HTA Austria
Austrian Institute for
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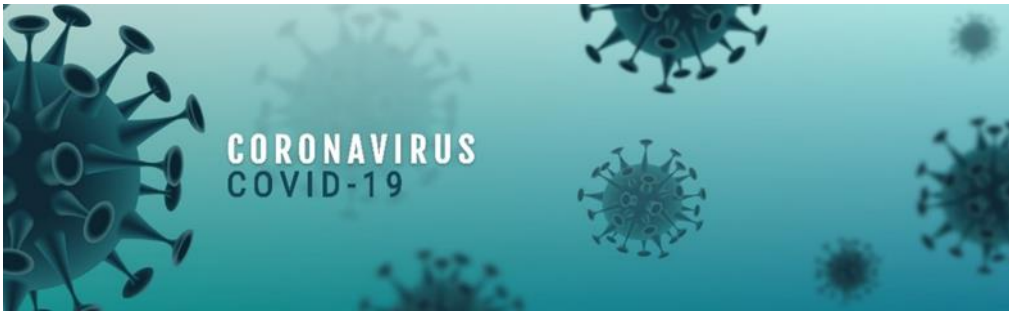
GmbH

Covid-19



HSS/ Horizon Scanning
Living Document **V18 October/**
November 2021

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Covid-19

HSS/ Horizon Scanning
Living Document **V18 October/ November** 2021

Vienna, November 2021

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Content

Figures

Tables

History of Changes	V18 October/November 2021
Oct and Nov 2021	Addition chapters on AT-527 (chapter 3.2.35), Plonmarlimab (TJM2) (chapter 3.2.36), Mavrilimumab (chapter 3.2.37) and SAB-185 (chapter 3.2.38)
Oct and Nov 2021	Update Methodology (1.2)
Oct and Nov 2021	Vaccine (chapter 2) – reporting is stopped, see earlier version (V17_August and September 2021) for more details
Oct and Nov 2021	Update Remdesivir (chapter 3.2.1)
Oct and Nov 2021	Favipiravir (chapter 3. 2.3) - see earlier version (V17_August and September 2021) for more details
Oct and Nov 2021	Darunavir (chapter 3. 2.4) – no changes
Oct and Nov 2021	Camostat Mesilate (chapter 3. 2.7) – no changes
Oct and Nov 2021	Update APN01/rhACE2 (chapter 3. 2.8)
Oct and Nov 2021	Update Tocilizumab (chapter 3. 2.9)
Oct and Nov 2021	Update Sarilumab (chapter 3. 2.10)
Oct and Nov 2021	Interferon beta (chapter 3. 2.11) – no changes
Oct and Nov 2021	Concalescent plasma (chapter 3. 2.12) - see earlier version (V17_August and September 2021) for more details
Oct and Nov 2021	Update Plasma derived medicinal products (chapter 3. 2.13) – REGN-COV2 (Ronapreve); LY-CoV555 and LY-CoV016 (Bamlanivimab and etesevimab); AZD7422 (Evusheld); Sotrovimab (VIR-7831; Xevudy) Regdanvimab (Regkirona)
Oct and Nov 2021	Combination therapy (chapter 3. 2.14) – no changes
Oct and Nov 2021	Solnatide (chapter 3. 2.15) – no changes
Oct and Nov 2021	Umifenovir (chapter 3. 2.16) – see earlier version (V17_August and September 2021) for more details
Oct and Nov 2021	Inhaled corticosteroids (chapter 3. 2.17.1) – no changes
Oct and Nov 2021	Update Anakinra (chapter 3. 2.18)
Oct and Nov 2021	Update Colchicine (chapter 3. 2.19)
Oct and Nov 2021	Update Nafamostat (chapter 3. 2.20)
Oct and Nov 2021	Gimsilumab (chapter 3. 2.21) – no changes
Oct and Nov 2021	Canakinumab (chapter 3. 2.22) – see earlier version (V17_August and September 2021) for more details
Oct and Nov 2021	Lenzilumab (chapter 3. 2.23) – no changes
Oct and Nov 2021	Vitamin D (chapter 3. 2.24) – see earlier version (V17_August and September 2021) for more details
Oct and Nov 2021	Update Baricitinib (chapter 3. 2.25)
Oct and Nov 2021	Update Molnupiravir (chapter 3. 2.26)
Oct and Nov 2021	Ivermectin (chapter 3. 2.27) – see earlier version (V17_August and September 2021) for more details

Oct and Nov 2021	Aspirin (chapter 3. 2.28) – see earlier version (V17_August and September 2021) for more details
Oct and Nov 2021	Aviptadil (RLF-100) (chapter 3. 2.29) – see earlier version (V17_August and September 2021) for more details
Oct and Nov 2021	Dimethyl fumarate (chapter 3. 2.30) – see earlier version (V17_August and September 2021) for more details
Oct and Nov 2021	Artesunate (chapter 3. 2.31) – see earlier version (V17_August and September 2021) for more details
Oct and Nov 2021	Update Tofacitinib (chapter 3. 2.32)
Oct and Nov 2021	Fluvoxamine (chapter 3. 2.33) – see earlier version (V17_August and September 2021) for more details
Oct and Nov 2021	Update PF-07321332 (PF-07321332/ritonavir – Paxlovid) (chapter 3. 2.34)

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	https://covid-19.ebscomedical.com/research

Information portal	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).

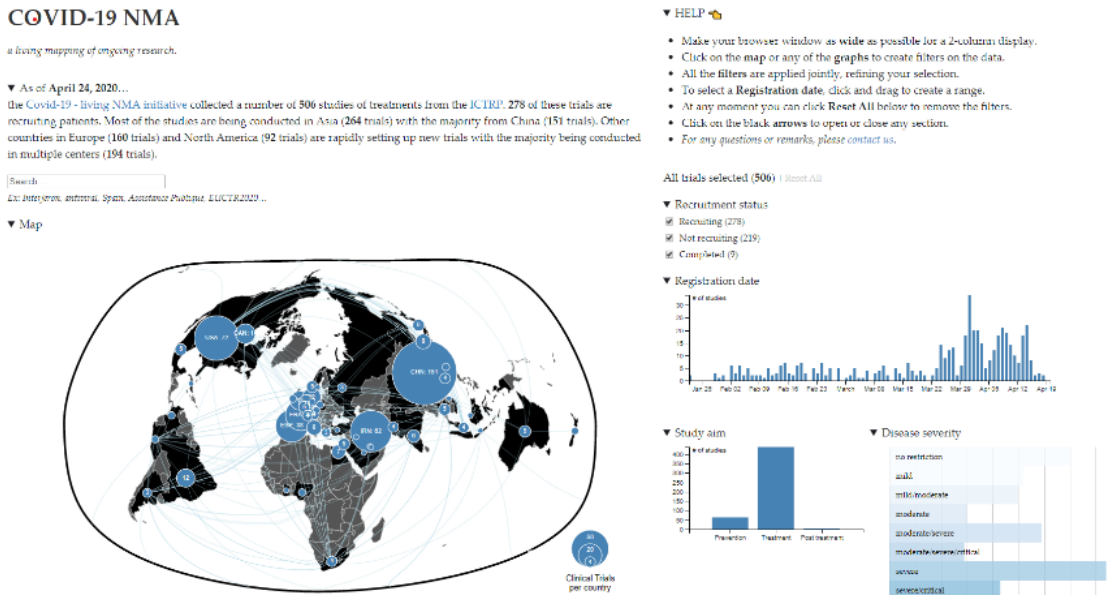

Figure 1.2-1: A living mapping of ongoing randomized trials, living systematic reviews with pairwise meta-analyses and network meta-analyses

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].

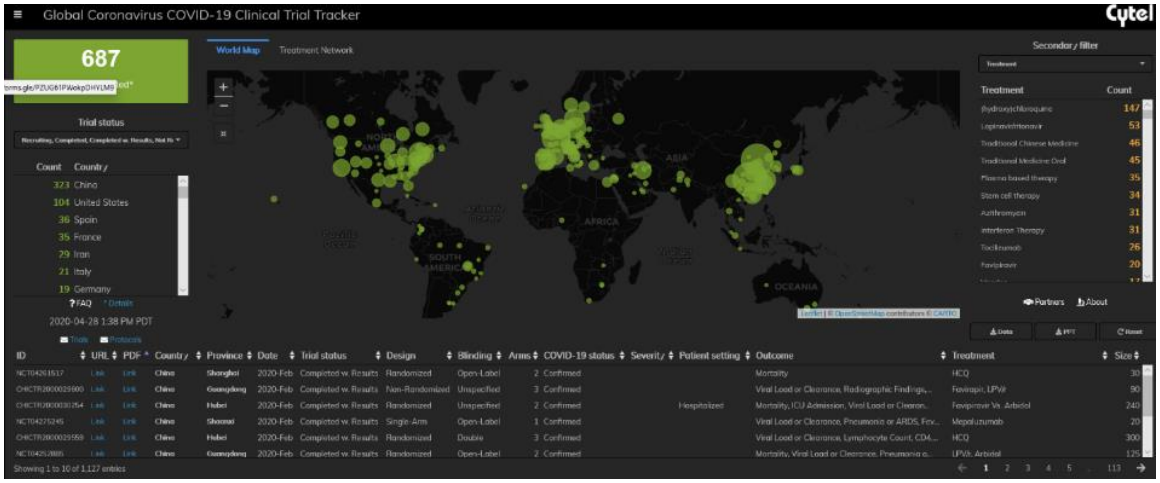

Figure 1.2-2: Global Coronavirus COVID-19 Clinical Trial Tracker - a real-time dashboard of clinical trials for COVID-19

1.3 Selection of Products for "Vignettes"

Vignetten zu Produkte, in "fortgeschrittenen" Stadien oder häufig diskutiert/ publiziert

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

Regeln, wann das Monitoring beendet wird folgen EUnetHTA

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.

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.

From October-November 2021 (v18) onwards the reporting related to Vaccines is stopped according to a decision of the Austrian Ministry of Health.

ab Jän 2021: nur Impfstoffe, für die EC Verträge abgeschlossen hat
ab April 2021: Fokus auf Impfungen für Kinder und auf Wirksamkeit bei unterschiedlichen Mutationen
ab Okt/Nov 2021: nur mehr Medikamente, keine Impfungen

2 Results: Vaccines

The reader is referred to the earlier version (v17_August and September 2021) for more details on **Vaccines.**

ab Okt/Nov 2021: nur mehr Medikamente, keine Impfungen

Reporting related to Vaccines is stopped according to decision of the Austrian Ministry of Health.

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 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.

Oktober 2021: EC veröffentlicht Portfolio von 10 Hoffnungsträgern

AIHTA war Mitglied der EC-Kommission

Details zu den Produkten auch in diesem Bericht

On **October 22, 2021** the EC established a portfolio of **10 potential COVID-19 therapeutics**. The list established is based on independent scientific advice, and focuses on COVID-19 treatment candidates that are likely to be authorised and therefore available on the European market soon. The list of ten is divided in three categories of treatments and will continue to evolve as new scientific evidence emerges: 1) **Antiviral monoclonal antibodies** that are most efficacious in the earliest stages of infection: Ronapreve, a **combination of two monocolonal antibodies casirivimab and imdevimab** from Regeneron harmaceuticals and Roche; Xevudy (**sotrovimab**) from Vir Biotechnology and GlaxoSmithKline; Evusheld, a **combination of two monoclonal antibodies tixagevimab and cilgavimab** from AstraZeneca; 2) **Oral antivirals** for use as quickly as possible after the infection: **Molnupiravir** from Ridgeback Biotherapeutics and MSD; **PF-07321332** from Pfizer; **AT-527** from Atea Pharmaceuticals and Roche and 3) **Immunomodulators** to treat hospitalised patients: Actemra (**tocilizumab**) from Roche Holding; Kineret (**anakinra**) from Swedish Orphan Biovitrum; Olumiant (**baricitinib**) from Eli Lilly; **Lenzilumab** from Humanigen.

These therapeutics will bring treatment to patients across the EU as fast as possible provided that their safety and effectiveness has been confirmed by the European Medicines Agency, https://ec.europa.eu/commission/presscorner/detail/en/ip_21_5366.

Details of Report of the COVID-19 therapeutics subgroup - list of 10 - 22.10.2021. could be found on the website https://ec.europa.eu/transparency/expert-groups-register/screen/meetings/consult?lang=en&meetingId=31115&fromExpertGroups=true.

3.1 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)

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

nicht aber für Pts ohne Beatmung

Therapieoptionen für invasiv und auch nicht-invasiv beatmete Pts

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.**

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.**

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**.

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 **hydrocortisone** 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)

EMA vorläufige Zulassung: 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.

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.**

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

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.

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

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).** 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**).

Molnupiravir

Molnupiravir seit Oktober im EMA-Rolling Review

On October 14, 2021 **EMA**'s human medicines committee has started a **rolling review** of the oral antiviral medicine molnupiravir for the **treatment of COVID-19 in adults**.

Furthermore, on November 8, 2021 EMA starts review to support possible national decisions on early use of molnupiravir prior to its authorisation, https://www.ema.europa.eu/en/news/covid-19-ema-heads-medicines-agencies-update-molnupiravir.

Baricitinib (Olumiant)

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).**

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

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**.

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)**.

Tofacitinib (Xeljanz)

vgl. Text zu Baricitinib

See text above related to US COVID-19 Treatment Guidelines Panel on baricitinib.

Casirivimab and imdevimab (REGN-COV2, Ronapreve)

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**.

On October 11, 2021, EMA has started evaluating an application for marketing authorisation for the monoclonal antibody combination Ronapreve (casirivimab/imdevimab). The applicant is Roche Registration GmbH. On **November 11, 2021** EMA's human medicines committee (**CHMP**) **has recommended authorising Ronapreve** for **treating COVID-19** in adults and adolescents (from 12 years of age and weighing at least 40 kilograms) who **do not require supplemental oxygen** and who are **at increased risk of their disease becoming severe**. Ronapreve can also be used for **preventing COVID-19** in people aged 12 years and older weighing at least 40 kilograms.

The **WHO living guideline** (24 September 2021) provided **conditional recommendation** to use casirivimab/imdevimab combination **in non-severe COVID-19 patients at the highest risk** of severe disease **and** conditional recommendation to use casirivimab/imdevimab combination **in severe and critically ill COVID-19 patients with seronegative status**.

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 and they may change based on circulating variants):

Bamlanivimab plus etesevimab or 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 in combination with 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). In the revised EUA on September 16, 2021 bamlanivimab and etesevimab administered together for **post-exposure prophylaxis (prevention)** for COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) who are at **high risk for progression to severe COVID-19, including hospitalization or death.**

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

Sept 2021 (EUA): auch für Post-Exposure Prophylaxe für Hochrisiko-Pts.

On **November 02, 2021 EMA has ended the rolling review of bamlanivimab and etesevimab, after the company Eli Lilly informed EMA that it was withdrawing from the process.**

Nov 2021: EMA beendet Rolling Review, Eli Lilly zieht Zulassungsantrag zurück

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

On **May 7, 2021 EMA** starts **rolling review of 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** 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 and they may change based on circulating variants):

Bamlanivimab plus etesevimab or 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

On **October 04, 2021 EMA** has **started evaluating an application for marketing authorisation** for the monoclonal antibody Regkirona. On **November 11, 2021** EMA's human medicines committee (**CHMP**) has **recommended authorising** Regkirona (regdanvimab) to **treat adults with COVID-19 who do not require**

Zulassungsantrag

supplemental oxygen therapy and who are at increased risk of progressing to severe COVID 19.

AZD7442 – tixagevimab/cilgavimab combination (Evusheld)

On October 14, 2021 **EMA**'s human medicines committee has started a **rolling review** of Evusheld (AZD7442), for the **prevention of COVID-19 in adults**.

Okt 2021: Tixagevimab/Cilgavimab Kominationstherapie in Rolling Review

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 (RoActemra)

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

Sarilumab (Kevzara)

See text above related to US COVID-19 Treatment Guidelines Panel and the WHO recommendations on tocilizumab.

vgl. Text zu Tocilizumab

Anakinra (Kineret)

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 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.

EMA scientific advice für viele unterschiedliche Medikamente

3.2 Individual therapeutics

3.2.1 Remdesivir (Veklury®)

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

Details in V13_April

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].

PRAC: Sinusbradykardie

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

Aug 2021: EMA-Verlängerung der konditionalen Zulassung

Abd-Elsalam et al. 2021 [120] published mixed results from RCT conducted in hospitalised Egyptian patients with COVID-19. 209 Patients were randomly assigned at a 1:1 ratio to receive either remdesivir (200 mg on the first day followed by 100mg daily for the next 9 days intravenously infused over 30–60 minutes) in addition to standard care or standard care alone. The primary outcomes were the length of hospital stay and mortality rate. The need for mechanical ventilation was assessed as a secondary outcome. Two hundred patients (100 in each group) completed the study and were included in the final analysis. The remdesivir group showed a significantly lower

RCT (Ägypten): 209 Pts. kein Unterschied bei Mortalität Unterschied bei Dauer des Spitalsaufenthalts

median duration of hospital stay (10 days) than the control group (16 days; p<0.001). Eleven of the patients in the remdesivir group needed mechanical ventilation compared with eight patients in the control group (p=0.469). The mortality rate was comparable between the two groups (p=0.602).

DisCoVeRy RCT

kein Unterschied zwischen den 5 Therapiearmen :

SoC allein vs.
Soc + remdesivir
SoC+lopinavir–ritonavir
lopinavir–ritonavir + interferon beta-1a oder hydroxychloroquine

Ader et al. 2021 [121] published negative results from **DisCoVeRy trial** (NCT04315948, EudraCT2020-000936-23) - a phase 3, open-label, adaptive, multicentre, randomised, controlled trial conducted in 48 sites in Europe (France, Belgium, Austria, Portugal, Luxembourg). Adult patients (aged ≥18 years) admitted to hospital with laboratory-confirmed SARS-CoV-2 infection and illness of any duration were eligible if they had clinical evidence of hypoxaemic pneumonia, or required oxygen supplementation. Participants were randomly assigned (1:1:1:1:1) to receive standard of care alone or in combination with remdesivir, lopinavir–ritonavir, lopinavir–ritonavir and interferon beta-1a, or hydroxychloroquine. Remdesivir was administered as 200 mg intravenous infusion on day 1, followed by once daily, 1-h infusions of 100 mg up to 9 days, for a total duration of 10 days. It could be stopped after 5 days if the participant was discharged. The primary outcome was the clinical status at day 15 measured by the WHO seven-point ordinal scale, assessed in the intention-to-treat population. Safety was assessed in the modified intention-to-treat population and was one of the secondary outcomes. Regarding primary outcome, the difference between treatment groups was not significant (odds ratio 0.98 [95% CI 0.77–1.25]; p=0.85). There was no significant difference in the occurrence of serious adverse events between treatment groups (remdesivir, 135 [33%] of 406 *vs* control, 130 [31%] of 418; p=0.48). Three deaths (acute respiratory distress syndrome, bacterial infection, and hepatorenal syndrome) were considered related to remdesivir by the investigators, but only one by the sponsor's safety team (hepatorenal syndrome). No clinical benefit was observed from the use of remdesivir in patients who were admitted to hospital for COVID-19, were symptomatic for more than 7 days, and required oxygen support.

3.2.2 Lopinavir + Ritonavir (Kaletra®)

wegen erwiesenem Mangel an Wirksamkeit wurde Beobachtung beendet

Due to the lack of effectiveness of lopinavir/ritonavir in treating adults hospitalised 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

3.2.3 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).**

They **recommends against** using the **Lopinavir/ritonavir (AI) or other HIV protease inhibitors** for the treatment of COVID-19 in **nonhospitalised patients (AIII)** [122].

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

3.2.4 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).**

They **recommends against** using the **Lopinavir/ritonavir (AI) or other HIV protease inhibitors** for the treatment of COVID-19 in **nonhospitalised patients (AIII)** [122].

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

3.2.5 Chloroquine (Resochin®) and

3.2.6 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 2020:
https://eprints.aihta.at/1234/10/Policy_Brief_002_Update_07.2020.pdf

3.2.7 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 [124]. Studies showed effects on the cell-entry mechanism of coronaviruses (e.g. SARS-CoV and SARS-CoV-2) in in-vitro human cells [125, 126] as well as in pathogenic mice-models [127] 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

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 [128].

vom dt. BMG für schwere Erkrankungen zentral eingekauft

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. **Gunst et al. 2021** [129] 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 ($p<0.05$).

1 Publikation zu RCT: kein Unterschied zwischen den Gruppen

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

Hersteller Kommunikation zu klinischer Studie mit 342 mild erkrankten Pts.

raschere Gesundung (-3 Tage)

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/.

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

Drug under consideration

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) [130], [131], [132].

aus SARS-Forschung hervorgegangen

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

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

Withdrawn, suspended or terminated studies

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

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

Results of publications

No relevant finished publications or finished trials assessing the efficacy and safety could be identified.

First results, related to a **phase 2/3 study** of hrsACE2 in 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 beatmungsfreien 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. On October 12, 2021 APEIRON Biologics announced the start of this phase 1 trial: double-blind, placebo-controlled, dose-escalation study plans to enroll about 40 healthy volunteers in Austria to assess the safety, tolerability, pharmacokinetics, and pharmacodynamics of inhaled APN01, https://www.apeiron-biologics.com/wp-content/uploads/20211012_APEIRON-Biologics_PR_Trial-Start-Inhalation-APN01_ENG.pdf.

Phase 1 Studie Erprobung von APN01 als Inhalation

Okt: Dosisfindungsstudie 40 Pts in Österreich

3.2.9 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)** [133] .

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 [134].

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) [135].**

Aug. 2021: EMA beginnt Evaluation der Indikationsausweitung

Declercq et al. 2021 [137] published negative results from a prospective, multicentre, open-label, randomised, controlled trial, in **hospitalised** patients with **COVID-19, hypoxia, and signs of a cytokine release syndrome** across 16 hospitals in Belgium (**NCT04330638, EudraCT 2020-001500-41**). The **COV-AID trial** has a 2×2 factorial design to evaluate IL-1 blockade versus no IL-1 blockade and IL-6 blockade versus no IL-6 blockade. Patients were randomly assigned by means of permuted block randomisation with varying block size and stratification by centre. In a first randomisation, patients were assigned to receive subcutaneous anakinra once daily (100 mg) for 28 days or until discharge, or to receive no IL-1 blockade (1:2). In a second randomisation step, patients were allocated to receive a single dose of siltuximab (11 mg/kg) intravenously, or a single dose of **tocilizumab** (8 mg/kg) intravenously, or to receive no IL-6 blockade (1:1:1). The primary outcome was the time to clinical improvement, defined as time from randomisation to an increase of at least two points on a 6-category ordinal scale or to discharge from hospital alive. The primary and supportive efficacy endpoints were assessed in the intention-to-treat population. Safety was assessed in the safety population. Drugs targeting IL-1 or IL-6 did not shorten the time to clinical improvement in this

RCT (Belgien): Pts mit Lungenversagen, niedrigem SOFA score

keine Unterschied in Dauer zur klinischen Verbesserung

sample of patients with COVID-19, hypoxic respiratory failure, low SOFA score, and low baseline mortality risk.

3.2.10 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 [138]. 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 [134].

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, [139].

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

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,**

Juli 2020: Pressemeldung zu RCT mit 194 Pts

kein Unterschied mehr SAE in Sarilumab Gruppe

Publikation der Ergebnisse März 2021:

keine Unterschiede, negative Ergebnisse

EudraCT 2020-001162-12)[140] 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.

REMAP-CAP Studienarm 48 Pts.

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

As already described in Tocilizumab Section above, **Gordon et al. 2021 [141](REMAP-CAP, NCT02735707)** published **preliminary report** as preprint, and then in scientific journal [142], 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.

Platform Studie: REMAP-CAP 2.274 kritsch Erkrankte

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

Derde et al. 2021 published **final report** as **preprint** [143] 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.

Phase 2/ 3 RCT

457 Pts hase 2
1.365 Pts Phase 3

geringfügig bessere Ergebnisse

Sivapalasingam et al. 2021 [144] 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 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 9 RCTS: unsichere Evidenz zu Sarilumab zu allen Endpunkten

Summary of finding Table 3.2-1 related to these four RCTs mentioned above and some additional non-published trials can be found below (last update 04/10/2021), https://covid-nma.com/living_data/index.php?allcomp#comparisons_div. In summary, evidence is uncertain or very uncertain about the effect of sarilumab on further outcomes: sarilumab compared to standard care may reduce All-cause mortality D28 (RR 0.88, 95% CI 0.65 to 1.18, 7 RCTs, low certainty of evidence); the evidence is very uncertaint about the effect of sarilumab on outcome All-cause mortality D60 (RR 0.94, 95% CI 0.84 to 1.06, 7 RCTs, very low certainty of evidence); evidence is uncertaint on WHO progression score (level 7 or above) (RR 1.18, 95% CI 0.79 to 1.79, 5 RCTs, low certainty of evidence) and AEs (RR 1.08, 95% CI 0.99 to 1.17, 3 RCTs, low certainty of evidence), and very uncertaint on SAEs (RR 1.06, 95% CI 0.95 to 1.18, 9 RCTs, very low certainty of evidence), compared to standard care for hospitalised COVID-19 patients. Sarilumab compared to standard care probably does not increase Clinical improvement D28 (RR 0.97, 95% CI 0.91 to 1.02, 6 RCTs, moderate certainty of evidence).

Table 3.2-1: Summary of findings table on Sarilumab compared to Standard Care for Hospitalised COVID-19

Sarilumab compared to Standard Care for Hospitalised COVID-19 (last update 04/10/2021), details on https://covid-nma.com/living_data/index.php?allcomp#comparisons_div

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	257 per 1000	226 per 1000	**RR: 0.88** (0.65 - 1.18)	2580 (7 RCTs)	⊕⊕◯◯ LOW	**Absolute effect (95% CI) 31 fewer per 1000** (from 90 fewer to 46 more)
All-cause mortality D60	297 per 1000	279 per 1000	**RR: 0.94** (0.84 - 1.06)	3365 (7 RCTs)	⊕◯◯◯ VERY LOW	**Absolute effect (95% CI) 18 fewer per 1000** (from 48 fewer to 18 more)
Clinical improvement D28	1000 per 1000	970 per 1000	**RR: 0.97** (0.91 - 1.02)	1840 (6 RCTs)	⊕⊕⊕◯ MODERATE	**Absolute effect (95% CI) 30 fewer per 1000** (from 90 fewer to 20 more)
WHO progression score (level 7 or above) D28	140 per 1000	166 per 1000	**RR: 1.18** (0.79 - 1.79)	510 (5 RCTs)	⊕⊕◯◯ LOW	**Absolute effect (95% CI) 25 more per 1000** (from 29 fewer to 111 more)
Number of patients with any adverse event	574 per 1000	619 per 1000	**RR: 1.08** (0.99 - 1.17)	2207 (3 RCTs)	⊕⊕◯◯ LOW	**Absolute effect (95% CI) 46 more per 1000** (from 6 fewer to 98 more)

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				
Number of patients with serious adverse events	230 per 100	244 per 1000	**RR: 1.06** (0.95 - 1.18)	3177 (9 RCTs)	⊕◯◯◯ VERY LOW	**Absolute effect (95% CI)** **14 more per 1000** (from 12 fewer to 41 more)

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)

3.2.11 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 [145].

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) [146, 147]. 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) [148] **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 [149].

Kombinationstherapie: Ergebnisse in 3.14

Results from **Huang et al. 2020** (**ChiCTR2000029387**) [150] 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 [151] 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) [152]. 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)** [153]. 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 [154] 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

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

nicht aber Dauer der Hospitalisierung und in ICU

were not significantly different between the groups. All-cause 28-day mortality was 6.06% and 18.18% in the IFN and control groups respectively (p = 0.12).

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 [155, 156]. 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 [157] 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 [158] 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. [159] published as preprint as well as scientific article [160] 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 3.2-2. 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 3.2-2: 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

3.2.12 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 [161]. 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.

3.2.13 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 [176] 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 [176].

3.2.13.1 REGN-COV2 - combination of two monoclonal antibodies casirivimab/imdevimab (REGN10933 and REGN10987, Ronapreve)

Kombination aus 2 monoklonalen Antikörpern: Casirivimab + Imdevimab

REGN-COV2 (Ronapreve) is combination of two monoclonal antibodies (REGN10933 casirivimab and REGN10987 imdevimab) 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

FDA Analyse zur Wirksamkeit bei unterschiedlichen Mutationen:

gleiche Wirksamkeit

In the FDA new revision in September 2021 [178], related to REGN-COV2 and new variants, casirivimab and imdevimab individually and together retained neutralization activity against Alpha (UK origin) (Table 3.2-3), 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), Delta plus, Kappa, Lambda and Mu.

Table 3.2-3: 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: [178]

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

US COVID-19 Treatment Guidelines Panel

- 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 and they may change based on circulating variants):

Empfehlung FÜR Antikörper Kombinationstherapien

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

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

symptomatische Patient*innen

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

The **WHO living guideline** (the latest 6th version, 24 September 2021) [179] provided

WHO Guideline (Sept 2021)

Conditional recommendation to use casirivimab/imdevimab combination **in non-severe COVID-19 patients at the highest risk** of severe disease:

konditionale Empfehlung für Ronapreve in mild Erkrankten:

- Whereas casirivimab and imdevimab achieves a substantial reduction in the relative risk of hospitalization, the absolute benefit will be trivial or unimportant in absolute terms for all but those at highest risk for which the intervention should be reserved.
- The panel identified a risk beyond 10% of being hospitalized for COVID-19 to represent a threshold at which most people would want to be treated with casirivimab and imdevimab.
- In the absence of credible tools to predict risk for hospitalization in people infected with COVID-19, typical characteristics of people at highest risk include lack of vaccination, older people, or those with immunodeficiencies and/or chronic diseases (e.g. diabetes).

große relative Effekte, die aber absolut irrelevant sein können

Pts-Selektion ist wichtig nach Risikoeinschätzung

and

konditionale Empfehlung für Ronapreve in schwer/ kritisch Erkrankten:

Conditional recommendation to use casirivimab/imdevimab combination **in severe and critically ill COVID-19 patients with seronegative status:**

nur in sero-negativen Pts. und in Kombination mit SoC (Kortikosteroiden)

- With benefits of casirivimab and imdevimab observed only in patients with seronegative status, clinicians will need to identify these patients by credible tests available at the point of care to appropriately apply this recommendation.
- Treatment with casirivimab and imdevimab is in addition to the current standard of care, which includes corticosteroids and IL-6 receptor blockers.

Results of publication

On December 17 2020, Weinreich et al. [180] 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.

Teilergebnisse von Phase 1–3 RCT

275 Pts.

Vorteile bei Viruslastreduktion Reduktion von Arztbesuchen

On May 21, 2021 Weinreich et al. [181] published as preprint, and then in scientific journal [182], 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
4.057 ambulante Pts
Risiko auf Progression

signifikante Reduktion der Hospitalisierungen in allen Subgruppen

On June 14, 2021 O'Brien et al. [183] published as preprint, and then in scientific journal [184] **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.

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

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

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 3.2-4. 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)

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

wenig sichere Evidenz

and may not increase SAEs (RR 0.11, 95% CI 0.01 to 2.07, low certainty of evidence).

*Table 3.2-4: 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**) [185]. 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 [186]. 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 [187].

Juli 2021 FDA EUA als Post Exposure Prophylaxe

In **new revision of EUA, July 2021** [178] 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 [188]. 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 [189, 190].

On **October 11, 2021, EMA has started evaluating an application for marketing authorisation** for the monoclonal antibody combination Ronapreve (casirivimab / imdevimab). Ronapreve is intended for the treatment of COVID-19 in adults and adolescents from 12 years of age who do not require supplemental oxygen therapy and who are at increased risk of progressing to severe COVID 19, and for the prevention of COVID-19 in adults and adolescents aged 12 years and older [191]. On **November 11, 2021** EMA's human medicines committee (**CHMP**) has **recommended authorising Ronapreve** for these indications, https://www.ema.europa.eu/en/news/covid-19-ema-recommends-authorisation-two-monoclonal-antibody-medicines.

Okt 2021: Zulassungsantrag für Ronapreve

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

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

The reader is referred to the earlier version (V17_August and September 2021) for more details on **bamlanivimab and etesevimab.**

Verweis auf v17

Our reporting on bamlanivimab and etesevimab was stopped because on **November 02, 2021 EMA has ended the rolling review of bamlanivimab and etesevimab,** developed by Eli Lilly Netherlands BV, **after the company informed EMA that it was withdrawing from the process** [192].

da Antrag auf Marktzulassung zurückgezogen wurde: Ende des Monitoring hier

3.2.13.3 AZD7442 - combination f two monoclonal antibodies (tixagevimab AZD8895 + cilgavimab AZD1061) - Evusheld

AZD7442 is a combination of two mAbs (tixagevimab - AZD8895 + cilgavimab - AZD1061, Evusheld) 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.

AZD7442 Kombination aus 2 monoklonalen Antikörpern Vanderbilt University/ AstraZeneca

The half-life extension more than triples the durability of its action compared to conventional antibodies and could afford up to 12 months of protection from COVID-19 following a single administration; data from the phase 1 trial show high neutralising antibody titres for at least nine months. Evusheld neutralises recent emergent SARS-CoV-2 viral variants, including the Delta and Mu variants, according in vitro findings. It is administered by intramuscular injection.

längere Halbwertszeit im Vegleich zu anderen Antikörpern: möglicherweise Schutz bis zu 12 Monaten

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

Phase 1 Ende Sept 2021

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-

Phase 2 & 3 laufend

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.

Regulatory update:

Okt 2021:
EUA Antrag (USA)
Rolling Review (EMA)

On **5 October 2021**, the Company announced that it had **submitted a request** to the US Food and Drug Administration (**FDA**) for Emergency Use Authorisation (**EUA**) for AZD7442 for **prophylaxis of COVID-19**.

On **October 14, 2021** EMA announced that **EMA's** human medicines committee has started a **rolling review** of Evusheld (AZD7442), for the **prevention of COVID-19** in **adults** [210].

Results of publications

keine Publikation von klinschen Studien

There are no publications from RCTs related to AZD7442.

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

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.

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-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.

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

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.

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

Results from the **TACKLE phase 3 trial** showed that AZD7442 achieved a statistically significant reduction in severe COVID-19 or death compared to placebo in **non-hospitalised patients with mild-to-moderate symptomatic COVID-19** [211]. The AZD7442 was well tolerated in both trials.

TACKLE RCT
signifikante Reduktion von Progression in mild Erkrankten

3.2.13.4 Sotrovimab (VIR-7831 monoclonal antibody, Xevudy)

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.

monoklonaler Antikörper

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.

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

Endpunkt: Verhinderung der Progression

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 published results from the preplanned interim analysis of this trial can be found below.

März 2021:
COMET-ICE
Zwischenauswertung

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/TICO** (NCT04501978) 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 enrollment 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**

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

to moderate COVID-19 . Details could be seen in section on bamlanivimab above.

One **phase 3** randomised clinical trial (**NCT04913675**) is ongoing to assess efficacy and safety of VIR-7831 given **intramusculary vs intravenously** for the treatment of mild to moderate COVID-19 in high-risk non-hospitalised patients.

RCT zu IM vs. IV Verabreichung läuft

Regulatory update:

April/ Mai: EMA beginnt Review von VIR-7831

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**.[212]. 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** [213].

VIR-7831 = Sotrovimab

On **May 7, 2021 EMA** starts **rolling review of VIR-7831**, called now **sotrovimab** [214]. 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.

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

keine Resistenzen

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, 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), as well as against variants of interest according to the new EUA revision issued in November 2021 [215].

Table 3.2-5: Pseudovirus neutralization data for SARS-CoV-2 variant substitutions with sotrovimab

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 (Colombia)	R346K, E484K, N501Y	No change

No change: <5-fold reduction in susceptibility; **Source**: [215]

US COVID-19 Treatment Guidelines (last update October 19, 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 and they may change based on circulating variants):

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

Bamlanivimab plus etesevimab *or* Casirivimab plus imdevimab; *or* Sotrovimab 500 mg intravenous (IV) infusion [122].

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 [216] published as **preprint,** and then in **scientific journal** [217] preplanned **interim analysis** from ongoing, multicenter, double-blind, **phase 3** trial (NCT04545060, **COMET-ICE trial**), 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

3.2.13.5 Regdanvimab (CT-P59, Regkirona)

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 [218].

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

Regulatory update:

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

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

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 [219, 220].

Okt. 2021: EMA Zulassungsantrag

On **October 04, 2021 EMA** has **started evaluating an application for** marketing authorisation for the monoclonal antibody Regkirona (regdanvimab, also known as CT-P59) to **treat adults with COVID-19 who do not require supplemental oxygen therapy and who are at increased risk of progressing to severe COVID 19**. The applicant is Celltrion Healthcare Hungary Kft [221]. On **November 11, 2021** EMA's human medicines committee (**CHMP**) has **recommended authorising Regkirona** for this indication, https://www.ema.europa.eu/en/news/covid-19-ema-recommends-authorisation-two-monoclonal-antibody-medicines.

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 [222] 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=

3.2.14 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.**

3.2.15 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.

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 [223].

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

Withdrawn, suspended or terminated studies

No withdrawn, suspended or terminated studies related to solnatide in COVID-19 patients were found in ClinicalTrials.gov and EUdraCT registers [223].

ClinicalTrials.gov & EUdraCT: keine klinischen Studien registriert,

Results of publications

keine Publikation von RCT

No publications related to the RCTs of solnatide in COVID-19 patients were found [223].

3.2.16 Umifenovir (Arbidol®)

The reader is referred to the earlier version (V17_August and September 2021) for more details on **umifenovir (Arbidol).**

Verweis auf v17

3.2.17 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

3.2.17.1 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 [229].

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 [230]. 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 [231]. On August 10, 2021 results are published in scientific article [232]. 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 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.

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

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 3.2-6 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 3.2-6: 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

3.2.18 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** [233].

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 [148].

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 [174].

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 [234]. 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 [235] (**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

As described in Sarilumab Section, **Derde et al. 2021** published **final results** as preprint [143] 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.

Anakinra zeigte keine Wirksamkeit

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 3.2-7 (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) [236].

RCT:
negative Ergebnisse bei Pts. mit Lungenversagen und niedrigem SOFA

Declercq et al. 2021 [137] published negative results from prospective, multicentre, open-label, randomised, controlled trial, in **hospitalised** patients with **COVID-19, hypoxia, and signs of a cytokine release syndrome across** 16 hospitals in Belgium (**NCT04330638, EudraCT 2020-001500-41**). The **COV-AID trial** has a 2×2 factorial design to evaluate IL-1 blockade versus no IL-1 blockade and IL-6 blockade versus no IL-6 blockade. Patients were randomly assigned by means of permuted block randomisation with varying block size and stratification by centre. In a first randomisation, patients were assigned to receive subcutaneous **anakinra** once daily (100 mg) for 28 days or until discharge, or to receive no IL-1 blockade (1:2). In a second randomisation step, patients were allocated to receive a single dose of siltuximab (11 mg/kg) intravenously, or a single dose of tocilizumab (8 mg/kg) intravenously, or to receive no IL-6 blockade (1:1:1). The primary outcome was the time to clinical improvement, defined as time from randomisation to an increase of at least two points on a 6-category ordinal scale or to discharge from hospital alive. The primary and supportive efficacy endpoints were assessed in the intention-to-treat population. Safety was assessed in the safety population. Drugs

targeting IL-1 or IL-6 did not shorten the time to clinical improvement in this sample of patients with COVID-19, hypoxic respiratory failure, low SOFA score, and low baseline mortality risk.

*Table 3.2-7: 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: [237];-**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 [234] c [235] ; d Imprecision: Very serious due to very wide confidence interval consistent with the possibility for benefit and the possibility for harm; e [143, 234] 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.

3.2.19 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)** [122].

US COVID-19 Treatment Guidelines Panel insuffiziente Datenlage

There is **insufficient evidence** for the COVID-19 Treatment Guidelines Panel to **recommend either for or against** the use of colchicine for the treatment of **nonhospitalized patients** with COVID-19.

Results of publications

Non-hospitalised patients

Tardif et al. 2021 [238] 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 [238]. 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

PRINCIPLE Trial Collaborative Group published as preprint [239] **negative results** from prospective, multicentre, open-label, multi-arm, adaptive platform randomised trial of treatments in the community for epidemic and pandemic illnesses (**PRINCIPLE**, ISRCTN86534580). Colchicine did not improve time to recovery in **outpatients** at **higher risk** of complications with COVID-19. COVID-19 related hospitalisations/deaths were similar in the colchicine group versus usual care, with an estimated odds ratio of 0.76 [0.28 to 1.89] and an estimated difference of -0.4% [-2.7% to 2.4]. One serious adverse event occurred in the colchicine group and one in usual care.

PRINCIPLE RCT: negative Ergebnisse bei ambulanten Pts. mit hohem Risiko

3.2.20 Nafamostat (Futhan©)

The reader is referred to the earlier version (V17_August and September 2021) for more details on nafamostat (Futhan).

Details in v17

Zhuravel et al. 2021 [240] published results from a **phase 2** open-label, randomised, multicentre, controlled trial (NCT04623021) that evaluated nafamostat (4.8 mg/kg/ day) plus standard-of-care (SOC) in hospitalised patients with COVID-19 pneumonia (i.e., those requiring nasal high-flow oxygen therapy and/or non-invasive mechanical ventilation). The primary outcome was the time to clinical improvement. Key secondary outcomes included the time to recovery, rates of recovery and National Early Warning

Phase 2 (Russland)
104 hospitalisierte Pts. mit Lungenentzündung und Bedarf an nicht-invasiver Beatmung

Score (NEWS). A total of 104 patients, mean age 58.6 years were enrolled in 13 clinical centres in Russia between 25/9/2020 and 14/11/2020 and randomised to nafamostat plus SOC (n=53) or SOC alone (n=51).

There was no significant difference in time to clinical improvement (primary endpoint) between the nafamostat and SOC groups (median 11 [interquartile range (IQR) 9 to 14) vs 11 [IQR 9 to 14] days; Rate Ratio [RR; the ratio for clinical improvement], 1.00; 95% CI, 0.65 to 1.57; p=0.953). In 36 patients with baseline NEWS ≥7 (high-risk COVID-19 patients requiring oxygen treatment), nafamostat was superior to SOC alone in median time to clinical improvement (11 vs 14 days; RR, 2.89; 95% CI, 1.17 to 7.14; p=0.012). Patients receiving nafamostat in this subgroup had a significantly higher recovery rate compared with SOC alone (61.1% (11/18) vs 11.1 % (2/18) by Day 11, p=0.002). The 28-day mortality was 1.9% (1/52) for nafamostat and 8.0% (4/50) for SOC (95% CI, -17.0 to 3.4; p=0.155). No case of COVID-19 related serious adverse events leading to death was recorded in the patients receiving nafamostat.

wirksam (Mortalität) nur in Subgruppe an Pts. mit Bedarf an Sauerstoff

3.2.21 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 [241, 242].

keine veröffentlichten Studien

1 Phase 2 Studie läuft

3.2.22 Canakinumab

The reader is referred to the earlier version (V17_August and September 2021) for more details on **canakinumab.**

Verweis auf v17

The **US COVID-19 Treatment Guidelines Panel** (update October 19, 2021), **recommends against** the use of **canakinumab** for the treatment of COVID-19, except in a clinical trial **(BIIa)**.

US COVID-19 Treatment Guidelines Panel: Empfehlung gegen canakinumab

3.2.23 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 [246, 247].

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** [248] 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).

Sept 2021: FDA lehnt für Lenzilumab EUA ab

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.

3.2.24 Vitamin D

Verweis auf v17

The reader is referred to the earlier version (V17_August and September 2021) for more details on **Vitamin D.**

3.2.25 Baricitinib (Olumiant)

About the drug under consideration

Januskinase-Inhibitor

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

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 [255, 256].

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) [257].

EMA: keine Zulassung für covid-19

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

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)** [258]. 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.

Juli 2021 Revision der FDA Zulassung:

auch als Monotherapie möglich

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** [259].

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 [122]. The Panel recommends **tofacitinib** as an alternative to **baricitinib** only when baricitinib is not available or not feasible to use **(BIIa)**.

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

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 [122].

Empfehlung gegen eine Kombinationstherapie Baricitinib + Tocilizumab

Withdrawn, suspended or terminated studies

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 [174].

mehrere laufende Studien

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.** [260] 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 3.2-8. 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 [261]: 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.** [262] publised as **pre-print** and on September 3, 2021 **in scientific journal** [263], 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.

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. The results are now posted in **preprint article** by **Ely et al. 2021** [264]. In this sub-study, in **patients with COVID-19 on mechanical ventilation or extracorporeal membrane oxygenation (ECMO) who received baricitinib plus standard of care** (baseline systemic corticosteroid use in 86% of participants) **all-cause mortality at day 28 was significantly reduced** (39·2% vs 58·0%; hazard ratio [HR]=0·54 [95%CI 0·31–0·96]; p=0·030). One additional death was prevented for every six baricitinib-treated participants. **Significant reduction in 60-day mortality** was also observed (45·1% vs 62·0%; HR=0·56 [95%CI 0·33–0·97]; p=0·027). Baricitinib-treated participants showed numerically more ventilator-free days (8.1 vs 5.5 days, p=0.21) and spent over 2 days less in the hospital than placebo-treated participants (23·7 vs 26·1 days, p=0·050).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 [264, 265].

SoF: moderate Sicherheit, dass Baricitinib Mortalität senkt

Summary of Findings Table 3.2-9 related to these 2 articles mentioned above, can be found below. In Summary, baricitinib probably reduce All-cause mortality at Day28 (RR 0.62, 95% CI 0.46 to 0.83, moderate certainty of evidence) and may reduce All-cause mortality at Day60 (RR 0.69, 95% CI 0.56 to 0.86, low certainty of evidence) compared to placebo. Baricitinib monotherapy compared to placebo probably does not increase clinical improvement (RR 1.00, 95% CI 0.95 to 1.05, moderate certainty of evidence). Evidence is uncertain on further outcomes: baricitinib may decrease WHO progression score level 7 or above (RR 0.82, 95% CI 0.64 to 1.04, low certainty of evidence), and may not increase Adverse events (RR 0.96, 95% CI 0.88 to 1.05, low certainty of evidence) and Serious adverse events (RR 0.77, 95% CI 0.64 to 0.94, low certainty of evidence).

*Table 3.2-8: 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

*Table 3.2-9: Summary of findings table, on **baricitinib monotherapy vs placebo in hospitalised COVID-19 patients** (Marconi 2021, Ely 2021)*

Baricitinib vs Placebo in Hospitalised patients, last update 03/11/2021, details on https://covid-nma.com/living_data/index.php?allcomp#comparisons_div

Patient or population: COVID-19 patients **Setting**: Worldwide **Intervention**: Baricitinib **Comparison**: Placebo

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of evidence	Comments
	Risk with Placebo	Risk with Baricitinib				
All-cause mortality D28	131 per 1000	81 per 1000	**RR: 0.62** (0.46 - 0.83)	1525 (1 RCT)	⊕⊕⊕◯ MODERATE	**Absolute effect (95% CI) 50 fewer per 1000** (from 71 fewer to 22 fewer)
All-cause mortality D60	181 per 1000	125 per 1000	**RR: 0.69** (0.56 - 0.86)	1626 (2 RCTs)	⊕⊕◯◯ LOW	**Absolute effect (95% CI) 56 more per 1000** (from 80 fewer to 25 fewer)
Clinical improvement D28	778 per 1000	778 per 1000	**RR: 1.00** (0.95 - 1.05)	1525 (1 RCT)	⊕⊕⊕◯ MODERATE	**Absolute effect (95% CI) 0 fewer per 1000** (from 39fewer to 39 more)
WHO progression score (level 7 or above) D28	167 per 1000	137 per 1000	**RR: 0.82** (0.64 - 1.04)	1525 (1 RCT)	⊕⊕◯◯ LOW	**30 fewer per 1000** (from 60 fewer to 7 more)
Number of patients with any adverse event	470 per 1000	451 per 1000	**RR: 0.96** (0.88 - 1.05)	1626 (2 RCTs)	⊕⊕◯◯ LOW	**Absolute effect (95% CI) 19 fewer per 1000** (from 56 fewer to 23 more)
Number of patients with serious adverse events	210 per 100	161 per 1000	**RR: 0.77** (0.64 - 0.94)	1626 (2 RCTs)	⊕⊕◯◯ LOW	**Absolute effect (95% CI) 48 fewer per 1000** (from 75 fewer to 13 fewer)

3.2.26 Molnupiravir

About the drug under consideration

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 [266, 267].

antivirales Medikament ähnlich Remdesivir aber orale Verabreichung

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 [267].

frühere Verabreichung zu Hause daher möglich

hospitalisierte, aber auch milde und moderate Erkrankung

Molnupiravir is not approved by the European Medicines Agency (EMA) or the American Food and Drug Administration (FDA) [267].

weder von EMA noch FDA zugelassen

On **October 25, 2021** EMA's human medicines committee **(CHMP)** has started a **rolling review of molnupiravir** (also known as MK 4482 or Lagevrio), developed by Merck Sharp & Dohme in collaboration with Ridgeback Biotherapeutics for the **treatment of COVID-19 in adults** [268].

Okt 2021: EMA beginnt Rolling Review

Furthermore, on November 8, 2021, EMA starts review to support possible national decisions on early use of molnupiravir prior to its authorisation, https://www.ema.europa.eu/en/news/covid-19-ema-heads-medicines-agencies-update-molnupiravir.

Withdrawn, suspended or terminated studies

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

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/.

Sept 2021: Phase 3 MOVe-AHEAD mit 1.332 Pts gestartet

Results of publications

There are one published RCT (as preprint) related to effectiveness and safety of molnupiravir for Covid-19 (NCT04405570).

keine RCTs derzeit in Phase 1/ 2

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** [269]. 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

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 (NCT04575597, MOVe-OUT) and hospitalised patients (NCT04575584, 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.

Okt 2021:
Interim Analyse von Phase 3 MOVe-OUT,
775 Pts.

hohe relative Reduktion der Hospitaliserung

On **October 01, 2021 Manufacturer announced** that molnupiravir significantly reduced the risk of hospitalization or death at a planned **interim analysis on 775 patients** initially enroled in the **phase 3 MOVe-OUT trial**: 7.3% of patients who received molnupiravir were either hospitalized or died through Day 29 following randomization (28/385), compared with 14.1% of placebo-treated patients (53/377); p=0.0012. Through Day 29, no deaths were reported in patients who received molnupiravir, as compared to 8 deaths in patients who received placebo. At the recommendation of an independent Data Monitoring Committee and in consultation with the U.S. Food and Drug Administration (FDA), recruitment into the study is being stopped early due to these positive results, https://www.merck.com/news/merck-and-ridgebacks-investigational-oral-antiviral-molnupiravir-reduced-the-risk-of-hospitalization-or-death-by-approximately-50-percent-compared-to-placebo-for-patients-with-mild-or-moderat/. The incidence of any adverse event and the incidence of drug-related adverse events were comparable in the molnupiravir and placebo groups.

3.2.27 Ivermectin

The reader is referred to the earlier versions (V15_June 2021 and V17_August and September 2021) for more details on ivermectin treatment in COVID-19 patients.

Verweis auf v15

The **US COVID-19 Treatment Guidelines Panel** Statement (February 11, 2021) [148] [122] 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** [270, 271] 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)

3.2.28 Aspirin

The reader is referred to the earlier version (V17_August and September 2021) for more details on **Aspirin.**

Verweis auf v17

3.2.29 Aviptadil (Zysami)

The reader is referred to the earlier version (V17_August and September 2021) for more details on **aviptadil (Zysami).**

Verweis auf v17

3.2.30 Dimethyl fumarate

The reader is referred to the earlier version (V17_August and September 2021) for more details on **dimethyl fumarate.**

Verweis auf v17

3.2.31 Artesunate

The reader is referred to the earlier version (V17_August and September 2021) for more details on **artesunate.**

Verweis auf v17

3.2.32 Tofacitinib (Xeljanz)

About the drug under consideration

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 [288].

JAK-Inhibitor

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

ev. Verbesserung der entzündungsbedingten Lungenschädigung bei hospitalisierten Patient*innen

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

The **US COVID-19 Treatment Guidelines Panel** Statement (August 25, 2021) [122] is: the Panel recommends **tofacitinib** as an alternative to **baricitinib** only when baricitinib is not available or not feasible to use **(BIIa)** for recently hospitalised patients with rapidly increasing oxygen needs and systemic inflammation (see Section on baricitinib).

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

Withdrawn, suspended or terminated studies

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

Results of publications

Guimaraes et al. 2021 [289] 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

RCT
STOP-COVID
289 hospitalisierte Pts.

bessere Ergebnisse bei Überleben und Atemwegsversagen

Nebenwirkungen

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).

3.2.33 Fluvoxamine

The reader is referred to the earlier version (V17_August and September 2021) for more details on **fluvoxamine.**

Verweis auf v17

3.2.34 PF-07321332; ritonavir (Paxlovid)

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 [293].

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. One **phase 3** RCT (**NCT05047601**)

Phase 1:
Studie zur Sicherheit

Phase 2/3:
an nicht-hospitalisierten Pts.

PF-07321332/ ritonavir

auch Post-Exposure Prophylaxe

evaluates effectiveness and safety of **PF-07321332/ritonavir** in **post-exposure prophylaxis.**

Results of publications

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

Nov 2021: Firmenkommunikation zu Interim-Analyse von Phase 2/3 EPIC-HR an ambulanten Pts mit hohem Risiko für Progression

89% (relative) Reduktion des Risiko für Hospitalisierung und Tod

On **November 05, 2021** Pfizer **announced** that its investigational novel COVID-19 oral antiviral candidate, **PAXLOVID™**, significantly reduced hospitalisation and death, based on an **interim analysis of the phase 2/3 EPIC-HR** (**E**valuation of **P**rotease **I**nhibition for **C**OVID-19 in **H**igh-**R**isk Patients, **NCT04960202**) randomized, double-blind study of **non-hospitalised adult patients** with COVID-19, who are **at high risk of progressing to severe illness**. The scheduled interim analysis showed an **89% reduction in risk of COVID-19-related hospitalisation or death from any cause compared to placebo** in patients treated within three days of symptom onset (primary endpoint); 0.8% of patients who received PAXLOVID™ were hospitalised through Day 28 following randomization (3/389 hospitalised with no deaths), compared to 7.0% of patients who received placebo and were hospitalised or died (27/385 hospitalised with 7 subsequent deaths) ($p<0.0001$). Similar reductions in COVID-19-related hospitalisation or death were observed in patients treated within five days of symptom onset; 1.0% of patients who received PAXLOVID™ were hospitalised through Day 28 following randomization (6/607 hospitalised, with no deaths), compared to 6.7% of patients who received a placebo (41/612 hospitalised with 10 subsequent deaths), $p<0.0001$. In the overall study population through Day 28, no deaths were reported in patients who received PAXLOVID™ as compared to 10 (1.6%) deaths in patients who received placebo.

Pfizer plant EUA (FDA) Einreichung

Pfizer will cease further enrollment into the study (according the recommendation of an independent Data Monitoring Committee and in consultation with the FDA), and plans to submit the data as part of its ongoing rolling submission to the U.S. FDA for Emergency Use Authorization (EUA) as soon as possible [294].

3.2.35 AT-527

About the drug under consideration

antivirales Medikament für HepC entwickelt

AT-527 is a a guanosine nucleotide analogue, a small molecule broad-spectrum antiviral against RNA viruses, which was initially developed to treat hepatitis C infection (flavivirus). It is administered orally as a pro-drug, which inside the cell is converted by phosphorylation into its active form (AT-9010). The compound interferes with the activity of the viral enzyme, which is carrying out the replication of the viral genome, by unique dual mechanisms targeting both RNA dependent RNA polymerase (RdRP) and the nidovirus RdRp-associated nucleotidyltransferase (NiRAN) of viral non-structural protein (nsp12) polymerase [295, 296].

für milde und moderate Covid-19 Erkrankung

AT-527 is being developed for patients with mild to moderate COVID-19. The medicine is administered orally at 550 mg (two tablets) twice daily for five days.

AT-527 is not authorised in Covid-19 patients (EMA, FDA).

Withdrawn, suspended or terminated studies

No withdrawn, suspended or terminated studies were found for AT-527 in COVID-19 patients.

2 laufende Studien: Phase 2 MOONSONG Phase 3 MORNINGSKY

It is now tested in **two phase 2** clinical trials (NCT04396106 and NCT04709835 – MOONSONG trial) for its safety and efficacy [297, 298].

AT-527 is being tested in **one phase 3** global multicenter trial (NCT04889040, MORNINGSKY trial) evaluating efficacy and safety in patients with mild to moderate COVID-19 in outpatient setting; the results are expected in second half of 2022 [299].

Results of publications

kein veröffentlichter RCT

Currently, no published results were found from phase 3 RCTs related to AT-527.

Firmenkommunikation zu Zwischenauswertung (MOONSONG)

Announced by Manufacturer, the **interim analysis** in **phase 2** RCT (NCT04396106) showed a rapid decrease in the virus load (starting on day 2) and faster virus clearance [300].

in HochrisikoPts: rasche Reduktion der Viruslast

On **October 19, 2021** Manufacturer announced results from **phase 2 MOONSONG trial** [301]: study did not meet the primary endpoint of reduction from baseline in the amount of SARS-CoV-2 virus in patients with mild or moderate COVID-19 compared to placebo in the overall study population, of which approximately two thirds of patients were low-risk with mild symptoms. In high-risk patients with underlying health conditions, a reduction of viral load of approximately 0.5 log10 at Day 7 was observed at 550 mg (prespecified subgroup analysis) and 1,100 mg BID (exploratory subgroup analysis) compared with placebo. AT-527 was generally safe and well tolerated. The proportion of patients experiencing any adverse event (AE) was 20% in the placebo group, 20% in the AT-527 550 mg BID group (Cohort A) and 27% in the AT-527 1100 mg BID group (Cohort B). There were 3 non-drug related serious adverse events (SAEs) in each of the treatment groups and all other AEs were grade 1 or 2. Gastrointestinal (GI)-related AEs were the most commonly reported AEs: 8% in the placebo group; 7% in the AT-527 550 mg BID group (Cohort A); 17% in the AT-527 1100 mg BID group (Cohort B), with mild to moderate nausea/vomiting resulting in premature study drug discontinuation of 3% in the placebo group, 0% in the AT-527 550 mg BID group (Cohort A) and 17% in the AT-527 1100 mg BID group (Cohort B). No clinically significant differences in laboratory abnormalities were observed in the treatment arms as compared to placebo.

3.2.36 Plonmarlimab (TJM2)

About the drug under consideration

Inhibitor von Entzündungsreaktionen

Plonmarlimab (or TJM2) was discovered and developed by I-Mab to target human granulocyte-macrophage colony-stimulating factor (GM-CSF), a cytokine that plays a critical role in acute and chronic inflammation. Plonmarlimab specifically binds to human GM-CSF with high affinity and can block GM-CSF from binding to its receptor, thereby preventing downstream signalling and target cell activation. As a result, it can effectively

inhibit inflammatory responses mediated by macrophages, neutrophils, and dendritic cells, leading to reduced tissue inflammation and damage.

Withdrawn, suspended or terminated studies

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

Results of publications

Aug 2021: Firmenkommunikation zu Zwischenauswertung von Phase 2/3, Pts mit schwerer Erkrankung

Höhere Rat von beatmungsfreien Tagen, raschere Erholung

On August 11 2021, Manufacturer I-Mab **announced positive interim data** from its U.S. phase **2/3** double-blind, placebo-controlled, randomized trial (NCT04341116) of plonmarlimab for the treatment of cytokine release syndrome (CRS) in 91 patients with **severe COVID-19**. The study aimed to determine the safety, efficacy and effects on cytokine levels following a single dose of 6 mg/kg of plonmarlimab or placebo in patients with severe COVID-19. Plonmarlimab treatment resulted in a higher mechanical ventilation free (MVF) rate (83.6% vs 76.7%) by day 30, lower mortality rate (4.9% vs 13.3%) by day 30, higher recovery rates (68.9% vs 56.7% at day 14 and 80.3% vs 70.0% at day 30), as well as reduced time to recovery and hospitalisation duration, as compared to placebo. A transient increase in Neutrophil to Lymphocyte Ratio (NLR) that is commonly associated with disease exacerbation was only observed in placebo. Plonmarlimab was well tolerated in all patients with no significant safety concerns [302].

3.2.37 Mavrilimumab

About the drug under consideration

monoklonaler Antikörper

Mavrilimumab is a monoclonal antibody (human isoform lgG4) that binds to GM-CSF receptor alpha and disrupts downstream signalling. Before COVID-19, mavrilimumab was already in study as a potential treatment for giant cell arteritis, a chronic inflammatory disease of medium-large arteries [247, 303, 304].

FDA: Orphan Drug Designation

On September 9, 2020, the U.S. Food and Drug Administration (FDA) granted Orphan Drug designation for mavrilimumab for giant cell arteritis [305]. Kiniksa Pharmaceuticals has received advice from the European Medicines Agency (EMA) during the clinical phase development of mavrilimumab as a potential immunomodulator for COVID-19 [306].

Mavrilimumab has not received approval by the EMA or the FDA for Covid-19 indication.

Withdrawn, suspended or terminated studies

2 laufende RCTs: Phase2 und Phase 2/3

There are two ongoing RCTs evaluating the efficacy of mavrilimumab against placebo in COVID-19 patients according to clinicaltrials.gov: a phase 2 trial (NCT04397497 EudraCT Number: 2020-001795-15) and a large phase 2/3 trial NCT04447469 to be completed in February 2022.

Results of publications

There is one RCT with published results by **Cremer et al. 2021** that compared mavrilimumab against placebo, the **MASH-COVID** study (NCT04399980, NCT04463004, NCT04492514) [307]. The trial was terminated earlier than planned with 40 patients enrolled [308]. Regarding the effectiveness of mavrilimumab, the trial did not find differences between arms for any outcome. Regarding the safety, all patients completed the infusion without reaction, there were not any cases of neutropenia nor bacteraemia, and there were no treatment related deaths. Bacterial pneumonia was diagnosed in one patient who received placebo (5%) and two patients who received mavrilimumab (10%) [307, 309].

RCT MASH-COVID
40 Pts.
frühzeitiger Abbruch

kein Unterschied zwischen den Studienarmen

On April 12, 2021 a **press release** by the pharmaceutical company [310] announced preliminary results of the **phase 2 portion of the largest trial**, in a cohort of non-mechanically-ventilated patients with severe COVID-19 pneumonia and hyperinflammation (n=116). According to the press release: the proportion of patients alive and free of mechanical ventilation at **day 29** was higher in the mavrilimumab group than in the placebo group (86.7% vs. 74.4%; p=0.1224); the mortality rate at day 29 was lower in the mavrilimumab group than in the placebo group (8% vs. 20.5%; p=0.0718); "no apparent differences were observed between the 10 mg/kg and 6 mg/kg IV treatment arms"; and, regarding to safety, "one treatment-emergent serious adverse event related to study drug was reported on placebo", "infections were noted in all groups including placebo recipients" and "all thrombotic events occurred in placebo recipients" [309]. Data are presented also at EULAR 2021 Virtual Congress in June 2021 [311].

April 2021: Firmenkommunikation zu vorläufigen Ergebnissen an schwer Erkrankten von Phase 2 Studie: geringere Mortalität

Follow-up overal survival data from the cohort of non-mechanically ventilated patients through **Day 90** demonstrated persistent clinical effect, confirming and extending the previously-reported Day 29 data. Kiniksa continues to enroll non-mechanically ventilated patients in the **phase 3** clinical trial of mavrilimumab in COVID-19 related ARDS, and expects data in the 1st quarter of 2022 [312].

Phase 3 Ergebnisse in Q1/2022 erwartet

3.2.38 SAB-185

About the drug under consideration

SAB-185 is a fully-human, specifically-targeted, broadly-neutralizing polyclonal antibody therapeutic candidate for the treatment of non-hospitalised patients with mild to moderate COVID-19. It was developed in collaboration with the US government using SAB's novel proprietary DiversitAb™ Rapid Response Antibody Program, as part of the Countermeasures Acceleration Group, formerly Operation Warp Speed. The recent publication of nonclinical data demonstrating SAB-185's potent neutralization of multiple emerging SARS-CoV-2 variants including Delta and Lambda [313]. Preclinical data has also indicated that SAB-185 is significantly more potent than human-derived convalescent immunoglobulin G (IgG).

polyklonaler Antikörper entwicklet in Operation Warp Speed

Withdrawn, suspended or terminated studies

No withdrawn, suspended or terminated studies were found for SAB-185 in COVID-19 patients.

ACTIV-2 , Phase 3
Pts mit milder oder moderater Erkrankung

It is being assessed in the ACTIV-2 trial funded and conducted by the National Institute of Allergy and Infectious Diseases (NIAID), part of the US National Institutes of Health (NIH) in collaboration with the AIDS Clinical Trials Group. SAB-185 advanced to the phase 3 trial based on meeting pre-defined graduation criteria. The phase 3 portion of the ACTIV-2 trial (NCT04518410) is a randomized, unblinded, active comparator-controlled adaptive platform study that assessing the clinical safety and efficacy of SAB-185 compared to active control monoclonal antibody treatment in people with mild to moderate COVID-19 who are at higher risk for progression to hospitalisation, enrolling approximately 600 participants to receive the investigational agent SAB-185 and 600 to receive an active comparator. The primary outcome measures of the phase 3 trial include safety and non-inferiority for the prevention of a composite endpoint of either hospitalisation or death from any cause through study day 28.

Results of publications

kein veröffentlichter RCT

Currently, no published results were found from phase 3 RCTs related to SAB-185 in COVID-19 patients.

Sept/Okt 2021:
Firmenkommunikation
Beginn von ACTIV-2

Announced by Manufacturer on September 24, 2021, both the low and high doses of SAB-185 tested in **phase 2** met the pre-defined efficacy goal for advancement to **phase 3** and appeared safe at the interim analysis [314]. On October 4, 2021 it was announced that the 1st patient has been dosed in the in phase 3 ACTIV-2 trial. The preferred dose to assess is the lower dose of SAB-185 (3,840 Units/kg) [315].

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