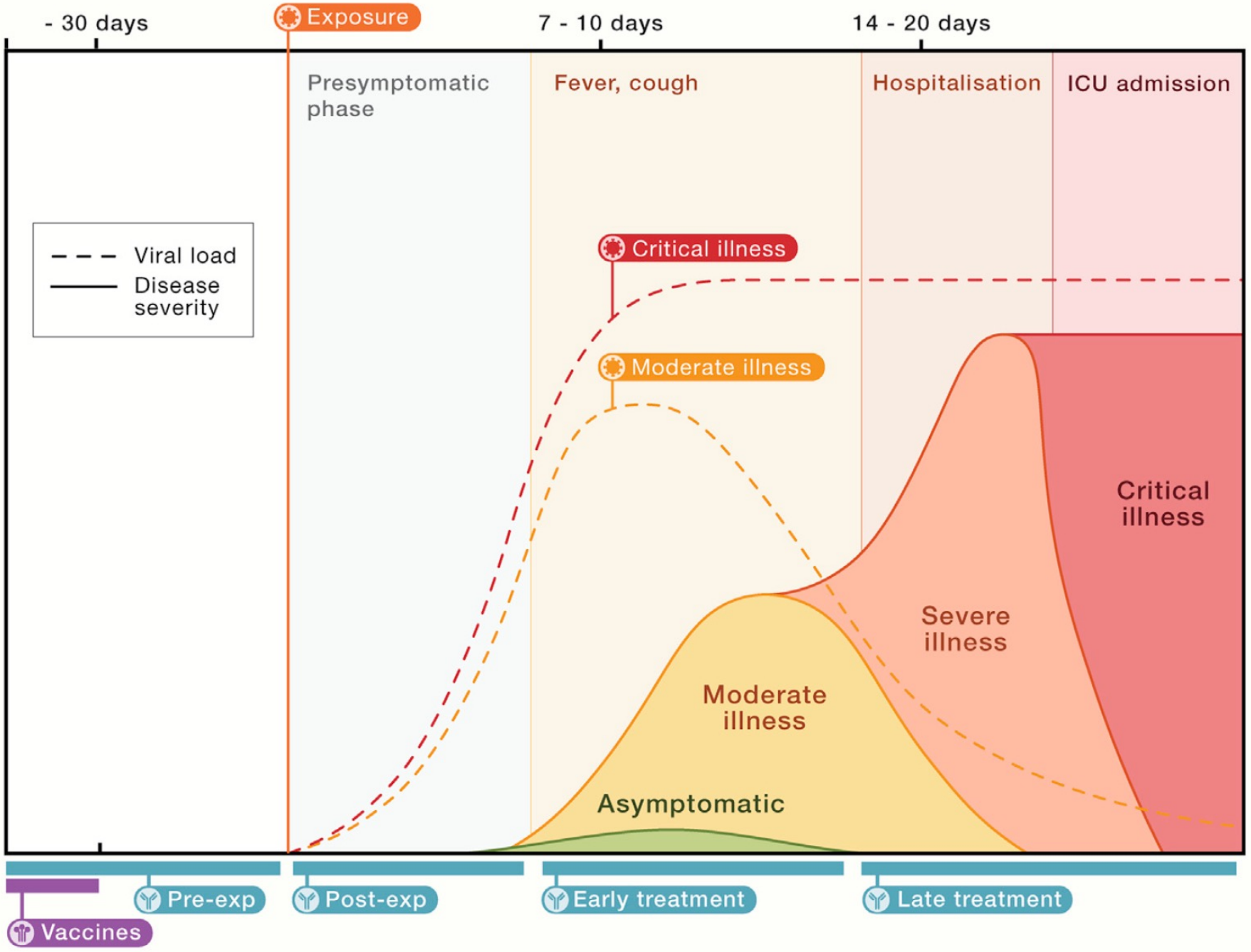
Nuovi scenari terapeutici nel trattamento di COVID-19: antivirali e monoclonali

Dr.ssa Francesca Bai
Clinica di Malattie Infettive
Ospedale San Paolo, ASST Santi Paolo e Carlo
Dipartimento di Scienze della Salute, Università degli Studi di Milano

Outline

- Quali trattamenti con **anticorpi monoclonali** e **antivirali** sono disponibili?
- Quali pazienti sono candidabili a tali trattamenti?
- Terapie con **anticorpi monoclonali** per SARS CoV-2
- Terapie **antivirali** per SARS CoV-2
- Azione antivirale su VOCs (Omicron) e resistenze virali
- Come scegliere i trattamenti?
- Combinazioni di trattamenti e opzioni future



Vaccines

- mRNA-1273 (Moderna)
- BNT162b2 (Pfizer/BioNTech)
- ChAdOx1-S (Astrazeneca)
- Ad26.COV2.S (Johnson&Johnson)
- Sputnik V (GRIEM)

Pre-exposure

- AZD8895+AZD1061 (Ph. 3)

Post-exposure

- Casirivimab+imdevimab (Ph. 3)
- Etesevimab+bamlanivimab (Ph. 3)
- AZD8895+AZD1061 (Ph. 3)

Early treatment

- Bamlanivimab (EUA)
- Etesevimab+bamlanivimab (EUA)
- Casirivimab+imdevimab (EUA)
- Regdanvimab (EUA in South Korea)
- Sotrovimab (EUA)
- AZD8895+AZD1061 (Ph. 3)

Late treatment

- Casirivimab+imdevimab (Ph. 3)
- AZD8895+AZD1061 (Ph. 3)

Corti D et al, Cell 2021;184(12):3086-3108.

Population

This recommendation applies only to people with these characteristics:



Patients with confirmed covid-19

Disease severity

Non-severe	Severe	Critical
Absence of signs of severe or critical disease	Oxygen saturation <90% on room air	Requires life sustaining treatment
	Signs of pneumonia	Acute respiratory distress syndrome
	Signs of severe respiratory distress	Sepsis
		Septic shock

Infographic co-produced by the BMJ and MAGIC; designer Will Stahl-Timmins (see BMJ Rapid Recommendations).

Therapeutics and COVID-19: living guideline - World Health Organization (WHO), April 2022

How to identify non-severe patients at highest risk of hospitalization?

- Several recommendations for drugs are only for those at highest risk for hospitalization; some treatments should be reserved for those at highest risk of hospitalization and given early in the disease course.
- A risk beyond 10% of being hospitalized for COVID-19 to represent a threshold at which most patients with non-severe illness would want to be treated.
- Reliably identifying those at highest risk is challenging because of the changing global context with evolution of the virus, patterns of vaccination.
- A systematic review of 232 risk prediction models for COVID-19 did not identify sufficiently credible and applicable risk prediction tools.
- In the absence of tools to predict risk for hospitalization, typical characteristics of people at highest risk include those with older age, immunosuppression and/or chronic diseases, with lack of vaccination as an additional risk factor.

Therapeutics and COVID-19: living guideline - World Health Organization (WHO), April 2022. Ref 18

How to identify non-severe patients at highest risk of hospitalization?

- Up to 10% of initially asymptomatic, minimally symptomatic progressed to severe disease.
- While 78% of patients admitted to hospital have at least one comorbidity, there continue to be patients lacking any identified comorbidity who subsequently become critically ill.
- Given that persistently high SARS CoV-2 viral loads may be associated with severe clinical outcomes, it is possible that **early reassessment of viral loads** might help guide who among the 'lower- risk' population might be helped by neutralizing mAbs.
- RCT evidence indicates that the clinical value of neutralizing mAb therapy is more pronounced in individuals who are **seronegative at diagnosis**

For more information on medical conditions and factors associated with increased risk for progression to severe COVID-19, please visit the Centers for Disease Control and Prevention (CDC) website.

Un gruppo di esperti scientifici indipendenti ha esaminato 82 strumenti terapeutici candidati in fase avanzata di sviluppo clinico e ha individuato i 10 candidati più promettenti per il portafoglio di cure anti COVID-19 dell'UE, tenendo conto del fatto che sono necessari tipi di prodotti differenti a seconda delle popolazioni di pazienti e delle fasi e della gravità della malattia. L'elenco è suddiviso in 3 categorie terapeutiche e continuerà a evolvere con l'emergere di nuove prove scientifiche.

- Anticorpi monoclonali antivirali più efficaci nelle prime fasi dell'infezione:
  - Ronapreve, una combinazione dei 2 anticorpi monoclonali casirivimab e imdevimab, di Regeneron Pharmaceuticals e Roche;
  - Xevudy (sotrovimab) di Vir Biotechnology e GlaxoSmithKline;
  - Evusheld, una combinazione dei 2 anticorpi monoclonali tixagevimab e cilgavimab, di AstraZeneca.
- Antivirali orali da utilizzare il più rapidamente possibile dal momento dell'infezione:
  - Molnupiravir, di Ridgeback Biotherapeutics e MSD;
  - PF-07321332 di Pfizer;
  - AT-527 di Atea Pharmaceuticals e Roche.
- Immunomodulatori per la cura dei pazienti ricoverati:
  - Actemra (tocilizumab) di Roche Holding;
  - Kineret (anakinra) di Swedish Orphan Biovitrum;
  - Olumiant (baricitinib) di Eli Lilly;
  - Lenzilumab di Humanigen.

Therapeutics and COVID-19

LIVING GUIDELINE

22 APRIL 2022

World Health Organization

Population

This recommendation applies only to people with these characteristics:



Disease severity

Non-severe	Severe	Critical
Absence of signs of severe or critical disease	Oxygen saturation <90% on room air Signs of pneumonia Signs of severe respiratory distress	Requires life sustaining treatment Acute respiratory distress syndrome Sepsis Septic shock

Interventions

Strong recommendations in favour

- **Nirmatrelvir and ritonavir** (Non-severe)
- **Corticosteroids** (Severe, Critical)
- **IL-6 receptor blockers** or **Baricitinib** (Severe, Critical)

Depending on availability as well as clinical and contextual factors

Weak or conditional recommendations in favour

- **Molnupiravir** (Non-severe)
  - Mitigation strategies to reduce potential harms should be implemented
- **Sotrovimab** (Non-severe)
- **Remdesivir** C (Non-severe)

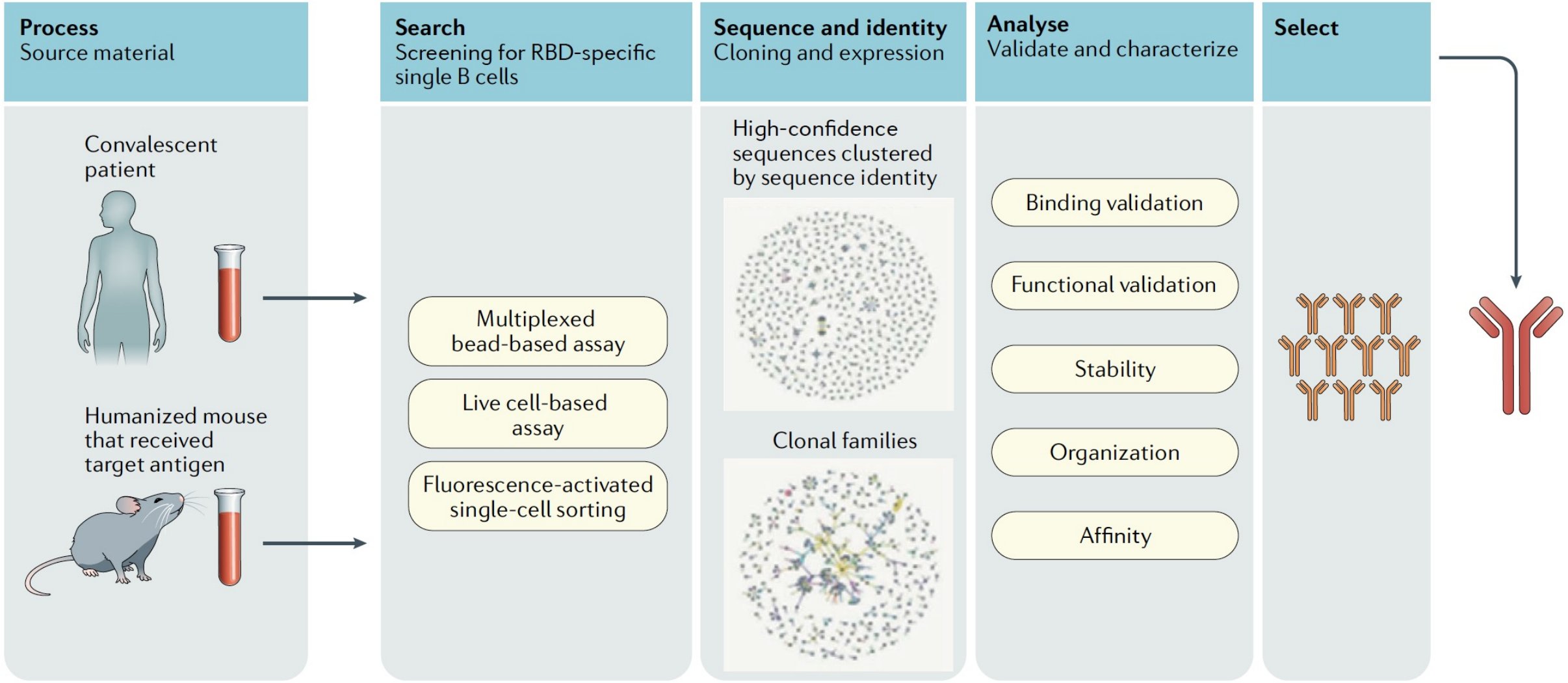
For those with highest risk of hospital admission

Use the interactive multiple comparison tool to compare and choose treatments

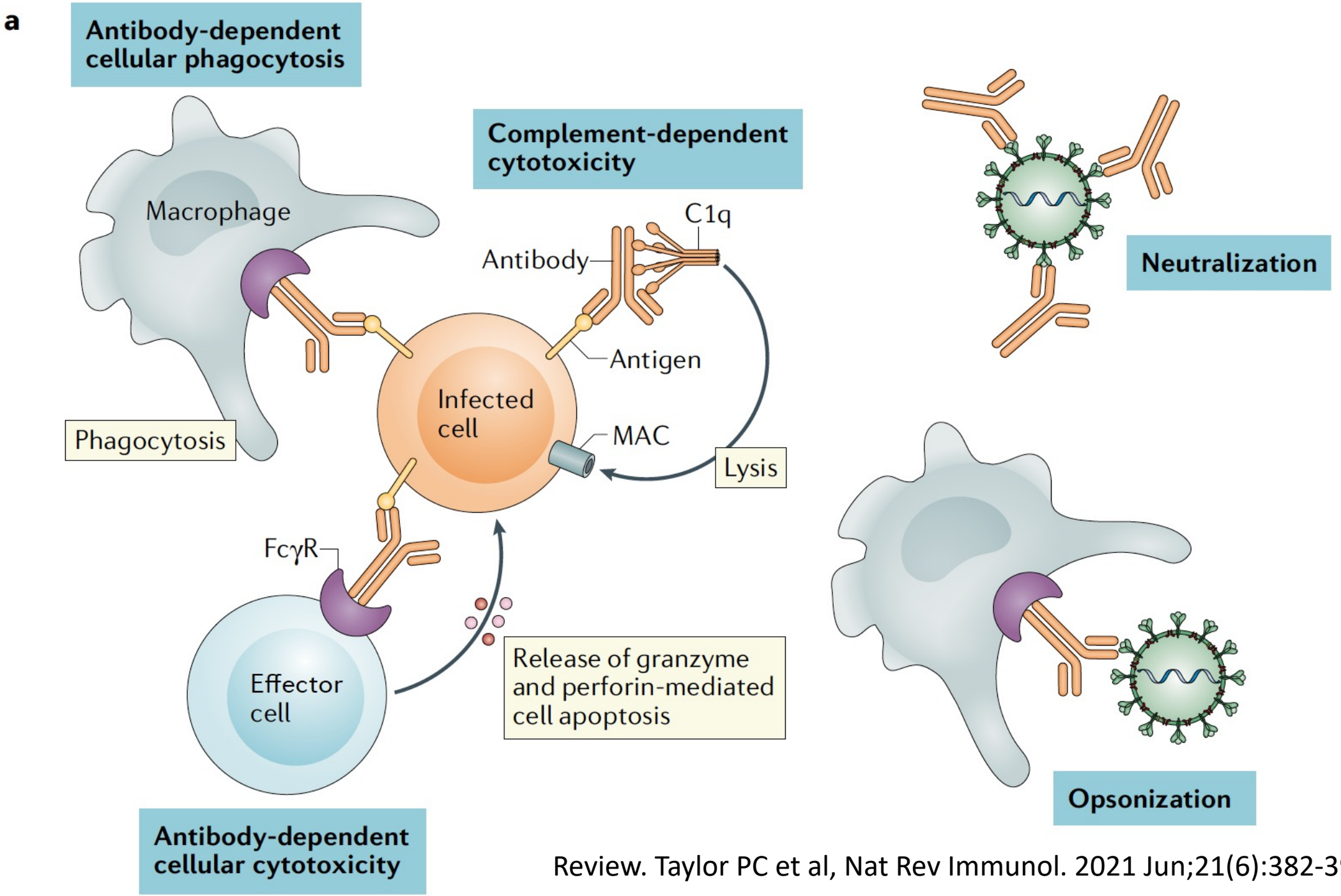
MATCH-IT

- **Casirivimab and imdevimab** (Non-severe)
  - Evidence of limited efficacy against Omicron BA1 variant
- **Casirivimab and imdevimab** (Severe, Critical)
  - For those with seronegative status for SARS-CoV-2 antibodies

Monoclonal Antibodies (mAbs) for SARS COV-2



Review. Taylor PC et al, Nat Rev Immunol. 2021 Jun;21(6):382-393.

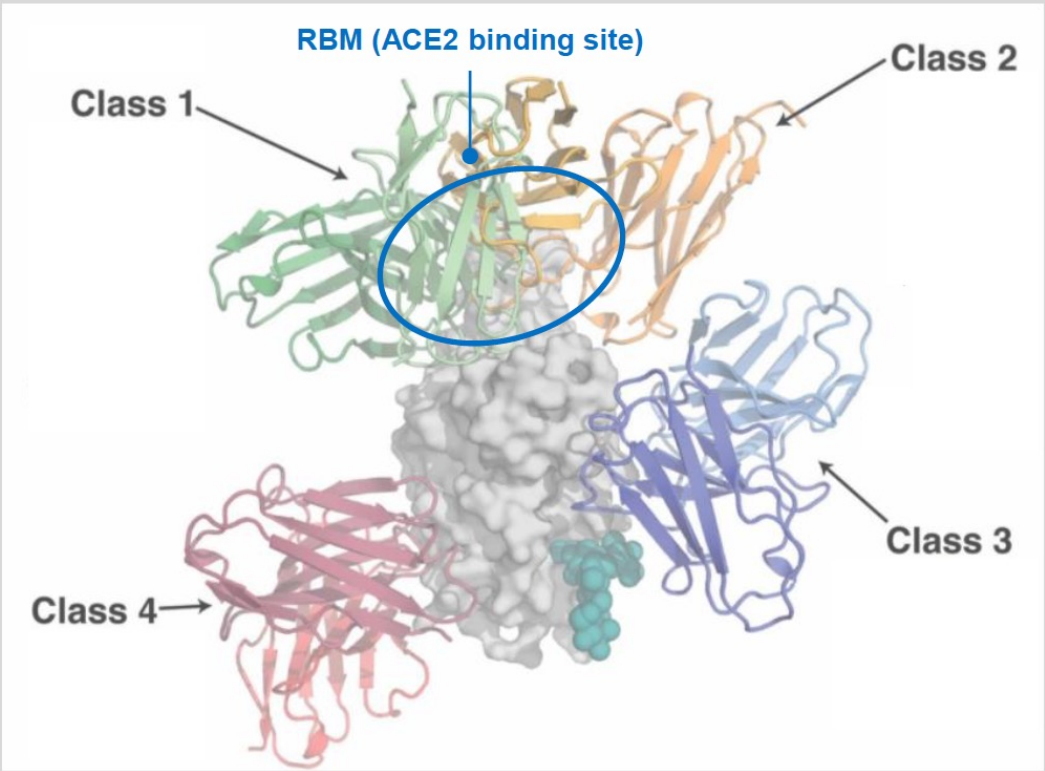


Review. Taylor PC et al, Nat Rev Immunol. 2021 Jun;21(6):382-393.

Closed and open conformation of spike protein

- The spike protein normally exists in a **pre-fusion, closed (down) conformation**; in this conformation some parts of the protein are hidden.
- Upon viral infection, the RBD undergoes a transient conformational change to the **open (up) combinations**, allowing SARS CoV-2 to interact with the host cell receptor.
- In the open conformation, the RBD points upwards, exposing the RBM and allowing the virus to bind ACE2.

Classification of mABs against Spike protein according to their binding site



The illustration has been reproduced with permission from Barnes CO, et al. *Nature* 2020;588:682–7

Classification	Structural characteristics
Class 1	• Blocks ACE2 • Binds only to 'up' RBDs
Class 2	• Blocks ACE2 • Binds both 'up' and 'down' RBDs • Can contact adjacent RBDs
Class 3	• Binds outside the RBM (ACE2 binding site) • Recognises both 'up' and 'down' RBDs
Class 4	• Does not block ACE2 • Binds only to 'up' RBDs

Barnes CO et al, Nature 2020; 588: 682-687

Classification of mAbs

Name	RBD site
Sotrovimab (VIR-7831)[1,2] **VIR-7832[1,2]**	Class 3
REGN-COV2 (REGN10933 and REGN10987, not co-formulated)[3,4,5]	Class 1 Class 2
LY-CoV555 and LY-CoV16[6,7]	Class 2
AZD7442[8] (cocktail of AZD8895 and AZD1061)	Class 1 Class 2

Only sotrovimab† binds to a Class 3 RBD site, distinct from the RBM (ACE2 binding site)[1,2]

1. Barnes CO, et al. *Nature* 2020;588:682–7; 2. Pinto D, et al. *Nature* 2020;583:290–5; 3. Baum A, et al. *Science* 2020;369:1014–18; 4. Baum A, et al. *Science* 2020;370:1110–5; 5. Hansen J, et al. *Science* 2020;369:1010–14; 6. Jones BE, et al. *bioRxiv preprint* 2020; doi: https://doi.org/10.1101/2020.09.30.318972; 7. Shi R, et al. *Nature* 2020;584:120–4; 8. Zost SJ, et al. *Nature* 2020;584:443–9.

Neutralizing monoclonal antibodies for treatment of COVID-19

Peter C. Taylor[1] ✉, Andrew C. Adams[2], Matthew M. Hufford[2], Inmaculada de la Torre[2], Kevin Winthrop[3] and Robert L. Gottlieb[4,5]

combination therapy[3–5]. Therefore, several questions need to be addressed about the potential clinical use of neutralizing SARS-CoV-2 mAbs: who should get them; what is the best dose and frequency; when in the course of the infection will they be most effective; what is the duration of the protection they provide; and what is their associated benefit-to-risk ratio? In addition, neutraliz-

Review. Nat Rev Immunol. 2021 Jun;21(6):382-393.

Criteri di eleggibilità all'uso di anticorpi monoclonali in pazienti con COVID-19

La somministrazione degli anticorpi monoclonali è riservata a pazienti non ospedalizzati, di età >12 aa, e con peso > 40 kg con diagnosi di infezione da SARS-CoV-2 confermata da tampone molecolare o antigenico di terza generazione e con malattia di grado lieve-moderato ma a rischio di progressione ed ospedalizzazione, e comunque entro 10 gg dall'esordio dei sintomi. I pazienti devono avere almeno una delle seguenti condizioni:

- indice di massa corporea (Body Mass Index, BMI) > 30 kg/m2 in pazienti di età >/= 18 anni oppure > 95° per età e genera in caso di pazienti di età < 18 anni
- presenza d'insufficienza renale cronica, incluse dialisi peritoneale o emodialisi
- essere portatori di diabete mellito non controllato (HbA1c>9,0% 75 mmol/mol) o con complicanze croniche
- avere una immunodeficienza primaria o secondaria
- avere un'età> 65 anni
- presenza di malattia cardio-cerebrovascolare (inclusa ipertensione con concomitante danno d'organo)
- presenza di epatopatia cronica
- presenza di broncopneumopatia cronica ostruttiva e/o altra malattia respiratoria cronica (ad es. soggetti affetti da asma, fibrosi polmonare o che necessitano di ossigenoterapia per ragioni differenti da SARS-CoV-2)
- presenza di emoglobinopatie
- patologie del neurosviluppo e patologie neurodegenerative

Sono eleggibili al trattamento oltre il 10° giorno i soggetti con immunodeficienza primitiva o secondaria e coloro che risultano positivi al tampone molecolare e sierologia negativa.

mAbs: main RCT

Antibody therapies				
Sotrovimab (NCT04545060)	Multiple countries (92% USA)	Hospitalization for ≥24 h or death	Age ≥18 unvaccinated Positive test with: ≤5 d of symptoms Criterion for high risk	Median age 53; 54% female; 87% White; mean BMI 32; N/A hypertension; 22% diabetes 59% had duration of symptoms ≤3 d
Casirivimab/imdevimab (NCT04425629)	USA and Mexico	COVID-19-related hospitalization or death from any cause	Age ≥18 unvaccinated Positive test with: ≤7 d of symptoms Criterion for high risk	Median age 48–50; 52% female; 84% White; 57% BMI ≥30; 36% hypertension; 15% diabetes Median duration of symptoms 3 d
Bamlanivimab/ etesevimab (NCT04427501)	USA	COVID-19-related hospitalization or death from any cause	Age ≥12 unvaccinated Positive test with: Symptoms Criterion for high risk	Mean age 54; 52% female; 87% White; mean BMI 34; 34% hypertension; 28% diabetes Median duration of symptoms 4 d

Todd CL et al, OFID 2022; 9(3):ofac008.

Eli Lilly Netherlands BV (Lilly) would like to inform you of the decision to no longer continue with the ongoing submissions and responses under rolling review for an eventual marketing authorisation application for bamlanivimab and etesevimab for the treatment of confirmed COVID-19 in patients aged 12 years and older that do not require supplemental oxygen for COVID-19 and who are at increased risk of progressing to severe COVID-19.

The decision to no longer pursue a marketing authorisation application is based on the following reason:

- CHMP has determined that prospective concurrent validation is required for submission of a formal marketing authorisation application. Given the current demand from EU member states, Lilly forecasts that no additional / new drug substance manufacturing campaigns will be needed for the foreseeable future. Therefore, at this point Lilly is not in a position to generate the additional data required by the CHMP to progress to a formal marketing authorization application.

Lilly would like to thank the Rapporteurs, EMA, and the scientific committees involved for the time dedicated to assessing the rolling review, and the valuable support and helpful guidance provided during this novel process.

mentre l'attività neutralizzante della combinazione bamlanivamb/etesevimab, differentemente dagli altri anticorpi monoclonali disponibili (casirivimab/imdevimab e sotrovimab), è fortemente inibita nei confronti delle varianti beta (B.1.351) e gamma (P.1).

Agenzia Italiana del Farmaco

Uso degli anticorpi monoclonali per COVID-19

La Commissione europea, su parere dell'Agenzia europea per i medicinali (EMA), ha autorizzato i seguenti medicinali contenenti anticorpi monoclonali, da soli o in associazione, contro la proteina spike del virus SARS-CoV-2:

- associazione **casirivimab-imdevimab** denominata **Ronapreve** (dell'azienda farmaceutica Regeneron/Roche) per il trattamento e la prevenzione di COVID-19;
- **regdanvimab** denominato **Regkirona** (dell'azienda farmaceutica Celltrion Healthcare Hungary Kft) per il trattamento di COVID-19;
- **sotrovimab** denominato **Xevudy** (dell'azienda GSK) per il trattamento di COVID-19.

Casirivimab/Imdevimab: non-severe COVID-19 patients at highest risk of clinical progression

For patients with non-severe COVID-19 at highest risk of hospitalization

Conditional recommendation for

Updated

We suggest treatment with casirivimab-imdevimab where viral genotyping can confirm a susceptible SARS-CoV-2 variant (i.e. excluding Omicron BA.1) *(conditional recommendation for)*.

Therapeutics and COVID-19: living guideline - World Health Organization (WHO), April 2022

Casirivimab/Imdevimab: SEVERE or CRITICAL COVID-19 disease

For patients with severe or critical COVID-19

Conditional recommendation for

Updated

We suggest treatment with casirivimab-imdevimab for patients with seronegative status, and where viral genotyping can confirm a susceptible SARS-CoV-2 variant (i.e. excluding Omicron BA.1) *(conditional recommendation for).*

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

Therapeutics and COVID-19: living guideline - World Health Organization (WHO), April 2022

Sotrovimab: conditional recommendation for patients with NON-SEVERE disease at highest risk of clinical progression

Conditional recommendation for

We suggest treatment with sotrovimab *(conditional recommendation for)*.

- *The Omicron BA.2 variant may substantially reduce clinical efficacy of sotrovimab; the GDG is currently assessing this issue.*
- *Patients with severe or critical COVID-19: based on current evidence, the benefit of sotrovimab in seronegative patients with severe or critical COVID-19 (see casirivimab-imdevimab recommendation in Section 6.8) remains unclear. This means that careful clinical judgment needs to be applied if casirivimab-imdevimab is unavailable and sotrovimab is considered.*

Therapeutics and COVID-19: living guideline - World Health Organization (WHO), April 2022

Sotrovimab

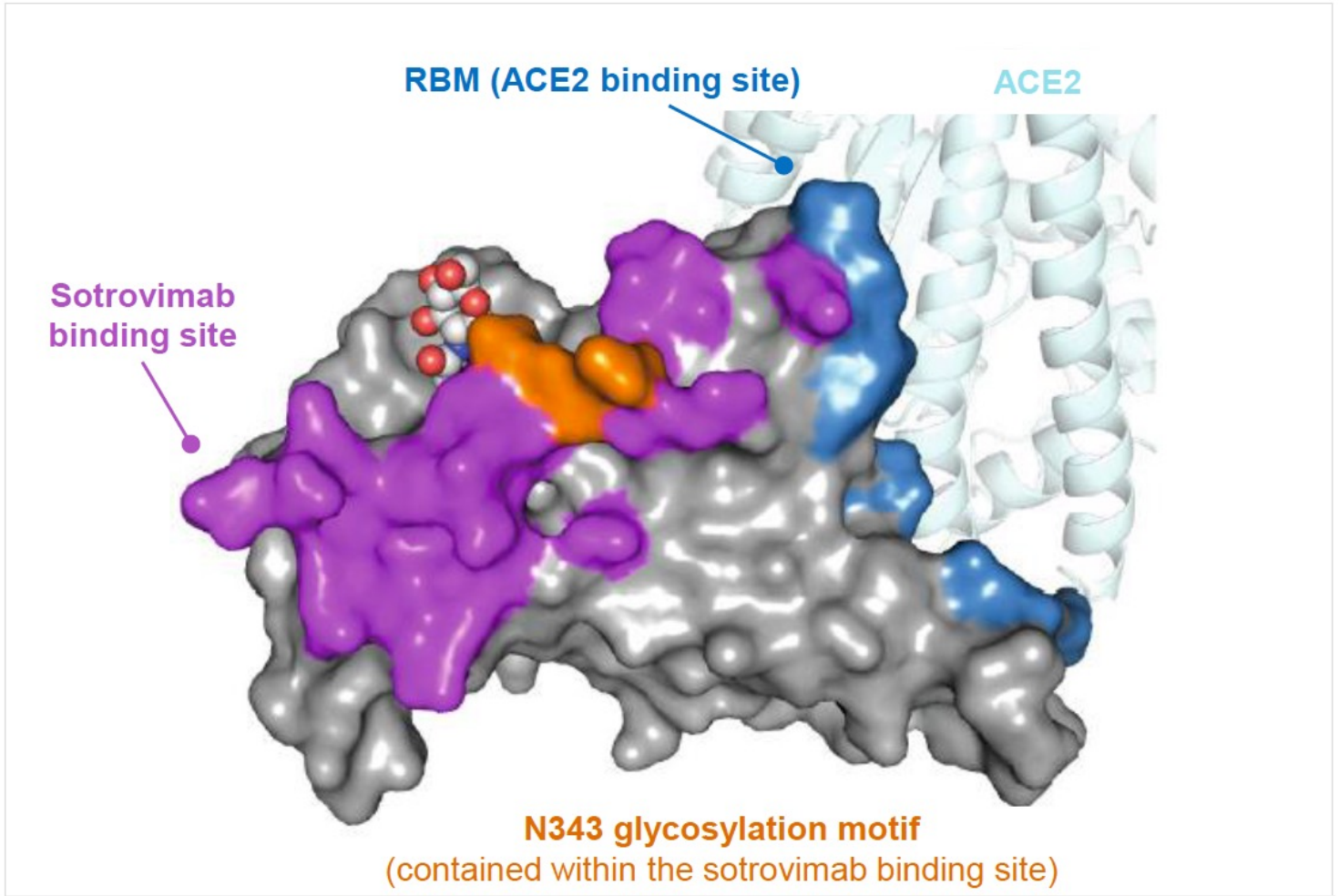
- Sotrovimab (VIR-7831; GSK4182136) is a single human monoclonal antibody that binds to a conserved epitope of the SARS-CoV-2 spike protein, preventing the virus from entering cells.

- High affinity for the SARS CoV-2 spike protein, able to bind to the virus in both the up (open) and down (closed) conformations

- Potent neutralisation activity

Barnes CO et al, Nature 2020; 588: 682-687; GSK press release

Sotrovimab



The illustration has been reproduced with the permission of Springer: Pinto D, et al. *Nature* 2020;583:290–5. Copyright © 2020

*Sotrovimab is based on parental mAb S309

The recognition of epitopes that are conserved across different viruses of the same lineage may be important to **reduce the risk of viral escape** under drug selection, as well as provide **long-term coverage of circulating and emerging variants** and strains.

Sotrovimab has preserved effector functions that may recruit the host immune system to fight viral infection[1]

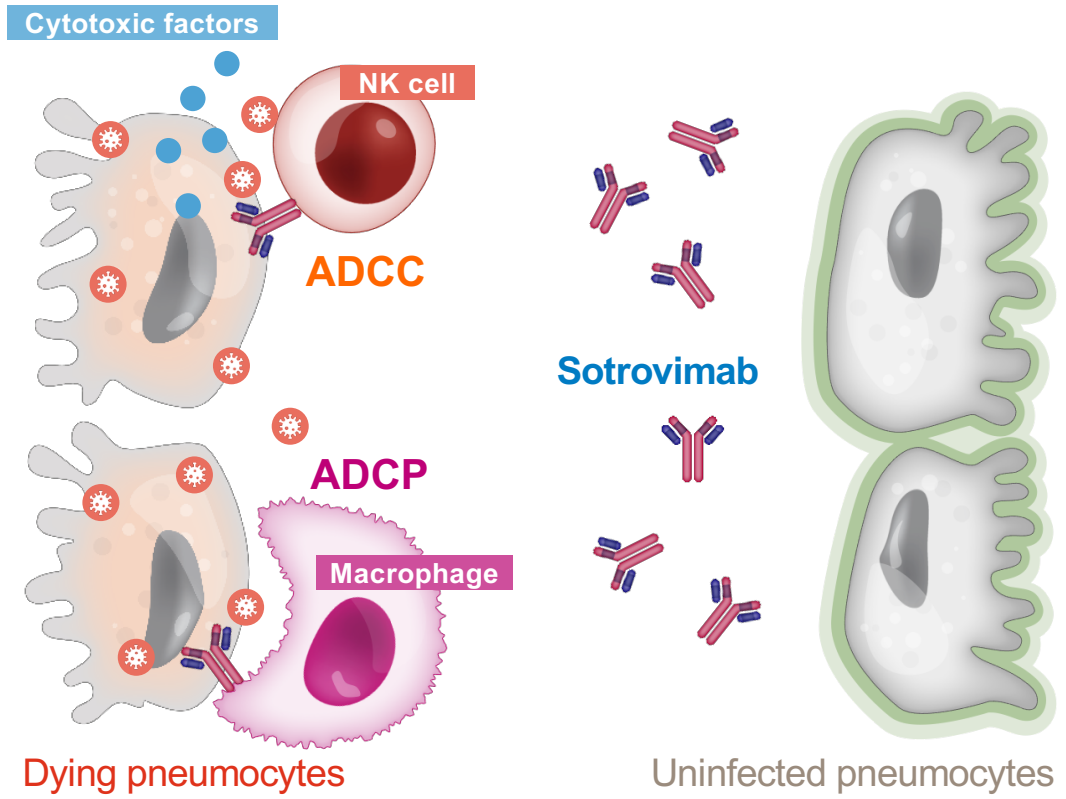
Antibody-dependent cell cytotoxicity (ADCC):[2–4]

- mediated by NK cells
- **triggers apoptosis** of virus-infected target cells (pneumocytes)

Antibody-dependent cell phagocytosis (ADCP):[2,4]

- mediated by macrophages or dendritic cells
- potential to **clear virus** and infected cells by engulfing/destroying viral particles and by stimulating a T-cell response

Antibody effector mechanisms[2-4]



NK, natural killer.

1. Cathcart AL, et al. bioRxiv (preprint). February 18, 2022. doi:10.1101/2021.03.09.434607v11; 2. Pinto D, et al. *Nature.* 2020;583(7815):290-295; 3. Jegaskanda S, et al. *J Immunol.* 2014;193(2):469-475; 4. Sicca F, et al. *Expert Rev Vaccines.* 2018;17(9):785-795.

This Document Contains GSK Proprietary Information – Not For Onward Distribution

QUESTION Among patients at risk of disease progression, does early treatment of mild to moderate COVID-19 with the neutralizing antibody sotrovimab prevent progression to severe disease?

CONCLUSION The findings support sotrovimab as a treatment option for nonhospitalized, high-risk patients with mild to moderate COVID-19, although efficacy against SARS-CoV-2 variants that have emerged since the study was completed is unknown.

POPULATION



572 Women
485 Men

Adults with symptomatic SARS-CoV-2 infection

Median age: 53 years

LOCATIONS



57
Clinic sites worldwide

INTERVENTION



1057 Patients analyzed

528
Sotrovimab
Single intravenous infusion with 500 mg of sotrovimab given over 1 hour on day 1



529
Placebo
Equal volume of saline placebo given over 1 hour on day 1

PRIMARY OUTCOME

All-cause hospitalization longer than 24 hours for acute illness management or death through day 29

FINDINGS

COMET-ICE

All-cause hospitalization or death

Sotrovimab
1% (6 of 528 patients)

Placebo
6% (30 of 529 patients)

Sotrovimab vs placebo was significant:

Adjusted relative risk, **0.21**
(95% CI, 0.09 to 0.50)

Absolute difference, **−4.53%**
(95% CI, -6.70% to -2.37%)

© AMA

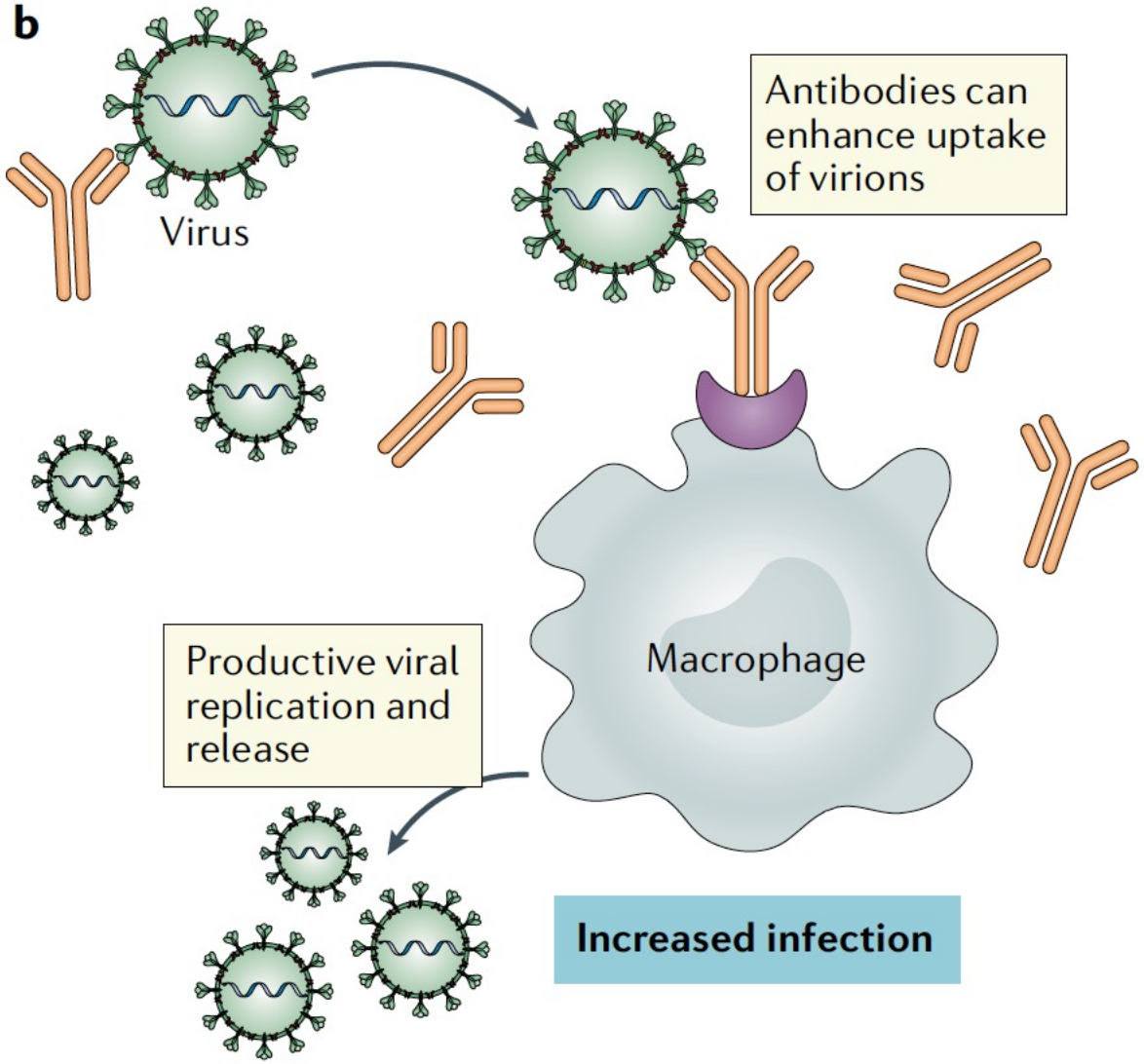
Gupta A, Gonzalez-Rojas Y, Juarez E, et al; for the COMET-ICE Investigators. Effect of sotrovimab on hospitalization or death among high-risk patients with mild to moderate COVID-19: a randomized clinical trial. *JAMA*. Published online March 14, 2022. doi:10.1001/jama.2022.2832

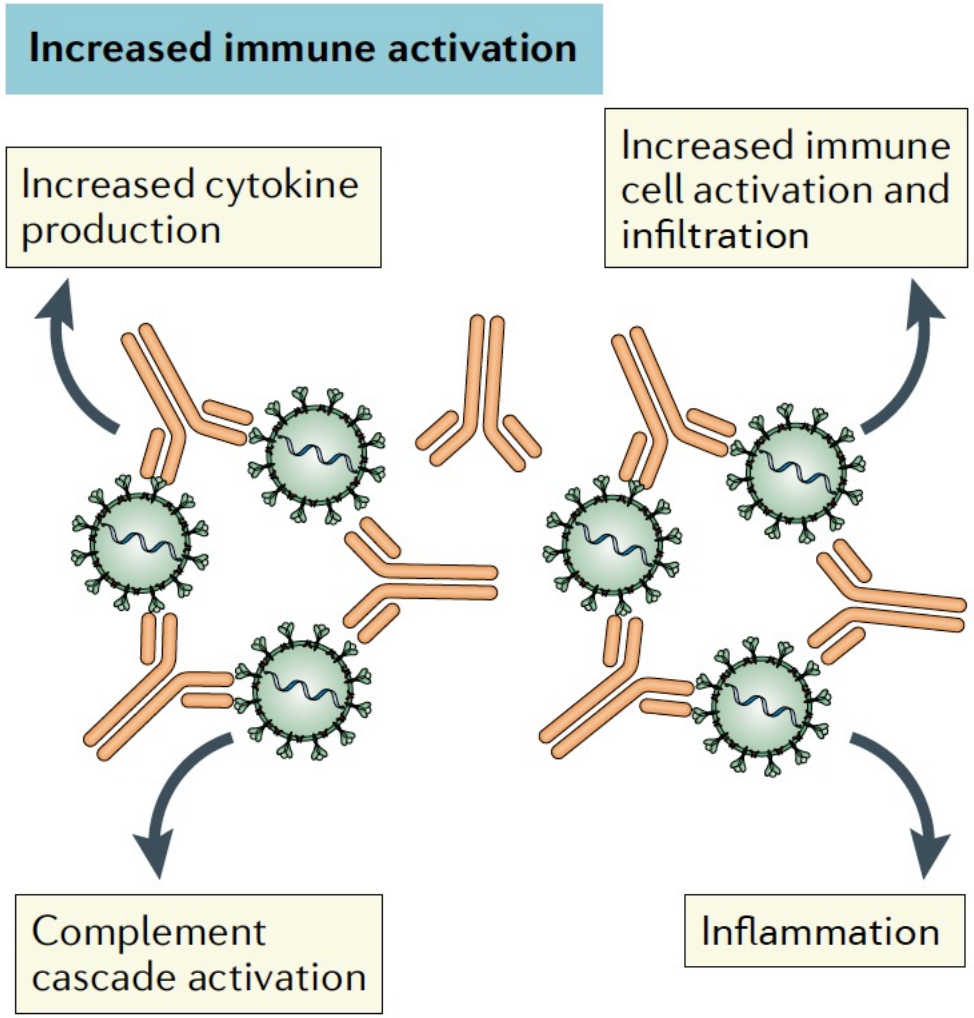
Conclusions

Among nonhospitalized patients with mild to moderate COVID-19 and at risk of disease progression, a single intravenous dose of sotrovimab, compared with placebo, significantly reduced the risk of a composite end point of all-cause hospitalization or death through day 29. The findings support sotrovimab as a treatment option for nonhospitalized, high-risk patients with mild to moderate COVID-19, although efficacy against SARS-CoV-2 variants that have emerged since the study was completed is unknown.

Adverse events associated with monoclonal antibody therapies. In terms of risk associated with mAb treatment of COVID-19, treatment-associated adverse events were comparable to those with placebo. The most frequent side effects observed in RCTs include nausea, diarrhoea, dizziness, headache and vomiting[24,25,78]. One per cent of patients receiving casirivimab and imdevimab reported a grade 2 or higher infusion-related reaction within 4 days of administration (comparable to 1% reported for placebo treatment)[78]. In the phase II portion of BLAZE-1,

Convalescent serum and mAbs: antibody-dependent enhancement (ADE)?





Review. Taylor PC et al, Nat Rev Immunol. 2021 Jun;21(6):382-393.

dose related[25]. Regarding evidence of ADE, in vitro data indicate neutralizing mAbs do not enhance productive infection of immune cells with SARS-CoV-2 (REFS[3,4]). From the clinical data available to date, there is no clear evidence these therapies result in enhanced immune responses consistent with ADE[24,25,78]. Furthermore, the safety profiles of modified and modified plus unmodified mAbs to treat SARS-CoV-2 infection are similar, suggesting that ADE may not play a role in clinical outcomes[25].

zation, spanning both neutralizing mAbs and CPT. First, does their use as a prophylactic or treatment potentially affect natural long-term immunity? Considering the large doses used and the relative half-life of antibodies (~3 weeks for IgG molecules), there is a pertinent consideration whether the presence of circulating neutralizing mAbs could impact active immunity, whether through memory from infection or vaccination. In RSV infection, rodent and primate infection models indicate that the passive transfer of antibodies does diminish the development of humoral immunity in the recipient; however, long-term memory was sufficient to protect the hosts from reinfection, largely owing to an intact T cell memory compartment[39,40]. Considering the limitations in translating data from animal models (where RSV replication is attenuated relative to that in its human host), additional data, particularly from clinical trials, will provide critical insight with regard to this potential challenge.

Second, could resistant viral variants emerge that limit the effectiveness of the therapies? The polyclonal nature of CPT, in which a spectrum of differentiated antibodies target multiple epitopes of the pathogen, may help to reduce this risk. Nevertheless, emerging preclinical data suggest SARS-CoV-2 spike (S) protein mutations escape from polyclonal serum[41], and convalescent plasma has reduced neutralizing activity against some viral variants[42]. For mAbs, however, depending on the infectious agent and the epitope targeted, combinations of mAbs may be necessary to maintain efficacy and prevent treatment failure. Experience with mAbs targeting human immunodeficiency virus (HIV), which has a very high mutation rate, suggests that it may be more effective and durable to use multiple neutralizing antibodies (that is, combinational mAb therapy) rather than a single one[43–46]. These particular mAbs to HIV also need

Paxlovid (Nirmatrelvir/Ritonavir) and Lagevio (Molnupiravir): oral antivirals

mild to moderate COVID-19 in adults and pediatric patients 12 years of age and older for Paxlovid and adults 18 and older for Molnupiravir who are at risk for progression to severe COVID-19 including hospitalization or death

Saravolats LD et al, Clin Infect Dis 2022; ciac180.

Recentemente sono stati resi disponibili tre antivirali (remdesivir, nirmatrelvir/ritonavir e molnupiravir) per il trattamento di soggetti adulti con COVID-19 che non necessitano di ossigenoterapia supplementare e che sono a maggior rischio di progressione verso forme severe di COVID-19.

Il paziente **non deve essere ospedalizzato** a causa di COVID-19, deve presentare una forma di **grado lieve-moderato** e almeno uno fra i seguenti fattori di rischio associati all'evoluzione in malattia severa:

- Patologia oncologica/oncoematologica in fase attiva
- Insufficienza renale cronica
- Broncopneumopatia severa
- Immunodeficienza primaria o acquisita
- Obesità [(Body Mass Index, BMI) ≥30]
- Malattia cardiovascolare grave (scompenso cardiaco, malattia coronarica, cardiomiopatia)
- Diabete mellito non compensato

RACCOMANDAZIONI AIFA SUI FARMACI
per la gestione domiciliare di COVID-19
Vers. 7 – Agg. 09/02/2022

Nirmatrelvir-Ritonavir

Nirmatrelvir is a SARS-CoV-2 main protease inhibitor (Mpro), and ritonavir is an HIV-1 protease inhibitor and CYP3A inhibitor [6]. Inhibition of SARS-CoV-2 Mpro renders it incapable of processing polyprotein precursors, preventing viral replication.

Nirmatrelvir inhibited the activity of recombinant SARS-CoV-2 Mpro in a biochemical assay with a Ki value of 3.1 nM and an IC50 value of 19.2 nM. Ritonavir is an HIV-1 protease inhibitor that is administered to increase the level of nirmatrelvir and has no activity against SARS-CoV-2 Mpro.

Saravolats LD et al, Clin Infect Dis 2022; ciac180.

Nirmatrelvir-ritonavir: strong recommendation for non-severe patients at highest risk of hospitalization

Strong recommendation for

New

We recommend treatment with nirmatrelvir-ritonavir *(strong recommendation for)*.

- *See Section 6.1 for help to identify patients at highest risk.*
- *Several therapeutic options are available: see decision support tool that displays benefits and harms of nirmatrelvir-ritonavir, molnupiravir, remdesivir and monoclonal antibodies.*
- *The GDG concluded that nirmatrelvir-ritonavir represents a superior choice because it may have greater efficacy in preventing hospitalization than the alternatives, has fewer concerns with respect to harms than does molnupiravir; and is easier to administer than intravenous remdesivir and the antibodies.*
- *The strong recommendation in favour does not apply to pregnant women, children, or those with possible dangerous drug interactions (many drugs interact with nirmatrelvir-ritonavir, see mechanism of action).*
- *Nirmatrelvir-ritonavir should be administered as soon as possible after onset of symptoms, ideally within 5 days.*

Therapeutics and COVID-19: living guideline - World Health Organization (WHO), April 2022

Drug-drug interactions

Nirmatrelvir is a substrate and potential inhibitor for P-gp and CYP3A4 enzymes.

Ritonavir is a substrate and inhibitor primarily for CYP3A4 but also CYP2D6.

Ritonavir induces CYP3A, CYP1A2, CYP2C9, CYP2C19, CYP2B6, and other enzymes such as glucuronosyl transferase. Ritonavir provides boosting to ensure sufficient levels of nirmatrelvir and is required for the latter's use [3].

monitoring while on nirmatrelvir-ritonavir therapy) [10]. One free, comprehensive drug interaction resource available is COVID-19 Drug Interactions by the University of Liverpool (https://www.covid19-druginteractions.org/).

Saravolats LD et al, Clin Infect Dis 2022; ciac180.

Study	Publication status	Location	Median age	Percent male	Severity	Dose	N randomized
EPIC-SR NCT05011513	Not published, ongoing (interim data)	Multicontinental	NA		All non-severe	Nirmatrelvir 300 mg and ritonavir 100 mg twice daily for 5 days	673
EPIC-HR NCT04960202	Published	Multicontinental	46	51	All non-severe	Nirmatrelvir 300 mg and ritonavir 100 mg twice daily for 5 days	2246

All patients were unvaccinated and were randomized within 5 days of symptom onset
No patients received therapeutic co-interventions
No pregnant women or children

Oral Nirmatrelvir for High-Risk, Nonhospitalized Adults with Covid-19

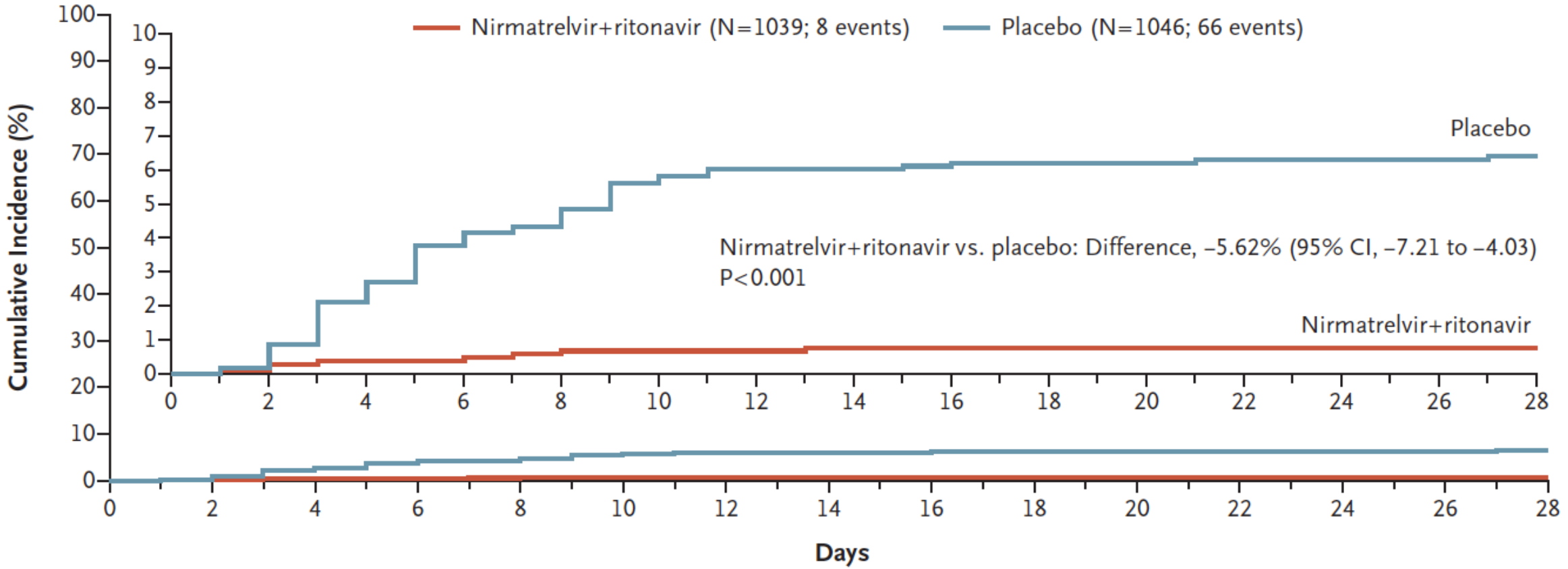
Hammond J et al, NEJM 2022; 386(15):1397-1408.2022

Jennifer Hammond, Ph.D., Heidi Leister-Tebbe, B.S.N., Annie Gardner, M.P.H., M.S.P.T., Paula Abreu, Ph.D., Weihang Bao, Ph.D., Wayne Wisemandle, M.A., MaryLynn Baniecki, Ph.D., Victoria M. Hendrick, B.Sc., Bharat Damle, Ph.D., Abraham Simón-Campos, M.D., Rienk Pypstra, M.D., and James M. Rusnak, M.D., Ph.D., for the EPIC-HR Investigators*

- Phase 2–3, double-blind, randomized, placebo-controlled trial
- Primary outcome: to evaluate the efficacy, viral load and safety associated with the use of nirmatrelvir plus ritonavir among nonhospitalized, symptomatic adults with COVID-19 who were at high risk for progression to severe disease.
- Eligible patients:
- at least 18 years old;
- symptom onset no more than 5 days before randomization
- with at least one sign or symptom of COVID-19 on the day of randomization
- to have at least one characteristic or coexisting condition associated with high risk of progression to severe COVID-19.

Characteristic	Nirmatrelvir plus Ritonavir (N=1120)	Placebo (N=1126)	Total (N=2246)
Median age (range) at randomization — yr	45.00 (18.00–86.00)	46.50 (18.00–88.00)	46.00 (18.00–88.00)
Sex — no. of patients (%)			
Male	566 (50.5)	582 (51.7)	1148 (51.1)
Female	554 (49.5)	544 (48.3)	1098 (48.9)
Race or ethnic group — no. of patients (%)†			
White	800 (71.4)	807 (71.7)	1607 (71.5)
Black	60 (5.4)	50 (4.4)	110 (4.9)
Asian	154 (13.8)	161 (14.3)	315 (14.0)
American Indian or Alaska Native	96 (8.6)	95 (8.4)	191 (8.5)
Multiracial	1 (0.1)	2 (0.2)	3 (0.1)
Not reported	8 (0.7)	9 (0.8)	17 (0.8)
Other or unknown	1 (0.1)	2 (0.2)	3 (0.1)
Time since first symptom			
≤3 days — no. of patients (%)	754 (67.3)	735 (65.3)	1489 (66.3)
>3 days — no. of patients (%)	366 (32.7)	391 (34.7)	757 (33.7)
Mean±SD — days	2.93±1.12	2.99±1.09	2.96±1.10
Median (range) — days	3.00 (0.00–7.00)	3.00 (0.00–9.00)	3.00 (0.00–9.00)
Covid-19 monoclonal antibody treatment — no. of patients (%)			
Received or expected to receive	70 (6.2)	70 (6.2)	140 (6.2)
Not received or did not expect to receive	1050 (93.8)	1056 (93.8)	2106 (93.8)
Serology status — no. of patients (%)			
Negative	518 (46.2)	537 (47.7)	1055 (47.0)
Positive	581 (51.9)	568 (50.4)	1149 (51.2)
Median viral load (range) — $\log_{10}$ copies per milliliter	5.41 (0.00–9.16)	5.30 (0.00–9.15)	5.35 (0.00–9.16)
Viral load ≥10^4 copies per milliliter — no. of patients (%)	677 (60.4)	676 (60.0)	1353 (60.2)

B **Covid-19–Related Hospitalization or Death from Any Cause through Day 28 among Patients Treated ≤5 Days after Symptom Onset**



No. at Risk

NMV-r	1039	1034	1023	1013	1007	1004	1002	1000	997	995	993	993	993	993	992
Placebo	1046	1042	1015	990	977	963	959	959	955	953	951	948	948	948	945

Hammond J et al, NEJM 2022;386(15):1397-1408.2022

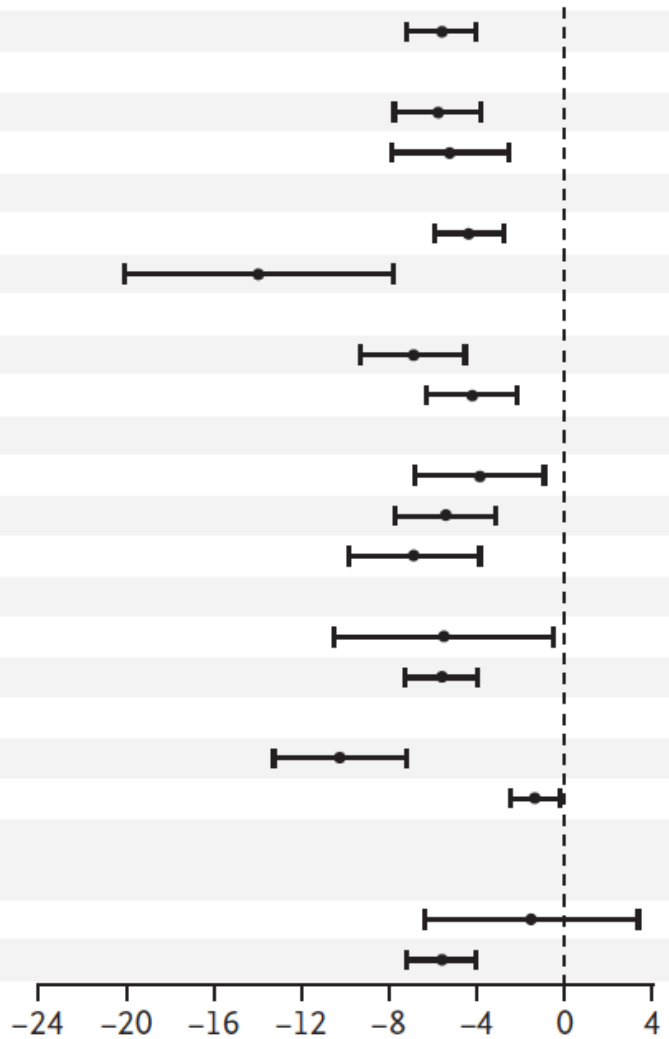
A Outcomes According to Time Since Onset of Covid-19 Symptoms

	Treated ≤3 Days after Onset of Symptoms (modified intention-to-treat population)		Treated ≤5 Days after Onset of Symptoms	
	Nirmatrelvir+ritonavir (N=697)	Placebo (N=682)	Nirmatrelvir+ritonavir (N=1039)	Placebo (N=1046)
Patients with event — no. (%)	5 (0.72)	44 (6.45)	8 (0.77)	66 (6.31)
Hospitalization for Covid-19	5 (0.72)	44 (6.45)	8 (0.77)	65 (6.21)
Death from any cause	0	9 (1.32)	0	12 (1.15)
Average time at risk for event — days	27.29	26.19	27.05	25.97
Average follow-up — days	27.45	27.25	27.20	27.05
Estimated percentage with event (95% CI) — %	0.72 (0.30 to 1.73)	6.53 (4.90 to 8.68)	0.78 (0.39 to 1.56)	6.40 (5.06 to 8.08)
Difference (±SE) from placebo — percentage points	−5.81±1.01		−5.62±0.81	
95% CI of difference	−7.78 to −3.84		−7.21 to −4.03	
P value	<0.001		<0.001	

Hammond J et al, NEJM 2022;386(15):1397-1408.2022

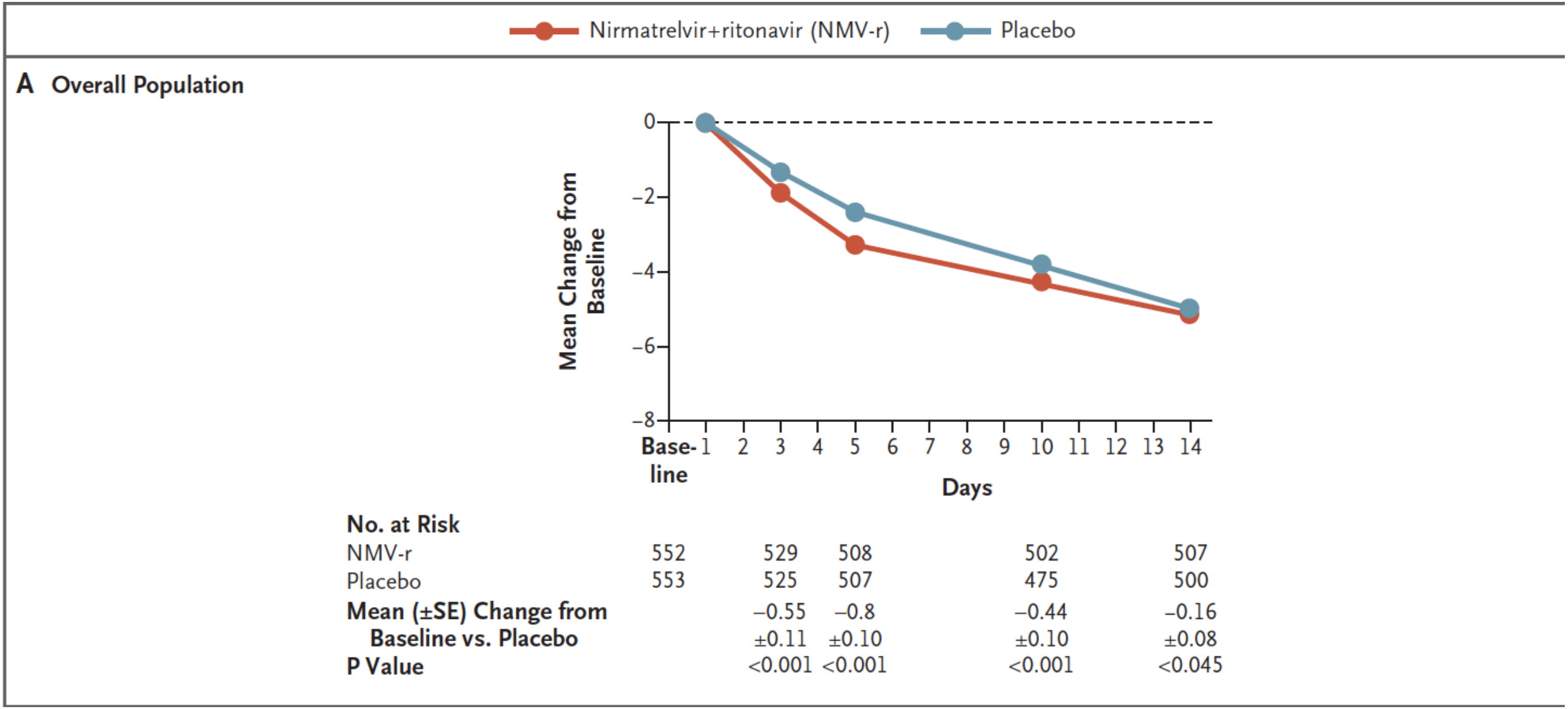
C Subgroup Analysis

Subgroup	Nirmatrelvir+Ritonavir (no. of events/total no.)	Placebo (no. of events/total no.)	Difference from Placebo (95% CI) (percentage points)
Overall	8/1039	66/1046	−5.62 (−7.21 to −4.03)
Time since symptom onset			
≤3 days	5/697	44/682	−5.81 (−7.78 to −3.84)
>3 days	3/342	22/364	−5.23 (−7.91 to −2.55)
Age			
<65 yr	7/908	46/909	−4.35 (−5.91 to −2.79)
≥65 yr	1/131	20/137	−13.93 (−20.07 to −7.80)
Sex			
Male	4/520	41/540	−6.93 (−9.32 to −4.53)
Female	4/519	25/506	−4.23 (−6.29 to −2.17)
Body-mass index			
<25	1/209	9/207	−3.88 (−6.83 to −0.94)
25 to <30	3/458	28/466	−5.44 (−7.75 to −3.13)
≥30	4/371	29/373	−6.85 (−9.82 to −3.87)
Diabetes mellitus			
Yes	2/125	9/127	−5.51 (−10.51 to −0.52)
No	6/913	57/919	−5.63 (−7.30 to −3.96)
Baseline SARS-CoV-2 serology status			
Negative	7/487	58/505	−10.25 (−13.28 to −7.21)
Positive	1/540	8/528	−1.34 (−2.45 to −0.23)
Received or expected to receive Covid-19 monoclonal antibody treatment			
Yes	1/70	2/69	−1.51 (−6.40 to 3.37)
No	8/1039	66/1046	−5.62 (−7.21 to −4.03)



Hammond J et al, NEJM 2022;386(15):1397-1408.2022

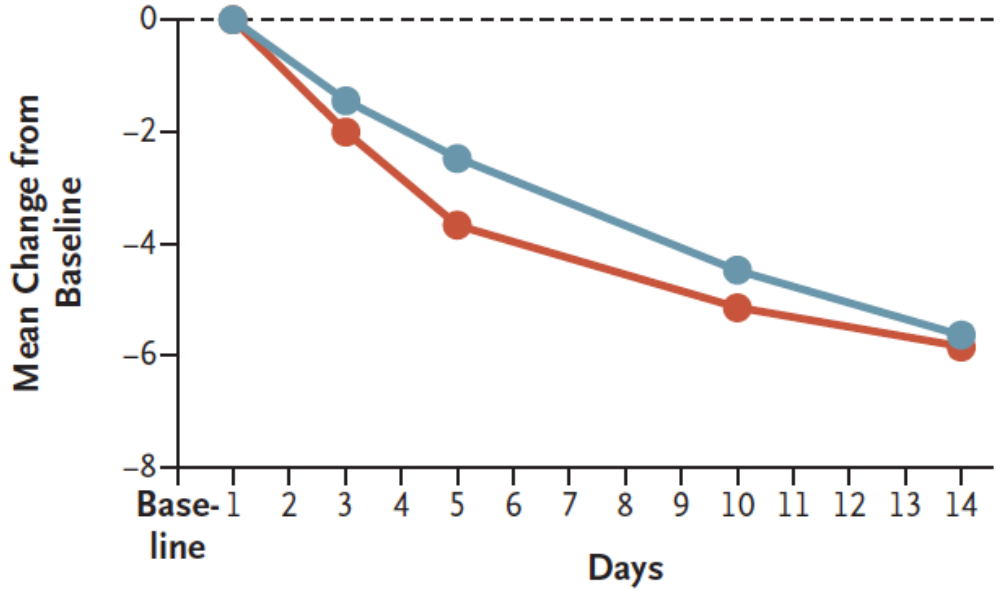
Change from Baseline in Log_{10}-Transformed Viral Load over Time (Modified Intention to-Treat Population, within 3 days after symtpoms onset)



No. at Risk					
NMV-r	552	529	508	502	507
Placebo	553	525	507	475	500
Mean (±SE) Change from Baseline vs. Placebo		−0.55 ±0.11	−0.8 ±0.10	−0.44 ±0.10	−0.16 ±0.08
P Value		<0.001	<0.001	<0.001	<0.045

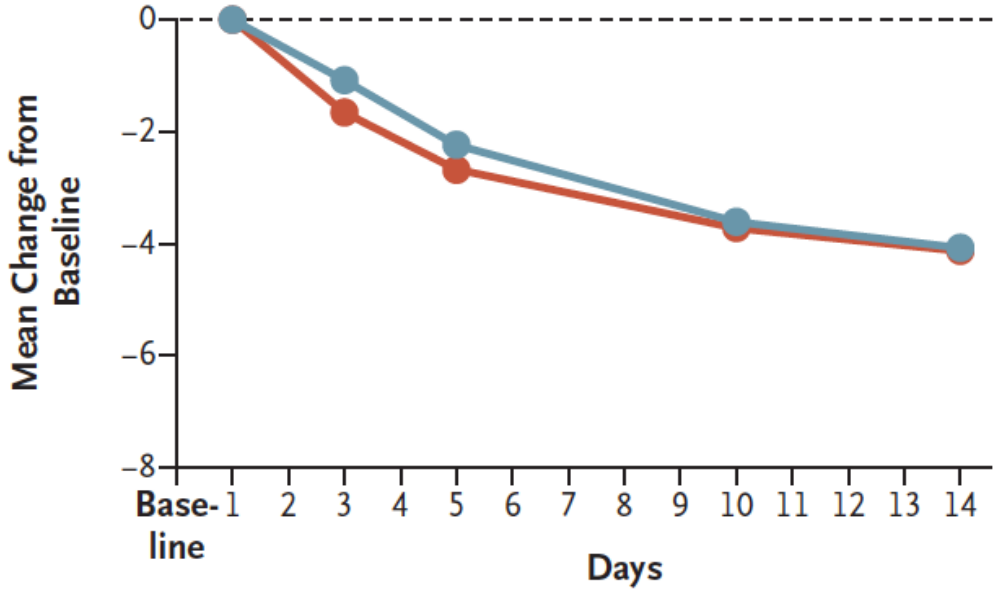
Hammond J et al, NEJM 2022;386(15):1397-1408.2022

B Seronegative



No. at Risk					
NMV-r	318	304	297	296	293
Placebo	312	294	284	267	273
Mean (±SE) Change from Baseline vs. Placebo		−0.56 ±0.14	−1.20 ±0.13	−0.67 ±0.14	−0.21 ±0.12
P Value		<0.001	<0.001	<0.001	0.07

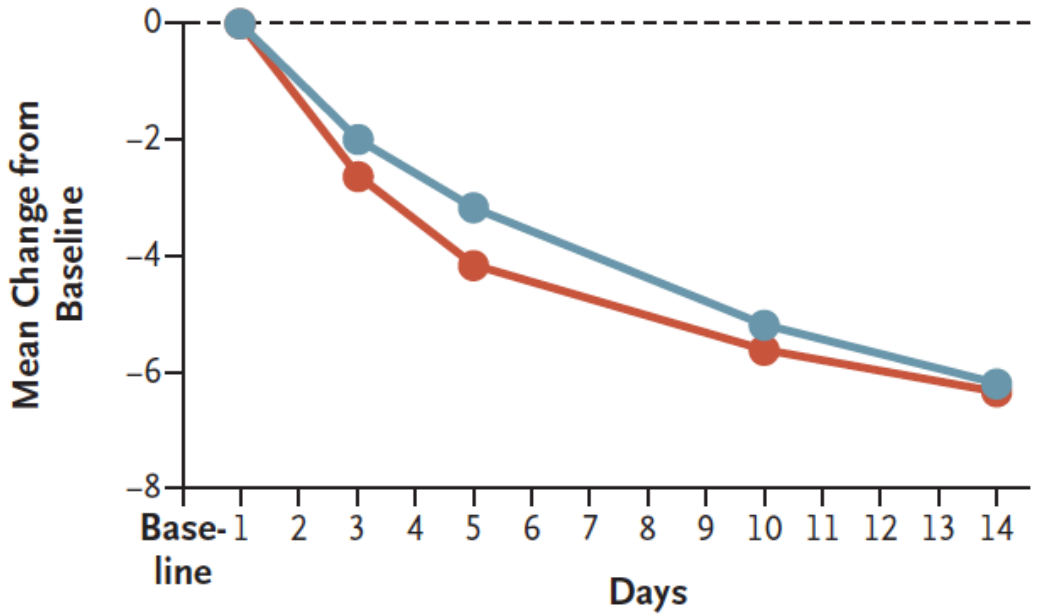
C Seropositive



No. at Risk					
NMV-r	231	222	208	203	211
Placebo	233	223	215	200	219
Mean (±SE) Change from Baseline vs. Placebo		−0.58 ±0.18	−0.44 ±0.16	−0.11 ±0.12	−0.06 ±0.11
P Value		0.001	0.01	0.37	0.60

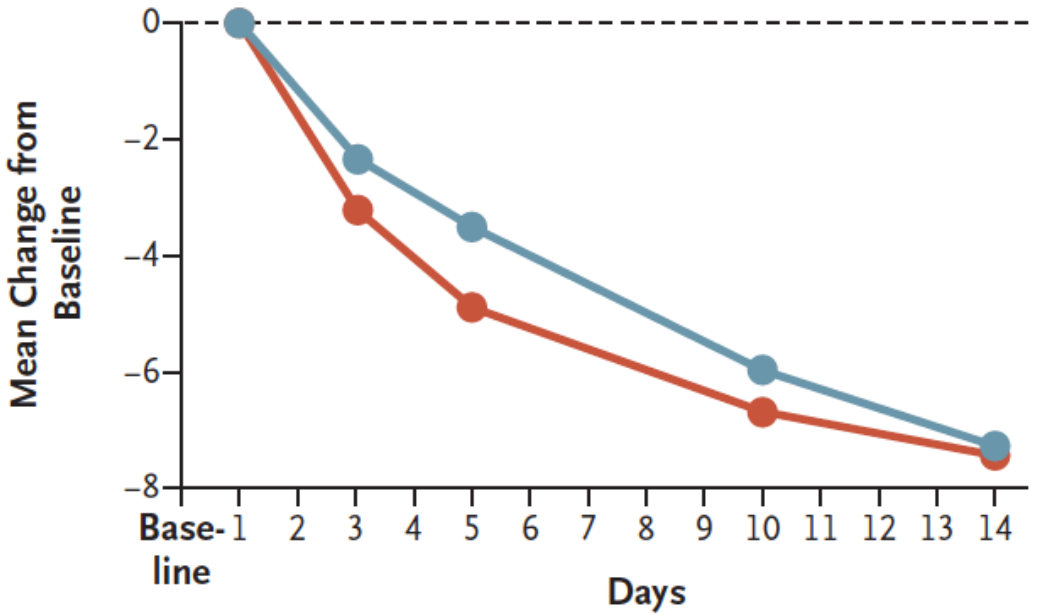
Hammond J et al, NEJM 2022;386(15):1397-1408.2022

D Baseline Viral Load >10^4 copies/ml



No. at Risk					
NMV-r	443	424	408	408	408
Placebo	442	419	402	379	396
Mean (±SE) Change from Baseline vs. Placebo		−0.66 ±0.12	−1.00 ±0.12	−0.43 ±0.12	−0.15 ±0.10
P Value		<0.001	<0.001	<0.001	0.13

E Baseline Viral Load >10^7 copies/ml



No. at Risk					
NMV-r	224	213	209	204	208
Placebo	202	191	185	171	176
Mean (±SE) Change from Baseline vs. Placebo		−0.88 ±0.16	−1.39 ±0.15	−0.73 ±0.17	−0.16 ±0.14
P Value		<0.001	<0.001	<0.001	0.25

Hammond J et al, NEJM 2022;386(15):1397-1408.2022

Adverse Event Category	Nirmatrelvir plus Ritonavir (N = 1109)	Placebo (N = 1115)
Events that emerged during treatment period		
No. of adverse events	476	525
Patients with adverse events — no. (%)		
Any adverse event	251 (22.6)	266 (23.9)
Serious adverse event	18 (1.6)	74 (6.6)
Maximum grade 3 or 4 adverse event	45 (4.1)	93 (8.3)
Maximum grade 5 adverse event	0	13† (1.2)
Discontinued drug or placebo because of adverse event	23 (2.1)	47 (4.2)
Had dose reduction or temporary discontinuation owing to adverse event	4 (0.4)	4 (0.4)
Events considered to be related to drug or placebo		
No. of adverse events	123	52
Patients with adverse events — no. (%)		
Any adverse event	86 (7.8)	42 (3.8)
Serious adverse event	1 (<0.1)	0
Maximum grade 3 or 4 adverse event	5 (0.5)	5 (0.4)
Maximum grade 5 adverse event	0	0
Discontinued drug or placebo because of adverse event	9 (0.8)	7 (0.6)
Had dose reduction or temporary discontinuation owing to adverse event	2 (0.2)	3 (0.3)

Hammond J et al, NEJM 2022;386(15):1397-1408.2022

Safety

Adverse events considered by the site investigator to be related to the trial drug or placebo were more common among recipients of nirmatrelvir plus ritonavir (7.8%) than among placebo recipients (3.8%).
This difference was largely attributed to dysgeusia (4.5% vs. 0.2%) and diarrhea (1.3% vs. 0.2%), which were the only treatment-related adverse events reported in at least 1% of recipients of nirmatrelvir plus ritonavir;
the majority of such events were resolved and were grade 1 or 2, with the exception of one case of grade 3 dysgeusia.

There were 13 deaths among placebo recipients, and all the deaths were Covid-19-related.

Hammond J et al, NEJM 2022;386(15):1397-1408.2022

EPIC HR: conclusions

- Results from this phase 2–3 trial in unvaccinated persons demonstrate the efficacy of oral administration of nirmatrelvir (300 mg) with ritonavir (100 mg) every 12 hours for 5 days
- **relative risk reductions of 88.9% and 87.8% were observed among patients commencing treatment within 3 days and within 5 days after symptom onset**, respectively, with 0 deaths occurring in the group that received nirmatrelvir plus ritonavir and 13 deaths occurring in the placebo group
- patients treated with nirmatrelvir plus ritonavir either had no Covid-19–related hospitalization or death from any cause or had a risk that was significantly lower than that with placebo
- *EPIC-Standard Risk [SR]; NCT05011513) includes vaccinated, high risk persons*.

Hammond J et al, NEJM 2022;386(15):1397-1408.2022

Mortality

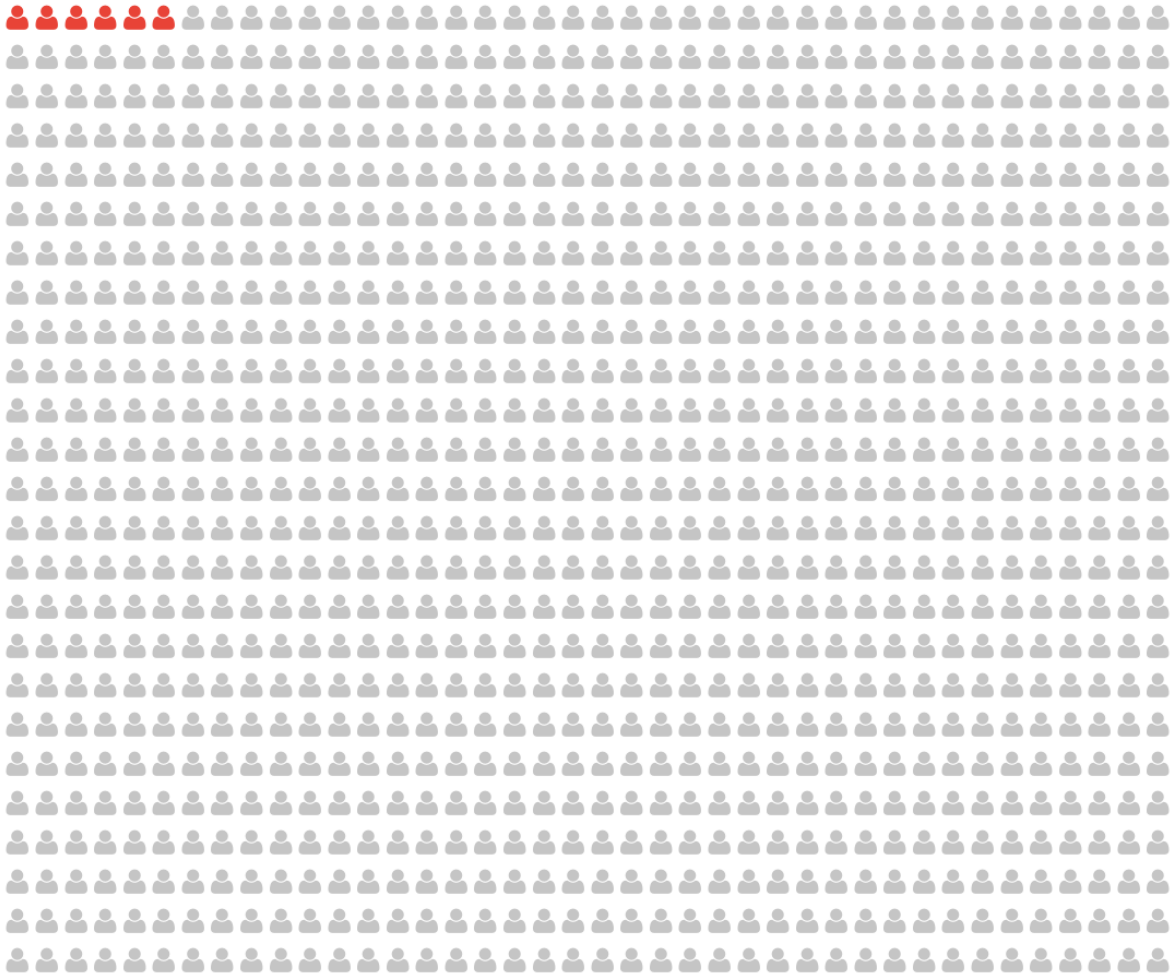
Among a 1000 people

6 fewer

Standard care	Nirmatrelvir
6	0
per 1000	per 1000

Certainty

LOW



994

Admission to hospital

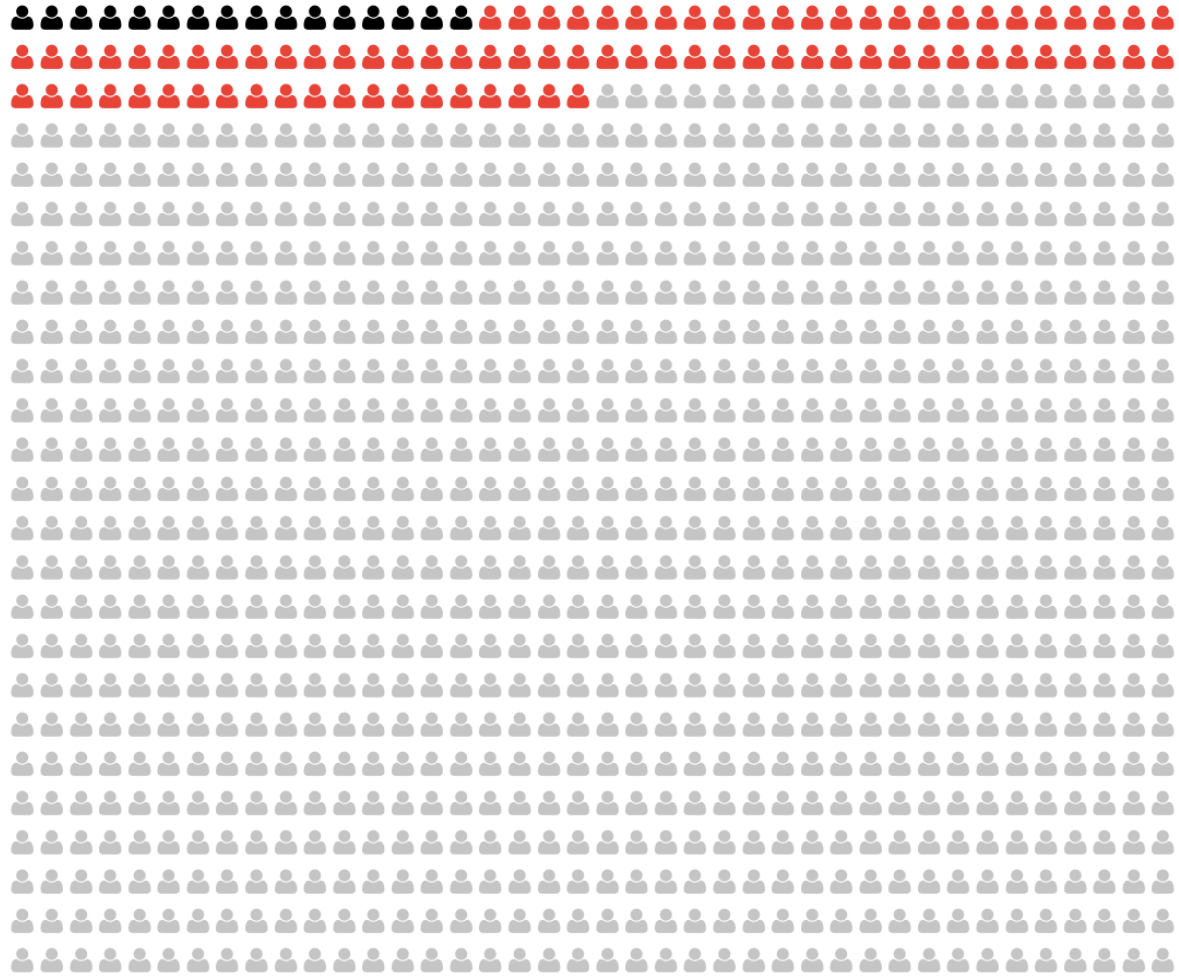
84 fewer

Standard care	Nirmatrelvir
100 per 1000	16 per 1000

Certainty

MODERATE

Among a 1000 people



900

Among a 1000 people

	Nirmatrelvir	Remdesivir	Molnupiravir	Sotrovimab	Casirivimab-imdevimab	Standard care
Mortality 90 days	0 per 1000	**4 more**	**No difference**	**1 more**	**3 more**	**6 more**
	certainty → ⊘⊘○○	⊘⊘○○	⊘⊘○○	⊘⊘⊘○	⊘⊘⊘○	⊘⊘⊘⊘
Admission to hospital 28 days	16 per 1000	**11 more**	**41 more**	**5 more**	**15 more**	**84 more**
	certainty → ⊘⊘⊘○	⊘⊘⊘○	⊘⊘⊘○	⊘⊘⊘○	⊘⊘⊘○	⊘⊘⊘⊘
Mechanical ventilation 90 days	n/a per 1000	**No data**	**No data**	**No data**	**No data**	**No data**
	certainty →					
Adverse effects leading to drug discontinuation 28 days	0 per 1000	**9 more**	**No difference**	**No difference**	**6 more**	**No difference**
	certainty → ⊘⊘⊘○	⊘⊘⊘⊘	⊘⊘⊘⊘	⊘⊘⊘⊘	⊘⊘⊘○	⊘⊘⊘⊘
Time to symptom resolution	n/a days	**No data**	**No data**	No data	**No data**	**No data**
	certainty →					
Practical issues	Oral twice daily for 5 days, administered early from symptom onset. Numerous potential drug interactions.	IV infusion daily for 3 days, administered early from symptom onset with monitoring (feasibility challenges).	Oral twice daily for 5 days, administered early from symptom onset. Risk mitigation strategies warranted.	Single IV infusion, administered early, needing monitoring. Only indicated for susceptible SARS-CoV-2 variant.	Single IV or SC infusion, administered early, needing monitoring. Only indicated for susceptible SARS-CoV-2 variant.	N/A

Remdesivir: nucleotide prodrug that binds to viral RNA polymerase and inhibits viral replication

Remdesivir è un profarmaco analogo nucleotidico dell'adenosina che viene metabolizzato nelle cellule ospiti per formare il metabolita trifosfato nucleosidico farmacologicamente attivo. Remdesivir trifosfato agisce come un analogo dell'adenosina trifosfato (ATP) e compete con il substrato naturale dell'ATP per l'incorporazione nelle catene di RNA nascente da parte della RNA-polimerasi RNA-dipendente del SARS-CoV-2, causando la terminazione della catena ritardata durante la replicazione dell'RNA virale.

Remdesivir ha mostrato un'attività in vitro contro un isolato clinico del SARS-CoV-2 nelle cellule primarie dell'epitelio respiratorio umano.

Remdesivir: conditional recommendation for non severe COVID-19 at highest risk of hospitalization

For patients with non-severe COVID-19 at highest risk of hospitalization

Conditional recommendation for

New

We suggest treatment with remdesivir *(conditional recommendation for).*

- *See Section 6.1 for help to identify patients at highest risk for hospitalization.*
- *Several therapeutic options are available: see decision support tool that displays benefits and harms of nirmatrelvir-ritonavir, molnupiravir, remdesivir and the monoclonal antibodies.*
- *The GDG concluded that nirmatrelvir-ritonavir represents a superior choice because it may have greater efficacy in preventing hospitalization than the alternatives, has fewer concerns with respect to harms than does molnupiravir; and is easier to administer than intravenous remdesivir and the antibodies.*
- *Remdesivir should be administered as soon as possible after onset of symptoms, ideally within 7 days.*

Therapeutics and COVID-19: living guideline - World Health Organization (WHO), April 2022

AGENZIA ITALIANA DEL FARMACO

Soggetti non ospedalizzati per COVID-19

Trattamento della malattia da coronavirus 2019 (COVID-19), negli adulti non ospedalizzati per COVID-19 e non in ossigeno-terapia per COVID-19 con insorgenza di sintomi da non oltre 7 giorni e in presenza di condizioni cliniche predisponenti che rappresentino dei fattori di rischio per lo sviluppo di COVID-19 grave.

Il paziente non deve essere ospedalizzato a causa di COVID-19 e deve presentare almeno uno fra i seguenti fattori di rischio associati all'evoluzione in malattia grave:

- Patologia oncologica/oncoematologica in fase attiva
- Insufficienza renale cronica (esclusi pazienti in dialisi o con eGFR <30 mL/min/1.73 m^2)
- Broncopneumopatia severa
- Immunodeficienza primaria o acquisita
- Obesità [(Body Mass Index, BMI) ≥30]
- Malattia cardiovascolare grave (scompenso cardiaco, malattia coronarica, cardiomiopatia)
- Diabete mellito non compensato

AGENZIA ITALIANA DEL FARMACO

Durata del trattamento

Soggetti non ospedalizzati per COVID-19

Il trattamento deve essere iniziato il prima possibile dopo la diagnosi di COVID-19 ed entro 7 giorni dalla comparsa dei sintomi.

La durata totale del trattamento deve essere di 3 giorni.

I pazienti devono essere monitorati durante il trattamento con remdesivir.

La somministrazione del farmaco in ambiente ambulatoriale deve essere monitorata secondo la pratica locale. L'utilizzo deve avvenire in condizioni in cui è possibile trattare le reazioni di ipersensibilità severe, inclusa l'anafilassi.

AIFA
AGENZIA ITALIANA DEL FARMACO

Soggetti ospedalizzati per COVID-19

Fin dall'inizio AIFA, tramite il registro di monitoraggio, ha concesso **la rimborsabilità al remdesivir esclusivamente per i soggetti con polmonite da COVID-19 in ossigenoterapia che non richiedono ossigeno ad alti flussi o ventilazione meccanica o ECMO e con insorgenza dei sintomi da meno di 10 giorni**.

AIFA stabilisce, alla luce delle nuove evidenze disponibili, che l'utilizzo del remdesivir nella popolazione ammessa alla rimborsabilità **potrà essere considerato esclusivamente in casi selezionati, dopo una accurata valutazione del rapporto benefici/rischi**.

I dati attualmente disponibili su remdesivir, infatti, non sono concordanti e complessivamente non dimostrano un chiaro beneficio clinico in termini di mortalità o ricorso alla ventilazione meccanica. L'OMS, dopo aver condotto uno studio randomizzato ed aver eseguito una metanalisi delle prove di efficacia su oltre 7.000 pazienti, ha formulato una **raccomandazione NEGATIVA DEBOLE** sull'utilizzo di tale farmaco nell'intera popolazione dei pazienti con COVID-19 a prescindere dalla gravità.

Sebbene nel sottogruppo di soggetti in ossigenoterapia standard (a bassi flussi) dello studio registrativo ACTT-1 sia stata dimostrata una riduzione del tempo al recupero e della mortalità, tale risultato non è stato confermato dallo studio Solidarity e dalla metanalisi dei quattro studi disponibili. Secondo l'OMS, inoltre, i risultati per sottogruppi non possono essere considerati affidabili per stime accurate.

Tutti gli studi concordano sulla mancanza di efficacia nei pazienti più gravi (che richiedono l'erogazione di ossigeno attraverso *device* ad alti flussi, ventilazione meccanica -non invasiva/invasiva- o ECMO).

I principali rischi connessi all'utilizzo del farmaco sono rappresentati da una possibile tossicità epatica e renale (quest'ultima è al momento oggetto di approfondimento presso l'EMA).

Infine, in ottemperanza a quanto riportato in scheda tecnica, il farmaco non è raccomandato in pazienti con funzionalità renale fortemente compromessa (eGFR<30mL/min) e non deve essere usato in pazienti che presentano livelli di ALT $\geq$ 5 volte il limite superiore della norma al basale (paragrafo 4.4 RCP).

Si ricorda che il farmaco non è autorizzato prima dei 12 anni di età.

Soggetti ospedalizzati per COVID-19

La durata totale del trattamento deve essere di almeno 5 giorni e non deve eccedere i 10 giorni.

Gli studi finora condotti non hanno evidenziato una differenza in termini di efficacia tra il trattamento a 5 giorni ed il trattamento a 10, sia nei pazienti con malattia moderata sia nella coorte di malattia severa.

Per situazioni particolari si rimanda alla scheda tecnica del medicinale Veklury®.

Admission to hospital Highest risk	Odds ratio 0.25 (CI 95% 0.06 — 0.88) Based on data from 562 participants in 1 studies. (Randomized controlled)	**100** per 1000 Difference:	**27** per 1000 **73 fewer per 1000** (CI 95% 93 fewer — 11 fewer)	**Moderate** Due to serious imprecision [5]	Remdesivir probably reduces hospitalization
Adverse effects leading to drug discontinuation	Based on data from 1,379 participants in 4 studies. (Randomized controlled)	**0** per 1000 Difference:	**9** per 1000 **9 more per 1000** (CI 95% 3 fewer — 21 more)	**Moderate** Due to serious imprecision [6]	There is probably little or no difference in adverse effects leading to drug discontinuation
Time to symptom resolution	Lower better Based on data from 138 participants in 1 studies. (Randomized controlled)	**9** days (Median) Difference:	**7.2** days (Mean) **MD 1.8 fewer** (CI 95% 5.7 fewer — 3.5 more)	**Very low** Due to extremely serious imprecision [7]	The impact of remdesivir on time to symptom resolution is uncertain

Study	Publication status	Country	Number of participants	Mean age	% Male	Type of care	Interventions	Outcomes
Ali, 2022 CATCO NCT04330690	Published	Canada	1282 (122 non-severe)	65.5	59.8	Inpatient	Remdesivir 200mg IV once, then 100mg IV daily for 9 days	Mortality, mechanical ventilation
Beigel, 2020 ACTT-1 NCT04280705	Published	United States, Denmark, United Kingdom, Greece, Germany, Korea, Mexico, Spain, Japan, Singapore	1062 (138 non-severe)	58.9	64.4	Inpatient	Remdesivir 200mg IV once, then 100mg IV daily for 9 days	Mortality, mechanical ventilation, adverse events, time to symptom resolution
Criner, 2020 NCT04252664	Abstract published	China	584 (all non-severe)	57	61	Inpatient	Remdesivir 200mg IV once, then 100mg IV daily for 4 OR 9 days	Mortality, adverse events
Gottlieb, 2021 PINETREE NCT04501952	Published	United States, Spain, Denmark, United Kingdom	562 (all non-severe)	50.5	52.1	Outpatient	Remdesivir 200mg IV once, then 100mg for 2 days	Mortality, admission to hospital, adverse effects
Pan, 2020 SOLIDARITY NCT04315948	Published	Multicontinental	5475 (1325 non-severe)	NR	62.9	Inpatient	Remdesivir 100mg IV for 10 days	Mortality

all patients were unvaccinated within 7 days of symptom onset did not receive therapeutic co-interventions

Early Remdesivir to Prevent Progression to Severe Covid-19 in Outpatients

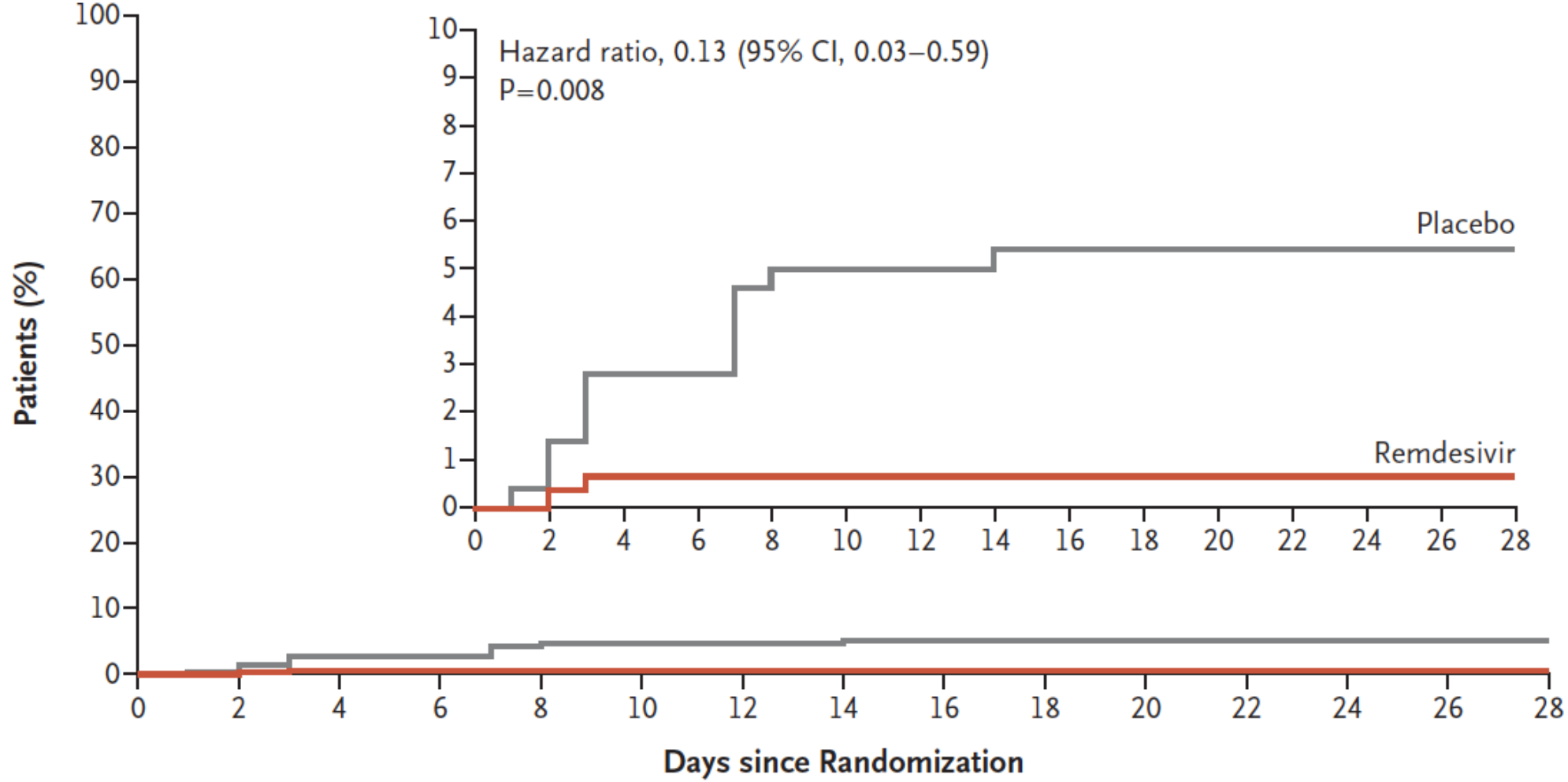
R.L. Gottlieb, C.E. Vaca, R. Paredes, J. Mera, B.J. Webb, G. Perez, G. Oguchi, P. Ryan, B.U. Nielsen, M. Brown, A. Hidalgo, Y. Sachdeva, S. Mittal, O. Osiyemi, J. Skarbinski, K. Juneja, R.H. Hyland, A. Osinusi, S. Chen, G. Camus, M. Abdelghany, S. Davies, N. Behenna-Renton, F. Duff, F.M. Marty,* M.J. Katz, A.A. Ginde, S.M. Brown, J.T. Schiffer, and J.A. Hill, for the GS-US-540-9012 (PINETREE) Investigators†

- Eligible patients were 12 years of age or older and had at least one preexisting risk factor for progression to severe COVID-19 or were 60 year of age or older, regardless of whether they had other risk factors.
- Risk factors included: hypertension, cardiovascular or cerebrovascular disease, diabetes mellitus, obesity (BMI≥30), immune compromise, chronic mild or moderate kidney disease, chronic liver disease, chronic lung disease, current cancer, or sickle cell disease.
- Eligible patients had at least one ongoing symptom consistent with Covid-19, with onset of the first symptom within 7 days before randomization (given that hospitalization typically occurs at or after 7 days of symptoms).

N Engl J Med 2022;386(4):305-315.

Characteristic	Remdesivir (N=279)	Placebo (N=283)	Total (N=562)
Age — yr	50±15	51±15	50±15
Age category — no. (%)			
≥60 yr	83 (29.7)	87 (30.7)	170 (30.2)
<18 yr	3 (1.1)	5 (1.8)	8 (1.4)
Female sex — no. (%)	131 (47.0)	138 (48.8)	269 (47.9)
Residence in the United States — no. (%)	264 (94.6)	267 (94.3)	531 (94.5)
Race or ethnic group — no. (%)†			
White	228 (81.7)	224 (79.2)	452 (80.4)
Black	20 (7.2)	22 (7.8)	42 (7.5)
American Indian or Alaska Native	15 (5.4)	21 (7.4)	36 (6.4)
Asian, Native Hawaiian, or Pacific Islander	7 (2.5)	7 (2.5)	14 (2.5)
Hispanic or Latinx	123 (44.1)	112 (39.6)	235 (41.8)
Other	3 (1.1)	2 (0.7)	5 (0.9)
Body-mass index	31.2±6.7	30.8±5.8	31.0±6.2
Coexisting conditions — no. (%)			
Diabetes mellitus	173 (62.0)	173 (61.1)	346 (61.6)
Obesity	154 (55.2)	156 (55.1)	310 (55.2)
Hypertension	138 (49.5)	130 (45.9)	268 (47.7)
Chronic lung disease	67 (24.0)	68 (24.0)	135 (24.0)
Current cancer	12 (4.3)	18 (6.4)	30 (5.3)
Cardiovascular or cerebrovascular disease	20 (7.2)	24 (8.5)	44 (7.8)
Immune compromise	14 (5.0)	9 (3.2)	23 (4.1)
Chronic kidney disease, mild or moderate	7 (2.5)	11 (3.9)	18 (3.2)
Chronic liver disease	1 (0.4)	1 (0.4)	2 (0.4)
Residence in skilled nursing facility — no. (%)	8 (2.9)	7 (2.5)	15 (2.7)
Median duration of symptoms before first infusion (IQR) — days	5 (3–6)	5 (4–6)	5 (3–6)
Median time since RT-PCR confirmation of SARS-CoV-2 (IQR) — days	2 (1–3)	3 (1–4)	2 (1–4)
Mean SARS-CoV-2 RNA nasopharyngeal viral load — $\log_{10}$ copies/ml‡	6.31±1.75	6.28±1.79	6.29±1.77

A **Covid-19–Related Hospitalization or Death from Any Cause**



No. at Risk

Placebo	283	280	272	271	265	264	264	263	262	261	261	260	256	250	227
Remdesivir	279	276	272	272	271	268	268	268	264	264	264	264	260	252	226

Subgroup	Remdesivir	Placebo	Hazard Ratio (95% CI)
	no./total no. of patients (%)		
Residence in the United States	2/264 (0.8)	12/267 (4.5)	0.17 (0.04–0.76)
Age ≥60 yr	1/83 (1.2)	9/87 (10.3)	0.11 (0.01–0.86)
Male sex	1/148 (0.7)	9/145 (6.2)	0.11 (0.01–0.84)
Diabetes mellitus	2/173 (1.2)	14/173 (8.1)	0.14 (0.03–0.63)
Obesity	1/154 (0.6)	9/156 (5.8)	0.11 (0.01–0.88)
Hypertension	2/138 (1.4)	10/130 (7.7)	0.17 (0.04–0.76)
Ethnic group			
Not Hispanic or Latinx	2/146 (1.4)	8/158 (5.1)	0.26 (0.06–1.22)
Hispanic or Latinx	0/123	6/112 (5.4)	—
Chronic lung disease	0/67	4/68 (5.9)	—
Cardiovascular or cerebrovascular disease	0/20	2/24 (8.3)	—
Current cancer	0/12	2/18 (11.1)	—

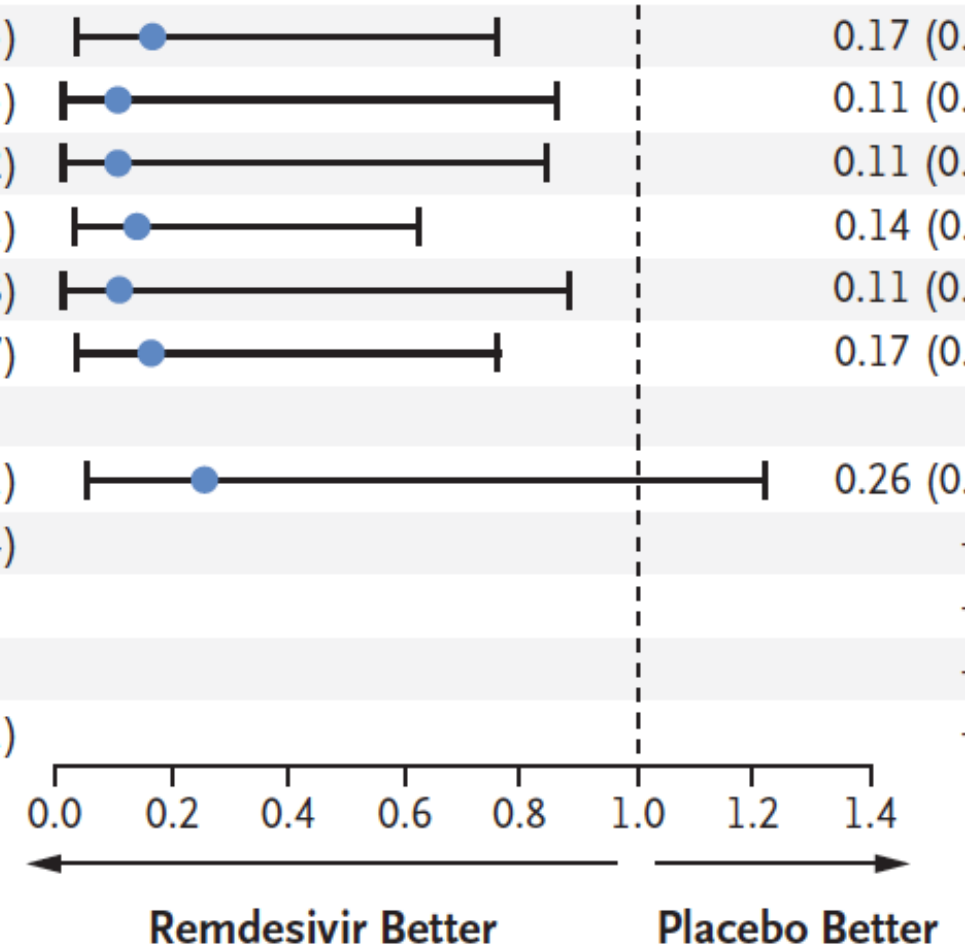


Table 3. Adverse Events.*

Event	Remdesivir (N = 279)	Placebo (N = 283)
	no. of patients (%)	
Primary safety end point: any adverse event	118 (42.3)	131 (46.3)
Adverse events		
Nausea	30 (10.8)	21 (7.4)
Headache	16 (5.7)	17 (6.0)
Cough	10 (3.6)	18 (6.4)
Diarrhea	11 (3.9)	11 (3.9)
Dyspnea	7 (2.5)	15 (5.3)
Fatigue	10 (3.6)	11 (3.9)
Ageusia	8 (2.9)	7 (2.5)
Anosmia	9 (3.2)	6 (2.1)
Dizziness	5 (1.8)	10 (3.5)
Chills	6 (2.2)	8 (2.8)
Pyrexia	1 (0.4)	11 (3.9)
Covid-19 pneumonia	2 (0.7)	8 (2.8)
Adverse event related to trial regimen	34 (12.2)	25 (8.8)
Serious adverse event†	5 (1.8)	19 (6.7)
Adverse event leading to discontinuation of trial regimen	2 (0.7)	5 (1.8)
Death	0	0

PINETREE trial: conclusions

In this trial involving non hospitalized patients with COVID-19 who were at high risk for severe disease,

we found that patients who received a 3-day course of remdesivir had an 87% lower risk of COVID-19–related hospitalization or death from any cause by day 28 and an 81% lower risk of COVID-19–related medically attended visits or death from any cause by day 28 than patients who received placebo.

Principali criticità:

- *bias* di imprecisione per interruzione precoce dello studio (è stata arruolata meno della metà dei pazienti rispetto alla dimensione del campione pianificata).

RDV in hospitalized patients

- **A phase 3 trial of remdesivir showed that both a 10-day course and a 5-day course of remdesivir shortened the recovery time in patients hospitalized with COVID-19**.

Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the treatment of Covid-19 — final report. N Engl J Med 2020; 383: 1813-26. Goldman JD, Lye DCB, Hui DS, et al. Remdesivir for 5 or 10 days in patients with severe Covid-19. N Engl J Med 2020; 383: 1827-37.

- November 2020, suggesting not to use remdesivir for patients with COVID-19, regardless of illness severity. This was based on data from four RCTs which were available at the time, with 7333 participants hospitalized for COVID-19. WHO **Solidarity trial: No difference regarding mortality or need for mechanical ventilation**

- **RDV was shown to be superior to placebo in shortening the time to recovery in hospitalized adults with evidence of lower respiratory tract infection and requiring supplemental oxygenation**

22/05/2020 - Beigel JH et al. 2020 (ACTT-1 Trial; NCT04280705): Si tratta di un grosso trial clinico randomizzato, in doppio-cieco, multinazionale, sponsorizzato dai National Health Institutes negli USA che ha valutato l'efficacia del remdesivir vs placebo (entrambi somministrati per 10 giorni) in una popolazione che comprendeva soggetti ricoverati, in gran parte con necessità di ossigenoterapia. I risultati pubblicati si riferiscono ad una analisi preliminare effettuata quando era stato raggiunto il campione previsto ma non tutti i soggetti arruolati avevano completato il follow-up di 28 giorni. I principali criteri di inclusione erano i seguenti: pazienti adulti ospedalizzati con polmonite dimostrata radiologicamente, oppure con saturazione O2<94% in aria ambiente o necessità di supplementazione con ossigeno ventilazione meccanica o ECMO (ossigenazione extracorporea). L'esito primario era il tempo alla guarigione (dimissione o ricovero senza necessità di cure aggiuntive), mentre esito secondario era la mortalità a 14 giorni. Lo studio ha arruolato 1.063 soggetti, mentre i risultati pubblicati si riferivano in totale a 1.059 soggetti (538 nel gruppo remdesivir e 521 nel gruppo placebo). In totale, l'88.7% della popolazione in studio aveva una patologia severa, in particolare il 25.6% era sottoposto a ventilazione meccanica o ECMO, il 18.5% riceveva ventilazione non invasiva o ossigeno ad alto flusso, il 39.6% riceveva ossigeno supplementare, e il rimanente 11.9%, pur ricevendo assistenza ospedaliera, non necessitava di ossigeno;

una superiorità statisticamente significativa del remdesivir rispetto al placebo, nella popolazione generale di pazienti ospedalizzati con COVID-19, con una differenza di 4 giorni nel tempo di recupero nei pazienti del gruppo remdesivir rispetto a quelli nel gruppo placebo (11 vs 15 giorni HR: 1,32, 95% CI 1,12-1,55; p<0,001). Nello strato di popolazione con polmonite e necessità di ossigeno supplementare la differenza nel tempo mediano di recupero è stata di 12 giorni nel gruppo remdesivir contro i 18 del gruppo placebo (RR 1,36; 95% CI 1,143–1,623; p<0,001). Nessuna differenza è stata osservata nello strato di popolazione con malattia 'lieve-moderata' (stadio 4; RR 1.38; 0.94-2.03). Non sono inoltre emerse differenze, rispetto al placebo, nei pazienti ospedalizzati in supporto ventilatorio (ventilazione non invasiva e device ad alti flussi; RR 1.20; 95%CI 0.79-1.81) ed in ventilazione meccanica (ventilazione meccanica invasiva ed ECMO; RR0.95; 95%CI 0.64-1.42). Nella popolazione generale in trattamento con remdesivir è stato osservato un andamento più favorevole in termini di mortalità a 14 rispetto al gruppo placebo senza raggiungere la significatività statistica; HR 0.70; 95%CI 0.47-1.04), ma lo studio non era dimensionato per la valutazione di quest'ultimo esito, anche considerando la sua interruzione precoce.

Principali criticità

- Interruzione precoce
- Lo studio non è stato dimensionato per valutare una riduzione della mortalità
- Non sono state descritte le terapie associate

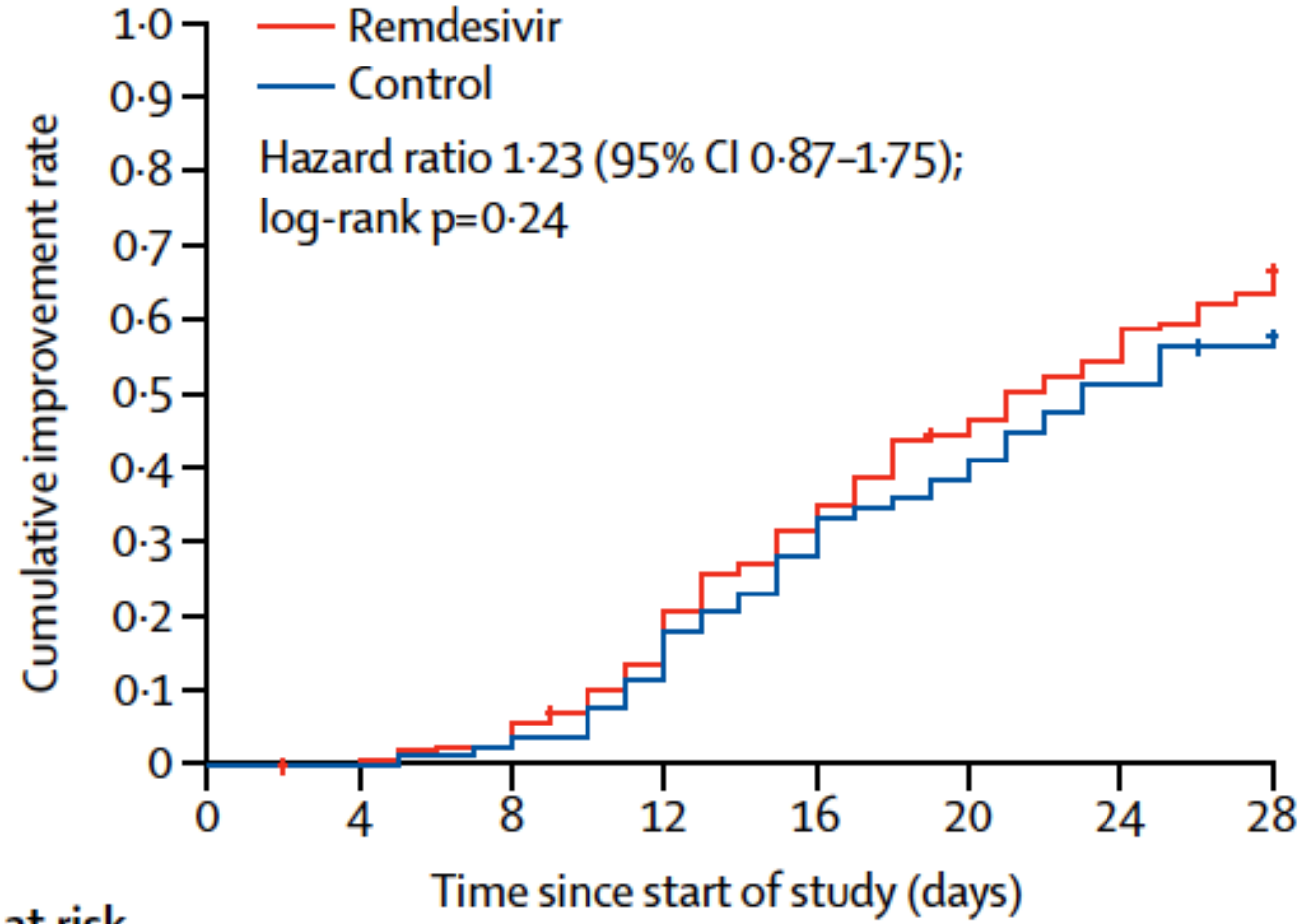
Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial

Yeming Wang, Dingyu Zhang*, Guanhua Du*, Ronghui Du*, Jianping Zhao*, Yang Jin*, Shouzhi Fu*, Ling Gao*, Zhenshun Cheng*, Qiaofa Lu*, Yi Hu*, Guangwei Luo*, Ke Wang, Yang Lu, Huadong Li, Shuzhen Wang, Shunan Ruan, Chengqing Yang, Chunlin Mei, Yi Wang, Dan Ding, Feng Wu, Xin Tang, Xianzhi Ye, Yingchun Ye, Bing Liu, Jie Yang, Wen Yin, Aili Wang, Guohui Fan, Fei Zhou, Zhibo Liu, Xiaoying Gu, Jiuyang Xu, Lianhan Shang, Yi Zhang, Lianjun Cao, Tingting Guo, Yan Wan, Hong Qin, Yushen Jiang, Thomas Jaki, Frederick G Hayden, Peter W Horby, Bin Cao, Chen Wang*

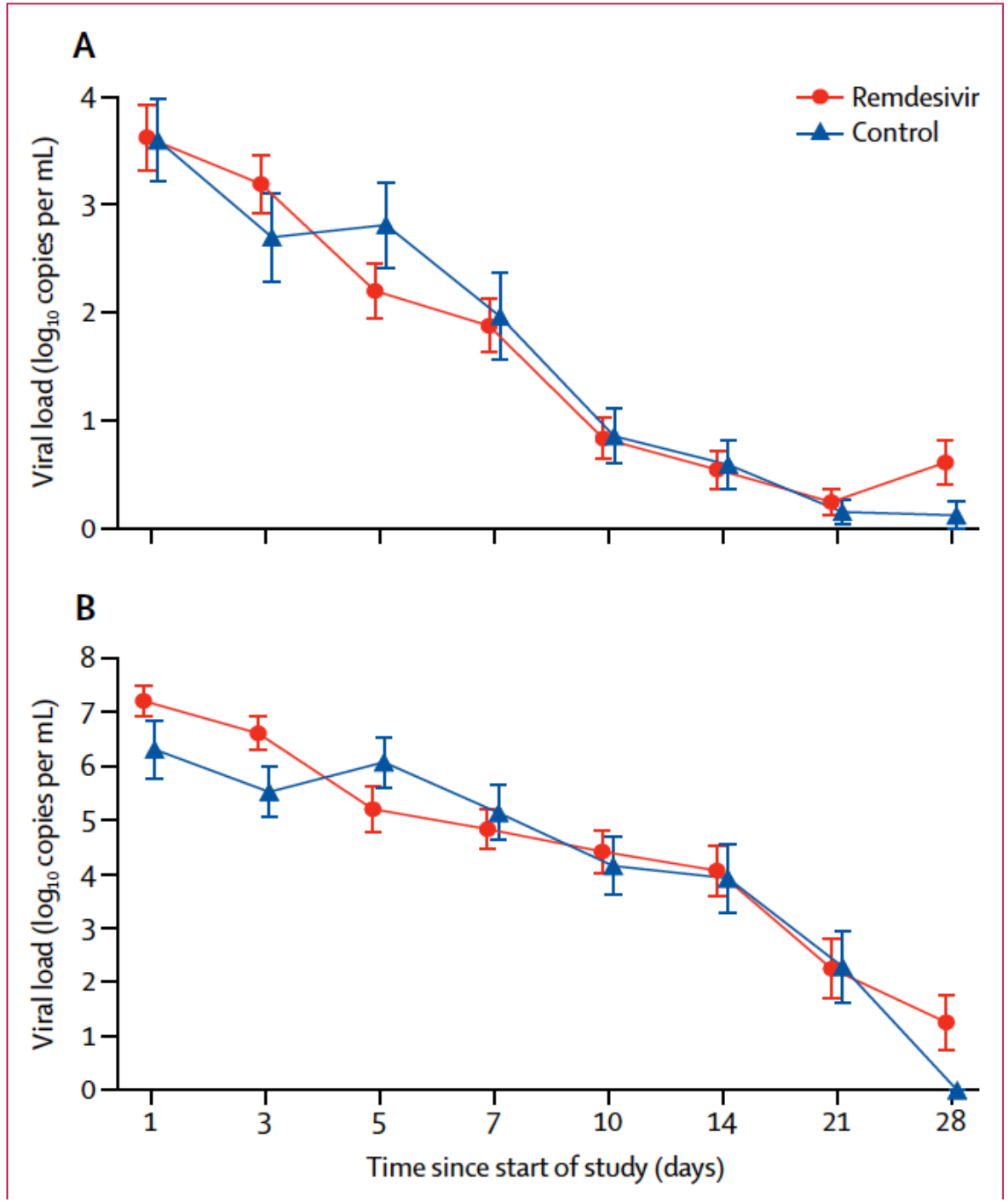
Methods We did a randomised, double-blind, placebo-controlled, multicentre trial at ten hospitals in Hubei, China. Eligible patients were adults (aged ≥18 years) admitted to hospital with laboratory-confirmed SARS-CoV-2 infection, with an interval from symptom onset to enrolment of 12 days or less, oxygen saturation of 94% or less on room air or a ratio of arterial oxygen partial pressure to fractional inspired oxygen of 300 mm Hg or less, and radiologically confirmed pneumonia. Patients were randomly assigned in a 2:1 ratio to intravenous remdesivir (200 mg on day 1 followed by 100 mg on days 2–10 in single daily infusions) or the same volume of placebo infusions for 10 days.

Wang J et al, Lancet 2020; 395: 1569–78

	Remdesivir group (n=158)	Placebo group (n=78)	Difference*
Time to clinical improvement	21·0 (13·0 to 28·0)	23·0 (15·0 to 28·0)	1·23 (0·87 to 1·75)†
Day 28 mortality	22 (14%)	10 (13%)	1·1% (−8·1 to 10·3)
Early (≤10 days of symptom onset)	8/71 (11%)	7/47 (15%)	−3·6% (−16·2 to 8·9)
Late (>10 days of symptom onset)	12/84 (14%)	3/31 (10%)	4·6% (−8·2 to 17·4)
Clinical improvement rates			
Day 7	4 (3%)	2 (3%)	0·0% (−4·3 to 4·2)
Day 14	42 (27%)	18 (23%)	3·5% (−8·1 to 15·1)
Day 28	103 (65%)	45 (58%)	7·5% (−5·7 to 20·7)
Duration of invasive mechanical ventilation, days	7·0 (4·0 to 16·0)	15·5 (6·0 to 21·0)	−4·0 (−14·0 to 2·0)
Duration of invasive mechanical ventilation in survivors, days‡	19·0 (5·0 to 42·0)	42·0 (17·0 to 46·0)	−12·0 (−41·0 to 25·0)
Duration of invasive mechanical ventilation in non-survivors, days‡	7·0 (2·0 to 11·0)	8·0 (5·0 to 16·0)	−2·5 (−11·0 to 3·0)
Duration of oxygen support, days	19·0 (11·0 to 30·0)	21·0 (14·0 to 30·5)	−2·0 (−6·0 to 1·0)
Duration of hospital stay, days	25·0 (16·0 to 38·0)	24·0 (18·0 to 36·0)	0·0 (−4·0 to 4·0)
Time from random group assignment to discharge, days	21·0 (12·0 to 31·0)	21·0 (13·5 to 28·5)	0·0 (−3·0 to 3·0)
Time from random group assignment to death, days	9·5 (6·0 to 18·5)	11·0 (7·0 to 18·0)	−1·0 (−7·0 to 5·0)
Six-category scale at day 7			
1—discharge (alive)	4/154 (3%)	2/77 (3%)	OR 0·69 (0·41 to 1·17)§
2—hospital admission, not requiring supplemental oxygen	21/154 (14%)	16/77 (21%)	..
3—hospital admission, requiring supplemental oxygen	87/154 (56%)	43/77 (56%)	..
4—hospital admission, requiring high-flow nasal cannula or non-invasive mechanical ventilation	26/154 (17%)	8/77 (10%)	..
5—hospital admission, requiring extracorporeal membrane oxygenation or invasive mechanical ventilation	6/154 (4%)	4/77 (5%)	..
6—death	10/154 (6%)	4/77 (5%)	..
Six-category scale at day 14			
1—discharge (alive)	39/153 (25%)	18/78 (23%)	OR 1·25 (0·76 to 2·04)§
2—hospital admission, not requiring supplemental oxygen	21/153 (14%)	10/78 (13%)	..
3—hospital admission, requiring supplemental oxygen	61/153 (40%)	28/78 (36%)	..
4—hospital admission, requiring high-flow nasal cannula or non-invasive mechanical ventilation	13/153 (8%)	8/78 (10%)	..
5—hospital admission, requiring extracorporeal membrane oxygenation or invasive mechanical ventilation	4/153 (3%)	7/78 (9%)	..
6—death	15/153 (10%)	7/78 (9%)	..



Number at risk (number censored)								
Remdesivir	158 (0)	155 (2)	147 (0)	123 (1)	101 (0)	82 (1)	63 (0)	25 (26*)
Control	78 (0)	78 (0)	75 (0)	64 (0)	52 (0)	46 (0)	38 (0)	17 (16*)


A
Remdesivir
Control
Viral load (log10 copies per mL)
4
3
2
1
0
B
Viral load (log10 copies per mL)
8
7
6
5
4
3
2
1
0
1
3
5
7
10
14
21
28
Time since start of study (days)

In summary, we found that this dose regimen of intravenous remdesivir was adequately tolerated but did not provide significant clinical or antiviral effects in seriously ill patients with COVID-19. However, we could not exclude clinically meaningful differences and saw numerical reductions in some clinical parameters. Ongoing studies with larger sample sizes will continue to inform our understanding of the effect of remdesivir on COVID-19. Furthermore, strategies to enhance the antiviral potency of remdesivir (eg, higher-dose regimens, combination with other antivirals, or SARS-CoV-2 neutralising antibodies) and to mitigate immunopathological host responses contributing to COVID-19 severity (eg, inhibitors of IL-6, IL-1, or TNFα) require rigorous study in patients with severe COVID-19.

Wang J et al, Lancet 2020; 395: 1569–78

mortalità a 28 giorni. Nella popolazione studiata, rappresentata prevalentemente da soggetti con malattia COVID-19 severa, che in gran parte richiedevano ossigenoterapia al ricovero, remdesivir non ha migliorato gli esiti clinici e non ha ridotto la mortalità in modo statisticamente significativo. Nell'interpretazione dei risultati occorre tuttavia tenere conto del fatto che, a causa dell'andamento epidemiologico della malattia in Cina con la riduzione dei casi a seguito delle politiche di distanziamento sociale, lo studio è stato interrotto precocemente per difficoltà nel reclutamento dei pazienti e il campione è risultato quindi ridotto rispetto alle previsioni iniziali. Lo studio non era quindi dimensionato per la valutazione degli esiti in studio e i risultati ottenuti non consentono di definire il profilo benefico/rischio del medicinale.

Principali criticità:

- lo studio non ha raggiunto il sample size preventivato.

- Nella meta-analisi che si accompagna alla *living guideline* sul remdesivir (aggiornata al 20/11/2020), il WHO prende in esame 7.333 soggetti trattati nei 4 principali studi clinici che hanno valutato l'efficacia di remdesivir (ACTT-1; SOLIDARITY; SIMPLE-MODERATE, e Wang et al.). L'analisi dei dati non ha consentito di evidenziare alcun effetto né in termini di mortalità (OR 0.90; 95% 0.70-1.12), né di ricorso alla ventilazione meccanica (OR 0. 89; 0.76-1.03), né di tempo al miglioramento clinico (9.0 nel gruppo SOC vs 11.0 giorni nel gruppo remdesivir; differenza media di -2 giorni; 95%CI da -4.2 a +0.9), o di durata dell'ospedalizzazione (12.8 nel gruppo SOC vs 12. 3 nel gruppo remdesivir; differenza media di -0.5 giorni; 95%CI da -3.3 a +2.3)
- In una delle *living systematic review* disponibili, curata dal gruppo Cochrane in collaborazione con numerose istituzioni universitarie e di ricerca (https://covid-nma.com/living_data/index.php), l'analisi dei dati disponibili, aggiornata al 09/12/2021, conferma la sostanziale assenza di beneficio clinico del remdesivir in termini di mortalità a 28 giorni nei soggetti ospedalizzati (RR 0.92; 95%CI 0.78-1.07).

In conclusione i principali studi randomizzati che hanno valutato l'efficacia clinica del remdesivir nel trattamento dei soggetti ospedalizzati, seppur in aperto e con endpoint primari differenti, mostrano risultati coerenti tra loro nell'escludere un beneficio clinico del remdesivir in termini di mortalità. In un unico studio si conferma un effetto positivo in termini di tempo al recupero, soprattutto nella popolazione più a basso rischio (soggetti in ossigenoterapia a bassi flussi e con inizio del trattamento entro 10 giorni dalla comparsa dei sintomi).

Molnupiravir: nucleoside analogue

- Molnupiravir is a prodrug with antiviral activity that is metabolized to the cytidine nucleoside analogue, NHC, which is taken up by cells and phosphorylated to form the active ribonucleoside triphosphate (NHC-TP).
- NHC-TP is incorporated into SARS-CoV-2 RNA by the viral RNA polymerase causing an accumulation of errors in the viral genome thus inhibiting replication.
- NHC is incorporated by the SARS-CoV-2 RdRp, instead of either C or U nucleosides, into the genomic or subgenomic RNA during copying of the RNA template genome. The resultant NHC-containing RNAs are then themselves used as a template for production of subsequent RNAs which are predicted to be mutated and therefore not believed to form functional viruses.
- This agent has a different mechanism of action than nirmatrelvir

Saravolats LD et al, Clin Infect Dis 2022; ciac180.

Molnupiravir: conditional recommendation for non severe patients at highest risk of hospitalization

Conditional recommendation for

New

We suggest treatment with molnupiravir *(conditional recommendation for).*

- *See Section 6.1 for help to identify patients at highest risk for hospitalization.*
- *Several therapeutic options are available: see decision support tool that displays benefits and harms of nirmatrelvir-ritonavir, molnupiravir, remdesivir and the monoclonal antibodies.*
- *The longer-term harms of molnupiravir remain unknown in the absence of clinical evidence, both for individual patients and at the population level. These include genotoxicity, emergence of resistance, and emergence of new variants (see Mechanism of action).*
- *The conditional recommendation reflects the concern for widespread treatment with molnupiravir before more safety data become available.*
- *Use of molnupiravir should be accompanied by mitigation strategies such as avoiding the drug in younger adults, active pharmacovigilance programmes, and monitoring viral polymerase and spike sequences (see Justification).*

Therapeutics and COVID-19: living guideline - World Health Organization (WHO), April 2022

Drug Interactions

Molnupiravir

No clinical drug interaction trials have been conducted with molnupiravir and concomitant medications; however, it has been shown that molnupiravir and NHC are not substrates, inhibitors, or inducers of a variety of CYP enzymes, human P-gp, or assessed transport proteins. Therefore, no drug interactions have yet been identified with molnupiravir [1].

Molnupiravir: 60 fewer hospitalization per 1000 patients

Benefits and harms

In patients with non-severe COVID-19, molnupiravir probably reduces admission to hospital and time to symptom resolution, and may reduce mortality. The effect of molnupiravir on mechanical ventilation is very uncertain. Treatment does not increase the likelihood of adverse effects leading to drug discontinuation.

However, potential long-term harms of molnupiravir remain uncertain and a matter of concern, in the absence of clinical data. Potential harms include emergence of resistance, and the potential harm coming from the risk of molnupiravir-induced mutagenesis. These deliberations (see Justification section) were based on molnupiravir's mechanism of action and available pre-clinical data (see Mechanism of action section).

The balance between benefits and potential harms was close, but favoured treatment in the highest risk group, if implemented with other mitigation strategies to avoid harm at individual and population level (see Mitigation strategies section). There is a risk that monotherapy with molnupiravir (as for other antiviral monotherapies) may be associated with emergence of drug resistance, as has been seen with other antivirals (see Mechanism of action section).

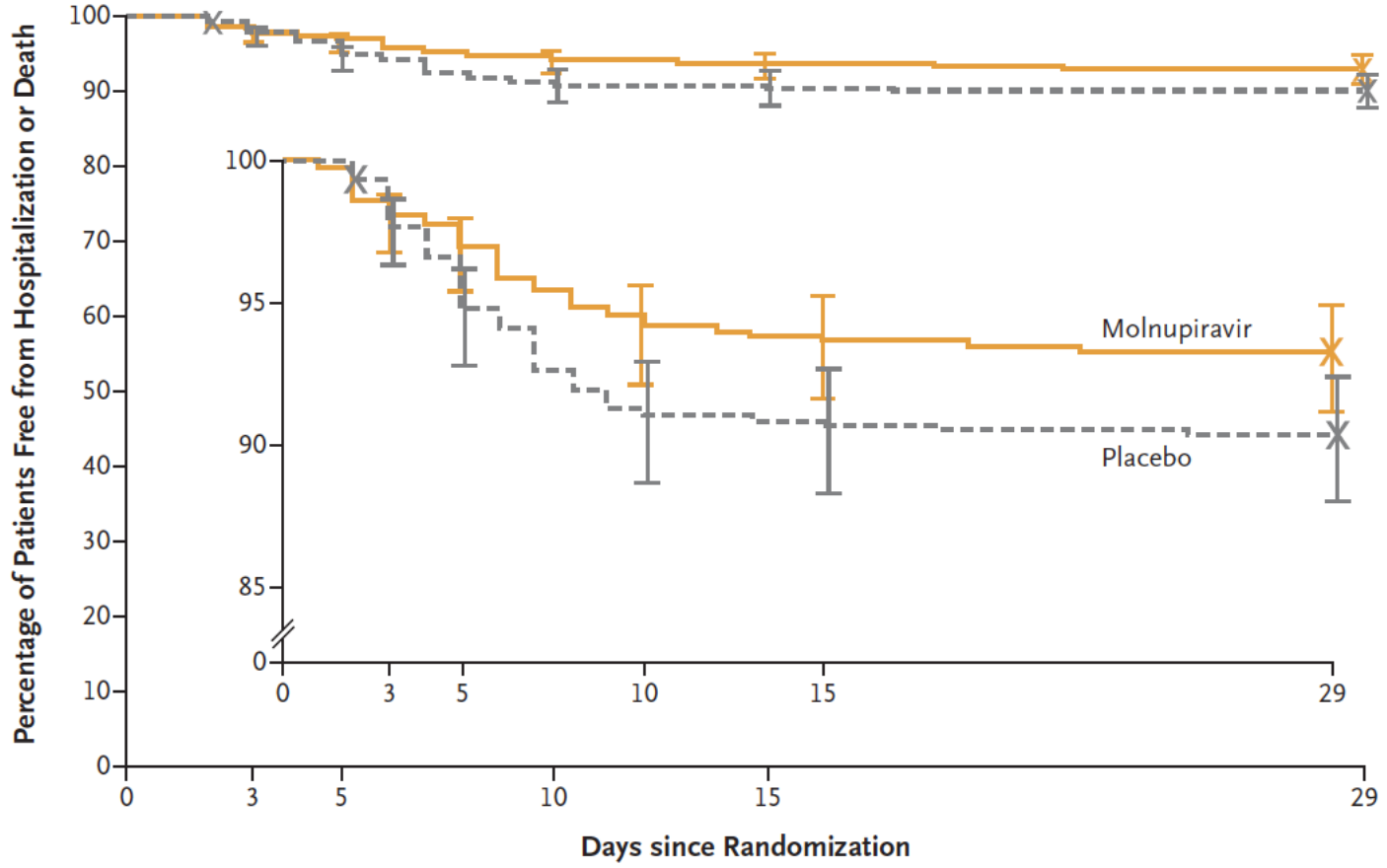
The absolute benefits of molnupiravir on hospital admission depend on the prognosis. The GDG defined a threshold of a 6% absolute reduction in hospital admission to represent what most patients would value as an important benefit. Molnupiravir would exert such a benefit in patients at highest risk of hospitalization (above 10% baseline risk), such as those that lack COVID-19 vaccination, older people, or those with immunodeficiencies and/or chronic diseases. The conditional recommendation for the use of molnupiravir in those at highest risk reflects this threshold: 60 fewer hospitalizations per 1000 patients, and a greater anticipated absolute survival benefit, although this was not possible to quantify in the absence of data.

Therapeutics and COVID-19: living guideline - World Health Organization (WHO), April 2022

Study	Publication status Registration	Number of participants	Country	Mean age	% Male	Comorbidities	Type of care	Severity	% Mechanical ventilation (at baseline)	Detailed ventilation (%)	Treatments (dose and duration)	Outcomes
Bernal, 2021 MOVe-OUT	Published NCT04575597	1433	Multicontinental	44.9	48.7	Copd (4.0%) Heart failure, coronary artery disease, or cardiomyopathies (11.7%) Diabetes (15.9%)	Outpatient	Mild/Moderate (99.3%) Severe (0.3%)	NR	NR	molnupiravir (800 mg twice daily for 5 days) vs standard care/placebo	Mortality Mechanical ventilation Admission to hospital Adverse effects leading to discontinuation
Fischer, 2021	Published NCT04405570	202	United States	40.1	48.5	NR	Outpatient	NR	NR	NR	molnupiravir (200 mg twice per day for 5 days) molnupiravir (400 mg twice per day for 5 days) molnupiravir (800 mg twice per day for 5 days) standard care/placebo	Mortality Admission to hospital Adverse effects leading to discontinuation Viral clearance Time to symptom/clinical improvement Time to viral clearance
Khoo, 2021 AGILE	Pre-print NCT04746183	18	United Kingdom	56	27.8	NR	Outpatient	NR	NR	NR	molnupiravir (300 mg twice daily for 5 days) molnupiravir (600mg twice daily for 5 days) molnupiravir (800mg twice daily for 5 days) standard care/placebo	Mortality Adverse effects leading to discontinuation

Characteristic	Molnupiravir (N=716)	Placebo (N=717)	Total (N=1433)
Female sex — no. (%)	384 (53.6)	351 (49.0)	735 (51.3)
Age group — no. (%)			
18–49 yr	484 (67.6)	465 (64.9)	949 (66.2)
≥50 yr	232 (32.4)	252 (35.1)	484 (33.8)
Median age (range) — yr	42.0 (18–90)	44.0 (18–88)	43.0 (18–90)
Risk factors for severe illness from Covid-19 — no. (%)			
At least one risk factor	712 (99.4)	712 (99.3)	1424 (99.4)
Obesity†	538 (75.1)	518 (72.2)	1056 (73.7)
Age >60 yr	119 (16.6)	127 (17.7)	246 (17.2)
Diabetes mellitus	107 (14.9)	121 (16.9)	228 (15.9)
Serious heart condition	86 (12.0)	81 (11.3)	167 (11.7)
Chronic kidney disease	38 (5.3)	46 (6.4)	84 (5.9)
Chronic obstructive pulmonary disease	22 (3.1)	35 (4.9)	57 (4.0)
Active cancer	13 (1.8)	16 (2.2)	29 (2.0)
Covid-19 severity — no. (%)			
Mild	395 (55.2)	390 (54.4)	785 (54.8)
Moderate	315 (44.0)	323 (45.0)	638 (44.5)
Severe or unknown‡	6 (0.8)	4 (0.6)	10 (0.7)
Clade designation; variant — no. (%)			
20H; beta	5 (0.7)	6 (0.8)	11 (0.8)
20I; alpha	12 (1.7)	9 (1.3)	21 (1.5)
20J; gamma	37 (5.2)	48 (6.7)	85 (5.9)
21A, 21I, 21J; delta	237 (33.1)	223 (31.1)	460 (32.1)
21G; lambda	14 (2.0)	7 (1.0)	21 (1.5)
21H; mu	76 (10.6)	86 (12.0)	162 (11.3)
Other§	16 (2.2)	16 (2.2)	32 (2.2)
Evaluable sequence data not yet available	319 (44.6)	322 (44.9)	641 (44.7)
Time from onset of Covid-19 signs or symptoms to randomization of ≤3 days — no. (%)¶	342 (47.8)	342 (47.7)	684 (47.7)

Bernal AJ et al, NEJM 2022; 386:509-20.



No. at Risk						
Molnupiravir	709	699	693	670	665	661
Placebo	699	693	674	637	634	631
No. of Events						
Molnupiravir	10	6	23	5	4	0
Placebo	5	19	37	3	3	0

Figure 2. Time-to-Event Analysis of Hospitalization or Death through Day 29 in the Modified Intention-to-Treat Population.

Bernal AJ et al, NEJM 2022; 386:509-20.

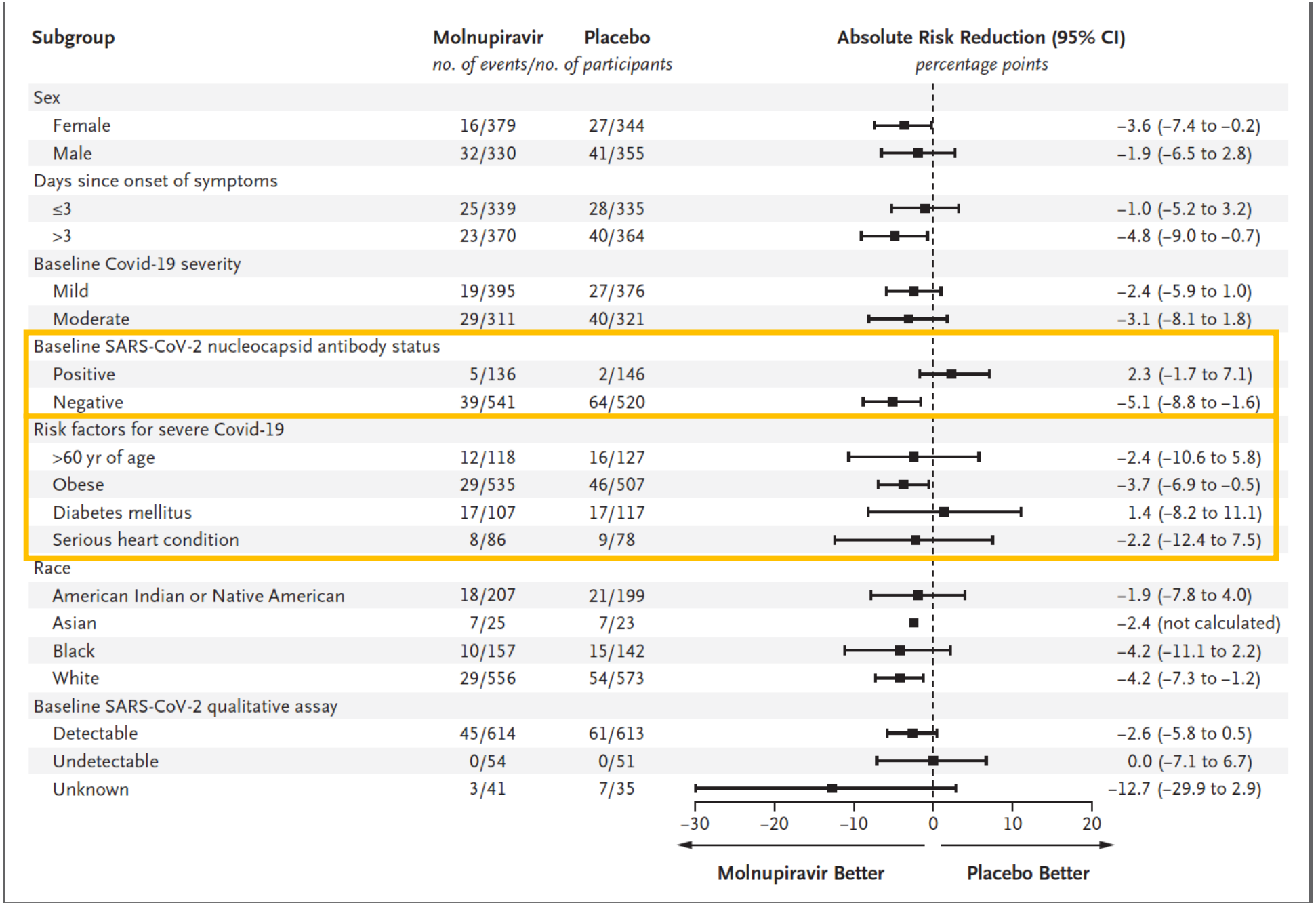


Figure 3. **Incidence of Hospitalization or Death at Day 29 in the Modified Intention-to-Treat Population, According to Subgroup.**

Table 2. Incidence of Adverse Events in the Safety Population.

Adverse Events and Discontinuation	Molnupiravir (N=710)	Placebo (N=701)	Estimated Difference (95% CI)*
	number (percent)		*percentage points*
Participants with adverse events			
≥1 Adverse event	216 (30.4)	231 (33.0)	−2.5 (−7.4 to 2.3)
≥1 Adverse event related to the assigned regimen†	57 (8.0)	59 (8.4)	−0.4 (−3.3 to 2.5)
≥1 Serious adverse event	49 (6.9)	67 (9.6)	−2.7 (−5.6 to 0.2)
≥1 Serious adverse event related to the assigned regimen†	0	1 (0.1)	−0.1 (−0.8 to 0.4)
Death	2 (0.3)	12 (1.7)	−1.4 (−2.7 to −0.5)
Participants who discontinued the assigned regimen because of an adverse event			
Adverse event	10 (1.4)	20 (2.9)	−1.4 (−3.1 to 0.1)
Adverse event related to the assigned regimen†	4 (0.6)	3 (0.4)	0.1 (−0.8 to 1.1)
Serious adverse event	5 (0.7)	13 (1.9)	−1.2 (−2.5 to 0.0)
Serious adverse event related to the assigned regimen†	0	0	0.0 (−0.5 to 0.5)

Safety

- Adverse events were those reported while subjects were on study intervention or within 14 days of study intervention completion/discontinuation.
- The most common adverse reactions in the molnupiravir treatment group were
  - diarrhea (2%)
  - nausea (1%)
  - dizziness (1%)
- Grade 3 and 4 laboratory abnormalities in chemistry (alanine aminotransferase, aspartate aminotransferase, creatinine, and lipase) and hematology (hemoglobin, platelets, and leukocytes) parameters all occurred at a similar rate across both the groups (<2%).
- Most serious events were COVID-19 related in 7% of subjects receiving Molnupiravir and in 10% of patients receiving placebo.

MOVe-OUT phase 3 trial: conclusions

- In non hospitalized at-risk adults with Covid-19 molnupiravir, initiated within 5 days after the onset of symptoms, reduces the risk of hospitalization for any cause or death through day 29
- The risk of hospitalization or death at day 29 was 6.8 percentage points lower with molnupiravir than with placebo at the interim analysis and 3.0 percentage points lower in the all-randomized analysis

In this trial, oral molnupiravir was found to be effective for the treatment of Covid-19, without evident safety concerns, when initiated within 5 days after the onset of signs or symptoms in this population of nonhospitalized, unvaccinated adults who were at risk for progression to severe disease.

Bernal AJ et al, NEJM 2022; 386:509-20.

Figure 3. Forest plot: Mechanical ventilation.

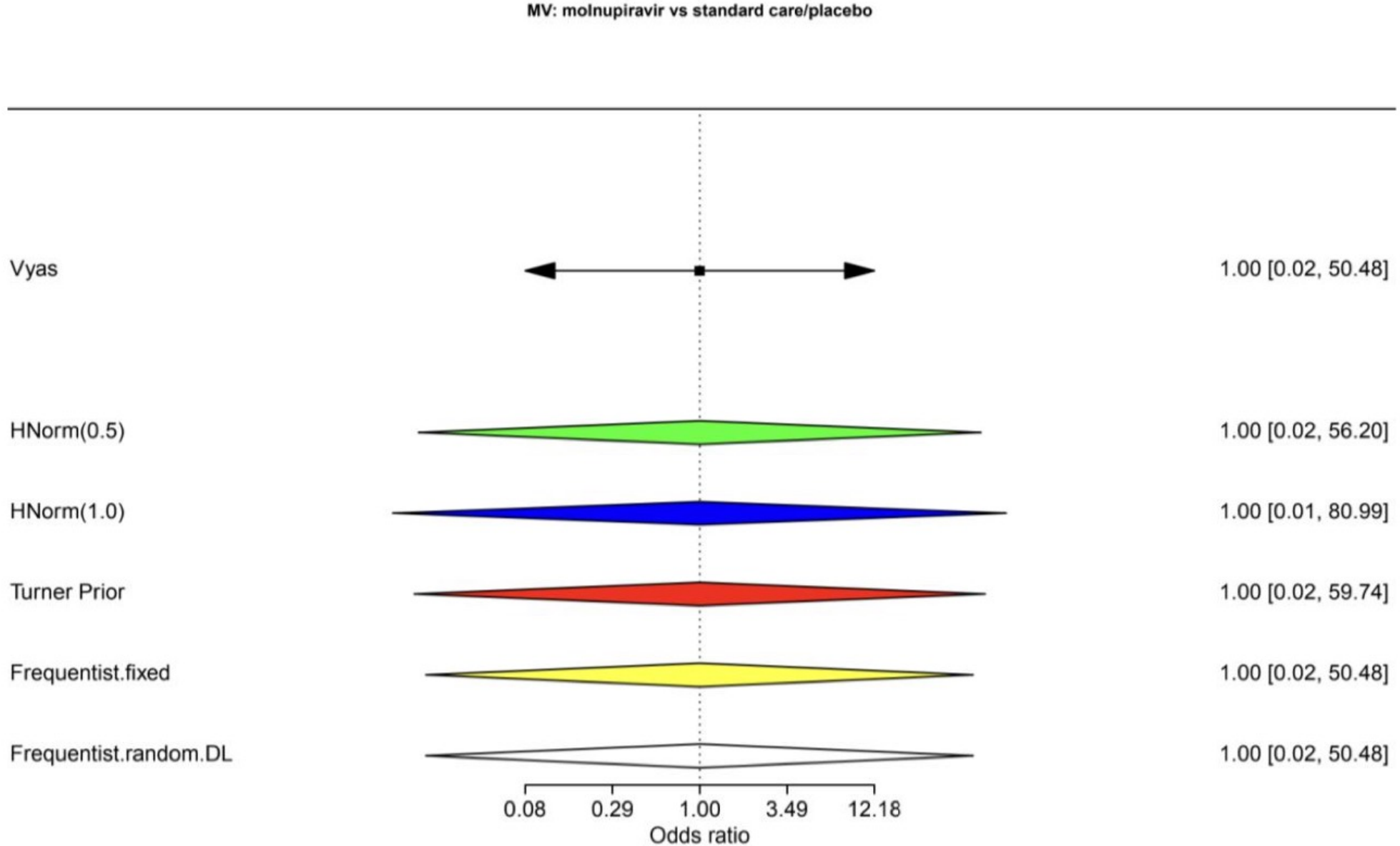
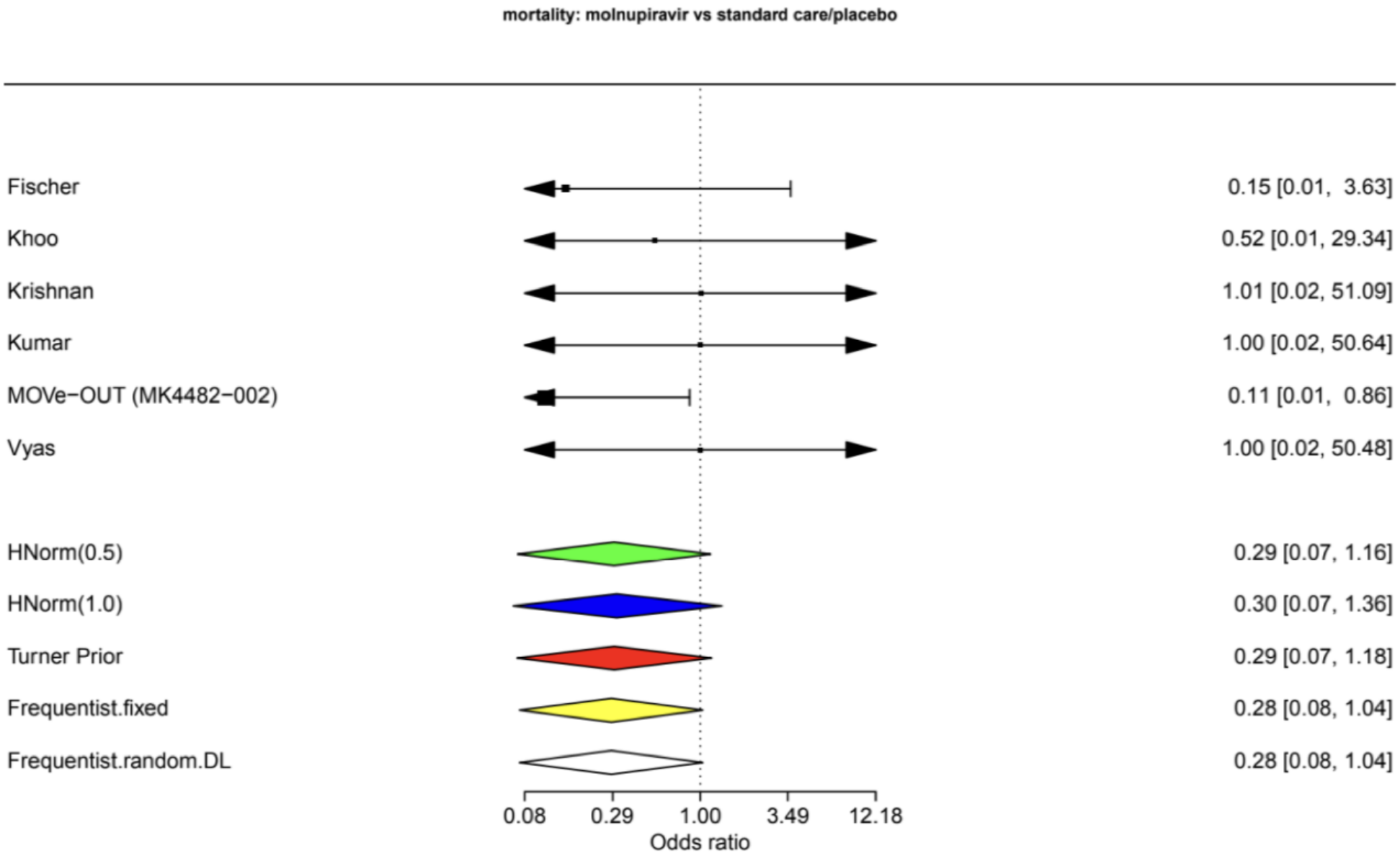


Figure 4. Forest plot: Mortality.



Molnupiravir: safety

- Molnupiravir should not be given to pregnant or breastfeeding women or to children. In case of doubt about pregnancy, a pregnancy test should be performed prior to treatment initiation.
- If a woman of child bearing age is considered for treatment, counselling regarding **birth control during treatment and for 4 days after the last dose** of molnupiravir should be facilitated.
- Men planning to conceive should be oriented on the potential for temporary genotoxic effect on sperm cell production, and those who are sexually active with females should be counselled to use **birth control during treatment and for at least 3 months after the last dose of molnupiravir**.
- The **unknown long-term risk of genotoxicity** is likely to be higher in younger patients as compared with older patients; thus use in younger adults who are not at high risk should be limited.
- **Active sequence monitoring of SARS-CoV-2 detected in clinical respiratory samples** (i.e. may include polymerase and spike) **should be arranged for patients receiving therapy**, including higher risk individuals (immunocompromised).
- **Pharmacovigilance**: use of molnupiravir should be accompanied by a robust, active pharmacovigilance programme.

Mutagenicity in vitro but not in animal models

As a mutagenic ribonucleoside antiviral agent, there is a theoretical risk that molnupiravir will be metabolized by the human host cell and incorporated into the host DNA, leading to mutations. Molnupiravir has been evaluated in vivo rodent mutagenicity assays. One study produced results that were equivocal; in the other study, there was no evidence for mutagenicity.

Saravolats LD et al, Clin Infect Dis 2022; ciac180.

Data from real-life settings

Neutralizing Monoclonal Antibody Treatment Reduces Hospitalization for Mild and Moderate COVID-19: A Real-World Experience

John Paul Verderese MD,[1] Maria Stepanova PhD,[1] Brian Lam PA,[1] Andrei Racila,[1] Andrej

The study included 707 COVID-19 patients who received a NmAb infusion and 1709 historic COVID-19 controls. Patients in NmAb group received BAM (n=553, or 78%) or REGN-COV2 (n=154). Patients in NmAb group were slightly older than controls (mean age 60 vs. 58 years, p=0.0044), were more commonly male, white, and obese (**Table 1**). Of NmAb recipients, 42% were eligible for an infusion based on their age (≥65 years), another 28% based on BMI ≥ 35 kg/m2, and 30% met other eligibility criteria (**Table 1**). The mean time from the onset of symptoms to infusion was 6 days (SD 3 days); 35% were referred to the infusion from an ED (**Table 1**).

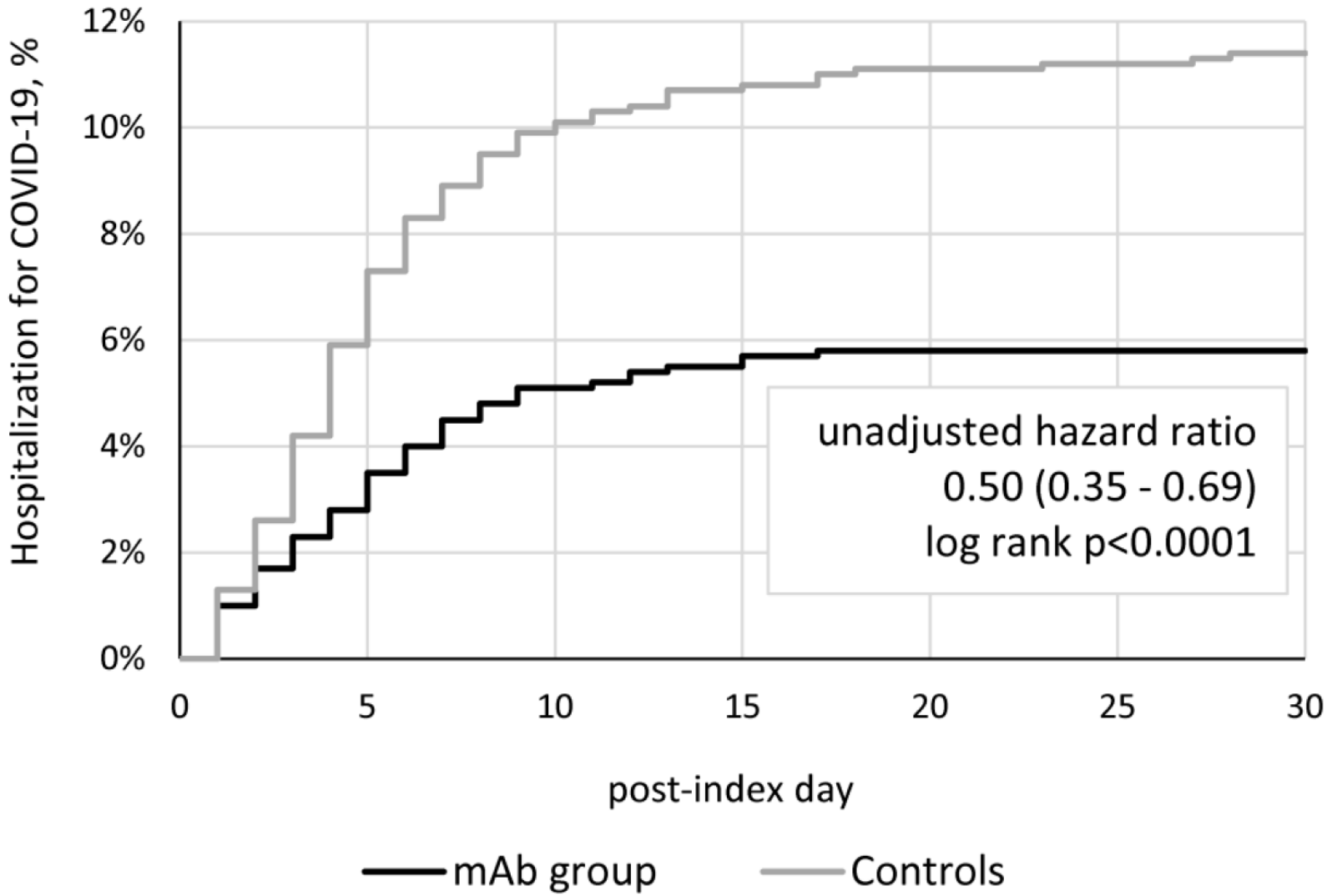
Manuscript

Clin Infect Dis 2022 Mar 23;74(6):1063-1069.

Table 1. Comparison of COVID-19 patients who received NmAb infusion to controls.

	NmAb group	Controls	P
N	707	1709	
Bamlanivimab	553 (78.2%)	0 (0.0%)	
Casirivimab and imdevimab (REGN-COV2)	154 (21.8%)	0 (0.0%)	
Age, years	59.8 ± 15.9	58.1 ± 15.2	0.0044
Male sex	31.7 ± 7.8	29.5 ± 6.2	<0.0001
Non-Hispanic white or Caucasian	357 (50.6%)	762 (44.6%)	0.0067
Non-Hispanic black or African-American	340 (56.2%)	644 (41.9%)	<0.0001
Hispanic	94 (15.5%)	263 (17.1%)	0.38
Asian	111 (17.8%)	507 (32.4%)	<0.0001
Other race/ethnicity	57 (9.4%)	118 (7.7%)	0.18
BMI, kg/m2	3 (0.5%)	6 (0.4%)	0.73
Morbid obesity (BMI ≥ 40)	109 (15.4%)	99 (5.8%)	<0.0001
BMI ≥ 35	232 (32.8%)	306 (17.9%)	<0.0001

Accepted Manuscript


Hospitalization for COVID-19, %
12%
10%
8%
6%
4%
2%
0%
0
5
10
15
20
25
30
post-index day
unadjusted hazard ratio
0.50 (0.35 - 0.69)
log rank p<0.0001
mAb group
Controls

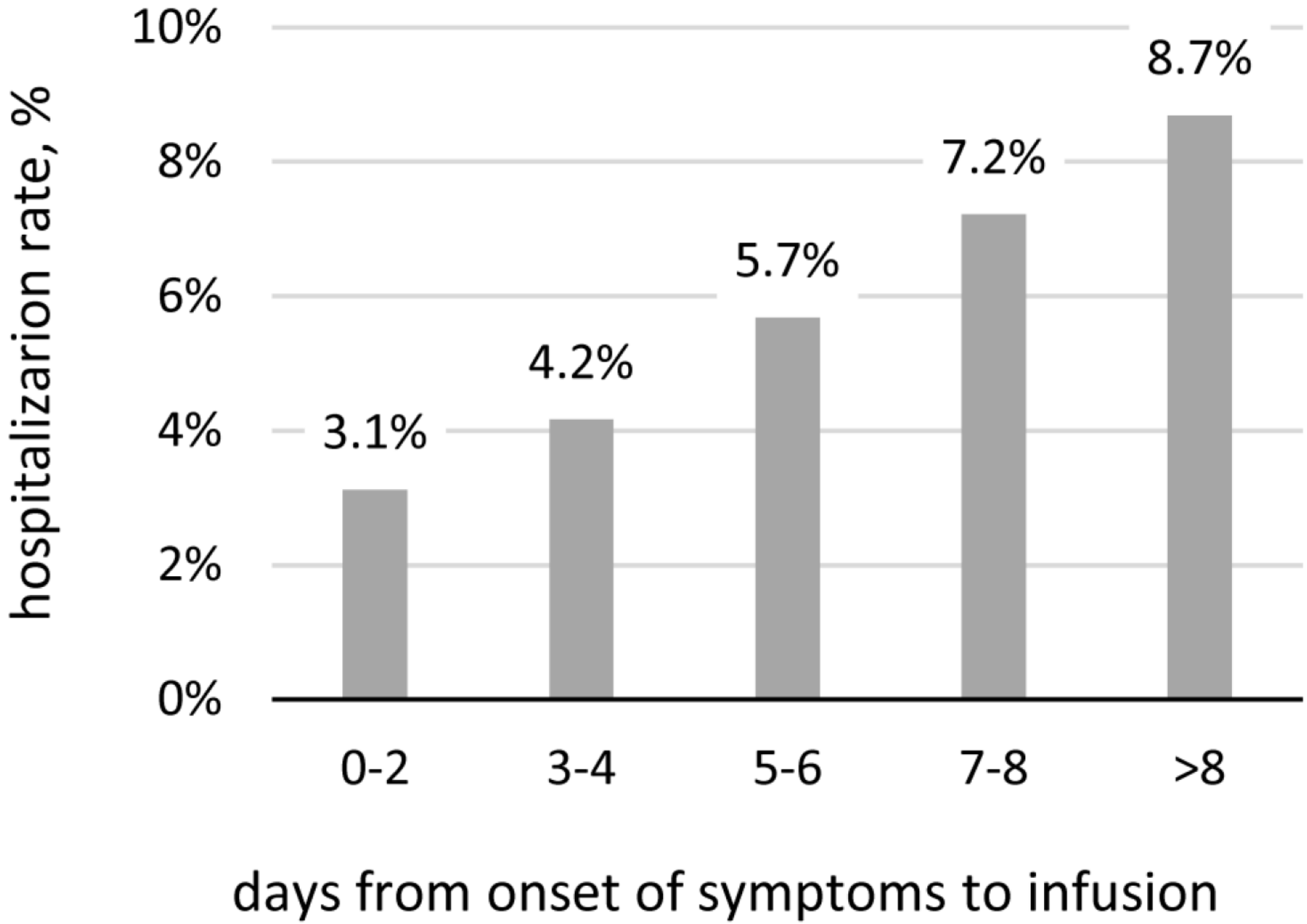
Outcomes

	NmAb group	Controls	P
N	707	1709	
Outcomes:			
Hospitalized with COVID-19 in 1-30 days post-index	41 (5.8%)	195 (11.4%)	<0.0001
Period from index to hospitalization, days (for hospitalized only)	5.29 ± 4.01	5.70 ± 4.95	0.83
Length of inpatient stay, days (for hospitalized only)	5.24 ± 4.55	7.44 ± 8.10	0.0186
Returned to ED in 1-30 days post-index	57 (8.1%)	210 (12.3%)	0.0026
Died in follow-up	4 (0.6%)	24 (1.4%)	0.08

Table 3. Independent predictors of time to hospitalization for COVID-19 patients.

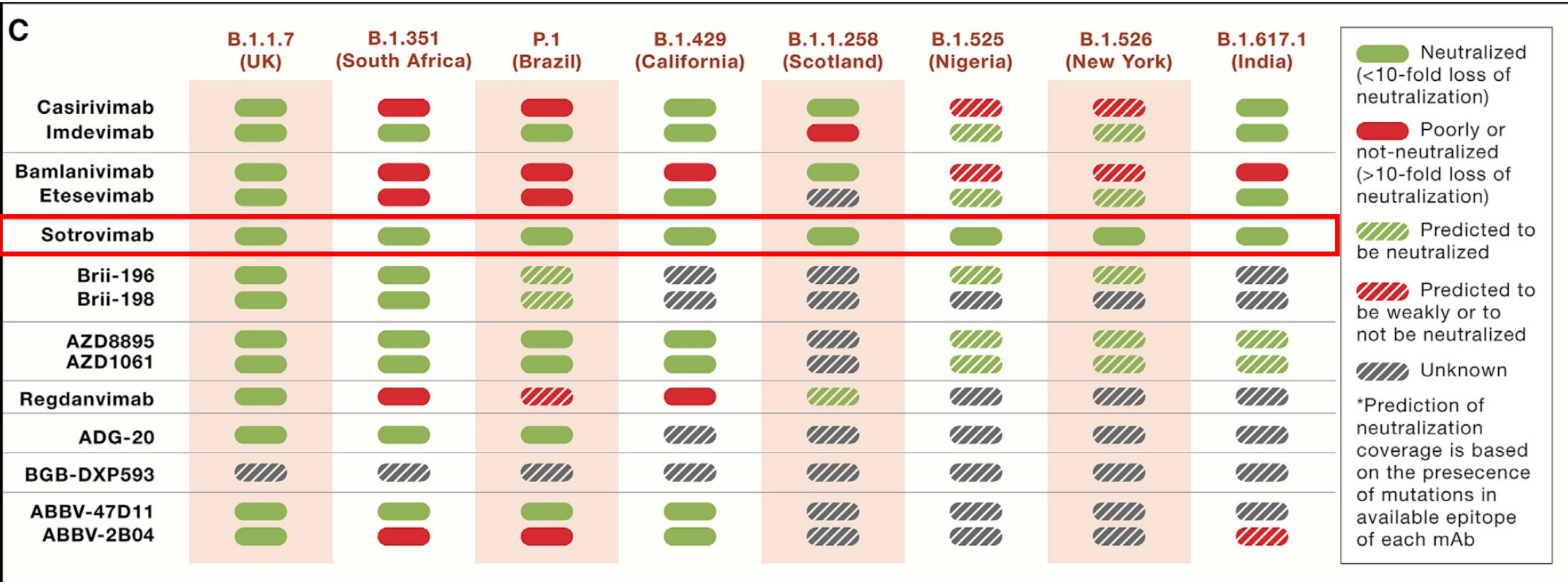
predictor	Adjusted hazard ratio	P
Model 1		
Receiving NmAb infusion	0.54 (0.38 - 0.79)	0.0012
Age, per 5 years	1.18 (1.12 - 1.24)	<.0001
Male sex	1.53 (1.16 - 2.02)	0.0025
White race	0.55 (0.41 - 0.76)	0.0002
Referral from ED*	2.11 (1.57 - 2.82)	<.0001
BMI ≥ 35 kg/m2	1.10 (0.76 - 1.58)	0.62
Model 2		
Receiving NmAb infusion	0.57 (0.38 - 0.84)	0.0045
Age, per 5 years	1.04 (0.97 - 1.13)	0.26
Male sex	1.45 (1.07 - 1.95)	0.0150
White race	0.48 (0.34 - 0.68)	<.0001
Referral from ED*	2.11 (1.53 - 2.90)	<.0001
BMI ≥ 35 kg/m2	1.08 (0.74 - 1.58)	0.69
Charlson's comorbidity index, per 1 point	1.22 (1.10 - 1.36)	0.0003

Manuscript


10%
8%
6%
4%
2%
0%
hospitalizarion rate, %
3.1%
4.2%
5.7%
7.2%
8.7%
0-2
3-4
5-6
7-8
>8
days from onset of symptoms to infusion

Antiviral activity against VOCs (Omicron)
and
viral resistance

Loss of in vitro activity against some VOCs



Efficacia in vitro rispetto alle VOC circolanti degli anticorpi monoclonali disponibili in Italia
(https://www.idsociety.org/covid-19-real-time-learning-network/emerging-variants/emerging-covid-19-variants/)

Variante (WHO label/ Pango lineage)	**Bamlanivimab + etesevimab**	**casirivimab + imdevimab (Ronapreve)**	**Sotrovimab (Xevudy)**
Omicron B.1.1.529	Attività neutralizzante assente	Attività neutralizzante assente	Attività neutralizzante conservata
Delta B.1.617.2	Attività neutralizzante conservata	Attività neutralizzante conservata	Attività neutralizzante conservata
Gamma P.1	Attività neutralizzante marcatamente ridotta	Attività neutralizzante conservata	Attività neutralizzante conservata
Beta B.1.351	Attività neutralizzante marcatamente ridotta	Attività neutralizzante conservata	Attività neutralizzante conservata
Alpha B.1.1.7	Attività neutralizzante conservata	Attività neutralizzante conservata	Attività neutralizzante conservata

Check for updates

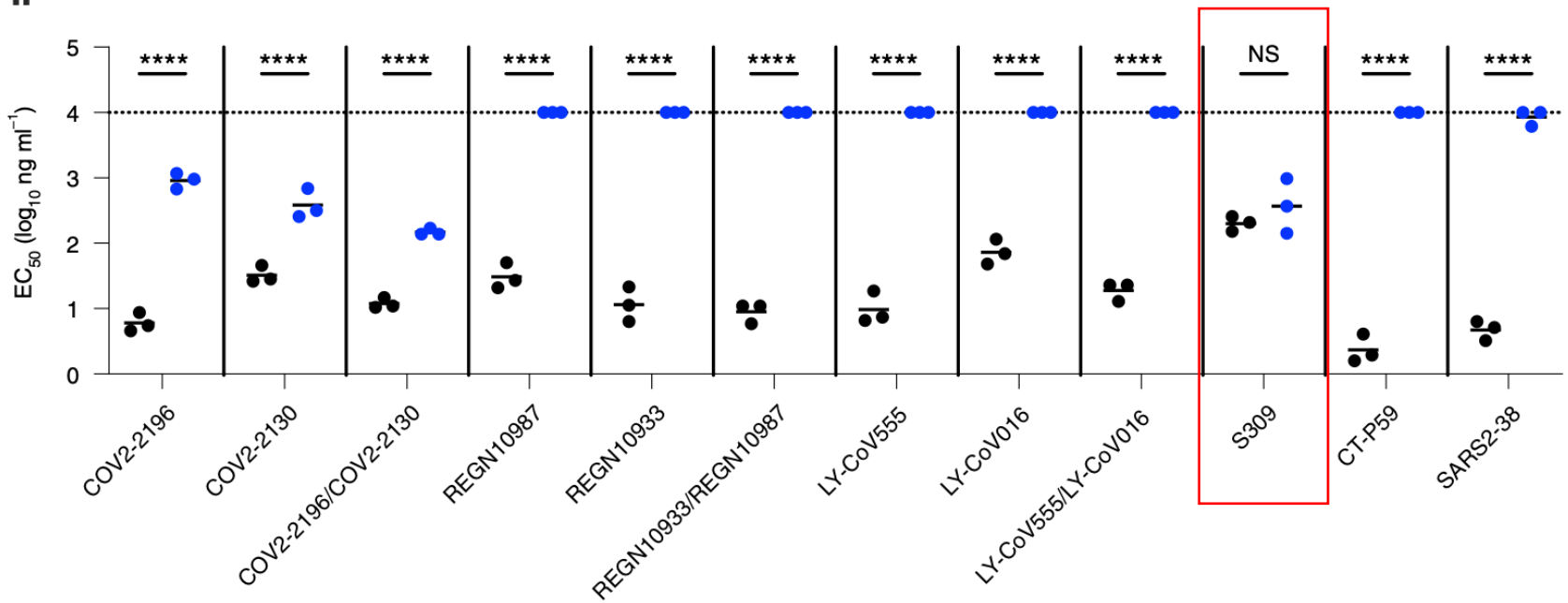
An infectious SARS-CoV-2 B.1.1.529 Omicron virus escapes neutralization by therapeutic monoclonal antibodies

g

Vero-TMPRSS2 cells

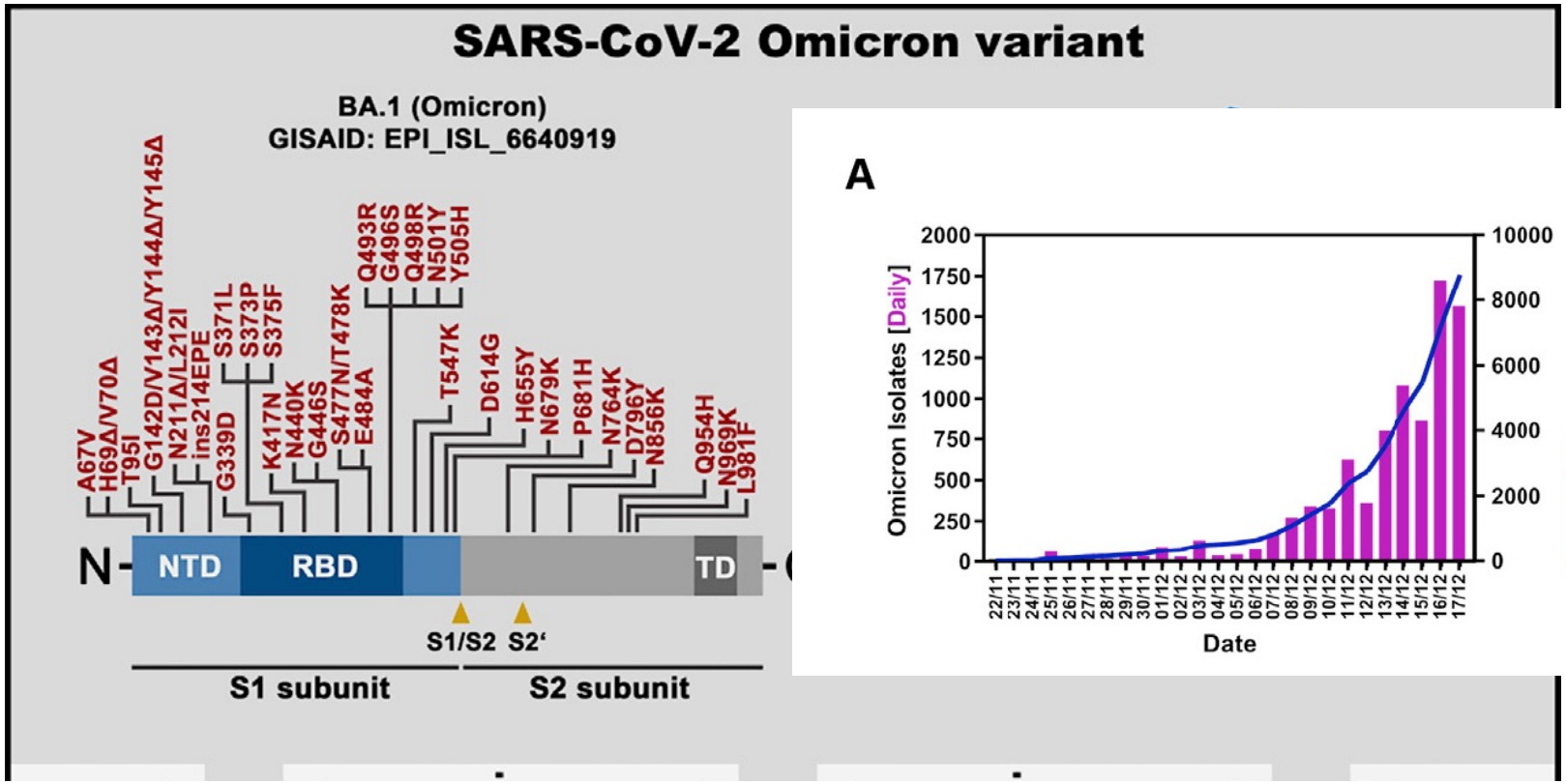
mAb	SARS2-COV-2	
	WA1/2020 D614G	B.1.1.529
COV2-2196	6	913
COV2-2130	32	381
COV2-2196/COV2-2130	12	147
REGN10987	31	>10,000
REGN10933	11	>10,000
REGN10933/REGN10987	9	>10,000
LY-CoV555	10	>10,000
LY-CoV016	72	>10,000
LY-CoV555/LY-CoV016	19	>10,000
S309	202	373
CT-P59	2	>10,000
SARS2-38	5	8,520

h



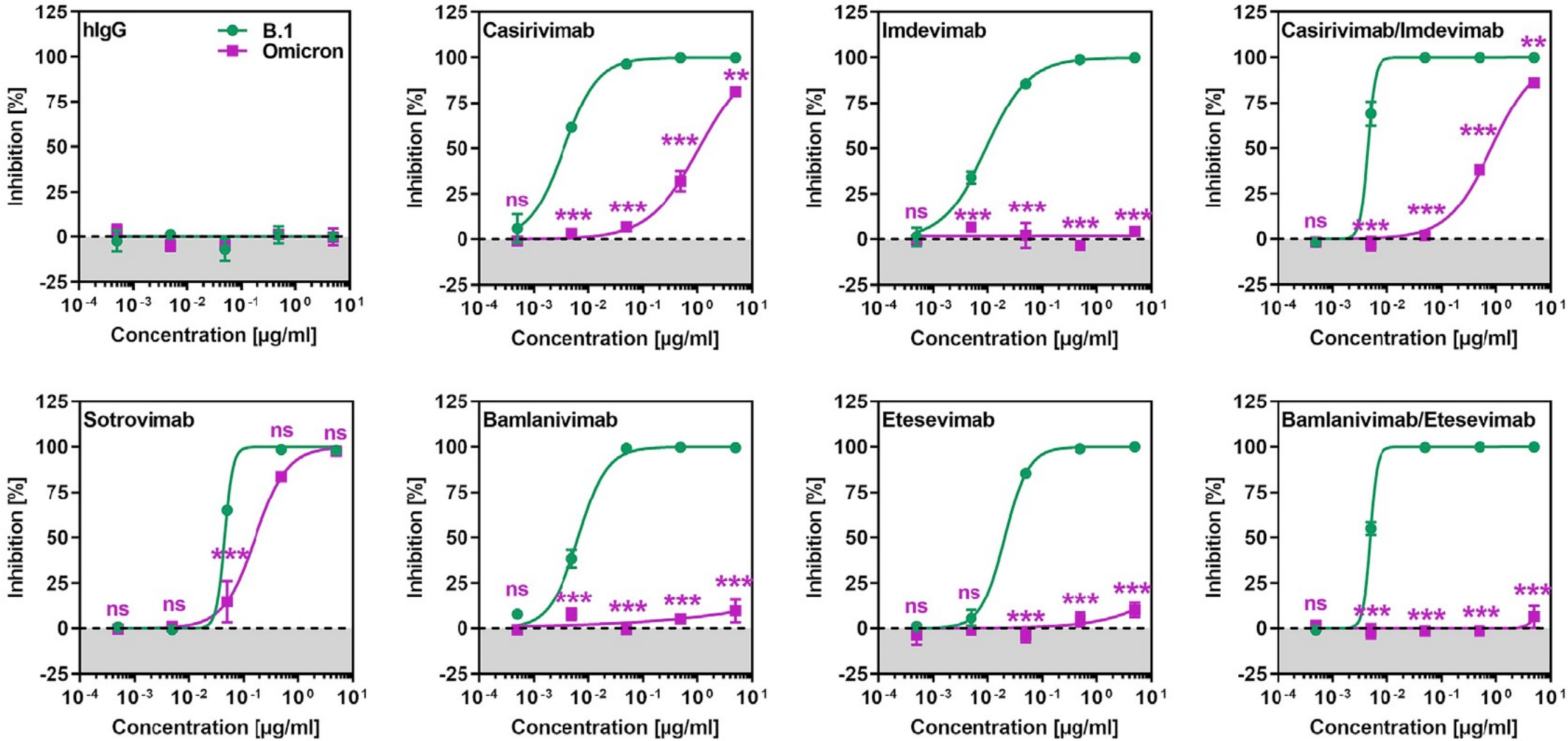
Cell

The Omicron variant is highly resistant against antibody-mediated neutralization: Implications for control of the COVID-19 pandemic



Hoffmann et al., 2022, Cell *185*, 447–456
February 3, 2022 © 2021 Elsevier Inc.
https://doi.org/10.1016/j.cell.2021.12.032

C



Sotrovimab: viral variants and resistance

- Information in the FDA Emergency Use Authorization state **“no change” in activity of sotrovimab against Alpha, Beta, Gamma, Epsilon, Iota, Kappa, Delta (including with K417N), Lambda and Mu** in pseudo-typed virus-like particle neutralization assays.

- **Sotrovimab has been reported to retain activity against BA.1 Omicron** in pseudovirus assays, but with **higher concentrations** being required for neutralization compared with the wild-type virus. Several reports have indicated that the **neutralization of the BA.2 sub-lineage of Omicron is more severely impacted** than it is for BA.1

  (https://www.biorxiv.org/content/10.1101/2021.03.09.434607v10).

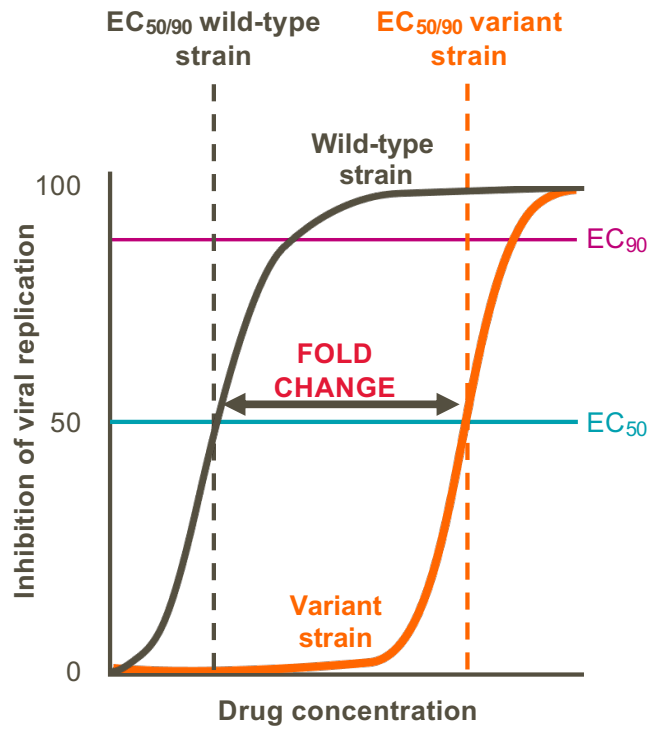
Therapeutics and COVID-19: living guideline - World Health Organization (WHO), April 2022; Ref 67-71

In vitro neutralization assays

Neutralization assays can be used to examine:[1,2]

- The potential for reduced mAb efficacy against emerging VOIs/VOCs[1]
- Effectiveness of neutralizing antibodies in patients with varying severities of COVID-19[2]
- Antibody response in humans post-vaccination and post-infection[2,3]
- Emergence of resistant variants under real or simulated selective pressure[1]

Determining viral susceptibility to treatment[4]



Calculating FC

$$\frac{EC_{50/90}\ \text{variant}}{EC_{50/90}\ \text{wild-type}}$$

Figure adapted with permission from National HIV Curriculum. Evaluation and Management of Virologic Failure.

The clinical implications of pseudotyped neutralization assays are not known.

EC_{50}, half maximal effective concentration; EC_{90}, 90% maximal effective concentration FC, fold-change; mAb, monoclonal antibody; VOC, variant of concern; VOI, variant of interest.

1. Cathcart AL, et al. bioRxiv (preprint). February 18, 2022. doi:10.1101/2021.03.09.434607v11; 2. Cantoni D, et al. *Oxf Open Immunol.* 2021;2(1):doi:10.1093/oxfimm/iqab005; 3. Liu C, et al. *Cell*. 2021;184(16):4220-4236; 4. National HIV Curriculum. Evaluation and Management of Virologic Failure (accessed March 28, 2022).

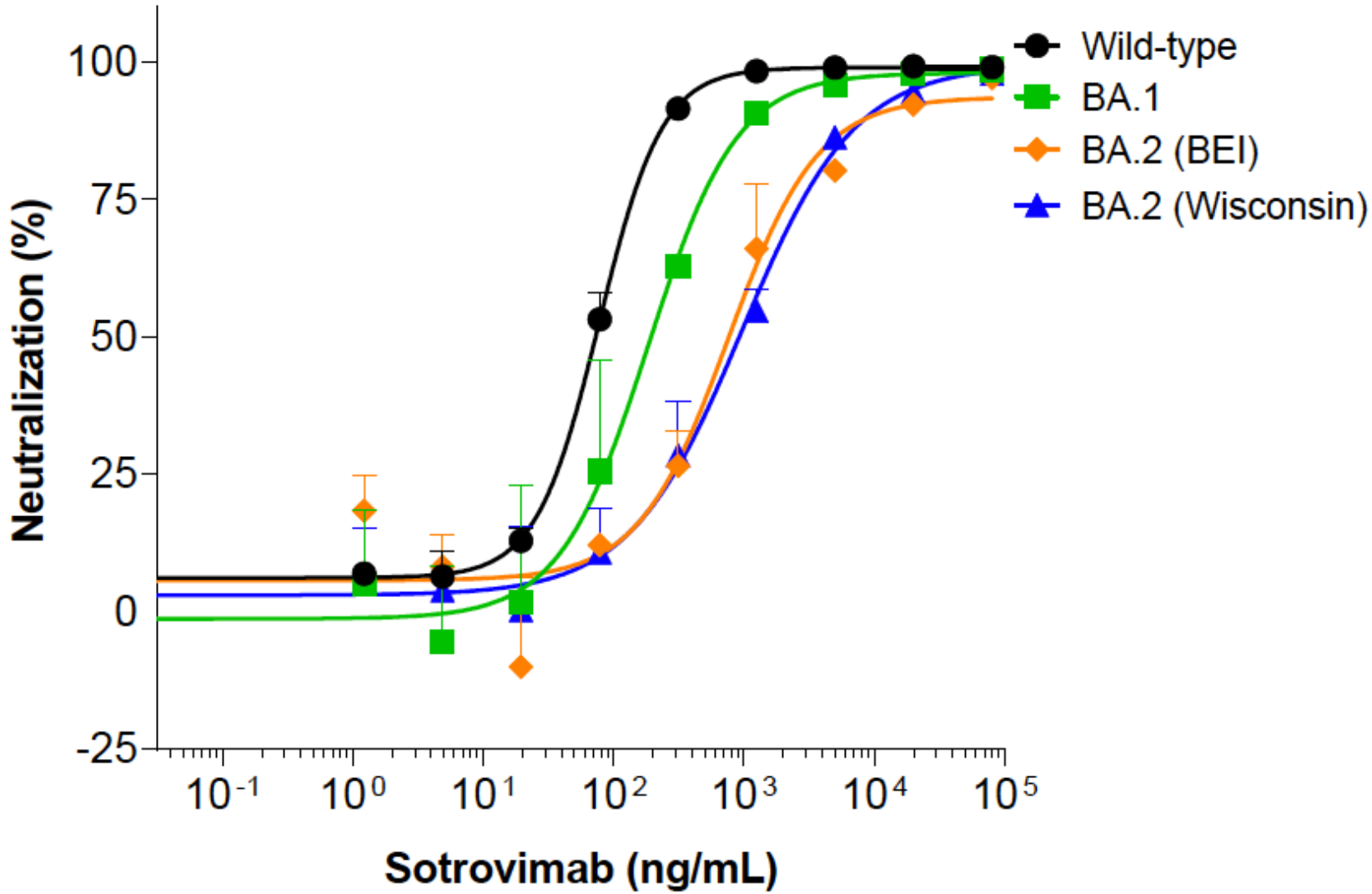
This Document Contains GSK Proprietary Information – Not For Onward Distribution

- To examine neutralization capacity, sotrovimab and VIR-7832 were tested in a VeroE6 or Vero E6-94 TMPRSS2 cell-based live SARS-CoV-2 virus system against the Washington 2019 (wild-type) virus as well as against the Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), Delta (B.1.617.2), Kappa (B.1.617.1) and Omicron (BA.1, BA.1.1 and BA.2) variants.

- Sotrovimab was tested against an extended panel of pseudotyped 112 viruses incorporating emerging variants as well as variants currently or previously deemed as VOC or VOI.
- Sotrovimab neutralized all variants tested with fold changes in IC50s of ≤3.3-fold observed for 21 of 23 variants assessed, while a 7.3-fold change in IC50 was observed for Omicron BA.3 and a 16-fold change in IC50 was observed for the Omicron BA.2 variant

Andrea L. Cathcart[1], bioRxiv preprint doi: https://doi.org/10.1101/2021.03.09.434607; this version posted April 1, 2022.

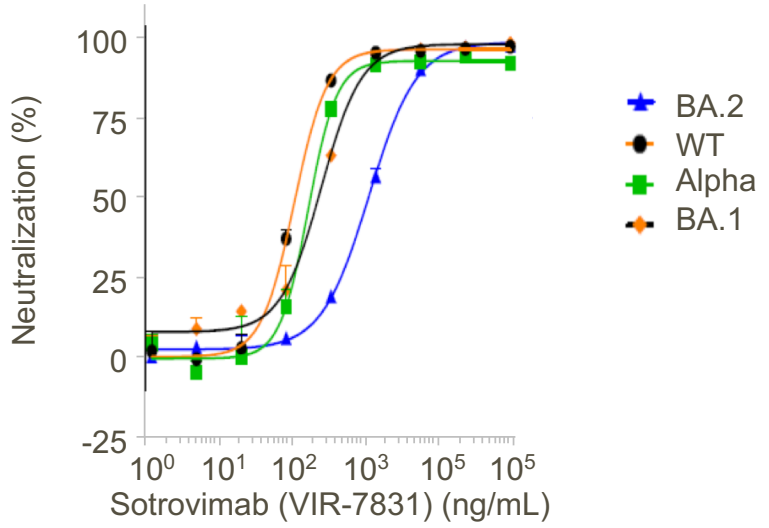
e)


Neutralization (%)
100
75
50
25
0
-25
10^{-1}
10^{0}
10^{1}
10^{2}
10^{3}
10^{4}
10^{5}
Sotrovimab (ng/mL)
Wild-type
BA.1
BA.2 (BEI)
BA.2 (Wisconsin)

Sotrovimab in vitro neutralization activity against Omicron SARS-CoV-2 variant and sublineages: Pseudotyped virus data

Sotrovimab neutralized pseudotyped virus expressing the Omicron BA.2 spike variant in vitro with a 16-fold reduction in EC_{50} compared with WT[1,2]

In vitro neutralization of Omicron BA.1 and BA.2 pseudotyped virus with Alpha variant and wild-type pseudotyped controls[1]



Results shown are from one experiment and are representative of 10 independent experiments[1]

Figure adapted with permission from Cathcart AL, et al. bioRxiv (preprint). February 18, 2022. doi:10.1101/2021.03.09.434607v11.

In vitro pseudotyped virus-like particle assessment of sotrovimab activity[2]

WHO label[3]	SARS-CoV-2 lineage[2]	Average FC in EC_{50} vs WT[2,*,†]
Omicron (B.1.1.529)	BA.1	2.7
	BA.1.1	3.3
	BA.2	16.0‡
	BA.3	7.3‡

Table adapted with permission from Cathcart AL, et al. bioRxiv (preprint). February 18, 2022. doi:10.1101/2021.03.09.434607v11.

*Average change in activity for sotrovimab vs wild-type control for spike variants tested in a pseudotyped virus system;[2] the clinical significance of pseudovirus neutralization data is not known; †A <5-fold reduction in susceptibility is considered no change in activity;[2] ‡Clinical relevance of 7.3-fold and 16.0-fold reductions in susceptibility are not known.[4] EC_{50}, half maximal effective concentration; FC, fold-change; WHO, World Health Organization; WT, wild-type. [See notes for references].

This Document Contains GSK Proprietary Information – Not For Onward Distribution

Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

In vitro activity of therapeutic antibodies against SARS-CoV-2 Omicron BA.1 and BA.2

Franck Touret (franck.touret@univ-amu.fr)

The replacement of the Omicron BA.1 variant of SARS-CoV-2 by the BA.2 sub lineage, which has a different set of mutations in the spike glycoprotein, alters the spectrum of activity of therapeutic antibodies. In this study, we compared the neutralising power of monoclonal antibodies against the Omicron BA.1 and BA.2 variants, with an ancestral strain (D614G) and a Delta variant as reference. Sotrovimab is less active against BA.2 than against BA.1 (fold change reduction ~1,5). Within the Evusheld/ AZD744 cocktail, Cilgavimab is more active against BA.2 than against BA.1 (fold change increase ~32), whilst activity of Tixagevimab remains very low. In total, the activity of Evusheld is significantly improved (fold change increase ~10 compared to BA.1).

antigenic shift[2,,] We are currently witnessing the replacement of the Omicron BA.1 variant by a new sub lineage, BA.2, which also emerged in South Africa in late 2021. Omicron BA.2 has fewer mutations than BA.1 in the spike glycoprotein, some of which are shared with BA.1 and others are original. This new mutation pattern has the potential to alter the activity of therapeutic monoclonal antibodies currently in clinical use against Omicron BA.1.

Our results support previous studies reporting that Sotrovimab retains some neutralising activity against the BA.1 sub lineage *in vitro*[2,3,9,10]. In the case of the BA.2 variant (Table 1, supplemental Fig.1), with an EC_{50} increasing from 55.2 (B.1) to 441(BA.2) ng/mL, we observe a decrease in neutralisation activity by a factor of ~8 (Table 1) compared to the ancestral B.1 strain, and ~1.5 compared to BA.1. This result is consistent with data from Vir Biotechnology using a pseudotype virus harboring all Omicron BA.2 spike mutations[11].

Update [4/5/2022] 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

This statement updates the statements below.

The Centers for Disease Control and Prevention (CDC) Nowcast data from April 5, 2022, estimates that the proportion of COVID-19 cases caused by the Omicron BA.2 variant is above 50% in all Health and Human Services (HHS) U.S. regions. Data included in the health care provider fact sheet show the authorized dose of sotrovimab is unlikely to be effective against the BA.2 sub-variant. Due to these data, sotrovimab is not authorized in any U.S. state or territory at this time.

Health care providers should use other approved or authorized products as they choose appropriate treatment options for patients.

FDA will continue to monitor BA.2 in all U.S. regions and will provide follow-up communication when appropriate.

Sotrovimab: viral variants and resistance

- An E340A amino acid substitution in the conserved epitope of the spike protein emerged rapidly under a selective pressure with sotrovimab in cell culture, and subsequent characterization using a pseudovirus assay resulted in a **>100-fold reduction in susceptibility to sotrovimab**.
- Sixteen other substitutions introduced into the epitope were also described as reducing neutralization by sotrovimab by **between 5.4 and > 297-fold**. Therefore, **resistance to sotrovimab can emerge under experimental conditions**. Additionally, 4 of the first 1000 consecutive patients treated with sotrovimab during a Delta wave in Australia are reported to have developed E340 mutations in their viral sequences, and remained culture positive for 12–24 days after dosing.

Therapeutics and COVID-19: living guideline - World Health Organization (WHO), April 2022; Ref 67-71

LETTER TO THE EDITOR OPEN

Check for updates

SARS-CoV-2 Omicron variant is highly sensitive to molnupiravir, nirmatrelvir, and the combination

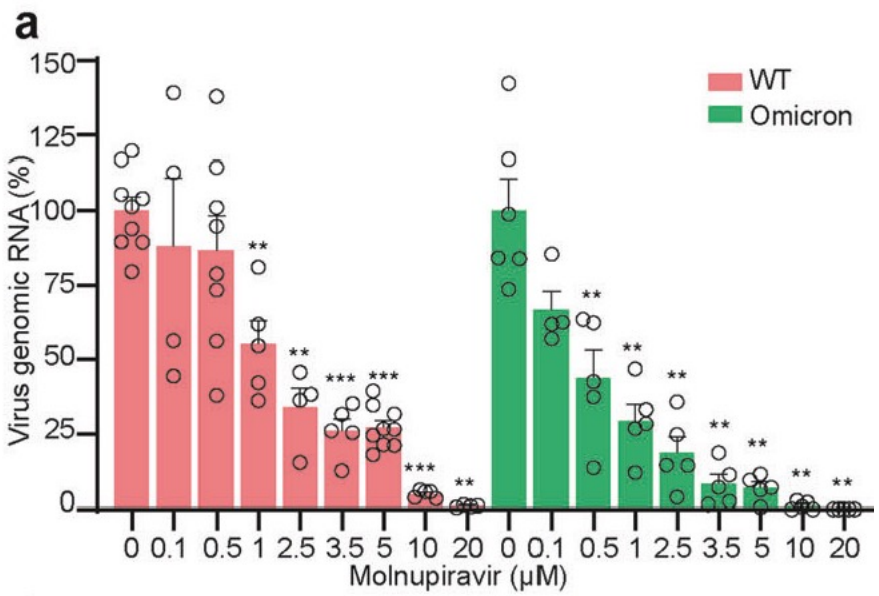
© The Author(s) 2022

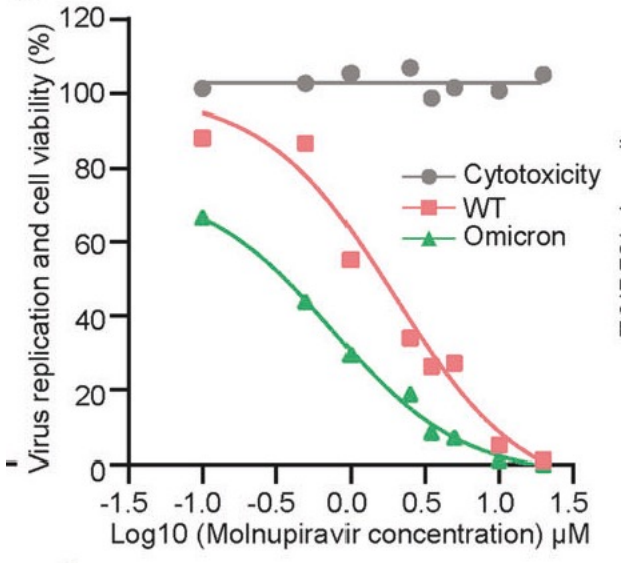
Cell Research (2022) 32:322–324; https://doi.org/10.1038/s41422-022-00618-w

In Calu-3 cells inoculated with the virus and treated with molnupiravir, we found potent and dose-dependent inhibition of viral replication based on qRT-PCR quantification of intracellular viral genomic RNA.

At clinically relevant concentration of 1 μM, molnupiravir already reduced Omicron RNA by 70.4% ± 12.5%, p=0.0043.

The dose response curves indicated that Omicron, as compared to WT SARS-CoV-2, appears to be more sensitive to the treatment, especially at low concentrations ranging from 0.5 μM to 5μM, and no cytotoxicity was observed.

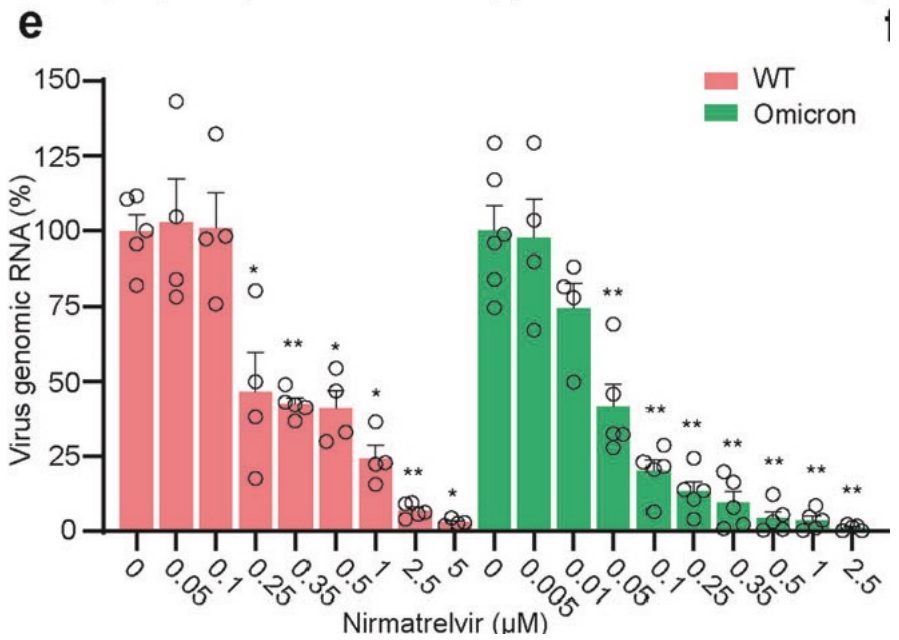


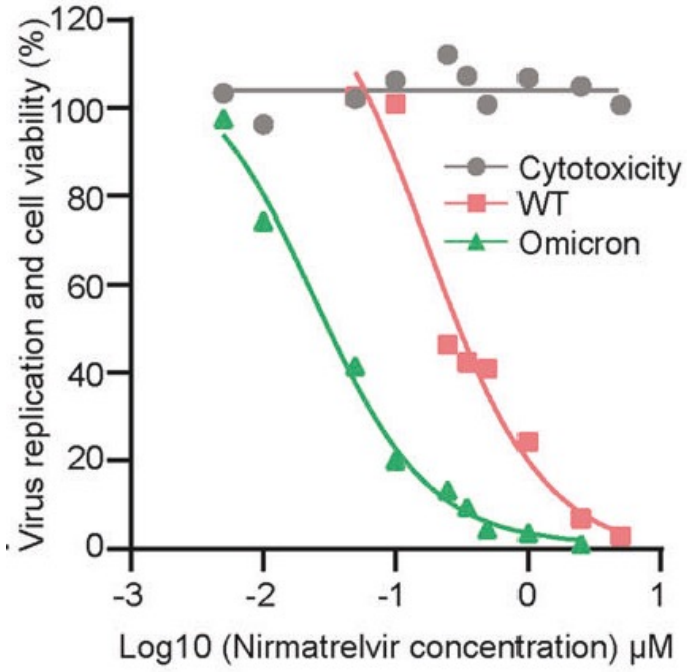


Potent and dose-dependent inhibition of intracellular viral genomic RNA was observed.

A low concentration of 0.1 µM has already reduced Omicron viral RNA by 79.9% ± 8.3% (p=0.0043).

The dose response curves calculated the IC50 of 0.1765 µM to WT and 0.02462 µM to Omicron SARS-CoV-2. These curves suggest that Omicron, compared to the parental WT SARS CoV-2, is slightly more sensitive to nirmatrelvir in Calu-3 cell model,





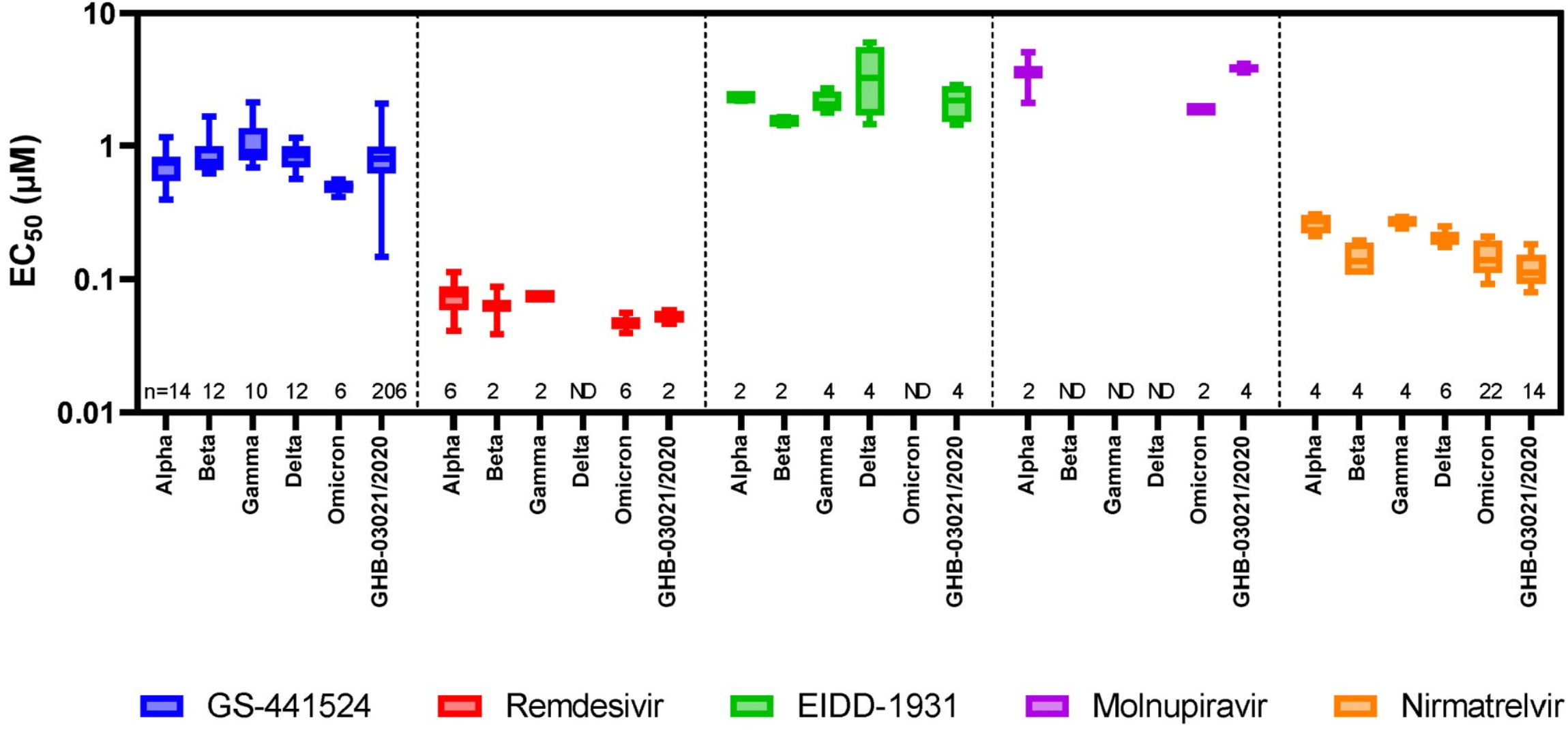
Remdesivir, Molnupiravir and Nirmatrelvir remain active against SARS-CoV-2 Omicron and other variants of concern

Laura Vangeel [a], Winston Chiu [a], Steven De Jonghe [a], Piet Maes [b], Bram Slechten [c], Joren Raymenants [c,d], Emmanuel André [c,d], Pieter Leyssen [a], Johan Neyts [a,1,**], Dirk Jochmans [a,1,*]

[a] *KU Leuven, Department of Microbiology, Immunology and Transplantation, Rega Institute, Laboratory of Virology and Chemotherapy, Leuven, Belgium*
[b] *KU Leuven, Department of Microbiology, Immunology and Transplantation, Rega Institute, Laboratory of Clinical and Epidemiological Virology, Leuven, Belgium*
[c] *University Hospitals Leuven, Department of Laboratory Medicine, Leuven, Belgium*
[d] *KU Leuven, Department of Microbiology, Immunology and Transplantation, Rega Institute, Laboratory of Clinical Bacteriology and Mycology, Leuven, Belgium*

A B S T R A C T

We assessed the *in vitro* antiviral activity of remdesivir and its parent nucleoside GS-441524, molnupiravir and its parent nucleoside EIDD-1931 and the viral protease inhibitor nirmatrelvir against the ancestral SARS-CoV2 strain and the five variants of concern including Omicron. VeroE6-GFP cells were pre-treated overnight with serial dilutions of the compounds before infection. The GFP signal was determined by high-content imaging on day 4 post-infection. All molecules have equipotent antiviral activity against the ancestral virus and the VOCs Alpha, Beta, Gamma, Delta and Omicron. These findings are in line with the observation that the target proteins of these antivirals (respectively the viral RNA dependent RNA polymerase and the viral main protease Mpro) are highly conserved.


10
1
0.1
0.01
EC50 (μM)
n=14 12 10 12 6 206 6 2 2 ND 6 2 2 2 4 4 ND 4 2 ND ND ND 2 4 4 4 4 6 22 14
Alpha
Beta
Gamma
Delta
Omicron
GHB-03021/2020
GS-441524
Remdesivir
EIDD-1931
Molnupiravir
Nirmatrelvir

Nirmatrelvir-ritonavir: activity against Omicron and resistance

- No data are available for activity against Omicron variants in cell cultures currently. However, nirmatrelvir retains activity against BA.1 Omicron in vitro, but in vivo data are currently unavailable.
- Based upon genome sequence of Omicron, there appears to be no molecular basis for a loss of activity.
- Much more data are required to ascertain the rate at which resistance will emerge for nirmatrelvir. Single amino acid changes introduced into the protease sequence can reduce activity of nirmatrelvir by between 23.6- and 39-fold.
- Mouse hepatitis virus (used as a betacoronavirus surrogate) acquired several mutations under a selective pressure in vitro, and these reduced nirmatrelvir activity by between 4- and 91-fold.
- Two amino substitutions were described in clinical trials, one of which did not impact nirmatrelvir activity.

Therapeutics and COVID-19: living guideline - World Health Organization (WHO), April 2022; ref 27 e 25

Remdesivir: resistance

- **Emergence of antiviral resistance**: under a selective pressure in vitro, SAR-CoV-2 resistance to remdesivir emerged and was associated with a mutation (E802D) within the sequence coding for the polymerase.

- The E802D mutation was also reported in a case study describing an immunocompromised patient receiving remdesivir who experienced recrudescence of high-grade viral shedding following a transient virological response to the drug.

- The clinical significance of these observations if remdesivir were widely used in an outpatient setting is unclear.

Therapeutics and COVID-19: living guideline - World Health Organization (WHO), April 2022 Ref 33 34

Molnupiravir: viral variant and resistance

- NHC, the nucleoside analogue metabolite of molnupiravir, had similar activity against the variants including alpha (B.1.1.7), beta (B.1.351), gamma (P.1), and delta (B.1.617.2).
- Molnupiravir retains activity against Omicron variants *in vitro*.
- No data are available for activity against Omicron variants in vivo currently.
- While there appears to be no molecular basis for a loss of activity, there is residual uncertainty around whether a higher replication or transmission rate may impact efficacy of the drug.
- Insufficient data are currently available to ascertain how high the barrier of resistance is with SARS-CoV-2 for molnupiravir. Based on experiences with other nucleoside antiviral drugs, molnupiravir will place a selective pressure for viral resistance mutations within an individual, with the potential to spread at a population level. Non-clinical and/or clinical data are therefore needed, but are not currently available for molnupiravir.

Therapeutics and COVID-19: living guideline - World Health Organization (WHO), April 2022, Ref 47-49

Molnupiravir: viral variant and resistance

- There have been no amino acid substitutions in the SARS-CoV-2 associated with resistance to NHC in the phase 2 clinical trials of molnupiravir performed.

- Following the 30 passages in cell culture, only a twofold decrease in the susceptibility was observed.

- NHC also demonstrated good activity in cell culture against the virus with polymerase substitutions associated with decreased remdesivir sensitivity, indicating a lack of cross resistance

Saravolats LD et al, Clin Infect Dis 2022; ciac180.

Which treatment to choose?

- Choices will depend on
  - availability of the drugs
  - routes of administration (only intravenous for remdesivir and the monoclonal antibodies)
  - duration of treatment
  - time from onset of symptoms to starting treatment

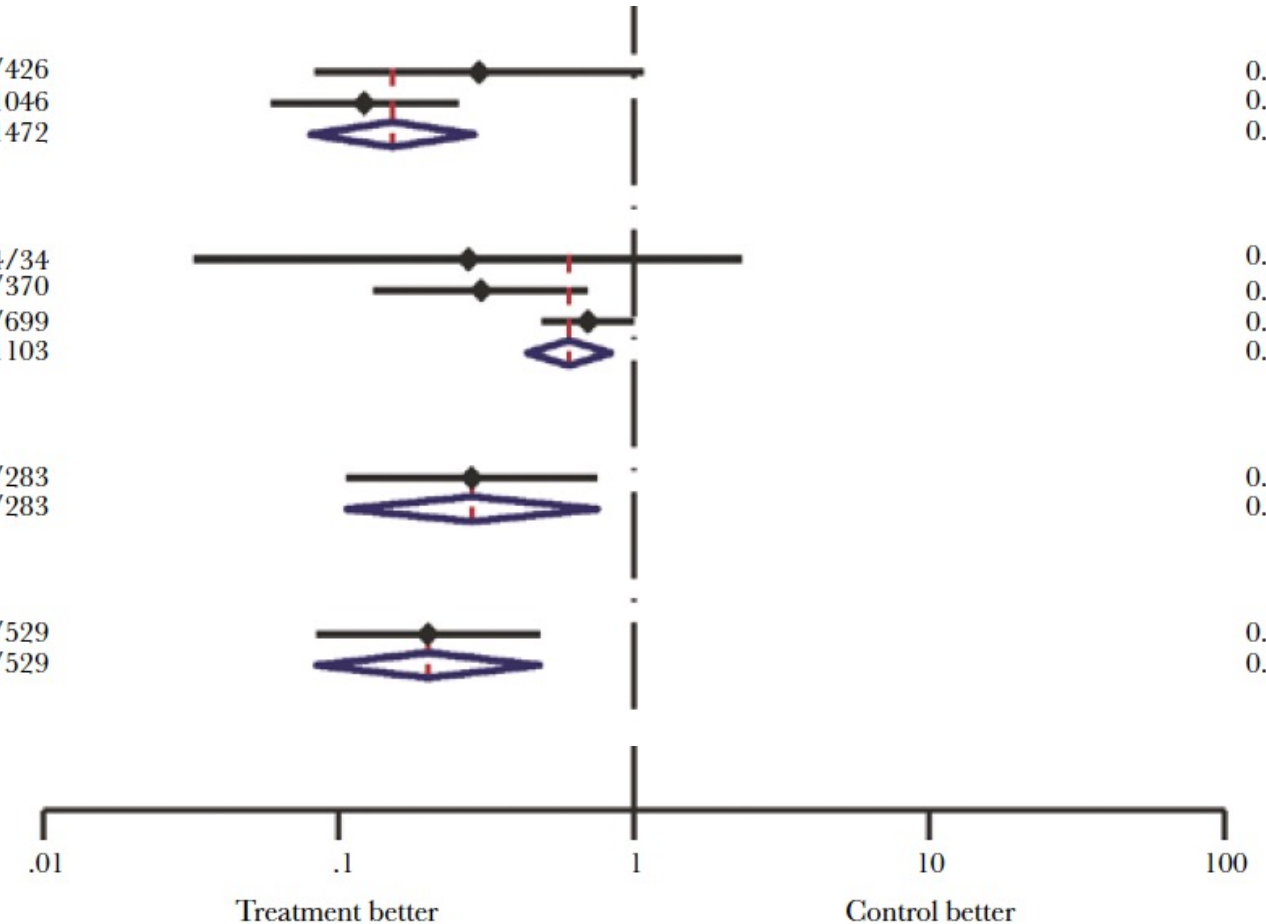
- In the absence of direct comparisons of the various therapeutics in trials, indirect comparisons from the LNMA have been used to inform use of one drug over another with a related mechanism of action.

Therapeutics and COVID-19: living guideline - World Health Organization (WHO), April 2022

Reduction in COVID-19-related hospitalizations

- ✓In the high-risk, non hospitalized population, **Molnupiravir achieving a 30% reduction in Covid-19–related hospitalization or death through 29 days** after randomization.
- ✓Covid-19 therapeutic **monoclonal antibodies are associated with relative risk reductions of approximately 70 to 85%** against mild-to-moderate Covid-19 in outpatient settings; however, monoclonal antibodies require intravenous or subcutaneous/intramuscolar administration in a health care setting, and they may be less effective against emerging variants harboring mutations in the monoclonal antibody–targeted SARS-CoV-2 spike protein.
- ✓**Remdesivir,** an agent administered intravenously, has shown an **87% reduction in the risk of progression to severe disease** in the outpatient setting

Active agent and study	Treatment n/N	Control n/N	Risk ratio (95% CI)	% Weight
Nirmatrelvir; ritonavir				
EPIC-SR (Unpublished)[b]	3/428	10/426	0.30 (0.08, 1.08)	24.38
EPIC-HR (Unpublished)[b]	8/1039	66/1046	0.12 (0.06, 0.25)	75.62
Subgroup, IV	11/1467	76/1472	0.15 (0.08, 0.29)	100.00
(I^2 = 29.2%, P = .235)				
Molnupiravir				
MOVE-Out (Ph 2- NEJM Evidence 2021)[c]	1/31	4/34	0.27 (0.03, 2.32)	2.28
HETERO (Unpublished)	7/371	23/370	0.30 (0.13, 0.70)	14.96
MOVE-Out (NEJM 2021)	48/709	68/699	0.70 (0.49, 0.99)	82.77
Subgroup, IV	56/1111	95/1103	0.60 (0.44, 0.83)	100.00
(I^2 = 46.7%, P = .153)				
Remdesivir				
PINETREE (NEJM 2021)	5/279	18/283	0.28 (0.11, 0.75)	100.00
Subgroup, IV	5/279	18/283	0.28 (0.11, 0.75)	100.00
(I^2 = 0.0%, P = .)				
Sotrovimab				
NCT04545060 (MedRxiv)	6/528	30/529	0.20 (0.08, 0.48)	100.00
Subgroup, IV	6/528	30/529	0.20 (0.08, 0.48)	100.00
(I^2 = 0.0%, P = .)				
Heterogeneity between groups: P = .000				



Lee TC et al, OFID 2022; 9(3):ofac008.

summarized in Table 3[1-4,11]. Molnupiravir has relatively lower efficacy and has not been evaluated in transplant recipients. In addition, due to significant drug interactions and the difficulty with outpatient therapeutic drug monitoring nirmatrelvir-ritonavir will be challenging to use in most transplant recipients with COVID-19. This may also be enhanced by the theoretical concern of mutagenicity for the virus in the immunocompromised patients. Thus, since neither drugs has been studied among compromised hosts, to prevent progression in transplant recipients, sotrovimab or intravenous remdesivir may be preferable as first line outpatient therapy [12].

nuscript

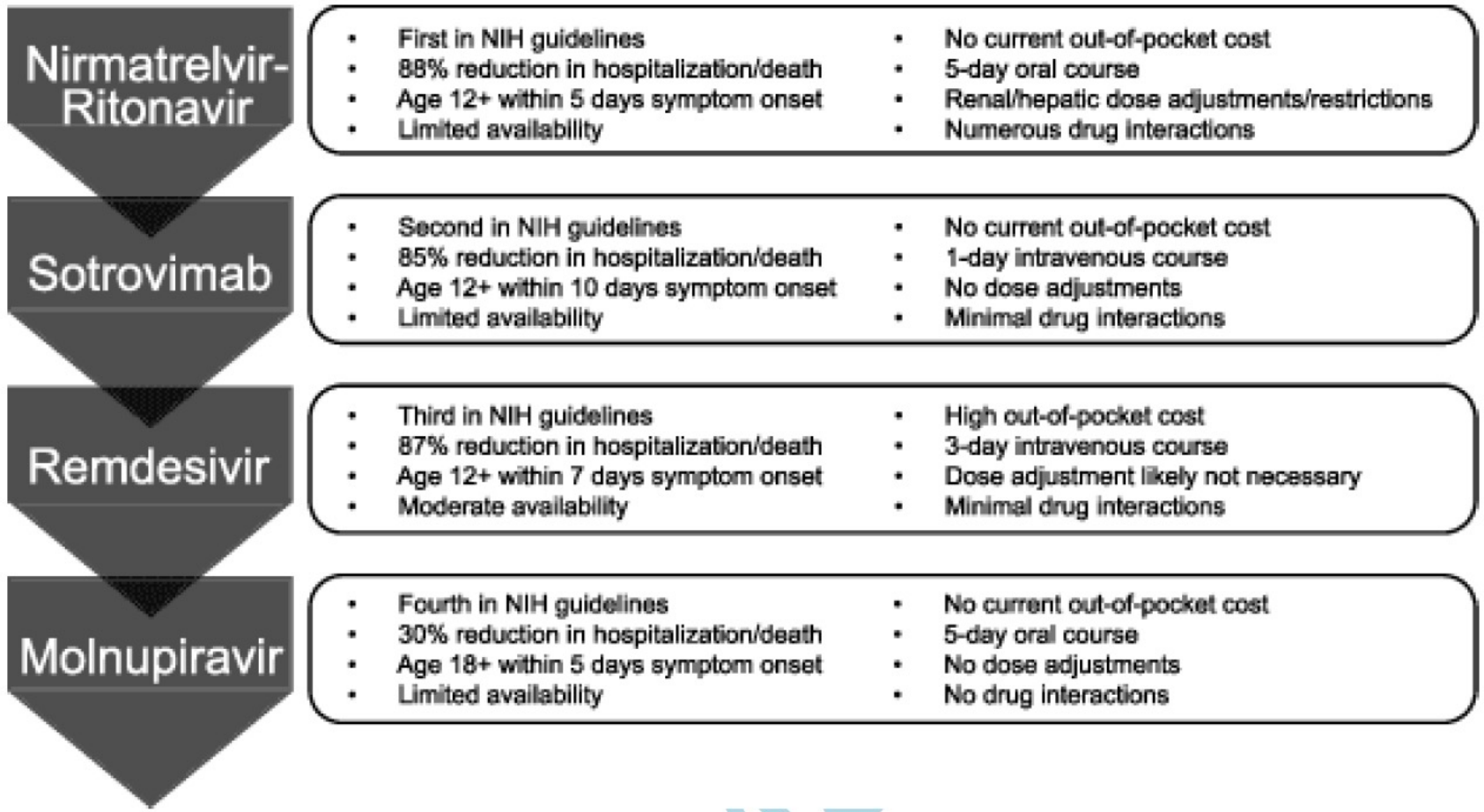
Saravolats LD et al, Clin Infect Dis 2022; ciac180.

Drug	Cost/Patient	Number Needed to Treat			Cost per Hospitalization Prevented		
		2.5% Risk	5% Risk	10% Risk	2.5% Risk	5% Risk	10% Risk
Fluvoxamine (meta-analysis)	14	160 (96–1334)	80 (48–667)	40 (24–334)	2244 (1346–18 709)	1122 (673–9355)	561 (337–4684)
Colchicine (meta-analysis)	37	182 (103–40 000)	91 (52–20 000)	46 (26–10 000)	6667 (3773–1 465 200)	3333 (1905–732 600)	1685 (952–366 300)
Inhaled corticosteroids (meta-analysis)[a]	132	143 (89–800)	72 (45–400)	36 (23–200)	18 819 (11 712–105 280)	9475 (5922–52 640)	4738 (3027–26 320)
Nirmatrelvir/ritonavir (meta-analysis)[b]	530	48 (44–57)	24 (22–29)	12 (11–15)	25 440 (23 320–30 210)	12 720 (11 660–15 370)	6360 (5830–7950)
Molnupiravir (meta-analysis)[a]	700	100 (72–236)	50 (36–118)	25 (18–59)	70 000 (50 400–165 200)	35 000 (25 200–82 600)	17 500 (12 600–41 300)
Remdesivir (phase 3)	1872	56 (45–160)	28 (23–80)	14 (12–40)	104 832 (84 240–299 520)	52 416 (43 056–149 760)	26 208 (22 464–74 880)
Sotrovimab (phase 3)	2100	50 (44–77)	25 (22–39)	13 (11–20)	105 000 (92 400–161 700)	52 500 (46 200–81 900)	27 300 (23 100–42 000)
Casirivimab/imdevimab (phase 3)	2100	57 (50–73)	29 (25–37)	15 (13–19)	119 700 (105 000–153 300)	60 900 (52 500–77 700)	31 500 (27 300–39 900)
Bamlanivimab/ etesevimab (phase 3)[b]	2100	58 (48–99)	29 (24–50)	15 (12–25)	121 800 (100 800–207 900)	60 900 (50 400–105 000)	31 500 (25 200–52 500)

Lee TC et al, OFID 2022; 9(3):ofac008.

Figure 1. Therapy options for treatment of mild-to-moderate COVID-19

Add as a footnote: These recommendations have not been established for the severely immunocompromised host and organ transplant recipients.



Neutralizing mAbs: prophylactic role?

associated benefit-to-risk ratio? In addition, neutralizing mAbs may have a prophylactic role in individuals deemed to be at high risk of severe COVID-19. Indeed, preliminary non-peer-reviewed preprint data suggest that mAbs prevent COVID-19 in high-risk individuals potentially exposed to SARS-CoV-2 in nursing homes or within households[6,7].

Review. Taylor PC et al, Nat Rev Immunol. 2021 Jun;21(6):382-393.

Insufficient immune response to vaccination: Tixagevimab/Cilgavimab (Evusheld)

- In Italia, ne è stata autorizzata la temporanea distribuzione per la profilassi di COVID-19 in soggetti adulti
- EVUSHELD (tixagevimab e cilgavimab) è indicato per la **profilassi pre-esposizione** dell'infezione da SARS-CoV-2 in soggetti adulti ed adolescenti di età pari o superiore a 12 anni e con peso corporeo di almeno 40 kg
- La popolazione trattabile deve essere rappresentata unicamente da soggetti con grave stato di compromissione del sistema immunitario e in presenza di sierologia negativa.

- *Profilassi pre-esposizione dell'infezione da SARS-CoV-2 in soggetti adulti ed adoloscenti di età pari o superiore a 12 anni e con peso corporeo di almeno 40kg, con un controllo sierologico completamente negativo (anticorpi IgG anti-Spike negativi) e che presentano almeno uno dei seguenti fattori di rischio:*
  - *Pazienti che abbiano assunto nell'ultimo anno terapie che comportano deplezione dei linfociti B (ad es. rituximab, ocrelizumab, ofatumumab, alemtuzumab)*
  - *Pazienti in trattamento con inibitori della tirosin-chinasi Bruton*
  - *Pazienti trattati con CarT*
  - *Pazienti trapiantati di cellule ematopoietiche che hanno una malattia di rigetto o che stanno assumendo farmaci immunosoppressori*
  - *Pazienti con malattia onco-ematologica in fase attiva*
  - *Pazienti trapiantati di polmone*
  - *Pazienti trapiantati di organo solido (diverso dal trapianto di polmone) entro 1 anno dal trapianto*
  - *Pazienti trapiantati di organi solidi con recente trattamento per rigetto acuto con agenti che riducono le cellule T o B*
  - *Pazienti con immunodeficienze combinate gravi*
  - *Pazienti con infezione da HIV non in trattamento e una conta dei linfociti T CD4 <50 cellule/mm3*
  - *pazienti con altra compromissione del sistema immunitario che ha determinato mancata sieroconversione.*

AIFA AGENZIA ITALIANA DEL FARMACO

FDA autorizza il nuovo dosaggio di Evusheld (tixagevimab in confezione con cilgavimab)

24 febbraio 2022. FDA authorizes revisions to Evusheld dosing (tixagevimab co-packaged with cilgavimab)

La Food and Drug Administration statunitense ha rivisto l'autorizzazione all'uso di emergenza di Evusheld (tixagevimab in confezione con cilgavimab) per modificare la dose iniziale come profilassi pre-esposizione (prevenzione) a COVID-19 in alcuni adulti e pazienti pediatrici.

Sulla base delle informazioni e dei dati più recenti disponibili, Evusheld potrebbe essere meno attivo contro alcune sottovarianti di Omicron. Il regime di dosaggio è stato rivisto perché i dati disponibili indicano che una dose più elevata di Evusheld può prevenire l'infezione da parte delle sottovarianti COVID-19 Omicron BA.1 e BA.1.1 rispetto alla dose di Evusheld originariamente autorizzata. In precedenza, il dosaggio autorizzato di Evusheld era di 150 mg di tixagevimab + 150 mg di cilgavimab somministrati come due iniezioni intramuscolari consecutive separate, con dosi ripetute ogni sei mesi mentre SARS-CoV-2 rimane in circolazione. Con questa revisione, la FDA ha aumentato la dose iniziale autorizzata a 300 mg di tixagevimab + 300 mg di cilgavimab.

Tixagevimab/Cilgavimab: viral variant

- The complementary binding of tixagevimab and cilgavimab to distinct regions of the viral spike protein receptor-binding domain presents a barrier to virus escape
- *In vitro* studies have shown that AZD7442 retain some neutralizing activity against the BA.1 subvariant of the Omicron variant, with neutralizing activity reduced by a factor of 12 to 30 in live virus
- Emerging evidence suggests that the neutralizing activity of AZD7442 against the BA.2 subvariant is only minimally lower than that against the wild-type virus (lower by a factor of 5 in live-virus assays and by a factor of 3 in pseudovirus assays)
- In February 2022, the FDA recommended an increase in the dose of AZD7442 to 600 mg because of the emergence of the BA.1 subvariant; recommendations for repeat dosing intervals have yet to be confirmed, pending further data.

Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

In vitro activity of therapeutic antibodies against SARS-CoV-2 Omicron BA.1 and BA.2

Franck Touret (franck.touret@univ-amu.fr)

The neutralising activity of Tixagevimab is very low against both BA.1 and BA.2 (EC_{50} >5000 ng/L, see Table 1). In contrast, Cilgavimab regains neutralizing power against BA.2 with an EC_{50} increasing only from 32.8 (B.1) to 49.8 ng/mL (BA.2), which represents a very limited loss of neutralising activity (B.1/BA.2 ratio: ~1.5, Table 1). In comparison, a 49-fold B.1/BA.1 reduction in neutralisation activity was observed with this monoclonal antibody. In short, this indicates that Cilgavimab exhibited 32-fold greater activity against BA.2 compared to BA.1 in our assays. This could be due to the absence in the BA.2 RBD of the G446S mutation, which is located in a region identified as critical for Cilgavimab neutralising activity[4]. When Cilgavimab was tested in combination with Tixagevimab, as proposed in the Evusheld therapeutic cocktail[12], the EC_{50} shifted from 27 (B.1) to 73.3 ng/mL (BA.2), *i.e.* a 2.7-fold decrease in neutralisation activity when comparing BA.2 with B.1, but a 10-fold increase when comparing BA.2 with BA.1 (Table 1). This is in line with results recently produced using spike protein-pseudotyped lentiviruses[13,14].

Future options

- Cross resistance would not be expected between nirmatrelvir, molnupiravir, monoclonal antibodies, or remdesivir based upon different mechanisms of action.
- Combination of different treatments (antivirals or monoclonal antibodies) are not recommended

- New oral antiviral treatments: AT-527
- Sotrovimab: higher doses or intramuscolar injection?
- VIR-73832
- BRII-196 + BRII-198

AT-527

Seeking to combat COVID-19 with an oral RNA viral polymerase inhibitor.

Leveraging our purine nucleotide prodrug platform, we are developing AT-527 – an orally administered, direct-acting antiviral drug candidate for the treatment of patients with COVID-19. AT-527 is designed to inhibit viral replication by interfering with viral RNA polymerase, a key component in the replication machinery of enveloped positive single-stranded RNA viruses, such as human flaviviruses and human coronaviruses.

ARTICLE

https://doi.org/10.1038/s41467-022-28113-1 OPEN

A dual mechanism of action of AT-527 against SARS-CoV-2 polymerase

Ashleigh Shannon[1], Véronique Fattorini[1], Bhawna Sama[1], Barbara Selisko[1], Mikael Feracci[1], Camille Falcou[1], Pierre Gauffre[1], Priscila El Kazzi[1], Adrien Delpal[1], Etienne Decroly[1], Karine Alvarez[1], Cécilia Eydoux[1], Jean-Claude Guillemot[1], Adel Moussa[2], Steven S. Good[2], Paolo La Colla[3], Kai Lin[2], Jean-Pierre Sommadossi[2], Yingxiao Zhu[4], Xiaodong Yan[4], Hui Shi[4], François Ferron[1,5] & Bruno Canard[1,5]✉

19 ottobre 2021 - 15:04

(Keystone-ATS) Battuta d'arresto inaspettata per AT-527, la cosiddetta pillola anti-Covid sviluppata dalla società americana Atea Pharmaceuticals, partner della svizzera Roche.

Il preparato antivirale non ha soddisfatto gli obiettivi di uno studio di fase II su pazienti che presentavano una forma moderata della malattia.

Il trattamento con AT-527 non ha raggiunto il traguardo primario, in quanto i pazienti non hanno mostrato una riduzione significativa della carica virale del coronavirus rispetto a coloro che hanno ricevuto un placebo, ha indicato oggi Atea.

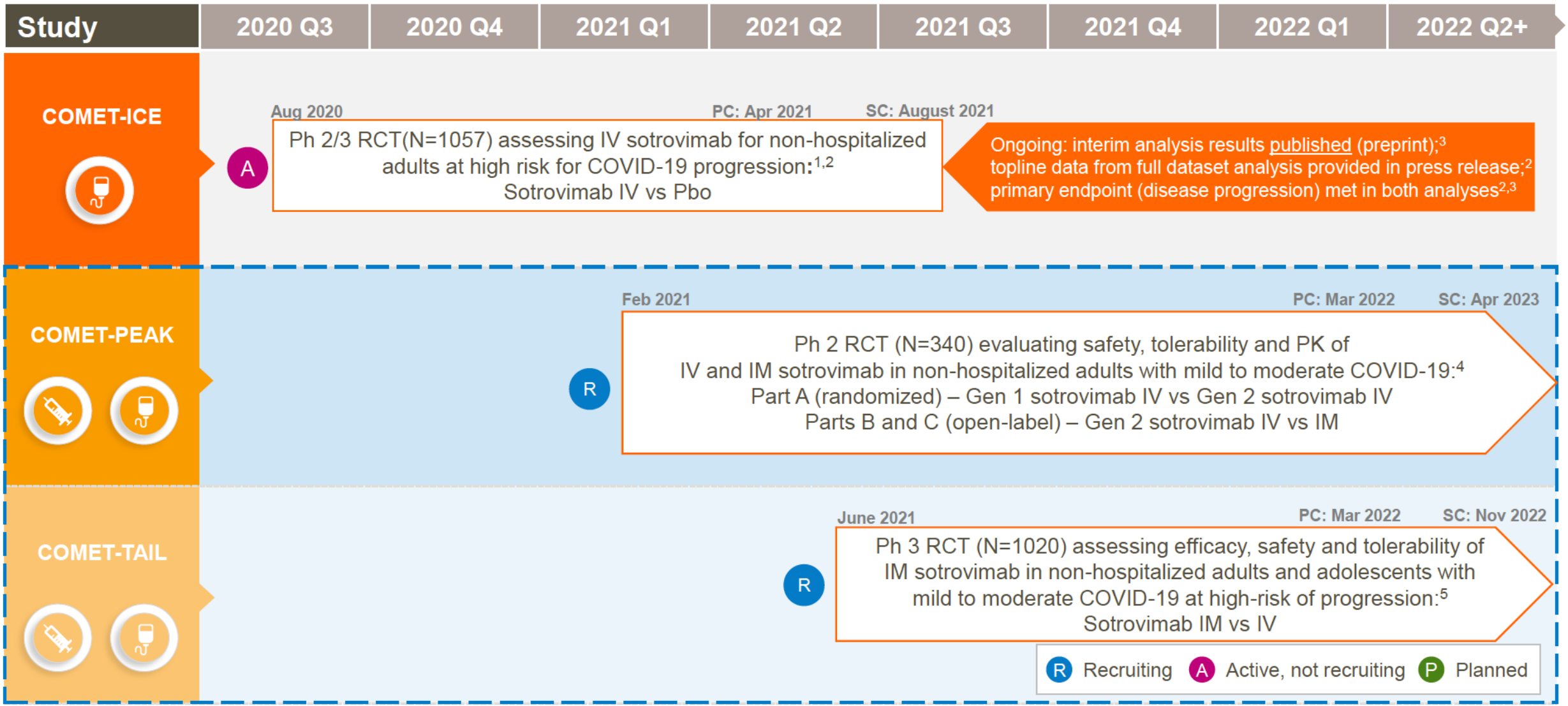
Roche e Atea ora rivedranno congiuntamente i potenziali cambiamenti alla sperimentazione globale di fase III. I dati di questo programma saranno disponibili solo nella seconda parte del 2022.

It is now in phase III and II clinical trials for the treatment of COVID-19 and hepatitis C virus (HCV) infections, respectively (**www.clinicaltrials.gov/ct2/**).

1	☐	Terminated	Study to Evaluate the Effects of RO7496998 (**AT-527**) in Non-Hospitalized Adult and Adolescent Participants With Mild or Moderate **COVID-19**	• **COVID-19**	• Drug: RO7496998 • Drug: Placebo	• Instituto Medico Rio Cuarto Cordoba, Argentina • Instituto Ave Pulmo Mar Del Plata, Argentina • Clínica Independencia Munro, Argentina • (and 94 more...)
2	☐	Completed	Study to Evaluate the Effects of **AT-527** in Non-Hospitalized Adult Patients With Mild or Moderate **COVID-19**	• **COVID-19**	• Drug: **AT-527** • Drug: Placebo	• Multiprofile Hospital for Active Treatment Puls AD PPDS Blagoevgrad, Bulgaria • Multiprofile Hospital For Active Treatment Dr. Tota Venkova JSC Gabrovo, Bulgaria • MHAT Dr. Atanas Dafovski AD Kardzhali, Bulgaria • (and 40 more...)
3	☐	Recruiting	Safety and Efficacy of **AT-527** in Subjects With Moderate Coronavirus Disease (**COVID-19**) in a Hospital Setting	• **COVID-19**	• Drug: **AT-527** • Other: Placebo	• Atea Study Site Scottsdale, Arizona, United States • Atea Study Site Davis, California, United States • Atea Study Site Los Angeles, California, United States • (and 34 more...)
4	☐	Completed	A Six-Month Follow-Up Study of Participants With **Coronavirus Disease 2019** (**COVID-19**) Previously Enrolled in a RO7496998 (**AT-527**) Study	• **COVID-19** • Long **COVID**		• Instituto Ave Pulmo Mar Del Plata, Argentina

COMET-PEAK and COMET-TAIL: Investigating IM sotrovimab

For more information see 'Deck 5'
NX-GBL-SOT-PPT-210014



IM, intramuscular; IV, intravenous; Pbo, placebo; PC, primary completion; Ph, phase; PK, pharmacokinetics; RCT, randomized controlled trial; SC, study completion.

1. ClinicalTrials.gov, NCT04545060 (accessed August 05, 2021); 2. GSK, Press Release June 21, 2021 (accessed August 05, 2021); 3. Gupta A, et al. *MedRxiv* (preprint). doi:10.1101/2021.05.27.21257096; 4. ClinicalTrials.gov, NCT04779879 (accessed August 05, 2021); 5. ClinicalTrials.gov. NCT04913675 (accessed August 05, 2021).

Safety data related to doses of sotrovimab higher than 500mg

Sotrovimab is an engineered human monoclonal that acts against an exogenous viral target[1]

- As a class, anti-SARS-CoV-2 mAbs have demonstrated a consistent safety profile in studies evaluating higher doses[2–4]

To date, there are no clinical data for higher doses of IV-administered sotrovimab in the licensed population[5]

Preclinical data[1,6]

- No adverse, drug-related findings were observed up to the highest dose tested (500mg/kg/week) in a 2-week repeat, IV-dose toxicology study in cynomolgus monkeys

Clinical data[1,5]

- To date, safety data from the clinical program (500mg IV dose) have demonstrated a low rate of AEs (including SAEs and Grade 3–4 AEs)

A 1000mg IV dose of sotrovimab is currently being explored in the RECOVERY UK platform trial (hospitalized patients with COVID-19; sotrovimab n=358)[5,7]

- As of March 21, 2022, one SAE has been reported in the sotrovimab arm;[5] no trial changes were recommended by the public DMC[5,*]

*As of March 04, 2022; SAE was noted as a suspected allergic reaction.[1]

AE, adverse event; DMC, data monitoring committee; IV, intravenous; mAb, monoclonal antibody; SAE, severe adverse event. [See notes for references].

This Document Contains GSK Proprietary Information – Not For Onward Distribution

Vir Biotechnology and GSK announce NHS-supported AGILE study to evaluate VIR-7832 in the early treatment of COVID-19

Vir Biotechnology, Inc. (Nasdaq: VIR) and GlaxoSmithKline plc (LSE/NYSE: GSK) today announced an agreement with the U.K.-based AGILE initiative to evaluate VIR-7832 in patients with mild to moderate COVID-19 in a Phase 1b/2a clinical trial. VIR-7832 is a neutralising COVID-19 antibody that preclinical data suggests has two distinguishing properties: an enhanced ability to clear infected cells and the potential to enhance virus-specific T cell function, which could help treat and/or prevent COVID-19 infection.

VIR-7832

About VIR-7832 / GSK4182137

VIR-7832 is a dual-action monoclonal antibody. Preclinical data suggest it has the potential to both block viral entry into healthy cells and an enhanced ability to clear infected cells. The antibody binds to an epitope on SARS-CoV-2 that is shared with SARS-CoV-1 (the virus which causes SARS), indicating that the epitope is highly conserved, which may make it more difficult for resistance to develop. VIR-7832 also has been designed to achieve high concentration in the lungs to ensure optimal penetration into airway tissues affected by SARS-CoV-2 and to have an extended half-life. Importantly, VIR-7832, has been engineered to potentially enhance virus-specific T cell function, which could help treat and/or prevent COVID-19 infection.

Efficacy and safety of two neutralising monoclonal antibody therapies, sotrovimab and BRII-196 plus BRII-198, for adults hospitalised with COVID-19 (TICO): a randomised controlled trial

ACTIV-3/Therapeutics for Inpatients with COVID-19 (TICO) Study Group†*

function.[14,15] BRII-196 and BRII-198 are two monoclonal antibodies isolated from COVID-19 survivors that bind distinct and complementary epitopes of the SARS-CoV-2 spike protein.[16] The Fc regions of BRII-196 and BRII-198 are engineered with triple amino acid modifications (Met252Tyr, Ser254Thr, and Thr256Glu) to extend half-life and reduce the binding affinity to Fc-γ receptors with the goal of reducing the potential for antibody-dependent enhancement.

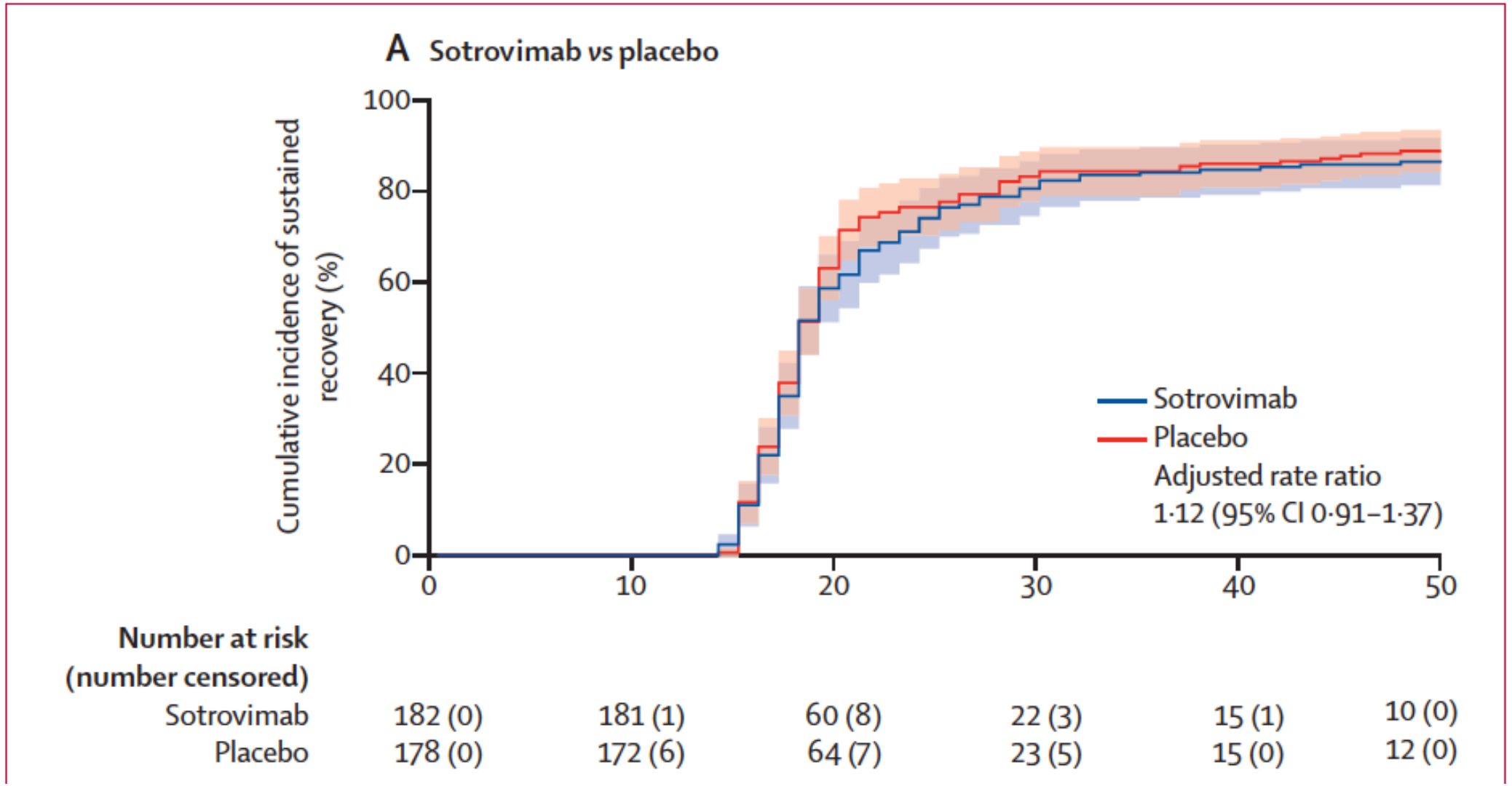
Lancet Infect Dis 2022; 22: 622–35

Study population

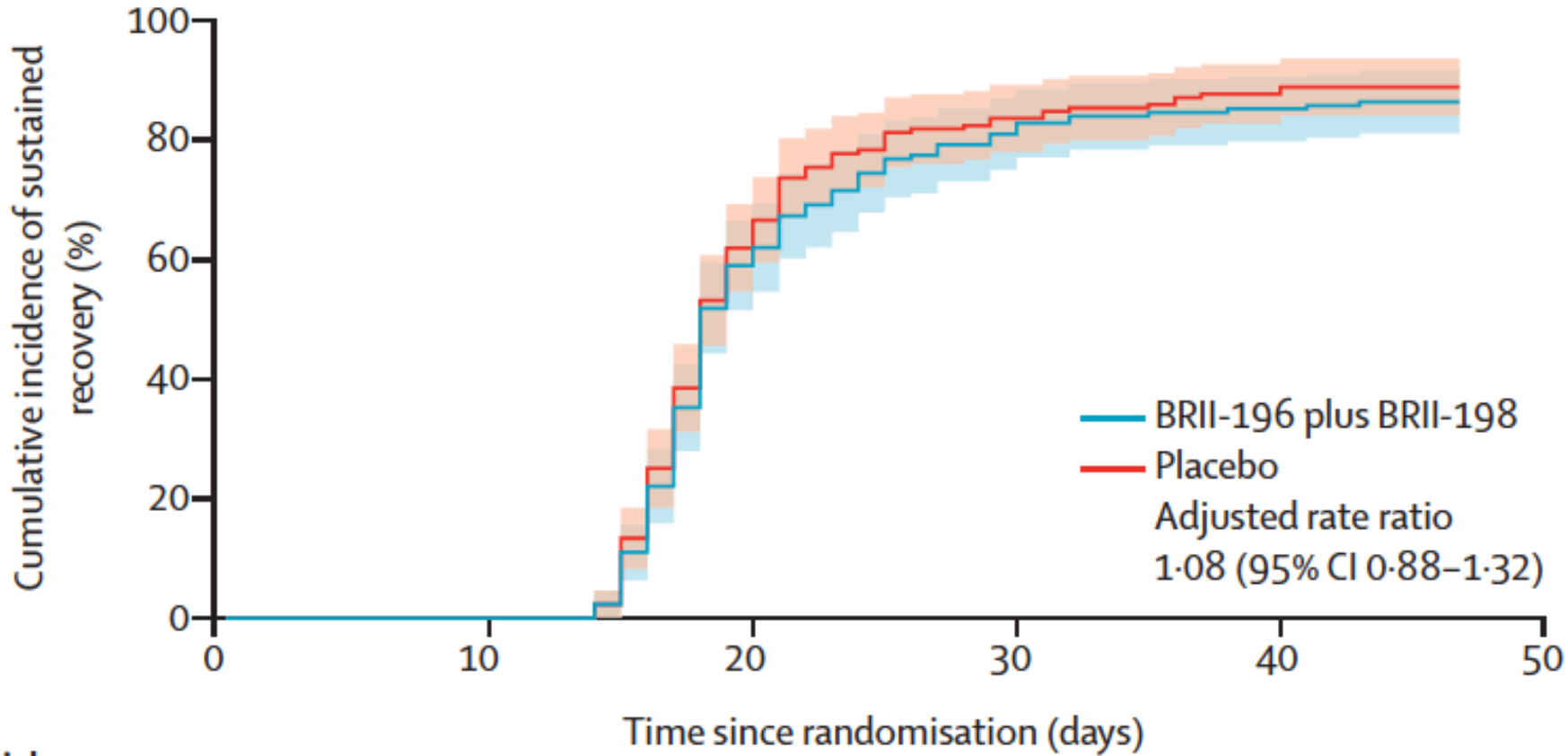
Methods In this multinational, double-blind, randomised, placebo-controlled, clinical trial (Therapeutics for Inpatients with COVID-19 [TICO]), adults (aged ≥18 years) hospitalised with COVID-19 at 43 hospitals in the USA, Denmark, Switzerland, and Poland were recruited. Patients were eligible if they had laboratory-confirmed SARS-CoV-2 infection and COVID-19 symptoms for up to 12 days. Using a web-based application, participants were randomly assigned (2:1:2:1), stratified by trial site pharmacy, to sotrovimab 500 mg, matching placebo for sotrovimab, BRII-196 1000 mg plus BRII-198 1000 mg, or matching placebo for BRII-196 plus BRII-198, in addition to standard of care. Each study

	Sotrovimab group (n=182)	Placebo group (n=178)*	BRII-196 plus BRII-198 group (n=176)
Age, years	61 (50–74)	60 (49–70)	61 (50–71)
Sex			
Female	75 (41%)	75 (42%)	78 (44%)
Male	107 (59%)	103 (58%)	98 (56%)
Race or ethnicity†			
Asian	7 (4%)	9 (5%)	12 (7%)
Non-Hispanic Black	40 (22%)	37 (21%)	37 (21%)
Hispanic	30 (16%)	32 (18%)	34 (19%)
Non-Hispanic White	101 (55%)	92 (52%)	87 (49%)
Other	4 (2%)	8 (4%)	6 (3%)
Body-mass index category			
≥30 kg/m² (obese)	102 (56%)	99 (56%)	90 (51%)
≥40 kg/m² (severely obese)	31 (17%)	25 (14%)	26 (15%)
Co-existing chronic illness			
Any	134 (74%)	136 (76%)	133 (76%)
Hypertension treated with medication	103 (57%)	104 (58%)	97 (55%)
Diabetes treated with medication	71 (39%)	62 (35%)	59 (3%)
Renal impairment	27 (15%)	19 (11%)	13 (7%)
Asthma	19 (10%)	17 (10%)	23 (13%)
Heart failure	13 (7%)	8 (4%)	15 (9%)
Chronic supplemental oxygen use before COVID-19	2 (1%)	5 (3%)	4 (2%)

	Sotrovimab group (n=182)	Placebo group (n=178)*	BRII-196 plus BRII-198 group (n=176)
Previous receipt of ≥1 dose of a COVID-19 vaccine	15 (8%)	10 (6%)	16 (9%)
Time since symptom onset, days	8 (5–9)	8 (5–9)	8 (6–9)
Medication use before randomisation			
Remdesivir	120 (66%)	112 (63%)	108 (61%)
Antibacterial agent	46 (2%)	54 (30%)	42 (24%)
Corticosteroid	109 (60%)	120 (67%)	98 (56%)
Therapeutic anticoagulation‡	25 (14%)	16 (9%)	18 (10%)
Prophylactic or intermediate anticoagulation	122 (67%)	126 (71%)	115 (65%)
Pulmonary ordinal scale category§			
Category 2: unable to do usual activities and no supplemental oxygen	64 (35%)	52 (29%)	60 (34%)
Category 3: supplemental oxygen <4 L/min	76 (42%)	80 (45%)	74 (42%)
Category 4: supplemental oxygen ≥4 L/min	42 (23%)	46 (26%)	42 (24%)
Neutralising anti-spike antibody positive	68/173 (39%)	76/171 (44%)	68/169 (40%)
Anti-nucleocapsid antibody positive	100/173 (58%)	108/171 (63%)	104/169 (62%)
Negative on both anti-nucleocapsid and neutralising anti-spike antibody assays	67/173 (39%)	54/171 (32%)	57/169 (34%)
Nucleocapsid antigen concentration >1450 pg/mL	84/173 (49%)	80/171 (47%)	82/169 (49%)


A Sotrovimab vs placebo
Cumulative incidence of sustained recovery (%)
100
80
60
40
20
0
0
10
20
30
40
50
Sotrovimab
Placebo
Adjusted rate ratio
1·12 (95% CI 0·91–1·37)
Number at risk (number censored)
Sotrovimab 182 (0) 181 (1) 60 (8) 22 (3) 15 (1) 10 (0)
Placebo 178 (0) 172 (6) 64 (7) 23 (5) 15 (0) 12 (0)

B BRII-196 plus BRII-198 *vs* placebo



Number at risk (number censored)						
BRII-196 plus BRII-198	176 (0)	172 (4)	60 (6)	19 (4)	11 (1)	9 (0)
Placebo	177 (0)	171 (6)	63 (7)	22 (5)	14 (0)	11 (0)

	Sotrovimab group (n=182)	Placebo group (n=178)*	BRII-196 plus BRII-198 group (n=176)	Sotrovimab *vs* placebo†		BRII-196 plus BRII-198 *vs* placebo†	
				Point estimate (95% CI)	p value	Point estimate (95% CI)	p value
Efficacy outcomes							
Pulmonary ordinal outcome scale at day 5 (futility assessment)	..	..	..	aOR 1·07 (0·74–1·56)‡	0·72	aOR 0·98 (0·67–1·43)‡	0·91
Category 1: can independently do usual activities	42/181 (23%)	40/178 (22%)	44/173 (25%)	..	..	..	..
Category 2: no supplemental oxygen; symptomatic and unable to do usual activities	66/181 (36%)	58/178 (33%)	58/173 (34%)	..	..	..	..
Category 3: supplemental oxygen <4 L/min	42/181 (23%)	42/178 (24%)	33/173 (19%)	..	..	..	..
Category 4: supplemental oxygen ≥4 L/min	19/181 (10%)	20/178 (11%)	18/173 (10%)	..	..	..	..
Category 5: high-flow nasal canula or non-invasive ventilation	10/181 (6%)	14/178 (8%)	15/173 (9%)	..	..	..	..
Category 6: invasive ventilation, ECMO, mechanical circulatory support, or RRT	2/181 (1%)	3/178 (2%)	4/173 (2%)	..	..	..	..
Category 7: death	0/181 (0%)	1/178 (1%)	1/173 (1%)	..	..	..	..

Conclusions

In conclusion, in this multinational, double-blind, effect in the BRII-196 plus BRII-198 group by baseline endogenous neutralising antibody status, suggesting potential opportunity for monoclonal antibody therapies to be targeted to patients hospitalised with COVID-19 who have not developed endogenous antibodies.

Covid, ricadute dopo il Paxlovid: casi sotto osservazione negli Usa

Il virus riprende forza dopo che i pazienti hanno concluso il ciclo di 5 giorni previsto per l'antivirale Pfizer

Non sono ancora quantificabili statisticamente ma sono **sotto osservazione alcuni casi** di **ricadute nel Covid** di pazienti che hanno preso **Paxlovid,** l'antivirale della Pfizer. Sscienziati della **Food and drug administration (Fda) Usa,** dei Centri per il controllo e la prevenzione delle malattie (Cdc) e della stessa azienda produttrice hanno iniziato ad indagare **le cause e la frequenza** della ripresa della malattia.

Secondo la **Pfizer,** si tratterebbe di casi rari che rispecchiano la stessa frequenza di ricadute osservata nei trial in pazienti che avevano preso un placebo. Tuttavia le segnalazioni sono in aumento: la Fda ha voluto sottolineare che i rapporti di una riattivazione virale negli stessi pazienti che dopo la malattia erano risultati negativi "non cambiano le conclusioni raggiunte nei trial sugli effetti di Paxlovid, che continua a dimostrare una riduzione significativa nei ricoveri e nei decessi" dei malati che assumono l'antivirale.

Opinion: Rebound after taking Paxlovid is the latest twist in the Covid-19 puzzle

Opinion by Kent Sepkowitz

Updated 0040 GMT (0840 HKT) May 11, 2022



What is clear is that the hope for a game changer from this particular drug is overly optimistic. Add viral rebound to the list of concerns already raised about the drug: the many drug-drug interactions, frequent appearance of a metallic taste in the mouth and its failure to prevent infection among uninfected close contacts (usually the easiest task for an antiviral). Plus, its efficacy has been shown only in the unvaccinated. Now comes an unexpected and still poorly understood new phenomenon that may create additional public health confusion regarding contagiousness.

FDA U.S. FOOD & DRUG ADMINISTRATION

What do we know about the case reports of patients developing symptoms again after completing a course of Paxlovid?

FDA is aware of the reports of some patients developing recurrent COVID-19 symptoms after completing a treatment course of Paxlovid. In some of these cases, patients tested negative on a direct SARS-CoV-2 viral test and then tested positive again.

The benefit of a 5-day treatment course of Paxlovid was demonstrated in the clinical trial that supported the EUA. This study showed that among non-hospitalized patients at high risk of progression to severe disease, treatment with Paxlovid reduced the risk of hospitalization or death by 88%. Reductions in hospitalization and death were also demonstrated in clinical trials of other available approved (Veklury [remdesivir]) or authorized (Lagevrio [molnupiravir]) antiviral agents.

In light of these reports, additional analyses of the Paxlovid clinical trial data have been performed. In the Paxlovid clinical trial, some patients (range 1-2%) had one or more positive SARS-CoV-2 PCR tests after testing negative, or an increase in the amount of SARS-CoV-2 detected by PCR, after completing their treatment course. This finding was observed in patients treated with the drug as well as patients who received placebo, so it is unclear at this point that this is related to drug treatment. Additional analyses show that most of the patients did not have symptoms at the time of a positive PCR test after testing negative, and, most importantly, there was no increased occurrence of hospitalization or death or development of drug resistance.

These reports, then, do not change the conclusions from the Paxlovid clinical trial which demonstrated a marked reduction in hospitalization and death.

We are continuing to review data from clinical trials and will provide additional information as it becomes available. However, there is no evidence of benefit at this time for a longer course of treatment (e.g., 10 days rather than the 5 days recommended in the Provider Fact Sheet for Paxlovid) or repeating a treatment course of Paxlovid in patients with recurrent COVID-19 symptoms following completion of a treatment course.

In summary, Paxlovid reduces the risk of hospitalization and death for patients with mild-to-moderate COVID-19 at high risk of disease progression. Health care providers should consider treatment with Paxlovid or other approved or authorized therapeutics in accordance with the approved labeling or authorized Health Care Provider Fact Sheets. Patients who test positive for SARS-CoV-2 who have symptoms should discuss treatment options with their health care provider as soon as possible after testing positive. Health care providers and patients should refer to CDC recommendations regarding patient isolation, *and* should wear a mask and isolate if they have any symptoms regardless of whether or not they have been treated with an antiviral agent.

Conclusioni

- ✓Chi dovrebbe essere candidato al trattamento?

  mancano dati su pazienti VACCINATI

- ✓Dose ottimale in corso di VOC?

  Sotrovimab 500 mg / 1000 mg

  Evusheld 300 mg / 600 mg

- ✓In che fase di malattia?

  severi/critici; > 10 giorni di trattamento

- ✓Durata della protezione post mAbs neutralizzanti?

  non dati emivita mAbs in vivo

Conclusioni

- ✓VOC: ridotta capacità neutralizzante verso Omicron BA.2, BA.3, BA.4, BA.5?
- ✓La terapia accelera il tempo alla guarigione virologica?
- ✓Gravidanza/età pediatrica
- ✓Farmacovigilanza Molnupiravir

GRAZIE PER L'ATTENZIONE