MEDICATIONS FOR NON-HOSPITALIZED PATIENTS
Bamlanivimab

- Recombinant anti-spike neutralizing monoclonal antibody that binds to spike protein and blocks spike protein attachment to human receptor.
Bamlanivimab EUA

- **Treatment of 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 (one of the following):**
  - Have a body mass index (BMI) ≥35
  - Have chronic kidney disease
  - Have diabetes
  - Have immunosuppressive disease or 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.
  - See EUA for criteria for Pediatric patients 12-17 years
Bamlanivimab should NOT be used for:

- Patients who are hospitalized due to COVID-19
- Require oxygen therapy due to COVID-19
- Require an increase in baseline oxygen flow rate due to COVID-19 in those on chronic oxygen therapy due to underlying non-COVID-19 related comorbidity.
- Benefit of treatment with bamlanivimab has not been observed in patients hospitalized due to COVID-19. Monoclonal antibodies, such as bamlanivimab, may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation.
Bamlanivimab Dose

- Single intravenous (IV) infusion of 700 mg administered as soon as possible after positive viral test for SARS-CoV2 and within 10 days of symptom onset. (Note in the clinical trial the median time from symptom onset was 4 days)

- Bamlanivimab 700 mg via IV infusion over at least 60 minutes via pump or gravity.

- No dosage adjustment is recommended based on age, sex, race, body weight, renal or mild hepatic impairment, during pregnancy or while lactating, or for disease severity or inflammation.
Bamlanivimab Preparation

- Remove the bamlanivimab vial from refrigerated storage and allow to equilibrate to room temperature for approximately 20 minutes before preparation.
- Do not expose to direct heat. Do not shake the vial.
- Inspect bamlanivimab visually for particulate matter and discoloration: It is a clear to opalescent and colorless to slightly yellow to slightly brown solution.
- Dilute bamlanivimab using a 250 mL prefilled 0.9% Sodium Chloride.
- Injection bag for intravenous infusion according to Table below
  Gently invert IV bag by hand approximately 10 times to mix. Do not shake.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dose/Volume of Bamlanivimab (# of vials)</th>
<th>Volume of 0.9% Sodium Chloride to Discard from a 250 mL IV bag</th>
<th>Total Volume for Infusion</th>
<th>Maximum Infusion Rate</th>
<th>Minimum Infusion Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bamlanivimab</td>
<td>700 mg/20 mL (1 vial)</td>
<td>70 mL</td>
<td>200 mL</td>
<td>200 mL/hr</td>
<td>60 minutes</td>
</tr>
</tbody>
</table>
Stability

• This product is preservative-free and therefore, the diluted infusion solution should be administered immediately.

• If immediate administration is not possible, store the diluted bamlanivimab infusion solution:
  • for up to 24 hours at refrigerated temperature (2°C to 8°C [36°F to 46°F])
  • for up to 7 hours at room temperature (20°C to 25°C [68°F to 77°F]) including infusion time.
  • If refrigerated, allow the infusion solution to equilibrate to room temperature for approximately 20 minutes prior to administration.
Nursing Information

- Gather the recommended materials for infusion: (Polyvinylchloride (PVC) infusion set containing a 0.20/0.22 micron in-line polyethersulfone (PES) filter.)
- Attach the infusion set to the IV bag
- Prime the infusion set
- Administer the infusion solution via pump or gravity over at least 60 minutes
- Once infusion is complete, flush the infusion line to ensure delivery of the required dose
- Discard unused product
- Clinically monitor patients during administration and observe patients for at least 1 hour after infusion is complete
- No premedications are required. Should have access to allergic reaction rescue medications
- Patient Information sheet available at: www.fda.gov/media/143604/download
Bamlanivimab ADEs

- Hypersensitivity Including Anaphylaxis and Infusion-Related Reactions
  - If signs and symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue administration and initiate appropriate medications and/or supportive therapy.

- Infusion-related reactions have been observed with administration of bamlanivimab.
  - Signs and symptoms of infusion related reactions may include: fever, chills, nausea, headache, bronchospasm, hypotension, angioedema, throat irritation, rash including urticaria, pruritus, myalgia, dizziness.
  - If an infusion-related reaction occurs, consider slowing or stopping the infusion and administer appropriate medications and/or supportive care.
Bamlanivimab Monitoring

- Clinically monitor patients during administration and observe patients for at least 1 hour after infusion is complete.

- Patients treated with bamlanivimab should continue to self-isolate and use infection control measures (e.g., wear mask, isolate, social distance, avoid sharing personal items, clean and disinfect “high touch” surfaces, and frequent handwashing) according to CDC guidelines.
Pregnancy/Lactation

- There are insufficient data to evaluate a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Pregnancy was an exclusion trial in the BLAZE-1 Trial.

- Bamlanivimab should only be used during pregnancy if the potential benefit outweighs the potential risk for the mother and the fetus.

- Nonclinical reproductive toxicity studies have not been performed with bamlanivimab.

- In a tissue cross reactivity study with bamlanivimab using human fetal tissues, no binding of clinical concern was detected. Human immunoglobulin G1 (IgG1) antibodies are known to cross the placental barrier; therefore, bamlanivimab has the potential to be transferred from the mother to the developing fetus.

- Lactation Risk Summary There are no available data on the presence of bamlanivimab in human or animal milk, the effects on the breastfed infant, or the effects on milk production. Maternal IgG is known to be present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for bamlanivimab and any potential adverse effects on the breastfed child from bamlanivimab or from the underlying maternal condition. Breastfeeding individuals with COVID-19 should follow practices according to clinical guidelines to avoid exposing the infant to COVID-19.
Mandatory Requirements

- Healthcare providers (to the extent practicable given the circumstances of the emergency) must document in the patient's medical record that the patient/caregiver has been:
  - Given the “Fact Sheet for Patients, Parents and Caregivers”
  - Informed of alternatives to receiving authorized bamlanivimab
  - Informed that bamlanivimab is an unapproved drug that is authorized for use under this Emergency Use Authorization
  - Patients with known hypersensitivity to any ingredient of bamlanivimab must not receive bamlanivimab
  - The prescribing health care provider and/or the provider's designee are/is responsible for mandatory reporting of all medication errors and serious adverse events* potentially related to bamlanivimab treatment within 7 calendar days from the onset of the event.
Clinical Data BLAZE I Trial – Methods

**Study Design:**
- Randomized double blind, placebo controlled phase II trial
- Bamlanivimab
  - 700mg IV x 1
  - 2800mg IV x 1
  - 7000mg IV x 1
- Placebo

**Inclusion Criteria:**
- Ambulatory Pts
- Had to have at least 1 symptom
- Initiated within 3 days of obtaining a positive COVID-19 NP swab – RT-PCR

**Exclusion Criteria:**
- SpO2 ≤ 93% RA
- RR ≥ 30 bpm
- HR ≥ 125 bpm
- Need for MV/pressors
- Concomitant infection
- Comorbidty requiring surgery within 7 days or life-threatening within 29 days
Demographics in Treatment group:
- Median age = 45 yo
- ≥ 65 yo = 10.7%
- Female = 55%
- White = 88%
- Hispanic = 44%
- Black = 7%
- High Risk = 70%
  (Defined as age ≥ 65 or BMI ≥ 35 or at least one relevant coexisting illness)

Symptoms in Treatment group:
- Mild = 75%
  (defined as not moderate)
- Moderate = 25%
  - Defined as
    - SOB present or
    - RR ≥ 20 bpm and
    - HR ≥ 95 bpm
- Median Duration of symptoms = 4 days

Outcomes Studied:
Primary Outcome: Change in viral load from baseline at day 11

Secondary Outcomes:
- Safety
- Time to symptom resolution
Blaze 1: Primary Outcome

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 (Figure 1).

**Figure 1: SARS-CoV-2 viral load change from baseline by visit.**

Not a good outcome since most patients cleared virus by day #11

Patients with a higher viral load on day 7 had a higher rate of hospitalization

Patients hospitalized had higher viral load
### Secondary Outcome: COVID related: Hospital/ED Visits

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Total Number of Patients per group</th>
<th>All Patients N (%) Hospital/ED visit</th>
<th>High Risk Patients per Group</th>
<th>High Risk N (%) Hospital/ED visit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>156</td>
<td>9 (6%)</td>
<td>69</td>
<td>7 (10%)</td>
</tr>
<tr>
<td>Bamlanivimab 700mg</td>
<td>101</td>
<td>1 (1%)</td>
<td>46</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Bamlanivimab 2800mg</td>
<td>107</td>
<td>2 (2%)</td>
<td>46</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Bamlanivimab 7000mg</td>
<td>101</td>
<td>2 (2%)</td>
<td>44</td>
<td>2 (5%)</td>
</tr>
<tr>
<td>All Bamlanivimab</td>
<td>309</td>
<td>5 (2%)</td>
<td>136</td>
<td>4 (3%)</td>
</tr>
<tr>
<td>patients</td>
<td></td>
<td></td>
<td></td>
<td>*4/95 (4%)</td>
</tr>
</tbody>
</table>

* # differ from the EUA data and the NEJM 2020 article: these patients were ≥ 65 years or BMI ≥ 35
Secondary Outcome: COVID related: Hospital/ED Visits

Patients recorded their symptoms daily as:
None or absent = 0
Mild = 1
Moderate = 2
Severe = 3

Symptoms evaluated included:
Cough
SOB
Feverish
Fatigue
Body aches
Sore throat
Chills
Headache
Loss of appetite
Loss of taste and smell

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.
Clinical Trial: ADEs

Only 1 serious ADE occurred in the placebo group

Infusion related reactions occurred in 7/309 2.3% of Bamlanivimab patients: pruritus, flushing, rash, and facial swelling. All patients completed the infusions and in some instances antihistamines were given.

Per the protocol pre-medications were not routinely given.

Table 2: Treatment-emergent Adverse Events Reported in at Least 1% of All Subjects in BLAZE-1

<table>
<thead>
<tr>
<th>Preferred term</th>
<th>Placebo N=156 %</th>
<th>Bamlanivimab 700 mg N=101 %</th>
<th>2,800 mg N=107 %</th>
<th>7,000 mg N=101 %</th>
<th>Total N=309 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>4%</td>
<td>3%</td>
<td>4%</td>
<td>5%</td>
<td>4%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5%</td>
<td>1%</td>
<td>2%</td>
<td>7%</td>
<td>3%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>2%</td>
<td>3%</td>
<td>3%</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>Headache</td>
<td>2%</td>
<td>3%</td>
<td>2%</td>
<td>0%</td>
<td>2%</td>
</tr>
<tr>
<td>Pruritus</td>
<td>1%</td>
<td>2%</td>
<td>3%</td>
<td>0%</td>
<td>2%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3%</td>
<td>1%</td>
<td>3%</td>
<td>1%</td>
<td>2%</td>
</tr>
</tbody>
</table>

Most frequent adverse event in the treatment group was Nausea.
NIH Recommendations

**Disease Severity**
Not Hospitalized, Mild to Moderate COVID-19

**Panel’s Recommendations**
There are insufficient data to recommend either for or against any specific antiviral or antibody therapy. SARS-CoV-2 neutralizing antibodies (bamlanivimab or casirivimab plus imdevimab) are available through EUAs for outpatients who are at high risk of disease progression. These EUAs do not authorize use in hospitalized patients.

Dexamethasone should not be used (AIII).
Summary

- Bamlanivimab has shown to decrease viral load and hospitalizations in ambulatory patients with COVID-19 with mild to moderate disease that are in a high risk group.
- This should not be used in hospitalized patients!
- Bamlanivimab was well tolerated with nausea and infusion related reactions being the most common side effects.
- Study population received bamlanivimab within 3 days of positive NP RT-PCR. It was not studied in patients whose symptom onset was greater than 10 days.
Casirivimab/Imdevimab

Are 2 antibodies better than 1?

- Binds non-competitively to the critical receptor binding domain (RBD) of the virus spike protein
- Decreases the ability of mutant viruses to escape treatment and protects against spike variants
Casirivimab and Imdevimab EUA

- Indication: Administered together for the treatment of mild to moderate (COVID-19) in adults and pediatric patients (≥12 years of age and ≥ 40 kg) with positive COVID-19 testing, and who are at high risk for progressing to severe COVID-19 and/or hospitalization. Not after 10 days from symptom onset.

Casirivimab
REGN10933
Recombinant human IgG (1) monoclonal antibody that target the receptor binding domain of the spike protein

Imdevimab
REGN10987
Recombinant human IgG (1) monoclonal antibody that target the receptor binding domain of the spike protein
High Risk is defined as one of the following:

- Body mass index (BMI) $\geq 35$
- Chronic kidney disease
- Diabetes
- Immunosuppressive disease/Receiving immunosuppressive treatment
- $\geq 65$ years of age
- $\geq 55$ years of age AND have:
  - cardiovascular disease OR hypertension OR chronic obstructive pulmonary disease/other chronic respiratory disease
- 12 – 17 years of age AND have:
  - BMI $\geq 85^{th}$ percentile for their age and gender based on CDC growth charts, (www.cdc.gov/growthcharts/clinical_charts.htm), OR sickle cell disease, OR congenital or acquired heart disease, OR neurodevelopmental disorders, for example, cerebral palsy, OR a medical-related technological dependence, for example, tracheostomy, gastrostomy, or positive pressure ventilation (not related to COVID-19), OR asthma, reactive airway or other chronic respiratory disease that requires daily medication for control.
Casirivimab/Imdevimab should NOT be used in:

- Patients who are hospitalized due to COVID-19
- Patients who require oxygen therapy due to COVID-19
- Patients who require an increase in baseline oxygen flow rate due to COVID-19 in those on chronic oxygen therapy due to underlying non-COVID-19 related comorbidity
- Benefit of treatment with casirivimab and imdevimab has not been observed in patients hospitalized due to COVID-19. Monoclonal antibodies, such as casirivimab and imdevimab, may be associated with worse clinical outcomes when administered to hospitalized patients requiring high flow oxygen or mechanical ventilation with COVID-19.
Dose

- 1,200 mg of casirivimab AND 1,200 mg of imdevimab administered together as a single intravenous (IV) infusion over 60 minutes.

- Casirivimab supplied as:
  - 300mg/2.5 mL or 1332mg/11.1 mL (120mg/mL)

- Imdevimab supplied as:
  - 300mg/2.5 mL or 1332mg/11.1 mL (120mg/mL)

- Solutions must be diluted prior to administration.
## Preparation

- Remove vials from refrigerated storage and allow to equilibrate to room temperature for approximately 20 minutes.
- Do not expose to direct heat/Do not shake the vials.
- Inspect vials visually for particulate matter and discoloration. If present discard and prepare fresh solution. The solution for each vial should be clear to slightly opalescent, colorless to pale yellow.
- Discard any product remaining in the vial.
- Gently invert infusion bag by hand approximately 10 times to mix. Do not shake.

<table>
<thead>
<tr>
<th>Antibody Dose</th>
<th>Volume to Withdraw from Vial</th>
<th>Number of Vials Needed</th>
<th>Volume of 0.9% Sodium Chloride to Discard from a 250 mL Infusion Bag</th>
<th>Total Volume for Infusion</th>
<th>Maximum Infusion Rate</th>
<th>Minimum Infusion Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Casirivimab 2,400 mg Dose</td>
<td>10 mL</td>
<td>1 vial of 11.1 mL OR 4 vials of 2.5 mL</td>
<td>20 mL</td>
<td>250 mL/hr</td>
<td>60 minutes</td>
<td></td>
</tr>
<tr>
<td>REGN10933 1,200 mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Imdevimab 2,400 mg Dose</td>
<td>10 mL</td>
<td>1 vial of 11.1 mL OR 4 vials of 2.5 mL</td>
<td>20 mL</td>
<td>250 mL/hr</td>
<td>60 minutes</td>
<td></td>
</tr>
<tr>
<td>REGN10987 1,200 mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NOTE: casirivimab = REGN10933; imdevimab = REGN10987

a 1,200 mg of Casirivimab and 1,200 mg of Imdevimab are to be administered together as a single intravenous infusion for a combined 2,400 mg dose.

b One 11.1 mL vial of one antibody may be prepared with four 2.5 mL vials of the other antibody to create one treatment course.
Stability

- Refrigerate unopened vials at 2°C to 8°C (36°F to 46°F) in the individual original carton to protect from light. Do NOT freeze, shake, or expose to direct light.

- This product is preservative-free and therefore, the diluted infusion solution should be administered immediately.

- If immediate administration is not possible:
  Store the diluted casirivimab and imdevimab infusion solution in the refrigerator between 2°C to 8°C (36°F to 46°F) for no more than 36 hours and at room temperature up to 25°C (77°F) for no more than 4 hours, including infusion time.

- If refrigerated, allow the infusion solution to equilibrate to room temperature for approximately 30 minutes prior to administration.
Nursing Information for Administration

- Gather the recommended materials for infusion:
  - Polyvinyl chloride (PVC), Polyethylene (PE)-lined PVC, or Polyurethane (PU) infusion set
  - In-line or add-on 0.2 micron polyethersulfone (PES) filter
- Attach the infusion set to the IV bag
- Prime the infusion set
- Administer as an IV infusion via pump or gravity over at least 60 minutes through an intravenous line containing a sterile, in-line or add-on 0.2-micron polyethersulfone (PES) filter
- The prepared infusion solution should not be administered simultaneously with any other medication.
- The compatibility of casirivimab and imdevimab injection with IV solutions and medications other than 0.9% Sodium Chloride Injection is not known.
- After infusion is complete, flush with 0.9% Sodium Chloride Injection
- Discard unused product
- Clinically monitor patients during administration and observe patients for at least 1 hour after infusion is complete.
- Patient information sheet available:
  www.regeneron.com/sites/default/files/treatment-covid19-eua-fact-sheet-for-hcp.pdf (also available in Spanish)
Drug Interactions

- None reported
Adverse Drug Reactions

• Serious hypersensitivity reaction, including anaphylaxis
  • If a significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue administration and initiate appropriate medications and/or supportive therapy.

Infusion-related reactions have been observed:
  • fever, chills, nausea, headache, bronchospasm, hypotension, angioedema, throat irritation, rash including urticaria, pruritus, myalgia, dizziness.
  • If an infusion-related reaction occurs, consider slowing or stopping the infusion and administer appropriate medications and/or supportive care.
### R10933-10987-CoV-2067: ADEs

<table>
<thead>
<tr>
<th>Dose</th>
<th>N=</th>
<th>Serious Adverse Reactions *</th>
<th>Infusion Related Reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>2400mg (1200mg + 1200mg)</td>
<td>258</td>
<td>4 (1.6%)</td>
<td>0</td>
</tr>
<tr>
<td>8000mg (4000mg + 4000mg)</td>
<td>260</td>
<td>2 (0.8%)</td>
<td>4 (1.5%):</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1 patient: anaphylaxis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2 patients permanently discontinued drug</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Other reactions: pyrexia, chills, urticarial, pruritus, abdominal pain, flushing</td>
</tr>
<tr>
<td>Placebo</td>
<td>262</td>
<td>6 (2.3%)</td>
<td>1 (nausea)</td>
</tr>
</tbody>
</table>

* None were considered to be study drug related
Use in Pregnancy/Breast Feeding

- Insufficient data to evaluate a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes.

- Weigh potential benefit outweighs versus risk for the mother and the fetus.

- In a tissue cross-reactivity study with casirivimab and imdevimab using human fetal tissues, no binding of clinical concern was detected. Human immunoglobulin G1 (IgG1) antibodies are known to cross the placental barrier; therefore, casirivimab and imdevimab have the potential to be transferred from the mother to the developing fetus. It is unknown whether the potential transfer of casirivimab and imdevimab provides any treatment benefit or risk to the developing fetus.

- There are no available data on the presence of casirivimab and/or imdevimab in human milk or animal milk, the effects on the breastfed infant, or the effects of the drug on milk production.
Health Care Provider must:

- As the health care provider, communicate to your patient or parent/caregiver, as age appropriate, information consistent with the “Fact Sheet for Patients, Parents and Caregivers” prior to the patient receiving casirivimab and imdevimab.

- Health care providers (to the extent practicable given the circumstances of the emergency) must document in the patient’s medical record that the patient/caregiver has been:
  a. Given the “Fact Sheet for Patients, Parents and Caregivers”
  b. Informed of alternatives to receiving casirivimab and imdevimab,
  c. Informed that casirivimab and imdevimab are unapproved drugs that are authorized for use under this Emergency Use Authorization

- The prescribing health care provider and/or the provider’s designee are/is responsible for mandatory responses to requests from FDA for information about adverse events and medication errors following receipt of casirivimab and imdevimab.

- The prescribing health care provider and/or the provider’s designee are/is responsible for mandatory reporting of all medication errors and serious adverse events* potentially related to casirivimab and imdevimab treatment within 7 calendar days from the onset of the event.
Clinical Data R10933-10987-CoV-2067 – Methods

**Study Design:**
- Randomized double blind, placebo controlled phase I/II trial
- Casirivimab/Imdevimab
  - 2400 (1200 + 1200mg) IV x 1
  - 8000 (4000 + 4000mg IV x 1
- Placebo

**Inclusion Criteria:**
- Ambulatory Pts
- Had to have at least 1 symptom
- Initiated within 3 days of obtaining a positive COVID-19 NP swab – RT-PCR

**Exclusion Criteria:**
- Hospital Admission
- IVIG within 3 months
- Systemic steroids (any indication)
Clinical Data R10933-10987-CoV-2067– Interim Analysis

Demographics in Treatment group:
- Median age = 45 yo
- ≥ 65 yo = 7%
- Female = 53%
- White = 85%
- Hispanic = 50%
- Black = 9%
- High Risk = 34%

Symptoms in Treatment group:
- Mild = 13%
- Moderate = 36%
- Severe = 31%
- Median Duration of symptoms = 3 days

Outcomes Studied:
Primary Outcome:
Change in viral load from baseline at day 11

Secondary Outcomes:
- Safety
- Time to symptom resolution
Primary Outcome

Greatest Benefit seen in patients:

- Higher Viral Loads
- No detectable antibodies at baseline

Figure 1. Mean Change from Baseline in SARS-COV-2 Viral Load Over Time
Secondary Outcome: COVID related: Hospital/ED Visits

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Total Number of Patients per group</th>
<th>All Patients N (%) Hospital/ED visit</th>
<th>High Risk Patients per Group</th>
<th>High Risk N (%) Hospital/ED visit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>231</td>
<td>10 (4%)</td>
<td>78</td>
<td>7 (9%)</td>
</tr>
<tr>
<td>C/I 2400mg</td>
<td>215</td>
<td>4 (2%)</td>
<td>70</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>C/I 8000mg</td>
<td>219</td>
<td>4 (2%)</td>
<td>81</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>All C/I patients</td>
<td>434</td>
<td>8 (2%)</td>
<td>151</td>
<td>4 (3%)</td>
</tr>
</tbody>
</table>

Regeneron Press Release: 10/28/20
N=799

Reduced COVID medical visits by 57% through day 29 (2.8% All C/I pts versus 6.5% placebo p=0.024)
Decreased medical visits by 72% in patients with one or more risk factors: > 50 years old, BMI > 30, cardiovascular, metabolic, lung, liver, kidney disease or immunosuppression
Change in Symptom Scores compared to Placebo

Median time to symptom improvement:

Treatment arms: 5 days versus Placebo arm: 6 days

 Patients recorded their symptoms daily

Symptoms evaluated included:

- shortness of breath or difficulty breathing
- chills, feverish
- sore throat
- cough
- nausea, vomiting, diarrhea
- headache
- red or watery eyes
- body and muscle aches
- loss of taste or smell
- fatigue, loss of appetite
- confusion, dizziness, pressure or tight chest
- chest pain, stomach ache, rash, sneezing, sputum/phlegm, runny nose.
NIH Recommendations

**DISEASE SEVERITY**
Not Hospitalized, Mild to Moderate COVID-19

**PANEL’S RECOMMENDATIONS**
There are insufficient data to recommend either for or against any specific antiviral or antibody therapy. SARS-CoV-2 neutralizing antibodies (bamlanivimab or casirivimab plus imdevimab) are available through EUAs for outpatients who are at high risk of disease progression. These EUAs do not authorize use in hospitalized patients.

Dexamethasone should not be used (AIII).
Casirivimab/Imdevimab has shown to decrease viral load and hospitalizations/ED visits in ambulatory patients with COVID-19 with mild to moderate disease that are in a high risk group.

**This should not be used in hospitalized patients!**

Casirivimab/Imdevimab was well tolerated with infusion related reactions being the most common side effects.

Study population received Casirivimab/Imdevimab within 3 days of positive NP RT-PCR. It was not studied in patients whose symptom onset was greater than 10 days.
MEDICATIONS FOR HOSPITALIZED PATIENTS
Baricitinib (Olumiant®): inhibits cytokine release/viral cell entry
Baricitinib (Olumiant®) + Remdesivir EUA

- **Indication:**
  Hospitalized patients ≥ 2 years requiring supplemental oxygen, invasive mechanical ventilation, or ECMO

**Baricitinib:**
- small molecule reversible Janus-associated kinase (JAK)-inhibitor
- Decreases risk of cytokine storm

**Remdesivir:**
- Decreases viral replication
EUA Requirements

- Only patients ≥ 2 years of age, hospitalized and on supplemental oxygen, invasive mechanical ventilation, or ECMO receive treatment with this combination

- Fact Sheet for Patients must document in the medical record that sheet was given, patients informed of alternative therapy, informed that Baricitinib is an approved medication that is authorized for the unapproved use: Available at: www.fda.gov/media/143824/download

- eGFR, Liver function tests, CBC with differential are done prior to first dose

- All medication errors and serious events must be reported within 7 calendar days from onset of event. (online, Form FDA 3500)
Baricitinib (Olumiant)

- Supplied as: 1 and 2mg tablets film coated immediate release
  - 2mg/30 tabs = $2265  $75/tab x 28 tabs = $2100 treatment course

Can be given with or without food

Dose:
  - >9 years old/adults: 4mg po daily x 14 days or until hospital discharge

Renal Dysfunction: (cleared filtration/active secretion)

<table>
<thead>
<tr>
<th>eGFR ml/min/1.73m²</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 60</td>
<td>No adjustment</td>
</tr>
<tr>
<td>30 – 59</td>
<td>2mg po once daily</td>
</tr>
<tr>
<td>15-29</td>
<td>1mg po once daily</td>
</tr>
<tr>
<td>&lt; 15/ESRD/Acute Renal Failure</td>
<td>Not Recommended</td>
</tr>
</tbody>
</table>
### Baricitinib – Dosing Adjustments

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absolute Lymphocyte Count</td>
<td></td>
</tr>
<tr>
<td>≥ 200 cells/μL</td>
<td>Continue recommended dose</td>
</tr>
<tr>
<td>&lt; 200 cells/μL</td>
<td>Hold until increase to ≥ 200</td>
</tr>
<tr>
<td>Absolute Neutrophil Count</td>
<td></td>
</tr>
<tr>
<td>≥ 500</td>
<td>Continue recommended dose</td>
</tr>
<tr>
<td>&lt; 500</td>
<td>Hold until increase to ≥ 500</td>
</tr>
<tr>
<td>Liver Function Tests</td>
<td></td>
</tr>
<tr>
<td>Increase in ALT or AST or drug induced liver disease is suspected</td>
<td>Hold Therapy</td>
</tr>
</tbody>
</table>

**Note:** Prescribing data states not to use if the hemoglobin < 8 g/dL
Use in Pregnancy

- It is not known if baricitinib crosses the placenta in humans
- Skeletal malformation and developmental toxicity has been observed in offspring of rats exposed to supratherapeutic doses
- EUA states: Risk versus Benefit
Use in patients with feeding tubes

- Intact tablets are not hazardous. Not known if crushed tablets may be a reproductive hazard. Use ventilated enclosure or personal protective equipment. (N95 respirator).

- Dispersed tablets are stable in water for 4 hours.

<table>
<thead>
<tr>
<th>Gastrostomy Feeding tube</th>
<th>Add dose to 10-15 mL of room temperature water</th>
<th>Repeat with 10-15 mL of room temperature water</th>
</tr>
</thead>
<tbody>
<tr>
<td>NG tube</td>
<td>Add dose to 30 mL of room temperature water. The syringe can be held horizontally and shaken during administration</td>
<td>Rinse syringe with 15 mL of room temperature water</td>
</tr>
</tbody>
</table>
Drug Interactions

- Substrate of P-glycoprotein, BCRP, MATE2-K, OAT3
- Probenecid (strong OAT3 inhibitor) – decreases renal clearance and increases baricitinib AUC by 2 fold
  - Dose decreased by 50%
    - If on 4mg: decrease to 2mg
    - If on 2mg: decrease to 1mg
    - If on 1mg: discontinue probencid

- Avoid Live Vaccinations
Adverse Reactions

- Increased risk of thrombosis: (arterial/venous)
  - Make sure patients are on appropriate DVT prophylaxis

- Increased risk of infections including tuberculosis and herpes zoster

- Other reported ADEs
  - Rapid and sustained decrease in neutrophils and lymphocyte count
  - Increase in platelet counts (peaks around 2 weeks ≈ increase 50 x 109/L)
Monitoring

- Serum creatinine
- CBC and differential: absolute lymphocyte count/absolute neutrophil count, hemoglobin, platelets
- Liver function tests
- CPK
- LDL/HDL: more with long term use
- Signs of infections
- Signs of thrombosis
Clinical Data ACTT-2 – Methods

Study Design:
- Randomized double blind, placebo controlled trial
- Baricitinib + remdesivir
- Placebo + Remdesivir

Inclusion Criteria:
- Hospitalized Patients
- Had to have at least 1 of the following:
  - Infiltrates on imaging
  - SpO2 ≤ 94% on Room Air
  - Requirement for Supplemental oxygen or mechanical ventilation

Exclusion Criteria:
- ALT/AST > 5x ULN
- eGFR < 30 ml/min
- Neutropenia (<1000 ANC)
- Leukopenia (< 200)
- Pregnancy/breastfeeding
- Probenecid
- Active TB/untreated latent TB
- Active Infections
- Live vaccines
- VTE within 12 weeks
- Hx of recurrent VTE
Clinical Data ACTT-2– Interim Analysis

Demographics:
- Median age = 55 yo
- ≥ 65 yo = 30%
- Female = 37%
- White = 48%
- Hispanic = 51%
- Black = 15%
- Asian = 10%

Oxygen Status:
- 14% no oxygen requirement
- 55% required oxygen
- 21% required noninvasive ventilation or high flow oxygen
- 11% required MV/ECMO

Outcomes Studied:
**Primary Outcome:**
Time to recovery within 29 days

Secondary Outcomes:
- Clinical status on day #15
- ADEs
* not all listed
## ACTT-2 Available Results

<table>
<thead>
<tr>
<th></th>
<th>Baricitnib + Remdesivir</th>
<th>Placebo + Remdesivir</th>
<th>HR/OR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Outcome</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time to Recovery</td>
<td>7 days</td>
<td>8 days</td>
<td>1.15 (95% CI 1-1.31) p=0.47</td>
</tr>
<tr>
<td><strong>Secondary Outcome</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical status Day #15</td>
<td>Favors B/R</td>
<td></td>
<td>1.26 (95% CI 1.01 – 1.57) p=0.44</td>
</tr>
<tr>
<td>Death at Day 29</td>
<td>4.7% (24/515)</td>
<td>7.1% (37/518)</td>
<td>-2.6 (95% CI -5.8 – 0.5)</td>
</tr>
<tr>
<td>Died or progressed to noninvasive ventilation, high flow, or MV on day 29</td>
<td>23%</td>
<td>28%</td>
<td>0.74 (95% CI 0.56-0.99) p=0.039</td>
</tr>
</tbody>
</table>
### Table 3: Comparisons and Confidence Intervals for Adverse Events in the As-Treated Population

<table>
<thead>
<tr>
<th>Patients with at least 1:</th>
<th>PBO + RDV (N = 509) n (%)</th>
<th>BARI + RDV (N = 507) n (%)</th>
<th>Risk Difference % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AE</td>
<td>242 (48)</td>
<td>210 (41)</td>
<td>-6 (-12, 0)</td>
</tr>
<tr>
<td>Grade 3-4 AE</td>
<td>238 (47)</td>
<td>207 (41)</td>
<td>-6 (-12, 0)</td>
</tr>
<tr>
<td>SAE</td>
<td>103 (20)</td>
<td>77 (15)</td>
<td>-5 (-10, 0)</td>
</tr>
<tr>
<td>SAE with fatal outcome</td>
<td>31 (6)</td>
<td>19 (4)</td>
<td>-2 (-5, 0)</td>
</tr>
<tr>
<td>AE leading to discontinuation of study drug</td>
<td>59 (12)</td>
<td>34 (7)</td>
<td>-5 (-8, -1)</td>
</tr>
<tr>
<td>Infections</td>
<td>50 (10)</td>
<td>32 (6)</td>
<td>-4 (-7, 0)</td>
</tr>
<tr>
<td>VTE</td>
<td>16 (3)</td>
<td>21 (4)</td>
<td>1 (-1, 3)</td>
</tr>
<tr>
<td>Pulmonary Embolism</td>
<td>2 (0.4)</td>
<td>5 (1)</td>
<td>0.6 (-0.4, 1.6)</td>
</tr>
</tbody>
</table>

---

**Abbreviations:** AE = adverse event; BARI + RDV = baricitinib plus remdesivir; NIAID = National Institute of Allergy and Infectious Disease; N = number of patients in the As-Treated Population; n = number of patients reporting at least 1 event; PBO + RDV = placebo plus remdesivir; SAE = serious adverse event; VTE = venous thromboembolic events.

**Note:** Patients are counted once for each category regardless of the number of events.
**NIH Recommendations**

**Hospitalized\(^a\) But Does Not Require Supplemental Oxygen**

**Dexamethasone** should not be used (Ala).

There are insufficient data to recommend either for or against the routine use of **remdesivir**. For patients at high risk of disease progression, the use of remdesivir may be appropriate.

**Hospitalized\(^a\) and Requires Supplemental Oxygen**

(But Does Not Require Oxygen Delivery Through a High-Flow Device, Noninvasive Ventilation, Invasive Mechanical Ventilation, or ECMO)

Use one of the following options:

- **Remdesivir**\(^b,c\) (e.g., for patients who require minimal supplemental oxygen) (Bla)
- **Dexamethasone**\(^d\) plus **remdesivir**\(^b,c\) (e.g., for patients who require increasing amounts of supplemental oxygen) (BII)\(^e,f\)
- **Dexamethasone**\(^d\) (e.g., when combination therapy with remdesivir cannot be used or is not available) (Bl)

**Hospitalized\(^a\) and Requires Oxygen Delivery Through a High-Flow Device or Noninvasive Ventilation**

Use one of the following options:

- **Dexamethasone**\(^d,f\) (Al)
- **Dexamethasone**\(^d\) plus **remdesivir**\(^b,c\) (BIII)\(^e,f\)
Summary

- Based on the available data, difficult to know who would be the best patient to recommend this therapy in.
- If ordered make sure to review CBC with differential and renal function.
- Increases risk of VTEs, make sure patients are on appropriate DVT prophylaxis if ordered.