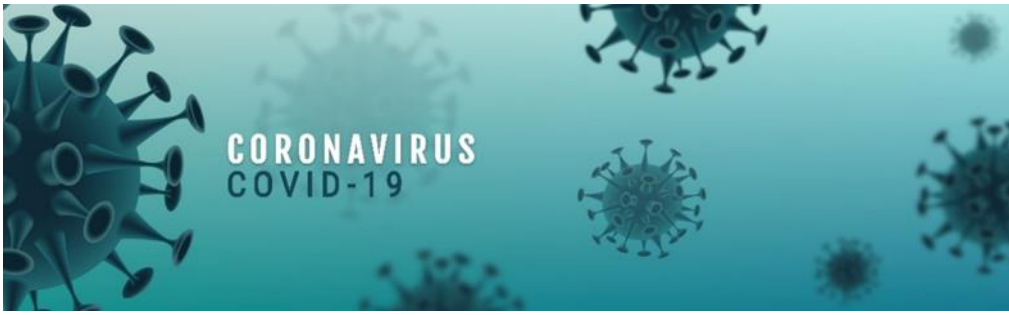
HTA Austria
Austrian Institute for
Health Technology Assessment
GmbH

Covid-19



HSS/ Horizon Scanning
Living Document **V17 August/**
September 2021

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HSS/ Horizon Scanning
Living Document **V17 August/ September** 2021

Vienna, September 2021

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History of Changes	V17 August/ September 2021
Aug and Sept 2021	Addition chapter on Fluvoxamine (chapter 3.33) and PF-07321332 (chapter 3.34)
Aug and Sept 2021	Methodology (1.2) – no changes
Aug and Sept 2021	Update Vaccine (chapter 2)
Aug and Sept 2021	Update Remdesivir (chapter 3.1)
Aug and Sept 2021	Update Favipiravir (chapter 3.3)
Aug and Sept 2021	Darunavir (chapter 3.4) – no changes
Aug and Sept 2021	Update Camostat Mesilate (chapter 3.7)
Aug and Sept 2021	Update APN01/rhACE2 (chapter 3.8)
Aug and Sept 2021	Update Tocilizumab (chapter 3.9)
Aug and Sept 2021	Update Sarilumab (chapter 3.10)
Aug and Sept 2021	Update Interferon beta (chapter 3.11)
Aug and Sept 2021	Update Concalescent plasma (chapter 3.12)
Aug and Sept 2021	Update Plasma derived medicinal products (chapter 3.13) – REGN-COV2; LY-CoV555 and LY-CoV016 (Bamlanivimab and etesevimab); AZD7422; VIR-7831 (Sotrovimab); Regdanvimab
Aug and Sept 2021	Combination therapy (chapter 3.14) – no changes
Aug and Sept 2021	Solnatide (chapter 3.15) – no changes
Aug and Sept 2021	Umifenovir (chapter 3.16) – no changes
Aug and Sept 2021	Update Inhaled corticosteroids (chapter 3.17.1)
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Aug and Sept 2021	Nafamostat (chapter 3.20) – no changes
Aug and Sept 2021	Gimsilumab (chapter 3.21) – no changes
Aug and Sept 2021	Update Canakinumab (chapter 3.22) – no changes
Aug and Sept 2021	Update Lenzilumab (chapter 3.23) – no changes
Aug and Sept 2021	Vitamin D (chapter 3.24) – no changes
Aug and Sept 2021	Update Baricitinib (chapter 3.25)
Aug and Sept 2021	Update Molnupiravir (chapter 3.26)
Aug and Sept 2021	Update Ivermectin (chapter 3.27)
Aug and Sept 2021	Update Aspirin (chapter 3.28) – no changes
Aug and Sept 2021	Update Aviptadil (RLF-100) (chapter 3.29)
Aug and Sept 2021	Dimethyl fumarate (chapter 3.30) – no changes
Aug and Sept 2021	Artesunate (chapter 3.31) – no changes
Aug and Sept 2021	Update Tofacitinib (chapter 3.32)

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

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.

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

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

1.2 Methodology

To respond to this request,

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

mehrstufige Methodik

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 laufenden 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).

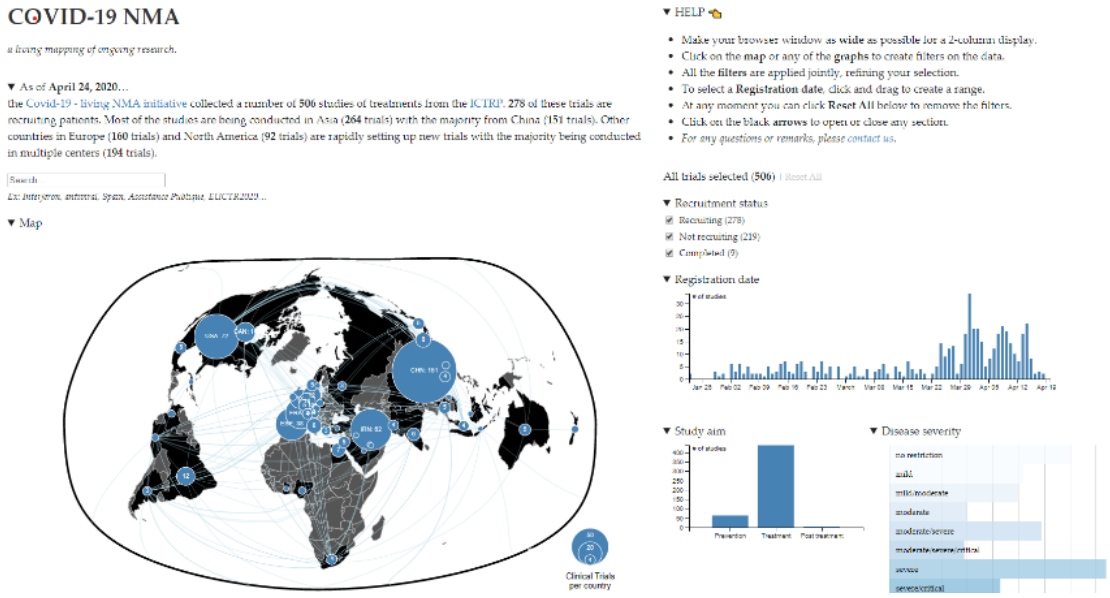
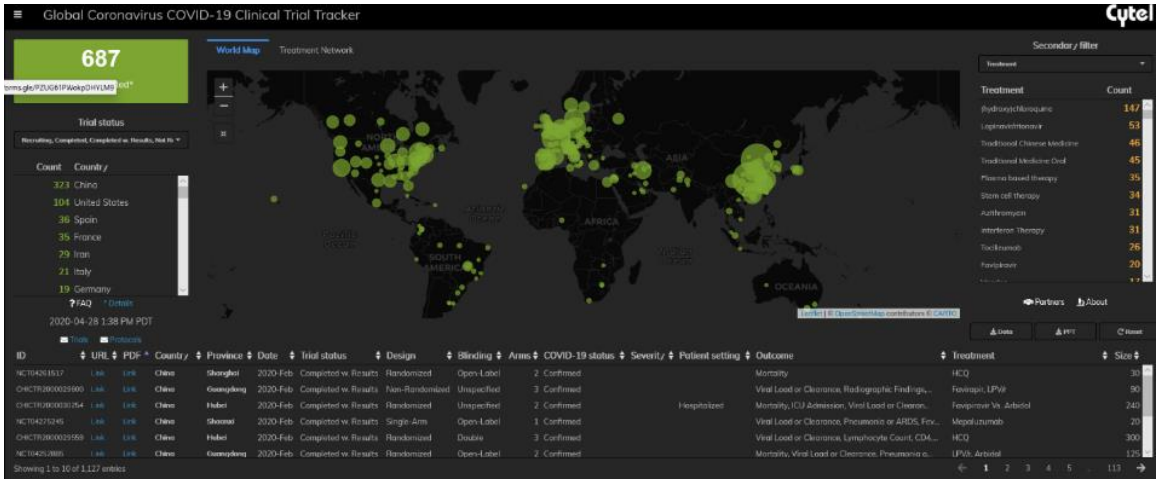


Figure 1.2-1: A living mapping of ongoing randomized trials, living systematic reviews with pairwise meta-analyses and network meta-analyses

Clinical Trial Tracker real-time dashboard

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"

Vignetten zu Produkte, in "fortgeschrittenen" Stadien oder

häufig diskutiert/ publiziert

Regeln, wann das Monitoring beendet wird folgen EUnetHTA

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

Decision to stop further investigation will be based on modified EUnetHTA stopping rules, https://eunethta.eu/covid-19-treatment/: 1) the compound has a positive marketing authorization decision or 2) no clinical benefit: ≥ 2 RCTs OR treatment arms in platform trials (e.g., RECOVERY) with negative efficacy and/or safety results in the indication and population under review (phase III, of high or moderate quality/ high or moderate certainty of evidence, well powered) OR ≥1 RCT with negative efficacy and/or safety results in the indication and population under review (phase III, of high or moderate quality/ high or moderate certainty of evidence, well powered) AND stopped enrollment of participants to the treatment arm of

interest in a platform trial (e.g., RECOVERY) because no evidence of beneficial effects.

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

From January 2021 (v10) only vaccines for which the European Commission (EC) concluded contracts or exploratory talks with their manufactures, to build a diversified portfolio of COVID-19 vaccines for EU citizens, will be presented in detail.

v10: nur Impfstoffe, für die EC Verträge abgeschlossen hat/ abschließt

From April 2021 (V13) focuse will be also on COVID-19 vaccines which clinical trials are conducted in children, on vaccines effectiveness related to SARS-CoV-2 new variants as well as on COVID-19 intranasal vaccines in development.

ab April 2021: Fokus auf Impfungen für Kinder und auf Wirksamkeit bei unterschiedlichen Mutationen

2 Results: Vaccines

As of June 13, 2021, the **European Commission** (EC) has given the **conditional marketing authorisation** for the vaccines developed by **BioNTech and Pfizer – Comirnaty® (vaccine efficacy 94.6%)** on **21 December 2020**, and **Moderna – now Spikevax (previously COVID-19 Vaccine Moderna - vaccine efficacy 94.1%)** on **6 January 2021**, following EMA positive assessment of its safety and efficacy.

Conditional Approval von EMA für 4 Impfstoffe:
BioNTech/ Pfizer
Moderna
AstraZeneca
Janssen/J&J

On **29 January 2021**, the EC has given the **conditional** marketing authorisation for the vaccine developed by **AstraZeneca – now Vaxzevria (previously COVID-19 Vaccine AstraZeneca) (vaccine efficacy around 60%).**

On **11 March 2021,** the **European Commission** (EC) has given the **conditional** marketing authorisation for the **COVID-19 Vaccine Janssen (vaccine efficacy 67%)** developed by **Janssen Pharmaceutica NV/Johnson & Johnson**, following evaluation by EMA.

On **February 03 2021** CHMP has started a **rolling review** of **NVX-CoV2373**, a COVID-19 vaccine being developed by **Novavax** CZ AS (a subsidiary of Novavax, Inc.), and on **February 12th** a rolling review of **CVnCoV**, a COVID-19 vaccine being developed by **CureVac** AG [6, 7]. On **March 4, 2021** CHMP has started a rolling review of **Sputnik V COVID-19** vaccine developed by **Russia's Gamaleya National Centre of Epidemiology and Microbiology** [8].

5 weitere in "Rolling Reviews" bei EMA:

Novavax
CureVac
Sputnik
Sinovac
Vidprevtyn

On **May 4 2021,** CHMP has started a **rolling review** of **COVID-19 Vaccine (Vero Cell) Inactivated**, developed by **Sinovac Life Sciences Co., Ltd** [9]. On **July 20 2021**, CHMP has started a **rolling review** of **COVID-19 Vaccine Vidprevtyn,** developed by **Sanofi Pasteur** [10].

On **September 6 2021**, **EMA** has **started evaluating an application for the use of a booster dose of Comirnaty** to be given **6 months after the second dose in people aged 16 years and older**. Booster doses are given to vaccinated people (i.e. people who have completed their primary vaccination) to restore protection after it has waned. EMA's human medicines committee (CHMP) will carry out an accelerated assessment of data submitted by the company that markets Comirnaty, including results from an ongoing clinical trial in which around 300 adults with healthy immune systems received a booster dose approximately 6 months after the second dose. The CHMP will recommend whether updates to the product information are appropriate. The outcome of this evaluation is expected within the next few weeks, unless supplementary information is needed, and will be communicated by EMA. Separately, EMA is also **assessing data** from the literature on the **use** of an **additional, third dose of an mRNA vaccine (Comirnaty or SpikeVax) in severely immunocompromised people** (i.e., with weakened immune systems). People with severely weakened immune systems who do not achieve an adequate level of protection from their standard primary vaccination may need an 'additional' dose as part of their primary vaccination. EMA will also communicate on the outcome of these evaluations in due course [11].

außerdem:
Evaluation von "Booster" (Auffrischung) mit Comirnaty

bei ≥ 16 Jahren oder Immunsuppremierten

EC Verträge mit 6 Firmen

2 weitere in Verhandlung: Novavax Valneva

As of May 14, 2021, the **EC** concluded **contracts with different vaccine manufactures** to build a diversified portfolio of COVID-19 vaccines for EU citizens: with **AstraZeneca** (400 million doses), **Sanofi-GSK** (300 million doses), **Johnson and Johnson/Janssen Pharmaceuticals** (400 million doses), **BioNTech-Pfizer** (600 million doses), **CureVac** (405 million doses) and **Moderna** (460 million doses). The EC has concluded **exploratory talks** with the pharmaceutical company **Novavax** with a view to purchasing up to 200 million doses and with **Valneva** with a view to purchase up to 60 million doses,
https://ec.europa.eu/commission/presscorner/detail/en/QANDA_20_2467.

Mai 2021: weiterer Vertrag EC-BioNTech für 900 Mio Dosen

On May 2021, the European Commission signed a third contract with **BioNTech-Pfizer**. It reserves an **additional 1.8 billion doses** on behalf of all EU Member States, **between the end of 2021 to 2023**. It will allow for the purchase 900 million doses of the current vaccine and option to purchase an additional 900 million doses,
https://ec.europa.eu/commission/presscorner/detail/en/ip_21_2548.

8 Impfstoffe: 4 in Phase 4 4 in Phase 3

As of September 12, 2021, out of these eight **COVID-19 candidate vaccines contracted** or **exploratory talks** has concluded **for EU, four are investigate in phase 4, and four are investigated in phase 3 RCTs:**

1. **Moderna Therapeutics/NIAID** (RNA LNP-encapsulated mRNA vaccine encoding S protein);
2. **University of Oxford/AstraZeneca** (Non-Replicating Viral Vector ChAdOx1 (AZD1222) vaccine);
3. **BioNTech/Fosun Pharma/Pfizer** (RNA 3 LNP-mRNAs vaccine);
4. **Janssen Pharmaceuticals/Johnson & Johnson** (Non-Replicating Viral Vector Ad26COVS1 vaccine); all in phase 4 RCTs;
5. **Novavax** (Protein Subunit, VLP-recombinant protein nanoparticle vaccine + Matrix M);
6. **CureVac** (RNA based vaccine, CVnCov2) vaccine,
7. **Sanofi-GSK** (Protein Subunit, with adjuvant 1 vaccine)
8. **Valneva** (Inactivated virus), all in phase 3 RCTs.

26 Publikationen zu Impfstudien

Out of these 8 coronavirus vaccines, the following articles were published for 7 vaccines, with results related to early phases vaccine trials (phase 1, 1/2 or phase 2) or phase 2/3 and phase 3 trials:

1. Three on **Moderna Therapeutics/NIAID** vaccine: a preliminary report with the results from the phase 1 study (NCT04283461) [12],
2. The results from the expanded phase 1 study (NCT04283461) in older adults [13] and
3. The results from phase 3 RCT (NCT04470427) [14];
4. Results from phase 3 RCT in adolescent (NCT04649151) [15]
5. Four on **Novavax** vaccine: the results from the phase 1/2 RCT (NCT04368988) [16];
6. The results from phase 2 component of 1/2 RCT (NCT04368988) trial [17]; and
7. The preliminary results from phase 2a/b in South Africa (NCT04533399) [18] and
8. Results from phase 3 RCT in UK (EudraCT 2020-004123-16) [19]

9. Eight 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) [20],
10. A report from the same RCT, on subgroups of volunteeres who were subsequesntly allocated to recive a homologous full-dose or half-dose ChAdOx1 booster vaccine 56 d following prime vaccination [21],
11. Pooled interim analysis phase 2/3 trials (ISRCTN89951424, NCT04324606, NCT04400838, and NCT04444674) [22], and
12. Pooled primary analysis phase 2/3 trials (ISRCTN89951424, NCT04324606, NCT04400838, and NCT04444674) [23], and
13. Phase 2 component of phase 2/3 trial COV002 (ISRCTN90906759, NCT04400838) [24];
14. Phase 3 component of phase 2/3 trials (ISRCTN89951424, NCT04324606, NCT04400838, and NCT04444674) [25];
15. Phase 3 trial in South Africa (NCT04444674) [26]
16. Exploratory analysis of a RCT (NCT04400838) [27]
17. Five on **BioNTech/Fosun Fharma/Pfizer** vaccine**:** Three with results from two phase 1/2 trials on **BNT162b1** vaccine, one in US (NCT04368728/EudraCT 2020-001038-36) [28], and
18. One in Germany (NCT04380701, EudraCT 2020-001038-36) [29] as well as
19. Additional safety and immunogenicity results from the US phase 1 trial (NCT04368728/EudraCT 2020-001038-36) [52, 53] and
20. One pivotal RCT efficacy trial on BNT162b2 (NCT04368728) [30] and
21. One RCT in adolescent (NCT04368728) [31] [32]
22. Two on **Janssen Pharmaceuticals/Johnson & Johnson** vaccine**:** interim results of a **phase ½** trial (NCT04436276) [41] and
23. Phase 3 RCT (NCT04505722) [33]
24. Two on **CureVac**: preliminary results of **phase 1** trial (NCT04449276) [34] and
25. Interim results of phase 3 RCT in adults (NCZ04582344) [35] and
26. One on **Sanofi and GSK**: interim results of phase ½ trial (NCT04537208) [36].

Regulatory Guidances and position paper:

Positionspapier der Internationalen Regulatoren zu Impfstudien

stringente klinische Studien vonnöten !

On 09/07/2020, Medicines Regulatory Authorities published the report related to phase 3 COVID-19 vaccine trials [37]. 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.

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.

März 2021: EMA (PRAC) beginnt Untersuchung zu Nebenwirkungen von AstraZeneca

Thromboembolien

On April 7, 2021 EMA's safety committee (PRAC) has concluded that **unusual blood clots with low blood platelets** should be listed as very rare side effects of **Vaxzevria (formerly COVID-19 Vaccine AstraZeneca**). EMA is reminding healthcare professionals and people receiving the vaccine to remain aware of the possibility of very rare cases of blood clots combined with low levels of blood platelets occurring within 2 weeks of vaccination. So far, most of the cases reported have occurred in women under 60 years of age within 2 weeks of vaccination. Based on the currently available evidence, specific risk factors have not been confirmed. One plausible explanation for the combination of blood clots and low blood platelets is an immune response, leading to a condition similar to one seen sometimes in patients treated with heparin (heparin induced thrombocytopenia, HIT). The PRAC has requested new studies and amendments to ongoing ones to provide more information and will take any further actions necessary, https://www.ema.europa.eu/en/news/astrazenecas-covid-19-vaccine-ema-finds-possible-link-very-rare-cases-unusual-blood-clots-low-blood.

Anaphylaxis

Following the assessment of a safety signal regarding cases of **anaphylaxis** (severe allergic reactions) with **COVID-19 Vaccine AstraZeneca**, **PRAC has recommended** an **update to the product information** to **include anaphylaxis and hypersensitivity** (allergic reactions) as **side effects** in section 4.8, with an unknown frequency, and to **update the existing warning** to reflect that cases of anaphylaxis have been reported. The update is based on a review of 41 reports of possible anaphylaxis seen among around 5 million vaccinations in the United Kingdom. After careful review of the data, PRAC considered that a link to the vaccine was likely in at least some of these cases, https://www.ema.europa.eu/en/news/meeting-highlights-pharmacovigilance-risk-assessment-committee-prac-8-11-march-2021.

weiters: Kapillarlecksyndrom

neuer Name: Vaxzevria (AstraZeneca)

Guillain-Barre syndrome (GBS)

On April 9, 2021 PRAC has started a review of a safety signal to assess reports of **capillary leak syndrome** in people who were vaccinated with **Vaxzevria (previously COVID-19 Vaccine AstraZeneca).** On June 11, 2021 EMA stated that EMA's safety committee (PRAC) has concluded that people who have previously had capillary leak syndrome must not be vaccinated with Vaxzevria. The Committee also concluded that capillary leak syndrome should be added to the product information as a **new side effect of the vaccine**, together with a warning to raise awareness among healthcare professionals and patients of this risk [38]. The PRAC has recommended a **change** to the **product information** for **Vaxzevria** (formerly COVID-19 Vaccine Astrazeneca) to include a warning to raise awareness among healthcare professionals and people taking the vaccine of cases of **Guillain-Barre syndrome (GBS)** reported following vaccination [39].

PRAC Untersuchung von BioNTech, AstraZeneca und Moderna zu Thrombozytopenie

PRAC has **started a review of a safety signal** to assess reports of **immune thrombocytopenia** in patients who received any of the three COVID-19 vaccines: **Comirnaty, COVID-19 Vaccine AstraZeneca and COVID-19 Vaccine Moderna**.

PRAC Untersuchung von BioNTech: lokale Schwellingen

PRAC has **started a review of a safety signal** to assess reports of **localised swelling after vaccination with COVID-19 vaccine Comirnaty** in people with a **history of injections with dermal fillers** (soft, gel-like substances injected under the skin), https://www.ema.europa.eu/en/news/meeting-highlights-pharmacovigilance-risk-assessment-committee-prac-8-11-march-2021. On May 7, 2021 PRAC concluded that facial swelling in people with a history of injections with dermal fillers should be included as a side effect and recommended a change to product information,

https://www.ema.europa.eu/en/news/meeting-highlights-pharmacovigilance-risk-assessment-committee-prac-3-6-may-2021.

PRAC Untersuchung von Moderna und Comirnaty:

Myokarditis, Perikarditis

On July 09, 2021 PRAC has concluded that **myocarditis and pericarditis** can occur in **very rare cases** following vaccination with **Comirnaty** and **Spikevax** (previously **COVID-19 Vaccine Moderna**). The Committee is therefore recommending listing myocarditis and pericarditis **as new side effects** in the **product information** for these vaccines, together with a warning to raise awareness among healthcare professionals and people taking these vaccines [39]. On June 25, 2021 the **FDA revised** the patient and provider **fact sheets** for the **Moderna** and **Pfizer-BioNTech COVID-19 vaccines** regarding the suggested increased risks of **myocarditis and pericarditis** following vaccination [40].

For **Vaxzevria** and **COVID-19 Vaccine Janssen**, the PRAC is reviewing the cases of **myocarditis and pericarditis** in the context of the vaccines' **Monthly Summary Safety Reports**, also referred to as pandemic summary safety reports, which are compiled by the marketing authorisation holders to support timely and continuous benefit-risk evaluations of COVID-19 vaccines used during the pandemic [41].

PRAC Untersuchung von Johnson & Johnson

Thromboembolien

On April 9, 2021 PRAC has started a review of a safety signal to assess reports of **thromboembolic events** (formation of blood clots, resulting in the obstruction of a vessel) in people who received **COVID-19 Vaccine Johnson & Johnson (Janssen)**. https://www.ema.europa.eu/en/news/meeting-highlights-pharmacovigilance-risk-assessment-committee-prac-6-9-april-2021.

Risiko: Thromboembolien innerhalb von 3 Wochen nach Impfung

On April 20, 2021 PRAC concluded that a warning about unusual blood clots with low blood platelets should be added in the product information. On May 7, 2021 PRAC concluded that product information will also include advice that patients who are diagnosed with thrombocytopenia within three weeks of vaccination should be actively investigated for signs of thrombosis. Patients who present with thromboembolism within three weeks of vaccination should be evaluated for thrombocytopenia. Thrombosis with thrombocytopenia syndrome will be added as an 'important identified risk' in the risk management plan for the vaccine. Furthermore, the marketing authorisation holder will provide a plan to further study the possible underlying mechanisms for these very rare events, https://www.ema.europa.eu/en/news/meeting-highlights-pharmacovigilance-risk-assessment-committee-prac-3-6-may-2021.

Anfang April 2021: FDA: Pausierung von Impfung mit Johnson & Johnson (J&)

Ende April: FDA Fortsetzung von J&J

Guillain-Barré syndrome
Kapillarlecksyndrom
Anaphylaxis

On April 13, 2021 FDA and CDC are recommending a pause in the use of **Johnson & Johnson (Janssen)** COVID-19 vaccine out of an abundance of caution. https://www.fda.gov/news-events/press-announcements/joint-cdc-and-fda-statement-johnson-johnson-covid-19-vaccine. On April 23, 2021 the use of the vaccine was resumed and FDA amended the emergency use authorization of the Johnson & Johnson (Janssen) COVID-19 vaccine to include information about a very rare and serious type of blood clot in people who receive the vaccine, https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/janssen-covid-19-vaccine. On July 08, 2021 in revised fact sheet of COVID-19 Vaccine Janssen increased risk of **Guillain-Barré syndrome** during the 42 days following vaccination is written in warning section [42], as well in adverse events section together with severe allergic reactions (including anaphylaxis), thrombosis with thrombocytopenia and capillary leak syndrome, following administration during mass vaccination outside of clinical trials.

Immunthrombo-zytopenie

venöse Thromboembolie

On July 09, 2021 the PRAC has recommended that people who have previously had capillary leak syndrome must not be vaccinated with COVID-19 Vaccine Janssen. The Committee also recommended that capillary leak syndrome should be added to the product information as a new side effect of the vaccine, together with a warning to raise awareness among healthcare professionals and patients of this risk [39]. In August 2021, the PRAC recommended updating the product information of COVID-19 Vaccine Janssen to include **immune thrombocytopenia** as an adverse reaction, as well as a warning to alert healthcare professionals and people taking the vaccine of this possible side effect. The PRAC concluded that cases of **dizziness and tinnitus** (ringing or other noises in one or both ears) are linked to the administration of COVID-19 vaccine Janssen [43]. As part of the ongoing close safety monitoring of the COVID-19 vaccines, PRAC is reviewing data on cases of **venous thromboembolism** (blood clots in the veins) with **COVID-19 Vaccine Janssen**. This safety issue is distinct from the very rare side effect of thrombosis with thrombocytopenia syndrome(TTS) (i.e. blood clots with low blood platelets) [44].

Comirnaty: Multisystem-Entzündungssyndrom (MIS)

On September 03, 2021 the PRAC is assessing whether there is a risk of **multisystem inflammatory syndrome (MIS)** with **COVID-19 vaccines** following a report of MIS with Comirnaty. The case occurred in a 17-year old male in Denmark who has since fully recovered. Some cases of MIS were also reported in the EEA following vaccination with other COVID-19 vaccines.

EMA Guidance für Vazzinehersteller bez. Veränderungen wegen Mutanten

B.1.1.7 (UK)
B.1.351 (SA)
P.1 (BR)

On February 10, 2021 **EMA** stated that it is **developing guidance for manufacturers planning changes to the existing COVID-19 vaccines** to tackle the **new virus variants**. In order to consider options for additional testing and development of vaccines that are effective against new virus mutations, the Agency has requested all vaccine developers to investigate if their vaccine can offer protection against any new variants, e.g., those identified in the United Kingdom - variant called **B.1.1.7**, South Africa - **B.1.351** and Brazil - variant called **P.1**, and submit relevant data. There are concerns that some of these mutations could impact to different degrees the ability of the vaccines to protect against infection and disease. A reduction in protection from mild disease would however not necessarily translate into a reduction in protection from serious forms of the disease and its complications, for which Agency need to collect more evidence [45]. On June 28, 2021 EMA provided procedural guidance on submitting a **variation** application to address **SARS-CoV-2 variants** by updating the composition of an authorised COVID-19 vaccine, including recommendations on how to name the variant vaccine [46].

Vaccine and SARS-CoV-2 variants (in June 2021 new names given by WHO)

Impfwirksamkeit bei Mutationen (Alpha, Beta, Gamma, Delta)

neu: Mu und Lambda

in Tabelle 2-2

So far, studies suggest that effectiveness may be reduced against some SARS-CoV-2 variants and more data are needed [18, 27, 47-60] [19, 61] [62] [63-77] [78] [79, 80] Current data related to clinical effectiveness and in vitro neutralisation, on **Alpha** (**B.1.1.7**), **Beta (B.1.351), Gamma** (**P.1**) and **Delta** (**B.1.617.2**) **SARS-CoV-2 variants** can be found in Table 2-2. Updated vaccines will be necessary to eliminate the virus. Recently, in addition to B.1.1.7, B.1.351 and P.1, two more SARS-CoV-2 variants, **B.1.427** and **B.1.429,** which were first detected in California, have been shown to be approximately 20% more transmissible than preexisting variants and have been classified by the CDC as **variants of concern**. Currently in EU (as of September 9, 2021), variants of concern are **Beta (B.1.351)**, **Gamma** (**P.1**) and **Delta** (**B.1.617.2**).

At this time, ECDC maintains its assessment of **B.1.620, Mu (B.1.621, Colombia)** and **Lambda (C.37, Peru)** as **variants of interest** and will continue to actively monitor the situation [81].

Publikation zum Umgang mit Varianten

Krause et al. 2021 published a special report related to variants and vaccines, pointed four major priorities for the global response to variants of concern; Evaluate existing vaccines for efficacy against variants; If current vaccines are inadequate, assess the effectiveness of new vaccines or modified vaccines against variants; Reduce the risk that additional variants of concern will emerge; Coordinate the worldwide response [82].

AstraZeneca arbeitet an neuem Impfstoff als Booster für neue Varianten

On 27 June 2021, **AstraZeneca** announced that the first participants in a phase II/III trial for the new COVID-19 variant vaccine AZD2816 were vaccinated to assess its safety and immunogenicity in both previously vaccinated and unvaccinated adults. AZD2816 has been designed using the same adenoviral vector platform as Vaxzevria, with minor genetic alterations to the spike protein based on the Beta (B.1.351, South African) variant. The trial will recruit approximately 2,250 participants across UK, South Africa, Brazil and Poland. AZD2816 will be administered to individuals who have previously been fully vaccinated with two doses of Vaxzevria or an mRNA vaccine, at least three months after their last injection. In non-vaccinated individuals, AZD2816 will be given as two doses, four or twelve weeks apart, or given as a second dose following a first dose of Vaxzevria four weeks apart. Initial data from the trial is expected later this year and, once available, will be submitted to regulators for assessment as a next-generation booster vaccine and through an expedited regulatory pathway, https://www.astrazeneca.com/media-centre/press-releases/2021/first-covid-19-variant-vaccine-azd2816-phase-ii-iii-trial-participants-vaccinated/

Vaccine in development in children

klinische Studien zu Pfizer, Moderna, AstraZeneca, J& J, Sinovac bei Kindern in Tabelle 2-3

Clinical trials are currently under way to test the Pfizer, Moderna, Oxford-AstraZeneca, Jansenn/Johnson&Johnson and Sinovac vaccines in children [83-86]. Details can be found in Table 2-3.

EMA: Zulassung von Comirnaty für 12-15J und Spikevax: 12-17 J

On May 3, 2021 **EMA** has started evaluating an **application** to **extend the use** of the COVID-19 vaccine **Comirnaty** to include young people **aged 12 to 15** [88]. On May 10, 2021 **FDA** authorised **Pfizer/BionTech COVID-19 vaccine** for **emergency use** in **adolescents 12-15 years old [89].**

On May 28, 2021 **EMA**'s CHMP recommended **granting** an **extension of indication** for the COVID-19 vaccine **Comirnaty** to include **children aged 12 to 15** [90]. On June 08, 2021 **EMA** has started evaluating an **application** to **extend the use** of the COVID-19 Vaccine **Moderna (Spikevax)** to include young people **aged 12 to 17** [91]. On June 23, 2021 **EMA**'s CHMP recommended **granting** an **extension of indication** for the **Moderna** COVID-19 vaccine **Spikevax** to include **children aged 12 to 15** [92].

As original size of the **Pfizer/BioNTech and Moderna** studies was too small to detect rare side effects, such as myocarditis and pericarditis, both manufacturers are expanding the size of their COVID-19 vaccine studies in children 5 to 11 years.

Intranasal vaccines in development

intranasale Verabreichung: 7 Impfstoffe in Entwicklung (1 Abbruch)

As of September 12, 2021, seven COVID-19 intranasal vaccines in development were found. Altimmune, Inc. has discontinued further development of AdCOVID. Nasal delivery is easier for administration, without needles and and can be self administered. Intranasal vaccines could boost immune 20efences in mucosa. As example, Oxford is launching a phase 1 trial of a nasal spray COVID-19 vaccine, including 30 volunteers aged 18-40. The spray will use the same ChAdOx1 nCoV-19 compound as the AstraZeneca shot. Details can be found in Table 2-4.

in Tabelle 2-4

Phase 1 trial (China)

Wu et al. 2021 [93] published **preliminary results** from a randomised, single-centre, open-label, **phase 1** trial done in Zhongnan Hospital (Wuhan, China), to evaluate the safety and immunogenicity of the **Ad5-nCoV vaccine by aerosol inhalation in adults** (≥18 years) seronegative for SARS-CoV-2 (NCT04552366). 130 (56%) participants were enrolled into the trial and randomly assigned into one of the five groups (26 participants per group) to be vaccinated via intramuscular injection, aerosol inhalation, or both. Within 7 days after vaccination, adverse events occurred in 18 (69%) participants. The most common adverse events reported 7 days after the first or booster vaccine were fever (62 [48%] of 130 participants), fatigue (40 [31%] participants), and headache (46 [35%] participants). More adverse events were reported in participants who received intramuscular vaccination, including participants in the MIX group (49 [63%] of 78 participants), than those who received aerosol vaccine (13 [25%] of 52 participants) after the first vaccine vaccination. No serious adverse events were noted within 56 days after the first vaccine. Authors concluded that aerosolised Ad5-nCoV is well tolerated, and two doses of aerosolised Ad5-nCoV elicited neutralising antibody responses, similar to one dose of intramuscular injection. An aerosolised booster vaccination at 28 days after first intramuscular injection induced strong IgG and neutralising antibody responses.

Table 2-1: Vaccines contracted or exploratory talks have concluded for EU, in the R&D pipeline (Phase 1 - Phase 4 clinical trials, not preclinical stages)

Source: Adapted from DRAFT landscape of COVID-19 candidate vaccines – September 10, 2021, https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines and Creech et al. 2021 [94]

Developers	Vaccine / Vaccine type	Number of doses	Study phase	Storage conditions	Efficacy against severe COVID-19	Overall efficacy	EC (EU) Current approval or EMA "rolling review"
Moderna + National Institute of Allergy and Infectious Diseases (NIAID)	**COVID-19 Vaccine Moderna (mRNA -1273) / m RNA**	2 IM	Phase 4	-25° to -15°C; 2-8°C for 30 d; room temperature ≤12 h	100% 14 d after 2nd dose	92.1% after 1st dose; 94.1% 14 d after 2nd dose	**Conditional marketing authorisation**
AstraZeneca + University of Oxford	**COVID-19 Vaccine AstraZeneca (ChAdOx1-S - (AZD1222) / Viral vector**	2 IM	Phase 4	2-8° C for 6 mo	100% 21 d after 1st dose	64.1% after 1st dose; 70.4% 14 d after 2nd dose	**Conditional marketing authorisation**
BioNTech + Pfizer	**Comirnaty (BNT162b2) / mRNA**	2 IM	Phase 4	-80° to -60°C; 2-8° C for 5 d; room temperature ≤2 h	88.9% after 1st dose	52% after 1st dose; 94.6% 7 d after 2nd dose	**Conditional marketing authorisation**
Janssen Pharmaceutical/Johnson&Johnson	**COVID-19 Vaccine Janssen (Ad26.COV2.S) / Viral vector**	1 IM	Phase 4	-25°C to -15°C; 2-8° C for 3 mo	85% after 28 d; 100% after 49 d	72% in US; 66% in Latin America; 57% in South Africa (at 28 d)	**Conditional marketing authorisation**
CureVac AG	**CVnCoV / mRNA**	2 IM	Phase 3	2-8° C for 3 mo; room temperature for 24 h	Unknown	Phase 3 ongoing	**EMA "rolling review"**
Sanofi Pasteur + GSK	**Vidprevtyn**; SARS-CoV-2 vaccine formulation 1 with adjuvant 1 (S protein (baculovirus production) / **Protein subunit**	2 IM	Phase 3	2-8° C	N.A – Phase 3 ongoing	Phase 3 ongoing	**EMA "rolling review"**
Novavax	**NVX-CoV2373 / Protein subunit**	2 IM	Phase 3	2-8° C for 6 mo	100%	89.3% in UK after 2nd dose; 60% in South Africa	**EMA "rolling review"**
Valneva	**VLA2001 / Inactivated virus**	2 IM	Phase 3	2-8° C	N.A – Phase 3 ongoing	N.A – Phase 3 ongoing	N.A – Phase 3 ongoing

Table 2-2: SARS-CoV-2 variants of concern in EU and vaccines contracted or exploratory talks have concluded for EU, and some vaccines not contracted nor exploratory talks have concluded for EU: clinical effectiveness (VE) and in-vitro neutralisation

Developers	Vaccine / Vaccine type	Clinical Efficacy against Alpha (B.1.1.7.) (UK) / Neutralisation	Clinical Efficacy against Beta (B.1.351) (South Africa) / Neutralisation	Clinical Efficacy against Gamma (P.1) (Brazil) / Neutralisation	Clinical Efficacy against Delta (B.1.617.2) (India) / Neutralisation
Vaccines contracted or exploratory talks have concluded for EU					
Moderna + National Institute of Allergy and Infectious Diseases (NIAID)	COVID-19 Vaccine Moderna (mRNA -1273) / m RNA	>90% against symptomatic COVID-19 Decrease by 1.8x	<10% reduction in VE Decrease by ≤8.6x	Not yet available Decrease by 4.5x	<10% reduction in VE 2 to <5-fold reduction
AstraZeneca + University of Oxford	COVID-19 Vaccine AstraZeneca (ChAdOx1-S - (AZD1222) / Viral vector (Non-replicating)	70.4% against symptomatic COVID-19 Decrease by 9x	10.4% against symptomatic COVID-19 Decrease by ≤86× to complete immune escape	Not yet available Decrease by 2.9x	Real word data: 60% effective at two weeks after the second dose; 33% effective against symptomatic disease three weeks after the first dose 2 to <5-fold reduction; 5 to <10-fold reduction
BioNTech + Pfizer	Comirnaty (BNT162b2) / mRNA	Real-word data: 72% (95% CI 58-86) 21 days after first dose and 86% (95% CI 76-97) seven days after two doses Decrease by 2x	100% in South Africa Decrease by ≤6.5x to 10.3x	Not yet available Decrease by 2.6X, 6.7x to 14x	Real word data: 88% effective, two weeks after the second dose; 33% effective against symptomatic disease three weeks after the first dose 2 to <5-fold reduction to 5 to <10-fold reduction
Janssen Pharmaceutical/Johnson&Johnson	COVID-19 Vaccine Janssen (Ad26.COV2.S) / Viral vector (Non-replicating)	Not yet available <2-fold reduction in neutralization to 2 to <5-fold reduction	57% against moderate to severe COVID-19; 85% against severe COVID-19 and hospitalisation 2 to <5-fold reduction to 5 to <10-fold reduction	68.1% against moderate to severe disease 2 to <5-fold reduction	Not yet available <2-fold reduction; 2 to <5-fold reduction
CureVac AG	CVnCoV / mRNA	Not yet available	Not yet available (Strong results variant when tested on mice; CureVac would expand a trial in Europe and Latin America to analyse the vaccine's efficacy against select variants)	Not yet available	Not yet available
Sanofi Pasteur + GSK	VAT00002; SARS-CoV-2 vaccine formulation 1 with adjuvant 1 (S protein (baculovirus production) / Protein subunit	Not yet available	Not yet available	Not yet available	Not yet available

Novavax	NVX-CoV2373 / Protein subunit	89.3% against symptomatic COVID-19 Decrease by 1.8x	60% against symptomatic COVID-19 ≥10-fold reduction	Not yet available	Not yet available
Valneva	VLA2001 / Inactivated virus	Not yet available	Not yet available	Not yet available	Not yet available
Vaccines not contracted nor exploratory talks have concluded for EU					
CoronaVac (Sinovac)	CoronaVac; SARS-CoV-2 vaccine (inactivated) / Inactivated virus	Decreased by 0.5X <2-fold reduction; 2 to <5-fold reduction	Decrease 2.5 to 3.3x to complete or partial loss of neutralization, 2 to <5-fold reduction to 5 to <10-fold reduction	<10% to 10 to <20% reduction in efficacy for symptomatic disease <2-fold reduction in neutralisation, 2 to <5-fold reduction	Not yet available <2-fold reduction to ≥10-fold reduction
Brazil		Not yet available	Not yet available	Real word data efficacy 36·8% (–54·9 to 74·2) Not yet available	Not yet available
Turkey		Not yet available	Not yet available	Not yet available	Not yet available
BBIBP-CorV (Sinopharm)	Inactivated SARS-CoV-2 vaccine (Vero cell) / Inactivated virus	Not yet available <2-fold reduction in neutralization	Not yet available Complete or partial loss of neutralization, 2 to <5-fold reduction	Decrease by 1.6x	Not yet available
Gamaleya (Sputnik V)	Gam-COVID-Vac Adeno-based (rAd26-S+rAd5-S) / Viral vector (Non-replicating)	Not yet available <2-fold reduction	Not yet available Decrease 6.1X, 2 to <5-fold reduction to 5 to <10-fold reduction	Not yet available Decrease 2.8X, 2 to <5-fold reduction	Not yet available 2 to <5-fold reduction

Table 2-3: COVID-19 Vaccines in development in children

Developers	Vaccine / Vaccine type	
Moderna + National Institute of Allergy and Infectious Diseases (NIAID)	COVID-19 Vaccine Moderna (mRNA -1273) / m RNA	**NCT04796896 (KidCOVE)** Phase 2/3 RCT in 6,750 children ages 6 months through 11 years in U.S. and Canada Two parts: 1. **Part 1**: open label, dose-escalation, age de-escalation study. 2 yo – up to 12 yo: each participant may receive either 50 µg or 100 µg dose of the vaccine. 6 mo – up to 2 yo: each participant may receive either 25 µg, 50 µg, or 100 µg dose. 2. **Part 2**: randomised, observer-blind, placebo-controlled expansion study based on the preliminary evaluation of the Part 1 results. The participants will receive two doses of the vaccine 28 days apart. To evaluate the medicine's safety, tolerability, reactogenicity and effectiveness, the company will observe the participants for 12 months after the second jab. Moderna expects authorization for the 5 to 11-year-old in winter 2021 or early 2022. **NCT 04649151 (TeenCOVE)** Phase 2/3 RCT, to evaluate the safety, reactogenicity, and effectiveness of mRNA-1273 SARS CoV 2 vaccine in 3000 healthy adolescents 12 to <18 years of age in US. See Press Release from 15 May 2021, on results related to primary endpoint below. See scientific publication below, Ali et al. 2021 [15] On June 08, 2021 **EMA** has started evaluating an **application** to **extend the use** of the COVID-19 Vaccine **Moderna** to include young people **aged 12 to 17.** On June 23, 2021 **EMA**'s CHMP recommended **granting** an **extension of indication** for the COVID-19 vaccine **Spikevax** to include **children aged 12 to 15.**
AstraZeneca + University of Oxford	COVID-19 Vaccine AstraZeneca (ChAdOx1-S - (AZD1222) / Viral vector	**Phase 2 RCT** in 300 **children aged 6-17**, in UK Currently has been **paused** while the **EMA** investigates the link between the shot and rare blood clots
BioNTech + Pfizer	Comirnaty (BNT162b2) / mRNA	**NCT 04368728 Phase 2/3 RCT in 2200 volunteers ages 12 to 15** On March 31, 2021 announced adolescent trials have shown efficacy of 100% in protecting adolescents ages 12-15, with no significant safety concerns. About 2,260 adolescents ages 12-15 years participated in the trial, with roughly half receiving the vaccine and half receiving a placebo. There were 18 cases of COVID-19 reported, all within the placebo group. One month after a second dose, the vaccine elicited SARS-CoV-2-neutralizing antibody geometric mean titers of 1,239.5 in a subset of adolescents, compared to 705.1 in an earlier group of 16- to 25-year-olds, according to the news release. Scientific publication in NEJM [31], see details below. On May 10, 2021 **FDA** authorised **Pfizer/BionTech COVID-19 vaccine** for **emergency use** in **adolescents 12-15 years old.** On May 28, 2021 **EMA**'s CHMP recommended **granting** an **extension of indication** for the COVID-19 vaccine **Comirnaty** to include **children aged 12 to 15.** **NCT 04816643, Phase 1/2/3 Study in 4644 children 6 months to 11 years old in US** Evaluating the safety, tolerability, and immunogenicity of the Pfizer-BioNTech COVID-19 vaccine on a two-dose schedule (approximately 21 days apart) in three age groups: children aged 5 to 11 years, 2 to 5 years, and 6 months to 2 years. The 5 to 11 year-old cohort started dosing last week and the companies plan to initiate the 2 to 5 year-old cohort next week. Manufacturer hope to submit for potential EUA to the FDA in September-October timeframe for children 5-11 years, and soon after for 6 months to 5 years. https://www.pfizer.com/news/press-release/press-release-detail/pfizer-biontech-announce-positive-topline-results-pivotal?linkId=114996658
Janssen Pharmaceutical/Johnson&Johnson	COVID-19 Vaccine Janssen (Ad26.COV2.S) / Viral vector	**RCT, phase 2a** Has begun in April 2021 testing its Covid-19 vaccine in 1700 adolescents aged 12; Initially will be tested in a small number

		of adolescents aged 16-17 years (following the review of initial data in this phase 2a trial, the study will be expanded to a larger group of younger adolescents in a stepwise approach). Currently enrolling participants in Spain and the United Kingdom; enrollment will commence shortly in the United States, the Netherlands and Canada, with Brazil and Argentina to follow https://www.wsj.com/articles/j-j-starts-testing-covid-19-vaccine-in-adolescents-11617379165
CureVac AG	CVnCoV / mRNA	Not available
Sanofi Pasteur + GSK	VAT00002; SARS-CoV-2 vaccine formulation 1 with adjuvant 1 (S protein (baculovirus production) / Protein subunit	Not available
Novavax	NVX-CoV2373 / Protein subunit	Pediatric and adolescent arms of the trials expected to initiate later in the second quarter 2021 https://www.marketwatch.com/story/novavax-to-expand-covid-19-vaccine-trials-to-children-teens-2021-04-05 The placebo-controlled portion of **PREVENT-19** RCT **(NCT04611802) continues in adolescents from 12 to less than 18 years of age**, which recently completed enrollment with 2248 participants
Valneva	VLA2001 / Inactivated virus	Not available
Sinovac Biotech	CoronaVac; SARS-CoV-2 vaccine (inactivated) / Inactivated virus	**RCT on 500 children in China ages 3 to 17; preliminary results from phase ½ trials announced** safe and could induce immune responses among children and adolescents; The lower dose of the vaccine could induce favourable antibody responses in children aged three to 11 years while the medium dose worked well for those aged 12 to 17 years. https://www.clinicaltrialsarena.com/news/sinovac-vaccine-immune-responses-children/, and **published**, see scientific publication below Han et al. 2021 [95]

Table 2-4: Intranasal vaccine in development

Developers	Vaccine platform	Vaccine type	No of doses	Study Phase	Registry number
AstraZeneca + University of Oxford	Viral vector (Non-replicating)	ChAdOx1-S - (AZD1222) (Covishield)	1-2	1	NCT04816019
University of Hong Kong, Xiamen University and Beijing Wantai Biological Pharmacy	Viral vector (Replicating)	DelNS1-2019-nCoV-RBD-OPT1 (Intranasal flu-based-RBD)	2	2	ChiCTR2000039715
Codagenix/Serum Institute of India	Live attenuated virus	COVI-VAC	1-2	1	NCT04619628
Center for Genetic Engineering and Biotechnology (CIGB)	Protein subunit	CIGB-669 (RBD+AgnHB)	3	1/2	RPCEC00000345
Bharat Biotech International Limited	Viral vector (Non-replicating)	BBV154, Adenoviral vector COVID-19 vaccine	1	1	NCT04751682
Meissa Vaccines, Inc.	Live attenuated virus	MV-014-212, a live attenuated vaccine that expresses the spike (S) protein of SARS-CoV-2	3	1	NCT04798001
CyanVac LLC	Viral vector (Non-replicating)	PIV5 vector that encodes the SARS-COV-2 spike protein	1	1	NCT04954287

Source: Adapted from DRAFT landscape of COVID-19 candidate vaccines – September 10, 2021, https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines

2.1 Moderna Therapeutics—US National Institute of Allergy

The reader is referred to the earlier version (V13_April) for more details on the Moderna vaccine (now Spikevax, previously COVID-19 Vaccine Moderna).

Details zu Moderna in V13_April

Current data related to clinical effectiveness and in vitro neutralisation, on Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1) and Delta (B.1.617.2) SARS-CoV-2 variants can be found in Table 2-2.

Wirksamkeit bei Mutanten in Tabelle 2-2

Moderna has announced that it is developing two new approaches to emerging variants of covid-19 after studies showed that its vaccine had a reduced level of neutralising titres to the South African variant, suggesting that immunity might wane. Although the studies showed that Moderna's current vaccine was effective against both the UK and South African variants, a sixfold reduction was seen in neutralising titre levels to the South African variant. In the first approach Moderna said that it would see whether a third "booster dose" of the current mRNA-1273 vaccine added to the approved two dose regimen would further increase neutralising titres against the emerging variants. In a second approach the company said that it had developed a booster vaccine candidate called mRNA-1273.351 against the emerging South African variant. It said that it was beginning phase I studies in the US to see whether this modified vaccine with variant specific proteins would increase the immunological effect [96].

Studie zu Wirksamkeit von mRNA Impfstoffen gegen Delta

Edara et al. 2021 [77] published results from an analysis aimed to assess neutralizing activity against the SARS-CoV-2 delta variants in a live-virus assay using serum samples obtained from infected and vaccinated persons with two mRNA vaccines (Moderna and Pfizer). The B.1.617.1 variant was 6.8 times less susceptible, and the B.1.617.2 variant was 2.9 times less susceptible, to neutralization by serum from persons who had recovered from Covid-19 and from vaccinated persons than was the WA1/2020 variant. Despite this finding, a majority of the convalescent serum samples (79% [19 of 24 samples] against B.1.617.1 and 96% [23 of 24 samples] against B.1.617.2) and all serum samples from vaccinated persons still had detectable neutralizing activity above the threshold of detection against both variants through 3 months after infection or after the second dose of vaccine.

Data related to development of vaccine in children can be found in Table 2-3.

TeenCove Phase 2/3 RCT: 3.700 Jugendliche 12-17 J

Ergebnisse publiziert

On May 25, 2021 Moderna announced that TeenCove phase 2/3 study of its COVID-19 vaccine (mRNA-1273) in adolescents has met its primary immunogenicity endpoint, successfully bridging immune responses to the adult vaccination. In the study, no cases of COVID-19 were observed in participants who had received two doses of the Moderna COVID-19 vaccine using the primary definition. In addition, a vaccine efficacy of 93% in seronegative participants was observed starting 14 days after the first dose using the secondary CDC case definition of COVID-19, which tested for milder disease. This study, known as the TeenCOVE study, enrolled more than 3,700 participants ages 12 to less than 18 years in the U.S. [97]. Results of this trial (NCT04649151) are published on August by Ali et al. 2021 [15]. A total of 3732 participants were randomly assigned to receive mRNA-1273 (2489 participants) or placebo (1243 participants). In the mRNA-1273 group, the most common solicited adverse reactions after the first or second injections were injection-site pain (in 93.1% and 92.4%, respectively),

headache (in 44.6% and 70.2%, respectively), and fatigue (in 47.9% and 67.8%, respectively); in the placebo group, the most common solicited adverse reactions after the first or second injections were injection-site pain (in 34.8% or 30.3%, respectively), headache (in 38.5% and 30.2%, respectively), and fatigue (in 36.6% and 28.9%, respectively). No serious adverse events related to mRNA-1273 or placebo were noted. The geometric mean titer ratio of pseudovirus neutralizing antibody titers in adolescents relative to young adults was 1.08 (95% confidence interval [CI], 0.94 to 1.24), and the absolute difference in serologic response was 0.2 percentage points (95% CI, −1.8 to 2.4), which met the noninferiority criterion. No cases of Covid-19 with an onset of 14 days after the second injection were reported in the mRNA-1273 group, and four cases occurred in the placebo group.

2.2 University of Oxford/ Astra Zeneca

Details zu Vaxzevria in V13_April

The reader is referred to the earlier version (V13_April) for more details on the **Vaxzevria,** previously **COVID-19 Vaccine AstraZeneca.**

RCT (Südafrika) 1467 Geimpfte geringe Wirksamkeit gegen B.1.351

Madhi et al. 2021 [26] published results from **RCT** (NCT04444674) **in South Africa.** Participants 18 to less than 65 years of age were assigned in a 1:1 ratio to receive two doses of vaccine containing 5×1010 viral particles or placebo (0.9% sodium chloride solution) 21 to 35 days apart. Serum samples obtained from 25 participants after the second dose were tested by pseudovirus and live-virus neutralization assays against the **original D614G virus and the B.1.351 variant.** The primary end points were safety and efficacy of the vaccine against laboratory-confirmed symptomatic coronavirus 2019 illness (Covid-19) more than 14 days after the second dose. Both the pseudovirus and the live-virus neutralization assays showed greater resistance to the B.1.351 variant in serum samples obtained from vaccine recipients than in samples from placebo recipients. In the primary end-point analysis, mild-to-moderate Covid-19 developed in 23 of 717 placebo recipients (3.2%) and in 19 of 750 vaccine recipients (2.5%), for an efficacy of 21.9% (95% confidence interval [CI], −49.9 to 59.8). Among the 42 participants with Covid-19, 39 cases (92.9%) were caused by the B.1.351 variant; vaccine efficacy against this variant, analyzed as a secondary end point, was 10.4% (95% CI, −76.8 to 54.8). The incidence of serious adverse events was balanced between the vaccine and placebo groups. two-dose regimen of the ChAdOx1 nCoV-19 vaccine did not show protection against mild-to-moderate Covid-19 due to the B.1.351 variant.

post-hoc Analyse: geringere Wirksamkeit gegen B.1.1.7 (70%) als gegen andere Mutationen (82%)

Emary et al. 2021 [27] published results from **post-hoc analysis** of the efficacy of the adenoviral vector vaccine, ChAdOx1 nCoV-19 (AZD1222), revealed that laboratory virus neutralization activity by vaccine-induced antibodies was lower against **B.1.1.7 variant**. However, clinical vaccine efficacy against symptomatic NAAT positive infection was good, with 70% (95% CI 44–85) for B.1.1.7 and 82% (68–89) for other lineages.

Current data related to clinical effectiveness and in vitro neutralisation, on **Alpha** (**B.1.1.7**), **Beta** (**B.1.351**), **Gamma** (**P.1**) and **Delta** (**B.1.617.2**) can be found in Table 2-2.

Wirksamkeit von BioNTech + Vaxzevria gegen B.1.617.2 (Delta)

Lopez Bernal et al. 2021 published as preprint, and later in scientific journal, results from observational study related to the effectiveness of the BNT162b2 and ChAdOx1 COVID-19 vaccines against B.1.617.2 COVID-19 variant [61] [79]. Effectiveness was notably lower after 1 dose of vaccine with

B.1.617.2 cases 33.5% (95%CI: 20.6 to 44.3) compared to B.1.1.7 cases 51.1% (95%CI: 47.3 to 54.7) with similar results for both vaccines. With BNT162b2 2 dose effectiveness reduced from 93.4% (95%CI: 90.4 to 95.5) with B.1.1.7 to 87.9% (95%CI: 78.2 to 93.2) with B.1.617.2. With ChAdOx1 2 dose effectiveness reduced from 66.1% (95% CI: 54.0 to 75.0) with B.1.1.7 to 59.8% (95%CI: 28.9 to 77.3) with B.1.617.2. Sequenced cases detected after 1 or 2 doses of vaccination had higher odds of infection with B.1.617.2 compared to unvaccinated cases (OR 1.40; 95%CI: 1.13-1.75).

vergleichende Studien zur Wirksamkeit BioNTech + Vaxzevria gene Alpha und Delta

Vorteil für BioNTech

Sheikh et al. 2021 published results from observational study in Scotland [78]: they report 19% reduced AZD1222 efficacy following two doses (60%) relative to two doses of BNT162b2 (79%) against the B.1.617.2 variant and similar to reduced efficacy against the B.1.1.7 variant following two doses (73% for AZD1222 *vs* 92% for BNT162b2). Wall et al. 2021 [98] published results of their analysis aimed to determine B.1.617.2 sensitivity to AZD1222-induced neutralising antibodies (NAbs) and to compare this to our previous measurements of NAbs induced by BNT162b2 (Pfizer–BioNTech): AZD1222 recipients have lower NAbTs than BNT162b2 recipients against SARS-CoV-2 variants, including B.1.617.2. Liu et al. 2021 [73] published results from analysis tested neutralization of B.1.617.1 and B.1.617.2 using serum from individuals who had received 2 doses of the BNT162b2 Pfizer-BioNTech or ChAdOx1 nCoV-19 Oxford- AstraZeneca vaccine. Geometric mean neutralization titres against B.1.617.1 were reduced 2.7-fold ($p<0.0001$) relative to the Victoria virus for the Pfizer-BioNTech vaccine serum and 2.6-fold ($p<0.0001$) for the Oxford-AstraZeneca vaccine. For B.1.617.2 titres were reduced 2.5-fold ($p<0.0001$) relative to the Victoria virus for the Pfizer-BioNTech vaccine serum and 4.3-fold ($p<0.0001$) for the Oxford-AstraZeneca vaccine.

Wirkung einer verzögerten Veabreichung der 2. oder 3. Impfdosis

Flaxman et al. 2021 [99] published as preprint results related to reactogenicity and immunogenicity of a delayed second dose or a third dose of ChAdOx1 nCoV-19 vaccine. A longer delay before the second dose of ChAdOx1 nCoV-19 leads to an increased antibody titre after the second dose. A third dose of ChAdOx1 nCoV-19 induces antibodies to a level that correlate with high efficacy after second dose and boosts T-cell 33 responses.

Data related to development of vaccine in children can be found in Table 2-3.

2.3 BioNTech/Fosun Pharma/Pfizer

Details zu Comirnaty in V13_April

The reader is referred to the earlier version (V13_April) for more details on the vaccines developed by BioNTech and Pfizer – Comirnaty.

On May 3, 2021 EMA's human medicines committee started an accelerated assessment of data submitted on Comirnaty, including results from a large ongoing clinical study involving adolescents from 12 years of age, in order to decide whether to recommend the extension of indication [88].

On May 10, 2021 FDA authorised expanded the emergency use authorization (EUA) for the Pfizer-BioNTech COVID-19 Vaccine for the prevention of COVID-19 to include adolescents 12 through 15 years of age [89].

Current data related to clinical effectiveness and in vitro neutralisation, on **Alpha** (**B.1.1.7**), **Beta** (**B.1.351**), **Gamma** (**P.1**) and **Delta** (**B.1.617.2**) **SARS-CoV-2 variants** can be found in Table 2-2.

Wirksamkeit bei Mutanten in Tabelle 2-2

Real-world observational studies found high effectiveness of the BNT162b2 Covid-19 Vaccine against the **B.1.1.7** (in Israel: vaccine effectiveness at 7 days or longer after the second dose was 95% against SARS-CoV-2 infection, 97% against symptomatic COVID-19, 97% against hospitalisation, and 98% against severe or critical disease) and **B.1.351** variants: in Qatar (estimated effectiveness against any documented infection with the B.1.1.7 variant was 89.5% at 14 days or more after the second dose; effectiveness against any documented infection with the B.1.351 variant was 75%; effectiveness against severe, critical, or fatal disease with the B.1.1.7 and B.1.351 variants was very high, at 97%) [100, 101].

RWD: Wirksamkeit von BioNTech gegen B.1.1.7 (Aplpha), B.1.351 (Beta)

Lopez Bernal et al. 2021 published as preprint, and later in scientific journal, results from observational study related to the effectiveness of the BNT162b2 and ChAdOx1 COVID-19 vaccines against B.1.617.2 COVID-19 variant [61] [79]. Effectiveness was notably lower after 1 dose of vaccine with B.1.617.2 cases 33.5% (95%CI: 20.6 to 44.3) compared to B.1.1.7 cases 51.1% (95%CI: 47.3 to 54.7) with similar results for both vaccines. With BNT162b2 2 dose effectiveness reduced from 93.4% (95%CI: 90.4 to 95.5) with B.1.1.7 to 87.9% (95%CI: 78.2 to 93.2) with B.1.617.2. With ChAdOx1 2 dose effectiveness reduced from 66.1% (95% CI: 54.0 to 75.0) with B.1.1.7 to 59.8% (95%CI: 28.9 to 77.3) with B.1.617.2. Sequenced cases detected after 1 or 2 doses of vaccination had higher odds of infection with B.1.617.2 compared to unvaccinated cases (OR 1.40; 95%CI: 1.13-1.75).

Wirksamkeit von BioNTech + Vaxzevria gegen B.1.617.2 (Delta)

On **July 5, 2021** according to a preliminary study announced by Israel's health ministry, BioNTech/Pfizer vaccine is less effective at halting the spread of the Delta variant: the vaccine is 64% effective at preventing infection among those who are fully inoculated but 93% effective against serious illness and hospitalisation, https://www.timesofisrael.com/israel-confirms-vaccine-less-effective-against-delta-variant-eyes-third-dose/. Based on these data, on July 8, 2021 Pfizer announced that it will seek FDA authorisation for a booster shot.

BioNTech weniger wirksam, Infektion mit Delta zu verhinden, aber wirksam gegen schwere Erkrankungen

Data related to development of vaccine in children can be found in Table 2-3.

Frenck et al. 2021 [31] [32] published results from ongoing multinational, placebo-controlled, observer-blinded trial (NCT04368728) in which **12-to-15-year-old participants** were randomly assigned in a 1:1 ratio to receive two injections, 21 days apart, of 30 μg of BNT162b2 or placebo. Noninferiority of the immune response to BNT162b2 in 12-to-15-year-old participants as compared with that in 16-to-25-year old participants was an immunogenicity objective. Safety (reactogenicity and adverse events) and efficacy against confirmed coronavirus disease 2019 (Covid-19; onset, ≥7 days after dose 2) in the 12-to-15-year-old cohort were assessed. 2260 adolescents 12 to 15 years of age received injections; 1131 received BNT162b2, and 1129 received placebo. As has been found in other age groups, BNT162b2 had a favorable safety and side-effect profile, with mainly transient mild to-moderate reactogenicity (predominantly injection-site pain [in 79 to 86% of participants], fatigue [in 60 to 66%], and headache [in 55 to 65%]); there were no vaccine related serious adverse events and few overall severe adverse events. The geometric mean ratio of SARS-CoV-2 50% neutralizing titers after dose 2 in 12-to-15-year-old participants relative to 16-to-25-year-old participants was 1.76 (95% confidence interval [CI], 1.47 to 2.10), which met the noninferiority criterion of a lower boundary of the two-sided 95%

laufender RCT: 12-15 J 2.260 Teilnehmer*innen

confidence interval greater than 0.67 and indicated a greater response in the 12-to-15-year-old cohort. Among participants without evidence of previous SARS-CoV-2 infection, no Covid-19 cases with an onset of 7 or more days after dose 2 were noted among BNT162b2 recipients, and 16 cases occurred among placebo recipients. The observed vaccine efficacy was 100% (95% CI, 75.3 to 100).

2.4 Janssen Pharmaceutical/ Johnson & Johnson

Details zu J&J in V13_April

The reader is referred to the earlier version (V13_April) for more details on the **COVID-19 Vaccine J&J**

Phase 3 RCT
19.630 Geimpfte

Auswertung der Mutanten und Analyse der Wirksamkeit

Sadoff et al. 2021[33] published results from an international, randomized, double-blind, placebo-controlled, **phase 3 trial**, in which adult participants were randomly assigned in a 1:1 ratio to receive a single dose of Ad26.COV2.S (5×1010 viral particles) or placebo (**ENSEMBLE**, NCT04505722). The per-protocol population included 19,630 SARS-CoV-2–negative participants who received Ad26.COV2.S and 19,691 who received placebo. On the basis of interim sequencing data from 512 unique RT-PCR–positive samples obtained from 714 participants (71.7%) with SARS-CoV-2 infection, the reference sequence (Wuhan-Hu-1 including the D614G mutation) was detected predominantly in the United States (190 of 197 sequences [96.4%]) and the 20H/501Y. V2 variant (also called **B.1.351**) was detected predominantly in South Africa (86 of 91 sequences [94.5%]), whereas in Brazil, the reference sequence was detected in 38 of 124 sequences (30.6%) and the reference sequence with the E484K mutation (**P.2 lineage**) was detected in 86 of 124 sequences (69.4%).

Wirksamkeit bei Mutanten in Tabelle 2-2

Ad26.COV2.S protected against moderate to severe–critical Covid-19 with onset at least 14 days after administration (116 cases in the vaccine group vs. 348 in the placebo group; efficacy, 66.9%; adjusted 95% confidence interval [CI], 59.0 to 73.4) and at least 28 days after administration (66 vs. 193 cases; efficacy, 66.1%; adjusted 95% CI, 55.0 to 74.8). Vaccine efficacy was higher against severe–critical Covid-19 (76.7% [adjusted 95% CI, 54.6 to 89.1] for onset at ≥14 days and 85.4% [adjusted 95% CI, 54.2 to 96.9] for onset at ≥28 days). Despite 86 of 91 cases (94.5%) in South Africa with sequenced virus having the 20H/501Y.V2 **variant** (also called **B.1.351**), vaccine efficacy was 52.0% and 64.0% against moderate to severe–critical Covid-19 with onset at least 14 days and at least 28 days after administration, respectively, and efficacy against severe–critical Covid-19 was 73.1% and 81.7%, respectively. Reactogenicity was higher with Ad26.COV2.S than with placebo but was generally mild to moderate and transient. The incidence of serious adverse events was balanced between the two groups. Three deaths occurred in the vaccine group (none were Covid-19–related), and 16 in the placebo group (5 were Covid-19–related).

Daten, dass J&J gegen Delta wirksamer ist als gegen Beta, Dauer der Immunantwort: zumindest 8 Monate

On **July 1, 2021** Johnson & Johnson **announced** data that demonstrated its single-shot COVID-19 vaccine generated strong, persistent activity against the rapidly spreading **Delta variant** and other highly prevalent SARS-CoV-2 viral variants. It elicited neutralizing antibody activity against the Delta variant at an even higher level than what was recently observed for the Beta (B.1.351) variant in South Africa where high efficacy against severe/critical disease was demonstrated (see above ENSEMBLE trial results). In addition, the data showed that the durability of the immune response lasted through at least eight months, the length of time evaluated to date,

https://www.jnj.com/positive-new-data-for-johnson-johnson-single-shot-covid-19-vaccine-on-activity-against-delta-variant-and-long-lasting-durability-of-response.

Current data related to clinical effectiveness and in vitro neutralisation, on **Alpha** (**B.1.1.7**), **Beta** (**B.1.351**), **Gamma** (**P.1**) and **Delta** (**B.1.617.2**) **SARS-CoV-2 variants** can be found in Table 2-2.

Data related to development of vaccine in children can be found in Table 2-3.

2.5 Novavax

About the vaccine

CEPI
Matrix-M™

The Novavax COVID-19 vaccine being developed by Novavax and co-sponsored by CEPI [102] is a recombinant protein nanoparticle technology platform that is to generate antigens derived from the coronavirus spike (S) protein [103]. Matrix-M™ is Novavax patented saponin-based adjuvant that has the potential to boost the immune system by stimulating the entry of antigen-presenting cells into the injection site and enhancing antigen presentation in local lymph nodes, boosting immune responses [104, 105].

Estimated timeline for approval

Phase 1:
131 gesunde Erwachsene

Juli 2021

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 [106-109]. This RCT will be conducted from May 15, 2020 to July 31, 2021. Estimated Primary Completion Date is December 31, 2020.

Phase 2b RCT
2.904 Südafrika
bis 2021

A **phase 2b** RCT trial (NCT04533399) aims to evaluate the effectiveness and safety in South Africans adults; 2904 participants are planned to enrolled, with estimated primary completion date in November 2021 [109].

Phase 3
9.000 Teilnehmer*innen
in UK

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.

Results of publications

Publikation der Phase 1/2

keine schwerwiegenden
NW beobachtet

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 [16]. 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).

Phase 2 RCT Publikation
250 Teilnehmer*innen
in 4 Gruppen

Formica et al. 2021 [17] published, as preprint, results from **phase 2 component** of above mentioned RCT (NCT04368988): participants were randomly assigned to receive either one or two intramuscular doses of 5-µg or 25-µg NVX-CoV2373 or placebo, 21 days apart. Approximately 250 participants each were assigned to one of four vaccine groups or placebo. Of these, approximately 45% were older participants. Reactogenicity was predominantly mild to moderate in severity and of short duration (median <3 days) after first and second vaccination with NVX-CoV2373, with higher frequencies and intensity after second vaccination and with the higher dose, and occurred less frequently and was of lower intensity in older participants. The two-dose regimen of 5-µg NVX-CoV2373 induced robust geometric mean titer (GMT) IgG anti-spike protein (65,019 and 28,137 EU/mL) and wild-type virus neutralizing antibody (2201 and 981 titers) responses in younger and older participants, respectively, with seroconversion rates of 100% in both age groups.

On January 28, 2021 Novavax, Inc. **announced** that NVX-CoV2373, its protein-based COVID-19 vaccine candidate, met the primary endpoint, with a vaccine efficacy of **89.3%**, in its **phase 3** clinical trial conducted in the United Kingdom. The study assessed efficacy during a period with high transmission and with a **new UK variant strain** of the virus emerging and circulating widely. It was conducted in partnership with the UK Government's Vaccines Taskforce.

Novavax also announced successful results of its **phase 2b** study conducted in South Africa in which approximately 90% of COVID-19 cases attributed to **South Africa** escape **variant**: **60% efficacy** for the prevention of mild, moderate and severe COVID-19 disease was observed [110].

Phase 3 RCT: UK
15.187 Teilnehmer*innen

89,7% Wirksamkeit
(auch bei hohem Anteil
von UK-Mutation)

Heath et al. 2021 [19] published results as preprint from this **phase 3** RCT in **UK** mentioned above (EudraCT 2020-004123-16): A total of 15,187 participants were randomized, of whom 7569 received NVXCoV2373 and 7570 received placebo. NVX-CoV2373 was 89.7% (95% confidence interval, 80.2 to 94.6) effective in preventing Covid-19, with no hospitalisations or deaths reported. There were five cases of severe Covid-19, all in the placebo group. Post hoc analysis revealed efficacies of 96.4% (73.8 to 99.5) and **86.3%** (71.3 to 93.5) against the prototype strain and **B.1.1.7 variant**, respectively. Vaccine efficacy was similar across subgroups, including participants with comorbidities and those ≥65 years old. Reactogenicity was generally mild and transient. The incidence of serious adverse events was low and similar in the two groups.

Phase 2a/b RCT
4.387 Teilnehmer*innen

Wirksamkeit
bei Mutanten in
Tabelle 2-2

Shinde et al. 2021 [18] published as preprint, and then as scientific publication [111] **preliminary results** from phase **2a/b** RCT in **South Africa,**: a total of 4387 participants were randomized and dosed at least once, 2199 with NVX-CoV2373 and 2188 with placebo. Vaccine efficacy was 49.4% (95% confidence interval [CI]: 6.1 to 72.8). Efficacy in HIV-negative participants was 60.1% (95% CI: 19.9 to 80.1), and did not differ by baseline serostatus. Of the primary endpoint cases with available whole genome sequencing, 38 (92.7%) of 41 were the B.1.351 variant. Post-hoc vaccine efficacy against B.1.351 was 51.0% (95% CI: - 0.6 to 76.2) in HIV-negative participants. Preliminary local and systemic reactogenicity events were more

common in the vaccine group; serious adverse events were rare in both groups.

Phase 3 RCT
PREVENT-19
29.960 Teilnehmer*innen
Teil von PREVENT-19
an 12-18 jährigen
vorläufige Ergebnisse:
hohe Wirksamkeit

On 16 June 2021 Novavax announced preliminary positive results from **PREVENT-19, phase 3** trial (NCT04611802) [112] (a 2:1 randomized, placebo-controlled, observer-blinded study to evaluate the efficacy, safety and immunogenicity of NVX-CoV2373 with Matrix-M™ adjuvant in 29,960 participants 18 years of age and older in 119 locations in the **United States and Mexico**, compared with placebo): NVX-CoV2373 demonstrated overall efficacy of 90.4% (95% CI: 82.9, 94.6), achieving its primary endpoint; 93% efficacy against predominantly circulating Variants of Concern and Variants of Interest; 91% efficacy in high-risk populations; 100% efficacy against variants "not considered Variants of Concern/Interest"; All COVID-19 hospitalizations/death occurred in the placebo group. Preliminary safety data from PREVENT-19 showed the vaccine to be generally well-tolerated. Serious and severe adverse events were low in number and balanced between vaccine and placebo groups. No single adverse event term was reported by more than 1% of participants. In assessing reactogenicity 7 days after Dose 1 and Dose 2, injection sitepain and tenderness, generally mild to moderate in severity, were the most common local symptoms, lasting less than 3 days. Fatigue, headache and muscle pain were the mostcommon systemic symptoms, lasting less than 2 days. The **placebo-controlled portion of PREVENT-19 continues in adolescents from 12 to less than 18 years of age**, which recently completed enrollment with 2,248 participants.
Current data related to clinical effectiveness and in vitro neutralisation, on **Alpha** (**B.1.1.7**), **Beta** (**B.1.351**), **Gamma** (**P.1**) and **Delta** (**B.1.617.2**) **SARS-CoV-2 variants** can be found in Table 2-2.

Data related to development of vaccine in children can be found in Table 2-3.

2.6 CureVac

About the vaccine

mRNA

The vaccine candidate CVnCoV, developed by CureVac, is a protamine-complexed mRNA-based vaccine expressing undisclosed SARS-CoV-2 protein(s). Each CureVac product is a tailored molecular creation that contains 5' and 3' untranslated regions and the open reading frame to make sure translation of the messenger RNA (mRNA) sequence results in appropriate levels of proteins in the body. This means that CureVac's technology uses mRNA as a data carrier in order to train the human body to produce ideal levels of proteins. Thereby the immune system is stimulated and can respond to antigens [113, 114].

Jänner 2021: CureVac kooperiert mit Bayer

CureVac and Bayer joint forces in January 2021 on COVID-19 vaccine candidate CVnCoV to ramp up the production and distribution of vaccine. Vaccine remains stable and within defined specifications for at least three months when stored at a standard refrigerator temperature of +5°C (+41°F) and for up to 24 hours as ready-to-use vaccine when stored at room temperature, https://www.curevac.com/en/covid-19/.

Estimated timeline for approval

Phase 1:
Beginn klinische Studie:
Sommer 2020

Phase 1 (NCT04449276) study aims to evaluate the safety and reactogenicity profile after 1 and 2 dose administrations of CVnCoV at different dose levels. Is is funded by Coalition for Epidemic Preparedness Innovations (CEPI), and located in Belgium and Germany. More then 250 healthy participants are enrolled in the trial. Preliminary results reported as preprint in November 2020 strongly supported the decision to advance a 12μg dose in the pivotal phase 2b/3 study [34], https://www.curevac.com/en/covid-19/.

Phase 2

Phase 2, RCT (NCT04515147) initiated in September 2020 aims to evaluate the safety and reactogenicity profile after 1 and 2 dose administrations of investigational SARS-CoV-2 mRNA vaccine (CVnCoV) at different dose levels and to evaluate the humoral immune response after 1 and 2 dose administrations of CVnCoV. 691 participants are planned to be enroll in the trial, with estimated study completion date in November 2021 [109].

Phase 2/3

Pivotal **phase 2b/3** study (NCT04652102/EUdraCT 2020-00399822), initiated in December 2020, assesses a 12μg dose of CVnCoV in two parts: an initial phase 2b trial which is expected to seamlessly merge into a phase 3 efficacy trial. Both the phase 2b and phase 3 trials are randomized, observer-blind, placebo-controlled studies in adults over 18 years of age or older. While the objective of the phase 2b study is to further characterize the safety, reactogenicity and immunogenicity of CVnCoV, the phase 3 assesses CVnCoV efficacy. Subjects will be enrolled at multiple sites and vaccinations follow a two-dose schedule on day 1 and day 29 of either CVnCoV or a placebo. In total, more than 35,000 participants will be included in the phase 2b/3 **HERALD study** at multiple sites in Europe and Latin America, https://www.curevac.com/en/covid-19/.

Phase 3

A **phase 3** RCT (NCT04674189) aims to evaluate the safety and immunogeneity of CVnCoV vaccine in adult health care workers in Germany. Estimated enrollments is 2520 participants, with estimated primary completion date in June 2021 [109].

Results of publications

Phase 1:
akzeptable
Sicherheitsdaten

Preliminary results related to **phase 1** (NCT04449276) reported as **preprint** in November 2020 showed that two doses of CVnCoV ranging from 2 µg to 12 µg per dose, administered 28 days apart were safe. No vaccine-related serious adverse events were reported. There were dose-dependent increases in frequency and severity of solicited systemic adverse events, and to a lesser extent of local reactions, but the majority were mild or moderate and transient in duration. Median titers measured in assays two weeks after the second 12 µg dose were comparable to the median titers observed in convalescent sera from COVID-19 patients. Seroconversion (defined as a 4-fold increase over baseline titer) of virus neutralizing antibodies two weeks after the second vaccination occurred in all participants who received 12 µg doses [34].

Phase 2b/3 RCT
HERALD
40.000 Teilnehmer*innen

moderate Wirksamkeit

On **June 30, 2021** CureVac **announced** results from the final analysis of its 40,000 subject international pivotal **phase 2b/3 study** (the **HERALD** study, NCT04652102/EUdraCT 2020-00399822) of the first-generation COVID-19 vaccine candidate, CVnCoV [115]. In the context of 15 strains circulating within the study population at the time of final analysis, CVnCoV demonstrated an **overall vaccine efficacy of 48%** (vaccine 83 vs. 145 placebo) against COVID-19 disease of any severity, including single non-respiratory mild symptoms. Significant protection was demonstrated among participants in the age group of 18 to 60, with an efficacy of 53% (vaccine 71

vs. 136 placebo) against disease of any severity and across all 15 identified strains; protection against moderate to severe disease was calculated to be 77% (9 vaccine vs. 36 placebo). In the same age group, CVnCoV provided 100% protection (vaccine 0 vs. 6 placebo) against hospitalization or death. In participants above 60 years, who represented 9% of the analysed cases, the available data did not enable a statistically significant determination of efficacy. The data confirm the favorable safety profile of CVnCoV in all age groups. The study will continue to complete follow-up analyses for trial participants. Available data have been communicated to the European Medicines Agency (EMA).

Current data related to clinical effectiveness and in vitro neutralisation, on **Alpha** (**B.1.1.7**), **Beta** (**B.1.351**), **Gamma** (**P.1**) and **Delta** (**B.1.617.2**) **SARS-CoV-2 variants** can be found in Table 2-2.

Data related to development of vaccine in children can be found in Table 2-3.

2.7 Sanofi and GSK

About the vaccine

Protein subunit

In April 2020, Sanofi and GSK agreed to develop an adjuvanted vaccine for COVID-19, using innovative technology from both companies. Sanofi through its S-protein COVID-19 antigen, based on recombinant DNA technology (this technology has produced an exact genetic match to proteins found on the surface of the virus, and the DNA sequence encoding this antigen has been combined into the DNA of the baculovirus expression platform, the basis of Sanofi's licensed recombinant influenza product in the US). GSK through its proven pandemic adjuvant technology which can be of particular importance in a pandemic situation since it may reduce the amount of vaccine protein required per dose, allowing more vaccine doses to be produced and therefore contributing to protect more people. Development of the recombinant-based COVID-19 vaccine candidate is being supported through funding and a collaboration with the Biomedical Advanced Research and Development Authority (BARDA), part of the office of the Assistant Secretary for Preparedness and Response at the U.S. Department of Health and Human Services, https://www.sanofi.com/en/media-room/press-releases/2020/2020-04-14-13-00-00. Vaccine could be kept in standard refrigerators, making it easier to distribute.

Estimated timeline for approval

Phase 1/2

On December 11, 2020 Sanofi and GSK announced a delay in their adjuvanted recombinant protein-based COVID-19 vaccine program to improve immune response in older adults. https://www.sanofi.com/en/media-room/press-releases/2020/2020-12-11-07-00-00.

Phase 1/2 study

Zwischenauswertung

Antikörperbildung am besten bei 18-49 J,

weniger bei ≥ 50 J oder gar bei ≥ 60 J

The interim RCT, **phase 1/2** results (NCT04537208, as preprint, and now as scientific publication) showed a level of neutralising antibody titers after two doses comparable to sera from patients who recovered from COVID-19, a balanced cellular response in adults aged 18 to 49 years, but insufficient neutralising antibody titers in adults over the age of 50. The candidate showed transient but higher than expected levels of reactogenicity likely due to the suboptimal antigen formulation, with no serious adverse events related to the vaccine candidate. The most favorable results were observed in the group which tested the highest antigen concentration, combined with the GSK adjuvant, showing neutralisation titers in 88% of participants. Seroconversion was observed in 89.6% of the 18 to 49 age group; 85% in the >50 age group; and 62.5% in the >60 age group [36] [116].

Phase 2b and phase 3 studies

Phase 2b, 722 Teilnehmer*innen

Phase 3: 35.000 Teilnehmer*innen

The Companies initiate a **phase 2b** study with an improved antigen formulation in February 2021. On May 17, 2021 Sanofi and GSM announced in a press release that adjuvanted recombinant COVID-19 vaccine candidate achieved strong rates of neutralizing antibody responses, in line with those measured in people who have recovered from COVID-19, in all adult age groups in a phase 2 study with 722 volunteers. The phase 2 interim results showed 95% to 100% seroconversion following a second injection in all age groups (18 to 95 years old) and across all doses, with acceptable tolerability and with no safety concerns. Overall, the vaccine candidate elicited strong neutralizing antibody levels that were comparable to those generated by natural infection, with higher levels observed in younger adults (18 to 59 years old). After a single injection, high neutralizing antibody levels were generated in participants with evidence of prior SARS-CoV-2 infection, suggesting strong potential for development as a booster vaccine. Based on these positive phase 2 interim results, the companies initiates a global phase 3, randomized, double-blind study with the 10µg dose, in combination with GSK's pandemic adjuvant. This phase 3 trial is expected to enroll more than 35000 adult participants from a broad range of countries and will assess the efficacy of two vaccine formulations including the D614 (Wuhan) and B.1.351 (South African) variants.

Zulassung Q4 2021 geplant

In parallel, the companies intend to conduct booster studies with various variant formulations in order to assess the ability of a lower dose of the vaccine to generate a strong booster response regardless of the initial vaccine platform received. Pending positive phase 3 outcomes and regulatory reviews, the vaccine is expected to be approved in the fourth quarter of 2021 [117].

Current data related to clinical effectiveness and in vitro neutralisation, on **Alpha** (**B.1.1.7**), **Beta** (**B.1.351**), **Gamma** (**P.1**) and **Delta** (**B.1.617.2**) **SARS-CoV-2 variants** can be found in Table 2-2.

Data related to development of vaccine in children can be found in Table 2-3.

2.8 Valneva

About the vaccine

Valneva vaccine candidate VLA2001 consists of inactivated whole virus particles of SARS-CoV-2 with high S-protein density, in combination with two adjuvants, alum and CpG 1018. This adjuvant combination has consistently induced higher antibody levels in preclinical experiments than alum-only formulations and shown a shift of the immune response towards Th1. VLA2001 is produced on Valneva's established Vero-cell platform, leveraging the manufacturing technology for Valneva's licensed Japanese encephalitis vaccine, IXIARO®. The process, which has already been upscaled to final industrial scale, includes inactivation with BPL to preserve the native structure of the S-protein.

inaktivierte SARS-CoV-2-Viren

VLA2001 is expected to conform with standard cold chain requirements (2-8° C).

Estimated timeline for approval

Valneva initiated **phase 1/2** clinical study in December 2020; randomised, double blind trial evaluating the safety and immunogenicity for three dose levels in approximately 150 healthy adults. The primary endpoint read-out will be two weeks after completion of the two-dose primary immunization (day 0, 21). Subject to analysis of this data, additional trials are expected to commence immediately thereafter. A total of 150 healthy adults aged 18 to 55 years have been recruited. Initial results are expected in April 2021, https://valneva.com/press-release/valneva-commences-manufacturing-of-its-inactivated-adjuvanted-covid-19-vaccine-completes-phase-1-2-study-recruitment/.

Phase 1/ 2 RCT began im Dez 2020
150 Teilnehmer*innen

Ergebnisse im April 2021

On 6 April 2021, Valneva announced results from above mentioned RCT, suggested the vaccine is immunogenic, with more than 90% of all study participants developing significant levels of antibodies to the SARS-CoV-2 virus spike protein across three dose groups tested. In the high dose group, after two doses, antibody titres were at or above levels for a panel of convalescent sera, 2021 https://valneva.com/press-release/valneva-reports-positive-phase-1-2-data-for-its-inactivated-adjuvanted-covid-19-vaccine-candidate-vla2001/.

Presseaussendung: 90% der Impfstudien-Teilnehmer*innen entwickelten Antikörper

The Company currently plans to include more than 4,000 participants in additional trials, which it believes could support an initial regulatory approval as soon as the fourth quarter of 2021. Valneva completed recruitment for the **phase 3** clinical trial: over 4,000 volunteers have been recruited in the United Kingdom for the phase 3 immunogenicity trial **Cov-Compare**, which compares **VLA2001 against** AstraZeneca's conditionally approved vaccine, **Vaxzevria**. Topline data are expected early in fourth quarter 2021. In August 2021, Valneva initiated a further **phase 3, VLA2001-304**, to generate data in the **elderly** and to potentially enable variant-bridging through immune-comparability. Data from this study are expected to complement ongoing clinical trials and support additional regulatory submissions. Valneva is **participating in a UK government-funded clinical trial** looking at **different COVID-19 'booster' vaccines**. The **Cov-Boost trial**, led by University Hospital Southampton NHS Foundation Trust, will look at **seven different COVID-19 vaccines, including VLA2001, as potential boosters**. It will be the first trial in the world to provide vital data on how effective a booster of each vaccine is in protecting individuals from the virus, https://valneva.com/research-development/covid-19-vla2001/.

Planung von Phase 3 RCT mit 4.000 Teilnehmer*innen

VLA2001 komparative Studie (vs. Vaxzevria) sowie Cov-Booster Trial

Current data related to clinical effectiveness and in vitro neutralisation, on **Alpha** (**B.1.1.7**), **Beta** (**B.1.351**), **Gamma** (**P.1**) and **Delta** (**B.1.617.2**) **SARS-CoV-2 variants** can be found in Table 2-2.

Data related to development of vaccine in children can be found in Table 2-3.

2.9 Sinovac Life Science Co., Ltd

Details zu J&J in V13_April

The reader is referred to the earlier version (V09_December 2020, subsection 2.5) for more details on the inactivated **CoronaVac vaccine** developed by **Sinovac Life Sciences Co., Ltd.**

Mai EMA beginnt "Rolling Review"

On **May 4, 2021, EMA**'s human medicines committee has started a **rolling review** of COVID-19 Vaccine (Vero Cell) Inactivated, developed by Sinovac Life Sciences Co., Ltd. The EU applicant for this medicine is Life'On S.r.l [9].

Phase 1/ 2 RCT
Kinder 3-17 J

Phase 1: Dosisfindung
Phase 2: 2.480 Teilnehmer*innen

Studie läuft noch

Han et al. 2021 [118] published results (as preprint) and then as scientific article [95] from randomised, double-blind, placebo-controlled **phase 1/2** clinical trial of CoronaVac in **healthy children and adolescents aged 3-17 years old** in Zanhuang (Hebei, China) (NCT04551547). CoronaVac was well tolerated and induced strong neutralising antibody responses in children and adolescents aged 3-17 years. Vaccine (in 0·5ml aluminum 10 hydroxide adjuvant) or placebo (adjuvant only) was given by intramuscular injection in two doses (day 0 and day 28). Phase 1 trial was conducted in 72 participants with an age de-escalation in tree groups and dose-escalation in two blocks (1.5ug or 3ug per injection). Within each block, participants were randomly assigned (3:1) using block randomisation to receive CoronaVac or placebo. In phase 2, 480 participants were randomly assigned (2:2:1) using block randomisation to receive either CoronaVac at 1.5ug or 3ug per dose, or placebo. The primary safety endpoint was adverse reactions within 28 days after each injection in all participants who received at least one dose. The primary immunogenicity endpoint was seroconversion rate at 28 days after the second injection and its GMT as the secondary endpoint.

Nebenwirkungen: mild
hohe Wirksamkeit

This study is ongoing and is registered with ClinicalTrials.gov (NCT04551547). 2550 participants received at least one dose of vaccine or placebo (n=71 for phase 1 and n=479 for phase 2; safety population). In the combined safety profile of phase 1 and phase 2, any adverse reactions within 28 days after injection occurred in 56 (26%) of 219 participants in the 1·5ug group, 63 (29%) of 217 in the 3ug group and 27 (24%) of 114 in the placebo group, without significant difference. Most **adverse reactions were mild** and moderate in severity and injection site pain (73[13%]) of 550 participants was the most frequently reported event. As of June 12, 2021, only one serious adverse event of pneumonia has been reported in the alum-only group, which was considered unrelated to vaccination. In phase 1, seroconversion after the second dose was observed in 27 of 27 participants (100.0% [95%CI 87.3-100.0]) in the 1.5ug groups and 26 of 26 participants (100.0% [86.8-100.0]) in the 3ug group, with the geometric mean titers of 55.0 (95%CI 38.9-77.9) and 117.4 (87.8-157.0). In phase 2, **seroconversion** was seen in 180 of 186 participants (**96.8%** [93.1-98.8]) in the 1.5ug group and 180 of 180 participants (**100.0%** [98.0-100.0]) in the 3ug group, with the geometric mean titers of 86.4 (73.9-101.0) and 142.2 (124.7-162.1). There were no detectable antibody responses in the placebo groups. Neutralising antibody titres induced by the 3·0 μg dose were higher than those of the 1·5 μg dose.

The results support the use of 3·0 µg dose with a two-immunisation schedule for further studies in children and adolescents.

Wirksamkeit bei Mutanten in Tabelle 2-2

Current data related to clinical effectiveness and in vitro neutralisation, on **Alpha** (**B.1.1.7**), **Beta** (**B.1.351**), **Gamma** (**P.1**) and **Delta** (**B.1.617.2**) **SARS-CoV-2 variants** can be found in Table 2-2.

Data related to development of vaccine in children can be found in Table 2-3.

3 Results: Therapeutics

EU-Strategie: Unterstützung bei Medikamenten-entwicklung entlang des gesamten Lebenszyklus

öffentliche F&E

On **May 5, 2021** the **European Commission proposed EU Strategy for the development and availability of COVID-19 therapeutics,** to support the development and availability of much-needed COVID-19 therapeutics, including for the treatment of 'long COVID'. This Strategy covers the full lifecycle of medicines: from research, development and manufacturing to procurement and deployment. It includes clear actions and targets in the research, development and innovation; access to and swift approval of clinical trials; scanning for candidate therapeutics; supply chains and delivery of medicine; regulatory flexibility; joint procurement and financing and international cooperation to make medicine available to all, https://ec.europa.eu/commission/presscorner/detail/en/IP_21_2201.

Ende Juni 2021: EC EV verlautbart EU Strategie für Therapeutika – zentraler Ankauf

5 Hoffnungsträger

On **June 29, 2021** the EC announced that the EU Strategy on COVID-19 Therapeutics delivers its first outcome: the first portfolio of **five promising therapeutics identified** that **could soon be available** to treat patients across the **EU**. Four of these therapeutics are monoclonal antibodies under rolling review by the European Medicines Agency (**combination of bamlanivimab and etesevimab**; **combination of casirivimab and imdevimab**; **regdanvimab**; and **sotrovimab**.) Another one is an immunosuppressant, which has a marketing authorisation that could be extended to include the treatment of COVID-19 patients (**baricitinib**), https://ec.europa.eu/commission/presscorner/detail/en/ip_21_3299.

Current therapeutic management of patients with COVID-19 (outpatients and hospitalised patients): Summary

derzeitige Therapien im Management von Covid-19 Patient*innen

zugelassen:

Dexamethasone (und andere Korikosteroide)

Dexamethasone (and other systemic corticosteroids)

In **EU, dexamethasone use** is endorsed by **EMA** following referral procedure: it is **indicated** 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.**

von WHO & US COVID-19 Treatment Guidelines Panel empfohlen für Pts mit Beatmung,

In current **WHO living guidance** 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.**

nicht aber für Pts ohne Beatmung

The **US COVID-19 Treatment Guidelines Panel recommends against** the use of **dexamethasone (AIIa)** or **other corticosteroids (AIII)** for the treatment of COVID-19 in **patients who do not require supplemental oxygen**.

Therapieoptionen für invasiv und auch nicht-invasiv beatmete Pts

In patients who require supplemental oxygen one of the following options for these patients is **recommended**: **Remdesivir** (e.g., for patients who require minimal supplemental oxygen) **(BIIa)**; **Dexamethasone plus remdesivir** (e.g., for patients who require increasing amounts of oxygen) **(BIII)**; **or Dexamethasone** (when combination therapy with remdesivir cannot be used or is not available) **(BI)**. If dexamethasone is not available, an alternative corticosteroid such as **prednisone, methylprednisolone,** or **hydrocorti-sone** can be used **(BIII)**.

For patients who require delivery of oxygen through a high-flow device or noninvasive ventilation one of the following options for these patients is recommended: **Dexamethasone (AI); or Dexamethasone plus remdesivir (BIII)**. For recently hospitalized patients (i.e., those within 3 days of hospital admission) who have rapidly increasing oxygen needs, andsystemic inflammation, add either **baricitinib (BIIa)** or IV **tocilizumab (BIIa)** (drugs are listed alphabetically and not in order of preference) to one of the two options above. If neither baricitinib nor IV tocilizumab is available or feasible to use, **tofacitinib** can be used **instead of baricitinib** (**BIIa**) or IV **sarilumab instead of IV tocilizumab (BIIa**).

For patients who require Invasive Mechanical Ventilation or Extracorporeal Membrane Oxygenation the Panel recommends the use of **dexamethasone** in hospitalized patients with COVID-19 who require invasive mechanical ventilation or ECMO **(AI)**. The Panel recommends the use of **dexamethasone plus IV tocilizumab** for patients who are within 24 hours of admission to the ICU **(BIIa)**. If IV tocilizumab is not available or feasible to use, IV **sarilumab can be used (BIIa**).

Daily regimen of dexamethasone 6 mg once daily is equivalent to 160 mg of hydrocortisone, 40 mg of prednisone, and 32 mg of methylprednisolone.

Remdesivir (Veklury)

Remdesivir (Veklury) is an antiviral medicine for systemic use which received a **conditional marketing authorisation** in **EU.** It 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.** On June 11, 2021 **EMA** stated that PRAC has recommended a **change to the product information to include sinus bradycardia** as an **adverse reaction of unknown frequency** for this medicine.

EMA vorläufige Zulassung: Remdesivir (Veklury)

PRAC: Sinusbradykardie

The **FDA 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 hospitalisation.**

von WHO nicht empfohlen

Current WHO living guidance on remdesivir for COVID-19 has a **conditional recommendation against the use of remdesivir in hospitalised patients with COVID-19, regardless of disease severity.**

The US COVID-19 Treatment Guidelines Panel issued new recommendations on remdesivir treatment for patients with COVID-19: There are unsufficient data to recommend either for or against the routine use of remdesivir in hospitalised but does not require supplemental oxygen. For patients at high risk of disease progression, the use of remdesivir may be appropriate.

US COVID-19 Treatment Guidelines Panel: insuffiziente Datenlage bei Pt ohne Sauerstoff Hochrisiko Pt: ev. angemessen

Remdesivir is **recommended for use in hospitalised patients who require supplemental oxygen (BIIa); Dexamethasone plus remdesivir** (e.g., for patient who required increasing amounts of supplemental oxygen) (**BIII**); **Dexamethasone** (e.g., when combination therapy with remdesivir cannot be used or is not available) (**BI**). For hospitalized patients with COVID-19 who require oxygen delivery through a high-flow device or, noninvasive ventilation use one of the following options: **Dexamethasone (AI); Dexamethasone plus remdesivir** (e.g., for patients who require increasing amounts of oxygen) **(BIII).** For patients who were recently hospitalised with rapidly increasing oxygen needs and systemic inflammation: **Add** either **baricitinib** (**BIIa**) or IV **tocilizumab** to one of the two options above **(BIIa).**

Empfehlung: Pts, die zusätzlich Sauerstoff benötigen, nicht aber für jene, die bereits künstlich beatmet werden

If neither baricitinib nor IV tocilizumab is available or feasible to use, **tofacitinib** can be used **instead of baricitinib** (**BIIa**) or IV **sarilumab instead of IV tocilizumab (BIIa**).

For hospitalised patients with COVID-19 who require invasive mechanical ventilation or extracorporeal membrane oxygenation: **Dexamethasone (AI)**. For patients who are within 24 hours of administration to the ICU **dexamethasone plus tocilizumab (BIIa)**. If IV tocilizumab is not available or not feasible to use IV **sarilumab** can be used (**BIIa**).

Baricitinib

zugelassen nur in USA (EUA): Baricitinib als Kombinationstherapie mit Remdesivir

The **FDA** recently issued **revision to Emergency Use Authorization (EUA)** for the distribution and emergency use of **baricitinib to be used alone for the treatment of COVID-19 in hospitalised adults and pediatric patients two years of age or older requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).**

EMA is **evaluating** an **application to extend the use** of baricitinib (Olumiant) to include treatment of COVID-19 in **hospitalised patients from 10 years of age who require supplemental oxygen**.

US COVID-19 Treatment Guidelines Panel: Empfehlung für Baricitinib oder Tocilizumab in Kombination mit Dexamethasone

The **US COVID-19 Treatment Guidelines Panel** recommends using either **baricitinib (BIIa)** or **tocilizumab (BIIa)** in combination with **dexamethasone** alone or **dexamethasone plus remdesivir** for the treatment of COVID-19 patients who were recently hospitalised with rapidly increasing oxygen needs and systemic inflammation. If neither baricitinib nor IV tocilizumab is available or feasible to use, **tofacitinib** can be used **instead of baricitinib** (**BIIa**) or IV **sarilumab instead of IV tocilizumab (BIIa**).

The Panel **recommends against** the use of **baricitinib** in combination with **tocilizumab** for the treatment of COVID-19 **(AIII)**.

Casirivimab and imdevimab (REGN-COV2)

EUA zugelassen nur in USA (EUA): Casirivimab and imdevimab (REGN-COV2)

The **U.S. Food and Drug Administration** issued an **emergency use authorization (EUA)** for casirivimab and imdevimab (REGN-COV2) to be administered together for the **treatment** of **mild to moderate COVID-19** in **adults and pediatric patients** (12 years of age or older weighing at least 40 kilograms [about 88 pounds]) with positive results of direct SARS-CoV-2 viral testing and who are **at high risk for progressing to severe COVID-19.**

In **new revision of EUA, July 2021** FDA has issued an **EUA** to permit the emergency use of the unapproved product, REGN-COV (casirivimab and imdevimab) co-formulated product and REGN-COV (casirivimab and imdevimab) supplied as individual vials to be administered together, in adult and pediatric individuals (12 years of age and older weighing at least 40 kg) for **post-exposure prophylaxis of COVID-19** in individuals who are at **high risk for progression to severe COVID-19**, including hospitalization or death, and are:

- not fully vaccinated **or** who are not expected to mount an adequate immune response to complete SARS-CoV-2 vaccination (for example, individuals with immunocompromising conditions including those taking immunosuppressive medications

and

- have been exposed to an individual infected with SARS-CoV-2 consistent with close contact criteria per Centers for Disease Control and Prevention (CDC)
or
- who are at high risk of exposure to an individual infected with SARS-CoV-2 because of occurrence of SARS-CoV-2 infection in other individuals in the same institutional setting (for example, nursing homes, prisons).

Feb - EMA rolling review: nur bestätigte Covid-19, die keine Beatmung brauchen, aber Hochrisiko für Fortschreiten zu schwerer Erkrankung

On **February 26, 2021 EMA** stated that the CHMP has completed its review to provide a **harmonised scientific opinion** at EU level to support national decision making on the possible use of the antibodies **before a formal authorisation is issued**. The Agency concluded that the combination (REGN-COV2) **can be used** for the treatment of **confirmed COVID-19 in patients who do not require supplemental oxygen and who are at high risk of progressing to severe COVID-19**.

US COVID-19 Treatment Guidelines Panel: Empfehlung FÜR Verwendung von Kombinationstherapien bei mild/ moderater Erkr.

The **US COVID-19 Treatment Guidelines Panel recommends** using one of the following combination anti-SARS-CoV-2 monoclonal antibodies to **treat outpatients with mild to moderate COVID-19** who are **at high risk of clinical progression**, as defined by the Emergency Use Authorization (EUA) criteria (listed in alphabetical order):

Casirivimab plus imdevimab; or Sotrovimab 500 mg intravenous (IV) infusion.

Kombinationstherapien

nur bestätigte Covid-19, die keine Beatmung brauchen, aber Hochrisiko für Fortschreiten zu schwerer Erkrankung

The Panel recommends using casirivimab 600 mg plus imdevimab 600 mg administered as subcutaneous (SQ) injections (AI) or an intravenous (IV) infusion (BIII) as **Post-Exposure Prophylaxis (PEP)** for people who are at high risk for progression to severe COVID-19 if infected with SARSCoV-2 AND who have the following vaccination status AND exposure history.

Vaccination Status: Not fully vaccinated (defined as people who were never vaccinated or those who received the second vaccine dose in a two-dose series or a single-dose vaccine <2weeks ago); *or* Fully vaccinated, but not expected to mount an adequate immune response (e.g., those with immunocompromising conditions, including those who are taking immunosuppressive medications),
AND
Exposure History to SARS-CoV-2: Had a recent exposure to an individual with SARS-CoV-2 infection that is consistent with the Centers for Disease Control and Prevention (CDC) close contact criteria; *or* At high risk of exposure to an individual with SARS-CoV-2 infection because of recent occurrence of SARS-CoV-2 infection in other individuals in the same institutional setting (e.g., nursing homes, prisons).

Bamlanivimab monotherapy or in combination with etesevimab

Widerruf der EUA in USA: Bamlanivimab Monotherapie

The **U.S. Food and Drug Administration revoked an Emergency Use Authorization (EUA)** for the investigational monoclonal antibody therapy **bamlanivimab** (previously LY-CoV555), when administered **alone**, for the treatment of **mild-to-moderate COVID-19** in adult and pediatric patients due to sustained increase of SARS-CoV-2 viral variants that are resistant to bamlanivimab alone resulting in the increased risk for treatment failure.

Feb 2021: zugelassen in USA (EUA) als Kombinationstherapie bamlanivimab + etesevimab

On February 9, 2021 the **FDA** issued an **EUA** for **bamlanivimab and etesevimab administered together** for the treatment of **mild to moderate COVID-19** in adults and pediatric patients (12 years of age or older weighing at least 40 kilograms [about 88 pounds]) who test positive for SARS-CoV-2 and who are **at high risk for progressing to severe COVID-19,** including hospitalization or death. Bamlanivimab and etesevimab are not authorized for use in states, territories, and US jurisdictions in which the

combined frequency of variants resistant to bamlanivimab and etesevimab exceeds 5% (last revision of EUA August 2021).

On March 5, 2021 **EMA** stated that the CHMP has completed its review started in February 2021, to provide a **harmonised scientific opinion** at EU level to support national decision making on the possible use of the antibodies **before a formal authorisation is issued**. The Agency concluded that **bamlanivimab monotherapy** and **bamlanivimab and etesevimab combination** can be used together to treat confirmed COVID-19 in patients who **do not require supplemental oxygen and who are at high risk of their COVID-19 disease becoming severe.**

März - EMA rolling review: nur für bestätigte Covid-19, die keine Beatmung brauchen, aber Hochrisiko für Fortschreiten zu schwerer Erkrankung

The **US COVID-19 Treatment Guidelines Panel recommends against** using **Bamlanivimab plus etesevimab** to treat outpatients with mild to moderate COVID-19 who are at high risk of clinical progression, as defined by the Emergency Use Authorization (EUA) criteria due to increase in the proportion of potentially resistant variants (**AIII**). The distribution of bamlanivimab plus etesevimab was paused on June 25, 2021, because both the Gamma (P.1) and Beta (B.1.351) variants of concern (VoC) that are currently circulating in the United States have reduced susceptibility to bamlanivimab and etesevimab.

US COVID-19 Treatment Guidelines Panel: Empfehlung GEGEN Verwendung bei ambulanten Pts mit mild/ moderater Erkr. (wegen Resistenzen)

Sotrovimab (VIR-7831)

On **May 21, 2021 EMA** stated that the CHMP has completed its review started in April 2021, to provide a **harmonised scientific opinion** at EU level to support national decision making on the possible use of the antibodies **before a formal authorisation is issued**. **EMA** concluded that sotrovimab can be **used** to treat confirmed COVID-19 in **adults** and **adolescents (aged 12 years and above and weighing at least 40 kg) who do not require supplemental oxygen therapy and who are at risk of progressing to severe COVID-19.**

Mai - EMA rolling review: nur für bestätigte Covid-19, die keine Beatmung brauchen, aber Hochrisiko für Fortschreiten zu schwerer Erkrankung

On **May 26, 2021 FDA** issued **EUA** for sotrovimab for the **treatment of mild-to-moderate COVID-19 in adults andpediatric patients** (12 years of age and older weighing at least 40 kilograms [about 88pounds]) with positive results of direct SARS-CoV-2 viral testing and who are at **high risk** for **progression to severe COVID-19**, including **hospitalization or death**.

US COVID-19 Treatment Guidelines Panel: Empfehlung FÜR Verwendung von Kombinationstherapien bei mild/ moderater Erkr.

The **US COVID-19 Treatment Guidelines Panel recommends** using one of the following combination anti-SARS-CoV-2 monoclonal antibodies to **treat outpatients with mild to moderate COVID-19** who are at **high risk of clinical progression**, as defined by the Emergency Use Authorization (EUA) criteria (listed in alphabetical order):

Casirivimab plus imdevimab; or Sotrovimab 500 mg intravenous (IV) infusion.

Regdanvimab (Regkirona)

On 26 March 2021 **EMA** announced that CHMP has completed a review of Celltrion's monoclonal antibody regdanvimab (CT-P59) to **support national authorities** who may decide on the use of this medicine for COVID-19 prior to authorisation. EMA **concluded** that regdanvimab can be used for the **treatment of confirmed COVID-19 in adult patients that do not require supplemental oxygen for COVID-19 and who are at high risk of progressing to severe COVID19**.

März - EMA rolling review: nur für bestätigte Covid-19, die keine Beatmung brauchen, aber Hochrisiko für Fortschreiten zu schwerer Erkrankung

Convalescent plasma

On **February 4 2021**, **FDA** announced that former **EUA** is **being revised** to authorize **only the use of high titer COVID-19 convalescent plasma**, for the treatment of **hospitalised patients** with COVID-19, **early in the disease course** and those hospitalised with **impaired humoral immunity**.

FDA-Revision der Zulassung von Reconvalezentenplasma: nur mit hohem Titer

Tocilizumab

RECOVERY Collaborative Group published **results** from the **RECOVERY trial** related to tocilizumab arm: tocilizumab improved survival and other clinical outcomes in severe and critical COVID-19 patients. These benefits were seen regardless of the level of respiratory support and were additional to the benefits of systemic corticosteroids.

RECOVERY Ergebnisse: bessere Ergebnisse bei schwerer/ kritischer Erkrankung unter tocilizumab

On 24 June 2021 FDA issued an **emergency use authorization** (EUA) for the drug Actemra (tocilizumab) for the treatment of **hospitalised adults and pediatric patients** (2 years of age and older) who are **receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO)**.

Juni 2021: FDA EUA Verwendung bei hospitalisierten Pts. mit nicht invasiver Beatmung

On **August 18, 2021 EMA** has started **evaluating** the anti-inflammatory medicine RoActemra (tocilizumab) **to extend its use** to include treatment of **hospitalised adult patients with severe COVID-19 who are already receiving treatment with corticosteroids and require extra oxygen or mechanical ventilation (breathing assisted by a machine).**

Aug 2021: EMA Evaluation

The **US COVID-19 Treatment Guidelines Panel** recommendations: For patients who were recently hospitalised with rapidly increasing oxygen needs and systemic inflammation: **Add** either **baricitinib** (**BIIa**) or IV **tocilizumab (BIIa)** to one of the two options, dexamethasone or dexamethasone plus remdesivir. If neither baricitinib nor IV tocilizumab is available or feasible to use, **tofacitinib** can be used **instead of baricitinib** (**BIIa**) or IV **sarilumab instead of IV tocilizumab (BIIa**).

US COVID-19 Treatment Guidelines Panel: Empfehlung in Kombinaion mit Dexamethasone in einigen Patientengruppen,

For hospitalised patients with COVID-19 who require invasive mechanical ventilation or extracorporeal membrane oxygenation: **Dexamethasone (AI)**. For patients who are within 24 hours of administration to the ICU **dexamethasone plus tocilizumab (BIIa)**. If IV tocilizumab is not available or not feasible to use IV **sarilumab** can be used (**BIIa**).

ICU, beatmet, etc.

On **July 6, 2021 the WHO recommends treatment with IL-6 receptor blockers (tocilizumab or sarilumab) for patients with severe or critical COVID-19 infection (strong recommendation).** Corticosteroids have previously been strongly recommended in patients with severe and critical COVID-19, and WHO recommends patients meeting these severity criteria should now receive both corticosteroids and IL-6 receptor blockers.

Juli 2021: WHO empfiehlt Interleukin-6-Rezeptorblocker für Pts. mit schwere Erkrankung

Anakinra

On **July 19, 2021 EMA has started evaluating an application to extend the use** of anakinra (Kineret) to include treatment of COVID-19 in **adult patients with pneumonia who are at risk of developing severe respiratory failure.**

Juli 2021: für Erwachsene mit Lungenentzündung

Lopinavir + ritonavir, chloroquine and hydroxychloroquine

Lopinavir + ritonavir, chloroquine and hydroxychloroquine are **not effective** in treating **COVID-19 patients.**

keine Wirksamkeit

Other pharmaceuticals listed in this document

Related to other pharmaceuticals listed in this document the **current evidence** is **uncertain or very uncertain** about their effect on different clinical outcomes in **COVID-19 patients**, or **not yet published in scientific journals** or **medicinal products** are **not yet in regulatory process**. Further RCTs are currently ongoing.

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/treatments-covid-19/covid-19-treatments-research-development.

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
ABBV-47D11	AbbVie	Antiviral	Clinical phase
AT-527	Roche	Antiviral	Clinical phase
Aviptadil	Relief Therapeutics Holding S.A	Other therapeutics	Clinical Phase
BI 764198	Boehringer Ingelheim International GmbH	Other therapeutic	Clinical phase
Emiplacel	Biopharma Excellence GmbH	Other therapeutic	Clinical Phase
Itolizumab	Biocon Biologics Limited	Immunomodulator (monoclonal antibody)	Clinical phase
SCTA01	Sinocelltech Ltd.	Antiviral (monoclonal antibody)	Clinical phase
Colchicine	Pharmascience Inc. / Montreal Health Institute	Immunomodulator	Clinical phase
IgM enriched human immune globulin (Trimodulin) (BT588)	Biotest AG	Antiviral	Clinical phase
Vilobelimab	InflaRx Pharma GmbH	Immunomodulator	Clinical phase
Vidofludimus calcium (IMU-836)	Immunic AG	Immunomodulator/Antiviral	Clinical phase
Proxalumatide	Suzhou Kintor Pharmaceuticals / Applied Biology	Other	Clinical phase
Opaganib	RedHill Biopharma	Other	Clinical phase
Nezulcitinib	Therevance Biopharma	Immunomodulator	Clinical phase
MK-7110	MSD	Immunomodulator	Clinical phase
MAD0004J08	Menarini Richerce	Antiviral Monoclonal antibody	Clinical phase
Imlifidase	Hansa Biopharma AB	Immunomodulator	Clinical phase
FBR-002	Fabentech	Antiviral Monoclonal antibody	Clinical phase
CoviFab	Immunova SA/mAbxience	Antiviral	Clinical phase
C-21	Vicore Pharma	Immunomodulator	Clinical phase
Bemcentinib	BergenBio	Antiviral	Clinical phase
Azelastine	Ursapharm	Immunomodulator	Clinical phase
BMS986414 and BMS986413	Rockefeller University and Bristol Myers Squibb	Antiviral Monoclonal antibody	Clinical phase
Calcifediol	Vifor Fresenius Medical Care Renal Pharma France	Other	Clinical phase
Camostat	Daewoong	Antiviral	Clinical phase

Lenzilumab	Humanigen	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 (September 13, 2021)

Drug	Mechanism of operation	Approval Status or Regulatory process status Withdrawn, suspended or terminated
Remdesivir (Veklury®)	Antiviral agent	**EMA: Conditional marketing authorisation granted** **FDA: Marketing authorisation granted** 2 RCTs (suspended and terminated)
Favipiravir (Avigan, T-705)	Antiviral agent	No withdrawn or terminated studies found, 1 suspended
Darunavir (Prezista®)	Antiviral agent	No withdrawn, suspended or terminated studies found
Camostat Mesilate (Foipan®)	Antiviral cell-entry inhibitor	1 RCT withdrawn, no suspended or terminated studies found
APN01 (rhACE2)	Antiviral cell-entry inhibitor	1 RCT withdrawn
Tocilizumab (RoActemra®)	Monoclonal antibody	**FDA Emergency Use Authorisation (EUA): Tocilizumab** **EMA: Marketing authorisation application submitted** 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, 1 RCTs terminated
Convalescent Plasma	Convalescent Plasma	**FDA revised Emergency Use Authorisation (EUA): only the use of high titer COVID-19 convalescent plasma**, for **hospitalised patients**, **early in the disease course,** with **impaired humoral immunity)** 1 RCT terminated, 1 RCT withdrawn
Plasma derived medicinal products: REGN-COV2; LY-CoV555 (bamlanivimab); LY-CoV016 (etesevimab); AZD7442; sotrovimab (VIR-7831); regdanvimab	Neutralizing monoclonal antibodies	**FDA Emergency Use Authorisation (EUA): REGN-COV2 (casirivimab+imdevimab)** **EMA: Use endorsed after Article 5(3) review: REGN-COV2 (casirivimab+imdevimab), currently under rolling review** **FDA revoked Emergency Use Authorisation (EUA): Bamlanivimab** **EMA: Use endorsed after Article 5(3) review: Bamlanivimab** **FDA Emergency Use Authorisation (EUA): Bamlanivimab+etesevimab** **EMA: Use endorsed after Article 5(3) review: Bamlanivimab+etesevimab, currently under rolling review** **FDA Emergency Use Authorisation (EUA): Sotrovimab** **EMA: Use endorsed after Article 5(3) review: Sotrovimab, currently under rolling review** **EMA: Use endorsed after Article 5(3) review Regdanvimab, currently under rolling review** 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 Inhaled corticosteroids: Budesonide	Glucocorticoid	**EMA: Dexamethasone use endorsed after Article 5(3) review** 2 RCTs terminated, 1 RCT suspended, 1 RCT withdrawn 1 RCT terminated
Anakinra (Kyneret®)	Interleukin 1 receptor antagonist	**EMA: Marketing authorisation application submitted** 1 RCT suspended, 2-RCT terminated
Colchicine	An alkaloid, with anti-gout and anti-inflammatory activities	1 RCT withdrawn, no 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	**FDA Emergency Use Authorisation (EUA): declined (as Sept 08, 2021)** No withdrawn, suspended or terminated studies found
Vitamin D	Vitamin	No withdrawn or suspended, 1 terminated studies found

Baricitinib	Inhibitor of Janus kinase (JAK)1 and JAK2	**FDA Emergency Use Authorisation (EUA): Baricitinib** **EMA: Marketing authorisation application submitted** 1 withdrawn, no suspended and 1 terminated studies found
Molnupiravir	Pro-drug of the nucleoside analogue *N*4-hydroxycytidine (NHC)	No withdrawn, suspended or terminated studies found
Ivermectin	Antiparasitic	No withdrawn, suspended or terminated studies found
Aspirin (acetylsalicylic acid)	Antitrombotic	1 RCT withdrawn, no suspended or terminated studies found
Aviptadil (RLF-100)	Synthetic form of Human Vasoactive Intestinal Polypeptide (VIP)	No withdrawn, suspended or terminated studies found
Artesunate	Anti-malaria drug	No withdrawn, suspended or terminated studies found
Tofacitinib	Selective inhibitor of the JAK family	No withdrawn, suspended or terminated studies found
Fluvoxamine	Antidepresant (SSRI)	No withdrawn, suspended or terminated studies found
PF-07321332	Antiviral protease inhibitor	No withdrawn, suspended or terminated studies found

3.1 Remdesivir (Veklury®)

Details in V13_April

The reader is referred to the earlier version (V13_April) for more details on **remdesivir (Veklury).**

PRAC: Sinusbradykardie

On June 11, 2021 **EMA** stated that PRAC has recommended a **change to the product information** for Veklury (remdesivir) **to include sinus bradycardia** (heart beats more slowly than usual) as an **adverse reaction of unknown frequency** for this medicine. The majority of events of sinus bradycardia resolved a few days after the treatment with Veklury was discontinued [119].

Aug 2021: EMA-Verlängerung der konditionalen Zulassung

On August 18, 2021 **EMA** published the clinical data supporting a **renewal** of the **conditional marketing authorisation** for Veklury (remdesivir).

3.2 Lopinavir + Ritonavir (Kaletra®)

wegen erwiesenem Mangel an Wirksamkeit wurde Beobachtung beendet

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

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

3.3 Favipiravir (Avigan®)

Beobachtung bis v15 (Juni)

The reader is referred to the earlier version (V15_June 2021) for more details on favipiravir treatment in hospitalised or nonhospitalised COVID-19 patients.

The US COVID-19 Treatment Guidelines Panel (last update February 11, 2021) **recommends against** using the **Lopinavir/ritonavir (AI) or other HIV protease inhibitors** for the treatment of COVID-19 in **hospitalised patients (AI).**

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

They **recommends against** using the **Lopinavir/ritonavir (AI) or other HIV protease inhibitors** for the treatment of COVID-19 in **nonhospitalised patients (AIII)** [120].

Shinkai et al. 2021 [121] published results from **phase 3 RCT** assessing the efficacy and safety of favipiravir (1800 mg twice a day on Day 1, followed by 800 mg twice a day for up to 13 days vs placebo in a ratio 2:1) in 156 **hospitalised moderate COVID-19** patients with moderate pneumonia not requiring oxygen therapy (JapicCTI-205238). The primary endpoint was a composite outcome defined as the time to improvement in temperature, oxygen saturation levels (SpO2), and findings on chest imaging, and recovery to SARS-CoV-2-negative. The median time of the primary endpoint was 11.9 days in the favipiravir group and 14.7 days in the placebo group, with a significant difference (p = 0.0136). Favipiravir-treated patients with known risk factors such as obesity or coexisting conditions provided better effects. Patients with early-onset in the favipiravir group showed higher odds ratio. No deaths were documented. Adverse events in the favipiravir group were predominantly transient, but the incidence was significantly higher. Favipiravir-specific AEs associated with hyperuricemia occurred in 87 (76.3%) of 114 patients. Four serious adverse events (SAEs) were documented in the favipiravirgroup: cardiopulmonary arrest, cerebral infarction, liver disorder, and COVID-19-related pneumonia.

Phase 3 RCT
156 hsopitalisierte Pts. moderate Erkrankung

raschere Gesundung (-2,6 Tage)

3.4 Darunavir

The reader is referred to the earlier version (V15_June 2021) for more details on darunavir treatment in hospitalised or nonhospitalised COVID-19 patients.

Beobachtung bis v15 (Juni)

The US COVID-19 Treatment Guidelines Panel (last update February 11, 2021) **recommends against** using the **Lopinavir/ritonavir (AI) or other HIV protease inhibitors** for the treatment of COVID-19 in **hospitalised patients (AI).**

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

They **recommends against** using the **Lopinavir/ritonavir (AI) or other HIV protease inhibitors** for the treatment of COVID-19 in **nonhospitalised patients (AIII)** [120].

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 [122]. Studies showed effects on the cell-entry mechanism of coronaviruses (e.g. SARS-CoV and SARS-CoV-2) in in-vitro human cells [123, 124] as well as in pathogenic mice-models [125] 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 [126].

Withdrawn, suspended or terminated studies

One withdrawn RCT was found (NCT04338906) related to combination therapy camostat + hydroxychloroquine because hydroxychloroquine not being standard of care anymore); no suspended or terminated studies were found in ClinicalTrials.gov and EUdraCT registers.

in ClinicalTrials.gov and EUdraCT keine abgeschlossenen klinischen Studien registriert

Results of publications

One scientific publication on a RCT of Camostat Mesilate (Foipan®) in **hospitalised** Covid-19 patients is currently identified.

1 Publikation zu RCT: kein Unterschied zwischen den Gruppen

Gunst et al. 2021 [127] published results from investigator-initiated, double-blind, randomized, placebo-controlled multicenter trial in patients hospitalised with confirmed SARS-CoV-2 infection (NCT04321096, EudraCT 2020-001200-42). Within 48 h of admission, 205 participants were randomly assigned in a 2:1 ratio to receive camostat mesilate 200 mg three times daily for 5 days or placebo. The primary outcome was time to discharge or clinical improvement measured as ≥2 points improvement on a 7-point ordinal scale. Other outcomes included 30-day mortality, safety and

change in oropharyngeal viral load. 137 patients were assigned to receive camostat mesilate and 68 to placebo. Median time to clinical improvement was 5 days (interquartile range [IQR], 3 to 7) in the camostat group and 5 days (IQR, 2 to 10) in the placebo group (p= 0.31). The hazard ratio for 30-day mortality in the camostat compared with the placebo group was 0·82 (95% confidence interval [CI], 0.24 to 2.79; p=0.75). The frequency of adverse events was similar in the two groups. Median change in viral load from baseline to day 5 in the camostat group was -0.22 log_{10} copies/mL (p<0.05) and -0.82 log_{10} in the placebo group (p<0.05).

Hersteller Kommunikation zu klinischer Studie mit 342 mild erkrankten Pts.

raschere Gesundung (-3 Tage)

On July 29, 2021 Manufacturer Daewoong Pharmaceutical Co., Ltd **announced** its **phase 2b** clinical trial results performed at 24 different clinical institutions in South Korea. Among 342 **mild COVID-19 patients**, 327 patients were administered with either camostat or a placebo. The primary endpoint aimed to assess the time taken to improve clinical symptoms with major secondary endpoints being treatment safety and rate of exacerbation. A total of seven clinical symptoms including fever, cough, shortness of breath, chills, muscle pain, headache, and sore throat were evaluated as modeled from various COVID-19 clinical trials. Symptoms were scored based on their severity (1-3) and was determined to be improved when a score of 0 (none) or 1 (mild) was reached and maintained for 24 hours. Concomitant uses of antipyretic analgesics were allowed for a conservative treatment. The analysis results demonstrated safety being confirmed in all patients receiving camostat. While varying medication adherence hindered statistical significant for the entire patient pool, a general trend of clinical symptom improvement was observed in the treatment group in seven days as opposed to eight days for the placebo group. None of the participants required advanced treatments including high-flow oxygen therapy. Among 175 medication-compliant patients (86 patients from the treatment group, 89 patients from the placebo group) who experienced at least one respiratory symptom indicative of exacerbation, statistically significant symptom improvement was observed on day 5 in the treatment group as opposed to the placebo group taking eight days to recover, suggesting a 40% faster recovery rate. A greater rate of 50% was reported to be statistically significant from seniors over the age of 50 who were at risk of developing severe COVID-19, https://www.biospace.com/article/releases/daewoong-pharmaceutical-announces-camostat-achieving-50-percent-faster-recovery-time-for-mild-covid-19-patients-over-age-of-50-in-topline-results-from-phase-2b-clinical-trial/.

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

Drug under consideration

aus SARS-Forschung hervorgegangen

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

APN01 (alunacedase alfa) 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) [128], [129], [130].

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

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 178 hospitalised patients with **severe COVID-19**, with primary composite outcome – All-cause mortality or invasive mechanical ventilation are recently announced (NCT04335136). Both groups, APN01 (n=88) and placebo (n=90), also additionally received standard of care (SOC). Patients received treatment for 7 days with follow-ups until day 28. The data showed that fewer patients treated with APN01 (n=9) died or received invasive ventilation compared to placebo (n=12), although statistical significance was not achieved due to the low total number of events. The data demonstrated a statistically significant improvement in mechanical ventilator-free days in alive patients and reduction in viral load in the group treated with APN01 compared to placebo. APN01 also demonstrated a positive impact on key biomarkers of the renin angiotensin system (RAS), demonstrating in vivo efficacy of the drug. Treatment with APN01 was safe and well tolerated and no drug-related severe adverse events were observed during the study.

Phase 2/3 RCT
178 Pt. hospitalisiert, schwere Erkrankung

besser bei beatmiungsfreien Tagen

In addition, APEIRON was invited to participate in the US **ACTIV-4d RAAS trial**, part of Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV), initiated and funded by the National Heart Lung and Blood Institute (NHLBI), part of the United States' National Institutes of Health (NIH). APN01 was prioritized for study by a broad panel of clinical trial experts through the Collaborative Network of Networks for Evaluating COVID19 Therapeutic Strategies (CONNECTS). The trial is anticipated to begin in Q2-2021, https://www.apeiron-biologics.com/wp-content/uploads/20210519_PR_APN01-development_ENG.pdf.

APN01 in ACTIV-4 Plattform Studie aufgenommen

In parallel to the US clinical trial with APN01 as intravenous application, APEIRON is preparing a company-sponsored **phase 1** trial to evaluate drug delivery of APN01 through **inhalation** in order to target **all infected or at-risk patients earlier in the course of the disease**. Preliminary data from ongoing evaluations with inhalation of ACE2 based therapeutics show high efficacy in SARS-CoV-2 animal models.

Phase 1 Studie Erprobung von APN01 als Inhalation

3.9 Tocilizumab (Roactemra®)

The reader is referred to the earlier version (V14_May 2021) for more details on **tocilizumab** (**RoActemra**).

Beobachtung bis v14 (Mai)

On 24 June 2021 FDA issued an **emergency use authorization** (EUA) for the drug Actemra (tocilizumab) for the treatment of **hospitalised adults and pediatric patients** (2 years of age and older) who are **receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO)** [131] .

Juni 2021: FDA EUA für hospitalisierte Pts mit nicht-invasiver Beatmung

On July 6, 2021 the WHO recommends treatment with **IL-6 receptor blockers (tocilizumab or sarilumab)** for **patients with severe or critical COVID-19 infection (strong recommendation).** Corticosteroids have previously been strongly recommended in patients with severe and critical COVID-19, and WHO recommends patients meeting these severity criteria should now receive both corticosteroids and IL-6 receptor blockers [132].

Juli 2021: WHO Empfehlung Interleukin-6-Rezeptorblocker für schwer+ kritisch Erkrankte

On **August 18, 2021 EMA** has started evaluating the anti-inflammatory medicine RoActemra (tocilizumab) **to extend its use** to include treatment of **hospitalised adult patients with severe COVID-19 who are already receiving treatment with corticosteroids and require extra oxygen or mechanical ventilation (breathing assisted by a machine) [133].**

Aug 2021: EMA beginnt mit Evaluation – hospitalisierte Pts, die bereits mit Dexamethasone behandelt werden basierned auf CORIMUNO-19 TCZ+DEX vs. DEX

CORIMUNO-19 study group published as preprint results from the **CORIMUNO-TOCI-DEX trial** (**NCT04476979**) [134], the first large-scale randomised clinical trial to report the effects of TCZ+DEX in comparison to DEX alone in **hospitalised patients** with moderate to severe **COVID-19 pneumonia requiring at least 3L/mn oxygen** but **not receiving non-invasive or invasive mechanical ventilation at randomisation**. The primary endpoint was survival without the need for invasive ventilation at day 14. Secondary endpoints were clinical status as assessed with the WHO progression scale at 7 and 14 days, overall survival up to day 14, 28, 60, and 90, survival without needs of ventilator utilization (including NIV and high-flow oxygen) at day 14, and the rate of oxygen supply independency and of hospital discharged at day 14 and 28. Safety outcomes included adverse events during treatment and follow up, serious adverse events, and premature treatment discontinuation.The study was arrested after the DSMB advised stopping the inclusions despite the absence of crossing the planned futility boundaries because of the dramatic decrease of inclusions occurring at the end of the third wave in France when infection rate had become very low. Authors found no difference between the two arms in terms of mechanical ventilation need and mortality up to day 90 (32/226 (14%) and 27/224 (12%) in the DEX and TCZ+DEX arms, respectively (Hazard ratio (HR) [90% credible interval (CrI)], 0.85 [0.55-1.31]). WHO CPS was significantly improved in the TCZ+DEX arm (OR 0.69, (95% CrI, 0.49 to 0.97). Safety was similar in both arms.

Studie wurde angehalten wegen Ende der 3. Welle (Schwierigkeiten bei Rekrutierung von Pts.)

bis dahin eingeschlossene Pts.
kein Unterschied bei Beatmung und Mortalität

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 [135]. 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-Rezeptorblocker für rheumatoide Arthritis zugelassen (EMA)
Covid-10: bei erhöhten IL-6-Spiegeln

The **US COVID-19 Treatment Guidelines Panel** Statement (last update August 25, 2021) [169]: The Panel recommends **IV sarilumab** as an alternative to **IV tocilizumab** only when IV tocilizumab is not available or not feasible to use **(BIIa)**.

US COVID-19 Treatment Guidelines Panel (Aug) Sarilumab als Alternative zu Tocilizumab

On July 6, 2021 the WHO recommends treatment with IL-6 receptor blockers (tocilizumab or sarilumab) for patients with severe or critical COVID-19 infection (strong recommendation). Corticosteroids have previously been strongly recommended in patients with severe and critical COVID-19, and WHO recommends patients meeting these severity criteria should now receive both corticosteroids and IL-6 receptor blockers [132].

Juli 2021: WHO Empfehlung Interleukin-6-Rezeptorblocker für schwer+ kritisch Erkrankte

The prospective and living network meta-analyses showed that in severely or critically ill patients, administering these drugs reduce the odds of death by 13%, compared to standard care: will be 15 fewer deaths per thousand patients, and as many as 28 fewer deaths for every thousand critically ill patients. The odds of mechanical ventilation among severe and critical patients are reduced by 28%, compared with standard care. This translates to 23 fewer patients out of a thousand needing mechanical ventilation, [136].

Network Metaanalyse RR Tod -13% RR künstliche Beatmung -28%

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

Juli 2020: Pressemeldung zu RCT mit 194 Pts

kein Unterschied mehr SAE in Sarilumab Gruppe

Publikation der Ergebnisse März 2021:

keine Unterschiede, negative Ergebnisse

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 was continuing, in hospitalised patients with severe and critical Covid-19 using a different dosing regimen, with published **negative results** in March 2021 by **Lescure et al.** (NCT04327388, EudraCT 2020-001162-12)[137] 420 patients were randomly assigned and 416 received placebo (n=84 [20%]), **sarilumab 200 mg** (n=159 [38%]), or **sarilumab 400 mg** (n=173 [42%]). At day 29, no significant differences were seen in median time to an improvement of two or more points between placebo (12·0 days [95% CI 9·0 to 15·0]) and sarilumab 200 mg (10·0 days [9·0 to 12·0]; hazard ratio [HR] 1·03 [95% CI 0·75 to 1·40]; log-rank p=0·96) or sarilumab 400 mg (10·0 days [9·0 to 13·0]; HR 1·14 [95% CI 0·84 to 1·54]; log-rank p=0·34), or in proportions of patients alive (77 [92%] of 84 patients in the placebo group; 143 [90%] of 159 patients in the sarilumab 200 mg group; difference −1·7 [−9·3 to 5·8]; p=0·63 *vs* placebo; and 159 [92%] of 173 patients in the sarilumab 400 mg group; difference 0·2 [−6·9 to 7·4]; p=0·85 *vs* placebo). At day 29, there were numerical, non-significant survival differences between sarilumab 400 mg (88%) and placebo (79%; difference +8·9% [95% CI −7·7 to 25·5]; p=0·25) for patients who had critical disease. No unexpected safety signals were seen. The rates of treatment-emergent adverse events were 65% (55 of 84) in the placebo group, 65% (103 of 159) in the sarilumab 200 mg group, and 70% (121 of 173) in the sarilumab 400 mg group, and of those leading to death 11% (nine of 84) were in the placebo group, 11% (17 of 159) were in the sarilumab 200 mg group, and 10% (18 of 173) were in the sarilumab 400 mg group.

As already described in Tocilizumab Section above, **Gordon et al. 2021 [138](REMAP-CAP, NCT02735707)** published **preliminary report** as preprint, with **positive results** related to IL-6 receptor antagonist, tocilizumab and sarilumab, to improve outcome, including survival, in **critical COVID-19 patients** who were randomised to receive either tocilizumab (8mg/kg) or **sarilumab** (**400mg**) or standard care (control). At the time of full analysis 353 patients had been assigned to tocilizumab, 48 to sarilumab and 402 to control. Median organ support-free days were 11 (IQR 0, 16) sarilumab and and 0 (IQR -1, 15) for control. Relative to control, median adjusted odds ratio was 1.76 (95%CrI 1.17, 2.91) for sarilumab, compared with control. Hospital mortality was 22.2% (10/45) for sarilumab and 35.8% (142/397) for control. All secondary outcomes and analyses supported efficacy of these IL-6 receptor antagonists. There were no serious adverse events in the sarilumab group.

REMAP-CAP Studienarm
48 Pts.

Vorteile bei Soitalsmortalität, 90-Tages Überleben, Zeit bis zur Intensivmedizin Spitalsentlassung klinische Verbesserung

Derde et al. 2021 published **final report** as **preprint** [139] from above mentioned **REMAP-CAP** RCT (**NCT02735707**): Adult participants with **critical COVID-19** were randomized to receive **tocilizumab, sarilumab, anakinra, or standard care (control)**. In addition, a small group (n=21) of participants were randomized to interferon-β1a. The primary outcome was an ordinal scale combining in-hospital mortality (assigned -1) and days free of organ support to day 21. The trial used a Bayesian statistical model with pre-defined triggers for superiority, equivalence or futility. Statistical triggers for equivalence between tocilizumab and sarilumab; and for inferiority of anakinra to the other active interventions were met at a planned adaptive analysis. Of the 2274 critically ill participants enrolled, 972 were assigned to tocilizumab, **485 to sarilumab 400 mg as a single intravenous infusion**, 378 to anakinra and **418 to control**. Median organ support-free days were 7 (interquartile range [IQR] –1, 16), 9 (IQR –1, 17), 0 (IQR –1, 15) and 0 (IQR –1, 15) for tocilizumab, sarilumab, anakinra and control, respectively. Median adjusted odds ratios were 1.46 (95%CrI 1.13, 1.87), 1.50 (95%CrI 1.13, 2.00), and 0.99 (95%CrI 0.74, 1.35) for tocilizumab, sarilumab and anakinra, yielding 99.8%, 99.8% and 46.6% posterior probabilities of superiority, respectively, compared to control. Median adjusted odds ratios for hospital survival were 1.42 (95%CrI 1.05,1.93), 1.51 (95%CrI 1.06, 2.20) and 0.97 (95%CrI 0.66, 1.40) for tocilizumab, sarilumab and anakinra respectively, compared to control, yielding 98.8%, 98.8% and 43.6% posterior probabilities of superiority, respectively, compared to control. All treatments appeared safe. In critical COVID-19, tocilizumab and sarilumab are similarly effective at improving survival and reducing duration of organ support. Anakinra is not effective in this population.

Platform Studie: REMAP-CAP
2.274 kritsch Erkrankte

Tocilizumab & Sarilumab gleichermaßen wirksam bei Überleben und Dauer der Unterstützung bei Beatmung

Sivapalasingam et al. 2021 [140] published as **preprint** results from adaptive, phase 2/3, randomized, double-blind, placebo-controlled trial of intravenous sarilumab **200 mg or 400 mg** in adults **hospitalised** with Covid-19 **requiring supplemental oxygen and/or assisted ventilation** (**NCT04315298**). The **phase 3** primary analysis population (cohort 1) was patients with **critical Covid-19** receiving mechanical ventilation (MV) randomized to sarilumab 400 mg or placebo. The primary end point for phase 3 was the proportion of patients with ≥1-point improvement in clinical status from baseline to day 22. 457 and 1365 patients were randomized and treated in phases 2 and 3, respectively. Among phase 3 critical patients receiving MV (n=289; 34.3% on corticosteroids), the proportion with ≥1-point improvement in clinical status (alive not receiving MV) at day 22 was 43.2% in sarilumab 400 mg and 35.5% in placebo (risk difference [RD] +7.5%; 95% confidence interval [CI], –7.4 to 21.3; p=0.3261), representing a relative risk improvement of 21.7%. Day 29 all-cause mortality was 36.4% in sarilumab 400 mg versus 41.9% in placebo (RD –5.5%; 95% CI, –20.2 to 8.7; relative risk reduction 13.3%). In post hoc analyses pooling phase 2 and 3 critical patients receiving

Phase 2/ 3 RCT

457 Pts hase 2
1.365 Pts Phase 3

geringfügig bessere Ergebnisse

MV, the hazard ratio (HR) for death in sarilumab 400 mg compared with placebo was 0.76 (95% CI, 0.51 to 1.13) overall, improving to 0.49 (95% CI, 0.25 to 0.94) in patients receiving corticosteroids at baseline.

SoF von 4 RCTS: unsichere Evidenz zu Sarilumab

Summary of finding table 3.10-1. related to these four RCTs mentioned above can be found below. In summary, evidence is very uncertain about the effect of sarilumab on outcomes All-cause mortality D28 (RR 0.94, 95% CI 0.63 to 1.41, 3 RCTs, very low certainty of evidence); All-cause mortality D60 (RR 0.96, 95% CI 0.85 to 1.09, 4 RCTs, very low certainty of evidence); Clinical improvement D28 (RR 0.98, 95% CI 0.87 to 1.10, 1 RCT, very low certainty of evidence) and SAEs (RR 1.06, 95% CI 0.94 to 1.20, 4 RCTs, very low certainty of evidence), compared to standard care for severe/critical COVID-19 patients. Sarilumab compared to standard care may not increase AEs (RR 1.08, 95% CI 0.99 to 1.17, 3 RCTs, moderate certainty of evidence).

*Table 3.10-1: Summary of findings table on **Sarilumab compared to Standard Care for Severe/Critical COVID-19** (4 RCTs: Gordon REMAP-CAP, Lescure, Sivapalasingam, Derde REMAP-CAP)*

Sarilumab compared to Standard Care for Severe/Critical COVID-19 (last update 11/07/2021)

Patient or population: Hospitalised (Severe/Critical COVID-19)
Setting: Worldwide
Intervention: Sarilumab
Comparison: Standard Care

Outcome	Anticipated absolute effects (95% CI)[a]		Relative effect (95% CI)	Number of participants (studies)	Certainty of evidence	Comments
	Risk with Standard treatment	Risk with Sarilumab				
All-cause mortality D28	272 per 1000	255 per 1000	**RR: 0.94** (0.63 - 1.41)	2210 (3 RCTs) [b, c, d]	⊕⊕⊕◯ VERY LOW [e]	**Absolute effect (95% CI) 16 fewer per 1000** (from 101 fewer to 111 more)
All-cause mortality D60	305 per 1000	292 per 1000	**RR: 0.96** (0.85 - 1.09)	3110 (4 RCTs) [f]	⊕⊕⊕◯ VERY LOW [g]	**Absolute effect (95% CI) 12 fewer per 1000** (from 46 fewer to 27 more)
Clinical improvement D28	559 per 1000	548 per 1000	**RR: 0.98** (0.87 - 1.10)	1330 (1 RCTs) [h]	⊕⊕⊕◯ VERY LOW [i]	**Absolute effect (95% CI) 11 fewer per 1000** (from 73 more to 56 more)
Number of patients with any adverse event	574 per 1000	619 per 1000	**RR: 1.08** (0.99 - 1.17)	2207 (3 RCTs) [j]	⊕⊕◯◯ LOW [k]	**Absolute effect (95% CI) 46 more per 1000** (from 6 fewer to 98 more)
Number of patients with serious adverse events	225 per 100	239 per 1000	**RR: 1.97** (0.94 - 1.20)	2667 (4 RCTs) [l]	⊕◯◯◯ VERY LOW [m]	**Absolute effect (95% CI) 14 more per 1000** (from 14 fewer to 45more)

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: aThe 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); b Lescure, 2021; c Gordon, REMAP-CAP, 2021; d Sivapalasingam, 2021 (2); e Risk of bias: Serious Risk of bias downgraded by 1 level: regarding adequate randomisation, deviation from intended intervention and missing data Imprecision: Very serious Imprecision downgraded by 2 level: due to wide confidence interval consistent with the possibility for benefit and the possibility for harm low number of participants f Lescure, 2021; Sivapalasingam, 2021 (1); Sivapalasingam, 2021(2); Derde, 2021; g Risk of bias: Serious Risk of bias downgraded by 1 level: some concerns regarding adequate randomization, deviation from intended intervention, missing data and selection of reported results Imprecision: Very serious Imprecision downgraded by 2 level: due to wide confidence interval consistent with the possibility for benefit and the possibility for harm and low number of participants; h Sivapalasingam, 2021 (2); i Risk of bias: Serious Risk of bias downgraded by 1 level: some concerns or high risk regarding adequate randomization, missing data and selection of reported results Indirectness: Serious despite a multicentre design this is a single study from a single country, therefore results in this population might not be generalizable to other settings. Imprecision: Serious due to low number of participants; j Lescure, 2021;Sivapalasingam, 2021 (1); Sivapalasingam, 2021 (2); k Risk of bias: Serious Risk of bias downgraded by 1 level: some concerns regarding adequate randomization, missing data and selection of reported results Imprecision: Serious due to low number of participants; l Lescure FX, 2021; Gordon AC, REMAP-CAP, 2021; Sivapalasingam S, 2021(1); Sivapalasingam S, 2021 (2); m Risk of bias: Serious Risk of bias downgraded by 1 level: some concerns regarding adequate randomization, deviation from intended intervention, missing data and outcome measurement Imprecision: Very serious Imprecision downgraded by 2 level: Imprecision downgraded by 2 level: due to wide confidence interval consistent with the possibility for no effect and the possibility for harm and low number of participants.

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 [141].

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) [142, 143]. 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 (last update August 27, 2021) [144] **recommends against** use of the **interferons (alfa or beta)** for the treatment of **severely or critically ill** patients with COVID-19, except in the context of a clinical trial (AIII).

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

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

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). One RCT, on interferon beta 1a, was found as terminated (NCT04449380, INTERCOP) due to futility.

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 [145].

Kombinationstherapie: Ergebnisse in 3.14

Results from **Huang et al. 2020** (**ChiCTR2000029387**) [146] 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 [147] 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) [148]. 101 COVId-19 hospitalized adult patients were randomly assigned (1:1) to receive **inhaled nebulised interferon beta-1a (**SNG001) (6 MIU) or **placebo** by 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.

1 RCT
101 Pts
inhaltiertes INF

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)** [149]. 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 [150] 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

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

nicht aber Dauer der Hospitalisierung und in ICU

mortality was 6.06% and 18.18% in the IFN and control groups respectively (p = 0.12).

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

keine Unterscheide bei den Endpunkten

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 [151, 152]. 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.

RCT
40 Pts.
geringe Unterschiede bei Endpunkten

Pandit et al. 2021 [153] published results of RCT conducted in 40 patients with moderate COVID-19 (**PEG IFN-α2b** plus SOC, vs SOC alone). The primary endpoint was improvement in clinical status on day 15, measured by the WHO 7-point ordinal scale. Overall, 19 (95.00%) subjects in PEG IFN-α2b plus SOC had achieved clinical improvement on day 15 compared to 13 (68.42%) subjects in SOC (p< 0.05); 80% and 95% of subjects in the PEG IFN-α2b plus SOC group had a negative RT-PCR result on day 7 and day 14, respectively, compared to 63% and 68% in the SOC group. Adverse events were reported for eleven subjects in the PEG IFN-α2b plus SOC group and eight subjects in the SOC group. All reported AEs were mild.

RCT
250 Pts.
geringe Unterschiede bei klinischem Status

Bhushan et al. 2021 [154] published results from RCT (CTRI/2020/12/029855) related to efficacy and safety of pegylated interferon alfa-2b (**PEG IFN-α2b**) along with the standard of care (SOC) vs SOC alone, in 250 hospitalised adults with moderate COVID-19 in India. PEG IFN-α2b induced early viral clearance (80.36% vs 68.18%, p=0.037 on Day 8), improved the clinical status (median, 5 days, as compared with 6 days; p<0.05) and decreased the duration of supplemental oxygen (median, 56.00 hours, as compared with 84.00 hours; p<0.05).

3-armiger RCT:
60 Patient*innen schwer Erkrankung

bessere klin. Ergebnnisse und Mortalität unter IFNβ1a und IFNβ1b

Darazam et al. [155] published as preprint as well as scientific article [156] results from three-armed, individually-randomized, open-label, controlled trial of **IFNβ1a** and **IFNβ1b**, comparing them against each other and a **control** group (**NCT04343768**). Patients were randomly assigned in a 1:1:1 ratio to IFNβ1a (subcutaneous injections of 12,000 IU on days 1, 3, 6), IFNβ1b (subcutaneous injections of 8,000,000 IU on days 1, 3, 6), or the control group. A total of 60 severely ill patients with positive RT-PCR and Chest CT scans underwent randomization (20 patients to each arm). In the Intention-To-Treat population, IFNβ1a was associated with a significant difference against the control group, in the outcome Time to clinical improvement (; (HR; 2.36, 95% CI=1.10-5.17, p=0.031) while the IFNβ1b indicated no significant difference compared with the control; HR; 1.42, (95% CI=0.63-3.16, p=0.395). The mortality was numerically lower in both of the intervention groups (20% in the IFNβ1a group and 30% in the IFNβ1b group vs. 45% in the control group). There were no significant differences between the three arms regarding the adverse events.

SoF Tabelle zu 4 RCTs: niedrige Aussagesicherheit der Studien zur Verbesserungen und Gesamtmortalität

Summary of Findings table related to **meta-analysis** on results of **4 RCTs** (Davoudi-Monfared, Rahmani, SOLIDARITY-INF, Darazam COVIFERON), 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 currently available very low certainty of evidence, the evidence is very uncertain about the effect of interferon beta-1a on outcomes: WHO progression score level 7 or above D28 (RR 0.46, 95% CI 0.24 to 0.90, 2 RCTs) and All-cause mortality D28 (RR 0.67, 95% CI 0.38 to 1.18, 4 RCTs).

*Table 3.11-1: Summary of findings table on **Interferon β-1a compared to Standard Care for Hospitalised COVID-19 patients** (4 RCTs: Davoudi-Monfared, Rahmani, SOLIDARITY-INF, Darazam COVIFERON) – https://covid-nma.com/living_data/index.php*

Interferon β compared to Standard Care for Hospitalised COVID-19 patients
Patient or population: COVID-19
Setting: Worldwide Hospital
Intervention: Interferon β
Comparison: Standard Care/Placebo

Outcome	Anticipated absolute effects (95% CI) [a]		Relative effect (95% CI)	Number of participants (studies)	Certainty of evidence	Comments
	Risk with Standard treatment/Placebo	Risk with Interferon Beta				
All-cause mortality D28	115 per 1,000	77 per 1,000	**RR: 0.67** (0.38 - 1.18)	4352 (4 RCTs) b	Very low certainty d	**38 fewer per 1000** (from 71 fewer to 21 more)
Viral negative conversion D7	Outcome not yet measured or reported	Outcome not yet measured or reported	Outcome not yet measured or reported	Outcome not yet measured or reported	Outcome not yet measured or reported	Outcome not yet measured or reported
Clinical improvement D28	Outcome not yet measured or reported	Outcome not yet measured or reported	Outcome not yet measured or reported	Outcome not yet measured or reported	Outcome not yet measured or reported	Outcome not yet measured or reported
WHO progression score (level 7 or above) D28	268 per 1,000	123 per 1,000	**RR: 0.46** (0.24 - 0.9)	165 (2RCTs) c	Very low certainty e	**145 fewer per 1000** (from 204 fewer to 27 fewer)
Number of patients with adverse events	Outcome not yet measured or reported	Outcome not yet measured or reported	Outcome not yet measured or reported	Outcome not yet measured or reported	Outcome not yet measured or reported	Outcome not yet measured or reported
Number of patients with serious adverse events	Outcome not yet measured or reported	Outcome not yet measured or reported	Outcome not yet measured or reported	Outcome not yet measured or reported	Outcome not yet measured or reported	Outcome not yet measured or reported

Explanations: a The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI); b Davoudi-Monfared E, 2020; Rahmani H, 2020; Pan H, SOLIDARITY, 2020; Darazam IA, COVIFERON, 2021; c Davoudi-Monfared E, 2020; Rahmani H, 2020; d Risk of bias: Serious some concerns regarding adequate randomization, deviation from intended intervention and selection of reported results, and high risk regarding missing data Inconsistency: Serious I^2=66% Imprecision: Serious due to wide confidence interval consistent with the possibility for benefit and the possibility for no effect and low number of participants and events; e Risk of bias: Serious Risk of bias downgraded by 1 level: some concerns regarding adequate randomization, deviation from intended intervention, selection of reported results and high risk regarding missing data Indirectness: Serious Indirectness downgraded by 1 level: studies from a single country, therefore results in this population might not be generalizable to other settings Imprecision: Serious due to low number of events and/or participants. **GRADE Working Group grades of evidence: High certainty:** We are very confident that the true effect lies close to that of the estimate of the effect; **Moderate certainty:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different; **Low certainty:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect; **Very low certainty**: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

3.12 Convalescent plasma transfusion

The reader is referred to the earlier version (V15_June 2021) for more details on Convalescent plasma treatment in COVID-19 patients.

FDA im August 2020: Emergency UseAuthorization (EUA)

Feb 2021: EUA Revision

Verabreichung von Rekonvalszentenplasma nur mehr im frühen Stadium von hospitaliserten Patient*innen und mit Plasma mit hohem Titer zugelassen

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 [157]. On **February 4 2021, FDA** announced that this **EUA** is **being revised** to authorize **only the use of high titer COVID-19 convalescent plasma**, for the treatment of **hospitalized patients** with COVID-19, **early in the disease course** and those hospitalized with **impaired humoral immunity**. The use of low titer COVID-19 convalescent plasma is no longer authorized under this EUA. COVID-19 convalescent plasma should not be considered a new standard of care for the treatment of patients with COVID-19. Given that the clinical evidence supporting this EUA remains limited, data from additional randomized, controlled trials are needed. Under this EUA, authorized COVID-19 convalescent plasma will be obtained from registered or licensed blood establishments from donors in the United States or its territories in accordance with applicable regulations, policies, and procedures. Testing for relevant transfusion-transmitted infections must be performed and the donation must be found suitable. Plasma donations must be tested by registered or licensed blood establishments for anti-SARSCoV-2 antibodies as a manufacturing step to determine suitability before release, using one of the tests listed in the EUA document, https://www.fda.gov/media/141477/download.

US NIH COVID-19 Treatment Guidelines:

Empfehlung gegen CVP oder insuffiziente Datenlage

Current US **NIH COVID-19 Treatment Guidelines** (last updated April 21, 2021)**:** The Panel **recommends against** the use of **low-titer COVID-19 convalescent plasma** for the treatment of COVID-19 **(AIIb)**.

For hospitalised patients with COVID-19 who do not have impaired immunity

1. The Panel **recommends against** the use of COVID-19 **convalescent plasma** for the treatment of COVID-19 in mechanically ventilated patients **(AI)**.
2. The Panel **recommends against** the use of **high-titer COVID-19 convalescent plasma** for the treatment of COVID-19 in hospitalised patients who do not require mechanical ventilation, except in a clinical trial **(AI)**.

For hospitalised patients with COVID-19 who have impaired immunity

- There are insufficient data for the Panel to recommend either for or against the use of high-titer COVID-19 convalescent plasma for the treatment of COVID-19.

For nonhospitalised patients with COVID-19

- There are insufficient data for the Panel to recommend either for or against the use of high-titer COVID-19 convalescent plasma for the treatment of COVID-19 in patients who are not hospitalised, except in a clinical trial.

Results of publications

The reader is referred to the earlier version (V15_June 2021) for more details on previously published results from RCTs.

Two more studies were published from previous version (June 2021).

Estcourt et al. 2021 on behalf of the **REMAP-CAP Investigators** published as preprint [158] negative results from ongoing adaptive platform trial (NCT02735707), in which **critically ill patients** with confirmed Covid-19, defined as receiving intensive care-level organ support, were randomized to open-label convalescent plasma or not (i.e., control group). The primary end point was organ support-free days (i.e., days alive and free of ICU-based organ support) up to day 21. The convalescent plasma intervention was stopped after pre-specified criteria for futility were met. At that time, 1084 participants had been randomized to convalescent plasma and 916 to no convalescent plasma (control). The median organ support-free days were 0 (interquartile range, -1 to 16) for the convalescent plasma group and 3 (interquartile range, -1 to 16) days for the control group. The median adjusted odds ratio (OR) was 0.97 (95% credible interval 0.83 to 1.15) and posterior probability of futility (OR < 1.2) was 99.4% for convalescent plasma compared to control. In-hospital mortality was 37.3% (401/1075) in convalescent plasma group, and 38.4% (347/904) in controls. The observed treatment effects were consistent across primary and secondary outcomes. Authors concluded that in critically ill adults with confirmed Covid-19, treatment with convalescent plasma, did not improve clinical outcomes.

Platform Studie
REMAP-CAP
2.000 Patient*innen, schwere Erkrankungen
1.084 bekamen CVP

früher Stopp des Studienarms, weil CVP bei diesen Pts keine Verbesserungen zeigte

Begin et al. 2021 on behalf of **CONCOR-1 Study Group** [159] published, as preprint, negative results from RCT of convalescent plasma for adults with **COVID-19 receiving oxygen** within 12 days of respiratory symptom onset. Patients were allocated 2:1 to 500 mL of convalescent plasma or standard of care. The composite primary outcome was intubation or death by 30 days. The trial was terminated at 78% of planned enrollment after meeting stopping criteria for futility. 940 patients were randomized and 921 patients were included in the intent-to-treat analysis. Intubation or death occurred in 199/614 (32.4%) in the convalescent plasma arm and 86/307 (28.0%) in the standard of care arm; relative risk (RR) 1.16 (95% confidence interval (CI) 0.94-1.43; p=0.18). Patients in the convalescent plasma arm had more serious adverse events (33.4% vs.26.4%; RR=1.27, 95% CI 1.02-1.57, p=0.034).

RCT CONCOR-1
940 Patient*innen
CVP-Therapiebeginn innerhalb von 12 Tagen nach ersten Symtome
früher Stopp, weil CVP bei diesen Pts keine Verbesserungen zeigte

Two additional RCTs from Brazil (NCT04547660, PLACOVID) and Uganda (NCT04542941) published negative results on convalescent plasma vs standard care in **hospitalised** COVID-19 patients (moderate to critical and mild to severe) [160, 161].

2 weitere RCTs (Uganda, Brasilien) mit negativen Ergebnissen

In August 2021, **Korley et al.** [162] published negative results from randomized, multicenter, single-blind trial (**SIREN-C3PO, NCT04355767**): patients who were being treated in an emergency department for Covid-19 symptoms were assigned to receive either one unit of convalescent plasma with a high titer of antibodies against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or placebo. All the patients were either 50 years of age or older or had one or more risk factors for disease progression. In addition, all the patients presented to the emergency department within 7 days after symptom onset and were in stable condition for **outpatient** management. The primary outcome was disease progression within 15 days after randomization, which was a composite of hospital admission for any reason, seeking emergency or urgent care, or death without hospitalization. Secondary outcomes included the worst severity of illness on an 8-category ordinal scale, hospital-free days within 30 days after randomization, and death from any cause. A total of 511 patients were enrolled in the trial (257 in the convalescent-plasma group and 254 in the placebo group). The median age of the patients was 54 years; the median symptom duration was 4 days. In the donor plasma samples, the median titer of SARS-CoV-2 neutralizing antibodies was 1:641. Disease progression occurred in 77 patients (30.0%) in the convalescent-plasma group and in 81 patients

RCT
511 Pts
ambulante Pts

kein Unterschied bei Fortschreiten der Erkrankung

(31.9%) in the placebo group (risk difference, 1.9 percentage points; 95% credible interval, −6.0 to 9.8; posterior probability of superiority of convalescent plasma, 0.68). Five patients in the plasma group and 1 patient in the placebo group died. Outcomes regarding worst illness severity and hospital-free days were similar in the two groups. The administration of Covid-19 convalescent plasma to high-risk outpatients within 1 week after the onset of symptoms of Covid-19 did not prevent disease progression.

Zusammenfassung von 17 RCTs: niedrige Aussagsicherheit

kein Unterschied bei Gesamtmortalität, bei klinischer Verbesserung

The **Living Systematic Review with meta-analysis**, related to **17 RCTs:** Li et al. 2020 [163], Gharbharan et al. 2020 [164], Avendano-Sola et al. 2020 [141], Agarwal et al. 2020 [165], Simonovich [166], AlQahtani et al. 2020, Libster et al. 2020 [167], Ray et al. 2020, Rasheed et al. 2020 [168], Salman et al. 2020 [169], Horby RECOVERY [170], O'Donnell [171], Bajpai et al. 2021, Pouladzadeh et al. 2021, Bennett-Guerrero et al. 2021, Koerper et al. 2021 and Etscourt REMAP-CAP Investigators 2021 [158] with **Summary of findings** table is provided in Table 3.12-1. In summary, according to currently available evidence, convalescent plasma probably does not reduce All-cause mortality D28 (RR 0.97, 95% CI 0.92 to 1.03, 13 RCTs, moderate certainty of evidence); probably does not increase incidence of clinical improvement D28 (RR 1.00, 95% CI 0.97 to 1.03, 6 RCTs, moderate certainty of evidence); may not decrease WHO progression score level 7 or above D28 (RR 0.77, 95% CI 0.56 to 1.07, 4 RCTs, low certainty of evidence); probably does not increase incidence of Adverse events (RR 1.05, 95% CI 0.94 to 1.18, 6 RCTs, moderate certainty of evidence) and may not increase Serious adverse events (RR 1.09, 95% CI 0.77 to 1.53, 10 RCTs, low certainty of evidence). The evidence is very uncertain about the effect of convalescent plasma on further outcome: Viral negative conversion D7 (RR 1.64, 95% CI 0.88 to 3.06, 3 RCTs, very low certainty of evidence).

Table 3.12-1: Summary of findings table on ***Convalescent plasma compared to Standard Care for Mild/Moderate/Severe/Critical COVID-19***
(16 RCTs: Li, Gharbharan, Avendano-Sola, Agarwal, AlQahtani, Simonovich, Libster, Ray, Rasheed, Salman, Horby RECOVERY, ODonnell, Bajpai, Pouladzadeh, Bennett-Guerrero, Koerper, Estcourt REMAP-CAP)

Convalescent plasma compared to Standard Care for Hospitalised COVID-19 patients (update 28/06/2021)

Patient or population:-Hospitalised COVID-19
Setting: Worldwide
Intervention: Convalescent plasma
Comparison: Standard Care/Placebo

Outcome	Anticipated absolute effects (95% CI) [a]		Relative effect (95% CI)	Number of participants (studies)	Certainty of evidence	Comments
	Risk with Standard treatment/Placebo	Risk with Convalescent plasma				
All-cause mortality D28	253 per 1,000	245 per 1,000	**RR: 0.97** (0.92 - 1.03)	15253 (13 RCTs) b	Moderate certainty h	**8 fewer per 1000** (from 20 fewer to 8 more)
Viral negative conversion D7	482 per 1,000	791 per 1,000	**RR: 1.64** (0.88 - 3.06)	459 (3 RCTs) c	Very low certainty i	**309 more per 1000** (from 58 fewer to 993 more)
Clinical improvement D28	650 per 1,000	650 per 1,000	**RR: 1.00** (0.97 - 1.03)	12195 (6 RCTs) d	Moderate certainty j	**0 fewer per 1000** (from 19 fewer to 19 more)
WHO progression score (level 7 or above) D28	166 per 1,000	127 per 1,000	**RR: 0.77** (0.56 - 1.07)	798 (4 RCTs) e	Low certainty k	**38 fewer per 1000** (from 73 fewer to 12 more)
Number of patients with adverse events	397 per 1,000	417 per 1,000	**RR: 1.05** (0.94 - 1.18)	956 (6 RCTs) f	Moderate certainty l	**20 more per 1000** (from 24 fewer to 71 more)
Number of patients with serious adverse events	67 per 1,000	73 per 1,000	**RR: 0.94** (0.72 - 1.23)	3197 (10 RCTs) g	Low certainty m	**6 more per 1000** (from 15 fewer to 35 more)

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 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); b AlQahtani M, 2020; Avendaño-Solà C, 2020; Agarwal A, PLACID, 2020; Horby P, RECOVERY, 2021; Li L, 2020; Simonovich VA, PlasmAr, 2020; Ray Y, 2020, O Donnell M, 2021; Bajpai M, 2020; Koerper S, 2021; Bennett-Guerrero E, 2021; Libster 2021; Estcourt REMAP-CAP 2021; c Agarwal A, PLACID, 2020; Li L, 2020; Salman OH, 2020; d Horby P, RECOVERY, 2021; AlQahtani M, 2020; Gharbharan A, 2020; Li L, 2020; Simonovich VA, PlasmAr, 2020; Bennet-Guerrero E, 2021; e Avendaño-Solà C, 2020; Simonovich VA, 2020, O Donnell M, 2021, Libster 2021; f Li L, 2020; Libster R, 2020; Simonovich VA, 2020, O Donnell M, 2021; Bajpai M, 2020; Koerper S, 2021; g Avendaño-Solà C, 2020; Gharbharan A, 2020; Li L, 2020; Libster R, 2020; Simonovich VA, 2020, O Donnell M, 2021; Bajpai M, 2020; Koerper S, 2021; Bennet-Guerrero E, 2021; Estcourt REMAP-CAP 2021; h Imprecision: Serious Imprecision downgraded by 1 level: due to wide confidence interval consistent with the possibility for benefit and the possibility for no effect; i Risk of bias: Serious Risk of bias downgraded by 1 level:some concerns regarding adequate randomization, deviations from intended interventions, missing data and selection of the reported result Inconsistency: Serious Inconsistency downgraded by 1 level: I^2=76% Imprecision: Very serious Imprecision downgraded by 2 levels: due to wide confidence interval consistent with the possibility for benefit and the possibility for no effect and low number of participants. j Risk of bias: Serious Risk of bias downgraded by 1 level: some concerns regarding adequate randomization, deviation from intended intervention, outcome measurement and selection of reported results; k Imprecision: Very serious due to wide confidence interval consistent with the possibility for benefit and the possibility for no effect and low number of participants; l Imprecision: Serious due to low number of participants; m Imprecision: Very serious Imprecision downgraded by 2 level: due to wide confidence interval consistent with the possibility for benefit and the possibility for no effect and low number of participants

3.13 Plasma derived medicinal products

Neutralizing monoclonal antibodies

neutralisierende monoklonale Antikörper: Prävention und Behandlung

Halbwertszeit bis 3 Wochen von Vorteil

Nachteil: unbekannte Bioverfügbarkeit der infundierten Antikörper

As Marovich et al. 2020 [172] 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.

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 [172].

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

Kombination aus 2 monoklonalen Antikörpern: Casirivimab + Imdevimab

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.

New SARS-CoV-2 Variants

in präklinischer Forschung: REGN-COV auch gegen Mutationen wirksam

On January 27, 2021, Regeneron Pharmaceuticals, Inc. announced that researchers in Columbia University lab [173] and Regeneron scientists have independently confirmed that REGEN-COV™ (casirivimab and imdevimab antibody cocktail) successfully neutralizes the circulating SARS-CoV-2 variants first identified in the UK (B.1.1.7) and South Africa (B.1.351), in preclinical research. Both antibodies retaining their potency against the B.1.1.7 variant; against the B.1.351 variant, imdevimab retained its potency and, while the casirivimab potency was reduced, it was still comparable to the potency that other single antibodies in development have against the original virus. Regeneron is conducting additional preclinical research against the variant first identified in Brazil (1.1.248), https://investor.regeneron.com/news-releases/news-release-details/regen-covtm-antibody-cocktail-active-against-sars-cov-2-variants.

In the FDA new revision in September 2021 [174], related to REGN-COV2 and new variants, casirivimab and imdevimab individually and together retained neutralization activity against Alpha (UK origin) (Table 3.13-1), Beta (South Africa origin), Gamma (Brazil origin) and Epsilon (USA [California] origin). Casirivimab and imdevimab, individually and together, also retained neutralization activity against Delta (India origin).

FDA Analyse zur Wirksamkeit bei unterschiedlichen Mutationen:

gleiche Wirksamkeit

Table 3.13-1. Pseudovirus neutralization data for SARS-CoV-2 variant substitutions with Casirivimab and Imdevimab together

Lineage with Spike Protein Substitution	Key substitutions tested	Fold reduction in susceptibility
Alpha - B.1.1.7 (UK origin)	N501Y	no change
Beta - B.1.351 (South Africa origin)	K417N, E484K, N501Y	no change
Gamma - P.1 (Brazil origin)	K417T + E484K + N501Y	no change
Delta- B.1.617.2/AY.3	L452R+T478K	no change
Delta plus - AY.1/AY.2f	K417N+L452R+T478K	no change
Epsilon - B.1.427/B.1.429 (California origin)	L452R	no change
Iota - B.1.526 (New York origin)	E484K	no change
Kappa/no designation- B.1.617.1/B.1.617.3 (India)	L452R+E484Q	no change
Lambda- C.37 (Peru)	L452Q+F490S	no change
Mu- B.1.621/B.1.621.1 (Colombia)	R346K, E484K, N501Y	no change

Source: [174]

US COVID-19 Treatment Guidelines (last update August 4, 2021)

- The **US COVID-19 Treatment Guidelines Panel** recommends using one of the following combination anti-SARS-CoV-2 monoclonal antibodies to treat outpatients with mild to moderate COVID-19 who are at high risk of clinical progression, as defined by the EUA criteria (listed in alphabetical order):

US COVID-19 Treatment Guidelines Panel

Empfehlung FÜR Antikörper Kombinationstherapien

Casirivimab plus imdevimab; *or* **Sotrovimab 500 mg intravenous (IV) infusion**.

Casirivimab + Imdevimab oder Sotrovimab

GEGEN Bamlanivimab + Etesevimab

- At this time, the Panel **recommends against** the use of **bamlanivimab plus etesevimab (AIII)** because the Gamma (P.1) and Beta (B.1.351) VoC, which have reduced susceptibility to both agents, are circulating in the United States.
- The use of anti-SARS-CoV-2 monoclonal antibodies should be considered for patients with mild to moderate COVID-19 who are hospitalized for a reason other than COVID-19 if they otherwise meet the EUA criteria for outpatient treatment.
- Anti-SARS-CoV-2 monoclonal antibodies are not currently authorized for use in patients who are hospitalized with severe COVID-19; however, they may be available through expanded access programs for patients who have not developed an antibody response or who are not expected to mount an effective immune response to SARS-CoV-2 infection [120].

Empfehlung FÜR Pts, die wegen anderen Gründen hospitalisiert sind

Also, the Panel recommends (last update: August 17, 2021):

Recommendation for individuals with symptoms that are consistent with COVID-19

symptomatische Patient*innen

The COVID-19 Treatment Guidelines Panel (the Panel) recommends that individuals who have recently been exposed to SARS-CoV-2 and have symptoms that are consistent with COVID-19 be evaluated for SARS-CoV-2

infection by either a nucleic acid amplification test (NAAT) or antigen testing (**AIII**).
Individuals with positive SARS-CoV-2 NAAT or antigen test results who meet the
Emergency Use Authorization (EUA) criteria for therapeutic use of anti-SARS-CoV-2 monoclonal antibodies should be referred for treatment.
Those with negative test results should be considered for post-exposure prophylaxis (PEP) as discussed below.

Post-Exposure Prophylaxe

Recommendations for Post-Exposure Prophylaxis
The Panel recommends using casirivimab 600 mg plus imdevimab 600 mg administered as subcutaneous (SQ) injections (**AI**) or an intravenous (IV) infusion (**BIII**) as PEP for people who are at high risk for progression to severe COVID-19 if infected with SARSCoV-2 AND who have the following vaccination status AND exposure history.
Vaccination Status: Not fully vaccinated (defined as people who were never vaccinated or those who received the second vaccine dose in a two-dose series or a single-dose vaccine <2weeks ago); *or* Fully vaccinated, but not expected to mount an adequate immune response (e.g., those with immunocompromising conditions, including those who are taking immunosuppressive medications)
AND
Exposure History to SARS-CoV-2: Had a recent exposure to an individual with SARS-CoV-2 infection that is consistent with the Centers for Disease Control and Prevention (CDC) close contact criteria; *or* At high risk of exposure to an individual with SARS-CoV-2 infection because of recent occurrence of SARS-CoV-2 infection in other individuals in the same institutional setting (e.g., nursing homes, prisons)

Results of publication

Teilergebnisse von Phase 1–3 RCT

275 Pts.

Vorteile bei Viruslastreduktion Reduktion von Arztbesuchen

On December 17 2020, Weinreich et al. [176] published **preliminary results of phase 1-2 portion** of ongoing double-blind, **phase 1–3 trial (NCT04425629)** involving **nonhospitalised** patients with **Covid-19**, randomly assigned (1:1:1) to receive placebo, **2.4 g** of REGN-COV2, or **8.0 g** of REGN-COV2 and were prospectively characterized at baseline for endogenous immune response against SARS-CoV-2 (serum antibody–positive or serum antibody–negative). In this interim analysis, data from 275 patients are reported: the REGN-COV2 antibody cocktail reduced viral load, with a greater effect in patients whose immune response had not yet been initiated or who had a high viral load at baseline. The same is true for medically attended visit, with a greater effect among patients who were serum antibody–negative at baseline. The percentages of patients with hypersensitivity reactions, infusion-related reactions, and other adverse events were similar in the combined REGN-COV2 dose groups and the placebo group.

Phase 3 RCT
4.057 ambulante Pts
Risiko auf Progression

signifikante Reduktion der Hospitalisierungen in allen Subgruppen

On May 21, 2021 Weinreich et al. [177] published as preprint results from **phase 3 portion** of above mentioned adaptive, randomized, master protocol, included 4057 Covid-19 outpatients **with one or more risk factors for severe disease (NCT04425629)**. Patients were randomized to a single treatment of **intravenous** placebo, or various doses of REGEN-COV, and followed for 28 days. The prespecified hierarchical analysis first compared REGEN-COV **2400mg dose** vs concurrent placebo, then compared the **1200mg dose** vs concurrent placebo, for endpoints assessing risk of hospitalization or death, and time to symptom resolution. Safety was evaluated in all treated patients. Demographic and baseline medical characteristics were balanced between the placebo and REGEN-COV groups. Both REGEN-COV 2400mg and 1200mg significantly reduced Covid-19-related hospitalization or all-cause death compared to placebo (71.3% reduction [1.3% vs 4.6%; p<0.0001] and 70.4% reduction [1.0% vs 3.2%; p=0.0024], respectively). The median time

to resolution of Covid-19 symptoms was 4 days shorter in both dose arms vs placebo (10 vs 14 days; p<0.0001). Efficacy of REGEN-COV was consistent across subgroups, including patients who were SARS-CoV-2 serum antibody-positive at baseline. REGEN-COV more rapidly reduced viral load than placebo. Serious adverse events occurred more frequently in the placebo group (4.0%) than in the 1200mg (1.1%) and 2400mg (1.3%) groups and grade ≥2 infusion-related reactions were infrequent (<0.3% in all groups).

Phase 3 RCT
314 asymtomatische (covid-19 positive) Erwachsene
subkutane Verabreichung

signifikant geringere Progression zu symptomatischer Erkrankung
raschere Gesundung (-14 Tage)

On June 14, 2021 O'Brien et al. [178] published as preprint, and then in scientific journal [179] **phase 3 results** of early treatment of **asymptomatic, SARS-CoV-2–positive** adults and adolescents with **subcutaneous** REGN-COV (**NCT04452318**). Individuals ≥12 years of age were eligible if identified within 96 hours of a household contact being diagnosed as SARS-CoV-2-positive; 314 were randomized 1:1 to receive subcutaneous REGEN-COV **1200 mg** or placebo. The primary endpoint was the proportion of infected participants without evidence of prior immunity (i.e., SARS-CoV-2-RT-qPCR–positive/seronegative) who subsequently developed symptomatic Covid-19 during a 28-day efficacy assessment period. Symptomatic SARS-CoV-2 infection developed in 11 of 753 participants in the REGN-COV group (1.5%) and in 59 of 752 participants in the placebo group (7.8%) (RRR, 81.4%; p<0.001). In weeks 2 to 4, a total of 2 of 753 participants in the REGN-COV group (0.3%) and 27 of 752 participants in the placebo group (3.6%) had symptomatic SARS-CoV-2 infection (RRR, 92.6%). REGEN-COV also prevented symptomatic and asymptomatic infections overall (RRR, 66.4%). Among symptomatic infected participants, the median time to resolution of symptoms was 2 weeks shorter with REGEN-COV than with placebo (1.2 weeks and 3.2 weeks, respectively), and the duration of a high viral load (>104 copies per milliliter) was shorter (0.4 weeks and 1.3 weeks, respectively). No dose-limiting toxic effects of REGN-COV were noted. Autors concluded that subcutaneous REGN-COV prevented symptomatic Covid-19 and asymptomatic SARS-CoV-2 infection in previously uninfected household contacts of infected persons. Among the participants who became infected, REGN-COV reduced the duration of symptomatic disease and the duration of a high viral load.

SoF von 2 RCTs zu ambulanen Patient*innen, asymptomatische/ mile Erkrankung

wenig sichere Evidenz

Data on moderate to very low certainty of evidence, related to effectiveness and safety of **REGN-COV2 1200 mg** compared to placebo, reported in these 2 RCTs mentioned above, can be found in the Table 3.13-2. In summary, based on the results of the phase 3 portion of two RCTs in **outpatients** with asymptomatic or mild Covid-19, the evidence is very uncertain about the effect of REGN-COV2 on outcome All-cause mortality D28 (RR 1.00, 95% CI 0.06 to 16.00, very low certainty of evidence). REGN-COV2 probably does not increase AEs (RR 0.70, 95% CI 0.53 to 0.93, moderate certainty of evidence) and may not increase SAEs (RR 0.11, 95% CI 0.01 to 2.07, low certainty of evidence).

*Table 3.13-2: Summary of findings table, on **REGN-COV2 1200 mg vs placebo** (2 RCTs: O'Brien; Weinreich)*

REGN-COV2 compared to Placebo for Asymptomatic and Mild outpatients (last update 27/06/2021)

Patient or population: Mild COVID-19
Setting: Worldwide Outpateint
Intervention: REGN-COV2 1200 mg
Comparison: Placebo

Outcome	Anticipated absolute effects (95% CI) [a]		Relative effect (95% CI)	Number of participants (studies)	Certainty of evidence	Comments
	Risk with Placebo	Risk with REGN-COV2				
All-cause mortality D28	1 per 1000	1 per 1000	**RR: 1.00** (0.06 - 16.00)	1992 (2 RCTs) [b]	OOO⊕ VERY LOW [c]	**Absolute effect (95% CI)** 0 fewer per 1000 (from 1 fewer to 15 more)
Number of patients with adverse events	475 per 1000	332 per 1000	**RR: 0.70** (0.53 - 0.93)	314 (1 RCT) [d]	⊕⊕⊕O MODERATE [e]	**Absolute effect (95% CI)** 142 fewer per 1000 (from 223 fewer to 33 fewer)
Number of patients with serious adverse events	25 per 1000	3 per 1000	**RR: 0.11** (0.01 - 2.07)	314 (1 RCT) [d]	⊕⊕OO LOW [f]	**Absolute effect (95% CI)** 23 fewer per 1000 (from 25 fewer to 27 more)

CI: Confidence interval; **RR**: Risk ratio; a The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI) b O'Brien, 2021; Weinreich, 2021 c Risk of bias: Serious Risk of bias downgraded by 1 level: some concerns regarding adequate randomization and missing data Imprecision: Very serious due to very wide confidence interval consistent with the possibility for benefit and the possibility for harm and low number of participants; d O'Brien, 2021; e Imprecision: Serious due to low number of participants; f Imprecision: Very serious due to very wide confidence interval consistent with the possibility for benefit and the possibility for harm and low number of participants

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

On June 16, 2021 **RECOVERY** Collaborative Group published as preprint results from randomised, controlled, open-label platform trial, in which eligible and consenting **hospitalised COVID-19** patients were randomly allocated (1:1) to either usual standard of care alone (usual care group) or usual care plus a single dose of **REGN-COV 8 g (casirivimab 4 g and imdevimab 4 g)** by **intravenous** infusion (REGEN-COV group). The primary outcome was 28-day mortality assessed first among patients without detectable antibodies to SARS-CoV-2 at randomisation (seronegative) and then in the overall population (**ISRCTN 50189673, NCT04381936**) [180]. 9785 patients were randomly allocated to receive usual care plus REGEN-COV or usual care alone, including 3153 (32%) seronegative patients, 5272 (54%) seropositive patients and 1360 (14%) patients with unknown baseline antibody status. In the primary efficacy population of **seronegative patients**, 396 (24%) of 1633 patients allocated to REGEN-COV and 451 (30%) of 1520 patients allocated to usual care died within 28 days (rate ratio 0.80; 95% CI 0.70-0.91; p=0.0010). In an analysis involving all randomised patients (regardless of baseline antibody status), 944 (20%) of 4839 patients allocated to REGEN-COV and 1026 (21%) of 4946 patients allocated to usual care died within 28 days (rate ratio 0.94; 95% CI 0.86-1.03; p=0.17). The proportional effect of REGEN-COV on mortality differed significantly between seropositive and seronegative patients (p value for heterogeneity =0.001). For the **seronegative patients**, the **duration of hospital stay was four days shorter** (median 13 days vs. 17 days) among those allocated to the antibody combination than the usual care group, and the **proportion of patients discharged alive by day 28 was greater** (64% vs. 58%; rate ratio 1.19, 95% confidence interval 1.08 to 1.30). Among the seronegative patients not on invasive mechanical ventilation at baseline, **the risk of progressing to the composite endpoint of invasive mechanical ventilation or death was lower** among those allocated to the antibody combination than the usual care group (30% vs. 37%; risk ratio 0.83, 95% confidence interval 0.75 to 0.92). No such benefits were seen in the overall study population (combining patients with negative, positive, or unknown serostatus).

Platform Studie RECOVERY 9.785 hospitalisierte Pts.

kein Unterschied in Mortalität bei seropositiven, wohl aber bei seronegativen Pts.

ebenso bei frühere Spitalsentlassung, Progression, invasive Beatmung

Dose-ranging Virology Trial

A companion dose-ranging phase 2 trial of 803 outpatient COVID-19 patients was conducted to evaluate the antiviral effect of several different REGEN-COV doses (IV: 2,400 mg, 1,200 mg, 600 mg and 300 mg; SC: 1,200 mg and 600 mg). All tested doses met the primary endpoint, rapidly and significantly reducing patients' viral load (log10 copies/mL) compared to placebo (p<0.001). Each dose demonstrated similar efficacy, including the lowest doses tested (IV: 300 mg; SC: 600 mg). In addition, a companion phase 2 trial showed that even the lowest doses tested (IV: 300 mg; subcutaneous [SC]: 600 mg) had significant viral load reductions over the first 7 study days, comparable to the 2,400 mg and 1,200 mg IV doses. A safety assessment conducted on all available patient data up to day 169 identified no new safety signals. Serious adverse events (SAEs) were largely related to COVID-19 and occurred in 1.1% of patients in the 1,200 mg group, 1.3% in the 2,400 mg group and 4.0% in the placebo group.

Phase 2 Dosisfindungsstudie 803 Pts.

auch niedrige Dosierungen reduzieren Viruslast

geringe Nebenwirkungen

Safety issue in hospitalised patients

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 **hospitalised 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

Sicherheitswarnung für Kohorte hospitalisierte und künstlich beatmete Pts.

analysis of further data on patients already enrolled. The IDMC also recommends continuing enrollment of hospitalised 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.

Regulatory update:

FDA: Notzulassung von von REGN-COV2

für milde bis moderate Erkrankung

seit Juni 2012: alternative Applikationsmöglichkeit

subkutan

On November 21, 2020, the U.S. Food and Drug Administration issued an **emergency use authorization (EUA)** for casirivimab and imdevimab to be administered together for the **treatment** of **mild to moderate COVID-19** in adults and pediatric patients (12 years of age or older weighing at least 40 kilograms [about 88 pounds]) with positive results of direct SARS-CoV-2 viral testing and who are **at high risk for progressing to severe COVID-19, including hospitalisation or death**. This includes those who are 65 years of age or older or who have certain chronic medical conditions [181]. In the **revised June 2021 version**, updates on authorized dosage (600 mg of casirivimab and 600 mg of imdevimab), routes of administration (subcutaneous route as an alternative for those who cannot receive intravenous infusion), as well as additional phase 3 results and safety with subcutaneous dosing are provided [182].

Juli 2021 FDA EUA als Post Exposure Prophylaxe

In **new revision of EUA, July 2021** [174] FDA has issued an Emergency Use Authorization (EUA) to permit the emergency use of the unapproved product, REGN-COV (casirivimab and imdevimab) in adult and pediatric individuals (12 years of age and older weighing at least 40 kg) for **post-exposure prophylaxis of COVID-19** in individuals who are at high risk for progression to severe COVID-19, including hospitalization or death, and are:

- not fully vaccinated OR who are not expected to mount an adequate immune response to complete SARS-CoV-2 vaccination (for example, individuals with immunocompromising conditions including those taking immunosuppressive medications

AND

- have been exposed to an individual infected with SARS-CoV-2 consistent with close contact criteria per Centers for Disease Control and Prevention (CDC)

OR

- who are at high risk of exposure to an individual infected with SARS-CoV-2 because of occurrence of SARS-CoV-2 infection in other individuals in the same institutional setting (for example, nursing homes, prisons)

Feb 2021: EMA beginnt "Rolling Review" zu REGN-COV

On **February 1st, 2021** EMA's human medicines committee (CHMP) has started a '**rolling review**' of data on REGN-COV2 antibody combination (casirivimab / imdevimab), based on preliminary results from a study that indicate a beneficial effect of the medicine in reducing the amount of virus in the nose and throat of non-hospitalised patients with COVID-19 [183]. Once finalised it will be the **basis for an EU marketing authorisation for this combination**.

EMA: REGN-COV2 kann für bestätigte Covid-19 Pts, die hohes Risiko auf Fortschreiten zu schwerer Erkrankung haben, eingestzt werden

On **February 26, 2021** EMA stated that the CHMP has completed its review to provide a **harmonised scientific opinion** at EU level to support national decision making on the possible use of the antibodies **before a formal authorisation is issued**. The Agency concluded that the combination (REGN-COV2) **can be used** for the treatment of **confirmed COVID-19 in patients who do not require supplemental oxygen and who are at high risk of progressing to severe COVID-19**. Risk factors may include but are not

limited to advanced age; obesity; cardiovascular disease, including hypertension; chronic lung disease, including asthma; type 1 or type 2 diabetes mellitus; chronic kidney disease, including those on dialysis; chronic liver disease; immunosuppressed, based on prescriber's assessment [184, 185].

Regeneron is collaborating with Roche to increase global supply of REGEN-COV2. Regeneron is responsible for development and distribution of the treatment in the U.S., and Roche is primarily responsible for development and distribution outside the U.S.

Regeneron Koperation mit Roche

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 hospitalised 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 **hospitalised** 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 in Planung

On 27 January 2021, **Eli Lilly and Company**, **Vir Biotechnology, Inc.** and **Glaxo Smith Kline plc** announced a collaboration to evaluate a **combination of two COVID-19 therapies** in **low-risk patients with mild to moderate COVID-19**. Lilly has expanded its ongoing **BLAZE-4** trial to evaluate the administration of **bamlanivimab (LY-CoV555) 700mg** with **VIR-7831** (**dual-action monoclonal antibody**, also known as **GSK4182136**) **500mg**, two neutralizing antibodies that bind to different epitopes of the SARS-CoV-2 spike protein [186].

EliLilly Kooperation mit GSK zu Kombinations-therapie Bamlanivimab + VIR-7831

bei milder/moderater Erkrankung

New SARS-CoV-2 Variants

Bamlanivimab plus etesevimab combination

FDA Analyse zur Wirksamkeit bei unterschiedlichen Mutationen: Potential für Resistenz

In the FDA new revision published on August 2021 [187], related to bamlanivimab plus etesevimab combination and new variants, there is a potential risk of treatment failure due to the development of viral variants that are resistant to bamlanivimab and/or etesevimab (Table 3.13-3). There are other authorized monoclonal antibody treatments available and healthcare providers should choose an authorized therapeutic option with activity against circulating variants in their state, territory, or US jurisdiction.

reduzierte Aktivität

Bamlanivimab and etesevimab together retained activity against the Alpha (UK origin) virus variant. For Beta (South Africa origin), Gamma (Brazil origin) reduced susceptibility to bamlanivimab and etesevimab was observed. Bamlanivimab and etesevimab together and etesevimab alone retained activity against Delta (India origin), but bamlanivimab alone had reduced activity.

Table 3.13-3: Pseudovirus neutralization data for SARS-CoV-2 variant substitutions with bamlanivimab plus etesevimab together (1:2 molar ratio)

Lineage with Spike Protein Substitution	Key substitutions tested	Fold reduction in susceptibility
Alpha - B.1.1.7 (UK origin)	N501Y	no change
Beta - B.1.351 (South Africa origin)	K417N, E484K, N501Y	431
Gamma - P.1 (Brazil origin)	K417T + E484K + N501Y	252
Delta- B.1.617.2/AY.3	L452R+T478K	no change
Delta plus - AY.1/AY.2f	K417N+L452R+T478K	1235
Epsilon - B.1.427/B.1.429 (California origin)	L452R	9
Iota - B.1.526 (New York origin)	E484K	30
Kappa/no designation- B.1.617.1/B.1.617.3 (India)	L452R+E484Q	6

Source: [187]

US COVID-19 Treatment Guidelines (last update August 4, 2021)

US COVID-19 Treatment Guidelines Panel: Empfehlung GEGEN Bamlanivimab Eetesevimab Kombinationstherapie

- The **US COVID-19 Treatment Guidelines Panel** recommends **against** using **Bamlanivimab plus etesevimab**-combination to treat outpatients with mild to moderate COVID-19 who are at high risk of clinical progression, as defined by the EUA criteria due to an increase in the prevalence of potentially resistant variants **(AIII)** [120]. The distribution of bamlanivimab plus etesevimab was paused on June 25, 2021, because both the Gamma (P.1) and Beta (B.1.351) variants of concern (VoC) that are currently circulating in the United States have reduced susceptibility to bamlanivimab and etesevimab.

Results of publications

Outpatients

ambulante
Phase 2/ 3 RCT Pts.

BLAZE-1
613 Patient*innen
milde/ moderate Erkrankung

Monotherapie vs. Kombinationstherapie mit Etesevimab

Ergebnisse von Phase 2 Kohorte

Final results of the **phase 2 portion of BLAZE-1**, randomised, double-blind, placebo-controlled trial **(NCT04427501)** were published by Gottlieb et al. 2021 [190]. The BLAZE-1 study is a randomized phase 2/3 trial at 49 US centers including **ambulatory patients** (n = 613) who tested positive for SARS-CoV-2 infection and had 1 or more **mild to moderate** COVID-19 symptoms. Patients who received **bamlanivimab** (LY-CoV555) **monotherapy** or placebo were enrolled first followed by patients who received **bamlanivimab** (LY-CoV555) **and etesevimab** (LY-CoV016) **combination** or **placebo**. Patients were randomized to receive a single infusion of bamlanivimab (700 mg [n=101], 2800 mg [n=107], or 7000 mg [n=101]), the combination treatment (**2800mg of bamlanivimab and 2800 mg of etesevimab** [n=112]), or placebo (n=156). The primary end point was change in SARS-CoV-2 log viral load at day 11 (±4 days). Nine prespecified secondary outcome measures were evaluated with comparisons between each treatment group and placebo, and included 3 other measures of viral load, 5 on symptoms, and 1 measure of clinical outcome (the proportion of patients with a COVID-19–related hospitalization, an emergency department [ED] visit, or death at day 29).

kein Unterschied bei Mortalität

signifikante Unterschiede bei Hospitalisierung, Besuch in Notfallambulanz unter Kombinationstherapie und Monotherapie

bessere Symtomkontrolle, aber unter beiden Interventionen

Data on high and moderate certainty of evidence, related to effectiveness and safety of bamlanivimab monotherapy and bamlanivimab + etesevimab compared to placebo and each other, reported in this RCT, prepared by Cruciani et al. [191-194], can be found in the Summary of Findings tables 3.13-3, 4 and 5. In summary, based on the final results of the phase 2 portion of one RCT in **outpatients** with recently diagnosed mild or moderate Covid-19, no deaths occurred in bamlanivimab, bamlanivimab + etesevimab combination and placebo group (high certainty of evidence).

Bamlanivimab 700 mg monotherapy and bamlanivimab 2800 mg + etesevimab 2800 mg treatment compared to placebo reduces COVID-19 related hospitalisation or visit to an emergency department at day 29 (high certainty of evidence). The change in mean total symptom score from baseline to day 11 was favouring the 700 mg monotherapy group (high certainty of evidence) and the bamlanivimab + etesevimab combination group (moderate certainty of evidence).

aber: keine raschere Viruslastreduktion

gleiche Nebenwirkungen

Bamlanivimab and bamlanivimab + etesevimab treatment compared to placebo does not increase number of patients with adverse events or number of serious adverse events (high certainty of evidence). The same is true for bamlanivimab compared to bamlanivimab + etesevimab treatment. Bamlanivimab monotherapy or bamlanivimab + etesevimab treatment, compared to placebo, does not accelerate the natural decline in viral load over time (high certainty of evidence). The same is true for bamlanivimab compared to bamlanivimab + etesevimab treatment.

Phase 2/ 3 RCT
BLAZE-1
1.035 Patient*innen
Ergebnisse von Phase 3 Kohorte
milde/ moderate Erkrankung, aber Risiko progredienter Erkrankung

On January 26, 2021 Eli Lilly and Company announced **unpublished results from phase 3 BLAZE-1 RCT** on the combination therapy arms enrolled **mild to moderate**, recently diagnosed **COVID-19 patients** who are at **high risk for progressing to severe COVID-19 and/or hospitalisation**, studying **bamlanivimab 2800 mg plus etesevimab 2800 mg versus placebo**. The primary outcome measure for the phase 3 portion of the BLAZE-1 trial was the percentage of participants who experience COVID-related hospitalizations or death from any cause by day 29. The key secondary endpoints were change from baseline to day 7 in SARS-CoV-2 viral load, persistently high SARS-CoV2 viral load on day 7, time to sustained symptom resolution, and COVID-related hospitalization, ER visit or death from any cause from baseline by day 29. Additional endpoints include

change from baseline in viral load at other time points, symptom improvement, symptom resolution, as well as safety.

signifikante Reduktion von Hospitalisierung und Mortalität

On July 14, 2021 results are published as scientific article [195]: Bamlanivimab (LY-CoV555) 2800 mg and etesevimab (LY-CoV016) 2800 mg together significantly reduced COVID-19-related hospitalisations and deaths in high-risk patients recently diagnosed with COVID-19. Across 1,035 patients, there were 11 events (out of 518 patients, 2.1%) in patients taking therapy and 36 events (out of 517 patients, 7.0%) in patients taking placebo, representing a 70 percent risk reduction (p=0.0004). There were 10 deaths total, all of which occurred in patients taking placebo, and no deaths in patients taking bamlanivimab and etesevimab together.

von 1.035 Pts 2,1% Ereignisse in Interventionsgruppe, 7% in Kontrollgruppe

Todesfälle nur in Plazebogruppe

Bamlanivimab and etesevimab together also demonstrated statistically significant improvements on all key secondary endpoints, providing strong evidence that the therapy reduced viral load and accelerated symptom resolution. At day 7, a greater reduction from baseline in the log viral load was observed among patients who received bamlanivimab plus etesevimab than among those who received placebo (difference from placebo in the change from baseline, −1.20; 95% CI, −1.46 to −0.94; p<0.001). Twelve of 518 patients (2.3%) who received bamlanivimab plus etesevimab had a Covid-19–related hospitalization, an emergency department visit, or death from any cause by day 29, as compared with 37 of 517 patients (7.2%) who received placebo (difference from placebo in the decrease from baseline, −4.8 percentage points; 95% CI, −7.4 to −2.3; p<0.001). The median time to sustained resolution of symptoms after two consecutive assessments was 1 day shorter in the bamlanivimab–etesevimab group (8 days; 95% CI, 7 to 8) than in the placebo group (9 days; 95% CI, 8 to 10) (p=0.007).

gleiche Nebenwirkungen

The safety profile of bamlanivimab and etesevimab together was consistent with observations from other phase 1, phase 2 and phase 3 trials evaluating these antibodies. Serious adverse events were reported at a similar frequency in the bamlanivimab and etesevimab together and placebo groups. Serious adverse events occurred in 7 of 518 patients (1.4%) in the bamlanivimab–etesevimab group and in 5 of 517 patients (1.0%) in the placebo group. Adverse events that occurred after the infusion was initiated were reported in 69 of 518 patients (13.3%) in the bamlanivimab–etesevimab group and in 60 of 517 patients (11.6%) in the placebo group. In both groups, the most common adverse events were nausea, rash, dizziness, diarrhea, and hypertension.

SoF-Tabelle Reduktion der Hospitalisierungen raschere Gesundung

Summary of Findings table 3.13-4 related to effectiveness and safety of bamlanivimab + etesevimab combination compared to placebo published in these 2 RCTs mentioned above can be found below. In summary, bamlanivimab + etesevimab combination may reduce number of hospitalisation (RR 0.33, 95% CI 0.16 to 0.59, low certainty of evidence) and may increase clinical improvement D28 (RR 1.20, 95% CI 0.99 to 1.46, low certainty of evidence) as well as viral negative conversion D7 (RR 1.67, 95% CI 1.22 to 2.30, low certainty of evidence). Evidence is very uncertain related to all cause mortality (RR 0.05, 95% CI 0.00 to 0.81, very low certainty of evidence), AEs (RR 0.88, 95% CI 0.50 to 1.56, very low certainty of evidence) and SAEs (RR 1.40, 95% CI 0.49 to 4.02, very low certainty of evidence).

EUnetHTA Bericht

On May 31, 2021 EUnetHTA Rapid Review was published on this topic [196].

Phase 3 RCT BLAZE-1
769 Pts
milde/ moderate Erkrankung
Kombinationstherapie

70%ige Reduktion der Hospitalisierungen und Notfallambulanz-Besuche

On March 10, 2021 Eli Lilly and Company announced new data from the **BLAZE-1 phase 3 study**, demonstrating **bamlanivimab** (LY-CoV555) **700 mg** and **etesevimab** (LY-CoV016) **1400 mg together** significantly reduced COVID-19 related hospitalizations and deaths ("events") in **high-risk patients** recently diagnosed with COVID-19.

This phase 3 cohort of BLAZE-1 included 769 high-risk patients, aged 12 and older with **mild to moderate COVID-19** (therapy: n=511; placebo: n=258). There were four events in patients taking bamlanivimab with etesevimab and 15 events in patients taking placebo, representing an 87 percent risk reduction (p<0.0001). Bamlanivimab and etesevimab together also demonstrated statistically significant improvements on key secondary endpoints. These results are consistent with those seen in other data sets from BLAZE-1: in the previous phase 3 cohort, bamlanivimab 2800 mg with etesevimab 2800 mg reduced the risk of hospitalizations and deaths by 70 percent and in the phase 2 cohort, bamlanivimab alone reduced the risk of hospitalizations and ER visits by approximately 70 percent. The viral load reductions were also consistent with what was observed in the previous phase 3 cohort of the study. In this phase 3 cohort, there were four deaths total, all of which were deemed related to COVID-19 and all of which occurred inpatients taking placebo; no deaths occurred in patients receiving treatment with bamlanivimab and etesevimab together. Across the two phase 3 cohorts of the study that have been analyzed to date, there have been no deaths in patients receiving treatment withbamlanivimab and etesevimab together, and 14 deaths in patients receiving placebo, 13 of which were deemed COVID-19 related. In this data set, the safety profile of bamlanivimab and etesevimab together was consistent with observations from other phase 1, phase 2 and phase 3 trials evaluating these antibodies, https://investor.lilly.com/news-releases/news-release-details/lillys-bamlanivimab-and-etesevimab-together-reduced..

BLAZE-4 laufend
Dosisfindung

Additionally, initial results from the **ongoing BLAZE-4 trial** (**NCT04634409**) provide viral load and pharmacodynamic/pharmacokinetic data which demonstrated lower doses, including bamlanivimab 700 mg and etesevimab 1400 mg together, are similar to bamlanivimab 2800 mg and etesevimab 2800 mg together [197].

Pressemeldung:

Phase 2 BLAZE-4
Kombinationstherapie mit VIR-7831
in mild/ moderater Erkrankung

-70% Viruslastreduktion

On March 29, 2021 Eli Lilly and Company, Vir Biotechnology, Inc. and GlaxoSmithKline plc announced data from the **expanded phase 2 BLAZE-4** trial studying **low-risk adult patients** with **mild to moderate COVID-19**. Results showed that investigational **bamlanivimab** (LY-CoV555) **700 mg co-administered with VIR-7831** (also known as GSK4182136) **500 mg** demonstrated a 70 percent (p<0.001) relative reduction in persistently high viral load (> 5.27; cycle threshold value < 27.5) at day 7 compared to placebo, meeting the primary endpoint. Bamlanivimab administered with VIR-7831 demonstrated a statistically significant reduction compared to placebo in the key virologic secondary endpoints of mean change from baseline to days 3, 5 and 7 in SARS-CoV-2 viral load. There were no events for the secondary endpoint of COVID-19 related hospitalization or death by day 29 in either study arm. One patient (in the treatment arm) visited the emergency room for COVID-19 related symptoms. No serious adverse events were seen with co-administration of bamlanivimab and VIR-7831. Bamlanivimab and VIR-7831 bind to different regions of the spike protein of SARS-CoV-2. Preclinical data suggest the administration of these two investigational antibodies together may provide protection against current variants of SARS-CoV-2 that are resistant to bamlanivimab.

Hospitalised COVID-19 patients

hospitalisierte Pts

Lundgren et al. 2020 (**ACTIV-3/TICO** LY-CoV555 Study group) published **preliminary** negative results from RCT (**NCT04501978**) compared LY-CoV555 with placebo in **hospitalised patients** who had Covid-19 without end-organ failure [199]. In addition, all the patients received high-quality supportive care as background therapy, including the antiviral drug remdesivir (95% of patients) and, when indicated, supplemental oxygen and glucocorticoids. The data and safety monitoring board recommended stopping enrollment for futility after 314 patients (163 in the LY-CoV555 group and 151 in the placebo group) had undergone randomization and infusion.

RCT mit hospitalisierten Pts. mit Organversagen

Kombinationstherapie Bamlanivimab + Remdesivir

kein Unterschied/ keine Wirksamkeit

Data on high certainty of evidence, related to effectiveness and safety of bamlanivimab reported in this one RCT mentioned above, prepared by Cruciani et al. [200, 201], can be found in the Table 3.13-5. Based on the interim results from one RCT with high certainty of evidence, in **hospitalised** patients, bamlanivimab compared to standard treatment does not reduce all-cause mortality, does not increase the number of patients with AEs and SAEs, and does not increase the number of patients discharged.

Daten zu hospitalisierten Patient*innen

keine Reduktion der Gesamtmortalität

*Table 3.13-4: Summary of findings (SoF) table for published RCTs related to effectiveness and safety of bamlanivimab + etesevimab combination compared to placebo – **OUTPATIENT** (2 RCTs: Gottlieb 2021, Dougan 2021)*

Outpatients (last update 10/08/2021)

Patient or population: COVID-19 patients
Setting: Worldwide
Intervention: Bamlanivimab+Etesevimab (LY-CoV555+LY-CoV016)
Comparison: Placebo

Outcome	Anticipated absolute effects (95% CI) [a]		Relative effect (95% CI)	Number of participants (studies)	Certainty of evidence	Comments
	Risk with Placebo	Risk with Bamlanivimab + etesevimab				
All-cause mortality	0 per 1000	0 per 1000	RR 0.05 (0.00 to 0.81)	1310 (2 RCTs) [b c]	⊕◯◯◯ VERY LOW [d]	/
Hospitalisation or death 29	70 per 1000	21 per 1000 (1 to 69)	RR 0.3 (0.16 to 0.59)	1035 (1 RCT) [c]	⊕⊕◯◯ LOW [e]	**Absolute effect (95% CI)** 49 fewer per 1000 (from 58 fewer to 29 fewer)
Clinical improvement D28	547 per 1000	656 per 1000	RR 1.20 (0.99 to 1.46)	275 (1 RCT) [b]	⊕⊕◯◯ LOW [e]	**Absolute effect (95% CI)** 109 more per 1000 (from 5 fewer to 251 fewer)
WHO progression score (level 7 or above) D28	Outcome not yet measured or reported	Outcome not yet measured or reported	Outcome not yet measured or reported	Outcome not yet measured or reported	Outcome not yet measured or reported	Outcome not yet measured or reported
Viral negative conversion D7	84 per 1000	140 per 1000	RR 1.67 (1.22 to 2.30)	1310 (2 RCTs) [b c]	⊕⊕◯◯ LOW [e]	**Absolute effect (95% CI)** 56 more per 1000 (from 18 more to 109 more)
Number of patients with any adverse events	150 per 1000	132 per 1000	RR 0.88 (0.50 to 1.56)	1310 (2 RCTs) [b c]	⊕◯◯◯ VERY LOW [d]	**Absolute effect (95% CI)** 18 fewer per 1.000 (from 75 fewer to 84 more)
Number of patients with serious adverse events	9 per 1000	12 per 1000	RR 1.40 (0.49 to 4.02)	1310 (2 RCTs) [b c]	⊕◯◯◯ VERY LOW [d]	**Absolute effect (95% CI)** 4 more per 1.000 (from 5 fewer to 27 more)

Source: https://covid-nma.com/living_data/index.php?allcomp#comparisons_div **Explanations:** [a] The risk in the intervention group is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI) [196] b Gottlieb et al [190] c Dougan et al [195] ; d Indirectness: Serious studies from a single country, therefore results in this population might not be generalizable to other settings. Imprecision: Very serious due to wide confidence interval consistent with the possibility for benefit and the possibility for no effect and very low number of participants e Indirectness: Serious despite a multicentre design this is a single study from a single country, therefore results in this population might not be generalizable to other settings. Imprecision: Serious due to low number of participants

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
Abbreviations: CI=confidence interval; RR=risk ratio; SAE=serious adverse event; AE=adverse event; RCT=randomised controlled trial; SD=standard deviation

Table 3.13-5: Summary of findings (SoF) table for published RCTs related to effectiveness and safety of bamlanivimab compared to standard treatment/placebo – ***HOSPITALISED*** *(1 RCT: Lundgren et al. 2020)*

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of evidence	Comments
	Risk with Standard treatment/Placebo	**Risk with Bamlanivimab** (previously neutralizing antibody LY-CoV555)				
All-cause mortality	32 per 1000	53 per 1000	**RR 1.67** (0.57 to 4.88)	326 (1 RCT) [a]	⊕⊕⊕⊕ HIGH	**Absolute effect (95% CI) 21 more per 1.000** (from 14 fewer to 124 more)
Number of patients with adverse events	172 per 1000	219 per 1000	**RR 1.27** (0.82 to 1.99)	326 (1 RCT) [a]	⊕⊕⊕⊕ HIGH	**Absolute effect (95% CI) 46 more per 1.000** (from 31 fewer to 170 more)
Number of patients with serious adverse events	32 per 1000	30 per 1000	**RR 0.93** (0.27 to 3.15)	326 (1 RCT) [a]	⊕⊕⊕⊕ HIGH	**Absolute effect (95% CI) 2 fewer per 1.000** (from 23 fewer to 68 more)
Number of patients discharged	866 per 1000	846 per 1000	**RR 0.98** (0.89 to 1.07)	326 (1 RCT) [a]	⊕⊕⊕⊕ HIGH	**Absolute effect (95% CI) 17 fewer per 1.000** (from 95 fewer to 61 more)

Source: Ref Cruciani F, De Crescenzo F, Vecchi S, Saulle R, Mitrova Z, Amato L, Davoli M. Should LY-CoV555 antibody compared to Standard treatment be used for hospitalised COVID-19 patients? 2020.

[a] ref Lundgren et al 2020 (ACTIV-3/TICO LY-CoV555 Study group) [199]
Abbreviations: CI=Confidence interval; RR=Risk ratio

Regulatory update:

In **August 2021** revision of EUA [187] , **FDA** the authorised use is: FDA has issued an Emergency Use Authorization (**EUA**) to permit the emergency use of the unapproved products **bamlanivimab and etesevimab administered together** for the treatment of **mild to moderate** coronavirus disease 2019 (COVID-19) in **adults and pediatric patients** (12 years of age and older weighing at least 40 kg) with positive results of direct SARSCoV-2 viral testing, and who are at **high risk for progression to severe COVID-19, including hospitalization or death**.

Aug 2021:
FDA EUA Zulassung als Kombinationstherapie für milde/moderat Erkrankte mit hohem Risiko zur Progression

Bamlanivimab and etesevimab are **not authorized for use in states, territories, and US jurisdictions in which the combined frequency of variants resistant to bamlanivimab and etesevimab exceeds 5%**.

Resistenz gegen Virus-Varianten

Bamlanivimab and etesevimab are not authorized for use in patients: who are hospitalized due to COVID-19, OR who require oxygen therapy due to COVID-19, OR who require an increase in baseline oxygen flow rate due to COVID-19 in those on chronic oxygen therapy due to underlying non-COVID-19 related comorbidity. Treatment with bamlanivimab and etesevimab has not been studied in patients hospitalized due to COVID-19. Monoclonal antibodies, such as bamlanivimab and etesevimab, may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation.

nicht für hospitalisierte mit Bedarf nach Beatmung

On **March 5, 2021 EMA** stated that the CHMP has completed its review started in February 2021[203], to provide a **harmonised scientific opinion** at EU level to support national decision making on the possible use of the antibodies **before a formal authorisation is issued**. The Agency concluded that **bamlanivimab monotherapy** and **bamlanivimab and etesevimab combination** can be used together to treat confirmed COVID-19 in patients who **do not require supplemental oxygen and who are at high risk of their COVID-19 disease becoming severe** [204, 205]. Risk factors may include but are not limited to: advanced age; obesity; cardiovascular disease, including hypertension; chronic lung disease, including asthma; type 1 or type 2 diabetes mellitus; chronic kidney disease, including those on dialysis; chronic liver disease; immunosuppressed, based on prescriber's assessment. Examples include: cancer treatment, bone marrow or organ transplantation, immune deficiencies, HIV (if poorly controlled or evidence of AIDS), sickle cell anemia, thalassemia, and prolonged use of immune-weakening medications.

März 2021
EMA: Bamlanivimab kann sowohl als Monotherapie wie auch als Kombinations-therapie mit Etesevimab eingesetzt werden
bei Pts mit bestätigtem Covid-19, nicht beatmungspflichtig, aber hohem Risiko auf Fortschreiten auf schweren Verlauf der Erkrankung

On **March 11, 2021** EMA's CHMP has started a '**rolling review**' of data on the antibodies bamlanivimab and etesemivab to be used in combination for the treatment of COVID-19. The review will also look at bamlanivimab used alone. The rolling review will continue until enough evidence is available to support formal marketing authorisation applications, https://www.ema.europa.eu/en/news/ema-starts-rolling-review-eli-lilly-antibodies-bamlanivimab-etesemivab-covid-19.

Rolling Review

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

AZD7442 Kombination aus 2 monoklonalen Antikörpern Vanderbilt University/ AstraZeneca

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

Phase 1 Ende Sept 2021

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

Phase 2 & 3 laufend

Larger late-stage **phase 2** and **phase 3** (NCT047233394, TACKLE, in outpatient adults) trials are ongoing to evaluate its 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.

ACTIV-2 phase 2/3 RCT

ACTIV-2 phase 2/3 RCT (NCT04518410) in ambulant patients is also ongoing.

Feb 2021: Phase 3 RCT begonnen

Studie ist Arm in ACTIV-3

An international randomized, controlled **phase 3** clinical trial has begun in February 2021, evaluating the safety and efficacy of AZD7442 for treating people hospitalised with COVID-19. The trial, **part of a master protocol - ACTIV-3**, has an adaptive design allowing investigators to add new sub-studies of additional investigational agents. ACTIV-3 is sponsored by the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health, https://www.nih.gov/news-events/news-releases/clinical-trial-hospitalized-covid-19-patients-evaluates-long-acting-antibody-therapy.

auch in DisCoVeRy Plattform Studie

AZD7442 is currently evaluated in **DisCoVeRy** clinical trial (NCT04315948), in hospitalised patients with COVID-19. The 1240 patients enrolled in the study in Europe will be followed up over a 15-month period until November 2022. An initial analysis of the results is expected to take place at the end of 2021.

Results of publications

There are no publications from RCTs related to AZD7442.

keine Publikation von klinschen Studien

Manufacturers announcements on pre- and post-exposure prophylaxis results: On June 2021, AstraZeneca announced results from the phase 3 RCT, STORM CHASER (NCT04625972), assessing the safety and efficacy of AZD7442 for the prevention of symptomatic COVID-19 in participants recently exposed to the SARS-CoV-2 virus. The trial did not meet the primary endpoint of post-exposure prevention of symptomatic COVID-19 with AZD7442 compared to placebo, https://www.astrazeneca.com/content/astraz/media-centre/press-releases/2021/update-on-azd7442-storm-chaser-trial.html. STORM CHASER is a phase III, randomised, double-blind, placebo-controlled, multi-centre trial assessing the safety and efficacy of a single 300mg dose of AZD7442 compared to placebo for the post-exposure prevention of COVID-19. The trial was conducted in 59 sites in the UK and US. 1,121 participants were randomised in a 2:1 ratio to receive a single intramuscular (IM) dose of either 300mg of AZD7442 (n=749) or saline placebo (n=372), administered in two separate, sequential IM injections. The primary efficacy endpoint is the first case of SARS-CoV-2 RT-PCR-positive symptomatic illness occurring post dose to Day 183. The primary analysis was to be conducted 30 days after 25 events meeting the primary efficacy endpoint definition had occurred. This primary analysis includes data and additional events accumulated up to 7 April 2021, 30 days after the symptom assessment date of the 25th event; participants will continue to be followed for 15 months. Trial participants were unvaccinated adults 18 years and over with confirmed exposure to a person with a case of the SARS-CoV-2 virus within the past eight days. In the overall trial population, AZD7442 reduced the risk of developing symptomatic COVID-19 by 33% (95% confidence interval (CI): -26, 65) compared to placebo, which was not statistically significant. Additional analyses were performed and are being communicated: in a pre-planned analysis of SARS-CoV-2 PCR positive (detectable virus) and PCR negative (no detectable virus) participants, AZD7442 reduced the risk of developing symptomatic COVID-19 by 73% (95% CI: 27, 90) compared with placebo, in participants who were PCR negative at time of dosing. In a post-hoc analysis, in participants who were PCR negative at baseline, AZD7442 reduced the risk of developing symptomatic COVID-19 by 92% (95% CI: 32, 99) versus placebo more than seven days following dosing, and by 51% (95% CI: -71, 86) up to seven days following dosing.

Hersteller Kommunikation zu RCT STORM CHASER
1.121 Teilnehmer*innen
Post Exposure Prophylaxe (bei Ungeimpften)

bei Endpunkt Entwicklung von symptomatischer Erkrankung: nicht stat. signif. Ergebnisse

bei post-hoc Analysen an Subgruppen: signifikant bessere Ergebnisse

On **August 2021**, Astra Zeneca announced positive high-level results from the PROVENT (NCT04625725), phase 3 trial, in **pre-exposure prophylaxis** trial. This randomised, double-blind, placebo-controlled, multi-centre trial is assessing the safety and efficacy of a single 300mg dose of AZD7442 compared to placebo for the prevention of COVID-19. The trial was conducted in 87 sites in the US, UK, Spain, France and Belgium. 5,197 participants were randomised in a 2:1 ratio to receive a single intramuscular (IM) dose of either 300mg of AZD7442 (n=3460) or saline placebo (n=1737), administered in two separate, sequential IM injections. Participants were adults 18 years-old and over who would benefit from prevention with the LAAB, defined as having increased risk for inadequate response to active immunisation (predicted poor responders to vaccines or intolerant of vaccine) or having increased risk for SARS-CoV-2 infection, including those whose locations or circumstances put them at appreciable risk of exposure to the SARS-CoV-2 virus. Participants at the time of screening were unvaccinated and had a negative point-of-care SARS-CoV-2 serology test. Approximately 43% of participants were 60 years and over. In addition, more than 75% had baseline co-morbidities and other characteristics that are associated with an increased risk for severe COVID-

RCT PROVENT
5.197 Teilnehmer*innen mit Risiko für inadequate Immunantwort bei Impfung
Pre-Exposure Prophylaxe

19 should they become infected, including those with immunosuppressive disease or taking immunosuppressive medications, diabetes, severe obesity or cardiac disease, chronic obstructive pulmonary disease, chronic kidney and chronic liver disease.

bei Endpunkt Entwicklung von symptomatischer Erkrankung: stat. signif. Ergebnisse

AZD7442 achieved a statistically significant reduction in the incidence of symptomatic COVID-19, the trial's primary endpoint. AZD7442 reduced the risk of developing symptomatic COVID-19 by 77% (95% confidence interval (CI): 46, 90), compared to placebo. The trial accrued 25 cases of symptomatic COVID-19 at the primary analysis. There were no cases of severe COVID-19 or COVID-19-related deaths in those treated with AZD7442. In the placebo arm, there were three cases of severe COVID-19, which included two deaths. More than 75% of participants had co-morbidities, which include conditions that have been reported to cause a reduced immune response to vaccination. The AZD7442 was well tolerated and preliminary analyses show adverse events were balanced between the placebo and AZD7442 groups, https://www.astrazeneca.com/content/astraz/media-centre/press-releases/2021/azd7442-prophylaxis-trial-met-primary-endpoint.html.

3.13.4 Sotrovimab (VIR-7831 monoclonal antibody)

monoklonaler Antikörper

VIR-7831 (Vir Biotechnology company) is a **dual-action monoclonal antibody** that was selected for clinical development based on its potential to both block viral entry into healthy cells and clear infected cells, as well as its potential to provide a high barrier to resistance. It has shown the ability to neutralize SARS-CoV-2 live virus in vitro. The antibody binds to an epitope on SARS-CoV-2 shared with SARS-CoV-1, indicating that the epitope is highly conserved, which may make it more difficult to escape mutants to develop. VIR-7832 has been engineered with the potential to enhance lung bioavailability, have an extended half-life, and function as a **therapeutic** and/or prophylactic T cell vaccine.

Phase 2/3 im Sept 2020 begonnen
COMET-ICE
1.300 Patient*innen nicht-hospitalisiert

Endpunkt: Verhinderung der Progression

A **phase 2/3 COMET-ICE** (COVID-19 Monoclonal antibody Effcacy Trial - Intent to Care Early) trial was launched on September 10, 2020, in which subjects with COVID-19 will receive VIR-7831 or placebo and be assessed for safety, tolerability, efficacy, and pharmacokinetics. The **phase 3 part** of the COMET-ICE trial is assessing the safety and effacy of a single intravenous (IV) infusion of VIR-7831 or placebo in approximately 1,300 **non-hospitalised** participants globally. The primary efficacy endpoint is the proportion of adults who have progression of COVID-19 as defined by the need for hospitalization or death within 29 days of randomization. The COMET clinical development program for VIR-7831 also includes a planned phase 3 trial for the prevention of symptomatic infection.

März 2021:
COMET-ICE Zwischenauswertung

Studie wegen positive Ergebnisse angehalten: 85% Reduktion von Hospitaliseirung und Tod

On March 10, 2021 Vir Biotechnology, Inc. and GlaxoSmithKline plc **announced** that an Independent Data Monitoring Committee (IDMC) recommended that the phase 3 COMET-ICE be stopped for enrollment due to evidence of profound efficacy. The IDMC recommendation was based on an **interim analysis** of data from 583 patients enrolled in the COMET-ICE trial, which demonstrated an **85% (p=0.002) reduction in hospitalisation or death in patients receiving VIR-7831 as monotherapy compared to placebo**, the primary endpoint of the trial. VIR-7831 was well tolerated. As the trial remains ongoing and blinded with patients continuing to be followed for 24 weeks, additional results, including epidemiology and virology data, will be forthcoming once the trial is completed. Based on these results, Vir and GSK

plan to submit an Emergency Use Authorization (EUA) application to the FDA and for authorizations in other countries, https://www.globenewswire.com/news-release/2021/03/11/2190921/0/en/Vir-Biotechnology-and-GSK-Announce-VIR-7831-Reduces-Hospitalization-and-Risk-of-Death-in-Early-Treatment-of-Adults-with-COVID-19.html.

The COMET clinical development programme for VIR-7831 includes two additional trials – one for the treatment of hospitalised patients and another for the prevention of symptomatic infection, https://www.gsk.com/en-gb/media/press-releases/vir-biotechnology-and-gsk-announce-global-expansion-to-phase-3-of-comet-ice-study-evaluating-vir-7831-for-the-treatment-of-covid-19/.

weitere Studien: Prävention symptom. Erkrankung hospitalisierte Pts.

The **ACTIV-3** randomized, placebo-controlled, multicenter, global phase 3 trial investigates the safety and effacy of VIR-7831 in **hospitalised** adults with COVID-19. The trial has closed enrollement in arm examining VIR-7831 on March 1, 2021 (due to futility), following an interim review and recommendations from the independent Data and Safety Monitoring Board (DSMB), https://www.nih.gov/news-events/news-releases/nih-sponsored-activ-3-clinical-trial-closes-enrollment-into-two-sub-studies

ACTIV-3 RCT: hospitalisierte Pts. Studie wegen negativer Ergebnisse angehalten

On 27 January 2021, **Eli Lilly and Company**, **Vir Biotechnology, Inc.** and **Glaxo Smith Kline plc** announced a collaboration to evaluate a **combination of two COVID-19 therapies** in **low-risk patients with mild to moderate COVID-19**. On March 29, 2021 Eli Lilly and Company, Vir Biotechnology, Inc. and GlaxoSmithKline plc announced data from this expanded phase 2 BLAZE-4 trial studying **low-risk adult patients** with **mild to moderate COVID-19** . Details could be seen in section on bamlanivimab above.

Pressemeldung: EliLilly + GSK Kooperation zu Kombinationstherapie bei milder/ moderater Erkrankung

On **April 15, 2021 EMA** starts **review of VIR-7831** in the treatment of patients with COVID-19. EMA is starting this review to **support national authorities** who may decide on the use of this medicine for COVID-19 **prior to marketing authorisation**.[206]. On **May 21, 2021 EMA** concluded that sotrovimab can be **used** to treat confirmed COVID-19 in **adults** and **adolescents (aged 12 years and above and weighing at least 40 kg) who do not require supplemental oxygen therapy and who are at risk of progressing to severe COVID-19** [207].

April/ Mai: EMA beginnt Review von VIR-7831

On **May 7, 2021 EMA** starts **rolling review of VIR-7831**, called now **sotrovimab** [208]. The decision to start the rolling review is based on preliminary results from an ongoing study looking at the ability of the medicine to prevent hospitalisation or death in non-hospitalised patients with COVID-19.

VIR-7831 = Sotrovimab

On **May 26, 2021 FDA** issued **EUA** for sotrovimab for the treatment of mild-to-moderate COVID-19 in adults andpediatric patients (12 years of age and older weighing at least 40 kilograms [about 88pounds]) with positive results of direct SARS-CoV-2 viral testing and who are at high risk forprogression to severe COVID-19, including hospitalization or death, https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-additional-monoclonal-antibody-treatment-covid-19. The EUA submission included data from published in vitro studies, which demonstrated that sotrovimab **maintains activity** against all known circulating **variants of concern**, including the variants from Brazil (P.1), California (B.1.427/B.1.429), India (B.1.617), New York (B.1.526), South Africa (B.1.351) and the UK (B.1.1.7). GSK and Vir will continue to evaluate the ability of sotrovimab to maintain activity against new and emerging variants, https://www.gsk.com/en-gb/media/press-releases/gsk-and-vir-

Mai: FDA erlässt EUA (Notfallszulassung): Sotrovimab für Pts., die keine zusätzlichen Sauerstoff brauchen, aber Risiko für progrediente Erkrankung haben

keine Resistenzen

biotechnology-announce-sotrovimab-vir-7831-receives-emergency-use-authorization-from-the-us-fda/.

US COVID-19 Treatment Guidelines (last update August 04, 2021)

- The **US COVID-19 Treatment Guidelines Panel** recommends using one of the following combination anti-SARS-CoV-2 monoclonal antibodies to treat outpatients with mild to moderate COVID-19 who are at high risk of clinical progression, as defined by the EUA criteria (listed in alphabetical order):

US COVID-19 Treatment Guidelines: Empfehlung FÜR Casirivimab + Imdevimab oder Sotrovimab bei milder/ moderater Erkrankung, aber Risiko für progrediente Erkrankung

Casirivimab plus imdevimab; *or* Sotrovimab 500 mg intravenous (IV) infusion [120].

Details related to use of other neutralising mABs with EUA and other treatment details are written in subsections above.

Results of publications

There is one publication (preprint) from RCTs related to AZD7442.

Gupta et al. 2021 [209] published as **preprint** preplanned **interim analysis** from ongoing, multicenter, double-blind, **phase 3** trial (NCT04545060), in 583 (sotrovimab, 291; placebo, 292) nonhospitalised patients with symptomatic Covid-19 and at least one risk factor for disease progression (randomized (1:1) to an intravenous infusion of sotrovimab 500 mg or placebo). The primary efficacy endpoint was the proportion of patients with Covid-19 progression, defined as hospitalisation longer than 24 hours or death, through day 29. The risk of Covid-19 progression was significantly reduced by 85% (97.24% CI, 44% to 96%; p=0.002) with a total of three (1%) patients progressing to the primary endpoint in the sotrovimab group versus 21 (7%) patients in the placebo group. All five patients admitted to intensive care, including one who died by day 29, received placebo. Safety was assessed in 868 patients (sotrovimab, 430; placebo, 438). Adverse events were reported by 17% and 19% of patients receiving sotrovimab and placebo, respectively; serious adverse events were less common with sotrovimab (2%) versus placebo (6%).

Phase 3 RCT (interim Analyse) 583 Pts nicht-hospitalisiert, aber symptomatische Erkrankung

signifikante Reduktion der Progression

3.13.5 Regdanvimab (CT-P59)

Regdanvimab (from Celltrion Healthcare) is a monoclonal antibody with activity against COVID-19. In pre-clinical data the treatment candidate demonstrated a 100-fold reduction in viral load of SARS-CoV-2, as well as a reduction in lung inflammation [210].

monoklonaler Antikörper

Results from the global **phase 1** clinical trial of CT-P59 demonstrated promising safety, tolerability, antiviral effect and efficacy profile in patients with mild symptoms of COVID-19.

Phase 1

On **January 13, 2021** Celltrion Group **announced** positive efficacy and safety results from global **phase 2/3** clinical trial of COVID-19 treatment candidate CT-P59: CT-P59 (40mg/kg) treated patients reported reduced progression rates to severe COVID-19 by 54% for patients with mild-to-moderate symptoms and 68% for moderate patients aged 50 years and over; a significantly shortened time to clinical recovery ranging from 3.4 to 6.4 days quicker compared to placebo and a significant reduction of viral load compared to placebo was reported at Day7 in patients treated with CT-P59. No drug-related serious adverse events reported,

Presseaussendung von Celltrion zu Phase 2/3 positive Ergebnisse

https://www.celltrionhealthcare.com/en-us/board/newsdetail?modify_key=433

März 2021: EMA „rolling review" von Regdanvimab für Patient*innen mit Risiko auf progrediente Erkrankung, aber ohne Bedarf nach Beatming

On **March 26, 2021 EMA** announced that the CHMP has completed its ~~a~~ **review** of Celltrion's monoclonal antibody regdanvimab (CT-P59) to **support national authorities** who may decide on the use of this medicine for COVID-19 **prior to authorisation**. EMA concluded that regdanvimab **can be used** for the treatment of confirmed COVID-19 in **adult patients who do not require supplemental oxygen therapy and who are at high risk of progressing to severe COVID-19**. Risk factors may include but are not limited to: advanced age; obesity; cardiovascular disease, including hypertension; chronic lung disease, including asthma; type 1 or type 2 diabetes mellitus; chronic kidney disease, including those on dialysis; chronic liver disease; immunosuppressed, based on prescriber's assessment. Examples include: cancer treatment, bone marrow or organ transplantation, immune deficiencies, HIV (if poorly controlled or evidence of AIDS), sickle cell anemia, thalassemia, and prolonged use of immune-weakening medications. The recommended dosage of regdanvimab is a single intravenous (IV) infusion of 40 mg/kg [211, 212].

Pressebericht: keine Resistenzen

On **May 18, 2021 Celltrion announced** that its regdanvimab (CT-P59) demonstrated neutralising potency against emerging **SARS-CoV-2 variants** first detected in New York, US (B.1.526), Nigeria (B.1.525) and India (B.1.617). The company plans to study neutralising titers against additional emerging strains, including the Brazil variant (P.1), in order to proactively address the pandemic as the virus continues to evolve. Regdanvimab is known to successfully neutralise the SARS-CoV-2 variants first identified in the UK (B.1.1.7), California (B.1.427/B.1.429), Brazil (P.2), in addition to the previously identified six variant genome mutations of SARS-CoV-2 (variants S·L·V·G·GH·GR), https://www.celltrionhealthcare.com/en-us/board/newsdetail?modify_key=482&pagenumber=1&keyword=&keyword_type=

Results of publications

Teil 1 des Phase 2/3 RCT 307 ambulante Pts mit milder/ moderater Erkrankung

raschere Gesundung (-3,4 Tage) weniger Hospitalisierungen

There is one publication (preprint) from RCTs related to regdanvimab. Eom et al. 2021 [213] reported 28-day results, as **preprint**, from **part 1** of a **two-part phase 2/3 study** of CT-P59 in 307 **outpatients with mild to moderate** SARS-CoV-2 infection (NCT04602000; EudraCT:2020-003369-20). Outpatients with mild-to-moderate COVID19 received a single dose of CT-P59 40 mg/kg (n=101), CT-P59 80 mg/kg (n=103), or placebo (n=103). Median (95% condence interval [CI]) time to conversion to negative RT-qPCR result (coprimary endpoint) was 12.8 days (9.00–12.84) with CT-P59 40 mg/kg, 11.9 days (8.94–12.91) with CT-P59 80 mg/kg, and 12.9 days (12.75–13.99) with placebo. Median (95% CI) time to clinical recovery (coprimary endpoint) was 5.4 days (3.97–6.78) with CT-P59 40 mg/kg, 6.2 days (5.53–7.85) with CT-P59 80 mg/kg, and 8.8 days (6.72–11.73) with placebo. The proportion (95% CI) of patients requiring hospitalisation or oxygen therapy was lower with CT-P59 40 mg/kg (4.0% [1.6–9.7%]) and CT-P59 80 mg/kg (4.9% [2.1–10.9%]) versus placebo (8.7% [4.7–15.8%). CT-P59 was well tolerated and no serious treatment-emergent adverse events or deaths occurred. CT-P59 accelerated viral and clinical recovery from COVID-19 and was well tolerated in patients with mild-to-moderate infection.

Hersteller Kommunikation zu Phase 3 RCT

weniger Hospitalisierungen bei Hochrisiko-Pts

In **June 2021**, Celltrion Healthcare **announced** efficacy and safety data based on the global **phase 3** clinical trial, demonstrating that regdanvimab (RegkironaTM), met all primary and key secondary endpoints in patients with mild to moderate symptoms of COVID-19 (**sample size 1315**). The research showed RegkironaTM significantly reduced the risk of COVID-19 related hospitalisation or death by 72% for patients at high risk of progressing to severe COVID-19 by day 28, meeting the primary efficacy endpoint [3.1 vs. 11.1 %, p-value< 0.0001]. RegkironaTM also reduced the risk of COVID-19 related hospitalisation or death by 70% for all patients, meeting the first key secondary endpoint [2.4 vs. 8.0 %, p-value <0.0001]. The trial also met the other key secondary endpoints, including faster and persistent reduction in symptom duration. Patients treated with CT-P59 (40mg/kg) recovered at least 4.7 days earlier than those in the placebo-treated patients [median 9.3 vs. minimum 14 days, p-value < 0.0001] for patients at high- risk of progressing to severe COVID-19. For all patients treated with CT-P59 (40mg/kg), patients recovered 4.9 days earlier than those in the placebo-treated patients [median 8.4 vs. 13.3 days, p-value < 0.0001]. The results also showed CT-P59 to have a positive safety profile, with no clinically meaningful differences between patients treated with CT-P59 (40mg/kg) and placebo-treated patients. Infusion related reactions were mild and transient, with most patients recovering within 1~3 days, https://www.celltrionhealthcare.com/en-us/board/newsdetail?modify_key=498&pagenumber=1&keyword=&keyword_type=

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

Details in V13_April

The reader is referred to the earlier version (V13_April) for more details on **Combination therapy** related to **interferon beta-1b, lopinavir and ribavirin or other triple combination of interferons.**

3.15 Solnatide

About the treatment under consideration

Medikament gegen akutes Atemnotsyndrom

Verabreichung: Inhalation

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.

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

In April 2020, solnatide has been approved for Compassionate Use by the Austrian Federal Office for Safety in Health Care (BASG) for the treatment of patients infected by the novel coronavirus SARS-CoV-2 and subsequently developing severe pulmonary dysfunction (severe COVID-19), as well as by

the Italian Medicines Agency and the Ethics Committee of the National Institute for Infectious Diseases (Lazzaro Spallanzani-Rome), within the compassionate use program of drugs undergoing clinical trials for the treatment of COVID-19 patients suffering from pulmonary oedema and acute respiratory distress syndrome.

EC-Grant seit April für Covid-19

bis Dezember 2021

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. The main goal of the H2020 SOLNATIDE project is to demonstrate safety, tolerability and clinical efficacy of solnatide in treatment of COVID-19 patients.

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

One ongoing randomised, double-blind, placebo controlled, parallel assignment trial with aim to assess efficacy and safety of 7 days orally inhaled 100 mg solnatide to treat pulmonary permeability oedema of 40 SARS-Cov-2 positive patients with moderate-to-severe ARDS is registered in EUdraCT register (EudraCT number 2020-001244-26), https://www.clinicaltrialsregister.eu/ctr-search/trial/2020-001244- 26/AT [214].

Withdrawn, suspended or terminated studies

ClinicalTrials.gov & EUdraCT: keine klinischen Studien registriert,

keine Publikation von RCT

No withdrawn, suspended or terminated studies related to solnatide in COVID-19 patients were found in ClinicalTrials.gov and EUdraCT registers [214].

Results of publications

No publications related to the RCTs of solnatide in COVID-19 patients were found [214].

3.16 Umifenovir (Arbidol®)

About the treatment under consideration

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

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.

1 in vitro Publikation

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) [215].

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**) [216] 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 [216].

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

kein Unterschied zwischen den Gruppen in einigen Surrogatendpunkten

mehr AE

One publication [217] 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 [218], 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 after seven days of admission across two groups significantly (94% versus 92% in umifenovir and lopinavir-ritonavir groups respectively) ($p=0.02$).

Okt 2020:
RCT (Iran)
100 Pts.

in Kombinationstherapie kleine Vorteile

Yethindra et al. 2020 [219] 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.

November 2020
RCT, 30 Pts. Kirgistan

Zusammenfassung von 2 RCTs: unsichere Evidenz zu den Effekten von Umifenovir

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 presented in Table 3.16-1. According to currently available very low quality of evidence, the evidence is very uncertain about the effect of umifenovir on further outcomes: All-cause mortality D14-D28; WHO progression score level 6 or above D14-28; WHO progression score level 7 or above D14-28; Serious adverse events and Viral negative conversion D7 (RR 0.90, 95% CI 0.44 to 1.84, 1 RCT, very low certainty of evidence).

*Table 3.16-1: Summary of findings table, on **umifenovir vs standard care** (2 RCTs:Yueping, Yethindra)*

Umifenovir compared to Standard Care for Mild/Moderate COVID-19

Patient or population: Mild/Moderate COVID-19
Setting: Worldwide
Intervention: Umifenovir
Comparison: Standard Care

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Standard Care	Risk with Umifenovir				
Viral negative conversion D3 - not reported	-	-	-	-	-	outcome not yet measured or reported
Viral negative conversion D7	412 per 1,000	**371 per 1,000** (181 to 758)	**RR 0.90** (0.44 to 1.84)	52 (1 RCT) [b]	⨁◯◯◯ VERY LOW [c,d]	
Clinical improvement D7 - not reported	-	-	-	-	-	outcome not yet measured or reported
Clinical improvement D14-D28 - not reported	-	-	-	-	-	outcome not yet measured or reported
WHO progression score (level 6 or above) D7	63 per 1,000	**46 per 1,000** (8 to 248)	**RR 0.73** (0.13 to 3.96)	82 (2 RCTs) [e]	⨁◯◯◯ VERY LOW [d,f,g]	
WHO progression score (level 6 or above) D14-D28	0 per 1,000	**0 per 1,000** (0 to 0)	not estimable	30 (1 RCT) [h]	⨁◯◯◯ VERY LOW [c,i,j]	zero events in both groups
WHO progression score (level 7 or above) D7	0 per 1,000	**0 per 1,000** (0 to 0)	not estimable	82 (2 RCTs) [e]	⨁◯◯◯ VERY LOW [g,j,k]	zero events in both groups
WHO progression score (level 7 or above) D14-D28	0 per 1,000	**0 per 1,000** (0 to 0)	not estimable	30 (1 RCT) [h]	⨁◯◯◯ VERY LOW [c,j,l]	zero events in both groups
All-cause mortality D7	0 per 1,000	**0 per 1,000** (0 to 0)	not estimable	82 (2 RCTs) [e]	⨁◯◯◯ VERY LOW [j,k,m]	zero events in both groups
All-cause mortality D14-D28	0 per 1,000	**0 per 1,000** (0 to 0)	not estimable	82 (2 RCTs) [e]	⨁◯◯◯ VERY LOW [j,k,m]	zero events in both groups
Adverse events	0 per 1,000	**0 per 1,000** (0 to 0)	**RR 5.50** (0.32 to 94.06)	52 (1 RCT) [b]	⨁⨁◯◯ LOW [d,n]	zero events in control group
Serious adverse events	0 per 1,000	**0 per 1,000** (0 to 0)	not estimable	82 (2 RCTs) [e]	⨁◯◯◯ VERY LOW [j,k,n]	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

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 13, 2020; b. Yueping L, 2020; c. Indirectness downgraded by 1 level: single study from a single institution, therefore results in this population might not be generalizable to other settings; d. Imprecision downgraded by 2 level: due to wide confidence interval consistent with the possibility for benefit and the possibility for harm and very low number of participants; e. Yethindra V, 2020; Yueping L, 2020; f. Risk of bias downgraded by 1 level: some concerns around deviation from intended intervention in both studies, some concerns in one study regarding randomization, outcome measurement, and selection of reported result; g. Indirectness downgraded by 1 level: results are mainly from a single study from a single institution, therefore results in this population might not be generalizable to other settings.; h. Yethindra, 2020; i. Risk of bias downgraded by 1 level: some concerns regarding randomization, deviations from intended intervention, outcome measurement, and selection of the reported results; j. Imprecision downgraded by 2 levels: no events in both groups and very low number of participants; k. Risk of bias downgraded by 1 level: some concerns regarding deviations from intended intervention in both studies, some concerns regarding randomization and selection of reported result in one study; l. Risk of bias downgraded by 1 level: some concerns regarding randomization, deviations from intended intervention, and selection of the reported results; m. Indirectness downgraded by 1 level: results from two single-institution studies, therefore results in the population might not be generalizable to other settings.; n. We presume that the adverse event rates, and the corresponding relative risks, is similar across diverse settings; therefore not downgraded for indirectness

3.17 Dexamethasone and other corticosteroids

The reader is referred to the earlier version (V13_April) for more details on **dexamethasone and other systemic corticosteroids** (except for inhaled corticosteroids).

Details in V13_April

3.17.1 Inhaled corticosteroids: Budesonide

About the drug under consideration

Budesonide is a type of medicine known as a steroid (also called a corticosteroid). Inhaled budesonide is a medicine used for asthma and chronic obstructive pulmonary disease (COPD).

Budesonid: Glucocorticoid zum Inhalieren bei COPD

On May 27, 2021 **EMA** issued **advice to healthcare professionals** that there is currently **insufficient evidence** that inhaled corticosteroids are beneficial for people with COVID-19 [220].

EMA: insuffiziente Datenlage

Results of publications

On April 9th, the results of an open-label, parallel-group, phase 2, randomised controlled trial (Steroids in COVID-19; **STOIC**, NCT04416399) of inhaled budesonide, compared with usual care, in adults within 7 days of the onset of **mild COVID-19** symptoms was published [221]. From July 16 to Dec 9, 2020, 146 participants were randomly assigned—73 to usual care and 73 to budesonide. The number needed to treat with inhaled budesonide to reduce COVID-19 deterioration was eight. Clinical recovery was 1 day shorter in the budesonide group compared with the usual care group (median 7 days [95% CI 6 to 9] in the budesonide group vs 8 days [7 to 11] in the usual care group; log-rank test p=0·007). The mean proportion of days with a fever in the first 14 days was lower in the budesonide group (2%, SD 6) than the usual care group (8%, SD 18; Wilcoxon test p=0·051) and the proportion of participants with at least 1 day of fever was lower in the budesonide group when compared with the usual care group. As-needed antipyretic medication was required for fewer proportion of days in the budesonide group compared with the usual care group (27% [IQR 0–50] vs 50% [15–71]; p=0·025) Fewer participants randomly assigned to budesonide had persistent symptoms at days 14 and 28 compared with participants receiving usual care (difference in proportions 0·204, 95% CI 0·075 to 0·334; p=0·003). Budesonide was safe, with only five (7%) participants reporting self-limiting adverse events.

Phase 2 RCT (STOIC)
167 Pts.
milde Erkrankung

NNT 8
-1 Tag weniger lang krank

weniger andauerende Symptome unter Budesonid

On April 12th a pre-print of an interim analyses from the **PRINCIPLE trial** (ISRCTN86534580) was published [222]. On August 10, 2021 results are published in scientific article [223]. PRINCIPLE is a multicentre, open-label, multi-arm, randomised, controlled, adaptive platform trial done remotely from a central trial site and at primary care centres in the UK. Eligible participants in **outpatient setting** were aged 65 years or older or 50 years or older with comorbidities, and unwell for up to 14 days with suspected COVID-19 but not admitted to hospital. Participants were randomly assigned to usual care, usual care plus inhaled budesonide (800 µg twice daily for 14 days), or usual care plus other interventions, and followed up for 28 days. Participants were aware of group assignment. The coprimary endpoints are time to first self-reported recovery and hospital admission or

RCT Interim Auswertung PRINCIPLE
4663 Pts.,
davon 751 mit Budesonid
frühzeitiger Abbruch

Verkürzung der Zeit der Erkrankung um ca 3 Tage

geringe Effekte auf Hospitalisierung/ Tod

death related to COVID-19, within 28 days.. The primary analysis population included all eligible SARS-CoV-2-positive participants randomly assigned to budesonide, usual care, and other interventions, from the start of the platform trial until the budesonide group was closed. 4700 participants were randomly assigned to budesonide (n=1073), usual care alone (n=1988), or other treatments (n=1639). The primary analysis model includes 2530 SARS-CoV-2-positive participants, with 787 in the budesonide group, 1069 in the usual care group, and 974 receiving other treatments. There was a benefit in time to first self-reported recovery of an estimated 2.94 days (95% Bayesian credible interval [BCI] 1.19 to 5.12) in the budesonide group versus the usual care group (11.8 days [95% BCI 10.0 to 14.1] *vs* 14.7 days [12.3 to 18.0]; hazard ratio 1.21 [95% BCI 1.08 to 1.36]). For the hospital admission or death outcome, the estimated rate was 6.8% (95% BCI 4.1 to 10.2) in the budesonide group versus 8·8% (5.5 to 12.7) in the usual care group (estimated absolute difference 2.0% [95% BCI –0.2 to 4.5]; odds ratio 0.75 [95% BCI 0.55 to 1.03]). Two participants in the budesonide group and four in the usual care group had serious adverse events (hospital admissions unrelated to COVID-19). Inhaled budesonide improves time to recovery, with a chance of also reducing hospital admissions or deaths (although results did not meet the superiority threshold), in people with COVID-19 in the community who are at higher risk of complications.

SoF von 2 RCTs ev. Reduktion der Hospitalisierungen

Summary of findings related to **inhaled budesonide compared to standard care** for COVID-19 patients in **outpatient setting**, related to 2 RCTs mentioned above, is presented in Summary of findings table 3.17-1 below. Inhaled budesonide may decrease number of hospitalisation ((RR 0.71, 95% CI 0.54 to 0.93, 1 RCT, low certainty of evidence). The evidence is very uncertain about the effect of inhaled budesonide on outcomes: All-cause mortality D28 (RR 0.83, 95% CI 0.34 to 2.03, 1 RCT, very low certainty of evidence); WHO progression score (level 7 or above) D28 (RR 1.06, 95% CI 0.58 to 1.91, 1 RCT, very low certainty of evidence) and serious Adverse events (RR 5.23, 95% CI 0.25to 108.86, 1 RCT, very low certainty of evidence).

*Table 3.17-1: Summary of findings table, on **budesonide vs standard care** (2 RCTs: Ramakrishnan, Yu)*

Budesonide compared to Standard Care for Mild COVID-19 (last update 30/08/2021)

Patient or population: Mild COVID-19
Setting: Worldwide Outpatients
Intervention: Budesonide
Comparison: Standard Care

Outcome	Anticipated absolute effects (95% CI) [a]		Relative effect (95% CI)	Number of participants (studies)	Certainty of evidence	Comments
	Risk with Standard treatment/Placebo	Risk with Budesonide				
All-cause mortality D28	10 per 1000	8 per 1000	**RR: 0.83** (0.34 - 2.03)	2060 (1 RCT) b	OOO⊕ VERY LOW c	**Absolute effect (95% CI) 2 fewer per 1000** (from 7 fewer to 10 more)
Clinical improvement D28	Outcome not yet measured or reported	Outcome not yet measured or reported	Outcome not yet measured or reported	Outcome not yet measured or reported	Outcome not yet measured or reported	Outcome not yet measured or reported
WHO progression score (level 7 or above) D28	20 per 1000	21 per 1000	**RR: 1.06** (0.58 - 1.91)	2060 (1 RCT) b	OOO⊕ VERY LOW c	**Absolute effect (95% CI) 1 more per 1000** (from 9 fewer to 18 more)
Hospitalisation or death	105 per 1000	75 per 1000	**RR: 0.71** (0.54 - 1.93)	2060 (1 RCT) b	OO⊕⊕ LOW d	**Absolute effect (95% CI) 31 fewer per 1000** (from 48 fewer to 7 more)
Number of patients with adverse events	Outcome not yet measured or reported	Outcome not yet measured or reported	Outcome not yet measured or reported	Outcome not yet measured or reported	Outcome not yet measured or reported	Outcome not yet measured or reported
Number of patients with serious adverse events	0 per 1000	0 per 1000	**RR: 5.23** (0.25 - 108.86)	2112 (1 RCT) b	OOO⊕ VERY LOW e	**Absolute effect (95% CI)** Zero events in both groups

a The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI) b Yu, 2021 c Risk of bias: Serious. Risk of bias downgraded by 1 level: some concerns deviation from intended intervention and missing data Indirectness: Serious despite a multicentre design this is a single study from a single country, therefore results in this population might not be generalizable to other settings. Imprecision: Very serious due to very wide confidence interval consistent with the possibility for benefit and the possibility for harm and low number of participants d Risk of bias: Serious Risk of bias downgraded by 1 level: some concerns regarding deviation from intended intervention and missing data Indirectness: Serious despite a multicentre design this is a single study from a single country, therefore results in this population might not be generalizable to other settings. e Risk of bias: Serious. Risk of bias downgraded by 1 level: some concerns deviation from intended intervention, missing data and outcome measurement Imprecision: Very serious due to very wide confidence interval consistent with the possibility for benefit and the possibility for harm and low number of participants

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

On July 19, 2021 **EMA has started evaluating an application to extend the use** of anakinra (Kineret) to include treatment of coronavirus disease 2019 (COVID-19) in **adult patients with pneumonia who are at risk of developing severe respiratory failure** [224].

Juli 2021: EMA beginnt Evaluierung für Pts mit Lungenentzündung

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 [144].

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. In December 2020, ANSM lifted the suspension of trials with anakinra because after further analysis in France and the EU, the risk was not confirmed.

ANACONDA (Frankreich) 71 hospitaliserte Pts

wegen Sicherheitsbdenken abgebrochen

nun aber die Aussetzung der Studie aufgehoben

Two RCTs were found as terminated: NCT04366232 (JAKINCOV), due investigator decision in France, on anakinra alone and in combination with ruxolitinib, and NCT04324021 in Italy and US because of recruitment issues.

2 RCTs abgebrochen

Currently, anakinra is investigated as a third option in the second randomisation for children >1 year old with hyperinflammatory syndrome associated with COVID-19 in children (PIMS-TS) in the RECOVERY (Randomised Evaluation of COVid-19 thERapY) trial, led by the University of Oxford [170].

Studiengruppe in RECOVERY

Results of publications

Currently, three publications related to an RCT of anakinra treatment in hospitalised COVID-19 patients were found.

3 Publikation eines RCTs

RCT, CORIMUNO-19

Rekrutierung nach 116 Pts. angehalten

The CORIMUNO-19 Collaborative group published results from a multicentre, open-label, Bayesian randomised clinical trial (**CORIMUNO-ANA-1, NCT04341584**), nested within the CORIMUNO-19 cohort, in France with mild-to-moderate COVID-19 pneumonia, severe acute respiratory syndrome coronavirus 2 infection confirmed by real-time RT-PCR, requiring at least 3 L/min of oxygen by mask or nasal cannula but without ventilation assistance, a score of 5 on the WHO Clinical Progression Scale (WHO-CPS), and a C-reactive protein serum concentration of more than 25 mg/L not requiring admission to the intensive care unit at admission to hospital [225]. Eligible patients were randomly assigned (1:1), stratified by centre and blocked with varying block sizes (randomly of size two or four), to either usual care plus anakinra (200 mg twice a day on days 1–3, 100 mg twice on day 4, 100 mg once on day 5) or usual care alone. The study was **stopped early,** following the recommendation of the data and safety monitoring board, after the recruitment of 116 patients: 59 were assigned to the anakinra group and 57 were assigned to the usual care group.

RCT, SAVE-MORE
594 Pts, hospitalisiert, moderate/ schwere Erkrankung

raschere Erholung
geringere Mortalität
kürzere Hospitalisierung

Kyriazopoulou et al. 2021 [226] (**NCT04680949, EUdraCT 2020-005828-11**) published as preprint results from the **SAVE-MORE** multicenter trial, 594 hospitalised patients with moderate and severe COVID-19 pneumonia and plasma suPAR 6 ng/ml or more and receiving standard-of-care were 1:2 randomized to subcutaneous treatment with placebo or 100 mg anakinra once daily for 10 days. The primary endpoint was the overall clinical status of the 11-point World Health Organization ordinal Clinical Progression Scale (WHO-CPS) at day 28. The changes of the WHO-CPS and of the sequential organ failure assessment (SOFA) score were the main secondary endpoints. Baseline characteristics and co-administered treatments were similar between the two arms. Majority of patients (81.6%) has severe COVID-19. Patients with severe disease by the WHO definition were also receiving intravenous 6 mg daily dexamethasone for 10 days. Remdesivir treatment was left at the discretion of the attending physicians.Anakinra-treated patients were distributed to lower strata of WHO-CPS by day 28 (adjusted odds ratio-OR 0.36; 95%CI 0.26-0.50; $p<0.001$); anakinra protected from severe disease or death (6 or more points of WHO-CPS) (OR: 0.46; $p=0.010$). The median absolute decrease of WHO-CPS in the placebo and anakinra groups from baseline was 3 and 4 points respectively at day 28 (OR 0.40; $p<0.001$); 2 and 3 points at day 14 (OR 0.63; $p=0.003$); the absolute decrease of SOFA score was 0 and 1 points (OR 0.63; $p=0.004$). 28-day mortality decreased (hazard ratio: 0.45; $p=0.045$). Hospital stay was shorter for 1 day and the time until ICU discharge was 4 days shorter. The incidence of serious TEAEs through day 28 was lower in patients in the anakinra and SoC group (16.5%) compared to the placebo and SoC group (21.2%). The non-serious TEAEs were similar in both treatment groups.

Platform Studie
REMAP-CAP
2.274 schwer Erkrankte

Anakinra zeigte
keine Wirksamkeit

As described in Sarilumab Section, **Derde et al. 2021** published **final results** as preprint [139] from **REMAP-CAP** RCT (**NCT02735707**): Adult participants with **critical COVID-19** were randomized to receive tocilizumab, sarilumab, anakinra, or standard care (control). In addition, a small group (n=21) of participants were randomized to interferon-β1a. The primary outcome was an ordinal scale combining in-hospital mortality (assigned -1) and days free of organ support to day 21. The trial used a Bayesian statistical model with pre-defined triggers for superiority, equivalence or futility. Statistical triggers for equivalence between tocilizumab and sarilumab; and for inferiority of anakinra to the other active interventions were met at a planned adaptive analysis. Of the 2274 critically ill participants enrolled, 972 were assigned to tocilizumab, 485 to sarilumab, 378 to anakinra and 418 to control. Median organ support-free days were 0 (IQR –1, 15) and 0 (IQR –1, 15) for anakinra and control, respectively. Median adjusted odds ratios was 0.99 (95%CrI 0.74, 1.35) for anakinra, yielding 46.6% posterior probability of superiority, compared to control. Median adjusted odds ratios for hospital survival was 0.97 (95%CrI 0.66, 1.40) for anakinra, compared to control, yielding 43.6% posterior probability of superiority, compared to control. All treatments appeared safe. Authors concluded that in patients with severe COVID-19 receiving organ support, anakinra is not effective. Anakinra is inferior compared to tocilizumab and sarilumab in this group of patients.

SoF von 2 RCTs
sehr unsichere Evidenz
Wirksamkeit:
Reduktion der 28-Tage
keine Reduktion 60-Tage
Gesamtsterblichkeit

ev.raschere klinische
Verbesserung

Nebenwirkungen

Effectiveness and safety data summary can be found in the **Summary of Findings** Table 3.18-1 (last update 07/09/2021): Low certainty evidence from two published RCTs (CORIMUNO-19, SAVE-MORE) in hospitalised patients with moderate to severe COVID-19 showed that anakinra, compared to standard care/placebo, may reduce all-cause mortality at day 28 (RR 0.69, 95% CI 0.34 to 1.39; 32 fewer per 1.000, 95% CI from 68 fewer to 40 more). Low certainty evidence from two published RCTs in hospitalised patients with severe and critical COVID-19 (CORIMUNO-19, REMAP-CAP) showed that anakinra, compared to standard care/placebo, may not reduce all-cause mortality at day 60 (RR 1.16, 95% CI 0.98 to 1.37; 56 more per 1000, 95% CI from 7 fewer to 129 more).

In hospitalised patients with moderate to severe COVID-19 showed that anakinra probably increases clinical improvement at day 28 (RR 1.06, 95% CI 1.00 to 1.12; 40 more per 1.000, 95% CI from 0 fewer to 97 more, moderate certainty of evidence, 2 RCTs: CORIMUNO-19, SAVE-MORE).

Anakinra, compared to standard care/placebo, may reduce WHO progression score (level 7 or above) at day 28 (RR 0.67, 95% CI 0.36 to 1.22; 55 fewer per 1000, 95% CI from 107 fewer to 37 more, low certainty of evidence, 2 RCTs: CORIMUNO-19, SAVE-MORE). The evidence is very uncertain about the effect of anakinra on viral negative conversion at day 7 (RR 0.93, 95% CI 0.63 to 1.37; 12 fewer per 1000, 95% CI from 61 fewer to 61 more, very low certainty of evidence, 1 RCT: SAVE-MORE).

Anakinra probably does not increase the number of patients with any adverse events (RR 0.99, 95% CI 0.88 to 1.11; 8 fewer per 1000, 95% CI from 92 fewer to 85 more, moderate certainty of evidence, 2 RCTs: CORIMUNO-19, SAVE-MORE). The evidence is very uncertain about the effect of anakinra on the number of patients with serious adverse events (RR 0.97, 95% CI 0.61 to 1.52; 7 fewer per 1000, 95% CI from 96 fewer to 128 more, very low certainty of evidence, 2 RCTs: CORIMUNO-19, SAVE-MORE) [227].

*Table 3.18-1: Summary of findings table, on **anakinra** (3 RCTs: CORIMUNO-19 Collaborative group, Kyriazopoulou - SAVE-MORE, Derde - REMAP-CAP)*

Patient or population: COVID-19 patients (moderate to critical, last update 07/09/2021)

Setting: Worldwide Hospitalised patients
Intervention: Anakinra
Comparison: Standard care/Placebo

Outcome	Anticipated absolute effects (95% CI)[a]		Relative effect (95% CI)	Number of participants (studies)	Certainty of evidence	Comments
	Risk with Standard treatment	Risk with Anakinra				
All-cause mortality D28	104 per 1000	71 per 1000	**RR: 0.69** (0.34 - 1.39)	722 (2 RCTs) [b, c]	⊕⊕◯◯ LOW [d]	**Absolute effect (95% CI) 32 fewer per 1000** (from 68 fewer to 40 more)
All-cause mortality D60	349 per 1000	405 per 1000	**RR: 1.16** (0.98 - 1.37)	912 (2 RCTs) [e]	⊕⊕◯◯ LOW [f]	**Absolute effect (95% CI) 56 more per 1000** (from 7 fewer to 129 more)
Clinical improvement D28	809 per 1000	857 per 1000	**RR: 1.06** (1.00 - 1.12)	722 (2 RCTs) [b, c]	⊕⊕⊕◯ MODERATE [g]	**Absolute effect (95% CI) 49 more per 1000** (from 0 fewer to 97 more)
WHO progression score (level 7 or above) D28	167 per 1000	112 per 1000	**RR: 0.67** (0.36 - 1.22)	722 (2 RCTs) [b, c]	⊕⊕◯◯ LOW [h]	**55 fewer per 1000** (from 107 fewer to 37 more)
Number of patients with any adverse event	769 per 1000	761 per 1000	**RR: 0.99** (0.88 - 1.11)	722 (2 RCTs) [b, c]	⊕⊕⊕◯ MODERATE [i]	**Absolute effect (95% CI) 8 fewer per 1000** (from 92 fewer to 85 more)
Number of patients with serious adverse events	247 per 100	240 per 1000	**RR: 0.97** (0.61 - 1.52)	722 (2 RCTs) [b, c]	⊕◯◯◯ VERY LOW [j]	**Absolute effect (95% CI) 7 fewer per 1000** (from 96 fewer to 128 more)
Viral negative conversion D7	165 per 1000	153 per 1000	**RR: 0.93** (0.63 – 1.37)	606 (1 RCT) [c]	⊕◯◯◯ VERY LOW [k]	**Absolute effect (95% CI) 12 fewer per 1000** (from 61 fewer to 61 more)

Source: [228];-**Abbreviations**: CI=Confidence interval; RR=Risk ratio; **Explanations**: a The risk in the intervention group is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI); b [225] c [226] ; d Imprecision: Very serious due to very wide confidence interval consistent with the possibility for benefit and the possibility for harm; e [139, 225] f Imprecision: Very serious due to wide confidence interval consistent with the possibility for no effect and the possibility for harm and low number of participants g Risk of bias: Serious Risk of bias downgraded by 1 level:some concerns regarding adequate randomization and outcome measurement; h Inconsistency: Serious Inconsistency downgraded by 1 level: I^2=60%; Imprecision: Serious due to wide confidence interval consistent with the possibility for benefit and the possibility for no effect; I Risk of bias: Serious Risk of bias downgraded by

1 level: Imprecision: Serious due to wide confidence interval consistent with the possibility for no effect and the possibility for harm; j Risk of bias: Serious Risk of bias downgraded by 1 level: some concerns regarding adequate randomization, outcome measurement, and selection of the reported result Inconsistency: Serious Inconsistency downgraded by 1 level: I^2=62% Imprecision: Serious due to wide confidence interval consistent with the possibility for benefit and the possibility for harm; k Risk of bias: Indirectness: Serious despite a multicentre design this is a single study from a single country, therefore results in this population might not be generalizable to other settings. Imprecision: Very serious due to wide confidence interval consistent with the possibility for benefit and the possibility for harm and low number of participants.

3.19 Colchicine

The reader is referred to the earlier version (V15_June 2021) for more details on colchicine treatment in **hospitalised** COVID-19 patients.

The **US COVID-19 Treatment Guidelines Panel** (update July 8, 2021), based on negative results from RECOVERY trial **recommends against** the use of colchicine in **hospitalised patients (AI)** [120].

US COVID-19 Treatment Guidelines Panel insuffiziente Datenlage

Results of publications

Non-hospitalised patients

Tardif et al. 2021 [229] published as preprint results from randomized, double-blind trial involving **non-hospitalised** patients with COVID-19 diagnosed by polymerase chain reaction (PCR) testing or clinical criteria (COLCORONA, NCT04322682). The patients were randomly assigned to receive colchicine (0.5 mg twice daily for 3 days and once daily thereafter) or placebo for 30 days. The primary efficacy endpoint was the composite of death or hospitalization for COVID-19 [229]. Among the 4159 patients with PCR-confirmed COVID-19, the primary endpoint occurred in 4.6% and 6.0% of patients in the colchicine and placebo groups, respectively (odds ratio, 0.75; 95% CI, 0.57 to 0.99; p=0.04). The odds ratios were 0.75 (95% CI, 0.57 to 0.99) for hospitalization due to COVID-19, 0.50 (95% CI, 0.23 to 1.07) for mechanical ventilation, and 0.56 (95% CI, 0.19 to 1.66) for death. Serious adverse events were reported in 4.9% and 6.3% in the colchicine and placebo groups (p=0.05); pneumonia occurred in 2.9% and 4.1% of patients (p=0.02). Diarrhea was reported in 13.7% and 7.3% in the colchicine and placebo groups (p<0.0001).

RCT
4.159 Patient*innen
nicht-hospitalisiert

Tod oder Hospitalisierung in
4,6% vs. 6% zugunsten von Colchicine

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

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 [230, 231].

keine veröffentlichten Studien

1 Phase 2 Studie läuft

3.22 Canakinumab

About the drug under consideration

Canakinumab is a human monoclonal anti-human interleukin-1 beta (IL-1 beta) antibody of the IgG1/κ isotype manufactured by Novartis Pharma AG. Canakinumab binds with high affinity specifically to human IL-1 beta and neutralises the biological activity of human IL-1 beta by blocking its interaction with IL-1 receptors, thereby preventing IL-1 beta-induced gene activation and the production of inflammatory mediators [232].
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 2 published RCTs related to effectiveness and safety of canakinumab for Covid-19.

Caricchio et al. 2021 published **negative results** [236] from RCT trial **CAN-COVID** (**NCT04362813**) among patients hospitalised with **severe COVID-19**. Patients were randomly assigned 1:1 to receive a single intravenous infusion of canakinumab (450mg for body weight of 40-<60 kg, 600mg for 60-80 kg, and 750mg for >80 kg; n=227) or placebo (n=227). The primary outcomewas survival without IMV from day 3 to day 29. Secondary outcomes were COVID-19–related mortality, measurements of biomarkers of systemic hyperinflammation, and safety evaluations. Among 454 patients who were randomized (median age, 59 years; 187 women [41.2%]), 417 (91.9%) completed day 29 of the trial. Between days 3 and 29, 198 of 223

RCT
454 hospitalisierte Pts.

kein Unterschied bei Mortalität

patients (88.8%) survived without requiring IMV in the canakinumab group and 191 of 223 (85.7%) in the placebo group, with a rate difference of 3.1% (95%CI, −3.1%to 9.3%) and an odds ratio of 1.39 (95%CI, 0.76 to 2.54; p=0.29). COVID-19–related mortality occurred in 11 of 223 patients (4.9%) in the canakinumab group vs 16 of 222 (7.2%) in the placebo group, with a rate difference of −2.3%(95%CI, −6.7%to 2.2%) and an odds ratio of 0.67 (95%CI, 0.30 to 1.50). Serious adverse events were observed in 36 of 225 patients (16%) treated with canakinumab vs 46 of 223 (20.6%) who received placebo. Among patients hospitalized with severe COVID-19, treatment with canakinumab, compared with placebo, did not significantly increase the likelihood of survival without IMV at day 29.

RCT
45 hospitalisierte Pts

kein Unterschied bei klinischer Verbesserung

Cremer et al. 2021 [237] published **negative results** from **proof-of concept trial** (**NCT04365153**,The three C study) in 45 patients with **COVID-19, myocardial injury,** and heightened **inflammation**. This trial required hospitalization due to COVID-19, elevated troponin, and a C-reactive protein concentration more than 50 mg/L. The primary endpoint was time to clinical improvement at Day 14, defined as either an improvement of two points on a seven-category ordinal scale or discharge from the hospital. The secondary endpoint was mortality at Day 28. Forty-five patients were randomly assigned to canakinumab 600 mg (n=15), canakinumab 300 mg (n=14), or placebo (n=16). There was no difference in time to clinical improvement compared to placebo [recovery rate ratio (RRR) for canakinumab 600 mg 1.15, 95% confidence interval (CI) 0.46–2.91; RRR for canakinumab 300 mg 0.61, 95% CI 0.23–1.64]. At Day 28, 3 (18.8%) of 15 patients had died in the placebo group, compared with 3 (21.4%) of 14 patients with 300 mg canakinumab, and 1 (6.7%) of 15 patients with 600 mg canakinumab. There were no treatment-related deaths, and adverse events were similar between groups.

3.23 Lenzilumab

About the drug under consideration

monoklonaler Antikörper

für keine Indikation bislang zugelassen

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

Lenzilumab is a first-in-class Humaneered® recombinant monoclonal antibody targeting human GM-CSF, with potential immunomodulatory activity, high binding affinity in the picomolar range, 94% homology to human germline, and has low immunogenicity. Following intravenous administration, lenzilumab binds to and neutralizes GM-CSF, preventing GM-CSF binding to its receptor, thereby preventing GM-CSF-mediated signaling to myeloid progenitor cells. The inhibition of GM-CSF signaling may be beneficial in improving the hyperinflammation-related lung damage in the most severe cases of COVID-19. This blockade can be achieved through antagonism of the GM-CSF receptor or the direct binding of circulating GM-CSF [238, 239].

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.

ACTIV-5 RCT: laufend
200 hospitalisierte Pts

Lenzilumab was selected for investigation within **ACTIV-5**, as a concomitant therapy with remdesivir compared with remdesivir alone. The study began in October 2020 and was comprised of 200 adult hospitalised patients who need medical care for COVID-19 pneumonia and randomized (1:1) to the treatment groups. Patients receive a loading dose of 200-mg intravenous (IV) remdesivir on day 1 followed by a 100-mg once-daily IV maintenance dose up to a 10-day total course while hospitalized. Lenzilumab (or placebo) is administered at 600-mg IV lenzilumab infusion every 8 hours starting on Day 1 for a total of 3 doses. On July 30, 2021 Humanigen announced that NIH has advanced the ACTIV-5/BET-B study to a **phase 2/3** study and modied the primary endpoint to survival without ventilation ("SWOV"), the same endpoint used in the Phase 3 LIVE-AIR study. The amended ACTIV-5/BET-B study now includes 400 patients overall. Up to sixty US sites will be participating in the study, https://s28.q4cdn.com/539885110/files/doc_news/NIH-Advances-ACTIV-5BET-B-Trial-Evaluating-Lenzilumab-from-a-Phase-2-Exploratory-Study-to-a-Phase-23-Study-for-the-Treatment-of-COVID-CML3P.pdf.

Results of publications

Phase 3 RCT
LIVE-AIR
520 Pts
mit schwerer Erkrankung

deutlich bessere klinische Ergebnisse in der Lenzilumab-Gruppe

Currently, results from one RCT were published as preprint related to effectiveness and safety of lenzilumab for Covid-19. **Temesgen et al. 2021** [240] published results from **LIVE-AIR phase 3** randomized, double-blind, placebo-controlled trial investigated the efficacy and safety of lenzilumab to assess the potential for lenzilumab to improve the likelihood of ventilator-free survival (referred to herein as survival without ventilation, SWOV), beyond standard supportive care, in hospitalised subjects with severe COVID-19 (NCT04351152). Subjects with COVID-19 (n=520), ≥18 years, and ≤94% oxygen saturation on room air and/or requiring supplemental oxygen, but not invasive mechanical ventilation, were randomized to receive lenzilumab (600 mg, n=261) or placebo (n=259) via three intravenous infusions administered 8 hours apart. Subjects were followed through Day 28 following treatment. Baseline demographics were comparable between the two treatment groups: male, 64.7%; mean age, 60.5 years; mean BMI, 32.5 kg/m^2; mean CRP, 98.36 mg/L; CRP was <150 mg/L in 77.9% of subjects. The most common comorbidities were obesity (55.1%), diabetes (53.4%), chronic kidney disease (14.0%), and coronary artery disease (13.6%). Subjects received steroids (93.7%), remdesivir (72.4%), or both (69.1%). Lenzilumab improved the likelihood of SWOV by 54% in the mITT population (HR: 1.54; 95%CI: 1.02-2.31, p=0.041) and by 90% in the ITT population (HR: 1.90; 1.02-3.52, nominal p=0.043) compared to placebo. SWOV also relatively improved by 92% in subjects who received both corticosteroids and remdesivir (1.92; 1.20-3.07, nominal p=0.0067); by 2.96-fold in subjects with CRP<150 mg/L and age <85 years (2.96; 1.63–5.37, nominal p=0.0003); and by 88% in subjects hospitalized ≤2 days prior to randomization (1.88; 1.13-3.12, nominal p=0.015). Survival was improved by 2.17-fold in subjects with CRP<150 mg/L and age <85 years (2.17; 1.04-4.54, nominal p=0.040).

Humanigen plans to use the data to seek emergency use authorisation from the FDA, https://www.businesswire.com/news/home/20210329005301/en/Humanigen-Reports-Positive-Phase-3-Topline-Results-Demonstrating-That-Lenzilumab%E2%84%A2-Improves-Survival-Without-Need-for-Mechanical-Ventilation-in-Hospitalized-Patients-With-COVID-19.

Hersteller plant EUA Antrag,

der aber von FDA abgelehnt wurde wegen Nutzen-Risken Abwägung

On **September 08, 2021** Humanigen announced the U.S. **FDA** has **declined** its request for emergency use authorization of lenzilumab to treat newly hospitalized COVID-19 patients. In its letter, FDA stated that it was unable to conclude that the known and potential benefits of lenzilumab outweigh the known and potential risks of its use as a treatment for COVID-19, https://s28.q4cdn.com/539885110/files/doc_news/FDA-has-declined-Humanigens-Emergency-Use-Authorization-EUA-Request-for-Lenzilumab-in-Hospitalized-COVID-19-Patients-2021.pdf. NIH's ACTIV-5/BET-B study is expected to provide further data that may support a new EUA request.

3.24 Vitamin D

About the drug under consideration

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 (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 [241]. 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 [242]. RCTs to assess efficacy and safety of vitamin D in COVID-19 patients are underway.

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

US COVID-19 Treatment Guidelines Panel: insuffiziente Datenlage

The **US COVID-19 Treatment Guidelines Panel** stated that there are **insufficient data** to recommend either **for or against** the use of vitamin D for the prevention or treatment of COVID-19 [120].

Withdrawn, suspended or terminated studies

No withdrawn or suspended, and 1 terminated (NCT04810949, enrolled patients were vaccinated agains COVID-19) interventional studies were found on Vitamin D in ClinicalTrials.gov and EUdraCT registers.

Results of publications

Entrenas Castillo et al. 2020 [243] published results from parallel pilot randomized open label, double-masked clinical trial on 76 consecutive **patients hospitalised** 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

Rastogi et al. 2020 [244] published results from randomized, placebo-controlled trial (NCT04459247, SHADE) on 40 COVID-19 adult **asymptomatic or mildly symptomatic** SARS-CoV-2 RNA positive vitamin D deficient individuals (intervention (n=16) or control (n=24) group), with outcomes measure: Proportion of patients with SARSCoV-2 RNA negative before day-21 and change in inflammatory markers. 10 (62.5%) participants in the intervention group and 5 (20.8%) participants in the control arm ($p<0.018$) became SARS-CoV-2 RNA negative. Fibrinogen levels significantly decreased with cholecalciferol supplementation (intergroup difference 0.70 ng/ml; $p=0.007$) unlike other inflammatory biomarkers.

RCT
40 Patient*innen asymptomatisch oder mild symptomatisch

Reduktion Entzündungsmarker Fibrinogen

Murai et al. 2020 [245] presented as pre-print results from double-blind, randomised, placebo-controlled trial involving 240 **hospitalised patients** with **severe COVID-19**, in Brasil (NCT04449718). A single dose of 200,000 IU of vitamin D3 supplementation was safe and effective in increasing 25-hydroxyvitamin D levels, but did not significantly reduce hospital length of stay (hazard ratio, 1.12) or any other 10 clinically-relevant outcomes compared with placebo.

RCT
240 hospitalisierte Patient*innen
kein Unterschied bei Dauer des Krankenhausaufenthalts

Sabico et al. 2021 [246] published results from RCT aims to determine the effects of 5000 IU versus 1000 IU daily oral vitamin D3 supplementation in the recovery of symptoms and other clinical parameters among mild to moderate COVID-19 patients with sub-optimal vitamin D status. A total of 69 reverse transcriptase polymerase chain reaction (RT-PCR) SARSCoV-2 positive adults who were **hospitalized** for **mild to moderate COVID-19 disease** were allocated to receive once daily for 2 weeks either 5000 IU oral vitamin D3 (n=36) or 1000 IU oral vitamin D3 (standard control) (n=33). Kaplan–Meier survival analysis revealed that the 5000 IU group had a significantly shorter time to recovery (days) than the 1000 IU group in resolving cough, even after adjusting for age, sex, baseline BMI, and D-dimer (6.2 ± 0.8 versus 9.1 ± 0.8; $p = 0.039$), and ageusia (loss of taste) (11.4 ± 1.0 versus 16.9 ± 1.7; $p=0.035$).

RCT
69 hospitalisierte Pts, milde/ moderate Erkrankung

verschiedene Dosierungen

Summary of Finding table related to **Vitamin D compared to Standard care/Placebo** for **hospitalised** COVID-19 patients, related to 2 RCTs mentioned above, is presented in Table 3.24-1 below. The evidence is very uncertain about the effect of Vitamin D on outcomes: All-cause mortality D14-D28 (RR 0.59, 95% CI 0.05 to 7.08, 2 RCTs, very low certainty of evidence); Clinical improvement D28 (RR 1.09, 95% CI 0.96 to 1.23, 1 RCT, very low certainty of evidence) and WHO progression score (level 7 or above) D28 (RR 0.04, 95% CI 0.01 to 0.29, 1 RCT, very low certainty of evidence). Vitamin D may increase Adverse events (RR 3.00, 95% CI 0.12 to 72.91, 1 RCT, low certainty of evidence).

SoF von 2 RCTs
sehr unsichere Evidenz
ev. Verhinderung von Verschlechterung

*Table 3.24-1: Summary of findings table on **Vitamin D compared to standard care** (2 RCT:Entrenas Castillo, Murai) - https://covid-nma.com/living_data/index.php)*

Vitamin D compared to Standard care/Placebo for Hospitalised COVID-19 (last update 14/06/2021)

Patient or population: Hospitalised COVID-19 patients
Setting: Worldwide
Intervention: Vitamin D
Comparison: Standard care/Placebo

Outcome	Anticipated absolute effects (95% CI) [a]		Relative effect (95% CI)	Number of participants (studies)	Certainty of evidence	Comments
	Risk with Standard treatment/Placebo	Risk with Vitamin D				
All-cause mortality D28	55 per 1000	32 per 1000	**RR: 0.59** (0.05 - 7.06)	316 (2 RCTs) b	OOO⊕ VERY LOW f	**Absolute effect (95% CI)** **22 fewer per 1000** (from 52 fewer to 332 more)
Clinical improvement D28	923 per 1000	1006 per 1000	**RR: 1.09** (0.96 - 1.23)	76 (1 RCT) c	OOO⊕ VERY LOW g	**Absolute effect (95% CI)** **83 more per 1000** (from 37 fewer to 212 more)
WHO progression score (level 7 or above) D28	500 per 1000	20 per 1000	**RR: 0.04** (0.01 - 0.29)	76 (1 RCT) d	OOO⊕ VERY LOW h	**Absolute effect (95% CI)** **480 fewer per 1000** (from 495 fewer to 355 fewer)
Viral negative conversion D7	Outcome not yet measured or reported	Outcome not yet measured or reported	Outcome not yet measured or reported	Outcome not yet measured or reported	Outcome not yet measured or reported	Outcome not yet measured or reported
Number of patients with adverse events	0 per 1000	0 per 1000	**RR 3.00** (0.12 to 72.91)	240 (1 RCT) e	OO⊕⊕ LOW i	**Absolute effect (95% CI)** Not calculated due to zero events in control group
Number of patients with serious adverse events	Outcome not yet measured or reported	Outcome not yet measured or reported	Outcome not yet measured or reported	Outcome not yet measured or reported	Outcome not yet measured or reported	Outcome not yet measured or reported

CI: Confidence interval; **RR**: Risk ratio; Explanations: a. The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI); b. Entrenas Castillo 2020**,** Murai 2020; c. Entrenas Castillo, 2020; d. Entrenas Castillo, 2020**;** e. Murai 2020; f. Inconsistency: Serious Inconsistency downgraded by 1 level: I^2=62.9%, Imprecision: Very serious 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; g. Risk of bias: Serious Risk of bias downgraded by 1 level: some concerns regarding adequate randomization, deviation from intended intervention and outcome measurement Indirectness: Serious single study from a single institution therefore results in this population might not be generalizable to other settings Imprecision: Serious due to low number of participants; h. Risk of bias: Serious Risk of bias downgraded by 1 level: some concerns regarding adequate randomization and deviations from intended interventions.

Indirectness: Serious

Indirectness downgraded by 1 level: single study from a single institution therefore results in this population might not be generalizable to other settings Imprecision: Serious due to low number participants; i. Imprecision: Very serious 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

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

3.25 Baricitinib (Olumiant)

About the drug under consideration

Januskinase-Inhibitor

Baricitinib is a selective and reversible inhibitor of Janus kinase (JAK)1 and JAK2. Janus kinases (JAKs) are enzymes that transduce intracellular signals from cell surface receptors for a number of cytokines and growth factors involved in haematopoiesis, inflammation and immune function. Baricitinib (Olumiant) is indicated in EU for the treatment of moderate to severe active rheumatoid arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more disease-modifying anti-rheumatic drugs and for the treatment of moderate to severe atopic dermatitis in adult patients who are candidates for systemic therapy [247, 248].

Baricitinib (Olumiant) in EU für moderate bis schwere rheumatoide Arthritis zugelassen

EMA: keine Zulassung für covid-19

Baricitinib (Olumiant) has not been approved by the European Medicines Agency (EMA). On November 19, 2020, the U.S. Food and Drug Administration (**FDA**) issued an **Emergency Use Authorization** (**EUA**) for the distribution and emergency use of baricitinib to be used **in combination with remdesivir** in **hospitalised adult and pediatric patients two years of age or older** with suspected or laboratory confirmed COVID-19 **who require supplemental oxygen, invasive mechanical ventilation, or extracorporeal membrane oxygenation** (ECMO) [249].

FDA Zulassung (EUA) als Kombinations-therapie mit Remdesivir hospitalisierte Pts mit Bedarf zur Beatmung

Juli 2021 Revision der FDA Zulassung:

auch als Monotherapie möglich

On **July 28, 2021** the **FDA** issued **revision to EUA** for the distribution and emergency use of **baricitinib to be used alone for the treatment of COVID-19 in hospitalised adults and pediatric patients two years of age or older requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO)** [250]. The EUA for baricitinib no longer requires baricitinib be used in combination with remdesivir. The use of baricitinib in combination with remdesivir is not contraindicated under the terms and conditions of this authorization.

On April 29, 2021 EMA starts evaluating an application to extend the use of baricitinib (Olumiant) to include treatment of COVID-19 in hospitalised patients from 10 years of age who require supplemental oxygen [251].

US COVID-19 Treatment Guidelines Panel: Empfehlung für Kombinationstherapie mit Dexamethasone in hospitalisierten Pts., die Sauerstoff baruche

The **US COVID-19 Treatment Guidelines Panel** (last update August 25, 2021), recommends using either **baricitinib (BIIa)** or **tocilizumab (BIIa)** (listed alphabetically) in combination with **dexamethasone** alone or **dexamethasone plus remdesivir** for the treatment of COVID-19 patients who were recently hospitalised with rapidly increasing oxygen needs and systemic inflammation [120]. The Panel recommends **tofacitinib** as an alternative to **baricitinib** only when baricitinib is not available or not feasible to use **(BIIa)**.

Empfehlung gegen eine Kombinationstherapie Baricitinib + Tocilizumab

The Panel **recommends against** the use of **baricitinib** in combination with **tocilizumab** for the treatment of COVID-19, **(AIII)**. Because both baricitinib and tocilizumab are potent immunosuppressants, there is the potential for an additive risk of infection [120].

Withdrawn, suspended or terminated studies

mehrere laufende Studien

One withdrawn (NCT04340232, could not make FDA required changes), no suspended and one terminated RCTs (NCT04373044, after the release of results of ACTT-2 trial) were found on baricitinib in ClinicalTrials.gov and EUdraCT registers. There are several ongoing RCTs, evaluating baricitinib alone or in combination with other pharmaceuticals in Covid-19

hospitalised patients. One is the RECOVERY (Randomised Evaluation of COVid-19 thERapY) trial, led by the University of Oxford [170].

Results of publications: Baricitinib in combination with remdesivir

RCT, ACTT-2
hospitalisierte Pts
Kombinationstherapie + Remdesivir

keine Reduktion der Gesamtmortalität
aber Reduktion der Zeit zur Erholung um 1 Tag

Pts. mit nicht-invasiver Beatmung: größter Nutzen

Reduktion der Zeit zur Erholung um 8 Tage (statt 18, nur 10 Tage)

On December 11, 2020, **Kalil et al.** [252] published results from the Adaptive COVID-19 Treatment Trial (**ACTT-2**) (**NCT04401579**), multicentre, double-blind, randomised, placebo-controlled trial evaluating **baricitinib plus remdesivir with remdesivir alone** in **hospitalised adults** with Covid-19 in eight countries. Effectiveness and safety data summary, related to three outcomes (All-cause mortality; Number of patients with AEs and Number of patients with SAEs), can be found in the **Summary of Findings** Table 3.25-1. High certainty evidence from one published RCT, ACTT-2 trial, showed that baricitinib in combination with remdesivir does not reduce All-cause mortality, and does not increase the number of patients with any adverse events as well as the number of patients with serious adverse events (high certainty of evidence). Combination of baricitinib and remdesivir significantly reduced median time to recovery in hospitalised COVID-19 patients from eight days to seven days, compared to remdesivir treatment alone. Patients who required high-flow oxygen or non-invasive ventilation during hospitalisation appeared to have had the largest benefit: their median time to recovery was shortened from eighteen days to ten days. Participants' conditions at day 15 was significantly improved when they received the two therapeutics combined. The incidence of progression to death or non-invasive or invasive ventilation was statistically significant lower in the combination of baricitinib and remdesivir vs remdesivir alone, as was the incidence of progression to death or invasive ventilation [253]: Risk ratio (95% CI) for outcome WHO progression score level 7 or above D14-28 is 0.59 (0.44 to 0.80) (COVID-NMA Meta-analysis, https://covid-nma.com/living_data/index.php?allcomp#comparisons_div). New Summary of finding table and certainty of evidence will be provided in the next versions of this report, https://covid-nma.com/living_data/index.php?allcomp#comparisons_div.

Results of publications: Baricitinib monotherapy (in addition to standard care)

Phase 3 RCT
COV-BARRIER
1.525 hospitalisierte Pts
bessere Ergebnisse bei

28-Tage und Gesamtmortalität mit Baricitinib

On May 3, 2021 **Marconi et al.** [254] publised as **pre-print** and on September 3, 2021 **in scientific journal** [255], results from phase 3, global, double-blind, randomized, placebo-controlled trial **COV-BARRIER** (**NCT04421027**). 1525 **hospitalised adults** with COVID-19 **receiving standard of care (SOC)** were randomly assigned (1:1) to once-daily **baricitinib 4-mg** (n=764) or **placebo** (n=761) for up to 14 days. **SOC included systemic corticosteroids in ~79% of participants (dexamethasone ~90%).** The primary endpoint was the proportion who progressed to high-flow oxygen, non-invasive ventilation, invasive mechanical ventilation, or death by day 28. A key secondary endpoint was all-cause mortality by day 28. All-cause mortality by day 60 was an exploratory endpoint. 27.8% of participants receiving baricitinib vs 30.5% receiving placebo progressed (primary endpoint, odds ratio 0.85, 95% CI 0.67-1.08; p=0.18). The 28-day all-cause mortality was 8% (n=62) for baricitinib and 13% (n=100) for placebo (hazard ratio [HR] 0.57 [95% CI 0.41–0.78]; nominal p=0.0018), a 38.2% relative reduction in mortality; one additional death was prevented per 20 baricitinib-treated participants. Reduction in mortality was seen for all pre-specified subgroups of baseline severity (most pronounced for participants on high-flow oxygen/non-invasive ventilation at baseline [17.5%, baricitinib vs 29.4%, placebo; HR 0.52, 95% CI 0.33-0.80; nominal p=0.007]).

Nebenwirkungen

The 60-day all-cause mortality was 10% (n=79) for baricitinib and 15% (n=116) for placebo (HR 0.62 [95% CI 0.47–0.83]; p=0.0050). The frequencies of serious adverse events (110 [15%] of 750 in the baricitinib group *vs* 135 [18%] of 752 in the placebo group), serious infections (64 [9%] *vs* 74 [10%]), and venous thromboembolic events (20 [3%] *vs* 19 [3%]) were similar between the two groups.

Metaanalyse zu Monotherapie Reduktion der Gesamtmortalität, aber nicht klinische Verbesserung

Results from **COVID-NMA Meta-analysis** show that baricitinib monotherapy compared to placebo significantly reduced COVID-19 related all-cause mortality at day 28 (Risk ratio 0.62, 95% CI 0.46 to 0.83). Baricitinib monotherapy compared to placebo does not significantly increase clinical improvement (Risk ratio 1.00, 95% CI 0.95 to 1.05), adverse events (Risk ratio 1.00, 95% CI 0.89 to 1.12) and serious adverse events (Risk ratio 0.81, 95% CI 0.64 to 1.02). Summary of finding table and certainty of evidence will be provided in the next versions of this report, https://covid-nma.com/living_data/index.php?allcomp#comparisons_div.

Hersteller Kommunikation

Pts mit kritischer Erkrankung in COV-BARRIER

28-Tage und 60-Tage Mortalität geringer

On **August 3, 2021** Eli Lilly and Company **announced results** from an **additional cohort of 101 adult critical COVID-19 patients** from the above mentioned COV-BARRIER trial. In this sub-study, **patients with COVID-19 on mechanical ventilation or extracorporeal membrane oxygenation (ECMO) who received baricitinib plus standard of care** were 46 percent **less likely to die by Day 28** compared to patients who received placebo plus standard of care (nominal p-value=0.0296; hazard ratio [HR] [95% CI] = 0.54 [0.31, 0.96]; analysis not adjusted for multiplicity). The cumulative proportion of patients who died by Day 28 was 39.2 percent (n/N: 20/51) in the baricitinib arm versus 58 percent in the placebo arm (n/N: 29/50). **Similar mortality benefit was observed by Day 60** (HR [96% CI] = 0.56 [0.33, 0.97]) with a cumulative proportion of death of 45.1 percent (n/N: 23/51) for baricitinib compared to 62.0 percent for placebo (n/N: 31/50). These findings are consistent with the reduction in mortality observed in the overall COV-BARRIER patient population. By Day 28, the frequency of adverse events, serious adverse events and serious infections were similar in the baricitinib group (88%, 50% and 44%, respectively) compared to placebo (95.9%, 71.4% and 53.1%, respectively). Venous thromboembolic events were reported in 6% of patients treated with baricitinib and 6.1% of patients treated with placebo. No new safety signals were identified [256].

*Table 3.25-1: Summary of findings table, on **baricitinib + remdesivir** (1 RCT: Kalil 2020)*

Question: Should Baricitinib-Remdesivir compared to Standard treatment (placebo/remdesivir) be used for COVID-19 patients?
Setting: Inpatient

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Absolute effect (95% CI)	Number of participants (studies)	Certainty of evidence	Comments
	Risk with placebo+remdesivir	Risk with baricitinib+remdesivir					
All-cause mortality	71 per 1000	46 per 1000	**RR 0.65** (0.40 to 1.07)	**25 fewer per 1.000** (from 43 fewer to 5 more)	1033 (1 RCT)[a]	⊕⊕⊕⊕ HIGH	Baricitinib in combination with remdesivir does not reduce All-cause mortality
Number of patients with any adverse event	432 per 1000	367 per 1000	**RR 0.85** (0.73 to 0.99)	**65 fewer per 1.000** (from 117 fewer to 4 fewer)	1016 (1 RCT)[a]	⊕⊕⊕⊕ HIGH	Baricitinib in combination with remdesivir reduces the risk of AE
Number of patients with serious adverse events	210 per 1000	159 per 1000	**RR 0.76** (0.59 to 0.99)	**50 fewer per 1.000** (from 86 fewer to 2 fewer)	1013 (1 RCT)[a]	⊕⊕⊕⊕ HIGH	Baricitinib in combination with remdesivir reduces the risk of serious AE

Source: ref Cruciani F., De Crescenzo F., Vecchi S., Saulle R., Mitrova Z., Amato L., et al. Should Baricitinib-Remdesivir compared to Standard treatment (placebo/remdesivir) be used for COVID-19 patients?. 2020.
[a] ref Kalil AC, Patterson TF, Mehta AK, Tomashek KM, Wolfe CR, Ghazaryan V, et al. Baricitinib plus Remdesivir for Hospitalized Adults with Covid-19. New England Journal of Medicine. 2020. 10.1056/NEJMoa2031994.
***Abbreviations**: RR=Risk ratio; CI=Confidence interval; AE=Adverse event; SAE=Serious adverse event*

3.26 Molnupiravir

About the drug under consideration

antivirales Medikament ähnlich Remdesivir aber orale Verabreichung

Molnupiravir is the orally available pro-drug of the nucleoside analogue N4-hydroxycytidine (NHC), which has shown potent anti-influenza virus activity in mice, guinea pigs, ferrets and human airway epithelium organoids. Animal study in ferrets showed that therapeutic treatment of infected animals with molnupiravir (MK-4482/EIDD-2801) twice a day significantly reduced the SARS-CoV-2 load in the upper respiratory tract and completely suppressed spread to untreated contact animals [257, 258].

frühere Verabreichung zu Hause daher möglich

hospitalisierte, aber auch milde und moderate Erkrankung

Molnupiravir attacks the same viral enzyme as Gilead's Remdesivir, but it can be taken orally. This would allow an administration at home and, therefore, earlier in the course of the disease. According to Ridgeback Biotherapeutics, molnupiravir has an extremely high barrier to resistance. According to Merck Sharp & Dohme/ MSD, molnupiravir is aimed at the treatment of Covid-19 in patients hospitalised due to mild, moderate or severe disease, and non-hospitalized patients with mild or moderate disease [258].

weder von EMA noch FDA zugelassen

Molnupiravir is not approved by the European Medicines Agency (EMA) or the American Food and Drug Administration (FDA) [258].

Withdrawn, suspended or terminated studies

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

Results of publications

keine RCTs derzeit in Phase 1/ 2, 2 und 1/ 3 Studien mit verschiedenen Pts. Populationen

There are one published RCT (as preprint) related to effectiveness and safety of molnupiravir for Covid-19 (NCT04405570). It is currently investigated in phase 1/2, 2 and 2/3 clinical trials (NCT04405739, NCT04575584, NCT04575597, ISRCTN27106947), in hospitalised and non-hospitalised aduls with COVID-19.

Presseaussendung von Merck & Ridgeback 2a RCT positive Ergebnisse

Juni 2021 Publikation zu Surrogatendpunkten

On March 6, 2021 Merck and Ridgeback Biotherapeutics, LP **announced preliminary positive results** from Ridgeback's **phase 2a** randomized, double-blind, placebo-controlled trial (NCT04405570) to evaluate the safety, tolerability, and efficacy to eliminate SARS-CoV-2 viral RNA of molnupiravir (EIDD-2801/MK-4482), on one secondary objective, showing a reduction in time (days) to negativity of infectious virus isolation in nasopharyngeal swabs from participants with symptomatic SARS-CoV-2 infection, as determined by isolation in Vero cell line culture. In June 2021, results from above mentioned trial are published as **preprint** by **Fisher et al. 2021** [259]. Among 202 treated participants, virus isolation was significantly lower in participants receiving 800 mg molnupiravir (1.9%) versus placebo (16.7%) at Day 3 (p=0.02). At Day 5, virus was not isolated from any participants receiving 400 or 800 mg molnupiravir, versus 11.1% of those receiving placebo (p=0.03). Time to viral RNA clearance was decreased and a greater proportion overall achieved clearance in participants administered 800 mg molnupiravir versus placebo (p=0.01). Molnupiravir was generally well tolerated, with similar numbers of adverse events across all groups. Four serious adverse events occurred and resulted in hospitalization, comprising one (1.6%) participant administered placebo who had hypoxia, two (3.2%) participants administered 400 mg molnupiravir (cerebrovascular accident and decreased oxygen saturation), and one (1.8%) participant

administered 800 mg molnupiravir who had acute respiratory failure. Treatment was discontinued in all 4 participants.

Presseaussendung: 2 laufende 2/3 RCTs MOVe-OUT, MOVe-IN ambulante, hospitalisierte Pts

keine Wirksamkeit bei hospitalisierten Pts

Phase 3 RCT: nur ambulante Pts

On April 15, 2021 Merck and Ridgeback Biotherapeutics provided an update on the clinical development program for molnupiravir. Based on a planned interim analysis of data from the phase 2, dose-finding portion (Part 1) of two ongoing placebo-controlled phase 2/3 trials evaluating molnupiravir administered twice a day for five days in outpatients (MOVe-OUT) and hospitalised patients (MOVe-IN) with COVID-19, and from a previously completed phase 2a dose-ranging study in outpatients, the decision has been made to proceed with the phase 3 portion (Part 2) of MOVe-OUT in outpatients with COVID-19, evaluating the 800 mg dose of molnupiravir twice daily. Data from MOVe-IN indicate that molnupiravir is unlikely to demonstrate a clinical benefit in hospitalised patients, who generally had a longer duration of symptoms prior to study entry; therefore, the decision has been made not to proceed to phase 3. Final data from the Phase 3 portion (Part 2) of the MOVe-OUT study is estimated to be available in September/ October 2021, https://www.merck.com/news/merck-and-ridgeback-biotherapeutics-provide-update-on-progress-of-clinical-development-program-for-molnupiravir-an-investigational-oral-therapeutic-for-the-treatment-of-mild-to-moderate-covid-19/

Beschaffungs-verhandlungen in USA

On June 09, 2021 Merck announced that it has entered into a procurement agreement with the United States government for molnupiravir. Merck pending favorable results from MOVe-OUT, so the earliest possible submission for an Emergency Use Authorization for molnupiravir will be in the second half of 2021, https://www.businesswire.com/news/home/20210609005142/en/Merck-Announces-Supply-Agreement-with-U.S.-Government-for-Molnupiravir-an-Investigational-Oral-Antiviral-Candidate-for-Treatment-of-Mild-to-Moderate-COVID-19

In August 2021, the Canadian regulator, Health Canada, has started a rolling review of molnupiravir in **outpateints with COVID-19**.

Phase 3 RCT MOVe-AHEAD zur Prävention geplant

On September 01, 2021 Merck and Ridgeback Biotherapeutics announced the initiation of the **phase 3 MOVe-AHEAD** (**NCT04939428**) clinical trial to evaluate molnupiravir for the **prevention** of COVID-19 infection. The global study is enrolling individuals who are at least 18 years of age and reside in the same household as someone with laboratory-confirmed SARS-CoV-2 infection with symptoms. The trial will enroll approximately 1332 participants who will be randomized to receive either molnupiravir (800 mg) or placebo orally every 12 hours for five days. The primary endpoints of the trial include percentage of participants with COVID-19 (laboratory-confirmed SARS-CoV-2 infection with symptoms) through Day 14, percentage of participants with an adverse event and percentage of participants who discontinued study intervention due to an adverse event, https://www.merck.com/news/merck-and-ridgeback-biotherapeutics-announce-initiation-of-pivotal-phase-3-move-ahead-study-evaluating-molnupiravir-for-post-exposure-prophylaxis-of-covid-19-infection/.

3.27 Ivermectin

The reader is referred to the earlier version (V15_June 2021) for more details on ivermectin treatment in COVID-19 patients.

The **US COVID-19 Treatment Guidelines Panel** Statement (February 11, 2021) [144] [120] is: Currently there are **insufficient data** to **recommend either for or against** the use of ivermectin for the treatment of COVID-19. Results from adequately powered, well-designed, and well-conducted clinical trials are needed to provide more specific, evidence-based guidance on the role of ivermectin for the treatment of COVID-19.

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

The **WHO Therapeutics and COVID-19 living guideline** [260, 261] includes a **recommendation not to use ivermectin except in the context of a clinical trial**. Such recommendation is based on the living systematic review and network meta-analysis (NMA) that pooled data from 16 randomized controlled trials (RCTs) with 2407 participants, including both inpatients and outpatients with COVID-19. The effects of ivermectin on mortality, need for invasive mechanical ventilation, hospital admission, duration of hospitalization and time to viral clearance all remain very uncertain (all very low certainty evidence). The uncertainty results from important concerns related to risk of bias in the included studies, and imprecision from a very low number of events and, in some cases, wide confidence intervals (CIs) in pooled estimates. Ivermectin may increase the risk of serious adverse events (SAEs) leading to drug discontinuation (odds ratio [OR] 3.07; 95% CI: 0.77–12.09; low certainty evidence) and may have little or no impact on time to clinical improvement (mean difference [MD] 0.5 fewer days; 95% CI: 1.7 fewer days to 1.1 more days; low certainty evidence). There was no credible subgroup effect based on dose. Subgroup analyses were not performed examining between-study differences in age or illness severity as per our pre-defined decision to limit subgroup analysis to within-study comparisons.

WHO Therapeutics and COVID-19 living guideline (basieremnd auf NMA vbon 16 RCTs):

Empfehlung gegen Ivermectin (außer in klin. Studien)

Results of publications

Ivermectin administered orally

mehrere RCTs

Several RCTs compared **ivermectin vs standard care**, published in scientific journals or as preprint, showed positive or negative results on different clinical outcomes in COVID-19 patients. The reader is referred to the earlier version (V15_June 2021) for more details on these publications.

RCT, 62 Pts. milde bis moderate Krankheit

kein Unterschied

One new study was published in outpatient setting. **Vallejos et al. 2021** [262] published negative results from RCT conducted in **nonhospitalised** individuals with COVID-19 in Corrientes, Argentina (NCT0452952). Patients were randomized to ivermectin (n=250) or placebo (n=251) arms in a staggered dose, according to the patient's weight, for 2 days. The primary outcome of hospitalisation was met in 14/250 (5.6%) individuals in ivermectin group and 21/251 (8.4%) in placebo group (odds ratio 0.65; 95% confidence interval, 0.32–1.31; p=0.227). The mean time from study enrolment to invasive mechanical ventilatory support (MVS) was 5.25 days (SD ± 1.71) in ivermectin group and 10 days (SD ± 2) in placebo group, (p=0.019). There were no statistically significant differences in the other secondary outcomes including polymerase chain reaction test negativity and safety outcomes.

RCT(Argentinien) 501 nicht-hospitalisierte Pts

weniger Hospitalisierungen

According the meta-analysis of 5 RCTs (Khan Chachar, 2020; Chaccour, 2021; Lopez-Medina, 2021; Biber, 2021; Vallejos, 2021) related to ivermectin vs standard care in **mild COVID-19 patients in outpatient setting** the evidence is uncertain about the effect of ivermectin on several outcomes: Clinical improvement D28 (RR 1.05, 95% CI 0.93 to 1.19); WHO progression score (level 7 or above) D28 (RR 1.43, 95% CI 0.55 to 3.72); All-cause mortality D28 (RR 1.05, 95% CI 0.27 to 4.02); Hospitalisation or death (RR 0.62, 95% CI 0.31 to 1.21) and Serious adverse events (RR 1.00, 95% CI 0.14 to 7.04) (low certainty of evidence). Ivermectin probably does not

Metaanalyse von 5 RCTs ambulante Pts mit milder/ moderater Erkr.

unsichere Evidenz zur Wirksamkeit

increase Adverse events (RR 0.96, 95% CI 0.85 to 1.08) (moderate certainty of evidence). The evidence is very uncertain about the effect of ivermectin on Viral negative conversion D7 (RR 1.21, 95% CI 0.19 to 1.63) (very low certainty of evidence). The Summary of findings table could be found below (last update 30/08/2021) (Table 3.27-1).

Metaanalyse von 8 RCTs hospitalisierte Pts

unsichere Evidenz zur Wirksamkeit

According the meta-analysis of 8 RCTs (Shah Bukari, 2021; Ahmed, 2020; Mohan, 2021; Podder, 2020; Kirti, 2021; Okumus, 2021, Pott-Junior H, 2021; Kishoria N, 2020) related to ivermectin vs standard care in **hospitalised COVID-19 patients** the evidence is uncertain (low certainty of evidence) about the effect of ivermectin on outcomes: Clinical improvement D28 (RR 1.00, 95% CI 0.90 to 1.11); WHO progression score (level 7 or above) D28 (RR 1.55, 95% CI 0.07 to 35.89). The evidence is very uncertain about the effect of ivermectin on further outcomes: All-cause mortality D28 (RR 0.53, 95% CI 0.21 to 1.31); Viral negative conversion D7 (RR 1.01, 95% CI 0.81 to 1.26); Adverse events (RR 0.86, 95% CI 0.59 to 1.24) and Serious adverse events (RR 1.11, 95% CI 0.19 to 6.44) (very low certainty of evidence) (last update 10/08/2021).

The Summary of findings table could be found below (Table 3.27-1).

*Table 3.27-1: Summary of findings table, on **Ivermectin vs placebo** (5 RCTs: Khan Chachar; Chaccour; Lopez-Medina; Biber; Vallejos)*

Ivermectin compared to Standard care/Placebo for Mild outpatients (last update 30/08/2021)

Patient or population: Mild COVID-19
Setting: Worldwide Outpateint
Intervention: Ivermectin
Comparison: Standard care/Placebo

Outcome	Anticipated absolute effects (95% CI) [a]		Relative effect (95% CI)	Number of participants (studies)	Certainty of evidence	Comments
	Risk with Standard care/Placebo	Risk with Ivermectin				
All-cause mortality D28	6 per 1000	7 per 1000	**RR: 1.05** (0.27 – 4.02)	1255 (4 RCTs) [b]	OO⊕⊕ LOW [c]	**Absolute effect (95% CI)** 0 fewer per 1000 (from 5 fewer to 19 more)
Clinical improvement D28	650 per 1000	683 per 1000	**RR: 1.05** (0.93 - 1.19)	526 (2 RCTs) d	OO⊕⊕ LOW e	**Absolute effect (95% CI)** 33 more per 1000 (from 46 fewer to 124 more)
WHO progression score (level 7 or above) D28	14 per 1000	20 per 1000	**RR: 1.43** (0.55 – 3.72)	1001 (3 RCTs) f	OO⊕⊕ LOW g	**Absolute effect (95% CI)** 6 more per 1000 (from 6 fewer to 38 more)
Hospitalisation or death	60 per 1000	8 per 1000	**RR: 0.62** (0.31 – 1.21)	601 (2 RCTs) h	OO⊕⊕ LOW i	**Absolute effect (95% CI)** 30 fewer per 1000 (from 55 fewer to 17 more)
Viral negative conversion D7	517 per 1000	626 per 1000	**RR: 1.21** (0.90 – 1.63)	805 (5 RCTs) j	OOO⊕ VERY LOW k	**Absolute effect (95% CI)** 109 more per 1000 (from 52 fewer to 326 more)
Number of patients with adverse events	359 per 1000	345 per 1000	**RR: 0.96** (0.85 - 1.08)	1167 (5 RCTs) [l]	⊕⊕⊕O MODERATE [m]	**Absolute effect (95% CI)** 14 fewer per 1000 (from 54 fewer to 29 more)
Number of patients with serious adverse events	3 per 1000	3 per 1000	**RR: 1.00** (0.14 – 7.04)	1167 (5 RCTs) [l]	⊕⊕OO LOW [n]	**Absolute effect (95% CI)** 0 fewer per 1000 (from 3 fewer to 21 more)

CI: Confidence interval; RR: Risk ratio; a The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI) b Chaccour, 2021; Lopez-Medina, 2021; Chahla, 2021; Vallejos, 2021; c Imprecision: Very serious due to very wide confidence interval consistent with the possibility for benefit and the possibility for harm and low number of participants; d Khan Chachar, 2020; Lopez-Medina, 2021; e Risk of bias: Serious Risk of bias downgraded by 1 level:high risk regarding adequate randomization and some concerns regarding outcome measurement and selection of the reported results Imprecision: Serious due to low number of participants; f Chaccour, 2021; Lopez-Medina, 2021; Vallejos, 2021; g Imprecision: Very serious due to very wide confidence interval consistent with the possibility for benefit and the possibility for harm and low number of participants; h Samaha, 2021; Vallejos, 2021; i Risk of bias: Serious Risk of bias downgraded by 1 level:some concerns regarding adequate randomization, deviation

from intended intervention and selection of the reported results -Imprecision: Serious due to wide confidence interval consistent with the possibility for benefit and the possibility for no effect; j Biber, 2021; Khan Chachar , 2020; Chaccour, 2021; Aref, 2021; Vallejos, 2021; k Risk of bias: Serious Risk of bias downgraded by 1 level: some concerns regardingdeviation from intended intervention, missing data and selection of the reported results Inconsistency: Serious Inconsistency downgraded by 1 level: I^2=:70.6% Imprecision: Serious due to low number of participants; l Khan Chachar, 2020; Chaccour, 2021; Lopez-Medina, 2021; Biber, 2021; Vallejos, 2021; m Imprecision: Serious due to low number of participants; n Imprecision: Very serious due to very wide confidence interval consistent with the possibility for benefit and the possibility for harm and low number of participants

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

*Table 3.27-2: Summary of findings table, on **Ivermectin vs Standard care/placebo** (8 RCTs)*

Ivermectin compared to Standard care/Placebo for Hospitalised COVID-19 patients (last update 10/08/2021)

Patient or population: Hospitalised COVID-19
Setting: Worldwide Outpateint
Intervention: Ivermectin
Comparison: Standard care/Placebo

Outcome	Anticipated absolute effects (95% CI) [a]		Relative effect (95% CI)	Number of participants (studies)	Certainty of evidence	Comments
	Risk with Standard care/Placebo	Risk with Ivermectin				
All-cause mortality D28	60 per 1000	32 per 1000	**RR: 0.53** (0.21 - 1.31)	850 (8 RCTs)	OOO⊕ VERY LOW [b]	**Absolute effect (95% CI)** 28 fewer per 1000 (from 47 fewer to 19 more)
Clinical improvement D28	756 per 1000	756 per 1000	**RR: 1.00** (0.90 - 1.11)	372 (4 RCTs)	OO⊕⊕ LOW c	**Absolute effect (95% CI)** 0 fewer per 1000 (from 76 fewer to 83 more)
WHO progression score (level 7 or above) D28	0 per 1000	0 per 1000	**RR: 1.55** (0.07 - 35.89)	245 (3 RCTs)	OO⊕⊕ LOW d	**Absolute effect (95% CI)** not calculated due to zero events in the control group
Viral negative conversion D7	318 per 1000	321 per 1000	**RR: 1.01** (1.81 - 1.26)	607 (8 RCTs)	OOO⊕ VERY LOW e	**Absolute effect (95% CI)** 3 more per 1000 (from 60 fewer to 83 more)
Number of patients with adverse events	222 per 1000	191 per 1000	**RR: 0.86** (0.59 - 1.24)	416 (6 RCTs)	OOO⊕ VERY LOW [f]	**Absolute effect (95% CI)** 31 fewer per 1000 (from 91 fewer to 53 more)
Number of patients with serious adverse events	12 per 1000	14 per 1000	**RR: 1.11** (0.19 - 6.44)	416 (6 RCTs)	OOO⊕ VERY LOW [g]	**Absolute effect (95% CI)** 1 more per 1000 (from 10 fewer to 67 more)

CI: Confidence interval; RR: Risk ratio; a The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI); Explanations will be provided in next version of this report.

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

Ivermectin mucoadhesive nanosuspension intranasal spray in treatment of patients with mild COVID-19

Verabreichung als intranasal Spray

RCT
114 Pts, milde Erkrankung
Krankheitssymptome kürzer

Aref et al. 2021 published effectiveness and safety results of ivermectin mucoadhesive nanosuspension intranasal spray in treatment of 114 patients with **mild COVID-19** (**NCT04716569**) [263]. Patients were divided randomly into two age and sex-matched groups; group A comprising 57 patients received ivermectin nanosuspension nasal spray twice daily plus the Egyptian protocol of treatment for mild COVID-19 and group B comprising 57 patients received the Egyptian protocol for mild COVID-19 only. In group A, 54 patients (94.7%) achieved 2 consecutive negative PCR nasopharyngeal swabs in comparison to 43 patients (75.4%) in group B, p=0.004. The durations of fever, cough, dyspnea and anosmia were significantly shorter in group A than group B, without significant difference regarding the duration of gastrointestinal symptoms. Duration taken for nasopharyngeal swab to be negative was significantly shorter in group A than in group B (8.3± 2.8 days versus 12.9 ± 4.3 days; p=0.0001).

3.28 Aspirin

About the drug under consideration

nicht-steroidales Antirheumatikum

schmerzstillender, entzündungshemmenderf iebersenkender und Thrombozyten-aggregationshemmender Arzneistoff

Aspirin (acetylsalicylic acid) is a non-steroidal anti-inflammatory drug with strong anti-inflammatory, anti-thrombotic and analgesic pharmacological effects. Long-term low-dose aspirin (75-150 mg daily) can effectively prevent the incidence of ischaemic cardiovascular and cerebrovascular event. Acetylsalicylic acid inhibits the platelet activation: blocking the platelet cyclooxygenase by acetylation, it inhibits thromboxane A2 synthesis, a physiological activating substance released by the platelets and which would play a role in the complications of the atheromatosic lesions. The repeated doses from 20 to 325 mg involve an inhibition of the enzymatic activity from 30 to 95%. Due to the irreversible nature of the binding, the effect persists for the lifespan of a thrombocyte (7-10 days). The inhibiting effect does not exhaust during prolonged treatments and the enzymatic activity gradually begins again upon renewal of the platelets 24 to 48 hours after treatment interruption, https://www.medicines.org.uk/emc/product/2408/smpc.

Patient*innen mit Covid-19 haben höheres Risiko für Bildung von Blutgerinnseln in Blutgefäßen

Patients with COVID-19 are at higher risk of blood clots forming in their blood vessels. Platelets, small cell fragments in the blood that stop bleeding, seem to be hyperreactive in COVID-19 and may be involved in the clotting complications. Since aspirin is an antiplatelet agent, it may reduce the risk of blood clots in patients with COVID-19.

retrospektive Kohortenstudie, 412 Pts

Vorteile bei künstlicher Beatmung und Intensivmedizin Spitalsmortalität

RCT für Nachweis einer Kausalität vonnöten

Chow et al. 2020 [264] published results from retrospective, observational cohort study of adult patients admitted with COVID-19 to multiple hospitals in the United States between March 2020 and July 2020. 412 patients were included in the study. 314 patients (76.3%) did not receive aspirin, while 98 patients (23.7%) received aspirin within 24 hours of admission or 7 days prior to admission. Aspirin use had a crude association with less mechanical ventilation (35.7% aspirin vs. 48.4% non-aspirin, p=0.03) and ICU admission (38.8% aspirin vs. 51.0% non-aspirin, p=0.04), but no crude association with in-hospital mortality (26.5% aspirin vs. 23.2% non-aspirin, p=0.51). After adjusting for 8 confounding variables, aspirin use was independently associated with decreased risk of mechanical

ventilation (adjusted HR 0.56, 95% CI 0.37-0.85, p=0.007), ICU admission (adjusted HR 0.57, 95% CI 0.38-0.85, p=0.005), and in-hospital mortality (adjusted HR 0.53, 95% CI 0.31-0.90, p=0.02). There were no differences in major bleeding (p=0.69) or overt thrombosis (p=0.82) between aspirin users and non-aspirin users. Authors concluded that a sufficiently powered randomized controlled trial is needed to assess whether a causal relationship exists between aspirin use and reduced lung injury and mortality in COVID-19 patients.

Aspirin is not approved for Covid-19 by the European Medicines Agency (EMA) or the American Food and Drug Administration (FDA).

Withdrawn, suspended or terminated studies

1 RCT zurückgezogen (keine Finanzierung)

One RCT was found as withdrawn (NCT04343001) because grant not obtained. No suspended or terminated interventional studies were found on Aspirin in COVID-19 patients in ClinicalTrials.gov and EUdraCT registers.

Results of publications

RCTs (4-armig)

900 Pts.

Atorvastatin

Aspirin

Atorvastatin + Aspirin

SoC

kein Unterschied zwischen den Gruppen

Ghati et al. 2021 [265] published results from a single-center, four-arm parallel design, open-label randomized controlled trial (CTRI/2020/07/026791) on RT-PCR positive Covid-19 patients, ≥ 40 years and < 75 years of age, requiring **hospitalisation** [World Health Organization (WHO) Ordinal Scale for Clinical Improvement 3to 5]. Patients were randomly assigned to either atorvastatin 40 mg (group A), aspirin 75 mg (group B), or both (group C) in addition to standard of care for 10 days or until discharge whichever was earlier or only standard of care (group D). The primary outcome variable was clinical deterioration to WHO Ordinal Scale for Clinical Improvement ≥ 6. The secondary outcome was change in serum inflammatory markers (C-reactive protein and Interleukin-6), and Troponin I. A total of 900 patients underwent randomization (with Groups A, B, C and D assigned 224, 225, 225 and 226 patients respectively). The primary outcome occurred in 25 (2.8%) patients: 7 (3.2%) in Group A, 3 (1.4%) in Group B, 8 (3.6%) in Group C and 7 (3.2%) in Group D. There was no difference in primary outcome across the study groups (p=0.463). Comparison of all patients who received atorvastatin or aspirin with the control group (Group D) also did not show any benefit [Atorvastatin: HR 1.0 (95% CI 0.41 - 2.46); Aspirin: HR 0.7 (95% CI 0.27-1.81)]. The secondary outcomes revealed lower serum IL-6 among patients in Groups B and C. There was no excess of adverse events.

RECOVERY

Studienarm mit Aspirin

From 06 November 2020, Aspirin is being investigated in the world's largest clinical trial of treatments for patients **hospitalised** with COVID-19. The Randomised Evaluation of COVid-19 thERapY (**RECOVERY**) trial is taking place in 176 hospital sites across the UK, and has so far recruited over 16,000 patients, https://www.recoverytrial.net/news/aspirin-to-be-investigated-as-a-possible-treatment-for-covid-19-in-the-recovery-trial.

Results are announced on June 08 2021 and published as **preprint**: a total of 7351 patients were randomised to aspirin 150 mg once daily and compared with 7541 patients randomised to usual care alone. There was no evidence that aspirin treatment reduced mortality. There was no significant difference in the primary endpoint of 28-day mortality (17% aspirin vs. 17% usual care; rate ratio 0.96 [95% confidence interval 0.89-1.04]; p=0.35). The results were consistent in all pre-specified subgroups of patients. Patients allocated to aspirin had a slightly shorter duration of hospitalisation (median 8 days vs. 9 days) and a higher proportion were discharged from hospital alive within 28 days (75% vs. 74%; rate ratio 1·06; 95% CI 1·02-1·10; p=0·0062). Among those not on invasive mechanical ventilation at baseline, there was no significant difference in the proportion who progressed to invasive mechanical ventilation or death (21% vs. 22%; risk ratio 0·96; 95% CI 0·90-1·03; p=0·23). For every 1000 patients treated with aspirin, approximately 6 more patients experienced a major bleeding event and approximately 6 fewer experienced a thromboembolic (clotting) event, https://www.recoverytrial.net/news/recovery-trial-finds-aspirin-does-not-improve-survival-for-patients-hospitalised-with-covid-19, [266].

Ergebnisse von 7.351 Pts im Aspirin Therapiearm

kein Unterschied bei Mortalität und Progression zu invasiver Beatmung

geringfügig kürzerer Spitalsaufenthalt

The **Summary of findings table** based on 2 RCTS can be found below (Table 3.28-1). In hospitalised COVID-19 patients Aspirin may not reduce All-cause mortality D28 (RR 0.86, 95% CI 0.49 to 1.50, low certainty of evidence) and does not increase Clinical improvement D28 (RR 1.02, 95% CI 1.00 to 1.04, high certainty of evidence). The evidence is very uncertain about the effect of Aspirin on outcome WHO progression score (level 7 or above) D28 (RR 0.43, 95% CI 0.1 to 1.64, very low certainty of evidence).

SoF von 2 RCTs

unsicher Evidenz wahrscheinlich kein Effekt

*Table 3.28-1: Summary of findings table, on **Aspirin vs Standard care** (2 RCTs: Horby RECOVERY, Ghanti)*

Ivermectin compared to Standard care for Hospitalised COVID-19 patients (last update 20/06/2021)

Patient or population: Hospitalised COVID-19
Setting: Worldwide Outpateint
Intervention: Aspirin
Comparison: Standard care

Outcome	Anticipated absolute effects (95% CI) [a]		Relative effect (95% CI)	Number of participants (studies)	Certainty of evidence	Comments
	Risk with Standard care	Risk with Aspirin				
All-cause mortality D28	168 per 1000	145 per 1000	**RR: 0.86** (0.49 - 1.50)	15343 (2 RCTs) b	OO⊕⊕ LOW c	**Absolute effect (95% CI)** 24 fewer per 1000 (from 86 fewer to 84 more)
Clinical improvement D28	736 per 1000	750 per 1000	**RR: 1.02** (1.00 - 1.04)	14892 (1 RCT) d	⊕⊕⊕⊕ HIGH	**Absolute effect (95% CI)** 15 more per 1000 (from 0 fewer to 29 more)
WHO progression score (level 7 or above) D28	31per 1000	13 per 1000	**RR: 0.43** (0.11 - 1.64)	451 (1 RCT) e	OOO⊕ VERY LOW f	**Absolute effect (95% CI)** 18 fewer per 1000 (from 28 fewer to 20 more)
Viral negative conversion D7	Outcome not yet measured or reported	Outcome not yet measured or reported	Outcome not yet measured or reported	Outcome not yet measured or reported	Outcome not yet measured or reported	Outcome not yet measured or reported
Number of patients with adverse events	Outcome not yet measured or reported	Outcome not yet measured or reported	Outcome not yet measured or reported	Outcome not yet measured or reported	Outcome not yet measured or reported	Outcome not yet measured or reported
Number of patients with serious adverse events	Outcome not yet measured or reported	Outcome not yet measured or reported	Outcome not yet measured or reported	Outcome not yet measured or reported	Outcome not yet measured or reported	Outcome not yet measured or reported

CI: Confidence interval; **RR**: Risk ratio; a The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI); b Horby RECOVERY, 2021; Ghanti, 2021 c Imprecision: Very serious due to very wide confidence interval consistent with the possibility for benefit and the possibility for harm; d Horby RECOVERY, 2021; e Ghanti, 2021; f Indirectness: Serioussingle study from a single institution therefore results in this population might not be generalizable to other settings Imprecision: Very seriousdue to very wide confidence interval consistent with the possibility for benefit and the possibility for harm and low number of participants

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

3.29 Aviptadil (Zysami)

About the drug under consideration

synthetisches menschliches vasoaktives intestinales Polypeptid (VIP)

soll Replikation des SARS-CoV-2-Virus in menschlichen Lungenzellen und Monozyten blockieren

Aviptadil (RLF-100) is a synthetic form of Human Vasoactive Intestinal Polypeptide (VIP). VIP acts on two receptors - VPAC1 and VPAC2, which are class B of G-protein-coupled receptors (GPCRs). Aviptadil is found to reduce viral replication in lung tissues, release of inflammatory cytokines and alveolar epithelial cell apoptosis in patients with corona virus infection. It is available both as intra venous and inhalational (nebulisation) preparations. It is found useful in conditions like asthma, chronic obstructive pulmonary disease (COPD), sarcoidosis, pulmonary fibrosis, acute lung injury, pulmonary hypertension, erectile dysfunction and ARDS. Intra venous administration is associated with side effects like tachycardia, flushing, hypotension, diarrhoea and alterations in ECG (bigeminy) [267]. Recent observational studies showed that treatment with aviptadil is associated with rapid recovery in Corona virus infected critically ill patients [267-270].
Aviptadil is not authorised in Covid-19 patients (EMA, FDA). On 14 July 2020 FDA granted Investigational New Drug (IND) permission for inhaled VIP and awarded FDA Orphan Drug Designation for intravenous VIP, to use in patients with COVID-19.

Withdrawn, suspended or terminated studies

2 laufende RCTs mit inhaltivem Aviptadil

No withdrawn, suspended or terminated studies were found. Two randomised controlled trials are ongoing with inhaled aviptadil.

In one RCT nebulized RLF-100 (aviptadil) 100 µg is given 3 times daily for moderate and severe COVID-19, with estimated enrolment of 288 patients (NCT04360096- AVICOVID-2). Another RCT with inhaled aviptadil with estimated enrolment in 80 patients in Switzerland (NCT04536350) is not yet recruiting patients.

Expanded Access Protokoll zur Verwendung von Aviptadil

In one study related to Expanded access protocol (NCT04453839, SAMICARE), aviptadil is given as 12 hour infusions at ascending doses of 50/100/150 pmol/kg/hr on 3 successive days. This expanded access protocol is designed to offer access to investigational use of RLF-100 to patients who do not qualify for inclusion in NCT04311697 either on the basis of specific medical exclusions or because there is no accessible study site available to the prospective participant.

Results of publications

Currently, published results were found from one RCT, COVID-AID.

Ergebnissen von 2b/3 RCT: COVID-AIV 196 Pts.

Youssef et al. 2021 [271] published **28-day interim report** from a **phase 2/3** RCT (NCT04311697 - **COVID-AIV**) of **intravenously-administered** ZYESAMI™ (aviptadil acetate, given as escalating doses from 50 -150 pmol/kg/hr over 12 hours for 3 days) for the treatment of respiratory failure in **critically-ill** patients with COVID-19. At 28 days, aviptadil patients treated with high flow nasal cannula (HFNC) were 35% - 46% more likely to recover, return home, and survive to 28 days compared to placebo-treated patients, with a trend level of significance. Aviptadil patients additionally demonstrated a statistically significant and clinically important ten day reduction in hospitalization time.

Hersteller Kommunikation zu Endergebnissen

schnellere klinische Verbesserung
Erholung vom Lungenversagen
schnellere Spitalsentalssung

On March 29, 2021 NeuroRx, Inc. reports **60-day** results of the completed above mentioned RCT. Across all 196 treated patients and all 10 clinical sites, aviptadil met the primary endpoint for successful recovery from respiratory failure at days 28 (p=0.014) and 60 (p=0.013) and also demonstrated a meaningful benefit in survival (p<0.001) after controlling for ventilation status and treatment site. In addition, the prespecified analysis of recovery from respiratory failure is clinically and statistically significant in the 127 patients treated by High Flow Nasal Cannula (HFNC) (p=0.02), compared to those treated with mechanical or non-invasive ventilation at tertiary care hospitals. In this group aviptadil patients had a 71% chance of successful recovery by day 28 vs. 48% in the placebo group (p=0.017) and a 75% rate of successful recovery by day 60 vs. 55% in the placebo group (p=0.036). Eighty-four percent (84%) of HFNC patients treated at tertiary medical centers with aviptadil survived to day 60 compared with 60% of those treated with placebo (p=0.007), https://www.prnewswire.com/news-releases/neurorx-announces-zyesami-aviptadil-rlf-100-met-the-primary-endpoint-of-its-phase-2b3-clinical-trial-and-also-demonstrated-a-meaningful-benefit-in-survival-from-critical-covid-19-301257291.html.

Beginn von Phase 2 I-SPY COVID Trial an kritisch Erkrankten

Inhalation

On July 12, 2021 NRx Pharmaceuticals and Quantum Leap Healthcare Collaborative™ have begun treating patients with **inhaled** Zyesami (Aviptadil), in the **I-SPY COVID Trial** (NCT04488081), a **phase 2 adaptive platform trial** aimed at improving treatment for **severely and critically ill** COVID-19 patients, https://www.nrxpharma.com/nrx-pharmaceuticals-and-quantum-leap-announce-treatment-of-severely-ill-covid-19-patients-with-zyesami%ef%83%94-aviptadil-in-the-i-spy-covid-trial/.

Phase 3 RCT ACTIV-3 an kritisch Erkrankten

On August 18, 2021 NRx Pharmaceuticals provided a **safety update** on Zyesami (aviptadil) which is being tested in the **ACTIV-3 critical care phase 3** study sponsored by the HIH. The study's Data Safety Monitoring Board found no new safety concerns in the trial and recommended continued enrollment. ACTIV-3 is a randomized, blinded, placebo-controlled clinical trial testing Zyesami and the antiviral remdesivir (Veklury) in hospitalised patients with acute respiratory failure due to COVID-19 who require high-flow supplemental oxygen, delivered by nasal cannula, mechanical ventilation, or extracorporeal membrane oxygenation. Study investigators are randomizing patients to receive one of four treatment regimens in addition to standard of care: both Zyesami and remdesivir, Zyesami and a placebo, remdesivir and placebo, or only placebo. Zyesami is administered as a daily 12 hour intravenous infusion over three days, https://www.nrxpharma.com/nrx-pharmaceuticals-announces-positive-safety-report-for-zyesami-aviptadil-in-nih-sponsored-activ-3-critical-care-study-in-patients-with-life-threatening-covid-19/.

3.30 Dimethyl fumarate

About the drug under consideration

Dimethylfumarat (DMF): antivirale und antientzündliche Effekte

Dimethyl fumarate (DMF) is thought to prevent NLRP3 inflammasome activation and the process of pyroptosis (inflammatory cell death) through its action on the protein gasdermin D. SARS-CoV-2 induces inflammasome activation and the degree of activation is thought to correlate with disease severity [272, 273]. DMF has demonstrated anti-viral and anti-inflammatory effects against SARS-CoV-2 in vitro [274].

In EU, dimethyl fumarate (Tecfidera) is authorised for the treatment of adult patients with relapsing remitting multiple sclerosis. DMF is not authorised in Covid-19 patients (EMA, FDA).

Zulassung in EU: bei Multipler Skelrose (MS)

Withdrawn, suspended or terminated studies

No withdrawn, suspended or terminated studies were found.

Currently effectiveness and safety of dimethyl fumarate are investigated in the RECOVERY trial (NCT04381936), in an early phase assessment among patients hospitalised with COVID-19, https://www.recoverytrial.net/.

Studienpräparat in RECOVERY

Results of publications

Currently, no published results were found from RCT related to dimethyl fumarate in COVID-19 patients.

3.31 Artesunate

About the drug under consideration

Artesunate is an artemisinin, a class of compounds originally derived from extracts of Artemisia annua (sweet wormwood) for the treatment of malaria and has since been adopted by the World Health Organization (WHO). The use of artesunate has surpassed the use of chloroquines for the treatment of malaria and more recently for COVID-19 [275] The anti-viral mechanism of artesunate is thought to hinge on suppression of nuclear factor kappa beta (NF-κβ) activation. Artesunate could therefore mitigate the inflammatory response and potentially improve patient outcome.

Pflanzenextrakt Medikament bei Malaria

Seven clinical trials have since been initiated to assess the efficacy of artesunate in different forms and administrations in reducing viral load and improving the prognosis of SARSCoV-2-positive patients. A preliminary report documents a significant decrease in viral load and duration of hospitalisation, and improved absorption of lung lesions in COVID-19 patients treated with 10 daily doses of 60 mg artesunate in addition to standard treatment [275, 276].

7 klinische Studien initiiert nach ersten vielversprechenden Daten

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

keine Zulassung

Withdrawn, suspended or terminated studies

No withdrawn, suspended or terminated studies were found for artesunate.

Effectiveness and safety of artesunate will be investigated in the WHO SOLIDARITY trial [277].

Studienpräparat in SOLIDARITY

derzeit keine abgeschlossenen RCTs

Results of publications

Currently, no published results were found from RCTs related to artesunate in COVID-19 patients.

3.32 Tofacitinib (Xeljanz)

About the drug under consideration

JAK-Inhibitor

Tofacitinib is a potent, selective inhibitor of the JAK family. In enzymatic assays, tofacitinib inhibits JAK1, JAK2, JAK3, and to a lesser extent TyK2. In human cells, tofacitinib preferentially inhibits signalling by heterodimeric cytokine receptors that associate with JAK3 and/or JAK1 with functional selectivity over cytokine receptors that signal via pairs of JAK2. Inhibition of JAK1 and JAK3 by tofacitinib attenuates signalling of interleukins (IL-2, -4, -6, -7, -9, -15, -21) and type I and type II interferons, which will result in modulation of the immune and inflammatory response [278].

ev. Verbesserung der entzündungsbedingten Lungenschädigung bei hospitalisierten Patient*innen

Acting on multiple critical pathways of the inflammatory cascade tofacitinib may ameliorate progressive, inflammation-driven lung injury in hospitalised patients with Covid-19.

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

US COVID-19 Treatment Guidelines Panel Statement – Alternative zu Baricitinib

The **US COVID-19 Treatment Guidelines Panel** Statement (August 25, 2021) [120] is: the Panel recommends **tofacitinib** as an alternative to **baricitinib** only when baricitinib is not available or not feasible to use **(BIIa)**.

Withdrawn, suspended or terminated studies

No withdrawn, suspended or terminated studies were found for tofacitinib in COVID-19 patients.

Results of publications

RCT
STOP-COVID
289 hospitalisierte Pts.

bessere Ergebnisse bei Überleben und Atemwegsversagen

Nebenwirkungen

Guimaraes et al. 2021 [279] published results from **STOP-COVID** RCT (**NCT04469114**), on **hospitalised adults** with Covid-19 pneumonia to receive either tofacitinib at a dose of 10 mg or placebo twice daily for up to 14 days or until hospital discharge. The primary outcome was the occurrence of death or respiratory failure through day 28 as assessed with the use of an eight level ordinal scale (with scores ranging from 1 to 8 and higher scores indicating a worse condition). All-cause mortality and safety were also assessed. A total of 289 patients underwent randomization at 15 sites in Brazil. Overall, 89.3% of the patients received glucocorticoids during hospitalisation. The cumulative incidence of death or respiratory failure through day 28 was 18.1% in the tofacitinib group and 29.0% in the placebo group (risk ratio, 0.63; 95% confidence interval [CI], 0.41 to 0.97; p=0.04). Death from any cause through day 28 occurred in 2.8% of the patients in the tofacitinib group and in 5.5% of those in the placebo group (hazard ratio, 0.49; 95% CI, 0.15 to 1.63). The proportional odds of having a worse score on the eight-level ordinal scale with tofacitinib, as compared with placebo, was 0.60 (95% CI, 0.36 to 1.00) at day 14 and 0.54 (95% CI, 0.27 to 1.06) at day 28. Serious adverse events occurred in 20 patients (14.1%) in the tofacitinib group and in 17 (12.0%) in the placebo group. Among the adverse events of special interest, deep-vein thrombosis, acute myocardial infarction, ventricular tachycardia, and myocarditis occurred in 1 patient each in the tofacitinib group; hemorrhagic stroke and cardiogenic shock occurred in 1 patient each in the placebo group. The incidence of serious infection was 3.5% in the tofacitinib group and 4.2% in the placebo group. Adverse events other than death that led to the discontinuation of the trial regimen

occurred in 11.3% of the patients in the tofacitinib group and in 3.5% of those in the placebo group; the most common such events were an increase in aminotransferase levels (in 4.2% of the patients in the tofacitinib group and in 0.7% of those in the placebo group) and lymphopenia (in 2.8% and 1.4%, respectively).

3.33 Fluvoxamine

About the drug under consideration

Serotonin-Wiederaufnahme-hemmer

Antidepressivum

Fluvoxamine is a selective serotonine re-uptake inhibitor (SSRI) indicated for major depression and/or obsessive compulsive disorder (OCD). Sukhatme and al. 2021 [280] published review article related to antiviral and anti-inflammatory mechanisms of action of fluvoxamine and other SSRIs that could play a role in COVID-19 treatment. These effects include: reduction in platelet aggregation, decreased mast cell degranulation, interference with endolysosomal viral trafficking, regulation of inositolrequiring enzyme 1α-driven inflammation and increased melatonin levels, which collectively have a direct antiviral effect, regulate coagulopathy or mitigate cytokine storm, which are known hallmarks of severe COVID-19.

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

Withdrawn, suspended or terminated studies

No withdrawn, suspended or terminated studies were found for fluvoxamine in COVID-19 patients.

Results of publications

Outpatient

RCT
STOP COVID
152 nicht-hospitalisierte Pts

besser bei Verhinderung von Verschlechterung

Lenze et al. 2020 [281] published results from double-blind, randomized, fully remote (contactless) clinical trial of fluvoxamine vs placebo **(STOP COVID, NCT04342663).** Participants were community-living, **nonhospitalised adults** with confirmed severe acute respiratory syndrome coronavirus 2 infection, with COVID-19 symptom onset within 7 days and oxygen saturation of 92% or greater. 152 participants were randomly assigned to receive 100 mg of fluvoxamine (n = 80) or placebo (n = 72) 3 times daily for 15 days. The primary outcome was clinical deterioration within 15 days of randomization defined by meeting both criteria of (1) shortness of breath or hospitalization for shortness of breath or pneumonia and (2) oxygen saturation less than 92% on room air or need for supplemental oxygen to achieve oxygen saturation of 92% or greater. Of 152 patients who were randomized (mean [SD] age, 46 [13] years; 109 [72%] women), 115 (76%) completed the trial. Clinical deterioration occurred in 0 of 80 patients in the fluvoxamine group and in 6 of 72 patients in the placebo group (absolute difference, 8.7% [95% CI, 1.8%-16.4%] from survival analysis; log-rank p=0.009). The fluvoxamine group had 1 serious adverse event and 11 other adverse events, whereas the placebo group had 6 serious adverse events and 12 other adverse events.

Reis et al. 2021 [282] published as **preprint, preliminary findings** from the ongoing **TOGETHER** randomized **platform clinical trial** (**NCT04727424**) for acutely symptomatic **nonhospitalised** patients with COVID-19, with a **known risk factor for progression to severe disease**, assessing the efficacy of fluvoxamine vs. placebo in preventing either extended emergency room observation or hospitalisation due to COVID-19. 3238 patients were randomly assigned to either fluvoxamine (100 mg twice daily for 10 days) or placebo. The primary endpoint was a composite outcome of emergency room observation for >6 hours or hospitalisation from COVID-19 up to 28 days post randomization using intention to treat. Modified intention to treat (mITT) explored patients receiving at least 24 hours of treatment before a primary outcome event. Secondary outcomes included viral clearance at day 7, time to hospitalization, mortality, and adverse drug reactions. On August 6th 2021 the trial arms were stopped for superiority. The average age of participants was 50 years (range 18-102 years); 57% were female. The proportion of patients observed in an emergency room for >6 hours or admitted to hospital due to COVID-19 was lower for the fluvoxamine group compared to placebo (77/739 vs 108/733; Relative Risk [RR]: 0.71; 95% Bayesian Credible Interval [95% BCI]: 0.54 - 0.93), with a probability of superiority of 99.4% surpassing the prespecified superiority threshold of 97.6% (risk difference 4.3%). Of the composite primary outcome events, 88% were hospitalisations. Findings were similar for the mITT analysis (RR0.68, 95% BCI: 0.50- 0.91). We found no significant relative effects between the fluvoxamine and placebo groups on viral clearance at day 7 (Odds ratio [OR]: 0.75; 95% Confidence Intervals [95% CI]: 0.53 - 1.07), mortality (OR: 0.70; 95% CI: 0.36 - 1.30), time to death (Hazard ratio [HR]: 0.79; 95% CI: 0.58 - 1.08), days hospitalised (Mean Difference (MD) 1.22 days; 95% CI: 0.98 - 1.53), number of days ventilated (MD 1.10; 95% CI: 0.70 -1.73) or other secondary outcomes. Data capturing all 28 days of follow-up will be reported after August 26th, 2021.

RCT
TOGETHER
3.238 nicht-hospitalisierte Pts mit Risiko

geringere Notfallaufnahmen und Hospitalisierungen

aber keine Effekte auf andere Endpunkte

3.34 PF-07321332

About the drug under consideration

PF-07321332, an orally bioavailable SARS-CoV-2 main protease inhibitor with in vitro pan-human coronavirus antiviral activity, and potent off-target selectivity and in vivo safety profiles. PF-07321332 has demonstrated oral activity in a mouse-adapted SARS-CoV-2 model and has achieved oral plasma concentrations exceeding the in vitro antiviral cell potency, in a phase 1 clinical trial in healthy human participants [283].

Proteaseinhibitor

PF-07321332 is not authorised in Covid-19 patients (EMA, FDA).

Withdrawn, suspended or terminated studies

No withdrawn, suspended or terminated studies were found for PF-07321332 in COVID-19 patients.

Global development program on PF-07321332 includes a **phase 1**, double blind, sponsor open, single and multiple ascending dose study to evaluate safety, tolerability and pharmacokinetics of PF-07321332 in healthy participants (NCT04756531); a **phase 2/3** study of **PF-07321332/ritonavir** in **nonhospitalised high risk** adults with COVID-19 (**NCT04960202**) to determine whether PF-07321332/ritonavir is safe and effective for the treatment of adults who are ill with COVID-19 and do not need to be in the hospital, but are at an increased risk of developing severe illness. On September 01, 2021 Pfizer announced that the first participant has been dosed in a pivotal **phase 2/3** clinical trial (**NCT05011513**) to evaluate the safety and efficacy of PF-07321332 in **non-hospitalised**, symptomatic adult participants who have a confirmed diagnosis of SARSCoV-2 infection and are **not at increased risk** of progressing to severe illness, which may lead to hospitalisation or death. The randomized, double-blind trial will enroll approximately 1,140 participants, who will receive **PF07321332/ritonavir** or placebo orally every 12 hours for five days.

Phase 1:
Studie zur Sicherheit

Phase 2/3:
an nicht-hospitalisierten Pts.
PF-07321332/ritonavir

Results of publications

Currently, no published results were found from RCTs related to PF-07321332 with/without ritonavir in COVID-19 patients.

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