

Monoclonal Antibodies—Clinical Trials, Safety and Efficacy Data and Considerations for Using Vaccines after Therapeutics

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12/20

Emergency Use Authorizations for Monoclonal Antibodies

- FDA has granted two Emergency Use Authorizations for monoclonal antibodies to treat high-risk outpatients with symptomatic COVID-19
 - Eli Lilly: bamlanivimab 700 mg
 - Regeneron: casirivimab 1.2g/imdevimab 1.2g
- Conditions of use very similar for both: require 1 hour infusion plus 1 hour monitoring post-infusion
- Safety data very similar for both: low risk of infusion reactions, including anaphylaxis (more common in highest dose used in trials, very uncommon in EUA dose)
- EUAs do NOT include hospitalized patients

High-Risk Criteria under each EUA

- At least 1 of the following:
 - BMI ≥ 35
 - Chronic kidney disease
 - Diabetes
 - Immunosuppressive disease
 - Receiving immunosuppressive treatment
 - Age ≥ 65 years
 - Age ≥ 55 years AND have any of the following
 - Cardiovascular disease
 - Hypertension
 - COPD/other chronic respiratory disease
- Adolescents (Age 12-17 years) who meet at least 1 of the following criteria:
 - BMI ≥ 85 th percentile for age/gender
 - Sickle cell disease
 - Congenital or acquired heart disease
 - Neurodevelopmental disorders (e.g. cerebral palsy)
 - Medical-related technological dependence [e.g., tracheostomy, gastrostomy, or positive pressure ventilation (not related to COVID-19)]
 - Asthma, reactive airway, or other chronic respiratory disease that requires daily medication for control

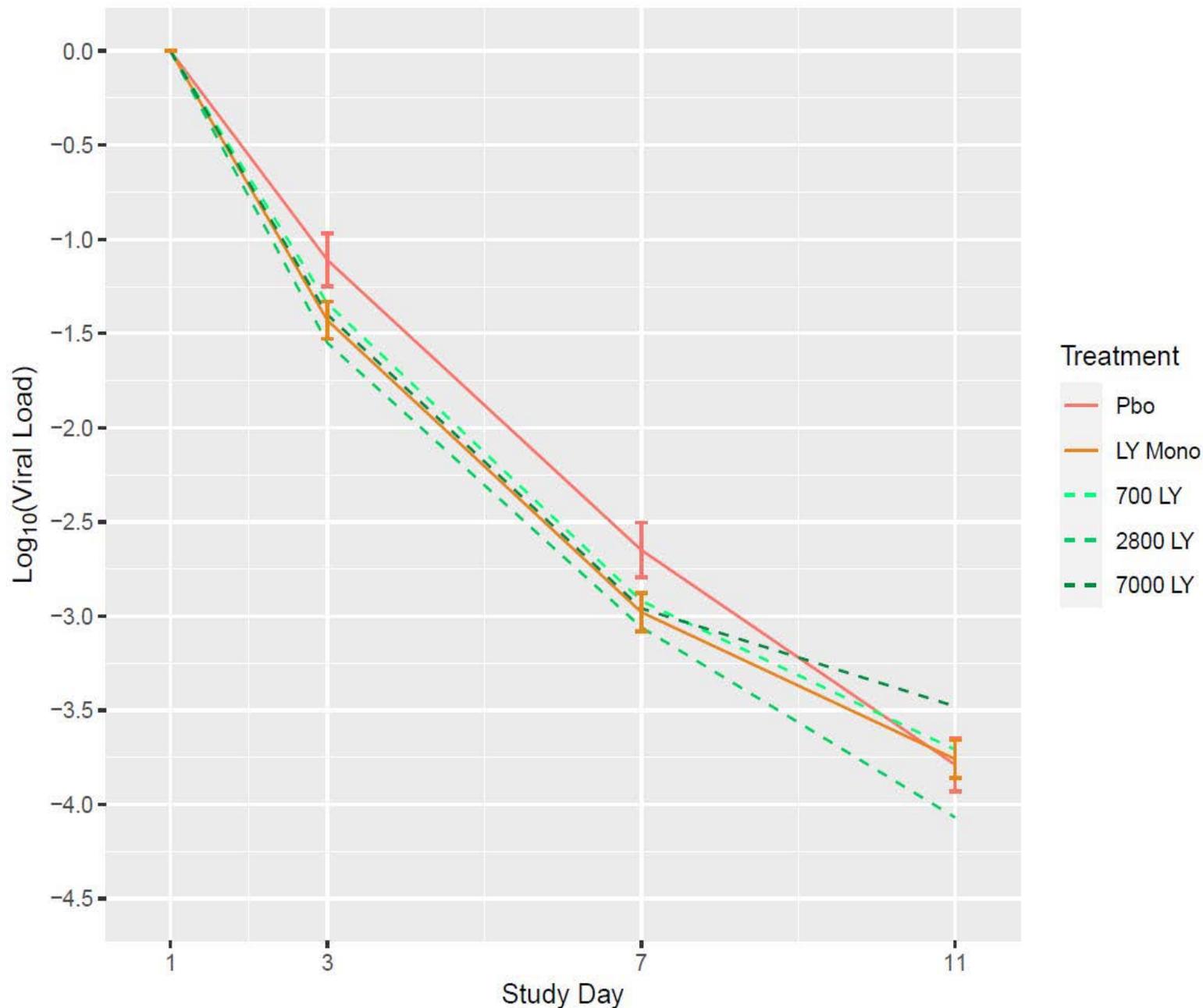
Lilly Development Program: Monoclonal Antibodies

- Two neutralizing antibodies
 - Bamlanivimab: highly potent neutralization at RBD of spike protein
 - Etesevimab: neutralizing antibody; different epitope; production schedule slightly later than for bamlanivimab
- Efficacy trials
 - BLAZE 1: multi-arm platform trial in mild-moderate outpatients; dose-comparison for bamlanivimab vs placebo; primary EP difference from baseline of day 11 viral load; later arms combo of 2 antibodies vs placebo; secondary EP duration of symptoms
 - BLAZE 2: post-exposure prophylaxis in nursing homes
 - ACTIV 2 (NIAID): mild-moderate outpatients, high and low dose; virologic EP
 - ACTIV 3 (NIAID): inpatients, high dose; terminated for futility

LY-CoV555 Monotherapy Data (bamlanivimab)

- The data supporting the EUA for bamlanivimab are based on an interim analysis from Part A of BLAZE-1 that occurred after all enrolled subjects completed at least Day 29 of the trial.
- BLAZE-1 Part A is a randomized, double-blind, placebo-controlled clinical trial studying bamlanivimab for the treatment of subjects with mild to moderate COVID-19 (subjects with COVID-19 symptoms who are not hospitalized). BLAZE-1 enrolled adult patients who were not hospitalized and had at least 1 or more COVID-19 symptoms that were at least mild in severity.
- Treatment was initiated within 3 days of obtaining the clinical sample for the first positive SARS-CoV-2 viral infection determination. Subjects were treated with a single infusion of bamlanivimab (at doses of 700 mg [N=101], 2,800 mg [N=107], or 7,000 mg [N=101]) or placebo (N=156).

The pre-specified primary endpoint in this Phase 2 trial was change in viral load from baseline to Day 11 for bamlanivimab versus placebo. Most subjects, including those receiving placebo, effectively cleared virus by Day 11.



SARS-CoV-2 viral load change from baseline by visit

The predefined secondary endpoint was COVID-19-related hospitalizations or emergency room visits within 28 days after treatment. A lower proportion of bamlanivimab-treated subjects progressed to COVID-19-related hospitalization or emergency room visits compared to placebo-treated subjects. Results for this endpoint were suggestive of a relatively flat dose-response relationship.

Treatment	N^a	Events	Proportion of Subjects %
Placebo	156	9	6%
bamlanivimab 700 mg	101	1	1%
bamlanivimab 2800 mg	107	2	2%
bamlanivimab 7000 mg	101	2	2%
All bamlanivimab doses	309	5	2%

N^a = number of treated patients in analysis

The absolute risk reduction for bamlanivimab compared to placebo is greater in subjects at higher risk of hospitalization according to the EUA high risk criteria.

Treatment	N^a	Events	Proportion of Subjects %
Placebo	69	7	10%
bamlanivimab 700 mg	46	1	2%
bamlanivimab 2800 mg	46	1	2%
bamlanivimab 7000 mg	44	2	5%
All bamlanivimab doses	136	4	3%

Na = number of treated patients in analysis

BLAZE-1 Combination Therapy

LY-CoV555 and LY-CoV016

- The BLAZE-1 randomized, double-blind, placebo-controlled Phase 2 study evaluated LY-CoV555 and LY-CoV016, which bind complementary regions of the SARS-CoV-2 spike protein, for the treatment of symptomatic COVID-19 in the outpatient setting.
- To be eligible, patients were required to have mild or moderate symptoms of COVID-19 as well as a positive SARS-CoV-2 test based on a sample collected no more than 3 days prior to drug infusion.
- The combination arm of the trial enrolled mild-to-moderate, recently diagnosed COVID-19 patients, studying LY-CoV555 2800 mg plus LY-CoV016 2800 mg (n=112) versus placebo (n=156).
- The primary outcome measure was change from baseline to day 11 in SARS-CoV-2 viral load.

Combination Therapy Data: Reduction of Viral Load

- The combination therapy significantly reduced viral load at day 11 ($p=0.011$), meeting the primary endpoint of the study.
- Combination treatment reduced viral levels at day 3 ($p=0.016$) and day 7 ($p<0.001$).
- An exploratory analysis showed that the proportion of patients with persistent high viral load at day 7 for combination therapy was lower (3.0 percent) versus placebo (20.8 percent), corresponding to a nominal p value of $p<0.0001$ without multiplicity adjustment.

Combination Therapy Data: Symptoms & Hospitalizations/ER Visits

- Combination therapy met prespecified clinical endpoints, including the time-weighted average change from baseline in total symptom score from day 1 to 11 ($p=0.009$).
- Improvement in symptoms was observed as early as 3 days after dosing.
- The rate of COVID-related hospitalization and ER visits was lower for patients treated with combination therapy (0.9 percent) versus placebo (5.8 percent), a relative risk reduction of 84.5 percent ($p=0.049$).

Regeneron Clinical Data

- Placebo-controlled RCT two doses of combination (8 g or 2.4 g) versus placebo
- Primary EP viral load through day 7; $p < 0.0001$
- Greatest difference in people with high viral load to start or seronegative at baseline by Regeneron's test
- Predefined secondary endpoint: medically attended visits 6.5% vs 2.8%
- Post-hoc analysis with EUA population, ER visits or hospitalization: 9% vs 3%

Bottom line: EUA population, ER visit or Hospitalization

Lilly single antibody: 10% vs 3%

Regeneron: 9% vs 3%

Lilly combo product (not EUA population): 5.8% vs 0.9%

Use of vaccine after monoclonal

- Most infected patients are mounting their own immune response at the time of antibody administration
- Therapeutic use in already infected patients unlikely to cause concern but will be studied as soon as vaccines available
- Prophylactic use (if effective, studies underway with multiple antibodies) will be more concerning
- Some antibodies have long half lives
- This setting will also be studied by vaccinating people post-monoclonal administration, if prophylactic studies are successful and when vaccines available