Prevenzione e ruolo degli antivirali nel COVID-19

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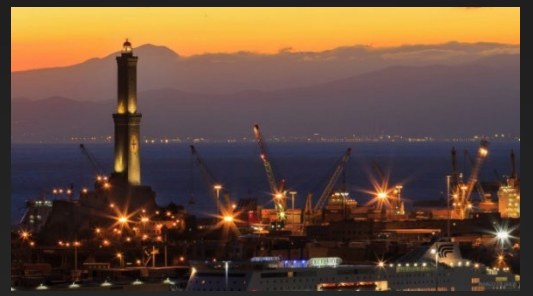

Disclosures
(past 5 years)

- Research grants
  - Astellas, Pfizer, MSD, Gilead
- Advisor/consultant/speaker bureau
  - Angelini, Astellas, Bayer, Biomerieux, Cidara, Gilead, Menarini, MSD, Pfizer, Shionogi

NO conflict of interest in COVID-19 vaccines area.

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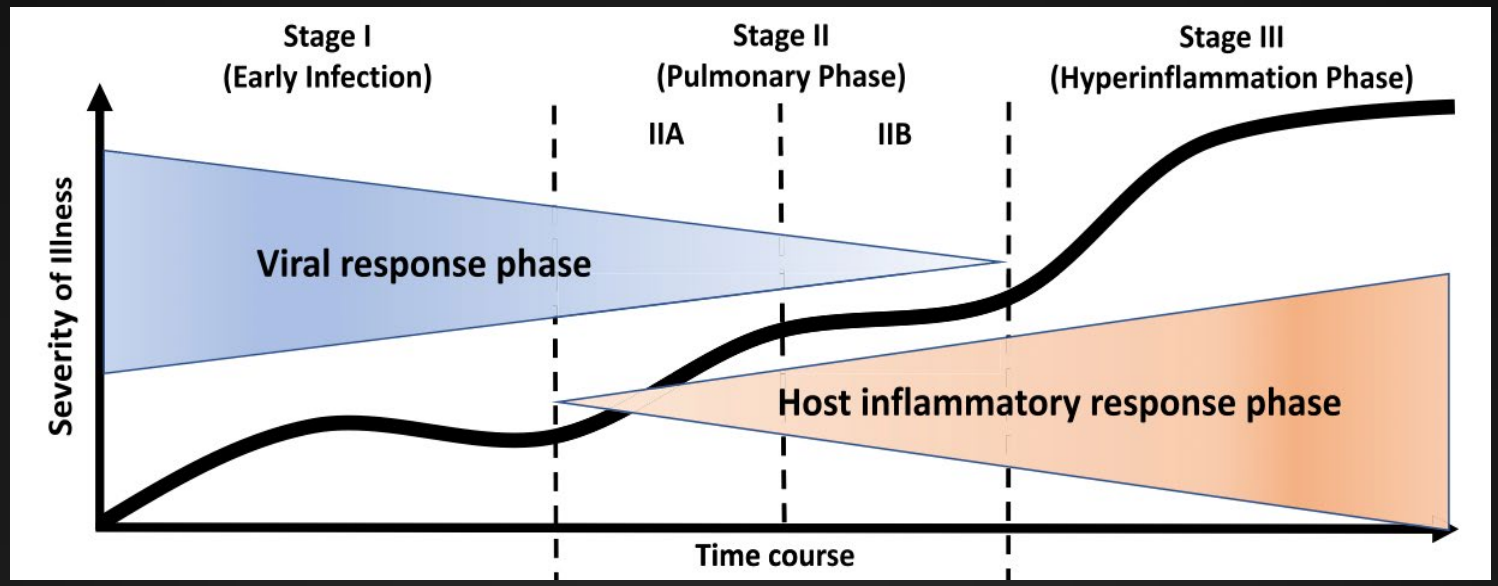
Da Maggio 2020 …ad oggi

Diversi Stadi di malattia e Terapie

Fase virale

Fase infiammatoria

- Nirmatrelvir/ritonavir (Paxlovid®)
- Molnupiravir (Lagevrio®)
- Remdesivir (Veklury®) 3 days
- NSAIDs
- Anticorpi monoclonali



- Remdesivir (Veklury®) 5-10 days
- Steroids
- Tocilizumab SD (Roactemra®)
- Anakinra (Kineret®)

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Siddiqi HK et al. The Journal of Heart and Lung Transplantation 2020

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The fast evolution of treatment during the COVID-19 pandemic……

2021

SITA & SIP 2021

2022

ESCMID
Nov 2021
Aug 2022

2023

WHO clinical guidelines Vers 13 Updated Jan 2023

IDSA guidelines. Vers 11 Updated Jun 2023

NIH COVID-19 Treatment guidelines Updated Oct 2023

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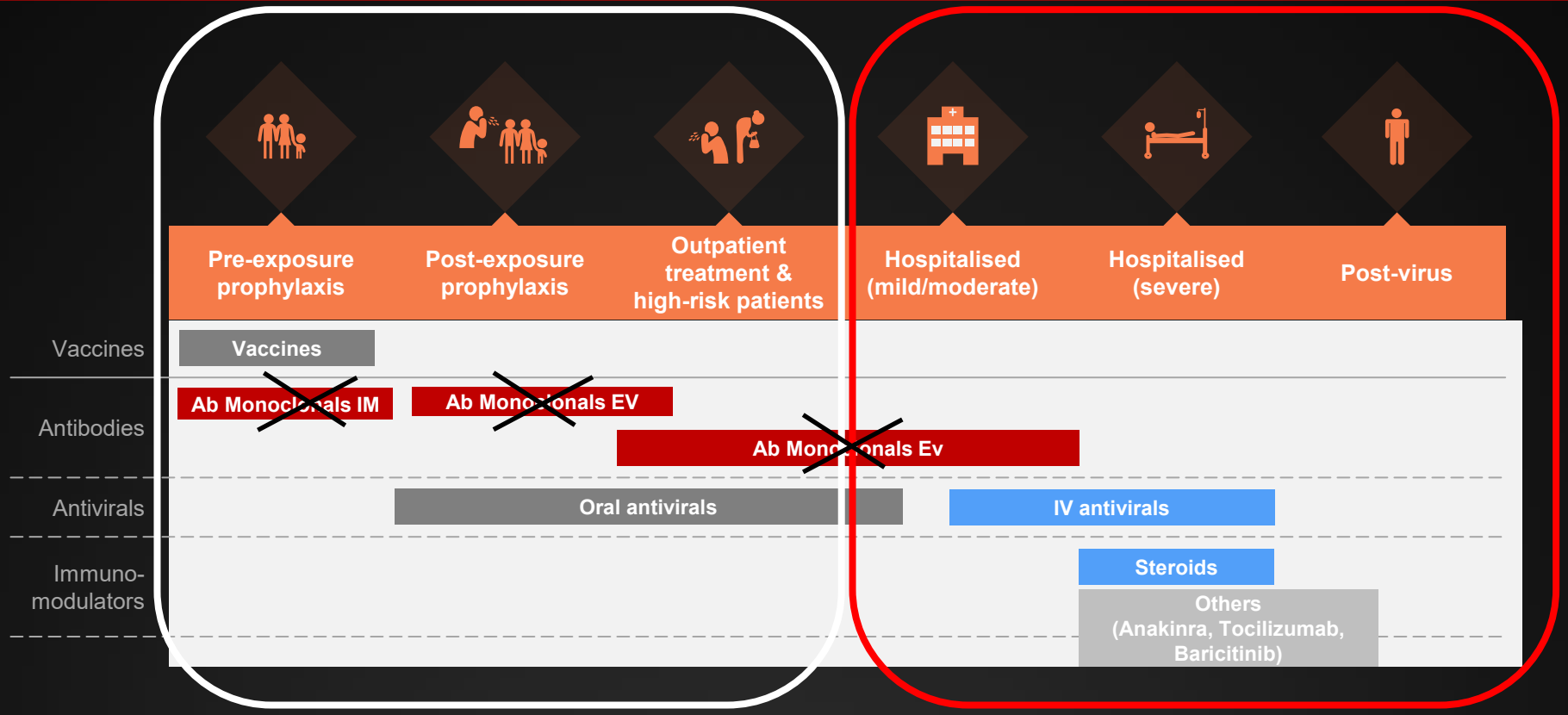
Potential role in the treatment of COVID-19
(based on available data)



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Song. Int J Antimicrob Agents 2020; Xu. Mil Med Res 2020; Pascarella. J Intern Med 2020

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New Perspectives on Antimicrobial Agents: Remdesivir Treatment for COVID-19

Aleissa M M et al, AAC 2020

Study	Method(s)	Study population	Key results	Strengths/limitations	Interpretation
Spinner et al., JAMA 2020 (SIMPLE Moderate Trial) (40)	Randomized, open-label, phase 3 trial (group 1, 200 mg loading dose, 100 mg maintenance dose for up to 4 days; group 2, 200 mg loading dose, 100 mg maintenance dose for up to 9 days; group 3, standard care)	Age ≥12 yrs; positive SARS-CoV-2 PCR; radiographic evidence of pulmonary infiltrates; SpO2 > 94% and breathing on room air at screening; ALT or AST < 5× ULN; eGFR > 50 ml/min	Those randomized to a 5-day course of remdesivir had a statistically significant difference in clinical status compared with standard of care at day 11, but not those randomized to a 10-day group; this difference was of uncertain clinical importance	Strengths: first study to evaluate remdesivir in patients with moderate COVID-19 pneumonia, had adequate power; limitations: did not evaluate SARS-CoV-2 loads, did not stratify by sites, which could have influenced the results, given the differences in patient care and discharge practices	A 5-day course of remdesivir may be sufficient to treat patients with moderate COVID-19 pneumonia
Pan et al. (SOLIDARITY Trial) (41)	Randomized, open-label, phase 3 trial (remdesivir 200 mg loading dose, 100 mg maintenance dose for up to 9 days or standard of care)	Age ≥18 yrs; diagnosis of definitive COVID-19	Remdesivir was not associated with a reduction in in-hospital mortality compared to standard of care (11% vs 11.2%); remdesivir was not associated with reduced initiation of ventilation or hospital length of stay	Strengths: large sample size; limitations: open-label study, no definition of COVID-19 or definitive COVID-19, did not stratify by oxygen requirements or site, has not reported duration of symptoms prior to start of treatment, inclusion criteria not clearly defined, patients who were discharged were not followed, did not use WHO ordinal scale	Remdesivir was not associated with improved in-hospital mortality among patients hospitalized with COVID-19
Goldman et al., NEJM 2020 (SIMPLE Severe Trial) (39)	Randomized, open-label, phase 3 trial (group 1, 200 mg loading dose, 100 mg maintenance dose for up to 4 days; group 2, 200 mg loading dose, 100 mg maintenance dose for up to 9 days)	Age ≥12 yrs; positive SARS-CoV-2 PCR; radiographic evidence of pulmonary infiltrates; SpO2 ≤ 94% or requiring supplemental oxygen; ALT or AST < 5× ULN; eGFR > 50 ml/min	difference in incidence of serious adverse events There was no difference in clinical improvement of at least 2 points in the ordinal scale between 5-day and 10-day courses (65% vs 54%); among patients receiving noninvasive ventilation or high-flow oxygen on day 5, day 14 mortality was 10% in the 5-day group vs 15% in the 10-day group; among patients receiving mechanical ventilation or ECMO on day 5, day 14 mortality was 40% in the 5-day group vs 17% in the 10-day group	Strengths: first study to evaluate optimal duration of remdesivir in COVID-19, adequate power, high protocol adherence; limitations: did not evaluate SARS-CoV-2 loads, excluded patients on mechanical ventilation or ECMO	5 days of remdesivir is sufficient to treat COVID-19 patients who are not receiving mechanical ventilation/ECMO; patients who progress to mechanical ventilation or ECMO may benefit from a 10-day course

New Microbiologica, 44, 4, 245-247, 2021, ISSN 1121-7138

SHORT COMMUNICATION

A comparative analysis of the first and second COVID-19 wave in Italy: evaluation of mortality in the Infectious Disease Unit of Genoa University Hospital

Chiara Dentone[1], Federica Portunato[1], Antonio Vena[1], Silvia Dettori[2], Sara Mora[3], Filippo Ansaldi[2,4], Matteo Bassetti[1,2]

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[2]Department of Health Sciences (DISSAL), University of Genoa, Italy;
[3]Department of Informatics, Bioengineering, Robotics and System Engineering, University of Genoa, Italy;
[4]Health Planning Unit, Azienda Ligure Sanitaria della Regione Liguria (A.Li.Sa.), Genoa, Italy

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Table 1 - *Clinical features, laboratory findings and treatment of hospitalized COVID-19 patients during first vs second wave.*

	First wave N= 285 (25.0%)	*Second wave N= 261 (15.7%)*	*P value*
Sex, Male (%)	188 (65.9)	167 (63.9)	.6279
Age, years, median (IQR[1])	68 (57-78)	66 (55-78)	.2543
Days from the onset of symptoms to ID Unit admission, median (IQR)	7 (4-10)	8 (5-12)	**.0238**
PaO2/FiO2[2] at hospital admission median (IQR)	250 (155-310)	265 (187-300)	.4237
Helmet CPAP[3] required (%)	101 (35.4)	86 (32.9)	.5405
IMV[4] required (%)	22 (7.7)	27 (10.3)	.2836
Remdesivir treatment	7 (2.4)	99 (37.9)	**<.00001**
Corticosteroids treatment	151 (52.9)	228 (87.3)	**<.00001**
Overall	60 (21.1)	27 (10.3)	**.0006**
In-Hospital mortality			
7-day	35 (12.3)	14 (5.4)	**.0047**
30-day	58 (20.3)	27 (10.3)	**.0013**
Length of ID[5] Unit hospitalization median (IQR)	11 (7-17)	8 (5-12)	**<.00001**
Days from the first nasal swab positive to the first negative median (IQR)	11 (7-20)	9 (6-13)	**.0083**

Abbreviations: [1]IQR: Interquartile Range, [2]PaO2/FiO2: arterial oxygen partial pressure/ fractional inspired oxygen, [3]CPAP: Continuous Positive Airway Pressure, [4]IMV: Invasive mechanical ventilation, [5]ID: Infectious Diseases.

COVID Original Research

Early Use of Remdesivir and Risk of Disease Progression in Hospitalized Patients With Mild to Moderate COVID-19

Falcone M et al. Clin Therap 2022

Studio prospettico osservazionale 312 pts ospedalizzati con COVID-19 tra sett 2020- Gen 2021
N=90 < 5 gg, N=222 > 5 gg da inizio sintomi
Primary composite outcome: HFNC, NIV or IMV, or death

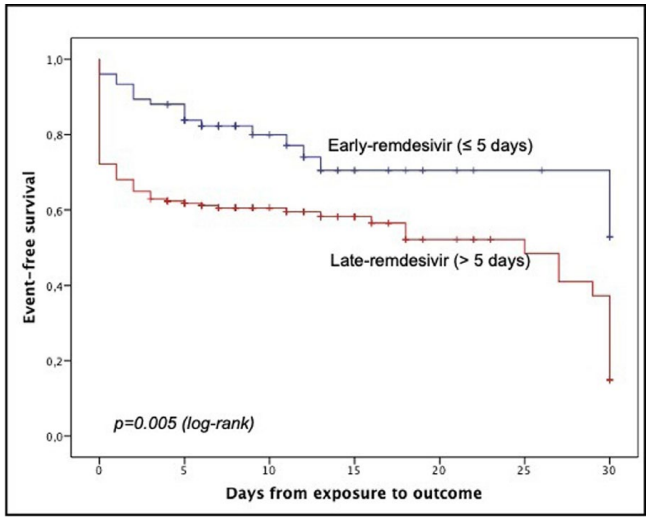


Figure. Kaplan-Meier analysis of disease progression between patients who received remdesivir within 5 days of symptoms onset and those who did not.

Table III. Multivariate logistic regression of factors independently associated with disease progression.*

Factor	OR (95% CI)	*P*
Early remdesivir (≤5 days from symptoms)	0.49 (0.27–0.87)	0.015
P/F ratio <300 on admission	2.22 (1.35–3.63)	0.002
History of dyspnea at home	2.53 (1.55–4.12)	<0.001
Age	1.02 (1.003–1.04)	0.025
C-reactive protein >5 mg/dL on admission	1.66 (1.01–2.72)	0.044

Real-life use of remdesivir in hospitalized patients with COVID-19

Garcia Vidal C, 2021

Studio osservazionale di coorte da lug-sett 2020

123/242 pts received Remdesivir and

Anti-inflammatory effect	
Tocilizumab (%)	33 (26.8%)
Anakinra (%)	7 (5.7%)
Methyl-prednisolone (%)	14 (11.4%)
Dexamethasone (%)	57 (46.3%)
Prednisone (%)	24 (19.5%)
Antibiotic treatment	
Ceftriaxone (%)	52 (42.8%)
Ceftaroline (%)	16 (13%)
Outcomes	
Median (IQR) of length of hospital stay	8 (6-12)
ICU admission (%)	24 (19.5%)
Need of mechanical ventilation (%)	9 (7.3%)
30-day mortality (%)	5 (4.1)

hospitalized patients with severe pneumonia due to SARS-CoV-2 documented by rRT-PCR, serology or antigen test, and all the following characteristics: 1) aged >12 years and >40 kg; 2) need of supplemental low-flow oxygen; 3) ≤7 days from symptom onset to remdesivir prescription; and 4) met at least two of these three criteria: respiratory rate ≥24 bpm, oxygen saturation at air ambient ≤94%, or PaO_2/FiO_2 <300 mmHg. Exclusion criteria included requirement of supplemental high-flow oxygen, mechanical ventilation, vasoactive drugs, extra-corporeal membrane oxygenation (ECMO), or meeting criteria

The most severe patients required co-administration of an anti-inflammatory therapy, and as expected they had the highest mortality rate. Interestingly, the concomitant use of remdesivir and tocilizumab was associated with the lowest mortality rate in this group (5.3%), in line with the recent report showing better outcomes among patients receiving remdesivir plus baricitinib [12]. Both inmune-modulators inhibit specific pathways of inflammatory cascade instead of the broad-spectrum inhibition induced by steroids with potential harmful consequences [13].

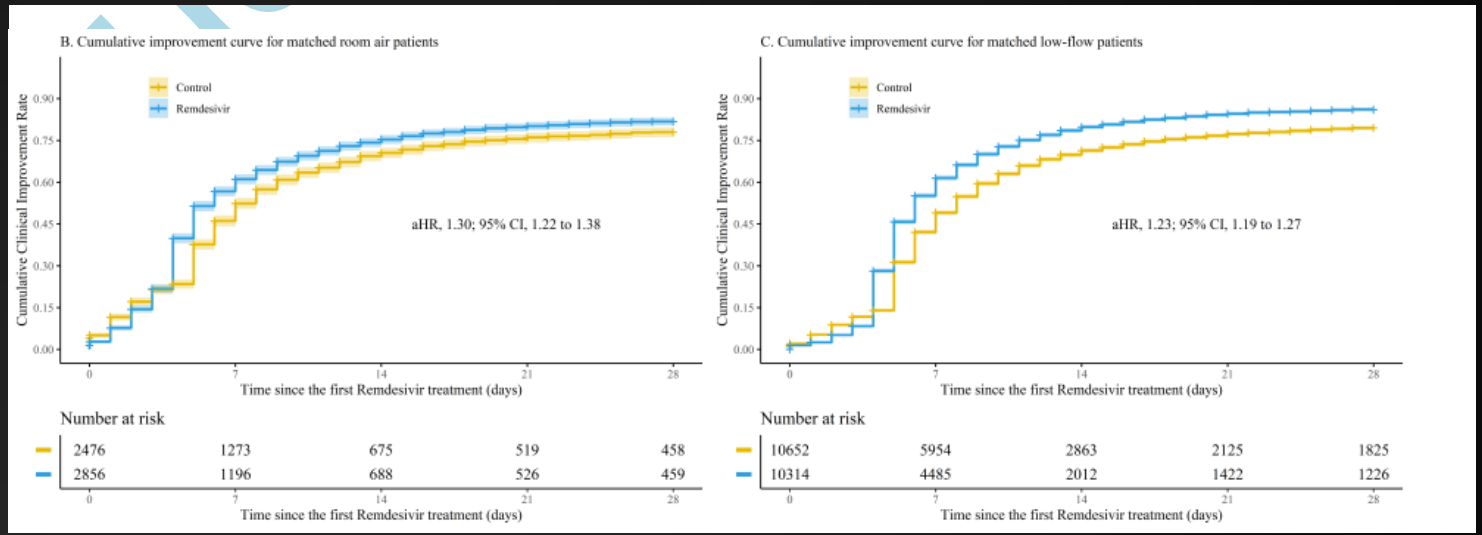
REAL-WORLD EFFECTIVENESS OF REMDESIVIR IN ADULTS HOSPITALIZED WITH COVID-19: A RETROSPECTIVE, MULTICENTER COMPARATIVE EFFECTIVENESS STUDY

Garibaldi BT, CID 2021

Studio retrospettivo, pts COVID-19 ospedalizzati Feb 20-Feb 21 US.
Remdesivir recipients matched to control using Time Dependent PS.
Primary outcome: time to improvement
Secondary outcome: time to death
42473 pts (44%) in Remdesivir

Remdesivir pts on:
no Oxygen (aHR 1.3 95%CI 1.22-1.38)
or low flow oxygen (aHR 1.23, 95% CI 1.19-1.27) were significantly more likely to achieve clinical improvement by 28 d and significantly reduced mortality in pts on low flow oxygen

Incidenza cumulativa per clinical improvement



…E survival probability

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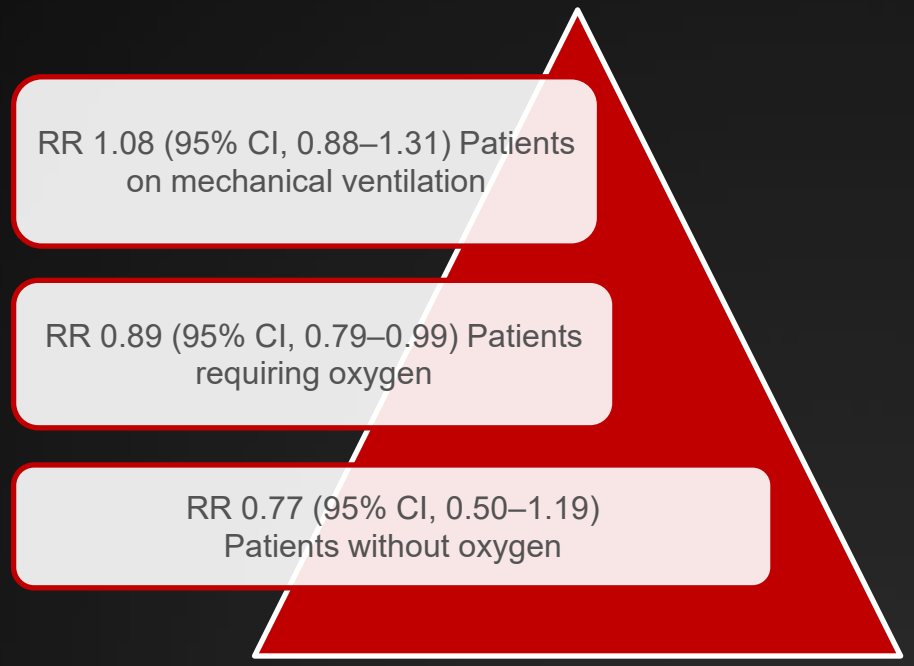
Strengthen of previous results

Eight randomized trials, totaling 10 751 participants

Primary outcome: mortality
Treatment with remdesivir was associated with:



Probability of any mortality benefit on the risk difference scale was:

- 14.8% in patients on mechanical ventilation
- 93.8% for those requiring oxygen
- 76.8% for patients without oxygen

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Remdesivir effectiveness and safety profile have been assessed across a broad range of patient populations and disease severity

Non-hospitalized population

Reduces hospitalisation or all-cause of death vs placebo

Pts high risk of severe disease:
RCT: PINETREE

Hospitalized population

Shortens time to recovery vs placebo

Overall population:
- RCT: ACTT-1

Reduces disease progression vs placebo

Overall population:
- **RCT: ACTT-1**
- **Solidarity**

Reduces mortality vs placebo or Soc

Low flow oxygen:
- **RCT: ACTT-1**

Metanalyses
Supplemental oxygen
- **RCT Solidarity**
- **RWE**

No oxygen
- **RWE**

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The REDPINE Study: Efficcy and Safety of Remdesivir in People With Moderately and Severely Reduced Kidney Function Hospitalised for COVID-19 Pneumonia

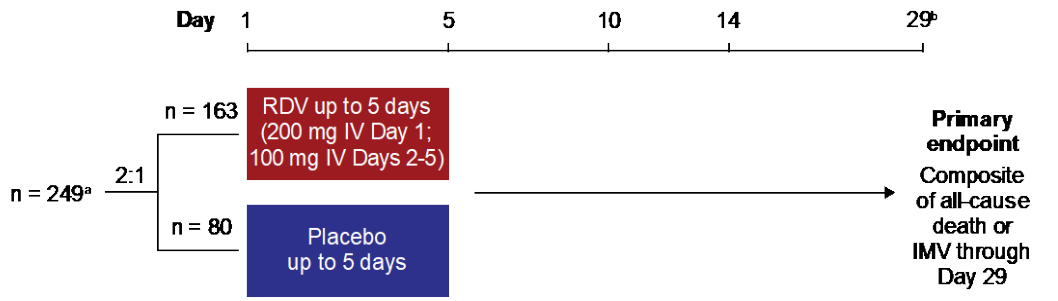
Poster 2635 33° ECCMID 2023

Jose Ramon Santos,[1,*] Jason D. Goldman,[2] Katherine R. Tuttle,[3] J. Pedro Teixeira,[4] Yiannis Koullias,[5] Joe Llewellyn,[5] Yang Zhao,[5] Hailin Huang,[5] Robert H. Hyland,[5] Anu Osinusi,[5] Rita Humeniuk,[5] Henry Hulter,[6] Robert L. Gottlieb,[7] Dahlene N. Fusco,[8] Rita Birne,[9] Fernando F. Stancampiano,[10] Claudia R. Libertin,[10] Mark J. McPhail,[11] Meghan Sise[12]

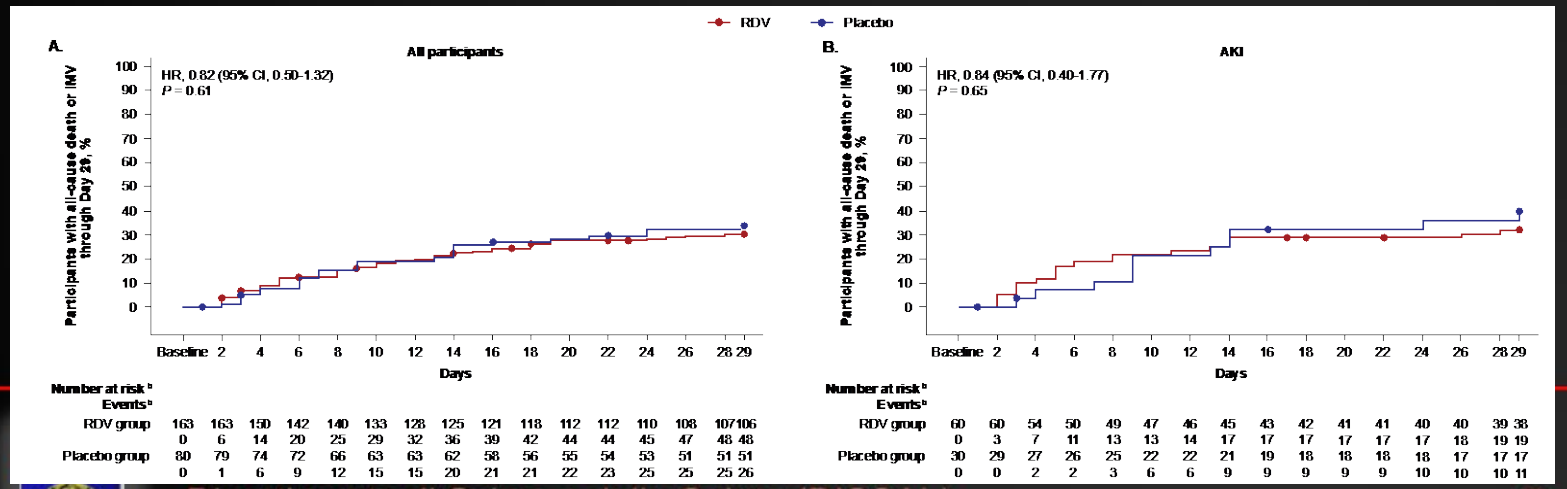
[1]Hospital Universitari Germans Trias i Pujol, Badalona, Spain; [2]Swedish Medical Center, Seattle, WA, USA; [3]Providence Inland Northwest Health, Spokane, WA, USA; [4]University of New Mexico Hospital, Albuquerque, NM, USA; [5]Gilead Sciences, Inc., Foster City, CA, USA; [6]University of California San Francisco, San Francisco, CA, USA; [7]Baylor University Medical Center and Baylor Scott & White Research Institute, Dallas, TX, USA; [8]Tulane University, New Orleans, LA, USA; [9]Centro Hospitalar de Lisboa Ocidental EPE, Lisbon, Portugal; [10]Mayo Clinic College of Medicine and Science, Jacksonville, FL, USA; [11]King's College Hospital, London, UK; [12]Massachusetts General Hospital, Boston, MA, USA.

- REDPINE was a Phase 3, randomised, double-blind, placebo-controlled, parallel-group, multicentre study conducted internationally at 55 centres across 5 countries (Brazil, Portugal, Spain, the United Kingdom, and the United States; EudraCT Registration Number: 2020-005416-22; ClinicalTrials.gov Identifier: NCT04745351)
- Eligible participants had confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, were hospitalised with severe COVID-19, were aged ≥12 years, weighed ≥40 kg, had oxygen saturation ≤94% on room air or required oxygen supplementation, and had eGFR <30 mL/min/1.73 m^2 due to either CKD or AKI

Figure 1. Study Design



RDV= 163 Placebo= 80



Conclusions:

- ✓ **No significant difference in all-cause death or IMV by Day 29 between the RDV and placebo groups;**
- ✓ **however, the study was underpowered for efficacy due to insufficient enrolment**
- ✓ **No dose adjustment is recommended in patients who have an eGFR <30 mL/min/1.73 m2, regardless of the need for dialysis**

Remdesivir Reduced Mortality in Immunocompromised Patients Hospitalized for Coronavirus Disease 2019 Across Variant Waves: Findings From Routine Clinical Practice

Essy Mozaffari,[1] Aastha Chandak,[2] Robert L. Gottlieb,[3,4,5,6] Chidinma Chima-Melton,[7] Stephanie H. Read,[8] Heng Jiang,[9] Mel Chiang,[1] EunYoung Lee,[1] Rikisha Gupta,[1] Mark Berry,[1] and Andre C. Kalil[10]

Clinical Infectious Diseases

MAJOR ARTICLE

August 2023

Retrospective Cohort

COVID19

Comparison of survival outcomes among immunocompromised patients hospitalized for COVID-19 and treated with remdesivir vs. not treated with remdesivir, across different variant waves of the pandemic

Remdesivir cohort: initiation of remdesivir upon hospital admission

n = 14,169

Non-remdesivir cohort: did not receive remdesivir during the hospitalization

n = 14,169

Immunocompromised adults hospitalized with a primary diagnosis of COVID-19

14-day all-cause in-hospital mortality

14

30% lower risk

p = <.0001

28-day all-cause in-hospital mortality

28

25% lower risk

p = <.0001

Dec 2020-Apr 2022

Immunocompromised patients are at high risk of COVID-19 mortality. Remdesivir treatment is associated with a significant reduction in 14- and 28-day mortality among immunocompromised patients hospitalized for COVID-19.

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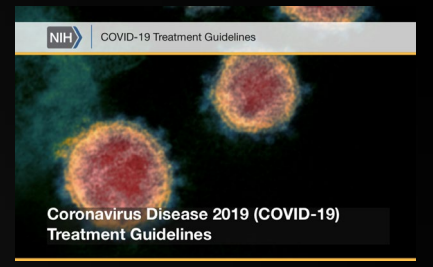
NIH, COVID-19 Guidelines, Feb 2022
Therapeutic Management of Adults Hospitalized for COVID-19 based on Disease Severity

Disease Severity	Recommendations for Antiviral or Immunomodulator Therapy	Recommendations for Anticoagulation Therapy
Hospitalized but Does Not Require Supplemental Oxygen	The Panel **recommends against** the use of **dexamethasone (AIIa)** or **other corticosteroids (AIII)**.[a] There is insufficient evidence to recommend either for or against the routine use of remdesivir. For patients who are at high risk of disease progression, remdesivir may be appropriate.	For patients without evidence of VTE: • **Prophylactic dose** of heparin, unless contraindicated **(AI)**
Hospitalized and Requires Supplemental Oxygen	Use 1 of the following options: • **Remdesivir**[b,c] (e.g., for patients who require minimal supplemental oxygen) **(BIIa)** • **Dexamethasone plus remdesivir**[b,c] **(BIIb)** • **Dexamethasone (BI)** For patients on dexamethasone with rapidly increasing oxygen needs and systemic inflammation, add a second immunomodulatory drug[d] (e.g., **baricitinib**[e] or **tocilizumab**[e]) **(CIIa)**.	For nonpregnant patients with D-dimer levels >ULN who are not at increased bleeding risk:[f] • **Therapeutic dose** of heparin[g] **(CIIa)** For other patients: • **Prophylactic dose** of heparin,[g] unless contraindicated **(AI)**
Hospitalized and Requires Oxygen Through a High-Flow Device or NIV	Use 1 of the following options: • **Dexamethasone (AI)** • **Dexamethasone plus remdesivir**[b] **(BIIb)** For patients with rapidly increasing oxygen needs and systemic inflammation, add either **baricitinib**[e] **(BIIa)** or **IV tocilizumab**[e] **(BIIa)** to 1 of the options above.[d,h]	For patients without evidence of VTE: • **Prophylactic dose** of heparin,[g] unless contraindicated **(AI)**
Hospitalized and Requires MV or ECMO	**Dexamethasone**[i] **(AI)** For patients who are within 24 hours of admission to the ICU: • **Dexamethasone plus IV tocilizumab (BIIa)** If IV tocilizumab is not available or not feasible to use, **IV sarilumab** can be used **(BIIa)**.	For patients without evidence of VTE: • **Prophylactic dose** of heparin,[g] unless contraindicated **(AI)** If patient is started on therapeutic heparin before transfer to the ICU, switch to a **prophylactic dose** of heparin, unless there is a non-COVID-19 indication **(BIII)**.

Rating of Recommendations: A = Strong; B = Moderate; C = Weak

Rating of Evidence: I = One or more randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion

NIH, COVID-19 Guidelines, Oct 2023



Hospitalized and Requires Conventional Oxygen[e]

CLOSE −

Clinical Scenario	Antiviral or Immunomodulator Therapy Recommendation	Anticoagulant Therapy Recommendation
Patients who require minimal conventional oxygen	**Remdesivir**[d,f] **(BIIa)**	For nonpregnant patients with D-dimer levels above the ULN who do not have an increased bleeding risk: • **Therapeutic dose of heparin**[h] **(CIIa)** For other patients: • **Prophylactic dose of heparin**, unless contraindicated **(AI)**; **(BIII)** for pregnant patients
Most patients	Use **dexamethasone plus remdesivir**[f] **(BIIa)**. If remdesivir cannot be obtained, use **dexamethasone (BI)**.	
Patients who are receiving dexamethasone and who have rapidly increasing oxygen needs and systemic inflammation	Add 1 of the following immunomodulators:[g] *Preferred* • **PO baricitinib (BIIa)** • **IV tocilizumab (BIIa)** *Alternatives* • **IV abatacept (CIIa)** • **IV infliximab (CIIa)**	

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Possible antiviral treatment for COVID-19 patients

	Remdesivir	Nirmatrelvir/ ritonavir
Age	≥ 12 yo	≥12 yo
Days from symptoms onset	≤ 7 days	≤ 5 days
Route of administration/ duration	IV/ 3 days 5 days or 10 days	PO/5 days
PROS	Good clinical experience; High efficacy	Oral; High efficacy against all VOCs
CONS	Need for hospital admission	Significant drug-drug interactions in SOT

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

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Therapeutic Management of Nonhospitalized Adults With COVID-19

Last Updated: April 20, 2023

COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. Available at https://www.covid19treatmentguidelines.nih.gov/.

Patients who are at the high risk:

- age >50 years and especially those aged ≥65 years)
- severe immunocompromising condition or receipt of immunosuppressive medications
- lack of vaccination or incomplete vaccination; a prolonged amount of time since the most recent vaccine dose (e.g., >6 months)
- obesity
- diabetes
- chronic respiratory, cardiac, and/or kidney disease

Table 2a. Therapeutic Management of Nonhospitalized Adults With Mild to Moderate COVID-19 Who Do Not Require Supplemental Oxygen

Patient Disposition	Panel's Recommendations
All Patients	• Symptom management should be initiated for all patients **(AIII)**. • The Panel **recommends against** the use of **dexamethasone**[a] or other systemic corticosteroids in the absence of another indication **(AIIb)**.
Patients Who Are at High Risk of Progressing to Severe COVID-19[b]	*Preferred therapies. Listed in order of preference:* • **Ritonavir-boosted nirmatrelvir (Paxlovid)**[c,d] **(AIIa)** • **Remdesivir**[d,e] **(BIIa)** *Alternative therapy. For use when the preferred therapies are not available, feasible to use, or clinically appropriate:* • **Molnupiravir**[d,f,g] **(CIIa)**
Each recommendation in the Guidelines receives a rating for the strength of the recommendation (A, B, or C) and a rating for the evidence that supports it (I, IIa, IIb, or III). See Guidelines Development for more information.	

The Panel favors the use of **ritonavir-boosted nirmatrelvir**; when it is not clinically appropriate (e.g., significant drug-drug interactions), the Panel recommends using remdesivir. The administration of **remdesivir** requires an IV infusion **once daily for 3 days. Molnupiravir** appears to have lower efficacy than the other options recommended by the Panel. Therefore, it should be considered when the other options are not available, feasible to use, or clinically appropriate.

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Nirmatrelvir/ritonavir

- Original RCT: symptomatic, unvaccinated, high risk adults
- N=1379 modified ITT
- Day 28 hosp/death: 0.72% in nirma/rito vs 6.45% placebo
- Relative risk reduction: 88.9%

NNT to avoid one event (hospitalization or death) 16 for nirmatrelvir

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Hammond J. NEJM. 2022;386:305.

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Nirmatrelvir Use and Severe Covid-19 Outcomes during the Omicron Surge

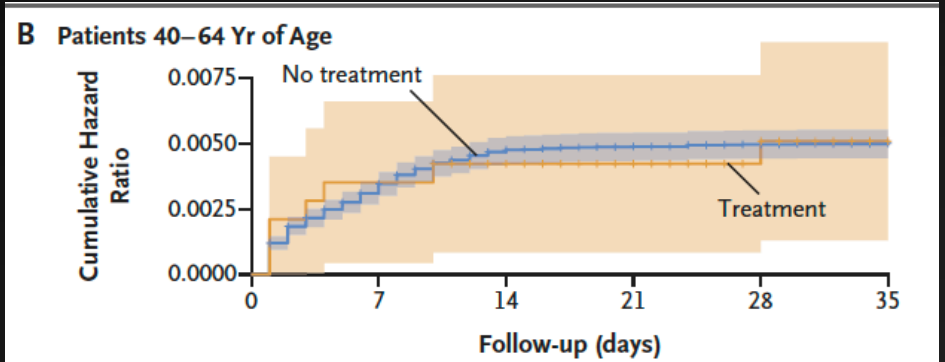
109,254 patients aged>40 yr at high risk for disease progression

78% vaccinated or prev infec or both

3902 **(4%)** received nirmatrelvir during the study period.

Median time from symptoms onset to nirmatrelvir: **2 days**

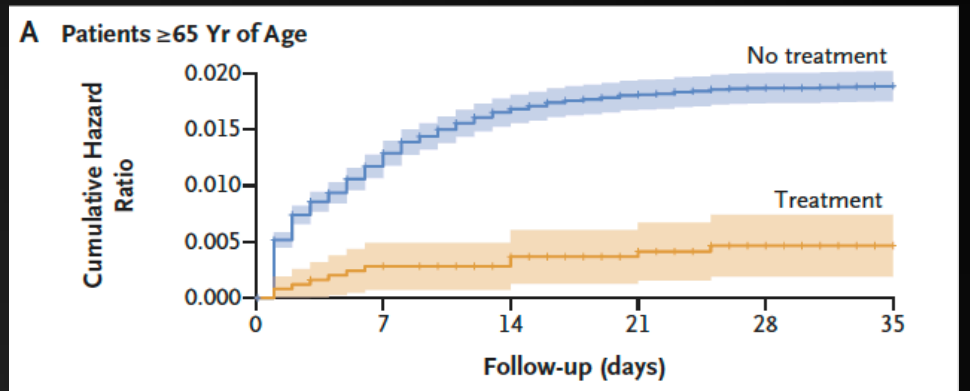
aHR 0.74 (95% CI 0.35 to 1.58)



No. at Risk						
No treatment	66,433	64,805	63,932	61,911	58,268	51,719
Treatment	1,418	1,413	1,368	1,268	1,153	950
Cumulative No. of Events						
No treatment	0	228	312	320	325	327
Treatment	0	5	6	6	7	7

Hospital admission: 15.2 cases NIRMA vs 15.8 NO NIRMA (per 100,000 person-days)

aHR 0.27 (95% CI 0.15 to 0.49)



No. at Risk						
No treatment	42,821	39,802	38,842	37,174	34,548	30,408
Treatment	2,483	2,475	2,370	2,117	1,841	1,498
Cumulative No. of Events						
No treatment	0	535	690	739	760	766
Treatment	0	7	9	10	11	11

Hospital admission: 14.7 cases NIRMA vs 58.9 NO NIRMA (per 100,000 person-days)

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Arbel R. NEJM. 2022;387:790-8.

JAMA Network Open

Lin Dan-Yu, et al. 2023

Nirmatrelvir or Molnupiravir Use and Severe Outcomes From Omicron Infections

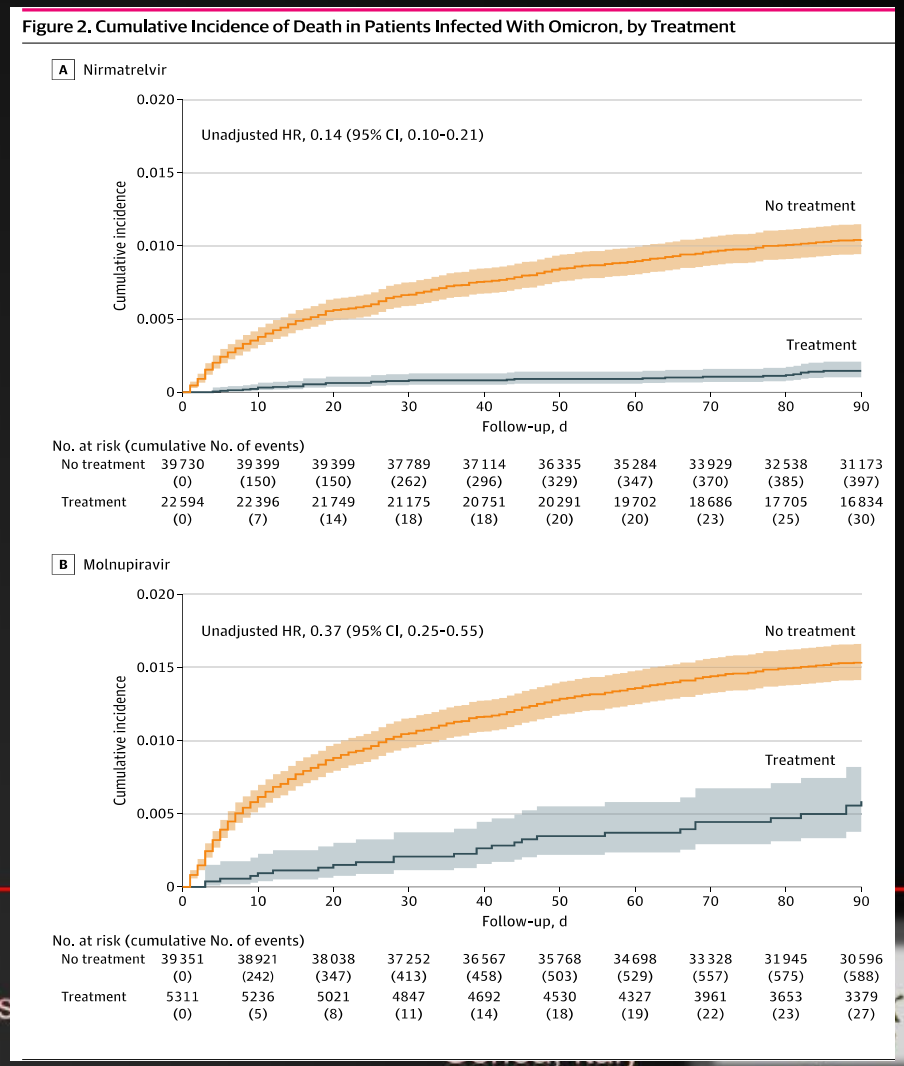
DESIGN, SETTING, AND PARTICIPANTS This was a cohort study of patients who received a diagnosis of COVID-19 at Cleveland Clinic from April 1, 2022, to February 20, 2023 (during which the Omicron variant evolved from BA.2 to BA.4/BA.5, then to BQ.1/BQ.1.1, and finally to XBB/XBB.1.5) and who were at high risk of progressing to severe disease, with follow-up through 90 days after diagnosis. The final date for follow-up data collection was February 27, 2023.

68867 patients (29386 [42.7%] aged>65years;26755[38.9%]males; 51452 [74.7%] non-Hispanic White patients).
22 594 received nirmatrelvir, and 5311 received molnupiravir.

30/22594 N/r, 27/5311 Molnu and 588/40962 no treatment died within 90 days of Omicron infection .

Conclusion: the use of either nirmatrelvir or molnupiravir is associated with reductions in mortality and hospitalization in patients infected with Omicron, regardless of age, race and ethnicity, virus strain, vaccination status, previous infection status, or coexisting conditions.

Figure 2. Cumulative Incidence of Death in Patients Infected With Omicron, by Treatment



Genoa, Italy

Nilmatrevir/ritonavir: The Evidence So Far

	EPIC-HR[1]	Lewnard et al, 2023[9]	Najjar-Debbiny et al, 2023[3]	Arbel et al, 2022[4]	Ganatra et al, 2022[5]	Wong et al, 2022[6*]	Yip et al, 2023[7*]	Dryden-Peterson et al, 2023[8]
Trial Type	RCT	RWE	RWE	RWE	RWE	RWE	RWE	RWE
Population	Non-hospitalised, unvaccinated, symptomatic adults with COVID-19 who were at high risk for progression to severe disease	Non-hospitalized COVID-19 patients (general population)	High-risk COVID-19 adult patients who were potentially candidates for PAXLOVID	COVID-19 patients eligible for PAXLOVID during Omicron surge	Non-hospitalised, vaccinated patients with COVID-19	Hospitalised adult patients with COVID-19 and without oxygen therapy on admission	Non-hospitalised COVID-19 patients attending COVID-19 clinics	Non-hospitalised COVID-19 patients eligible for PAXLOVID during Omicron surge
PAXLOVID efficacy	**RRR of 86.3%[2] in** COVID-19-related hospitalisation or death events by Day 28 versus placebo	**Estimated effectiveness of 89.2%** when administered within 0–5 days of symptom onset	Decreased risk of severe COVID-19 or mortality versus no PAXLOVID (**HR: 0.54**)	Lower rates of hospitalisation and death due to COVID-19 in adults ≥65 years than younger adults, regardless of SARS-CoV-2 immunity (**HR hospitalisation: 0.27; HR death: 0.21**)	Reduction in the composite outcome of all-cause ER visits, hospitalisation, or death in 30 days versus no PAXLOVID (**OR: 0.5; RRR: 45%**)	Lower risk of all-cause mortality versus matched controls (**HR: 0.34**)	Reduction in hospital admissions versus no antiviral treatment (**weighted HR: 0.79**)	Fewer hospitalisations and deaths versus no PAXLOVID treatment (**aRR: 0.56**)

*Studies with multiple outcomes, with only certain outcomes shown. This publication includes data relating to several outcomes, however only data and information concerning nirmatrelvir/ritonavir are shown. Please reference the original article for additional information.

ER, emergency room; HR, hazard ratio; OR, odds ratio; RCT, randomised controlled trial; RRR, relative risk reduction; RWE, real-world evidence.

1. Hammond J, et al. *N Engl J Med* 2022; 386:1397–1408; 2. Pfizer. Summary of Product Characteristics for PAXLOVID: https://www.ema.europa.eu/en/documents/product-information/paxlovid-epar-product-information_en.pdf (Accessed February 2023); 3. Najjar-Debbiny R, et al. *Clin Infect Dis* 2023;76:e342–e349; 4. Arbel R, et al. *N Engl J Med* 2022;387:790–798; 5. Ganatra S et al. *Clin Infect Dis* 2022;ciac673; 6. Wong CKH, et al. *Lancet Infect Dis* 2022;22:1681–1693; 7. Yip TCF, et al. *Clin Infect Dis* 2023;76:e26–e33; 8. Dryden-Peterson S, et al. *Ann Intern Med* 2023;176:77–84.

New perspectives…..

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In outpatients setting

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Efficacy and Safety of Ensitrelvir in Patients With Mild-to-Moderate Coronavirus Disease 2019: The Phase 2b Part of a Randomized, Placebo-Controlled, Phase 2/3 Study

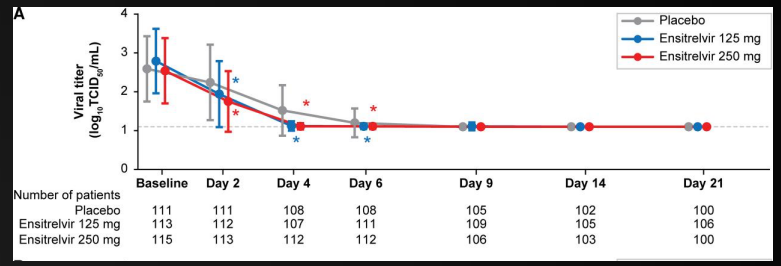
Mukae H, CID 2023

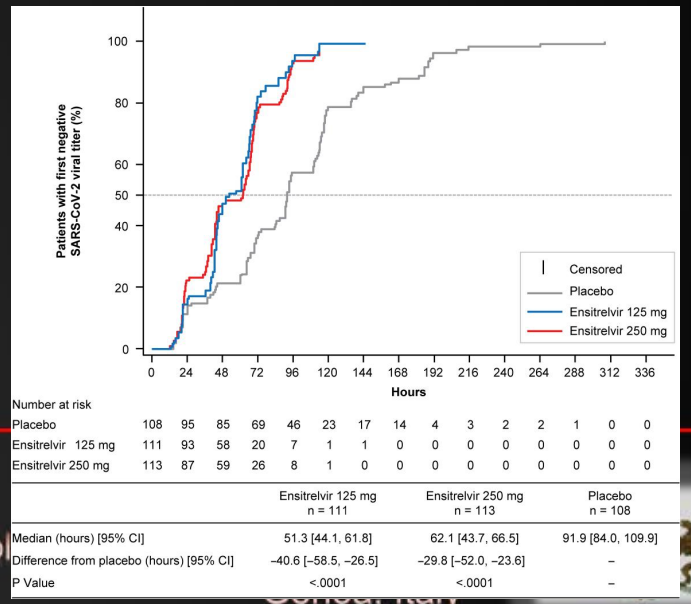
Background. This phase 2b part of a randomized phase 2/3 study assessed the efficacy and safety of ensitrelvir for mild-to-moderate coronavirus disease 2019 (COVID-19) during the Omicron epidemic.

Methods. Patients were randomized (1:1:1) to orally receive ensitrelvir fumaric acid 125 mg (375 mg on day 1) or 250 mg (750 mg on day 1) or placebo once daily for 5 days. The co-primary endpoints were the change from baseline in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) titer on day 4 and time-weighted average change from baseline up to 120 hours in the total score of predefined 12 COVID-19 symptoms. Safety was assessed through adverse events.

Results. A total of 341 patients (ensitrelvir 125-mg group: 114; ensitrelvir 250-mg group: 116; and placebo group: 111; male: 53.5–64.9%; mean age: 35.3–37.3 years) were included in the efficacy analyses. The change from baseline in SARS-CoV-2 titer on day 4 was significantly greater with both ensitrelvir doses than with placebo (differences from placebo: −0.41 $\log_{10}$ 50% tissue-culture infectious dose/mL; $P < .0001$ for both). The total score of the 12 COVID-19 symptoms did not show a significant difference between the ensitrelvir groups and placebo group. The time-weighted average change from baseline up to 120 hours was significantly greater with ensitrelvir versus placebo in several subtotal scores, including acute symptoms and respiratory symptoms. Most adverse events were mild in severity.

Conclusions. Ensitrelvir treatment demonstrated a favorable antiviral efficacy and potential clinical benefit with an acceptable safety profile.





The primary virologic outcome was change from baseline (day 1, before drug administration) in the SARS-CoV-2 viral titer on day 4 of treatment. The primary clinical outcome was time- weighted average change from baseline up to 120 hours in the total score of 12 COVID-19 symptoms

In conclusion, 5-day, once-daily, oral ensitrelvir treatment demonstrated rapid and favorable antiviral efficacy with an acceptable safety profile in patients with mild-to-moderate COVID-19, a majority of whom had been vaccinated.

Safety and Effectiveness of Ensitrelvir for the Treatment of COVID-19 in Japanese Clinical Practice: A Post-Marketing Surveillance (Interim Analysis).
Ogura E., *et al*. IDWeek 2023. Poster #537

New data evaluating the effectiveness and tolerability of ensitrelvir in clinical practice in Japan.

Following emergency regulatory approval from the MHLW in Japan, an ongoing post-marketing surveillance study is enrolling 3,000 Japanese patients.

As of July 20, 2023, a total of 1,682 patients were enrolled, of which, 1,589 were evaluated for safety and 1,584 for effectiveness.
After ensitrelvir administration, the median time to resolution of fever was about 1.5 days and median time to resolution of all symptoms was about 6.5 days, independent of age or presence of risk factors for severe disease.

There were no deaths due to COVID-19. No new concerns about tolerability or effectiveness of ensitrelvir have been identified.

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The NEW ENGLAND JOURNAL of MEDICINE

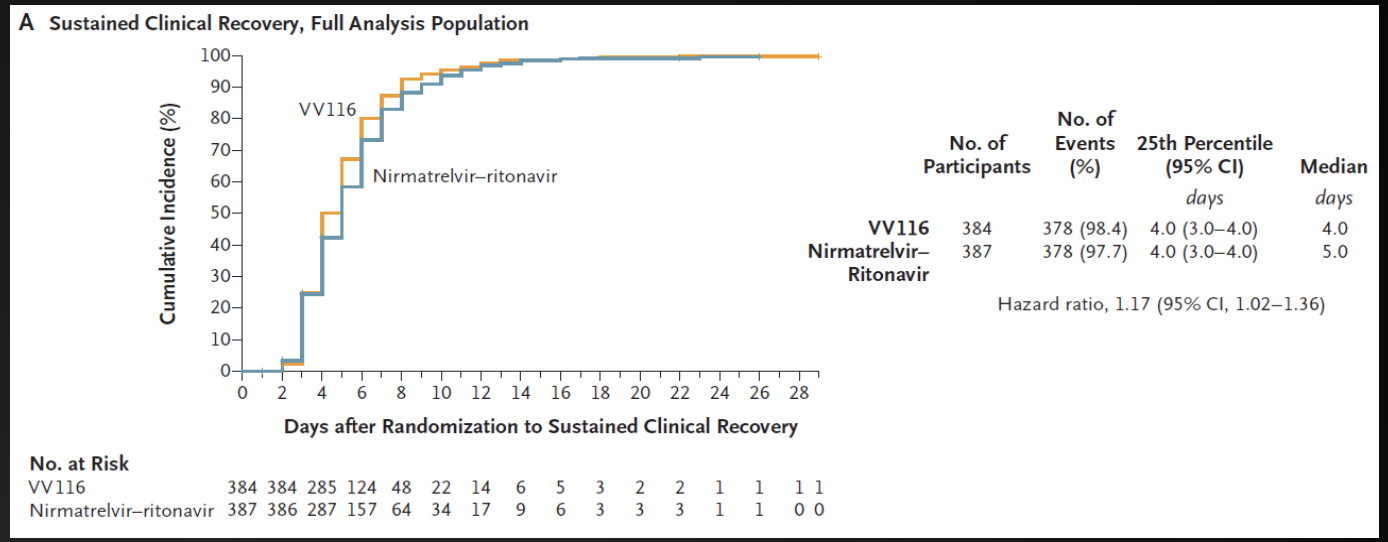
ORIGINAL ARTICLE

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

Cao Z, et al. NEJM 2022

VV116 is an oral analogues of remdesivir.
Study: phase 3, noninferiority, observer-blinded, randomized trial

Primary endpoint:
Time from randomization to **sustained clinical recovery** (alleviation of all COVID-19 symptoms according a predefined scale) through day 28.



	No. of Participants	No. of Events (%)	25th Percentile (95% CI)	Median
			days	*days*
VV116	384	378 (98.4)	4.0 (3.0–4.0)	4.0
Nirmatrelvir–Ritonavir	387	378 (97.7)	4.0 (3.0–4.0)	5.0

Hazard ratio, 1.17 (95% CI, 1.02–1.36)

The hazard ratio for the time from randomization to sustained clinical recovery indicated that the noninferiority of VV116 to nirmatrelvir–ritonavir was established.

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As we move into 2024…..

We need
‘effective care pathways’
In the hospital setting and
in outpatient clinic

Identify rapidly
outside the
Hospital
patients at risk

Network between
Hospital and GP
to avoid the
overcrowding of ED

Need of additional
data for the
management of
specific patient
groups

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Grazie!!!

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