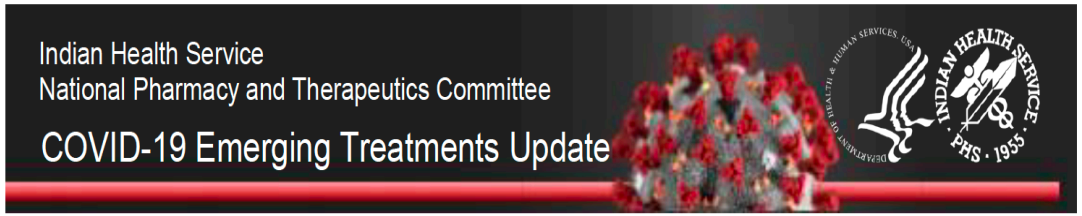
COVID-19 Update November 18, 2020

Jorge Mera, MD FACP

Whitney Essex, APRN

Bamla-nivimab EUA



November 10, 2020

Bamlanivimab (LY-CoV555)

- EMERGENCY USE AUTHORIZATION -

Mechanism of action[1]: Bamlanivimab is a neutralizing IgG1 monoclonal antibody that binds to the receptor binding domain of the spike protein of SARS-CoV-2 to reduce viral load, ameliorate symptoms and prevent hospitalization.

Current Status[1,2]: Bamlanivimab is an investigational drug and is not currently FDA-approved for any indication. On November 9th, 2020, the FDA issued an Emergency Use Authorization (EUA) for bamlanivimab for use in the outpatient setting to treat mild to moderate COVID-19 in adults and pediatric patients with positive results of direct SARS-CoV-2 viral testing who are 12 years of age and older weighing at least 40 kg, and who are at high risk for progressing to severe COVID-19 and/or hospitalization.

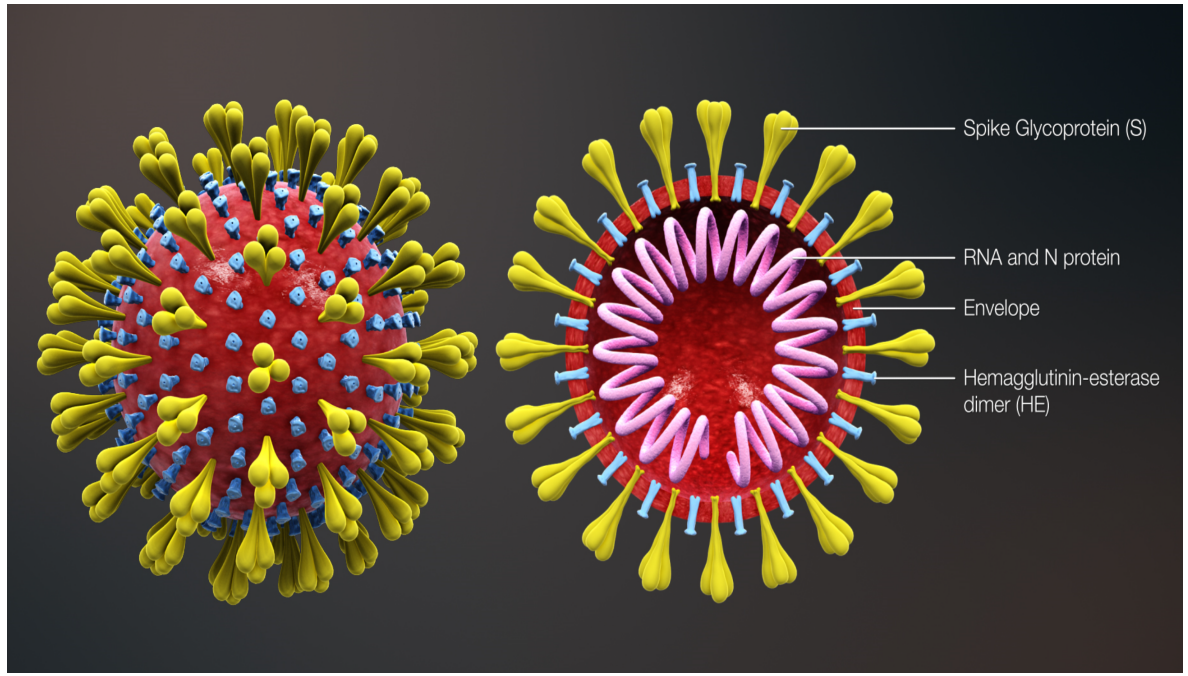
- High risk is defined as patients who meet at least one of the following criteria:
- Have a body mass index (BMI) ≥35
- Have chronic kidney disease
- Have diabetes
- Have immunosuppressive disease
- Are currently receiving immunosuppressive treatment
- Are ≥65 years of age
- Are ≥55 years of age AND have: cardiovascular disease, OR hypertension, OR chronic obstructive pulmonary disease/other chronic respiratory disease.
- ***Are 12–17 years of age AND have:***
  - BMI ≥85th percentile for their age and gender based on CDC growth charts, OR
  - Sickle cell disease, OR
  - Congenital or acquired heart disease, OR
  - Neurodevelopmental disorders, OR
  - A medical-related technological dependence or positive pressure ventilation (not related to COVID-19), OR
  - Asthma, reactive airway or chronic respiratory disease requiring daily medication.

Concept of Using a Bamlanivimab for COVID-19

Biological Plausibility

- Binds to the receptor binding domain in the spike protein
- Neutralizes the virus and prevents infection of tissue culture
- In animal models it has shown marked reductions in viral loads in the upper and lower respiratory tracts
- Passive protection against SARS-CoV-2 in nonhuman primates has been reported

SARS-CoV-2 Structure



SARS-CoV-2 Neutralizing Antibody LY-CoV555 in Outpatients with Covid-19

Inclusion Criteria

- Outpatients ≥ 18 years old, with recently diagnosed mild or moderate Covid-19
- Within 10 days of symptom initiation
- Within 3 days of positive SARS-CoV-2 PCR

Trial Design

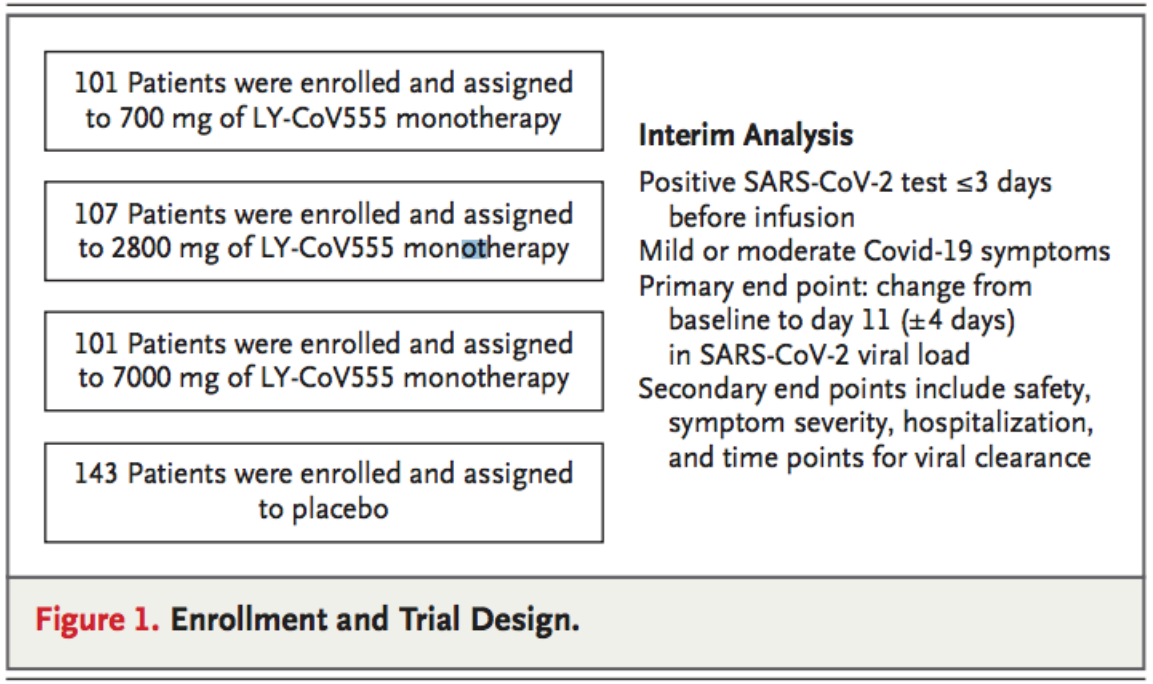


Figure 1. Enrollment and Trial Design.

NEJM October 28, 2020

SARS-CoV-2 Neutralizing Antibody LY-CoV555 in Outpatients with Covid-19

- **Primary Outcome:**
  - Change from baseline in the viral load at day 11
- **Secondary Outcome:**
  - Severity of symptoms
  - Covid-19 related hospitalization

NEJM October 28, 2020

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	LY-CoV555 (N=309)	Placebo (N=143)
Age		
Median (range) — yr	45 (18–86)	46 (18–77)
65 Yr or older — no. (%)	33 (10.7)	20 (14.0)
Female sex — no. (%)	171 (55.3)	78 (54.5)
Race or ethnic group — no./total no. (%)†		
White	269/305 (88.2)	120/138 (87.0)
Hispanic or Latino	135/309 (43.7)	63/143 (44.1)
Black	22/305 (7.2)	7/138 (5.1)
Body-mass index‡		
Median	29.4	29.1
≥30 to <40 — no./total no. (%)	112/304 (36.8)	56/139 (40.3)
≥40 — no./total no. (%)	24/304 (7.9)	9/139 (6.5)
Risk factors for severe Covid-19 — no. (%)§	215 (69.6)	95 (66.4)
Disease status — no. (%)		
Mild	232 (75.1)	113 (79.0)
Moderate	77 (24.9)	30 (21.0)
Median no. of days since onset of symptoms	4.0	4.0
Mean viral load — Ct value¶	23.9	23.8

SARS-CoV-2 Neutralizing Antibody LY-CoV555 in Outpatients with Covid-19

NEJM, October 28,2020

SARS-CoV-2 Neutralizing Antibody LY-CoV555 in Outpatients with Covid-19
NEJM October 28, 2020

Primary Outcome

- Mean decrease from baseline in the log viral load for the entire population was −3.81, (99.97% of viral RNA)

- **Only patients on the 2800 mg** arm had a significant difference VL decrease compared to placebo: −0.53 P=0.02

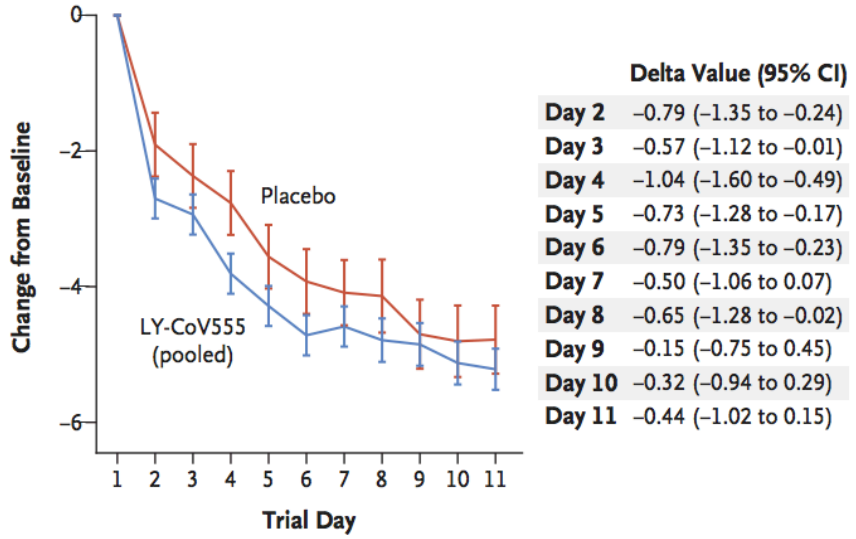
Table 2. Change from Baseline in Viral Load.

Variable	LY-CoV555 (N=309)	Placebo (N=143)	Difference (95% CI)
Primary outcome			
Mean change from baseline in viral load at day 11		−3.47	
	700 mg, −3.67		−0.20 (−0.66 to 0.25)
	2800 mg, −4.00		−0.53 (−0.98 to −0.08)
	7000 mg, −3.38		0.09 (−0.37 to 0.55)
	Pooled doses, −3.70		−0.22 (−0.60 to 0.15)
Secondary outcomes*			
Mean change from baseline in viral load at day 3		−0.85	
	700 mg, −1.27		−0.42 (−0.89 to 0.06)
	2800 mg, −1.50		−0.64 (−1.11 to −0.17)
	7000 mg, −1.27		−0.42 (−0.90 to 0.06)
	Pooled doses, −1.35		−0.49 (−0.87 to −0.11)
Mean change from baseline in viral load at day 7		−2.56	
	700 mg, −2.82		−0.25 (−0.73 to 0.23)
	2800 mg, −3.01		−0.45 (−0.92 to 0.03)
	7000 mg, −2.85		−0.28 (−0.77 to 0.20)
	Pooled doses, −2.90		−0.33 (−0.72 to 0.06)

SARS-CoV-2 Neutralizing Antibody LY-CoV555 in Outpatients with Covid-19
NEJM October 28, 2020

Secondary Outcomes

- Symptoms
  - On days 2 to 6, the patients who received LY-CoV555 had a slightly lower severity of symptoms than those who received placebo.



	Delta Value (95% CI)
Day 2	−0.79 (−1.35 to −0.24)
Day 3	−0.57 (−1.12 to −0.01)
Day 4	−1.04 (−1.60 to −0.49)
Day 5	−0.73 (−1.28 to −0.17)
Day 6	−0.79 (−1.35 to −0.23)
Day 7	−0.50 (−1.06 to 0.07)
Day 8	−0.65 (−1.28 to −0.02)
Day 9	−0.15 (−0.75 to 0.45)
Day 10	−0.32 (−0.94 to 0.29)
Day 11	−0.44 (−1.02 to 0.15)

Figure 3. Symptom Scores from Day 2 to Day 11.

Shown is the difference in the change from baseline (delta value) in symptom scores between the LY-CoV555 group and the placebo group from day 2 to day 11. The symptom scores ranged from 0 to 24 and included eight domains, each of which was graded on a scale of 0 (no symptoms) to 3 (severe symptoms). The I bars represent 95% confidence intervals. Details about the symptom-scoring methods are provided in the Supplementary Appendix.

SARS-CoV-2 Neutralizing Antibody LY-CoV555 in Outpatients with Covid-19: OUTCOMES

Secondary Outcomes

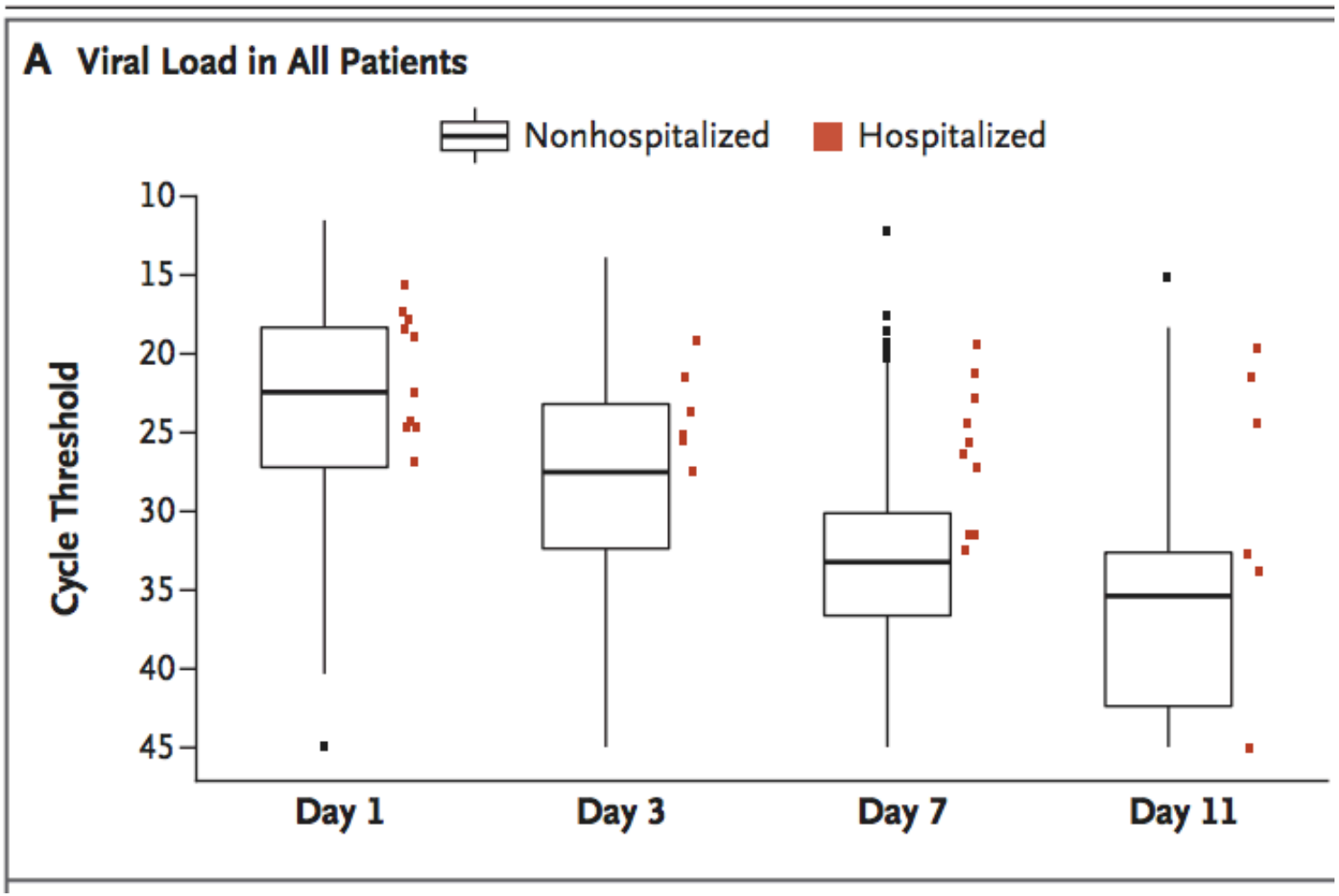
- Covid-19 related hospitalization or visit to an emergency department
  - **LY-CoV555 pooled group**: 1.6%
    - LY-CoV555 700 mg group: 1.0%
  - **Placebo group**: 6.3%

Post hoc analysis

Patients ≥ 65 years of age and those with a BMI ≥ 35 or more who received LY-CoV55 had 4% (4 of 95) hospitalization rate compared to 15% (7 of 48) of those who received placebo.

Table 3. Hospitalization.*

Key Secondary Outcome	LY-CoV555	Placebo	Incidence
	no. of patients/total no.		%
Hospitalization		9/143	6.3
	700 mg, 1/101		1.0
	2800 mg, 2/107		1.9
	7000 mg, 2/101		2.0
	Pooled doses, 5/309		1.6



Hospitalization was 12% (7 of 56 patients)among those who had a high viral load, as compared with a frequency of 0.9% (3 of 340 patients) among those with a lower viral load.

Association Between Viral Load and Hospitalization

NEJM
October 28,2020

SARS-CoV-2 Neutralizing Antibody LY-CoV555 in Outpatients with Covid-19: Conclusions

In this interim analysis of a phase 2 trial, one of three doses of neutralizing antibody LY-CoV555 appeared to accelerate the natural decline in viral load over time, whereas the other doses had not by day 11

NEJM October 28, 2020

Factors to Consider in the Blaze-1 Trial

- **Primary Outcome was change in viral load** within 4 days of day 11
  - Only one dose (2800mg achieved this but not the one approved in EUA)
- **Secondary outcomes**
  - COVID related ED visits and Hospitalization were combined
- The mean time of enrollment was within **4 days of symptoms**
- **Pediatric population not evaluated**

Caution with Phase II trials in General

- Phase II trials mainly tests safety, evaluates doses and may look at some measure of efficacy
- Measuring efficacy can be problematic when the outcome is infrequent because
  - The trial will have to be very long
  - The trial will need many patients
- To overcome this problem investigators look at other endpoints that correlate highly with the outcome we would like to measure
- The problem is that for COVID-19 we really don’t have strong predictors of treatment success

Factors to Consider in General

Monoclonal antibodies do not replicate the normal immune response and we don’t know if the spike protein is the main target.

Is Viral RNA a good measure of response?

- Is it a good surrogate for viral replication?
- Is it a good surrogate for clinical outcomes?

Are clinical symptoms a good clinical endpoint?

- They vary considerably from patient to patient
- They and resolve in the majority of patients

Challenges
Adapted From Paul Sax ID Observation Journal Watch

- **Supply is limited**
  - The supply could be exhausted in less than 2 weeks. How will we choose who gets it?
- **It must be given within 10 days of symptom onset.**
  - In the clinical trial the mean time to delivery was within 4 days of symptoms
  - Some experts think even 10 days is too long a wait for effective intervention — the sooner the better.
- **It must be given intravenously.**
  - How many outpatient clinicians can give infusions in their clinics?
- **People with early COVID-19 disease are at their most contagious.**
  - Most secondary transmissions happen between 1 day before and 5 days after the onset of symptoms, during which time respiratory viral load peaks. And this is precisely when we'll want to bring patients in for treatment.
- **Most infusion centers have a high proportion of patients who are immunocompromised.**

Challenges
Adapted From Paul Sax ID Observation Journal Watch

- **Many infusion centers are not set up for urgent referrals.**
  - Their regular patients have regularly scheduled infusions
- **Both the infusion and the post-treatment monitoring take a lot of time.**
  - This isn't a simple matter of showing up, getting one quick shot, then leaving. The infusion takes 1 hour, and there is a 1-hour monitoring period afterward to ensure no severe allergic reactions ensue. Budgeting 3 hours seems about right.
- **Emergency departments do not want a 3-hour treatment clogging up their patient flow — especially if they don't get paid.**
- **The formulation is tricky to prepare and not stable for very long.**
  - "Preparation of the IV admixture is not simple and is stable for just 7 hours at room temperature or 24 hours under refrigeration (including infusion time)."
- **Serious side effects may occur.**
  - Although not in the published paper, the package insert cites at least one case of anaphylaxis and another serious infusion reaction among bamlanivimab-treated patients.
  - As a result, we are advised that this treatment "may only be administered in settings in which health care providers have immediate access to medications to treat a severe infusion reaction, such as anaphylaxis."

Moving Forward

- Implementation planning in progress
- Will probably not include pediatric population due to lack of data
- Will monitor safety closely
- Not being able to do a randomized study will investigate the possibility of studying a control group to see if we can evaluate efficacy