 RCTs) [b]	⊕⊕◯◯ LOW [c,d]	
Incidence of clinical improvement D7	98 per 1.000	**96 per 1.000** (29 to 313)	**RR 0.98** (0.30 to 3.19)	103 (1 RCT) [e]	⊕◯◯◯ VERY LOW [f,g,h]	
Incidence of clinical improvement D14-D28	500 per 1.000	**540 per 1.000** (415 to 710)	**RR 1.08** (0.83 to 1.42)	189 (2 RCTs) [i]	⊕◯◯◯ VERY LOW [j,k]	
WHO progression score level 6 or above D7	47 per 1.000	**27 per 1.000** (2 to 279)	**RR 0.57** (0.05 to 5.99)	81 (1 RCT) [l]	⊕◯◯◯ VERY LOW [g,h,m]	
WHO progression score level 6 or above D14-28	70 per 1.000	**11 per 1.000** (1 to 211)	**RR 0.16** (0.01 to 3.02)	81 (1 RCT) [l]	⊕◯◯◯ VERY LOW [g,h,m]	
WHO progression score level 7 or above D7	47 per 1.000	**27 per 1.000** (2 to 279)	**RR 0.57** (0.05 to 5.99)	81 (1 RCT) [l]	⊕◯◯◯ VERY LOW [g,h,n]	
WHO progression score level 7 or above D14-28	23 per 1.000	**9 per 1.000** (0 to 209)	**RR 0.38** (0.02 to 8.97)	81 (1 RCT) [l]	⊕◯◯◯ VERY LOW [g,h,n]	
All-cause mortality D7	70 per 1.000	**11 per 1.000** (1 to 211)	**RR 0.16** (0.01 to 3.02)	81 (1 RCT) [l]	⊕◯◯◯ VERY LOW [g,h,n]	
All-cause mortality D14-D28	245 per 1.000	**147 per 1.000** (81 to 269)	**RR 0.60** (0.33 to 1.10)	189 (2 RCTs) [i]	⊕⊕◯◯ LOW [k,o]	
Adverse events	0 per 1.000	**0 per 1.000** (0 to 0)	**RR 2.94** (0.12 to 70.61)	103 (1 RCT) [e]	⊕◯◯◯ VERY LOW [f,h,p]	zero events in control group
Serious adverse events	0 per 1.000	**0 per 1.000** (0 to 0)	**RR 2.94** (0.12 to 70.61)	103 (1 RCT) [e]	⊕◯◯◯ VERY LOW [f,h,p]	zero events in control group

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

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

GRADE Working Group grades of evidence

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

Explanations

a. Last update: September 18, 2020
b. Agarwal A, 2020; Avendaño-Solà, 2020
c. Risk of bias downgraded by 1 level: some concerns or high risk due to concerns during the randomization process, deviation from intended intervention, missing data and selection of reported results
d. Imprecision downgraded by 1 level: due to low number of events and/or participants
e. Li L, 2020
f. Risk of bias downgraded by 1 level: some concerns or high risk due to concerns during the randomization process, deviation from intended intervention and outcome measurement
g. Indirectness downgraded by 1 level: despite a multicenter design it's a single study from a single country, therefore results in this population might not be generalizable to other settings
h. 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
i. Gharbharan A, 2020; Li L, 2020
j. 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 outcome measurement
k. 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
l. Avendaño-Solà, 2020
m. Risk of bias downgraded by 1 level: some concerns due to concerns during the randomization process, deviation from intended intervention, outcome measurement and selection of reported results
n. Risk of bias downgraded by 1 level: some concerns due to concerns during the randomization process, deviation from intended intervention and selection of reported results
o. Risk of bias downgraded by 1 level: some concerns or high risk due to concerns during the randomization process, deviation from intended intervention and missing data
p. We presume that the adverse event rates, and the corresponding relative risks, is similar across diverse settings; therefore not downgraded for indirectness

3.13 Plasma derived medicinal products

Neutralizing monoclonal antibodies

As Marovich et al. 2020 [139] 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.

neutralisierende monoklonale Antikörper: Prävention und Behandlung

Halbwertszeit bis 3 Wochen von Vorteil

Nachteil: unbekannte Bioverfügbarkeit der infundierten Antikörper

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 [139].

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

REGN-COV2 is combination of two monoclonal antibodies (REGN10933 and REGN10987) which 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.

A **phase 3 prevention trial** evaluates 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) 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.

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

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.

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

On September 14, 2020 the University of Oxford and Regeneron Pharmaceuticals, Inc. announced that **RECOVERY** (Randomised Evaluation of COVid-19 thERapY 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-

Sept 2020: RECOVERY nimmt REGNCOV2 als Studienmedikament auf

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.

Results of publication

On Oct 28, 2020 Regeneron Pharmaceuticals, Inc. announced **positive results** from an **ongoing phase 2/3 RCT** in the COVID-19 **outpatient setting** (ambulantory patients, n=799) on their website; the trial met the primary and key secondary endpoints. REGN-COV2 significantly reduced viral load and patient medical visits (hospitalizations, emergency room, urgent care visits and/or physician office/telemedicine visits), by 57% through day 29 (2.8% combined dose groups; 6.5% placebo; p=0.024) and by 72% in patients with one or more risk factor (including being over 50 years of age; body mass index greater than 30; cardiovascular, metabolic, lung, liver or kidney disease; or immunocompromised status) (combined dose groups; nominal p = 0.0065). Manufacturer will submit detailed results from this trial for publication, https://www.prnewswire.com/news-releases/regenerons-covid-19-outpatient-trial-prospectively-demonstrates-that-regn-cov2-antibody-cocktail-significantly-reduced-virus-levels-and-need-for-further-medical-attention-301162255.html.

Phase 2/3 RCT
799 ambulante Pts.

Firmenankündigung zu positive Efekten

Endpunkte:
Reduktion der Viruslast
Artzt-/ Notfall-/ Spitalsbesuche

Safety issue

On 30 October 2020, Regeneron Pharmaceuticals, Inc. received a recommendation from the independent data monitoring committee (IDMC) for the REGN-COV2 antibody cocktail treatment trials for COVID-19 that the current hospitalized patient trial be modified. Specifically, based on a potential safety signal and an unfavorable risk/benefit profile at this time, the IDMC recommends further enrollment of patients requiring high-flow oxygen or mechanical ventilation be placed on hold pending collection and analysis of further data on patients already enrolled. The IDMC also recommends continuing enrollment of hospitalized patients requiring either no or low-flow oxygen as the risk/benefit remains acceptable in these cohorts. Finally, the IDMC recommends continuation of the outpatient trial without modification, https://investor.regeneron.com/news-releases/news-release-details/regn-cov2-independent-data-monitoring-committee-recommends.

Sicherheitswarnung für Kohorte hospitalisierte und künstlich beatmete Pts.

Regulatory update: The U.S. FDA is reviewing an Emergency Use Authorization submission for the REGN-COV2 low dose in adults with mild-to-moderate COVID-19 who are at high risk for poor outcomes.

FDA: Prüfung von REGN-COV2 für EUA

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

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.

2 weitere mAb:
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)

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.

LY-CoV555: Phase 1

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.

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

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

BLAZE-2: RCT, Phase 3
initiiert

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.

NIH-Studien: ACTIV-2 and
ACTIV-3

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

pragmatic trial planned
by Eli Lilly

Results of publications

Chen et al. 2020 [140] published interim analysis results of BLAZE-1, phase 2 **RCT (NCT04427501),** in 452 mild or moderate Covid-19 patients. One of three doses of neutralizing antibody LY-CoV555 appeared to accelerate the natural decline in viral load over time, whereas the other doses had not by day 11: 2800-mg dose of LYCoV555, the difference from placebo in the decrease from baseline was -0.53 (95% confidence interval [CI], -0.98 to -0.08; p=0.02. On days 2 to 6, the patients who received LY-CoV555 had a slightly lower severity of symptoms than those who received placebo. The percentage of patients who had a Covid-19–related hospitalization or visit to an emergency department was 1.6% in the LY-CoV555 group and 6.3% in the placebo group. In a post hoc analysis that was focused on high-risk subgroups (an age of ≥65 years or a BMI of ≥35), the percentage of hospitalization was 4.2% in the LY-CoV555 group and 14.6% in the placebo group. The safety outcomes were similar in intervention and placebo groups.

Phase 2 RCT
452 Pts.
milde/moderate
Erkrankung

Vorteil bei Endpunkten:
Reduktion der Viruslast
Artzt-/ Notfall-/
Spitalsbesuche

On October 7, 2020 Eli Lilly and Company **announced** data from an 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 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.

BLAZE-1
268 Pts,
Zwischenauswertung

Vorteil bei Endpunkten:
Reduktion der Viruslast
Artzt-/ Notfall-/
Spitalsbesuche

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 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). Combination therapy has been generally well tolerated with no drug-related serious adverse events.

Ergebnisse in
Kombinationstherapie
gleich wie in
Monotherapie
LY-CoV555

Regulatory update:

On November 9, 2020, the **U.S. Food and Drug Administration** issued an **Emergency Use Authorization (EUA)** for the investigational monoclonal antibody therapy **bamlanivimab (previously LY-CoV555)** for the treatment of mild-to-moderate COVID-19 in adult and pediatric patients. Bamlanivimab is authorized for patients with positive results of direct SARS-CoV-2 viral testing who are 12 years of age and older weighing at least 40 kilograms (about 88 pounds), and who are at high risk for progressing to severe COVID-19 and/or hospitalization. This includes those who are 65 years of age or older, or who have certain chronic medical conditions, https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-monoclonal-antibody-treatment-covid-19. Bamlanivimab is not authorized for patients who are hospitalized due to COVID-19 or require oxygen therapy due to COVID-19. A benefit of bamlanivimab treatment has not been shown in patients hospitalized due to COVID-19. Monoclonal antibodies, such as bamlanivimab, may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation.

November: FDA EUA für bamlanivimab

für ambulante Pts mit Risiko auf Verschlechterung

Nicht für bereits hospitalisierte Pts.

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

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.

AZD7442 Kombination aus 2 monoklonalen Antikörpern Vanderbilt University/ AstraZeneca

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 1 Ende Sept 2021

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-and-treatment-of-covid-19.html.

Phase 2 & 3 in Vorbereitung

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

Hung et al. 2020 [113] 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). 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.

Reduktion der Dauer der Virusausscheidung, Symtomverbesserung, Dauer des Krankenhausaufenthalts

kein Unterschied bei AE keine Todesfälle in beiden Gruppen

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 3.14-1.

keine weiteren RCTs publiziert

Huang et al. 2020 [114] 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 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.

RCT: 101 Pts

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

kein Unterschied

Chinese RCT published by **Zheng et al. 2020** [141, 142] 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.

RCT (China)
89 Pts.

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

bessere Ergebnisse in IFN Gruppen

The **Living Systematic Review**, related to this RCT mentioned above, with **Summary of findings table** is provided in Table 3.14-1 continued.

Li C et al. 2020 [143] 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.

Okt 2020:
preprint RCT
China
94 Pts.

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

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.

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

Table 3.14-1: 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 3.14-1 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

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.

Medikament gegen akutes Atemnotsyndrom

Verabreichung: Inhalation

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

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

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

EC-Grant seit April für covid-19

bis Dezember 2021

One ongoing randomised, double-blind, placebo controlled, parallel assignment trial with aim to assess efficacy and safety of 7 days orally inhaled 100 mg solnatide to treat pulmonary permeability oedema of 40 SARS-Cov-2 positive patients with moderate-to-severe ARDS is registered in EUdraCT register (EudraCT number 2020-001244-26), https://www.clinicaltrialsregister.eu/ctr-search/trial/2020-001244- 26/AT [144].

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

Withdrawn, suspended or terminated studies

No withdrawn, suspended or terminated studies related to solnatide in COVID-19 patients were found in ClinicalTrials.gov and EUdraCT registers [144].

ClinicalTrials.gov & EUdraCT: keine klinischen Studien registriert,

Results of publications

keine Publikation von RCT

No publications related to the RCTs of solnatide in COVID-19 patients were found [144].

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 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

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) [145].

1 in vitro Publikation

Withdrawn, suspended or terminated studies

No 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**) [147] 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 [147].

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

kein Unterschied zwischen den Gruppen in einigen Surrogatendpunkten

mehr AE

One publication [71] on the completed RCT (**ChiCTR2000030254**) about the efficacy and safety of favipiravir, in comparison with umifenovir, to treat Covid-19 patients was identified; Summary of findings table can be found in Section related to favipiravir.

1 RCT nur im preprint (nicht peer-reviewed)

RCT (**IRCT20180725040596N2**) published by **Nojomi et al. 2020**, as preliminary report in the format of preprints [148], is an open label randomized controlled trial, on effectiveness of umifenovir on 100 patients with COVID-19, 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 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 similar across two groups (2.7 versus 3.1 days in umifenovir and lopinavir-ritonavir arms respectively). Peripheral oxygen saturation rate was different

Okt 2020: RCT (Iran) 100 Pts.

in Kombinationstherapie kleine Vorteile

after seven days of admission across two groups significantly (94% versus 92% in umifenovir and lopinavir-ritonavir groups respectively) (p=0.02).

November 2020
RCT, 30 Pts. Kirgistan

Yethindra et al. 2020 [149] published results from exploratory randomized controlled study recruited 30 mild and moderate COVID-19 patients in Kyrgyzstan. No patient progressed toward severe and critical illness in either category. Pneumonia was ameliorated in 76.6% (23/30) of the patients, with moderate and potential amelioration in 36.6% and 40% of the patients, respectively. Many patients were observed to have significantly ameliorated pneumonia in the umifenovir category (86.6%, 13 of 15) compared to the control category (66.6%, 10 of 15). In addition, 66.6% of patients in the umifenovir category had potential pneumonia absorption. Only one patient presented with mild side effects in the umifenovir category, while one patient had cephalalgia; notably, no patient experienced severe side effects.

The Living Systematic Review, related to these two RCTs mentioned above, with Summary of findings table (https://covid-nma.com/living_data/index.php) is underway.

3.17 Dexamethasone and other corticosteroids

About the drug under consideration

Glukokortikoide: entzündungshemmend

Dexamethasone is a long-acting glucocorticoid which is used principally as an anti-inflammatory or immunosuppressant agent. 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 [153, 154].

nationale, nicht EMA 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. The UK has approved dexamethasone for the treatment of Covid-19 on June 16, 2020 [156].

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 [157].

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 dexamethasone study arm. 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. 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 [158].

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)** [62]. If dexamethasone is not available, the Panel **recommends using** alternative glucocorticoids such as **prednisone**, **methylprednisolone**, or **hydrocortisone (AIII)** [61]. For more details, see also section on remdesivir.

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

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** [160, 161].

WHO-Empfehlung für Pts. mit schwerer oder kritischer Erkrankung

Withdrawn, suspended or terminated studies

Two RCTs were found as terminated: RCT - NCT04327401 (CoDEX), related to dexamethasone, 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. NCT04344288 (CORTI-Covid) on prednisone in France, terminated due Competent Authority decision. 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 [32]. 1 RCT in US (NCT04360876) is withdrawn because funding not received.

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

1 eingestellter RCT – wegen Magel an Rekrutierung

Results of publications

The RCT with the largest number of included COVID-19 patients is RCTs of dexamethasone arm of the **RECOVERY trail** in Covid-19 patients (**NCT04381936, EudraCT 2020-001113-21**) [164]. The primary outcome was all-cause mortality within 28 days after randomization; further analyses were specified at 6 months.

größter RCT: RECOVERY

2.104 Pts

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

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

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 [163, 164].

The **CoDEX trial** (**NCT04327401**) 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 and other secondary outcomes [162, 169].

CoDEX
299 Pt (Brasilien)

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

The **CAPE COVID trial** (**NCT02517489**) 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) [165, 169].

CAPE COVID
149 Pts (Frankreich)
bessere Ergebnisse mit hydrocortisone

The **REMAP-CAP trial** (**NCT02735707**), 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 [166, 169].

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

MetCOVID trial (**NCT04343729**) 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. 416 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. 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 [167].

MetCOVID
418 Pts (Brasilien)
methylprednisolone

kein Unterschied zwischen Gruppen bei Mortalität methylprednisolone

Subgruppenanalyse: >60 Jahre bessere Ergebnisse

GLUCOCOVID trial (**EudraCT 2020-001934-37**) 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 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 [167].

GLUCOCOVID
85 Pts (Spanien)
Methylprednisolone

bessere Ergebnisse bei „composite"Endpunkten

Ergebnisse sind ebenfalls alters-abhängig

Edalatifard et al. 2020 [173] 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**). 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.

Okt 2020:
RCT (Iran)
68 Pts.

schwere Erkrankung

signifikante Ergebnisse bei klinischer Verbesserung und bei Mortalität

Farahani et al. 2020 [174] 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**): 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. 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.

Phase 2 RCT (Iran)
29 Pts.

signifikante Vorteile bei Mortalität

Meta-analysis data on high, low and very low certainty of evidence, related to effectiveness and safety of dexamethasone and other corticosteroids reported in 7 RCTs, can be found in the Summary of Findings Table 3.17-1. In summary, according to the results of six RCTs with high certainty of evidence, corticosteroids reduce the risk of all-cause mortality D14-28 in COVID-19 patients /RR 0.90 (95% CI 0.83 to 0.97); absolute effect estimate 25 fewer per 1000 (95% CI from 23 fewer to 27 fewer). The same is true for outcomes WHO progression score level 6 or above D14-28 (RR 0.87, 95% CI 0.78 to 0.97, low certainty of evidence, 3 RCTs) and WHO progression score level 7 or above D14-28 RR 0.88, 95% CI 0.79 to 0.98, high certainty of evidence, 4 RCTs).

Table 3.17-1: Summary of findings table, on ***dexamethasone and other corticosteroids*** *(7 RCTs: Horbey, Tomazini, Dequin, REMAP-CAP Investigators, Jeronimo, Corral, Edalatifard)*

Corticosteroids compared to Standard Care/Placebo for Mild/Moderate/Severe/Critical COVID-19

Patient or population: Mild/Moderate/Severe/Critical COVID-19
Setting: Worldwide
Intervention: Corticosteroids
Comparison: Standard Care/Placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Standard Care/Placebo	Risk with Corticosteroids				
Viral negative conversion D3 - not reported	-	-	-	-	-	Outcome not yet measured or reported
Viral negative conversion D7	474 per 1,000	**478 per 1,000** (360 to 635)	**RR 1.01** (0.76 to 1.34)	212 (1 RCT) [b]	⊕◯◯◯ VERY LOW [c,d,e]	
Clinical improvement D7 - not reported	-	-	-	-	-	Outcome not yet measured or reported
Clinical improvement D14-28	620 per 1,000	**775 per 1,000** (508 to 1,000)	**RR 1.25** (0.82 to 1.90)	6724 (2 RCTs) [f]	⊕◯◯◯ VERY LOW [g,h,i]	
WHO progression score level 6 or above D7 - not reported	-	-	-	-	-	Outcome not yet measured or reported
WHO progression score level 6 or above D14-28	720 per 1,000	**626 per 1,000** (562 to 698)	**RR 0.87** (0.78 to 0.97)	512 (3 RCTs) [j]	⊕⊕◯◯ LOW [k,l]	
WHO progression score level 7 or above D7 - not reported	-	-	-	-	-	Outcome not yet measured or reported
WHO progression score level 7 or above D14-28	254 per 1,000	**224 per 1,000** (201 to 249)	**RR 0.88** (0.79 to 0.98)	6937 (4 RCTs) [m]	⊕⊕⊕⊕ HIGH	
All-cause mortality D7	246 per 1,000	**187 per 1,000** (128 to 271)	**RR 0.76** (0.52 to 1.10)	416 (1 RCT) [b]	⊕⊕◯◯ LOW [d,e]	
All-cause mortality D14-28	27 per 100	**25 per 100** (23 to 27)	**RR 0.90** (0.83 to 0.97)	7591 (6 RCTs) [n]	⊕⊕⊕⊕ HIGH	
Adverse events	68 per 1,000	**101 per 1,000** (7 to 1,000)	**RR 1.49** (0.11 to 20.63)	363 (2 RCTs) [o]	⊕◯◯◯ VERY LOW [k,p,q]	
Serious adverse events	86 per 1,000	**75 per 1,000** (41 to 137)	**RR 0.88** (0.48 to 1.60)	817 (5 RCTs) [r]	⊕◯◯◯ VERY LOW [q,s]	

***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: November 10, 2020
b. Prado Jeronimo CM, 2020
c. Risk of bias downgraded by 1 level: high risk due to missing data
d. Indirectness downgraded by 1 level: single study from a single institution, 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 no effect and low number of participants
f. Horby P (RECOVERY Trial), 2020; Tomazini BM, 2020
g. Risk of bias downgraded by 1 level: some concerns regarding deviations from intended intervention and outcome measurement
h. Inconsistency downgraded by 1 level: I^2=74.1%
i. Imprecision downgraded by 1 level: due to wide confidence interval consistent with the possibility for benefit and the possibility for no effect
j. Corral-Gudino L, 2020; Dequin P-F, 2020; Tomazini BM, 2020
k. Risk of bias downgraded by 1 level: some concerns or high risk regarding adequate randomization, deviations from intended interventions and outcome measurement
l. Imprecision downgraded by 1 level: due to low number of events and/or participants
m. Corral-Gudino L, 2020; Dequin P-F, 2020; Horby P (RECOVERY Trial), 2020; Tomazini BM, 2020
n. Angus DC, 2020; Corral-Gudino L, 2020; Dequin P-F, 2020; Horby P (RECOVERY Trial), 2020; Prado Jeronimo CM, 2020; Tomazini BM, 2020
o. Corral-Gudino L, 2020; Tomazini BM, 2020
p. Inconsistency downgraded by 1 level: I^2=81.6%
q. 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
r. Angus DC, 2020; Corral-Gudino L, 2020; Edalatifard M, 2020; Dequin P-F, 2020; Tomazini BM, 2020
s. Risk of bias downgraded by 1 level: some concerns or high risk regarding adequate randomization, deviations from intended interventions, missing data and outcome measurement

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 not authorised in Covid-19 patients (EMA, FDA).

Immunsuppressivum, humaner Interleukin-1 Rezeptorantagonist

EMA-Zulassung für Rheumatoide Arthritis seit 2002

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 [62].

mehrere laufende Studien, Empfehlung des US COVID-19 Treatment Guidelines Panel: insuffiziente Datenlage

Withdrawn, suspended or terminated studies

One RCT was found as suspended – ANACONDA (NCT04364009) –due to efficiency and safety reasons, after enrolment of 71 hospitalized COVID-19 patients in France. The intermediate review of data from this clinical trial showed early excess mortality in the group of patients treated with anakinra combined with standard optimized care, compared to the group of patients treated with standard optimized care alone. On October 29, 2020, the French National Agency for Medicines and Health Products Safety (ANSM) announced that inclusions in clinical trials evaluating anakinra in the treatment of COVID-19 are suspended due to safety information regarding the ANACONDA-COVID-19 clinical trial, https://ansm.sante.fr/S-informer/Actualite/Suspension-des-inclusions-en-France-dans-les-essais-clinique-evaluant-l-anakinra-dans-la-prise-en-charge-de-la-COVID-19-Point-d-information.

ANACONDA (Frankreich) 71 hospitaliserte Pts

wegen Sicherheit abgebrochen

One RCT was found as terminated: NCT04366232 (JAKINCOV), due investigator decision in France, on anakinra alone and in combination with ruxolitinib.

JAKINCOV (Frankreich) abgebrochen

Results of publications

Until now no scientific publication on RCTs of anakinra (Kineret®) in Covid-19 patients could be identified.

keine Publikation eines RCTs

3.19 Colchicine

About the drug under consideration

Colchicine is an alkaloid isolated from the autumn crocus, Colchicinum autumnale, with anti-gout and anti-inflammatory activities. Colchicine is available throughout the world in a generic form [182].

toxisches Alkaloid wirkt als Zellgift (Mitosehemmung)

Colchicine is not authorised in Covid-19 patients (EMA, FDA).

generisch

Withdrawn, suspended or terminated studies

No withdrawn, suspended or terminated interventional studies were found on colchicine in ClinicalTrials.gov and EUdraCT registers.

keine Studien

Results of publications

Deftereos et al. 2020 [184] 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 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. 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).

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 [185] 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. 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 [186], 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. 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.

RCT preprint (Brasilien) 38 Pt.

Reduktion von Sauerstoff Supplementierung und von Hospitalisierung

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) vidjeti DEPLazio i covid-nma*

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

Nafamostat mesilate (FUT-175, Futhan®, Nichi-Iko Pharmaceutical) is (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. Nafamostat is not approved for any use by EMA or FDA.

Futhan®

Withdrawn, suspended or terminated studies

No 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.

monoklonaler Antkörper in Entwicklung

EMA/ FDA: keine Zulassung

Withdrawn, suspended or terminated studies

No withdrawn, suspended or terminated interventional studies were found on gimsilumab in ClinicalTrials.gov and EUdraCT registers.

keine abgeschlossenen, abgebrochenen Studien

Results of publications

keine veröffentlichten Studien

There are no published results from RCTs related to effectiveness and safety of gimsilumab for Covid-19 treatment; one Phase II study of gimsilumab is ongoing, estimated study completion date is March 2021 [200, 201].

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 [202].
Canakinumab is not authorised in Covid-19 patients (EMA, FDA).

monoklonaler Antkörper

EMA Orphan Drug Zulassung für diverse Indikationen

Withdrawn, suspended or terminated studies

No withdrawn, suspended or terminated interventional studies were found on canakinumab in ClinicalTrials.gov and EUdraCT registers.

keine abgeschlossenen, abgebrochenen Studien

Results of publications

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 [204-206].

keine veröffentlichten Studien
1 Phase 3 Studie läuft

Manufacturer recently **announced preliminary interim results** from the CAN-COVID trial: the CAN-COVID trial failed to meet its primary endpoint showing that treatment with canakinumab plus standard of care (SoC) did not demonstrate a significantly greater chance of survival for patients without the need for invasive mechanical ventilation, compared with placebo plus SoC up to Day 29. The trial did not meet its key secondary endpoint of reducing the COVID-19-related death rate during the 4-week period after treatment. The safety profiles of canakinumab plus SoC and placebo plus SoC were comparable (https://www.novartis.com/coronavirus/can-covid-clinical-trial).

CAN-COVID negative Ergebnisse kein Unterschied

3.23 Lenzilumab

About the drug under consideration

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 [207, 208].

monoklonaler Antikörper

für keine Indikation bislang zugelassen

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

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.

Withdrawn, suspended or terminated studies

No withdrawn, suspended or terminated interventional studies were found on lenzilumab in ClinicalTrials.gov and EUdraCT registers.

Okt 2020: keine weiteren Studien

Results of publications

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

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 [32].

Phase 3 RCT an hospitalisierten Pts mit Lungenentzündung 300 Pts.

3.24 Vitamin D

About the drug under consideration

Vitamin D (ergocalciferol-D2, cholecalciferol-D3) is a fat-soluble vitamin increases the intestinal absorption of calcium and phosphate. Vitamin D is absorbed from the intestine and transported by protein binding in the blood to the liver (first hydroxylation to 25-hydroxycholecalciferol) and to the kidney (2nd hydroxylation to 1,25- dihydroxycholecalciferol, active metabolite responsible for increasing calcium absorption). It has been claimed as potentially protective against the infection since it may be associated with immunocompetence, inflammation, aging, and those diseases involved in determining the outcomes of COVID-19 [210]. VIOLET RCT (NCT03096314) of early high-dose enteral vitamin D3 supplementation in critically ill, vitamin D–deficient patients who were at high risk for death did not provide an advantage over placebo with respect to 90-day mortality or other, nonfatal outcomes among critically ill, vitamin D–deficient patients [211]. RCTs to assess efficacy and safety of vitamin D in COVID-19 patients are underway.

protektive Wirkung gegen Infekte bekannt

assoziiert mit guter Immunantwort

VIOLET
RCT zu hoch-dosiertem Vit D3 zur Supplementierung kein Vorteil

mehrere klinische Studien laufend

Vitamin D is not authorised in Covid-19 patients (EMA, FDA).

Withdrawn, suspended or terminated studies

No withdrawn, suspended or terminated interventional studies were found on Vitamin D in ClinicalTrials.gov and EUdraCT registers.

Results of publications

Entrenas Castillo et al. 2020 [212] published results from parallel pilot randomized open label, double-masked clinical trial on 76 consecutive patients hospitalized with COVID-19 infection in Spain (NCT04366908). Eligible patients were allocated at a 2 calcifediol:1 no calcifediol ratio, through electronic randomization on the day of admission to take oral calcifediol (0.532 mg), or not. Patients in the calcifediol treatment group continued with oral calcifediol (0.266 mg) on day 3 and 7, and then weekly until discharge or ICU admission. Of 50 patients treated with calcifediol, one required admission to the ICU (2%), while of 26 untreated patients, 13 required admission (50 %), $p < 0.001$. Calcifediol or 25-hydroxyvitamin D, a main metabolite of vitamin D, significantly reduced the need for ICU treatment of patients requiring hospitalization due to proven COVID-19: Univariate Risk Estimate Odds Ratio for ICU in patients with Calcifediol treatment versus without Calcifediol treatment: 0.02 (95 %CI 0.002- 0.17). Multivariate Risk Estimate Odds Ratio for ICU in patients with Calcifediol treatment vs Without Calcifediol treatment ICU (adjusting by Hypertension and T2DM): 0.03 (95 %CI: 0.003-0.25). Of the patients treated with calcifediol, none died, and all were discharged, without complications. The 13 patients not treated with calcifediol, who were not admitted to the ICU, were discharged. Of the 13 patients admitted to the ICU, two died and the remaining 11 were discharged.

RCT
76 hospitalisierte Pts

Vorteil bei Verhinderung von ICU Verschlechterung der Erkrankung

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