Supplementary Appendix

Clinical and Virological Response to a Neutralizing Monoclonal Antibody for Hospitalized Patients with COVID-19

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Section 1: TICO Study Group

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Section 2: Methods

The complete inclusion and exclusion criteria from the protocol are given below.

Inclusion Criteria

- Age ≥ 18 years;
- Informed consent by the patient or the patient's legally-authorized representative
- SARS-CoV-2 infection, documented by PCR or other nucleic acid test (NAT) within 3 days prior to randomization OR documented by NAT more than 3 days prior to randomization AND progressive disease suggestive of ongoing SARS-CoV-2 infection per the responsible investigator;
- Duration of symptoms attributable to COVID-19 ≤ 12 days per the responsible investigator;
- Requiring admission for inpatient hospital acute medical care for clinical manifestations of COVID-19, per the responsible investigator, and NOT for purely public health or quarantine purposes.

Exclusion Criteria

- Prior receipt of
  - Any SARS-CoV-2 hIVIG, convalescent plasma from a person who recovered from COVID-19 or
  - SARS-CoV-2 nMAb at any time prior to hospitalization;
- Not willing to abstain from participation in other COVID-19 treatment trials until after Day 5;
- In the opinion of the responsible investigator, any condition for which, participation would not be in the best interest of the participant or that could limit protocol-specified assessments;
- Expected inability to participate in study procedures;
- Women of child-bearing potential who are not already pregnant at study entry and who are unwilling to abstain from sexual intercourse with men or practice appropriate contraception through Day 90 of the study.

- Men who are unwilling to abstain from sexual intercourse with women of child-bearing potential or who are unwilling to use barrier contraception through Day 90 of the study.

- **[stage 1, prior to futility assessment, only]** Presence at enrollment of any of the following:
    a. stroke
    b. meningitis
    c. encephalitis
    d. myelitis
    e. myocardial infarction
    f. myocarditis
    g. pericarditis
    h. symptomatic congestive heart failure (NYHA class III-IV)
    i. arterial or deep venous thrombosis or pulmonary embolism

- **[stage 1, prior to futility assessment, only]** Current or imminent requirement for any of the following:
    a. invasive mechanical ventilation
    b. ECMO
    c. mechanical circulatory support
    d. vasopressor therapy
    e. commencement of renal replacement therapy at this admission (i.e. not patients on chronic renal replacement therapy).

Outcomes

Day 5 Ordinal Outcomes use for Early Futility

Two ordinal outcomes used to determine early futility were assessed at day 5. The first ordinal outcome is a 7-category outcome largely based on oxygen requirements. The highest category that applies on day 5 was assigned. This outcome is referred to as the "pulmonary" ordinal outcome and is defined below:

1. Can independently undertake usual activities with minimal or no symptoms
2. Symptomatic and currently unable to independently undertake usual activities but no need of supplemental oxygen (or not above premorbid requirements)
3. Supplemental oxygen (<4 liters/min, or <4 liters/min above premorbid requirements)
4. Supplemental oxygen (≥4 liters/min, or ≥4 liters/min above premorbid requirements, but not high-flow oxygen)
5. Non-invasive ventilation or high-flow oxygen
6. Invasive ventilation, extracorporeal membrane oxygenation (ECMO), mechanical circulatory support, or new receipt of renal replacement therapy
7. Death

The second ordinal outcome, also assessed at Day 5, captures the range of organ dysfunction that may be associated with progression of Coronavirus-Induced Disease 2019 (COVID-19), such as respiratory dysfunction and coagulation-related complications. Again, the highest category that applies on day 5 was assigned. This outcome is referred to as the "pulmonary+" ordinal outcome. The 7 categories of the pulmonary+ ordinal outcome assessed at Day 5 are:

1. Can independently undertake usual activities with minimal or no symptoms
2. Symptomatic and currently unable to independently undertake usual activities but no need of supplemental oxygen (or not above premorbid requirements)
3. Supplemental oxygen (<4 liters/min, or <4 liters/min above premorbid requirements)
4. Supplemental oxygen (≥4 liters/min, or ≥4 liters/min above premorbid requirements, but not high-flow oxygen) or any of the following: stroke (NIH Stroke Scale [NIHSS] ≤14), meningitis, encephalitis, myelitis, myocardial infarction, myocarditis, pericarditis, new onset CHF NYHA class III or IV or worsening to class III or IV, arterial or deep venous thromboembolic events.
5. Non-invasive ventilation or high-flow oxygen, or signs and symptoms of an acute stroke (NIHSS >14)
6. Invasive ventilation, ECMO, mechanical circulatory support, vasopressor therapy, or new receipt of renal replacement therapy
7. Death

Primary Efficacy Endpoint

The primary endpoint is ***time from randomization to sustained recovery,*** where sustained recovery is defined as being discharged from the index hospitalization, followed by being alive and *home* for 14 consecutive days prior to Day 90.

Home is defined as the level of residence or facility where the participant was residing prior to hospital admission leading to enrollment in this trial (the index hospitalization).

Residence or facility groupings to define home are:
1) **Independent/community dwelling** with or without help, including house, apartment, undomiciled/homeless, shelter, or hotel;
2) **Residential care facility** (e.g., assisted living facility, group home, other non-medical institutional setting);
3) **Other healthcare facility** (e.g., skilled nursing facility, acute rehab facility); and
4) L**ong-term acute care hospital** (hospital aimed at providing intensive, longer term acute care services, often for more than 28 days).

Lower (less intensive) level of residence or facility will also be considered as home. By definition, "home" cannot be a "short-term acute care" facility. Participants previously affiliated with a "long-term acute care" hospital recover when they return to the same or lower level of care.

Readmission from "home" may occur and if this occurs within 14 days of the first discharge to "home", then the primary endpoint will not be reached until such time as the participant has been at home for 14 consecutive days.

Participants residing in a facility solely for public health or quarantine purposes will be considered as residing in the lowest level of required residence had these public health measures not been instated.

Safety Outcome

Adverse events of any grade during the infusion and 2 hours post infusion were collection on a checklist. These events were summarized in the preliminary report (13). Composite safety outcomes were assessed through day 5, through day 28 and through day 90. The composite safety endpoints assessed through day 5 and day 28 included deaths, serious adverse events (SAEs), end organ dysfunction, serious infection and grade 3 or 4 AEs. As indicated in section 10.2.5 of the protocol, end organ dysfunction and serious infections were defined as "protocol-specified exempt events". Those events were systematically reported during follow-up but not reported as a SAE unless they were considered related to study agent. These events are listed below for ease of reference:

- Stroke
- Meningitis
- Encephalitis
- Myelitis
- Myocardial infarction
- Myocarditis
- Pericarditis
- New onset of worsening of CHF (NYHA class 3 or 4)
- Arterial or deep vein thromboembolic events
- Respiratory failure defined as receipt of high flow nasal oxygen, non-invasive ventilation, invasive mechanical ventilation or ECMO
- Hypotension requiring vasopressor therapy
- Renal dysfunction requiring renal replacement therapy
- Hepatic decompensation
- Neurologic dysfunction, including acute delirium and transient ischemic events
- Disseminated intravascular coagulation
- Major bleeding events
- Serious infections

Adverse events were graded for severity using a toxicity table of the Division of AIDS, NIAID (33). For adverse events not in the table, a generic grading scheme was used. Adverse events were categorized according to codes in the Medical Dictionary for Regulatory Activities (MedDRA®), version 23.1.

After day 28, grade 3 and 4 events were not collected. Thus, the composite safety outcome through day 90 includes deaths, SAEs, end organ dysfunction, and serious infection. Other safety outcomes included in the protocol and the data analysis plan were:

- Deaths through day 90; and

- A composite of SAEs, including the protocol-specified exempt events, or death through day 90.

In our earlier report (13), we speculated that one possibility why bamlanivimab failed the futility assessment is that harmful effects may have occurred such as antibody exaggerated inflammation. To address this, stored samples were used to measure plasma levels of interleukin-6 (IL-6), serum levels of C-reactive protein (CRP), and plasma levels of D-dimer.

Laboratory Methods

Laboratory specimens were collected for consenting participants and stored by clinical sites and periodically sent to a central biorepository, Advanced BioMedical Laboratories (ABML), for use in future research.

A nasal mid-turbinate swab was collected at baseline. Swabs were immediately placed into tubes containing 3 mL of sterile Universal Transport Medium (UTM). Samples were aliquoted into 3 cryovials, frozen, and shipped on a regular basis to ABML

Four 1.0 mL aliquots or serum and four 1 mL aliquots of plasma were collected at baseline, and on follow-up days 1, 3, 5, 28 and 90. Two 9mL tubes, one SST and one EDTA of blood was drawn to obtain the 8 aliquots.

SARS-CoV-2 RNA load

SARS-CoV-2 RNA load in the nasal swab material was determined using extraction, master mix preparation, and RT-PCR as described in the CDC 2019-Novel Coronavirus (2019-nCoV) Real-Time RT-PCR Diagnostic Panel. The lower limit of quantification (LLoQ) for this measurement is 399 copies/mL.

Viral RNA measurements were centrally determined by ABML.

SARS-CoV-2 Lineages and Variants

The nasal swab material was also used to determine viral lineages and variants. cDNA and amplicons were prepared as described in the ARTIC protocol (34). Qualitative Assessment of the amplicon was also performed by Bioanalyzer DNA 1000 Chip (Agilent, Santa Clara, CA). Library preparation and sequencing was carried out at the National Human Genome Research Institute. The Cecret pipeline (https://github.com/UPHL-BioNGS/Cecret) was adopted as our sequencing analysis workflow backbone with some modification and addition of new components. Sequence reads in FASTQ format were quality assessed using FastQC (v0.11.9) (35) with a minimum frequency threshold of 0.6 and a minimum depth of 10 reads. They were then adapter and quality trimmed with SeqyClean (v1.10.09) (36). Trimmed reads were aligned to the SARS-Cov2 reference (Genbank accession MN908947.3) using BWA (v0.7.17-r1188) (37) and primer sequences were masked and consensus sequences called using iVar (v1.3.1) (38). SARS-CoV-2 Nextstrain clade assignments and variants were determined by Nextclade (v0.14.0) (39) based on the consensus sequences. PANGO lineages were assigned by pangolin (v2.3.3) (40). Multiple sequence alignment of the consensus sequences was performed using MAFFT (v7.475) and a phylogenetic tree produced from the alignment with IQ-TREE (v1.6.7) and plotted with iTOL (v6; https://itol.embl.de/).

Antibody Levels

Stored plasma specimens were used to measure total anti-SARS-CoV-2 antibody levels. Antibody levels were determined using the BioRad Platelia SARS-CoV-2 Total Ab assay (BioRad, Hercules, California) (anti-N antibodies). Results of this assay are reported as "specimen ratios". Specimen ratios are defined as the specimen optical density (OD) divided by the OD of the control R4(OD_MR4). Specimen ratios ≥ 1.0 are considered positive, those between 0.8 and 1.0 equivocal, and those < 0.8 negative. In this report, we refer to those with levels < 1.0 specimen ratios as having "negative" anti-N Abs and those with specimen ratios ≥ 1.0 as having positive anti-N Abs.

Levels of neutralizing antibodies (nAbs) directed against the SARS-CoV-2 receptor binding domain (RBD) were determined using the GenScript SARS-CoV-2 Surrogate Virus Neutralization Test (sVNT) assay (GenScript, Piscataway, NJ) (nAbs). nAbs are expressed as percent binding inhibition; levels ≥ 30% are considered positive for nAbs as recommended by the manufacturer, and those < 30% are considered negative for nAbs.

Both antibody determinations were made centrally at the Frederick National Laboratory, blinded to treatment group.

Antigen Levels

SARS-CoV-2 nucleocapsid antigen levels were determined in 90 µL plasma in duplicate using a Quanterix assay (Quanterix, Billerica, MA). The lower level of quantification was determined to be 3 ng/L. Results below that level are imputed as 2.9 ng/L. The antigen determinations were made centrally at the Frederick National Laboratory, blinded to treatment group.

Interleukin-6, C-Reactive Protein and D-dimer

Plasma levels of interleukin-6 (IL-6) and serum levels of C-reactive protein (CRP) were measured using electrochemilumiescence (Meso Scale Discovery, Gaithersburg, MD) at baseline and at days 1, 3, and 5. D-dimer was measured by an enzyme-linked fluorescent assay on a VIDAS instrument (BioMerieux, Durham, NC). Upper limits of normal for IL-6, CRP, and D-dimer are 2 ng/L, 10 mg/L, and 0.5 mg/L, respectively.

Pre-Specified Hypotheses Based on Antibody and Viral Levels

Prior to unblinding the 90-day follow-up results for bamlanivimab, a supplemental analysis plan was developed for the centrally measured antibody, antigen, and viral RNA levels.
As part of that plan two subgroup hypotheses were stated:

1) Patients with negative or low positive neutralizing antibody levels at entry (GenScript) will benefit more from the investigational agent compared to placebo than patients with high antibody levels. Furthermore, those with low neutralizing antibody levels AND with high antigen levels, will benefit more from the investigational agent compared to placebo than other subgroups categorized by both antibody and antigen levels.
2) Patients with lower neutralizing antibody levels at entry (Genscript) AND with high levels of RNA in nasal turbinates will benefit more from the investigational agent compared to placebo than other subgroups categorized by both antibody and RNA levels.

While the primary hypotheses consider the neutralizing antibody levels (nAbs; Genscript), similar pre-specified analyses were stated for the total antibody levels (BioRad).

In addition to the primary endpoint, subgroup analyses are also carried out for the composite safety outcomes, for mortality, and for the day 5 ordinal pulmonary outcome.

This supplemental analysis plan which was prepared on 14 April 2021 is included as a separate appendix. The motivation for the two hypotheses is briefly stated on page 4 of the supplemental statistical analysis plan. There was a growing body of evidence since bamlanivimab failed the futility assessment that indicated that SARS-CoV-2 antibodies could alter pathogenesis when given early before an immune response to the infection had been initiated. The two hypotheses were based on this evidence and biological reasoning.

Both versions 1.0 (27 July 2020) and 2.0 (20 November 2020) of the TICO master protocol state that subgroups defined by SARS-CoV-2 neutralizing antibody level and by upper respiratory SARS-CoV-2 viral load will be carried out using stored specimens. Neither protocol provides details of the analysis or a specific hypothesis.

When we wrote the TICO master protocol there was no evidence overall or for subgroups on benefit and risks of monoclonal antibody treatment. Trials in hospitalized patients and outpatients were just beginning. Our trial of bamlanivimab was the first trial of a monoclonal antibody among hospitalized patients. The trial failed futility in October 2020 based on the overall results that considered a day 5 ordinal outcome. At that time none of the stored specimens had been analysed for baseline antibody, antigen or viral RNA levels.

Laboratory capabilities for central measurement of antibody and antinge levels became available in 2021.
By that time, outpatient trials of monoclonal antibody indicated clinical benefit in early disease and one of the outpatient trials had reported differential benefit according to antibody sero-status (3). Based on this information we developed the two hypotheses and prepared a plan for the analysis of the data in our final report of the bamlanivimab trial which was planned to include the complete 90 days of follow-up for all participants which occurred at the end of January 2021.

Sample Size to Assess Primary Endpoint
For the primary endpoint of sustained recovery we estimated that 843 primary events would be accrued if 1,000 patients were followed for 90 days; 843 primary events provides 90% power at the 0.025 (1-sided) level of significance to detect a sustained recovery rate ratio (RRR) (investigational agent/placebo) of 1.25

Early Termination Based on Futility
As previously reported, the TICO bamlanivimab trial was stopped for futility on October 26, 2020 (13). This was based on a planned interim analysis by the independent Data and Safety Monitoring Board

(DSMB). Futility was assessed based on the day 5 ordinal outcomes. The review on October 26 followed a review on October 13, 2020 that led the DSMB to recommend that enrollment be paused due to a possible safety problem. The October 26 futility assessment ensured that all randomzied participants had completed at least 5 days of follow-up. Following the recommendation to stop the study for futility, all participants were followed for at least 90 days, the planned duration of follow-up.

Statistical Methods

As previously described, following the DSMB recommendation on October 26, 2020 that no further participants be randomized based on a planned futility assessment that was pre-specified in the protocol, an analysis data set that administratively censored follow-up data on October 26, 2020 was locked in order to prepare a preliminary report (13). The median follow-up at the time of the preliminary report was 31 days.

Data collected after October 26, 2020 remained blinded to investigators until all participants completed the planned 90 days of follow-up. The statistical analysis plan for primary and secondary endpoints and for early futility analyses using the day 5 ordinal outcomes are included in the appendix of our earlier report (13).

Following unblinding of the day 90 clinical data, stored specimen analyses were planned as described in Methods of this supplement. After preliminary baseline levels of antibody and antigen data were generated (samples were analyzed in batches), a supplementary analysis plan was developed before carrying out the planned subgroup analyses by antibody level, antigen level, and viral RNA level.

A proportional odds model was used to summarize the 7-category ordinal outcome assessed at Day 5; this intermediate outcome was for assessing futility (see Figure S1) (13).

In addition, to summarizing antibody levels (nAb and anti-N Ab) as percentage positive during follow-up, box plots of levels reported, including those negative or indeterminate, are given and treatment differences at each time-point are summarized using analysis of covariance with the baseline antibody level as a covariate. Antigen levels are summarized with similar methods.

Treatment comparisons of the percentage of participants with antigen levels < 3 ng/L at each follow-up visit through day 5 are summarized. In addition, the percentage with antigen levels < 1000 ng/L (approximate median at baseline) and differences in $\log_{10}$ antigen levels are summarized. Logistic regression models with $\log_{10}$ antigen levels as a covariate are used to summarize the treatment differences for antigen levels < 3 and <1000 ng/L, and odds ratios (ORs) and 95% CIs are cited. Analysis of covariance with $\log_{10}$ antigen levels at baseline as a covariate is used to compare treatment differences in $\log_{10}$ antigen levels during follow-up.

Composite safety outcomes through day 28 and day 90 and mortality through day 90 are summarized using time-to-event methods, Kaplan-Meier curves and proportional hazards regression. Hazard ratios (HRs) and 95% confidence intervals (CIs) are cited. For completeness other safety outcomes, infusion reactions and day 5 composite safety outcomes are also cited. The percentage with these outcomes in each treatment group are compared using logistic regression models and ORs are cited.

The protocol listed 15 baseline-defined subgroups to be carried outanalyses for the primary endpoint of sustained recovery. In this report, we summarize sustained recovery, the day 90 composite safety outcome, and mortality through 90 days for nAb subgroups in the main report. Subgroups based on other baseline data for sustained recovery are given in the supplemental appendix; nAb and antigen/viral RNA measurements at entry are also givenfor the day 5 pulmonay ordinal outcome in the supplemental appendix. Heterogeneity of the treatment effect across subgroups was assessed by including interaction terms between treatment group and baseline subgroups in Fine-Gray, logistic or proportional hazards regression models for these outcomes.

Section 3: Results

This section briefly summarizes tables and figures included in this supplement. The tables and figures are summarized in the order they are cited in the main paper,

Figure S1. A few updates to the day 5 ordinal pulmonary outcome were made since the preliminary report was published (13). These final data indicate that the odds of a more favorable outcome for bamlanivimab compared to placebo is 0.86 favoring placebo (95% CI: 0.57-1.30; p=0.48).

Figure S2. 314 of the 326 randomized participants (169 bamlanivimab, 157 placebo) were infused and followed through 90 days. Patients were enrolled between August 5 and October 13, 2020. Most patients who were not infused (8 of 12) were randomized on October 13, the date the DSMB recommended pausing enrollment. The clinical database for this trial was locked after all participants completed the day 90 visit.

Figures S3A and S3B. Sequences from 255 participants identified no concerning mutations in codons 417, 452 or 484 in the spike protein; virus from 6 participants had deletions in codon 69-70. Coverage of 75% or more of genome was achieved in 204 of 255 samples; the insert displays phylogeny (with indication of Pango Lineage and Nextstrain clade) with genome coverage color coded (red: < 75% and ≥ 50 (n=21, 30 samples with coverage <50% not included in the plot); green: >75% general and 100% of spike (n=152); blue and yellow: >75% general and less than 100% (yellow; n=21) or 100% (blue; n=31) for RBD within spike). Samples color-coded green and red are displayed to illustrate coverage below (bottom sample is reference).

Mutations compared with reference genomic sequence (NCBI Accession: MN908947.3) were called with a minimum frequency threshold of 0.6 and a minimum depth of 10 reads with iVar. The most frequently found Spike mutations included: D614G (222), K1045R (11), A222V (8), H69-V70 deletion (6), P681H (5), N439K (5), L5F (4), Q677H (4), A688V (4), G946V (4).

In RBD, the following additional mutations were found: N439K (5), S477N (4), R346K (2), P384L (1), T385I (1), T470N (1), N501Y (1), A522V (1).

Table S1-S3. Characteristics at entry are given by treatment group for the 314 participants who were infused and and comprise the primary analysis cohort (Table S1), for the 153 participants who were nAb negative at entry (Table S2), and for the 152 participants who were nAb positive at entry (Table S3). For 9 participants a plasma sample was not available for analysis of antibody and antigen levels.

Figures S4A-S4C. NAb levels measured with the GenScript assay were determined at baseline (day 0) and days 1, 3, and 5. The percentage nAb positive (with binding inhibition ≥ 30%) are given at each time point and comparisons are made between treatment groups.

Figures S4D-S4F. The percentage with antigen levels below the level of quantification (3 ng/L) are summarized by treatment group at baseline (day 0), and day 1, 3 and 5 of follow-up, overall and by nAb status.

Table S4. According to the supplementary analysis plan developed, antigen levels < 3 and < 1000 ng/L for the bamlanivimab and placebo groups were to be compared at day 5 using logistic regression with baseline log10 transformed antigen level as a covariate. These results are summarized in Table S4 and complement the analyses shown in Figure S4D. At day 5 the OR (bamlanivimab versus placebo) for antigen levels < 3 ng/mL is 1.40 (95% CI: 0.74-2.66; p=0.30). The OR for antigen levels < 1000 ng/L at day 5 is 1.24 (95% CI: 0.23-6.64; p=0.80). At no timepoint did these ORs differ significantly from 1.0.

Figure S5A-S5C. Boxplots of nAb levels are given overall (A) and according to nAb status at entry: (B) negative and (C) positive. These figures complement Figure 4A, 4B and 4C which gives the percentage positive (≥ 30% for binding inhibition). In Figure S5, higher levels for those in the bamlanivimab compared to the placebo group are evident at each follow-up visits, overall and for those nAb negative and positive at baseline.

Figure S6A-S6C. Antigen levels at baseline and days 1, 3, and 5 after $\log_{10}$ transformation are summarized overall (A) and according to nAb antibody status at entry: (B) negative and (C) positive in Figure S6. Figure S6 complements Figure 4D, 4E, and 4F. Antigen levels < 3 ng/L, the lower level of quantification, are imputed as 2.9 ng/L in these analyses. Antigen levels during follow-up, like the percentage < 3 ng/L, did not differ significantly between treatment groups, overall or according to nAb sero-positive status at baseline.

Figure S7A-S7C. Anti-N antibody levels with the BioRad assay were determined at baseline (day 0) and days 1, 3, and 5. Figure S7 gives the percentage positive (≥ 1.0 for the specimen ratio). The percentatge positive for anti-N antibodies did not differ significantly between treatment groups, overall or according to anti-N Ab sero-postive status at baseline.

Figure S8A-S8C. This figure complements Figure S7. Boxplots for anti-N levels during follow-up, like the percentage positive shown in Figure S7, did not differ significantly between treatment groups, overall or according to anti-N Ab status at baseline.

Figure S9. Baseline-defined subgroups that consider demographic and clinical factors which were pre-specified for the primary endpoint of sustained recovered are summarized in Figure S9. There was no evidence of heterogeneity among the sHRs for any of the subgroups considered in Figure S9.

Figure S10. In the supplementary analysis plan, methods for evaluating subgroups using baseline anti-N Abs instead of nAbs were also stated. Figure S10 summarizes these subgroups for the sustained recovery outcome in a similar manner to those presented in Figure 2 of the main paper. Like the finding for negative and positive nAbs in Figure 2, sHRs for sustained recovery were significantly greater, favoring bamlanivimab, for those with negative anti-N Abs (< 1.0 specimen ratios) (sHR=1.27) compared to those with positive anti-N Abs (≥ 1.0 specimen ratios) (sHR=0.81) (nominal p=0.05 for the difference in sHRs.

In addition, as hypothesized, among those with negative anti-N abs and with antigen levels ≥ 1000 ng/L or those with viral RNA levels ≥ 10,000 copies/mL and antigen levels ≥ 1000 ng/L had higher sHRs than the other 3 groups defined by anti-N Abs and viral levels. The 3 df interactions for these groups

gave nominal p-values for the heterogeneity of sHRs of 0.06 and 0.04, for antigen and viral RNA, respectively.

An analysis was also carried out classifying participants as having high viral levels by either antigen levels ≥ 1000 ng/L or viral RNA ≥ 10,000. Findings were similar and the interaction nominal p-value was 0.06.

Figure S11. Given the similar subgroup findings for nAbs and anti-N Abs, a subgroup analysis for sustained recovery was also carried out classifying participants as negative on both nAbs and anti-N Abs versus positive on either. The percentage of participants negative to both antibodies was 34%. This subgroup yielded a 1df interaction nominal p-value of 0.008 (sHR for those negative to both = 1.47 and sHR for those positive to either = 0.78).

sHRs for those with both antibodies negative and with high viral levels were 1.93, 2.01, and 1.60 for high viral levels defined by antigen, viral RNA and either, respectively. The 3 df interaction nominal p-values for the 4 groups considered in each of these analyses were 0.01, 0.004, and 0.03.

For comparison with other studies, we also estimated the sHR of sustained recovery in the placebo group according to antigen and viral RNA level at entry. These sHRs were estimated with no other covariates in the regression model. The sHR for those with antigen ≥ 1000 vs < 1000 ng/L was 0.44 (95% CI: 0.32 – 0.62); for those with viral RNA ≥ 10000 vs <10000 copies/mL, the sHR was 0.63 (95% CI: 0.45 – 0.87); and for those with either antigen ≥ 1000 ng/L or viral RNA ≥ 10000 copies/mL versus both lower, the sHR was 0.50 (95% CI: 0.35 to 0.72).

Figure S12. Figure S12 gives subgroup findings for the day 5 pulmonary ordinal outcome that parallel those for sustained recovery shown in Figure 2 of the main paper. Proportional ORs, adjusted for baseline pulmonary status, are shown; ORs greater than 1.0 favor the bamlanivimab group. ORs were 0.62 (95% CI: 0.34-1.11) for those nAb positive and 1.07 (95% CI: 0.60-1.92) for those nAb negative.

Table S5. Overall and subgroup analyses by nAb status at entry for the day 90 composite safety outcome and mortality are given in the main paper (Figure 3). Table S5 summarizes the overall results for each of the pre-specified safety outcomes. We previously reported the percentage of participants with infusion reactions and with the primary composite safety outcome considered for the early futility analysis of death, SAEs, or grade 3 or 4 adverse events by day 5. Since that report 2 additional events were reported in the bamlanivimab group and the OR (bamlanivimab/placebo) is 1.66 (95% CI: 0.87-3.16). The previously reported OR was 1.56.

When this composite outcome at day 5 is expanded to include organ failure events and serious infections, serious events that according to protocol were exempt from SAE reporting unless they were considered related to treatment, the OR was 1.83 (95% CI: 1.01-3.29).

Point estimates for all of the pre-specified outcomes exceeded 1.0.

Table S6. Safety outcomes given in Table S5 are summarized by nAb status at baseline in Table S6. With the exception of the composite outcome at day 90 and mortality each of the ORs or HRs for

bamlanivimab versus placebo was greater 1.0 for both subgroups and there was no evidence of an interaction. The day 90 composite outcome and mortality are discussed in the main paper.

Table S7. The components of the day 90 safety outcome are summarized in Table S7, overall and by nAb status at entry. For each component among those with negative nAbs, HRs were less than 1.0 favoring bamlanivimab; for those with positive nAbs at entry, each HR was > 1.0. Organ failure was the most frequently occuring component of the composite outcomes and most of these events were categorized as respiratory failure events. Respiratory failure was defined as the receipt of high-flow nasal oxygen, non-invasive ventilation, invasive mechanical ventilation, or ECMO.

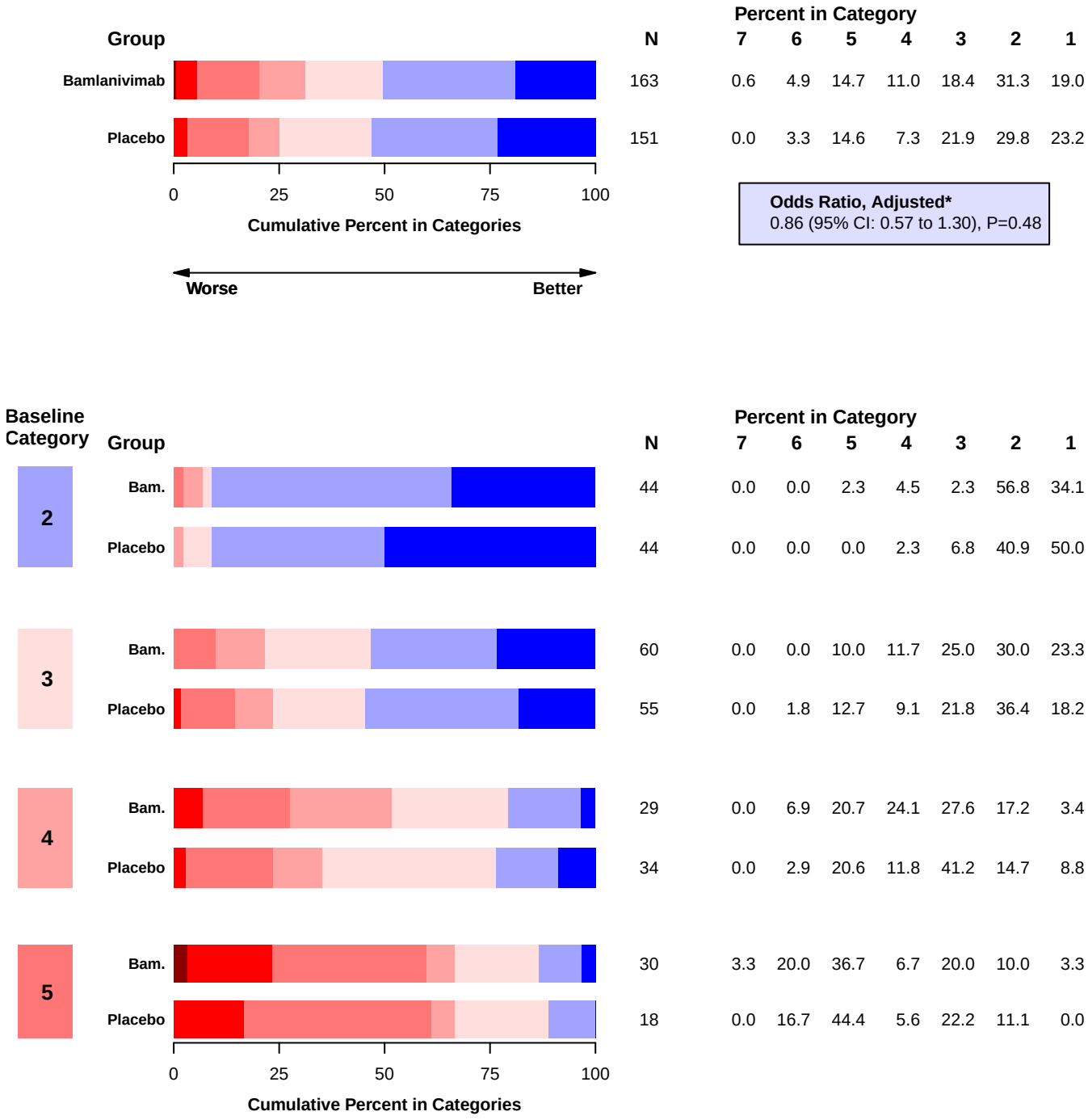
Figure S13A-S13F. Boxplots for $\log_2$ transformed IL-6 (A-C) and CRP (D-F) are shown in Figure S13. Both inflammatory markers declined over follow-up. Overall, median levels of IL-6 on the untransformed scale (data not shown) declined from 7.6 at baseline to 5.0 ng/L at Day 5 for bamlanivimab and from 5.7 to 3.6 ng/L for placebo. Median CRP declined from 153 to 38 mg/L for bamlanivimab and from 130 to 24 mg/L for placebo. Levels of these biomarkers did not differ significantly from one another at any follow-up visit either overall or by nAb subgroup.

Figure S14A-14C. Boxplots for $\log_2$ transformed D-dimer are given in Figure S14. D-dimer did not decline from baseline to day 5. At no time-point did levels differ between treatments, overall (A) or in the subgroups defined by nAb status at entry (B and C).

Section 4: Tables and Figures

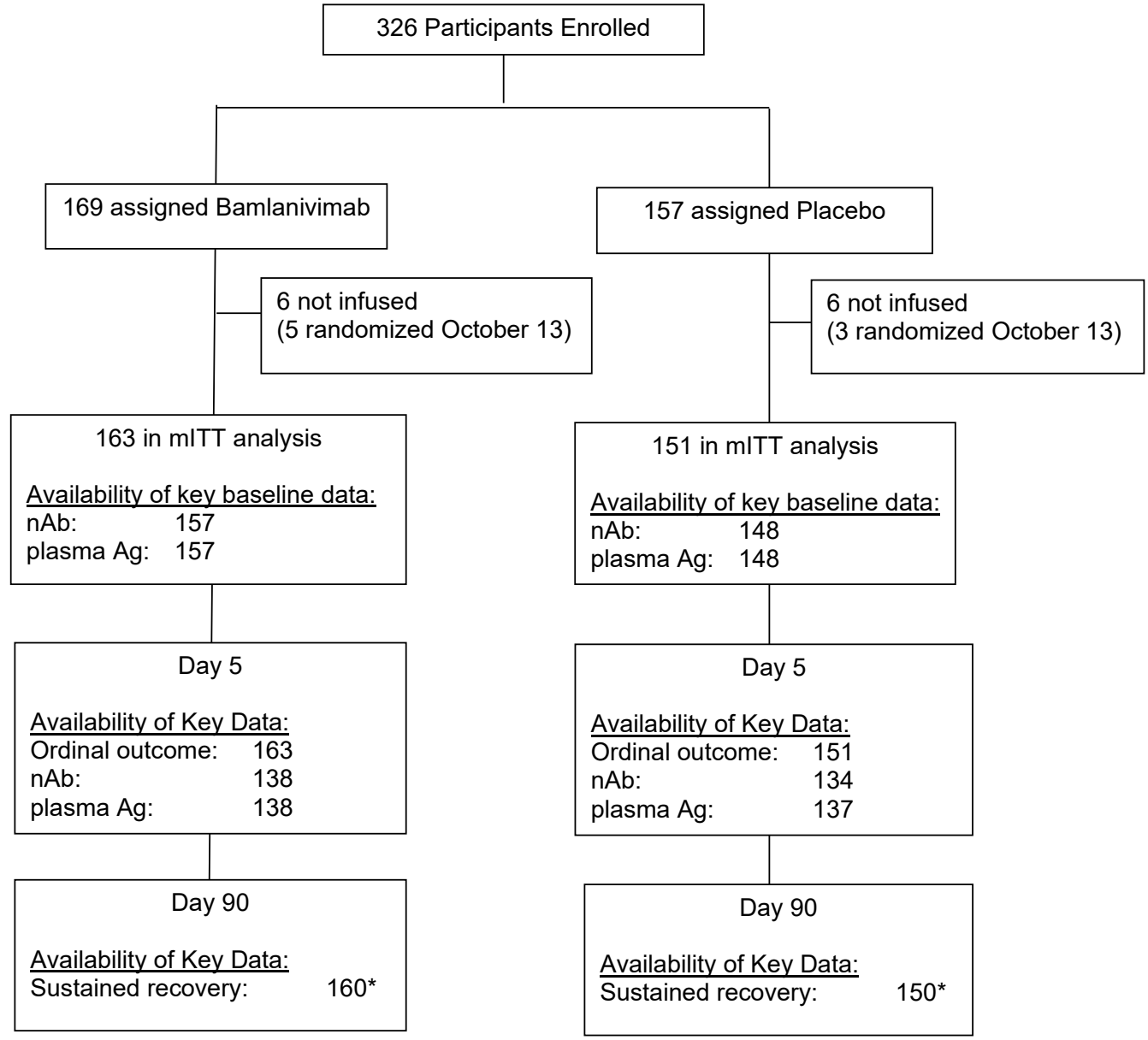
Contents

Figure S1: Pulmonary Outcome on Day 5



* OR of being in a better category with Bamlanivimab vs. placebo, estimated in a proportional odds model adjusted for baseline category and for study site pharmacy.

Figure S2: Consort Diagram



* Three participants in the Bamlanivimab group had followup for events censored at day 7, 16 and 76. One participant in the Placebo group has followup for events censored at day 79.

Figure S3: Viral Sequencing Summary, Panel A

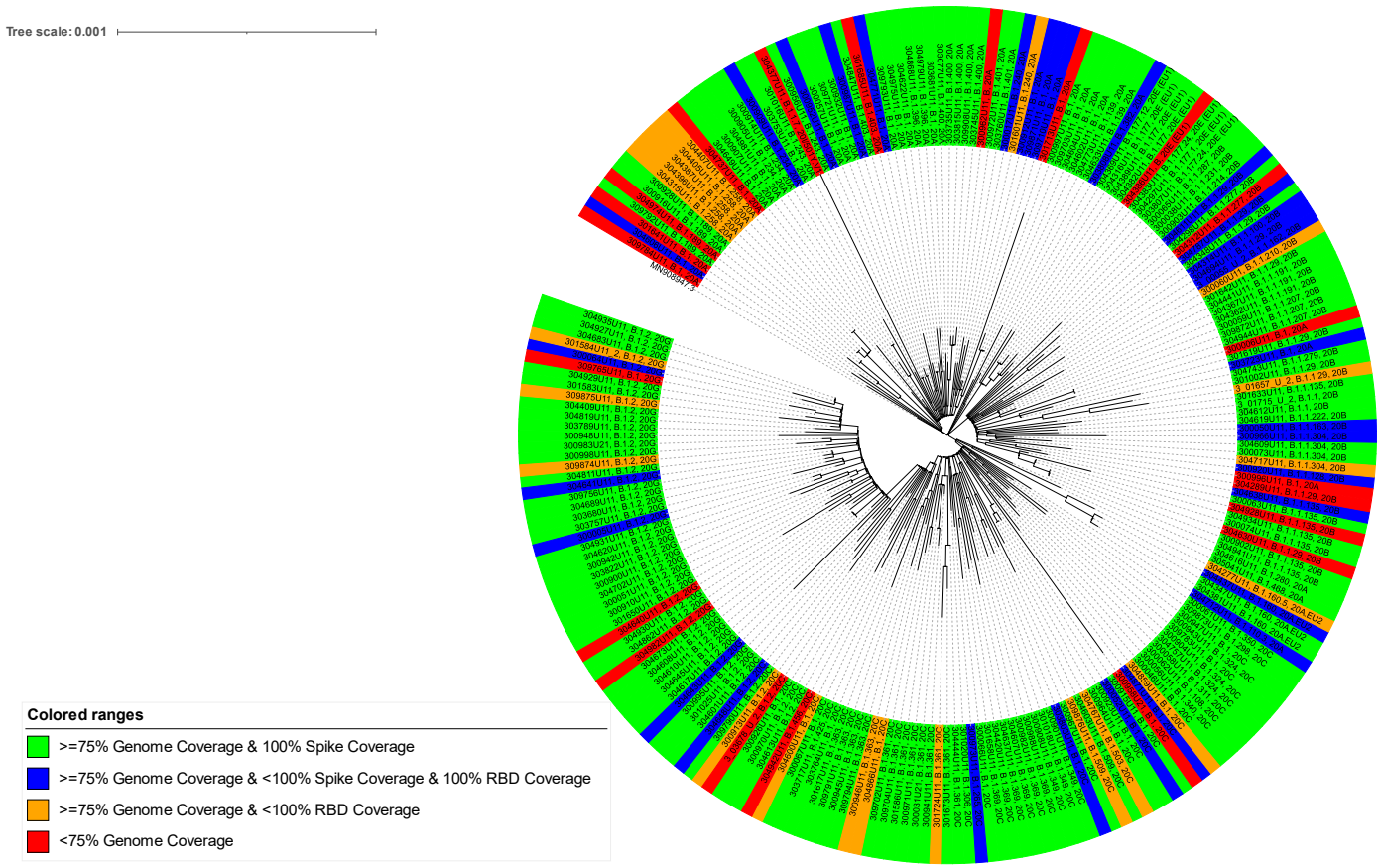


Figure S3: Viral Sequencing Summary, Panels B-E

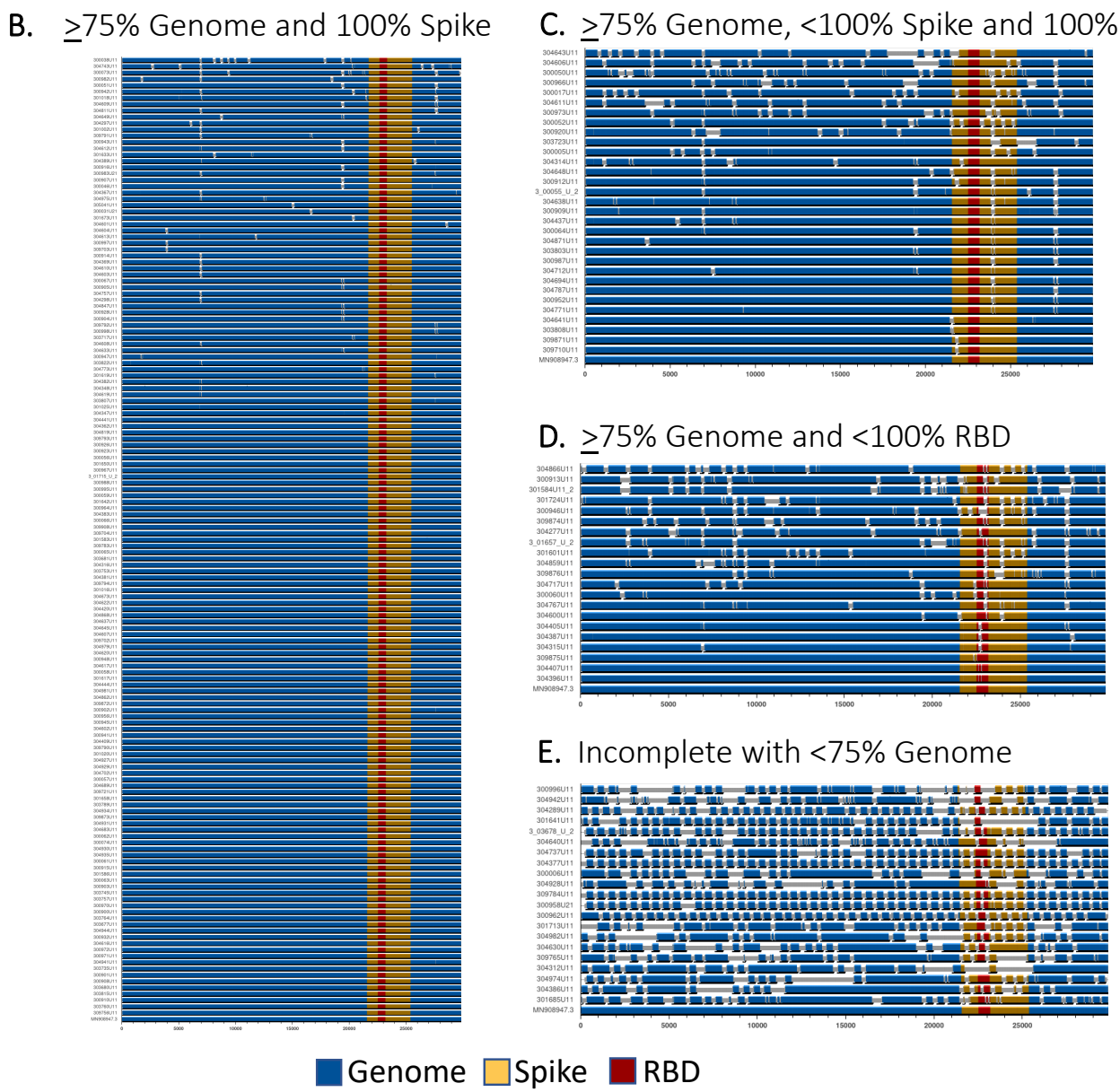


Table S1: Baseline Characteristics by Treatment Group - All Participants

		Bamlanivimab (n=163)	Placebo (n=151)
Age	Median (IQR) - yr	63 (50, 72)	59 (48, 71)
Female gender	No. (%)	66 (40%)	71 (47%)
Non-white race	No. (%)	87 (53%)	80 (53%)
History of:	No. (%)		
Hypertension requiring medication		84 (52%)	74 (49%)
Diabetes requiring medication		54 (33%)	36 (24%)
Renal impairment		24 (15%)	9 (6%)
Asthma and/or COPD		23 (14%)	22 (15%)
At least one co-morbidity		117 (72%)	100 (66%)
Days since symptom onset	Median (IQR)	7 (5, 9)	8 (5, 9)
Oxygen Requirement	No. (%)		
Not receiving supplemental oxygen		44 (27%)	42 (28%)
Supplemental oxygen < 4 L/min*		60 (37%)	56 (37%)
Supplemental oxygen ≥ 4 L/min*		29 (18%)	35 (23%)
Non-invasive ventilation or HFNC		30 (18%)	18 (12%)
Invasive ventilation or ECMO		0 (0%)	0 (0%)
Laboratory assessments			
Plasma nucleocapside antigen	Median ng/L	1240 (141, 3578)	856 (138, 3400)
≥ 3 ng/L (positive)	No. (%)	148 (94%)	142 (96%)
Nasal swab fluid viral RNA load	Mean±SD $\log_{10}$	4.59 ± 1.60	4.46 ± 1.63
<1000 copies	No. (%)	27 (22%)	27 (22%)
Anti-N antibody positive	No. (%)	93 (59%)	87 (59%)
Interleukin-6	Median (IQR) - ng/L	7.6 (3.2, 16.2)	5.7 (2.4, 14.8)
D-dimer	Median (IQR) - mg/L	0.95 (0.64, 1.38)	0.86 (0.62, 1.38)
C-reative protein	Median (IQR) - mg/L	49 (28, 88)	44 (22, 77)
B-Lymphocytes	Median (IQR) - 10^9	0.80 (0.56, 1.07)	0.81 (0.55, 1.31)

Table S2: Baseline Characteristics by Treatment Group - nAb Negative

		Bamlanivimab (n=74)	Placebo (n=79)
Age	Median (IQR) - yr	66 (51, 72)	63 (50, 75)
Female gender	No. (%)	30 (41%)	39 (49%)
Non-white race	No. (%)	36 (49%)	41 (52%)
History of:	No. (%)		
Hypertension requiring medication		41 (55%)	42 (53%)
Diabetes requiring medication		26 (35%)	17 (22%)
Renal impairment		16 (22%)	6 (8%)
Asthma and/or COPD		12 (16%)	11 (14%)
At least one co-morbidity		54 (73%)	55 (70%)
Days since symptom onset	Median (IQR)	6 (4, 8)	7 (4, 9)
Oxygen Requirement	No. (%)		
Not receiving supplemental oxygen		29 (39%)	25 (32%)
Supplemental oxygen < 4 L/min*		24 (32%)	28 (35%)
Supplemental oxygen ≥ 4 L/min*		11 (15%)	17 (22%)
Non-invasive ventilation or HFNC		10 (14%)	9 (11%)
Invasive ventilation or ECMO		0 (0%)	0 (0%)
Laboratory assessments			
Plasma nucleocapside antigen	Median ng/L	2473 (957, 5372)	1740 (614, 4940)
≥ 3 ng/L (positive)	No. (%)	74 (100%)	78 (99%)
Nasal swab fluid viral RNA load	Mean±SD $\log_{10}$	5.00 ± 1.52	4.65 ± 1.76
<1000 copies	No. (%)	10 (15%)	14 (20%)
Anti-N antibody positive	No. (%)	22 (30%)	27 (34%)
Interleukin-6	Median (IQR) - ng/L	8.4 (4.3, 17.2)	6.2 (2.9, 14.0)
D-dimer	Median (IQR) - mg/L	0.92 (0.61, 1.42)	0.82 (0.55, 1.28)
C-reative protein	Median (IQR) - mg/L	40 (22, 82)	38 (17, 61)
B-Lymphocytes	Median (IQR) - 10^9	0.77 (0.55, 0.99)	0.77 (0.51, 1.24)

Table S3: Baseline Characteristics by Treatment Group - nAb Positive

		Bamlanivimab (n=83)	Placebo (n=69)
Age	Median (IQR) - yr	59 (48, 70)	57 (45, 65)
Female gender	No. (%)	34 (41%)	30 (43%)
Non-white race	No. (%)	48 (58%)	37 (54%)
History of:	No. (%)		
Hypertension requiring medication		39 (47%)	31 (45%)
Diabetes requiring medication		26 (31%)	18 (26%)
Renal impairment		6 (7%)	3 (4%)
Asthma and/or COPD		11 (13%)	10 (14%)
At least one co-morbidity		57 (69%)	44 (64%)
Days since symptom onset	Median (IQR)	8 (5, 10)	8 (6, 9)
Oxygen Requirement	No. (%)		
Not receiving supplemental oxygen		13 (16%)	17 (25%)
Supplemental oxygen < 4 L/min*		35 (42%)	26 (38%)
Supplemental oxygen ≥ 4 L/min*		18 (22%)	18 (26%)
Non-invasive ventilation or HFNC		17 (20%)	8 (12%)
Invasive ventilation or ECMO		0 (0%)	0 (0%)
Laboratory assessments			
Plasma nucleocapside antigen	Median ng/L	300 (37, 2461)	294 (37, 1193)
≥ 3 ng/L (positive)	No. (%)	74 (89%)	64 (93%)
Nasal swab fluid viral RNA load	Mean±SD $\log_{10}$	4.09 ± 1.56	4.21 ± 1.40
<1000 copies	No. (%)	17 (31%)	13 (25%)
Anti-N antibody positive	No. (%)	71 (86%)	60 (87%)
Interleukin-6	Median (IQR) - ng/L	6.0 (3.0, 15.4)	4.4 (1.9, 15.0)
D-dimer	Median (IQR) - mg/L	0.97 (0.72, 1.36)	0.98 (0.71, 1.42)
C-reative protein	Median (IQR) - mg/L	50 (32, 89)	57 (27, 88)
B-Lymphocytes	Median (IQR) - 10^9	0.82 (0.56, 1.10)	0.88 (0.56, 1.34)

Figure S4: Percent nAb Positive and Antigen Negative Over Time by Baseline nAb Status

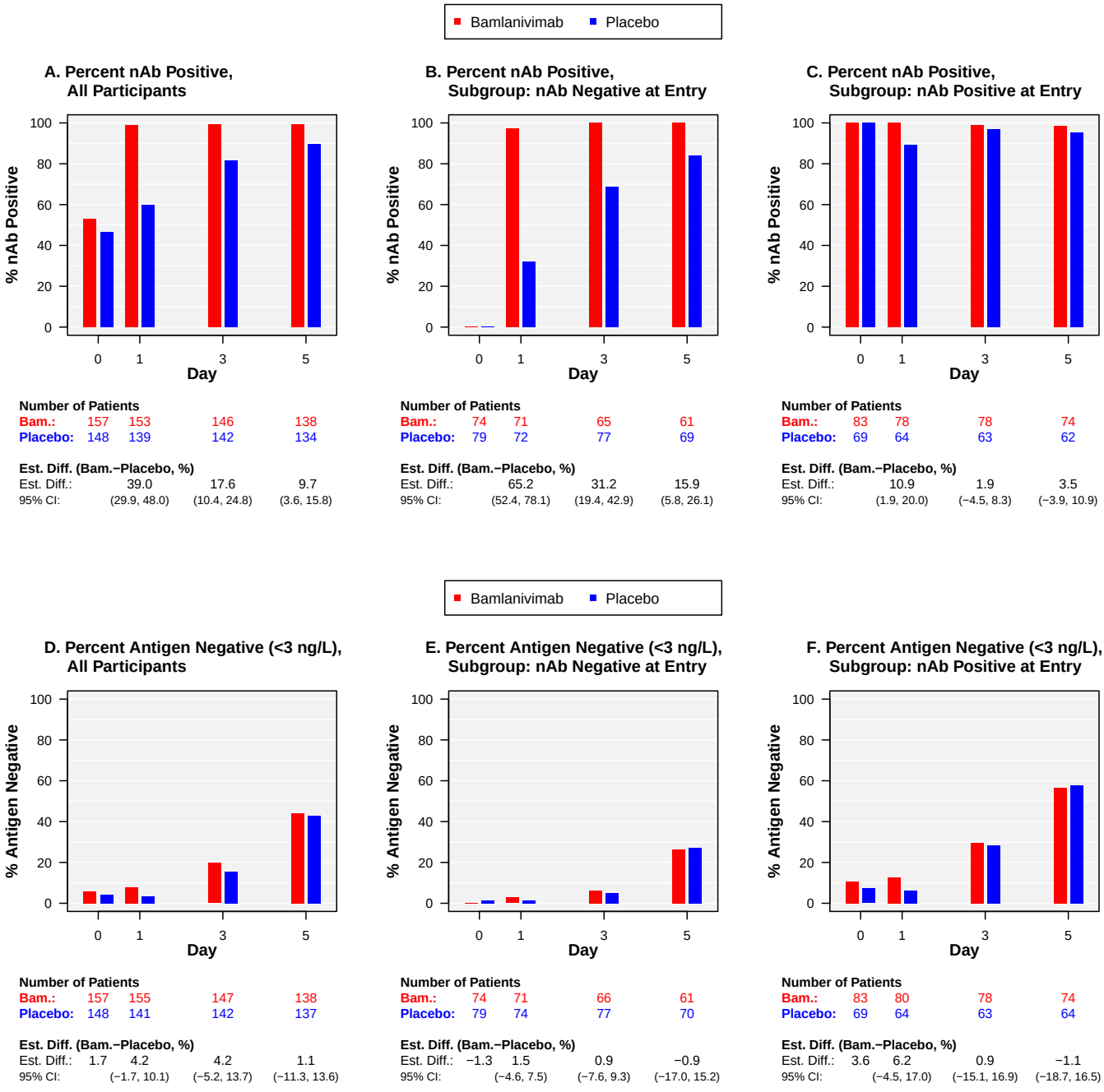


Table S4: Antigen Levels Below Selected Cutoffs by Study Day and Treatment Group

Antigen Levels Below the Level of Quantification*

	Banlanivimab			Placebo			Treatment Difference†		
Visit	N Pts	N	%	N Pts	N	%	OR	95% CI	P-value
Day 0	157	9	5.7	148	6	4.1			
Day 1	155	12	7.7	141	5	3.5	3.50	0.96, 12.76	0.06
Day 3	147	29	19.7	142	22	15.5	1.46	0.64, 3.30	0.37
Day 5	138	61	44.2	137	59	43.1	1.40	0.74, 2.66	0.30

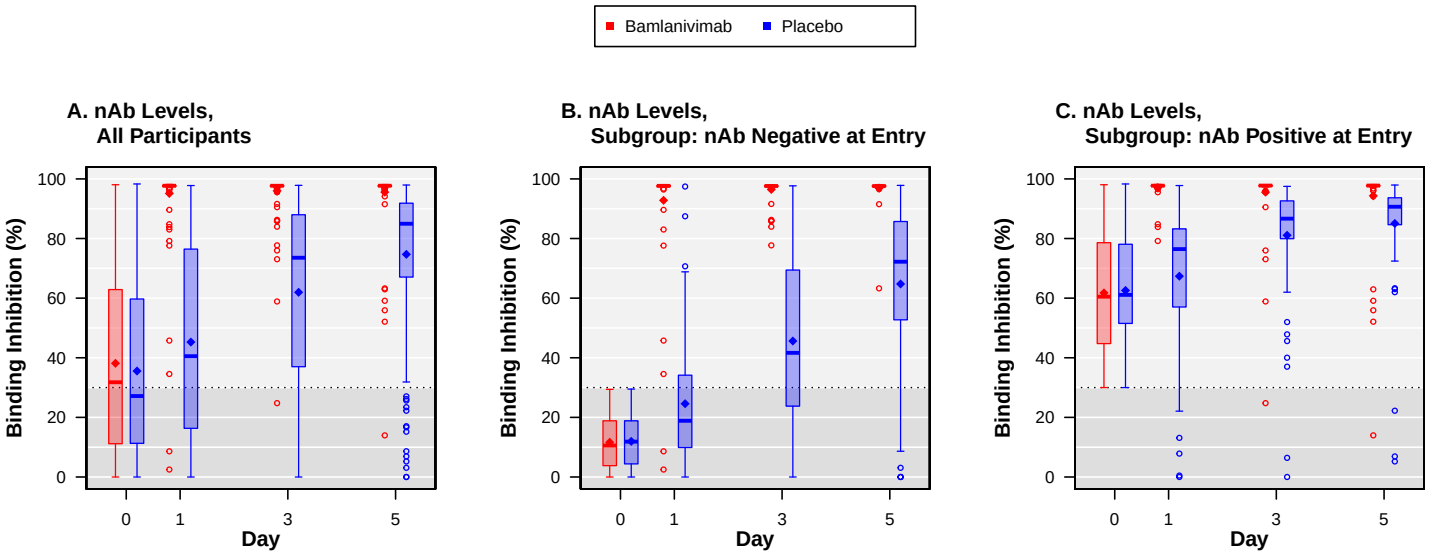
Antigen Levels < 1000 ng/L

	Banlanivimab			Placebo			Treatment Difference†		
Visit	N Pts	N	%	N Pts	N	%	OR	95% CI	P-value
Day 0	157	71	45.2	148	81	54.7			
Day 1	155	86	55.5	141	86	61.0	1.07	0.52, 2.21	0.85
Day 3	147	137	93.2	142	132	93.0	1.05	0.37, 2.94	0.93
Day 5	138	135	97.8	137	134	97.8	1.24	0.23, 6.64	0.80

* LOQ = 3.0 by Quanterix plasma antigen assay

† Odds ratio from logistic model with adjustment for baseline $\log_{10}$ antigen levels.

Figure S5: nAb Levels by Over Time by Baseline nAb Status



Number of Patients

	Day 0	Day 1	Day 3	Day 5
Bam.:	157	153	146	138
Placebo:	148	139	142	134

Est. Mean Diff. (Bam.−Placebo)

	Day 1	Day 3	Day 5
Est. Diff.:	50	33	21
95% CI:	(45, 54)	(28, 37)	(16, 25)
P−value:	<0.001	<0.001	<0.001

Number of Patients

	Day 0	Day 1	Day 3	Day 5
Bam.:	74	71	65	61
Placebo:	79	72	77	69

Est. Mean Diff. (Bam.−Placebo)

	Day 1	Day 3	Day 5
Est. Diff.:	68	51	32
95% CI:	(62, 75)	(44, 58)	(25, 39)
P−value:	<0.001	<0.001	<0.001

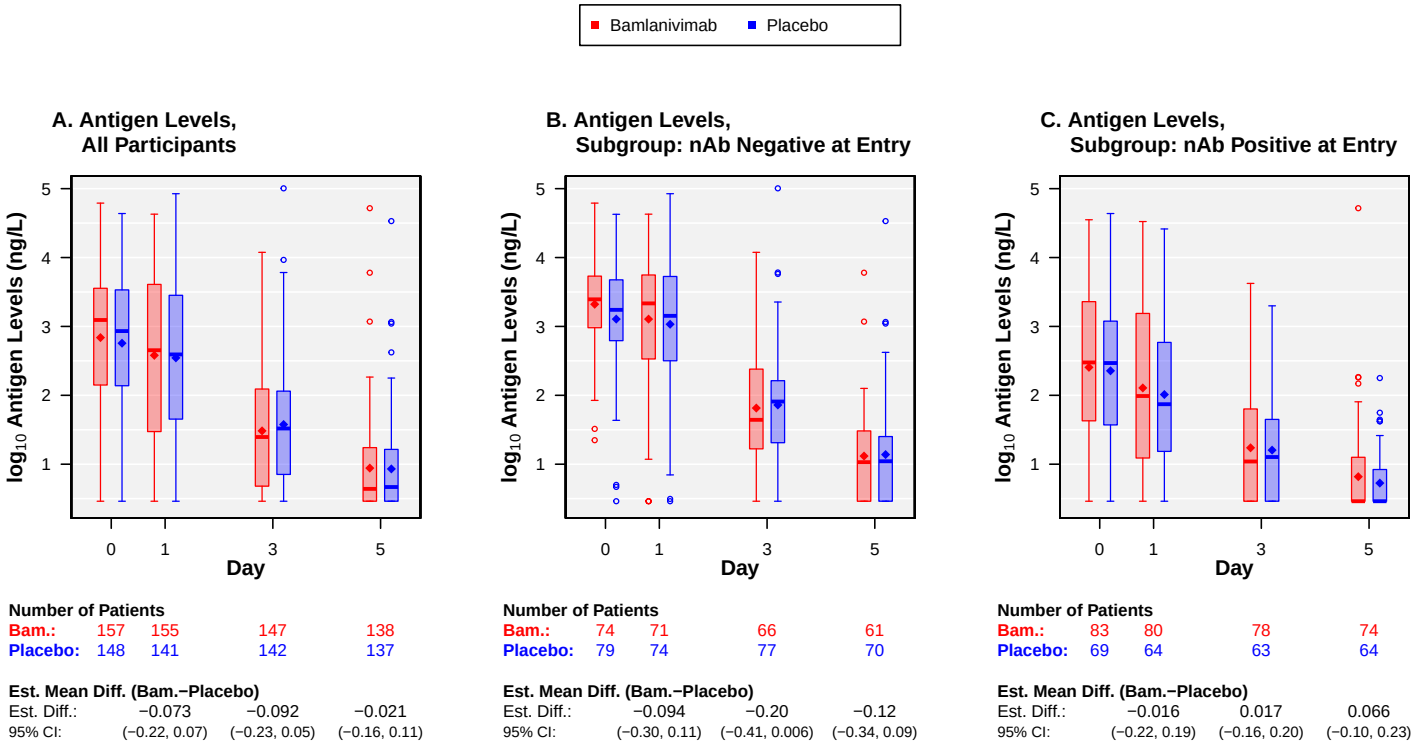
Number of Patients

	Day 0	Day 1	Day 3	Day 5
Bam.:	83	78	78	74
Placebo:	69	64	63	62

Est. Mean Diff. (Bam.−Placebo)

	Day 1	Day 3	Day 5
Est. Diff.:	30	14	9
95% CI:	(25, 36)	(10, 19)	(4, 15)
P−value:	<0.001	<0.001	<0.001

Figure S6: Antigen Levels Over Time by Baseline nAb Status



A. Antigen Levels, All Participants

Number of Patients				
Bam.:	157	155	147	138
Placebo:	148	141	142	137

Est. Mean Diff. (Bam.−Placebo)			
Est. Diff.:	−0.073	−0.092	−0.021
95% CI:	(−0.22, 0.07)	(−0.23, 0.05)	(−0.16, 0.11)

B. Antigen Levels, Subgroup: nAb Negative at Entry

Number of Patients				
Bam.:	74	71	66	61
Placebo:	79	74	77	70

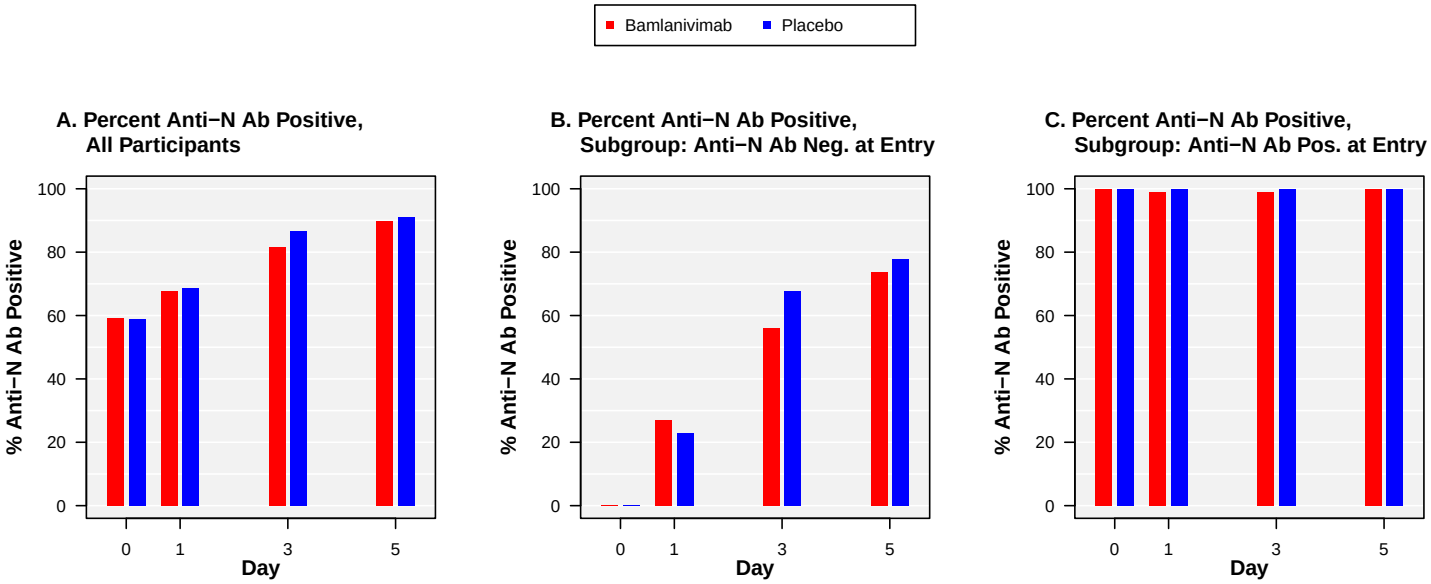
Est. Mean Diff. (Bam.−Placebo)			
Est. Diff.:	−0.094	−0.20	−0.12
95% CI:	(−0.30, 0.11)	(−0.41, 0.006)	(−0.34, 0.09)

C. Antigen Levels, Subgroup: nAb Positive at Entry

Number of Patients				
Bam.:	83	80	78	74
Placebo:	69	64	63	64

Est. Mean Diff. (Bam.−Placebo)			
Est. Diff.:	−0.016	0.017	0.066
95% CI:	(−0.22, 0.19)	(−0.16, 0.20)	(−0.10, 0.23)

Figure S7: Percent of Participants Positive for Anti-N Antibodies Over Time by Baseline Anti-N Status

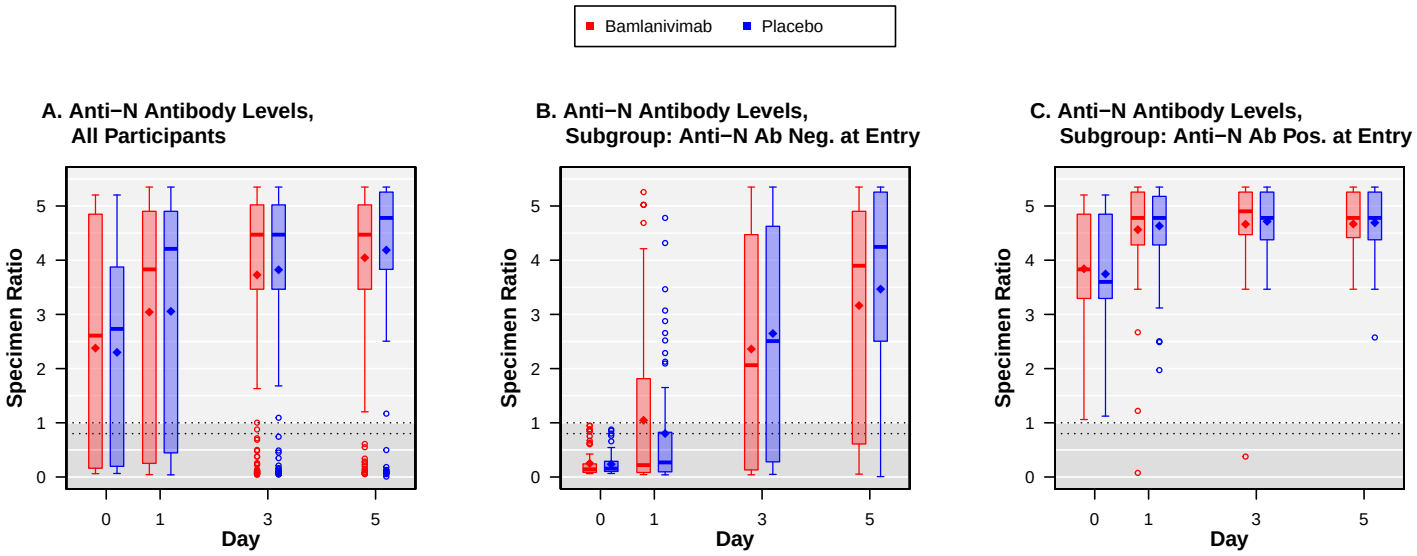


A. Percent Anti−N Ab Positive, All Participants				
Number of Patients				
Bam.:	157	155	147	138
Placebo:	148	140	141	136
Est. Diff. (Bam.−Placebo, %)				
Est. Diff.:		−0.8	−4.9	−1.3
95% CI:		(−12.2, 10.5)	(−14.0, 4.2)	(−9.0, 6.3)

B. Percent Anti−N Ab Positive, Subgroup: Anti−N Ab Neg. at Entry				
Number of Patients				
Bam.:	64	63	57	53
Placebo:	61	57	59	54
Est. Diff. (Bam.−Placebo, %)				
Est. Diff.:		4.2	−11.7	−4.2
95% CI:		(−12.9, 21.3)	(−30.9, 7.6)	(−22.3, 13.9)

C. Percent Anti−N Ab Positive, Subgroup: Anti−N Ab Pos. at Entry				
Number of Patients				
Bam.:	93	88	87	82
Placebo:	87	80	80	79
Est. Diff. (Bam.−Placebo, %)				
Est. Diff.:		−1.1	−1.1	0.0
95% CI:		(−4.5, 2.2)	(−4.5, 2.2)	.

Figure S8: Anti-N Antibody Levels Over Time by Baseline Anti-N Status



A. Anti−N Antibody Levels, All Participants

Number of Patients				
Bam.:	157	155	147	138
Placebo:	148	140	141	136

Est. Mean Diff. (Bam.−Placebo)			
Est. Diff.:	−0.007	−0.19	−0.14
95% CI:	(−0.30, 0.28)	(−0.53, 0.16)	(−0.47, 0.19)
P−value:	0.96	0.29	0.41

B. Anti−N Antibody Levels, Subgroup: Anti−N Ab Neg. at Entry

Number of Patients				
Bam.:	64	63	57	53
Placebo:	61	57	59	54

Est. Mean Diff. (Bam.−Placebo)			
Est. Diff.:	0.18	−0.33	−0.38
95% CI:	(−0.12, 0.47)	(−0.99, 0.33)	(−1.11, 0.36)
P−value:	0.23	0.32	0.31

C. Anti−N Antibody Levels, Subgroup: Anti−N Ab Pos. at Entry

Number of Patients				
Bam.:	64	63	57	53
Placebo:	61	57	59	54

Est. Mean Diff. (Bam.−Placebo)			
Est. Diff.:	−0.08	−0.053	−0.023
95% CI:	(−0.32, 0.16)	(−0.26, 0.15)	(−0.21, 0.16)
P−value:	0.51	0.61	0.81

Figure S9: Sustained Recovery Outcome for Baseline Demographic Subgroups

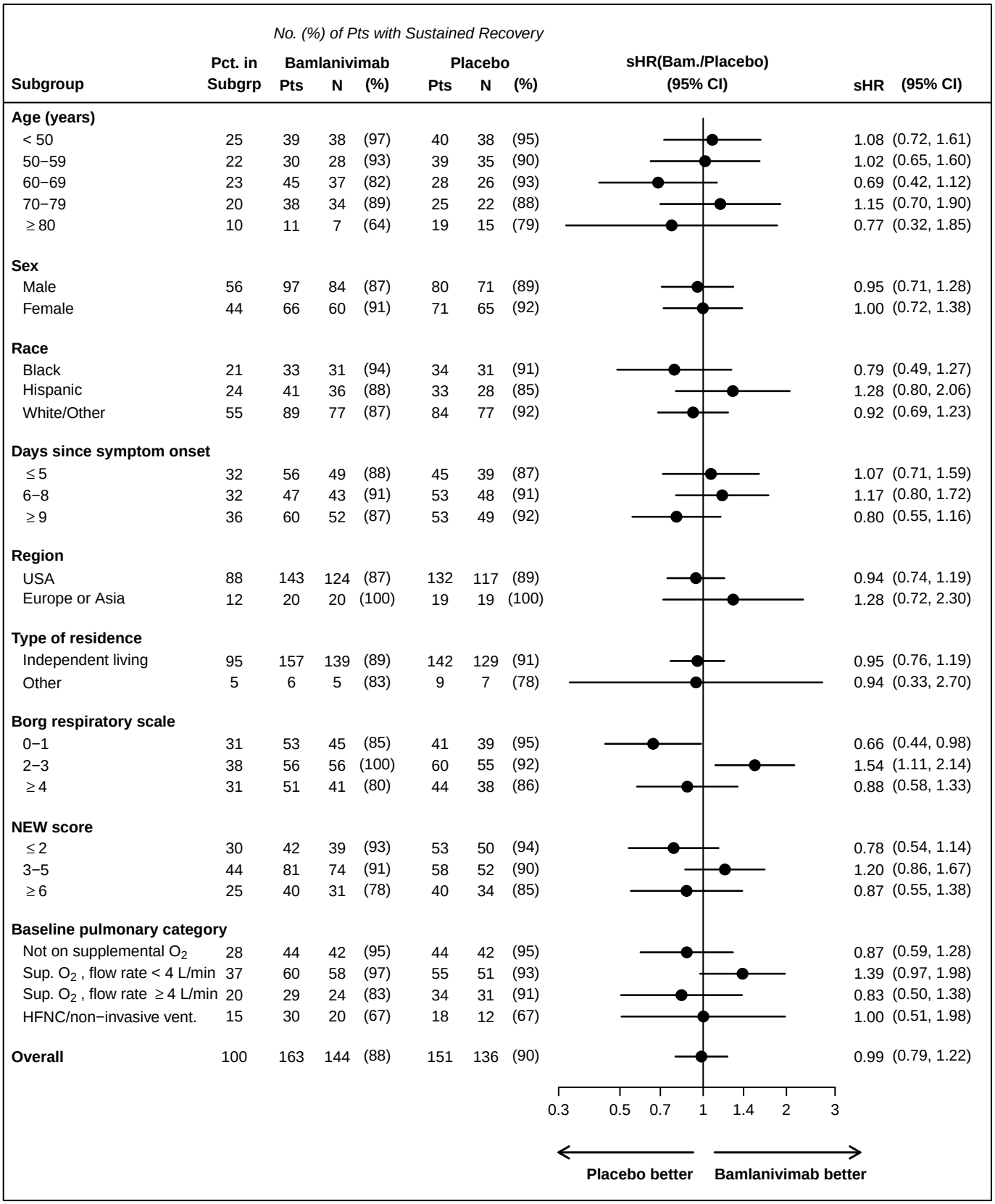


Figure S10: Sustained Recovery Outcome for Subgroups Defined by Baseline Anti-N Antibody Status and Levels of Viral Measures

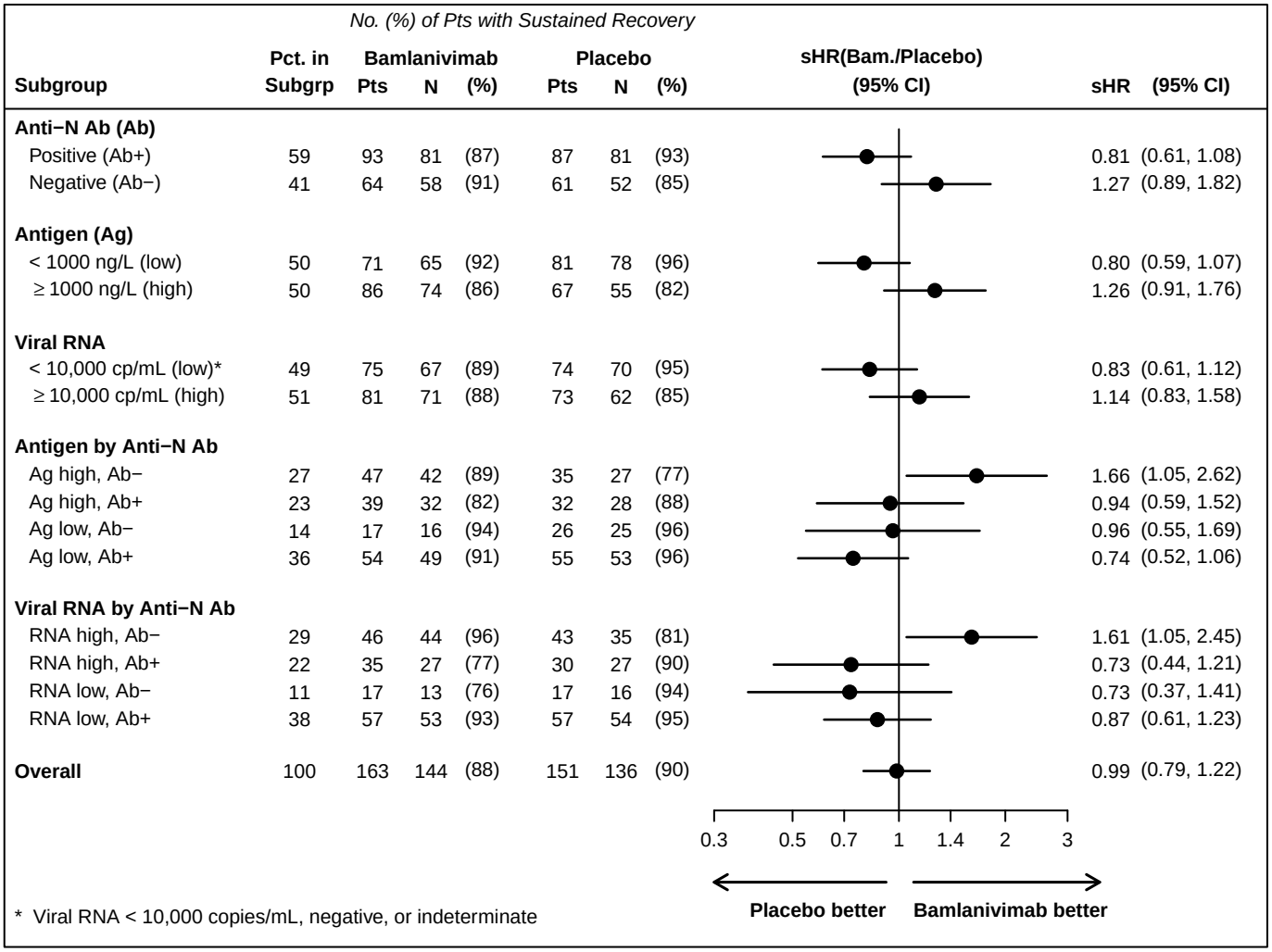


Figure S11: Sustained Recovery Outcome for Subgroups Defined by nAb and Anti-N Antibodies and Levels of Viral Measures

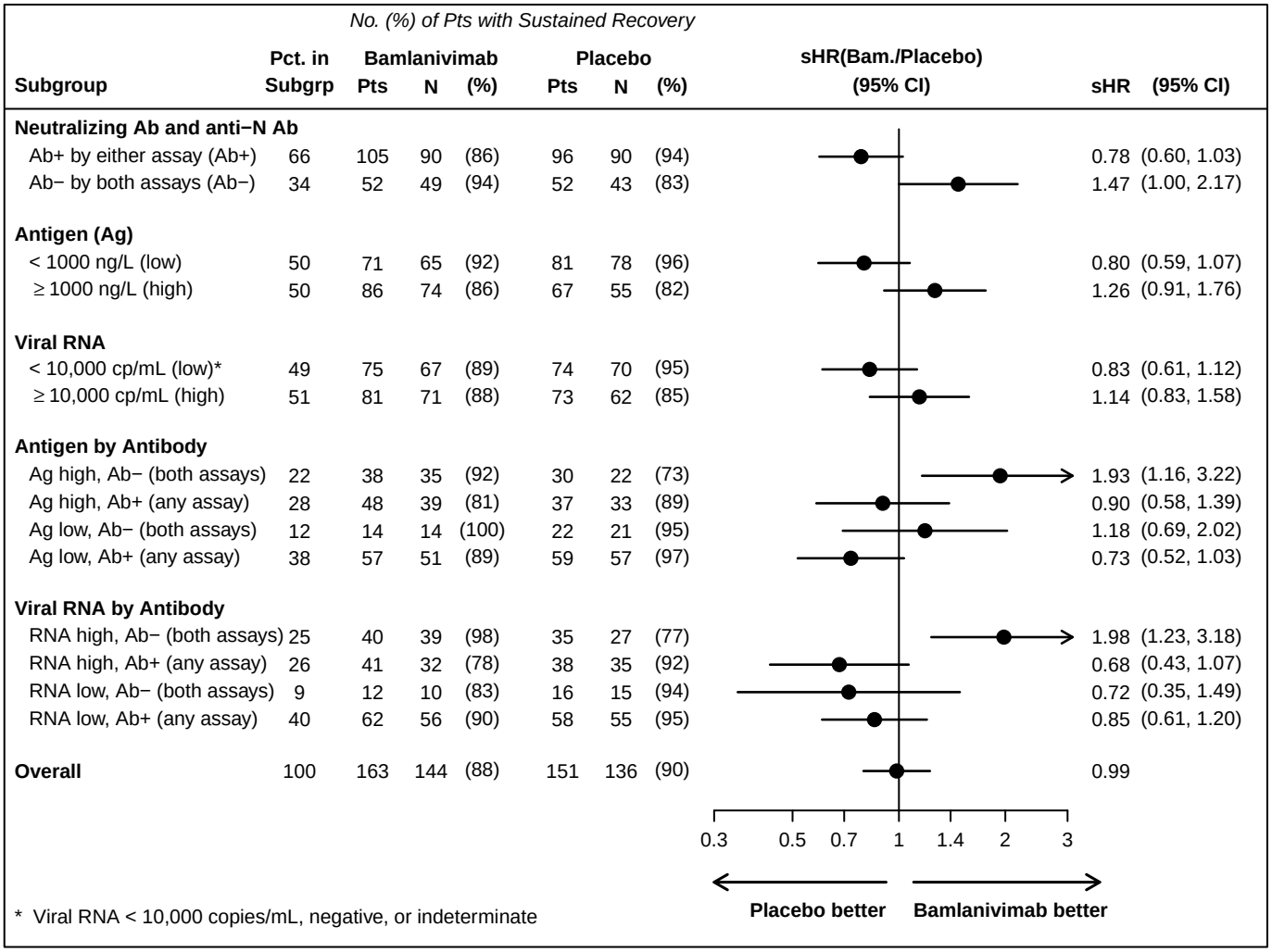


Figure S12: Day 5 Ordinal Pulmonary Outcome for Subgroups Defined by Baseline nAb Status and Levels of Viral Measures

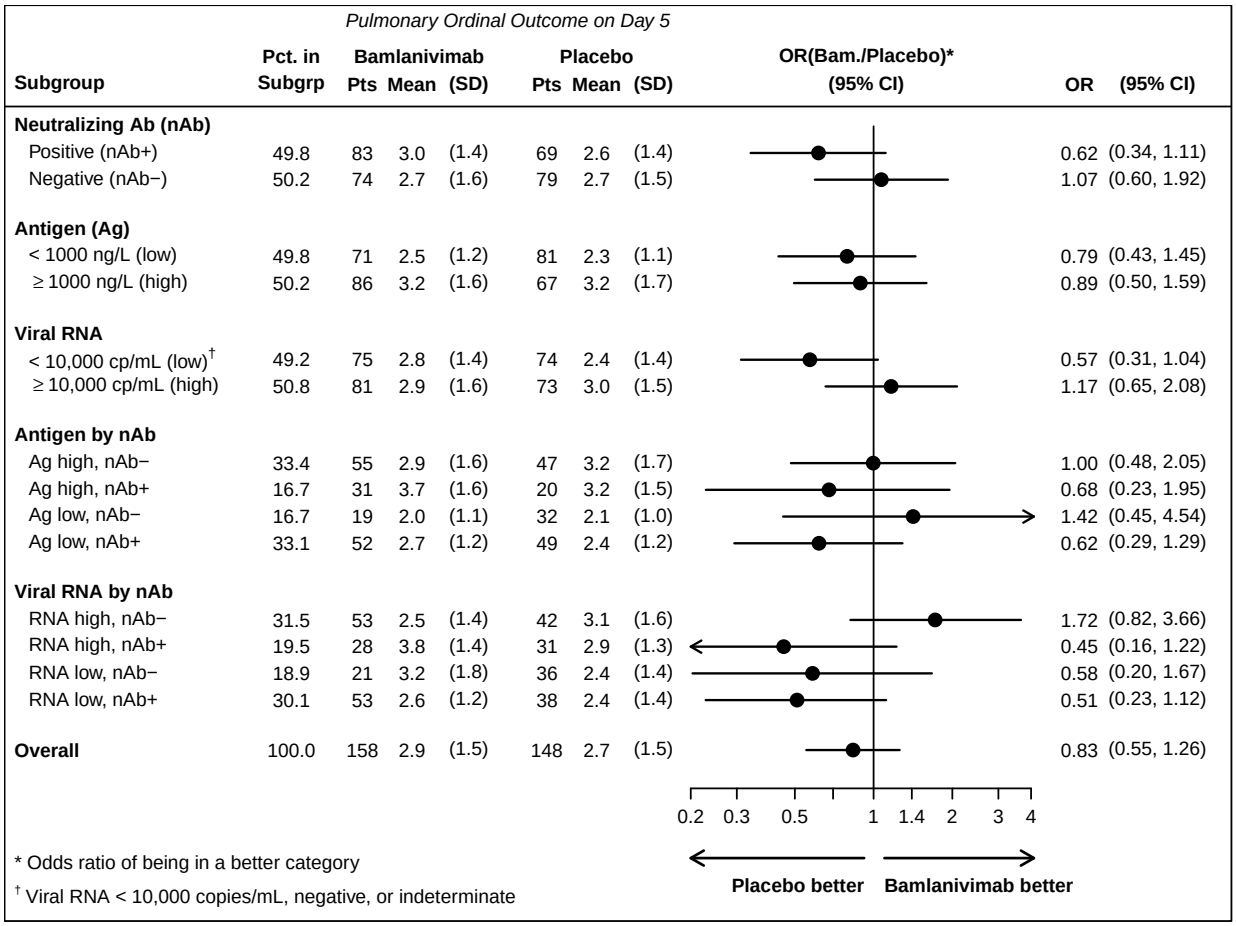


Table S5: Number of Participants with Safety Outcomes by Treatment Group

Event	Bamlanivimab	Placebo	OR or HR	95% CI	p-value
Infusion reaction *	23 (14.1%)	14 (9.3%)	1.62	0.79, 3.32	.19
Day 5 composite safety outcome †	33 (20.2%)	21 (13.9%)	1.66	0.87, 3.16	.13
Day 5 expanded safety outcome ‡	45 (27.6%)	28 (18.5%)	1.83	1.01, 3.29	.05
Day 28 composite safety outcome §	42 (25.8%)	32 (21.2%)	1.28	0.81, 2.02	.30
Day 28 expanded safety outcome ‖	52 (31.9%)	42 (27.8%)	1.21	0.81, 1.82	.35
Day 90 composite safety outcome ¶	45 (27.6%)	41 (27.2%)	1.05	0.68, 1.60	.83
Death **	13 (8.0%)	11 (7.3%)	1.09	0.49, 2.43	.84

* Infusion reactions during or within 2 hours following the infusion; odds ratio (OR) estimated from logistic model adjusted for site pharmacy.

† Death, SAE, or grade 3/4 AE through Day 5; odds ratio (OR) estimated from logistic model adjusted for site pharmacy.

‡ Death, SAE, or grade 3/4 AE, organ failure, or serious infection through Day 5; odds ratio (OR) estimated from logistic model adjusted for site pharmacy.

§ Death, SAE, or grade 3/4 AE through Day 28; hazard ratio (HR) estimated from Cox model with stratification by site pharmacy.

‖ Death, SAE, or grade 3/4 AE, organ failure, or serious infection through Day 28; hazard ratio (HR) estimated from Cox model with stratification by site pharmacy.

¶ Death, SAE, organ failure, or serious infection through Day 90; hazard ratio (HR) estimated from Cox model with stratification by site pharmacy.

** Death through Day 90; hazard ratio (HR) estimated from Cox model with stratification by site pharmacy.

Table S6: Safety Outcomes by Baseline nAb Status

Event	Bamlanivimab	Placebo	OR or HR	95% CI
Infusion reaction *				
Antibody positive	9 (10.8%)	3 (4.3%)	2.68	0.69, 10.30
Antibody negative	14 (18.9%)	10 (12.7%)	1.61	0.67, 3.89
Day 5 composite safety outcome †				
Antibody positive	15 (18.1%)	9 (13.0%)	1.47	0.60, 3.60
Antibody negative	16 (21.6%)	12 (15.2%)	1.54	0.67, 3.52
Day 5 expanded safety outcome ‡				
Antibody positive	23 (27.7%)	13 (18.8%)	1.65	0.76, 3.57
Antibody negative	20 (27.0%)	15 (19.0%)	1.58	0.74, 3.38
Day 28 composite safety outcome §				
Antibody positive	20 (24.1%)	12 (17.4%)	1.42	0.69, 2.91
Antibody negative	20 (27.0%)	20 (25.3%)	1.12	0.60, 2.08
Day 28 expanded safety outcome ‖				
Antibody positive	26 (31.3%)	16 (23.2%)	1.42	0.76, 2.65
Antibody negative	24 (32.4%)	26 (32.9%)	1.04	0.60, 1.81
Day 90 composite safety outcome ¶				
Antibody positive	26 (31.3%)	13 (18.8%)	1.79	0.92, 3.48
Antibody negative	18 (24.3%)	28 (35.4%)	0.67	0.37, 1.21
Death **				
Antibody positive	8 (9.6%)	2 (2.9%)	3.52	0.75, 16.58
Antibody negative	4 (5.4%)	9 (11.4%)	0.46	0.14, 1.48

* Infusion reactions during or within 2 hours following the infusion; odds ratio (OR) estimated from logistic model.

† Death, SAE, or grade 3/4 AE through Day 5; odds ratio (OR) estimated from logistic model.

‡ Death, SAE, or grade 3/4 AE, organ failure, or serious infection through Day 5; odds ratio (OR) estimated from logistic model.

§ Death, SAE, or grade 3/4 AE through Day 28; hazard ratio (HR) estimated from Cox model.

‖ Death, SAE, or grade 3/4 AE, organ failure, or serious infection through Day 28; hazard ratio (HR) estimated from Cox model.

¶ Death, SAE, organ failure, or serious infection through Day 90; hazard ratio (HR) estimated from Cox model.

** Death through Day 90; hazard ratio (HR) estimated from Cox model.

Table S7: Components of the Day 90 Safety Outcome by Baseline nAb Status

All Participants							
	Bamlanivimab (n= 163)		Placebo (n= 151)		Hazard Ratio*		
Events through Day 90	Pts	Pct.	Pts	Pct.	HR	95% CI	P-value
SAE	9	5.5	12	7.9	0.70	0.29, 1.65	.41
Death	13	8.0	11	7.3	1.09	0.49, 2.43	.84
SAE or Death	22	13.5	20	13.2	1.03	0.56, 1.89	.93
Organ Failure	37	22.7	31	20.5	1.14	0.71, 1.83	.60
Any of Above	45	27.6	41	27.2	1.05	0.68, 1.60	.83
Among Participants with Negative nAb at Baseline							
	Bamlanivimab (n= 74)		Placebo (n= 79)		Hazard Ratio*		
SAE	4	5.4	8	10.1	0.51	0.15, 1.70	.27
Death	4	5.4	9	11.4	0.46	0.14, 1.48	.19
SAE or Death	8	10.8	15	19.0	0.55	0.23, 1.29	.17
Organ Failure	15	20.3	20	25.3	0.78	0.40, 1.53	.48
Any of Above	18	24.3	28	35.4	0.67	0.37, 1.21	.18
Among Participants with Positive nAb at Baseline							
	Bamlanivimab (n= 83)		Placebo (n= 69)		Hazard Ratio*		
SAE	5	6.0	4	5.8	1.10	0.30, 4.11	.88
Death	8	9.6	2	2.9	3.52	0.75, 16.58	.11
SAE or Death	13	15.7	5	7.2	2.29	0.82, 6.43	.11
Organ Failure	22	26.5	11	15.9	1.78	0.86, 3.68	.12
Any of Above	26	31.3	13	18.8	1.79	0.92, 3.48	.09

* Hazard ratio by Cox regression. Overall is stratified by site pharmacy.

Figure S13: Plasma IL-6 and CRP Levels Over Time by Baseline nAb Status

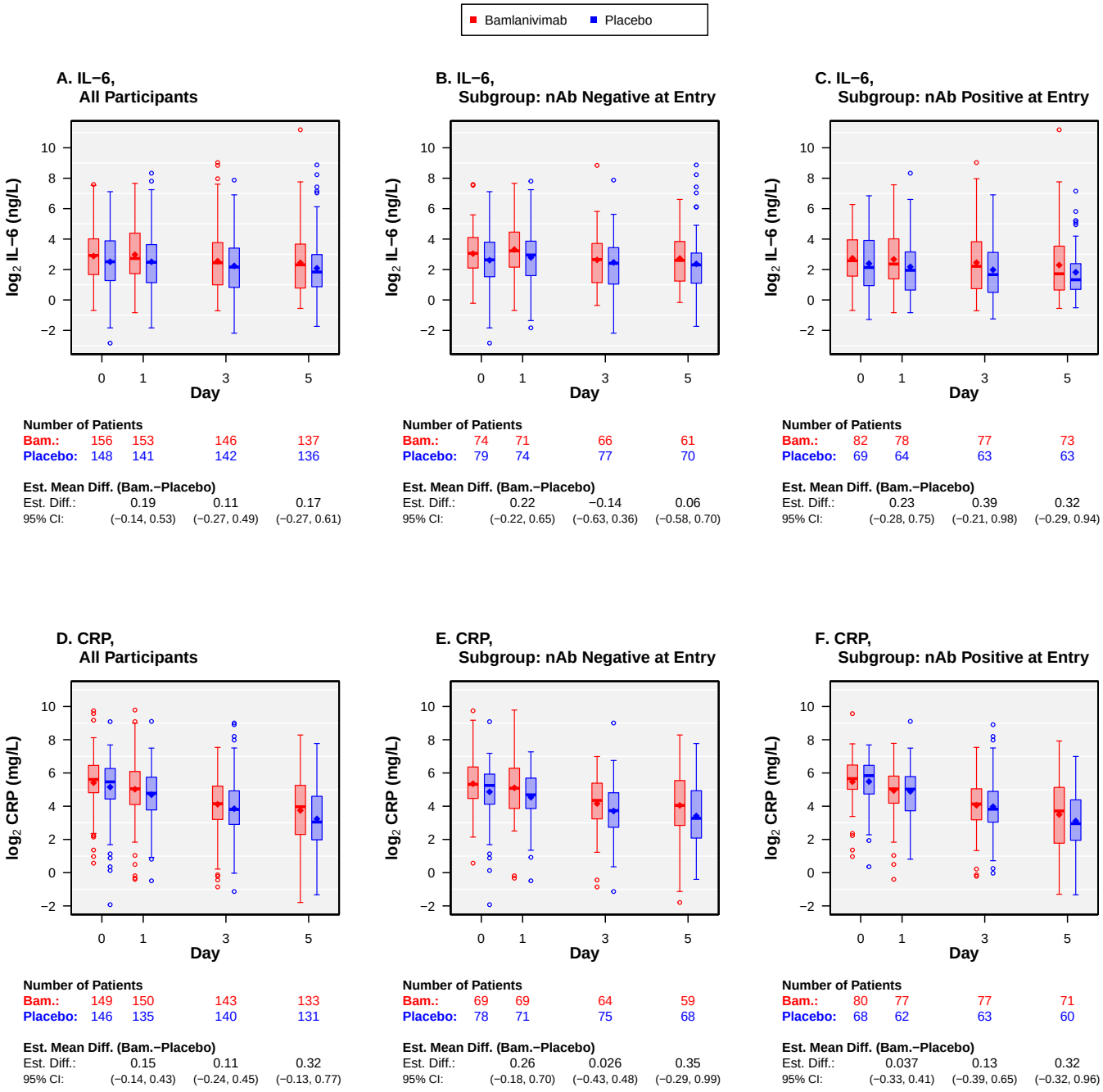
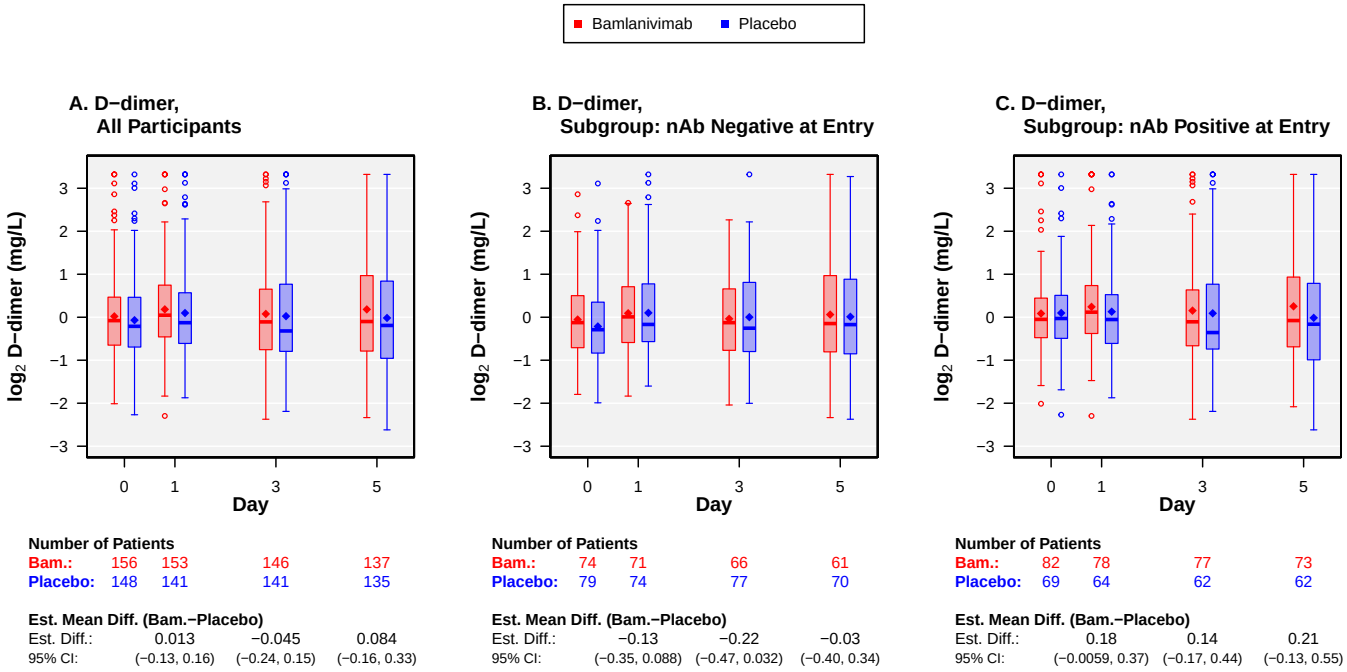


Figure S14: Plasma D-dimer Levels Over Time by Baseline nAb Status



Number of Patients

	Day 0	Day 1	Day 3	Day 5
Bam.:	156	153	146	137
Placebo:	148	141	141	135

Est. Mean Diff. (Bam.−Placebo)

	Day 1	Day 3	Day 5
Est. Diff.:	0.013	−0.045	0.084
95% CI:	(−0.13, 0.16)	(−0.24, 0.15)	(−0.16, 0.33)

Number of Patients

	Day 0	Day 1	Day 3	Day 5
Bam.:	74	71	66	61
Placebo:	79	74	77	70

Est. Mean Diff. (Bam.−Placebo)

	Day 1	Day 3	Day 5
Est. Diff.:	−0.13	−0.22	−0.03
95% CI:	(−0.35, 0.088)	(−0.47, 0.032)	(−0.40, 0.34)

Number of Patients

	Day 0	Day 1	Day 3	Day 5
Bam.:	82	78	77	73
Placebo:	69	64	62	62

Est. Mean Diff. (Bam.−Placebo)

	Day 1	Day 3	Day 5
Est. Diff.:	0.18	0.14	0.21
95% CI:	(−0.0059, 0.37)	(−0.17, 0.44)	(−0.13, 0.55)

Supplementary Appendix References

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