

SUPPLEMENTARY TEXT

First in Human Study of Bamlanivimab in a Randomized Trial of Hospitalized Patients with COVID-19

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Supplementary Methods

Inclusion criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

1. Are ≥ 18 and ≤ 85 years of age at the time of randomization

Type of Participant and Disease Characteristics

2. In the judgement of the investigator, have moderate or severe COVID-19 illness per the FDA resource page
3. Are hospitalized, or in the process of being admitted to hospital, and have an initial laboratory determination of current COVID-19 infection ≤ 14 days of randomization.

Sex

4. Are men or non-pregnant women.

Study Procedures

5. Understand and agree to comply with planned study procedures
6. Agree to the collection of nasopharyngeal swabs and venous blood

Informed Consent

7. The participant or legally authorized representative give signed informed consent, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

Exclusion criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

10. Require invasive mechanical ventilation or anticipated impending need for invasive mechanical ventilation
11. Anticipate transfer to another hospital which is not a study site within 5 days of randomization
12. Have known allergies to any of the components used in the formulation of the interventions
13. Have hemodynamic instability requiring use of pressors within 24 hours of randomization
14. Were resident in a nursing home or long-term care facility immediately prior to current hospitalization
15. Suspected or proven serious, active bacterial, fungal, viral, or other infection (besides COVID-19) that in the opinion of the investigator could constitute a risk when taking intervention
16. Have any co-morbidity requiring surgery within <7 days, or that is considered life threatening within 29 days
17. Have prior history of hepatic impairment, such as
 - a. severe liver cirrhosis Child-Pugh B or worse
 - b. cirrhosis with a history of hepatic encephalopathy
 - c. clinically meaningful ascites requiring ongoing treatment with diuretics and/or paracentesis, or
 - d. history of hepatorenal syndrome.
18. Have any serious concomitant systemic disorder that, in the opinion of the investigator, would preclude participation in the study
19. Current diagnosis of active malignancy that, in the opinion of the investigator, could constitute a risk when taking investigational product
20. Received convalescent COVID-19 plasma treatment prior to enrollment

Diagnostic assessments

21. Have an SpO₂ <88% while breathing room air at rest. If on supplemental oxygen at the time of screening, use the last time point of measurement on room air up to 48 hours prior
22. Have alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >5X upper limit of normal (ULN)

23. Have acute kidney disease with an eGFR <30 mL/min/1.73 m² based on the chronic kidney disease epidemiology collaboration equation (CKD-EPI).

Chronic kidney disease is allowable, if judged to be stable for the past 3 months, in the opinion of the investigator.

Other Exclusions

24. Are pregnant or breast feeding

25. Are concurrently enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study

26. Are Lilly employees

27. Are investigator site personnel directly affiliated with this study or their immediate families.

Sample size

Sample size was determined based on Monte Carlo simulations of mean AUC (28 day) of viral load using a viral dynamic PK/PD model and a preliminary variability estimate from literature. Success for the trial was claimed using a Bayesian criterion if any of the three bamlanivimab doses had at least 60% probability to reduce at least 30% mean AUC over placebo.

Viral resistance

All qPCR and nasal samples were subjected to next-generation sequencing. The full-length spike protein sequence was then inferred from the next-generation sequencing data and amino acid variations relative to the Wuhan reference sequence at an allelic frequency of $\geq 20\%$. Treatment emergent spike variations were identified by comparing post-baseline sequences to the respective baseline sequence (or reference sequence, if no baseline sequence was available) on a per patient basis.

PK Assay

Serum concentrations of bamlanivimab were determined using a validated hybrid LC-MS/MS method. Extraction was performed using Protein G coated magnetic beads for affinity capture of immunoglobulins, followed by sample purification, sequential reduction and alkylation of cysteines, and overnight on-beads enzymatic digestion with trypsin. A specific tryptic signature peptide from the Fab region of bamlanivimab was used for quantitation, with a stable isotope

labelled form used as the internal standard (IS). The signature peptide was identified and quantified using reversed-phase high-performance liquid chromatography with tandem mass spectrometry (HPLC-MS/MS) detection over an analyte concentration range of 5.00 to 500.00 µg/mL. Concentrations were calculated using peak area ratios of analyte to IS, and the linearity of the calibration curve determined using least squares regression analysis with a weighting factor of $1/x^2$. Samples were analysed on a weekly basis to facilitate PK and safety data review.

Surrogate Virus Neutralization Assay

Serum samples were co-incubated with biotinylated peptide from the receptor binding domain (RBD) of the SARS-CoV-2 spike protein, then added to plates coated with recombinant ACE2 extracellular domain (ECD). In the absence of antibody to RBD, the biotinylated RBD binds to the ACE2 ECD resulting in increased signal after colorimetric detection. Optical density value of diluted samples was interpolated against the bamlanivimab curve and multiplied by the dilution factor to generate the equivalent amount of bamlanivimab neutralization activity in the sample.

Serology

IgG antibodies against SARS-CoV-2 epitopes were detected using an in-house developed, Luminex-based, multiplex assay. Patient serum samples were titrated (1:800 – 1:1.6E7) in phosphate buffered saline-high salt solution (PBS-HS; 0.01 M PBS, 1% BSA, 0.02% Tween, 300 mM NaCl) and combined with Luminex MAGPlex microspheres coupled with SARS-CoV-2 antigens (RBD, NTD, NCP). These were incubated for 90 minutes at RT, washed, and then incubated for 60 minutes at RT with α IgG Fc-specific (#109-115-098, Jackson Labs) detector phycoerythrin-conjugated antibodies. Washed beads were then resuspended in a PBS-1% BSA solution and read using a Luminex L-200 System with xPONENT Software.

PK Data Analysis

Serum concentrations of bamlanivimab were analysed using descriptive summary statistics and the nonlinear mixed-effects modeling program NONMEM (Version 7.4.2). The PK data were well described by a 2-compartment structural model, parameterized in terms of systemic clearance (CL), central compartment volume of distribution (V1), peripheral volume of distribution (V2) and intercompartmental clearance (Q). Interpatient variability was included on both CL and V1. Weight was incorporated with fixed allometric exponents on CL, Q, V1 and

V2¹. Residual variability was accounted for with a proportional (bamlanivimab) error structure. No intrinsic or extrinsic patient factor was significant on key PK parameters.

References

- (1) Betts, A. *et al.* Linear pharmacokinetic parameters for monoclonal antibodies are similar within a species and across different pharmacological targets: A comparison between human, cynomolgus monkey and hFcRn Tg32 transgenic mouse using a population-modeling approach. *MAbs* **10**, 751-64 (2018).

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SUPPLEMENTARY FIGURES

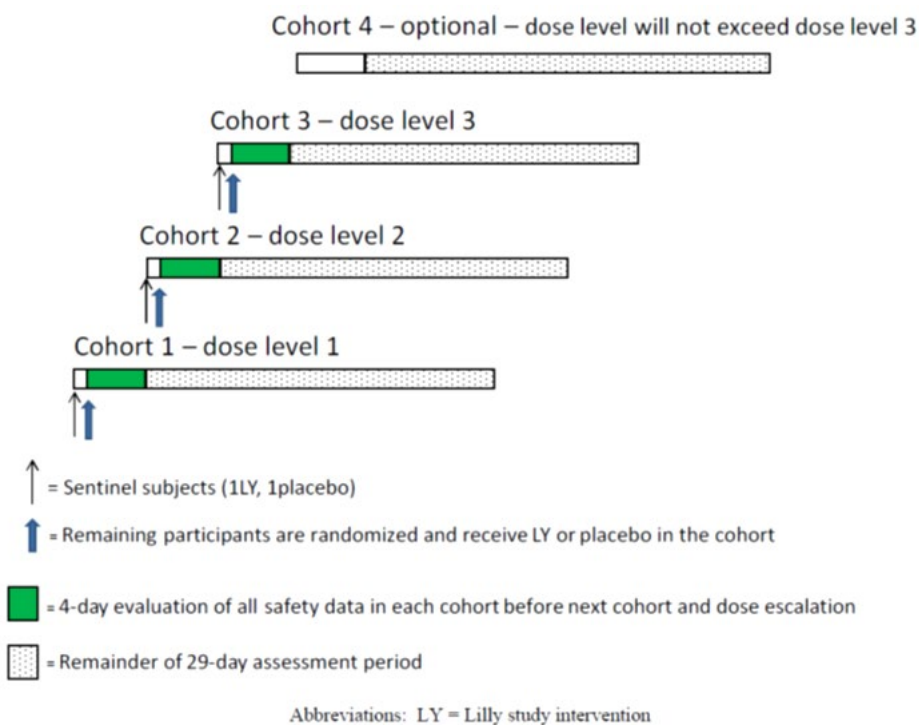


Figure S1: Study design

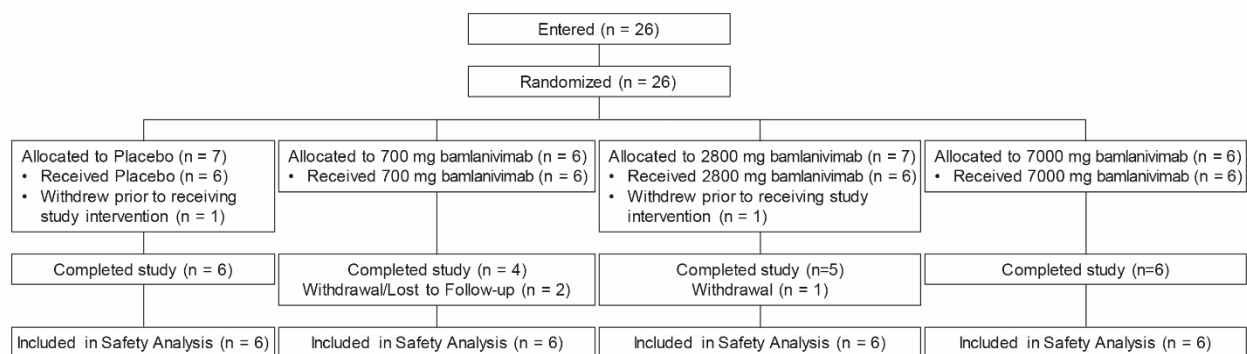


Figure S2: CONSORT diagram

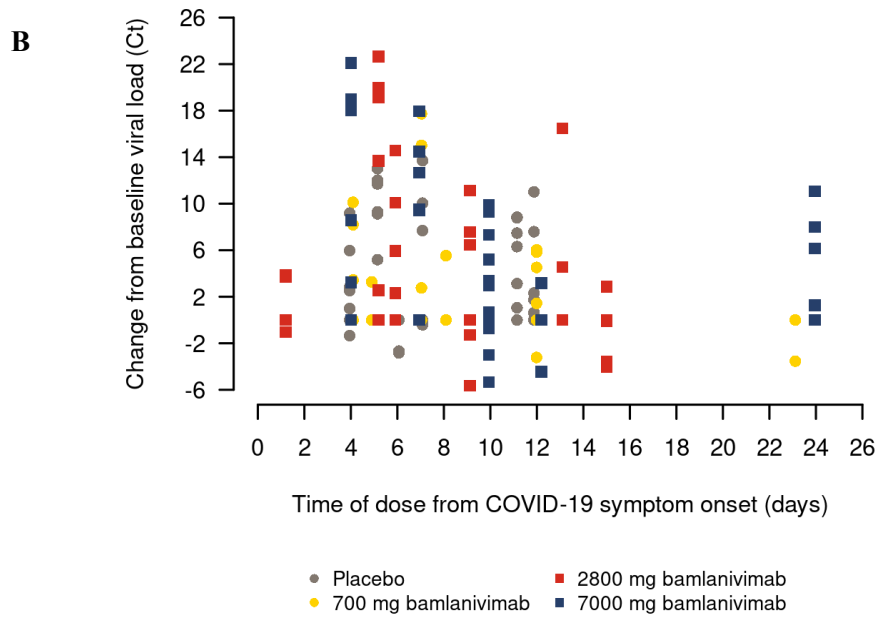
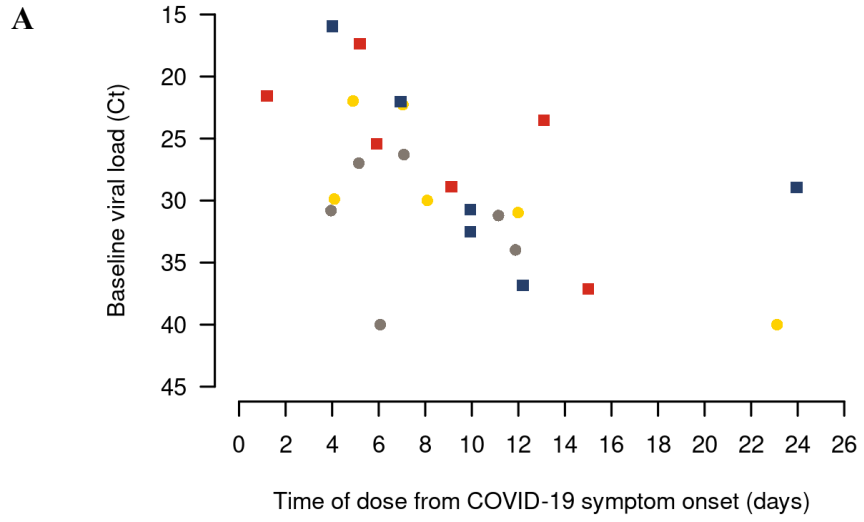


Figure S3: Baseline viral load vs time since symptom onset

SUPPLEMENTARY TABLES

Supplementary Table S1: Total symptom score

	Treatment Groups			
	Bamlanivimab			
	Placebo (N = 6)	700 mg (N = 6)	2800 mg (N = 6)	7000 mg (N = 6)
	Symptom score			
Day 1, n Mean symptom score (SD)	6 3.0 (2.1)	6 4.2 (2.2)	6 2.8 (1.2)	6 1.3 (1.8)
Day 2, n Mean symptom score (SD)	5 1.8 (1.6)	6 3.3 (1.8)	6 2.2 (1.7)	6 1.7 (1.9)
Day 3, n Mean symptom score (SD)	6 1.3 (0.5)	6 2.7 (1.6)	5 1.2 (1.8)	6 1.7 (1.5)
Day 4, n Mean symptom score (SD)	4 0.8 (0.5)	6 2.2 (1.8)	5 2.2 (0.4)	6 1.2 (1.0)
Day 7, n Mean symptom score (SD)	6 0.7 (0.5)	4 1.3 (1.5)	6 1.2 (1.2)	4 1.5 (1.3)
Day 11, n Mean symptom score (SD)	6 0.5 (0.5)	4 1.0 (1.4)	6 1.8 (1.8)	5 0.6 (0.5)
Day 15, n Mean symptom score (SD)	6 0.2 (0.4)	4 1.0 (1.4)	5 1.6 (1.8)	5 0.4 (0.5)
Day 22, n Mean symptom score (SD)	6 0.3 (0.5)	4 0.8 (1.5)	5 1.0 (1.0)	6 0.5 (0.5)
Day 29, n Mean symptom score (SD)	5 0.2 (0.4)	4 0.8 (1.5)	5 0.4 (0.9)	6 0.7 (0.5)

Total Symptom Score is derived as the sum all 3 symptom scores (fever, cough, shortness of breath) for each patient at each day.

Supplementary Table S2. NIAID Ordinal Scales

n (%)		Treatment Groups			
		Bamlanivimab			
		Placebo (N=6)	700 mg (N=6)	2800 mg (N=6)	7000 mg (N=6)
NIAID Ordinal Scale					
Screening					
1	0	0	0	0	0
2	0	0	0	0	0
3	0	0	0	0	0
4	2 (33.3)	5 (83.3)	4 (66.7)	4 (66.7)	4 (66.7)
5	0	1 (16.7)	0	0	0
6	4 (66.7)	0	2 (33.3)	2 (33.3)	2 (33.3)
7	0	0	0	0	0
8	0	0	0	0	0
Day 1					
1	0	0	0	0	0
2	0	0	0	0	0
3	0	0	0	0	0
4	2 (33.3)	5 (83.3)	3 (50.0)	2 (33.3)	2 (33.3)
5	0	1 (16.7)	0	0	0
6	3 (50.0)	0	2 (33.3)	3 (50.0)	3 (50.0)
7	1 (16.7)	0	1 (16.7)	1 (16.7)	1 (16.7)
8	0	0	0	0	0
Day 2					
1	0	0	0	0	0
2	0	0	0	0	0
3	0	0	0	0	0
4	1 (16.7)	4 (66.7)	3 (50.0)	1 (16.7)	1 (16.7)
5	0	0	0	0	0
6	3 (50.0)	2 (33.3)	1 (16.7)	4 (66.7)	4 (66.7)
7	1 (16.7)	0	2 (33.3)	1 (16.7)	1 (16.7)
8	0	0	0	0	0
Day 3					
1	0	0	0	0	0
2	0	0	0	0	0
3	0	0	0	0	0
4	1 (16.7)	3 (50.0)	1 (16.7)	1 (16.7)	1 (16.7)
5	0	0	0	0	0
6	1 (16.7)	2 (33.3)	1 (16.7)	3 (50.0)	3 (50.0)
7	3 (50.0)	1 (16.7)	4 (66.7)	0	0
8	1 (16.7)	0	0	2 (33.3)	2 (33.3)
Day 4					
1	0	0	0	0	0
2	0	0	0	0	0
3	0	0	0	0	0
4	1 (16.7)	3 (50.0)	1 (16.7)	1 (16.7)	1 (16.7)
5	0	0	0	0	0
6	1 (16.7)	0	1 (16.7)	2 (33.3)	2 (33.3)
7	1 (16.7)	2 (33.3)	3 (50.0)	1 (16.7)	1 (16.7)
8	1 (16.7)	1 (16.7)	0	2 (33.3)	2 (33.3)
Day 7					

	1	0	0	0	0
	2	0	0	0	0
	3	0	0	0	0
	4	1 (16.7)	1 (16.7)	0	0
	5	0	0	1 (16.7)	0
	6	0	0	1 (16.7)	1 (16.7)
	7	0	2 (33.3)	3 (50.0)	2 (33.3)
	8	5 (83.3)	1 (16.7)	1 (16.7)	1 (16.7)
Day 11					
	1	0	0	0	0
	2	0	0	0	0
	3	0	0	0	0
	4	0	0	0	0
	5	0	0	0	0
	6	0	0	0	0
	7	0	2 (33.3)	5 (83.3)	4 (66.7)
	8	6 (100.0)	2 (33.3)	1 (16.7)	1 (16.7)
Day 15					
	1	0	0	0	0
	2	0	0	0	0
	3	0	0	0	0
	4	0	0	0	0
	5	0	0	0	0
	6	0	0	0	0
	7	0	2 (33.3)	5 (83.3)	4 (66.7)
	8	6 (100.0)	2 (33.3)	0	1 (16.7)
Day 22					
	1	0	0	0	0
	2	0	0	0	0
	3	0	0	0	0
	4	0	0	0	0
	5	0	0	0	0
	6	0	0	0	0
	7	1 (16.7)	1 (16.7)	4 (66.7)	2 (33.3)
	8	5 (83.3)	3 (50.0)	1 (16.7)	4 (66.7)
Day 29					
	1	0	0	0	0
	2	0	0	0	0
	3	0	0	0	0
	4	0	0	0	0
	5	0	0	0	0
	6	0	0	0	0
	7	0	1 (16.7)	4 (66.7)	2 (33.3)
	8	5 (83.3)	3 (50.0)	1 (16.7)	4 (66.7)

Missing patient data for any cell where n does not equal 6; Score: 1 = Death; 2 = Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation; 3 = Hospitalized, on non-invasive ventilation or high flow oxygen devices; 4 = Hospitalized, requiring supplemental oxygen; 5 = Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19 related or otherwise); 6 = Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care; 7 = Not hospitalized, limitation on activities and/or requiring home oxygen; 8 = Not hospitalized, no limitations on activities

Supplementary Table S3. WHO Ordinal Scales

n (%)	Treatment Groups			
	Bamlanivimab			
	Placebo (N=6)	700 mg (N=6)	2800 mg (N=6)	7000 mg (N=6)
WHO Ordinal Scale				
Screening				
0	0	0	0	0
1	0	0	0	0
2	0	1 (16.7)	0	0
3	4 (66.7)	0	2 (33.3)	2 (33.3)
4	2 (33.3)	5 (83.3)	4 (66.7)	4 (66.7)
5	0	0	0	0
6	0	0	0	0
7	0	0	0	0
8	0	0	0	0
Day 1				
0	0	0	0	0
1	0	0	0	0
2	1 (16.7)	1 (16.7)	1 (16.7)	1 (16.7)
3	3 (50.0)	0	2 (33.3)	3 (50.0)
4	2 (33.3)	5 (83.3)	3 (50.0)	2 (33.3)
5	0	0	0	0
6	0	0	0	0
7	0	0	0	0
8	0	0	0	0
Day 2				
0	0	0	0	0
1	0	0	0	0
2	1 (16.7)	0	2 (33.3)	1 (16.7)
3	3 (50.0)	2 (33.3)	1 (16.7)	4 (66.7)
4	1 (16.7)	4 (66.7)	3 (50.0)	1 (16.7)
5	0	0	0	0
6	0	0	0	0
7	0	0	0	0
8	0	0	0	0
Day 3				
0	0	0	0	0
1	1 (16.7)	0	0	2 (33.3)
2	3 (50.0)	1 (16.7)	4 (66.7)	0
3	1 (16.7)	2 (33.3)	1 (16.7)	3 (50.0)
4	1 (16.7)	3 (50.0)	1 (16.7)	1 (16.7)
5	0	0	0	0
6	0	0	0	0
7	0	0	0	0
8	0	0	0	0
Day 4				
0	0	1 (16.7)	0	0
1	1 (16.7)	0	0	2 (33.3)
2	1 (16.7)	2 (33.3)	3 (50.0)	1 (16.7)
3	1 (16.7)	0	1 (16.7)	2 (33.3)

	4	1 (16.7)	3 (50.0)	1 (16.7)	1 (16.7)
	5	0	0	0	0
	6	0	0	0	0
	7	0	0	0	0
	8	0	0	0	0
Day 7	0	1 (16.7)	0	1 (16.7)	0
	1	4 (66.7)	1 (16.7)	1 (16.7)	1 (16.7)
	2	0	2 (33.3)	3 (50.0)	2 (33.3)
	3	0	0	1 (16.7)	1 (16.7)
	4	1 (16.7)	1 (16.7)	0	0
	5	0	0	0	0
	6	0	0	0	0
	7	0	0	0	0
	8	0	0	0	0
Day 11	0	3 (50.0)	1 (16.7)	1 (16.7)	0
	1	3 (50.0)	1 (16.7)	1 (16.7)	1 (16.7)
	2	0	2 (33.3)	4 (66.7)	4 (66.7)
	3	0	0	0	0
	4	0	0	0	0
	5	0	0	0	0
	6	0	0	0	0
	7	0	0	0	0
	8	0	0	0	0
Day 15	0	2 (33.3)	2 (33.3)	1 (16.7)	0
	1	4 (66.7)	0	0	1 (16.7)
	2	0	2 (33.3)	4 (66.7)	4 (66.7)
	3	0	0	0	0
	4	0	0	0	0
	5	0	0	0	0
	6	0	0	0	0
	7	0	0	0	0
	8	0	0	0	0
Day 22	0	2 (33.3)	2 (33.3)	1 (16.7)	3 (50.0)
	1	3 (50.0)	1 (16.7)	1 (16.7)	1 (16.7)
	2	1 (16.7)	1 (16.7)	3 (50.0)	2 (33.3)
	3	0	0	0	0
	4	0	0	0	0
	5	0	0	0	0
	6	0	0	0	0
	7	0	0	0	0
	8	0	0	0	0
Day 29	0	2 (33.3)	3 (50.0)	2 (33.3)	2 (33.3)
	1	3 (50.0)	0	0	2 (33.3)
	2	0	1 (16.7)	3 (50.0)	2 (33.3)
	3	0	0	0	0
	4	0	0	0	0

5	0	0	0	0
6	0	0	0	0
7	0	0	0	0
8	0	0	0	0
<p>Missing patient data for any cell where n does not equal 6; Score: 0 = No clinical or virological evidence of infection; 1 = No limitation of activities; 2 = Limitation of activities; 3 = Hospitalized, no oxygen therapy; 4 = Oxygen by mask or nasal prongs; 5 = Non-invasive ventilation or high-flow oxygen; 6 = Intubation and mechanical ventilation; 7 = Ventilation + additional organ support; 8 = Death</p>				

Supplementary Table S4. NEWS2 Scores

n (%)	Treatment Groups			
	Placebo (N=6)	Bamlanivimab		
		700 mg (N=6)	2800 mg (N=6)	7000 mg (N=6)
NEWS2 Score				
Day 1				
0-4	1 (16.7)	0	3 (50.0)	2 (33.3)
5-6	0	2 (33.3)	0	2 (33.3)
≥7	1 (16.7)	0	0	0
Day 2				
0-4	4 (66.7)	1 (16.7)	4 (66.7)	4 (66.7)
5-6	1 (16.7)	2 (33.3)	0	1 (16.7)
≥7	0	3 (50.0)	2 (33.3)	0
Day 3				
0-4	4 (66.7)	5 (83.3)	2 (33.3)	5 (83.3)
5-6	2 (33.3)	1 (16.7)	1 (16.7)	0
≥7	0	0	2 (33.3)	0
Day 4				
0-4	0	2 (33.3)	2 (33.3)	2 (33.3)
5-6	2 (33.3)	3 (50.0)	1 (16.7)	1 (16.7)
≥7	0	0	0	0
Day 7				
0-4	5 (83.3)	2 (33.3)	4 (66.7)	4 (66.7)
5-6	1 (16.7)	1 (16.7)	0	0
≥7	0	1 (16.7)	2 (33.3)	0
Day 11				
0-4	6 (100.0)	4 (66.7)	4 (66.7)	4 (66.7)
5-6	0	0	2 (33.3)	0
≥7	0	0	0	0
Day 15				
0-4	6 (100.0)	4 (66.7)	4 (66.7)	5 (83.3)
5-6	0	0	0	0
≥7	0	0	0	0
Day 22				
0-4	5 (83.3)	4 (66.7)	5 (83.3)	5 (83.3)
5-6	0	0	0	0
≥7	1 (16.7)	0	0	0
Day 29				
0-4	5 (83.3)	4 (66.7)	5 (83.3)	5 (83.3)
5-6	0	0	0	0
≥7	0	0	0	0
Missing patient data for any cell where n does not equal 6; NEWS2 = National Early Warning Score; Aggregate score 0-4 = low clinical risk; 5-6 = medium clinical risk; ≥7 = high clinical risk				