Supplemental Online Content

Geng LN, Bonilla H, Hedlin H, et al. Nirmatrelvir-Ritonavir and Symptoms in Adults With Postacute Sequelae of SARS-CoV-2 Infection: the STOP-PASC Randomized Clinical Trial. *JAMA Intern Med.* Published online June 7, 2024. doi:10.1001/jamainternmed.2024.2007

This supplemental material has been provided by the authors to give readers additional information about their work.

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eMethods

Randomization and Interventions

2:1 randomization ratio was chosen to aid in recruitment and potentially enhance early detection of safety signals. Ritonavir is an HIV protease inhibitor and has no known biological activity against SARS-CoV-2. At the low dose of 100 mg twice daily, ritonavir is a pharmacologic booster of nirmatrelvir via inhibition of CYP3A4 metabolism.[1–3] Ritonavir is associated with dysgeusia (a recognized side effect of nirmatrelvir-ritonavir for acute COVID-19 treatment) and, therefore, was included in the control comparator to minimize potential unmasking and its possible influence on self-reported outcomes.[4,5]

PASC Symptoms Questionnaire

The set of post-acute sequelae of SARS-CoV-2 (PASC) symptoms selected for this study were based on (1) *a priori* mechanistic rationale considering the types of symptoms that might be driven by viral persistence, (2) patient-informed clinical experience of most bothersome and impactful symptoms, and (3) reported prevalence and severity of these symptoms in PASC patient populations.[6–10] PASC symptoms questionnaire used in this study shares similarities with surveys used in clinical practice,[9] the NIH RECOVER study,[11] and other PASC symptom questionnaires informed by patient input.[12] Symptom severity rating was based a 4-point Likert scale (0: none, 1: mild, 2: moderate, 3: severe) considering the symptom at its worst during the past 7 days.

"Core" symptoms were defined as six symptoms or symptom clusters that were included in the primary outcome and assessed via electronic survey every week until 10 weeks and then every two weeks thereafter until end of study at 15 weeks (questions #1-6 in survey below). Six core symptoms were: fatigue, shortness of breath, brain fog, body aches, heart (or cardiovascular) symptoms, and stomach (or gastrointestinal) symptoms.

"Expanded" symptoms were 20 symptoms that included the six core symptoms, individual symptoms contained within the cardiovascular and gastrointestinal core symptom clusters, and additional common and/or potentially mechanistically-relevant PASC symptoms (e.g., headache, fever, sore throat, post-exertional malaise, etc.). The expanded 20 symptoms were assessed via electronic survey during in-person visit timepoints and shown below.

PASC Symptoms: Core 6 and Expanded 20 Symptoms Survey

For each symptom below, please indicate how severe it was for you **at its worst in the last 7 days**. Please answer ALL the questions.

1. **Fatigue** (low energy, tiredness, or exhaustion): [ ] 0 - none [ ] 1 - Mild [ ] 2 - Moderate [ ] 3 - Severe
2. **Shortness of breath** (including difficulty breathing, or feeling breathless, or air hunger): [ ] 0 - none [ ] 1 - Mild [ ] 2 - Moderate [ ] 3 - Severe
3. **Brain Fog** (including difficulty with focus, or memory, or word-finding, or processing, or orientation, or multitasking): [ ] 0 - none [ ] 1 - Mild [ ] 2 - Moderate [ ] 3 - Severe
4. **Body aches** (including pain in joints or muscles): [ ] 0 - none [ ] 1 - Mild [ ] 2 - Moderate [ ] 3 - Severe

5. **Heart symptoms** (including chest pain, or dizziness, or heart racing, or fast heart rate, or palpitations): [ ] 0 - none [ ] 1 - Mild [ ] 2 - Moderate [ ] 3 - Severe
6. **Stomach symptoms** (including nausea, or vomiting, or diarrhea, or constipation, or abdominal pain, or decreased appetite): [ ] 0 - none [ ] 1 - Mild [ ] 2 - Moderate [ ] 3 – Severe
7. **Post-exertional malaise** (worsening of symptoms or feeling unwell after physical or mental activity): [ ] 0 - none [ ] 1 - Mild [ ] 2 - Moderate [ ] 3 – Severe
8. **Headache**: [ ] 0 - none [ ] 1 - Mild [ ] 2 - Moderate [ ] 3 – Severe
9. **Fever**: [ ] 0 - none [ ] 1 – Mild (<101 deg F) [ ] 2 – Moderate (101-103 deg F) [ ] 3 – Severe (>103 deg F)
10. **Cough**: [ ] 0 - none [ ] 1 - Mild [ ] 2 - Moderate [ ] 3 – Severe
11. **Sore throat:** [ ] 0 - none [ ] 1 - Mild [ ] 2 - Moderate [ ] 3 – Severe
12. **Difficulty sleeping**: [ ] 0 - none [ ] 1 - Mild [ ] 2 - Moderate [ ] 3 – Severe
13. **Chest pain**: [ ] 0 - none [ ] 1 - Mild [ ] 2 - Moderate [ ] 3 – Severe
14. **Heart racing** (fast heart rate or palpitations): [ ] 0 - none [ ] 1 - Mild [ ] 2 - Moderate [ ] 3 – Severe
15. **Dizziness** (including lightheadedness or feeling faint): [ ] 0 - none [ ] 1 - Mild [ ] 2 - Moderate [ ] 3 – Severe
16. **Nausea or vomiting**: [ ] 0 - none [ ] 1 - Mild [ ] 2 - Moderate [ ] 3 – Severe
17. **Diarrhea**: [ ] 0 - none [ ] 1 - Mild [ ] 2 - Moderate [ ] 3 – Severe
18. **Constipation**: [ ] 0 - none [ ] 1 - Mild [ ] 2 - Moderate [ ] 3 – Severe
19. **Abdominal pain**: [ ] 0 - none [ ] 1 - Mild [ ] 2 - Moderate [ ] 3 – Severe
20. **Decreased appetite**: [ ] 0 - none [ ] 1 - Mild [ ] 2 - Moderate [ ] 3 – Severe

Clinical Assessments at In-Person Visits

The 1 minute sit-to-stand test is a widely used functional test for exercise capacity that is reliable, valid, and responsive and can be easily performed in many settings, particularly where space and time are limited.[25] It involves an armless chair and the performance of as many sit-to-stand actions as possible in 1 min without using the upper limbs.

Vital signs (temperature, heart rate, blood pressure, oxygen saturation, respiratory rate) were measured while patient is seated at rest and orthostatic blood pressure and heart rate were measured again after 1 minute of standing up. Abnormalities in vital signs such as hypertension, tachycardia, bradycardia, and fever have been reported in PASC.[8,13–16] Orthostatic vital sign abnormalities may suggest autonomic dysfunction, though these measures alone were not intended to be diagnostic of autonomic disorders.[10,17,18]

Stool Processing and RT-PCR

Stool Sample Collection

Participants enrolled in the study collected stool samples and mailed them back to the study site on days 0, +7, +15, and +70 post-enrollment. Stool samples were collected in both the OMNIgene Gut OMR-200 (DNA Genotek, OMR-200) and OMNIgene GUT DNA & RNA OMR-205 (DNA Genotek, OMR-205) stool collection kit for each timepoint. Participants received a set of stool collection and mailing supplies for each timepoint. This consisted of one OMR-200 stool collection kit, one OMR-205 DNA&RNA stool collection kit, a toilet accessory (DNA Genotek, OM-AC1), and a pre-addressed return mailer. Participants were instructed to write the date and

time of stool collection on the stool collection tubes and then mail them back to the study site within 24 hours of collection. Upon receipt, participant stool samples were vortexed to homogenize the tube contents for 30 seconds before 500 µL aliquots were made in Eppendorf tubes and immediately frozen at –80 °C.

Preparing Preserved Stool Sample Controls

Reconstituted bovine coronavirus (BCoV) was prepared *per the manufacturer's instructions* by resuspending one vial of lyophilized Zoetis Calf-Guard Bovine Rotavirus-Coronavirus Vaccine in 3 mL of 1X phosphate buffered saline. Stool samples collected in 2018 and immediately frozen at –80 °C were used to eliminate the possibility of a latent coronavirus infection in the stool donor.

Positive control stool standards were prepared by adding 4 biopsy punches of stool to each OMR-200 and OMR-205 DNA&RNA tube. 20 µL of SARS-CoV-2 viral RNA standard (ATCC Cat# VR-3276SD) at 10^6 copies/µL was added to each tube to reach a final concentration of 10^4 copies/µL. The tubes were homogenized by vortexing for 30 seconds before 500 µL of the stool slurry was aliquoted into 1.5 mL Eppendorf tubes. 10 µL of reconstituted attenuated Bovine coronavirus (BCoV) standard were added to each tube, the tubes were homogenized briefly and then immediately frozen at –80 °C until further use. Negative control stool standards were prepared the same way as described above without the addition of SARS-CoV-2 viral RNA. Positive control and negative control stool standards were prepared on different days so as to avoid cross contamination.

RNA Extraction Protocol for Participant Sample Analysis

RNA extractions from participant samples were performed in batches of 24 by two independent operators. Each batch included 10 OMR-200 participant samples, 10 OMR-205 participant samples, two negative control stool samples (one each OMR-200 and OMR-205), and two positive control samples (one each OMR-200 and OMR-205) prepared as described above.

All RNA extractions were performed using the Allprep PowerViral DNA/RNA Kit (Qiagen Cat # 28000-50) given that it yielded the highest detectable viral RNA for stool samples collected in both the OMR-200 and OMR-205. The following modified protocol was used. Stool sample aliquots were removed from the freezer. 10 µL of reconstituted attenuated Bovine coronavirus (BCoV) standard were added to each 500 µL aliquot of PASC participant stool and the tubes were homogenized for 15 seconds. The solid contents of the tubes were spun down by centrifugation at 10,000 x g for 2 minutes. For tubes in which less than 150 µL of liquid supernatant, 150 µL of sterile phosphate buffered saline was added, the stool slurry was re-homogenized and then spun again at 10,000 x g for 2 minutes. 200 µL of the liquid supernatant from each sample was added to a 2 mL Eppendorf tube pre-loaded with 500 µL of Solution PM1 pre-warmed to 55 °C and 6.5 µL of ß-mercaptoethanol. The remaining steps in the RNA extraction were carried out according to the kit protocol and eluted in 100µL of RNase free water from the kit. Extracted RNA was then transferred to 96 well plates in randomized order, briefly spun down, sealed and stored at −80 °C until further analysis.

RT-qPCR Protocol

RNA extracted from pariticipant stool samples was assayed for two SARS-CoV-2 genomic targets (E gene and N1 gene) and for the BCoV M gene. Each 20µL RT-qPCR reaction was composed of 5µL TaqPath 1-Step RT-qPCR Master Mix, CG, 1.5 µL of primer/probe mixture, 8.5 µL of nuclease-free water. The primer/probe mixture was prepared with a final concentration of 400 nM of each of the forward and reverse primers and 200 nM of the corresponding probe in 8.5 mM Tris-HCl pH 8.0 and 0.8 mM EDTA. Reactions were prepared in Micro-Amp Optical

384-well plates with 5 µL of stool RNA samples, synthetic RNA standards, nuclease free water, or 1X phosphate buffered saline using a Velocity 11 VPrep – 96 Tip Pipettor liquid handler. Each assay plate also included standard curves. Standard curves were prepared by serially diluting quantitative synthetic SARS-CoV-2 RNA from 10^5-10^{-1} copies per µL, dilutions 10^4 – 10^{-1} copies per µL selected for the plates. Nuclease free water and 1x phosphate buffered saline were used as negative controls.

RNA from each extracted stool sample was assayed in two technical replicates for each target. Standard curves were run in technical duplicates for all targets on every RT-qPCR assay plate. The location of participant sample RNA extracts were randomized on the assay plate. Similarly, the location and number of positive and negative controls were randomized on each assay plate. One positive and one negative control standard was analyzed for each stool collection kit (four total standards) per set of 20 participant samples (10 each OMR-200 and OMR-205) analyzed. Prior to the assay, plates were sealed with an optically clear seal and spun down at room temperature. The samples were assayed in a 12k Flex Applied Biosystems qPCR machine in standard mode using the following cycling conditions: 25°C for 2 minutes, 50°C for 15 minutes, and 95°C for 2 minutes, followed by 45 cycles of 95°C, 3 seconds, and 55°C, 30 seconds.

Blinding

The trial was conducted in a double-blind manner. The participants, treating clinicians, and study personnel including the blinded statisticians remained blinded to study drug versus placebo assignment until after the database was locked and blinded analysis was completed. Only the separate biostatistical team who generated the randomization allocation and prepared unblinded reports for the DSMB and the study pharmacists were aware of the treatment assignment. The blinded and unblinded statisticians were firewalled from the time the first participant was randomized until after database lock was completed.

Additional Statistical Analyses

Our pre-specified analysis plan (**Supplement 3**) was to adjust for the randomization stratification factors including the number of moderate/severe core symptoms at the baseline (2 or 3 vs >3) and vaccine status. However, only one participant in each group had not completed their primary vaccine series, so we were ultimately unable to adjust for vaccine status in the models.

We used a cumulative link mixed effects regression model with a participant-specific random intercept and an unstructured covariance matrix to compare the trajectory of symptoms between study arms in an exploratory analysis. Indicator variables for study week were included to allow for non-linear changes in symptom severity over time.

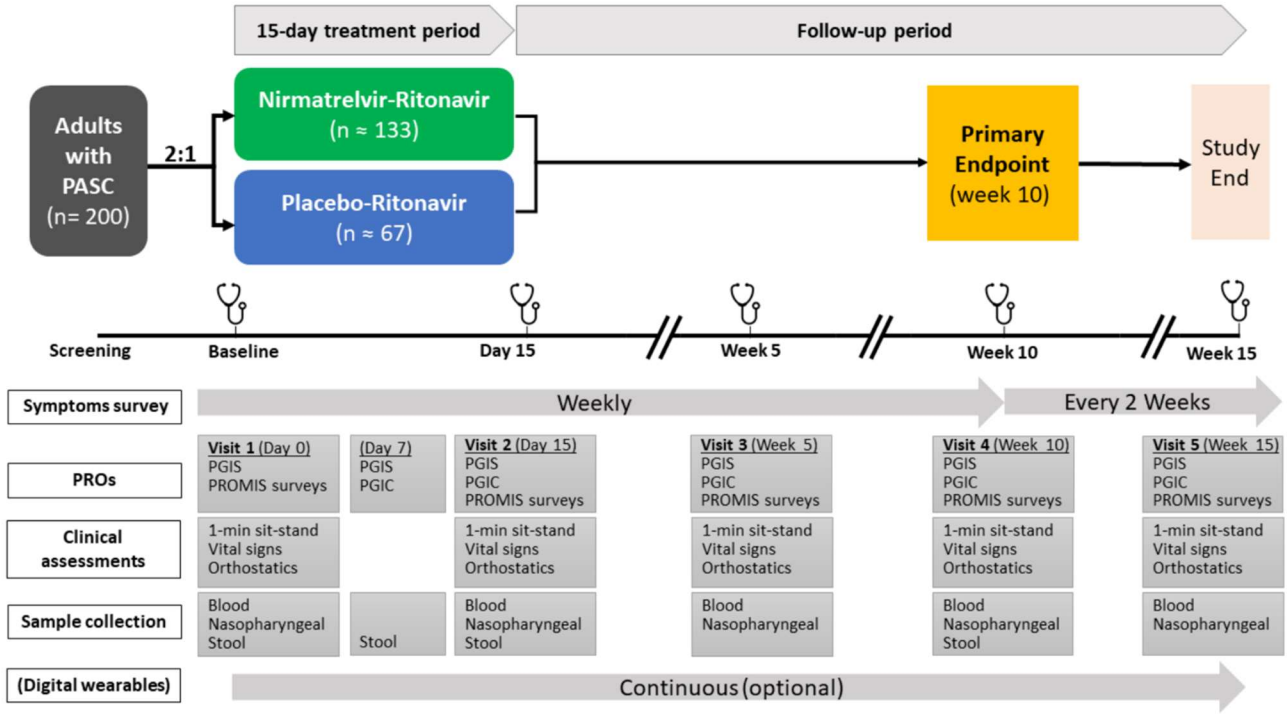
To adhere to the intent-to-treat (ITT) principle, all models were fit using multiply imputed data, with the exception of the mixed effects model. Ten imputed datasets were generated using proportional odds logistic regression models for ordinal outcomes and predictive mean matching for all other outcomes. The variance estimation after multiple imputations was adjusted with Rubin's rules.

We used several R packages, including 'mice' to perform multiple imputations for the ITT and modified ITT (mITT) analyses;[19] 'tidyverse',[20] 'tableone',[21] 'magrittr',[22] 'zoo',[23] and 'reshape2'[24] for data wrangling and visualization; and 'MASS',[25] 'lmtest',[26] 'survival',[27] 'nlme',[28] 'ordinal',[29] and 'RVAideMemoire'[30] for model-fitting and hypothesis testing.

Sample Size Calculation

We planned to enroll approximately 200 participants total with the expectation that 180 participants would complete the 10-week follow-up. The sample size calculation used the following simplifying assumptions: (a) for each core symptom, the Likert-scale at week 10 is uniformly distributed over 0, 1, 2, and 3 in the placebo-ritonavir group, (b) for each core symptom, the proportions of the participants in the nirmatrelvir/ritonavir group with a Likert-scale of 0, 1, 2, and 3 are 34.8%, 26.8%, 21.2%, and 17.2%, respectively, at Week 10, and (c) the z-scores of comparing 6 core symptoms using all participants are positively correlated with a pair-wise correlation coefficient of 0.25. Assumptions (a) and (b) satisfy the proportional odds model with an odds ratio of 1.6. Under this assumption, the z-score of individual comparison based on 60 participants in the placebo-ritonavir group and 120 participants in the nirmatrelvir-ritonavir group follows a normal distribution with mean of 1.66 and unit variance. The final test statistic is equivalent to the simple average of z-scores from analyses for individual symptoms, since the assumed alternatives are identical for all core symptoms. Under assumption (c) the Wald test statistic for the overall comparison follows a normal distribution with a mean of 2.71 and unit variance, providing a power of 77% at the two-sided significance level of 0.05. Our calculations were conservative because 1) the regression analysis excluding participants without the core symptom at baseline is expected to generate a z-score with a greater mean value and a higher power, since the potential dilution effect from participants without the core symptom at the baseline are reduced; and 2) the inverse variance weighting is expected to generate a more efficient combination of test statistics from individual test than equal weighting.

eFigure 1. Trial Schematic



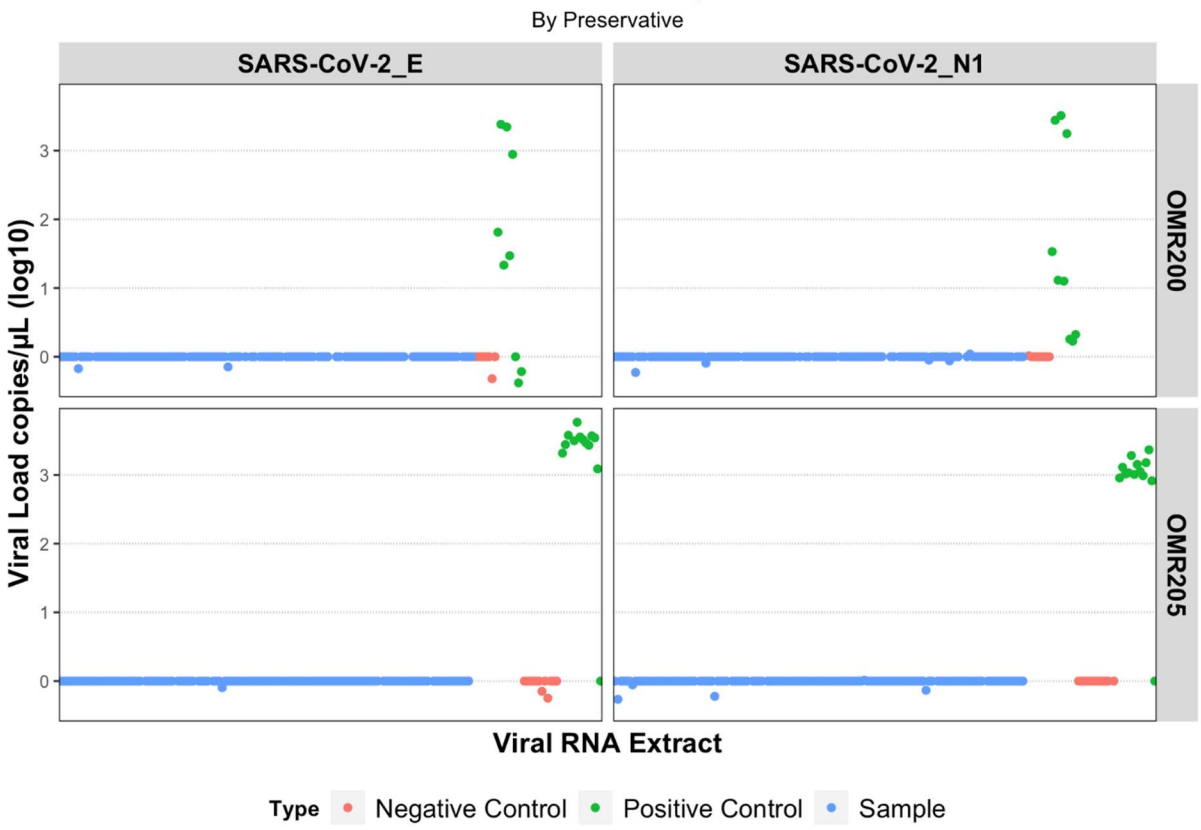
Study duration: 15 weeks with 5 in-person visits (baseline, Day 15, Week 5, Week 10, Week 15).
Intervention treatment period: 15 days of either nirmatrelvir-ritonavir or placebo-ritonavir.
Primary endpoint: 10 weeks post-randomization.
PASC symptoms surveys:

Core 6 symptoms: assessed weekly until 10 weeks, then biweekly thereafter.
Expanded 20 symptoms: assessed at baseline, Day 7, Day 15, Week 5, Week 10, Week 15.

Other PROs, clinical assessments, sample collection (blood, nasopharyngeal swab, stool) were completed on in-person visit timepoints with additional assessment of PGIS and PGIC on Day 7. Stool was additionally collected on Day 7.
Opt-in digital wearables sub-study with Apple smartwatch and automated blood pressure cuff.
Abbreviations:

PASC: Post-Acute Sequelae of SARS-CoV2
PROs: Patient-Reported Outcomes
PGIS: Patient Global Impression of Severity
PGIC: Patient Global Impression of Change
PROMIS: Patient-Reported Outcomes Measurement Information System

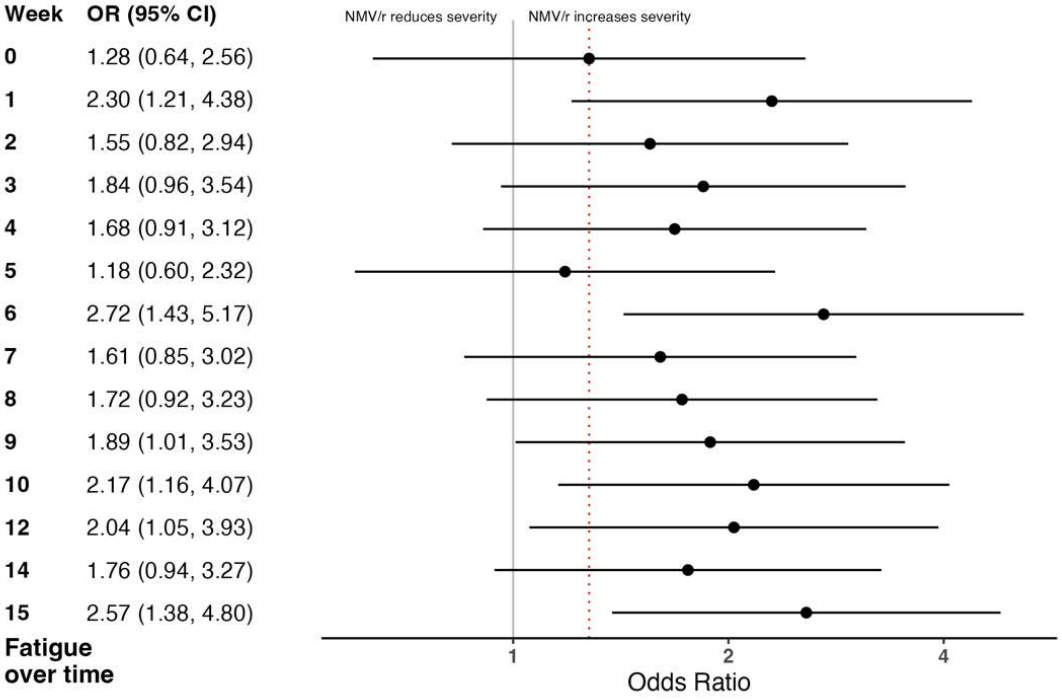
eFigure 2. Stool RT-PCR on Baseline Samples

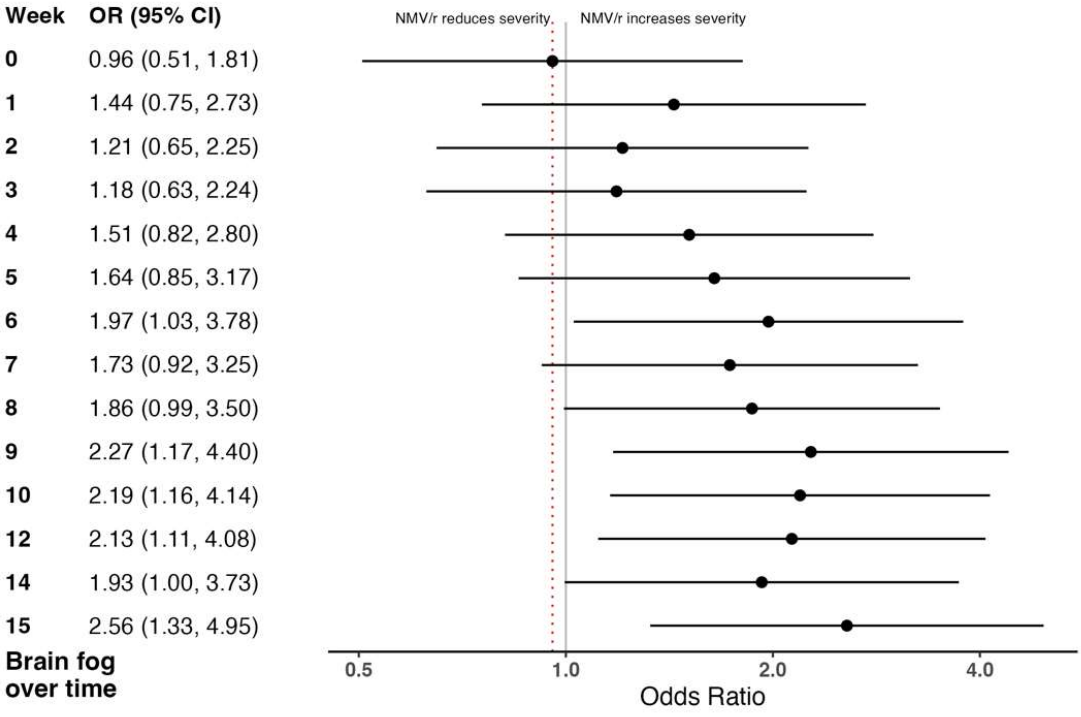


Viral Load calculated for the SARS-CoV-2 N1 and E gene for participant samples (blue), positive controls (green) and negative controls (red) collected in the OMR-200 or OMR-205 stool collection tubes. RNA extracts from 140 patient samples are shown dotted in blue along on the x-axis. Values of zero correspond to undetectable viral RNA.

eFigure 3: Forest Plots of Core Symptoms Severity at Different Time Points

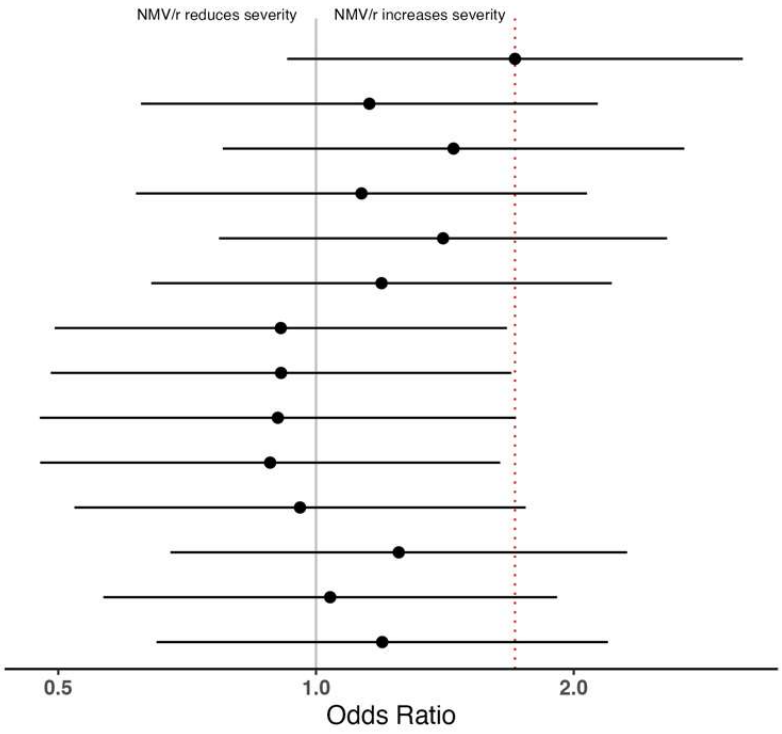
Red dotted line represents the baseline odds ratio for reference. For a given symptom and timepoint, an odds ratio (OR) of 1.5 corresponds to a 50% increase in the odds of being in a higher severity category, for those on NMV/r compared to those on PBO/r.





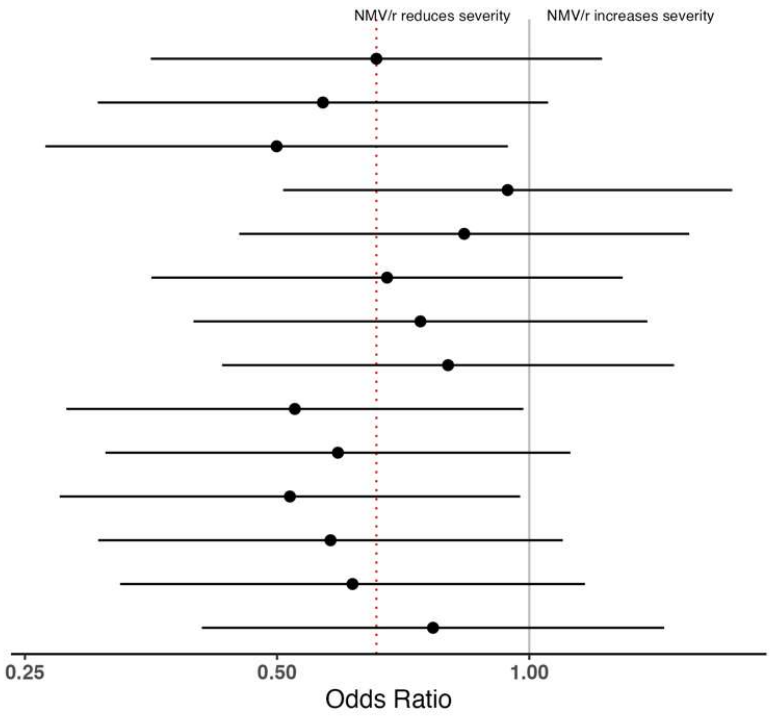
Week	OR (95% CI)
0	1.71 (0.93, 3.15)
1	1.15 (0.62, 2.13)
2	1.45 (0.78, 2.69)
3	1.13 (0.62, 2.07)
4	1.41 (0.77, 2.57)
5	1.19 (0.64, 2.22)
6	0.91 (0.50, 1.67)
7	0.91 (0.49, 1.69)
8	0.90 (0.48, 1.71)
9	0.88 (0.48, 1.64)
10	0.96 (0.52, 1.76)
12	1.25 (0.68, 2.31)
14	1.04 (0.56, 1.91)
15	1.19 (0.65, 2.19)

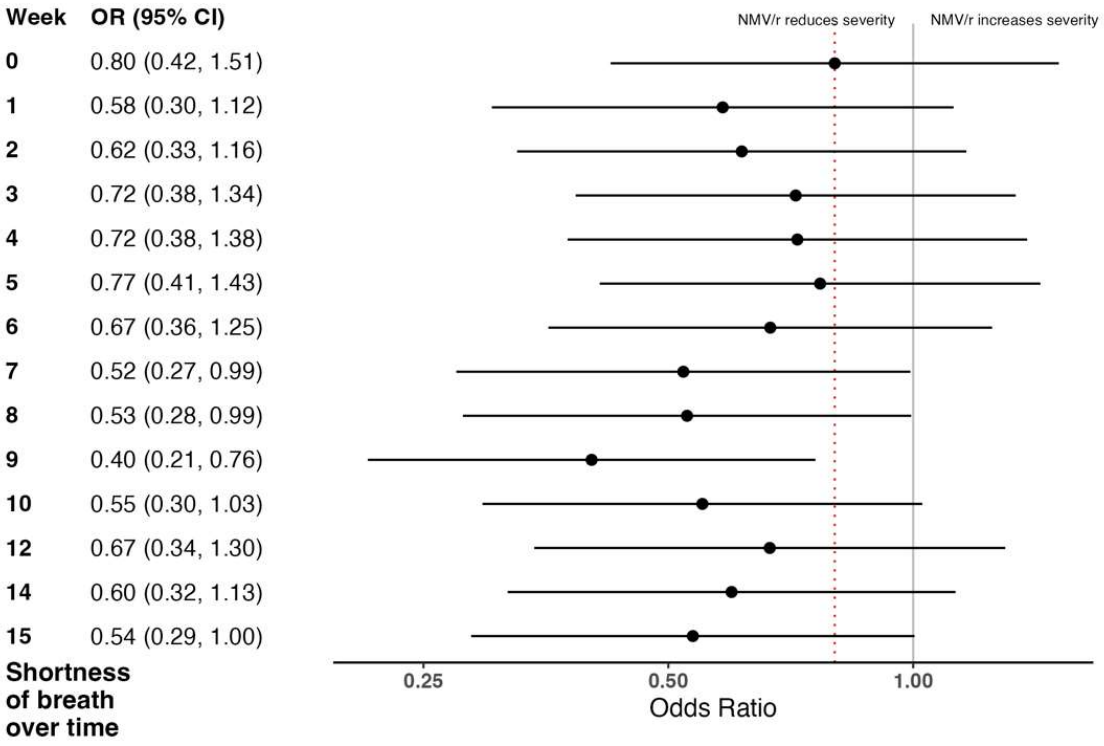
Body aches over time

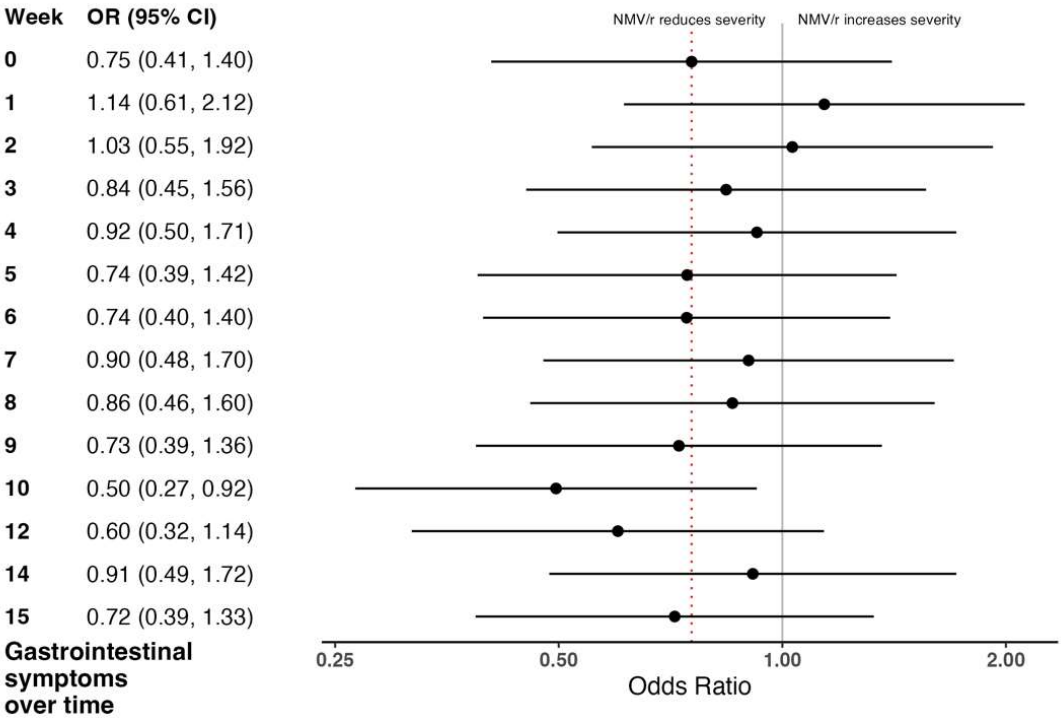


Week	OR (95% CI)
0	0.66 (0.35, 1.22)
1	0.57 (0.31, 1.05)
2	0.50 (0.26, 0.94)
3	0.94 (0.51, 1.75)
4	0.84 (0.45, 1.55)
5	0.68 (0.35, 1.29)
6	0.74 (0.40, 1.38)
7	0.80 (0.43, 1.49)
8	0.52 (0.28, 0.98)
9	0.59 (0.31, 1.12)
10	0.52 (0.28, 0.98)
12	0.58 (0.31, 1.10)
14	0.62 (0.32, 1.17)
15	0.77 (0.41, 1.45)

Cardiovascular symptoms over time

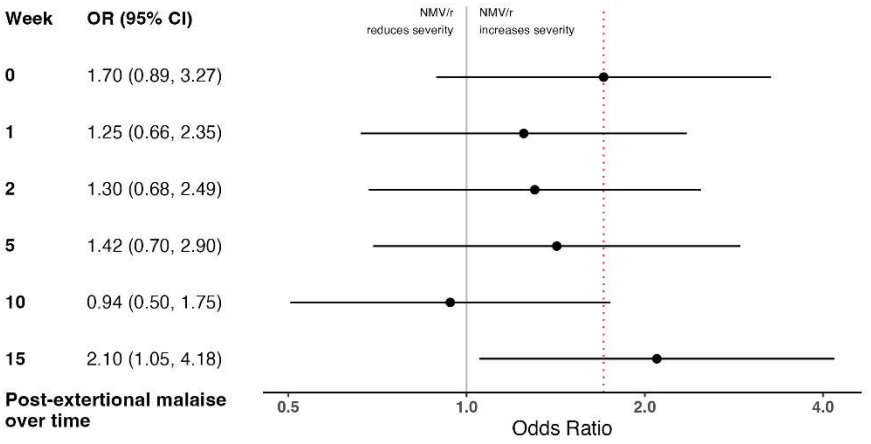


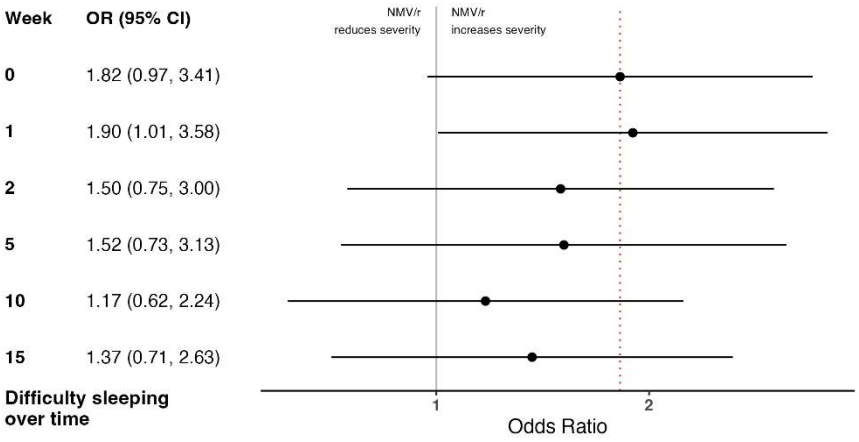


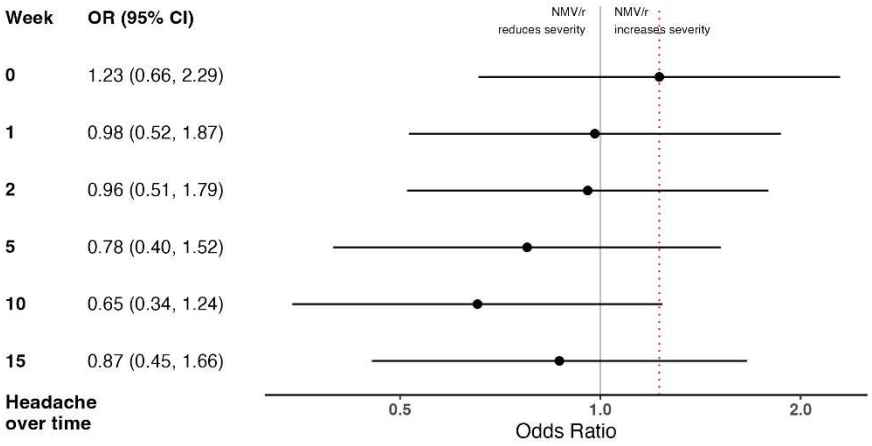


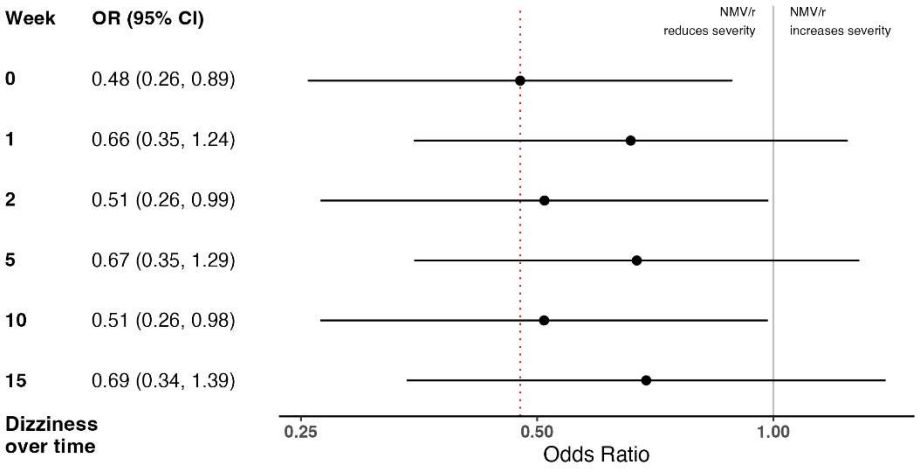
eFigure 4: Forest Plots of Expanded Symptoms Severity at Different Time Points

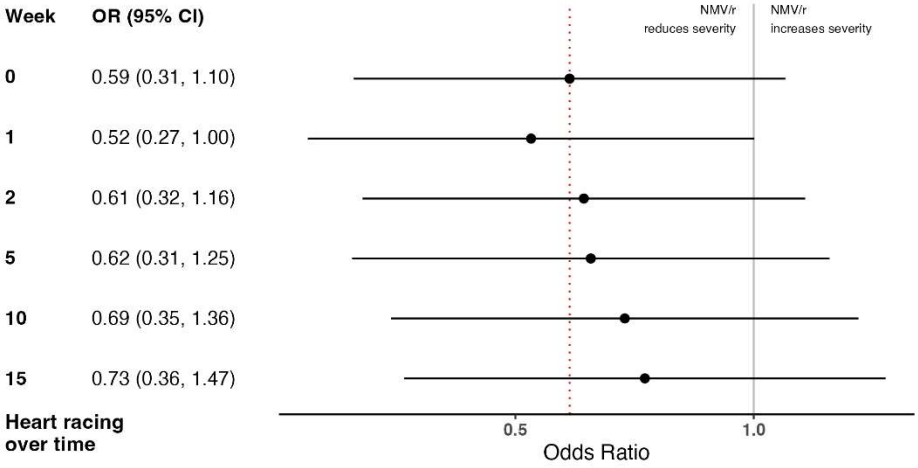
Red dotted line represents the baseline odds ratio for reference. For a given symptom and timepoint, an odds ratio (OR) of 1.5 corresponds to a 50% increase in the odds of being in a higher severity category, for those on NMV/r compared to those on PBO/r. No odds ratio could be estimated for fever at Week 0 because too few patients experienced the symptom.

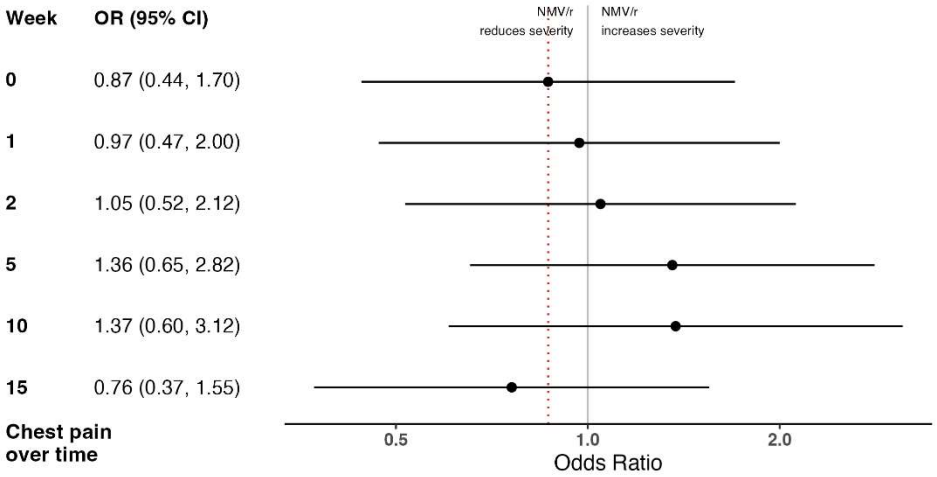


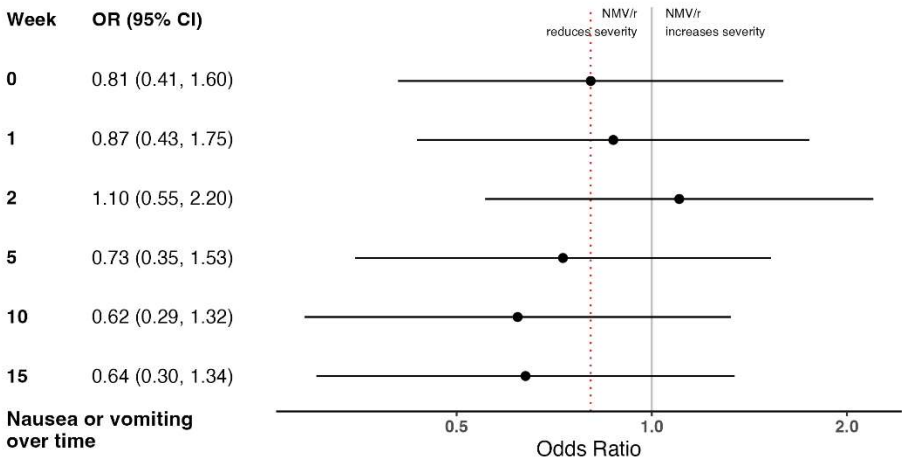


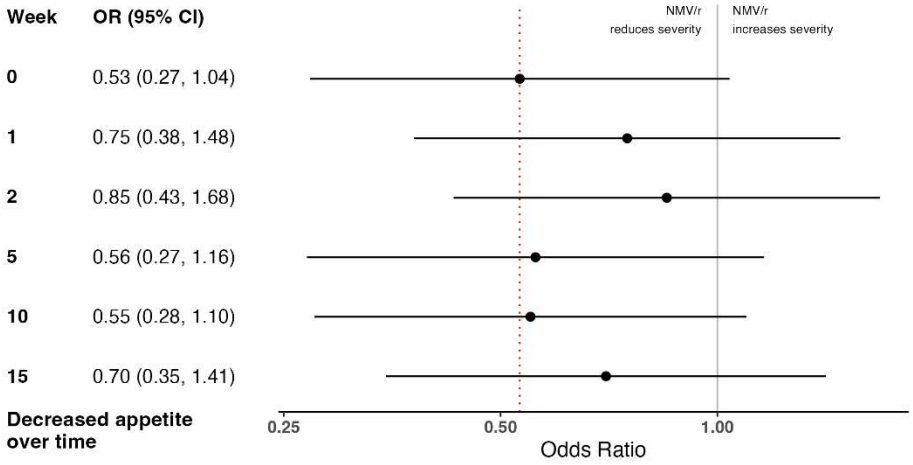


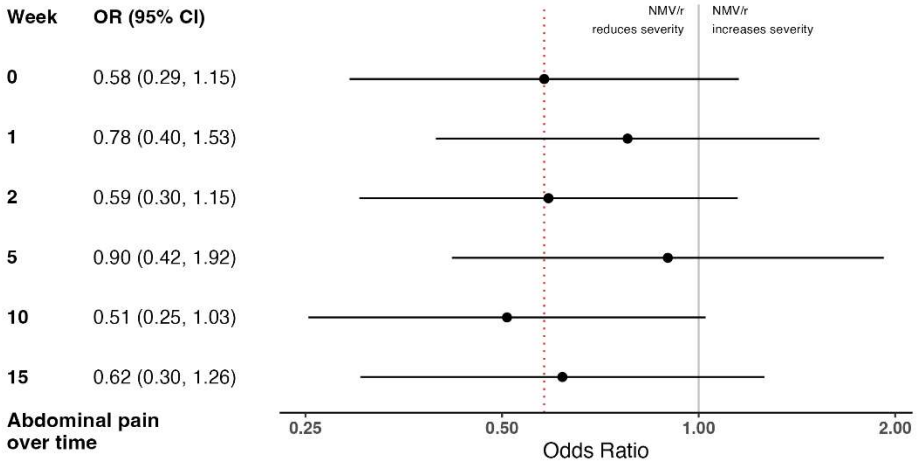


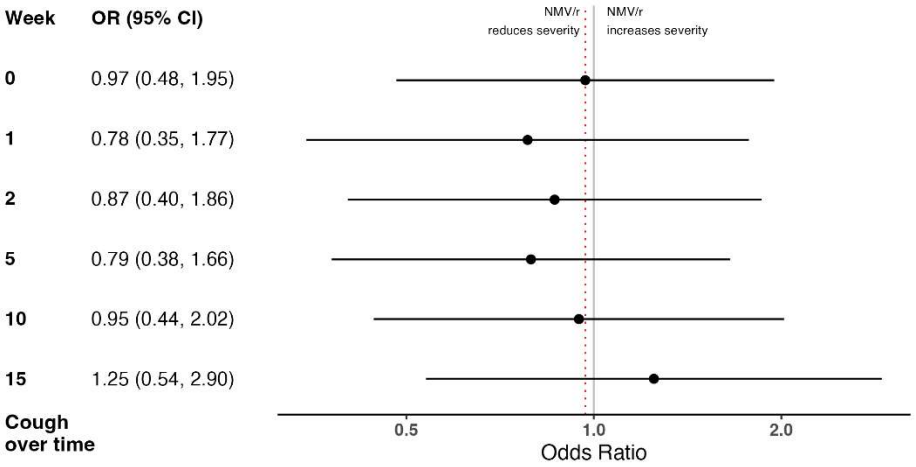


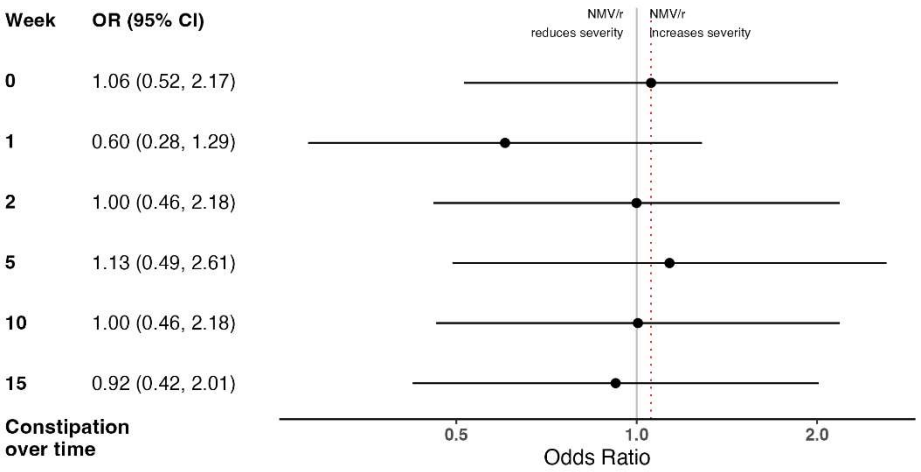


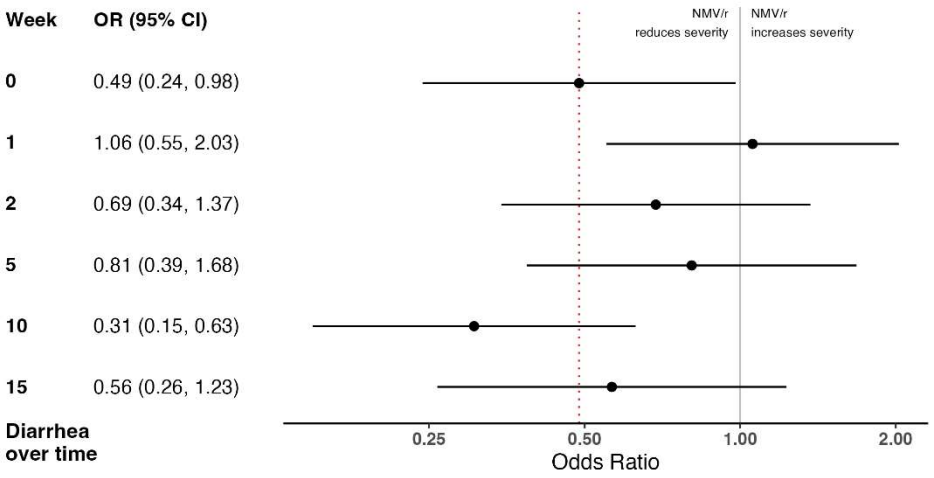


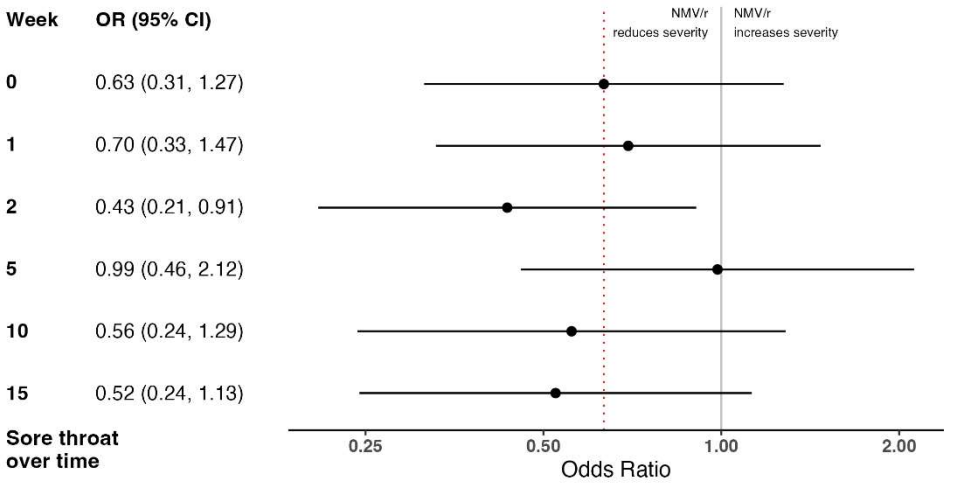


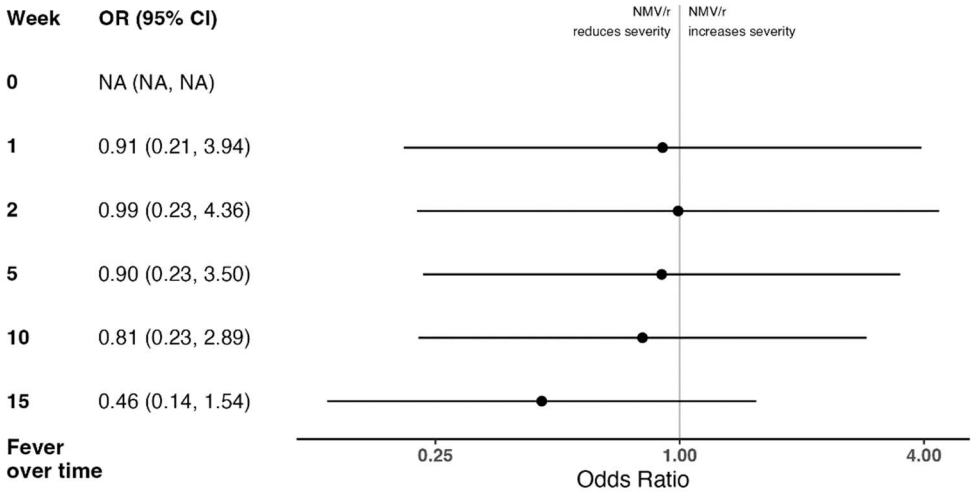






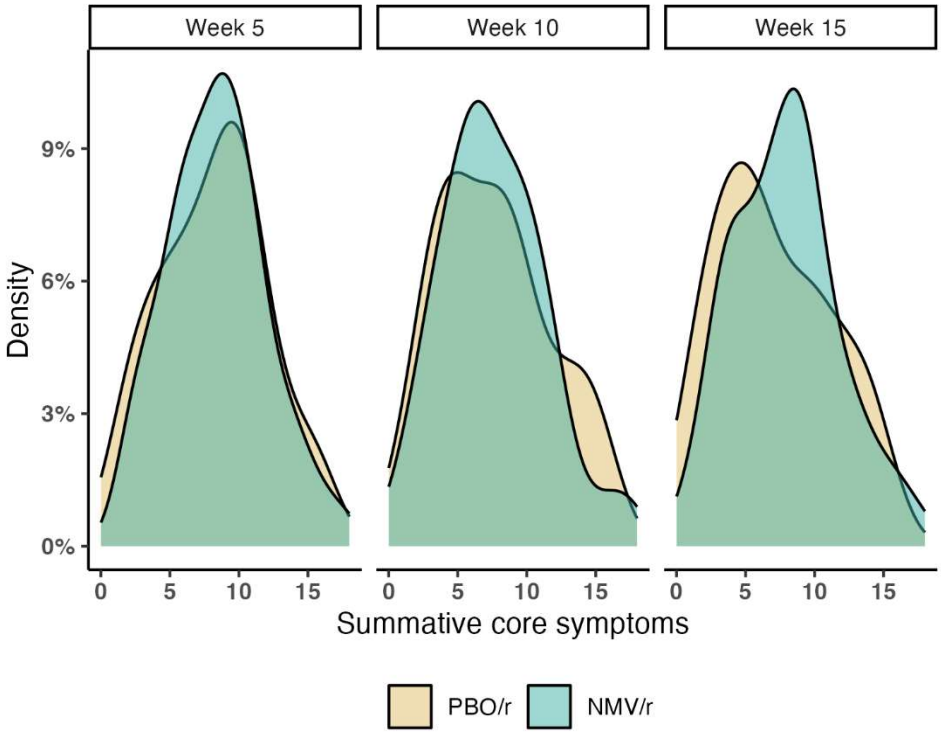




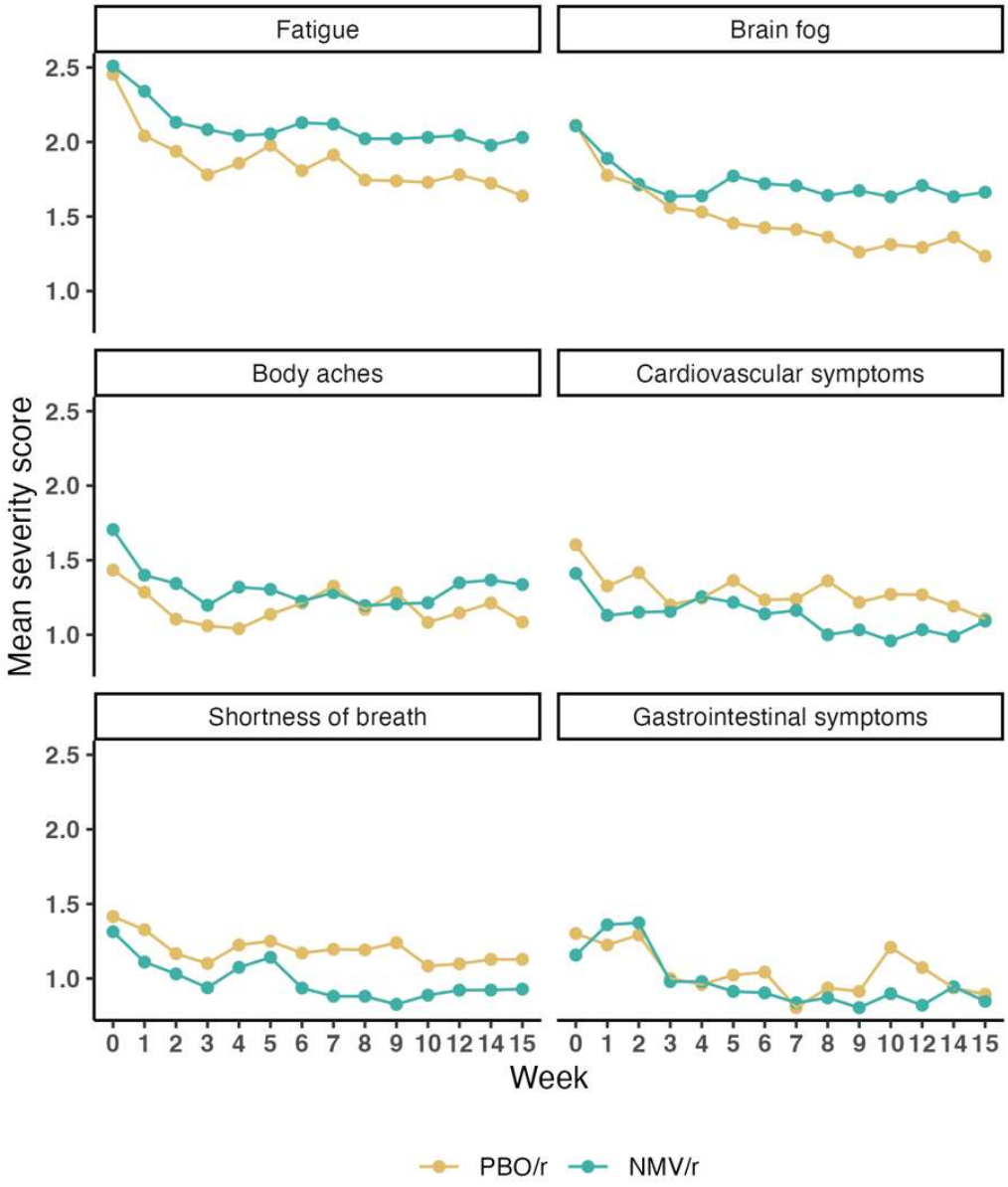


eFigure 5: Density Plots of Summative Severity Scores for Core Symptoms at 5, 10, and 15 Weeks by Group

Summation of six core symptoms' severity scores at different time points; maximum possible summative score is 18 at each time point. PBO/r: placebo-ritonavir; NMV/r: nirmaltrelvir-ritonavir.

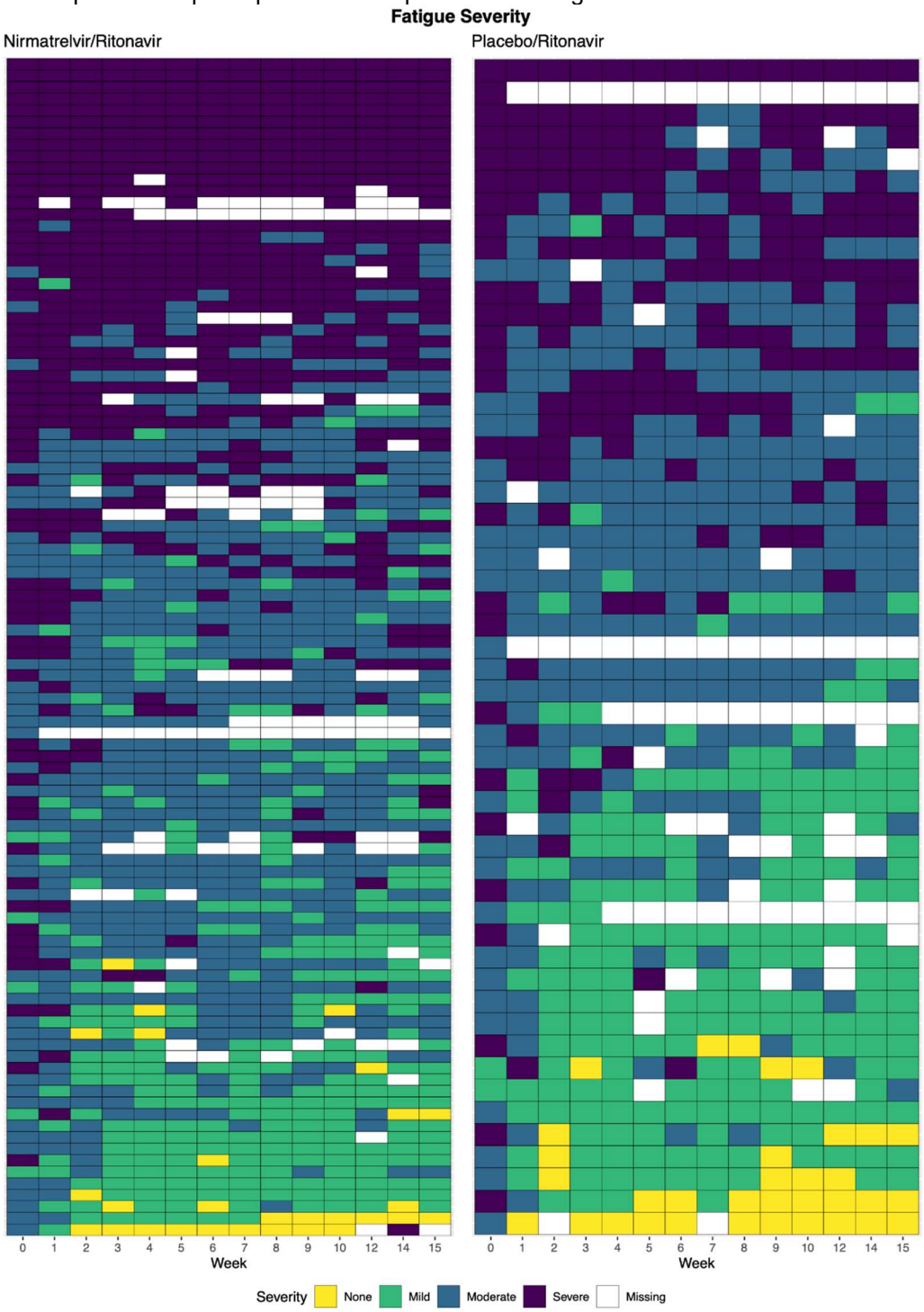


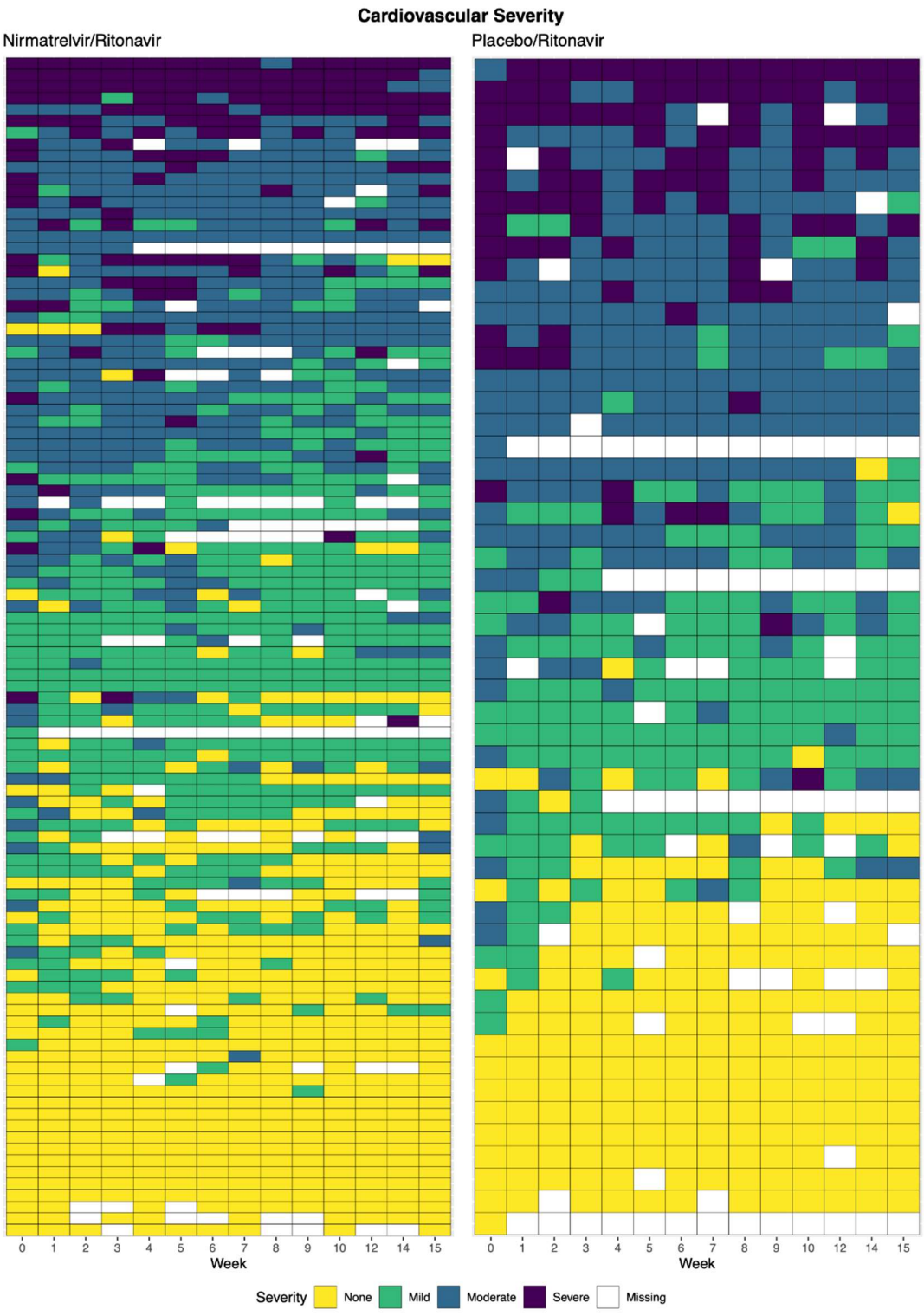
eFigure 6: Mean Core Symptoms Severity Score over Time by Group
Each core symptom's mean severity scores at different time points. PBO/r: placebo-ritonavir; NMV/r: nirmaltrelvir-ritonavir.

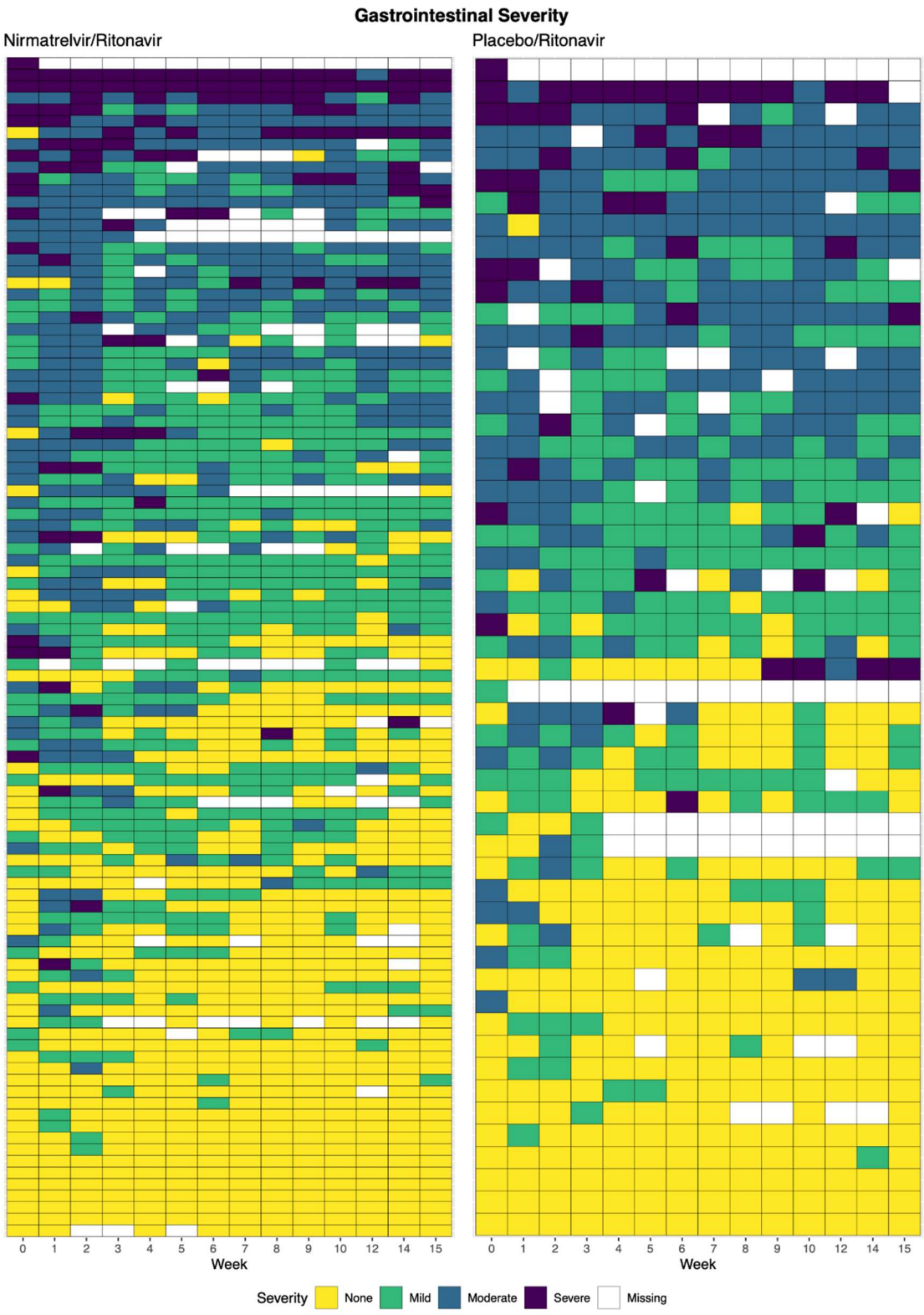


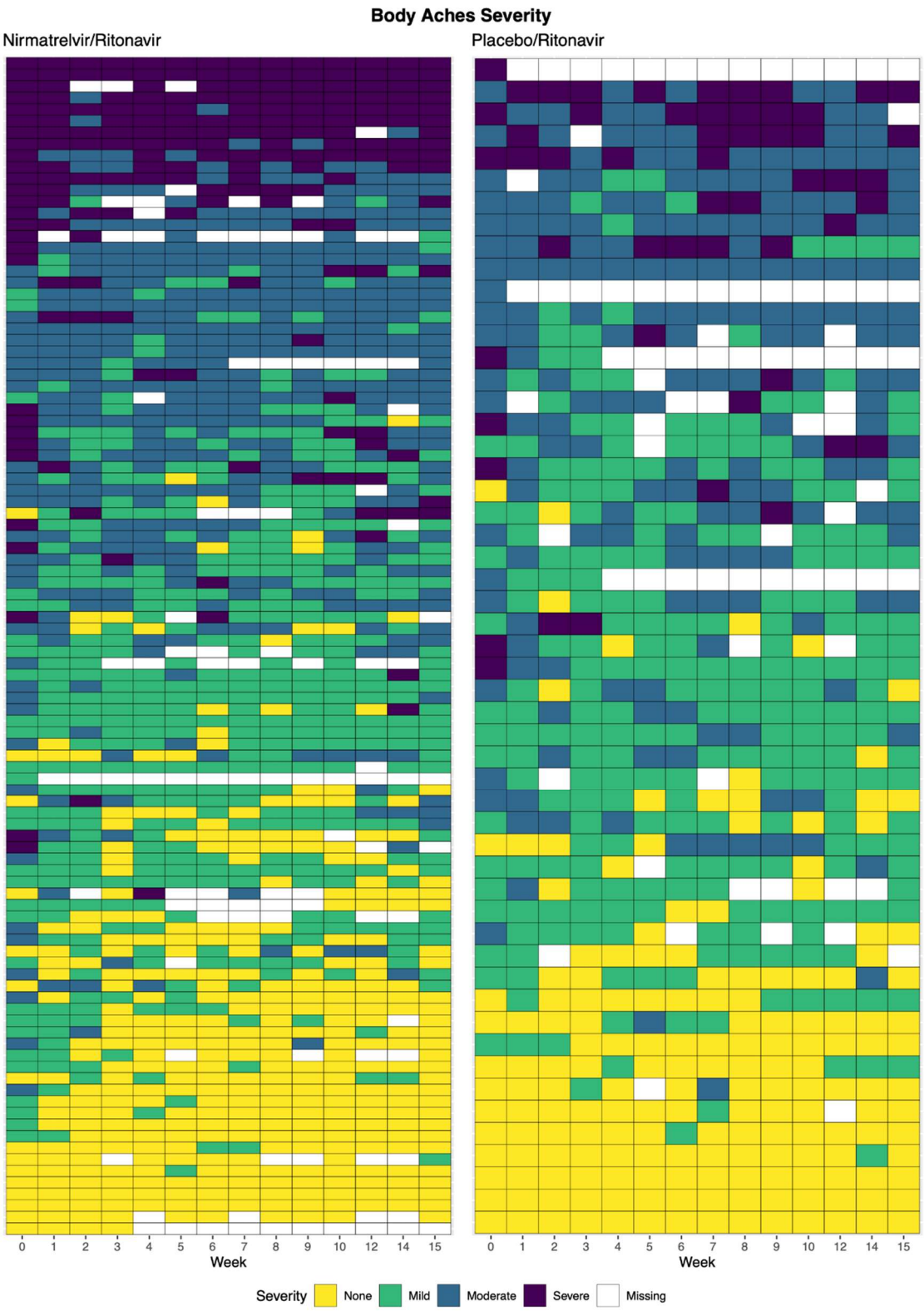
eFigure 7: Heatmaps of Raw Severity Scores for Each Core Symptom over Time

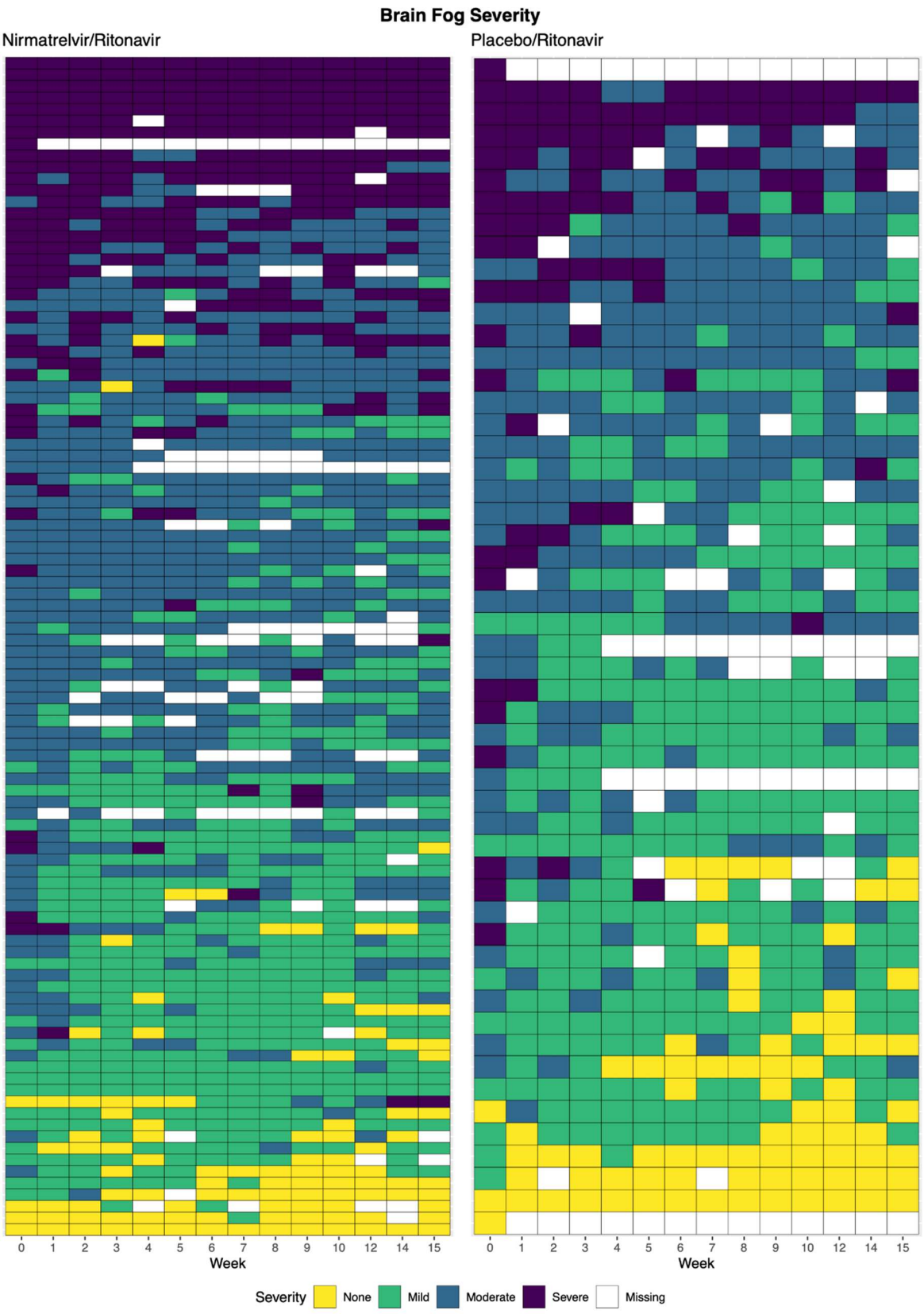
Each row corresponds to a participant. White represents missing data.

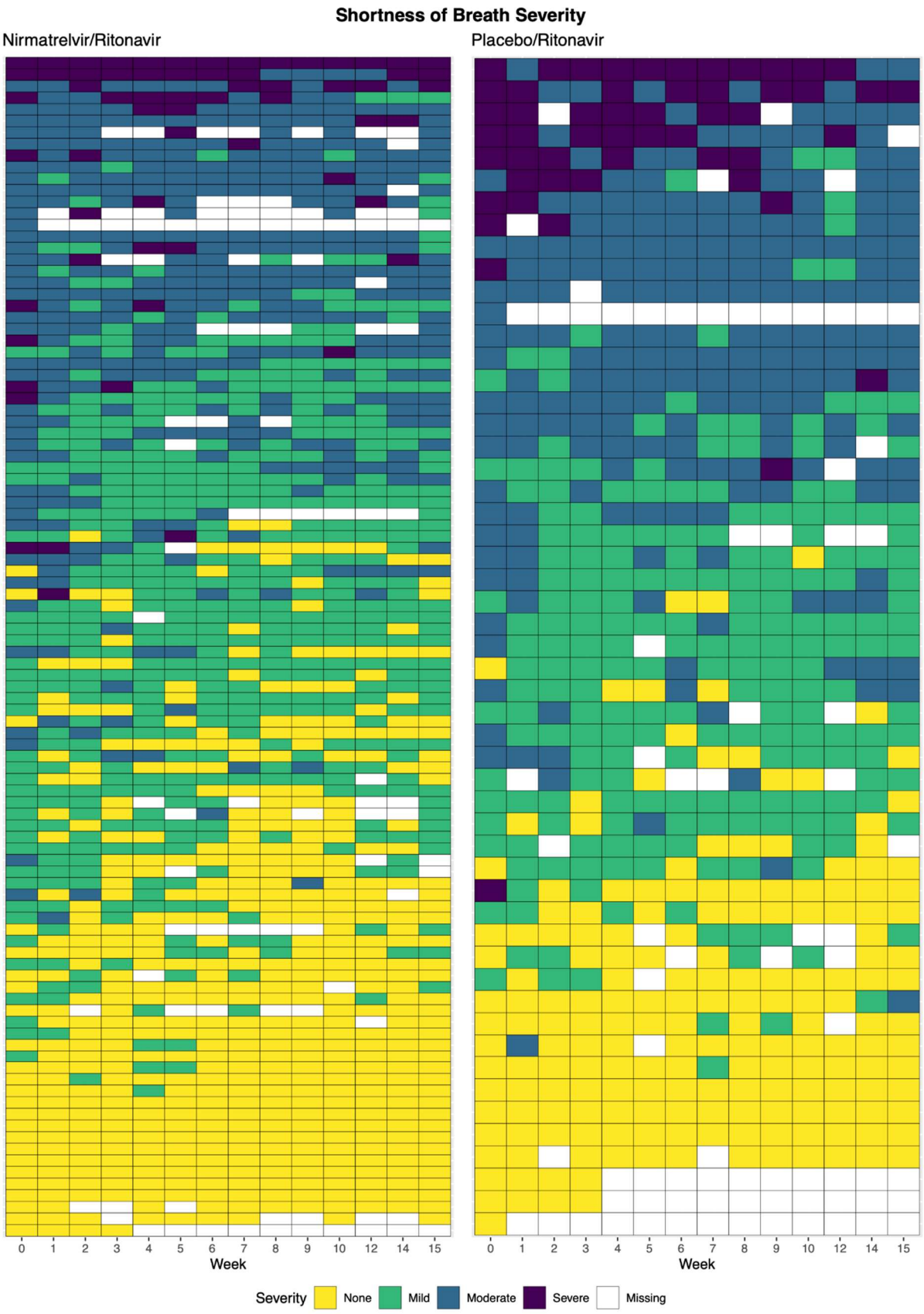






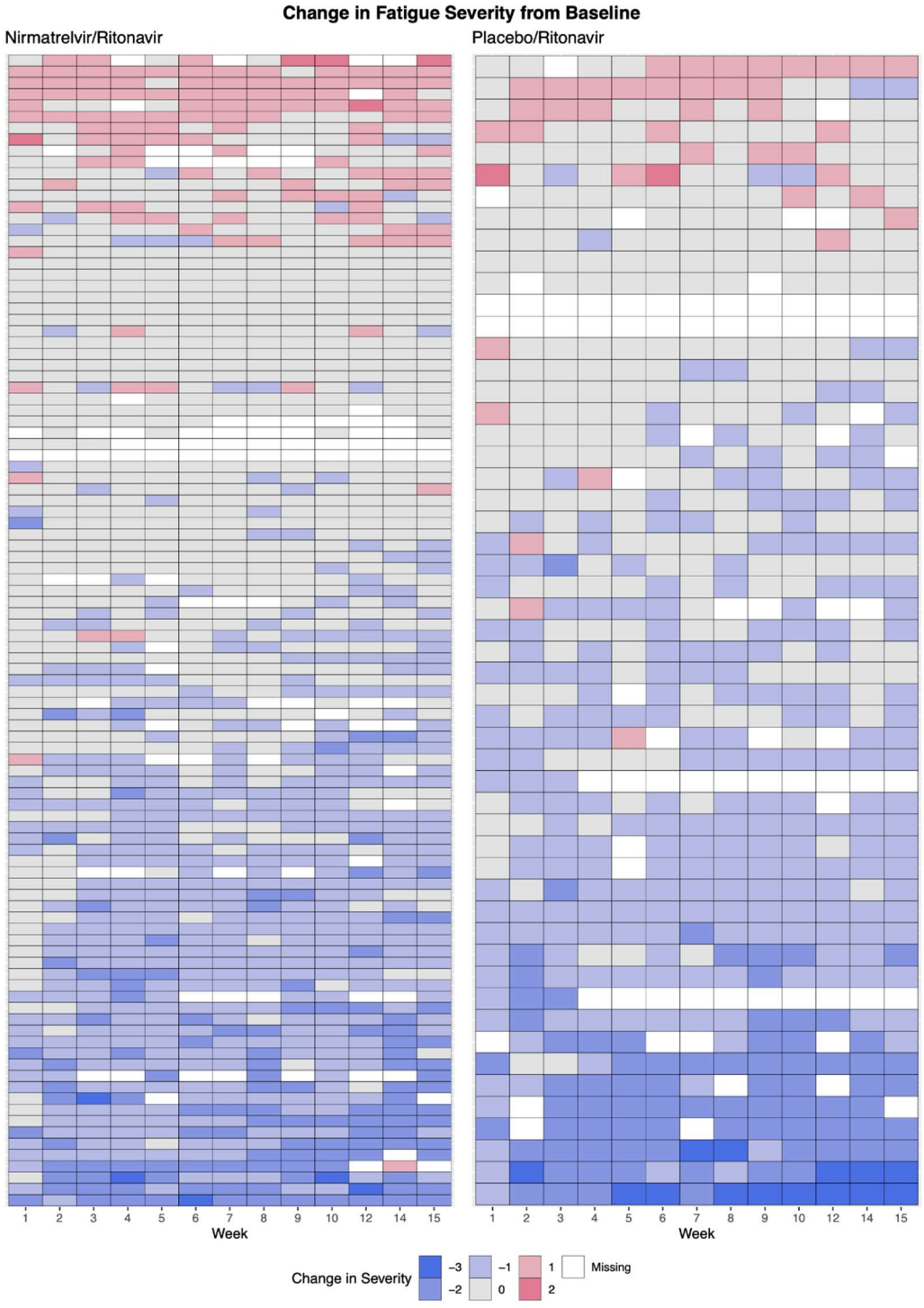


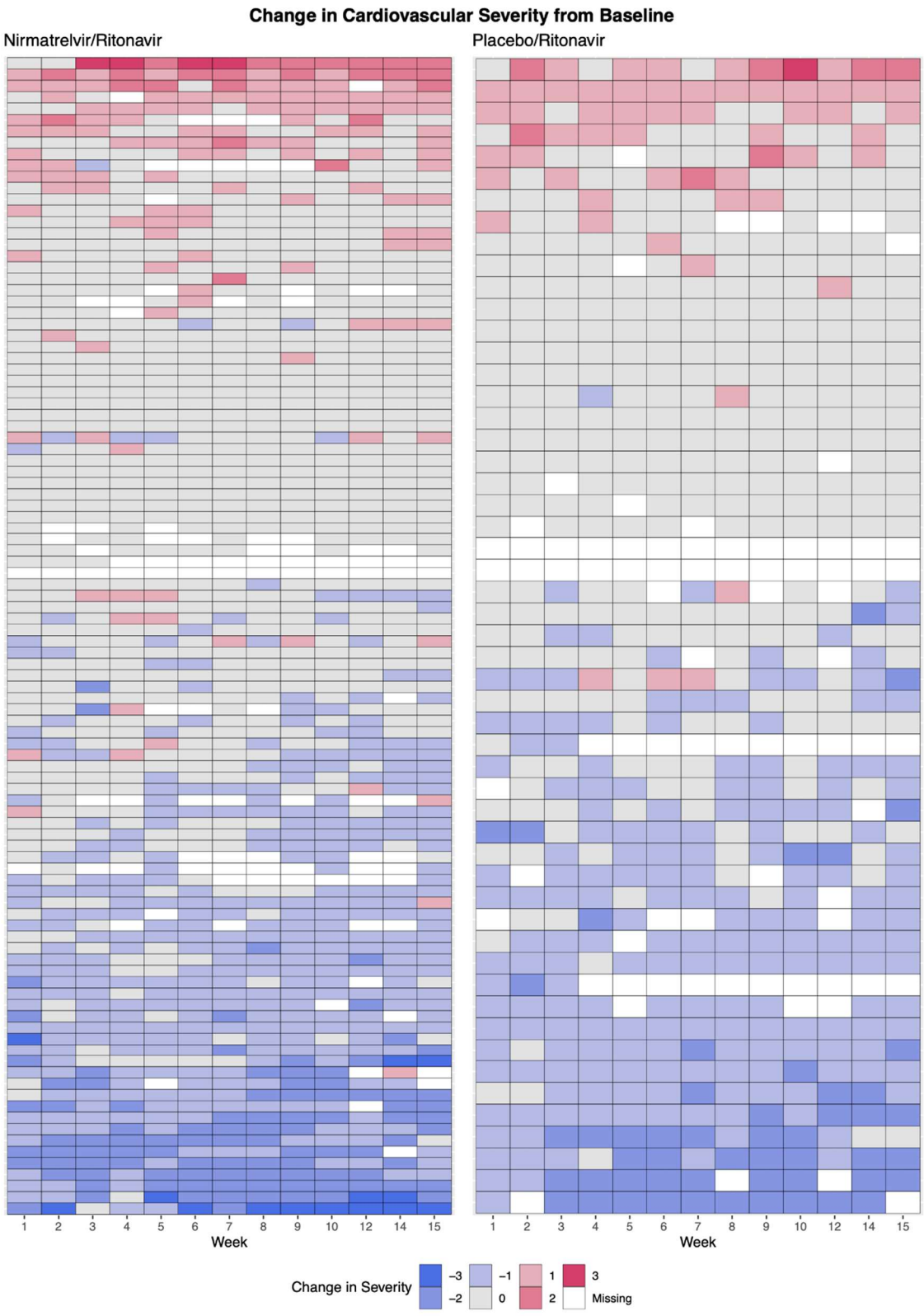


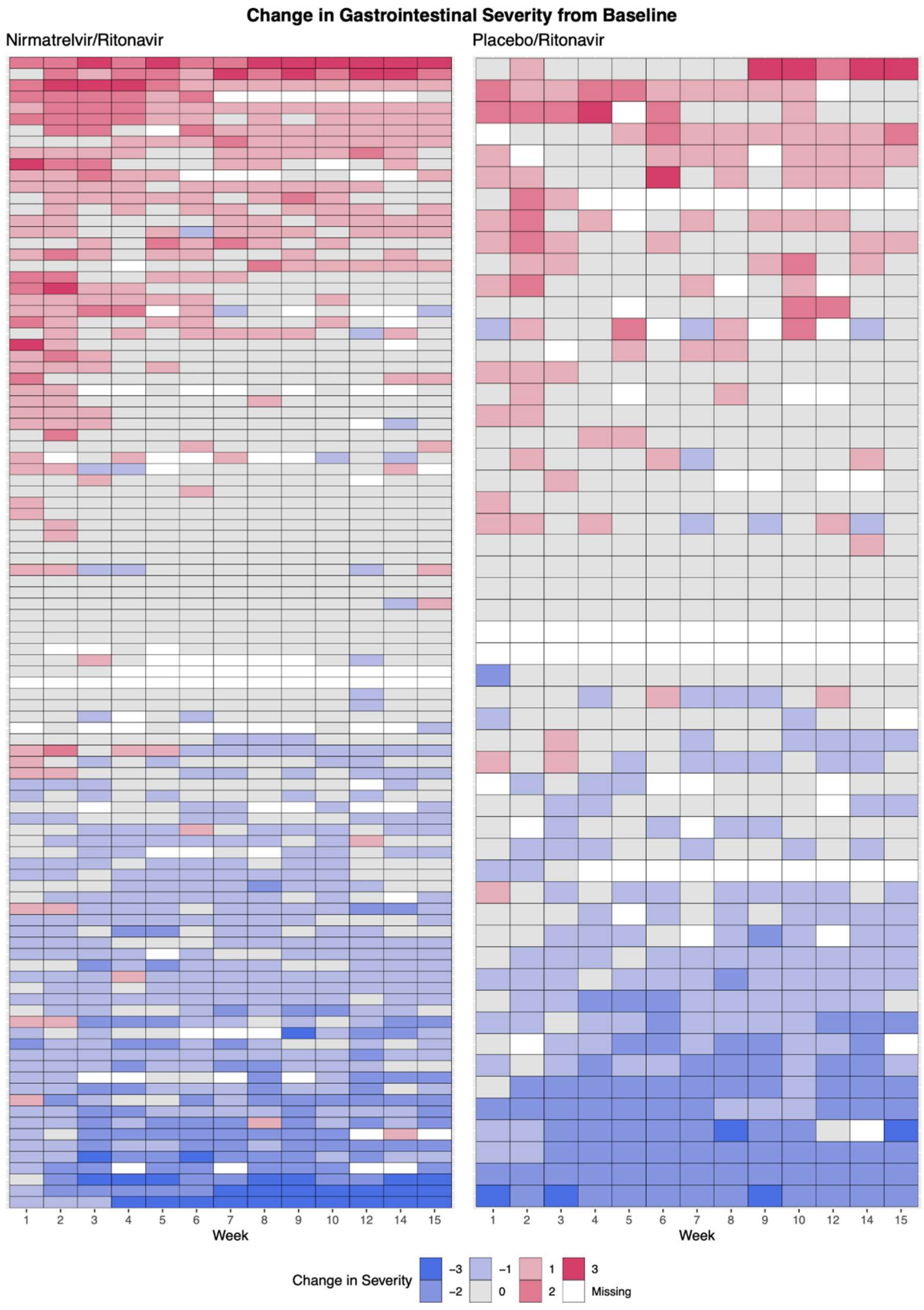


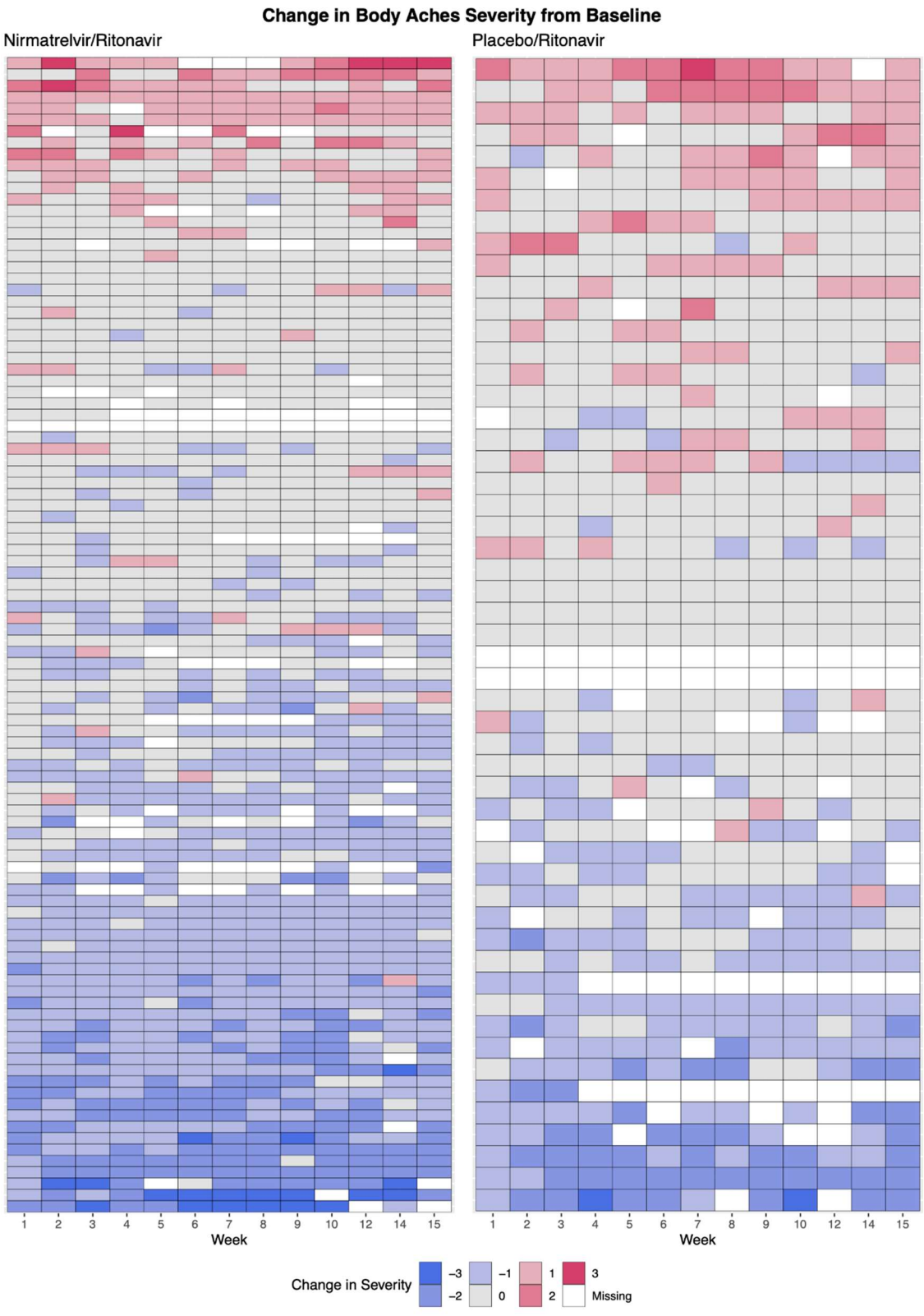
eFigure 8: Heatmaps of Change from Baseline Severity for Each Core Symptom over Time

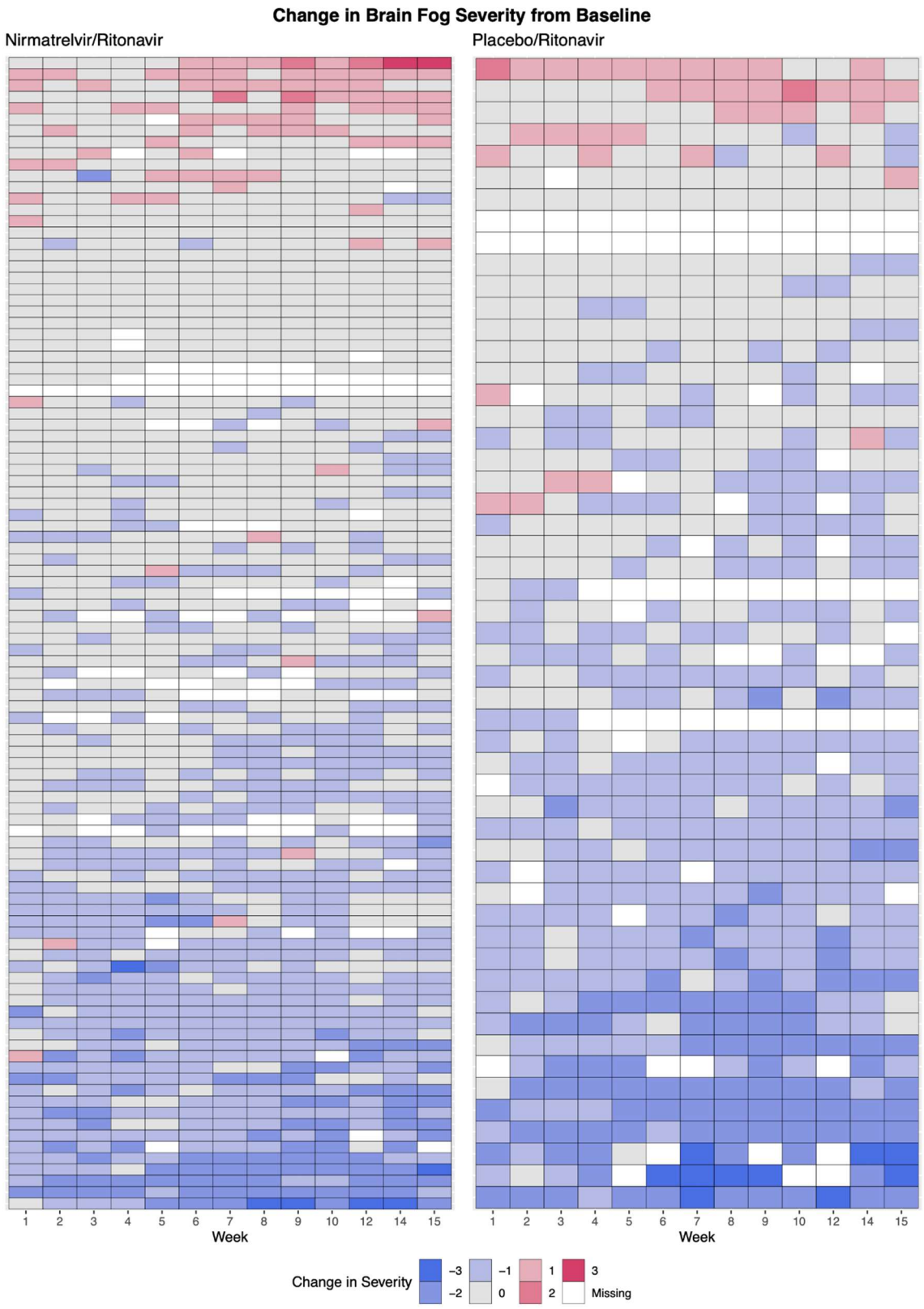
Each row corresponds to a participant. Red shades are increased symptom severity. Blue shades are decreased symptom severity. White represents missing data.

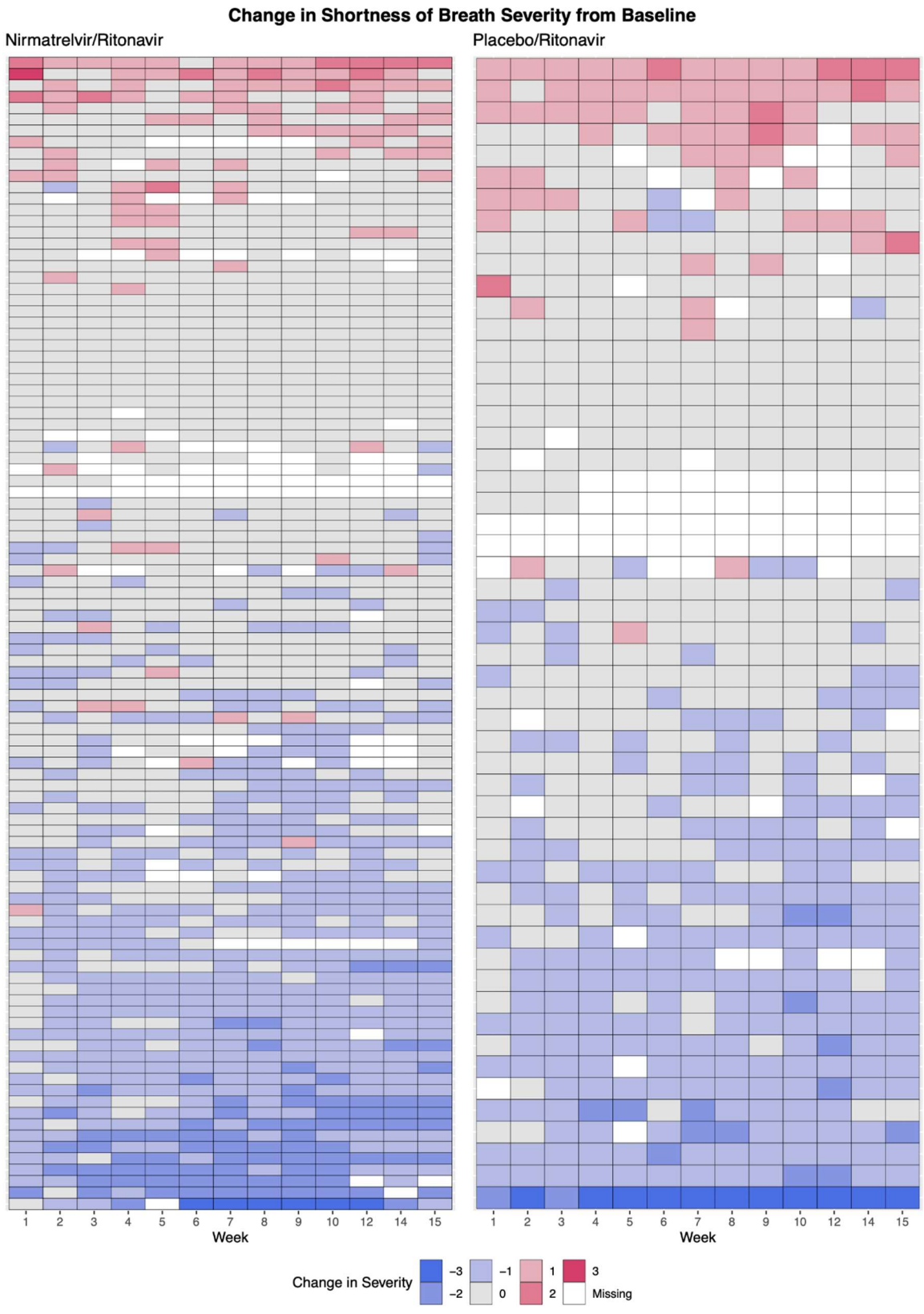








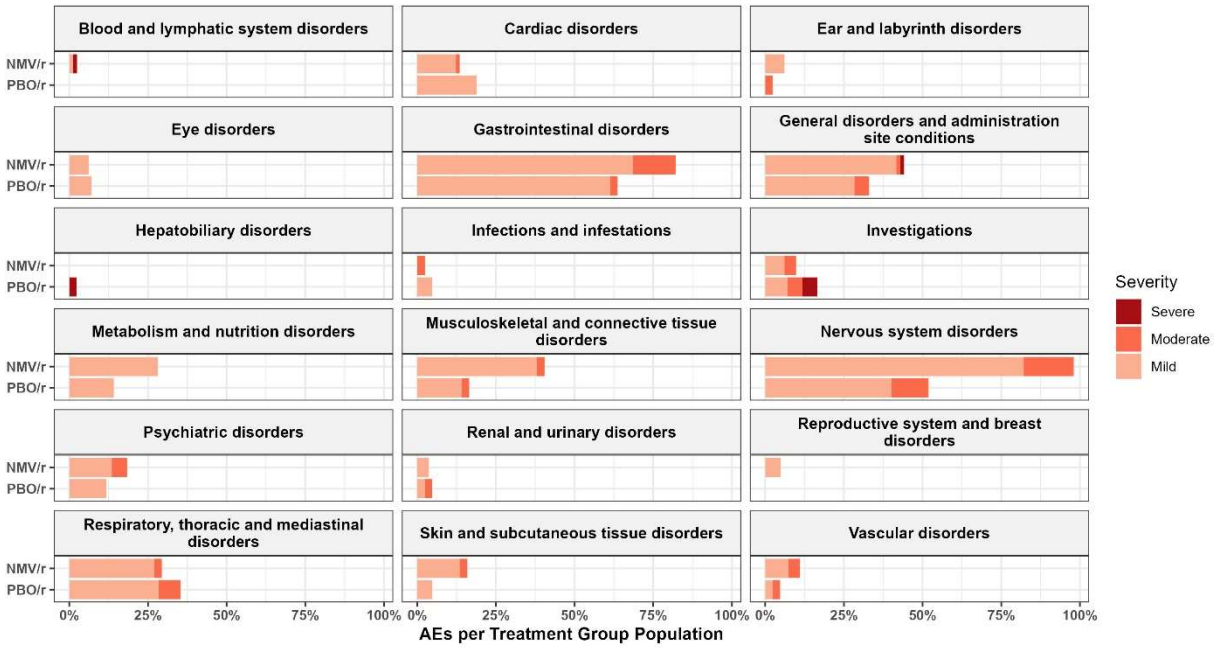




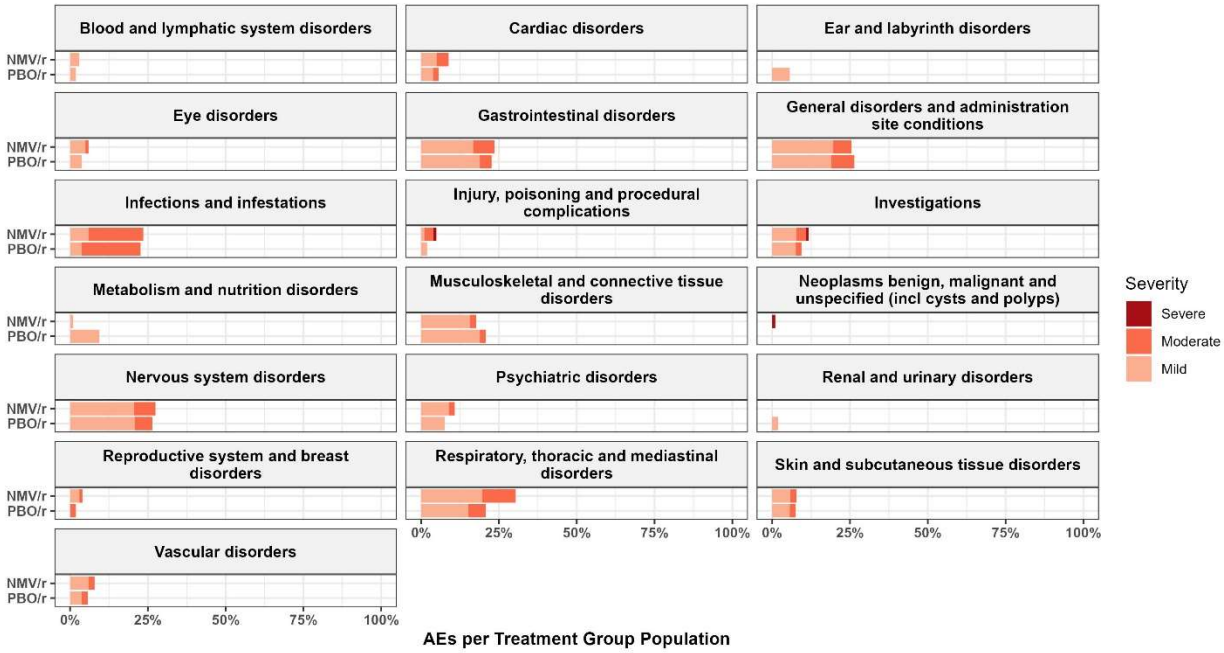
eFigure 9: Percentage of Participants Experiencing AEs for Each System Organ Class by Severity and Group

System Organ Class (SOC) classifications according to MedDRA v26.1 dictionary. (A) AEs occurring within 15-day treatment period; (B) AEs occurring after 15-day treatment period. NMV/r: nirmatrelvir-ritonavir; PBO/r: placebo-ritonavir.

A.



B.



eTable 1: Additional Secondary Outcomes

	NMV/r (N=102)	PBO/r (N=53)	
			HR (95% CI); p-value
Time to relief (weeks)			
Fatigue	-	-	0.90 (0.45, 1.77); 0.744
Brain fog	-	-	0.67 (0.32, 1.37); 0.259
Body aches	-	-	1.61 (0.65, 3.99); 0.286
Cardiovascular symptoms	-	-	0.92 (0.38, 2.24); 0.846
Shortness of breath	-	-	1.56 (0.51, 4.73); 0.410
Gastrointestinal symptoms	-	-	0.94 (0.42, 2.11); 0.880
	Mean (SD)	***Mean (SD)***	***Beta[a] (95% CI); p-value***
Change from baseline to 10 weeks			
Heart rate (supine to standing)	0.878 (14.2)	1.4 (11.5)	-0.51 (-6.15, 5.12); 0.856
SBP (supine to standing)	-2.86 (15.9)	-4.47 (14.1)	1.73 (-4.06, 7.53); 0.555
DBP (supine to standing)	-1.86 (10.9)	-1.51 (13.7)	-0.68 (-5.15, 3.79); 0.764
1 minute sit-to-stand	2.67 (10.8)	3.27 (7.25)	-0.41 (-4.24, 3.42); 0.833

CI = confidence interval; DBP = diastolic blood pressure; HR = hazard ratio; IQR = interquartile range [25th-75th percentile]; NMV/r = nirmatrelvir-ritonavir; PBO/r = placebo-ritonavir; SBP = systolic blood pressure

a The estimated coefficients can be interpreted as differences in the change score between groups, e.g. a coefficient estimate of -0.5 means those on NMV/r reported a 0.5 lower change between baseline to 10 weeks compared to those on PBO/r.

eTable 2: Post-hoc Subgroup Analyses for Select Outcomes

	Overall (N=155)	Pre-Omicron[a] (N=88)	Post-Omicron[a] (N=67)
	p-value	***p-value***	***p-value***
Primary outcome: Pooled core symptom severity	0.903	0.955	0.897
	OR[b] (95% CI); p-value	***OR[b] (95% CI); p-value***	***OR[b] (95% CI); p-value***
Proportion of weeks with mild or no symptoms			
Fatigue	0.55 (0.33, 0.92); 0.022	0.61 (0.30, 1.25); 0.173	0.50 (0.24, 1.05); 0.065
Brain fog	0.50 (0.31, 0.82); 0.006	0.47 (0.24, 0.92); 0.027	0.56 (0.26, 1.20); 0.131
Body aches	1.32 (0.74, 2.33); 0.342	1.16 (0.56, 2.38); 0.691	1.70 (0.63, 4.55); 0.285
Cardiovascular symptoms	1.37 (0.76, 2.48); 0.289	1.34 (0.63, 2.87); 0.439	1.35 (0.49, 3.69); 0.555
Shortness of Breath	1.32 (0.73, 2.38); 0.349	1.32 (0.60, 2.94); 0.486	1.26 (0.51, 3.10); 0.614
Gastrointestinal Symptoms	1.40 (0.79, 2.47); 0.249	1.68 (0.86, 3.27); 0.123	0.93 (0.29, 3.00); 0.896
	Beta[c] (95% CI); p-value	***Beta[c] (95% CI); p-value***	***Beta[c] (95% CI); p-value***
PGIC at 15 days	0.19 (-0.30, 0.67); 0.444	0.07 (-0.58, 0.72); 0.837	0.25 (-0.47, 0.98); 0.487
PGIC at 5 weeks	-0.25 (-0.78, 0.28); 0.346	-0.75 (-1.47, -0.04); 0.040	0.19 (-0.44, 0.83); 0.542
PGIC at 10 weeks	0.10 (-0.48, 0.67); 0.738	-0.14 (-0.93, 0.66); 0.728	0.17 (-0.52, 0.86); 0.622
PGIC at 15 weeks	0.17 (-0.43, 0.76); 0.578	0.03 (-0.84, 0.90); 0.947	0.22 (-0.48, 0.92); 0.531

CI = confidence interval; IQR = interquartile range [25th-75th percentile]; NMV/r = nirmatrelvir-ritonavir; OR = odds ratio; PBO/r = placebo-ritonavir;

[a] Participants who had their index infection prior to December 2021 were categorized as "Pre-Omicron" and participants who had their index infection in December 2021 or later were categorized as "Post-Omicron."

[b] An odds ratio of 1.5 corresponds to a 50% increase in the odds of experiencing mild/no symptoms, for those on NMV/r compared to those on PBO/r.

[c] The estimated coefficients can be interpreted as differences in PGIC scores between groups, e.g. an estimate of 0.3 means that on average, those on NMV/r reported PGIC 0.3 points higher than those on PBO/r. A higher score value corresponds to worsening status.

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