Efficacy of nirmatrelvir-ritonavir in high-risk trial participants with prior SARS-CoV-2 infection or vaccination: a pooled analysis

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Disclosure

- All authors are employees of Pfizer and may hold shares, stock options, or both

Background and rationale

- EPIC-HR showed >85% efficacy of oral nirmatrelvir-ritonavir (NMV/r) for preventing COVID-19 hospitalization and all-cause death in unvaccinated high-risk patients[1*]
- The applicability of these RCT findings to current settings of high population-level immunity, however, are not well understood
- We evaluated efficacy of NMV/r in a subset of high-risk trial participants with pre-existing SARS-CoV-2 immunity from either prior infection or vaccination

*≥1 risk factor for severe COVID-19.
NMV/r, nirmatrelvir-ritonavir; RCT, randomized controlled trial.
1. Hammond J, et al. N Engl J Med 2022;386:1397-408.

Methods: Design, setting, and population

- Efficacy of NMV/r received within 5 days of COVID-19 symptom onset was assessed vs placebo through 28 days against pre-specified outcomes:
  - Proportion with COVID-19-related hospitalization and all-cause death
  - COVID-19-related medical visits per 100 participants
  - Reduction from baseline in no. of participants with severe COVID-19 symptoms in 2–6 days and 7–28 days after treatment initiation
  - Time to sustained COVID-19 symptom alleviation*

- Data were pooled from two Phase 2/3 RCT (mITT1) populations:
  - High-risk† EPIC-HR patients who were unvaccinated and sero(+) at baseline[1]
  - High-risk† EPIC-SR patients who previously received COVID-19 vaccine[2]

* Sustained alleviation considered to have occurred on first of 4 consecutive days during which all symptoms scored as moderate or severe and as mild or absent at baseline were scored as mild or absent and as absent, respectively.
† ≥1 risk factor for severe COVID-19.
mITT1, modified intention-to-treat 1 defined as all participants randomly assigned to study intervention (within 5 days of symptom onset), who took at least 1 dose of study intervention, with at least 1 post-baseline visit through Day 28, and who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment; NMV/r, nirmatrelvir-ritonavir; RCT, randomized controlled trial.
1. Hammond J, et al. N Engl J Med 2022;386:1397-408; 2. Hammond J, et al. N Engl J Med 2024;390:1186-95.

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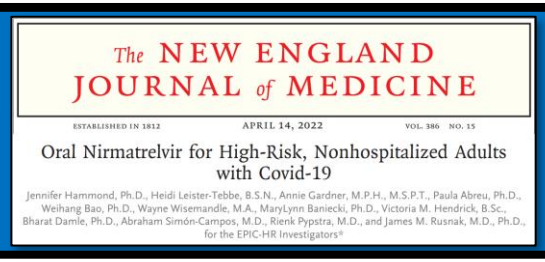
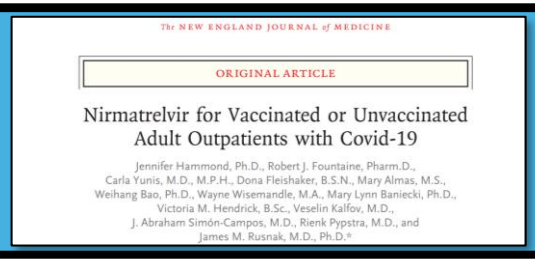
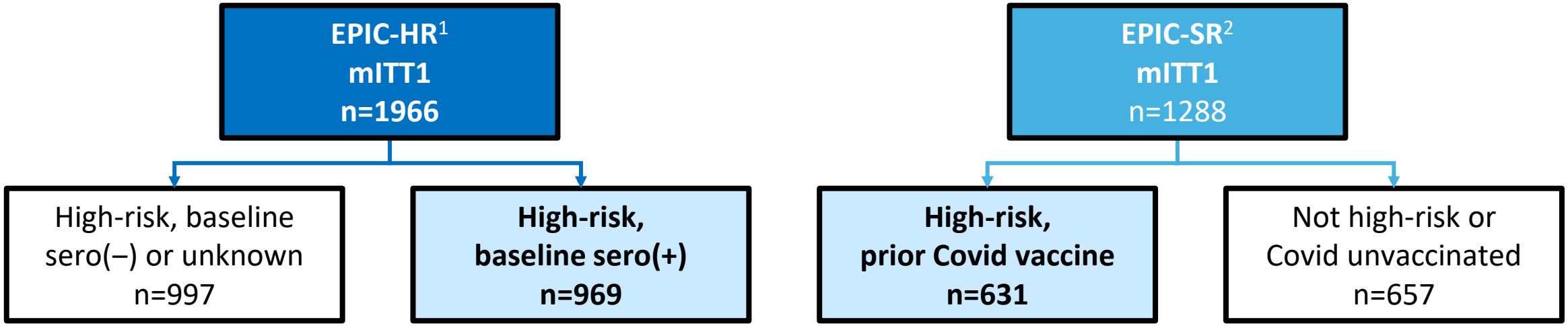
Methods: EPIC-HR and EPIC-SR trials

EPIC-HR[1]	EPIC-SR[2]
	
• High-risk and not vaccinated against COVID-19	• High-risk and COVID-19 vaccinated **<u>OR</u>** not high-risk irrespective of vaccine hx
• Jul 16, 2021 – Dec 9, 2021	• Aug 25, 2021 – Jul 25, 2022
• >85% significant relative efficacy against COVID-19 hospitalization and all-cause death	• No difference in median time to sustained alleviation of all targeted COVID-19 signs and symptoms • 51% (p=.18) relative reduction in COVID-19 hospitalization and all-cause death
Safety profile of NMV/r well-described in both studies, with dysgeusia the most frequent event reported by NMV/r recipients, followed by diarrhea and nausea	

1. Hammond J, et al. N Engl J Med 2022;386:1397-408; 2. Hammond J, et al. N Engl J Med 2024;390:1186-95.

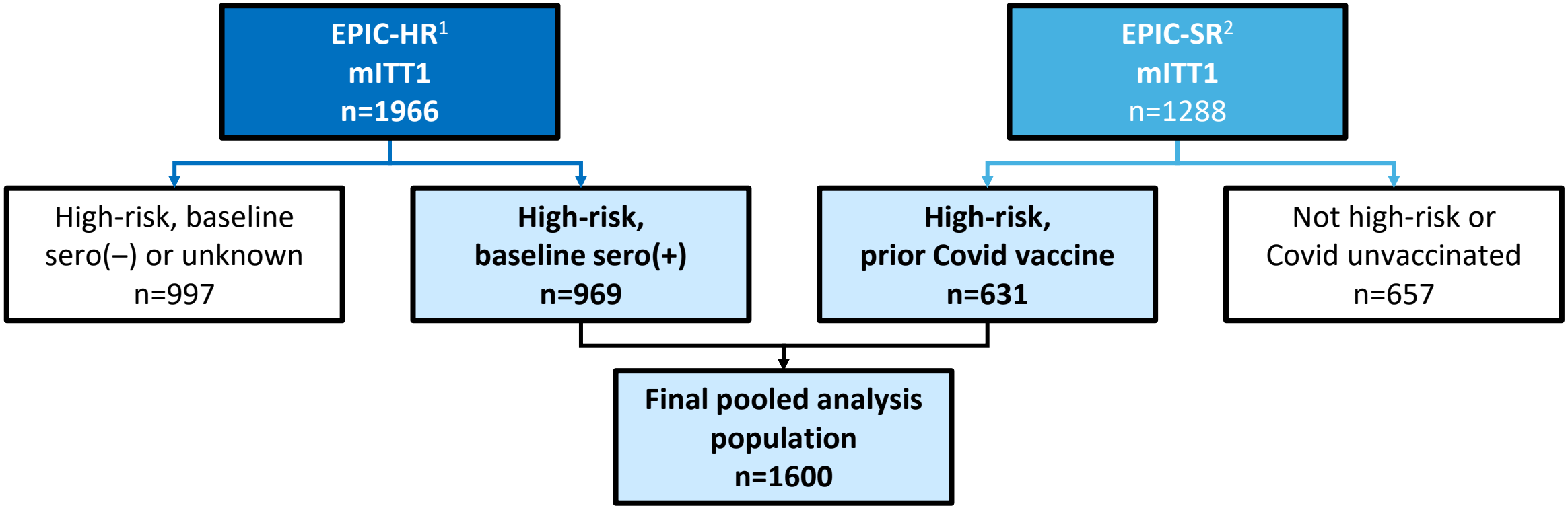
Results: Pooled analysis selection criteria (EPIC-HR and SR)



= pooled analysis study population

1. Hammond J, et al. N Engl J Med 2022;386:1397-408. Supplementary appendix; 2. Hammond J, et al. N Engl J Med 2024;390:1186-95.

Results: Pooled analysis selection criteria (EPIC-HR and SR)



1. Hammond J, et al. N Engl J Med 2022;386:1397-408. Supplementary appendix; 2. Hammond J, et al. N Engl J Med 2024;390:1186-95.

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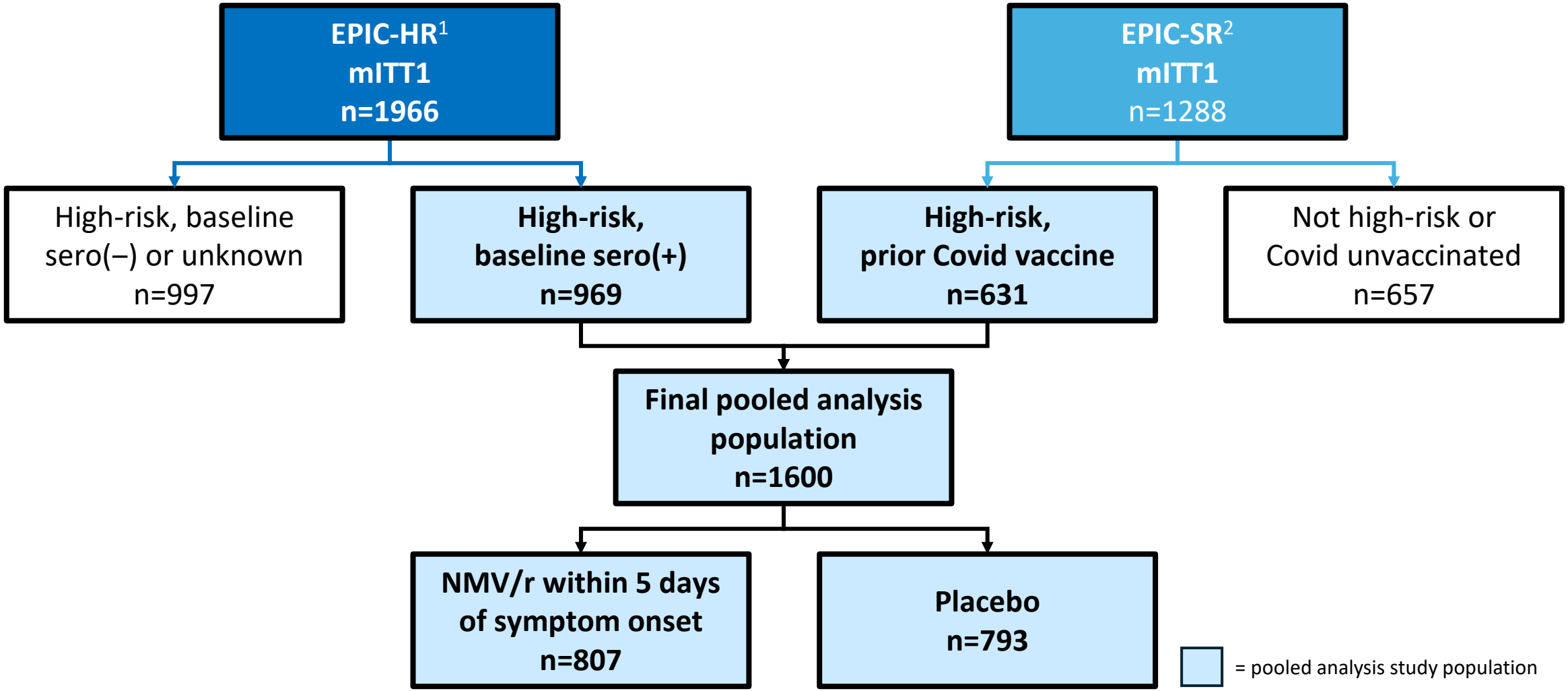

1. Hammond J, et al. N Engl J Med 2022;386:1397-408. Supplementary appendix; 2. Hammond J, et al. N Engl J Med 2024;390:1186-95.

Results: Study population

Characteristic	n (%)		
	NMV/r (n=807)	Placebo (n=793)	Total (n=1,600)
Age group in years	median = 44	median = 45	median = 45
18–44	406 (50.3)	385 (48.5)	791 (49.4)
45–59	253 (31.4)	266 (33.5)	519 (32.4)
60–64	54 (6.7)	69 (8.7)	123 (7.7)
≥65	94 (11.6)	73 (9.2)	167 (10.4)
Gender			
Male	402 (49.8)	406 (51.2)	808 (50.5)
Female	405 (50.2)	387 (48.8)	792 (49.5)
Race			
White	553 (68.5)	546 (68.9)	1099 (68.7)
Black or African American	40 (5.0)	29 (3.7)	69 (4.3)
Asian or Pacific Islander	134 (16.6)	138 (17.4)	272 (17.0)
Other or unknown*	80 (9.9)	80 (10.1)	160 (10.0)
Ethnicity			
Hispanic or Latino	426 (52.8)	437 (55.1)	863 (53.9)
Non-Hispanic or Latino	376 (46.6)	351 (44.3)	727 (45.4)
Not reported	5 (0.6)	5 (0.6)	10 (0.6)

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* Includes multiracial.
NMV/r, nirmatrelvir-ritonavir

Results: Study population (cont.)

Characteristic	n (%)		
	NMV/r (n=807)	Placebo (n=793)	Total (n=1,600)
Geography			
US	355 (44.0)	360 (45.4)	715 (44.7)
Europe	153 (19.0)	140 (17.7)	293 (18.3)
India	85 (10.5)	84 (10.6)	169 (10.6)
Rest of world	214 (26.5)	209 (26.4)	423 (26.4)
BMI (kg/m^2)			
<25, normal or underweight	167 (20.7)	153 (19.3)	320 (20.0)
25–29.9, overweight	381 (47.2)	352 (44.4)	733 (45.8)
30–34.9, obesity class I	179 (22.2)	187 (23.6)	366 (22.9)
≥35, obesity class II or III	80 (9.9)	100 (12.6)	180 (11.3)
Comorbidities			
Cardiovascular disorder	24 (3.0)	24 (3.0)	48 (3.0)
Chronic kidney disease	3 (0.4)	8 (1.0)	11 (0.7)
Chronic lung disease	36 (4.5)	28 (3.5)	64 (4.0)
Cigarette smoker	272 (33.7)	274 (34.6)	546 (34.1)
Diabetes mellitus	97 (12.0)	92 (11.6)	189 (11.8)
Hypertension	233 (28.9)	228 (28.8)	461 (28.8)

Results: Efficacy of NMV-r

Outcome	NMV/r	Placebo	Relative RR (95% CI)	Absolute RR (95% CI)
Proportion of participants with **COVID-19-related hospitalization and all-cause death**, n/N (%)	4 / 807 (0.5)	15 / 793 (1.9)	**73.7**[a] (21.4–91.3)[b]	**1.40**[a] (0.33–2.47)[c,*]
No. of (any) **COVID-19-related medical visits**, visits/N (visits per 100 participants)	21 / 807 (2.6)	53 / 793 (6.7)	**65.0**[d] (24.4–83.8)[*]	**4.10**[e]
Reduction from baseline in no. of participants with **severe COVID-19 symptoms in 2–6 days** after treatment initiation, n/N (%)	45 / 768 (5.9)	15 / 772 (1.9)	**22.1** (0.66–38.9)[f,*]	**3.92**[g]
Reduction from baseline in no. of participants with **severe COVID-19 symptoms in 7–28 days** after treatment initiation, n/N (%)	101 / 768 (13.2)	73 / 772 (6.9)	**46.6** (22.1–63.4)[f,*]	**6.28**[g]

CI, confidence interval; mITT, modified intention-to-treat; NMR-r, nirmatrelvir-ritonavir (Paxlovid); RR, risk reduction, which is 100%*(1 - risk ratio). *95% CI provided for pre-specified formal statistical analysis.
a Risk ratio determined using estimates obtained from Kaplan-Meier method. b 95% CI based on observed event rates. c Difference estimated using Kaplan-Meier method, variance estimated using Greenwood formula. d Comparison of event rates based on negative binomial regression model that included main effects of treatment, geographic region, days since symptom onset (0–3, 4–5 days), baseline SARS-CoV-2 serology status, COVID-19 vaccination status, baseline viral load (<4, ≥4 $\log_{10}$ copies/mL), and log number of days follow-up as participant offset variable. e Difference between treatment groups based on average number of medical visits per 100 participants. f Estimated using generalized estimating equations (GEE) model adjusted for geographic region, days since symptom onset, baseline SARS-CoV-2 serology status, COVID-19 vaccination status, and baseline viral load. g Difference between treatment groups based on observed change from baseline in proportion of participants with severe symptoms.

Results: Efficacy of NMV-r

Outcome	NMV/r	Placebo	Relative RR (95% CI)	Absolute RR (95% CI)	NNT
Proportion of participants with **COVID-19-related hospitalization and all-cause death**, n/N (%)	4 / 807 (0.5)	15 / 793 (1.9)	**73.7**[a] (21.4–91.3)[b]	**1.40**[a] (0.33–2.47)[c,*]	**71**
No. of (any) **COVID-19-related medical visits**, visits/N (visits per 100 participants)	21 / 807 (2.6)	53 / 793 (6.7)	**65.0**[d] (24.4–83.8)[*]	**4.10**[e]	**24**
Reduction from baseline in no. of participants with **severe COVID-19 symptoms in 2–6 days** after treatment initiation, n/N (%)	45 / 768 (5.9)	15 / 772 (1.9)	**22.1** (0.66–38.9)[f,*]	**3.92**[g]	**26**
Reduction from baseline in no. of participants with **severe COVID-19 symptoms in 7–28 days** after treatment initiation, n/N (%)	101 / 768 (13.2)	73 / 772 (6.9)	**46.6** (22.1–63.4)[f,*]	**6.28**[g]	**16**

CI, confidence interval; mITT, modified intention-to-treat; NMR-r, nirmatrelvir-ritonavir (Paxlovid); RR, risk reduction, which is 100%*(1 - risk ratio). *95% CI provided for pre-specified formal statistical analysis.
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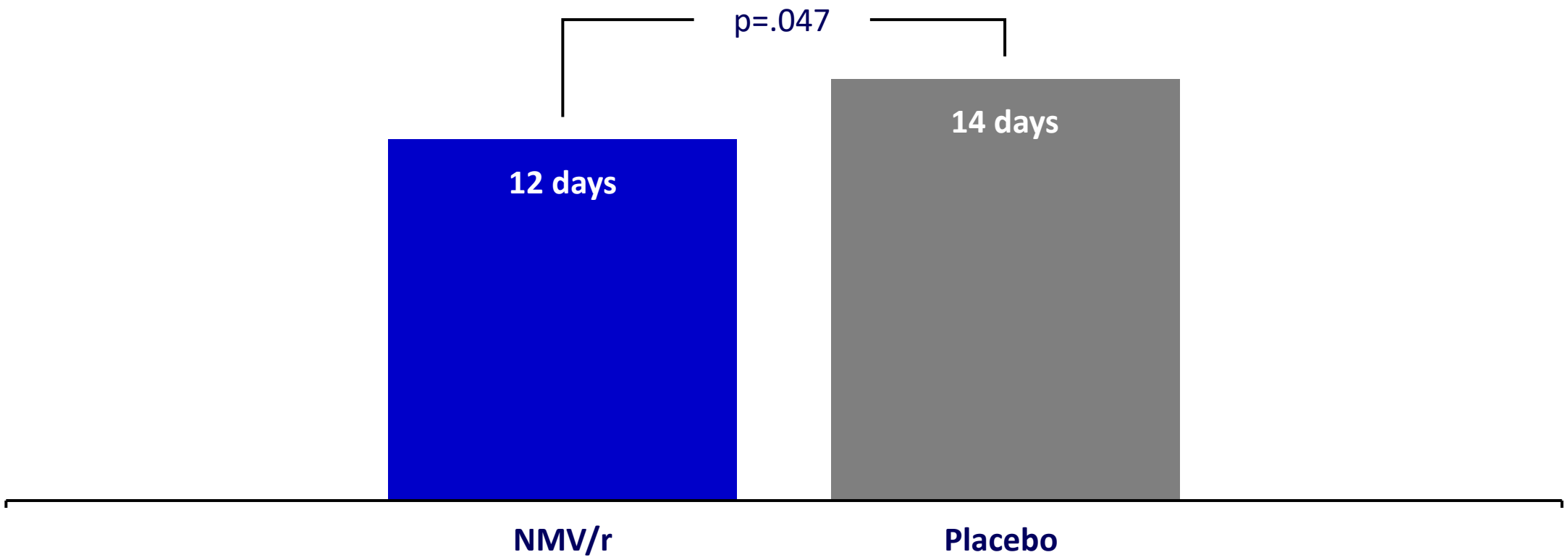
Results: Efficacy of NMV-r (cont.)

- Median **time to sustained symptom alleviation**† was **2 days shorter** for those who received NMV/r vs placebo



† Sustained alleviation considered to have occurred on first of 4 consecutive days during which all symptoms scored as moderate or severe and as mild or absent at baseline were scored as mild or absent and as absent, respectively.

Limitations

- Limited sample size to perform stratified analyses
- Limited number of Omicron infections
- No data from 2022–23 or 2023–24 seasons

Does COVID-19 still cause a significant health burden?

Cumulative rates of COVID-19 Hospitalization per 100,000 by age group and period, COVID-NET[1]

Age group	Oct 1, 2023 – Mar 31, 2024	Oct 1, 2023 – Aug 31, 2024
≥18	151.4 (0.15%)	217.8 (0.22%)
≥65	523.0 (0.52%)	753.9 (0.75%)
≥75	891.8 (0.89%)	1,292.1 (1.29%)

1. CDC. COVID-NET. Available at: https://covid.cdc.gov/covid-data-tracker/#covidnet-hospitalization-network. Accessed Sep 2024.

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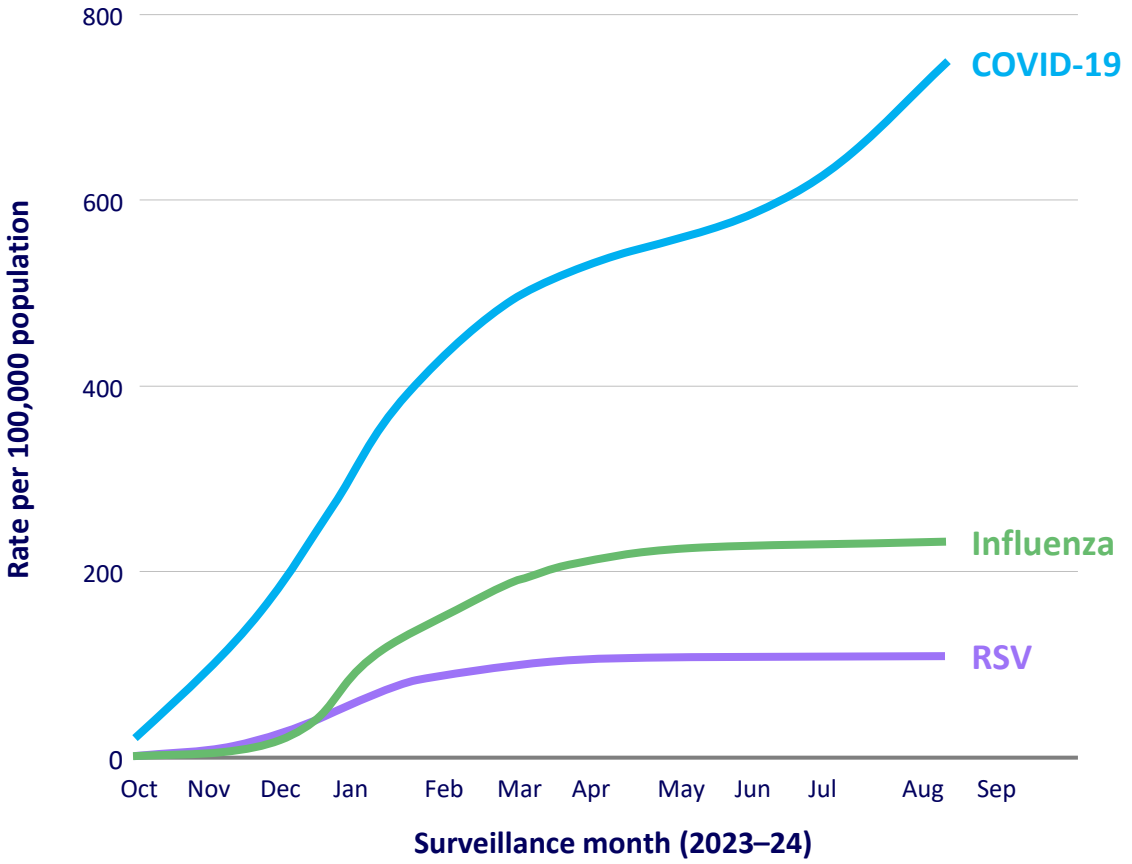
Cumulative US Hospitalizations 2023–24 (≥65 years)[2]



RSV, respiratory syncytial virus. RESP-NET is a CDC system that monitors laboratory-confirmed hospitalizations associated with COVID-19, RSV, and influenza. It does not collect data on all hospitalizations caused by respiratory illnesses. Surveillance is conducted through network of acute care hospitals in select counties or county equivalents in 12, 13 and 14 states for RSV, COVID-19, or influenza, respectively. Surveillance platforms for these viruses covers >30 million people and includes~8–10% of US population. 1. CDC. COVID-NET. Available at: https://covid.cdc.gov/covid-data-tracker/#covidnet-hospitalization-network. Accessed Sep 2024; 2. CDC. RESP-NET. https://www.cdc.gov/surveillance/resp-net/dashboard.html. Accessed Sep 2024.

Conclusions

- Post-pandemic burden of COVID-19 remains significant in adults (i.e., still higher than flu), especially for those eligible for NMV/r

- In a subset of RCT participants with pre-existing natural or vaccine-derived SARS-CoV-2 immunity, treatment with NMV/r significantly:
  - **Decreased risk** of COVID-19 hospitalization and all-cause death (NNT = 71)
  - **Decreased risk** of all COVID-19-related medical encounters (NNT = 24)
  - **Decreased risk** of severe symptoms 2–6 and 7–28 days post-treatment (NNTs = 26 and 16)
  - **Shortened time** to sustained symptom alleviation (by 2 days on average)

- Consistent with real-world observational studies conducted in the Omicron era,[1-3] our findings underscore the utility of NMV/r in high-risk patients with baseline SARS-CoV-2 immunity

1. Aggarwal NR, et al. Lancet Infect Dis. 2023;23(6):696-705; 2. Najjar-Debbiny R, et al. Clin Infect Dis. 2023;76(3):e342-e349; 3. Lewnard JA, et al. Lancet Infect Dis. 2023;23(7):806-15.