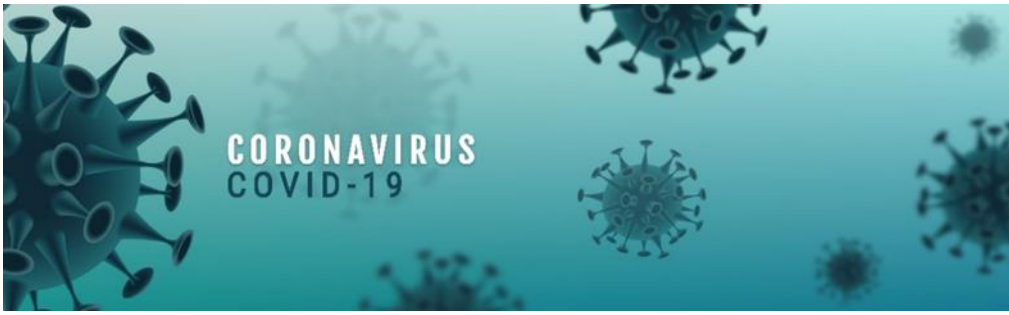
HTA Austria
Austrian Institute for
Health Technology Assessment
GmbH

Covid-19



HSS/ Horizon Scanning

Living Document **V19 December 2021/**

January 2022

HTA Austria
Austrian Institute for
Health Technology Assessment
GmbH

Covid-19

HSS/ Horizon Scanning
Living Document V19 December 2021/ January 2022

Vienna, January 2022

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Dec 2021 / Jan 2022	Addition chapters on Ensovibep (MP0420) (chapter 3.2.39) and Bemcetinib (chapter 3.2.40)
Dec 2021 / Jan 2022	Methodology (1.2) – no changes
Dec 2021 / Jan 2022	Vaccine (chapter 2) – reporting is stopped, see earlier version (V17_August and September 2021) for more details
Dec 2021 / Jan 2022	Update Remdesivir (chapter 3.2.1)
Dec 2021 / Jan 2022	Favipiravir (chapter 3. 2.3) - see earlier version (V17_August and September 2021) for more details
Dec 2021 / Jan 2022	Darunavir (chapter 3. 2.4) – see earlier version (V15_June 2021) for more details
Dec 2021 / Jan 2022	Camostat Mesilate (chapter 3. 2.7) – no changes
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Dec 2021 / Jan 2022	Nafamostat (chapter 3. 2.20) – no changes
Dec 2021 / Jan 2022	Gimsilumab (chapter 3. 2.21) – no changes
Dec 2021 / Jan 2022	Canakinumab (chapter 3. 2.22) – see earlier version (V17_August and September 2021) for more details
Dec 2021 / Jan 2022	Update Lenzilumab (chapter 3. 2.23)
Dec 2021 / Jan 2022	Vitamin D (chapter 3. 2.24) – see earlier version (V17_August and September 2021) for more details
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Dec 2021 / Jan 2022	Aviptadil (RLF-100) (chapter 3. 2.29) – see earlier version (V17_August and September 2021) for more details
Dec 2021 / Jan 2022	Dimethyl fumarate (chapter 3. 2.30) – see earlier version (V17_August and September 2021) for more details
Dec 2021 / Jan 2022	Artesunate (chapter 3. 2.31) – see earlier version (V17_August and September 2021) for more details
Dec 2021 / Jan 2022	Tofacitinib (chapter 3. 2.32) – no changes
Dec 2021 / Jan 2022	Fluvoxamine (chapter 3. 2.33) – see earlier version (V17_August and September 2021) for more details
Dec 2021 / Jan 2022	Update Nirmatrelvir (PF-07321332) and ritonavir – Paxlovid (chapter 3. 2.34)
Dec 2021 / Jan 2022	Update AT-527 (chapter 3.2.35)
Dec 2021 / Jan 2022	Plonmarlimab (TJM2) (chapter 3.2.36) – no changes
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1 Background: policy question and methods

1.1 Policy Question

On March 30th 2020, a request was raised by the Austrian Ministry of Health (BMASGK), the Health Funds of the Regions and the Federation of Social Insurances to set up a Horizon Scanning ystem (HSS) for medicines and vaccines. The establishment of a HSS/ Horizon Scanning System for Covid-19 interventions has the intentions of

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

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

a. informing health policy makers at an early stage which interventions (vaccinations and drugs) are currently undergoing clinical trials and
b. monitoring them over the next few months in order to support evidence-based purchasing, if necessary.

1.2 Methodology

To respond to this request,

mehrstufige Methodik

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

Bestandsaufnahme
selektive Suche
Vignetten
Monitoring

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

internationale/ europ. Zusammenarbeit

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

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

V1-V3: auch laufende Studien - Verweis auf EUnetHTA

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.

ab V4: nur abgeschlossene (oder beendete) Interventionsstudien aus 2 Studienregistern

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

ab V5: nur mehr best verfügbare Evidenz

Table 1.2-1: International Sources

Primary sources	Link
WHO Drugs: Vaccines:	https://www.who.int/teams/blueprint/covid-19 https://www.who.int/blueprint/priority-diseases/key-action/Table_of_therapeutics_Appendix_17022020.pdf?ua=1 https://www.who.int/who-documents-detail/covid-19-candidate-treatments https://www.who.int/who-documents-detail/draft-landscape-of-covid-19-candidate-vaccines
Danish Medicine Agency Drugs: Vaccines:	https://laegemiddelstyrelsen.dk/da/nyheder/temaer/ny-coronavirus-covid-19/~/media/5B83D25935DF43A38FF823E24604AC36.ashx https://laegemiddelstyrelsen.dk/da/nyheder/temaer/ny-coronavirus-covid-19/~/media/3A4B7F16D0924DD8BD157BBE17BFED49.ashx
Pang et al. 2020 [1] Drugs: Vaccines:	https://www.mdpi.com/2077-0383/9/3/623 Table 5+6, Table 3+4
SPS HS-report (UK)	unpublished
Secondary sources	
VfA/ Verband Forschender Arzneimittelhersteller Drugs: Vaccines:	https://www.vfa.de/de/arzneimittel-forschung/woran-wir-forschen/therapeutische-medikamente-gegen-die-coronavirusinfektion-covid-19 https://www.vfa.de/de/arzneimittel-forschung/woran-wir-forschen/impfstoffe-zum-schutz-vor-coronavirus-2019-ncov
EMA/ Europen Medicines Agency Medicines:	https://www.ema.europa.eu/ https://www.ema.europa.eu/en/medicines/medicines-under-evaluation
FDA/US Food and Drug Administration	https://www.fda.gov/emergency-preparedness-and-response/counterterrorism-and-emerging-threats/coronavirus-disease-2019-covid-19
Trial Registries	
US National Library of Medicine European Union Drug Regulating Authorities Clinical Trials Database WHO International Clinical Trials Registry Platform TrialsTracker	https://clinicaltrials.gov/ https://eudract.ema.europa.eu/ https://www.who.int/ictrp/en/ http://Covid-19.trialstracker.net/
Up-to-date information on clinical trials and literature searching resources relating to COVID-19	
Cochrane COVID-19 Study Register 21/04.20	https://covid-19.cochrane.org/
Living mapping of research and a living systematic review	https://covid-nma.com/ https://covid-nma.com/dataviz/
Dynamic meta-analysis of evidences about drug efficacy and safety for COVID19 - meta/Evidence – COVID-19	http://metaevidence.org/COVID19.aspx
CORDITE (CORona Drug InTEractions database)	https://cordite.mathematik.uni-marburg.de/#/
Living listing of interventional clinical trials in Covid-19/2019-nCoV produced by the Anticancer Fund	http://www.redo-project.org/covid19db/; http://www.redo-project.org/covid19_db-summaries/
Global Coronavirus COVID-19 Clinical Trial Tracker	https://www.covid-trials.org/
LitCovid	https://www.ncbi.nlm.nih.gov/research/coronavirus/
UK NIHR Innovation Observatory NIHR COVID-19 Studies COVID-19 Therapeutics Dashboard COVID-19: a living systematic map of the evidence	https://www.nihr.ac.uk/covid-studies/ http://www.io.nihr.ac.uk/report/covid-19-therapeutics/ http://eppi.ioe.ac.uk/cms/Default.aspx?tabid=3765
WHO COVID-19 Database new search interface	https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov
COVID-evidence Database	https://covid-evidence.org/database
Medical Library Association – COVID-19 Literature search strategies	https://www.mlanet.org/page/covid-19-literature-searching
Centre of Evidence Based Dermatology (CEBD) - Coronavirus Dermatology Online Resource	https://www.nottingham.ac.uk/research/groups/cebd/resources/Coronavirus-resource/Coronavirushom
Ovid Expert Searches for COVID-19	http://tools.ovid.com/coronavirus/

EBSCO Covid-19 Portal Literature searching section of portal Information portal	 https://covid-19.ebscomedical.com/research https://covid-19.ebscomedical.com/
NIH COVID-19 Treatment Guidelines. 2020.	https://covid19treatmentguidelines.nih.gov/introduction/
Tertiary sources	
NIPHNO	https://www.fhi.no/en/qk/systematic-reviews-hta/map/
INAHTA	http://www.inahta.org/covid-19-inahta-response/
EUnetHTA Covid-19 Rolling Collaborative Reviews (RCR)	https://eunethta.eu/rcr01-rcrxx/

"lebende" Dokumente mit up-to-date Informationen

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

Kartierung von laufenden RCTs

Boutron et al., 2020 [5] 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).

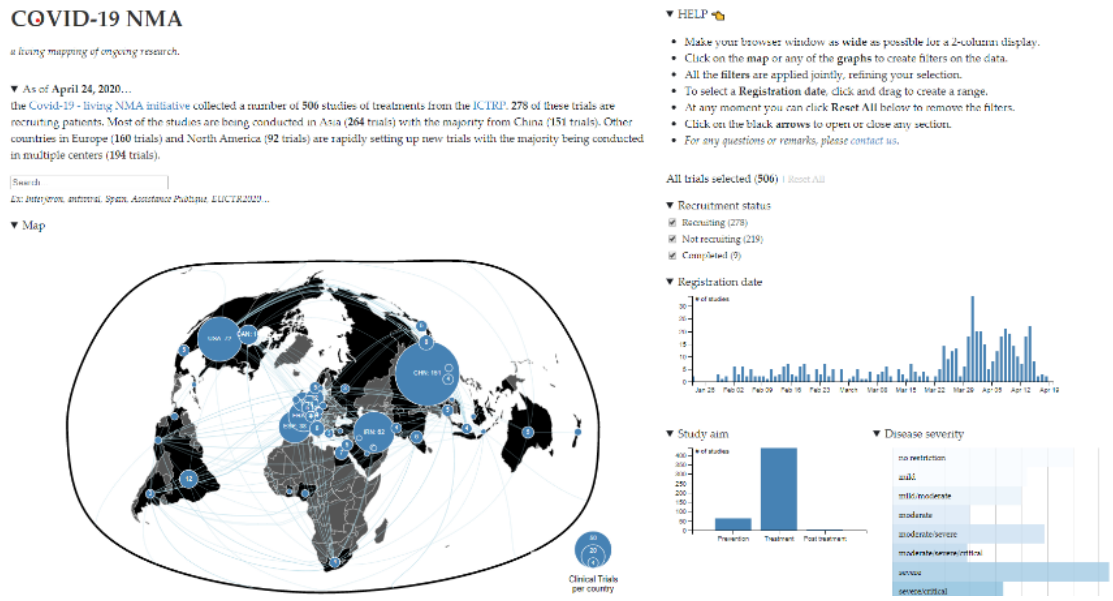

Figure 1.2-1: A living mapping of ongoing randomized trials, living systematic reviews with pairwise meta-analyses and network meta-analyses

Clinical Trial Tracker real-time dashboard

Thorlund et al., 2020 [6] 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 [7].

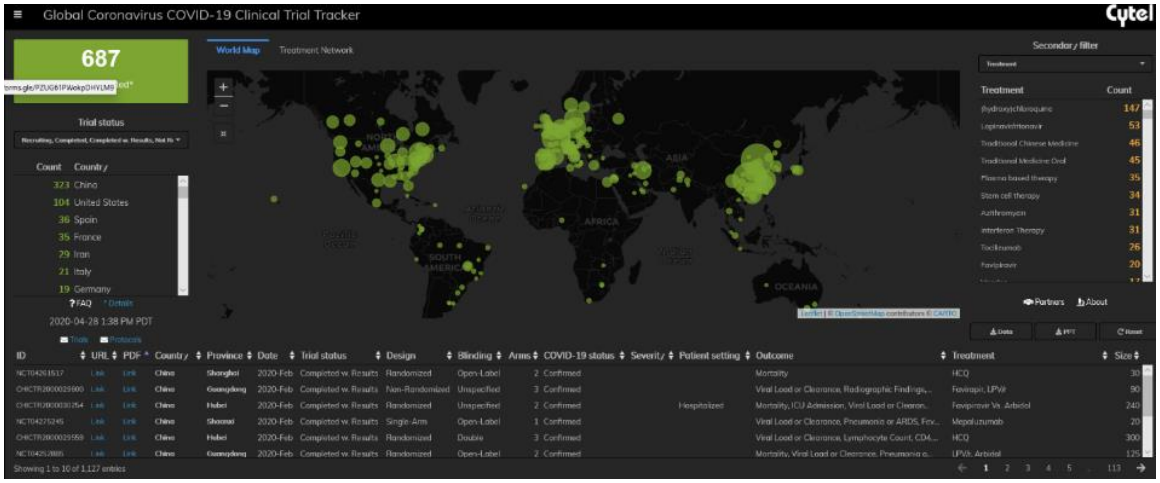

Figure 1.2-2: Global Coronavirus COVID-19 Clinical Trial Tracker - a real-time dashboard of clinical trials for COVID-19

1.3 Selection of Products for "Vignettes"

Vignetten zu Produkten, 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

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

SARS-CoV-2 variants and their susceptibility to anti-SARS-CoV-2 monoclonal antibodies

seit November: Omicron

In **November 2021**, the **Omicron (B.1.1.529) variant** was designated as the **new variant of concern** (VOC): it includes numerous mutations in the spike protein. Ongoing studies are evaluating the susceptibility of this VOC to the anti-SARS-CoV-2 mAbs. **This variant** is predicted to have **markedly reduced susceptibility to some anti-SARS-CoV-2 mAb products,** including **bamlanivimab plus etesevimab and casirivimab plus imdevimab. Sotrovimab** appears to **retain activity against this variant.**

Einfluss auf Wirksamkeit von Antikörper-Therapien

Dez. 2021: US COVID-19 Treatment Guidelines Panel neue Empfehlungen

On **December 30, 2021** the **US COVID-19 Treatment Guidelines Panel** current **outpatient treatment** recommendations are as follows (in order of preference):

- **Paxlovid** (**nirmatrelvir** 300 mg plus ritonavir 100 mg) orally twice daily for 5 days, initiated as soon as possible and within 5 days of symptom onset in those aged ≥12 years and weighing ≥40 kg **(AIIa)**.
- **Xevudy (Sotrovimab)** 500 mg administered as a single intravenous (IV) infusion, administered as soon as possible and within 10 days of symptom onset in those aged ≥12 years and weighing ≥40 kg who live in areas with a high prevalence of the Omicron VOC **(AIIa)**.
- **Veklury (Remdesivir)** 200 mg IV on Day 1 followed by remdesivir 100 mg IV on Days 2 and 3, initiated as soon as possible and within 7 days of symptom onset in those aged ≥12 years and weighing ≥40 kg **(BIIa)**.
- **Lagevrio (Molnupiravir)** 800 mg orally twice daily for 5 days, initiated as soon as possible and within 5 days of symptom onset in those aged ≥18 years **ONLY** when none oft he above options can be used **(CIIa)**.

Paxlovid

Xevudy

Veklury

Lagevrio

Dexamethasone (and other systemic corticosteroids)

derzeitige Therapien im Management von Covid-19 Patient*innen

zugelassen:

Dexamethasone (und andere Korikosteroide)

In **EU, dexamethasone use** is endorsed by **EMA** following referral procedure: it is **indicated** in **adults and adolescents (from 12 years of age and weighing at least 40 kg) who require supplemental oxygen therapy.** In all cases, the recommended dose in adults and adolescents is **6 milligrams once a day for up to 10 days.**

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

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

nicht aber für Pts ohne Beatmung

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

Therapieoptionen für invasiv und auch nicht-invasiv beatmete Pts

In patients who require supplemental oxygen one of the following options for these patients is **recommended**: **Remdesivir** (e.g., for patients who require minimal supplemental oxygen) **(BIIa)**; **Dexamethasone plus remdesivir** (e.g., for patients who require increasing amounts of oxygen) **(BIIb)**; **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**).

Tocilizumab und Sarilumab

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 **December 17 2021** the **CHMP recommended including** the **treatment of adults** who **do not require supplemental oxygen** and who are **at increased risk of progressing to severe COVID-19** to its indication.

Dez 2021: Indikationsausweitung

PRAC: Sinusbradykardie

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.

The **FDA approved** remdesivir for use in **adult and pediatric patients 12 years of age and older** and weighing at least 40 kilograms (about 88 pounds) for the treatment of **COVID-19 requiring hospitalisation.**

von WHO nicht empfohlen

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

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

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

Remdesivir is **recommended for use in hospitalised patients who require supplemental oxygen (BIIa); Dexamethasone plus remdesivir** (e.g., for patient who required increasing amounts of supplemental oxygen) (**BIII**); **Dexamethasone** (e.g., when combination therapy with remdesivir cannot be used or is not available) (**BI**). For hospitalized patients with COVID-19 who require oxygen delivery through a high-flow device or, noninvasive ventilation use one of the following options: **Dexamethasone (AI); Dexamethasone plus remdesivir** (e.g., for patients who require increasing amounts of oxygen) **(BIIb).** 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**).

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

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**).

For the **US COVID-19 Treatment Guidelines** Panel's December 30, 2021 **outpatient treatment** recommendations, see the above subsection related to **SARS-CoV-2 variants and their susceptibility to anti-SARS-CoV-2 monoclonal antibodies.**

Molnupiravir (Lagevrio)

On **November 19, 2021** CHMP has **issued advice** on the use of molnupiravir to **treat adults with COVID-19** who **do not require supplemental oxygen and who are at increased risk of developing severe COVID-19**. Lagevrio should be administered as soon as possible after diagnosis of COVID-19 and within 5 days of the start of symptoms. On **November 23, 2021**, EMA has **started evaluating as application** for **marketing authorisation**. On **December 14, 2021** EMA announced that it is reviewing **new data on effectiveness** of molnupiravir for the treatment of COVID-19.

EMA: in rolling review für mild bis moderat erkrankte Erwachsene, die Risko auf Krankheitsprogression haben

On **December 23, 2021 FDA** issued **EUA** for molnupiravir for **the treatment of mild-to-moderate COVID-19 in certain adults** (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, and **for whom alternative COVID-19 treatment options authorized by the FDA are not accessible or clinically appropriate**).

FDA: Notfallzulassung Dez. 2021: nur wenn andere Theapieoptionen ncht verfügbar sind

For the **US COVID-19 Treatment Guidelines** Panel's December 30, 2021 **outpatient treatment** recommendations, see the above subsection related to **SARS-CoV-2 variants and their susceptibility to anti-SARS-CoV-2 monoclonal antibodies.**

Nirmatrelvir (formerly PF-07321332) and ritonavir (Paxlovid)

On **December 16 2021, EMA issued advice** on use of Paxlovid for the **treatment of COVID-19.** Paxlovid, which is **not yet authorised in the EU**, **can be used** to **treat adults with COVID-19** who **do not require supplemental oxygen and who are at increased risk of progressing to severe disease**. Paxlovid should be administered as soon as possible after diagnosis of COVID-19 and within 5 days of the start of symptoms. On **December 22, 2021** EMA published the **conditions of use** for Paxlovid, following the CHMPs advice on ist use to treat COVID-19. In parallel to the provision of this advice, a more comprehensive **rolling review started** on **13 December 2021 ahead** of **application** for a **conditional marketing authorisation received on January 10, 2022.**

EMA: in rolling review für mild bis moderat erkrankte Erwachsene, die Risko auf Krankheitsprogression haben

On **December 22, 2021 FDA** issued **EUA** for Paxlovid (nirmatrelvir tablets and ritonavir tablets, co-packaged for oral use) for the **treatment of mild-to-moderate coronavirus disease** (COVID-19) in **adults and pediatric patients** (12 years of age and older weighing at least 40 kilograms or about 88 pounds) with **positive results of direct SARS-CoV-2 testing**, and who are at **high risk for progression to severe COVID-19**, including hospitalization or death. It should be initiated as soon as possible after diagnosis of COVID-19 and **within five days of symptom onset**.

FDA: Notfallzulassung Dez. 2021: Therapiebeginn innerhalb von 5 Tagen nach Symptomen

For the **US COVID-19 Treatment Guidelines** Panel's December 30, 2021 **outpatient treatment** recommendations, see the above subsection related to **SARS-CoV-2 variants and their susceptibility to anti-SARS-CoV-2 monoclonal antibodies.**

Baricitinib (Olumiant)

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).**

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

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**).

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

Empfehlung gegen: Baricitinib als Kombinationstherapie mit Tocilizumab

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

The Panel **recommends against** the use of **JAK inhibitors other than baricitinib or tofacitinib** for the treatment of COVID-19, except in a clinical trial **(AIII)**.

andere JAK-Inhibitoren (als Baricitinib und Tofacitinib)

Tofacitinib (Xeljanz)

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

vgl. Text zu Baricitinib

Casirivimab and imdevimab (REGN-COV2, Ronapreve)

FDA: EUA für mild bis moderat Erkrankte, die hohes Risko auf Krankheitsprogression haben

The **FDA** issued an **emergency use auth orization (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.**

Revision von EUA: auch für Post-Prophylaxe

In **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).

Nov 2021 EMA: Marktzulassung für mild bis moderat Erkrankte, die hohes Risko auf Krankheitsprogression haben

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. **Marketing authorisation** is **granted** by EC on **12 November 2021**.

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**.

Wirksamkeit gegen Omicron fraglich

When the Omicron variant represents the majority (e.g., >80%) of infections in a region, it is expected that bamlanivimab plus etesevimab and casirivimab plus imdevimab will not be active for treatment or post-exposure prophylaxis (PEP) of COVID-19.

For the **US COVID-19 Treatment Guidelines** Panel's December 30, 2021 **outpatient treatment** recommendations, see the above subsection related to **SARS-CoV-2 variants and their susceptibility to anti-SARS-CoV-2 monoclonal antibodies.**

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

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

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

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.**

Sotrovimab (Xevudy)

On **December 16 2021 CHMP has recommended authorisation of sotrovimab** 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 the disease becoming severe**. **Marketing authorisation** is **granted** by **EC** on **17 December 2021**.

EMA Marktzulassung Dez 2021 für mild bis moderat Erkrankte, die hohes Risko auf Krankheitsprogression haben

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**.

For the **US COVID-19 Treatment Guidelines** Panel's December 30, 2021 **outpatient treatment** recommendations, see the above subsection related to **SARS-CoV-2 variants and their susceptibility to anti-SARS-CoV-2 monoclonal antibodies.**

Regdanvimab (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 supplemental oxygen therapy and who are at increased risk of progressing to severe COVID 19. Marketing authorisation** is **granted** by **EC** on **12 November 2021**.

EMA Marktzulassung Nov 2021 für mild bis moderat Erkrankte, die hohes Risko auf Krankheitsprogression haben

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**.

seit Okt 2021 EMA Rolling Review, Prä-Exposition Prophylaxe

On **December 8, 2021** the **FDA** issued an emergency use authorisation (**EUA**) for the Evusheld for the **pre-exposure prophylaxis (prevention, PrEP)** of COVID-19 in certain adults and pediatric individuals.

US COVID-19 Treatment Guidelines (last update **January 5**, **2022**)

The Panel recommends using **tixagevimab plus cilgavimab** as SARS-CoV-2 **PrEP** for adults and adolescents (aged ≥12 years and weighing ≥40 kg) who do not have SARS-CoV-2 infection, who have not been recently exposed to an individual with SARS-CoV-2 infection, **AND** who: are moderately to severely immunocompromised and may have an inadequate immune response to

US COVID-19 Treatment Guidelines für Immunsuppremierte

COVID-19 vaccination **(BIIa)**; ***or*** are not able to be fully vaccinated with any available COVID-19 vaccines due to a documented history of severe reactions to a COVID-19 vaccine or any of its components **(AIIa)**.

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

The **US COVID-19 Treatment Guidelines Panel** (last updated December 16, 2021) **recommends against** the use of COVID-19 convalescent plasma for a **treatment of COVID-19 in hospitalised patients without impaired humoral immunity (AI).** There is **insufficient evidence** to recommend **either for or against** it use for the **treatment in nonhospitalised patients without impaired humoral immunity** and for the **treatment in nonhospitalised or hospitalised patients with impaired humoral immunity.**

US COVID-19 Treatment Guidelines und WHO : Empfehlung GEGEN CVP wegen insuffizienter Evidenz, nur in klinischen Studien

Current WHO living guidance (last updated December 6, 2021) on convalescent plasma for COVID-19 has a **strong recommendations against** administering convalescent plasma for the **treatment** of patients **with non-severe COVID-19**. It recommends **against** administering convalescent plasma for the **treatment** of patients **with severe or critical COVID-19 except** in the **context of a clinical trial**.

Tocilizumab (RoActemra)

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 **December 6 2021, CHMP has recommended** proposed **extension of indication** 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)** and **marketing authorisation** is **granted** by **EC** on **December 7, 2021**.

Dez 2021 EMA Indikationsausweitung/ Marktzulassung für hospitalisierte Pts mit nicht Beatmung

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,

ICU, beatmet, etc.

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**).

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 **December 16, 2021, CHMP** recommended **adding the treatment of COVID-19** in **adult patients** with **pneumonia requiring supplemental oxygen (low or high flow oxygen)** and who are **at risk of developing severe respiratory failure** (as determined by blood levels of a protein called suPAR, soluble urokinase plasminogen activator receptor, of at least 6 ng per ml), to its approved indications. Following evaluation by EMA, the **EC authorised** it use to treat COVID-19 on **December 17**, **2021**.

Dez 2021: EMA Marktzulassung für Pts. mit Lungenentzündung und zusätzlichm Sauerstoffbedarf

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®)

Details in V13_April

The reader is referred to the earlier version (V13_April and V18_October/November 2021) for more details on **remdesivir (Veklury).**

Aug 2021: EMA-Verlängerung der konditionalen Zulassung für Pts mit Lungenentzündung und zusätzlichem Sauerstoffbedarf
Dez. 2021: Indikationsausweitung auch für Pts. ohne Sauerstoffbedarf aber hohem Risiko

On August 18, 2021 **EMA** published the clinical data supporting a **renewal** of the **conditional marketing authorisation** for Veklury (remdesivir). 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 **December 17, 2021** the **CHMP recommended extending the use** of remdesivit for the **treatment of adults** who **do not require supplemental oxygen** and who are **at increased risk of progressing to severe COVID-19** to its indication [8].

The US COVID-19 Treatment Guidelines Panel (last update **December 30, 2021**)

This statement contains the Panel's recommendations for treating these **nonhospitalised patients** using the currently available therapies. The Panel's recommendations take into account the efficacies of these drugs and the high prevalence of the B.1.1.529 (Omicron) variant of concern (VOC). When resources are limited, therapy should be prioritized for patients who are at the highest risk of progressing to severe COVID-19.

US COVID-19 Treatment Guidelines Panel: Empfehlunge für ambulante Pts (Rangreihung nach Präferenz)

Paxlovid
Xevudy
Veklury
Lagevrio

The Panel's current **outpatient treatment recommendations** are as follows (in order of preference):

- **Paxlovid** (nirmatrelvir 300 mg plus ritonavir 100 mg) orally twice daily for 5 days, initiated as soon as possible and within 5 days of symptom onset in those aged ≥12 years and weighing ≥40 kg **(AIIa)**
- **Xevudy** (Sotrovimab) 500 mg administered as a single intravenous (IV) infusion, administered as soon as possible and within 10 days of symptom onset in those aged ≥12 years and weighing ≥40 kg who live in areas with a high prevalence of the Omicron VOC **(AIIa)**
- **Veklury** (Remdesivir) 200 mg IV on Day 1 followed by remdesivir 100 mg IV on Days 2 and 3, initiated as soon as possible and within 7 days of symptom onset in those aged ≥12 years and weighing ≥40 kg **(BIIa)**
- **Lagevrio** (Molnupiravir) 800 mg orally twice daily for 5 days, initiated as soon as possible and within 5 days of symptom onset in those aged ≥18 years **ONLY** when none oft he above options can be used **(CIIa)** [9].

Remdesivir in nonhospitalised patients

PINETREE RCT
562 nicht-hospitalisierte Pts. mit Risiko zur Krankheits-Progression

Gottlieb et al. 2021 published positive results from a randomized, double-blind, placebo-controlled trial (**PINETREE**, NCT04501952; EudraCT 2020-003510-12) involving **nonhospitalised patients** with Covid-19 who had symptom onset within the previous 7 days and who had at least one **risk factor for disease progression** (age ≥60 years, obesity, or certain coexisting medical conditions). Patients were randomly assigned to receive intravenous remdesivir (200 mg on day 1 and 100 mg on days 2 and 3) or placebo. The primary efficacy end point was a composite of Covid-19–related hospitalisation or death from any cause by day 28. The primary safety end point was any adverse event. A secondary end point was a composite of a Covid-19–related medically attended visit or death from any cause by day 28. Among nonhospitalised patients who were at high risk for Covid-19 progression, a 3-day course of remdesivir had an acceptable safety profile and resulted in an 87% lower risk of hospitalisation or death than placebo.

A total of 562 patients who underwent randomization and received at least one dose of remdesivir or placebo were included in the analyses: 279 patients in the remdesivir group and 283 in the placebo group. The most common coexisting conditions were diabetes mellitus (61.6%), obesity (55.2%), and hypertension (47.7%). Covid-19–related hospitalisation or death from any cause occurred in 2 patients (0.7%) in the remdesivir group and in 15 (5.3%) in the placebo group (hazard ratio, 0.13; 95% confidence interval [CI], 0.03 to 0.59; p=0.008). A total of 4 of 246 patients (1.6%) in the remdesivir group and 21 of 252 (8.3%) in the placebo group had a Covid-19–related medically attended visit by day 28 (hazard ratio, 0.19; 95% CI, 0.07 to 0.56). No patients had died by day 28. Adverse events occurred in 42.3% of the patients in the remdesivir group and in 46.3% of those in the placebo group [10].

Vorteil bei Hospitalisierung/Tod oder Arztbesuchen

3.2.2 Lopinavir + Ritonavir (Kaletra®)

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.

wegen erwiesenem Mangel an Wirksamkeit wurde Beobachtung beendet

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

3.2.3 Favipiravir (Avigan®)

The reader is referred to the earlier version (V15_June 2021) for more details on favipiravir 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)** [9].

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)** [9].

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

3.2.5 Chloroquine (Resochin®) and

3.2.6 Hydroxychloroquine (Plaquenil®)

wegen erwiesenem Mangel an Wirksamkeit wurde Beobachtung beendet

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

Last reporting V4/ July 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

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

Camostat Mesilate (Foipan®) is classified as a so-called serine protease inhibitor, blocking several pancreatic and plasmatic enzymes like trypsin, thrombin and plasmin [11]. Studies showed effects on the cell-entry mechanism of coronaviruses (e.g. SARS-CoV and SARS-CoV-2) in in-vitro human cells [12, 13] as well as in pathogenic mice-models [14] by inhibiting the enzyme Transmembrane protease, serine 2 (TMPRSS2).

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

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

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 [15].

Withdrawn, suspended or terminated studies

in ClinicalTrials.gov and EUdraCT keine abgeschlossenen klinischen Studien registriert

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.

Results of publications

1 Publikation zu RCT: kein Unterschied zwischen den Gruppen

One scientific publication on a RCT of Camostat Mesilate (Foipan®) in **hospitalised** Covid-19 patients is currently identified. **Gunst et al. 2021** [16] published results from investigator-initiated, double-blind, randomized, placebo-controlled multicenter trial in patients hospitalised with confirmed SARS-CoV-2 infection (NCT04321096, EudraCT 2020-001200-42). Within 48 h of admission, 205 participants were randomly assigned in a 2:1 ratio to receive camostat mesilate 200 mg three times daily for 5 days or placebo. The primary outcome was time to discharge or clinical improvement measured as ≥2 points improvement on a 7-point ordinal scale. Other outcomes included 30-day mortality, safety and change in oropharyngeal viral load. 137 patients were assigned to receive camostat mesilate and 68 to placebo. Median time to clinical improvement was 5 days (interquartile range [IQR], 3 to 7) in the camostat group and 5 days (IQR, 2 to 10) in the placebo group (p= 0.31). The hazard ratio for 30-day mortality in the camostat compared with the placebo group was 0·82 (95% confidence interval [CI], 0.24 to 2.79; p=0.75). The frequency of adverse events was similar in the two groups. Median change in viral load from baseline to day 5 in the camostat group was -0.22 log_{10} copies/mL ($p<0.05$) and -0.82 log_{10} in the placebo group ($p<0.05$).

Hersteller Kommunikation zu klinischer Studie mit 342 mild erkrankten Pts.

raschere Gesundung (-3 Tage)

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

https://www.biospace.com/article/releases/daewoong-pharmaceutical-announces-camostat-achieving-50-percent-faster-recovery-time-for-mild-covid-19-patients-over-age-of-50-in-topline-results-from-phase-2b-clinical-trial/.

3.2.8 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) [17], [18], [19].

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 versions (V14_May 2021 and V18_October and November 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)** [20] .

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

On **December 6 2021, EMA's CHMP** has **recommended extending of indication** of tocilizumab to include the **treatment** of **adults with COVID-19** who are **receiving systemic treatment with corticosteroids and require supplemental oxygen or mechanical ventilation**. **Marketing authorisation** is **granted** by **EC** on **December 7, 2021** [21].

Dez. 2021: EMA Marktzulassung für Ptsmit Sauerstoff-/ Beatmungsbedarf

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 [22].

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

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 [23]. 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

The **US COVID-19 Treatment Guidelines Panel** Statement (last update December 16, 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**, in hospitalised patients who require supplemental oxygen, high-flow oxygen, noninvasive ventilation (NIV), or mechanical ventilation **(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 [22].

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 [24].

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

Withdrawn, suspended or terminated studies

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

Results of publications

Juli 2020: Pressemeldung zu RCT mit 194 Pts

kein Unterschied mehr SAE in Sarilumab Gruppe

Publikation der Ergebnisse März 2021:

keine Unterschiede, negative Ergebnisse

On July 03, 2020 in press release related to sarilumab RCT conducted in US, https://www.clinicaltrialsarena.com/news/kevzara-us-covid19-trial-data/, Sanofi and Regeneron Pharmaceuticals have reported that this phase III clinical trial of sarilumab, compared 400mg dose of the drug plus best supportive care to best supportive care alone, failed to meet its primary and key secondary endpoints in 194 **critically ill Covid-19 patients** who required mechanical ventilation in the US. In the primary analysis arm, adverse events were reported in 80% of patients treated with sarilumab and 77% of those on placebo. Serious adverse events in at least 3% of patients, more frequent among sarilumab patients, were multi-organ dysfunction syndrome and hypotension. Based on the data, the companies have halted this US-based trial, including a second cohort of patients who were on a higher 800mg dose of the drug. The trial being conducted outside of the US was continuing, in hospitalised patients with severe and critical Covid-19 using a different dosing regimen, with published **negative results** in March 2021 by **Lescure et al.** (**NCT04327388, EudraCT 2020-001162-12**)[25] 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 [26](REMAP-CAP, NCT02735707)** published **preliminary report** as preprint, and then in scientific journal [27], 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.

Derde et al. 2021 published **final report** as **preprint** [28] from above mentioned **REMAP-CAP** RCT (**NCT02735707**): Adult participants with **critical COVID-19** were randomized to receive **tocilizumab, sarilumab, anakinra, or standard care (control)**. In addition, a small group (n=21) of participants were randomized to interferon-β1a. The primary outcome was an ordinal scale combining in-hospital mortality (assigned -1) and days free of organ support to day 21. The trial used a Bayesian statistical model with pre-defined triggers for superiority, equivalence or futility. Statistical triggers for equivalence between tocilizumab and sarilumab; and for inferiority of anakinra to the other active interventions were met at a planned adaptive analysis. Of the 2274 critically ill participants enrolled, 972 were assigned to tocilizumab, **485 to sarilumab 400 mg as a single intravenous infusion**, 378 to anakinra and **418 to control**. Median organ support-free days were 7 (interquartile range [IQR] –1, 16), 9 (IQR –1, 17), 0 (IQR –1, 15) and 0 (IQR –1, 15) for tocilizumab, sarilumab, anakinra and control, respectively. Median adjusted odds ratios were 1.46 (95%CrI 1.13, 1.87), 1.50 (95%CrI 1.13, 2.00), and 0.99 (95%CrI 0.74, 1.35) for tocilizumab, sarilumab and anakinra, yielding 99.8%, 99.8% and 46.6% posterior probabilities of superiority, respectively, compared to control. Median adjusted odds ratios for hospital survival were 1.42 (95%CrI 1.05,1.93), 1.51 (95%CrI 1.06, 2.20) and 0.97 (95%CrI 0.66, 1.40) for tocilizumab, sarilumab and anakinra respectively, compared to control, yielding 98.8%, 98.8% and 43.6% posterior probabilities of superiority, respectively, compared to control. All treatments appeared safe. In critical COVID-19, tocilizumab and sarilumab are similarly effective at improving survival and reducing duration of organ support. Anakinra is not effective in this population.

Platform Studie:
REMAP-CAP
2.274 kritsch Erkrankte

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

Sivapalasingam et al. 2021 [29] 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.

Phase 2/ 3 RCT

457 Pts hase 2
1.365 Pts Phase 3

geringfügig bessere Ergebnisse

CORIMUNO-19
Phase 2/3
148 hospitalisierte Pts.

kein Unterschied zwischen den Gruppen bei Mortalität und Nebenwirkungen

kein Vorteil von Sarilumab

The **CORIMUNO-19 Collaborative group, 2021** [30] published negative results from multicentric, open-label, Bayesian randomised, adaptive, **phase 2/3** clinical trial **CORIMUNO-SARI-1** (**NCT04324073**), nested within the CORIMUNO-19 cohort, to test a superiority hypothesis. Patients 18 years or older **hospitalised** with COVID-19 in six French centres, **requiring at least 3L/min of oxygen but without ventilation assistance and a WHO Clinical Progression Scale [CPS] score of 5** were enrolled. 148 patients were randomly assigned (1:1) via a web-based system, according to a randomisation list stratified on centre and with blocks randomly selected among 2 and 4, to receive usual care plus 400 mg of sarilumab intravenously on day 1 and on day 3 if clinically indicated (sarilumab group, n=68) or usual care alone (usual care group, n=80). Primary outcomes were the proportion of patients with WHO-CPS scores greater than 5 on the 10-point scale on day 4 and survival without invasive or non-invasive ventilation at day 14. 18 (26%) of 68 patients in the sarilumab group had a WHO-CPS score greater than 5 at day 4 versus 20 (26%) of 76 in the usual care group (median posterior absolute risk difference 0.2%; 90% credible interval [CrI] −11.7 to 12.2), with a posterior probability of absolute risk difference greater than 0 of 48.9%. At day 14, 25 (37%) patients in the sarilumab and 26 (34%) patients in the usual care group needed ventilation or died, (median posterior hazard ratio [HR] 1.10; 90% CrI 0.69–1.74) with a posterior probability HR greater than 1 of 3.4%. Serious adverse events occurred in 27 (40%) patients in the sarilumab group and 28 (37%) patients in the usual care group (p=0.73). Sarilumab treatment did not improve early outcomes in patients with moderate-to-severe COVID-19 pneumonia.

Phase 2 RCT
115 hospitalisierte Pts

kein Unterschied zwischen den Gruppen bei akutem Lungenversagen

kein Vorteil von Sarilumab

Merchante et al. 2021 [31] published negative results from **phase 2**, open-label, RCT of hospitalised patients with COVID-19 pneumonia and interleukin (IL)-6 levels ≥ 40 pg/mL and/or D-dimer > 1500 ng/mL (**SARICOR, EudraCT 2020-001531-27; NCT04357860**). Participants were randomized (1:1:1) to receive SOC (control group), SOC plus a single subcutaneous dose of sarilumab 200 mg (Sarilumab-200) or SOC plus a single subcutaneous dose of sarilumab 400 mg (Sarilumab-400). The primary outcome variable was the development of acute respiratory distress syndrome (ARDS) requiring high-flow nasal oxygenation (HFNO), non-invasive mechanical ventilation (NIMV) or invasive mechanical ventilation (IMV) at day 28. One-hundred and fifteen participants (control group, n=39; Sarilumab-200, n=37; Sarilumab-400, n=39) were included. At randomization, 104 (90%) patients had supplemental oxygen and 103 (90%) received corticosteroids. Eleven (28%) patients in the control group, ten (27%) in Sarilumab-200 and five (13%) in Sarilumab-400 developed the primary outcome (hazard ratio [95% CI] of Sarilumab-400 vs control group: 0.41 [0.14-1.18]; p=0.09). Seven (6%) patients died: three in the control group and four in Sarilumab-200. There were no deaths in Sarilumab-400 (p=0.079, log-rank test for comparisons with the control group).

SARTRE Phase 3 RCT
201 hospitalisierte Pts.

kein Unterschied zwischen den Gruppen bei aktum Lungenversagen

kein Vorteil von Sarilumab

Sancho-Lopez et al. 2021 [32] published negative results from **phase 3**, RCT (**SARTRE**, **EudraCT 2020-002037-15**), in which 201 patients underwent randomization: 99 patients in the sarilumab group and 102 patients in the control group. The rate of patients progressing to severe respiratory failure (Brescia-COVID scale score C 3) up to day 15 was 16.16% in the Sarilumab group versus 15.69% in the control group (RR 1.03; 95% CI 0.48–2.20). No relevant safety issues were identified. Authors concluded that in hospitalised patients with Covid-19 pneumonia, who were under standard oxygen therapy and who presented analytical inflammatory parameters, an early therapeutic intervention with sarilumab plus standard of care (including corticosteroids) was not shown to be more effective than current standard of care alone.

SoF von 9 RCTS: unsichere Evidenz zu Sarilumab zu allen Endpunkten

Summary of finding Table 3.2-1 related to RCTs mentioned above and some additional non-published trials can be found below (last update 09/12/2021), 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 0.89, 95% CI 0.66 to 1.18, 8 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 1.09, 95% CI 0.73 to 1.63, 5 RCTs, low certainty of evidence), Clinical improvement D28 (RR 0.99, 95% CI 0.93 to 1.05, 6 RCTs) and AEs (RR 1.08, 95% CI 0.99 to 1.17, 4 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.

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 09/12/2021), details on https://covid-nma.com/living_data/index.php?allcomp#comparisons_div

Patient or population: Hospitalised (Moderate/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	234 per 1000	208 per 1000	**RR: 0.89** (0.66 - 1.18)	2781 (8 RCTs)[b]	⊕⊕◯◯ LOW[h]	**Absolute effect (95% CI) 26 fewer per 1000** (from 79 fewer to 42 more)
All-cause mortality D60	297 per 1000	279 per 1000	**RR: 0.94** (0.84 - 1.06)	3365 (7 RCTs)[c]	⊕◯◯◯ VERY LOW[i]	**Absolute effect (95% CI) 18 fewer per 1000** (from 48 fewer to 18 more)
Clinical improvement D28	661 per 1000	655 per 1000	**RR: 0.99** (0.93 - 1.05)	1901 (6 RCTs)[d]	⊕⊕◯◯ LOW[j]	**Absolute effect (95% CI) 7 fewer per 1000** (from 46 fewer to 33 more)
WHO progression score (level 7 or above) D28	142 per 1000	155 per 1000	**RR: 1.09** (0.73 - 1.63)	571 (5 RCTs)[e]	⊕⊕◯◯ LOW[k]	**Absolute effect (95% CI) 13 more per 1000** (from 38 fewer to 90 more)
Number of patients with any adverse event	498 per 1000	538 per 1000	**RR: 1.08** (0.99 - 1.17)	2408 (4 RCTs)[f]	⊕⊕◯◯ LOW[l]	**Absolute effect (95% CI) 40 more per 1000** (from 5 fewer to 85 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) g	⊕◯◯◯ VERY LOW m	**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); b Lescure FX, 2021; Gordon AC, REMAP-CAP, 2021, Sivapalasingam S, 2021 (2)SARICOR, 2021; SARCOVID, 2021; CORIMUNO-SARI, 2021; CORIMUNO-SARI (ICU), 2021; Sancho-Lopez A, 2021; c Lescure FX, 2021; Sivapalasingam S, 2021 (1); Sivapalasingam S, 2021(2); Derde L, 2021; SARCOVID, 2021; CORIMUNO-SARI, 2021; CORIMUNO-SARI (ICU), 2021 ; d Sivapalasingam S, 2021 (2); SARICOR, 2021; SARCOVID, 2021; Sancho-Lopez A, 2021; CORIMUNO-SARI, 2021; CORIMUNO-SARI (ICU), 2021; e SARICOR, 2021; SARCOVID, 2021; Sancho-Lopez A, 2021; CORIMUNO-SARI, 2021; CORIMUNO-SARI (ICU), 2021; f Lescure FX, 2021;Sivapalasingam S, 2021 (1); Sivapalasingam S, 2021 (2); Sacho-Lopez A, 2021; g Lescure FX, 2021; Gordon AC, REMAP-CAP, 2021; Sivapalasingam S, 2021(1); Sivapalasingam S, 2021 (2); SARICOR, 2021; SARCOVID, 2021; SARTRE, 2021; CORIMUNO-SARI, 2021; CARIMUNO-SARI (ICU), 2021; h Imprecision: Very serious Imprecision downgraded by 2 level: due to wide confidence interval consistent with the possibility for benefit and the possibility for harm low number of participants; I Risk of bias: Serious Risk of bias downgraded by 1 level: some concerns regarding adequate randomization, deviation from intended intervention, missing data and selection of reported results Imprecision: Very serious Imprecision downgraded by 2 level: due to wide confidence interval consistent with the possibility for benefit and the possibility for harm and low number of participants; j Risk of bias: Serious Risk of bias downgraded by 1 level: some concerns regarding adequate randomization, deviation from intended intervention, missing data, outcome measurement and selection of the reported results Imprecision: Serious due to low number of participants; k 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; l Risk of bias: Serious. Risk of bias downgraded by 1 level: some concerns regarding adequate randomization, missing data, outcome measurement, and selection of reported results Imprecision: Serious due to low number of participants; m Risk of bias: Serious Risk of bias downgraded by 1 level: some concerns regarding adequate randomization, deviation from intended intervention, missing data and outcome measurement Imprecision: Very serious Imprecision downgraded by 2 level: due to wide confidence interval consistent with the possibility for no effect and the possibility for harm and low number of participants.

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

The reader is referred to the earlier version (V18_October and November 2021) for more details on **interferons.**

Empfehlung des US COVID-19 Treatment Guidelines Panel GEGEN INF-Therapie, nur in klinischen Studien

The **US COVID-19 Treatment Guidelines Panel** (last update December 16, 2021) [33] **recommends against** the use of **systemic interferon beta** for the treatment of **hospitalised patients** with COVID-19 **(AI).** The Panel **recommends against** the use of **interferon alfa** or **lambda** for the treatment of **hospitalised patients** with COVID-19, except in a clinical trial **(AIIa)**. The Panel **recommends against** the use of **interferons** for the treatment of **nonhospitalised patients** with mild or moderate COVID-19, except in a clinical trial **(AIIa)**.

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 [34]. 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 und WHO:

Empfehlung GEGEN CVP

The **US COVID-19 Treatment Guidelines Panel** (last update December 16, 2021) **recommends against** the use of COVID-19 convalescent plasma for a **treatment of COVID-19 in hospitalised patients without impaired humoral immunity (AI).** There is **insufficient evidence** to recommend **either for or against** it use for the **treatment in nonhospitalised patients without impaired humoral immunity** and for the **treatment in nonhospitalised or hospitalised patients with impaired humoral immunity.**

Current WHO living guidance (last updated December 6, 2021) on convalescent plasma for COVID-19 has a **strong recommendations against** administering convalescent plasma for the **treatment** of patients **with non-severe COVID-19**. It recommends **against** administering convalescent plasma for the **treatment** of patients **with severe or critical COVID-19 except** in the **context of a clinical trial** [35].

3.2.13 Plasma derived medicinal products

Neutralizing monoclonal antibodies

neutralisierende monoklonale Antikörper: Prävention und Behandlung

As Marovich et al. 2020 [36] stated, **neutralizing monoclonal antibodies** to SARS-CoV-2 have the potential to be used for both prevention and treatment of infection. They can help to guide vaccine design and development as well. The main target of SARS-CoV-2 neutralizing monoclonal antibodies is the surface spike glycoprotein that mediates viral entry into host cells. Some products will include of a combination of 2 monoclonal antibodies targeting different sites on the spike protein. Due to long half-life of most monoclonal antibodies (approximately 3 weeks for IgG1), a single infusion should be sufficient. A potential limitation of monoclonal antibodies for treatment of COVID-19 is the unknown bioavailability of passively infused IgG in tissues affected by the disease, especially the lungs, which serve as a key target of SARS-CoV-2 infection. Due to the effect of viral diversity it will be important to monitor for the emergence of resistant viral mutations under selective pressure of monoclonal antibody treatment.

Halbwertszeit bis 3 Wochen von Vorteil

Nachteil: unbekannte Bioverfügbarkeit der infundierten Antikörper

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 [36].

SARS-CoV-2 variants and their susceptibility to anti-SARS-CoV-2 monoclonal antibodies

Wirksamkeit von Antikörper Therapien bei Virus-Varianten: Laborstudien

In laboratory studies, some SARS-CoV-2 variants that harbor certain mutations have markedly reduced susceptibility to a number of the authorized anti-SARS-CoV-2 mAbs. The clinical relevance of reduced in vitro susceptibility of select variants to anti-SARS-CoV-2 mAbs is under investigation.

Omicron-Variante: reduzierte Wirksamkeit bamlanivimab + etesevimab und casirivimab plus imdevimab

In **November 2021**, the **Omicron (B.1.1.529) variant** was designated as the **new variant of concern** (VOC): it includes numerous mutations in the spike protein. Ongoing studies are evaluating the susceptibility of this VOC to the anti-SARS-CoV-2 mAbs. This variant is predicted to have **markedly reduced susceptibility to some anti-SARS-CoV-2 mAb products,** including **bamlanivimab plus etesevimab** and **casirivimab plus imdevimab. Sotrovimab** appears to **retain activity against this variant.** Ongoing population-based genomic surveillance of the types and proportions of circulating SARS-CoV-2 variants, as well as studies on the susceptibility of different variants to available anti-SARS-CoV-2 mAbs, will be important in defining the utility of specific mAbs in the future [37].

keine reduzierte Wirksamkeit: Sotrovimab

On **December 23, 2021** Office of the Assistant Secretary for Preparedness & Response (**ASPR**) and **FDA** released a **joint statement** on the circulating SARS-CoV-2 viral variants, including Omicron, and how the variants may be associated with resistance to monoclonal antibodies. Data show that it is unlikely that bamlanivimab and etesevimab administered together or REGEN-COV will retain activity against this variant. Based on similar cell culture data currently available, sotrovimab appears to retain activity against the Omicron variant. **ASPR will pause any further allocations of bamlanivimab and etesevimab together, etesevimab alone, and REGEN-COV pending updated data from the CDC** [38].

The US COVID-19 Treatment Guidelines Panel (last update **December 30, 2021**)

US COVID-19 Treatment Guidelines Panel Empfehlung bei ambulanten Pts. (Omicron):

This statement contains the Panel's recommendations for treating these **nonhospitalised patients** using the currently available therapies. The Panel's recommendations take into account the efficacies of these drugs and the high prevalence of the B.1.1.529 (Omicron) variant of concern (VOC). When resources are limited, therapy should be prioritized for patients who are at the highest risk of progressing to severe COVID-19.

The Panel's current **outpatient treatment recommendations** are as follows (in order of preference):

sortiert nach Präferenz im Therapieeinsatz

- **Paxlovid** (**nirmatrelvir** 300 mg plus ritonavir 100 mg) orally twice daily for 5 days, initiated as soon as possible and within 5 days of symptom onset in those aged ≥12 years and weighing ≥40 kg **(AIIa)**.
- **Xevudy (Sotrovimab)** 500 mg administered as a single intravenous (IV) infusion, administered as soon as possible and within 10 days of symptom onset in those aged ≥12 years and weighing ≥40 kg who live in areas with a high prevalence of the Omicron VOC **(AIIa)**.
- **Veklury (Remdesivir)** 200 mg IV on Day 1 followed by remdesivir 100 mg IV on Days 2 and 3, initiated as soon as possible and within 7 days of symptom onset in those aged ≥12 years and weighing ≥40 kg **(BIIa)**.
- **Lagevrio (Molnupiravir)** 800 mg orally twice daily for 5 days, initiated as soon as possible and within 5 days of symptom onset in those aged ≥18 years **ONLY** when none oft he above options can be used **(CIIa)**.

Paxlovid
Xevudy
Veklury
Lagevrio

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

The reader is referred to the earlier version (V18_October and November 2021) for more details on **casirivimab and imdevimab combination (Ronapreve).**

EMA-Marktzulassung im Nov 2021

Marketing authorisation for COVID-19 granted in EU on November 12, 2021.

3.2.13.1.2 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** [39].

da Antrag auf Marktzulassung zurückgezogen wurde: Ende des Monitoring hier

3.2.13.1.3 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. 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-clinical-trial-initiated-for-monoclonal-antibody-combination-for-the-prevention-and-treatment-of-covid-19.html.

Phase 2 & 3 laufend

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

ACTIV-2 phase 2/3 RCT

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.

Feb 2021:
Phase 3 RCT begonnen

Studie ist Arm in ACTIV-3

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.

auch in DisCoVeRy Plattform Studie

Regulatory update:

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 **8 December 2021**, the FDA **issued EUA** for **emergency use** as **pre-exposure prophylaxis for prevention of COVID-19 in adults and pediatric individuals** (12 years of age and older weighing at least 40 kg), who **are not currently infected with SARS-CoV-2** and who **have not had a known recent exposure** to an individual infected with SARS-CoV-2 and who **have moderate to severe immune compromise** due to a medical condition or receipt of immunosuppressive medications or treatments and **may not mount an adequate immune response to COVID-19 vaccination or for whom vaccination with any available COVID-19 vaccine**, according to the approved or authorized schedule, is **not recommended due to a history of severe adverse reaction** (e.g., severe allergic reaction) to a **COVID-19 vaccine(s) and/or COVID-19 vaccine component(s).** One dose of Evusheld, administered as two separate consecutive intramuscular injections (one injection per monoclonal antibody, given in immediate succession), may be effective for pre-exposure prevention for six months. Evusheld is not authorized for individuals for the treatment of COVID-19 or for post-exposure prevention of COVID-19 [40].

Okt 2021:
EUA Antrag (USA)
Rolling Review (EMA)
Dez 2021:
EUA für Prä-Expositions Prophylaxe bei Immunschwäche

Menschen mit (allergischen) Reaktionen auf Covid-19 Impfung

Wirksamkeit gegen Virus-Varianten

bei Omicron starke Reduktion der Wirksamkeit

The neutralizing activity of tixagevimab and cilgavimab in combination was tested against pseudotyped VLPs and/or authentic SARS-CoV-2 variant strains harboring all spike substitutions identified in Alpha (B.1.1.7, 0.5- to 5.2-fold), Beta (B.1.351, 1.0- to 3.8-fold), Gamma (P.1, 0.4- to 2.0- fold), Delta (B.1.617.2, 0.6- to 1.2-fold), and Delta [+K417N] (AY.1/ AY.2, 1.0-fold) variants of concern, and Eta (B.1.525, 3.1-fold), Iota (B.1.526, 0.3- to 3.4-fold), Kappa (B.1.617.1, 0.5- to 3.4- fold) Lambda (C.37, 0.7-fold), and Mu (B.1.621, 7.5-fold) variants of interest. Tixagevimab and cilgavimab in combination was also tested against Epsilon (B.1.427 / B.1.429, 0.8- to 3.5-fold), R.1 (3.5-fold), B.1.1.519 (1.4-fold), C.36.3 (2.3-fold), B.1.214.2 (0.8-fold), and B.1.619.1 (3.3-fold) variant alerts for further monitoring and B.1.616 (0.5-fold), A.23.1 (0.4-fold), A.27 (0.8-fold), and AV.1 (5.9- fold) variants de-escalated from further monitoring (Table 3.2-2). Preliminary data for the neutralizing activities of tixagevimab, cilgavimab, and their combination against the **Omicron (B.1.1.529) variant of concern** are available. VLPs pseudotyped with the SARSCoV-2 spike of Omicron showed **reduced susceptibility** to tixagevimab (>600- to >1,000-fold), cilgavimab (>700- to >1,000-fold), and to their combination (132- to 183-fold). Authentic Omicron viruses showed reduced susceptibility to tixagevimab (152- to 230-fold), cilgavimab (12- to 268-fold), and to their combination (12- to 30-fold) [41].

Table 3.2-2: Pseudovirus neutralization data for SARS-CoV-2 variant substitutions with tixagevimab and cilgavimab combination

Lineage with Spike Protein Substitution	Key substitutions tested	Fold reduction in susceptibility
Alpha - B.1.1.7 (UK origin)	N501Y	0.5 to 5.2 fold
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	7.5 fold
Omicron – B.1.1.529 (Botswana)	G339D+S371L +S373P+ S375F+K417N N440K+G446S +S477N+ T478K+E484A +Q493R+ G496S+Q489R +N501Y+ Y505H	**132 to 183-fold**

Source: [41]

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** [42].

EMA: in Rolling Review

US COVID-19 Treatment Guidelines (last update **January 5, 2022**)

The Panel recommends using **tixagevimab plus cilgavimab** as SARS-CoV-2 **PrEP** for adults and adolescents (aged ≥12 years and weighing ≥40 kg) who do not have SARS-CoV-2 infection, who have not been recently exposed to an individual with SARS-CoV-2 infection, **AND** who:

- Are moderately to severely immunocompromised and may have an inadequate immune response to COVID-19 vaccination **(BIIa)**; *or*
- Are not able to be fully vaccinated with any available COVID-19 vaccines due to a documented history of severe reactions to a COVID-19 vaccine or any of its components **(AIIa)** [9].

US COVID-19 Treatment Guidelines: Empfehlung für Immunschwache und nicht vollständig Geimpfte

Results of publications

There are no publications from RCTs related to AZD7442.

keine Publikation von klinschen Studien

Manufacturers announcements on pre- and post-exposure prophylaxis results: On June 2021, AstraZeneca announced results from the phase 3 RCT, **STORM CHASER** (NCT04625972), assessing the safety and efficacy of AZD7442 for the prevention of symptomatic COVID-19 in participants recently exposed to the SARS-CoV-2 virus. The trial did not meet the primary endpoint of **post-exposure** prevention of symptomatic COVID-19 with AZD7442 compared to placebo, https://www.astrazeneca.com/content/astraz/media-centre/press-releases/2021/update-on-azd7442-storm-chaser-trial.html. STORM CHASER is a phase III, randomised, double-blind, placebo-controlled, multi-centre trial assessing the safety and efficacy of a single 300mg dose of AZD7442 compared to placebo for the post-exposure prevention of COVID-19. The trial was conducted in 59 sites in the UK and US. 1,121 participants were randomised in a 2:1 ratio to receive a single intramuscular (IM) dose of either 300mg of AZD7442 (n=749) or saline placebo (n=372), administered in two separate, sequential IM injections.

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

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,

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

https://www.astrazeneca.com/content/astraz/media-centre/press-releases/2021/azd7442-prophylaxis-trial-met-primary-endpoint.html.

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** [43]**.** The AZD7442 was well tolerated in both trials.

TACKLE RCT
signifikante Reduktion von Progression in mild Erkrankten

3.2.13.2 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 enrollement in arm examining VIR-7831 on March 1, 2021 (due to futility), following an interim review and recommendations from the independent Data and Safety Monitoring Board (DSMB), https://www.nih.gov/news-events/news-releases/nih-sponsored-activ-3-clinical-trial-closes-enrollment-into-two-sub-studies

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

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

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

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

On December 2021 was announced that the **RECOVERY trial** is currently testing sotrovimab as a possible treatment for hospitalised COVID-19 patients. The trial aims to recruit at least 4000 patients to the sotrovimab treatment arm, to be compared with at least 4000 patients who receive usual standard of care only. The main aim is to assess whether the treatment reduces the risk of death among patients admitted to hospital with COVID-19. The trial will also investigate whether the treatment shortens the length of hospital stay or reduces the need for a mechanical ventilator [45].

Sotrovimab wird in RECOVERY Plattform Studie in hospitalisierten Pts. getestet

Regulatory update:

On **November 18, 2021 EMA** has **started evaluating an application for marketing authorisation** for the monoclonal antibody Xevudy (sotrovimab) [46]. On **December 16, 2021 CHMP has recommended authorisation of sotrovimab** for the **treatment of adults and adolescents** (aged 12 years and over and weighing at least 40 kg) with coronavirus disease 2019 (COVID-19) who **do not require oxygen supplementation** and who are **at increased risk of progressing to severe COVID-19**. **Marketing authorisation** is **granted** by **EC** on **17 December 2021** [47].

EMA Marktzulassung: Dez 2021 für Pts mit erhöhtem Risiko und ohne Bedarf nach zusätzlichem Sauerstoff

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), the UK (B.1.1.7) and recently found variant Omicron B.1.1.529/BA.1 (South Africa), as well as against variants of interest according to the new EUA revision issued in November and December 2021 [48] [49].

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

keine Resistenzen u.a. gegen Omicron

Table 3.2-3: 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
Omicron - B.1.1.529/BA.1 (South Africa)	G339D+S371L +S373P+ S375F+K417N N440K+G446S +S477N+ T478K+E484A +Q493R+ G496S+Q489R +N501Y+ Y505H	No change

No change: <5-fold reduction in susceptibility; Source: [48] [49]

The US COVID-19 Treatment Guidelines Panel (last update **December 30, 2021**)

This statement contains the Panel's recommendations for treating these **nonhospitalised patients** using the currently available therapies. The Panel's recommendations take into account the efficacies of these drugs and the high prevalence of the B.1.1.529 (Omicron) variant of concern (VOC). When resources are limited, therapy should be prioritized for patients who are at the highest risk of progressing to severe COVID-19.

US COVID-19 Treatment Guidelines Panel empfiehlt folgende Medikamente für ambulante Pts. (in der Reihenfolge der Präferenz)

The Panel's current **outpatient treatment recommendations** are as follows (in order of preference):

- **Paxlovid** (**nirmatrelvir** 300 mg plus ritonavir 100 mg) orally twice daily for 5 days, initiated as soon as possible and within 5 days of symptom onset in those aged ≥12 years and weighing ≥40 kg **(AIIa)**.
- **Xevudy (Sotrovimab)** 500 mg administered as a single intravenous (IV) infusion, administered as soon as possible and within 10 days of symptom onset in those aged ≥12 years and weighing ≥40 kg who live in areas with a high prevalence of the Omicron VOC **(AIIa)**.
- **Veklury (Remdesivir)** 200 mg IV on Day 1 followed by remdesivir 100 mg IV on Days 2 and 3, initiated as soon as possible and within 7 days of symptom onset in those aged ≥12 years and weighing ≥40 kg **(BIIa)**.
- **Lagevrio (Molnupiravir)** 800 mg orally twice daily for 5 days, initiated as soon as possible and within 5 days of symptom onset in those aged ≥18 years **ONLY** when none oft he above options can be used **(CIIa)**.

Paxlovid
Xevudy
Veklury
Lagevrio

Results of publications

There are two publications from RCTs related to AZD7442, one in nonhospitalised and one in hospitalised patients.

Gupta et al. 2021 [50] published as **preprint,** and then in **scientific journal** [51] 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

ACTIV-3/Therapeutics for Inpatients with COVID-19 (TICO) Study Group, 2021 published results from RCT in which a total of 546 **hospitalised patients** randomly assigned to sotrovimab (n=184), BRII-196 plus BRII-198 (n=183), or placebo (n=179). Neither sotrovimab nor BRII-196 plus BRII-198 showed efficacy for improving clinical outcomes among adults hospitalised with COVID-19 [52].

ACTIV-3/TICO, 546 hospitalisierte Pts keine Unterschiede zwischen den Gruppen

3.2.13.3 Regdanvimab (CT-P59, Regkirona)

monoklonaler Antikörper
Veweis auf v18

The reader is referred to the earlier version (V18_October and November 2021) for more details on **regdanvimab (Regkirona).**

Marketing authorisation for COVID-19 granted in EU on November 12, 2021.

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 [53].

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 [53].

ClinicalTrials.gov & EUdraCT: keine klinischen Studien registriert,

Results of publications

No publications related to the RCTs of solnatide in COVID-19 patients were found [53].

keine Publikation von RCT

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 [54].

EMA: insuffiziente Datenlage

The US COVID-19 Treatment Guidelines Panel (last update **December 16, 2021**)

For **nonhospitalised** patients with COVID-19: there is **insufficient evidence** for the Panel to recommend **either for or against** the use of **inhaled corticosteroids** for the treatment of COVID-19. For **hospitalised** patients with COVID-19: there is **insufficient evidence** for the Panel to recommend **either for or against** the use of **inhaled corticosteroids** for the treatment of COVID-19 [9].

US COVID-19 Treatment Guidelines Panel: insuffiziente Evidenz für nicht-hospitalisierte und für hospitalisierte Pts

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 [55]. 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 [56]. On August 10, 2021 results are published in scientific article [57]. 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
4.663 Pts.,
davon 751 mit Budesonid
frühzeitiger Abbruch

Verkürzung der Zeit der Erkrankung um ca 3 Tage

geringe Effekte auf Hospitalisierung/ Tod

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 3.2-4 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

SoF von 2 RCTs
ev. Reduktion der Hospitalisierungen

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 3.2-4: 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** [58].

Juli 2021: EMA beginnt Evaluierung für Pts mit Lungenentzündung

On **December 16 2021, CHMP** recommended **adding the treatment of COVID-19** in **adult patients** with **pneumonia requiring supplemental oxygen (low or high flow oxygen)** and who are **at risk of developing severe respiratory failure** (as determined by blood levels of a protein called suPAR, soluble urokinase plasminogen activator receptor, of at least 6 ng per ml), to its approved indications. Following evaluation by EMA, on **December 17, 2021** the **EC authorised** it use to treat **COVID-19** [59, 60]. The recommended dose of anakinra is 100 mg administered once a day by subcutaneous injection for 10 days [61]. Detailed information could be found in updated Summary of product characteristics document [62].

Dez. 2021: EMA Marktzulassung für Pts mit Lungenentzündung, die zusätzlichen Sauerstoff brauchen

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 [33].

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

Studiengruppe in RECOVERY

(Randomised Evaluation of COVid-19 thERapY) trial, led by the University of Oxford [63].

Results of publications

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

3 Publikation eines RCTs

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 [64]. 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, CORIMUNO-19

Rekrutierung nach 116 Pts. angehalten

Kyriazopoulou et al. 2021 [65] [66] [67](**NCT04680949, EUdraCT 2020-005828-11**) published as preprint, and then in scientific journal, 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.

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

raschere Erholung
geringere Mortalität
kürzere Hospitalisierung

As described in Sarilumab Section, **Derde et al. 2021** published **final results** as preprint [28] 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

Plattform Studie
REMAP-CAP
2.274 schwer Erkrankte

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.

COV-AID RCT: hospitalisierte Pts mit Anzeicen für Zytokinsturm

kein Unteschied zwischen den Gruppen bei Mortalität

Declercq et al. 2021 [68] 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. 55 patients died during the study, but no evidence for differences in mortality between treatment groups was found. The incidence of serious adverse events and serious infections was similar across study groups.

SoF von 24 RCTs sehr unsichere Evidenz

Wirksamkeit:

Reduktion der 28-Tage

keine Reduktion 60-Tage Gesamtsterblichkeit

ev.raschere klinische Verbesserung

Nebenwirkungen

Effectiveness and safety data summary related to these 4 RCTs mentioned above can be found in the **Summary of Findings** Table 3.2-5 (last update 08/12/2021): 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). The evidence from four published RCTs in hospitalised patients with moderate to critical COVID-19 (CORIMUNO-19, REMAP-CAP, SAVE-MORE, COV-AID) is very uncertain about the effect of anakinra on all-cause mortality at day 60 (very low certainty evidence, RR 1.03, 95% CI 0.68 to 1.56; 8 more per 1000, 95% CI from 84 fewer to 147 more). In hospitalised patients with moderate to critical COVID-19 showed that anakinra probably increases clinical improvement at day 28 (RR 1.08, 95% CI 0.97 to 1.20; 59 more per 1.000, 95% CI from 22 fewer to 147 more, moderate certainty of evidence, 3 RCTs: CORIMUNO-19, SAVE-MORE, COV-AID). 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 slightly increase the number of patients with any adverse events (RR 1.02, 95% CI 0.94 to 1.11; 14 more per 1000, 95% CI from 43 fewer to 78 more, moderate certainty of evidence, 2 RCTs: CORIMUNO-19, SAVE-MORE). Anakinra may not increase the number of patients with serious adverse events (RR 0.95, 95% CI 0.58 to 1.56; 12 fewer per 1000, 95% CI from 104 fewer to 138 more, low certainty of evidence, 2 RCTs: CORIMUNO-19, SAVE-MORE) [69].

*Table 3.2-5: Summary of findings table, on **anakinra** (4 RCTs: CORIMUNO-19 Collaborative group, Kyriazopoulou - SAVE-MORE, Derde - REMAP-CAP, Declercq - COV-AID)*

Patient or population: COVID-19 patients (moderate to critical, last update 08/12/2021)

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	262 per 1000	270 per 1000	**RR: 1.03** (0.68 - 1.56)	1633 (4 RCTs) [e]	⊕◯◯◯ VERY LOW [f]	**Absolute effect (95% CI) 8 more per 1000** (from 84 fewer to 147 more)
Clinical improvement D28	737 per 1000	796 per 1000	**RR: 1.08** (0.97 - 1.20)	837 (3 RCTs) [b, c]	⊕⊕⊕◯ MODERATE [g]	**Absolute effect (95% CI) 59 more per 1000** (from 22 fewer to 147 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	713 per 1000	727 per 1000	**RR: 1.02** (0.94 - 1.11)	722 (2 RCTs) [b, c]	⊕⊕⊕◯ MODERATE [i]	**Absolute effect (95% CI) 14 more per 1000** (from 43 fewer to 78 more)
Number of patients with serious adverse events	247 per 100	235 per 1000	**RR: 0.95** (0.58 - 1.56)	722 (2 RCTs) [b, c]	⊕⊕◯◯ LOW [j]	**Absolute effect (95% CI) 12 fewer per 1000** (from 104 fewer to 138 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: [70];-**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 [64] c [65] [68] ; d Imprecision: Very serious due to very wide confidence interval consistent with the possibility for benefit and the possibility for harm; e [28, 64] [235] [68] f Risk of bias: Serious Risk of bias downgraded by 1 level: some concerns regarding deviation from intended interventions and missing data; Inconsistency: Serious Inconsistency downgraded by 1 level: I^2=:63.2%; Imprecision: Serious Imprecision downgraded by 1 level: due to wide confidence interval consistent with the possibility for benefit and the

possibility for harm and low number of participants and events. This outcome was not downgraded an additional level for imprecision because it was downgraded one level for inconsistency, which is related to and would have contributed to the severity of the imprecision. g Imprecision: Serious due to low number of participants; 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 Inconsistency: Serious Inconsistency downgraded by 1 level: I^2=68.2% 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

Verweis auf v18

The reader is referred to the earlier version (V15_June 2021 and V18_October/November 2021) for more details on colchicine treatment in **hospitalised** and **nonhospitalised** COVID-19 patients.

US COVID-19 Treatment Guidelines Panel: Empfehlung GEGEN Colchicine bei hospitalisieten oder nicht-hospitalisierten Pts.

The **US COVID-19 Treatment Guidelines Panel** (update December 16, 2021), based on negative results from RECOVERY trial **recommends against** the use of colchicine in **hospitalised patients (AI).** The COVID-19 Treatment Guidelines Panel (the Panel) **recommends against** the use of **colchicine** for the treatment of **nonhospitalised patients** with COVID-19, except in a clinical trial **(BIIa)** [9].

3.2.20 Nafamostat (Futhan©)

Details in v17

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

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

Zhuravel et al. 2021 [71] 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 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).

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

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.

3.2.21 Gimsilumab

About the drug under consideration

monoklonaler Antkörper in Entwicklung

EMA/ FDA: keine Zulassung

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.

Withdrawn, suspended or terminated studies

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

keine abgeschlossenen, abgebrochenen Studien

Results of publications

keine veröffentlichten Studien

There are no published results from RCTs related to effectiveness and safety of gimsilumab for Covid-19 treatment; one Phase II study of gimsilumab is ongoing, estimated study completion date is March 2021 [72, 73].

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

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 [74, 75].

monoklonaler Antikörper

für keine Indikation bislang zugelassen

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

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

Withdrawn, suspended or terminated studies

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

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

ACTIV-5 RCT: laufend 200 hospitalisierte Pts

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

bessere klinische Ergebnisse in der Lenzilumab-Gruppe

Currently, results from one RCT were published as preprint, and then in scientific journal, related to effectiveness and safety of lenzilumab for Covid-19. **Temesgen et al. 2021** [76] [67] 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%). Survival without invasive mechanical ventilation to day 28 was achieved in 198 (84%; 95% CI 79–89) participants in the lenzilumab group and in 190 (78%; 72–83) patients in the placebo group, and the likelihood of survival was greater with lenzilumab than placebo (hazard ratio 1.54; 95% CI 1.02–2.32; p=0.040). 68 (27%) of 255 patients in the lenzilumab group and 84 (33%) of 257 patients in the placebo group experienced at least one adverse event that was at least grade 3 in severity based on CTCAE criteria. The most common treatment-emergent adverse events of grade 3 or higher were related to respiratory disorders (26%) and cardiac disorders (6%) and none led to death. Authors concluded that lenzilumab significantly improved survival without invasive mechanical ventilation in hospitalised patients with COVID-19, with a safety profile similar to that of placebo. The added value of lenzilumab beyond other immunomodulators used to treat COVID-19 alongside steroids remains unknown [67].

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

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

Verweis auf v17

3.2.25 Baricitinib (Olumiant)

About the drug under consideration

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 [77, 78].

Januskinase-Inhibitor

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

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) [79].

EMA: keine Zulassung für covid-19

FDA Zulassung (EUA) als Kombinationstherapie 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)** [80]. 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** [81].

The **US COVID-19 Treatment Guidelines Panel** (last update December 16, 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 [9]. 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 [9].

Empfehlung gegen eine Kombinationstherapie Baricitinib + Tocilizumab

Withdrawn, suspended or terminated studies

mehrere laufende Studien

One withdrawn (NCT04340232, could not make FDA required changes), no suspended and one terminated RCTs (NCT04373044, after the release of results of ACTT-2 trial) were found on baricitinib in ClinicalTrials.gov and EUdraCT registers. There are several ongoing RCTs, evaluating baricitinib alone or in combination with other pharmaceuticals in Covid-19 hospitalised patients. One is the RECOVERY (Randomised Evaluation of COVid-19 thERapY) trial, led by the University of Oxford [63].

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.** [82] 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 3.2-6. 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 [83]: 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.** [84] publised as **pre-print** and on September 3, 2021 **in scientific journal** [85], 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** [86]. 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 [86, 87].

SoF: ev. geringere 28-Tage und 60-Tage Mortalität, weitere Endpunkte sehr unsicher

Summary of Findings *Table 3.2-7* 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 3.2-6: 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 3.2-7: 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 (Lagevrio)

About the drug under consideration

antivirales Medikament ähnlich Remdesivir aber orale Verabreichung

Molnupiravir is the orally available pro-drug of the nucleoside analogue N4-hydroxycytidine (NHC), which has shown potent anti-influenza virus activity in mice, guinea pigs, ferrets and human airway epithelium organoids. Animal study in ferrets showed that therapeutic treatment of infected animals with molnupiravir (MK-4482/EIDD-2801) twice a day significantly reduced the SARS-CoV-2 load in the upper respiratory tract and completely suppressed spread to untreated contact animals [88, 89].

frühere Verabreichung zu Hause daher möglich

hospitalisierte, aber auch milde und moderate Erkrankung

Molnupiravir attacks the same viral enzyme as Gilead's Remdesivir, but it can be taken orally. This would allow an administration at home and, therefore, earlier in the course of the disease. According to Ridgeback Biotherapeutics, molnupiravir has an extremely high barrier to resistance. According to Merck Sharp & Dohme/ MSD, molnupiravir is aimed at the treatment of Covid-19 in patients hospitalised due to mild, moderate or severe disease, and non-hospitalized patients with mild or moderate disease [89].

weder von EMA noch FDA zugelassen

Molnupiravir is not approved by the European Medicines Agency (EMA) or the American Food and Drug Administration (FDA) [89].

Okt 2021: EMA beginnt Rolling Review

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** [90].

EMA: für mild bis moderat Erkrankte mit hohem Risiko auf Progression, innerhalb der ersten 5 Tage nach Krankheitsbeginn einzunehmen

On **November 19, 2021** CHMP has **issued advice** on the use of molnupiravir to **treat adults with COVID-19** who **do not require supplemental oxygen and who are at increased risk of developing severe COVID-19**. Lagevrio should be administered as soon as possible after diagnosis of COVID-19 and within 5 days of the start of symptoms. On **November 23, 2021**, EMA has **started evaluating as application** for **marketing authorisation**. On **December 14, 2021** EMA announced that it is reviewing **new data on effectiveness** of molnupiravir for the treatment of COVID-19 [91].

FDA: EUA, aber nur für Pts, die keinen Zugang zu anderen zugelassenen Medikamenten haben

nicht: für Prä- oder PostExpositions Prophylaxe

On **December 23, 2021 FDA** issued **EUA** for molnupiravir for the treatment of **mild-to-moderate** coronavirus disease (COVID-19) in **adults with positive results of direct SARS-CoV-2 viral testing**, and who are at **high risk for progression to severe COVID-19**, including hospitalisation or death, and **for whom alternative COVID-19 treatment options authorized by the FDA are not accessible or clinically appropriate**. It should be initiated as soon as possible after diagnosis of COVID-19 and within five days of symptom onset. Molnupiravir is not authorized for use in patients younger than 18 years of age because molnupiravir may affect bone and cartilage growth. It is not authorized for the pre-exposure or post-exposure prevention of COVID-19 or for initiation of treatment in patients hospitalized due to COVID-19 because benefit of treatment has not been observed in people when treatment started after hospitalisation due to COVID-19. Molnupiravir is a medication that works by introducing errors into the SARS-CoV-2 virus' genetic code, which prevents the virus from further replicating. It is administered as four 200 milligram capsules taken orally every 12 hours for five days, for a total of 40 capsules [92].

The US COVID-19 Treatment Guidelines Panel (last update **December 30, 2021**)

US COVID-19 Treatment Guidelines Panel:

This statement contains the Panel's recommendations for treating these **nonhospitalised patients** using the currently available therapies. The Panel's recommendations take into account the efficacies of these drugs and the high prevalence of the B.1.1.529 (Omicron) variant of concern (VOC). When resources are limited, therapy should be prioritized for patients who are at the highest risk of progressing to severe COVID-19.

Empfehlungen für ambulante, nicht-hospitalisierte Pts. (in Rangreihung nach Präferenz)

The Panel's current **outpatient treatment recommendations** are as follows (in order of preference):

Paxlovid
Xevudy
Veklury
Lagevrio

- **Paxlovid** (**nirmatrelvir** 300 mg plus ritonavir 100 mg) orally twice daily for 5 days, initiated as soon as possible and within 5 days of symptom onset in those aged ≥12 years and weighing ≥40 kg **(AIIa)**.
- **Xevudy (Sotrovimab)** 500 mg administered as a single intravenous (IV) infusion, administered as soon as possible and within 10 days of symptom onset in those aged ≥12 years and weighing ≥40 kg who live in areas with a high prevalence of the Omicron VOC **(AIIa)**.
- **Veklury (Remdesivir)** 200 mg IV on Day 1 followed by remdesivir 100 mg IV on Days 2 and 3, initiated as soon as possible and within 7 days of symptom onset in those aged ≥12 years and weighing ≥40 kg **(BIIa)**.
- **Lagevrio (Molnupiravir)** 800 mg orally twice daily for 5 days, initiated as soon as possible and within 5 days of symptom onset in those aged ≥18 years **ONLY** when none oft he above options can be used **(CIIa)**.

Withdrawn, suspended or terminated studies

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

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

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/.

Results of publications

4 Publikationen

There are one published phase 2a RCT (as preprint [93]) related to effectiveness and safety of molnupiravir for Covid-19 (NCT04405570); one published phase 2 component of MOVe-OUT (NCT04575597) RCT [94], one published phase 2/3 RCT in hospitalised patients (NCT04575584, MOVe-IN) [95], and one published phase 3 component of MOVe-OUT (NCT04575597) trial [96]

Phase 2a RCT
202 Pts.

deutlich raschere Reduktion der Virulslast unter Molnupiravir

In June 2021, results from **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) are published as **preprint** by **Fisher et al. 2021** [93]. Participants were randomized 1:1 to 200 mg molnupiravir or placebo, or 3:1 to molnupiravir (400 or 800 mg) or placebo, twice-daily for 5 days. 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.

Phase 2 (Dosisfindung) + Phase 2/3 MOVe-OUT
302 ambulante Pts.

geringere Hospitalisierungen
3,1% vs 5,4%

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) [94] 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. The **phase 2** component of **MOVe-OUT** randomly assigned 302 participants to treatment 1:1:1:1 to receive **200, 400, or 800mg of molnupiravir or placebo twice daily for 5 days**. Of 225 participants in the combined molnupiravir group, 7 (3.1%) were hospitalised or died, compared with 4 of 74 participants (5.4%) in the placebo group. Subgroup analyses suggested lower incidences of hospitalisation and/or death in the molnupiravir versus placebo groups in participants older than 60 years of age, those with increased risk for severe illness, those with symptom onset up to (and including) 5 days before randomization, and those with both symptom onset up to (and including) 5 days before randomization and increased risk for severe illness [94].

MOVe-IN
hospitalisierte Pts

keine Wirksamkeit

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. A 5-day course of molnupiravir up to 800 mg twice daily was not associated with dose-limiting side effects or adverse events. Median time to sustained recovery was 9 days in all groups, with similar day 29 recovery rates ranging from 81.5% to 85.2% [95].

Phase 3 von MOVe-OUT
1.433 ungeimpfte ambulante Pts.

geringere Hospitalisierungen (oder Tod)
6,8% vs 9,7%

Jayk Bernal et al. 2021 published results from the **phase 3 MOVe-OUT trial** (NCT04575597): a total of 1433 **unvaccinated** participants underwent randomization; 716 were assigned to receive **800 mg of molnupiravir** and 717 to receive placebo, **twice daily for 5 days**. The superiority of molnupiravir was demonstrated at the interim analysis; the risk of hospitalization for any cause or death through day 29 was lower with molnupiravir (28 of 385 participants [7.3%]) than with placebo (53 of 377 [14.1%]) (difference, −6.8 percentage points; 95% confidence interval, −11.3 to −2.4; p=0.001). In the analysis of all participants who had undergone randomization, the percentage of participants who were hospitalized or died through day 29 was lower in the molnupiravir group than in the placebo group (6.8% [48 of 709] vs. 9.7% [68 of 699]; difference, −3.0 percentage points; 95% confidence interval, −5.9 to

−0.1). Results of subgroup analyses were largely consistent with these overall results; in some subgroups, such as patients with evidence of previous SARS-CoV-2 infection, those with low baseline viral load, and those with diabetes, the point estimate for the difference favored placebo. One death was reported in the molnupiravir group and 9 were reported in the placebo group through day 29. Adverse events were reported in 216 of 710 participants (30.4%) in the molnupiravir group and 231 of 701 (33.0%) in the placebo group [96].

3.2.27 Ivermectin

Verweis auf v15

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.

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

The **US COVID-19 Treatment Guidelines Panel** Statement (February 11, 2021) [33] [9] 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.

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

Empfehlung GEGEN Ivermectin (außer in klin. Studien)

The **WHO Therapeutics and COVID-19 living guideline** [97, 98] 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.

3.2.28 Aspirin

Verweis auf v17

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

RECOVERY
7.351 hospitalisierte Pts

keine Unterschiede, kein Vorteil von Aspirin

The **final results** were published from **RECOVERY** trial. 7351 patients were randomly allocated (1:1) to receive aspirin and 7541 patients to receive usual care alone. Overall, 1222 (17%) of 7351 patients allocated to aspirin and 1299 (17%) of 7541 patients allocated to usual care died within 28 days (rate ratio 0.96, 95% CI 0.89–1.04; p=0.35). Consistent results were seen in all prespecified subgroups of patients. Patients allocated to aspirin had a slightly shorter duration of hospitalisation (median 8 days, IQR 5 to >28, *vs* 9 days,

IQR 5 to >28) and a higher proportion were discharged from hospital alive within 28 days (75% *vs* 74%; rate ratio 1.06, 95% CI 1.02–1.10; p=0.0062). Among patients not on invasive mechanical ventilation at baseline, there was no significant difference in the proportion meeting the composite endpoint of invasive mechanical ventilation or death (21% *vs* 22%; risk ratio 0.96, 95% CI 0.90–1.03; p=0.23). Aspirin use was associated with a reduction in thrombotic events (4.6% *vs* 5.3%; absolute reduction 0.6%, SE 0.4%) and an increase in major bleeding events (1.6% *vs* 1.0%; absolute increase 0.6%, SE 0.2%) [99].

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 [100].

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.

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

ev. Verbesserung der entzündungsbedingten Lungenschädigung bei hospitalisierten Patient*innen

The **US COVID-19 Treatment Guidelines Panel** Statement (August 25, 2021) [9] 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 [101] published results from **STOP-COVID** RCT (**NCT04469114**), on **hospitalised adults** with Covid-19 pneumonia to receive either tofacitinib at a dose of 10 mg or placebo twice daily for up to 14 days or until hospital discharge. The primary outcome was the occurrence of death or respiratory failure through day 28 as assessed with the use of an eight level ordinal scale (with scores ranging from 1 to 8 and higher scores indicating a worse condition). All-cause mortality and safety were also assessed. A total of 289 patients underwent randomization at 15 sites in Brazil. Overall, 89.3% of the patients received glucocorticoids during hospitalisation. The cumulative incidence of death or respiratory failure through day 28 was 18.1% in the tofacitinib group and 29.0% in the placebo group (risk ratio, 0.63; 95% confidence interval [CI], 0.41 to 0.97; p=0.04). Death from any cause through day 28 occurred in 2.8% of the patients in the tofacitinib group and in 5.5% of those in the placebo group (hazard ratio, 0.49; 95% CI, 0.15 to 1.63). The proportional odds of having a worse score on the eight-level ordinal scale with tofacitinib, as compared with placebo, was 0.60 (95% CI, 0.36 to 1.00) at day 14 and 0.54 (95% CI, 0.27 to 1.06) at day 28. Serious adverse events occurred in 20 patients (14.1%) in the tofacitinib group and in 17 (12.0%) in the placebo group. Among the adverse events of special interest, deep-vein thrombosis, acute myocardial infarction, ventricular tachycardia, and myocarditis occurred in 1 patient each in the tofacitinib group; hemorrhagic stroke and cardiogenic shock occurred in 1 patient each in the placebo group. The incidence of serious infection was 3.5% in the tofacitinib group and 4.2% in the placebo group. Adverse events other than death that led to the discontinuation of the trial regimen occurred in 11.3% of the patients in the tofacitinib group and in 3.5% of those in the placebo group; the most common such events were an increase in aminotransferase levels (in 4.2% of the patients in the tofacitinib group and in 0.7% of those in the placebo group) and lymphopenia (in 2.8% and 1.4%, respectively).

RCT
STOP-COVID
289 hospitalisierte Pts.

bessere Ergebnisse bei Überleben und Atemwegsversagen

Nebenwirkungen

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 Nirmatrelvir and ritonavir (Paxlovid)

About the drug under consideration

Proteaseinhibitor

PF-07321332 (now nirmatrelvir), 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 [102].

bislang nicht zugelassen

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

EMA: für mild bis moderat Erkrankte mit hohem Risiko auf Progression, innerhalb der ersten 5 Tage nach Krankheitsbeginn einzunehmen

On **December 16, 2021 EMA issued advice** on use of Paxlovid for the **treatment of COVID-19.** Paxlovid, which is **not yet authorised in the EU**, **can be used** to **treat adults with COVID-19** who **do not require supplemental oxygen and who are at increased risk of progressing to severe disease**. Paxlovid should be administered as soon as possible after diagnosis of COVID-19 and within 5 days of the start of symptoms. On **December 22, 2021** EMA published the **conditions of use** for Paxlovid, following the CHMPs advice on ist use to treat COVID-19. In parallel to the provision of this advice, a more comprehensive **rolling review started** on **13 December 2021** ahead of application for a conditional marketing authorisation received on January 10, 2022 [103].

FDA: EUA (auch für Kinder)

EPIC-HR RCT an Ungeimpften

On **December 22, 2021 FDA** issued **EUA** for Paxlovid (nirmatrelvir tablets and ritonavir tablets, co-packaged for oral use) for the **treatment of mild-to-moderate coronavirus disease** (COVID-19) in **adults and pediatric patients** (12 years of age and older weighing at least 40 kilograms or about 88 pounds) with **positive results of direct SARS-CoV-2 testing**, and who are at **high risk for progression to severe COVID-19**, including hospitalization or death. It should be initiated as soon as possible after diagnosis of COVID-19 and **within five days of symptom onset**. The primary data supporting this EUA for Paxlovid are from EPIC-HR, a randomized, double-blind, placebo-controlled clinical trial studying Paxlovid for the treatment of non-hospitalised symptomatic adults with a laboratory confirmed diagnosis of SARS-CoV-2 infection. Patients were adults 18 years of age and older with a prespecified risk factor for progression to severe disease or were 60 years and older regardless of prespecified chronic medical conditions. **All patients had not received a COVID-19 vaccine and had not been previously infected with COVID-19**. Paxlovid is not authorized for the pre-exposure or post-exposure prevention of COVID-19 or for initiation of treatment in those requiring hospitalization due to severe or critical COVID-19. It consists of nirmatrelvir, which inhibits a SARS-CoV-2 protein to stop the virus from replicating, and ritonavir, which slows down nirmatrelvir's breakdown to help it remain in the body for a longer period at higher concentrations. Paxlovid is administered as three tablets (two tablets of nirmatrelvir and one tablet of ritonavir) taken together orally twice daily for five days, for a total of 30 tablets. It is not authorized for use for longer than five consecutive days [104].

The US COVID-19 Treatment Guidelines Panel (last update **December 30, 2021**)

US COVID-19 Treatment Guidelines Panel:

This statement contains the Panel's recommendations for treating these **nonhospitalised patients** using the currently available therapies. The Panel's recommendations take into account the efficacies of these drugs and the high prevalence of the B.1.1.529 (Omicron) variant of concern (VOC). When resources are limited, therapy should be prioritized for patients who are at the highest risk of progressing to severe COVID-19.

Empfehlungen für ambulante, nicht-hospitalisierte Pts. (in Rangreihung nach Präferenz)

The Panel's current **outpatient treatment recommendations** are as follows (in order of preference):

Paxlovid
Xevudy
Veklury
Lagevrio

- **Paxlovid** (**nirmatrelvir** 300 mg plus ritonavir 100 mg) orally twice daily for 5 days, initiated as soon as possible and within 5 days of symptom onset in those aged ≥12 years and weighing ≥40 kg **(AIIa)**.
- **Xevudy (Sotrovimab)** 500 mg administered as a single intravenous (IV) infusion, administered as soon as possible and within 10 days of symptom onset in those aged ≥12 years and weighing ≥40 kg who live in areas with a high prevalence of the Omicron VOC **(AIIa)**.
- **Veklury (Remdesivir)** 200 mg IV on Day 1 followed by remdesivir 100 mg IV on Days 2 and 3, initiated as soon as possible and within 7 days of symptom onset in those aged ≥12 years and weighing ≥40 kg **(BIIa)**.
- **Lagevrio (Molnupiravir)** 800 mg orally twice daily for 5 days, initiated as soon as possible and within 5 days of symptom onset in those aged ≥18 years **ONLY** when none oft he above options can be used **(CIIa)**.

Withdrawn, suspended or terminated studies

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

Phase 1:
Studie zur Sicherheit

Phase 2/3:
an nicht-hospitalisierten Pts.

PF-07321332/ ritonavir

auch Post-Exposure Prophylaxe

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 (**EPIC-HR**, **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 (unvaccinated adults who were at standard risk, i.e., low risk of hospitalisation or death, as well as vaccinated adults who have an acute breakthrough symptomatic COVID-19 infection and one or more risk factors for progressing to severe illness), who will receive **PF07321332/ritonavir** or placebo orally every 12 hours for five days. One **phase 3** RCT (**NCT05047601**) 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.

On **December 14, 2021** Pfizer **announced final results** from an analysis of all **2,246 adults** enrolled in its **phase 2/3 EPIC-HR** (**E**valuation of **P**rotease **I**nhibition for **C**OVID-19 in **H**igh-**R**isk Patients, **NCT04960202**) trial of PAXLOVID™ (nirmatrelvir [PF-07321332] tablets and ritonavir tablets), randomized, double-blind study of **non-hospitalised adult patients** with COVID-19, who are **at high risk of progressing to severe illness**. These results were consistent with the interim analysis announced in November 2021 [105], showing Paxlovid significantly reduced the risk of hospitalisation or death for any cause by 89% compared to placebo in non-hospitalised, high-risk adult patients with COVID-19 treated within three days of symptom onset. In a secondary endpoint, Paxlovid reduced the risk of hospitalisation or death for any cause by 88% compared to placebo in patients treated within five days of symptom onset, an increase from the 85% observed in the interim analysis. A secondary endpoint, SARS-CoV-2 viral load at baseline and Day 5 have been evaluated for 499 patients. After accounting for baseline viral load, geographic region, and serology status, Paxlovid reduced viral load by approximately 10-fold, or 0.93 $\log_{10}$ copies/mL, relative to placebo, indicating robust activity against SARS-CoV-2. Treatment-emergent adverse events were comparable between Paxlovid (23%) and placebo (24%), most of which were mild in intensity. Fewer serious adverse events (1.6% vs. 6.6%) and discontinuation of study drug due to adverse events (2.1% vs. 4.2%) were observed in patients dosed with Paxlovid, compared to placebo, respectively [106].

Phase 2/3 EPIC-HR
2.246 ambulante Pts

Informationen aus Presseaussendung
89% Reduktion von Hospitalisierung/ Tod

Recent **in vitro data** confirm that **nirmatrelvir** is a **potent inhibitor of the Omicron 3CL protease**, which, combined with existing in vitro antiviral and protease inhibition data from other Variants of Concern (VoC) including Delta, indicates that Paxlovid will retain robust antiviral activity against current VoCs as well as other coronaviruses [106].

auch gegen Omicron wirksam

3.2.35 AT-527

About the drug under consideration

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 [107, 108].

antivirales Medikament für HepC entwickelt

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.

für milde und moderate Covid-19 Erkrankung orale Verabreichung

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

Withdrawn, suspended or terminated studies

No withdrawn, or terminated studies were found for AT-527 in COVID-19 patients. One suspended trial was found (NCT05126576, MORNINGSKY) in ClinicalTrials.gov register (posted November 19, 2021: the phase 3 MORNINGSKY study (CV43043) has been temporarily paused due to the recent readout of preliminary results from the phase 2 MOONSONG dose-

1 Studie angehalten wegen Protokoll-Veränderungen (Ungeimpfte)

ranging study. A protocol amendment is under development by the Sponsor and co-development partner.).

2 laufende Studien: Phase 2 MOONSONG

It is now tested in **two phase 2** clinical trials (NCT04396106 and NCT04709835 – MOONSONG trial) for its safety and efficacy [109, 110]. The phase 2 trial enrolling hospitalised Covid-19 patients will be amended for unvaccinated, high-risk individuals' recruitment in the outpatient setting to assess the safety, virological activity and tolerability of the oral antiviral in unvaccinated individuals with moderate disease. The amended phase 2 trial is expected to enroll up to 200 patients. Atea anticipates reporting data from this trial during 2022 [111].

Phase 3 MORNINGSKY

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 [112]. As recently announced, the company will close this international phase 3 MORNINGSKY trial of its oral antiviral AT-527 due to changing COVID-19 landscape with the anticipated availability of new antiviral treatment regimens.

präklinische Studien

AT-527 is being analysed for its potential to offer protection against Covid-19 disease progression and long-Covid complications development. Preclinical in vitro studies of AT-527 in combination with other compounds possessing different mechanisms of action to analyse additive and synergistic effects will be conducted also [111, 113].

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 [114].

in Hochrisiko Pts: rasche Reduktion der Viruslast

On **October 19, 2021** Manufacturer announced results from **phase 2 MOONSONG trial** [115]: 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 [116].

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 [75, 117, 118].

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 [119]. 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 [120].

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

RCT MASH-COVID 40 Pts. frühzeitiger Abbruch

kein Unterschied zwischen den Studienarmen

There is one RCT with published results by **Cremer et al. 2021** that compared mavrilimumab against placebo, the **MASH-COVID** study (NCT04399980, NCT04463004, NCT04492514) [121]. The trial was terminated earlier than planned with 40 patients enrolled [122]. 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%) [121, 123].

Phase 2/3 RCT hospitalisierte Pts.

65% Reduktion der künstlichen Beatmung 86,7% vs. 74,4% ohne Beatmung nach 1 Monat

geringere Mortalität

Results from the **phase 2 portion** of the on-going, global, randomized, double-blind, placebo-controlled seamless transition **phase 2/3 trial** designed to evaluate the efficacy and safety of mavrilimumab in adults hospitalised with severe COVID-19 pneumonia and hyperinflammation, showed that a single infusion of mavrilimumab **reduced progression to mechanical ventilation and improved survival**. Mavrilimumab recipients had a reduced requirement for mechanical ventilation and improved survival: at day 29, the proportion of patients alive and free of mechanical ventilation was 12.3 percentage points higher with mavrilimumab (86.7% of patients) than placebo (74.4% of patients) (Primary endpoint; p=0.1224). Mavrilimumab recipients experienced a **65% reduction in the risk of mechanical ventilation or death through Day 29 (Hazard Ratio (HR) = 0.35; p=0.0175)**. Day 29 mortality was 12.5 percentage points lower in mavrilimumab recipients (8%) compared to placebo (20.5%) (p=0.0718). Mavrilimumab recipients had a 61% reduction in the risk of death through Day 29 (HR= 0.39; p=0.0726). Adverse events occurred less frequently in mavrilimumab recipients compared to placebo, including secondary infections and thrombotic events (known complications of COVID-19). Thrombotic events occurred only in the placebo arm (5/40 [12.5%]) [124] [125].

Phase 3 Ergebnisse in Q1/2022 erwartet

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 [126].

3.2.38 SAB-185

About the drug under consideration

polyklonaler Antikörper entwicklet in Operation Warp Speed

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.

Laborstudie zu Omicron: wirksam

The recent publication of nonclinical data demonstrating SAB-185's potent neutralization of multiple emerging SARS-CoV-2 variants including Delta and Lambda [127]. On December 16, 2021 SAB Biotherapeutics announced data demonstrating that SAB-185 retains neutralization activity against the Omicron SARS-CoV-2 variant in an *in vitro* pseudovirus model. The data were generated by scientists at the US Food and Drug Administration (FDA) Center for Biologics Evaluation and Research (CBER) [128]. Preclinical data has also indicated that SAB-185 is significantly more potent than human-derived convalescent immunoglobulin G (IgG).

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 [129]. 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) [130].

3.2.39 Ensovibep (MP0420)

About the drug under consideration

Designed Ankyrin Repeat Protein (DARPin)

Antimikrtobiotikum

IV Verabreichung

Ensovibep is a small-molecule therapeutic designed by Molecular Partners in partnership with Novartis. It consists of a single kind of small molecule, from a novel class of antimicrobials known as DARPins (designed ankyrin repeat proteins). DARPins offer a differentiated approach to treating COVID-19 through a single molecule that can engage up to three parts of the SARS-CoV-2 virus simultaneously to neutralize the virus through multiple mechanisms. It is now being evaluated in clinical studies. Initial findings from the phase 1 trial of ensovibep showed it to be safe and well tolerated, with no significant adverse events amd with the expected half-life of two to three weeks [131-133]. Ensovibep should be administered intravenously, as infusion.

auch bei unterschiedlichen Virus-Varianten wirksam

According to results of in vitro studies using pseudovirion models of SARS-CoV-2 to analyse for infectivity in the presence of ensovibep, the drug continues to retain full potency against the new viral variants of SARS-CoV-2 (i.e., UK (B1.1.7), South Africa (B.1.351), Brazil (P.1), California (B.1.429), New York (B.1.526), emerging variants R.1 and A.23.1, the individual key mutations of the variants identified in India, B.1.617 and B.1.618, and other key spike mutations identified to date), and could have the potential for sustained binding to additional COVID-19 variants, as they may appear in the future [134].

Withdrawn, suspended or terminated studies

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

Phase 3, ACTIV-3 hospitalisierte Pts. angehalten (Unwirksamkeit)

On **November 17 2021**, Molecular Partners has announced to **stop** the **recruitment** of **hospitalised adult Covid-19 patients** in the **phase 3, ACTIV-3 clinical trial** of ensovibep (NCT04501978); after a futility analysis, it was found that ensovibep did not meet the thresholds needed to progress subject enrolment [135].

Phase 2/3 EMPHATY ambulante Pts.

Ensovibep is currently assessing in **phase 2/3 EMPHATY trial** (NCT04828161), in **outpatients** with early stages of infection, to prevent worsening symptoms and hospitalisation (adults, with a positive SARS-CoV-2 antigen test and who are experiencing at least two pre-determined mild/moderate symptoms of COVID-19 within 7 days of their diagnosis) [135].

Results of publications

keine veröffentlichten Studien

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

3.2.40 Bemcetinib

About the drug under consideration

selektiver AXL Inhibitor

orale Verabreichung

Bemcentinib (formerly known as BGB324), is a potential first-in-class, potent and highly selective AXL inhibitor. It exhibits potent anti-viral activity in preclinical models against several enveloped viruses, including Ebola and Zika virus. Preclinical data suggest that bemcentinib is potentially useful for the

treatment of early SARS-CoV-2 infection [136]. It targets a cell-surface protein called AXL, which is one of several cell surface receptors used by enveloped viruses to enter cells; it prevents inhibition of type I interferon, which is the cell's anti-viral defence mechanism, suggesting valuable utility in treatment of SARS-CoV-2 infection. New data investigating bemcentinib against SARS-CoV-2 mutations showed that bemcentinib is also efficacious in preventing SARS-CoV-2 infection by carrying circulating mutations [137]. It is administered as an oral capsule and taken once per day.

Withdrawn, suspended or terminated studies

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

2 laufende Studien Phase 2 RCTs hospitalisierte Pts.

Bemcetinib is investigated in **two phase 2 RCTs**, in **hospitalised COVID-19 patients**: one **BerGenBio's trial** conducted in South Africa and India (**NCT04890509**) is completed, but the results are not yet published.

ACCORD2 Plattform Studie

The other is **ACCORD2 study**, sponsored by University Hospital Southampton, UK: a multicentre, seamless, phase 2 adaptive randomisation platform study to assess the efficacy and safety of multiple candidate agents for the treatment of COVID-19 in hospitalised patients (**EudraCT 2020-001736-95**).

Results of publications

keine veröffentlichten Studien

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

Firmenankündigungen:

bessere Wirksamkeit mit Bemcetinib bei Reduktion der Progression

In July 2021, manufacturer BerGenBio has presented a combined analysis of data from these two phase 2 studies mentioned above, at the European Congress of Clinical Microbiology & Infectious Diseases (ECCMID). Results favoured bemcetinib and showed survival 96.6% vs 91.2%; significantly reduced likelihood (69%) of progression to ventilation in higher severity cohort; and significantly increased likelihood (88%) of shorter time to recovery or discharge in higher severity cohort. Patients in the subgroup (higher severity cohort) were receiving oxygen (Grade 4) or non-invasive ventilation (Grade 5) and recorded serum levels of the inflammatory marker C-Reactive Protein (CRP) greater than 30mg/L. This subgroup represents more than 60% of the patients in the combined study population, and the previously reported treatment benefit in this group of patients in India and South Africa is reproduced in analysis of the patients studied in the UK. Bemcentinib was well tolerated throughout both studies [138].

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