SITA
Società Italiana di Terapia Antinfettiva
Antibatterica Antivirale Antifungina

14° CONGRESSO NAZIONALE
GENOVA | 21-22 novembre 2024

TDM
Therapeutic Drug Monitoring

Sessione 7 | Focus su Sars-CoV-2

Futuro terapeutico dell'infezione da SarsCoV-2

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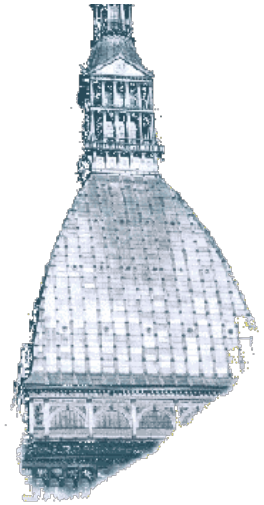
Clinica di Malattie Infettive
Università degli Studi di Torino
Ospedale Amedeo di Savoia



Ospedale Amedeo di Savoia

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- Abbvie
- Gilead Sciences
- MSD
- Janssen
- ViiV
- Pfizer
- Novartis
- Angelini
- HL Roche
- Astra Zeneca
- GSK

SARS – CoV – 2 EARLY TREATMENT (registration trials vs Placebo)

DRUG	Total Patients Enrolled	RRR Relative Risk Reduction	NNT Number Needed to be Treated to avoid 1 outcome	Age (Median)	Placebo with Primary end Point*	Deaths Drug / Placebo
REMDESIVIR	562	86.8%	21.73	50 ± 15 > 60: **30.2%**	5.3%	0 / 0
NIRMATRELVIR RITONAVIR	2246	88.9%	17.45	46 > 65: **14.7%**	6.45%	0 / 12 Death rate N/r = 0 Death rate P = 1.06
MOLNUPIRAVIR	1433	30.1%	34.48	42 > 60: **17.2%**	9.7%	1 / 9 Death rate M = 0.14 Death rate P = 1.25
SOTROVIMAB	583	85%	16.6	53 > 65: **22%**	7%	0 / 1 Death rate S = 0 Death rate P = 0.34

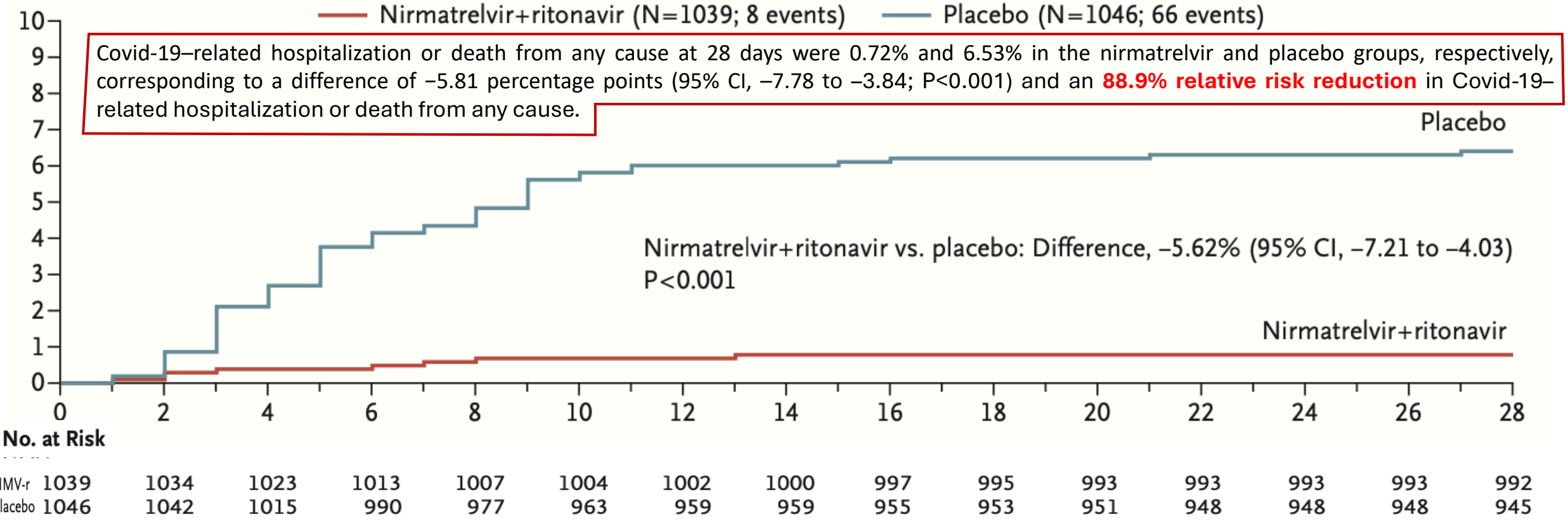
* Hospitalization or Death

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

Jennifer Hammond, et al. NEJM 2022; February 16, 2022, DOI: 10.1056/NEJMoa2118542 The NEW ENGLAND JOURNAL of MEDICINE

1120 Were assigned to receive nirmatrelvir (300 mg) and ritonavir (100 mg) bid x 5 d

1126 Were assigned to receive placebo



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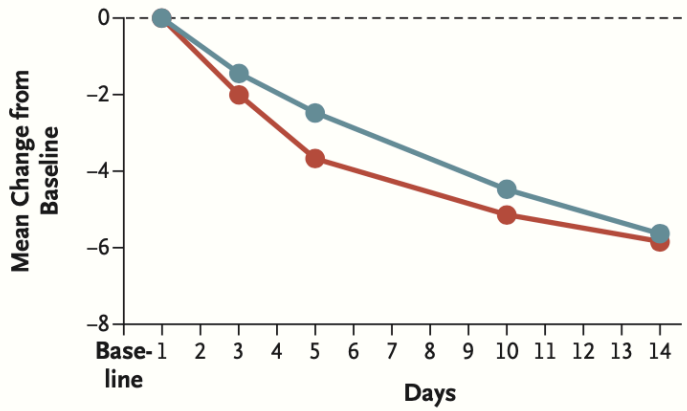
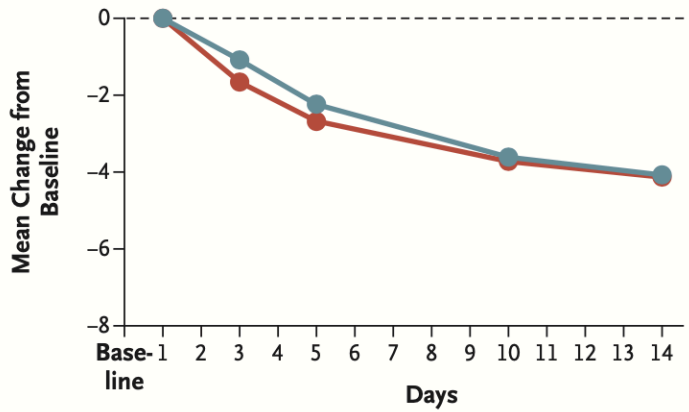
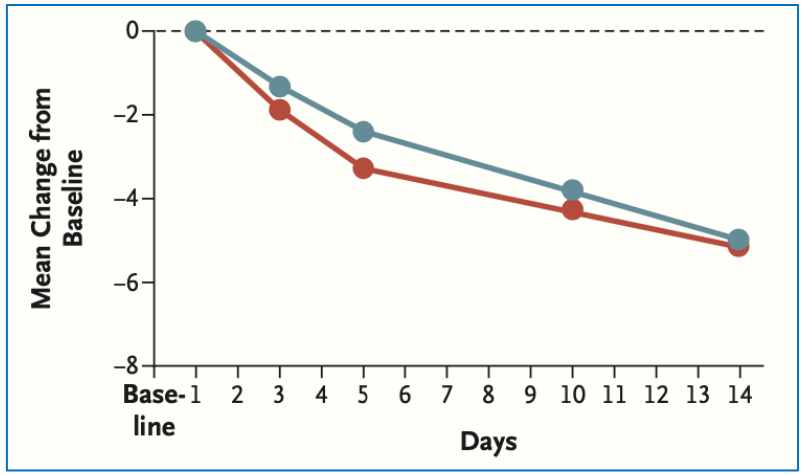
Seronegative



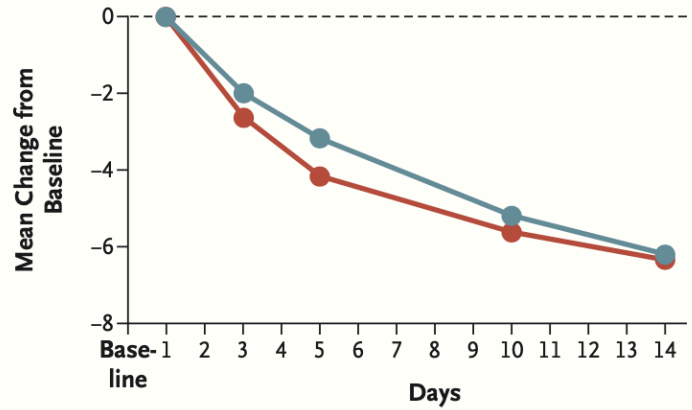
Seropositive



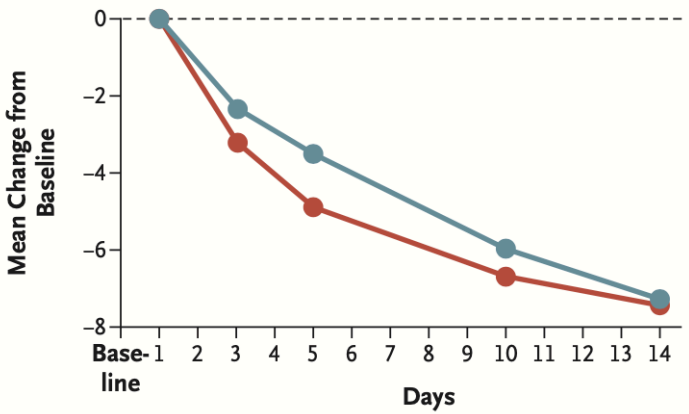
Overall Population

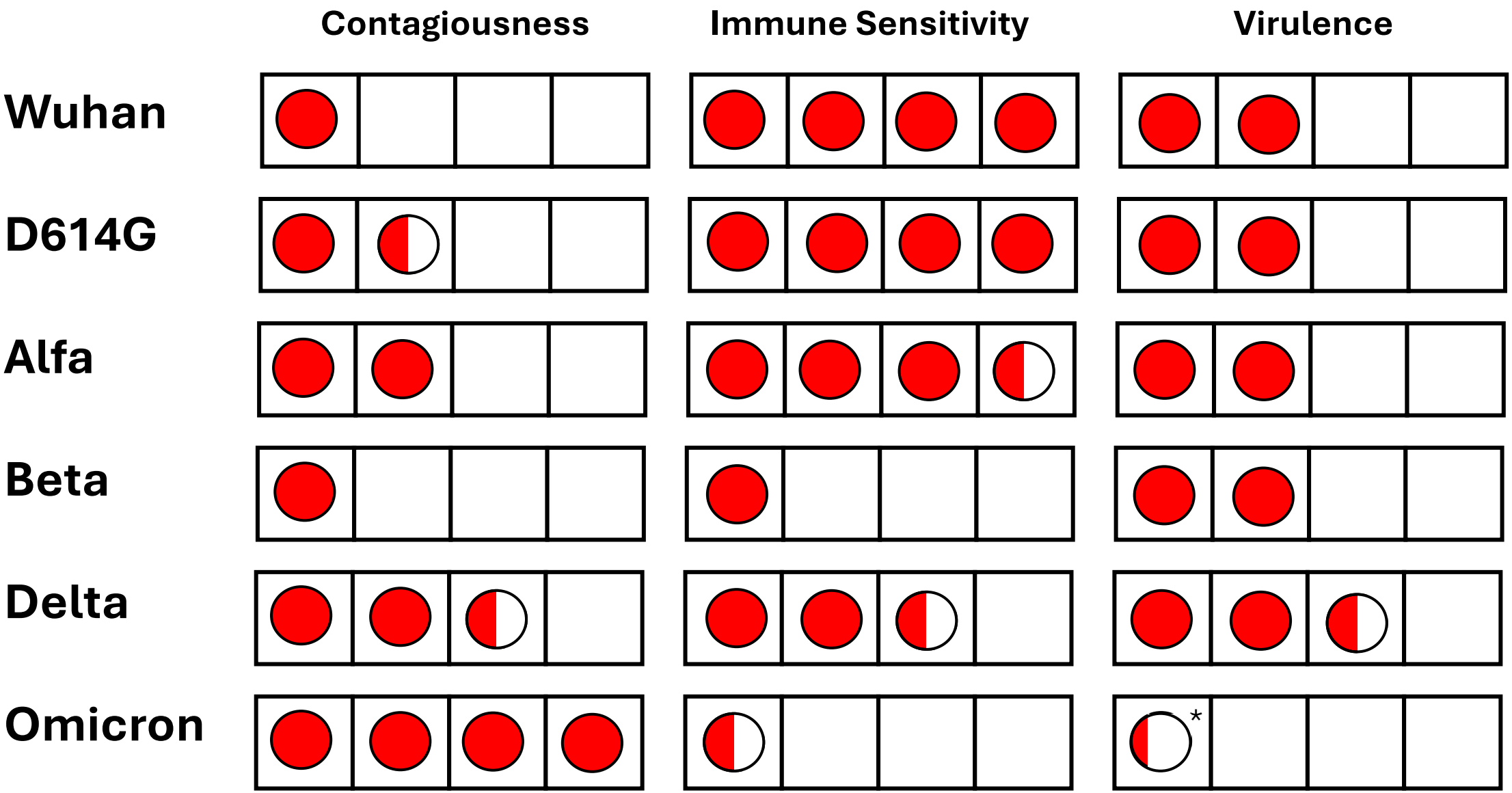


Baseline Viral Load >10^4 copies/ml



Baseline Viral Load >10^7 copies/ml




Contagiousness
Immune Sensitivity
Virulence
Wuhan
D614G
Alfa
Beta
Delta
Omicron
*
* Effect of Vaccination to be considered

Nirmatrelvir for Vaccinated or Unvaccinated Adult Outpatients with Covid-19

The NEW ENGLAND JOURNAL of MEDICINE

Jennifer Hammond, et al. **N Engl J Med 2024;390:1186-95.**

Adults who had:

- confirmed Covid-19;
- symptom onset within the past 5 days;
- fully vaccinated against Covid-19 and who had at least one risk factor for severe disease;
- patients without such risk factors who had never been vaccinated against Covid-19 or had not been vaccinated within the previous year,

1:1 ratio

nirmatrelvir– ritonavir → 658

placebo → 638

every 12 hours for 5 days

Characteristic	Nirmatrelvir–Ritonavir (N=658)	Placebo (N=638)	Total (N=1296)
Median age (range) — yr	41 (18–87)	42 (18–82)	42 (18–87)
Most common risk factors — no. (%)**			
BMI ≥30	109 (16.6)	122 (19.1)	231 (17.8)
Smoking	86 (13.1)	86 (13.5)	172 (13.3)
Hypertension	83 (12.6)	77 (12.1)	160 (12.3)
Diabetes mellitus	34 (5.2)	32 (5.0)	66 (5.1)
≥65 yr of age	36 (5.5)	29 (4.5)	65 (5.0)

Nirmatrelvir for Vaccinated or Unvaccinated Adult Outpatients with Covid-19

The NEW ENGLAND JOURNAL of MEDICINE

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Table 2. Time to Sustained Alleviation of All Targeted Signs and Symptoms through Day 28.*

Variable	Nirmatrelvir–Ritonavir (N=654)	Placebo (N=634)
Mean trial follow-up — days	27.4	27.5
Mean time at risk for event — days	13.1	13.7
No. of participants with sustained alleviation (%)	477 (72.9)	470 (74.1)
Time to sustained alleviation		
Median (95% CI) — days	12 (11–13)	13 (12–14)
Mean — days	13.8	14.1
P value by log-rank test	0.60	

Participants recorded daily symptom severity on a 4-point scale:

0, absent;
1, mild;
2, moderate;
3, severe)

- 5 of the 654 participants (0.8%) on NMT/r
- 10 of the 634 (1.6%) placebo

were hospitalized for Covid-19 or died from any cause through day 28

(−0.8 % - 95% CI −2.0 to 0.4)

0/5 NMT/r in ICU
3/10 placebo in ICU

In high-risk participants, hospitalization or death occurred in:

- 3 (0.9%) in the NMT/r group
- 7 (2.2%) in the placebo group

(−1.3 % ; 95% CI −3.3 to 0.7)

Treating Acute Covid-19 — Final Chapters Still Unwritten

N ENGL J MED 390;13 NEJM.ORG APRIL 4, 2024

Rajesh T. Gandhi, M.D., and Martin Hirsch, M.D.

As with many medical interventions, there is likely to be a ***gradient of benefit*** for nirmatrelvir–ritonavir, with the ***patients at highest risk for progression most likely to derive the greatest benefit.***

Thus, it appears reasonable to recommend nirmatrelvir– ritonavir primarily for the treatment of Covid-19 in ***older patients (particularly those ≥65 years of age)***, those who are ***immunocompromised***, and those who have conditions that substantially increase the risk of severe Covid-19, ***regardless of previous vaccination or infection status***.

Early combination therapy of COVID-19 in high-risk patients

Hans Martin Orth, et al. Infection (2023) 52:877–889

Retrospective, multicentre study

Inclusion:
n=144

144 patients were included with a median duration of SARS-CoV-2 viral load≥ 10^6 copies/ml of 8.0 days (IQR 6.0–15.3).

COVID-19 pneumonia [%] 13.2 (n = 19/144)

- **1x DAA plus 1x mAB:** n=96
- **2x DAAs:** n=29
- **2x DAAs plus 1x mAB:** n=19

Co-primary endpoints:

1) Days with SARS-CoV-2 viral load ≥10^6 RNA copies/ml
2) Occurrence of prolonged viral shedding

Omicron [%]	58.3 (n = 84/144)
Delta [%]	0.7 (n = 1/144)
No sequencing [%]	41.0 (n = 59/144)

Prolonged viral shedding was defined as SARS-CoV-2 viral load≥ 10^6 RNA copies/ ml 21 days after treatment initiation.

Early combination therapy of COVID-19 in high-risk patients

Hans Martin Orth, et al. Infection (2023) 52:877–889

1 × DAA plus 1 × mAB [%]	66.7 (n = 96/144)
Remdesivir + mAB [%]	66.7 (n = 64/96)
Nirmatrelvir/ritonavir + mAB [%]	19.8 (n = 19/96)
Molnupiravir + mAB [%]	13.5 (n = 13/96)
2 × DAAs [%]	20.1 (n = 29/144)
Remdesivir + molnupiravir [%]	79.3 (n = 23/29)
Remdesivir + nirmatrelvir/ritonavir [%]	17.3 (n = 5/29)
Molnupiravir + nirmatrelvir/ritonavir [%]	3.4 (n = 1/29)
2 × DAAs plus 1 × mAB [%]	13.2 (n = 19/144)
Remdesivir + molnupiravir + mAB [%]	84.2 (n = 16/19)
Remdesivir + nirmatrelvir/ritonavir + mAB [%]	10.5 (n = 2/19)
Molnupiravir + nirmatrelvir/ritonavir + mAB [%]	5.3 (n = 1/19)

Days with SARS-CoV-2 RNA ≥ 10^6 copies	
All [median]	8.0 (IQR 6.0–15.3)
Under 1 × DAA plus 1 × mAB [median]	9.5 (IQR 6.0–14.0)
Under 2 × DAAs [median]	8.0 (IQR 6.0–14.0)
Under 2 × DAAs plus 1 × mAB [median]	6.0 (IQR 5.0–8.0)

Therapeutical agents	
DAAs [absolute]	192
Remdesivir [%]	57.3 (n = 110/192)
Molnupiravir [%]	28.1 (n = 54/192)
Nirmatrelvir/ritonavir [%]	14.6 (n = 28/192)
mABs [absolute]	115
Sotrovimab [%]	74.8 (n = 86/115)
Tixagevimab/cilgavimab [%]	23.5 (n = 27/115)
Casirivimab/imdevimab [%]	1.7 (n = 2/115)

Prolonged viral shedding was observed in **14.6%** (n = 21/144). Clinical courses of COVID-19 were mild to moderate.

Underlying haematological malignancies (HM) (p = 0.03) and **treatment initiation later than five days after diagnosis** (p < 0.01) were significantly associated with longer viral shedding.

Oral Simnotrelvir for Adult Patients with Mild-to-Moderate Covid-19

Bin Cao, et al. N Engl J Med 2024;390:230-41.

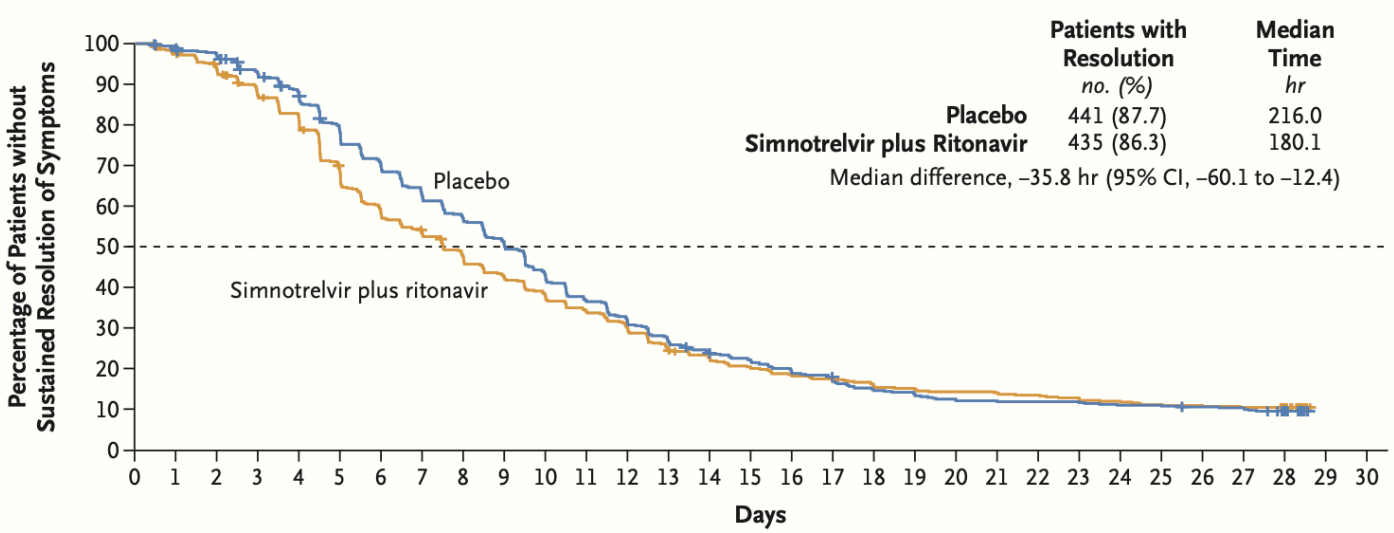
The primary efficacy end point was the time to **sustained resolution of symptoms**, defined as the absence of 11 Covid-19–related symptoms for 2 consecutive days.

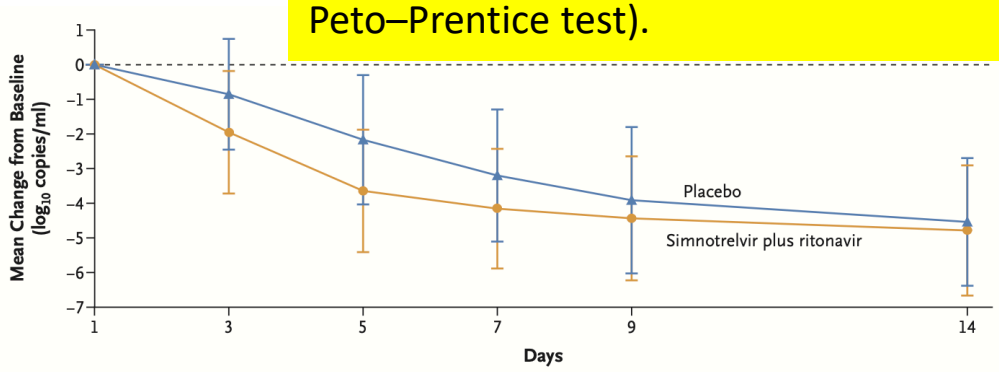
603 Were assigned to receive simnotrelvir (750 mg) plus ritonavir (100 mg)

605 Were assigned to receive placebo

Characteristic	Simnotrelvir plus Ritonavir (N=573)	Placebo (N=566)	Total (N=1139)
Median age (IQR) — yr	35 (28–47)	35 (28–47)	35 (28–47)
Age ≥60 yr	18 (3.1)	20 (3.5)	38 (3.3)
At least one risk factor	302 (52.7)	307 (54.2)	609 (53.5)

Patients who received the first dose of trial drug or placebo **within 72 hours after symptom onset**, the time to sustained resolution of Covid-19 symptoms was significantly shorter in the simnotrelvir group than in the placebo group (**180.1** hours [95% CI 162.1 to 201.6] vs. **216.0** hours [95% CI, 203.4 to 228.1]; median difference, −35.8 hours [95% CI, −60.1 to −12.4]; P=0.006 by Peto–Prentice test).





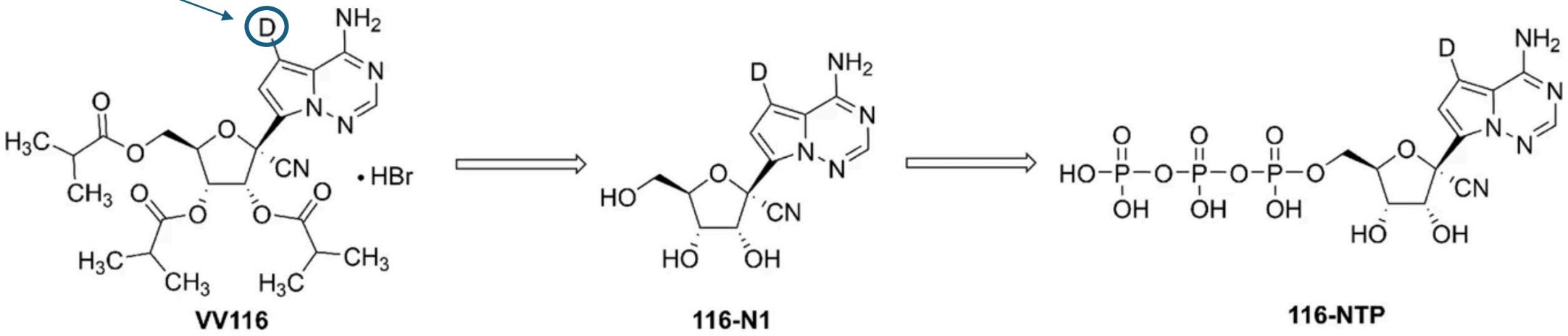
Safety, tolerability, and pharmacokinetics of VV116, an oral nucleoside analog against SARS-CoV-2, in Chinese healthy subjects

Hong-Jje Qian, et al. Acta Pharmacologica Sinica 2022; 43: 3130–3138

APS | Acta Pharmacologica Sinica

What VV116 is:

Deuterated remdesivir hydrobromide with oral bioavailability



After oral administration, VV116 is rapidly converted to 116-N1, which undergoes three successive enzymatic phosphorylation reactions in cells to yield the triphosphate active form, 116-NTP.

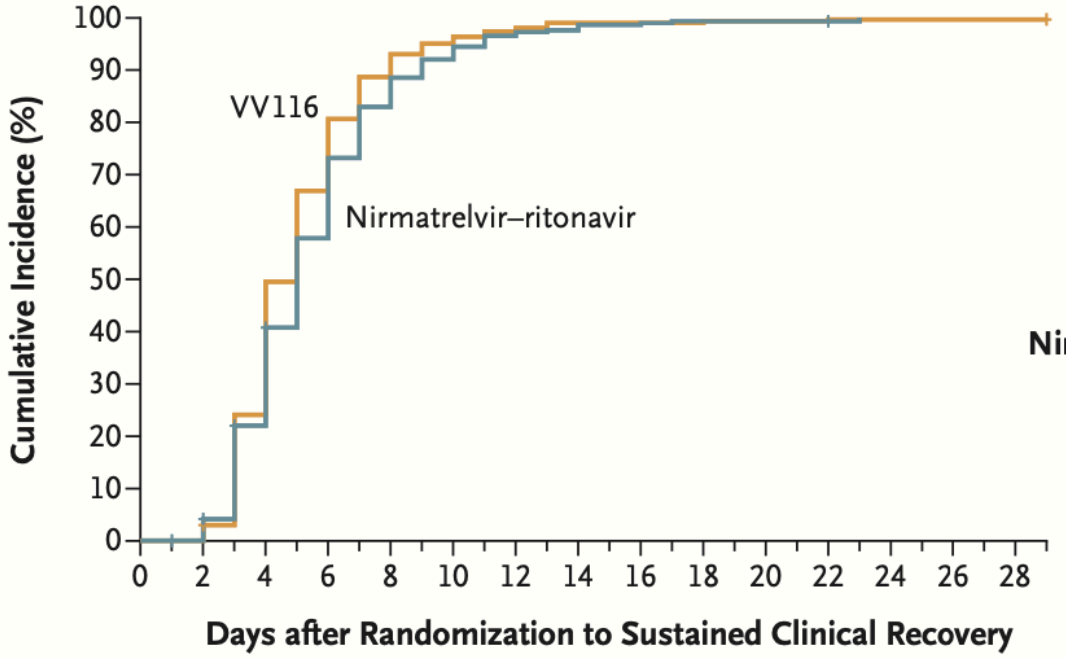
VV116 versus Nirmatrelvir–Ritonavir for Oral Treatment of Covid-19

The NEW ENGLAND JOURNAL of MEDICINE

Z. Cao, et al. N Engl J Med 2023;388:406-17.

Characteristic	VV116 (N=384)	Nirmatrelvir–Ritonavir (N=387)	Total (N=771)
Median age at randomization (range) — yr	53.0 (18–94)	53.0 (18–91)	53.0 (18–94)
Age of ≥60 yr	144 (37.5)	147 (38.0)	291 (37.7)

C Sustained Clinical Recovery, Participants Who Started Trial Regimen within 5 Days after Symptom Onset



	No. of Participants	No. of Events (%)	25th Percentile (95% CI)	Median
			days	*days*
VV116	303	298 (98.3)	4.0 (3.0–4.0)	5.0
Nirmatrelvir–Ritonavir	293	287 (98.0)	4.0 (3.0–4.0)	5.0

Hazard ratio, 1.21 (95% CI, 1.02–1.42)

No. at Risk

VV116	303	303	227	99	34	15	8	3	3	3	2	2	1	1	1	1
Nirmatrelvir–ritonavir	293	292	225	121	49	23	10	7	4	2	2	2	0	0	0	0

VV116 versus Nirmatrelvir–Ritonavir for Oral Treatment of Covid-19

The NEW ENGLAND JOURNAL of MEDICINE

Z. Cao, et al. N Engl J Med 2023;388:406-17.

Clinical recovery — no. (%)	VV116 (N=384)	Nirmatrelvir–Ritonavir (N=387)
By day 5	255 (66.4)	223 (57.6)
By day 7	331 (86.2)	316 (81.7)
By day 10	362 (94.3)	356 (92.0)
By day 14	374 (97.4)	374 (96.6)
By day 28	378 (98.4)	378 (97.7)
Symptom resolution — no. (%)		
By day 5	109 (28.4)	94 (24.3)
By day 7	207 (53.9)	191 (49.4)
By day 10	283 (73.7)	276 (71.3)
By day 14	334 (87.0)	334 (86.3)
By day 28	364 (94.8)	370 (95.6)
SARS-CoV-2 clearance — no. (%)		
By day 5	186 (48.4)	183 (47.3)
By day 7	288 (75.0)	275 (71.1)
By day 10	337 (87.8)	345 (89.1)
By day 14	364 (94.8)	358 (92.5)

Adverse Event	VV116 (N=384)	Nirmatrelvir–Ritonavir (N=387)
	no. of participants (%)	
Adverse events overall		
Any adverse event	259 (67.4)	299 (77.3)
Adverse event with maximum grade of ≥3†	10 (2.6)	22 (5.7)
Serious adverse event‡	1 (0.3)	2 (0.5)
Adverse event leading to discontinuation of trial regimen	6 (1.6)	9 (2.3)
Adverse event leading to dose reduction or temporary discontinuation of trial regimen	5 (1.3)	4 (1.0)
Adverse events considered by the investigator to be related to the assigned regimen		
Any adverse event	199 (51.8)	260 (67.2)
Adverse event with maximum grade of ≥3†	7 (1.8)	20 (5.2)
Serious adverse event	0	0
Adverse event leading to discontinuation of trial regimen	6 (1.6)	9 (2.3)
Adverse event leading to dose reduction or temporary discontinuation of trial regimen	4 (1.0)	4 (1.0)

Oral VV116* versus placebo in patients with mild-to-moderate COVID-19 in China: a multicentre, double-blind, phase 3, randomised controlled study

Xiaohong Fan, et al. Lancet Infect Dis 2024; 24: 129–39

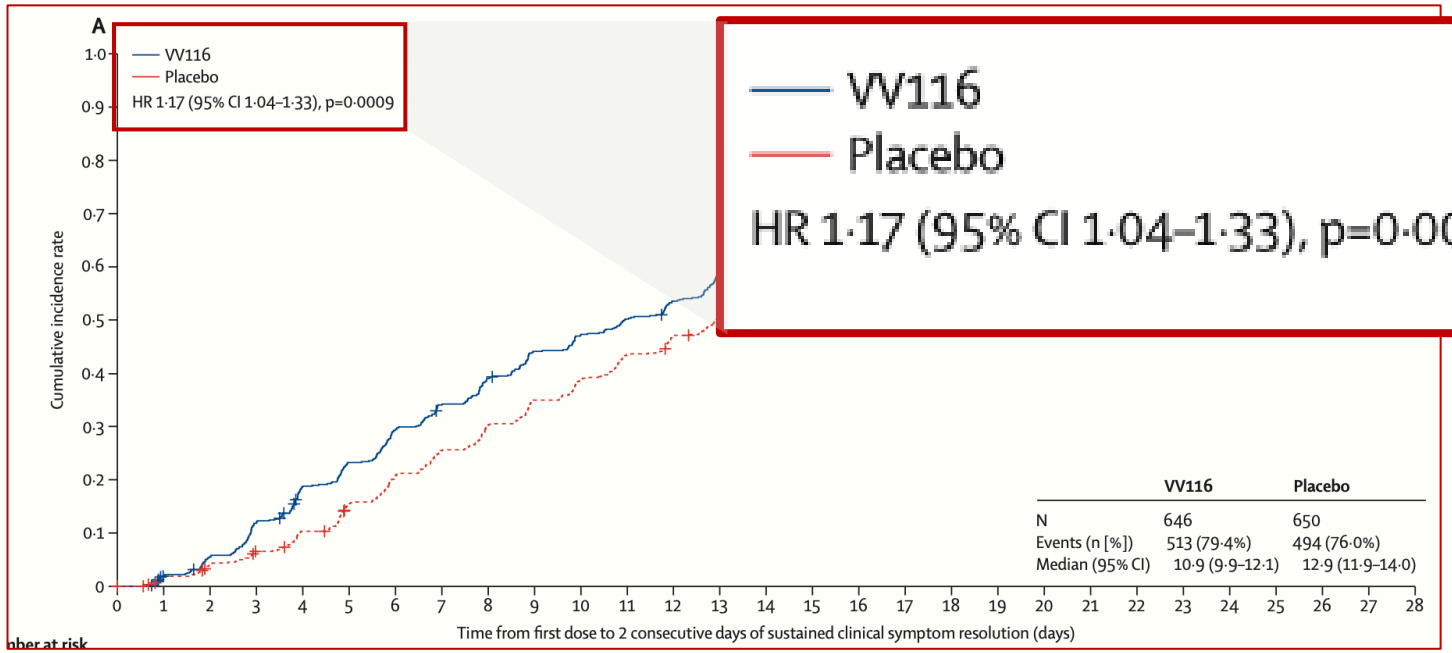
* mindeudesivir

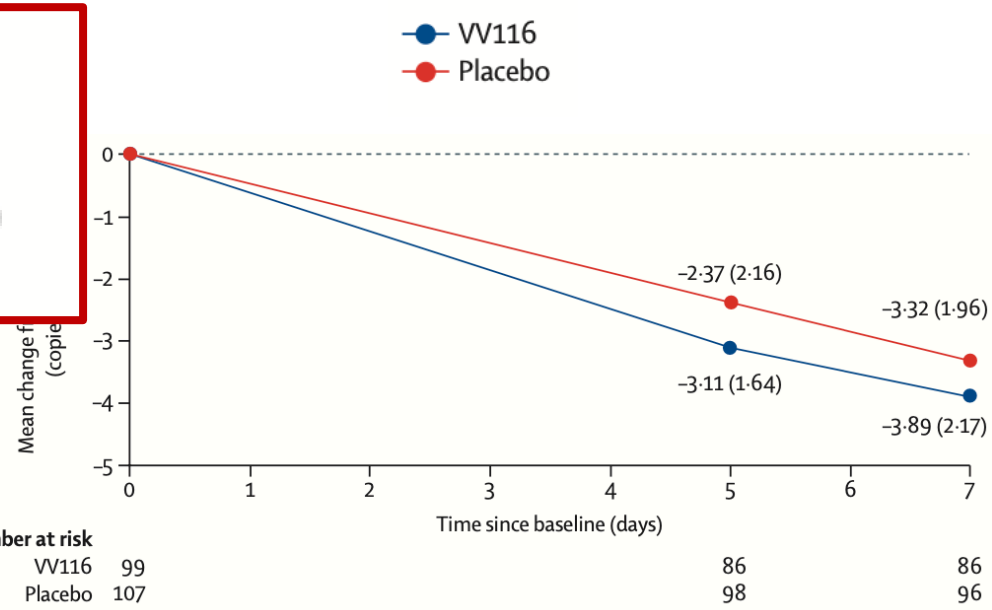
674 received VV116 (full analysis set)

673 received placebo (full analysis set)

0·6 g every 12 h on day 1 and 0·3 g every 12 h on days 2–5

	VV116 (n=646)	Placebo (n=650)
Age		
Median (IQR)	35·0 (29·0–46·0)	35·0 (28·0–47·0)
<60 years	600 (92·9%)	603 (92·8%)
≥60 years	46 (7·1%)	47 (7·2%)



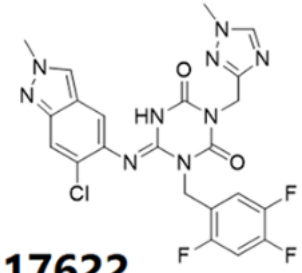


Sasaki *et al.*, *Sci. Transl. Med.* published First Release 3 November 2022

S-217622 (ensitrelvir), an inhibitor of SARS-CoV-2 main protease (M_{pro}, also known as 3C-like protease).

S-217622 inhibited viral proliferation at low nanomolar to sub-micromolar concentrations in cells.

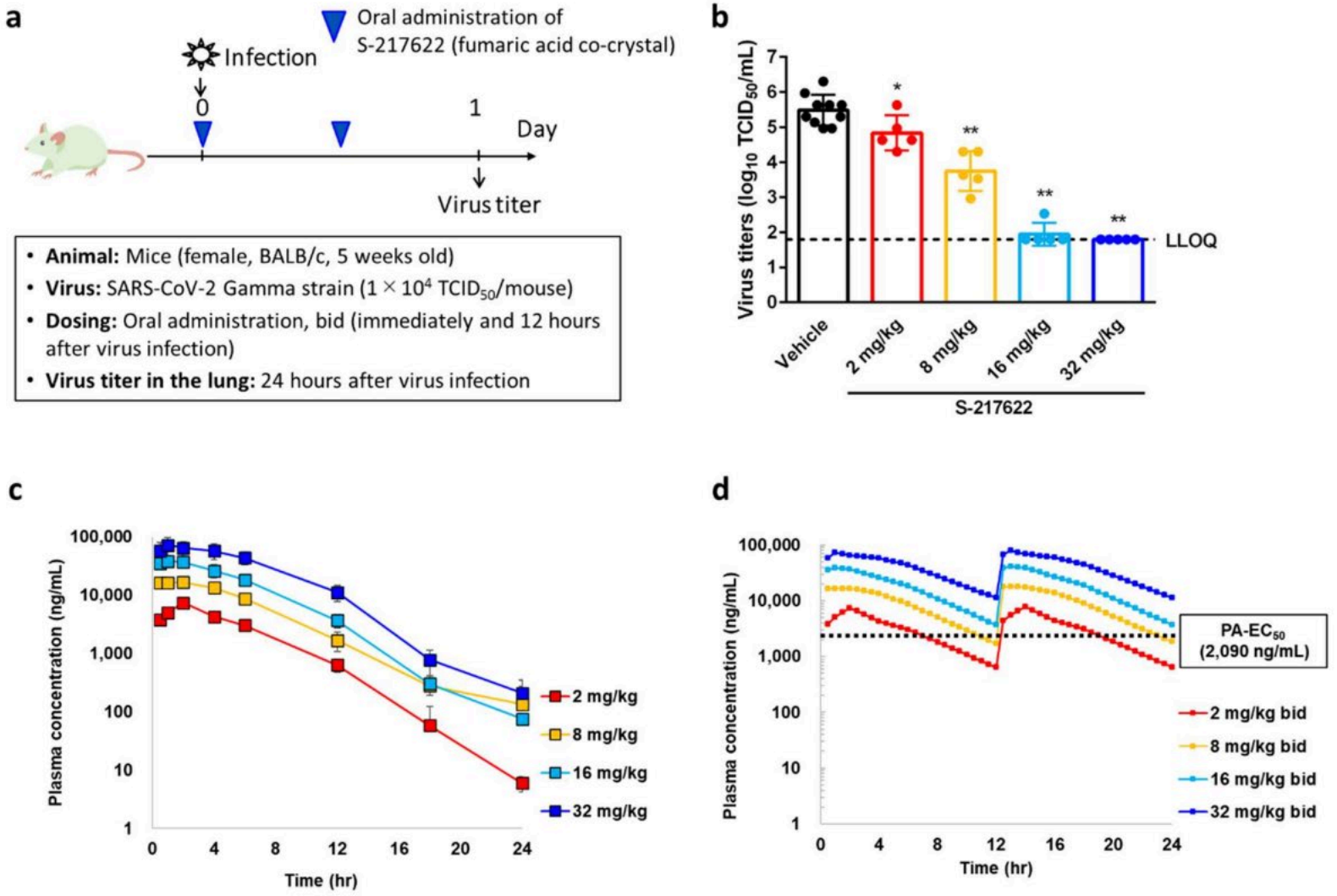
S-217622 (ensitrelvir) decreases viral load and ameliorates disease severity in SARS-CoV-2-infected hamsters.



S-217622
$3CL^{pro}$ IC_{50} : 0.013 μM
EC_{50} : 0.29 - 0.50 μM

S-217622 exerted antiviral activity against SARS-CoV-2 variants of concern (VOCs), including the highly pathogenic Delta variant and the recently emerged Omicron BA.5 and BA.2.75 variants.

Under evaluation in a phase 3 clinical trial (clinical trial registration no. jRCT2031210350)

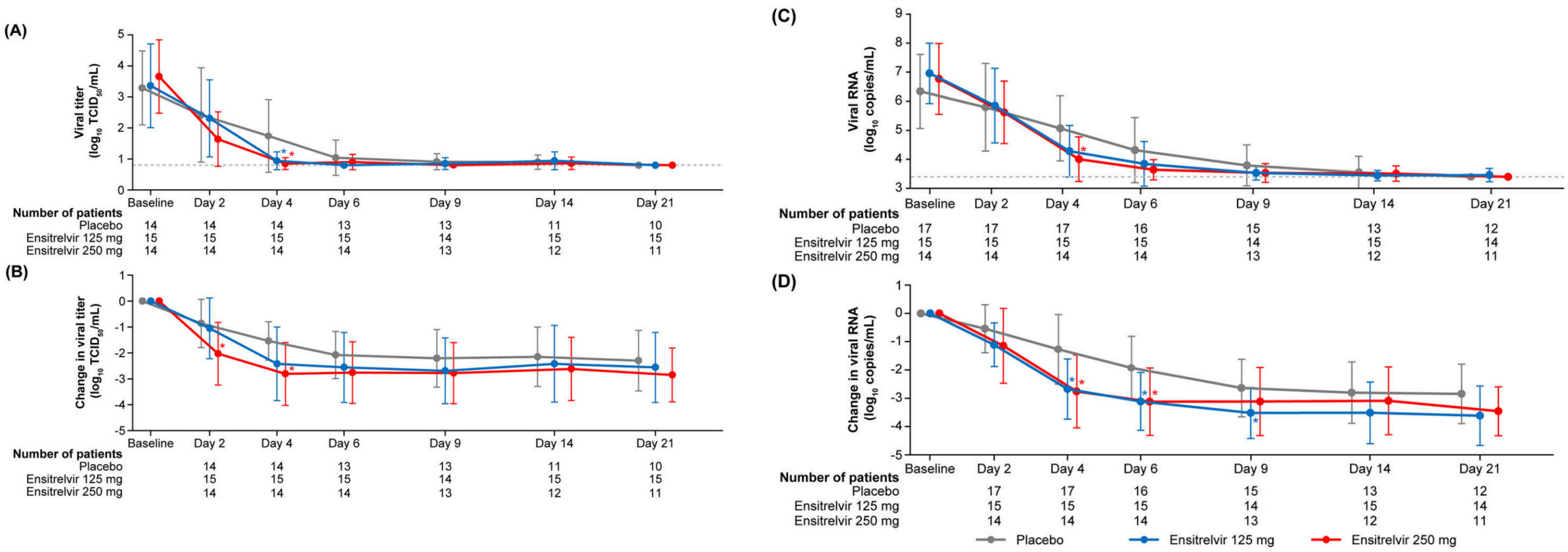


Dose-dependent in vivo antiviral efficacy of S-217622 in mice infected with SARSCoV-2. (a) Protocol for the in vivo study. bid = twice a day; (b) Effect of S-217622 (fumaric acid co-crystal) treatment on lung viral titers in SARS-CoV-2 Gamma strain (hCoV19/Japan/TY7-501/2021)-infected mice. TCID50 = 50% tissue culture infectious dose; each point represents an individual viral titer (n = 5–10). The broken line represents the lower limit of quantification (1.80 log10 TCID50/mL).

A Randomized Phase 2/3 Study of Ensitrelvir, a Novel Oral SARS-CoV-2 3C-Like Protease Inhibitor, in Japanese Patients with Mild-to-Moderate COVID-19 or Asymptomatic SARS-CoV-2 Infection: Results of the Phase 2a Part

AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy®

Hiroshi Mukae, et al. October 2022 Volume 66 Issue 10



SARS-CoV-2 viral titer as (A) absolute values and (B) change from baseline (mITT population), and SARSCoV-2 viral RNA level as (C) absolute values and (D) change from baseline (ITT population). Data are presented as mean 6 standard deviation (SD). *, P , 0.05 versus placebo. The gray, dotted, horizontal lines in panels (A) and (C) indicate the lower limit of detection of viral titer (0.8 log10 TCID50/mL) and lower limit of quantification of viral RNA (3.40 log10 copies/mL), respectively. TCID50, 50% tissue culture infectious dose.

PRESSRELEASE

Sept 28th, 2022

SHIONOGI

Shionogi Announces Achievement of the Primary Endpoint for Ensitrelvir Fumaric Acid (S-217622) in the Phase 3 part of the Phase 2/3 Clinical Trial in Asia

This study was conducted in patients with mild/moderate symptoms of COVID-19 and assessed clinical symptom resolution with ensitrelvir (2 dose groups; high dose and low dose), orally administered once daily for five days, compared to placebo.
A total of **1,821 patients** were enrolled, in Japan, South Korea, and Vietnam, **irrespective of risk factors for COVID-19 progression**. The majority of patients were previously vaccinated.
The primary endpoint in the study was the time to resolution of **five key COVID-19 symptoms** (stuffy or runny nose, sore throat, cough, feeling hot or feverish, and low energy or tiredness) which are characteristic of infection with the SARS-CoV-2 Omicron variant, in patients randomized within 72 hours from the onset of symptoms.

In this population, the **median time to resolution** of the five COVID-19 symptoms was significantly **reduced in those treated with the low dose of ensitrelvir** (the dose level submitted for approval in Japan) compared to placebo: **167.9 hours versus 192.2 hours**, a statistically significant difference of 24 hours (p=0.04).
In addition, with respect to the key secondary endpoint of **reduction in viral RNA on day 4** (following the third dose), **ensitrelvir showed a significant difference versus placebo** (p<0.0001) in the Least Squares mean change from baseline in viral RNA; a **reduction of more than 1.4 log10 copies/mL versus placebo**, similar to the results observed in previous studies.

In the low-dose group, the most common treatment- related adverse events were decreased high-density lipoprotein and increased blood triglycerides, as observed in previous studies.

PRESSRELEASE

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Release 2022/11/22

Xocova® (Ensitrelvir Fumaric Acid) Tablets 125mg Approved in Japan for the Treatment of SARS-CoV-2 Infection, under the Emergency Regulatory Approval System

Efficacy and Safety of 5-Day Oral Ensitrelvir for Patients With Mild to Moderate COVID-19

The SCORPIO-SR Randomized Clinical Trial

JAMA Network Open

Hiroshi Yotsuyanagi, et al. *JAMA Network Open.* 2024;7(2):e2354991.

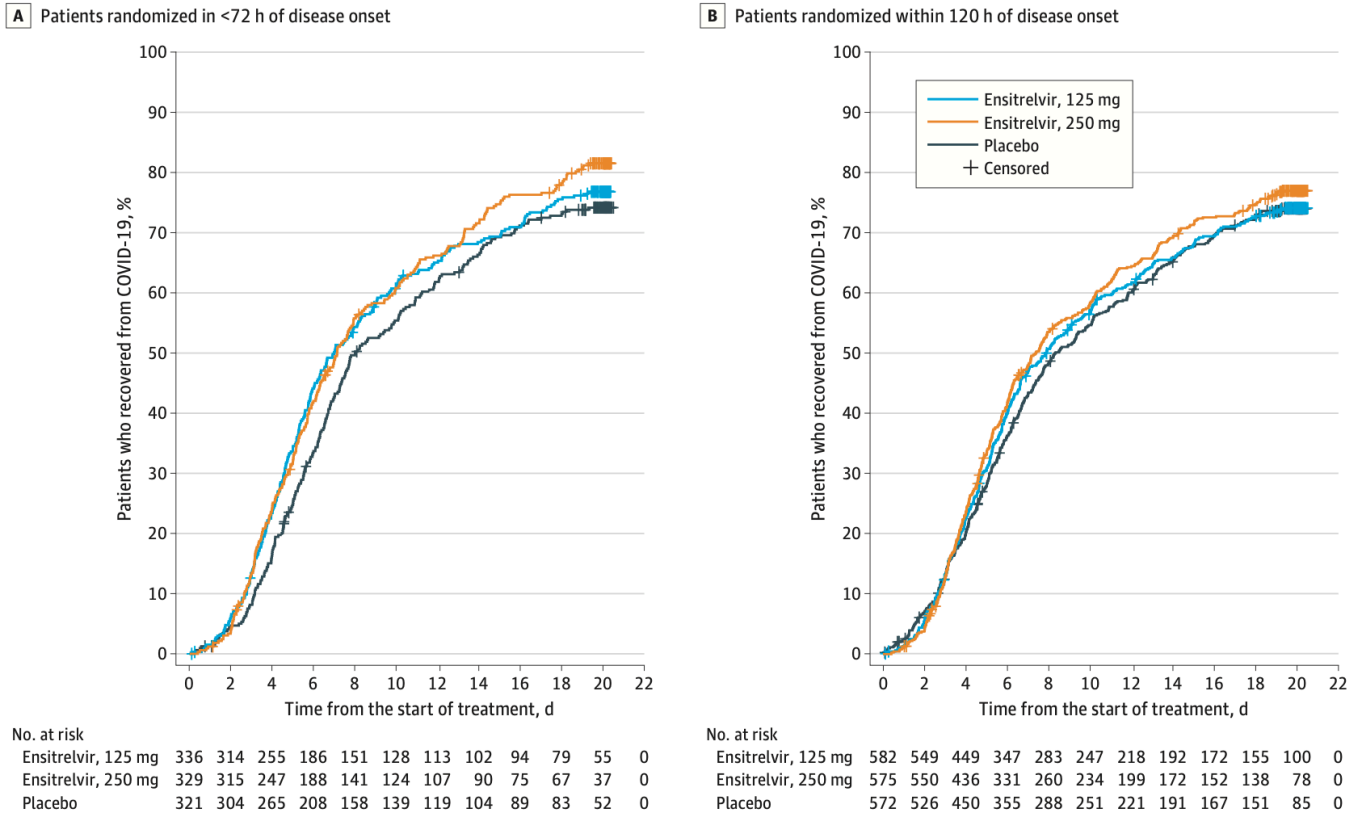
607 Randomized to receive ensitrelvir, 125 mg
604 Included in the safety analysis population
3 Excluded for not receiving the allocated intervention

606 Randomized to receive ensitrelvir, 250 mg
599 Included in the safety analysis population
7 Excluded for not receiving the allocated intervention

608 Randomized to receive placebo
605 Included in the safety analysis population
3 Excluded for not receiving the allocated intervention

Characteristic	
Age, mean (SD), y	35.2 (12.3)
Oxygen saturation, mean (SD), %[f]	97.3 (1.5)

None of the patients reported received mechanical ventilation or died, and only 1 patient each in the 125-mg ensitrelvir and placebo groups required COVID-19–related hospitalization or equivalent recuperation during the study period.



Efficacy and Safety of 5-Day Oral Ensitrelvir for Patients With Mild to Moderate COVID-19

The SCORPIO-SR Randomized Clinical Trial

JAMA Network Open

Hiroshi Yotsuyanagi, et al. *JAMA Network Open.* 2024;7(2):e2354991.

Variable	Ensitrelvir, 125 mg (n = 347)[b]	Ensitrelvir, 250 mg (n = 340)	Placebo (n = 343)
Change from baseline to day 4 in SARS-CoV-2 RNA level			
Patients, No.	340	333	337
LS mean (SE), log_{10} copies/mL[c]	−2.48 (0.08)	−2.49 (0.08)	−1.01 (0.08)
Difference from placebo, LS mean (SE) [95% CI], log_{10} copies/mL[c]	−1.47 (0.08) [−1.63 to −1.31]	−1.48 (0.08) [−1.64 to −1.32]	NA
P value[c]	<.001	<.001	NA
Time to resolution of 12 COVID-19 symptoms[d]			
Patients, No	336	330	321
Median (95% CI), h	179.2 (152.1 to 212.1)	184.9 (168.9 to 226.2)	213.2 (185.8 to 253.8)
Difference from placebo, median (95% CI), h	−34.0 (−85.9 to 8.3)	−28.3 (−72.8 to 14.7)	NA
P value[e]	.07	.08	
Time to resolution of 14 COVID-19 symptoms[f]			
Patients, No.	336	330	321
Median (95% CI), h	187.8 (156.4 to 217.0)	190.3 (171.4 to 244.0)	231.8 (192.1 to 265.8)
Difference from placebo, median (95% CI), h	−44.1 (−95.3 to 4.5)	−41.5 (−81.2 to 27.3)	NA
P value[e]	.03	.05	NA

d
1.Low energy or tiredness,
2.muscle or body aches,
3.headache,
4.chills or shivering,
5.feeling hot or feverish,
6.stuffy or runny nose,
7.sore throat,
8.cough,
9. shortness of breath
10.nausea,
11.vomiting, and
12.diarrhea.

f
1.Low energy or tiredness,
2.muscle or body aches,
3.headache,
4.chills or shivering,
5.feeling hot or feverish,
6.stuffy or runny nose,
7.sore throat,
8.cough,
9. shortness of breath
10.nausea,
11.vomiting,
12.Diarrhea
13.Anosmia
14.Dysgeusia

Leritrelvir for the treatment of mild or moderate COVID-19 without co-administered ritonavir: a multicentre randomised, double-blind, placebo-controlled phase 3 trial

www.thelancet.com Vol 67 January, 2024

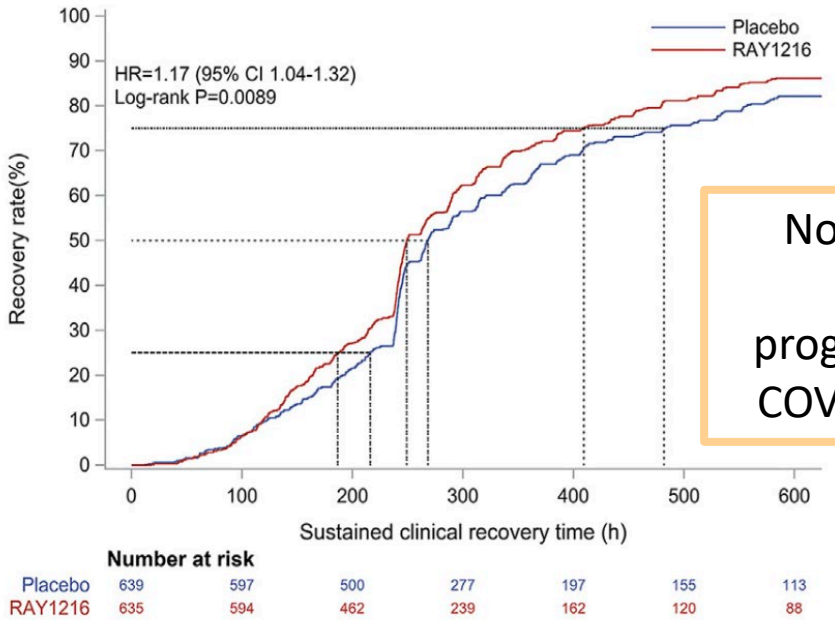
YangqingZhan, et al. eClinicalMedicine 2024;67: 102359

680 Were assigned to received Leritrelvir (Intention to treat)

679 Were assigned to received placebo (Intention to treat)

Characteristic	Leritrelvir (N = 680)	Placebo (N = 679)	Total (N = 1359)
Median age at randomization (IQR) — years	32.0 (26.0, 39.0)	31.0 (26.0, 38.0)	31.0 (26.0, 39.0)
Mean age (Range)— years	33.7 (18, 73)	33.4 (18, 70)	33.6 (18, 73)
Risk factors for severe illness of COVID-19 — no. (%)[d]			
Age of >60 years old	8 (11.3)	7 (9.3)	15 (10.3)

Sustained Clinical Recovery, Per-Protocol Population (N = 1274).



The median time to sustained clinical recovery in **leritrelvir** group was significantly **shorter** (251.02 h [IQR 188.95–428.68 h]) than that of Placebo (271.33 h [IQR 219.00–529.63 h], P = 0.0022, hazard ratio [HR] 1.20, 95% confidence interval [CI], 1.07–1.35).

No participants in either group progressed to severe COVID-19 by day 29.

	Leritrelvir (N = 680)	Placebo (N = 679)	P-value
Proportion of participants with SARS-CoV-2 virus turned negative (95% CI) (%)			
Leritrelvir reduced viral load by 0.82 log10 on day 4 compared to placebo.			
Day 4	5.95 (4.24, 8.07)	4.10 (2.70, 5.95)	0.14
Day 6	16.28 (13.50, 19.37)	10.09 (7.86, 12.71)	0.0011
Day 10	36.93 (33.18, 40.81)	32.33 (28.70, 36.13)	0.084
Day 15	66.04 (62.22, 69.71)	59.46 (55.53, 63.31)	0.016

Early treatment with fluvoxamine, bromhexine, cyproheptadine, and niclosamide to prevent clinical deterioration in patients with symptomatic COVID-19: a randomized clinical trial

www.thelancet.com Vol 70 April, 2024

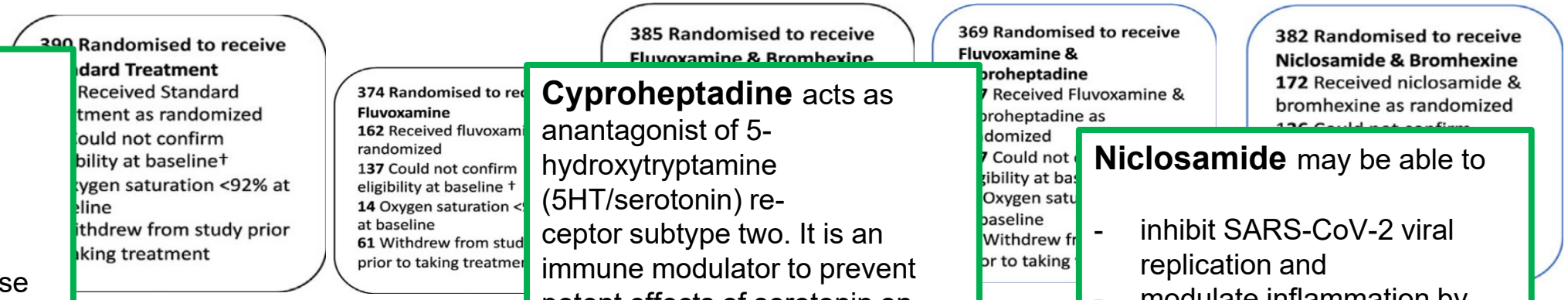
Dhammika Leshan Wannigama, et al. eClinicalMedicine 2024;70: 102517

Fluvoxamine, a selective serotonin reuptake inhibitor (SSRI):
- reducing damaging aspects of the inflammatory response to SARS-CoV-2 infection,
- lowering the risk of hypercoagulable state by reducing platelet serotonin levels,

Bromhexine hydrochloride acts as a - mucolytic and immune modulator to help clear chest congestion, and as a
- TMPRSS2 protease blocker

Cyproheptadine acts as anantagonist of 5-hydroxytryptamine (5HT/serotonin) receptor subtype two. It is an immune modulator to prevent potent effects of serotonin on
- lung vascular tone,
- respiratory rate, and
- -systemic vascular beds,

Niclosamide may be able to
- inhibit SARS-CoV-2 viral replication and
- modulate inflammation by markedly blunting calcium oscillations and membrane conductance in spike-expressing cells by suppressing the activity of TMEM16F, a calcium-activated ion channel, a scramblase responsible for theexposure of phosphatidylserine on the cell surface.



					randomised, N = 178[a]	randomised, N = 207[a]	randomised, N = 147[a]			
Age years	36.2			5.2 (13.1)	35.5 (13.1)	34.5 (13.2)	35.1 (13.2)			
Weight kg	63.6			1.8 (19.9)	64.8 (21.4)	64.4 (18.6)	64.8 (21.3)			
Height cm	161.8			61.5 (11.0)	162.4 (9.4)	162.7 (8.8)	161.4 (9.3)			
Body mass index (BMI), kg/m^2	24.2			3.6 (7.5)	24.4 (7.1)	24.2 (6.2)	24.9 (8.1)			
Body temperature celsius	37.8			7.6 (0.6)	37.7 (0.7)	37.6 (0.7)	37.7 (0.7)			
Systolic blood pressure mmHg	115.0 (9.8)	122.0 (13.4)	115.4 (9.5)	121.4 (14.3)	115.9 (9.9)	120.5 (14.1)	115.8 (9.6)			
Diastolic blood pressure mmHg	74.7 (9.4)	77.6 (10.8)	74.6 (9.2)	79.7 (10.8)	75.6 (9.0)	79.7 (11.3)	75.1 (8.9)			
Oxygen saturation	94.4 (1.1)	94.0 (1.5)	94.4 (1.1)	94.1 (1.4)	94.3 (1.1)	94.1 (1.2)	94.2 (1.0)	93.9 (1.7)	94.6 (1.1)	94.2 (1.6)
Respiratory rate PR breaths min.	17.8 (2.3)	17.7 (1.4)	18.3 (2.4)	18.0 (1.6)	17.8 (2.5)	18.1 (1.5)	17.8 (2.1)	17.9 (3.1)	18.1 (2.7)	17.9 (2.7)
Heart rate beats min.	86.6 (19.1)	87.6 (20.3)	88.2 (19.4)	86.4 (17.5)	88.1 (19.9)	85.3 (19.5)	88.1 (19.4)	89.9 (19.3)	85.8 (17.4)	86.1 (18.7)

Early treatment with fluvoxamine, bromhexine, cyproheptadine, and niclosamide to prevent clinical deterioration in patients with symptomatic COVID-19: a randomized clinical trial

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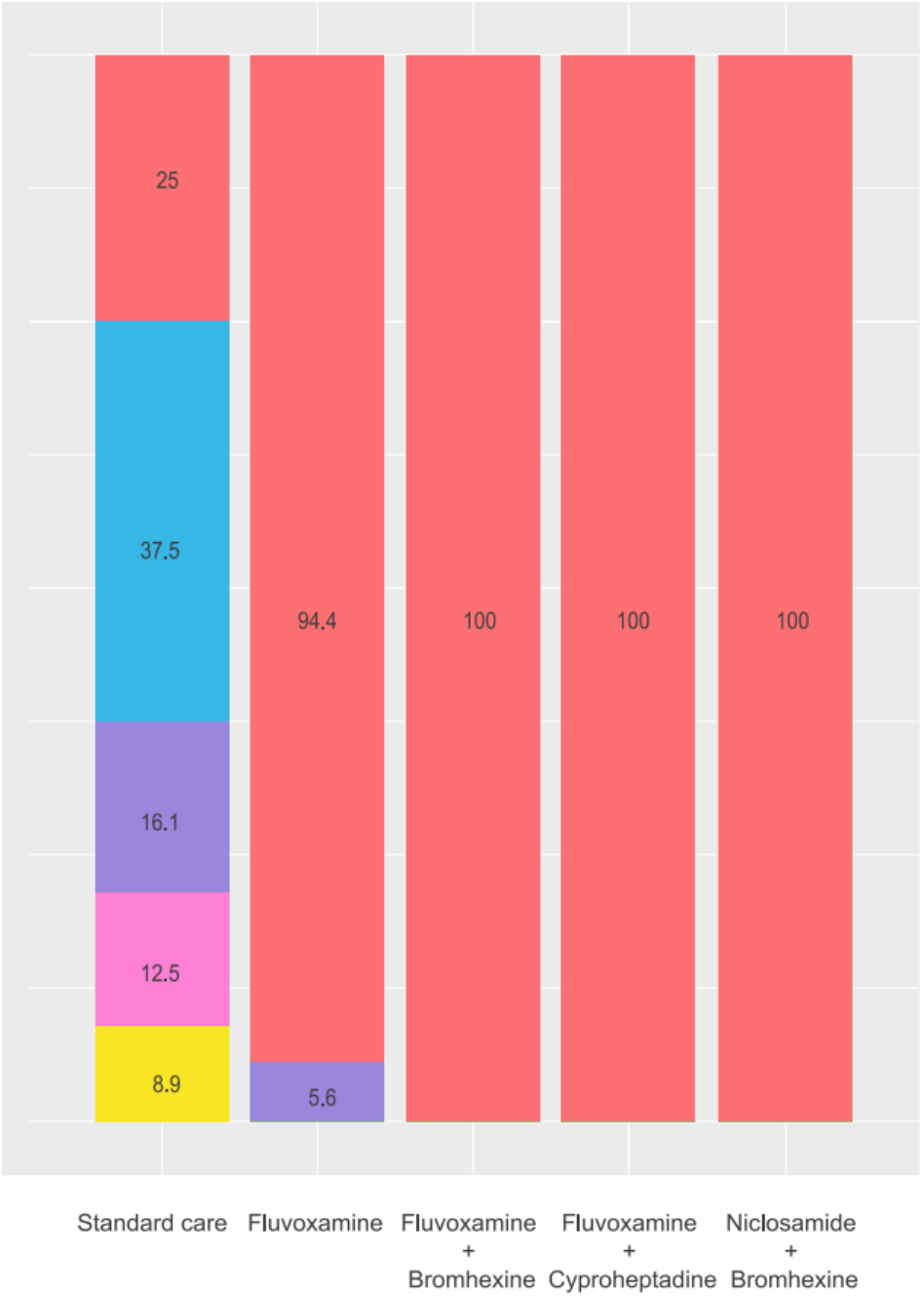


Clinical status

- Hospitalized, requiring invasive mechanical ventilation or ECMO
- Hospitalized, requiring noninvasive ventilation or high-flow oxygen
- Hospitalized, requiring low-flow supplemental oxygen
- Hospitalized, not requiring supplemental oxygen; requiring ongoing medical care (COVID-19-related or otherwise)
- Not hospitalized, not requiring supplemental oxygen or ongoing medical care (other than per-protocol drug administration)
- Death

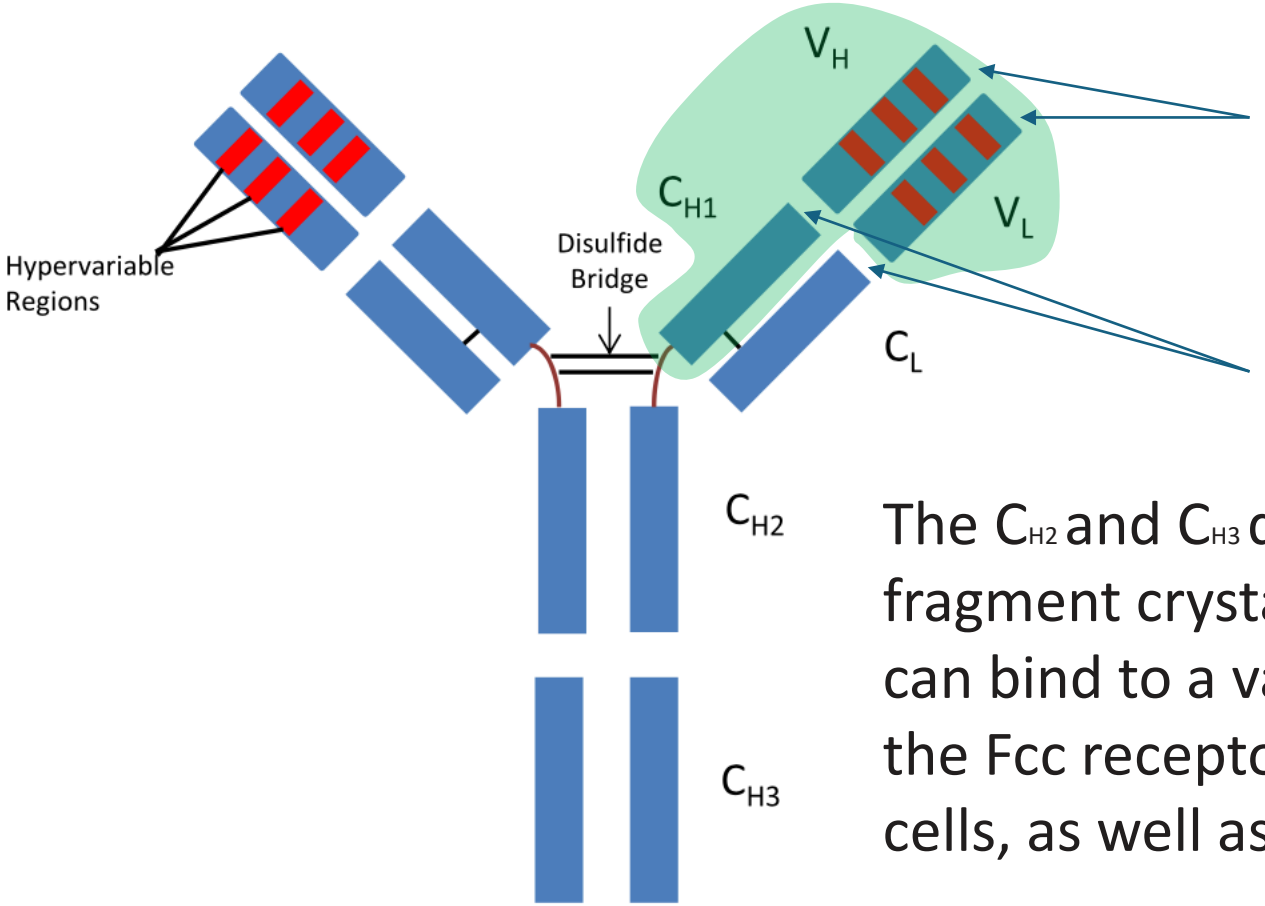
Early treatment within 48-h of symptoms onset

Open label

- All treated groups significantly differed from the standard care group by days 9, 14, and 28 ($p < 0.0001$).
- By day 28, the three 2-drug treatments were significantly better than the fluvoxamine arm ($p < 0.0001$).

All currently clinically used therapeutic antibodies are immunoglobulin G (IgG) monoclonal antibodies (mAbs) and possess the same basic structure

The two variable regions and the C_{H1} domains of the heavy chains comprise the **antigen binding fragment (Fab)** with each variable domain containing the complementarity- determining region, which is highly specific for the target antigen.

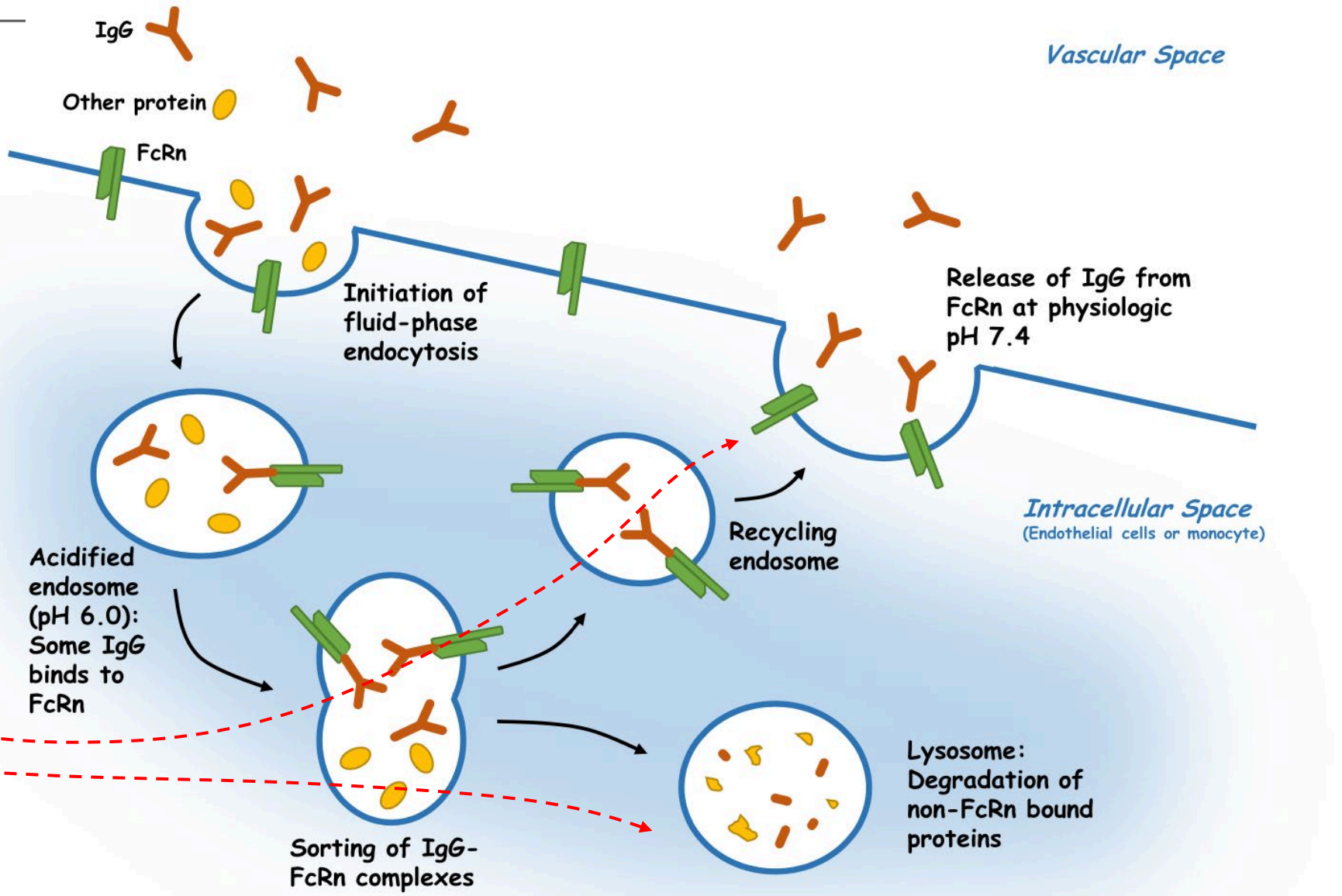


variable domains (V_H and V_L)

constant domains (C_H and C_L)

The C_{H2} and C_{H3} domains of the heavy chain make up the fragment crystallizable (Fc) region of the antibody and can bind to a variety of cell surface receptors, including the Fcc receptors and the neonatal Fc receptor (FcRn) on cells, as well as components of the complement system

Pharmacokinetics of Monoclonal Antibodies
Ryman and Meibohm



2 Pathways:

a. Recycling

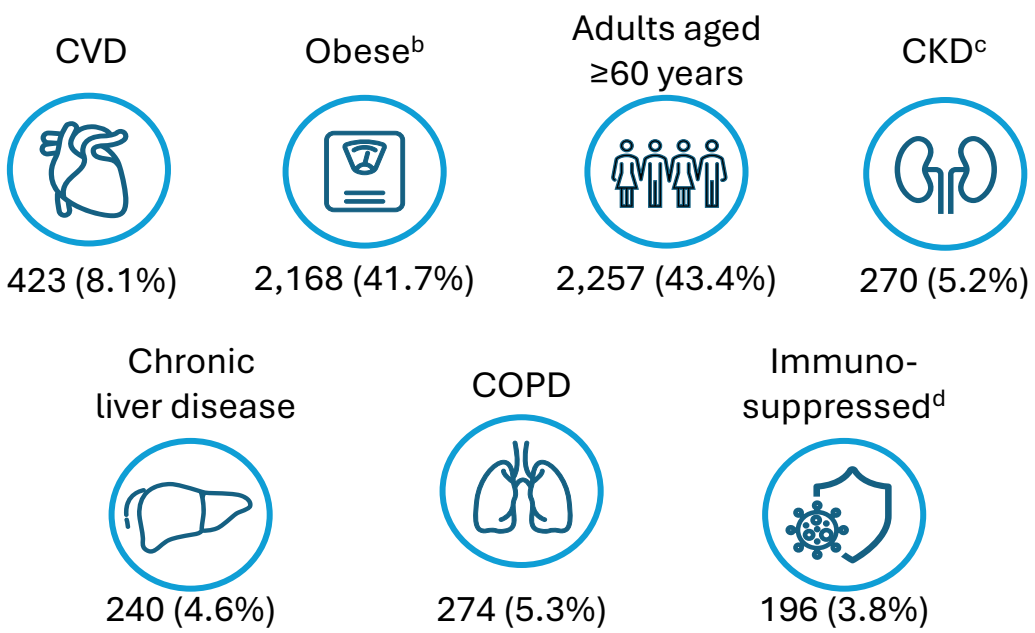
b. Degradation

PROVENT: Phase III Randomized, Double-Blind, Placebo-Controlled Study of AZD7442 for Pre-exposure Prophylaxis in 5197 Participants[1,2]

ClinicalTrials.gov identifier: NCT04625725
Status: active, not recruiting
Completion date: June 2022

Objective | Study design | Key inclusion criteria | **Demographics[3]** | Key exclusion criteria

PROVENT enrolled participants at increased risk for inadequate response to vaccination[a]



Characteristics were well-balanced between the treatment groups

Characteristic	AZD7442 (n=3460)	Placebo (n=1737)
Age, mean (SD), years	53.6 (15.0)	53.3 (14.9)
Age ≥60 years, no. (%)	1500 (43.4)	757 (43.6)
Sex, female, no. (%)	1595 (46.1)	802 (46.2)
Race, no. (%)		
White	2545 (73.6)	1249 (71.9)
Black or African American	597 (17.3)	302 (17.4)
Asian	110 (3.2)	60 (3.5)
Other	208 (6.0)	126 (7.3)
Ethnicity, Hispanic/Latino, no. (%)	539 (15.6)	215 (12.4)
BMI, mean (SD), kg/m^2	29.6 (6.9)	29.6 (7.0)

[a]Participants could have multiple risk characteristics so percentages total >100%. [b]BMI≥30 kg/m^2; [c]GFR <30 mL/min/1.73 m^2; [d]Caused by underlying/chronic disease or treatments.
CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; CVD = cardiovascular disease; GFR = glomerular filtration rate; SD = standard deviation.

1. AstraZeneca Pharmaceuticals LP press release. Published August 20, 2021; 2. Study NCT04625725. ClinicalTrials.gov website; 3. Levin M et al. Presentation at: IDWeek 2021; September 29-October 3, 2021; virtual conference.

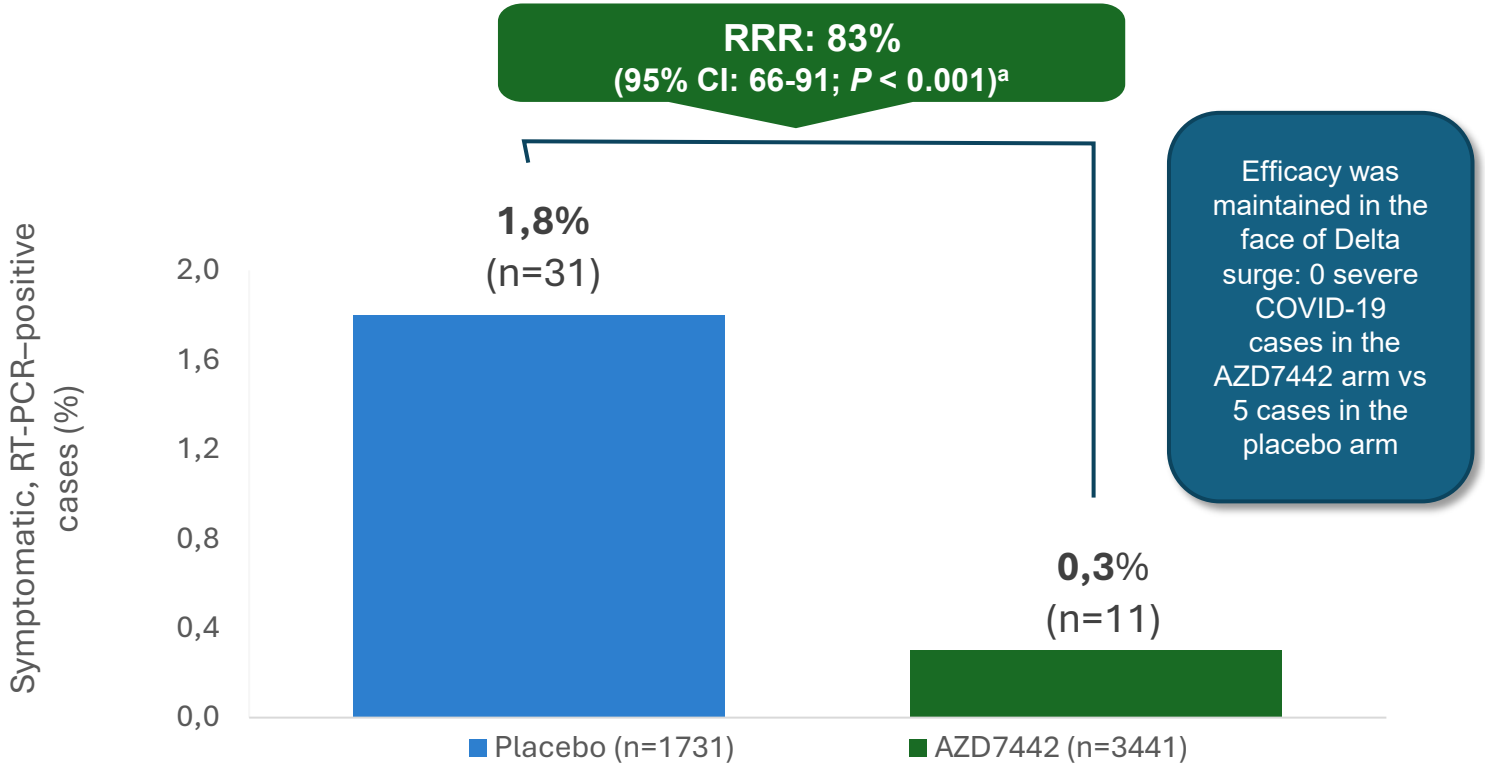
6-Month Data:
PROVENT: Phase III Randomized, Double-Blind, Placebo-Controlled Study of AZD7442 for Pre-exposure Prophylaxis in 5197 Participants[1,2]

ClinicalTrials.gov identifier: NCT04625725
Status: active, not recruiting
Completion date: June 2022

Primary outcome measures[1]

- Incidence of the first case SARS-CoV-2 RT-PCR–positive symptomatic illness
- Safety and tolerability of AZD7442 (incidence of AEs, SAEs, MAAEs, AESIs)

Reduction in the incidence of symptomatic COVID-19 with AZD7442 compared with placebo—6-month (median) follow-up[1,3]



[a]Poisson regression with robust variance, including covariate for treatment (AZD7442 vs placebo), age at informed consent (≥60 years old vs <60 years old), with log of the follow-up time as an offset.
AE = adverse event; AESI = adverse event of special interest; CI = confidence interval; COVID-19 = coronavirus disease 2019; MAAE = medically attended adverse event; RRR = relative risk reduction; RT-PCR = reverse transcriptase–polymerase chain reaction; SAE = severe adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

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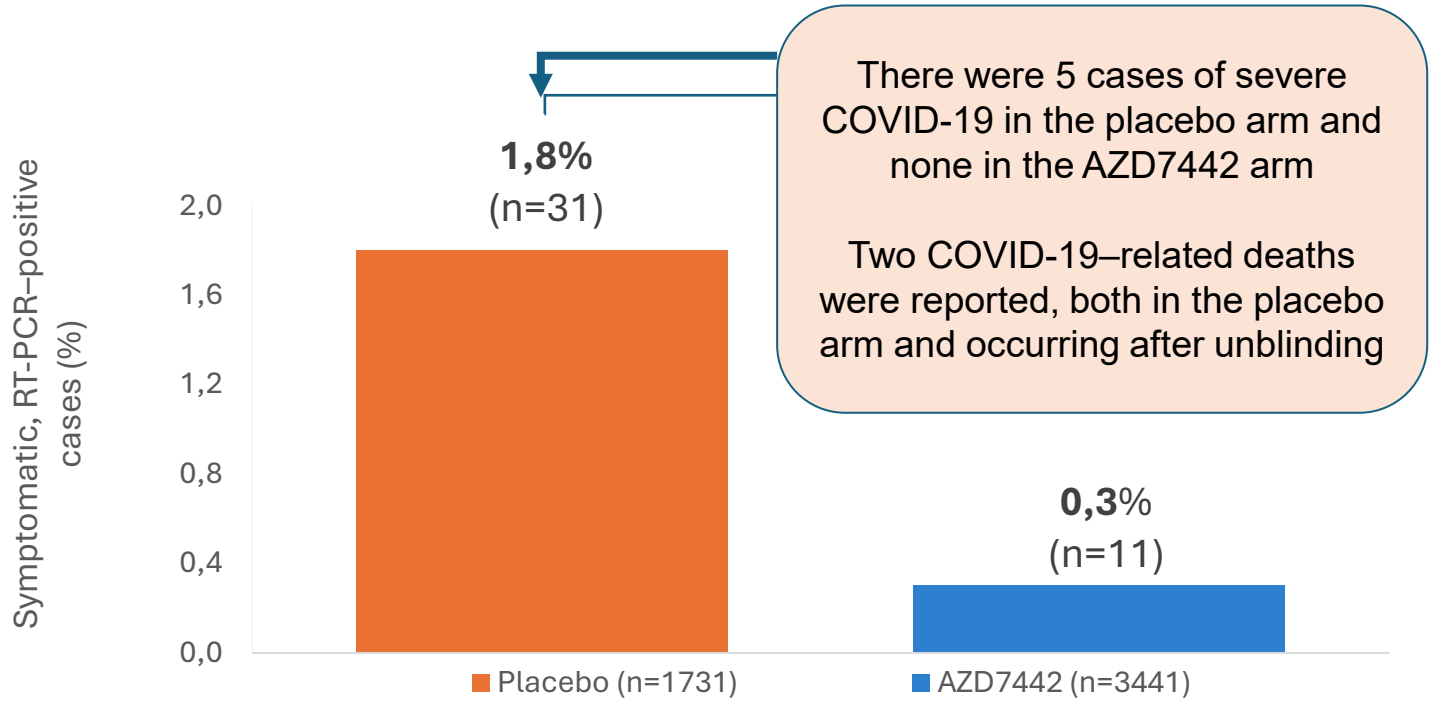


There were 5 cases of severe COVID-19 in the placebo arm and none in the AZD7442 arm

Two COVID-19–related deaths were reported, both in the placebo arm and occurring after unblinding

AE = adverse event; AESI = adverse event of special interest; COVID-19 = coronavirus disease 2019; MAAE = medically attended adverse event; RT-PCR = reverse transcriptase–polymerase chain reaction; SAE = severe adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

1. AstraZeneca Pharmaceuticals LP press release. Published August 20, 2021; 2. Study NCT04625725. ClinicalTrials.gov website; 3. Levin M et al. Presentation at: IDWeek 2021; September 29-October 3, 2021; virtual conference.

The U.S. FDA has issued an EUA for the emergency use of the unapproved product PEMGARDA (pemivibart), a SARS-CoV-2 spike protein-directed attachment inhibitor, for the pre-exposure prophylaxis of coronavirus disease 2019 (COVID-19) in adults and adolescents (12 years of age and older weighing at least 40 kg):

- who are not currently infected with SARS-CoV-2 and
- who have not had a known recent exposure to an individual infected with SARS-CoV-2 and
- who have moderate-to-severe immune compromise due to a medical condition or receipt of immunosuppressive medications or treatments and
- are unlikely to mount an adequate immune response to COVID-19 vaccination.

PEMGARDA has been authorized by FDA for the emergency use described above. PEMGARDA is not FDA-approved for any use, including use for preexposure prophylaxis of COVID-19.

This drug is derived from the parent mAb adintrevimab and is authorized as a 4,500 mg intravenous infusion every 3 months. **There are no published effectiveness data to date**; rather, pemivibart's approval was based on an **"immunobridging"** approach, similar to that used for vaccines. This demonstrated that ***pemivibart was able to neutralize the JN.1 variant to a similar degree as other mAbs*** (with effectiveness data) were able to neutralize prior variants

Cohort B: placebo-controlled, randomized trial in adults who do not have moderate-to-severe immune compromise.

Exploratory Clinical Efficacy Results in Randomized Participants without SARS CoV-2 Infection at Baseline in CANOPY Cohort B (Adults who do not have Moderate-to-Severe Immune Compromise)

	PEMGARDA n=317	Placebo n=160
RT-PCR-confirmed symptomatic COVID-19, COVID-19-related hospitalization, or all-cause death[a] through Month 3[b]		
Proportion: n (%)	1 (0.3)	8 (5.0)
Standardized Relative Risk Reduction (95% CI)	94% (50%, 99%)	
RT-PCR-confirmed symptomatic COVID-19, COVID-19-related hospitalization, or all-cause death[a] through Month 6[c]		
Proportion: n (%)	6 (1.9)	19 (11.9)
Standardized Relative Risk Reduction (95% CI)	84% (61%, 94%)	

Cohort A: single-arm, open-label trial in adults who have moderate-to-severe immune compromise.

Rates of RT-PCR-confirmed COVID-19, COVID-19-Related Hospitalizations, or All-Cause Death in Participants in CANOPY Cohort A (Adults who have Moderate-to-Severe Immune Compromise)

- 65% taking high-dose corticosteroids/other immunosuppressive medications
- 13% acute leukemia, chronic lymphocytic leukemia, non-Hodgkin, lymphoma, or multiple myeloma (regardless of treatment)
- 12% primary immunodeficiency
- 11% solid organ transplant recipient
- 9% advanced HIV infection
- 7% actively treated for solid tumor or hematologic malignancies

median age = 59 years,
aged 65 years or older = 31%

	PEMGARDA n=298
RT-PCR-confirmed symptomatic COVID-19, COVID-19-related hospitalization, or all-cause death[a] through Month 3[b]	
Proportion: n (%)	3 (1.0)
RT-PCR-confirmed symptomatic COVID-19, COVID-19-related hospitalization, or all-cause death[a] through Month 6[c]	
Proportion: n (%)	11 (3.7)

Sipavibart neutralises both historic and circulating SARS-CoV-2 variants

Sipavibart è stato progettato con la sostituzione YTE nel frammento Fc dell'anticorpo per estendere l'emivita dell'mAb arrivando a 90 giorni e la sostituzione TM sempre nel frammento Fc per ridurre il potenziale rischio teorico di potenziamento anticorpo-dipendente (ADE) dell'infezione (Dall'Acqua et al 2006, Oganesvan et al 2008, Loo et al 2022).

- Sipavibart neutralizes all historic and many circulating SARS-CoV-2 variants, however it does not retain in vitro neutralisation activity against SARS-CoV-2 variants that contain an F456L mutation.
- **Sipavibart retains neutralising activity against the Omicron BA.2.86 family of variants, including JN.1**

SARS-CoV-2 Variants	SARS-CoV-2 Pseudovirus Neutralization[a] IC_{50} (ng/mL) sipavibart
D614G	13.5
Alpha	11.0
Beta	10.7
Delta	17.9
Gamma	4.6
BA.1	5.4
BA.1.1	4.6
BA.2	10.7
BA.2.12.1	7.9
BA.4/5	4.7
BA.2.75	25.0
BA.4.6	14.5
BA.4.7	4.2
BA.5.9	4.7
BA.2.75.2	9.7
BF.7	3.8
BQ.1	11.6
BQ.1.1	9.2
XBB	3.8
XBB.1	3.6
XBB.1.5/ XBB.1.9[b]	5.8
XBB.1.16	1.3
XBB.2.3	3.4
XBB.1.5.10 / EG.5[b]	>1000
EG.5.1	>1000
BA.2.86 [c]	3.8
JN.1	83.1

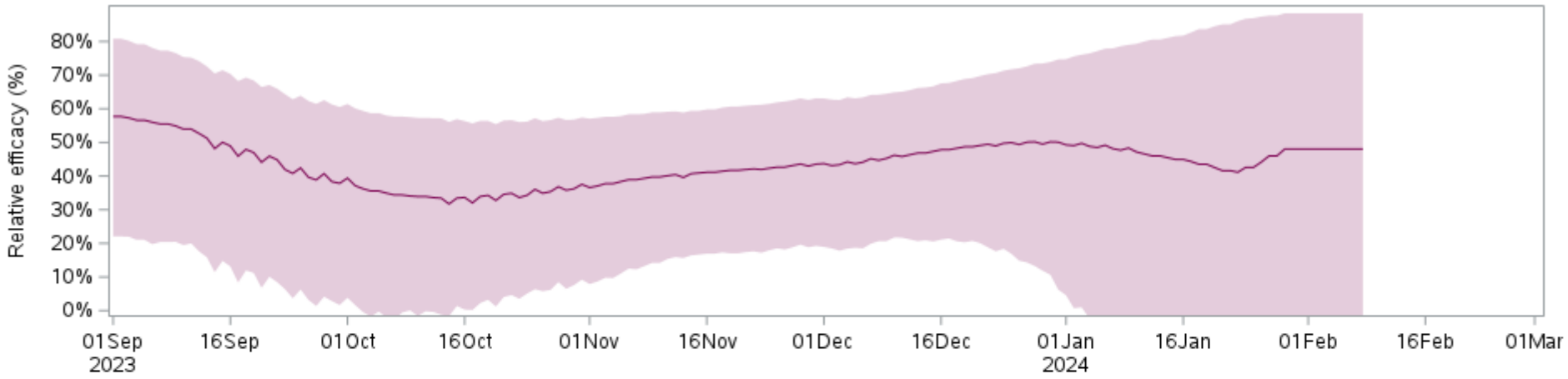
[a] IC_{50} values derived from AstraZeneca research-grade assay, except XBB.1.5, XBB.1.16, XBB.1.5.10 , EG.5.1, BA.2.86 and JN.1 (Monogram Biosciences, South San Francisco, CA)
[b] XBB.1.5 and XBB.1.9 have the same SARS-CoV-2 spike sequence. XBB.1.5.10 and EG.5 have the same SARS-CoV-2 spike sequence.
[c] BA.2.86 includes BA.2.86, BA.2.86.1, JN.2 and JN.3, which have the same SARS-CoV-2 protein sequence
IC_{50}: 50% inhibitory concentration

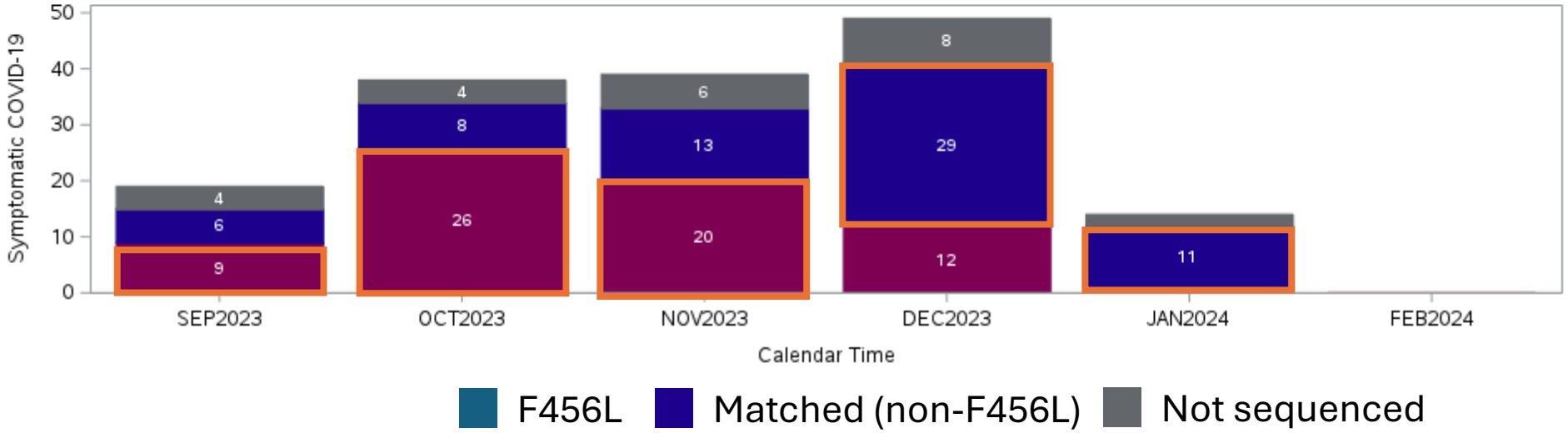
SUPERNOVA è lo studio di fase III internazionale che valuta la sicurezza e l'efficacia di Sipavibart per la PrEP del COVID-19 in individui immunocompromessi.

Finora, questo è l'unico studio di fase III che testa un anticorpo neutralizzante contro SARS-CoV-2 nell'era post insorgenza della variante Omicron in una popolazione immunocompromessa.

	Sipavibart N = 1669	**Comparator N = 1665**	**Totale N = 3334**
Assunzione di farmaci immunosoppressori	1228 (73.6)	1248 (75.0)	2476 (74.3)
Immunodeficienze secondarie moderate o gravi (es. emodialisi)	265 (15.9)	239 (14.4)	504 (15.1)
Neoplasie ematologiche	272 (16.3)	239 (14.4)	511 (15.3)
Trapianto di organi solidi	235 (14.1)	237 (14.2)	472 (14.2)
Somministrazione di terapie per la deplezione delle cellule B (entro 1 anno)	235 (14.1)	209 (12.6)	444 (13.3)
Tumore solido in trattamento	55 (3.3)	58 (3.5)	113 (3.4)
Trapianto di cellule staminali emopoietiche	36 (2.2)	30 (1.8)	66 (2.0)
Immunodeficienze primarie (moderate o gravi)	26 (1.6)	29 (1.7)	55 (1.6)
Infezione da HIV (avanzata o non trattata)	13 (0.8)	23 (1.4)	36 (1.1)
Pregressa terapia con cellule T chimeriche	4 (0.2)	5 (0.3)	9 (0.3)

Overall consistent efficacy seen across the winter season within 3 months of a 300mg IM dose independent of infecting variant





There were no events in Feb relative to the 3-month follow-up period.

Missing sequenced variants includes those that failed assay

Efficacy is maintained over the **winter season** even though the **variant landscape changed** with F456L variants predominant Sep to Nov and matched variants predominant Dec/Jan

La somministrazione di Sipavibart ha determinato una riduzione statisticamente significativa del rischio di COVID-19 sintomatico attribuito a qualsiasi variante di SARS CoV-2 rispetto al comparatore (EVUSHELD e/o placebo): efficacia 34,9% (97,5% CI 15,0, 50,1); p < 0,001.

Conclusions

- Current clinical research in therapeutics is oriented to large numbers of potential clients (mostly not at risk) instead of selecting out those who actually remain at risk of:

1. Hospitalization (COVID-associated, mostly due to decompensation of chronic comorbidities)
2. Severe COVID-19 (pneumonia)
3. Death (COVID-associated, mostly due to decompensation of chronic comorbidities)

- Such strategy, however, was commercially unsuccessful when Zanamivir, Oseltamivir and, more recently, Baloxavir Marboxil were developed for Influenza. The decrease in suffering of drug recipients (as measured by hours or days of fever) was judged to be insufficient to grant their widespread use. The average perception about these drugs is that they are barely useful.

- A different approach, such as a study design more focused on those at higher risk of severe disease, could have disclosed a better profile.

- The same applies to the last two years of clinical research in antivirals for SARS-CoV-2; the last series of clinical trials, although mostly successful in terms of primary end-point, are unlikely to convince payers to promote a widespread use of these drugs and the risk is that of missing good opportunities for the patients who might instead consistently benefit of an early antiviral approach.

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