COVID-19: come si cura oggi a casa?

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UNIVERSITÀ DEGLI STUDI DI GENOVA

IRCCS Azienda Ospedaliera Universitaria San Martino – IST
Istituto Nazionale per la Ricerca sul Cancro

Disclosures (past 5 years)

- Advisor/consultant/speaker bureau
  - Angelini, Gilead, Menarini, MSD, Pfizer, Shionogi

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FIRST MESSAGE

NOT with ANTIBIOTICS

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Who should be treated at home?

Stage	Characteristics
Asymptomatic infection	Positive virologic test for SARS-CoV-2 (ie, NAAT or antigen test) but no symptoms consistent with COVID-19
Mild illness	Varied symptoms (eg, fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, loss of taste or smell) but no shortness of breath, dyspnea, or abnormal chest imaging
Moderate illness	$SpO_2 \geq 94\%$ and lower respiratory disease evidenced by clinical assessment or imaging
Severe illness	$SpO_2 < 94\%$, $PaO_2/FiO_2 < 300$ mm Hg, respiratory rate > 30 breaths/min, or lung infiltrates > 50%
Critical illness	Respiratory failure, septic shock, and/or multiorgan dysfunction

NIH COVID-19 Treatment Guidelines Last Updated March 24, 2022

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The Pillars of COVID-19 Treatment

- Supportive care (antipyretics, analgesics, or antitussives)
- Oxygen, Non-invasive Support, Mechanical Ventilation.
- Antiviral Agents
- Monoclonal Antibodies
- Anticoagulants
- Immunomodulators

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The Pillars of COVID-19 treatment

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Supportive Care

ALL Patients

- Fever
- Headache
- Myalgias
- Cough

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Antiviral agents and Monoclonal Antibodies

At high risk patients

- Chronic renal failure
- Severe pulmonary disease
- Oncological/oncohematological pathology in the active phase
- Primary or acquired immunodeficiency
- Obesity [(Body Mass Index, BMI) ≥30]
- Severe cardiovascular disease (heart failure, cardiomyopathy)
- Uncompensated diabetes mellitus

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The landscape is changing

In Italy **> 90%** of the population is vaccinated

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Who Remains At Risk Of Severe Disease After Vaccination?

Medical Conditions Associated With Higher Risk for Severe COVID-19

Tier	Risk Group
1	• Immunocompromised individuals not expected to mount an adequate immune response to COVID-19 vaccination or SARS-CoV-2 infection due to their underlying conditions, regardless of vaccine status (see Immunocompromising Conditions below); *or* • Unvaccinated individuals at the highest risk of severe disease (anyone aged ≥75 years or anyone aged ≥65 years with additional risk factors).
2	• Unvaccinated individuals not included in Tier 1 who are at risk of severe disease (anyone aged ≥65 years or anyone aged <65 years with clinical risk factors)
3	• Vaccinated individuals at high risk of severe disease (anyone aged ≥75 years or anyone aged ≥65 years with clinical risk factors) **Note:** Vaccinated individuals who have not received a COVID-19 vaccine booster dose are likely at higher risk for severe disease; patients within this tier in this situation should be prioritized for treatment.
4	• Vaccinated individuals at risk of severe disease (anyone aged ≥65 years or anyone aged <65 years with clinical risk factors) **Note:** Vaccinated individuals who have not received a COVID-19 vaccine booster dose are likely at higher risk for severe disease; patients within this tier in this situation should be prioritized for treatment.

NIH COVID-19 Treatment Guidelines Last Updated March 24, 2022

Outpatient treatment for COVID-19

	Remdesivir	Sotrovimab	Nirmatrelvir/ ritonavir	Molnupiravir
Age	≥12 yo	≥12 yo	≥ 12	≥ 18yo
Days from symptoms onset	≤5 days	≤10 days	≤5 days	≤5 days
Route of administration/ Duration	IV/5 days	IV/ Single infusion	PO/5 days	PO/5 days
PROS	Good experience; High efficacy	Single infusion	Oral; High efficacy against all VOCs	Oral; No drug-drug interactions
CONS	Need for hospital admission	IV administration; Concerns against BA.2 variant	Drug-drug interactions	Lower efficacy in pivotal trial.

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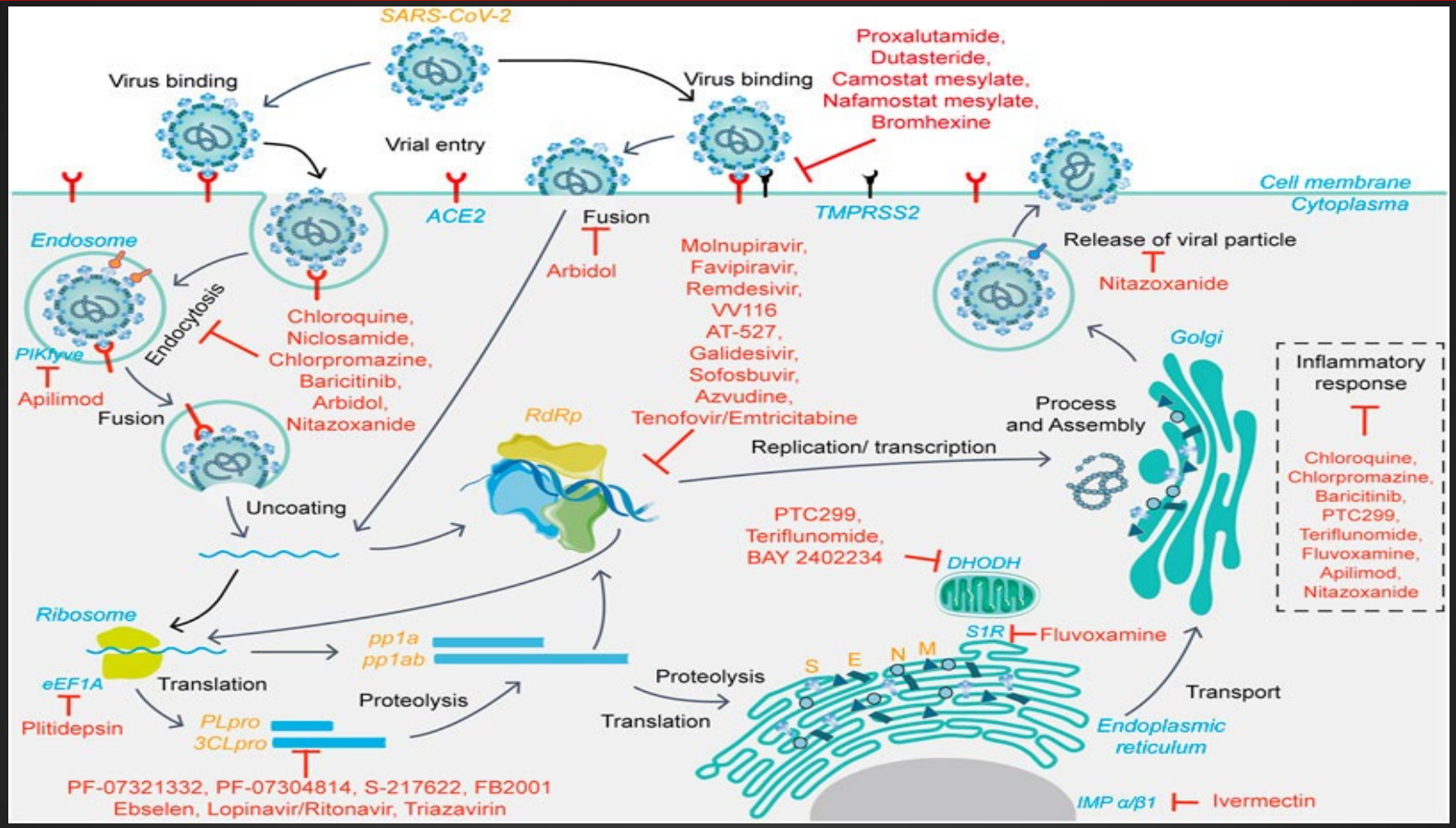
Potential Mechanisms Of Action Of Anti-SARS-COV-2 Antiviral Drugs



Zhao L, Front Pharmacol 2022;13:840639

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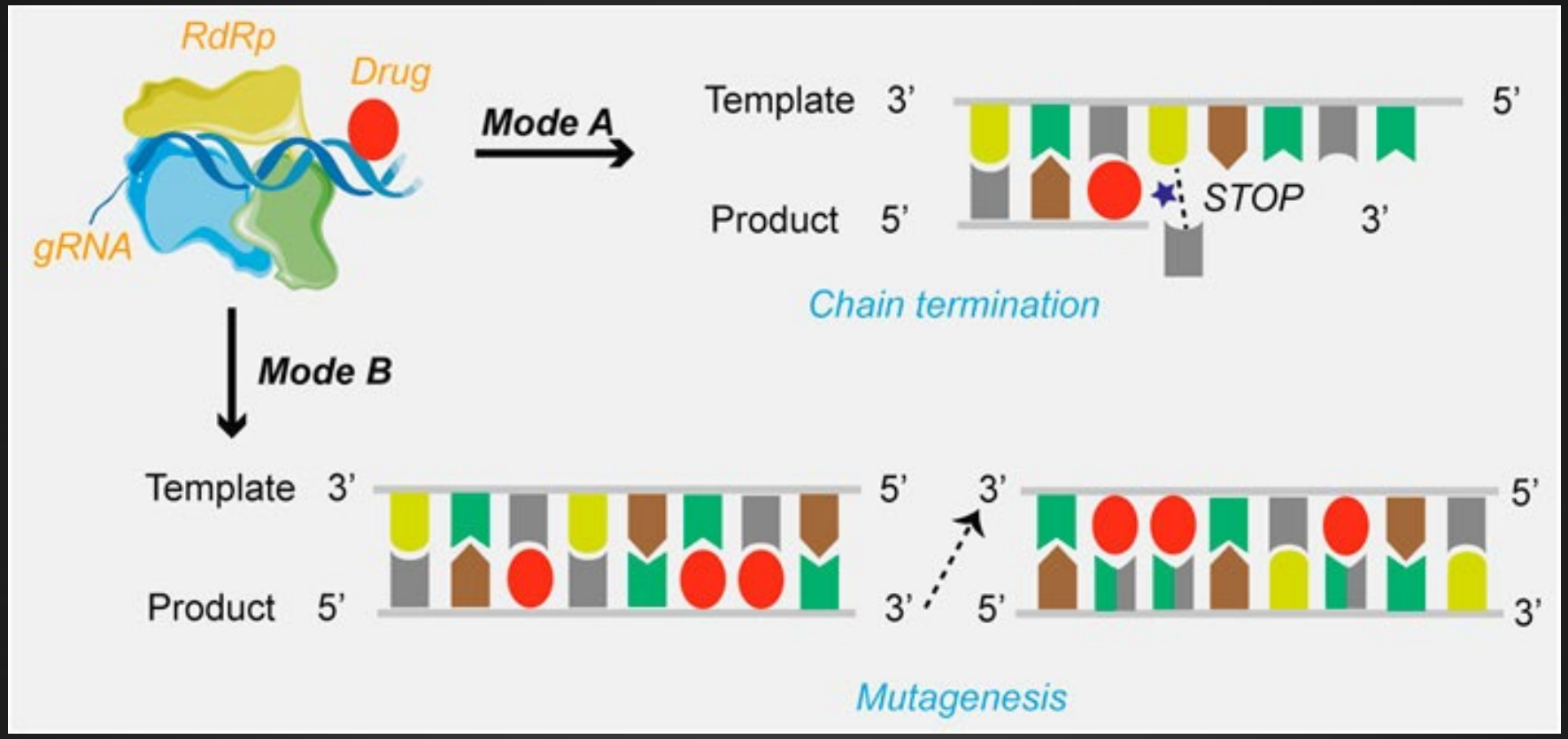

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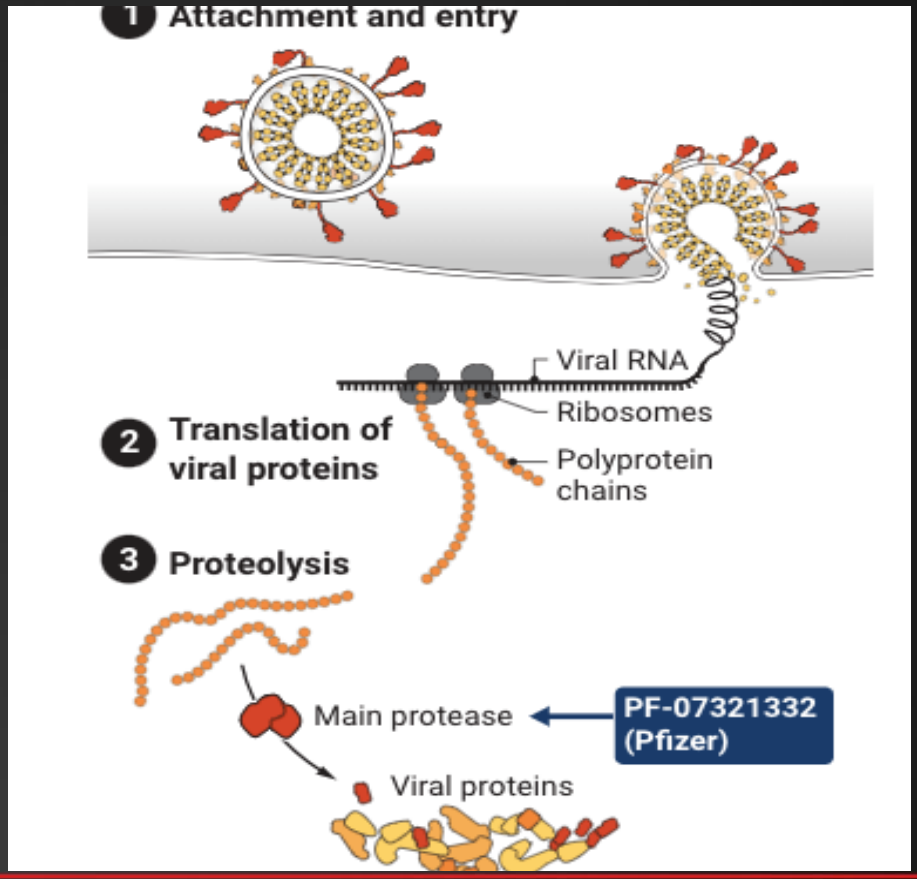

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ANTIVIRAL AGENTS
SUMMARY

	NIRMATRELVIR/r (Paxlovid)	MOLNUPIRAVIR (Lagevrio)	REMDESIVIR X 3 (Veklury)
Dosing	300-100 mg BID GFR ≥ 60 150-100 mg BID GFR ≥ 30- <60	800 mg BID	200 mg as a single dose on day 1, followed by 100 mg once daily on days 2 and 3
Route	Oral	Oral	IV
Trial	EPIC-HR	MOVE-OUT	PINE-TREE
N	2246	1433	563
Vaccinated	NOT INCLUDED	NOT INCLUDED	NOT INCLUDED
Symptoms (days)	< 5	< 5	< 7
Condition High Risk	≥ 1	≥ 1	≥ 1
Age (median)	46	43	50
Efficacy	89%	31%	87%
NNT	16	34.5	22
Deaths (Drug/Placebo)	0/13	1/9	0/0
Activity VOC	Yes	Yes	Yes
GFR	≥ 30	No adjustment	≥ 30
Pregnancy	No experience. Discuss	Contraindicated	Discuss

Key issues

Age of the patient

- 12 yo> Age< 18 yo
- Age <65 yo
- Age >65 yo

Underlying conditions

- Renal impairment
- Liver impairment
- Pregnancy
- Other comorbidities

Time from symptoms onset

Modality of infusion

Other concomitant medications

Vena a. Personal view

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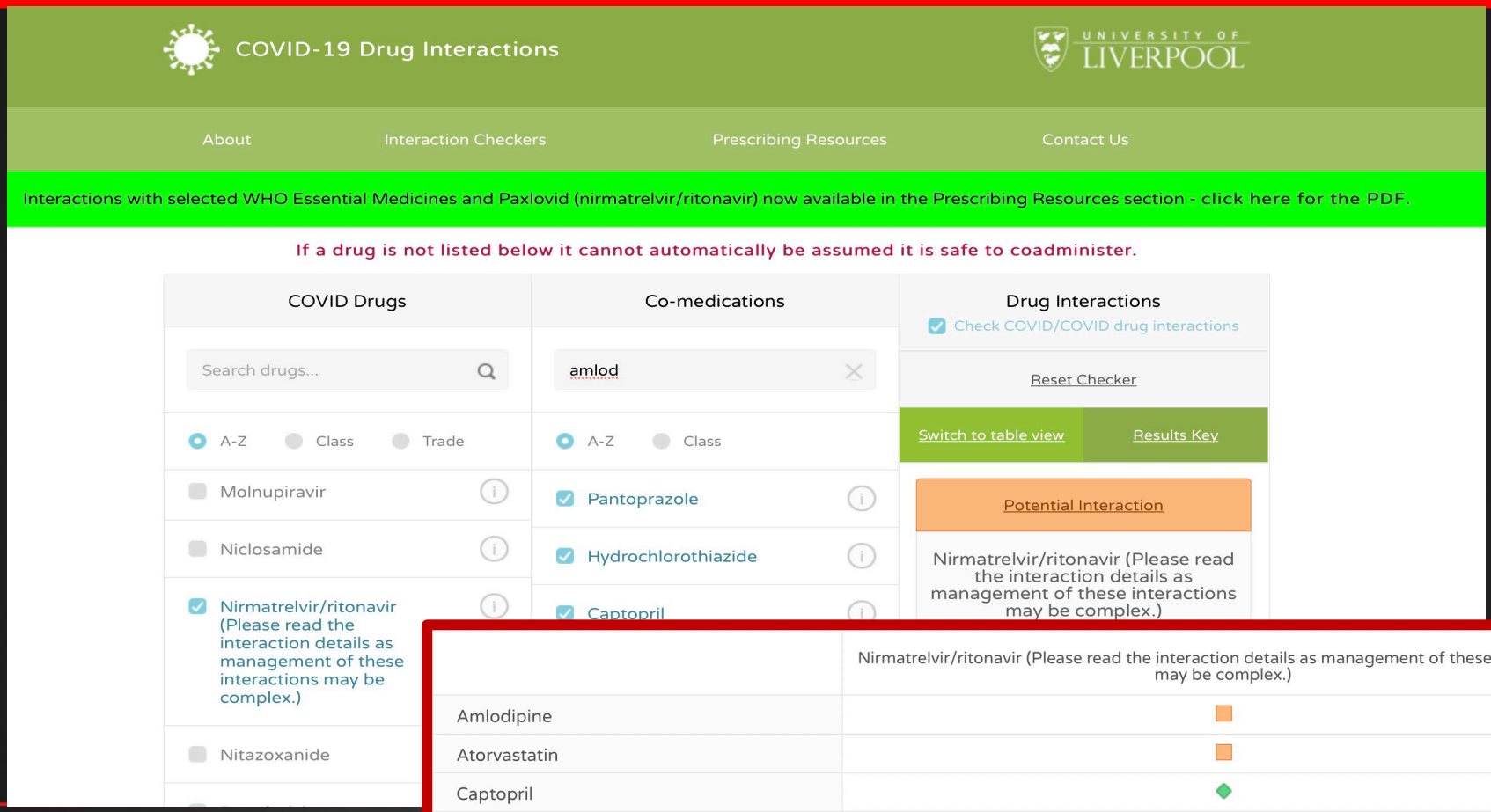
Clinical case



	Nirmatrelvir/ritonavir (Please read the interaction details as management of these interactions may be complex.)
Amlodipine	■
Atorvastatin	■
Captopril	◆
Carvedilol	◆
Furosemide	◆
Hydrochlorothiazide	◆
Pantoprazole	◆

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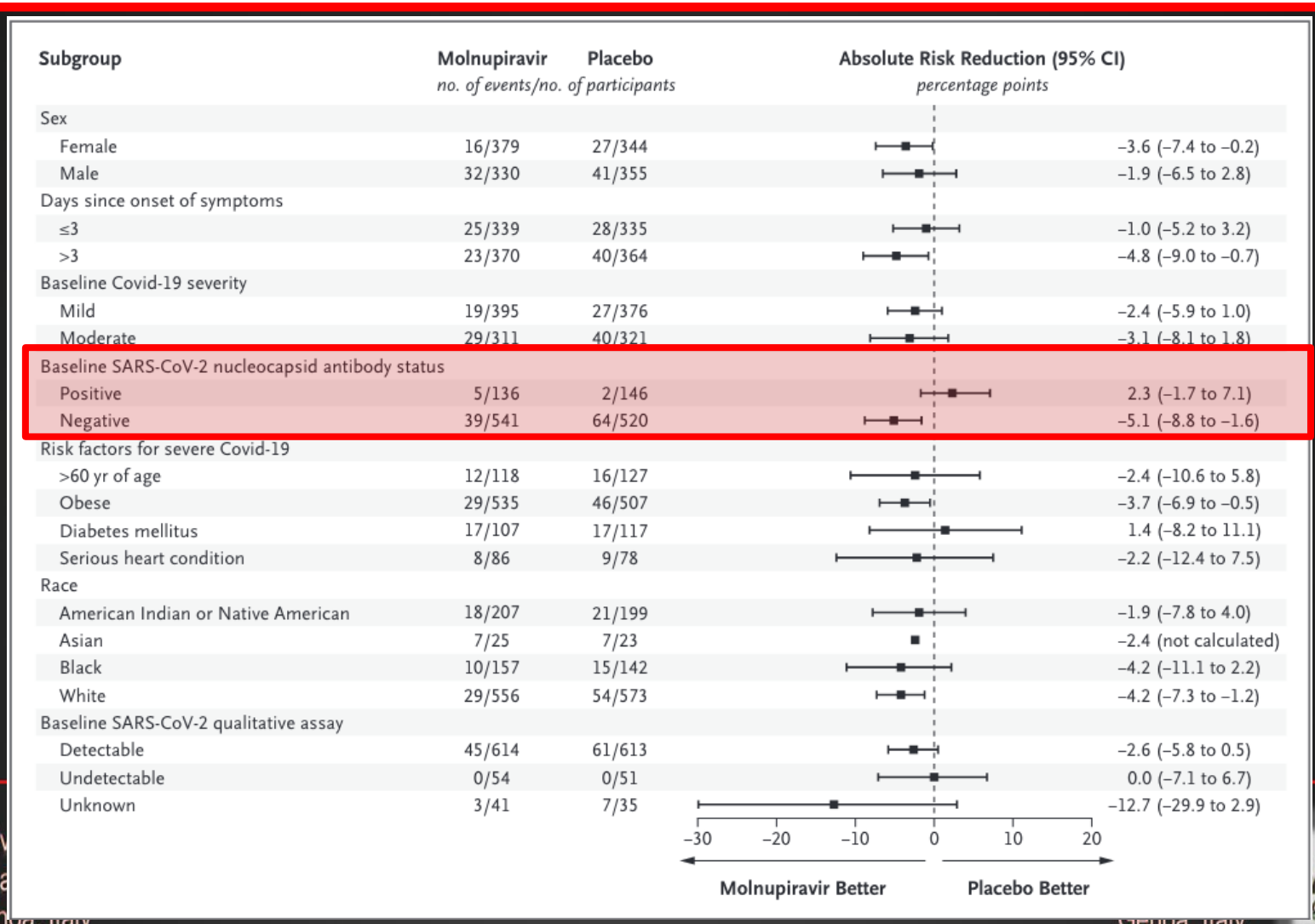
Molnupiravir for Oral Treatment of Covid-19 in Nonhospitalized Patients



Subgroup	Molnupiravir (no. of events/no. of participants)	Placebo (no. of events/no. of participants)	Absolute Risk Reduction (95% CI) (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)

Jayk Bernal A, N Engl J Med 2022

Our clinical experience

- Observational retrospective cohort study (January 2022 and February 2021)
- Aim: to describe our clinical experience with molnupiravir to treat patients with mild or moderate SARS-Cov-2 infections since its recent approval in Italy.

Bassetti M; Vena A; personal data

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Our clinical experience

Inclusion criteria

- Non-hospitalized adult (aged ≥18 years) patients
- Confirmed COVID-19 by polymerase chain reaction or by antigenic test;
- Had initial onset of signs/symptoms attributable to COVID-19 for ≤5 days prior to start molnupiravir;
- Mild or moderate illness at the time of the initial administration
- Had at least **one characteristic or underlying medical condition** associated with an **increased risk of severe illness** from COVID-19.

Bassetti M; Vena A; personal data

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Our clinical experience

Primary endpoint: composite of requirement of hospital admission and/ or need for supplemental oxygen during the 30-day follow-up period.

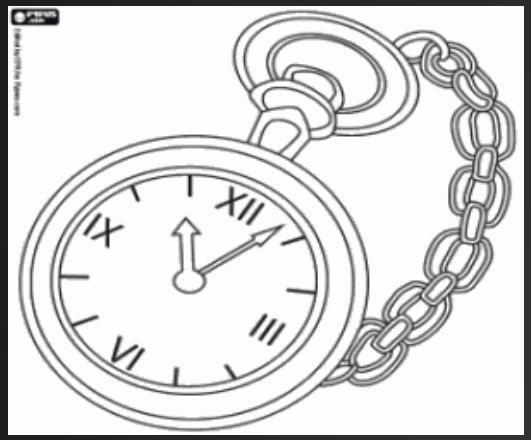
Secondary endpoints: included 30-day overall mortality and adverse events.

CHARACTERISTICS	Molnupiravir N= 169
Age, years	68.6 ± 17.6
Sex, male	97 (57.4)
Charlson comorbidity index	1.68±1.39
Previous anti-SARS-Cov-2 vaccination	146 (86.4)
McCabe Scale	
Ultimately fatal	72 (42.6)
Non-fatal	54 (32.0)
Rapidly fatal	43 (25.4)

Bassetti M; Vena A; personal data

Our clinical experience

Median time to study drug initiation from symptoms onset
2.3 days



CHARACTERISTICS	Molnupiravir N = 169
Risk factor for disease progression	
Cardiovascular disease	68 (40.2)
Onco-hematological disease	33 (19.5)
Primary or secondary immunodepression	36 (21.3)
Chronic obstructive pulmonary disease	27 (16.0)
Obesity (BMI≥30)	25 (14.8)
Diabetes mellitus	16 (9.5)
Chronic kidney failure	5 (3.0)

36 patients had more than 1 risk factor for disease progression

Bassetti M; Vena A; personal data

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Our clinical experience

Only 1 unvaccinated patient was admitted because of COVID-19

No patients died for Covid-19

Adverse events: rash with only one patient requiring treatment withdrawal

CHARACTERISTICS	Molnupiravir N= 169
Requirement for hospital admission or need for supplemental oxygen	7 (4.1)
Adverse events	2 (1.0)
30-day overall mortality	7 (4.1)

Our results suggest that molnupiravir is a well tolerated and effective drug for the treatment of mild moderate COVID-19

Bassetti M; Vena A; personal data

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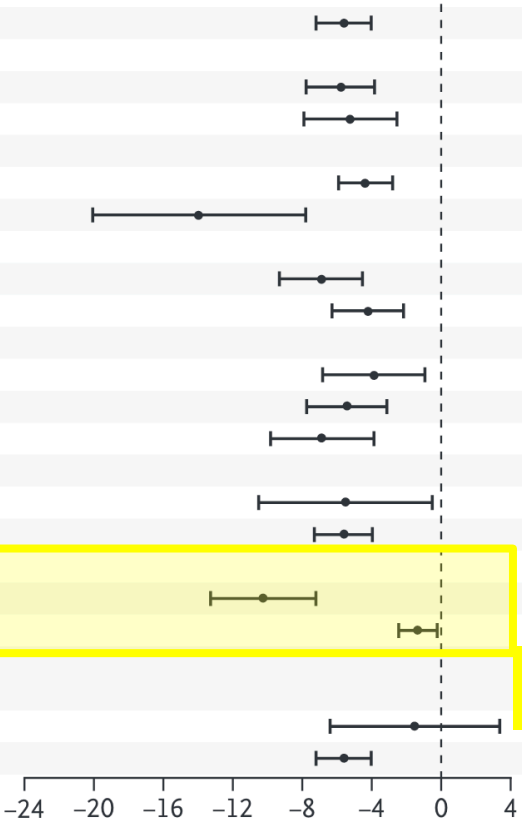
ESTABLISHED IN 1812 APRIL 14, 2022 VOL. 386 NO. 15

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

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	[illegible]
No	8/1039	66/1046	−5.62 (−7.21 to −4.03)



NNT 103

Genoa, Italy

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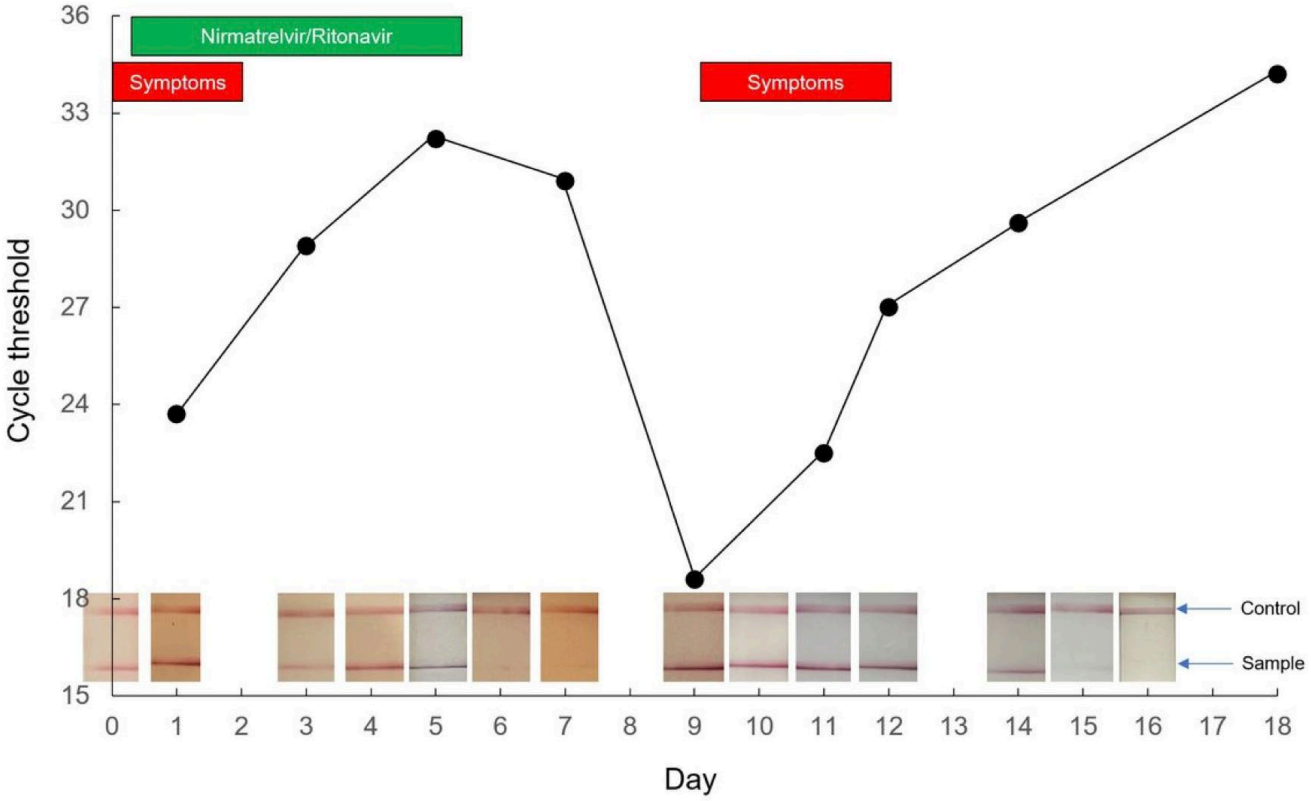
Hammond C; N Engl J Med 2022

Covid-19 Relapses after nirmatrelvir



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Gupta K; under Review; 2022

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What about monoclonal antibodies?

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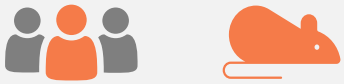
nAb-cocktail derived from a large pool of candidates

REGENERON

Antibodies collected

- **Convalescent plasma** from previously infected patients
- **Humanised mice** challenged with SARS-CoV-2 spike protein



Antibodies screened

- **Binding affinity**
- **Neutralisation potency**
- **3D structure**
- **Non-overlapping epitopes**

nAbs selected

Bind to distinct regions of the spike protein

Hansen. Science 2020
Baum. Science 2020
https://www.regeneron.com/covid19 (Accessed Sep 2020)

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MONOCLONAL ANTIBODIES

- **BAM**lanivimab
- **ETE**sevimab
- **CAS**irivimab
- **IMD**evimab
- **SOT**rovimab
- **CIL**gavimab
- **TIX**agevimab
- **REG**danvimab
- **BEB**telovimab

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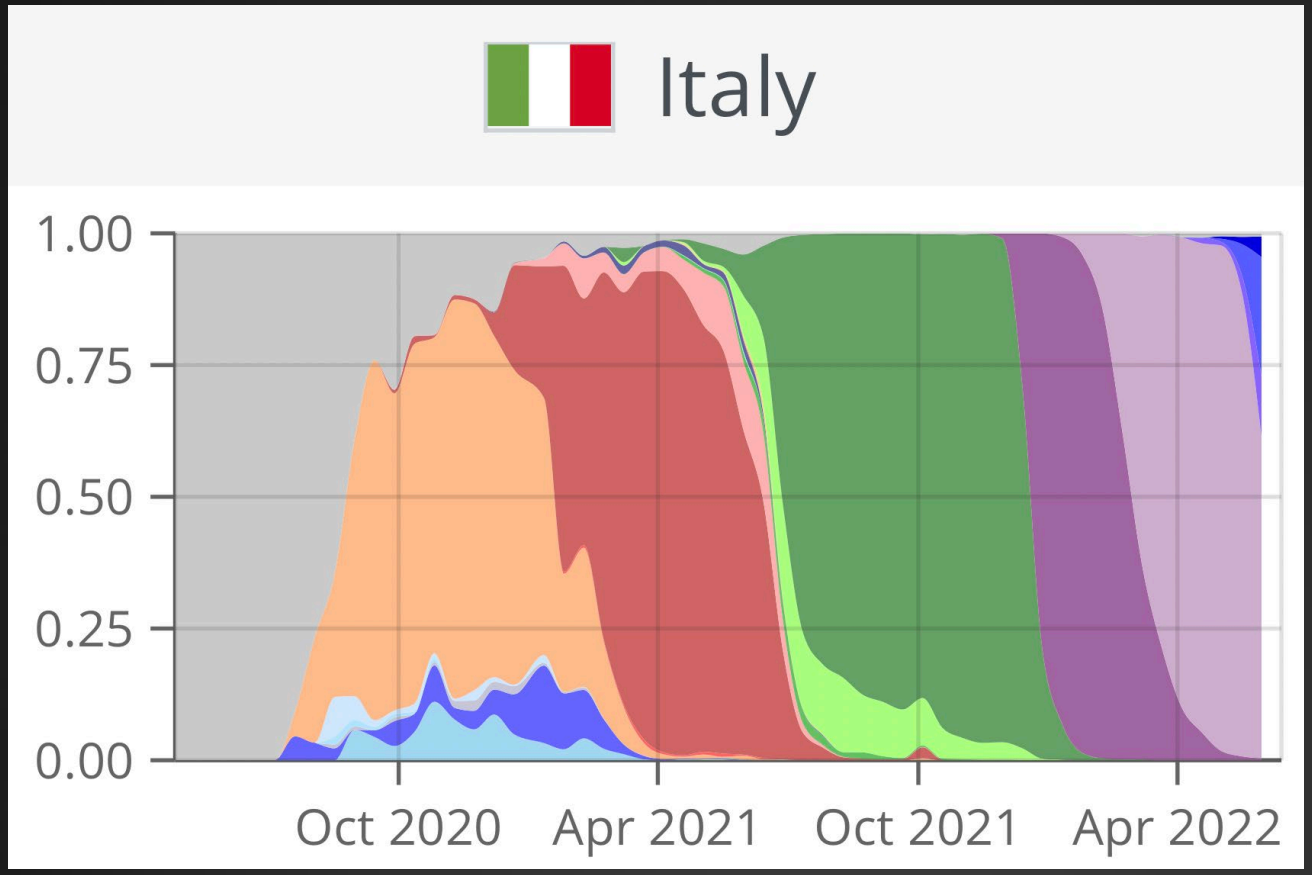
Variant of Concern
Italy



30 May 2022 - 13 Jun 2022

Variant	Num seq	Freq
21L (Omicron)	515	0.61
22B (Omicron)	192	0.23
22A (Omicron)	97	0.11
22C (Omicron)	33	0.04
others	5	0.01

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Monoclonal Antibodies Activity Against VOC

	BAM	ETE	BAM/ETE	CAS	IMD	CAS/IMD	CIL	TIX	CIL/TIX	SOT	REG	BEB	ADI
Alpha	1 21	13 18	1.3 9	1 27	0.6 28	1 13	0.6 12	1.5 11	0.8 11	2* 21	2.6 2	0.6 4	1.2 4
Beta	>1000 24	516 21	897 10	117 32	0.6 32	1.6 16	1.1 11	6.3 12	1.4 11	1 21	33 3	0.6 4	2.5 4
Gamma	>1000 15	313 15	404 4	154 21	0.4 21	1 8	0.5 11	5.9 10	0.9 8	1.2 16	61 3	0.7 3	1.8 4
Delta	>1000 20	0.5 20	1 8	0.8 22	1.5 23	1 9	2.5 8	0.9 8	1 9	1.6 15	9.8 3	0.7 4	1.5 4
Omicron/BA.1	>1000 23	340 22	794 9	>1000 26	>1000 27	>1000 12	305 24	306 25	75 15	4.5 29	>1000 7	0.7 7	108 10
Omicron/BA.2	>1000 3	444 3	897 2	>1000 4	161 4	344 3	1.8 6	674 5	5.4 6	32 7	-	0.8 2	638 2

BAMlanivimab, **ETE**sevimab, **CAS**irivimab, **IMD**evimab, **SOT**rovimab, **CIL**gavimab, **TIX**agevimab, **REG**danvimab, **BEB**telovimab

https://covdb.stanford.edu/page/susceptibility-data/

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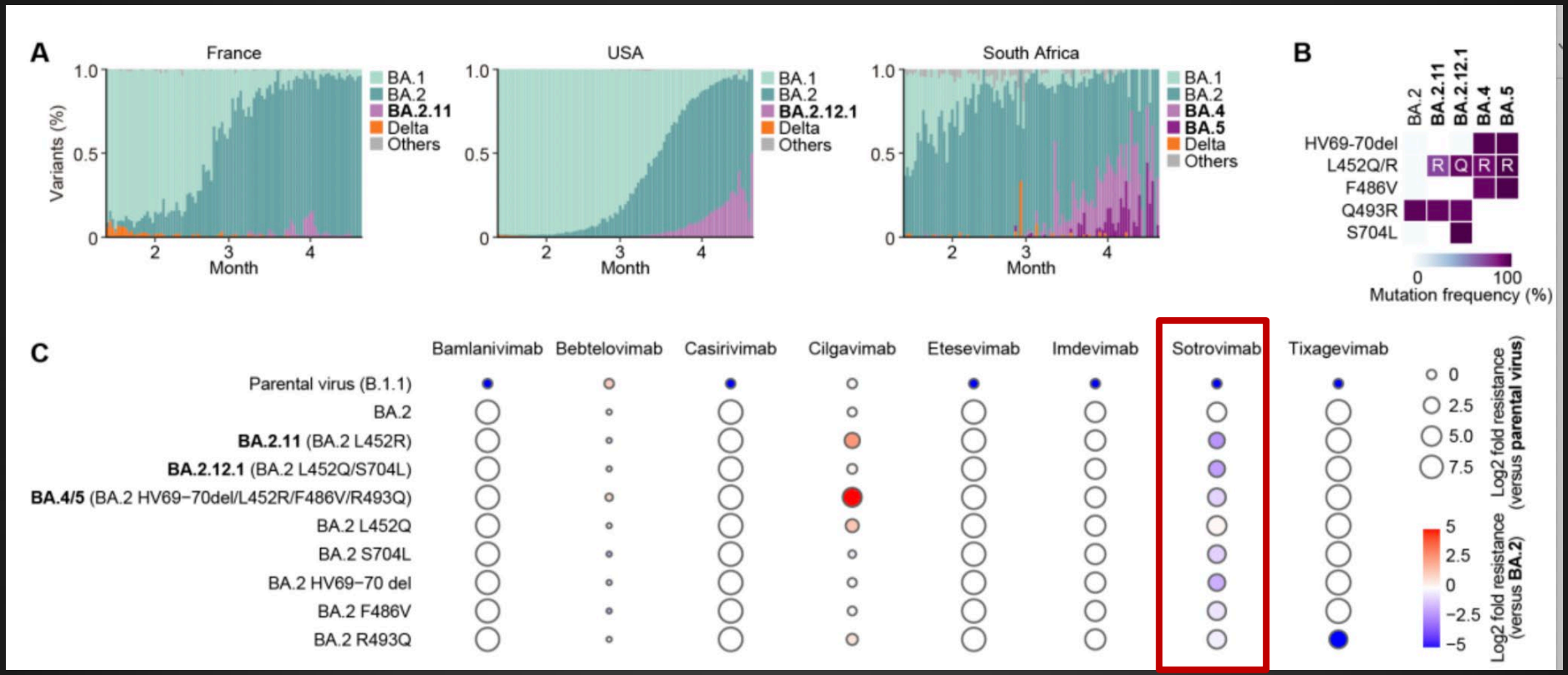
Sensitivity of novel SARS-CoV-2 Omicron subvariants, BA.2.11, BA.2.12.1, BA.4 and BA.5 to therapeutic monoclonal antibodies

Daichi Yamasoba, Ph.D.[1,2#], Yusuke Kosugi, M.S.[1#], Izumi Kimura, Ph.D.[1#], Shigeru Fujita, D.V.M.[1], Keiya Uriu, M.S.[1], Jumpei Ito, D.V.M., Ph.D.[1], Kei Sato, Ph.D.[1*], The



Yamasoba, Under Review bioRxiv.gov

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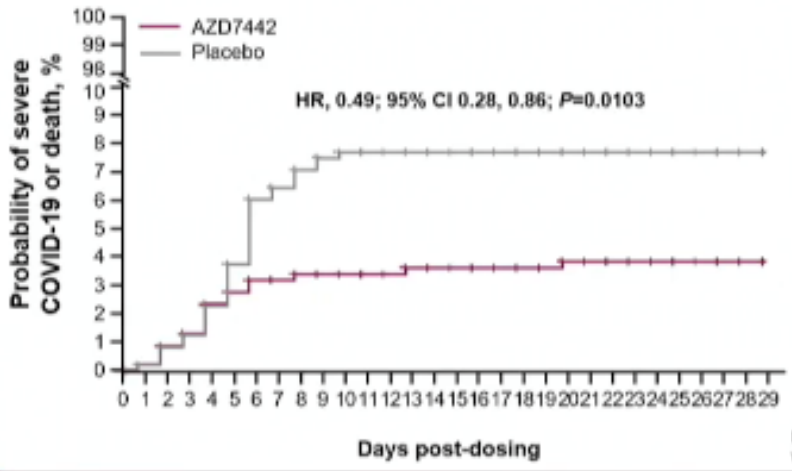
TIXAGEVIMAB/CILGAVIMAB

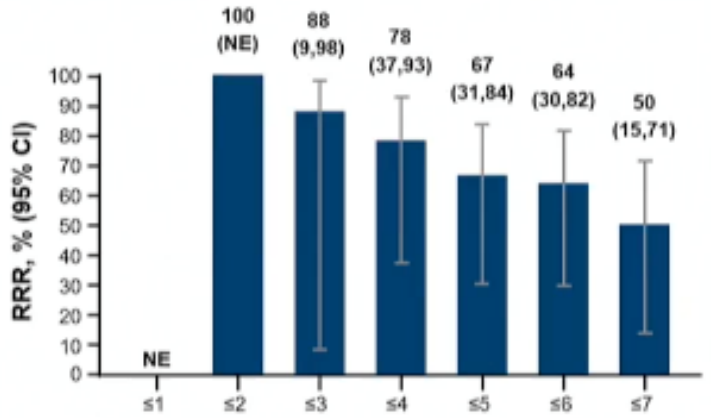
Primary endpoint met

(Reduction in severe COVID-19 or death when AZD7442 administered ≤7 days after symptom onset)

RRR of 50% (95% CI: 15, 71)
(*P*=0.010)* for AZD7442 vs placebo



Earlier treatment after symptom onset led to greater reductions in risk



No. of participants with event	≤1	≤2	≤3	≤4	≤5	≤6	≤7
AZD7442	0/6	0/29	1/90	4/172	9/253	11/329	18/407
Placebo	0/6	3/34	8/84	17/157	27/251	32/345	37/415

Conclusions A single 600 mg dose of intramuscular AZD7442 provided statistically and clinically significant protection against development of severe COVID-19 or death 28 days post-dose, with earlier treatment leading to more favourable outcomes

Montgomery; Lancet 2022

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ANYTHING ELSE?

FLUVAXIMINE

Table 1. Fluvoxamine COVID-19 Trial Details

Source	Dates	Original outcome	Inclusion criteria	Demographics	Fluvoxamine target dose[a]	Duration, d
Stop COVID 1[6] United States	April 10, 2020-August 5, 2020	Clinical deterioration: Hospitalization or new hypoxemia within 15 d	Age ≥18 unvaccinated positive test with: ≤7 d symptoms	Median age 46; 72% female; 70% White individuals; 56% BMI ≥ 30; 20% hypertension; 11% diabetes	100 mg	15
				Median 4 d of symptoms		
Stop COVID 2[9] United States and Canada	December 22, 2020-May 21, 2020	Clinical deterioration: Hospitalization or new hypoxemia within 15 d	Age ≥30 unvaccinated positive test with: ≤6 d symptoms	Median age 47; 62% female; 73% White individuals; 44% BMI ≥ 30; 21% hypertension; 9% diabetes	100 mg	15
			Criterion for high risk	Median 5 d of symptoms		
TOGETHER[10] Brazil	January 20, 2021-August 5, 2021	ED visit ≥6 h or hospitalization within 28 d	Age ≥18 unvaccinated positive test with: ≤7 d symptoms	Median age 50; 55% female; 96% mixed race; 51% BMI ≥ 30; 13% hypertension; 16% diabetes	100 mg	10
			Criterion for high risk	Mean 3.8 d of symptoms[b]		

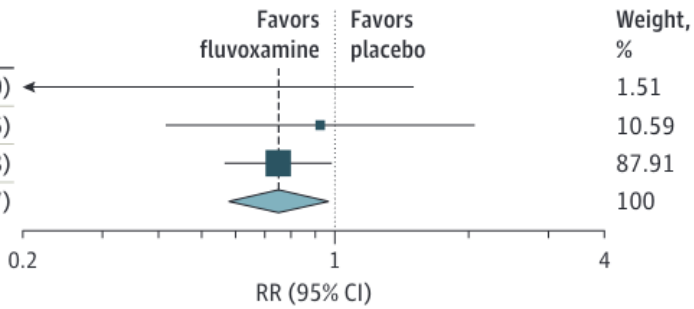
Abbreviations: BMI, body mass index; ED, emergency department.

[a] Target dose was to be taken orally twice a day.

[b] Median not provided; missing data on approximately 23% of participants.

Figure 2. Frequentist Random Effects Meta-analysis

Study	Fluvoxamine No./total No.	Control No./total No.	RR (95% CI)	Weight, %
STOP COVID 1	1/80	5/72	0.18 (0.02-1.50)	1.51
STOP COVID 2	11/272	12/275	0.93 (0.42-2.06)	10.59
Together	76/741	104/756	0.75 (0.56-0.98)	87.91
Overall REML: $I^2 = 0.2\%$, $P = .37$	88/1093	121/1103	0.75 (0.58-0.97)	100



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DISCUSSION

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