Utility of virologic assessments as a marker of progression to severe disease based on data from the ACTIV-2 trial

Michael Hughes
(Harvard TH Chan School of Public Health, Boston, USA)
on behalf of the ACTIV-2/A5401 Study

Disclosure: NIH COVID research funding

Goals of Analysis

1. Natural history: Are SARS-CoV-2 RNA levels in anterior nasal (AN) samples predictive of subsequent all-cause hospitalization/death in untreated participants (placebo recipients)?
   - AN RNA levels at Day 0 as a predictor of hospitalization/death from Day 0 to Day 28
   - AN RNA levels at Days 0 and 3 as predictors of hospitalization/death between Day 4 and Day 28

2. mAb-treated participants:

a) Is association between of AN RNA levels at Days 0 and 3 and subsequent hospitalization/death in participants receiving monoclonal antibodies (mAbs) by infusion similar to that among placebo recipients?

b) Does effect of mAbs on AN RNA levels at Day 3 explain effect of mAb on subsequent hospitalization/death?

ACTIV-2

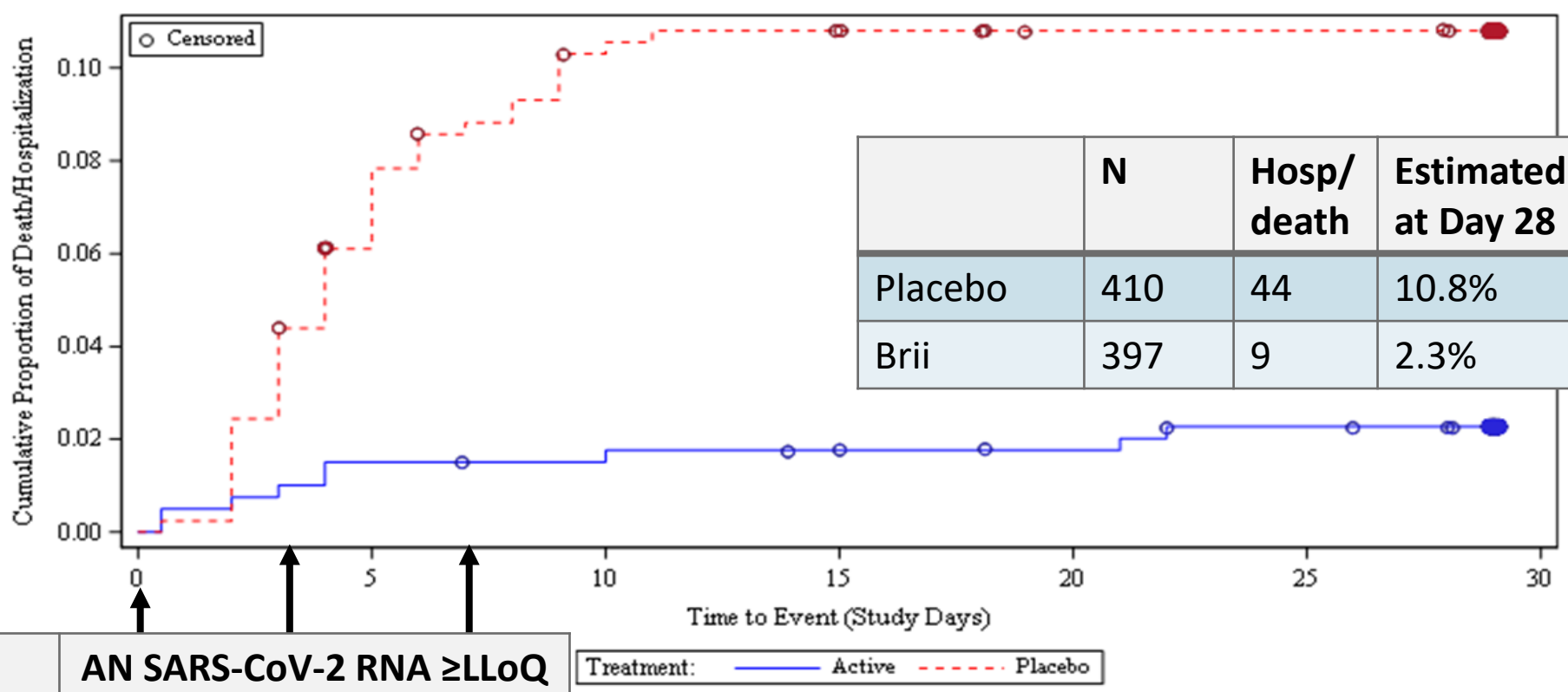
- Phase 2/3 platform trial to evaluate the safety and efficacy of investigational agents for the treatment of non-hospitalized adults (age 18+) with COVID-19.

- Key Eligibility Criteria
  - Positive for SARS-CoV-2 (antigen or nucleic acid test within 10 days prior to study entry)
  - Symptom duration ≤10 days, with ongoing symptoms at study entry

- Virology: AN swabs from Day 0 and Day 3 tested at central lab for quantitative SARS-CoV-2 RNA using Abbott m2000sp/rt platform; lower limit of quantification (LLoQ): 100 (2 $\log_{10}$) copies/mL

- Monoclonal antibody agents contributing to this presentation:
  - “Bam” (Bamlanivimab) vs Placebo [August to November 2020]; n=317
  - Bamlanivimab (uncontrolled cohort) [November 2020 to January 2021]; n=919
  - “Brii” (Amubarvimab + Romlusevimab) vs Placebo [January to July 2021]; n=808

Brii vs placebo: Hosp/death through to 28 days



	N	Hosp/ death	Estimated % at Day 28	Ratio (95% CI)
Placebo	410	44	10.8%	
Brii	397	9	2.3%	0.21 (0.10, 0.43)

	AN SARS-CoV-2 RNA ≥LLoQ		
	Day 0	Day 3	Day 7
Placebo	69%	55%	30%
Brii	69%	46%	21%
Difference		-9%	-9%

- In placebo group, about half of hosp/death in first 3-4 days, and almost all by 10 days
- Substantial effect of Brii mAbs on hosp/death
- Modest effect on AN RNA levels

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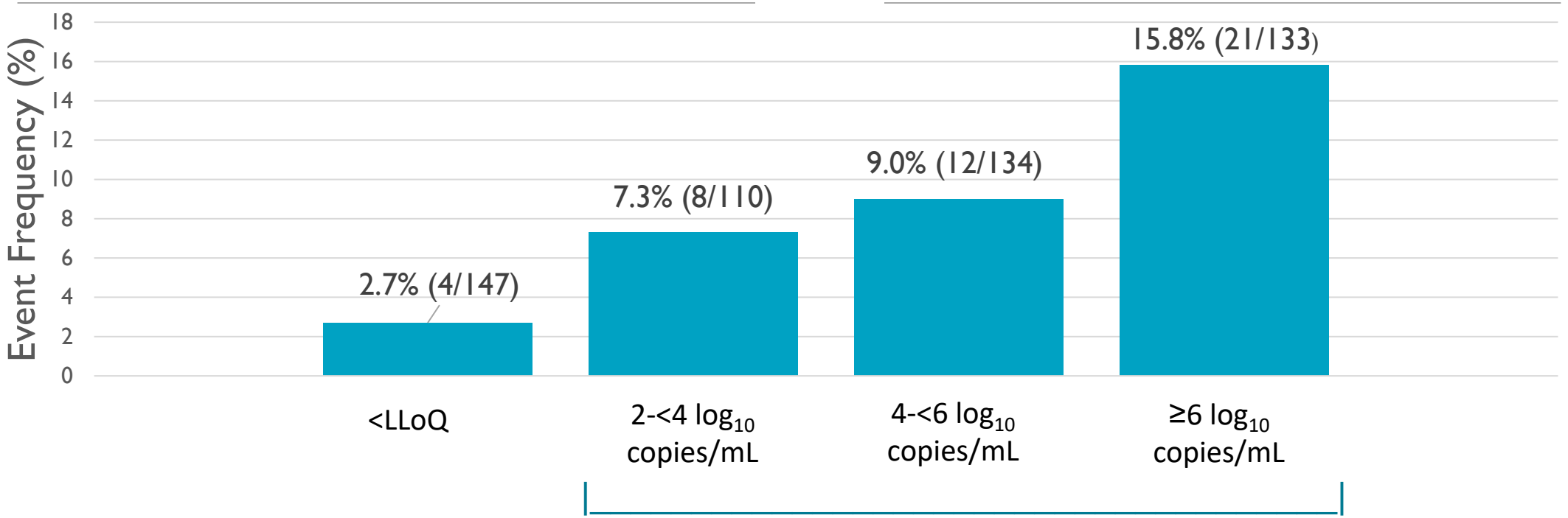
Characteristics of Placebo Recipients
(Enrolled August 2020 to July 2021 to Bam and Brii Evaluations)

	Placebo (n=561)
Age (y): median (quartiles)	49 (38, 57)
Sex: % female	51%
Race: % white	77%
Ethnicity: % Hispanic/Latino	45%
Country: % U.S.	77%
SARS-CoV-2 vaccination: %	7%
Higher risk of severe COVID: %	79%
Days from symptom onset to study entry: Median (quartiles)	6 (4, 7)

AN RNA level at Day 0 predicts hospitalization/death through Day 28 among untreated (placebo) participants

(n=524 with AN RNA values on day 0)



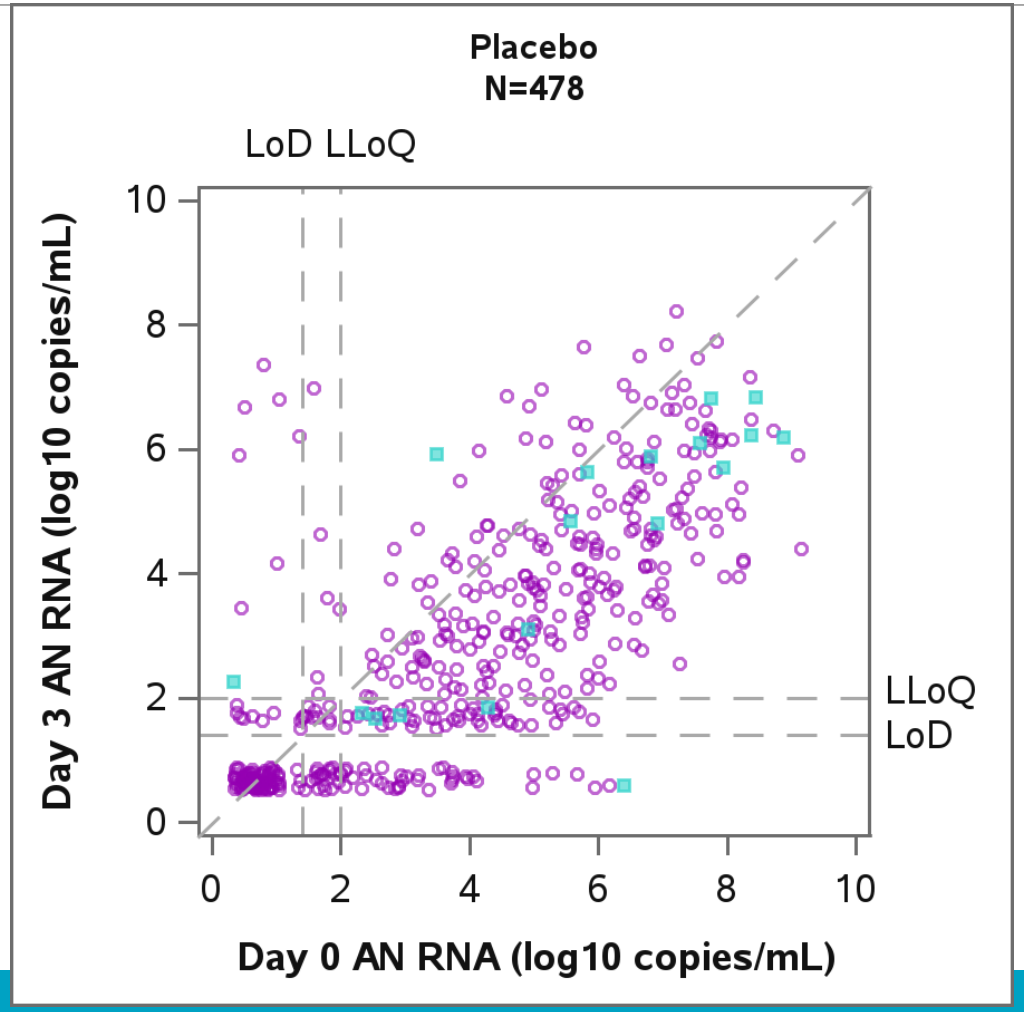
Relative Risk per 1.0 log_{10} copies/mL higher (95% CI):
1.24 (1.04, 1.49)

'< LLoQ' represents results below the lower limit of quantification (2 log_{10} copies/mL)

SARS-CoV-2 RNA levels on Days 0 and 3 showing participants who were hospitalized or died between Days 4 and 28

Untreated (Placebo) Participants Not Hospitalized by Day 3

Teal squares = participants hospitalized/died between day 4 and day 28



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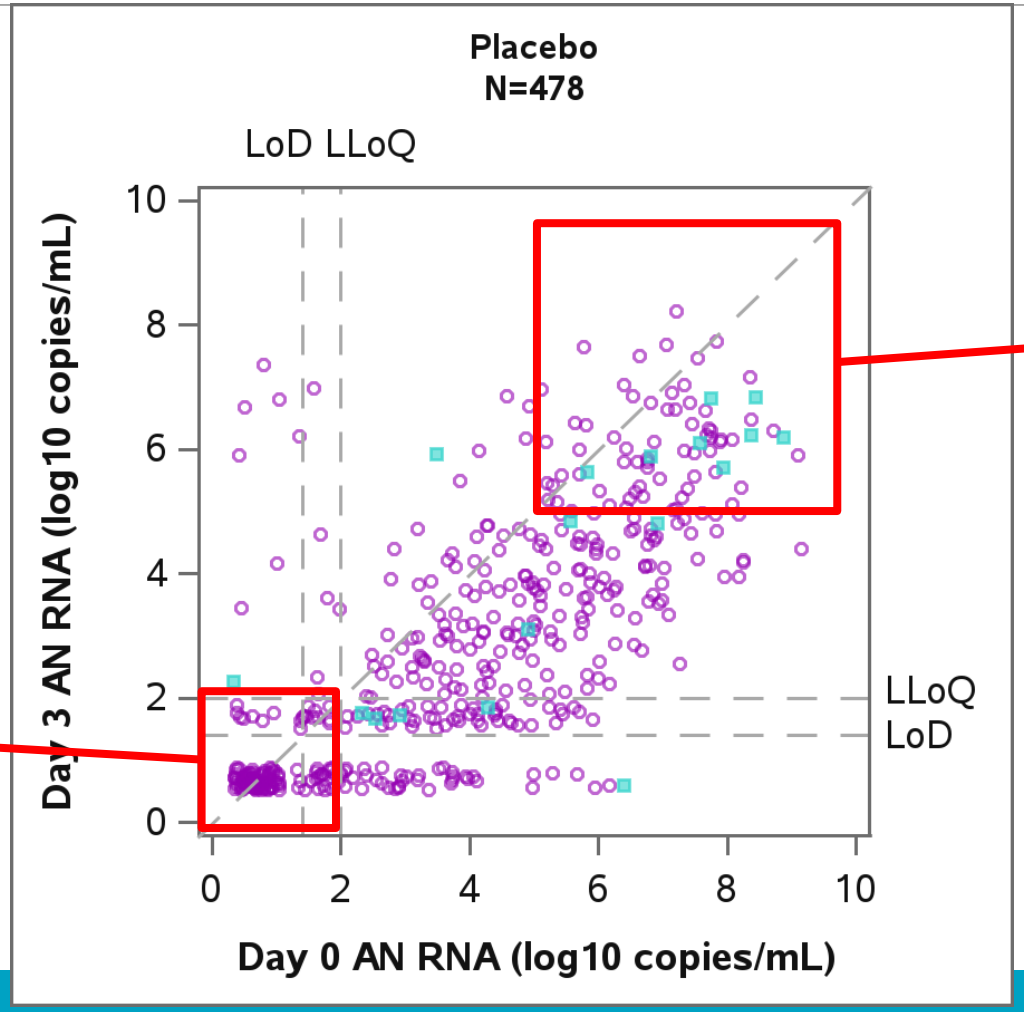

RNA <LLoQ at both Day 0 and Day 3

0% (0/123) subsequently hospitalized/died

RNA ≥5 $\log_{10}$ copies/mL at both Day 0 and Day 3

10% (8/77) subsequently hospitalized/died

AN RNA levels at Days 0 and 3 as predictors of subsequent hospitalization/death between Days 4 and 28

(Placebo recipients, N=478)

Covariate		**Risk Ratio for Hosp/Death during Days 4 to 28 (95% CI)**
Day 0 AN RNA	(per 1 $\log_{10}$ copies/mL above LLoQ higher)	1.3 (0.8, 2.0)
Day 3 AN RNA	(per 1 $\log_{10}$ copies/mL above LLoQ higher)	1.4 (1.0, 2.0)

Risk of hospitalization/death highest among those with persistently high RNA levels

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mAb/Placebo Analysis Population

2115 participants

- 1554 received one of two anti-SARS-CoV-2 mAb regimens (similar substantial efficacy in phase 3 trials)
  - “Brii”: Amubarvimab plus romlusevimab combination therapy
  - “Bam”: Bamlanivimab monotherapy (includes n=990 in uncontrolled cohort)
- 561 received placebo

102 participants (5%) were hospitalized or died through day 28

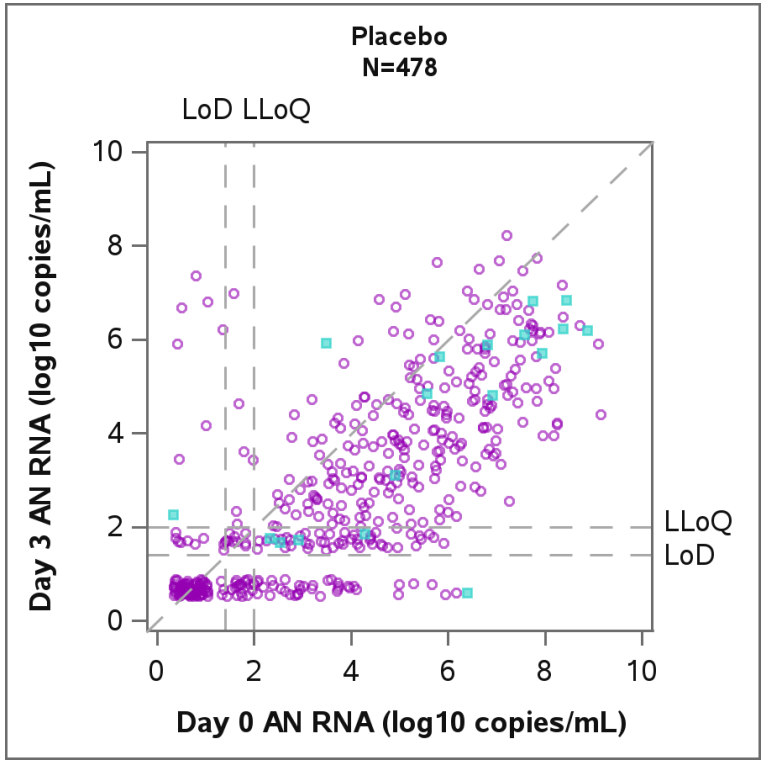
- 57 hospitalized/died within 3 days

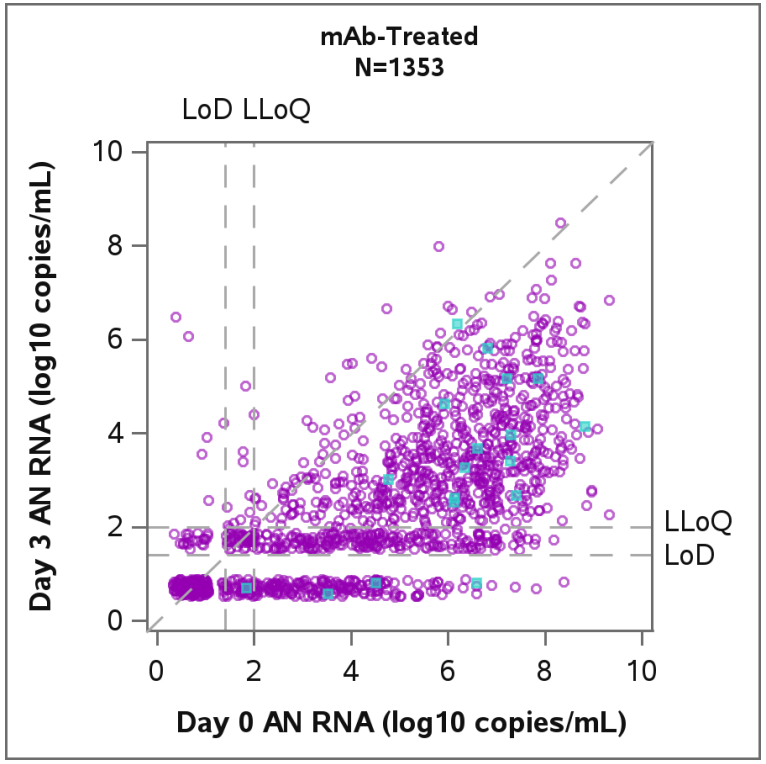
Participant Characteristics

(enrolled August 2020 to July 2021 in Bam and Brii evaluations)

		Placebo (N=561)	mAb-treated (N=1554)	Total (N=2115)
Age (years)	Median (Quartiles)	49 (38, 57)	50 (39, 60)	49 (39, 59)
Sex	Female	287 (51%)	797 (51%)	1084 (51%)
Race	White	430 (77%)	1263 (81%)	1693 (80%)
	Black Or African American	74 (13%)	159 (10%)	233 (11%)
	Asian	30 (5%)	75 (5%)	105 (5%)
	Other	26 (5%)	56 (4%)	82 (4%)
Ethnicity	Hispanic Or Latino	249 (45%)	564 (36%)	813 (39%)
Country	United States	432 (77%)	1415 (91%)	1847 (87%)
History of SARS-CoV-2 Vaccination		39 (7%)	32 (2%)	71 (3%)
Higher Risk of Severe COVID-19 Progression		442 (79%)	1101 (71%)	1543 (73%)
Days from Symptom Onset to Study Day 0	Median (Quartiles)	6 (4, 7)	5 (4, 7)	6 (4, 7)

Day 3 vs Day 0 SARS-CoV-2 AN RNA levels





Teal squares indicate participants who were hospitalized or died by day 28; purple circles indicate participants with no hospitalization/death.

AN RNA levels at Days 0 and 3 as predictors of subsequent hospitalization/death between Days 4 and 28

		Risk Ratio for Hosp/Death during Days 4 to 28 (95% CI)	
Covariate		**Placebo (N=478)**	**mAb-treated (N=1353)**
Day 0 AN RNA	(per 1 $\log_{10}$ copies/mL above LLoQ higher)	1.3 (0.8, 2.0)	1.3 (1.0, 1.8)
Day 3 AN RNA	(per 1 $\log_{10}$ copies/mL above LLoQ higher)	1.4 (1.0, 2.0)	1.0 (0.7, 1.6)

Possible different association of risk of hosp/death with Day 3 RNA among mAb-treated participants compared with placebo recipients (though difference not statistically significant)

Effect of mAb on Hospitalization/Death between Days 4 and 28 Without and With Adjustment for Effect on Day 3 AN RNA

	Risk Ratio for mAb versus Placebo* (95% CI)	p-value
Model 1: not adjusted for Day 3 AN RNA	0.29 (0.15, 0.55)	<0.001
Model 2: adjusted for Day 3 AN RNA	0.32 (0.16, 0.62)	<0.001
Proportion of Effect on Log Risk Scale Explained	8%	

* Adjusted for Day 0 RNA

Little evidence that effect of mAb on hospitalization/death is explained by effect of mAb on Day 3 RNA in AN samples

Summary

- AN SARS-CoV-2 RNA levels are predictive of hospitalization/death in the natural history setting (on placebo in this study)
- Possible evidence of different associations among mAb-treated versus placebo recipients when AN RNA levels at Day 0 and Day 3 were modeled jointly
- Limited ability of AN RNA level at Day 3 to explain the subsequent effect of mAb on hospitalization/death
- AN RNA at Day 3 may not be a good surrogate for hospitalization/death in evaluating mAbs
  - Caveat: Many hospitalizations before Day 3 so exploration of associations with very early viral dynamics (e.g., Day 1) might be useful though effect of mAbs on these dynamics still likely very modest