COVID-19 Update
December 4, 2020

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Outline

- Bamlanivimab EUA
- The concept of using monoclonal antibodies for COVID-19
- Blaze-1 Clinical Trial
- Questions, concerns and challenges
- CNHS working plan

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.

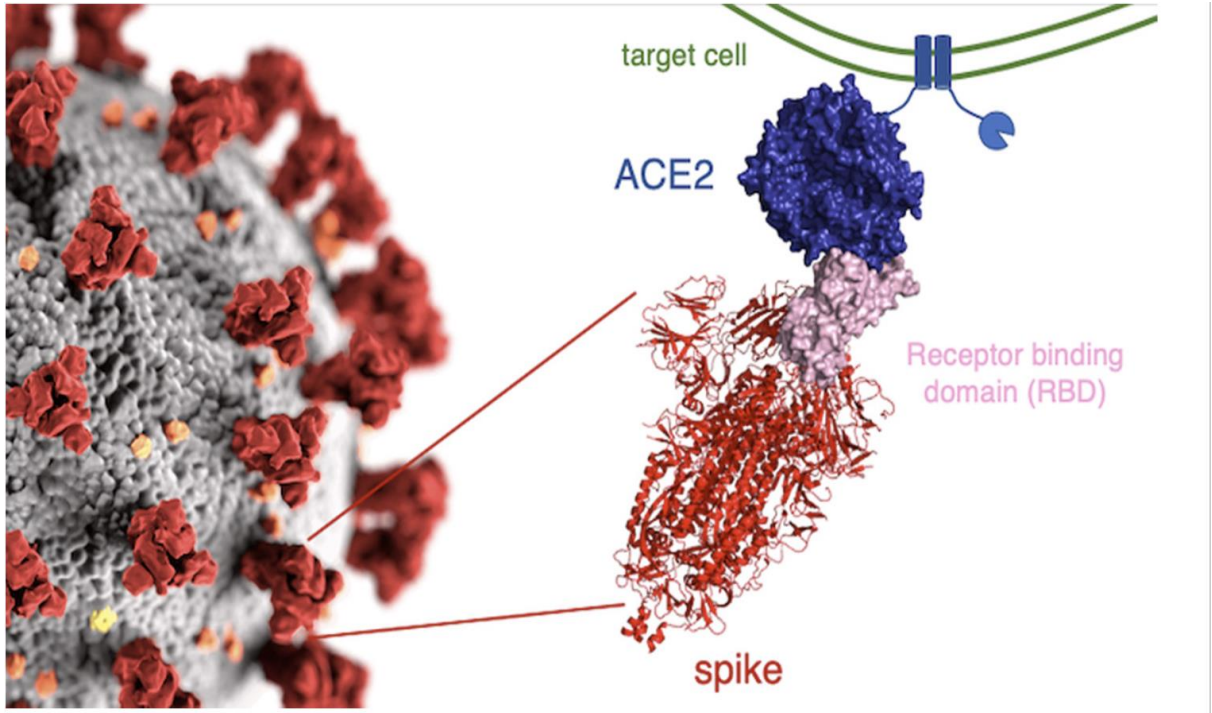
- High risk is defined as patients who meet at least one of the following criteria:
- Have a body mass index (BMI) ≥35
- Have chronic kidney disease
- Have diabetes
- Have immunosuppressive disease
- Are currently receiving immunosuppressive treatment
- Are ≥65 years of age
- Are ≥55 years of age AND 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

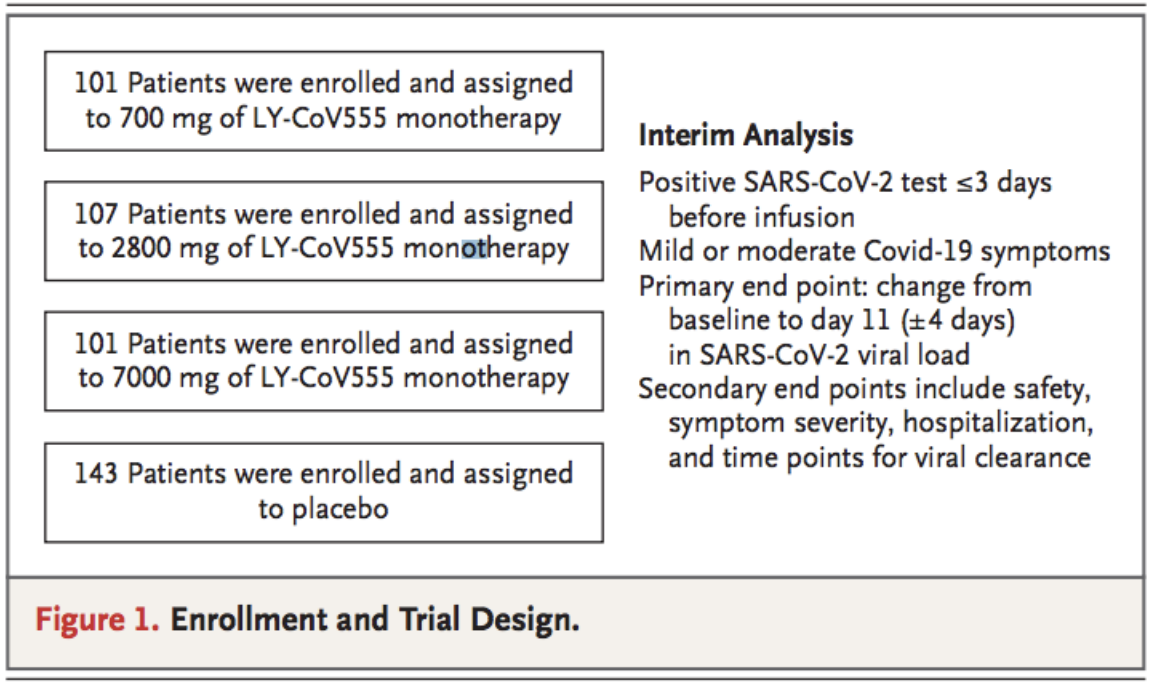


Figure 1. Enrollment and Trial Design.

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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

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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

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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
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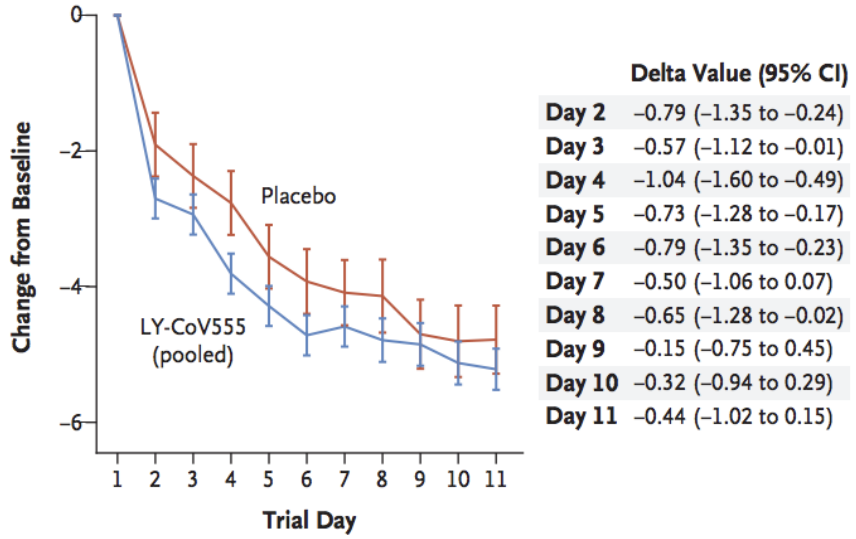
Secondary Outcomes

- 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

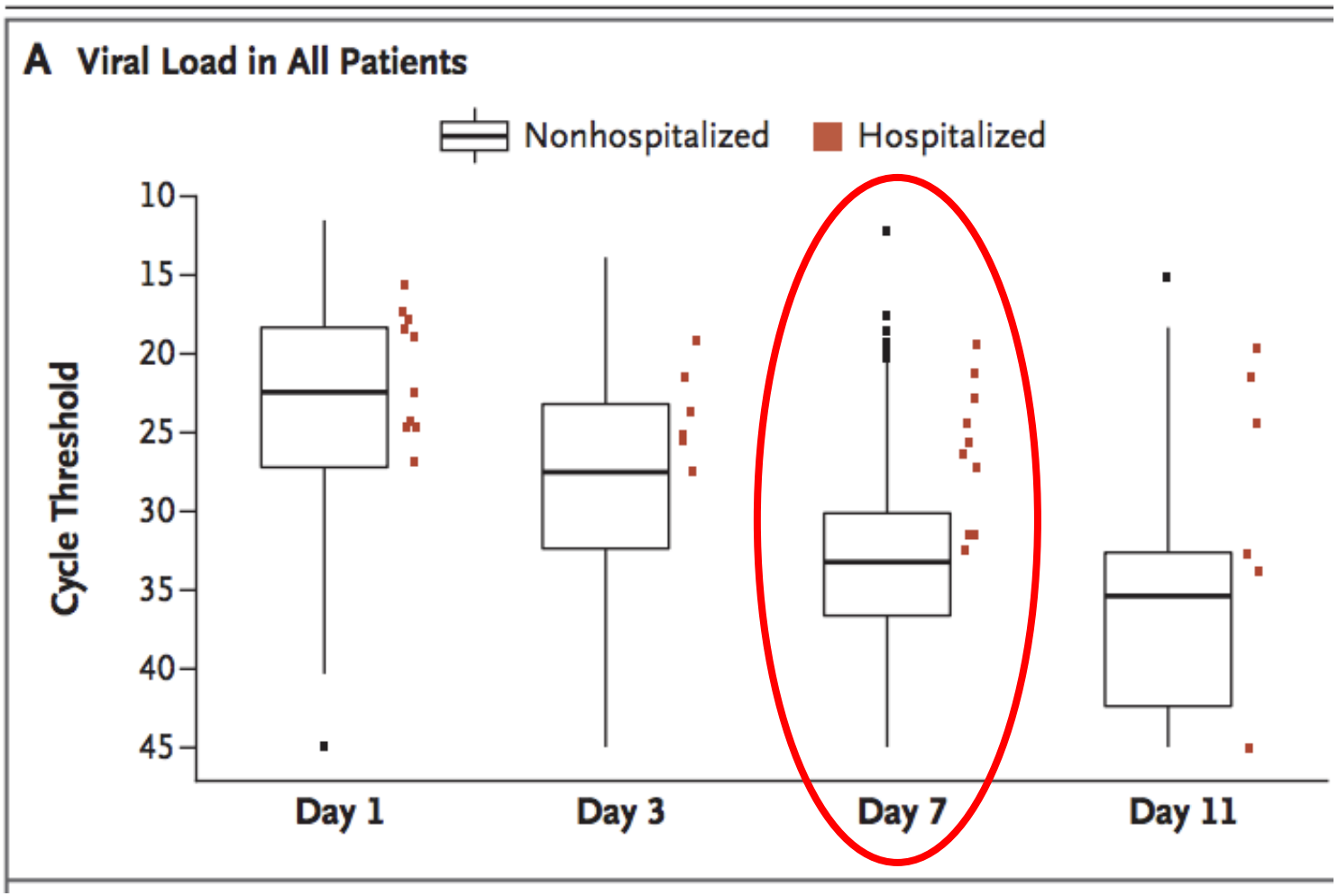
- Covid-19 related hospitalization or visit to an emergency department
  - **LY-CoV555 pooled group**: 1.6%
    - LY-CoV555 700 mg group: 1.0%
  - **Placebo group**: 6.3%

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

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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

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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**

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?
  - **CN have chosen the ones at highest risk**
    - **Age > 65**
    - **BMI > 35**
    - **Diabetes**
    - **Anyone who meets EUA and is very interested except for Peds for now**
- **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.

Challenges
Adapted From Paul Sax ID Observation Journal Watch

- **It must be given intravenously.**
  - How many outpatient clinicians can give infusions in their clinics?
  - **CN is infusing it at one clinic and the UC/ED if capacity allows**

- **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.
  - **CN is well equipped**
- **Most infusion centers have a high proportion of patients who are immunocompromised.**
  - **CN is not using the the infusion center**

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
    - **CN has a hot line, 2 ID providers on call 7 days a week and a dedicated case manager**
- **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.
  - **This is a problem if uptake of the medication increases**
- **ED do not want a 3-hour treatment clogging up their patient flow**
  - **Nobody does but "it is what it is"**

Challenges
Adapted From Paul Sax ID Observation Journal Watch

- **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)."
  - **Our Pharmacists are on board.**
- **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."
  - **BE PREPARED**

What?	Bamlanivimab 700mg IV (200mL total volume when mixed) One-time dose Infused over 1 hour Observation period 1-hour post-infusion
Who?	Age 65+ BMI 35+ Diabetes Others who meet EUA criteria and request it
Where?	Cherokee Nation Outpatient Health Center – 1st Floor - Screening Clinic Entrance WWH Emergency/Urgent Care Department
When?	CNOHC – Monday thru Friday (preferred) ED/UC – Evenings/Weekends if necessary
How?	ID nurse receives list of potential candidates and notifies patients of treatment option Schedules appointment for Provider visit/Infusion Provider to Provider: Call Dr. Mera or Whitney ED/UC: Offer and administer if able, or; Provider to Provider

NIH COVID-19 Guidelines

- At this time, **there are insufficient data to recommend either for or against the use of bamlanivimab** for the treatment of outpatients with mild to moderate COVID-19.
- Bamlanivimab **should not be considered the standard of care** for the treatment of patients with COVID-19.
- **An interim analysis of the BLAZE-1** study, a Phase 2, randomized, placebo-controlled trial, suggested a potential clinical benefit of bamlanivimab for outpatients with mild to moderate COVID-19..
- **More data are needed to assess the impact of bamlanivimab on the disease course of COVID-19** and to identify those people who are most likely to benefit from the drug. Health care providers are encouraged to discuss participation in bamlanivimab clinical trials with their patients.

https://www.covid19treatmentguidelines.nih.gov/statement-on-bamlanivimab-eua