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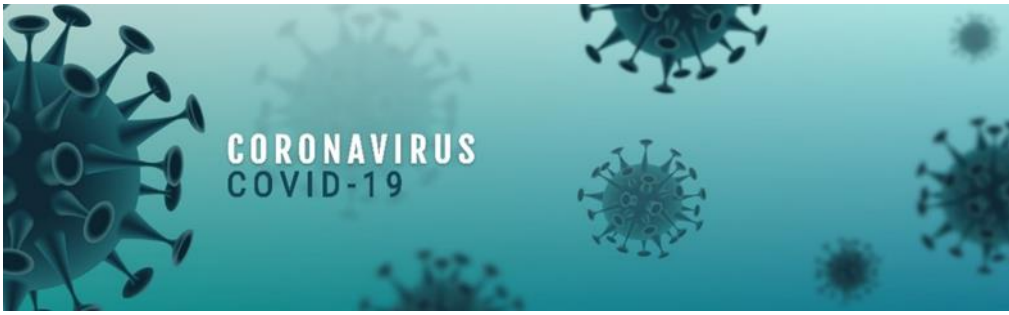
Covid-19



HSS/ Horizon Scanning

Living Document **V24**

October/November 2022

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Covid-19

HSS/ Horizon Scanning
Living Document **V24 October/November 2022**

Vienna, November 2022

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October/November 2022	Methodology (1.2) – no changes
October/November 2022	Vaccine (chapter 2) – reporting is stopped, see earlier version (V17_August and September 2021) for more details
October/November 2022	Update Summary (chapter 3.1)
October/November 2022	Update Remdesivir (chapter 3.2.1) - see earlier versions (V13_April and V18_October/November 2021, V22_June and July 2022) for more details
October/November 2022	Favipiravir (chapter 3. 2.3) - see earlier versions (V15_June 2021 and V17_August and September 2021) for more details
October/November 2022	Darunavir (chapter 3. 2.4) – see earlier version (V15_June 2021) for more details
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October/November 2022	Gimsilumab (chapter 3.2.21) – see earlier version (V22_June and July 2022) for more details

1 Background: policy question and methods

Fragestellung und Methodik: Details in früheren Versionen

The reader is referred to earlier versions (last: v22 June/ July 2022) for more details on

- Policy Question and
- Methodology

2 Results: Vaccines

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

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

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.

On **June 7, 2022 EMA's Medicine Shortages Steering Group adopted** the **list of critical medicines** for the **COVID-19 health emergency**. The published list contains all the approved vaccines and therapeutics: **dexamethasone-containing medicines**, **tixagevimab/cilgavimab** (Evusheld), **anakinra** (Kineret), **nirmatrelvir/ritonavir** (Paxlovid), **regdanvimab** (Regkirona), **tocilizumab** (RoActemra), **casirivimab/imdevimab** (Ronapreve), **remdesivir** (Veklury) and **sotrovimab** (Xevudy) in the European Union (EU) to prevent or treat COVID-19. It will be updated to reflect changes in the pandemic situation which may give rise to an increased risk of shortages of particular medicines, or following the authorisation of new medicines [1].

EMA Liste an knappen Arzneimitteln beinhaltet alle zugelassenen Medikamente

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 and oral antivirals

In **November 2021**, the **Omicron (B.1.1.529) variant** was designated as the **new variant of concern** (VOC) and in January 2022 has become the dominant VOC globaly: it includes numerous mutations in the spike protein. Omicron is comprised of several genetically related **sublineages**, including **BA.1**, **BA.2, BA.3, BA.4 and BA.5**. Ongoing studies are evaluating the susceptibility of this VOC to the anti-SARS-CoV-2 mAbs. **This variant has markedly reduced susceptibility to some anti-SARS-CoV-2 mAb products,** including **bamlanivimab plus etesevimab and casirivimab plus imdevimab. Sotrovimab** has substantially **decreased in vitro activity against** the Omicron **BA.2, BA.4 and BA.5 subvariants. BA.5** has become the dominant subvariant, with prevalence around 87%.

seit November 2021: Omicron

Einfluss auf Wirksamkeit von Antikörper-Therapien

Based on in vitro data, **bebtelovimab has activity against** a **broad range of SARS-CoV-2 variants**, including the **B.1.1.529 (Omicron) variant of concern (VOC)** and **its BA.1 and BA.2 sublineages**. The same is true for **BA.2.12.1** and **BA.4/BA.5 sublineages**. The new Omicron BA.5 (**BQ.1**), and Omicron BA.5 (**BQ.1.1**) variants showed a **large reduction** in susceptibility to bebtelovimab of **>672-fold** [2].

Tixagevimab and cilgavimab in **combination** retained full to nearly full neutralisation activity against pseudovirus and/or live virus SARS-CoV-2 variant strains: VLPs pseudotyped with the spike of **Omicron BA.2.12.1**, **BA.3**, or **BA.4/BA.5** showed **5-fold**, **16-fold**, and **33- to 65-fold reductions** in neutralizing activity, respectively. Omicron **BA.4.6** showed **>1000-fold reduction** in neutralizing activity [3].

These three Omicron **sublineages BA.4**, **BA.5** and **BA.2.12.1** have acquired a few additional mutations that may impact their characteristic. In some countries, the rise in cases has also led to a surge in hospitalisations and ICU admissions; however, the current evidence available does not indicate a change in severity associated with any of the three Omicron descendent lineages BA.2.12.1, BA.4 and BA.5.

3 Omikron Subtypen BA.4, BA.5, BA.2.12.1

keine Veränderung im Schweregrad

Recently, the **Centers for Disease Control and Prevention** (**CDC**) has reported a **rapid increase** in the circulation of **certain SARS-CoV-2 Omicron subvariants** in the United States that are **likely to be resistant to currently**

US-CDC: rasche Zunahme von Resistenzen

used anti-SARS-CoV-2 monoclonal antibodies (mAbs).The **subvariants BQ.1** and **BQ.1.1** are **likely to be resistant** to the anti-SARS-CoV-2 monoclonal antibody (mAb) **bebtelovimab**, and the **subvariants BA.4.6**, **BA.2.75.2**, **BF.7**, **BQ.1**, and **BQ.1.1**, are **likely to be resistant** to the mAbs **tixagevimab plus cilgavimab** (**Evusheld**) [4, 5]

EU-ECDC: Zunahme der Varianten BQ.1/BQ.1.1.

According to the **European Center for Disease Control and Prevention** (**ECDC**) [6] **two new variants of interest** (VOI) are **Omicron BA.2.75** and **BQ.1 sublineges** that could imply a significant impact on transmissibility, severity and/or immunity, realistically having an impact on the epidemiological situation in the EU/EEA. BQ.1 variant originates from the BA.5 Omicron Variant of Concern (VOC). BQ.1, including its sub-lineages, has been designated as Variant of Interest (VOI) by ECDC as of 20 October 2022. Based on modelling estimates, it is expected that by mid-November to beginning of December 2022, more than 50% of SARS-CoV-2 infections will be due to **BQ.1/BQ.1.1**. By the beginning of 2023, more than 80% of SARS-CoV-2 cases are expected to be due to BQ.1/BQ.1.1 [7].

WHO: Zunahme neuer Varianten

According the **WHO update** on **9 November 2022** [8], the global variant circulation indicates a replacement of previously dominating BA.5 descendent lineages by the most recently emerging variants BQ.1 and BA.5 + R346X. Among the variants under monitoring and during week 42 as compared to week 41, BQ.1 (BA.5.3.1.1.1.1) and its descendent lineages and BA.5 + R346X are the lineages that have had the largest increases. BQ.1 rose from 9.4% to 13.4%. BA.5 with additional mutations (R346X, K444X, V445X, N450D and/or N460X) rose from 20.8% to 22.9%, mainly due to BA.5 + R346X. BA.2.75 showed a rise in sequence prevalence from 3.5% to 4.3%. XBB and its descendent lineages rose from 1.1% to 2.0%. BA.2.3.20 is rising slowly, with a prevalence of <1%.

Nirmatrelvir zeigt bis bislang gleichbleibende antivirale Wirkung

Currently, **nirmatrelvir** has shown consistent in vitro antiviral activity against the following variants: Alpha, Beta, Delta, Gamma, Lambda, Mu, and Omicron BA.1 and BA.2.

auch Remdesivir, Molnupiravir

Current data indicate that **remdesivir, molnupiravir and nirmatrelvir** may have **therapeutic value** against the **sublineages BA.2.12.1, BA.4, and BA.5 of SARS-CoV-2 omicron variants**. Takashita et al. 2022 [9] tested antiviral drugs (**remdesivir, molnupiravir and nirmatrelvir**) by determining the in vitro 50% inhibitory concentration (IC50) of each compound against BA.2.12.1, BA.4, and BA.5. Positive results indicate that these three antiviral drugs may have **therapeutic value** against the **sublineages BA.2.12.1, BA.4, and BA.5 of SARS-CoV-2 omicron variants**.

The antiviral drugs **ritonavir-boosted nirmatrelvir, remdesivir,** and **molnupiravir** are **expected to be active against subvariants BQ.1, BQ.1.1**, **BA.4.6**, **BA.2.75.2**, **BF.7**, **BQ.1**, and **BQ.1.1.**

The US COVID-19 Treatment Guidelines Panel on Omicron subvariants and **treatment** of **non-hospitalised patients** (last update **November 10, 2022**)

August 2022:
US COVID-19 Treatment Guidelines Panel zur Behandlung nicht-hospitalisierter Hochrisiko-Patient*innen

Nirmatrelvir + ritonavir (Paxlovid) (AIIa)
Remdesivir (BIIa)

geringere Präferenz
Bebtelovimab (CIII)
Molnupiravir (CIIa)

The Panel has recommended **bebtelovimab** 175 mg intravenous (IV) injection in patients aged ≥12 years as an alternative therapy **ONLY** when ritonavir-boosted nirmatrelvir (Paxlovid) and remdesivir are not available, feasible to use, or clinically appropriate **(CIII)**. Treatment should be initiated as soon as possible and within 7 days of symptom onset. **When resistant Omicron subvariants** (e.g., **BQ.1**, **BQ.1.1**) **represent the majority of infections in the region**, clinicians **cannot rely on bebtelovimab** to be effective for the treatment of COVID-19. **Ritonavir-boosted nirmatrelvir, remdesivir,** and **molnupiravir** are **expected to be active against these resistant subvariants.**

Because the Omicron VOC and its subvariants have become the dominant variants in the United States, the Panel **recommends against** using **bamlanivimab plus etesevimab**, **casirivimab plus imdevimab**, or **sotrovimab** for the treatment of COVID-19 **(AIII)**.

This statement contains the Panel's recommendations for **treating nonhospitalised patients** who are **at high risk** of progressing to severe COVID-19 using the currently available therapies. The Panel recommends one of the following:

Preferred therapies (listed in order of preference):

- **Ritonavir-boosted nirmatrelvir (Paxlovid) (AIIa)**
- **Remdesivir (BIIa)**

Alternative therapies (for use ONLY if none of the preferred therapies are available, feasible to use, or clinically appropriate, listed in alphabetical order):

- **Bebtelovimab 175 mg,** but ONLY when the majority of circulating Omicron subvariants in the region are susceptible **(CIII)**; *or*
- **Molnupiravir 800 mg (CIIa)**

US COVID-19 Treatment Guidelines on **prophylaxis** (last update **November 10, 2022**)

Impfung ist Prophylaxe erster Wahl

Resistenz gegen Evusheld nimmt zu

Trotzdem:

zur pre-Exposure Prophylaxe bei schwer immun-komprimierten Pts:

Tixagevimab/ Cilgavimab (Evusheld)

Zusätzlich: Vorsichtsmaßnahmen

- The COVID-19 Treatment Guidelines Panel (the Panel) recommends that all patients who are eligible to receive tixagevimab plus cilgavimab (Evusheld) as pre-exposure prophylaxis (PrEP) should receive bivalent COVID-19 vaccines unless the use of these vaccines is contraindicated due to a history of severe adverse reactions to a COVID-19 vaccine or any of its components **(AIII)**.
- The prevalence of Omicron subvariants that are resistant to tixagevimab plus cilgavimab is rapidly increasing. The proportion of SARS-CoV-2 infections caused by these subvariants is currently estimated to exceed 45% in all regions in the United States.
- Tixagevimab plus cilgavimab is the only agent authorized by the Food and Drug Administration for use as COVID-19 PrEP in people who are not expected to mount an adequate immune response to COVID-19 vaccination or those with contraindications for COVID-19 vaccines.
    - In the absence of an alternative option for PrEP, the Panel continues to recommend the use of **tixagevimab plus cilgavimab** as PrEP for eligible individuals **(BIIb)**.
    - Given the increasing prevalence of these resistant SARS-CoV-2 subvariants, the decision to administer tixagevimab plus cilgavimab to a given patient should be based on the regional

prevalence of the resistant subvariants, the individual patient's risks, the available resources, and logistics.

- Individuals who receive tixagevimab plus cilgavimab as PrEP should continue to take precautions to avoid exposure to SARS-CoV-2. If they experience signs and symptoms consistent with COVID-19, they should be tested for SARS-CoV-2 infection and, if infected, promptly seek medical attention and treatment, if appropriate.

Dosierung von Tixagevimab/ Cilgavimab (Evusheld)

- The Panel recommends using **tixagevimab 300 mg plus cilgavimab 300 mg** administered as 2 consecutive 3-mL intramuscular injections **(BIII)** as SARS-CoV-2 **pre-exposure prophylaxis** (**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; *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.
- The Panel recommends repeat dosing of **tixagevimab 300 mg plus cilgavimab 300 mg** administered as IM injections **every 6 months** (**BIIb**).

FDA EUA: rasche Verabreichung von 2.Dosis

The FDA Emergency Use Authorization states that individuals who received tixagevimab 150 mg plus cilgavimab 150 mg should be given a second dose as soon as possible. The specific dose of tixagevimab plus cilgavimab that an **individual** should receive depends on the amount of time that has passed since the first dose was administered: If the initial dose was administered ≤3 months prior, the second dose should be tixagevimab 150 mg plus cilgavimab 150 mg. If the initial dose was administered >3 months prior, the second dose should be tixagevimab 300 mg plus cilgavimab 300 mg.

KEIN Ersatz für Impfung !

- **Tixagevimab plus cilgavimab is not a substitute for COVID-19 vaccination and should not be used in unvaccinated individuals for whom COVID-19 vaccination is recommended and who are anticipated to have an adequate response**.

Empfehlung GEGEN Bamlanivimab/ Etesevimab sowie Casirivimab/ Imdevimab

als Post-Exposure Prophylaxe

The Panel **recommends against** the use of **bamlanivimab plus etesevimab** and **casirivimab plus imdevimab** for **post-exposure prophylaxis** (PEP), as the B.1.1.529 (**Omicron**) variant **and its subvariants**, which are not susceptible to these agents, are currently the predominant variant circulating in the United States **(AIII)**.

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, nicht aber für Pts ohne 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.** In the **recent update** (**16 September 2022**) **corticosteroids and IL-6 receptor blockers** (**tocilizumab and sarilumab**) **may be administered in combination with baricitinib** to patients with **severe or critical COVID-19 (strong recommendation)** [10].

starke Empfehlung fürTocilizumab and Sarilumab pülud Baricitinib

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 most patients) **(BIIa)**; **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)**.

Kombinationstherapien

plus Remdesivir
plus Baricitinib
plus Tocilizumab

For patients who require delivery of oxygen through a high-flow device or noninvasive ventilation, the Panel recommends the use of a combination of 2 immunomodulators (either **dexamethasone plus baricitinib [AI]** or **dexamethasone plus tocilizumab [BIIa]**). If baricitinib, tofacitinib, tocilizumab, or sarilumab cannot be obtained, the Panel recommends starting dexamethasone while waiting for an additional immunomodulator to be acquired.

Tocilizumab und Sarilumab

For patients who require Invasive Mechanical Ventilation or Extracorporeal Membrane Oxygenation and who have not initiated 1 of the recommended immunomodulator combinations, the Panel recommends promptly starting either **dexamethasone plus baricitinib (BIIa)** or **dexamethasone plus tocilizumab (BIIa)**. If the second immunomodulator is not available, dexamethasone should be started while waiting for the second agent.

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

NICHT: für nicht-hospitalisierte Pts.

The Panel stresses that the use of corticosteroids in **nonhospitalised patients** with COVID-19 **is not recommended (AIIb).**

Remdesivir (Veklury)

Remdesivir (Veklury) is an antiviral medicine for systemic use which firstly received a **conditional marketing authorisation** in **EU,** and then **full approval.** According to the **last** EPAR - Product information **update** in **November 2022** [11] it is **indicated** for the treatment of coronavirus disease 2019 (**COVID-19)** in **adults and paediatric patients** (at least 4 weeks of age and weighing at least 3 kg) with **pneumonia requiring supplemental oxygen** (low- or high-flow oxygen or other noninvasive ventilation at start of treatment) and **adults and paediatric patients** (weighing at least 40 kg) who **do not require supplemental oxygen** and who are **at increased risk of progressing to severe COVID-19**.

EMA Zulassung: Remdesivir (Veklury): Indikationen

Lungenentzündung mit Bedarf nach Sauerstoff, aber auch nur bei Risiko für progredienete Erkrankung

On June 11, 2021 **EMA** stated that PRAC has recommended a **change to the product information to include sinus bradycardia** as an **adverse reaction of unknown frequency** for this medicine.

PRAC: Sinusbradykardie

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

On **January 21, 2022 FDA** has **expanded** the approved indication for Veklury to include its use in **adults and pediatric patients** with positive results of direct SARS-CoV-2 viral testing, and who are **not hospitalised** and have **mild-to-moderate COVID-19**, and are at **high risk for progression to severe COVID-19, including hospitalisation or death**.

Jän 2022: FDA- Indikations-ausweitung:

mild-moderate Pts. Kinder

On **April 25, 2022 FDA expanded** the approval of the COVID-19 treatment Veklury (remdesivir) to include **pediatric patients 28 days of age and older weighing at least 3 kilograms** (about 7 pounds) with positive results of direct SARS-CoV-2 viral testing, who are **hospitalised**, or **not hospitalised** and have **mild-to-moderate COVID-19** and are at **high risk for progression to severe COVID-19**, **including hospitalisation or death**. This action makes Veklury the first approved COVID-19 treatment for children less than 12 years of age.

In the tenth version of the guideline, the **WHO living guideline** (**22 April 2022**) provided **conditional recommendation** for the **use of remdesivir** in patients with **non-severe COVID-19** at the **highest risk of hospitalisation.**

WHO Guideline (April2022): auch für nicht schwer Erkrankte, aber Risiko für Hospitalisierung

In the **last update** on **16 September 2022** the **WHO living guideline** provided **conditional recommendation for** the **use of remdesivir** in patients with **severe COVID-19** and **conditional recommendation against** the **use of remdesivir** in patients with **critical COVID-19** [10].

US COVID-19 Treatment Guidelines Panel:

The US COVID-19 Treatment Guidelines Panel recommendations on remdesivir treatment for **hospitalised patients** with COVID-19:

bei hospitalisierten Pts. ohne Sauerstoff, aber Hochrisiko für Fortschreiten der Erkrankung

Remdesivir is **recommended** for use **in hospitalised patients who do not require oxygen supplementation,** but are **at high risk of progressing to severe COVID-19 (BIII).**

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

Remdesivir is **recommended for use in hospitalised patients who require minimal conventional oxygen (BIIa); Dexamethasone plus remdesivir** (e.g., for most patients) (**BIIa**); **Dexamethasone** (e.g., when combination therapy with remdesivir cannot be used or is not available) (**BI**). For patients who are receiving dexamethasone and who have **rapidly increasing oxygen needs** and **systemic inflammation** add **PO baricitinib** or **IV tocilizumab** to 1 of the options above **(BIIa)**. If PO baricitinib and IV tocilizumab are not available or not feasible to use, PO tofacitinib can be used instead of PO baricitinib **(BIIa)**, and IV sarilumab can be used instead of IV tocilizumab **(BIIa)**.

andere Therapieoptionen:

vgl. Dexamethasone

For hospitalised patients with COVID-19 who **require oxygen delivery through a high-flow device or, noninvasive ventilation** promptly start 1 of the following, if not already initiated: **Dexamethasone plus PO baricitinib (AI); Dexamethasone plus IV tocilizumab (BIIa).** If PO baricitinib and IV tocilizumab are not available or not feasible to use, PO tofacitinib can be used instead of PO baricitinib **(BIIa)**, and IV sarilumab can be used instead of IV tocilizumab **(BIIa)**. If **baricitinib, tofacitinib, tocilizumab,** or **sarilumab** cannot be obtained: **Dexamethasone (AI).** Add **remdesivir** to 1 of the options above in certain patients **(CIIa)**. The Panel **recommends against** the use of remdesivir without immunomodulators in these patients **(AIIa)**.

For hospitalised patients with COVID-19 who require **invasive mechanical ventilation or extracorporeal membrane oxygenation** promptly start 1 of the following, if not already initiated: **Dexamethasone plus PO baricitinib (BIIa); Dexamethasone plus IV tocilizumab (BIIa).** If PO baricitinib and IV tocilizumab are not available or not feasible to use, PO tofacitinib can be used instead of PO baricitinib **(BIIa)**, and IV sarilumab can be used instead of IV tocilizumab **(BIIa)**. If **baricitinib, tofacitinib, tocilizumab**, or **sarilumab** cannot be obtained: **Dexamethasone (AI).**

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

Molnupiravir (Lagevrio)

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

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.

On **December 23, 2021 FDA** issued **EUA**, and **reissued** on **March 23, 2022** 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 und erneuert März 2022: nur wenn andere Therapieoptionen ncht verfügbar sind

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

WHO: vorläufige Empfehlung für mild Erkrankte, aber mit hohem Risiko für Hospitalisierung

The **WHO living guideline** (3 March 2022) provided **conditional recommendation** to **use** molnupiravir **in non-severe COVID-19 patients at highest risk of hospitalisation (excluding pregnant and breastfeeding women, and children)**.

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

On **January 27, 2022 EMA's** human medicines committee (**CHMP**) has recommended granting a **conditional marketing authorisation** for the oral antiviral medicine Paxlovid (PF-07321332 / ritonavir) for the **treatment of COVID-19 in adults who do not require supplemental oxygen and who are at increased risk of the disease becoming severe.** The **European Commission authorised** the COVID-19 treatment Paxlovid, following evaluation by EMA on **January 28, 2022**.

Jän. 2022 EMA: vorläufige Zulassung von Paxlovid für Hochrisiko-Pts.

On **December 22, 2021 FDA** issued **EUA,** and **reissued** on **April 14, 2022** 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 und erneuert April 2022: Therapiebeginn innerhalb von 5 Tagen nach Symptomen

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

The **WHO living guideline** (**22 April 2022**) provided **strong recommendation** for the **use of nirmatrelvir-ritonavir** in patients with **non-severe COVID-19** at the **highest risk of hospitalisation** and **conditional recommendation against** the **use of nirmatrelvir-ritonavir** in patients **with non-severe COVID-19** at a **low risk of hospitalisation**.

WHO Guideline: Paxlovid NUR bei milder Erkrankung für Hochrisiko-Pts

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

In **May 2022, FDA approved** a **new indication for baricitinib** for the **treatment of COVID-19** in **hospitalised adults requiring supplemental oxygen, non-**

invasive or invasive mechanical ventilation, or extracorporeal membrane ohygenation (ECMO).

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

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

The **US COVID-19 Treatment Guidelines Panel** recommends using **baricitinib or tofacitinib in combination with dexamethasone** in **hospitalised patients** with **evidence of inflammation** and **increasing oxygen needs**.

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

For hospitalised patients with COVID-19 who **require oxygen delivery through a high-flow device or, noninvasive ventilation** promptly start 1 of the following, if not already initiated: **Dexamethasone plus PO baricitinib (AI); Dexamethasone plus IV tocilizumab (BIIa).** If PO baricitinib and IV tocilizumab are not available or not feasible to use, PO tofacitinib can be used instead of PO baricitinib **(BIIa)**, and IV sarilumab can be used instead of IV tocilizumab **(BIIa)**. If **baricitinib, tofacitinib, tocilizumab,** or **sarilumab** cannot be obtained: **Dexamethasone (AI).** Add **remdesivir** to 1 of the options above in certain patients **(CIIa)**. The Panel **recommends against** the use of remdesivir without immunomodulators in these patients **(AIIa)**.

Empfehlung GEGEN: Baricitinib als Kombinationstherapie mit Tocilizumab sowie gegen andere JAK-Inhibitoren (als Baricitinib und Tofacitinib)

For hospitalised patients with COVID-19 who require **invasive mechanical ventilation or extracorporeal membrane oxygenation** promptly start 1 of the following, if not already initiated: **Dexamethasone plus PO baricitinib (BIIa); Dexamethasone plus IV tocilizumab (BIIa).** If PO baricitinib and IV tocilizumab are not available or not feasible to use, PO tofacitinib can be used instead of PO baricitinib **(BIIa)**, and IV sarilumab can be used instead of IV tocilizumab **(BIIa)**. If **baricitinib, tofacitinib, tocilizumab**, or **sarilumab** cannot be obtained: **Dexamethasone (AI).**

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)**.

WHO: starke Empfehlung für Baricitinib auch in Kombination mit Tocilizumab and Sarilumab bei schwerer/ kritischer Erkrankung

The **WHO living guideline** (last updated **September 16, 2022** provided **strong recommendation** to **use** baricitinib **in severe and critically ill COVID-19 patients**. **Corticosteroids and IL-6 receptor blockers** (**tocilizumab and sarilumab**) are also recommended, and **may be administered in combination with baricitinib** to patients with severe or critical COVID-19 **(strong recommendation)**.

Tofacitinib (Xeljanz)

vgl. Text zu Baricitinib

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

WHO: vorläufige Empfehlung GEGEN Tofacitinib

The **WHO living guideline** (14 January 2022) provided **conditional recommendation against** the use of tofacitinib for treating severe and critical COVID-19.

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

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).

Jän 2022: REGEN-COV: nur bei bestimmten Virus-Varianten

As of **January 24, 2022** REGEN-COV is **not authorized** for **treatment** of mild to moderate COVID-19 in geographic regions **where infection is likely to have been caused by a non-susceptible SARS-CoV-2 variant based on available information such as variant susceptibility to this drug and regional variant frequency**. The same is true for **post-exposure prophylaxis** of COVID-19.

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 adults and adolescents (from 12 years of age and weighing at least 40 kilograms). **Marketing authorisation** is **granted** by EC on **12 November 2021**.

WHO/ US COVID-19 Treatment Guidelines: starke Empfehlung gegen Ronapreve

The **WHO living guideline** (last updated **16 Sept 2022** provided **strong recommendation against** the **use of casirivimab/imdevimab** combination in **patients with COVID-19** [10].

For the **US COVID-19 Treatment Guidelines** Panel's **outpatient treatment** recommendations, see the above subsection related to **SARS-CoV-2 variants and their susceptibility to anti-SARS-CoV-2 monoclonal antibodies and oral antivirals.** The Panel **recommends against** the use of **bamlanivimab plus etesevimab** and **casirivimab plus imdevimab** for **post-exposure prophylaxis** (PEP), as the B.1.1.529 (**Omicron**) variant, and **its subvariants**, which are not susceptible to these agents, are currently the predominant variant circulating in the United States **(AIII)**.

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

As of **January 24, 2022**, bamlanivimab and etesevimab are **not authorized** for **treatment** of mild to moderate COVID-19 **in geographic regions where infection is likely to have been caused by a non-susceptible SARS-CoV-2 variant based on available information including variant susceptibility to these drugs and regional variant frequency**. The same is true for **post-exposure prophylaxis** of COVID-19.

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 **hospitalisation or death**.

On **April 05, 2022 FDA** announced that sotrovimab is **no longer authorized** to treat COVID-19 in any U.S. region **due to increases** in the proportion of COVID-19 cases caused by the **Omicron BA.2 sub-variant**.

FDA April 2022: Sotrovimab nicht länger zugelassen

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

The **WHO living guideline** (last updated **16 Sept 2022** provided provided **strong recommendation against** the **use of sotrovimab** in **patients with non-severe COVID-19** [10].

WHO: starke Empfehlung gegen Sotrovimab Bei nicht-schwerer Erkrankung

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

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** and on **March 15 2022** started evaluating the **marketing authorisation application**. On 23 March 2022 EMA recommended granting a marketing authorisation and on **30 March 2022** the **EC authorised** Evusheld for the **pre-exposure prophylaxis** of COVID-19 in **adults** and **adolescents aged 12 years and older weighing at least 40 kg.**

EMA Zulassung März 2022: 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. According to the revised FDA EUA in **October 2022**, there is a potential risk of treatment failure due to the development of viral variants that are resistant to tixagevimab and cilgavimab. Prescribing healthcare providers should consider the prevalence of SARS-CoV-2 variants in their area, where data are available, when considering prophylactic treatment options [3].

FDA: Resistenzen

For the **US COVID-19 Treatment Guidelines** Panel's **outpatient pre-exposure prophylaxis** (**PrEP**) recommendations, see the above subsection related to **SARS-CoV-2 variants and their susceptibility to anti-SARS-CoV-2 monoclonal antibodies and oral antivirals.**

Bebtelovimab

On **February 11, 2022** the U.S. Food and Drug Administration (**FDA**) has issued an Emergency Use Authorization (**EUA**) for the emergency use of bebtelovimab for the treatment of **mild-to-moderate coronavirus disease 2019** (COVID-19) in **adults and pediatric patients (12 years of age and older weighing at least 40 kg**): with **positive results of direct 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 approved or authorized by FDA are not accessible or clinically appropriate**.

Feb 2022: FDA EUA für mild-moderat Erkrankte mit hohem Risiko für Progression, wenn alternative Therapien nicht verfügbar

Bebtelovimab retains activity against the omicron variant and its BA.1 and BA.2 sublineages, as well as BA.2.12.1 and BA.4/BA.5. According to the revised FDA EUA in November 2022, there is a potential risk of treatment failure due to the development of viral variants that are resistant to bebtelovimab [2].

auch gegen Omicron wirksam

The company did not apply for authorisation of bebtelovimab to market it in the EU.

Hersteller Lilly: bislang kein Antrag für EMA-Zulassung

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

US COVID-19 Treatment Guidelines Panel

Convalescent plasma (CVP)

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

The **new EUA revision** in **December 2021** authorised the use of **high titer COVID-19 convalescent plasma only** in **outpatients** or **inpatients with COVID-19** who have **immunosuppressive disease** or who are **receiving immunosuppressive treatment.**

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

The **US COVID-19 Treatment Guidelines Panel** (last updated April 29, 2022

- **recommends against** the use of COVID-19 convalescent plasma that was collected prior to the emergence of the Omicron variant for the treatment of COVID-19 **(AIII)**.
- The Panel **recommends against** the use of CCP for the treatment of COVID-19 in **hospitalised, immunocompetent patients (AI)**.
- There is **insufficient evidence** for the Panel to recommend **either for or against** the use of high-titer CCP that was collected after the emergence of Omicron for the **treatment of immunocompromised patients and nonhospitalised, immunocompetent patients** with COVID-19.

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)

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

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)**.

Dez 2021 EMA Indikationsausweitung/ Marktzulassung für hospitalisierte Pts mit nicht 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**.

US COVID-19 Treatment Guidelines Panel

The US COVID-19 Treatment Guidelines Panel recommendations for **hospitalised patients** with COVID-19:

Therapieoptionen mit Kombinationstherapien mit Tocilizumab

Remdesivir is **recommended** for use in hospitalised patients **who require minimal conventional oxygen (BIIa); Dexamethasone plus remdesivir** (e.g., for most patients) (**BIIa**); **Dexamethasone** (e.g., when combination therapy with remdesivir cannot be used or is not available) (**BI**). For patients who are receiving dexamethasone and who have rapidly increasing oxygen needs and systemic inflammation add **PO baricitinib** or **IV tocilizumab** to 1 of the options above **(BIIa)**. If PO baricitinib and IV tocilizumab are not available or not feasible to use, PO tofacitinib can be used instead of PO baricitinib **(BIIa)**, and IV sarilumab can be used instead of IV tocilizumab **(BIIa)**.

For hospitalised patients with COVID-19 who **require oxygen delivery through a high-flow device or, noninvasive ventilation** promptly start 1 of the following, if not already initiated: **Dexamethasone plus PO baricitinib (AI);**

Dexamethasone plus IV tocilizumab (BIIa). If PO baricitinib and IV tocilizumab are not available or not feasible to use, PO tofacitinib can be used instead of PO baricitinib **(BIIa)**, and IV sarilumab can be used instead of IV tocilizumab **(BIIa)**. If **baricitinib, tofacitinib, tocilizumab,** or **sarilumab** cannot be obtained: **Dexamethasone (AI).** Add **remdesivir** to 1 of the options above in certain patients **(CIIa)**. The Panel **recommends against** the use of remdesivir without immunomodulators in these patients **(AIIa)**.

For hospitalised patients with COVID-19 who require **invasive mechanical ventilation or extracorporeal membrane oxygenation** promptly start 1 of the following, if not already initiated: **Dexamethasone plus PO baricitinib (BIIa); Dexamethasone plus IV tocilizumab (BIIa).** If PO baricitinib and IV tocilizumab are not available or not feasible to use, PO tofacitinib can be used instead of PO baricitinib **(BIIa)**, and IV sarilumab can be used instead of IV tocilizumab **(BIIa)**. If **baricitinib, tofacitinib, tocilizumab**, or **sarilumab** cannot be obtained: **Dexamethasone (AI).**

Juli 2021: WHO empfiehlt Interleukin-6-Rezeptorblocker für Pts. mit schwere Erkrankung Auch in Kombination mit Baricitinib

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).** In the **recent update** (**16 September 2022**) **corticosteroids and IL-6 receptor blockers** (**tocilizumab and sarilumab**) **may be administered in combination with baricitinib** to patients with severe or critical COVID-19 (**strong recommendation**) [10].

Sarilumab (Kevzara)

vgl. Text zu Tocilizumab

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

Anakinra (Kineret)

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

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**.

Nov 2022: FDA EUA Zulassung

On **November 2022, FDA** issued an **emergency use authorization** (**EUA**) for the drug Kineret (anakinra) for the **treatment** of coronavirus disease 2019 (COVID-19) in **hospitalised adults with positive results of direct SARS-CoV-2 viral testing with pneumonia requiring supplemental oxygen (low- or high-flow oxygen)** who are **at risk of progressing to severe respiratory failure and likely to have an elevated plasma soluble urokinase plasminogen activator receptor (suPAR)** [12].

Lopinavir + ritonavir, chloroquine and hydroxychloroquine

keine Wirksamkeit

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

Favipiravir and Darunavir

US COVID-19 Treatment Guidelines Panel/ WHO Guideline:

Empfehlung GEGEN Behandlung mit:

Favipiravir, Darunavir

Ivermectin

Colchicine

Canakinumab

Interferone

Aspirin

The US COVID-19 Treatment Guidelines Panel **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).**

Ivermectin

The **US COVID-19 Treatment Guidelines Panel recommends against** the use of ivermectin for the treatment of COVID-19, except in clinical trials **(AIIa)**.

The **WHO Therapeutics and COVID-19 living guideline** includes a **recommendation not to use ivermectin except in the context of a clinical trial**.

Colchicine

The **US COVID-19 Treatment Guidelines Panel** 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).**

The **WHO living guideline** (**14 July 2022**) provided **strong recommendation against treatment with colchicine** in patients with **COVID-19.**

Canakinumab

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

Interferons

The **US COVID-19 Treatment Guidelines Panel 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)**.

Aspirin

The **US COVID-19 Treatment Guidelines Panel recommends against** the use of aspirin to prevent mortality or the need for organ support **(AI)**.

Tofacitinib

The **US COVID-19 Treatment Guidelines Panel**: **Baricitinib or tofacitinib** is recommended **in combination with dexamethasone** in **hospitalised patients** with evidence of **inflammation and increasing oxygen needs** (see Section on baricitinib). 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)**.

WHO Guidline: Empfehlung GEGEN die Verwendung von Tofacitinib bei schwerer Erkrankung

The **WHO living guideline** (**14 January 2022**) provided **conditional recommendation against** the use of tofacitinib for treating severe and critical COVID-19.

GEGEN Fluvoxamine

Fluvoxamine

The **WHO living guideline** (**14 July 2022**) provided **recommendation not to use fluvoxamine** in patients with **COVID-19** except in the context of a clinical trial (recommended **only in research settings**).

Other pharmaceuticals listed in this document

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

EMA scientific advice für viele unterschiedliche Medikamente

EMA is providing guidance to assist developers of potential COVID-19 medicines, to prepare for eventual applications for marketing authorisation. This includes scientific advice, as well as informal consultation with the COVID-19 EMA pandemic Task Force (COVID-ETF). The outcome of any consultation or advice from EMA is not binding on developers. COVID-19 medicines that have received EMA advice can be found at 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.

3.2 Individual therapeutics

3.2.1 Remdesivir (Veklury®)

Details in früheren Versionen

The reader is referred to the earlier versions (V13_April and V18_October/November 2021, V22_June and July 2022) and subchapter 3.1 for more details on **remdesivir (Veklury).**

3.2.2 Lopinavir + Ritonavir (Kaletra®)

wegen erwiesenem Mangel an Wirksamkeit wurde Beobachtung beendet

Due to the lack of effectiveness of lopinavir/ritonavir in treating adults hospitalised with COVID-19 patients and the decisions to stop enrolling participants to the lopinavir/ritonavir (Kaletra) arms of the RECOVERY,

SOLIDARITY and DISCOVERY studies in adults hospitalized with COVID-19, our reporting related to lopinavir/ritonavir was stopped also.

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

3.2.3 Favipiravir (Avigan®)

Beobachtung bis v15 (Juni)

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

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

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)** [4].

3.2.4 Darunavir

Beobachtung bis v15 (Juni)

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

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

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)** [4].

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®)

Details in früheren Versionen

The reader is referred to the earlier version (V22_June and July 2022) for more details on **camostat mesylate** (Foipan).

Camostat Mesilate (Foipan®) ist not approved for any anti-viral use (FDA, EMA) in COVID-19.

In addition to already published studies, **Tobback et al. 2022** [13] recently published **negative results** from a **phase 2 RCT** (NCT04625114) in symptomatic (maximum 5 days) and asymptomatic patients with confirmed COVID-19 infection which aimed to assess the efficacy and safety of 300 mg camostat mesylate three times daily in an **ambulatory setting**.

Phase 2 RCT: negative Ergebnisse

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

The reader is referred to the earlier version (V22_June and July 2022) for more details on **APN01**.

Details in früheren Versionen

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 (NCT05065645): 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-

Phase 1 Studie
Erprobung von APN01 als Inhalation

Okt: Dosisfindungsstudie
40 Pts in Österreich

biologics.com/wp-content/uploads/20211012_APEIRON-Biologics_PR_Trial-Start-Inhalation-APN01_ENG.pdf.

3.2.9 Tocilizumab (Roactemra®)

The reader is referred to the earlier versions (V14_May 2021 and V18_October and November 2021) and subchapter 3.1 for more details on **tocilizumab** (**RoActemra**).

Details in früheren Versionen

3.2.10 Sarilumab (Kevzara®)

The reader is referred to the earlier version (V22_June and July 2022) and subchapter 3.1 for more details on **sarilumab** (Kevzara).

Details in früheren Versionen

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

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.**

Details in früheren Versionen

3.2.12 Convalescent plasma (CVP) transfusion

The reader is referred to the earlier version (V15_June 2021) and subchapter 3.1 for more details on **Convalescent plasma** treatment in COVID-19 patients.

Details in früheren Versionen

3.2.13 Plasma derived medicinal products

Neutralizing monoclonal antibodies

The reader is referred to the earlier version (V22_June and July 2022) for more details on **neutralizing monoclonal antibodies.**

Details zu MoABs in früheren Versionen

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

The reader is referred to the subchapter 3.1 for more details.

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

The reader is referred to the earlier versions (V18_October and November 2021 and V22_June and July 2022) The reader is referred to the earlier version (V22_June and July 2022) and subchapter 3.1 for more details on **casirivimab and imdevimab combination (Ronapreve).**

Details in früheren Versionen

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) The reader is referred to the earlier version (V22_June and July 2022) and subchapter 3.1 for more details on **bamlanivimab and etesevimab.**

Details in früheren Versionen

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

The reader is referred to the earlier versions (V21_April and May 2022 and V22_June and July 2022) and subchapter 3.1 for more details on **tixagevimab + cilgavimab** (Evusheld).

Details in früheren Versionen

Results of publications

In addition to one publication from RCTs related to AZD7442 (**PROVENT** - NCT04625725, **phase 3** trial, in **pre-exposure prophylaxis)**, one publication from **phase 3** RCTs related to AZD7442 (**TACKLE** RCT, NCT04723394, for **early outpatient treatment**), the results from **ACTIV-3-TICO phase 3** RCT (NCT04501978) [14] are now published, comparing a single intravenous dose of tixagevimab–cilgavimab versus placebo, in **hospitalised COVID-19 patients** receiving remdesivir and other standard care. 1455 patients were randomly assigned and 1417 in the primary modified intention-to-treat population were infused with tixagevimab–cilgavimab (n=710) or placebo (n=707). The estimated cumulative incidence of sustained recovery was 89% for tixagevimab–cilgavimab and 86% for placebo group participants at day 90 in the full cohort (recovery rate ratio [RRR] 1.08 [95% CI 0.97–1.20]; p=0.21). Results were similar in the seronegative subgroup (RRR 1.14 [0.97–1.34]; p=0.13). Mortality was lower in the tixagevimab– cilgavimab group (61 [9%]) versus placebo group (86 [12%]; hazard ratio [HR] 0.70 [95% CI 0.50–0.97]; p=0.032). The composite safety outcome occurred in 178 (25%) tixagevimab–cilgavimab and 212 (30%) placebo group participants (HR 0.83 [0.68–1.01]; p=0.059). Serious adverse events occurred in 34 (5%) participants in the tixagevimab–cilgavimab group and 38 (5%) in the placebo group. The mortality signal was numerically larger in patients requiring high-flow oxygen or non-invasive mechanical ventilation at study entry and in patients infected with the delta SARS-CoV-2 variant. Authors concluded that among patients hospitalised with COVID-19 receiving remdesivir and other standard care, tixagevimab–cilgavimab did not improve the primary outcome of time to sustained recovery but was safe and mortality was lower.

PROVENT Phase 3 RCT (Prä-Expositions Pts.)

TACKLE Phase 3 RCT (ambulante Pts.)

ACTIV-3-TICO Phase 3 RCT: 1.455 Pts (hospitalisierte Pts. mit Remdesivir oder SoC)

kein Unterschied bei anhaltender Gesundung, aber Mortalität geringer

Sotrovimab (VIR-7831 monoclonal antibody, Xevudy)

The reader is referred to the earlier version (V19_December 2021/January 2022) and subchapter 3.1 for more details on **sotrovimab (Xevudy).**

Details in früheren Versionen

Marketing authorisation in EU is **granted** by **EC** on **17 December 2021**.

Regdanvimab (CT-P59, Regkirona)

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

Details in früheren Versionen

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

Bebtelovimab

The reader is referred to the earlier versions (V22_June and July 2022) and subchapter 3.1 for more details on **bebtelovimab**.

Details in früheren Versionen

On **February 11, 2022** the U.S. Food and Drug Administration (**FDA**) has issued an Emergency Use Authorization (**EUA**) for the emergency use of bebtelovimab for the treatment of **mild-to-moderate coronavirus disease 2019** (COVID-19) in **adults and pediatric patients (12 years of age and older weighing at least 40 kg**): with **positive results of direct 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 approved or authorized by FDA are not accessible or clinically appropriate**. Bebtelovimab (175 mg) must be administered as a single intravenous injection [15].

Feb 2022: FDA: EUA für mild-moderat Erkrankte mit hohem Risiko für Progression

Bebtelovimab is currently authorized in all U.S. regions until further notice by the Agency. **The company did not apply for authorisation of bebtelovimab to market it in the EU.**

keine Zulassung von EMA, kein Antrag vorgelegt

In **revised June 2022 EUA**, bebtelovimab **retains activity to Omicron subvariants BA.2.12.1 and BA.4/BA.5** [16]. According to the **new revision** in **November 2022**, the Omicron BA.5 [+N444T, N460K] (**BQ.1**), and Omicron BA.5 [+R346T, N444T, N460K] (**BQ.1.1**) variants showed a **large reduction** in susceptibility to bebtelovimab of **>672-fold** [2].

Zunahme der Resistenzen

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

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.**

Details in früheren Versionen

3.2.15 Solnatide

The reader is referred to the earlier versions (V22_June and July 2022) for more details on **Solnatide**.

Details in früheren Versionen

The therapeutic molecule solnatide (INN) has been designed by APEPTICO (a privately-held biotechnology company from Vienna/Austria) for the therapeutic treatment of patients with Acute Respiratory Distress Syndrome (ARDS) and various forms of life-threatening Pulmonary Oedema (PPO). Solnatide is a synthetic peptide of less than 20 amino acids applied directly in the lower airways in the form of a liquid aerosol, aims to accelerate the dissolution of alveolar oedema and reduce barrier damage caused by Covid-19 in the lungs.

Medikament gegen akutes Atemnotsyndrom

Verabreichung: Inhalation

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

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

treatment of COVID-19 patients suffering from pulmonary oedema and acute respiratory distress syndrome.

EC-Grant seit April für Covid-19

bis Dezember 2021

APEPTICO Forschung und Entwicklung GmbH has signed, together with the "solnatide consortium", the Grant Agreement ID: 101003595 with the European Commission to accelerate the process of making APEPTICO's proprietary investigational medicinal product (IMP) solnatide available for medical treatment of patients severely affected by the novel coronavirus 2019 (SARS-CoV-2) disease, COVID-19; the Grant Agreement was made available via the Horizon2020 programme "Advancing knowledge for the clinical and public health response to the 2019-nCoV epidemic" (https://ec.europa.eu/commission/presscorner/detail/en/ip_20_386). Project started on 1 April 2020 and will end on 31 December 2021. The main goal of the H2020 SOLNATIDE project is to demonstrate safety, tolerability and clinical efficacy of solnatide in treatment of COVID-19 patients.

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

One ongoing randomised, double-blind, placebo controlled, parallel assignment trial with aim to assess efficacy and safety of 7 days orally inhaled 100 mg solnatide to treat pulmonary permeability oedema of 40 SARS-Cov-2 positive patients with moderate-to-severe ARDS is registered in EUdraCT register (EudraCT number 2020-001244-26), https://www.clinicaltrialsregister.eu/ctr-search/trial/2020-001244- 26/AT [17].

Pressemeldung, dass Wirkmechanismus erkannt wurde

On **May 30, 2022** APEPTICO Forschung und Entwicklung GmbH **announced** that the **mechanism of action of solnatide**, a possible treatment for pulmonary oedema, has been disclosed by an international network of scientists from Austria, Spain and the United States. The collaborators propose a model to describe how the solnatide peptide may interact with the cytoplasmic C-terminal domain of the ENaC-α subunit via electrostatic complementarity. The sodium channel ENaC is responsible for the removal of pulmonary liquid in life-threatening conditions such as COVID19-associated and non-COVID ARDS,
file:///C:/Users/mirja/OneDrive/Radna%20povr%C5%A1ina/MH%20for%20AIHTA_2022/MH%20for%20AIHTA_June%20July%202022/Press%20Release%20APEPTICO_2022-05-30.pdf

Results of publications

keine Publikation von RCT

No withdrawn, suspended or terminated studies related to solnatide in COVID-19 patients were found in ClinicalTrials.gov and EUdraCT registers [17]. No publications related to the RCTs of solnatide in COVID-19 patients were found [17].

3.2.16 Umifenovir (Arbidol®)

Details in früheren Versionen

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

3.2.17 Dexamethasone and other corticosteroids (Budesonide)

Details in früheren Versionen

The reader is referred to the earlier version (V13_April) and subchapter 3.1 for more details on **dexamethasone and other systemic corticosteroids** (except for inhaled corticosteroids). The reader is referred to the earlier version (V22_June and July 2022) for more details on **inhaled corticosteroids: budesonide**.

auch zu Budesonide

3.2.18 Anakinra (Kineret®)

Details in früheren Versionen

The reader is referred to the earlier version (V20_February and March2022) for more details on anakinra (Kineret).

On **December 17, 2021** the **EC authorised** it use to treat **COVID-19,** in **adult patients with pneumonia who are at risk of developing severe respiratory failure.**

Nov 2022: FDA EUA Zulassung für Pts mit Lungenentzündung und Bedarf an Sauerstoff oder Risiko auf progrediente Erkrankung

On November 2022, FDA issued an **emergency use authorization** (**EUA**) for the **treatment** of coronavirus disease 2019 (COVID-19) in **hospitalised adults with positive results of direct SARS-CoV-2 viral testing with pneumonia requiring supplemental oxygen (low- or high-flow oxygen)** who are **at risk of progressing to severe respiratory failure and likely to have an elevated plasma soluble urokinase plasminogen activator receptor (suPAR)** [12].

3.2.19 Colchicine

Details in früheren Versionen

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.

3.2.20 Nafamostat (Futhan©)

Details in früheren Versionen

The reader is referred to the earlier versions (V17_August and September 2021 and V22_June and July 2022) for more details on **nafamostat** (Futhan).

3.2.21 Gimsilumab

Details in früheren Versionen

The reader is referred to the earlier version (V22_June and July 2022) for more details on **gimsilumab**.

Gimsilumab has no approvement for any indication by EMA or FDA yet.

3.2.22 Canakinumab

Details in früheren Versionen

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

3.2.23 Lenzilumab

Details in früheren Versionen

The reader is referred to the earlier version (V22_June and July 2022) for more details on **lenzilumab**.

Sept 2021: FDA lehnt für Lenzilumab EUA ab

Lenzilumab is not authorised in Covid-19 patients (EMA, FDA). On **September 08, 2021** Humanigen announced the U.S. **FDA** has **declined** its request for **emergency use authorization** of lenzilumab to treat newly hospitalised COVID-19 patients.

3.2.24 Vitamin D

Details in früheren Versionen

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

3.2.25 Baricitinib (Olumiant)

Details in früheren Versionen

The reader is referred to the earlier version (V22_June and July 2022) for more details on **Baricitinib**.

EMA: keine Zulassung für covid-19

Baricitinib (Olumiant) has not been approved by the European Medicines Agency (**EMA**). On November 19, 2020, the U.S. Food and Drug Administration (**FDA**) issued an **Emergency Use Authorization** (**EUA**) for the distribution and emergency use of baricitinib to be used **in combination with remdesivir** in **hospitalised adult and pediatric patients two years of age or older** with suspected or laboratory confirmed COVID-19 **who require supplemental oxygen, invasive mechanical ventilation, or extracorporeal membrane oxygenation** (ECMO) [18].

FDA Zulassung (EUA) als Kombinationstherapie mit Remdesivir hospitalisierte Pts mit Bedarf zur Beatmung

FDA Zulassung:

auch als Monotherapie möglich

On **July 28, 2021** the **FDA** issued **revision to EUA** for the distribution and emergency use of **baricitinib to be used alone for the treatment of COVID-19 in hospitalised adults and pediatric patients two years of age or older requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO)** [19]. 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. In **May 2022, FDA approved** a **new indication for baricitinib** for the **treatment of COVID-19 in hospitalised adults requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane ohygenation (ECMO)** [20].

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** [21].

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.** [22] 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 3.2-1 High certainty evidence from one published RCT, ACTT-2 trial, showed that baricitinib in combination with remdesivir does not reduce All-cause mortality, and does not increase the number of patients with any adverse events as well as the number of patients with serious adverse events (high certainty of evidence). Combination of baricitinib and remdesivir significantly reduced median time to recovery in hospitalised COVID-19 patients from eight days to seven days, compared to remdesivir treatment alone. Patients who required high-flow oxygen or non-invasive ventilation during hospitalisation appeared to have had the largest benefit: their median time to recovery was shortened from eighteen days to ten days. Participants' conditions at day 15 was significantly improved when they received the two therapeutics combined. The incidence of progression to death or non-invasive or invasive ventilation was statistically significant lower in the combination of baricitinib and remdesivir vs remdesivir alone, as was the incidence of progression to death or invasive ventilation [23]: 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.** [24] publised as **pre-print** and on September 3, 2021 **in scientific journal** [25], 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 posted in **preprint article** by **Ely et al. 2021** [26] and in February 2022 published in **scientific article** [27]. 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 [26, 28].

RECOVERY RCT
8.156 Pts
Mortalität
12% vs. 14% SoC

RECORY + 9 weitere RCTs zeigen ein 20%ige RRR

Results from **RECOVERY trial** are published as **preprint** [29] and recently in the **scientific journal** [30] in hospitalised patients with COVID-19, baricitinib significantly reduced the risk of death. Eligible and consenting patients (n=8156) were randomly allocated (1:1) to either usual standard of care alone (usual care group) or usual care plus baricitinib 4 mg once daily by mouth for 10 days or until discharge if sooner (baricitinib group). The primary outcome was 28-day mortality assessed in the intention-to-treat population. A meta-analysis was conducted that included the results from the RECOVERY trial and all previous randomised controlled trials of baricitinib or other JAK inhibitor in patients hospitalised with COVID-19. At randomisation, 95% of patients were receiving corticosteroids and 23% receiving tocilizumab (with planned use within the next 24 hours recorded for a further 9%). Overall, 513 (12%) of 4148 patients allocated to baricitinib versus 546 (14%) of 4008 patients allocated to usual care died within 28 days (age-adjusted rate ratio 0·87; 95% CI 0·77-0·98; p=0·026). This 13% proportional reduction in mortality was somewhat smaller than that seen in a meta-analysis of 8 previous trials of a JAK inhibitor (involving 3732 patients and 425 deaths) in which allocation to a JAK inhibitor was associated with a 43% proportional reduction in mortality (rate ratio 0.57; 95% CI 0.45-0.72). Including the results from RECOVERY into an **updated meta-analysis** of all 9 completed trials (involving 11,888 randomised patients and 1484 deaths) allocation to baricitinib or other JAK inhibitor was associated with a 20% proportional reduction in mortality (rate ratio 0.80; 95% CI 0.71-0.89; p<0.001). In RECOVERY, there was no significant excess in death or infection due to non-COVID-19 causes and no excess of thrombosis, or other safety outcomes.

Summary of Findings Table 3.2-2 related to 4 articles (Marconi 2021, Ely 2021, RECOVERY trial 2022, Troseid 2022), can be found below. In Summary, baricitinib may reduce All-cause mortality at Day28 (RR 0.76, 95% CI 0.60 to 0.96, low certainty of evidence) and probably reduces All-cause mortality at Day60 (RR 0.73, 95% CI 0.59 to 0.89, moderate certainty of evidence) compared to placebo. Baricitinib probably decreases WHO progression score level 7 or above (RR 0.81, 95% CI 0.68 to 0.97, moderate certainty of evidence) and increases clinical improvement (RR 1.02, 95% CI 1.00 to 1.05, high certainty of evidence).

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

Baricitinib probably does not increase Adverse events (RR 0.96, 95% CI 0.88 to 1.05, moderate certainty of evidence) and Serious adverse events (RR 0.80, 95% CI 0.67 to 0.95, moderate certainty of evidence).

Wolfe et al. 2022 [31] published results from randomised, double-blind, double placebo-controlled trial (NCT04640168), from 67 trial sites in the USA (60 sites), South Korea (two sites), Mexico (two sites), Singapore (two sites), and Japan (one site). **Hospitalised adults** (≥18 years) with COVID-19 who required supplemental oxygen administered by low-flow (≤15 L/min), high-flow (>15 L/min), or non-invasive mechanical ventilation modalities who met the study eligibility criteria (male or nonpregnant female adults ≥18 years old with laboratory-confirmed SARS-CoV-2 infection) were enrolled in the study. Patients were randomly assigned (1:1) to receive either baricitinib, remdesivir, and placebo, or dexamethasone, remdesivir, and placebo using a permuted block design. Randomisation was stratified by study site and baseline ordinal score at enrolment. All patients received **remdesivir** (≤10 days) **and either baricitinib** (or matching oral placebo) for a maximum of 14 days **or dexamethasone** (or matching intravenous placebo) for a maximum of 10 days. The primary outcome was the difference in mechanical ventilation-free survival by day 29 between the two treatment groups in the modified intention-to-treat population. Safety analyses were done in the as-treated population, comprising all participants who received one dose of the study drug. 1010 patients were enrolled and randomly assigned, 516 (51%) to baricitinib plus remdesivir plus placebo and 494 (49%) to dexamethasone plus remdesivir plus placebo. The mean age of the patients was 58·3 years (SD 14·0) and 590 (58%) of 1010 patients were male.

Wolfe 2022
RCT (USA, …)
1.010 hospitalisierte Pts mit Bedarf nach nicht-invasiver Beatmung

baricitinib, remdesivir + placebo, or dexamethasone, remdesivir + placebo

Mechanical ventilation-free survival by day 29 was similar between the study groups (Kaplan-Meier estimates of 87·0% [95% CI 83·7 to 89·6] in the baricitinib plus remdesivir plus placebo group and 87·6% [84·2 to 90·3] in the dexamethasone plus remdesivir plus placebo group; risk difference 0·6 [95% CI –3·6 to 4·8]; p=0·91). The odds ratio for improved status in the dexamethasone plus remdesivir plus placebo group compared with the baricitinib plus remdesivir plus placebo group was 1·01 (95% CI 0·80 to 1·27). At least one adverse event occurred in 149 (30%) of 503 patients in the baricitinib plus remdesivir plus placebo group and 179 (37%) of 482 patients in the dexamethasone plus remdesivir plus placebo group (risk difference 7·5% [1·6 to 13·3]; p=0·014). 21 (4%) of 503 patients in the baricitinib plus remdesivir plus placebo group had at least one treatment-related adverse event versus 49 (10%) of 482 patients in the dexamethasone plus remdesivir plus placebo group (risk difference 6·0% [2·8 to 9·3]; p=0·00041). Severe or life-threatening grade 3 or 4 adverse events occurred in 143 (28%) of 503 patients in the baricitinib plus remdesivir plus placebo group and 174 (36%) of 482 patients in the dexamethasone plus remdesivir plus placebo group (risk difference 7·7% [1·8 to 13·4]; p=0·012). Authors concluded that in hospitalised patients with COVID-19 requiring supplemental oxygen by low-

ähnliche Ergebnisse bei beatmungsfreiem Überleben

Dexamethason jedoch mit deutlich mehr unerwünschten Ereignissen verbunden

flow, high-flow, or noninvasive ventilation, baricitinib plus remdesivir and dexamethasone plus remdesivir resulted in similar mechanical ventilation-free survival by day 29, but dexamethasone was associated with significantly more adverse events, treatment-related adverse events, and severe or life-threatening adverse events. A more individually tailored choice of immunomodulation now appears possible, where side-effect profile, ease of administration, cost, and patient comorbidities can all be considered.

Karamitsakos 2022
RCT, 251 Pts
tocilizumab or baricitinib

kein Unterschied

Karamitsakos et al. 2022 [32] published as preprint results from randomized controlled trial (NCT05082714), on 251 patients with COVID-19 and PaO2/FiO2 < 200 to receive either **tocilizumab** (n=126) **or baricitinib** (n=125) plus standard of care. The primary outcome was mechanical ventilation or death by day 28. Secondary outcomes included time to hospital discharge by day 28 and change in WHO progression scale at day 10. Baricitinib was non-inferior to tocilizumab for the primary composite outcome of mechanical ventilation or death by day 28 (HR 0.83, 95% CI: 0.56 to 1.21, p=0.001 for non-inferiority). Baricitinib was non-inferior to tocilizumab for the time to hospital discharge within 28 days (discharged alive- tocilizumab: 52.4% vs baricitinib: 58.4%; HR 0.85, (95% CI: 0.61 to 1.18), p< 0.001 for non-inferiority). There was no significant difference between baricitinib and tocilizumab arm in the change in WHO scale at day 10 [0.0 (95% CI: 0.0 to 0.0) vs 0.0 (95% CI: 0.0 to 1.0), p=0.83]. Authors concluded that baricitinib was non-inferior to tocilizumab with regards to the composite outcome of mechanical ventilation or death by day 28 and the time to discharge by day 28 in patients with severe COVID-19. Cost-effectiveness should be taken into account to avoid a dramatic upswing in health system budgets.

Bari-SolidAct
Phase 3 RCT

angehalten, wegen Evidenz aus Recovery zu Überlebensvorteilen

aber in Bari-SolidAct: kein Vorteil bei Mortalität

viele SAE

Trøseid et al. 2022 [33] published as preprint results from a multinational, **phase 3**, randomised, double-blind, placebo-controlled trial of baricitinib in hospitalised patients with severe or critical COVID-19, **Bari-SolidAct trial** (NCT04891133), in 39 clinical sites (hospital wards and intensive care units) across 10 European countries, within an **adaptive platform trial EU-SolidAct**. The trial was **stopped for immunocompetent participants** before reaching the planned sample size of 1,900 **due to external evidence from the Recovery trial i**ndicating **survival benefit of baricitinib in the trial population**. 299 patients were screened, 284 randomised, and 275 participants received study drugs (139 baricitinib and 136 placebo). There were 21 deaths in each group, with a proportion of death at day 60 of 15.1% in the baricitinib group and 15.4% in the placebo group (adjusted absolute difference and 95% CI -0·1% [-8·3 to 8·0]). There were no differences between the study groups with regard to changes in viral load, lymphocyte count, neutrophil count, lactate dehydrogenase, D-Dimer, CRP, procalcitonin or ferritin levels. In subgroup analyses, there was a potential interaction between vaccination status and treatment allocation on 60-day mortality. There were 54 serious adverse events in 32 participants (23%) in the baricitinib group and 60 in 34 participants (25%) in the placebo group. In a post-hoc analysis, there was a significant interaction between vaccination status and treatment allocation on serious adverse events (interaction p-value=0.003), with an increased occurrence of respiratory complications and severe infections in vaccinated participants treated with baricitinib. Authors concluded that no difference in participants treated with baricitinib for the primary mortality endpoint at day 60. There was a potential interaction between vaccination status and treatment allocation on mortality and occurrence of serious adverse events, although these findings are not conclusive. Real world data and subgroup

analyses according to vaccination status and disease severity in larger trials, are warranted to assess the precise risk/benefit ratio of baricitinib in vaccinated patients with severe/critical COVID-19.

*Table 3.2-1: Summary of findings table, on **baricitinib + remdesivir** (1 RCT: Kalil 2020)*

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

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

Source: ref Cruciani F., De Crescenzo F., Vecchi S., Saulle R., Mitrova Z., Amato L., et al. Should Baricitinib-Remdesivir compared to Standard treatment (placebo/remdesivir) be used for COVID-19 patients?. 2020.

[a] ref Kalil AC, Patterson TF, Mehta AK, Tomashek KM, Wolfe CR, Ghazaryan V, et al. Baricitinib plus Remdesivir for Hospitalized Adults with Covid-19. New England Journal of Medicine. 2020. 10.1056/NEJMoa2031994. **Abbreviations**: RR=Risk ratio; CI=Confidence interval; AE=Adverse event; SAE=Serious adverse event

Table 3.2-2: Summary of findings table, on ***baricitinib monotherapy vs placebo in hospitalised COVID-19 patients*** *(Marconi 2021, Ely 2021, RECOVERY trial 2022, Troseid 2022)*

Baricitinib vs Placebo in Hospitalised patients, last update 13/10/2022, 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) [a]		Relative effect (95% CI)	Number of participants (studies)	Certainty of evidence	Comments
	Risk with Placebo	Risk with Baricitinib				
All-cause mortality D28	140 per 1000	106 per 1000	**RR: 0.76** (0.60 - 0.96)	10066 (4 RCTs)	⊕⊕OO LOW	**Absolute effect (95% CI) 34 fewer per 1000** (from 56 fewer to 6 fewer)
All-cause mortality D60	177 per 1000	129 per 1000	**RR: 0.73** (0.59 - 0.89)	1910 (3 RCTs)	⊕⊕⊕◯ MODERATE	**Absolute effect (95% CI) 48 fewer per 1000** (from 73 fewer to 20 fewer)
Clinical improvement D28	777 per 1000	792 per 1000	**RR: 1.02** (1.00 - 1.05)	9782 (3 RCTs)	⊕⊕⊕⊕ HIGH	**Absolute effect (95% CI) 16 more per 1000** (from 0 fewer to 39 more)
WHO progression score (level 7 or above) D28	200 per 1000	162 per 1000	**RR: 0.81** (0.68- 0.97)	1910 (3 RCTs)	⊕⊕⊕◯ MODERATE	**38 fewer per 1000** (from 64 fewer to 6 fewer)
Number of patients with any adverse event	470 per 1000	451 per 1000	**RR: 0.96** (0.88 - 1.05)	1626 (2 RCTs)	⊕⊕⊕◯ MODERATE	**Absolute effect (95% CI) 19 fewer per 1000** (from 56 fewer to 23 more)
Number of patients with serious adverse events	214 per 100	171 per 1000	**RR: 0.80** (0.67 - 0.95)	1910 (3 RCTs)	⊕⊕⊕◯ MODERATE	**Absolute effect (95% CI) 43 fewer per 1000** (from 71 fewer to 11 fewer)

3.2.26 Molnupiravir (Lagevrio)

The reader is referred to the earlier version (V22_June and July 2022) and subchapter 3.1 for more details on Molnupiravir.

Details in früheren Versionen

Molnupiravir is not approved by the European Medicines Agency (EMA) or the American Food and Drug Administration (FDA) [34].

weder von EMA noch FDA zugelassen

On **October 25, 2021 EMA**'s human medicines committee (**CHMP**) has started a **rolling review of molnupiravir** (also known as MK 4482 or Lagevrio), developed by Merck Sharp & Dohme in collaboration with Ridgeback Biotherapeutics for the **treatment of COVID-19 in adults** [35].

Okt 2021: EMA beginnt Rolling Review

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 [36].

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

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 [37].

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

nicht: für Prä- oder PostExpositions Prophylaxe

In the new revision of EUA for molnupiravir (August 2022) [38], data related to viral RNA rebound showed that viral RNA rebound post-treatment increases in SARS-CoV-2 RNA shedding levels (i.e., viral RNA rebound) in nasopharyngeal samples were observed on Day 10, Day 15, and/or Day 29 in a subset of molnupiravir and placebo recipients in the phase 3 MOVe-OUT trial. Approximately 1% of both molnupiravir and placebo recipients had evidence of recurrent COVID-19 symptoms coinciding with a rebound in viral RNA levels in nasopharyngeal samples. Post-treatment viral RNA rebound was not associated with the primary clinical outcome of hospitalisation or death through Day 29 following the single 5-day course of molnupiravir treatment. Post-treatment viral RNA rebound also was not associated with the detection of cell culture infectious virus in nasopharyngeal swab samples.

Rebound-Effekt

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/.

PANORAMIC trial läuft mit geimpften Pts.

Molnupiravir is now being evaluated in the **UK Panoramic trial**, coordinated by Oxford University (https://www.panoramictrial.org/). The inclusion criteria and primary efficacy endpoint are similar to the Move-Out trial, with two exceptions: Panoramic includes mainly vaccinated patients, and is being conducted during the Omicron wave, whereas Move-Out included only unvaccinated patients and was conducted in 2021, when previous variants led to more severe disease [39]. The preliminary analysis from this trial is available below [40].

Results of publications

Publikationen

There are one published phase 2a RCT (as preprint [41]) related to effectiveness and safety of molnupiravir for Covid-19 (NCT04405570); one published phase 2 component of MOVe-OUT (NCT04575597) RCT [42], one published phase 2/3 RCT in hospitalised patients (NCT04575584, MOVe-IN) [43], and one published phase 3 component of MOVe-OUT (NCT04575597) trial [44]. Two additional RCTs are published recently: **Khoo et al. 2022** [45], published as preprint, results from **AGILE CST-2** (NCT04746183; ISRCTN27106947) **phase 2** trial; **Zou et al. 2022** [46] published results from a RCT involving patients with **mild or moderate COVID-19** (ChiCTR2200056817). The preliminary analysis from the **PANORAMIC trial** is recently published as preprint [40], see below.

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** and then in **scientific article** by **Fisher et al. 2021** [41, 47] 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) [42] 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,** which results are published by **Caraco et al. 2021**, 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 [42].

MOVe-IN hospitalisierte Pts

keine Wirksamkeit

Data from **MOVe-IN** published by **Arribas et al. 2021**, 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% [43].

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 [44].

Johnson et al. 2022 [48] published results from **secondary analysis** of this randomized, double-blind, placebo-controlled phase 3 component of MOVe-OUT. Participants receiving molnupiravir showed faster normalization of CRP and Spo2 , with improvements observed on day 3 of therapy, compared with placebo. Molnupiravir-treated participants had a decreased need for respiratory interventions versus placebo-treated participants (relative risk reduction [RRR], 34.3% [95% CI, 4.3% to 54.9%]), with similar findings in participants who were hospitalized after randomization (RRR, 21.3% [CI, 0.2% to 38.0%]). Hospitalised participants who received molnupiravir were discharged a median of 3 days before those who received placebo. Acute care visits (7.2% vs. 10.6%; RRR, 32.1% [CI, 4.4% to 51.7%]) and COVID-19–related acute care visits (6.6% vs. 10.0%; RRR, 33.8% [CI, 5.6% to 53.6%]) were less frequent in molnupiravir versus placebo treated participants.

Sekundäranalyse von MOVe-OUT

RRR 34,4% bei repiratorischen Interventionen und Ambulanzbesuchen

Koudinya Tippabhotla et al. 2022 [49] published as preprint positive results from phase 3, randomized, open-label, parallel-group study in 1220 patients with laboratory-confirmed (RT-PCR positive) SARS-CoV-2 infection across 16 centres in India. 7.3% (90/1220) patients were with one risk factor (i.e. hypertension, diabetes mellitus, obesity, hypothyroidism, hyperthyroidism) presenting a risk for progression to severe COVID-19 (Clinical Trials Registry of India, CTRI/2021/07/034588). **Non-hospitalized adults with mild COVID-19** were randomized to receive either molnupiravir 800 mg (200 mg x 4 capsules administered orally every 12 hours for 5 days) with SOC or SOC alone and followed up at day 5 (end of treatment, and days 10, 14 and 28. Standard of care was provided as per the clinical guidance for management of adult COVID-19 patients by the Government of India or as per the Investigator's discretion.

RCT, Phase 3
1.220 Pts. (Indien)
nicht-hospitalisierte Pts.

The primary endpoint was the rate of hospitalisation of patients from randomization till day 14. Secondary endpoints included rate of hospitalisation of patients from randomization up to day 28; clinical improvement (2-point decrease in 11- point WHO Clinical Progression Scale) at days 5, 10, and 14; SARS-CoV-2 RT-PCR negativity at the end of treatment; and mortality rate at day 14 and day 28. 1220 patients were randomly assigned to receive molnupiravir + SOC (n=610) or SOC alone (n=610) and considered for the intent-to-treat (ITT) analysis. No patient met the hospitalisation-defined criteria during the 14-day duration as well as till day 28. Clinical improvement was observed significantly earlier in patients of molnupiravir + SOC group as compared to the SOC alone group at the end of treatment day 5 (29.0% vs 5.6%), and further at day 10 (67.4% vs 31.6%) and day 14 (89.0% vs 79.5%) in the ITT population ($p < 0.001$ for all). The median time to clinical improvement was 10 days in molnupiravir + SOC group vs. 14 days in SOC alone group ($p< 0.001$). Significantly higher proportion of patients in the molnupiravir + SOC group were associated with RT-PCR negativity as compared to SOC alone at day 5 (81.5% vs. 17.4%), day 10 (89.8% vs. 46.4%,), and day 14 (93.1% vs 83.1%) ($p < 0.0001$ for all). Mean viral load at day 5 was 4.8 in the molnupiravir + SOC vs. 21.8 in the SOC alone group ($p < 0.001$). There were no serious adverse events or deaths reported in the study till day 28.

frühere Genesung (10 vs. 14 Tage) mit Molnupiravir

keine SAE

Summary of Findings Table 3.2-3 related to 6 RCTs mentioned above and below in outpatients (Caraco, 2021; Jayk Bernal, 2021; Fischer, 2021; Koudinya Tippabhotla 2022; Khoo 2022; Kumarasamy 2022) can be found below. In Summary, molnupiravir probably reduces all-cause mortality at Day28 (RR 0.19, 95% CI 0.04 to 0.86, moderate certainty of evidence) compared to standard care/placebo. The same is true for the outcomes of

SoF von 6 RCTs: ev. Reduktion der 28-Tages Mortalität

hospitalisation or death (RR 0.67, 95% CI 0.49 to 0.92, moderate certainty of evidence); AEs and SAEs: molnupiravir probably does not increase adverse events (RR 0.99, 95% CI 0.90 to 1.09, moderate certainty of evidence) and serious adverse events (RR 0.73, 95% CI 0.52 to 1.02, moderate certainty of evidence), compared to standard care/placebo. Evidence is very uncertain on viral negative conversion D7 (RR 1.49, 95% CI 0.42 to 5.22, very low certainty of evidence).

Evidence is uncertain on clinical improvement D28 (RR 1.12, 95% CI 1.07 to 1.18, low certainty of evidence) and WHO progression score (level 7 or above) (RR - , with zero events in both groups, low certainty of evidence).

unsichere Evidenz bei einigen Endpunkten

Khoo et al. 2022 [45], published as preprint, and then in scientific journal [50], results from **AGILE CST-2** (NCT04746183; ISRCTN27106947) **phase 2 RCT**, related to safety and virological efficacy of molnupiravir in **vaccinated and unvaccinated** individuals. Authors found molnupiravir to be well-tolerated, with evidence for high probability of antiviral efficacy in a population of vaccinated and unvaccinated individuals infected with a broad range of viral variants. Of 180 participants randomised (90 molnupiravir, 90 placebo), 50% were vaccinated. Infections with SARS-CoV-2 variants Delta (40%), Alpha (21%), Omicron (21%) and EU1 (16%) were represented. The median time to negative-PCR was 8 versus 11 days for molnupiravir and placebo (HR=1·30, 95% CrI 0·92-1·71, p=0·07 by Logrank and p=0·03 by Breslow-Gehan tests). Although small numbers precluded subgroup analysis, no obvious differences were observed between vaccinated and unvaccinated participants. Using a two-point prior the probability of molnupiravir being superior to placebo (HR>1) was 75·4%, which was just below the defined threshold of 80% for establishing superiority. Using an uninformative continuous prior, the probability of HR>1 was 94·7%. As an exploratory analysis, the change in viral titre on day 5 (end of treatment) was significantly greater with molnupiravir compared with placebo. 73 (81%) of 90 participants in the molnupiravir group and 68 (76%) of 90 participants in the placebo group had at least one adverse event by day 29. A total of 4 participants reported severe adverse events (grade 3+), 3 of whom were in the placebo arm. No participants died (due to any cause) during the trial.

AGILE CST-2 Phase 2 180 Pts

in Geimpften ud Ungeimpften:

kein Unterschied

Zou et al. 2022 [46] published results from a **RCT** involving patients with **mild or moderate COVID-19** (ChiCTR2200056817). Patients were randomized to orally receive molnupiravir (800 mg) plus basic treatment or only basic treatment for 5 days (BID). The antiviral efficacy of the drug was evaluated using reverse transcriptase polymerase chain reaction. Results showed that the time of viral RNA clearance (primary endpoint) was significantly decreased in the molnupiravir group (median, 9 days) compared to the control group (median, 10 days) (Log-Rank p=0.0092). Of patients receiving molnupiravir, 18.42% achieved viral RNA clearance on day 5 of treatment, compared to the control group (0%) (p=0.0092). On day 7, 40.79%, and 6.45% of patients in the molnupiravir and control groups, respectively, achieved viral RNA clearance (p=0.0004). In addition, molnupiravir has a good safety profile, and no serious adverse events were reported.

RCT mit mild/ moderat Erkrankten

raschere Viruslastreduktion

Butler at al. 2022 [40] published as **preprint preliminary analysis results** from the UK **PANORAMIC RCT** (ISRCTN30448031): multicentre, open-label, adaptive, multi-arm, platform trial were aged ≥50, or ≥18 years with comorbidities, and unwell ≤5 days with confirmed COVID-19 in the community, randomised to usual care or usual care plus molnupiravir (800mg twice daily for 5 days). **99% had at least one dose of a SARS-CoV-2 vaccine**.

PANORAMIC RCT 25.000 Pts

The primary outcome measure was all-cause hospitalisation/death within 28 days, analysed using Bayesian models. The main secondary outcome measure was time to first self-reported recovery. A sub-set of participants in each group were assessed for the virology primary outcome measure of day seven SARS-CoV-2 viral load. In this preliminary analysis, authors found that molnupiravir did not reduce already low hospitalisations/deaths among higher risk, vaccinated adults with COVID-19 in the community, but resulted in faster time to recovery, and reduced viral detection and load.

raschere Erholung

More specifically, primary outcome measure data were available in 25000 (97%) participants and included in this analysis. 103/12516 (0.8%) hospitalisations/deaths occurred in the molnupiravir group versus 96/12484 (0.8%) in usual care alone with a posterior probability of superiority of 0.34 (adjusted odds ratio 1.061 (95% Bayesian credible interval [BCI]) 0.80 to 1.40). Estimates were similar for all subgroups. The observed median (IQR) time-to-first-recovery from randomisation was 9 (5–23) days in molnupiravir and 15 (7–not reached) days in usual care. There was an estimated benefit of 4.2 (95% BCI: 3.8 – 4.6) days in time-to-first-recovery (TTR) giving a posterior probability of superiority of >0.999 (estimated median TTR 10.3 [10.2 – 10.6] days vs 14.5 [14.2 – 14.9] days respectively; hazard ratio [95% BCI], 1.36 [1.3–1.4] days), which met the pre-specified superiority threshold. On day 7, SARS-CoV-2 virus was below detection levels in 7/34 (21%) of the molnupiravir group, versus 1/39 (3%) in the usual care group (p=0.039), and mean viral load was lower in the molnupiravir group compared with those receiving usual care [(SD) of log10(viral load) 3.82 (1.40) in the molnupiravir group and 4.93 (1.38) in the usual care group, (p<0.001)]. 59 (0.4%) participants experienced serious adverse events in the molnupiravir group and 52 (0.4%) in usual care.

RWE: positive Ergebnisse bei früher Anwendung

Additional, three **real-world effectiveness studies** showed positive results, conducted in a real-world setting during a pandemic wave dominated by the SARS-CoV-2 omicron variant, indicate effectiveness of the early use of molnupiravir, in patients with mild-to moderate COVID-19 who are at high risk [51-53].

Analyse von klinischen Studien zu Molnupiravir findet

90% der Daten wurden nicht veröffentlicht

Lawrence et al. 2022 [54] published as preprint results from **analysis of registered trials of molnupiravir in India**, to assess which clinical trials had been presented or published. According to the CTRI, 12 randomised trials of molnupiravir were conducted in India, in 13,694 patients, starting in late May 2021. By July 2022, none of the 12 trials has been published, one was presented at a medical conference, and two were announced in press releases suggesting failure of treatment. Results from three trials were shared with the World Health Organisation. One of these three trials had many unexplained results, with effects of treatment significantly different from the MSD MOVE-OUT trial in a similar population. Authors concluded that approximately 90% of the global data on molnupiravir has not been published in any form.

*Table 3.2-3: Summary of findings table, on **molnupiravir vs standard care/placebo** (6 RCTs: Caraco, 2021; Jayk Bernal, 2021; Fischer, 2021; Koudinya Tippabhotla 2022, Kumarasamy 2022, Khoo 2022)*

Molnupiravir compared to Standard Care/Placebo for Mild COVID-19 – Outpatients (last update 13/10/2022)

Patient or population: Mild COVID-19 - Outpatients
Setting: Worldwide
Intervention: Molnupiravir
Comparison: Standard Care/Placebo

Outcome	Anticipated absolute effects (95% CI) [a]		Relative effect (95% CI)	Number of participants (studies)	Certainty of evidence	Comments
	Risk with Standard treatment/Placebo	Risk with Molnupiravir				
All-cause mortality D28	7 per 1000	1 per 1000	**RR: 0.19** (0.04 - 0.86)	3100 (5 RCTs) b	⊕⊕⊕O MODERATE c	**Absolute effect (95% CI) 6 fewer per 1000** (from 7 fewer to 1 fewer)
Clinical improvement D28	795 per 1000	890 per 1000	**RR: 1.12** (1.07 - 1.18)	1220 (1 RCT)	⊕⊕OO LOW [l]	**Absolute effect (95% CI) 95 more per 1000** (from 56 more to 143 more)
WHO progression score (level 7 or above) D28	0 per 1000	0 per 1000	RR: (-)	1400 (2 RCT)	⊕⊕OO LOW [m]	Zero events in both groups
Hospitalisation or death	60 per 1000	40 per 1000	**RR: 0.67** (0.49 - 0.92)	2983 (4 RCTs) d	⊕⊕⊕O MODERATE e	**Absolute effect (95% CI) 20 fewer per 1000** (from 30 fewer to 5 fewer)
Viral negative conversion D7	115 per 1000	171 per 1000	**RR: 1.49** (0.42 - 5.22)	2819 (4 RCTs) f	⊕OOO VERY LOW g	**Absolute effect (95% CI) 56 more per 1000** (from 67 fewer to 485 more)
Number of patients with adverse events	273 per 1000	271 per 1000	**RR: 0.99** (0.90 - 1.09)	3016 (5 RCTs) h	⊕⊕⊕O MODERATE i	**Absolute effect (95% CI) 3 fewer per 1000** (from 27 fewer to 25 more)
Number of patients with serious adverse events	35 per 1000	26 per 1000	**RR: 0.73** (0.52 – 1.02)	4318 (6 RCTs) [j]	⊕⊕⊕O MODERATE [k]	**Absolute effect (95% CI)**

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 Molnupiravir				
						9 fewer per 1000 (from 17 fewer to 1 more)

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 Caraco Y, 2021; Jayk Bernal A, 2021; Fischer W, 2021; Koudinya Tippabhotla 2022; Khoo 2022; c Imprecision: Serious due to low number of participants; d Caraco Y, 2021; Jayk Bernal A, 2021; Koudinya Tippabhotla 2022; Khoo 2022; e Imprecision: Serious due to low number of participants/events; f Jayk Bernal A, 2021; Fische W, 2021; Koudinya Tippabhotla 2022; Khoo 2022; g Risk of bias: Very serious Risk of bias downgraded by 2 levels: some concerns or high risk regarding missing data, and selection of the reported results Imprecision: Serious due to low number of participants h Caraco Y, 2021; Jayk Bernal A, 2021; Fischer W, 2021; Koudinya Tippabhotla 2022; Khoo 2022; i Imprecision: Serious due to low number of participants; j Caraco Y, 2021; Jayk Bernal A, 2021; Fischer W, 2021; Koudinya Tippabhotla 2022; Khoo 2022; Kumarasamy 2022; k Imprecision: serious due to wide confidence interval consistent with the possibility for benefit and the possibility for no effect; l Indirectness: Serious despite a multicentre design this is a single study from a single country, therefore results in this population might not be generalizable to other settings. Imprecision: Serious due to low number of participants; m Imprecision: Very serious no events in both groups

3.2.27 Ivermectin

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

Details in früheren Versionen

3.2.28 Aspirin

The reader is referred to the earlier version (V17_August and September 2021 and V22_June and July 2022) for more details on **Aspirin.**

Details in früheren Versionen

3.2.29 Aviptadil (Zysami)

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

Details in früheren Versionen

3.2.30 Dimethyl fumarate

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

Details in früheren Versionen

3.2.31 Artesunate

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

Details in früheren Versionen

3.2.32 Tofacitinib (Xeljanz)

The reader is referred to the earlier version (V22_June and July 2022) for more details on **tofacitinib** (Xeljanz).

Details in früheren Versionen

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

3.2.33 Fluvoxamine

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

Details in früheren Versionen

3.2.34 Nirmatrelvir and ritonavir (Paxlovid)

The reader is referred to the earlier version (V22_June and July 2022) and subchapter 3.1 for more details on **nirmatrelvir and ritonavir** (**Paxlovid**).

Details in früheren Versionen

On **January 27, 2022 EMA's** human medicines committee (**CHMP**) has recommended granting a **conditional marketing authorisation** for the oral antiviral medicine Paxlovid (PF-07321332 / ritonavir) for the **treatment of COVID-19 in adults who do not require supplemental oxygen and who are at**

Jän 2022: EMA vorläufige Zulassung für mild-moderat Hoch-Risiko Erkrankte

increased risk of the disease becoming severe [55]. The **European Commission authorised** the COVID-19 treatment Paxlovid, following evaluation by EMA on **January 28, 2022**.

FDA: EUA (auch für Kinder)

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**.

EPIC-HR RCT an Ungeimpften mit (gewissen) Risikofaktoren

antivirale Resistenzen von Nirmatrelvir in Zellkulturen

In **June 2022 revision** of **EUA** [56], and in the new revision in **September 2022** [57] regarding **antiviral resistance**, SARS-CoV-2 Mpro residues potentially associated with nirmatrelvir resistance have been identified using a variety of methods, including SARS-CoV-2 resistance selection, testing of recombinant SARS-CoV-2 viruses with Mpro substitutions, and biochemical assays with recombinant SARS-CoV-2 Mpro containing amino acid substitutions. The clinical significance of these substitutions is unknown.

Juni 2022: Pfizer beantragt FDA Zulassung auch für Geimpfte

On **June 30, 2022** Pfizer **announced submission of New Drug Application to the FDA**: **approval** for the treatment of COVID-19 in **both vaccinated and unvaccinated individuals at high risk for progression to severe illness** from COVID-19; consistent with current emergency use authorization, https://www.pfizer.com/news/press-release/press-release-detail/pfizer-announces-submission-new-drug-application-us-fda

vermehrte Berichte zu Rebound/Wiederauftreten von COVID-19-Symptomen nach Paxlovid Thrapie

There are reports of SARS-CoV-2 viral **rebound and the recurrence of COVID-19 symptoms** in patients who completed a 5-day course of ritonavir-boosted nirmatrelvir. The frequency and clinical implications of these events are not yet known. According to a CDC analysis of electronic medical records from a large health care system, hospitalisations and emergency department visits for rebounding COVID-19 symptoms are rare after treatment with the antiviral therapy nirmatrelvir-ritonavir [58]. Data from EPIC-HR RCT on the occurrence of viral load rebound are published recently. The incidence of viral load rebound was similar in the nirmatrelvir–ritonavir group and the placebo group. The occurrence of viral load rebound was not retrospectively associated with low nirmatrelvir exposure, recurrence of moderate-to-severe symptoms, or development of resistance to nirmatrelvir [59].

signifikante Arneimittel-Interaktionen daher: sorgfältige Pts. Auswahl

Ritonavir-boosted nirmatrelvir has **significant drug-drug interactions**, primarily due to the ritonavir component of the combination. Before prescribing ritonavir-boosted nirmatrelvir, clinicians should carefully review the patient's concomitant medications**,** including over-the-counter medications, herbal supplements, and recreational drugs, to evaluate potential drug-drug interactions.

RWE bestätigt Zulassungsstudien mit Hochrisiko-Pts. keine Effekte aber bei jüngeren Pts.

Real-world effectiveness studies positive results (as in already published RCTs), conducted in a real-world setting during a pandemic wave dominated by the SARS-CoV-2 omicron variant, indicate effectiveness of the early use of nirmatrelvir plus ritonavir in patients with mild-to moderate COVID-19 who are at high risk [51, 53, 60-62]. Results from one of the studies mentioned above, related to analysis of data from all members of Clalit Health Services who were 40 years of age or older at the start of the study period and eligible to receive nirmatrelvir therapy during the omicron surge, showed that among patients 65 years of age or older, the rates of hospitalisation and death due to

Covid-19 were significantly lower among those who received nirmatrelvir than among those who did not. No evidence of benefit was found in younger adults [63].

Paxlovid is currently evaluated in the **UK Panoramic trial**, https://www.panoramictrial.org/.

Paxlovid wird derzeit in PANORAMIC evlauiert

3.2.35 AT-527

The reader is referred to the earlier version (V22_June and July 2022) for more details on **AT-527**.

Details in früheren Versionen

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

3.2.36 Plonmarlimab (TJM2)

The reader is referred to the earlier version (V22_June and July 2022) for more details on **Plonmarlimab** (or TJM2).

Details in früheren Versionen

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

Withdrawn, suspended or terminated studies

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

Results of publications

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 [64].

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

höhere Rat von beatmungsfreien Tagen, raschere Erholung

3.2.37 Mavrilimumab

The reader is referred to the earlier version (V22_June and July 2022) for more details on **mavrilimumab**.

Details in früheren Versionen

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

3.2.38 SAB-185

The reader is referred to the earlier version (V22_June and July 2022) for more details on **SAB-185**.

Details in früheren Versionen

Taiwo et al. 2022 published results as abstract [65] from **phase 2 ACTIV-2 RCT** conducted at 42 sites in the US received SAB-185 (n=107) or placebo (n=106). No differences were observed in the proportion with NP SARS-CoV-2 RNA< lower limit of quantification (LLoQ) in nasopharyngeal (NP) swab, time to improvement in targeted symptoms for 2 consecutive days after Day 0, and safety through Day 28. Antiviral or clinical efficacy and safety criteria for graduation to phase 3 were pre-specified.

As announced by Manufacturer, **NIH discontinued phase 3 ACTIV-2 trial on SAB-185** for treatment of COVID-19 due to declining COVID hospitalisations. While SAB-185 previously met the initial pre-specified safety and efficacy criteria to continue to the next phase of the phase 3 ACTIV-2 trial, the **independent Data and Safety Monitoring Board** (DSMB) recommended that the study be **stopped for reasons** of "**operational futility**", meaning that hospitalisation rates had declined to the point where the study was no longer large enough to ensure that statistically significant findings could be obtained, https://ir.sab.bio/news-releases/news-release-details/sab-biotherapeutics-reports-nih-discontinuing-phase-3-activ-2.

Hersteller beendet ACTIV-2 RCT wegen abnehmender Hospitalisierungen (Mangel an Pts.)

3.2.39 Ensovibep (MP0420)

The reader is referred to the earlier version (V22_June and July 2022) for more details on **Ensovibep** (MP0420).

Details in früheren Versionen

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

Withdrawn, suspended or terminated studies

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

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 [66]. Published results from this RCT can be found below.

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

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) [66]. EMPATHY Part A enrolled 407 patients to identify a dose of ensovibep with optimal safety and efficacy and recruited patients in the USA, South Africa, India, the Netherlands and Hungary to explore three doses: 75mg, 225mg and 600mg.

Phase 2/3 EMPHATY 407 ambulante Pts.

Results of publications

Currently, published results were found from one phase 3, ACTIV-3 clinical trial of ensovibep (NCT04501978) in COVID-19 patients.

ACTIV-3 -TICO
Phase 3 RCT
485 Pts.

In **August 2022, ACTIV-3/TICO Study Group** published negative results from **phase 3, ACTIV-3 clinical trial** of ensovibep (NCT04501978) [67] Compared with placebo, ensovibep did not improve clinical outcomes for **hospitalised participants** with COVID-19 receiving standard care, including remdesivir; no safety concerns were identified. An independent data and safety monitoring board recommended that enrollment be halted for early futility after 485 patients were randomly assigned and received an infusion of ensovibep (n=247) or placebo (n=238). The odds ratio (OR) for a more favorable pulmonary outcome in the ensovibep (vs. placebo) group at day 5 was 0.93 (95% CI, 0.67 to 1.30; p=0.68; OR > 1 would favor ensovibep). The 90-day cumulative incidence of sustained recovery was 82% for ensovibep and 80% for placebo (subhazard ratio [sHR], 1.06 [CI, 0.88 to 1.28]; sHR > 1 would favor ensovibep). The primary composite safety outcome at day 90 occurred in 78 ensovibep participants (32%) and 70 placebo participants (29%) (HR, 1.07 [CI, 0.77 to 1.47]; HR < 1 would favor ensovibep).

kein Unterschied

On January 10, 2022 Novartis and Molecular Partners **announced** that **Part A** of the **EMPATHY clinical trial** that compared single intravenous doses of ensovibep, met the primary endpoint of viral load reduction over eight days. The two secondary endpoints also showed clinically meaningful benefit over placebo – composite endpoint of hospitalisation and/or Emergency Room (ER) visits or death, and time to sustained clinical recovery. No deaths occurred in any of the patients treated with ensovibep. All doses were well-tolerated and no unexpected safety issues were identified for any of the doses. The lowest dose of 75mg is the planned dose for further development [68][70][57][57]https://www.novartis.com/news/media-releases/novartis-and-molecular-partners-report-positive-topline-data-from-phase-2-study-ensovibep-mp0420-darpin-antiviral-therapeutic-covid-19.

Presseaussendung zu EMPATHY

positive Ergebnisse

3.2.40 Bemcetinib

The reader is referred to the earlier version (V22_June and July 2022) for more details on **Bemcetinib**.

Details in früheren Versionen

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

Withdrawn, suspended or terminated studies

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

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.

2 laufende Studien
Phase 2 RCTs
hospitalisierte Pts.

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**).

ACCORD2 Plattform Studie

EU-SolidAct trial , Teil von EU-RESPONSE Adaptive Platform Trial:

500 hospitalisierte Pts.

On **January 27, 2022** BerGenBio ASA and Oslo University Hospital **announced** to study bemcentinib in hospitalised COVID-19 patients in the EU funded **EU-SolidAct trial – European DisCoVeRy for Solidarity**: An Adaptive Pandemic and Emerging Infection Platform Trial as a part of EU-RESPONSE, a pan-European research project involved with the rapid and coordinated investigation of medications to treat COVID-19 during the ongoing pandemic. The EU-SolidAct (**EudraCT 2021-000541-41; NCT04891133**) is a multi-center, randomized, adaptive phase 2 and 3 platform trial, the master protocol of which has been developed to evaluate potential treatments in hospitalised patients with COVID-19, the disease caused by the SARS-CoV2 virus (coronavirus). Under the trial, bemcentinib will be studied in up to 500 hospitalised COVID-19 patients [69]. On **27 September 2022** BerGenBio **announced** that the **first patient has been included** in this study [70].

Results of publications

keine veröffentlichten Studien

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

Firmenankündigung:

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 [71].

3.2.41 Y180 - M^{pro} inhibitor

Details in früheren Versionen

The reader is referred to the earlier version (V22_June and July 2022) for more details on **Y180 – Mpro Inhibitor**.

vielversprechende präklinische Daten

Y180 protected against wild-type SARS-CoV-2, B.1.1.7 (Alpha), B.1.617.1 (Kappa) and P.3 (Theta), with EC50 of 11.4, 20.3, 34.4 and 23.7 nM, respectively. Oral treatment with Y180 displayed a antiviral potency and substantially ameliorated the virus-induced tissue damage in both nasal turbinate and lung of B.1.1.7-infected K18-human ACE2 (K18-hACE2) transgenic mice. Therapeutic treatment with Y180 improved the survival of mice from 0 to 44.4% (p=0.0086) upon B.1.617.1 infection in the lethal infection model. Importantly, Y180 was also highly effective against the B.1.1.529 (Omicron) variant both in vitro and in vivo. Preliminary preclinical safety evaluation did not show obvious toxicity both in vitro and in vivo. The safety of Y180 in humans remains to be determined in clinical trials.

In a head-to-head in vivo antiviral assay, therapeutic treatment with Y180/ritonavir was more potent than PF-07321332/ ritonavir against SARS-CoV-2 Omicron in K18-hACE2 transgenic mice [72].

Y180 is not authorised in Covid-19 patients (EMA, FDA).

Withdrawn, suspended or terminated studies

As of September 2022, there are no clinical trials registered in ClinicalTrials.gov register or EU Clinical Trials Register.

keine klinischen Studien laufend

Results of publications

Currently, no published results were found from clinical trials related to Y180 in COVID-19 patients.

3.2.42 Ensitrelvir

The reader is referred to the earlier version (V22_June and July 2022) for more details on **Ensitrelvir**.

Details in früheren Versionen

Ensitrelvir fumaric acid (S-217622; hereafter, ensitrelvir) is a novel **oral**

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

Withdrawn, suspended or terminated studies

As of July 2022, there are no clinical trials on ensitrelvir registered in ClinicalTrials.gov register or EU Clinical Trials Register. No withdrawn, suspended or terminated studies in trial registers were found for ensitrelvir in COVID-19 patients.

One study registered in Japan Registry of Clinical Trials (jRCT2031210350) is currently ongoing (a multicenter, randomized, double-blind, placebo-controlled, phase 2/3 study to assess the efficacy, safety, and pharmacokinetics of 5-day oral administration of ensitrelvir) and the first results are published as preprint, see bellow.

1 Phase 2/3 Studie (Japan)

Results of publications

Currently, published results were found from one clinical trial related to ensitrelvir in COVID-19 patients.

Mukae et al. 2022 [73] published results as **preprint** from double-blind**, phase 2a part** of a phase 2/3 study (Japan Registry of Clinical Trials identifier: jRCT2031210350) assessed the efficacy and safety of ensitrelvir in Japanese patients with mild to-moderate COVID-19 or asymptomatic SARS-CoV-2 infection. Sixty-nine patients enrolled from 56 sites were randomized (1:1:1) to orally receive 5-day ensitrelvir fumaric acid (375 mg on day 1 followed by 125 mg daily or 750 mg on day 1 followed by 250 mg daily) or placebo and followed up until day 28. The primary outcome was change from baseline in SARS-CoV-2 viral titer. A total of 16, 14, and 17 patients in the ensitrelvir 125 mg, ensitrelvir 250 mg, and placebo groups, respectively, were included in the intention-to-treat population (mean age: 38.8, 40.4, and 38.0 years, respectively). On day 4, the change from baseline in SARS-CoV-2 viral titer (log10 50% tissue culture infectious dose/mL) in patients with positive viral titer and viral RNA at baseline was greater with ensitrelvir 125 mg (mean [standard deviation], -2.42 [1.42]; p = 0.0712) and 250 mg (-2.81 [1.21]; p = 0.0083) versus placebo (-1.54 [0.74]), and ensitrelvir treatment reduced SARS-CoV-2 RNA by -1.4 to -1.5 log10 copies/mL versus placebo. All adverse events were mild to moderate. Authors concluded that ensitrelvir treatment

Mukae 2022 Phase 2a (Dosisfindungsstudie) an mild-moderat Erkrankten

demonstrated rapid SARS-CoV-2 clearance and was well tolerated in patients with mild-to-moderate COVID-19 or asymptomatic SARS-CoV-2 infection.

Phase 2b RCT

deutlich höhere Titer unter Ensitrelvir

Mukae et al. 2022 [74] published results as **preprint** from double-blind**, phase 2b part** of a phase 2/3 above mentioned study: Patients were randomized (1:1:1) to orally receive ensitrelvir fumaric acid 125 mg (375 mg on day 1; *n*=140) or 250 mg (750 mg on day 1; n=140) or placebo (n=141) once daily for 5 days. Compared with placebo, the change from baseline in severe acute respiratory syndrome coronavirus 2 titer (measured as $\log_{10}$ 50% tissue-culture infectious dose) on day 4 was significantly greater with ensitrelvir 125 mg and 250 mg (differences from placebo: −0.41, p<0.0001 for both). The total score of predefined 12 COVID-19 symptoms showed an improving trend with ensitrelvir treatment without a significant intergroup difference. Most adverse events were mild in severity. Ensitrelvir treatment demonstrated a favorable antiviral efficacy and potential clinical benefit with an acceptable safety profile.

3.2.43 Poly-ICLC (Hiltonol)

Details in früheren Versionen

The reader is referred to the earlier version (V22_June and July 2022) for more details on **Poly-ICLC (Hiltonol®).**

Poly-ICLC (Hiltonol®) is an investigational drug and it is not authorised in Covid-19 patients (EMA, FDA).

Withdrawn, suspended or terminated studies

No withdrawn, suspended or terminated studies in trial registers were found for Poly-ICLC (Hiltonol®) in COVID-19 patients.

1 Phase 1 Studie registriert

Currently, in ClinicalTrials.gov register one **phase 1-1b study** (NCT04672291) in Canada is registered to evaluate the safety and tolerability of **nasally administered** Poly-ICLC (Hiltonol®) treatment in study participants who are **at high-risk for COVID-19**.

Results of publications

Currently, no published results were found from clinical trials related to Poly-ICLC in COVID-19 patients.

3.2.44 Nitric Oxide Nasal Sprey

Details in früheren Versionen

The reader is referred to the earlier version (V22_June and July 2022) for more details on Nitric Oxide **Nasal Spray** (NONS).

Nitric oxide is not authorised in Covid-19 patients (EMA, FDA). NONS has a marketing authorization as a Class I Medical Device in the EU.

Withdrawn, suspended or terminated studies

One withdrawn **phase 2** study was found (NCT04443868) in mild COVID-19 patients (no subjects enrolled).

2 Phase 3 Studien registriert an asymptomatisch oder mild Erkrankten

As of September 2022, there are 2 ongoing clinical trials registered in ClinicalTrials.gov register. One is **phase 3** RCT (NCT05012319) in Bahrain to evaluate the efficacy of NONS compared to placebo in 500 asymptomatic or mild covid-19 patients to reduce the need for urgent medical care in term

of the need of visiting the emergency room in participants with COVID-19 infection and reduce of symptoms. The other is a **phase 3** (NCT05109611) multicenter, randomized, double-blinded, placebo-controlled, clinical efficacy study evaluating nitric oxide nasal spray (NONS) as prevention for treatment of 13000 individuals at risk of exposure to COVID-19 infection in Canada and Sri Lanka. One is found in EU Clinical Trials Register (EudraCT 2020-004994-27).

Results of publications

Currently, three published studies's results were found from clinical trials related to nitric oxide in COVID-19 patients.

Winchester 2021
Phase 2 RCT
80 Pts

Administration des Sprays 5-6 x täglich

deutlich geringere Viruslast und raschere Symtombekämpfung

Winchester et al. 2021 [75] showed the reduction of viral load in the UK **phase 2** RCT (EudraCT 2020-004994-27) trials aimed to measure whether nitric oxide nasal spray (NONS) could accelerate the reduction in SARS-CoV-2 RNA load versus control with a saline spray. Study recruited 80 mild, symptomatic COVID-19 infection participants who were divided into a NONS treatment or a placebo arm to test the efficacy of NONS as a treatment for mild COVID-19 infection. The nasal sprays were self-administered 5–6 times daily (two sprays per nostril/dose, 120–140 μL of solution/spray) for 9 days. Patients in the NONS treatment arm demonstrated viral loads, as determined from PCR testing of nose and throat swab sampling, that were lower at days 2 and 4 by a factor of 16.2 than those on placebo, and symptom resolution was also found to be faster on NONS treatment than on placebo in this study.

Moni 2021
Phase 2 RCT
29 Pts.

deutlich raschere Verringerung der Viruslast

Moni et al. 2021 [76] published as **preprint** results from the **phase 2** open label, randomised controlled feasibility trial (ISRCTN 16806663) conducted at a South Indian tertiary care referral centre, recruited COVID-19 pneumonia patients with hypoxic respiratory failure and allocated them into iNO cases and control groups(1:1). iNO was administered as pulses for 30 minutes for three consecutive days at 12-hour intervals in cases, in addition to standard of care received by the control group. The primary outcome was decline in viral load, as defined by a surrogate change in the RT-PCR cycle threshold. The co-primary clinical outcome was time to improvement of >2 points on the WHO Ordinal Scale(WOS). Among the 29 patients enrolled, 14 iNO cases and 11 controls completed the study protocol. Longitudinal analysis revealed a significant difference in the decline ($p<0.002$, $n=23$) in viral load among the iNO cases compared to controls. The proportion of patients achieving 2-point improvement in the WOS within 14 days of randomisation was significantly higher in the iNO cases (n=11, 79%), as compared to the controls (n=4, 36%) ($p=0.05$).

1 Phase 2 RCT aus Kanada (ohne publizierten Ergebnisse)

One RCT in **Canada** is completed: a multi-center, randomized, controlled, **phase 2** clinical efficacy study evaluating a novel nitric oxide releasing solution (NORS) treatment for the **prevention and treatment of COVID-19 in healthcare workers at risk of infection** (NCT04337918) but results are not posted in the clinicaltrial.gov register.

RCT (Indien)
306 Pts

raschere Viruslastreduktion

Results are recently **published** in the scientific journal by **Tandon et al. 2022** [77]. In this randomized, double-blind, placebo-controlled, parallel-arm study at 20 clinical sites across India that evaluated 306 patients, NONS reduced the SARS-CoV-2 log viral load in COVID-19 patients by more than 94% within 24 hours of treatment, and by more than 99% in 48 hours as compared to saline control. Treatment also demonstrated, in the high-risk group (n=218), a statistically significant greater proportion of patients who

achieved a combination of clinical and virological cure, based on the World Health Organization (WHO) Progression Scale. The median time to negative PCR, in this group, was 4 days in the treatment group compared with 8 days in the control. Test subjects included patients infected with different variants, likely including Delta and Omicron. No adult COVID-19 infected patient in the study required hospitalisation (or supplemental oxygen) for the treatment of COVID-19 by study end. There were no significant adverse health events recorded in the phase 3 trial, or in over 500 subjects treated so far with NONS in clinical trials. All AEs were mild in severity: nasal discomfort was the only infrequently observed respiratory AE in NONS subjects.

Pressemitteilung Mai 2022

RWE (Thailand)
625 Teilnehmer*innen
Post-Expositions-prophylaxe

deutlich geringere Infektionsrate

In **May 2022**, manufacturer **announced** results from the **real-word study**, conducted at Srinakharinwirot University in Bangkok, Thailand, with an Omicron outbreak in February, 2022. Authors found that participants who took NONS after COVID-19 after high-risk exposure were 75% less likely to become infected when compared to the control group, with a statistically significant reduction in infection rate. After exclusion for being low-risk or testing positive via antigen test kit (ATK) within 24 hours, 625 student participants were included in the analysis. Of these, 203 participants used NONS at least four times per day and 422 volunteers did not use NONS. All volunteers were tested via ATK on the fifth, seventh, and tenth day of quarantine, and positive tests were confirmed by PCR. Among the 203 participants who used NONS, 13 tested positive (6.4% infection rate). Of the 422 in the control group, 108 participants tested positive (25.6% infection rate), a statistically significant difference from the treatment group ($p<0.0001$). Participants in the NONS group reported only a mild side effect of nasal irritation (8 of the 203, or 3.9%), https://www.businesswire.com/news/home/20220511005194/en/Clinical-Study-Suggests-SaNOtize-Nitric-Oxide-Nasal-Spray-Is-Effective-at-Preventing-COVID-19-after-High-Risk-Exposure.

3.2.45 Sabizabulin

About the drug under consideration

Mikrotubuli-Disruptor mit antiviraler und entzündungs-hemmender Wirkung

Sabizabulin is an **orally available** novel microtubule disruptor with dual antiviral and anti-inflammatory activities. Sabizabulin targets, binds, and crosslinks both the a- and b-tubulin subunits of microtubules to inhibit polymerization and to induce depolymerization of microtubules, which alters microtubule dynamics. Microtubules are intracellular transport structures important for coronavirus cellular entry, trafficking, replication, egress and for triggering the innate inflammatory response and cytokine storm responsible for ARDS, septic shock, and frequently death [78-80].

FDA Fast Track designation

The **US FDA** has granted Fast Track designation to the Veru's COVID-19 program in January 2022 and the Company submitted a **request for FDA emergency use authorization** on **June 7, 2022** [81].

Pressemitteilung zu FDA Abstimmung zum Nutzen-Risiko Abwägung

On **November 9, 2022** the Company **announced** that the FDA advisory committee voted 8-5 that the known and potential benefits of sabizabulin when used for the treatment of adult patients hospitalised with COVID-19 at high risk of ARDS do not outweigh the known and potential risks of sabizabulin. There was additional discussion around the clinical trial design aspects of an additional clinical trial as a potential post authorization requirement. FDA will consider the input of the advisory committee as part

of their review of the EUA and render a decision on the Emergency Use Authorization, https://ir.verupharma.com/news-events/press-releases/detail/164/veru-provides-update-on-fda-advisory-committee-meeting.

EMA Juli 2022 review

On **July 27, 2022 EMA's Emergency Task Force** (ETF) has **started a review** of data on the use of sabizabulin for treating COVID-19, under Article 18 of the new EU regulation (Reg 2022/123). Although the developer, Veru, has not yet applied to EMA for a marketing authorisation or a rolling review, the review (based on data from the company) **will assist EU Member States who may consider allowing use of the medicine before a possible authorisation** [82]

Withdrawn, suspended or terminated studies

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

Results of publications

1 RCT

Currently, results of a planned interim analysis from one phase 3 RCT were found related to sabizabulin in COVID-19 patients.

Interim Auswertung nach 150 Pts
hospitalisierte Pts. mit moderat-schwerer Erkrankung
hohem Risiko für ARDS

Barnette et al. 2022 [78] published **positive results** of a **planned interim analysis** for the first 150 randomized patients from a randomized, multicenter placebo-controlled **phase 3** clinical trial (NCT04842747) conducted with **hospitalised patients** with **moderate to severe Covid-19** who were **at high risk for acute respiratory distress syndrome (ARDS) and death**. Patients were randomly assigned (2:1) to 9 mg of oral sabizabulin or placebo daily (up to 21 days). The primary end point was all-cause mortality up to day 60. Key secondary end points were days in the intensive care unit (ICU), days on mechanical ventilation, and days in the hospital. A total of 204 patients were randomly assigned to treatment: 134 to sabizabulin and 70 to placebo. Baseline characteristics were similar. The distribution of common risk factors for ARDS and death was similar between treatment groups and included hypertension (59.2% for sabizabulin vs. 61.5% for placebo), 65 years of age or older (45.9% for sabizabulin vs. 50.0% for placebo), diabetes (35.7% for sabizabulin vs. 40.4% for placebo), and obesity (defined as a BMI of 35 or greater; 34.7% for sabizabulin vs. 27.5% for placebo). Covid-19 nonvaccinated rates were also similar (54.1% for sabizabulin vs. 57.7% for placebo). Receipt of standard of care was also similar between the two groups, in which dexamethasone (83.7% for sabizabulin vs. 80.7% for placebo) and remdesivir (34.7% for sabizabulin vs. 28.8% for placebo) were the most common treatments. In this planned interim analysis for the first 150 randomized patients sabizabulin treatment resulted in a 24.9 percentage point absolute reduction and a 55.2% relative reduction in deaths compared with placebo (odds ratio, 3.23; 95% CI confidence interval, 1.45 to 7.22; p=0.0042). The mortality rate was 20.2% (19 of 94) for sabizabulin versus 45.1% (23 of 51) for placebo. For the key secondary end points, sabizabulin treatment resulted in a 43% relative reduction in ICU days (p=0.0013), a 49% relative reduction in days on mechanical ventilation (p=0.0013), and a 26% relative reduction in days in the hospital (p=0.0277) versus placebo. Adverse and serious adverse events were lower in the sabizabulin group compared with the placebo group. **Study was stopped for efficacy at the direction of the independent data monitoring committee.**

hohe Reduktion der Mortalität, ICU, Beatmung, Spitalsaufenthaltstage

Studie wurde beendet aufgrund der Wirksamkeit

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