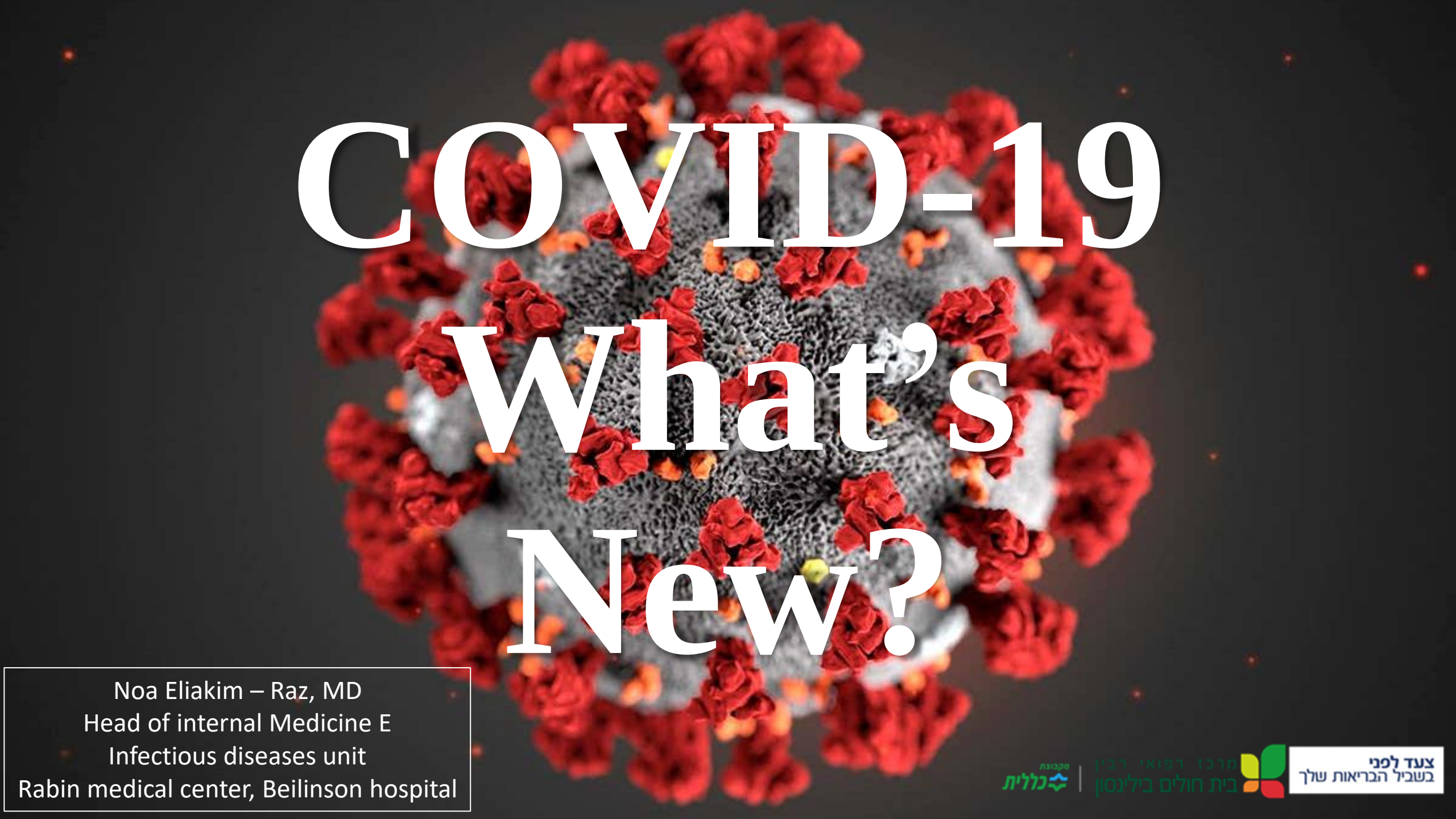


COVID-19 What's New?

Noa Eliakim – Raz, MD
Head of internal Medicine E
Infectious diseases unit
Rabin medical center, Beilinson hospital

פנימית ה ' קורונה
בילינסון

צעד לפני
בשביל הבריאות שלך

מרכז רפואי רבין
בית חולים בילינסון

מקבוצת כללית

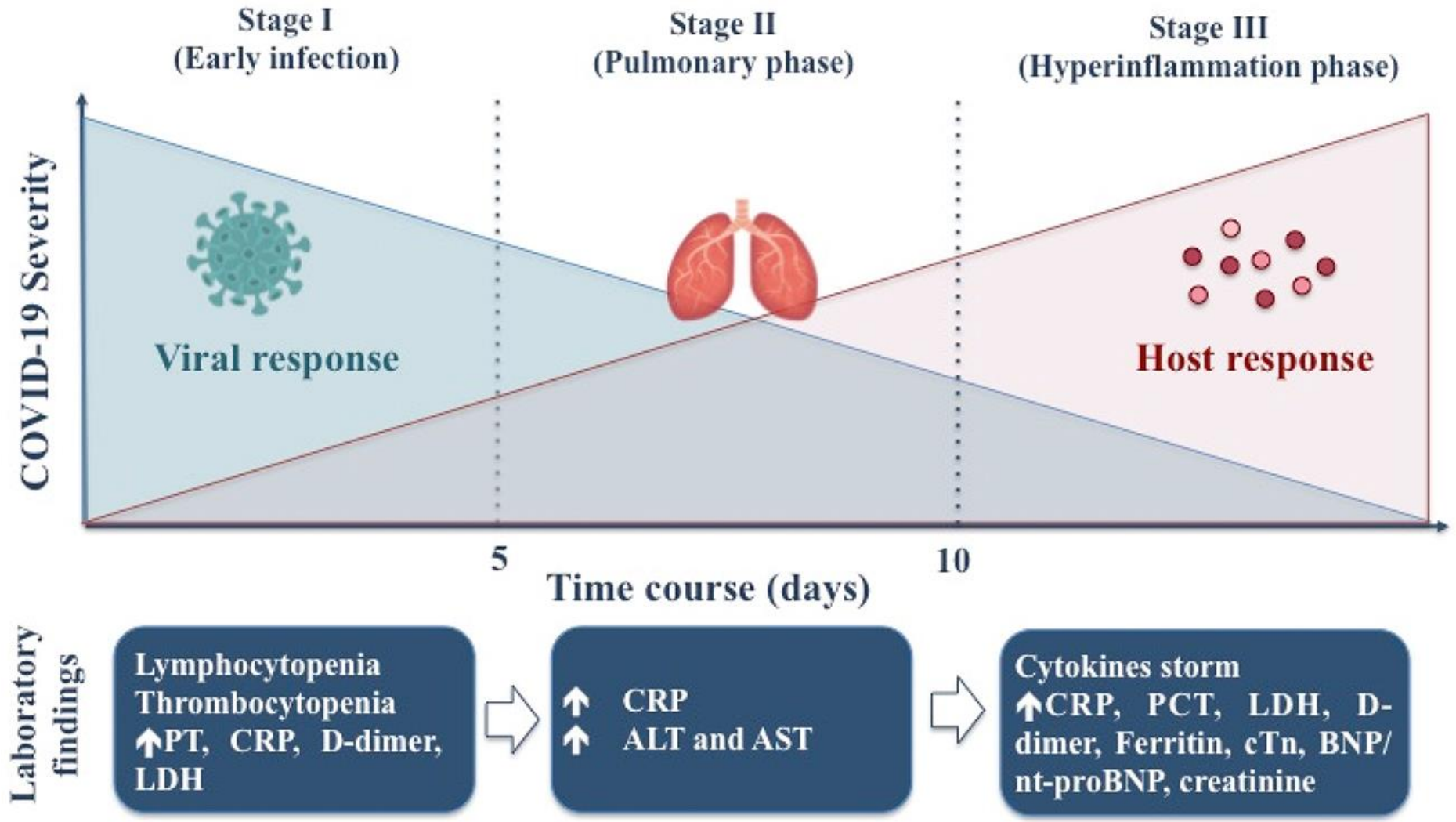
כ' בתמוז, התש"פ
12 יולי 2020
אסמכתא: 294754420

ההגדרה הנוכחית מבוססת על ההגדרות מטעם ה-NIH[1], ה- WHO[2] ומאמרי סקירה בעיתונים מ
הגדרה זו נידונה ואושרה על ידי הצוות לטיפול מגיפות (הצט"מ). להלן ההגדרות:

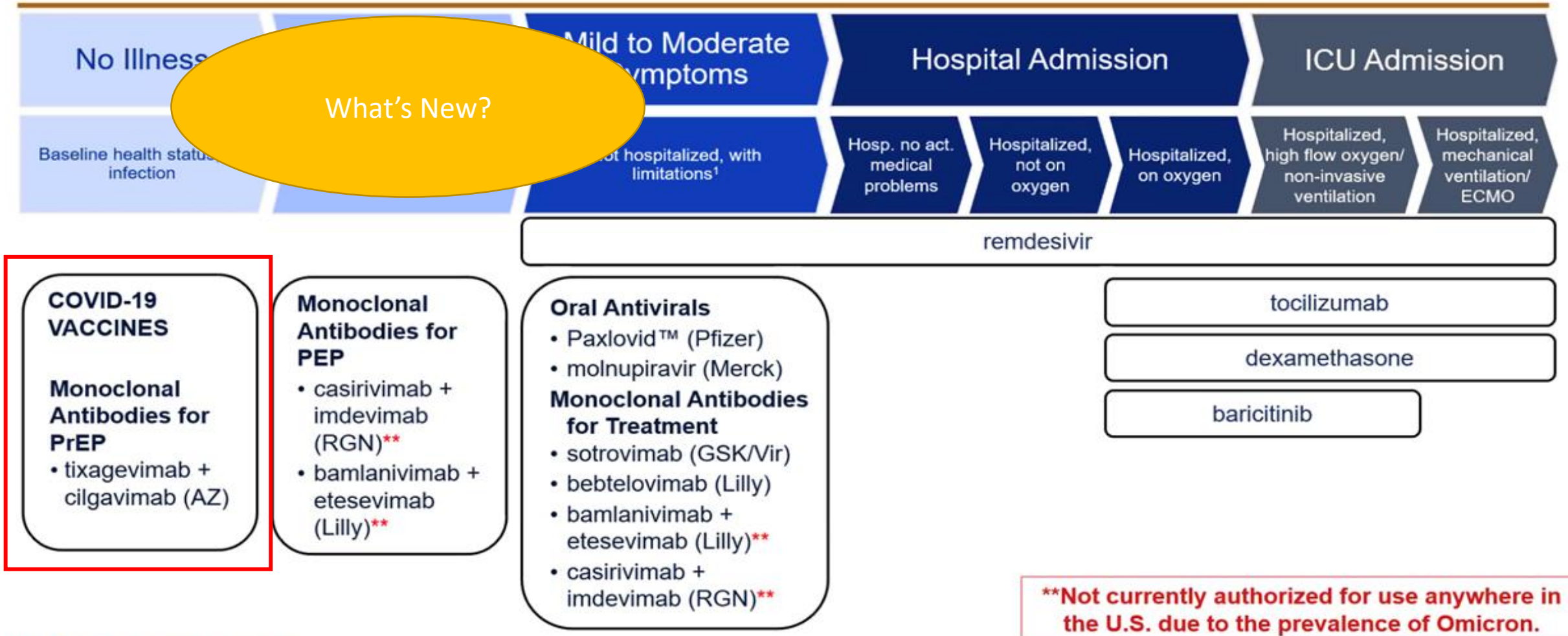
מצב המטופל	הגדרת המצב
קל	סימפטומים עם COVID 19 (נוכחות של חום, שיעול, חולשה, אובדן טעם וריח וכדומה).
בינוני	אבחנה קלינית או רנטגנית של COVID-19 Pneumonia.
קשה	COVID-19 ואחד מהקריטריונים הבאים: 1. נשימות של מעל 30 לדקה. 2. ריווי חמצן בדם של 93% ומטה ללא תמיכה בחמצן*. 3. יחס PaO2/FiO2 נמוך מ- 300.
מונשם/קריטי	1. חולה הזקוק לתמיכה מכנית נשימתית פולשנית או לא פולשנית. 2. פגיעה **קשה** בתפקוד מערכתי: הלם, פגיעה לבבית, פגיעה כבדית, פגיעה כלייתית.

*בסעיף 2 בהגדרת חולה קשה - יש לסייג חולה ריאה כרוני (COPD) הסובל מהיפוקסמיה קבועה – לגביו תיקבע החומרה על פי קצב הנשימות והערכה הקלינית של הרופא המטפל.

COVID-19 infection

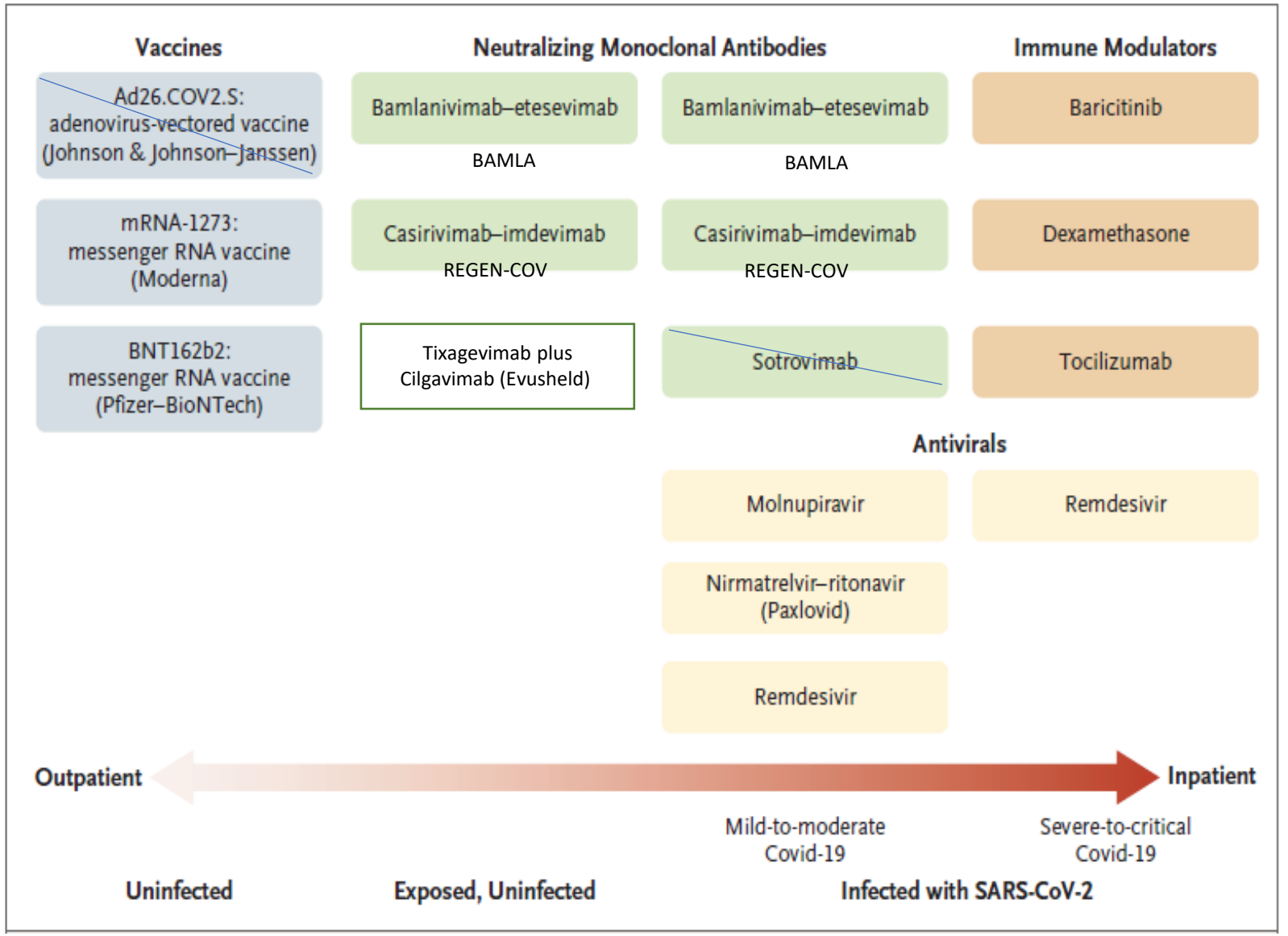


COVID-19: *Preventative Agents & Therapeutics*



**Not currently authorized for use anywhere in the U.S. due to the prevalence of Omicron.

[1] NIH COVID-19 Treatment Guidelines https://www.covid19treatmentguidelines.nih.gov/about-the-guidelines/whats-new/
Therapeutic Management of Nonhospitalized Adults With COVID-19 https://www.covid19treatmentguidelines.nih.gov/management/clinical-management/nonhospitalized-adults--therapeutic-management/



N Engl J Med. 2021 Dec 22 : NEJMe2118579

Article

Considerable escape of SARS-CoV-2 Omicron to antibody neutralization

Nature | Vol 602 | 24 February 2022 |

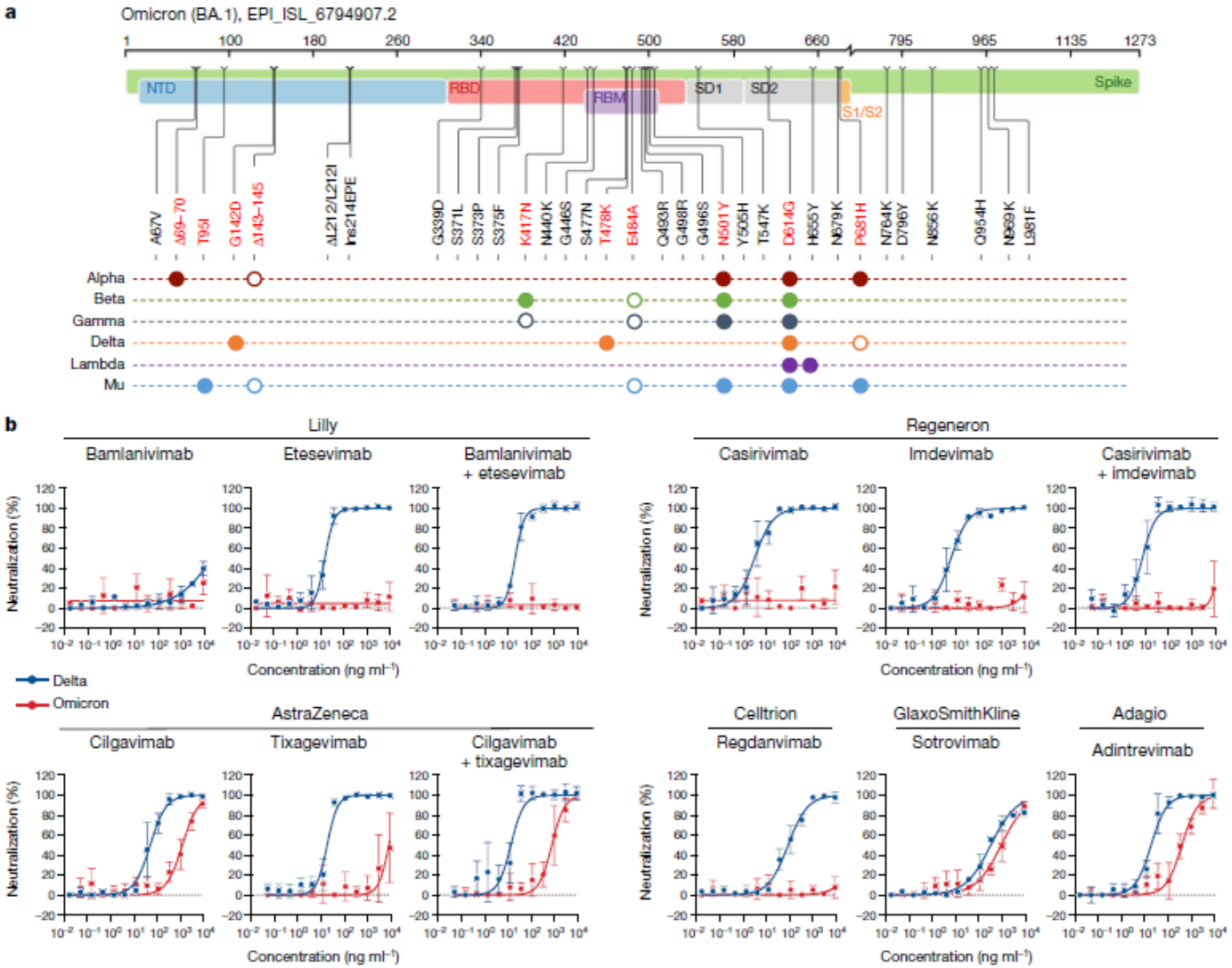
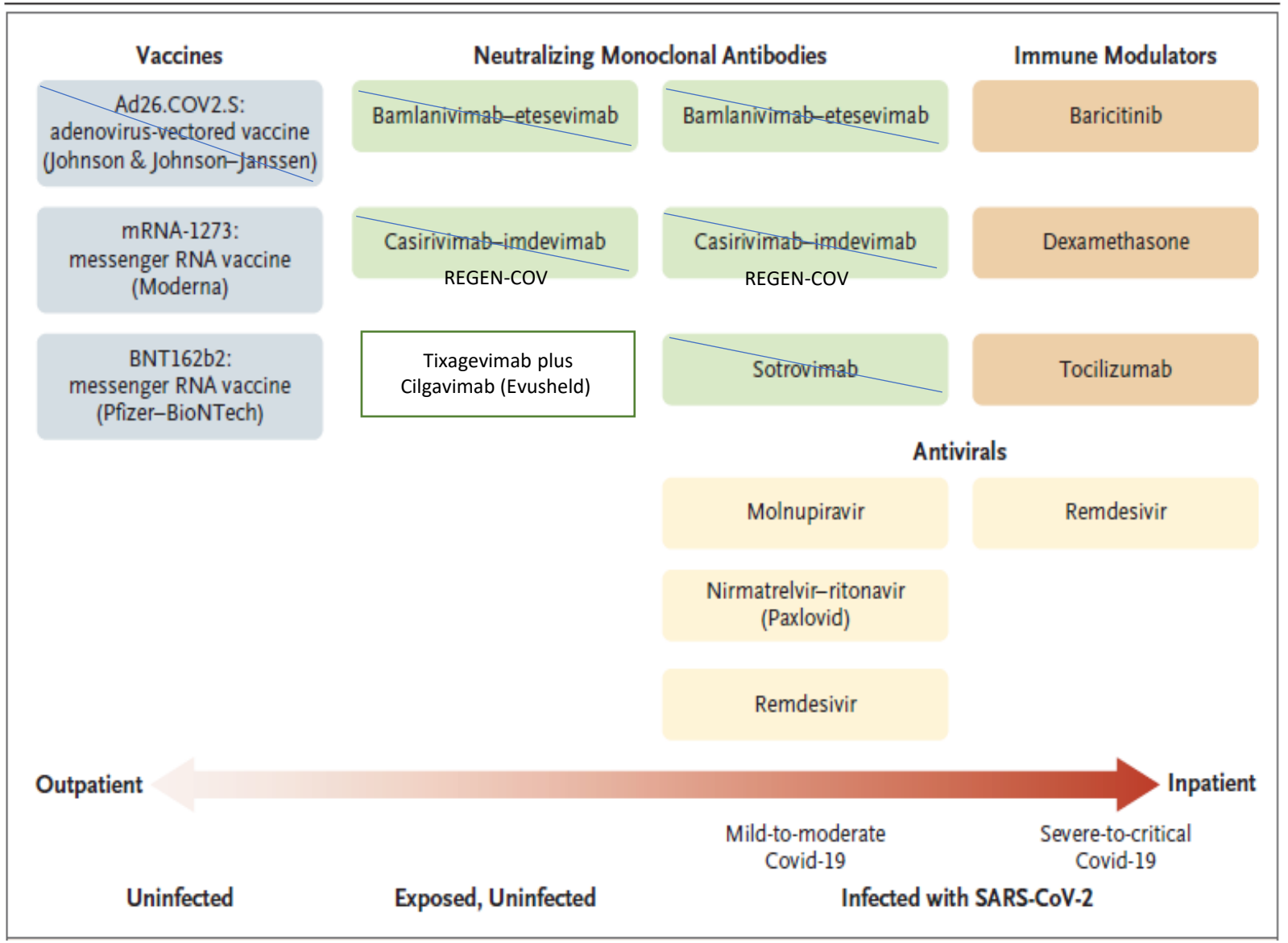


Fig. 1 | Neutralization of SARS-CoV-2 variants Delta and Omicron by clinical and preclinical monoclonal antibodies. a, The mutational landscape of the

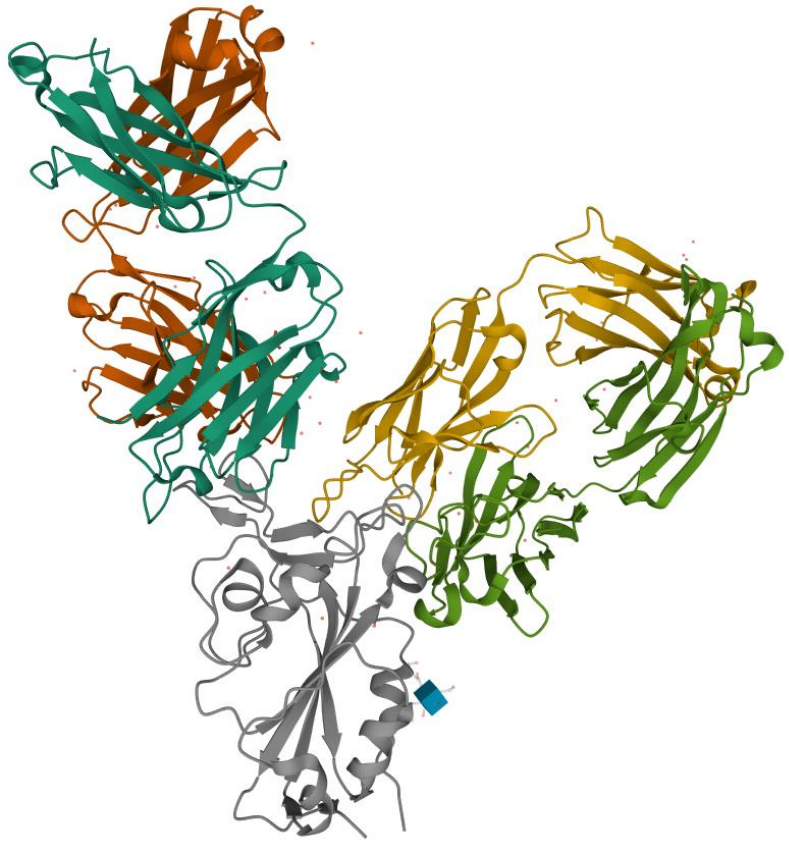
Dose–response analysis of the neutralization by clinical or preclinical monoclonal antibodies (bamlanivimab, etesevimab, casirivimab, imdevimab,



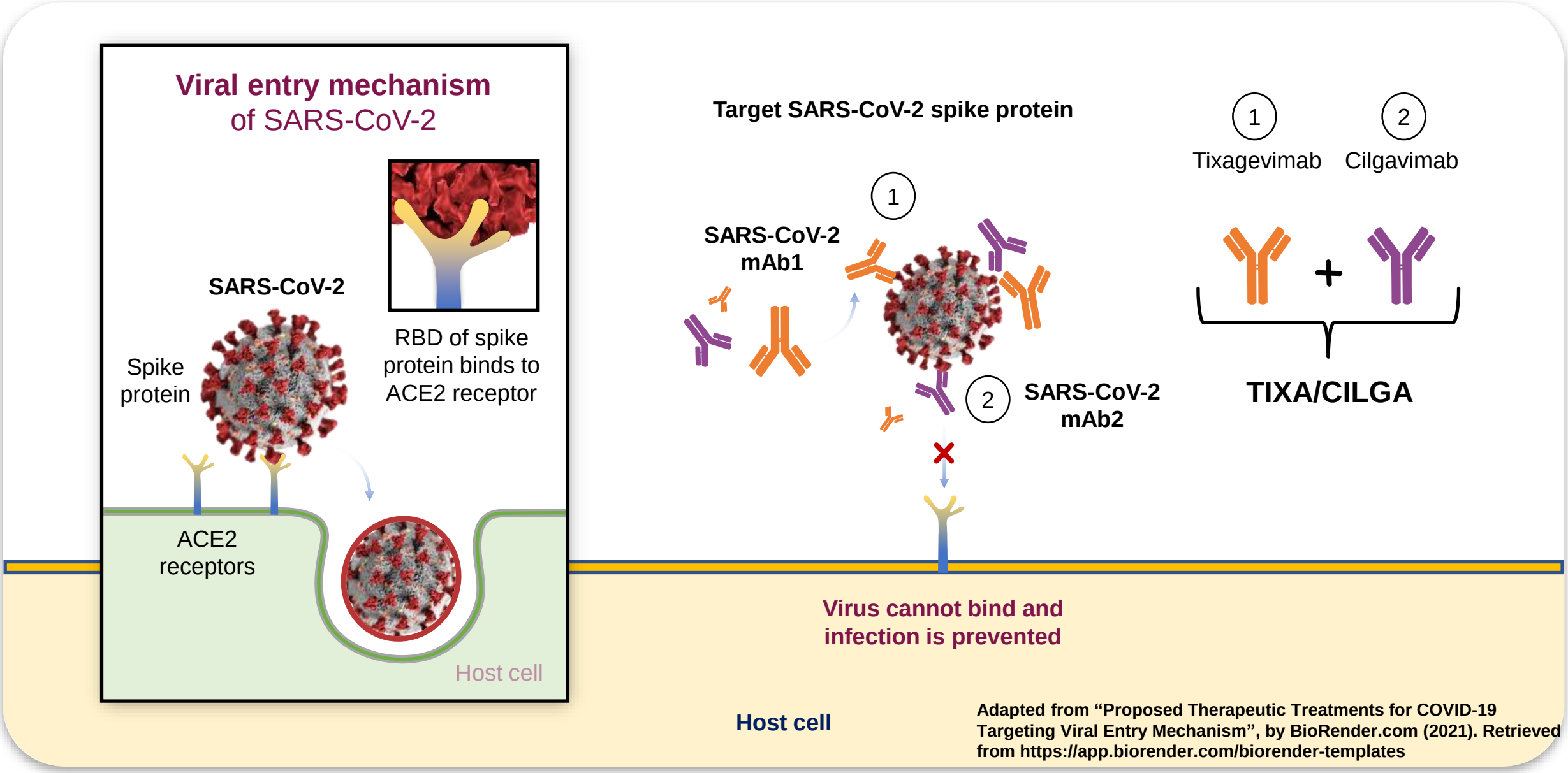
N Engl J Med. 2021 Dec 22 : NEJMe2118579

Tixagevimab/Cilgavimab: *Long acting antibody Combination*

- **2 human monoclonal antibodies**
- **Highly potent with favorable safety profile**
- **Retained neutralizing activity against VOC**
- **Extended half-life**
- **Efficacy was shown for pre-exposure prophylaxis in high-risk populations**



Tixagevimab/Cilgavimab: *Long acting antibody Combination*



Adapted from "Proposed Therapeutic Treatments for COVID-19 Targeting Viral Entry Mechanism", by BioRender.com (2021). Retrieved from https://app.biorender.com/biorender-templates

PROVENT: Phase III Randomized, Double-blind, Placebo-Controlled Study of Tixagevimab/Cilgavimab for PrEP (n=5197)

Inclusion criteria:

- Adults age ≥18 years at increased risk for inadequate response to vaccination or SARS-CoV-2 infection
- Negative point-of-care SARS-CoV-2 serology test and unvaccinated at screening
- Negative RT-PCR at dosing

Exclusion criteria:

- History of laboratory-confirmed COVID-19 infection, SARS, MERS
- Prior vaccine or mAb/biologic for COVID-19

TIXA/CILGA
300 mg single dose (×2 IM injections of 1.5 mL each)
n=3460

Randomization 2:1

Placebo (normal saline)
Single dose (×2 IM injections of 1.5 mL each)
n=1737

Primary endpoints:

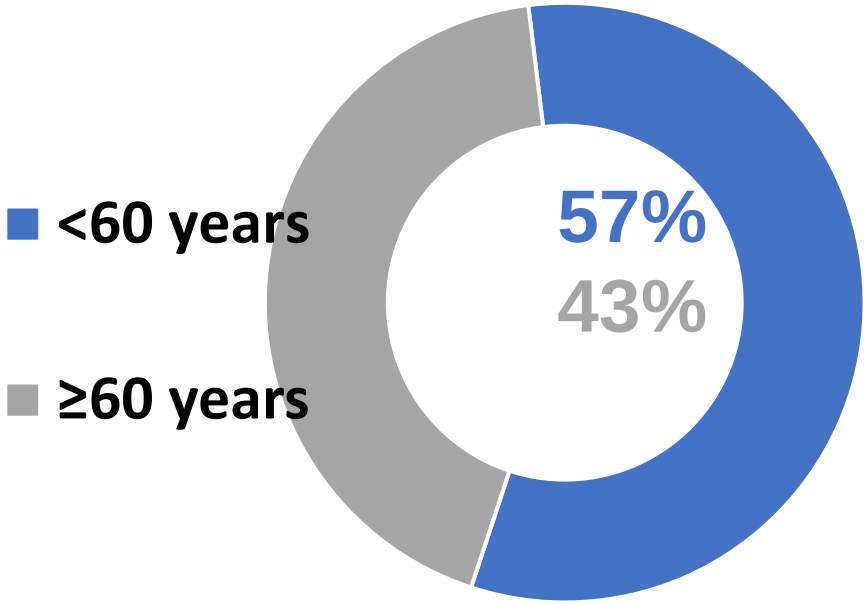
Efficacy endpoint:
SARS-CoV-2 RT-PCR-positive symptomatic illness within 183 days post-single dose

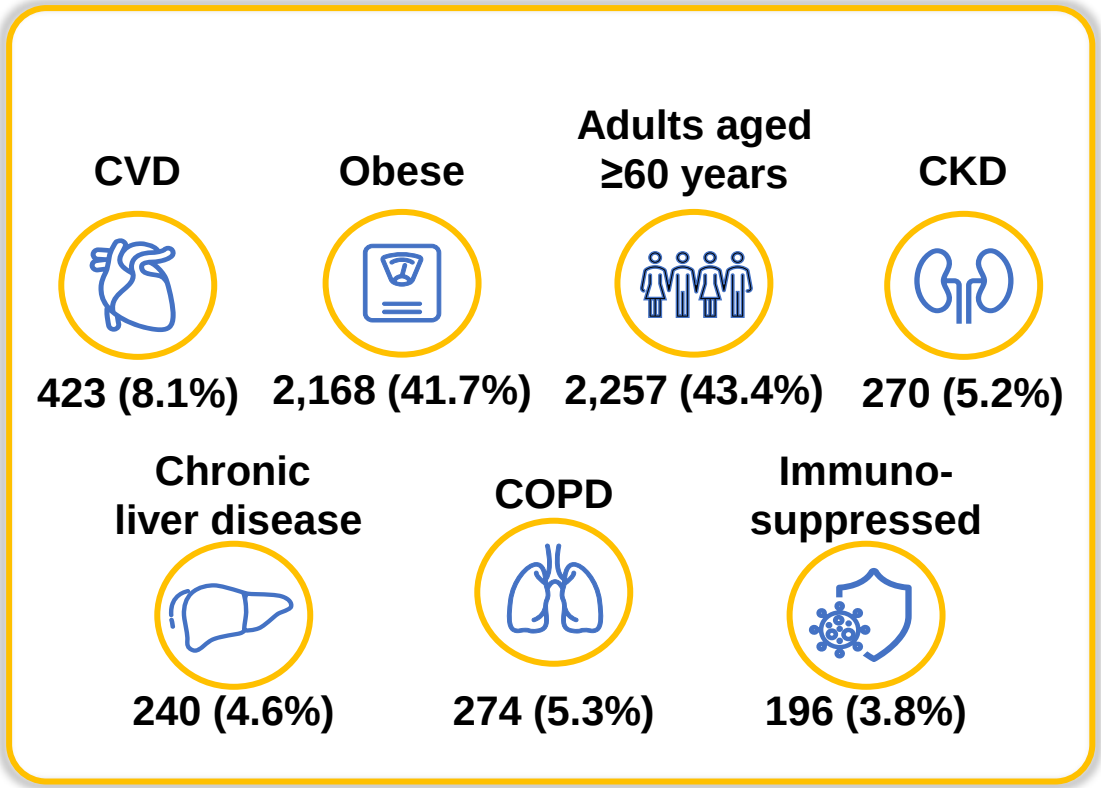
Safety Endpoint:
Adverse events through 457 days (15 mo) post-dose

Conducted in the UK, US, Spain, Belgium, and France

Results

78% of participants had baseline comorbidities

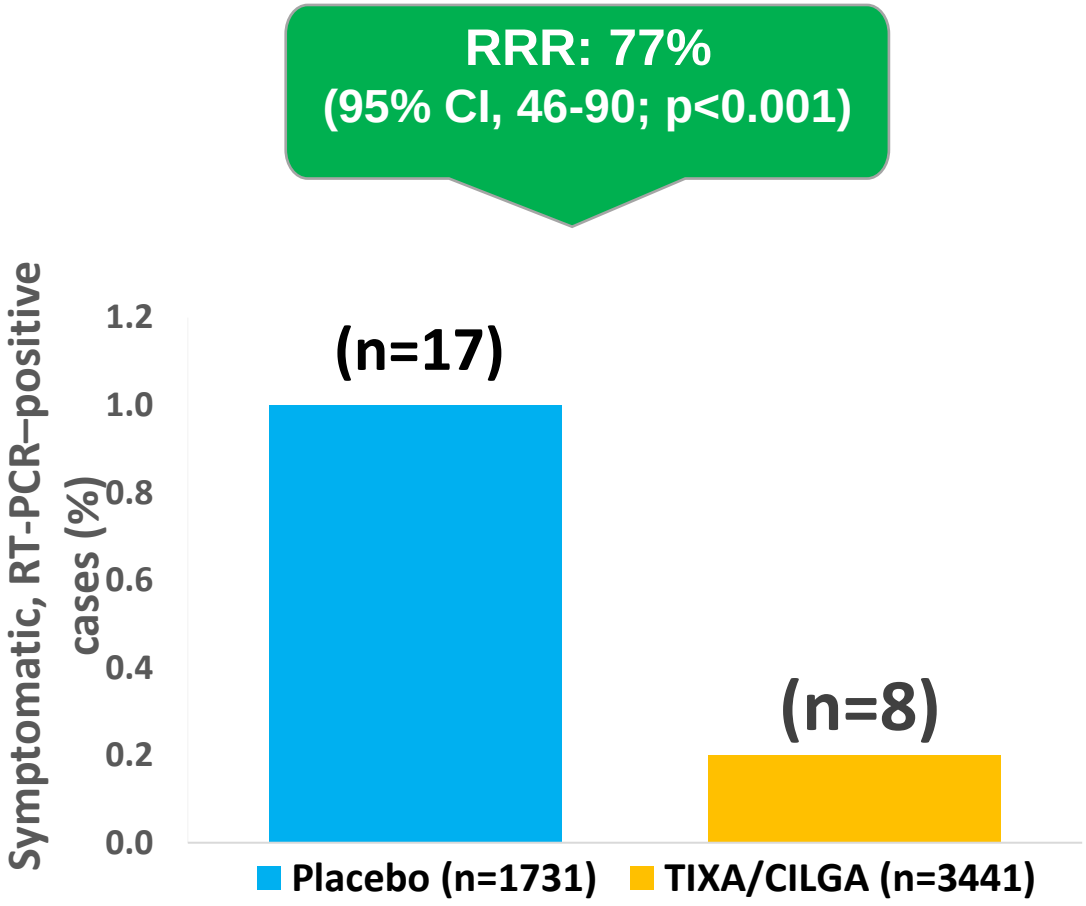




Results: *After 3 months follow up*

Reduction in the incidence of symptomatic COVID-19 with TIXA/CILGA compared with placebo

Case severity	Number of cases	
	TIXA/CILGA	Placebo
Severe/critical COVID-19	0	1
Total symptomatic cases	25/5172 RRR: 77% (95% CI, 46-90)	



Results: *Adverse events*

No. (%) of participants with:	TIXA/CILGA (n=3461)	Placebo (n=1736)
≥1 AE	1221 (35.3)	593 (34.2)
≥1 SAE	50 (1.4)	23 (1.3)
≥1 Treatment-related SAE	1 (<0.1)	0
≥1 AE leading to study withdrawal	1 (<0.1)	0
≥1 AESI	93 (2.7)	37 (2.1)
Injection site reaction	82 (2.4)	36 (2.1)
Anaphylaxis	1 (<0.1)	0
Immune complex disease	1 (<0.1)	0
Other	9 (0.3)	2 (0.1)

AEs were balanced between the TIXA/CILGA and placebo groups

Results: *Adverse events*

No. (%) of:	TIXA/CILGA (n=3461)	Placebo (n=1736)
Participants with mild AEs	761 (22.0)	369 (21.3)
Participants with moderate AEs	387 (11.2)	191 (11.0)
Participants with severe AEs	64 (1.8)	27 (1.6)
Deaths	4 (0.1)	4 (0.2)
Myocardial infarction	1 (<0.1)	0
Illicit drug overdose	2 (0.1)	2 (0.1)
Renal failure	1 (<0.1)	0
COVID-19/ARDS	0	2 (0.1)

Most AEs were of mild or moderate severity

6.5-month follow-up: Reduction in the incidence of symptomatic COVID-19 with TIXA/CILGA compared with placebo

Case severity	Number of cases		Relative Risk Reduction
	TIXA/CILGA	Placebo	
Severe COVID-19	0	5	--
Symptomatic cases	11/3441	31/1731	**83%** (95% CI, 66-91)

TIXA/CILGA reduced the risk of symptomatic disease by 83% through 6.5-month follow-up

From The Medical Letter on Drugs and Therapeutics

Tixagevimab and Cilgavimab (Evusheld) for Pre-Exposure Prophylaxis of COVID-19

The FDA has issued an Emergency Use Authorization (EUA) for the investigational long-acting monoclonal antibodies tixagevimab and cilgavimab (Evusheld – AstraZeneca) to be administered concomitantly by IM injection for pre-exposure prophylaxis of COVID-19 in persons ≥12 years old who weigh ≥40 kg and have either a history of severe allergy that prevents their vaccination against COVID-19 or moderate or severe immune compromise (see **Box**). They are the first drugs to be authorized by the FDA for this indication.[1] Two other pairs of antibodies, bamlanivimab plus etesevimab (Lilly) and casirivimab plus imdevimab (REGEN-COV), are authorized for post-exposure prophylaxis of COVID-19.[2,3]

Box. Some Moderately or Severely Immunocompromising Conditions[5]

- Moderate or severe primary immunodeficiency
- Advanced or untreated HIV infection
- Receipt of CAR T-cell therapy or hematopoietic cell transplant within the previous 2 years
- Active treatment for a solid tumor or hematologic malignancy
- Use of immunosuppressive therapy after a solid-organ transplant
- Active treatment with other immunosuppressive or immuno-modulatory drugs, such as high-dose corticosteroids (≥20 mg/d of prednisone or equivalent) and tumor necrosis factor (TNF) inhibitors.

Prevention of SARS-CoV-2 Infection

Last Updated: February 1, 2022

Summary Recommendations

- The COVID-19 Treatment Guidelines Panel (the Panel) recommends COVID-19 vaccination as soon as possible for everyone who is eligible according to the Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices **(AI)**.
- The Panel recommends using **tixagevimab plus cilgavimab (Evusheld)** administered as intramuscular injections as SARS-CoV-2 pre-exposure prophylaxis (PrEP) for adults and adolescents (aged ≥12 years and weighing ≥40 kg) who do not have SARS-CoV-2 infection, who have not been recently exposed to an individual with SARS-CoV-2 infection, **AND** who:
  - Are moderately to severely immunocompromised and may have inadequate immune response to COVID-19 vaccination **(BIIa)**; *or*
  - Are not able to be fully vaccinated with any available COVID-19 vaccines due to a documented history of severe adverse reaction to a COVID-19 vaccine or any of its components **(AIIa)**.
- **Tixagevimab plus cilgavimab is not a substitute for COVID-19 vaccination and should not be used in unvaccinated individuals for whom COVID-19 vaccination is recommended and who are anticipated to have an adequate response.**
- If supplies of tixagevimab plus cilgavimab are limited, priority for use as PrEP should be given to those who are at the highest risk for severe COVID-19.
- The Panel **recommends against** the use of **bamlanivimab plus etesevimab** and **casirivimab plus imdevimab** for post-exposure prophylaxis (PEP), as the B.1.1.529 (Omicron) variant, which is not susceptible to these agents, is currently the predominant variant circulating in the United States **(AIII)**.

IDSA Guidelines on the Treatment and Management of Patients with COVID-19

Published by IDSA on 4/11/2020. Last updated, 3/23/2022

Recommendation 19: In moderately or severely immunocompromised individuals* at increased risk for inadequate immune response to COVID-19 vaccine or for whom COVID-19 vaccine is not recommended due to a documented serious adverse reaction to the vaccine, the IDSA guideline panel suggests pre-exposure prophylaxis with tixagevimab/cilgavimab rather than no tixagevimab/cilgavimab. (Conditional recommendation, Low certainty of evidence)

IDSA Guidelines on the Treatment and Management of Patients with COVID-19

Published by IDSA on 4/11/2020. Last updated, 3/23/2022

Figure 2. FDA EUA criteria for the use of tixagevimab/cilgavimab for pre-exposure prophylaxis of COVID-19 in moderately or severely immunocompromised patients [1]

According to the FDA Emergency Use Authorization of Evusheld, medical conditions or treatments that may result in moderate to severe immune compromise include but are not limited to:

- Active treatment for solid tumor and hematologic malignancies
- Receipt of solid-organ transplant and taking immunosuppressive therapy
- Receipt of chimeric antigen receptor (CAR)-T-cell or hematopoietic stem cell transplant (within 2 years of transplantation or taking immunosuppression therapy)
- Moderate or severe primary immunodeficiency (e.g., DiGeorge syndrome, Wiskott-Aldrich syndrome)
- Advanced or untreated HIV infection (people with HIV and CD4 cell counts <200mm^3, history of an AIDS-defining illness without immune reconstitution, or clinical manifestations of symptomatic HIV)
- Active treatment with high-dose corticosteroids (i.e., ≥20 mg prednisone or equivalent per day when administered for ≥2 weeks), alkylating agents, antimetabolites, transplant-related immunosuppressive drugs, chancer chemotherapeutic agents classified as severely immunosuppressive, tumor-necrosis (TNF) blockers, and other biologic agents that are immunosuppressive or immunomodulatory (e.g., B-cell depleting agents)

הנדון: <u>תכשיר Evusheld מתוצרת אסטרהזניקה – עדכון התוויות מס' 1</u>
סימוכין: תכשיר Evusheld מתוצרת אסטרהזניקה – הנחיות שימוש מיום 14/2/22, מס' 239169722

בהמשך להנחיות למתן חיסון סביל נגד נגיף קורונה החדש מסוג Evusheld למדוכאי חיסון, להלן רשימת ההתוויות העדכנית:

1. בני 12 שנים ומעלה, השוקלים לפחות 40 ק"ג, אשר אינם מאומתים לנגיף SARS-CoV-2. למען הסר ספק, אין צורך לבדוק סטטוס מחלת קורונה לפני מתן התכשיר.
2. אדם עם דיכוי חיסוני בינוני – חמור מאחת או יותר מהסיבות המפורטות להלן, על פי המלצת רופא מטפל:

- חולי היפוגמאגלובולינמיה המטופלים באופן קבוע באימונגלובולינים
- חולי CLL הנזקקים לטיפול או עם היפוגאמאגלובולינמיה
- חולים המטופלים ב- B cell depleting therapy (כולל לדוגמא anti-CD20 כמו rituximab, obinatuzumab, ocrelizumab, ofatumumab, veltuzumab, Y-ibritumomab tiuxetan) גם ללא מחלה ממארת, עד חצי שנה ממתן הטיפול.
- מושתלי מח עצם מתורם זר עד שנה מההשתלה, או עם GVHD בדרגת חומרה 3-4
- מושתלי מח עצם בהשתלה עצמית עד חצי שנה מהשתלה
- חולים לאחר טיפול CAR-T (chimeric antigen receptor T-cell therapy) - עד חצי שנה מהטיפול
- מושתלים שקיבלו ATG (anti thymocyte globulin) בחצי השנה האחרונה
- חולי לימפומות אגרסיביות
- מושתלי אברים סולידיים (לב, ריאה, כליה, כבד, איברי מערכת העיכול)
- חולי מיאלומה נפוצה עם מחלה פעילה, המקבלים טיפול

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טל: 02-5080522 **פקס:** 02-5655950

Mild-moderate COVID high risk patients
Antivirals

- Remdesivir
- Paxlovid
- Molnupiravir

Remdesivir

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 27, 2022 VOL. 386 NO. 4

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†

562 PATIENTS
(PLANNED 632)

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

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

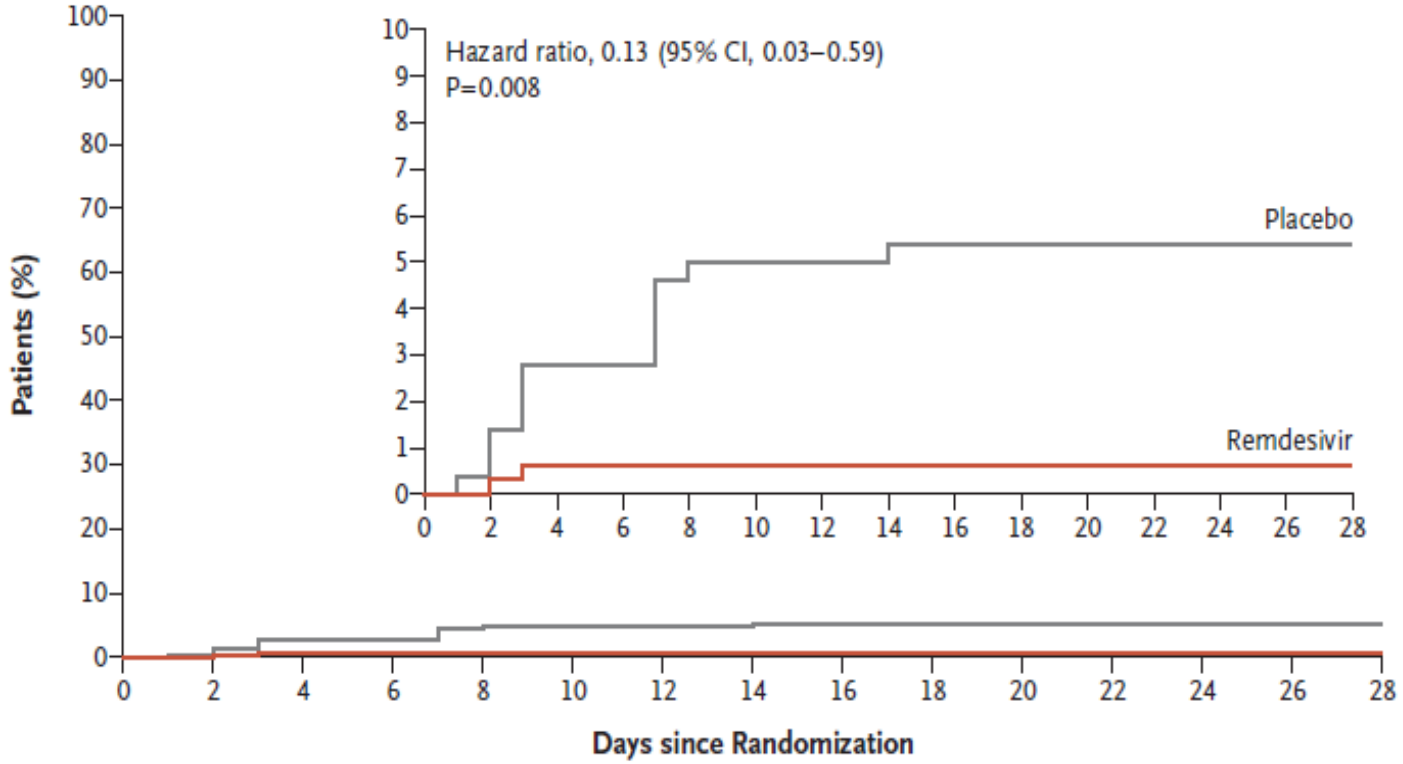
Table 2. Efficacy Calculated with the Use of a Cox Proportional-Hazards Model with Baseline Stratification Factors as Covariates.*

End Point	Remdesivir (N=279)	Placebo (N=283)	Hazard Ratio (95% CI)	P Value
Primary efficacy end point				
Covid-19–related hospitalization or death from any cause by day 28 — no. (%)†	2 (0.7)	15 (5.3)	0.13 (0.03 to 0.59)	0.008
Secondary efficacy end points				
Covid-19–related hospitalization or death from any cause by day 14 — no. (%)	2 (0.7)	15 (5.3)	0.13 (0.03 to 0.59)	
Covid-19–related medically attended visit or death from any cause — no./total no. (%)‡				
Day 14	2/246 (0.8)	20/252 (7.9)	0.10 (0.02 to 0.43)	
Day 28	4/246 (1.6)	21/252 (8.3)	0.19 (0.07 to 0.56)	
Death from any cause by day 28 — no.	0	0	NC	
Hospitalization for any cause by day 28 — no. (%)§	5 (1.8)	18 (6.4)	0.28 (0.10 to 0.75)	
Time-weighted average change in nasopharyngeal SARS-CoV-2 viral load from baseline to day 7 — $\log_{10}$ copies/ml	−1.24	−1.14	0.07 (−0.10 to 0.24)¶	
Alleviated baseline Covid-19 symptoms, according to FLU-PRO Plus questionnaire — no./total no. (%)‖				
Questionnaire completed before infusion on day 1	23/66 (34.8)	15/60 (25.0)	1.41 (0.73 to 2.69)**	
Questionnaire completed on day 1, either before or after infusion — no./total no. (%)§	61/169 (36.1)	33/165 (20.0)	1.92 (1.26 to 2.94)**	

ירידה של 87% סיכוי לאשפוז או תמותה (15 מול 2 חולים)

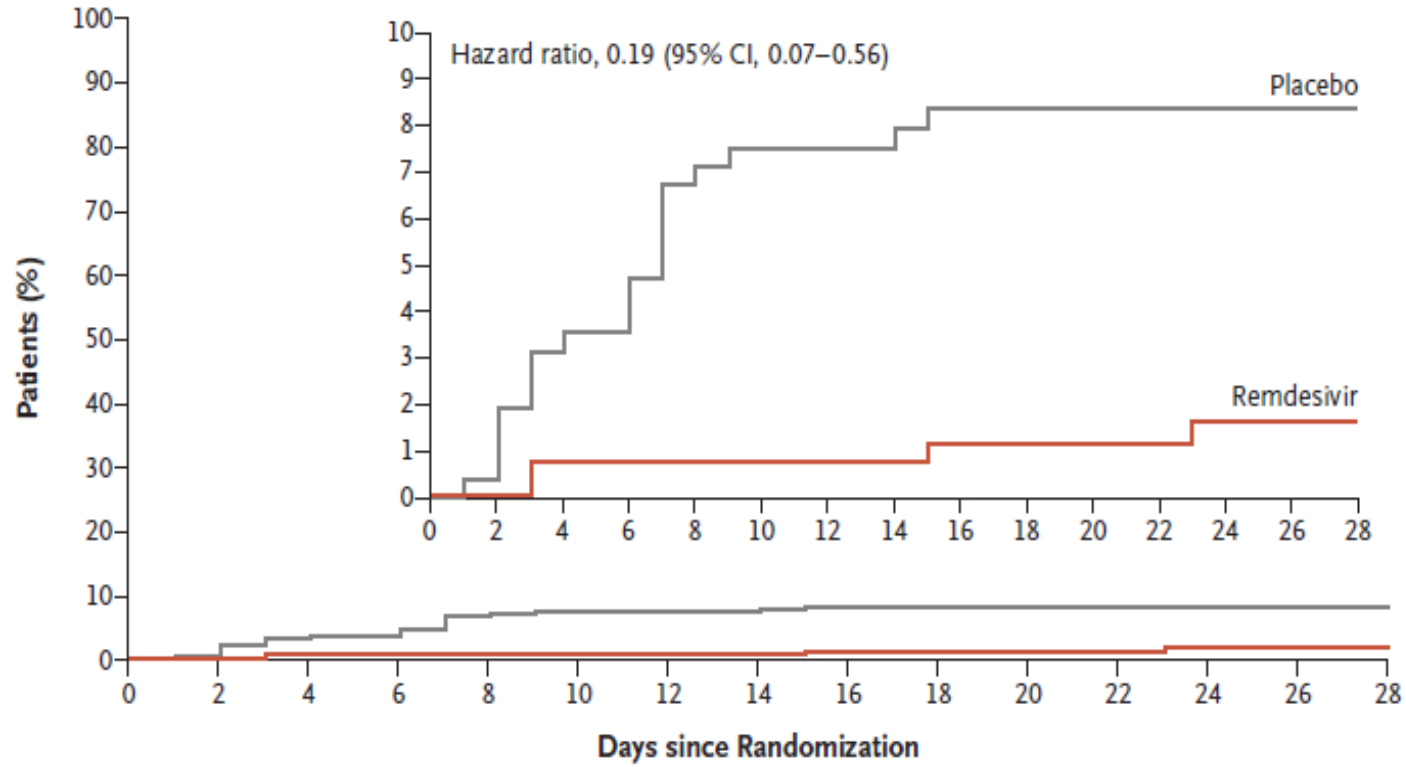
פחות ביקורים אצל הרופא המטפל

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

B **Covid-19–Related Medically Attended Visit or Death from Any Cause**



No. at Risk															
Placebo	252	249	241	239	230	228	228	227	225	224	224	223	219	213	193
Remdesivir	246	243	239	239	239	237	237	237	232	232	232	232	227	220	197

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)	—

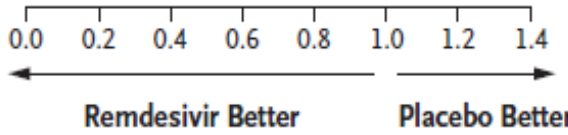


Figure 2. Covid-19–Related Hospitalization or Death from Any Cause at Day 28 in More Than 5% of the Trial Population, According to Demographic and Clinical Characteristics at Baseline.

Hazard ratios and two-sided 95% confidence intervals (I bars) were estimated with the use of Cox regression with the baseline stratification factors as covariates: residence in a skilled nursing facility (yes or no), age (<60 years or ≥60 years), and country (United States or outside the United States). Analyses with stratification according to Hispanic or Latinx ethnic group were conducted post hoc. Hazard ratios and 95% confidence intervals for subgroups with no events in the remdesivir group could not be accurately calculated and are therefore omitted. The dashed line indicates a hazard ratio of 1.0.

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

Molnupiravir

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Molnupiravir for Oral Treatment of Covid-19 in Nonhospitalized Patients

A. Jayk Bernal, M.M. Gomes da Silva, D.B. Musungaie, E. Kovalchuk, A. Gonzalez, V. Delos Reyes, A. Martín-Quirós, Y. Caraco, A. Williams-Diaz, M.L. Brown, J. Du, A. Pedley, C. Assaid, J. Strizki, J.A. Grobler, H.H. Shamsuddin, R. Tipping, H. Wan, A. Paschke, J.R. Butterton, M.G. Johnson, and C. De Anda, for the MOVe-OUT Study Group*

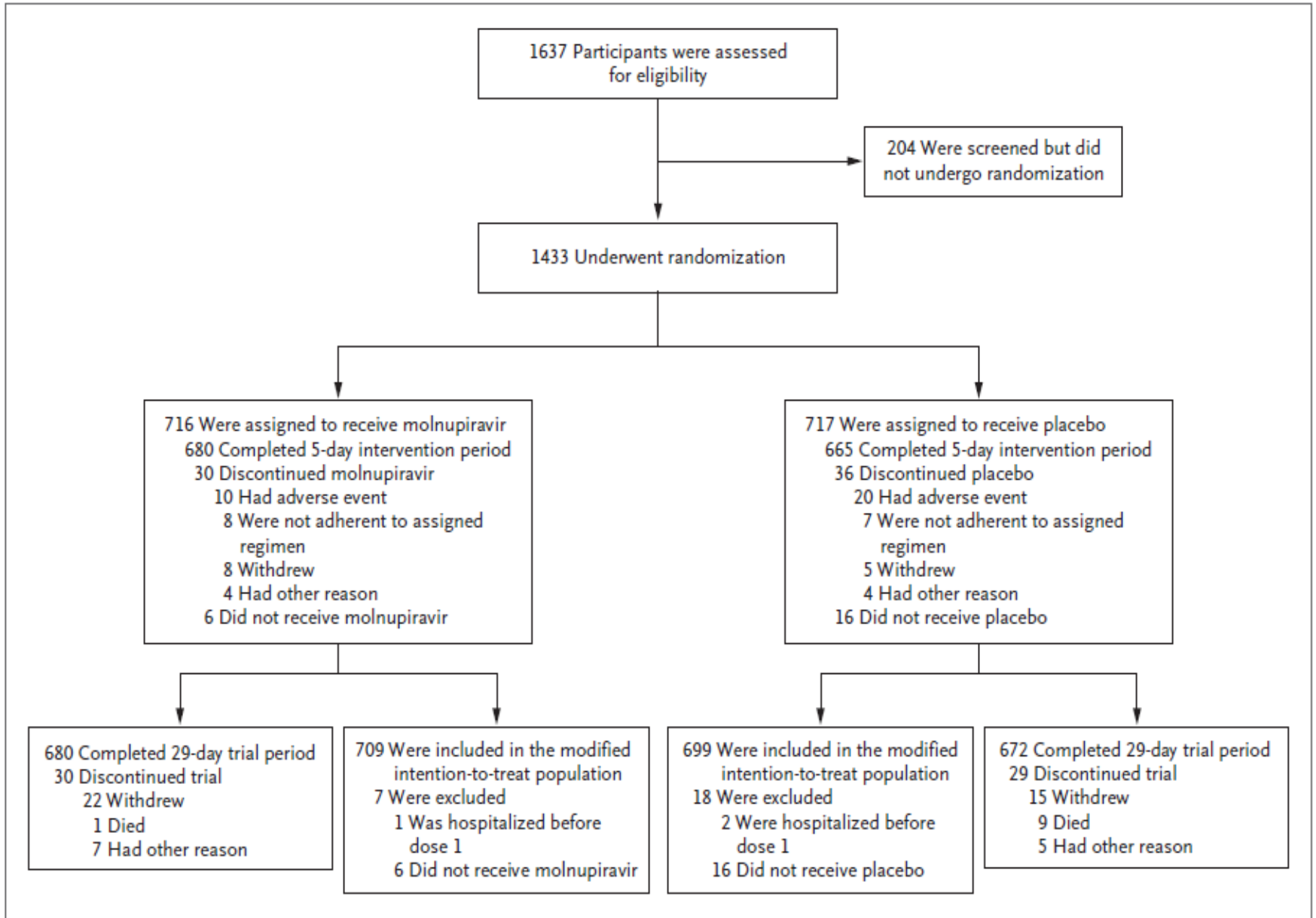


Figure 1. Randomization and Flow of Participants from Baseline through Day 29.

Table 1. Demographic and Clinical Characteristics of the Participants at Baseline.*

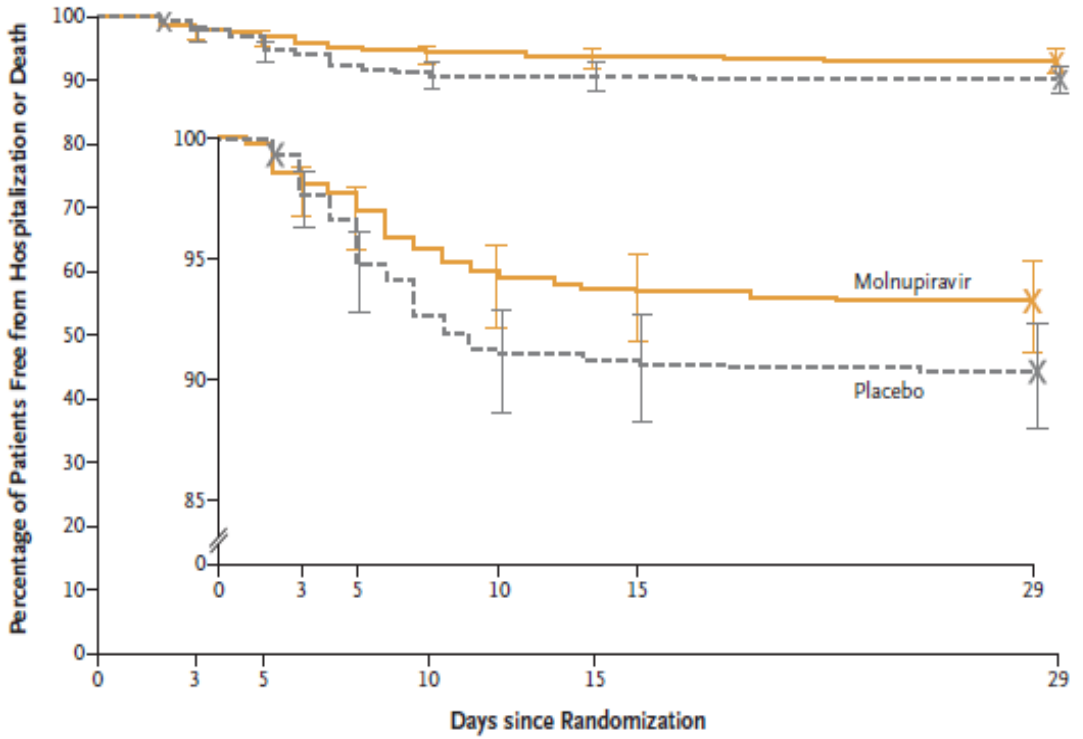
Characteristic	Molnupiravir (N=716)	Placebo (N=717)	Total (N=1433)
Female sex — no. (%)	384 (53.6)	351 (49.0)	735 (51.3)
Age group — no. (%)			
18–49 yr	484 (67.6)	465 (64.9)	949 (66.2)
≥50 yr	232 (32.4)	252 (35.1)	484 (33.8)
Median age (range) — yr	42.0 (18–90)	44.0 (18–88)	43.0 (18–90)
Risk factors 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)
SARS-CoV-2 RNA in nasopharyngeal sample, qualitative assay — no. (%)‡			
Detectable	615 (85.9)	615 (85.8)	1230 (85.8)
Undetectable	54 (7.5)	51 (7.1)	105 (7.3)
SARS-CoV-2 nucleocapsid antibody — no. (%)‡			
Positive	137 (19.1)	147 (20.5)	284 (19.8)
Negative	541 (75.6)	521 (72.7)	1062 (74.1)

<u>אשפוז</u>

מולנופיריביר – 6.8% פלצבו – 9.7%

<u>תמותה</u>

מולנופיריביר – 1/709 פלצבו – 9/699



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.

Shown are Kaplan–Meier curves with 95% confidence intervals (I bars). X indicates censored values. Data for the single participant with unknown survival status and no hospitalization reported were censored on the day when the participant was last known to be alive. The inset shows the same data on an expanded y axis.

Subgroup	Molnupiravir	Placebo	Absolute Risk Reduction (95% CI)
	no. of events/no. of participants		*percentage points*
Sex			
Female	16/379	27/344	−3.6 (−7.4 to −0.2)
Male	32/330	41/355	−1.9 (−6.5 to 2.8)
Days since onset of symptoms			
≤3	25/339	28/335	−1.0 (−5.2 to 3.2)
>3	23/370	40/364	−4.8 (−9.0 to −0.7)
Baseline Covid-19 severity			
Mild	19/395	27/376	−2.4 (−5.9 to 1.0)
Moderate	29/311	40/321	−3.1 (−8.1 to 1.8)
Baseline SARS-CoV-2 nucleocapsid antibody status			
Positive	5/136	2/146	2.3 (−1.7 to 7.1)
Negative	39/541	64/520	−5.1 (−8.8 to −1.6)
Risk factors for severe Covid-19			
>60 yr of age	12/118	16/127	−2.4 (−10.6 to 5.8)
Obese	29/535	46/507	−3.7 (−6.9 to −0.5)
Diabetes mellitus	17/107	17/117	1.4 (−8.2 to 11.1)
Serious heart condition	8/86	9/78	−2.2 (−12.4 to 7.5)
Race			
American Indian or Native American	18/207	21/199	−1.9 (−7.8 to 4.0)
Asian	7/25	7/23	−2.4 (not calculated)
Black	10/157	15/142	−4.2 (−11.1 to 2.2)
White	29/556	54/573	−4.2 (−7.3 to −1.2)
Baseline SARS-CoV-2 qualitative assay			
Detectable	45/614	61/613	−2.6 (−5.8 to 0.5)
Undetectable	0/54	0/51	0.0 (−7.1 to 6.7)
Unknown	3/41	7/35	−12.7 (−29.9 to 2.9)

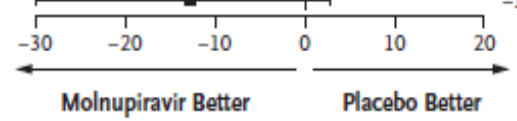


Figure 3. Incidence of Hospitalization or Death at Day 29 in the Modified Intention-to-Treat Population, According to Subgroup.

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)

* Differences shown are for molnupiravir as compared with placebo. Difference estimates were based on the Miettinen and Nurminen method.

† Related events were those determined by the investigators to be related to the assigned regimen.

Molnupiravir

- On December 23,2021,the FDA issued Emergency Use Authorization molnupiravir for mild to moderate COVID-19 in adult who are at high risk for progression and within 5 days of symptom onset, but only if other authorized therapeutic options are not “accessible or clinically appropriate.”
- Because of its mechanism of action, there have been theoretical concerns that molnupiravir may cause mutations in humanDNA10 or hasten development of new viral variants.
- The FDA concluded that the drug has a “low risk for genotoxicity” but is requiring the manufacturer to develop a process to evaluate genomic databases for new viral variants.
- Not for children or pregnancy.

Paxlovid Nirmatrelvir-Ritonavir

Nirmatrelvir-Ritonavir **reduced risk of hospitalization or death by 88% in interim analysis of phase 2/3 EPIC-HR study**

INH CYP3A4

The NEW ENGLAND JOURNAL of MEDICINE

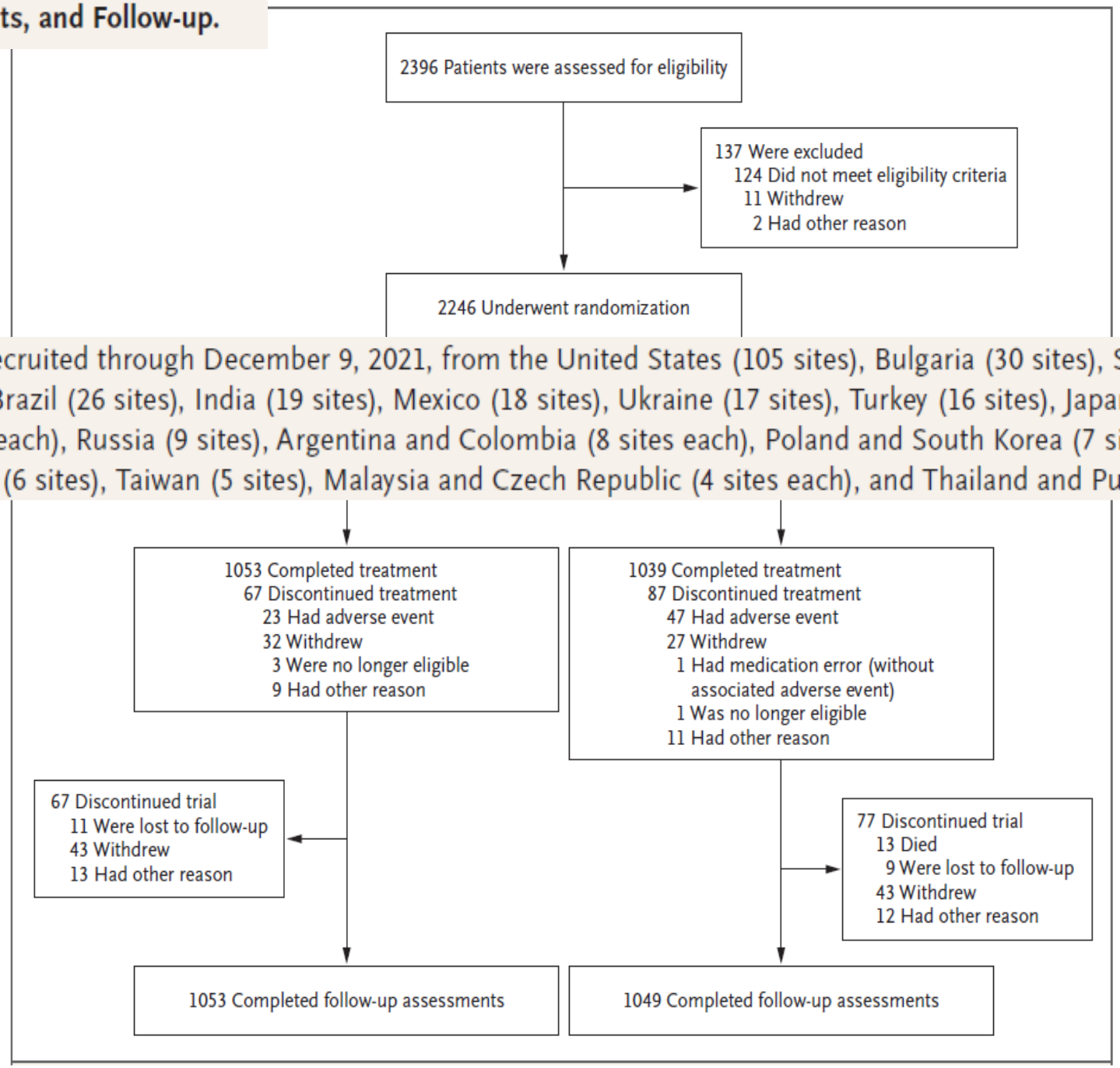
ORIGINAL ARTICLE

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

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*

N Engl J Med 2022 Feb 16;NEJMoa2118542

Figure 1. Randomization, Treatment Assignments, and Follow-up.

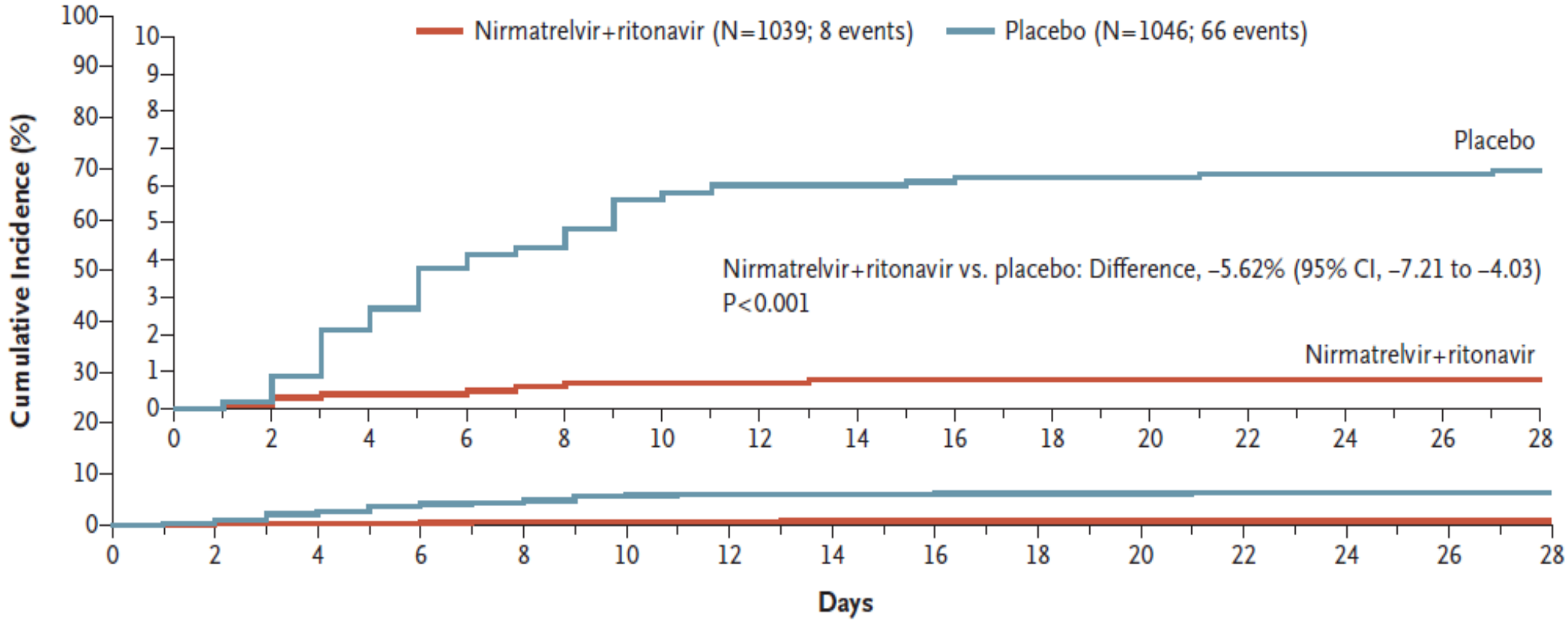


A Outcomes According to Time Since Onset of Covid-19 Symptoms

	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	

Participants who received nirmatrelvir-ritonavir had an **88% reduction** in **hospitalization or death** compared with the placebo group: **8 of 1039 (0.8%) (6.3%)vs 66 of 1046**

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

מעל גיל 65 16.3% מול 1.1% !

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)

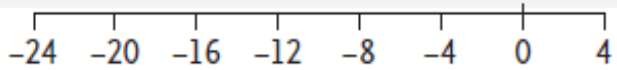


Table 2. Summary of Adverse Events, Serious Adverse Events, and Adverse Events Leading to Discontinuation through Day 34 (Safety Analysis Population).*

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)

The BMJ

Cite this as: *BMJ* 2021;375:n2713

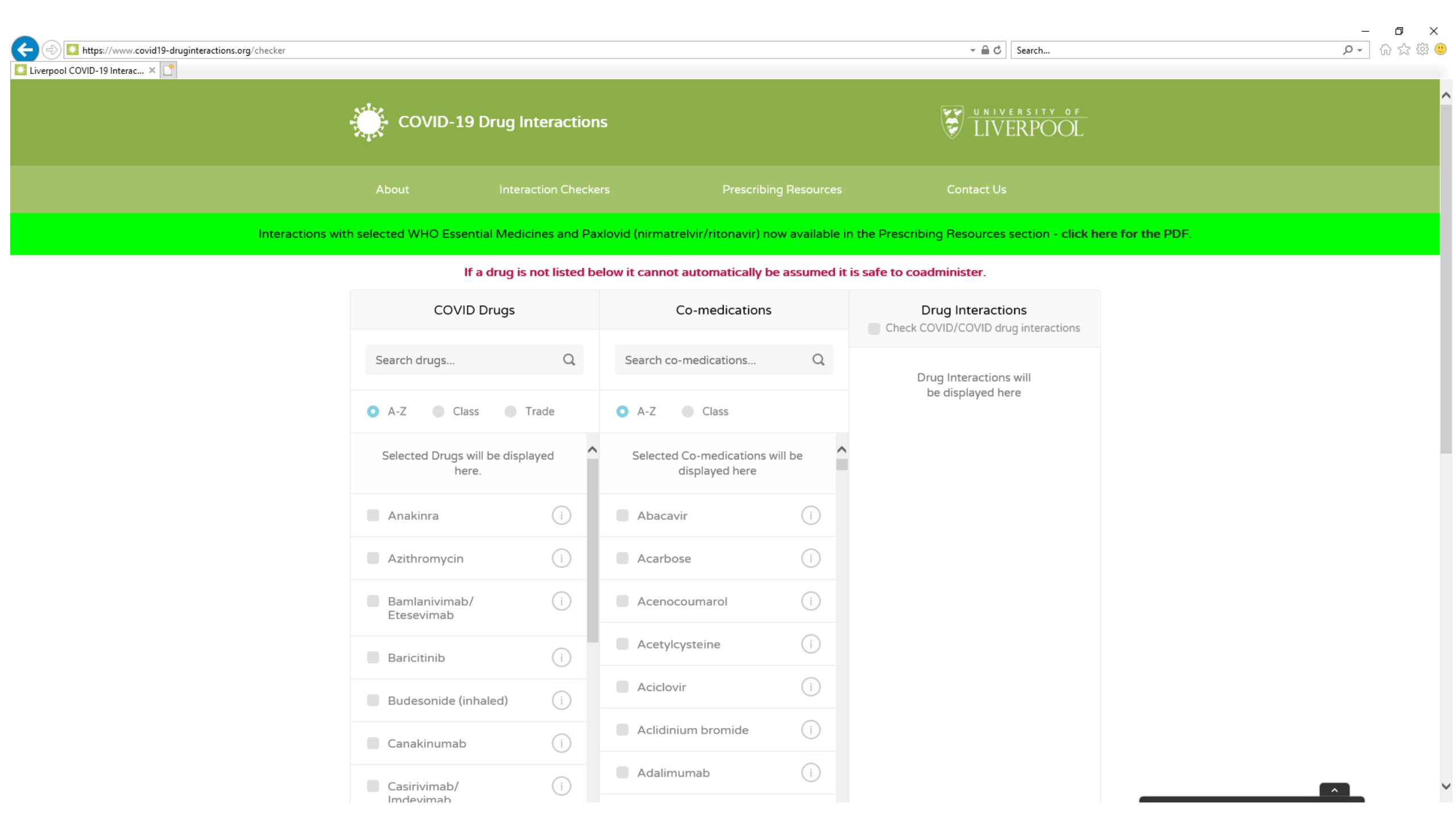
http://dx.doi.org/10.1136/bmj.n2713

Published: 8 November 2021

Covid-19: Pfizer's paxlovid is 89% effective in patients at risk of serious illness, company reports

Elisabeth Mahase

- On December 22,2021,the FDA issued Emergency Use Authorization for mild to moderate COVID-19 in adult and pediatric patients (age 12 years and 40kg) who are at high risk for progression and within 5 days of symptom onset.
- Inhibits CYP3A, alters the metabolism of many other drugs.
- Should not be administered with medications such as amiodarone (and several other antiarrhythmic drugs),rifampin,orrivaroxaban.
- Other medications, may need dose reduction or close monitoring.
- Medications such as statins may be temporarily stopped.
- Prior to prescribing, clinicians should assess potential drug interactions.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Prescribing Resources
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Interactions with selected WHO Essential Medicines and Paxlovid (nirmatrelvir/ritonavir) now available in the Prescribing Resources section - click here for the PDF.
If a drug is not listed below it cannot automatically be assumed it is safe to coadminister.
COVID Drugs
Search drugs...
A-Z
Class
Trade
Selected Drugs will be displayed here.
Anakinra
Azithromycin
Bamlanivimab/ Etesevimab
Baricitinib
Budesonide (inhaled)
Canakinumab
Casirivimab/ Imdevimab
Co-medications
Search co-medications...
A-Z
Class
Selected Co-medications will be displayed here
Abacavir
Acarbose
Acenocoumarol
Acetylcysteine
Aciclovir
Aclidinium bromide
Adalimumab
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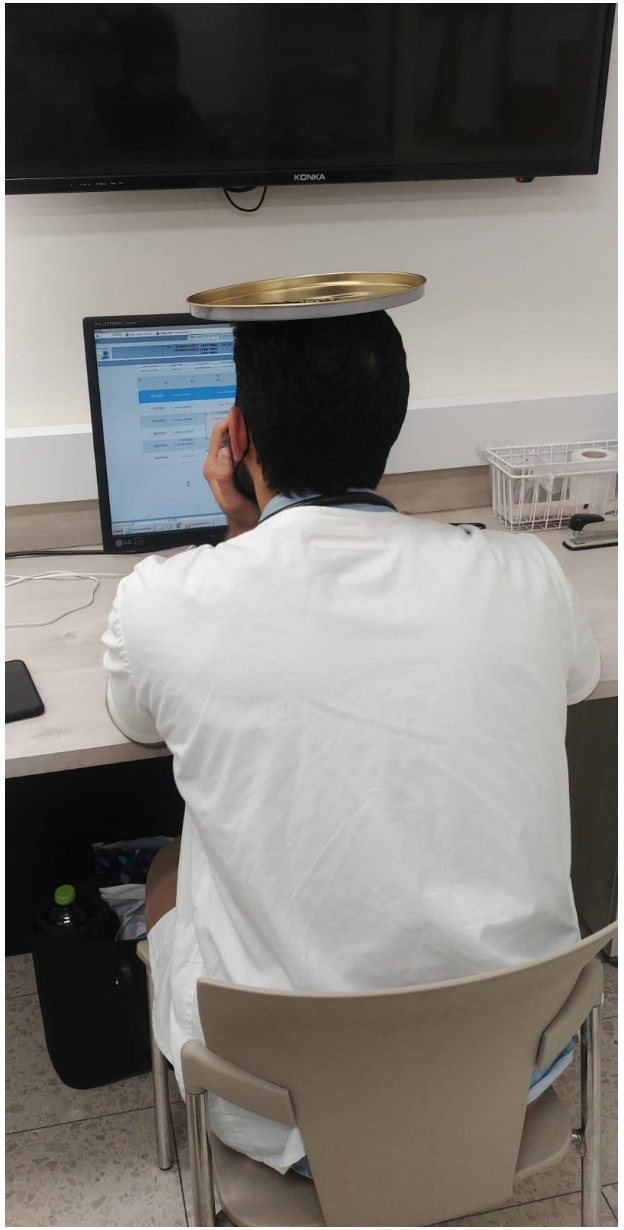
What to choose???

Take home message:

Find the Balance



eTable 1. Comparison of Treatment Options for High-Risk Nonhospitalized Patients With Mild to Moderate COVID-19

	Nirmatrelvir-ritonavir[1]	Sotrovimab[2]	Remdesivir[3]	Molnupiravir[4]
Efficacy (prevention of hospitalization or death)	• Absolute risk reduction: 6.3%→0.8% • Relative risk reduction: 88% • NNT: 18	• Absolute risk reduction: 7%→1% • Relative risk reduction: 85% • NNT: 17	• Absolute risk reduction: 5.3%→0.7% • Relative risk reduction: 87% • NNT: 22	• Absolute risk reduction: 9.7%→6.8% • Relative risk reduction: 30% • NNT: 35
Advantages	• Highly efficacious • Oral regimen • Ritonavir studied (safe) in pregnancy	• Highly efficacious • Monoclonal antibodies typically safe in pregnancy • Few/no drug interactions	• Highly efficacious • Studied in pregnancy • Few/no drug interactions	• Oral regimen • Not anticipated to have drug interactions
Disadvantages	• Drug-drug interactions	• Requires IV infusion followed by 1-h observation	• Requires IV infusion on 3 consecutive days	• Low efficacy • Concern: mutagenicity • Not recommended in pregnancy/childr en

Abbreviations: IV, intravenous; NNT, number needed to treat.

Gandhi RT, Malani PN, del Rio C. COVID-19 therapeutics for nonhospitalized patients. *JAMA*. doi:10.1001/jama.2022.0335

eTable 2. Outpatient Therapies and Potential Patient Populations

Medication	Examples of patient population
Nirmatrelvir, 300 mg, plus ritonavir, 100 mg, orally twice daily for 5 d	• Patient not taking interacting medications • Administer as soon as possible and within 5 d of symptom onset
Sotrovimab, 500 mg, intravenous infusion	• Patient taking medication that interacts with nirmatrelvir-ritonavir • Patient able to come to health care facility • Administer as soon as possible and within 10 d of symptom onset
Remdesivir intravenous infusion, 200 mg (day 1) and 100 mg (days 2 and 3)	• Patient in health care facility or through home infusion service • Administer as soon as possible and within 7 d of symptom onset
Molnupiravir, 800 mg, orally twice daily for 5 d	• Adult patient not able to be treated with one of the options above • Not pregnant (if given during pregnancy, shared decision-making) • Administer as soon as possible and within 5 d of symptom onset

Gandhi RT, Malani PN, del Rio C. COVID-19 therapeutics for nonhospitalized patients. *JAMA*. doi:10.1001/jama.2022.0335

OPEN FUTURE QUESTIONS

- What is the benefit of therapies in **lower-risk patients**, such as those after vaccination? The studies were conducted in **unvaccinated** individuals before the emergence of the Omicron variant.
- **What is the role of combination therapy?** To date, therapies have been evaluated as single agents
- **Monitoring for the emergence of resistance** among patients receiving monotherapies is needed along with trials to evaluate antiviral combinations.
- Does treatment of SARS-CoV-2prevent transmission and does early therapy reduce **post acute sequelae of SARS-CoV-2** infection?
- In addition, **equitable distribution** of these life-saving medications must be ensured, not just in wealthy countries but throughout the world. Infections with global morbidity and mortality must be addressed with a coordinated global response.

Together we ca..... Never mind, thank you for listening ☺