Supplemental Online Content

Cohen MS, Nirula A, Mulligan MJ, et al; BLAZE-2 Investigators. Effect of bamlanivimab vs placebo on incidence of COVID-19 among residents and staff of skilled nursing and assisted living facilities: a randomized clinical trial. *JAMA*. Published online June 3, 2021. doi:10.1001/jama.2021.8828

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

eAppendix. Supplemental Methods

RT-PCR for SARS-CoV-2

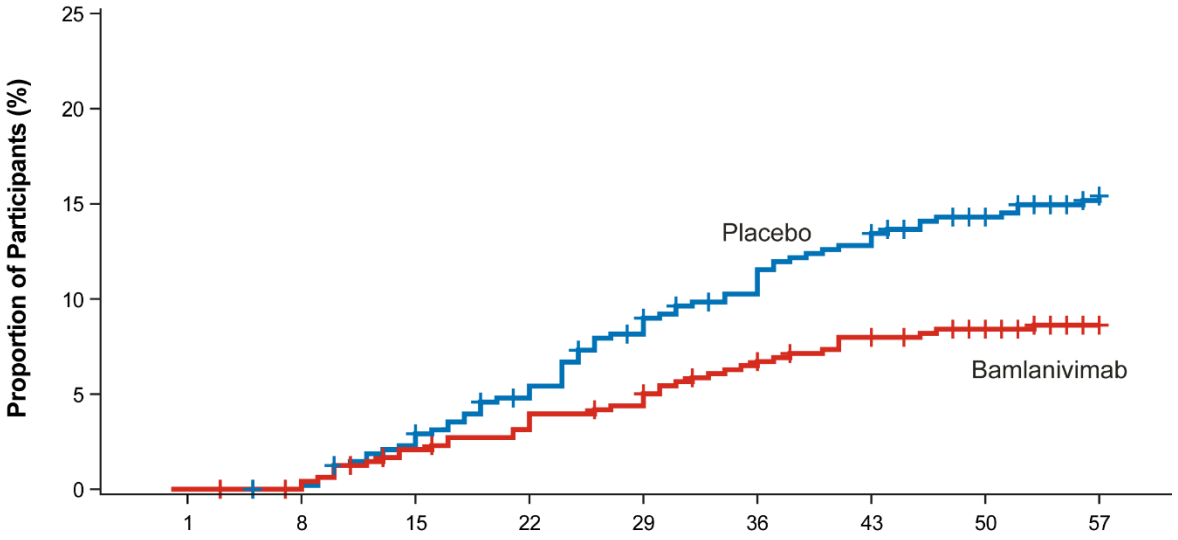
RT-PCR for detection of SARS-CoV-2 was performed on nasal or nasopharyngeal swabs collected in sterile viral transport media using the materials, extraction method, and RT-PCR protocol as described previously.[1] The SARS-CoV-2 specific primers "N1" and "N2" target different sequences of the SARS-CoV-2 nucleocapsid N gene, and are co-amplified with a human internal control target, RNase P, hereafter referred to as "RP," for 45 cycles of PCR. Primer and probe sequences are available in the "Lilly SARS-CoV-2 Assay EUA Summary" and were obtained from Integrated DNA Technologies (IDT, San Jose, CA). RT-PCR results were interpreted as follows. A clinical sample was "positive" for detection of SARS-CoV-2 if either or both of the SARS-CoV-2 specific N1 and N2 targets showed clear and unambiguous amplification with a cycle threshold (Ct) determined. A clinical sample was "negative" for detection of SARS-CoV-2 if neither of the N1 or N2 targets showed amplification, while the internal human control RP target showed clear and unambiguous amplification. A clinical sample was "invalid" if all three targets showed no amplification. Viral presence or absence and any quantitative determination was not scored for "invalid" samples. All amplification curves were reviewed by a board certified pathologist (AS, GJO) who were blinded to treatment assignment.

Serology testing for SARS-CoV-2

Serum was tested for anti-SARS-CoV-2 antibodies using the Elecsys Anti-SARS-CoV-2 electrochemiluminescence immunoassay intended for qualitative detection of antibodies to SARS-CoV-2 on a cobas e602 (Roche Diagnsotics, #09203095190), per the package insert. Results were reported as reactive (positive for anti-SARS-CoV-2 antibodies) or non-reactive (negative for anti-SARS-CoV-2 antibodies). Elecsys Anti-SARS-CoV-2 serology determined serology status, antibodies to the nucleocapsid protein of SARS-CoV-2 (combined IgA, IgG, and IgM) were detected.

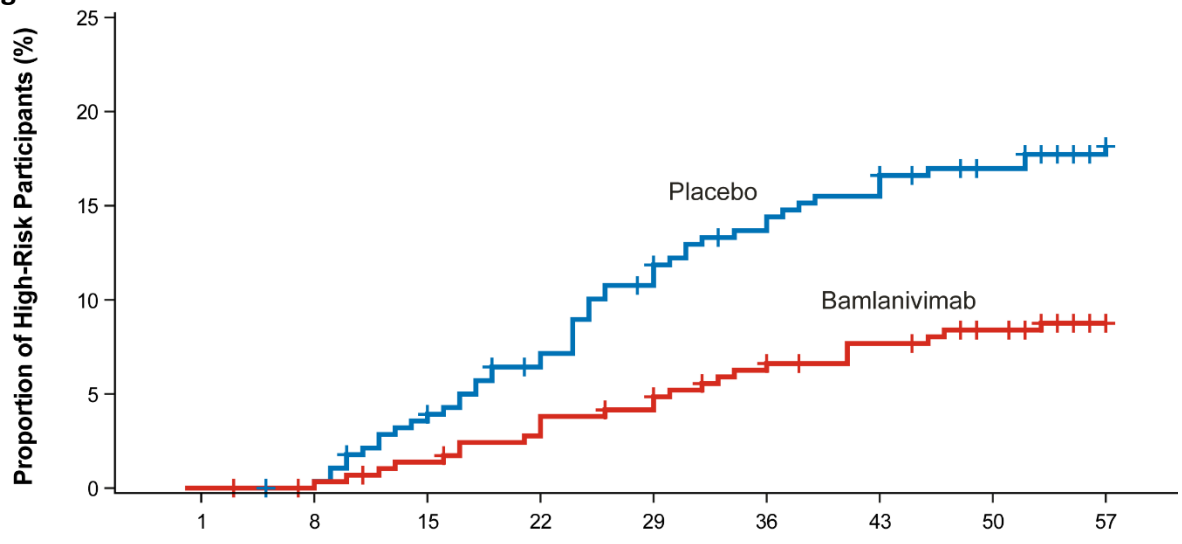
eFigure 1. Time From Infusion to Development of Mild or Worse Severity COVID-19 With Bamlanivimab Versus Placebo

All Prevention Population



No. at Risk									
Placebo	482 (1)	480 (13)	465 (12)	451 (17)	431 (12)	417 (9)	406 (4)	396 (5)	22 (0)
Bamlanivimab	484 (2)	479 (8)	469 (9)	458 (5)	450 (8)	440 (6)	432 (2)	425 (1)	20 (0)

High-Risk

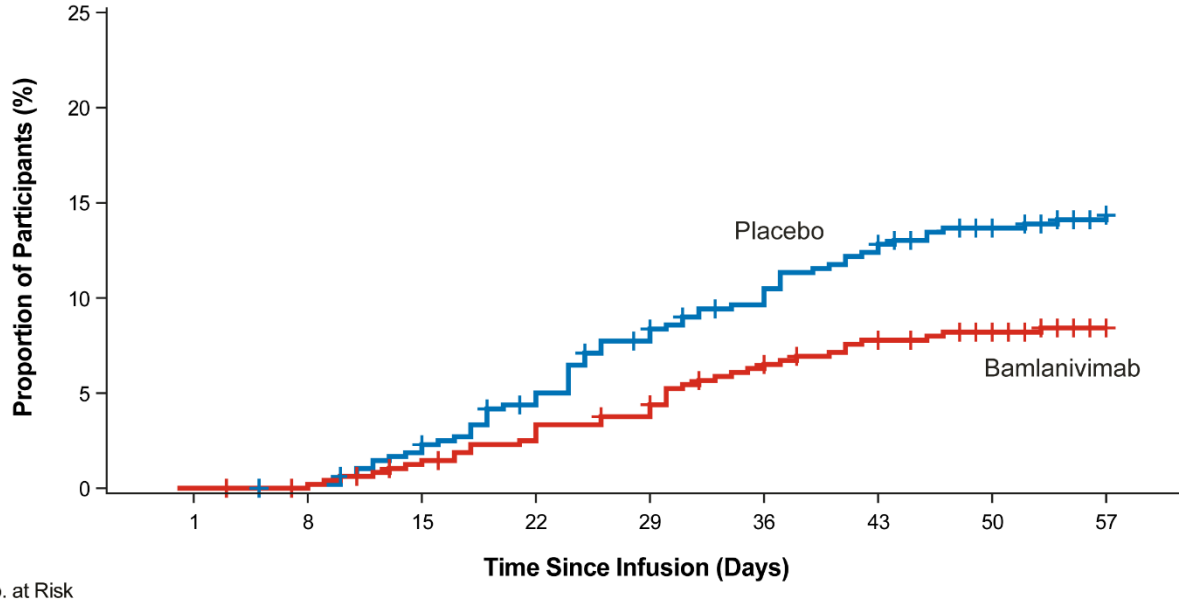


No. at Risk									
Placebo	282 (1)	280 (10)	268 (9)	257 (13)	242 (7)	234 (6)	226 (1)	221 (3)	9 (0)
Bamlanivimab	293 (1)	289 (3)	285 (7)	277 (3)	271 (5)	264 (3)	260 (2)	255 (1)	9 (0)

Time from infusion (days) to development of mild or worse COVID-19 with bamlanivimab versus placebo in the entire prevention population (top) and in the high-risk prevention population (bottom). Participants were SARS-CoV-2 RT-PCR negative and serology negative at baseline. The numbers below the figure represent the number of participants at risk (number of participants with events) in the interval of time after the current listed day through the following listed day.

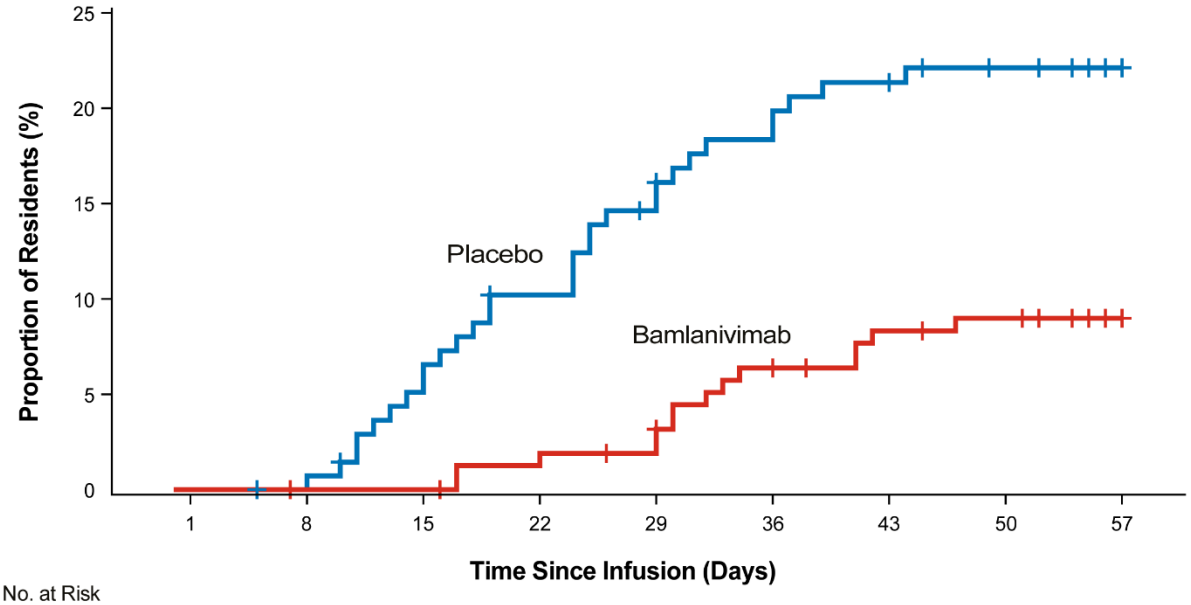
eFigure 2A. Time From Infusion to Development of Moderate or Worse Severity COVID-19 With Bamlanivimab Versus Placebo

All Prevention Population



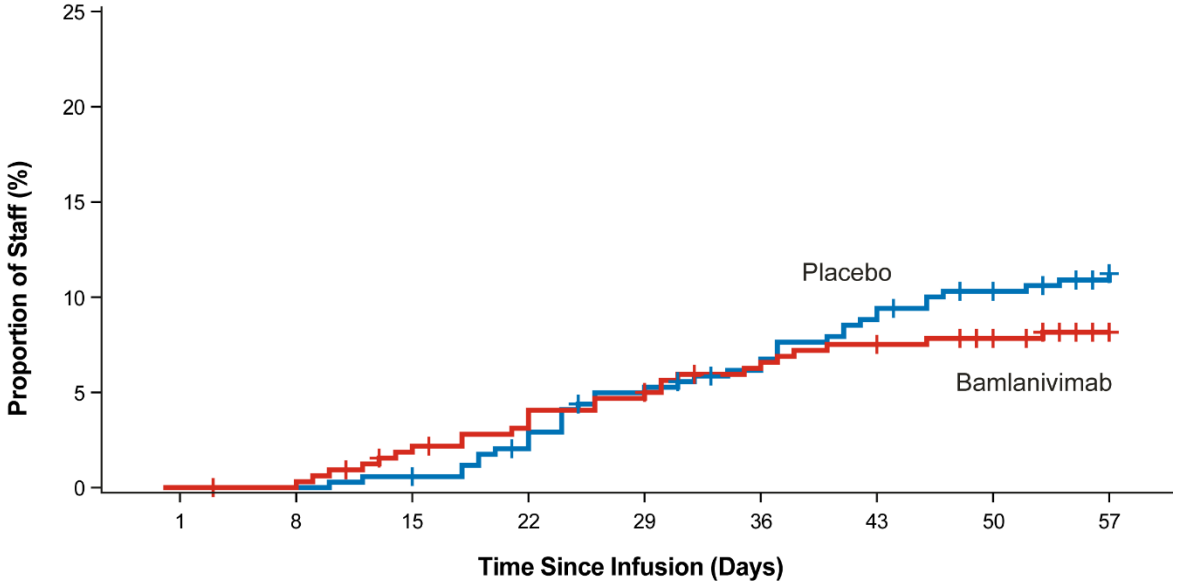
No. at Risk									
Placebo	482 (1)	480 (10)	468 (13)	453 (16)	434 (10)	422 (11)	409 (4)	399 (3)	23 (0)
Bamlanivimab	484 (1)	480 (6)	472 (9)	461 (5)	453 (10)	441 (6)	433 (2)	426 (1)	20 (0)

Residents



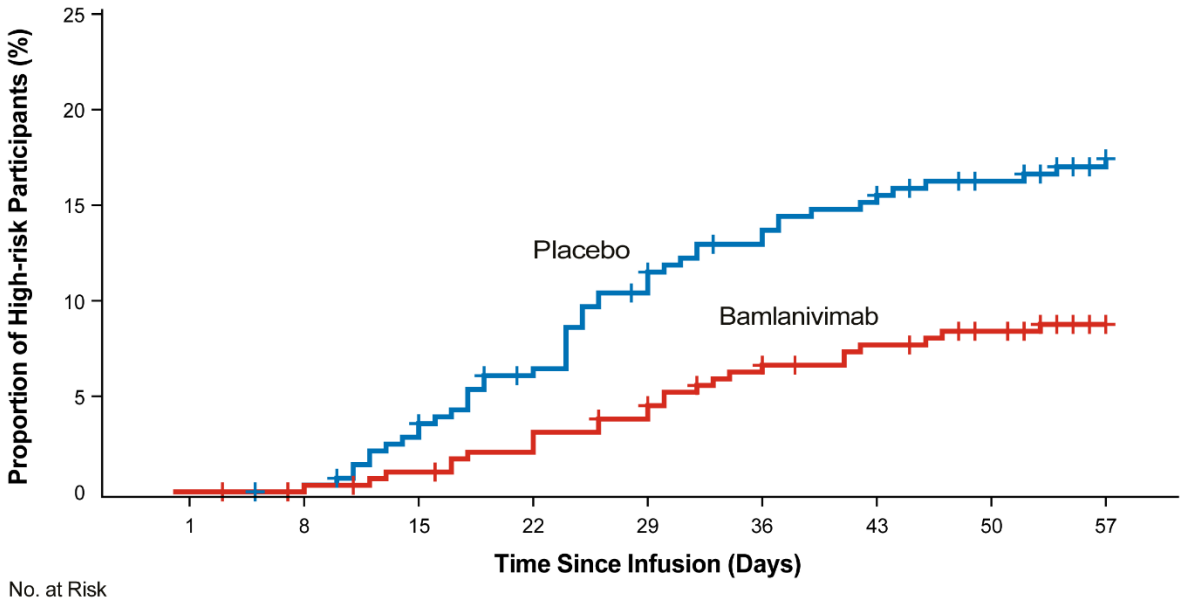
No. at Risk									
Placebo	139 (1)	137 (8)	128 (5)	122 (8)	112 (5)	107 (2)	103 (1)	99 (0)	2 (0)
Bamlanivimab	161 (0)	159 (0)	159 (3)	155 (2)	151 (5)	145 (3)	141 (1)	139 (0)	5 (0)

Staff



No. at Risk									
Placebo	343 (0)	343 (2)	340 (8)	331 (8)	322 (5)	315 (9)	306 (3)	300 (3)	21 (0)
Bamlanivimab	323 (1)	321 (6)	313 (6)	306 (3)	302 (5)	296 (3)	292 (1)	287 (1)	15 (0)

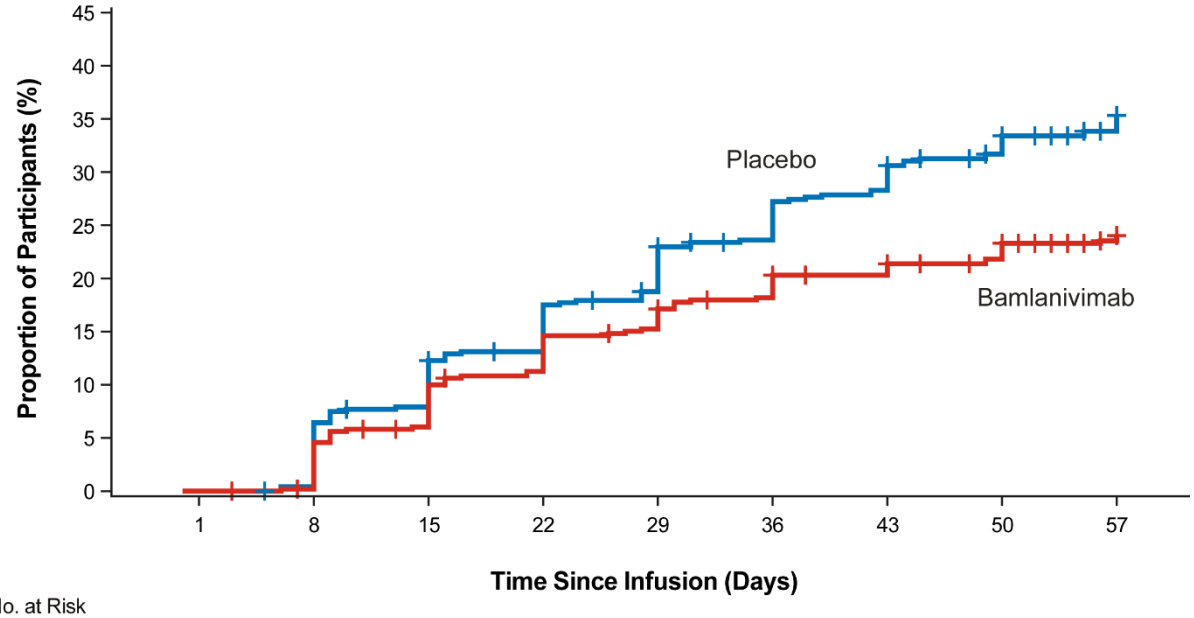
High-Risk



No. at Risk									
Placebo	282 (1)	280 (9)	269 (8)	259 (14)	243 (6)	236 (5)	229 (2)	223 (3)	9 (0)
Bamlanivimab	293 (1)	289 (2)	286 (6)	279 (4)	272 (6)	264 (3)	260 (2)	255 (1)	9 (0)

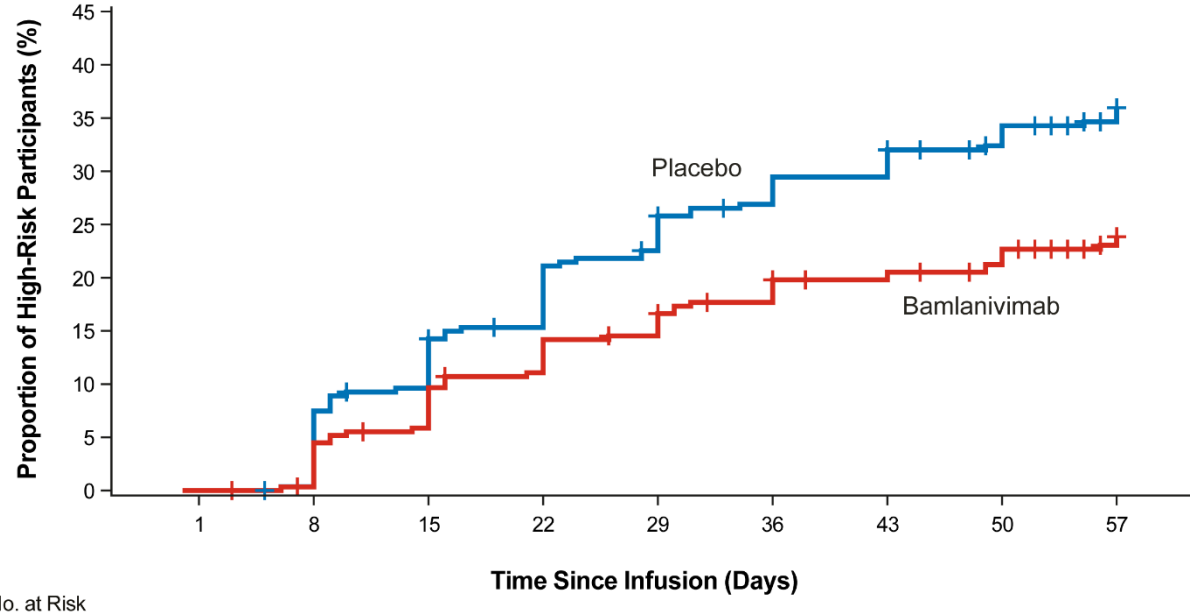
eFigure 2B. Time From Infusion to Detection of SARS-CoV-2 by RT-PCR With Bamlanivimab Versus Placebo

All Prevention Population



No. at Risk									
Placebo	482 (31)	450 (28)	420 (25)	394 (26)	365 (20)	343 (16)	325 (13)	307 (8)	19 (1)
Bamlanivimab	484 (22)	459 (26)	431 (22)	407 (12)	392 (15)	375 (5)	368 (9)	355 (3)	18 (0)

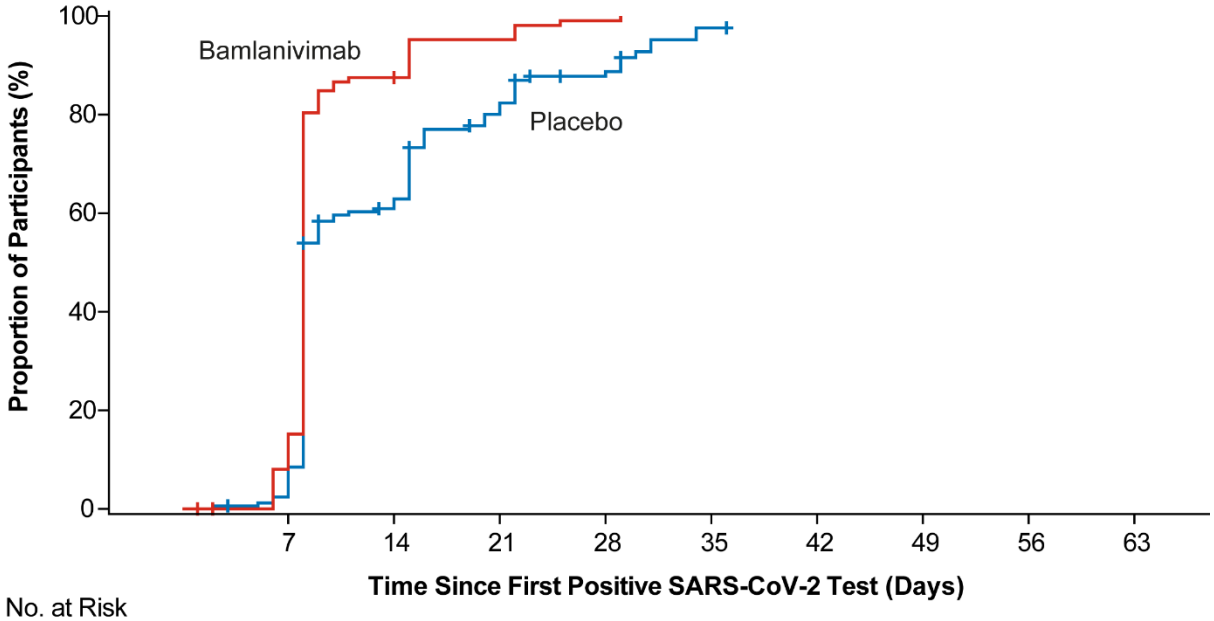
High-Risk



No. at Risk									
Placebo	282 (21)	260 (19)	239 (19)	219 (13)	204 (10)	193 (7)	184 (6)	174 (4)	9 (1)
Bamlanivimab	293 (13)	277 (15)	261 (13)	247 (7)	237 (9)	226 (2)	223 (6)	215 (3)	8 (0)

Panel A) time from infusion (days) to development of moderate or worse COVID-19 with bamlanivimab versus placebo in the entire prevention population, resident prevention population, the staff prevention population, and the high-risk population
Panel B) Time from infusion (days) to detection of SARS-CoV-2 detected by RT-PCR with bamlanivimab versus placebo in the prevention population (top) and the high-risk population (bottom).
Participants were SARS-CoV-2 RT-PCR negative and serology negative at baseline. The numbers below the figure represent the number of participants at risk (number of participants with events) in the interval of time after the current listed day through the following listed day.

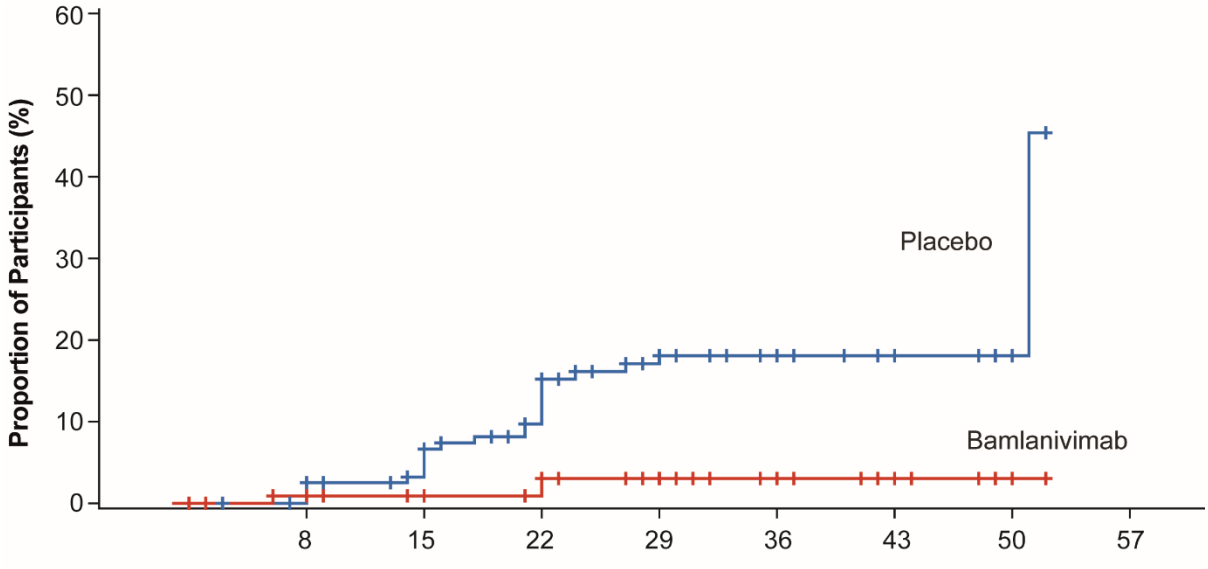
eFigure 3. Time From First Positive SARS-CoV-2 Test to Clearance



No. at Risk									
Placebo	151 (89)	57 (28)	23 (8)	12 (8)	2 (0)	0 (0)	0 (0)	0 (0)	0
Bamlanivimab	95 (81)	13 (8)	5 (4)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0

Time to SARS-CoV-2 clearance (a single negative SARS-CoV-2 RT-PCR test). Participants were SARS-CoV-2 RT-PCR negative and serology negative at baseline. The numbers below the figure represent the number of participants at risk (number of participants with events) in the interval of time after the current listed day through the following listed day.

eFigure 4. Time From First Positive RT-PCR for SARS-CoV-2 to Seropositivity



No. at Risk								
Placebo	147 (6)	125 (11)	92 (3)	69 (0)	45 (0)	25 (0)	3 (1)	0
Bamlanivimab	104 (0)	94 (2)	83 (0)	70 (0)	52 (0)	27 (0)	1 (0)	0

Time from first positive RT-PCR for SARS-CoV-2 to seropositivity. The numbers below the figure represent the number of participants at risk (number of participants with events) in the interval of time after the current listed day through the following listed day.

eTable 1. Definitions for COVID-19 Severity[a]

Severity	Symptoms	Clinical Signs
Mild[b]	Symptoms that could include fever, cough, sore throat, malaise, headache, muscle pain, gastrointestinal symptoms	No clinical signs indicative of moderate, severe, or critical severity
Moderate	Any symptom of mild illness or shortness of shortness of breath with exertion	Clinical signs suggestive of moderate illness with COVID-19, such as • Respiratory rate ≥ 20 breaths per minute • Heart rate ≥ 90 beats per minute • O2 utilization increase of ≥ 1L/min (for participants receiving O2 at baseline)[c] • IV fluid initiation[c]
Severe	Any symptom of moderate illness, shortness of breath at rest, or respiratory distress	Clinical signs indicative of severe systemic illness with COVID-19, such as • Respiratory rate ≥ 30 breaths per minute, • Heart rate ≥ 125 beats per minute, • SpO2 ≤ 93% on room air at sea level or PaO2/FiO2 < 300
Critical		Evidence of critical illness, defined by at least one of the following: • Respiratory failure defined based on resource utilization requiring at least one of the following: – Endotracheal intubation and mechanical ventilation – Oxygen delivered by high-flow nasal cannula (heated, humidified, oxygen delivered via reinforced nasal cannula at flow rates > 20 L/min with fraction of delivered oxygen ≥0.5) – Non-invasive positive pressure ventilation – Extracorporeal membrane oxygenation (ECMO) – Clinical diagnosis of respiratory failure (i.e., clinical need for one of the preceding therapies, but preceding therapies not able to be administered in setting of resource limitation) • Shock • Multi-organ dysfunction/failure
Death		

Abbreviations: COVID-19, coronavirus disease – 2019; FiO2, fraction of inspired oxygen in the air; IV, intravenous; PaO2, partial pressure of oxygen; SpO2, saturation of peripheral oxygen.

[a] Adapted from FDA 2020[2].

[b] Without shortness of breath or dyspnea.

[c] Addition to FDA Guidance applies only to residents at skilled nursing and assisted living facilities.

eTable 2. Demographics of Participants in the Safety Population at Baseline[a]

	Bamlanivimab (N=588)	**Placebo (N=587)**
Age		
Median (Range), y	53.0 (18-104)	51.0 (18-96)
≥65 y, No. (%)	170 (28.9)	170 (29.0)
Sex, No. (%)		
Female	434 (73.8)	443 (75.5)
Male	154 (26.2)	144 (24.5)
Self-reported race, No./total (%)[b]		
White	519/584 (88.9)	515/583 (88.3)
Black or African American	48/584 (8.2)	53/583 (9.1)
Asian	6/584 (1.0)	8/583 (1.4)
Native Hawaiian or other Pacific Islander	2/584 (0.3)	3/583 (0.5)
American Indian or Alaska Native	4/584 (0.7)	1/583 (0.2)
Multiple	5/584 (0.9)	3/583 (0.5)
Hispanic or Latino, No./total (%)[b]	26/587 (4.4)	36/587 (6.1)
BMI, Median (Range)[c]	29.0 (15.4-68.4)	29.7 (14.1-77.4)

Abbreviations: BMI, body mass index; COVID-19, coronavirus disease 2019.

[a] All participants randomly assigned to and received placebo or bamlanivimab (regardless of baseline serology status).

[b] Race and ethnic group were reported by the patients. Denominators used to calculate percentages did not include participants with missing data.

[c] The body-mass index is the weight in kilograms divided by the square of the height in meters.

eTable 3. Demographics of High-Risk Participants in the Prevention Population at Baseline[a]

	High-Risk Participants[b] Prevention Population	
	Bamlanivimab (N=293)	**Placebo (N=282)**
Age		
Median (Range), y	64.0 (18-104)	64.0 (18-96)
≥65 y, No. (%)	145 (49.5)	137 (48.6)
Sex, No. (%)		
Female	207 (70.6)	210 (74.5)
Male	86 (29.4)	72 (25.5)
Self-reported race, No./total (%)[c]		
White	267/292 (91.4)	257/281 (91.5)
Black or African American	20/292 (6.8)	22/281 (7.8)
American Indian or Alaska Native	1/292 (0.3)	0
Asian	2/292 (0.7)	1/281 (0.4)
Native Hawaiian or other Pacific Islander	1/292 (0.3)	0
Multiple	1/292 (0.3)	1/281 (0.4)
Hispanic or Latino, No./total (%)[b]	8/292 (2.7)	14/282 (5.0)
BMI, Median (Range)[c]	33.9 (15.4-64.7)	33.5 (14.1-77.4)
High risk for severe COVID-19, No. (%)[e]	293 (100)	282 (100)

Abbreviations: BMI, body mass index; COVID-19, coronavirus disease 2019.

[a] Participants negative at baseline for SARS-CoV-2 by RT-PCR and serology.

[b] The high-risk prevention population included all residents (300) and staff at high risk for the development of severe COVID-19 (275).

[c] Race and ethnic group were reported by the patients. Denominators used to calculate percentages did not include participants with missing data.

[d] The body-mass index is the weight in kilograms divided by the square of the height in meters.

[e] High-risk status was defined as resident status in a skilled nursing or assisted living facility, or staff who satisfied at least one of the following at the time of screening: aged ≥65 years, BMI ≥35, had chronic kidney disease, type 1 or type 2 diabetes, immunosuppressive disease, receiving immunosuppressive treatment, or were ≥ 55 years of age and have cardiovascular disease, hypertension, chronic obstructive pulmonary disease or other chronic respiratory disease.

eTable 4. Demographics of Participants With Positive SARS-CoV-2 Status by RT-PCR and Negative Serology at Baseline (Treatment Population)

	Treatment Population (All)		Resident Treatment Population		Staff Treatment Population	
	Bamlanivimab (N=66)	**Placebo (N=66)**	**Bamlanivimab (N=17)**	**Placebo (N=24)**	**Bamlanivimab (N=49)**	**Placebo (N=42)**
Age						
Median (Range), y	52.0 (19-96)	52.0 (22-94)	75.0 (58-96)	75.0 (42-94)	42.0 (19-74)	39.5 (22-65)
≥65 y, No. (%)	15 (22.7)	22 (33.3)	13 (76.5)	21 (87.5)	2 (4.1)	1 (2.4)
Sex, No. (%)						
Female	50 (75.8)	47 (71.2)	10 (58.8)	15 (62.5)	40 (81.6)	32 (76.2)
Male	16 (24.2)	19 (28.8)	7 (41.2)	9 (37.5)	9 (18.4)	10 (23.8)
Self-reported race, No./total (%)[a]						
White	58/66 (87.9)	59/66 (89.4)	16/17 (94.1)	22/24 (91.7)	42/49 (85.7)	37/42 (88.1)
Black or African American	7/66 (10.6)	5/66 (7.6)	1/17 (5.9)	2/24 (8.3)	6/49 (12.2)	3/42 (7.1)
Asian	0	1/66 (1.5)	0	0	0	1/42 (2.4)
Native Hawaiian or other Pacific Islander	0	1/66 (1.5)	0	0	0	1/42 (2.4)
Multiple	1/66 (1.5)	0	0	0	1/49 (2.0)	0
Hispanic or Latino, No./total (%)[a]	2/66 (3.0)	6/66 (9.1)	0	3/24 (12.5)	2/49 (4.1)	3/42 (7.1)
BMI, Median (Range)[b]	28.0 (16.1-68.4)	28.8 (16.5-72.4)	30.7 (17.6-68.4)	26.3 (16.5-72.4)	27.6 (16.1-52.9)	29.1 (17.9-48.7)
High risk for severe COVID-19, No. (%)[c]	38 (57.6)	38 (57.6)	17 (100)	24 (100)	21 (42.9)	14 (33.3)

Abbreviations: BMI, body mass index; COVID-19, coronavirus disease 2019.

[a] Race and ethnic group were reported by the patients. Number of subjects with non-missing data, used as denominator.

[b] The body-mass index is the weight in kilograms divided by the square of the height in meters.

[c] High-risk status was defined as resident status in a skilled nursing or assisted living facility, or staff who satisfied at least one of the following at the time of screening: aged ≥65 years, BMI ≥35, had chronic kidney disease, type 1 or type 2 diabetes, immunosuppressive disease, receiving immunosuppressive treatment, or were ≥ 55 years of age and have cardiovascular disease, hypertension, chronic obstructive pulmonary disease or other chronic respiratory disease.

eTable 5. Deaths Among Participants SARS-CoV-2 Serology Negative at Baseline[a]

	Prevention Population (All)		Treatment Population	
	Bamlanivimab (N=484)	**Placebo (N=482)**	**Bamlanivimab (N=66)**	**Placebo (N=66)**
Total deaths	5 (1.0)	6 (1.2)	0	4 (6.1)
Deaths resulting from adverse events[b]	5 (1.0)	2 (0.4)	0	3 (4.5)
Deaths resulting from COVID-19	0	4 (0.8)	0	1 (1.5)

[a] 1 death due to hypovolemic shock reported in participant SARS-CoV-2 serology positive at baseline who received placebo.

[b] Excluding study-specific clinical events related to COVID-19 as per Investigator, causes of deaths are listed in Table 2.

eTable 6. Adverse Events in the Prevention Population, Resident Prevention Population, and Staff Prevention Population

Adverse events, No. (%)[a]	All Prevention Population		Residents Prevention Population		Staff Prevention Population	
	Bamlanivimab (N=484)	Placebo (N=482)	Bamlanivimab (N=161)	Placebo (N=139)	Bamlanivimab (N=323)	Placebo (N=343)
Participants with ≥1 treatment-emergent adverse event[b]	97 (20.0)	86 (17.8)	30 (18.6)	30 (21.6)	67 (20.7)	56 (16.3)
Severity of treatment-emergent adverse event[b,c]						
Severe	15 (3.1)	12 (2.5)	11 (6.8)	8 (5.8)	4 (1.2)	4 (1.2)
Moderate	25 (5.2)	24 (5.0)	8 (5.0)	6 (4.3)	17 (5.3)	18 (5.2)
Mild	54 (11.2)	49 (10.2)	10 (6.2)	15 (10.8)	44 (13.6)	34 (9.9)
Missing	3 (0.6)	1 (0.2)	1 (0.6)	1 (0.7)	2 (0.6)	0
Most common treatment-emergent adverse events (occurring in ≥1% of bamlanivimab or placebo recipients)[d]						
Urinary tract infection	10 (2.1)	10 (2.1)	6 (3.7)	6 (4.3)	4 (1.2)	4 (1.2)
Pneumonia	2 (0.4)	4 (0.8)	2 (1.2)	3 (2.2)	0	1 (0.3)
Fall	2 (0.4)	3 (0.6)	1 (0.6)	3 (2.2)	1 (0.3)	0
Contusion	1 (0.2)	2 (0.4)	1 (0.6)	2 (1.4)	0	0
Gamma-glutamyl transferase increased	1 (0.2)	2 (0.4)	1 (0.6)	2 (1.4)	0	0

	All Prevention Population		Residents Prevention Population		Staff Prevention Population	
	Bamlanivimab (N=484)	**Placebo (N=482)**	**Bamlanivimab (N=161)**	**Placebo (N=139)**	**Bamlanivimab (N=323)**	**Placebo (N=343)**
Hyperkalemia	0	2 (0.4)	0	2 (1.4)	0	0
Arthralgia	4 (0.8)	4 (0.8)	0	2 (1.4)	4 (1.2)	2 (0.6)
Epistaxis	2 (0.4)	2 (0.4)	0	2 (1.4)	2 (0.6)	0
Hypertension	6 (1.2)	9 (1.9)	0	2 (1.4)	6 (1.9)	7 (2.0)
Sinusitis	2 (0.4)	4 (0.8)	0	0	2 (0.6)	4 (1.2)
Nasal congestion	1 (0.2)	4 (0.8)	0	0	1 (0.3)	4 (1.2)
Serious adverse events[e]	19 (3.9)	13 (2.7)	15 (9.3)	10 (7.2)	4 (1.2)	3 (0.9)
Deaths resulting from adverse events[f]	5 (1.0)	2 (0.4)	5 (3.1)	2 (1.4)	0	0
Discontinuation from study participation due to adverse event (including death)	5 (1.0)	2 (0.4)	5 (3.1)	2 (1.4)	0	0

[a] Study-specific clinical events related to COVID-19 were reported separately and not as Adverse Events (per protocol).

[b] A treatment-emergent adverse event was defined as an event that first occurred or worsened in severity after baseline.

[C] Patients with multiple occurrences of these categories were counted once for each category. Patients may be counted in more than one category.

[d] The preferred terms were defined according to the Medical Dictionary for Regulatory Activities, version 23.0.

[e] In the prevention population, the serious adverse events in the bamlanivimab group were urinary tract infection, pneumonia, acquired immunodeficiency syndrome, gastroenteritis, groin abscess, atrial fibrillation, cardio-respiratory arrest, acute myocardial infarction, cardiac failure congestive, coronary artery disease, cerebrovascular accident, headache, hypoesthesia, paresthesia, transient ischemic attack, vascular dementia, small intestinal obstruction, spinal compression fracture, anemia, iron deficiency anemia, ammonia increased, hypoglycaemia, bile duct stone, lumbar spinal stenosis, psychotic disorder. The serious adverse events in the placebo group were pneumonia, bacteremia, sepsis, septic shock, cardio-respiratory arrest, cerebrovascular accident, abdominal distension, ascites, mouth hemorrhage, femur fracture, injury corneal, open globe injury, blood creatinine increased, hyperkalemia, chronic kidney disease, ureterolithiasis, chronic kidney disease, ureterolithiasis, chronic obstructive pulmonary disease, epistaxis, thyrotoxic crisis.

[f] In the prevention population 5 deaths were reported in the bamlanivimab group, 2 deaths were reported in the placebo group.

eTable 7. Sensitivity Analysis – All Prevention Population

	Primary Analysis		**Sensitivity Analysis**	
	Bamlanivimab (N=480)	Placebo (N=481)	Bamlanivimab (N=480)	Placebo (N=481)
Primary outcome				
Participants with mild-or-worse COVID-19, No. (%)	41 (8.5)	73 (15.2)	38 (7.9)	72 (15.0)
Odds ratio, 95% CI	0.43 (0.28, 0.68)		0.41 (0.26, 0.64)	
P-value	<0.001		<0.001	
Absolute risk difference, 95% CI	-6.6 (-10.7, -2.6)		-7.1 (-11.1, -3.1)	

Abbreviations: CI, Confidence Interval; COVID-19, coronavirus disease 2019.

eTable 8. Sensitivity Analysis – Resident Prevention Population

	Primary Analysis		**Sensitivity Analysis**	
	Bamlanivimab (N=159)	Placebo (N= 138)	Bamlanivimab (N=159)	Placebo (N=138)
Primary outcome				
Residents with mild-or-worse COVID-19, No. (%)	14 (8.8)	31 (22.5)	11 (6.9)	30 (21.7)
Odds ratio, 95% CI	0.20 (0.08, 0.49)		0.13 (0.04, 0.36)	
P-value	<0.001		<0.001	
Absolute risk difference, 95% CI	-13.7 (-21.9, -5.4)		-14.8 (-22.8, -6.9)	

Abbreviations: CI, Confidence Interval; COVID-19, coronavirus disease 2019.

eReferences

1. Lilly SARS-CoV-2 Assay EUA Summary. EMERGENCY USE AUTHORIZATION (EUA) SUMMARY LILLY SARS-CoV-2 ASSAY. https://www.fda.gov/media/140543/download.
2. US Food and Drug Administration. COVID-19: Developing Drugs and Biological Products for Treatment or Prevention Guidance for Industry. May 2020. https://www.fda.gov/media/137926/download.