Supplementary Material – Symptom Alleviation/Resolution and Returns to Usual Health/Activities in Immunocompromised Adults with COVID-19 Treated with Nirmatrelvir-Ritonavir: Results from the EPIC-IC Trial

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CONSORT Checklist

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Open science			
Trial registration	2	Name of trial registry, identifying number (with URL) and date of registration	2, n/a
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Funding and conflicts of interest	5a	Sources of funding and other support (eg, supply of drugs), and role of funders in the design, conduct, analysis and reporting of the trial	19
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Outcomes	14	Prespecified primary and secondary outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome	5–6, Figure S1
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*We strongly recommend reading this statement in conjunction with the CONSORT 2025 Explanation and Elaboration and/or the CONSORT 2025 Expanded Checklist for important clarifications on all the items. We also recommend reading relevant CONSORT extensions. See www.consort-spirit.org.

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Comissao Nacional De Etica Em Pesquisa	Brasilia, Distrito Federal	Brazil
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Supplementary Methods

Clinical Trial Design

Participants were instructed to take one dose of their assigned study treatment, whether NMV/r or placebo, every 12 hours throughout the 15-day treatment period. Each dose of NMV/r or placebo was formulated as a set of tablets to be taken together orally. Placebo tablets were identical in appearance to active tablets. Double-blinding was retained throughout the study period. Further details on blinding are available in Weinstein et al., 2025 [1].

Randomization was stratified by whether participants were considered immunocompromised solely based on the use of corticosteroids or a tumor necrosis factor (TNF) blocker (see full definition of immunocompromise (IC) in Supplementary Methods, EPIC-IC participants). This subpopulation was capped at about 25%. Information on randomization sequence generation, allocation concealment, and randomization implementation is available in Weinstein et al., 2025 [1].

To confirm SARS-CoV-2 infection, a rapid antigen test was conducted at screening if the participant did not have results of a positive SARS-CoV-2 test obtained within 5 days prior to randomization. During the study, some individuals were enrolled based on positive rapid antigen test results but did not have a detectable viral load on RT-PCR at Baseline. The study protocol was therefore amended to clarify that nasopharyngeal swab collection for a RT-PCR test must occur before any rapid antigen assessment.

COVID-19 signs and symptoms used to determine eligibility for EPIC-IC were based on published FDA guidance and included cough, shortness of breath or difficulty breathing, feeling feverish, chills or shivering, fatigue, muscle or body aches, diarrhea, nausea, vomiting, headache, sore throat, stuffy or runny nose, loss of smell, and loss of taste [2].

Study visits were conducted at study sites, which were medical institutions, including hospitals and clinical research centers. Home health visits or mobile visits could be conducted if an in-person visit was not feasible. The study's US diversity strategy aimed to support the recruitment of diverse populations. US sites therefore included medical institutions with varying characteristics, like urban and suburban locations.

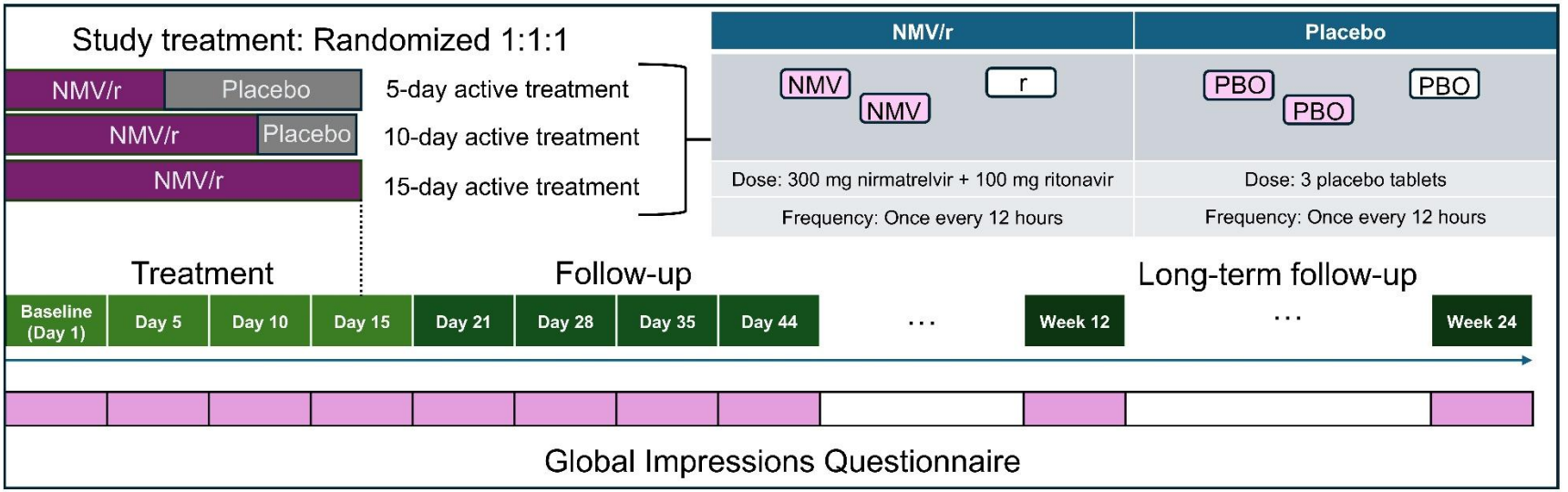

Figure S1. Schedule of treatment and Global Impressions Questionnaire assessment in the EPIC-IC trial

Participants were randomized 1:1:1 to receive active treatment with NMV/r for the first 5, 10, or 15 days of the study. The patient-reported Global Impressions Questionnaire was completed at each visit (indicated with pink shading). Abbreviations: NMV, nirmatrelvir; NMV/r, nirmatrelvir-ritonavir; PBO, placebo; r, ritonavir.

EPIC-IC Participants

Participants needed to be immunocompromised, with ≥1 of the following: recipient of solid organ transplant and receiving immunosuppressive therapy; receipt of chimeric antigen receptor (CAR)-T-cell therapy or hematopoietic cell transplantation and either within 2 years of transplantation or receiving immunosuppressive therapy; moderate or severe primary immunodeficiency (e.g., DiGeorge syndrome); active or recent use of ≥1 immune-weakening medications (e.g., corticosteroids, chemotherapy, TNF blockers, anti-CD20 biologics); active immunosuppressive treatment for a solid tumor or hematological malignancy; or HIV infection with CD4 cell count <200 mm^3 within 6 months before screening [1].

Subpopulations of participants with severe IC vs. non-severe IC were defined post hoc, with the definition of severe IC provided by the US FDA based on investigator requests for extended treatment [1].

Sample Size

The study aimed to randomize 150 participants in the main study population, partly due to practical considerations regarding the difficulty of recruiting immunocompromised patients. A power calculation was not conducted because EPIC-IC was an exploratory trial with a descriptive statistical approach; no formal hypothesis testing was planned. In addition, the authors determined that there was insufficient knowledge regarding the potential treatment effect on virologic endpoints to adequately estimate the appropriate power for inference testing. Primary analyses were conducted after the main study population was fully enrolled and all participants completed their Day 44 visit. Follow-up analyses were conducted after all participants in the main study population completed their Week 24 visit.

Supplementary Results

Table S1. Completion rates for the Global Impressions Questionnaire*

Completion rate, n (%)	Overall (N=150)	5-day NMV/r (n=52)	10-day NMV/r (n=48)	15-day NMV/r (n=50)
Baseline	141 (94.0)	48 (92.3)	47 (97.9)	46 (92.0)
Day 5	135 (90.0)	45 (86.5)	45 (93.8)	45 (90.0)
Day 10	135 (90.0)	46 (88.5)	46 (95.8)	43 (86.0)
Day 15	135 (90.0)	47 (90.4)	44 (91.7)	44 (88.0)
Day 21	128 (85.3)	43 (82.7)	42 (87.5)	43 (86.0)
Day 28	124 (82.7)	42 (80.8)	42 (87.5)	40 (80.0)
Day 35	131 (87.3)	44 (84.6)	43 (89.6)	44 (88.0)
Day 44	131 (87.3)	43 (82.7)	44 (91.7)	44 (88.0)
Week 12	127 (84.7)	44 (84.6)	42 (87.5)	41 (82.0)
Week 24	125 (83.3)	39 (75.0)	44 (91.7)	42 (84.0)

*All returned questionnaires were completed (i.e., all questions were answered).

Abbreviation: NMV/r, nirmatrelvir-ritonavir.

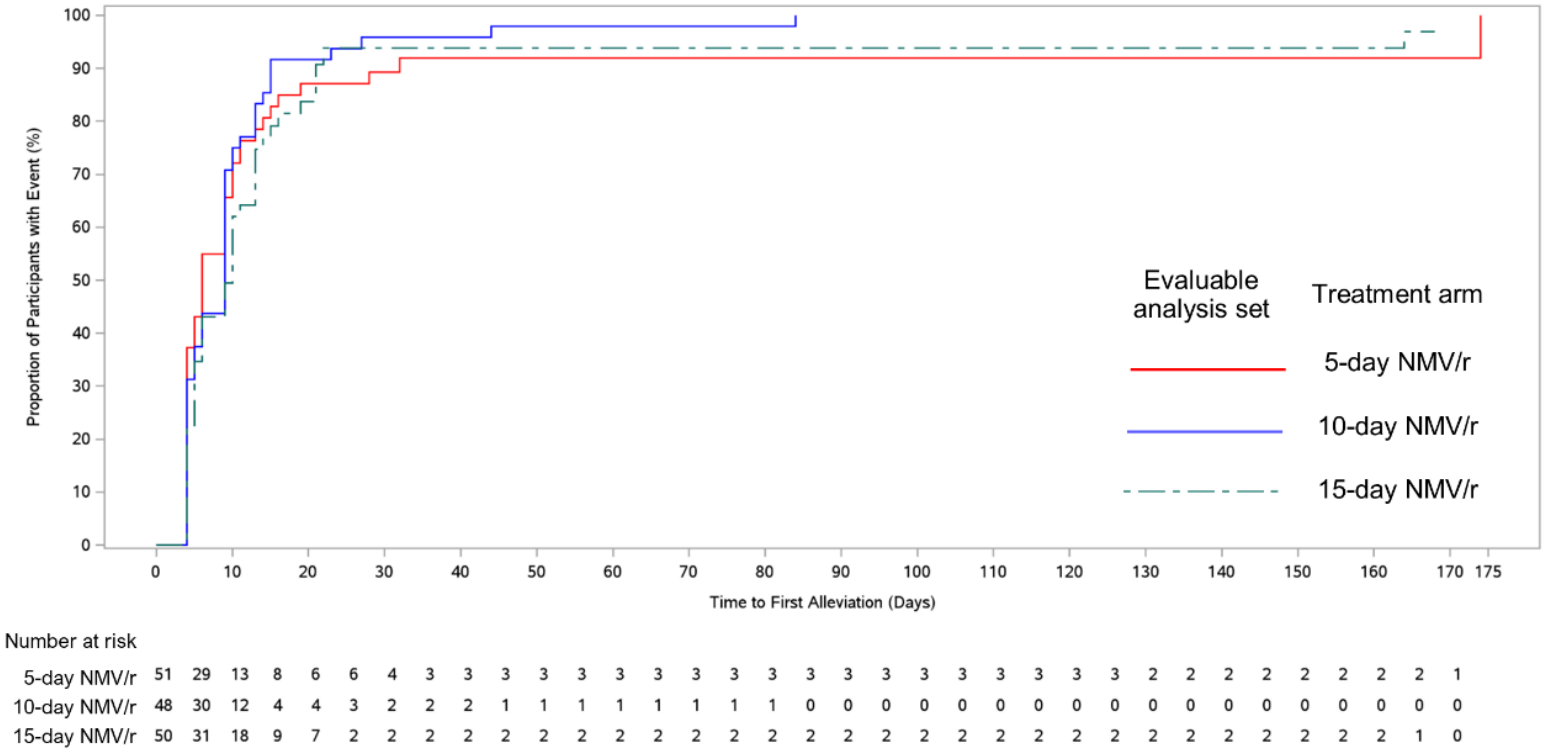

Figure S2. Estimated time to first alleviation of overall symptoms through Week 24

Kaplan-Meier estimates of the proportion of participants reporting the first alleviation of their overall symptoms by study day through Week 24. Estimates were based on participants in the evaluable analysis set with non-missing data (n=149). Abbreviation: NMV/r, nirmatrelvir-ritonavir.

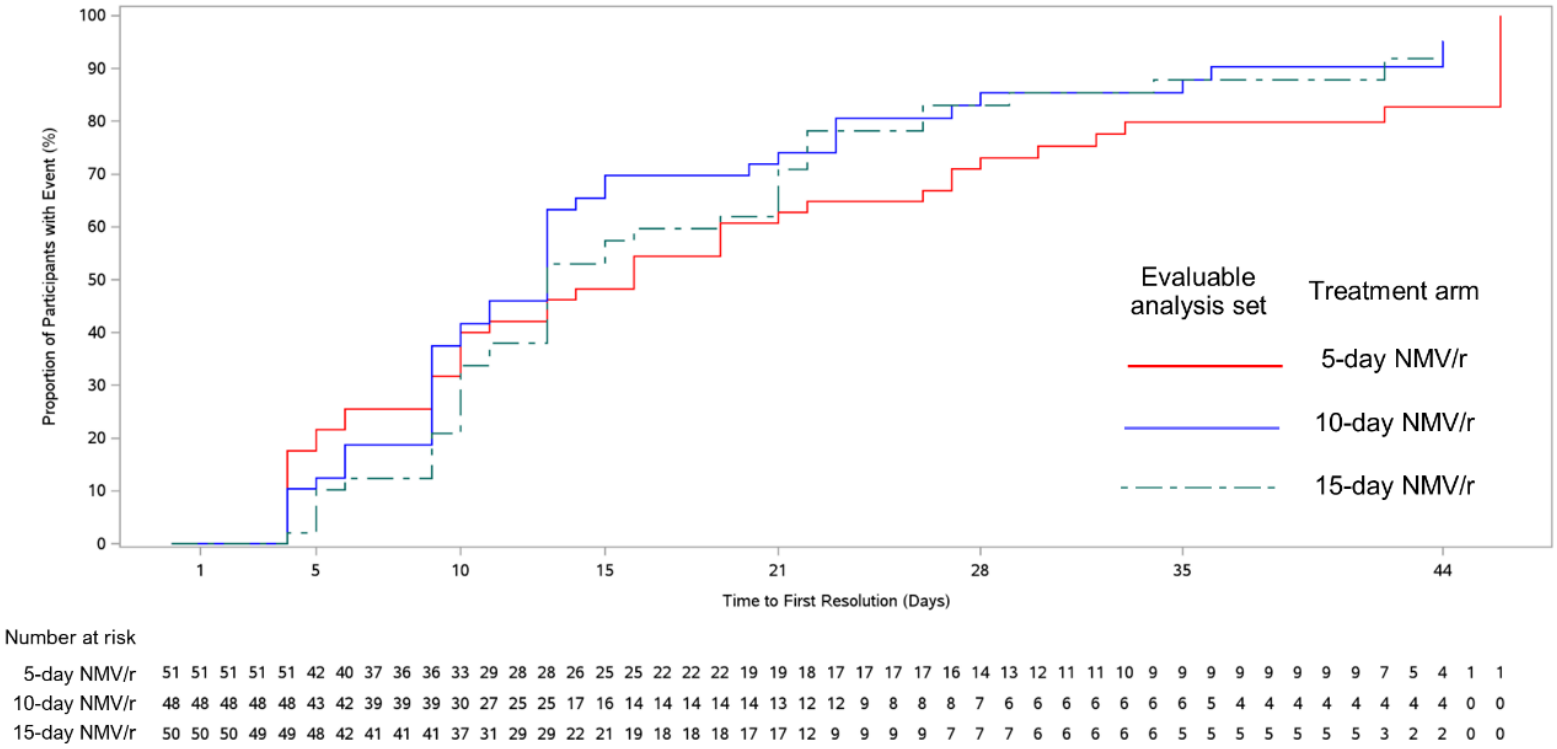

Figure S3. Estimated time to first resolution of overall symptoms through Week 24

Kaplan-Meier estimates of the proportion of participants reporting the first resolution of their overall symptoms by study day through Week 24 in the evaluable analysis set. Estimates were based on participants in the evaluable analysis set with non-missing data (n=149). Abbreviation: NMV/r, nirmatrelvir-ritonavir.

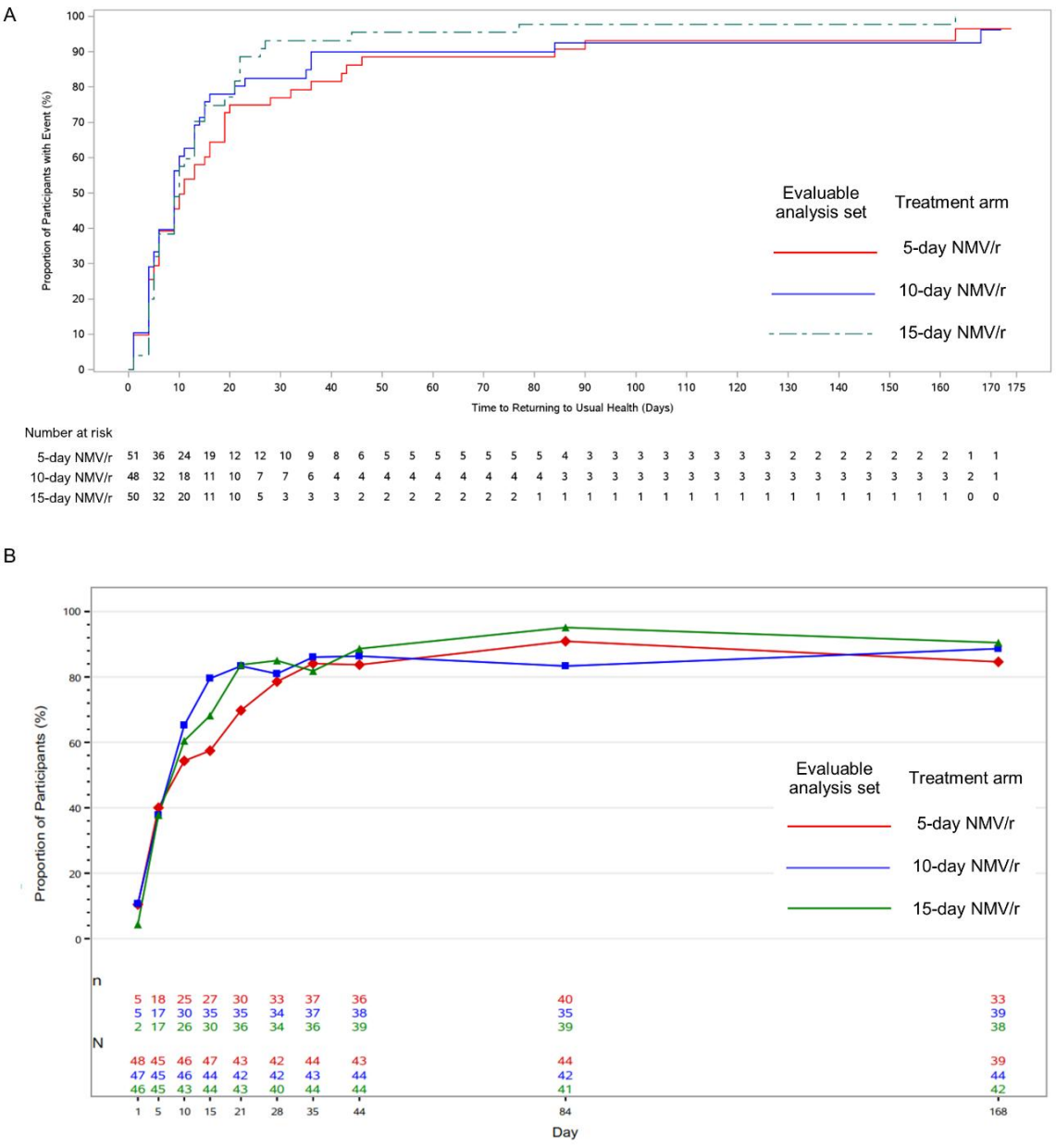

Figure S4. Return to usual health through Week 24

Participants experiencing return to their usual health by study day through Week 24. (A) Kaplan-Meier estimates were based on participants in the evaluable analysis set with non-missing data (n=149). (B) Proportions were calculated for each visit day as the number of participants with an event (n) divided by the number of participants with non-missing data (N). Abbreviation: NMV/r, nirmatrelvir-ritonavir.

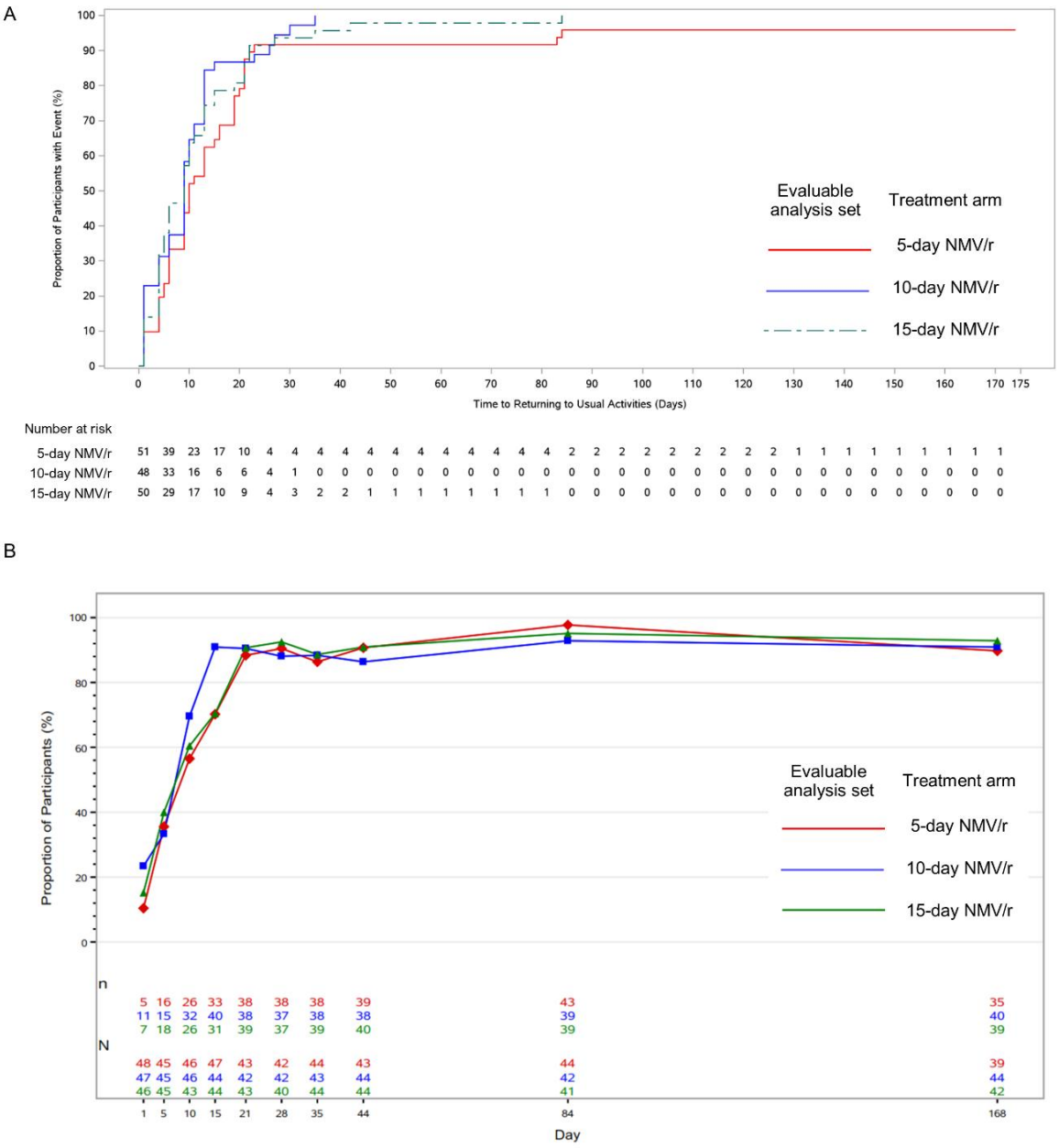

Figure S5. Return to usual activities through Week 24

Participants experiencing return to their usual activities by study day through Week 24. (A) Kaplan-Meier estimates were based on participants in the evaluable analysis set with non-missing data (n=149). (B) Proportions were calculated for each visit day as the number of participants with an event (n) divided by the number of participants with non-missing data (N). Abbreviation: NMV/r, nirmatrelvir-ritonavir.

References

[1] Weinstein E, Paredes R, Gardner A, et al. Extended nirmatrelvir–ritonavir treatment durations for immunocompromised patients with COVID-19 (EPIC-IC): a placebo-controlled, randomised, double-blind, phase 2 trial. Lancet Infect Dis. 2025. doi: 10.1016/S1473-3099(25)00221-X

[2] US Food and Drug Administration [Internet]. Assessing COVID-19-Related Symptoms in Outpatient Adult and Adolescent Subjects in Clinical Trials of Drugs and Biological Products for COVID-19 Prevention or Treatment: Guidance for Industry. 2024. Available from: https://www.fda.gov/media/167275/download