Viral and Symptom Rebound After COVID-19 Monoclonal Antibody Therapy in the ACTIV-2 Trial

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BACKGROUND

- Viral and symptom rebound following oral direct antiviral therapy for COVID-19 has been reported. Risk after COVID-19 monoclonal antibody (mAb) therapy is unknown.
- mAbs amubarvimab/romlusevimab reduced hospitalization/death by 79% in phase 2/3 randomized, placebo-controlled ACTIV-2/A5401 trial.
- mAb therapy may reduce risk of rebound given its longer half-life (~17 days vs ~6 hours for nirmatrelvir/ritonavir).
- We explored viral and symptom rebound with amubarvimab/romlusevimab vs placebo in the trial.

METHODS

Self-Collected Anterior Nasal Swabs	
Sparse	**Intensive**
Days: 0, 3, 7, 14, 28	Days: 0-14, 28
Phase 2+3	Phase 2 only

- Nasal SARS-CoV-2 viral RNA (vRNA) quantified by qPCR.
- **Primary viral rebound (VR) definition**: vRNA ≥3 $\log_{10}$ copies/mL (log) at day (d) 7, 14, or 28 and ≥0.5 log higher than d3 or at d14 or 28 and ≥0.5 log higher than d7
- VR in intensive sampled population assessed comparing to any prior measure d3 onward
- **Symptom rebound (SR) definition**: First occurrence of any mod/severe symptom (of 13 recorded daily, 29d diary) persisting for ≥2d, after achieving 2-days sustained symptom improvement or resolution

RESULTS

- No difference in VR by sparse sampling (4%/arm) (**Fig 1A-B**).
- Less VR with mAb vs placebo by intensive sampling (**Fig 1C-D**).
- Lower VR rate when requiring higher vRNA threshold (**Fig 1**).
- Viral rebounders, regardless of mAb treatment versus placebo, more likely to be immunocompromised (particularly higher-level rebound) and have fewer days since diagnosis and symptom onset, lower anti-N or anti-S Ab levels/seropositivity rates, and higher entry vRNA levels (**Table 1**).
- No difference in SR rates (6% vs 5%, mAb vs placebo; HR (95% CI) 0.95 (0.52, 1.75) for SR after symptom improvement) or time to SR (**Fig 3**).
- Co-occurring VR and SR rare (<1% of participants).

Acute COVID-19 mAb treatment reduced risk of viral rebound.

Viral rebound was associated with being earlier in the COVID-19 course, higher nasal viral levels, and less serologic response.

Figure 1. Viral rebound rates by treatment arm and definition

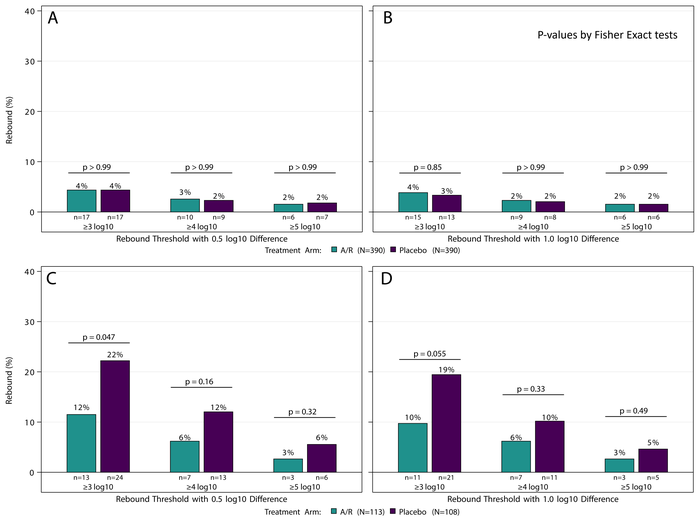
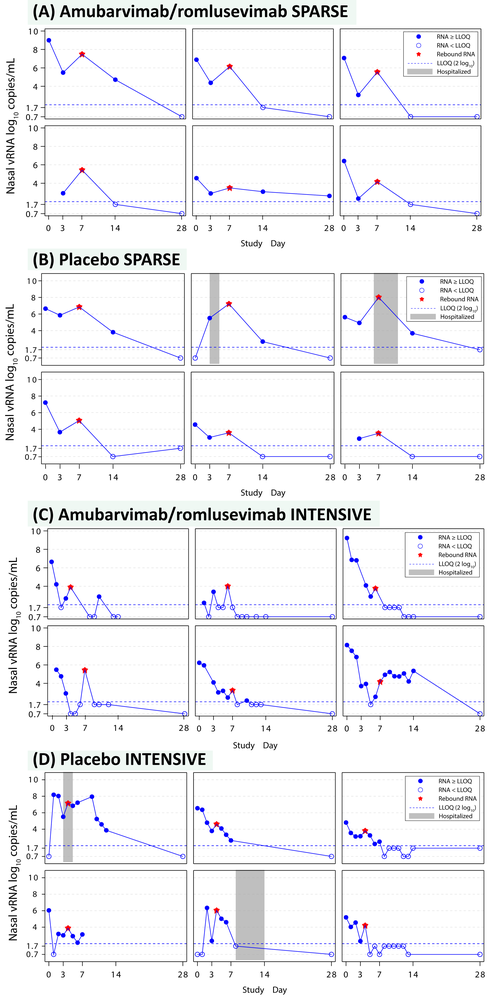


Table 1. Characteristics of viral rebounders vs non-rebounders

	Rebound to ≥3 log10 copies/mL			Rebound to ≥5 log10 copies/mL		
Characteristic	**Rebounders (N=34) Median (quartiles) or n (%)**	**Non-rebounders (N=746) Median (quartiles) or n (%)**	**p-value**	**Rebounders (N=13) Median (quartiles) or n (%)**	**Non-rebounders (N=767) Median (quartiles) or n (%)**	**p-value***
Age (years)	48 (39, 61)	49 (39, 58)	0.83	50 (39, 62)	49 (39, 58)	0.57
Sex						
Female	16 (47%)	390 (52%)	0.60	4 (31%)	402 (52%)	0.16
Male	18 (53%)	356 (48%)		9 (69%)	365 (48%)	
Immunocompromised (IC) status						
None	23 (68%)	563 (75%)	0.28	5 (38%)	581 (76%)	0.003
Mild	7 (21%)	138 (18%)		5 (38%)	140 (18%)	
Moderate	4 (12%)	36 (5%)		3 (23%)	37 (5%)	
Severe	0 (0%)	9 (1%)		0 (0%)	9 (1%)	
Any IC condition	11 (32%)	183 (25%)	0.31	8 (62%)	186 (24%)	0.005
Days from symptom onset to entry	4 (3, 7)	6 (4, 7)	0.10	4 (2, 5)	6 (4, 7)	0.030
Days from positive SARS-CoV-2 test to entry	1 (1, 3)	3 (1, 5)	<0.001	1 (0, 1)	3 (1, 5)	0.001
Serum anti-N antibody (COI)	0.08 (0.07, 0.11)	0.10 (0.07, 2.58)	0.003	0.07 (0.07, 0.09)	0.10 (0.07, 2.29)	0.011
Negative	30 (94%)	481 (70%)	0.002	13 (100%)	498 (71%)	0.025
Positive	2 (6%)	202 (30%)		0 (0%)	204 (29%)	
Serum anti-S antibody (U/mL)	0.3 (0.3, 0.3)	0.3 (0.3, 71.1)	<0.001	0.3 (0.3, 0.3)	0.3 (0.3, 60.1)	0.14
Negative	29 (88%)	383 (56%)	<0.001	10 (77%)	402 (57%)	0.17
Positive	4 (12%)	302 (44%)		3 (23%)	303 (43%)	
Day 0 viral RNA level	4.8 (3.8, 6.7)	3.8 (1.7, 5.8)	0.018	6.5 (4.2, 7.1)	3.9 (1.7, 5.8)	0.007

*Chi-square, Wilcoxon, or Fisher's exact tests. Not significantly different between rebounders vs non-rebounders: ethnicity, BMI, Delta vs non-Delta variant, history of SARS-CoV-2 vaccination, day 0 total symptom score

Figure 2. Example by-participant vRNA kinetics for participants with VR requiring ≥0.5 $\log_{10}$ increase to ≥3 $\log_{10}$ copies/mL



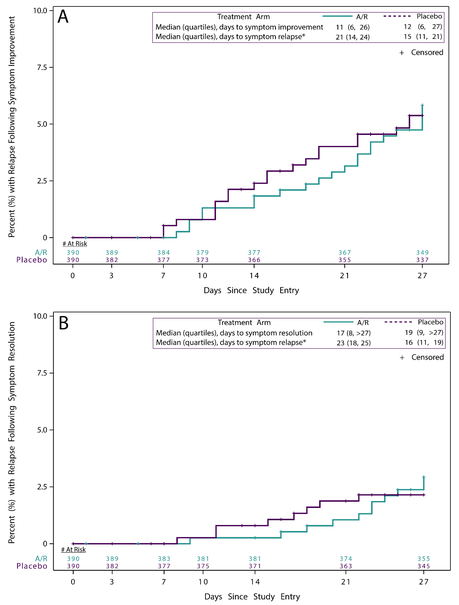


Figure 3. Joint modeling of time to SR among participants who achieved sustained symptom improvement (A) and sustained symptom resolution (B), by treatment arm, adjusting for baseline symptom score.

Time to symptom improvement/resolution estimated using Kaplan-Meier methods. Time from study entry to SR among participants who relapsed calculated using descriptive statistics.

CONCLUSIONS

- VR detection is influenced by sampling frequency and rebound definition.
- mAb therapy was associated with a lower VR rate than placebo in an intensely sampled subpopulation, potentially related to long half-life of mAbs suppressing vRNA.
- Association of VR with immunocompromise, early COVID-19 infection and lack of humoral immunity suggests VR is influenced by host-virus interaction prior to immunologic control

ADDITIONAL KEY INFORMATION

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