Antibody Therapy Literature Review: COVID-19 Clinical Advisory Group Update
April 2021

Background:
- The Food and Drug Administration has granted Emergency Use Authorization (EUA) to two combination antibody therapies (casirivimab & imdevimab, bamlanivimab & etesevimab) for use in non-hospitalized patients with mild to moderate COVID-19. The EUA for bamlanivimab monotherapy was revoked on April 16, 2021.
- Bamlanivimab and etesevimab bind to distinct but overlapping epitopes of the spike protein receptor binding domain. In contrast, casirivimab and imdevimab bind to non-overlapping epitopes of the spike protein receptor binding domain.¹

Data Summary:

Randomized Controlled Trials²⁴¹⁵
- There is no data to support the use of COVID-19 antibody therapies in patients hospitalized due to COVID-19. The study that evaluated bamlanivimab monotherapy in this setting was terminated early due to a lack of clinical benefit.
- In outpatients, bamlanivimab & etesevimab reduced the rate of hospitalizations or ED visits and viral load (surrogate markers for efficacy) when compared to placebo in a statistically significant way. The decrease associated with bamlanivimab monotherapy on these two outcomes was not considered statistically significant in the phase 2/3 study.
  - In one analysis of patients with high risk, the mortality rate was 0% in patients who received bamlanivimab & etesevimab vs. 1.9% in the placebo group (p< 0.001).
  - Recent unpublished results from the phase 3 BLAZE-1 study showed treatment with bamlanivimab & etesevimab reduced the rate of hospitalization and death by 5% (absolute risk reduction) when compared to placebo in high risk non-hospitalized patients with mild to moderate COVID-19.
- In outpatients, casirivimab & imdevimab (combined dose group) reduced the rate of medically attended visits and viral load (surrogate markers for efficacy) when compared to placebo.
  - Recent data from a phase 3 study showed treatment reduced hospitalization and death in high risk patients. The absolute risk reduction compared to placebo was 3.3% for the 2,400 mg dose group and 2.2% for the 1,200 mg dose group.
  - The benefit of antibody treatment in outpatients is increased in high risk patients, particularly in patients ≥65 years of age or with a BMI ≥ 35.

Resistant Variants¹⁰¹¹
- As of 3/27/2021, the major circulating variants of SARS-CoV-2 in the United States are: B.1.1.7 (44.1%), B.1.2 (10%), B.1.526 (9.2%), and B.1.429 (6.9%). Table 1 shows the neutralization activity of the EUA antibody therapies on pseudoviruses in the following lineage: B.1.1.7, B.1.351, P.1, B.1.427/B.1.429, and B.1.526. It is not known how closely this data correlates with clinical outcomes.
  - Casirivimab with imdevimab does not show decreased susceptibility to any of these variants.
  - Bamlanivimab alone retains susceptibility only to the B.1.1.7 variant. Bamlanivimab with etesevimab is active against the B.1.1.7 variant, have reduced activity against the B.1.526 & B.1.427/B.1.429 variants and likely have no activity against the B.1.351 & P.1 variants.
- One study showed that current EUA antibody therapies retain neutralizing activity against the B.1.1.7 variant of SARS-COV-2. However, both bamlanivimab and the combination of bamlanivimab and etesevimab were ineffective against the B.1.351 variant. Combination use of casirivimab & imdevimab on the B.1.351 variant also showed a decrease in neutralizing activity.

Guideline Recommendations:
- **IDSA guidelines**
  - Among ambulatory patients with mild to moderate COVID-19 at high risk for progression to severe disease, the IDSA guideline panel suggests bamlanivimab/etesevimab or casirivimab/imdevimab rather than no neutralizing antibodies. (Conditional recommendation, low certainty of evidence) (Last updated April 11, 2021)
    - Local variant susceptibility may be considered in the choice of the most appropriate neutralizing antibody therapy.
  - Bamlanivimab monotherapy is not recommended for hospitalized patients with severe COVID-19 (Strong recommendation, moderate certainty of evidence). (Last updated April 11, 2021)
- **NIH guidelines**
  - Both bamlanivimab 700 mg plus etesevimab 1,400 mg and casirivimab 1,200 mg plus imdevimab 1,200 mg are recommended for the treatment of outpatients with mild to moderate COVID-19 who are at high risk of clinical progression, as defined by the EUA criteria. (AIIa) (Last updated April 21, 2021)
  - Use of anti-SARS-CoV-2 monoclonal antibodies in patients who are hospitalized because of COVID-19 is not recommended. (AIIa) (Last updated April 21, 2021)

Recommendations:
- Until more data is available, reserve the use of casirivimab & imdevimab to non-hospitalized adult COVID-19 patients with a BMI ≥ 35 OR age ≥ 65 AND symptom onset of ≤ 4 days. Use is restricted to emergency departments and by the EUA limitations of authorized use.
  - Since the majority of non-hospitalized patients will not experience disease progression or be hospitalized, the clinical benefits of COVID-19 antibody therapies are limited. Current evidence suggests patients with BMI ≥ 35 OR age ≥ 65 will likely benefit the most from treatment.
  - Bamlanivimab monotherapy no longer has EUA status and should not be used.
- Monoclonal or polyclonal COVID-19 antibodies are not recommended in patients hospitalized for COVID-19.
- Additional Exclusion Criteria: Patients with recent administration of other COVID-19 EUA treatments including convalescent plasma or IVIG, patients who are hospitalized.
Analysis

**Phase 2: LOE 1b, n=452**

Chen et al. BLAZE-1 Study

2 Oct 2020

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**Interim Analysis**

**Baseline Demographics**
- Median age of 45-46; over 70% of patients had mild disease
- 44.7% of patients in the bamlanivimab groups had a BMI of ≥ 30 (median 29.4) vs. 46.8% in the placebo group
- Close to 70% of patients had risk factors for severe COVID-19 (e.g. age ≥ 65, BMI ≥ 35)
- Mean viral load: 23.9 vs. 23.8 (bamlanivimab vs. placebo)
- Median days from onset of symptoms: 4

**Treatment Groups:**
- Bamlanivimab 700 mg (BAM700), n = 101
- Bamlanivimab 2800 mg (BAM2800), n = 107
- Bamlanivimab 7000 mg (BAM7000), n = 101
- Placebo, n = 143

**Inclusion criteria**
- Non-hospitalized adult patients with ≥ 1 mild or moderate COVID-19 symptoms
- ≤ 3 days from confirmation of COVID-19 infection
- Male or non-pregnant female

**Key Exclusion criteria**
- SpO2 ≤ 93% on room air or PaO2/FiO2 < 300
- Respiratory rate ≥ 30/min, HR ≥ 125/min
- Allergy to any component of the treatment options
- On or anticipated need for mechanical ventilation
- Hemodynamic instability, co-morbidities that are life threatening or require surgery soon
- History of positive SARS-CoV-2 serology test
- Pregnancy or are breastfeeding

**Therapy Groups**

- **Primary outcome:**
  - Mean change in log viral load by day 11 compared to placebo
    - BAM700: -0.20 (-0.66 to -0.25, p = 0.38)
    - BAM2800: -0.53 (-0.98 to -0.08, p = 0.02)
    - BAM7000: 0.09 (-0.37 to 0.55, p = 0.70)
  - Both treatment and placebo groups had decreases in viral load over time

- **Secondary outcome:**
  - By day 3, only the BAM2800 group showed statistically significant improvement in mean log viral load reduction compared to placebo: -0.64 (-1.11 to -0.17). However, pool analysis of all doses suggests improvement in viral load with bamlanivimab.
  - By day 29, less patients were hospitalized (ED visit or inpatient hospitalization) for COVID-19 in the combined bamlanivimab group (1.6% vs. 6.3% in the placebo group)
  - Difference compared to placebo
    - BAM700: 5% (0 to 10, p = 0.09), BAM2800: 4% (-1 to 9, p = 0.21), BAM7000: 4% (-2 to 9, p = 0.21), **Pooled BAM: 4% (1 to 9%, p = 0.02)**
  - **Post-hoc analysis of patients ≥ 65 years of age or patients with BMI ≥ 35** showed a greater reduction in the rate of hospitalization with bamlanivimab vs. placebo (4% vs. 14.6%)
  - Patients who received bamlanivimab had improved symptom scores from baseline compared to patients who received placebo from day 2 to 6.

- **Adverse events:**
  - No serious adverse events were reported in the bamlanivimab groups.
  - 22.3% of patients experienced an adverse event in the bamlanivimab group vs. 24.5% in the placebo group. The most commonly reported adverse event in the bamlanivimab group was nausea.
  - Infusion related reactions occurred in 2.3% of bamlanivimab patients vs. 1.4% in patients who received placebo.

**Limitations:**
- **Interim analysis of an ongoing trial**
- **Did not adjust for multiple testing** in the statistical analyses which makes interpretation of statistical significance challenging
- **Use of surrogate markers for efficacy**
- **Use of nasopharyngeal swabs to determine viral load may not accurately reflect the viral load in the lower respiratory tract.**

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**Literature Review Table**

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### Analysis

**Phase 1/2:** LOE 1b, n=2020

Weinreich et al. (2020) - Study terminated early

Lundgren et al. (2021) - PMID: 333327780

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| Lundgren et al. March 2021<sup>1</sup> (ACTIV-3/TICO LY-CoV555) LOE= 1b, n = 314 Study terminated early | Multi-group, multi-stage, randomized, double-blind study  - Allows for assessment of multiple therapeutic options against placebo  - Incorporation of early futility and safety evaluation before enrollment of full sample size (phase 1)  

**Treatment Groups:**  
- BAM7000, n = 163  
- Placebo, n = 151

Patients received background therapy that included remdesivir and when appropriate, supplemental oxygen and glucocorticoids.

**Inclusion Criteria:**  
- Hospitalized adult patients with confirmed SARS-CoV-2 infection and duration of COVID-19 symptoms ≤ 12 days

**Key Exclusion Criteria:**  
- Has received convalescent plasma, SARS-CoV-2 IVIG or a monoclonal antibody against SARS-CoV-2  
- End organ failure (during phase 1)

**Baseline Demographics:**  
- Patients in the BAM7000 group appears to be at higher risk for disease progression based on baseline characteristics  
- 95% of patients were on remdesivir and 49% were receiving glucocorticoids

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<th>Casirivimab &amp; Imdevimab</th>
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| Weinreich et al. Dec 2020<sup>4</sup> (PMID: 333327780) Phase1/2: Interim Analysis | Randomized, double-blind, placebo-controlled multi-centered trial. Interim analysis of the first 275 patients enrolled in the study.  

**Treatment Options:**  
- REGN-COV2 2.4 g, n = 92  
- REGN-COV2 8 g, n = 90  
- Placebo, n = 93

REGN-COV2 = Casirivimab and imdevimab as a cocktail in equal doses.

Analysis includes a modified set of patients who were serum antibody-negative at baseline. (83% of the 275 patients)

**Inclusion Criteria:**  
- Non-hospitalized patients ≥ 18 years of age  
- Confirmed SARS-CoV-2 infection within 72 hours of randomization and symptom onset ≤ 7 days

**Key Exclusion Criteria:**  
- Hospitalized adult patients with confirmed SARS-CoV-2 infection and duration of COVID-19 symptoms ≤ 12 days

| Efficacy outcome: |  
- Pulmonary ordinal outcome at day 5 (based on oxygen requirements and ranges from death to the ability to perform normal daily activities)  
  - No difference between BAM7000 and placebo in the likelihood of being in the more favorable category (OR 0.85; CI 0.56 to 1.29, p = 0.45)  
  - Pulmonary-plus outcome at day 5 (range of organ dysfunctions that could be related the disease)  
  - No difference between BAM7000 and placebo (OR 0.87; CI 0.57 to 1.31, p = 0.50)

| Safety outcome: |  
- Rate of composite endpoint consisting of death, serious adverse events or grade 3/4 adverse events through day 5  
  - BAM7000: 19% vs. placebo: 14% (OR 1.56; CI 0.78 to 3.10, p = 0.2)  
  - Majority of the events were grade 3 or 4 adverse events  
  - 14 patients died in the BAM7000 group vs. 5 in the placebo group (HR 2; CI 0.67 to 5.99, p = 0.22)

| Adverse events: |  
- Infusion reactions occurred in 14% of BAM7000 patients vs. 9% in placebo patients. The majority of the infusion related side effects were grade 1 or 2 in severity.

| Viral load outcome: |  
- Time weighted average change from baseline in viral load through day 7 (in log<sub>10</sub> scale)  
  - Modified analysis set  
    - REGN-COV2 2.4 g: LS mean difference from placebo was -0.52 (-1.04 to 0)  
    - REGN-COV2 8 g: LS mean difference from placebo was -0.6 (-1.12 to -0.08)  
    - Combined REGN-COV2: LS mean difference from placebo was -0.56 (-1.02 to -0.11)  
  - Overall population set  
    - REGN-COV2 2.4 g: LS mean difference from placebo was -0.25 (CI -0.60 to 0.10)  
    - REGN-COV2 8 g: LS mean difference from placebo was -0.56 (CI -0.91 to -0.21)  
    - Combined REGN-COV2: LS mean difference from placebo was -0.41 (CI -0.71 to -0.10)  
  - Post-hoc analysis showed greater treatment benefit in patients with the highest viral loads. (i.e. baseline viral load > 10<sup>7</sup> copies/mL)

| Clinical outcome: |  
- Rate of medically attended visits through day 29 (include ambulatory/ED visits and hospitalizations)

| Conclusions |  
- REGN-COV2 did more effective in reducing viral load than placebo. However, this was mainly driving by the change observed with the 8 g dose.  
- A trend towards reduction in medically attend visits in the REGN-COV2 groups was observed when compared to placebo with greater reduction in patients with serum antibody negative status at baseline.

**Limitations:**  
- Interim analysis with no formal hypothesis testing to control for type I errors. As a result, the data is considered exploratory.  
- Use for surrogate markers for efficacy
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| ▪ Known hypersensitivity to any component of the treatment options  
▪ Pregnancy or are breastfeeding  
▪ Past, current or planned use of COVID-19 EUA approved treatments, IVIG, systemic corticosteroids or convalescent plasma  
▪ Continued sexual activity in women of childbearing potential or men who are unwilling to practice highly effective contraception for this study.  
Baseline demographics:  
▪ Median age of 44; 56% of the patients were Hispanic or Latino  
▪ The median number of days from reported COVID-19 symptoms to randomization was 3 days.  
▪ BMI of study population was 30.25  
▪ ≥ 1 risk factors for hospitalization: 64% of patients | ▪ Modified analysis set: combined REGN-COV2 (6%) vs. placebo (15%), difference of 9% (CI: -29 to 11); REGN-COV2 2.4 g (5%), difference of 10% (-32 to 13); REGN-COV2 8 g (8%), difference of 8% (-30 to 16)  
▪ Overall population set: combined REGN-COV2 (3%) vs. placebo (6%), difference of 3% (CI: -16 to 9); REGN-COV2 2.4 g (3%), difference of 3% (-18 to 11); REGN-COV2 8 g (3%), different of 3% (-18 to 11)  
▪ Adverse effects:  
  - Few adverse events were reported in the REGN-COV2 treatment groups and most were low grade in nature  
  - No reports of grade 2 or high infusion related reactions or hypersensitivity in the REGN-COV2 2.4 g group. | ▪ Study used a continual patient enrollment design and combined patients from phase 1 & 2 of the study.  
▪ Data only suggests a potential clinical benefit and the primary outcome included ambulatory care visits.  
▪ Sample size too small to accurately assess safety of treatment. |

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| R10933-10987-COV-2067 | Randomized, double-blind, placebo-controlled trial of the 799 patients who completed a minimum of 28 days of the study.  
Treatment Groups:  
▪ REGN-COV2 2.4 g, n = 266  
▪ REGN-COV2 8 g, n = 267  
▪ Placebo, n = 266  
Inclusion Criteria:  
▪ Non-hospitalized adult patients with at least 1 mild to moderate COVID-19 symptoms  
Key Exclusion Criteria  
▪ Past, current or planned use of COVID-19 treatments  
Baseline demographics  
▪ Mean age of 42  
▪ 31% of patients had 1 or more severe symptoms  
▪ Medium duration of symptoms was 3 days  
▪ Mean viral load 5.8 log10 copies/mL  
▪ Around 60% of patients had at least one high risk factor for COVID-19 progression | ▪ Primary outcome:  
  - Time weighted average change in viral load from baseline by day 7  
  - Modified full analysis set  
    - Difference between REGN-COV2 (pooled data) and placebo was -0.36 log10 copies/mL (p<0.0001)  
    - The greatest reduction compared to placebo was seen in patients with high viral load and in patients who were seronegative at baseline  
▪ Clinical outcome:  
  - The rate of medically attended visits for COVID-19 was lower in patients who received REGN-COV2 vs. placebo (2.8% vs. 6.5%, p = 0.02). The observed difference between the 2.4 g or 8 g dose and placebo was not statistically significant.  
  - In the post hoc analysis, lower rate of COVID-19 associated hospitalizations and ED visits were noted in the REGN-COV2 group vs. placebo. (1.8% vs. 4.3%, NS). The impact of treatment with REGN-COV2 was greater in patients at high risk for progression to severe disease or hospitalization  
    - REGN-COV2 2.4 g: 2.9%, REGN-COV2 8 g: 2.5%, combined REGN-COV2: 2.6%, placebo: 9%. The combined REGN-COV2 group showed a statistically significant difference when compared to placebo.  
    - Median time to symptom improvement was 5 days for the REGN-COV2 group vs. 6 days in the placebo group.  
▪ Adverse events:  
  - No serious adverse events were considered to be associated with the study drug  
  - One anaphylactic reaction was reported within 1 hour after infusion. Infusion-related reactions that were moderate in severity occurred in 1.5% of patients in the REGN-COV2 8 g group. None occurred in the 2.4 g group. | ▪ Treatment with REGN-COV2 reduced viral load and medically attended visits when compared to placebo.  
▪ Trend towards improved rate of hospitalizations and ED visits with greater improvement in patients at high risk of progression to severe disease or hospitalization.  
Limitation:  
▪ Data extracted from FDA documents and full publication of the data is not available for review. |

Bamlanivimab and Etesevimab

Gottlieb et al. Jan 2021 (BLAZE-1) | Randomized, double-blind, placebo-controlled trial of patients with mild to moderate COVID-19 in the outpatient setting. | ▪ Primary outcome:  
  - Change in log10 viral load from baseline to day 11:  
    - Difference of 3% (CI: -16 to 9); REGN-COV2 2.4 g (3%), difference of 3% (-18 to 11); REGN-COV2 8 g (3%), different of 3% (-18 to 11)  
▪ Adverse events:  
  - No serious adverse events were considered to be associated with the study drug  
  - One anaphylactic reaction was reported within 1 hour after infusion. Infusion-related reactions that were moderate in severity occurred in 1.5% of patients in the REGN-COV2 8 g group. None occurred in the 2.4 g group. | ▪ Combination therapy with bamlanivimab and etesevimab significantly decreased viral load compared to placebo. In
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| **Treatment Groups:** | - Change in viral load was not significantly different compared to placebo for the monotherapy groups  
- The combination therapy group showed a statistically significant difference compared to placebo (-0.57; CI -1.00 to -0.14, p = 0.01) | **Secondary outcome:**  
- No statistically significant difference between treatment groups and placebo on 74 of the 84 secondary end points.  
- Significant difference in change of viral load AUC from baseline to day 29 in the BAM2800 and combination groups.  
- In terms of change in symptom improvement, no statistically significant difference was observed for the BAM2800 and combination groups when compared to placebo.  
- Only the BAM700 group had a statistically significant change in symptom resolution from baseline to day 11 when compared to placebo.  
- Rate of COVID-19 related hospitalizations, ED visits at day 29: 1% BAM700, 1.9% BAM2800, 2% BAM7000, 0.9% combination therapy, 5.8% placebo. **The difference compared to placebo was statistically significant in the combination group only** (-4.9% CI -8.9% to -0.8%, p = 0.049)  
- **Post-hoc analysis:**  
  - Lower hospitalization rate in patients ≥ 65 years of age or in patients with BMI ≥ 35 for the BAM700 and combination therapy groups when compared to placebo.  
  - BAM700 2.7%, combination therapy 0%, placebo 13.5%  
- **Adverse events:**  
  - One patient who received combination therapy had a serious adverse event.  
  - The serious adverse event (UTI) was considered unrelated to the study drug.  
  - The most commonly reported adverse events were nausea and diarrhea  
  - Immediate hypersensitivity reactions occurred in 6 patients in the bamlanivimab groups, 2 patients in the combination group and 1 patient in the placebo group. The reactions were generally mild in severity. | **contrast to phase 1/2 results, bamlanivimab monotherapy no longer had a statistically significant impact on viral load reduction when compared to placebo.**  
**Combination therapy was also better than placebo in reducing the rate of COVID-19 related hospitalizations or ED visits. A larger impact of treatment was observed in patients ≥ 65 years of age or had a BMI ≥ 35.** |
| **Inclusion Criteria:**  
  - Non-hospitalized adult patients with at least one mild or moderate symptoms of COVID-19  
  - Within 3 days of first positive test for SARS-CoV-2  
  - Male or non-pregnant female | **Limitations:**  
- **Interim analysis**  
- Study population relatively small  
- No adjustments for multiple testing which makes interpretation of statistical significance challenging  
- Unknown how much of a benefit can be attributed to etesevimab alone vs. a synergistic effect of combination therapy  
- Assessment of viral load at day 11 may be too late in the clinical course. |  |
| **Key Exclusion Criteria:**  
  - SpO2 < 93% on room air or PaO2/FiO2 < 300, respiratory rate ≥ 30/min, HR ≥ 125/min  
  - Allergy to any component of the treatment options  
  - On or anticipated need for mechanical ventilation  
  - Hemodynamic instability, co-morbidities that are life threatening or require surgery soon  
  - History of positive SARS-CoV-2 serology test | **Baseline demographics:**  
  - Mean age of 44.7, 67.1% had 1 or more risk factors for severe disease  
  - Medium duration of symptom onset: 4. The majority of patients had mild symptoms  
  - Mean SARS-CoV-2 cycle threshold was 23.7  
  - Patients ≥ 65 years of age or patients with BMI ≥ 35 were excluded. Single dose of bamlanivimab 700mg/etesevimab 1,400 mg (n = 158), bamlanivimab 2,800 mg/etesevimab 2,800 mg (n = 101), bamlanivimab 700 mg (n = 103) or placebo (n = 153)  
  - Rates of viral load > 5.27 on day 7: placebo 31%, bamlanivimab 700 mg/etesevimab 1,400 mg 14% (p < 0.001), bamlanivimab 2,800 mg/etesevimab 2,800mg 10% (p<0.001) |  |
| **Study Population:** | - Rate of treatment-emergent bamlanivimab-resistant variants: 7.1% BAM700, 9.8% BAM2800, 11.3% BAM7000, 1% combination therapy, 4.8% placebo. |  |
| **Eli Lilly EUA Fact Sheet** | - **Phase 3 BLAZe 1 Data:** Single dose of bamlanivimab 2,800 mg & etesevimab 2,800 mg (n = 518) vs. placebo (n = 517)  
  - All patients met criteria for being high risk. Median age of 56, 77% had mild disease and the mean duration of symptoms was 4 days  
  - 70% reduction in rates of COVID-19 associated hospitalization (224 hours of acute care) or death by any cause by day 29 with bamlanivimab 2,800 mg & etesevimab 2,800 mg compared to placebo (2% vs. 7%, p = 0.001). There was no death in the treatment group vs. 10 deaths in the placebo group (p <0.001)  
  - More patients had high viral load (>5.27) at day 7 in the placebo group  
  - **Phase 4 Data:** Phase 2 randomized, double-blind, placebo-controlled study of non-hospitalized patients with mild to moderate COVID-19. Patients ≥ 65 years of age or patients with BMI ≥ 35 were excluded. Single dose of bamlanivimab 700mg/etesevimab 1,400 mg (n = 158), bamlanivimab 2,800 mg/etesevimab 2,800 mg (n = 101), bamlanivimab 700 mg (n = 103) or placebo (n = 153)  
  - Rates of viral load > 5.27 on day 7: placebo 31%, bamlanivimab 700 mg/etesevimab 1,400 mg 14% (p < 0.001), bamlanivimab 2,800 mg/etesevimab 2,800mg 10% (p<0.001) | **Bamlanivimab/etesevimab reduced the rate of COVID associated hospitalization or death**  
**Less patients had high viral load 7 days after receiving bamlanivimab/etesevimab** |
| **Eli Lilly, March 10, 2021 n=769** | **COVID-19 related hospitalizations and deaths**  
- Bamlanivimab/etesevimab: 4 events, placebo: 15 events; 87% risk reduction (p <0.0001)  
- Viral load reduction was similar to what was observed reported by Gottlieb et al.  
- **Adverse events:**  
  - Safety profile of bamlanivimab/etesevimab was consistent with data from earlier phases of the trial. | **Combination therapy with bamlanivimab/etesevimab lowered the risk of COVID-19 related hospitalizations and death**  
**Limitation:**  
- Full publication of result still pending |
Wang et al. Feb 2021
Pre-print (not peer reviewed yet)

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Results</th>
<th>Conclusions</th>
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</table>
| Testing of the neutralizing effect of 30 monoclonal antibodies against B.1.1.7 (UK) and B.1.351 (South Africa) variants of SARS-CoV-2. | ▪ **Key findings**
- B.1.1.7 variant is refractory to neutralization by most monoclonal antibodies that target the N-terminal domain (NTD) of the spike protein and to a few monoclonal antibodies that target the receptor-binding domain (RBD).
- B.1.351 variant is refractory to neutralization by most monoclonal antibodies that target the NTD but many that target the RBD.
  - Neutralizing activity of bamlanivimab and casirivimab were either completely or markedly abolished.
  - Etesevimab is also inactive against B.1.351
  - Imdevimab retains activity against the B.1.351 variant
  - Combination of bamlanivimab and etesevimab is ineffective in neutralizing the B.1.351 variant. Combination of casirivimab and imdevimab shows decreased activity against the B.1.351 variant. | ▪ Current EUA antibody therapies retain activity against the B.1.1.7 variant
▪ Out of the current EUA antibody therapies, only the combination of casirivimab and imdevimab will have some activity against the B.1.351 variant

Limitations:
▪ Data has not gone through the peer-review process yet

Tada et al. Feb 2021
Pre-print (not peer reviewed yet)

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</table>
| Test of neutralizing activity of REGN10933 (casirivimab) and REGN10987 (imdevimab) against SARS-COV-2 variant spike proteins. | ▪ Casirivimab maintains activity against B.1.1.7 but loses neutralizing activity against B.1.351 or mink cluster 5 spike proteins.
▪ Imdevimab has significantly decreased neutralizing activity against B.1.351 and mink cluster 5 spike protein
▪ Combination therapy with casirivimab and imdevimab had a decreased in neutralizing titer by 9.1 folds when used on the B.1.351 variants compared to the D614G variant (the predominant world-wide strain in May of 2020). | ▪ Combination of casirivimab and imdevimab exhibits reduced neutralizing activity against the B.1.351 spike protein variant.

Limitations:
▪ Has not gone through the peer-review process yet

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### Table 1 Neutralizing Activity of COVID-19 Antibody Therapies on SARS-CoV-2 Pseudovirus Variants

<table>
<thead>
<tr>
<th>Lineage with Spike Protein Substitution</th>
<th>Bamlanivimab <em>Fold Reduction in Susceptibility</em></th>
<th>Bamlanivimab &amp; Etesevimab <em>Fold Reduction in Susceptibility</em></th>
<th>Casirivimab &amp; Imdevimab <em>Fold Reduction in Susceptibility</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>B.1.1.7 (UK)</td>
<td>No change*</td>
<td>No change*</td>
<td>No change+</td>
</tr>
<tr>
<td>B.1.351 (South Africa)</td>
<td>&gt;2,360</td>
<td>&gt;45</td>
<td>No change+</td>
</tr>
<tr>
<td>P.1 (Brazil)</td>
<td>&gt;2,360</td>
<td>&gt;511</td>
<td>No change+</td>
</tr>
<tr>
<td>B.1.427/B.1.429 (California)</td>
<td>&gt;1,020</td>
<td>7.4</td>
<td>No change+</td>
</tr>
<tr>
<td>B.1.526 (New York)</td>
<td>&gt;2,360</td>
<td>17</td>
<td>No change+</td>
</tr>
</tbody>
</table>

* < 5 fold decrease in susceptibility; † < 2 fold decrease in susceptibility

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The percentage of pediatric patients in this data is unknown

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References