Monoclonal Antibody Treatment for COVID-19 High Risk Patients

July 6th, 2021

Ursula Baffigo MD MPH Medical Director, Medical Management

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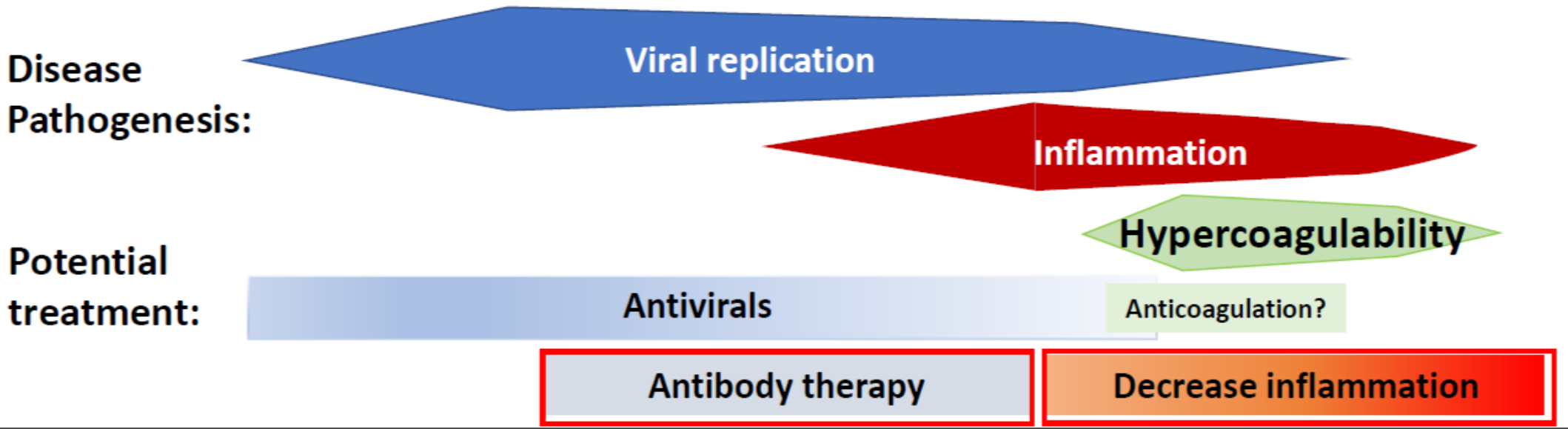
Treatment Across the COVID-19 Spectrum

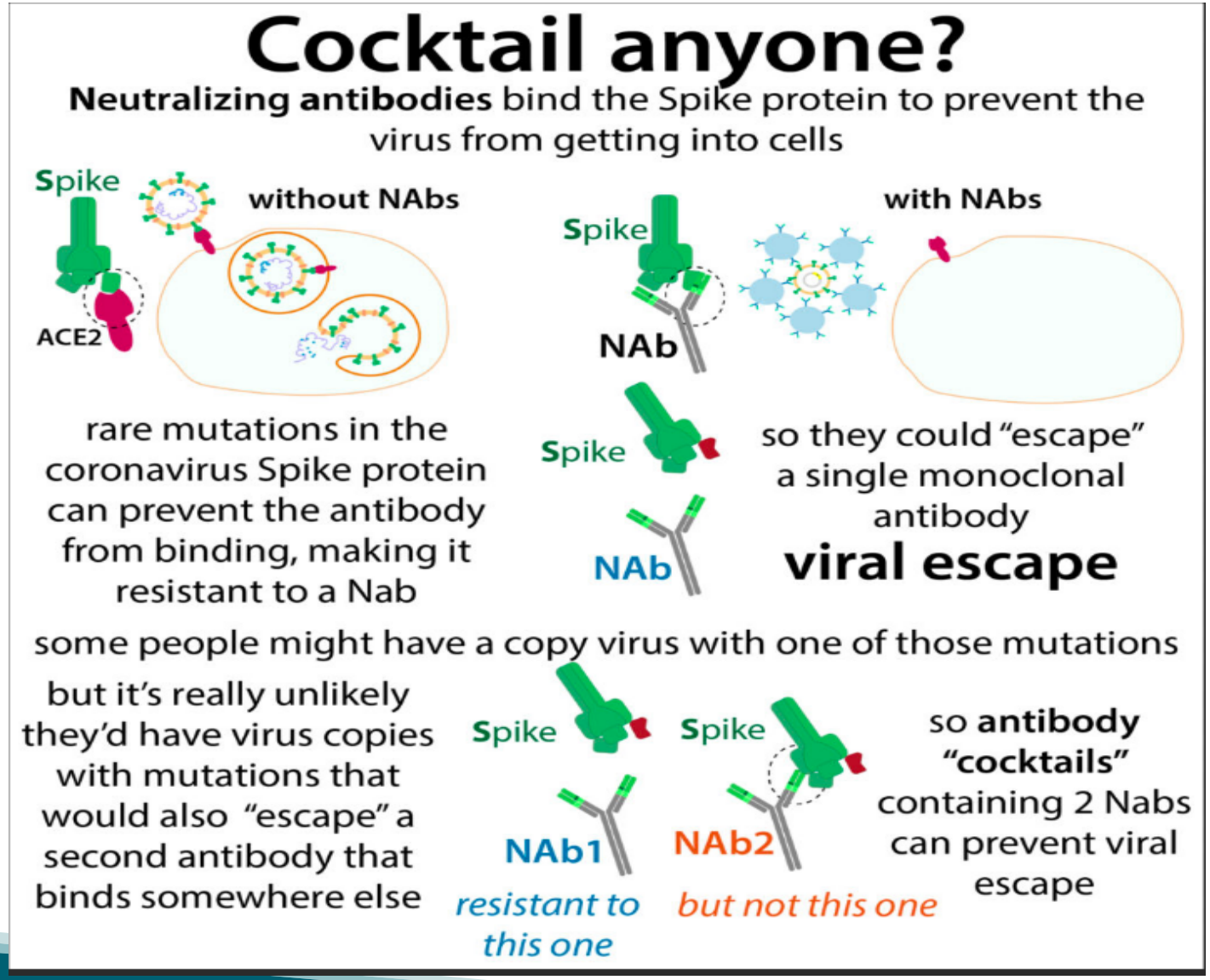
Stage/ Severity:	Asymptomatic/ Presymptomatic	Mild Illness	Moderate Illness	Severe Illness	Critical illness
	+ SARS-CoV-2 test but no symptoms	Mild symptoms (eg fever, cough, taste/smell changes); no dyspnea	O_2 saturation >=94%, lower respiratory tract disease	O_2 saturation <94%, respiratory rate >30/min; lung infiltrates >50%	Respiratory failure, shock, multi-organ dysfunction/failure



Gandhi RT, CID, 2020

Neutralizing Antibodies

- Reduce Escape



Casirivimab + Imdevimab (REGEN-COV)

- Casirivimab + Imdevimab (REGEN-COV) is the monoclonal antibody therapy choice for CA
- Dose: Casirivimab 600 mg plus Indevimab 600 mg
- Treatment should be started ASAP after a positive COVID result of a SARS-CoV-2 antigen or nucleic acid amplification (NAAT) and within 10 days of symptom onset

Reduced Hospitalization and Death

- “COVID-19 related hospitalization or all-cause death through Day 29 …, events occurred in 7 (1.0%) subjects treated with 600 mg of casirivimab and 600mg of imdevimab compared to 24 (3%) subjects currently randomized to placebo, demonstrating **a 70% reduction in COVID-19 related hospitalization or all-cause death compared to placebo (p=0.0024)”**

- Phase 3 data from ongoing COV-2067 trial; data from 4,567 randomized subjects. FDA-authorized Fact Sheet for Healthcare Providers (June 3, 2021)

FDA Emergency Use Authorization

- This EUA is for the use of the unapproved product, REGEN-COV (casirivimab and imdevimab) co-formulated product and REGEN-COV (casirivimab and imdevimab) supplied as individual vials to be administered together, for the treatment of mild to moderate COVID-19 in:
- adults and pediatric patients (12 years of age and older weighing at least 40 kg)
- with positive results of direct SARS-CoV-2 viral testing, and
- who are at high risk for progression to severe COVID-19, including hospitalization or death

High Risk Conditions

- Obesity or being overweight (BMI >25 or if age 12-17, have BMI ≥85th percentile for their age and gender)
- Pregnancy
- Chronic kidney disease
- Diabetes
- Immunosuppressive disease or immunosuppressive treatment
- Cardiovascular disease (including congenital heart disease) or hypertension
- Chronic lung diseases (for example, chronic obstructive pulmonary disease, asthma [moderate-to-severe], interstitial lung disease, cystic fibrosis and pulmonary hypertension)
- Sickle cell disease
- Neurodevelopmental disorders (for example, cerebral palsy) or other conditions that confer medical complexity (for example, genetic or metabolic syndromes and severe congenital anomalies)
- Having a medical-related technological dependence (for example, tracheostomy, gastrostomy, or positive pressure ventilation (not related to COVID 19)

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Effectiveness Data
REGEN-COV

COVID-2067 trial

- Randomized double-blinded, placebo controlled clinical trial
- Evaluating REGEN-COV (casirivimab and imdevimab) for the treatment of subjects with mild to moderate COVID-19 symptoms who are not hospitalized
- N= 4,567 subjects with at least one risk factor for severe COVID-19
- Median age= 50 yo (13% of subjects were 65+ yo)
- Gender: 52% female
- Race/ethnicity: 84% white, 36% Hispanic/Latino, 5% Black or African American
- Median duration of symptoms was 3 days
- Two treatment doses:
  - Casirivimab 600mg + Imdevimab 600mg
  - Casirivimab 1200mg + Imdevimab 1200mg

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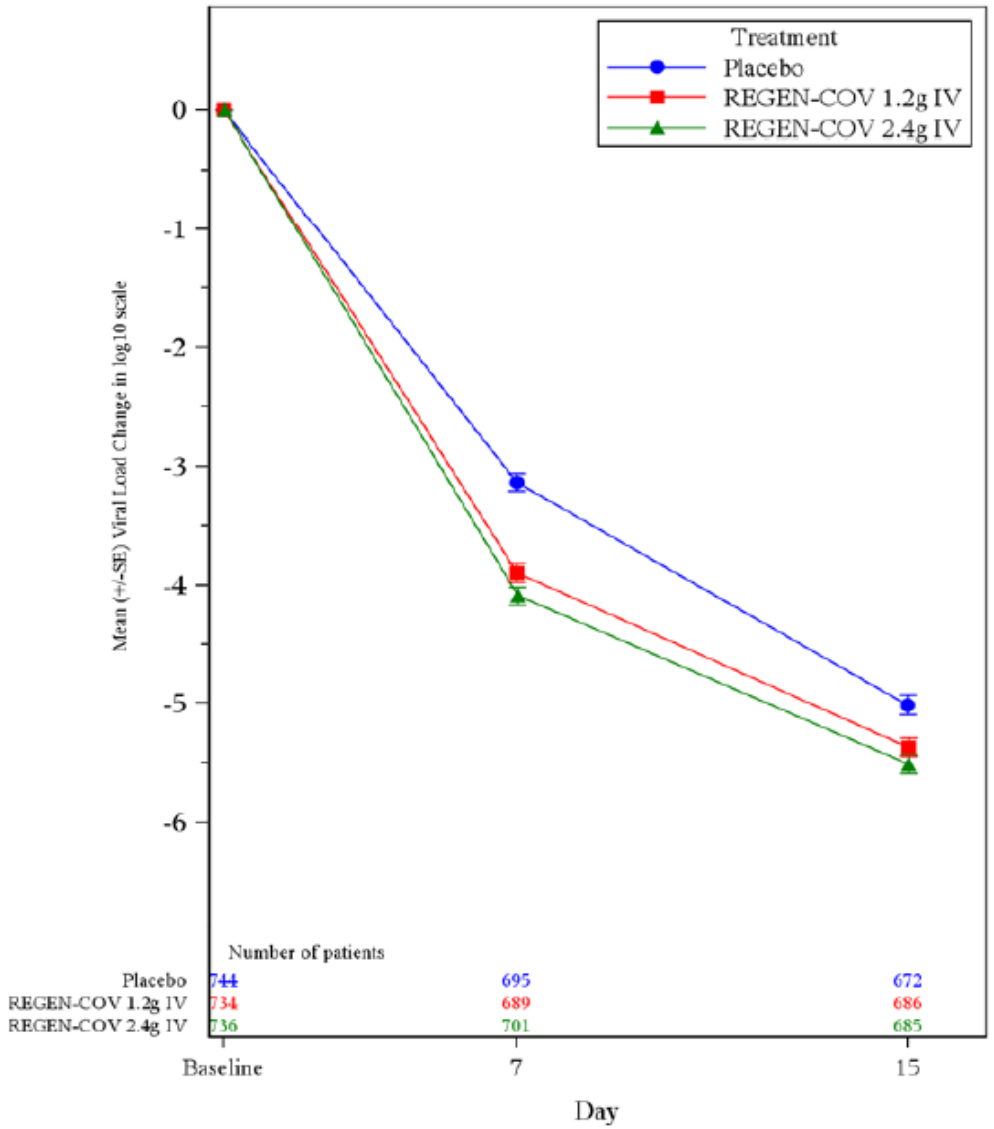
Figure 1: Change from Baseline in SARS-COV-2 Viral Load (log_{10} copies/mL) to Day 15



REGEN-COV 1.2 g IV = 600 mg of casirivimab and 600 mg of imdevimab administered intravenously
REGEN-COV 2.4 g IV = 1,200 mg of casirivimab and 1,200 mg of imdevimab administered intravenously

Table 7: Proportion of subjects with ≥1 COVID-19-related hospitalization or all-cause death through day 29

	600 mg of casirivimab and 600 mg of imdevimab (intravenous)	Placebo	1,200 mg of casirivimab and 1,200 mg of imdevimab (intravenous)	Placebo
	n=736	n=748	n=1,355	n=1,341
# of subjects with at least 1 event (COVID-19-related hospitalization or all-cause death)	7 (1.0%)	24 (3.2%)	18 (1.3%)	62 (4.6%)
Risk reduction	70% (p=0.0024)		71% (p<0.0001)	

Conclusion:

1. 70% reduction in COVID-19 related hospitalization or all-cause death compared to placebo
2. Absence of dose effect- Casirivimab 1200mg + Imdevimab 1200mg

is no longer authorized under EUA

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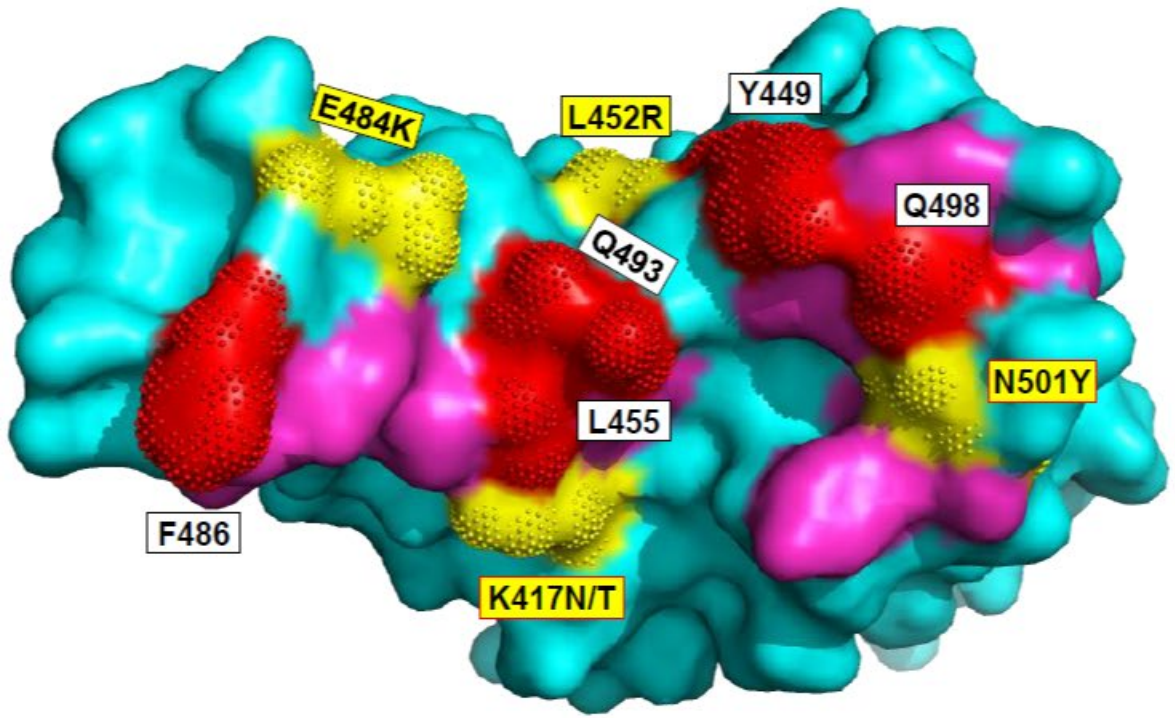
Is REGEN-COV Effective Against the Delta Variant?

RBD- ACE2 Interaction Sites With Variants



RBD

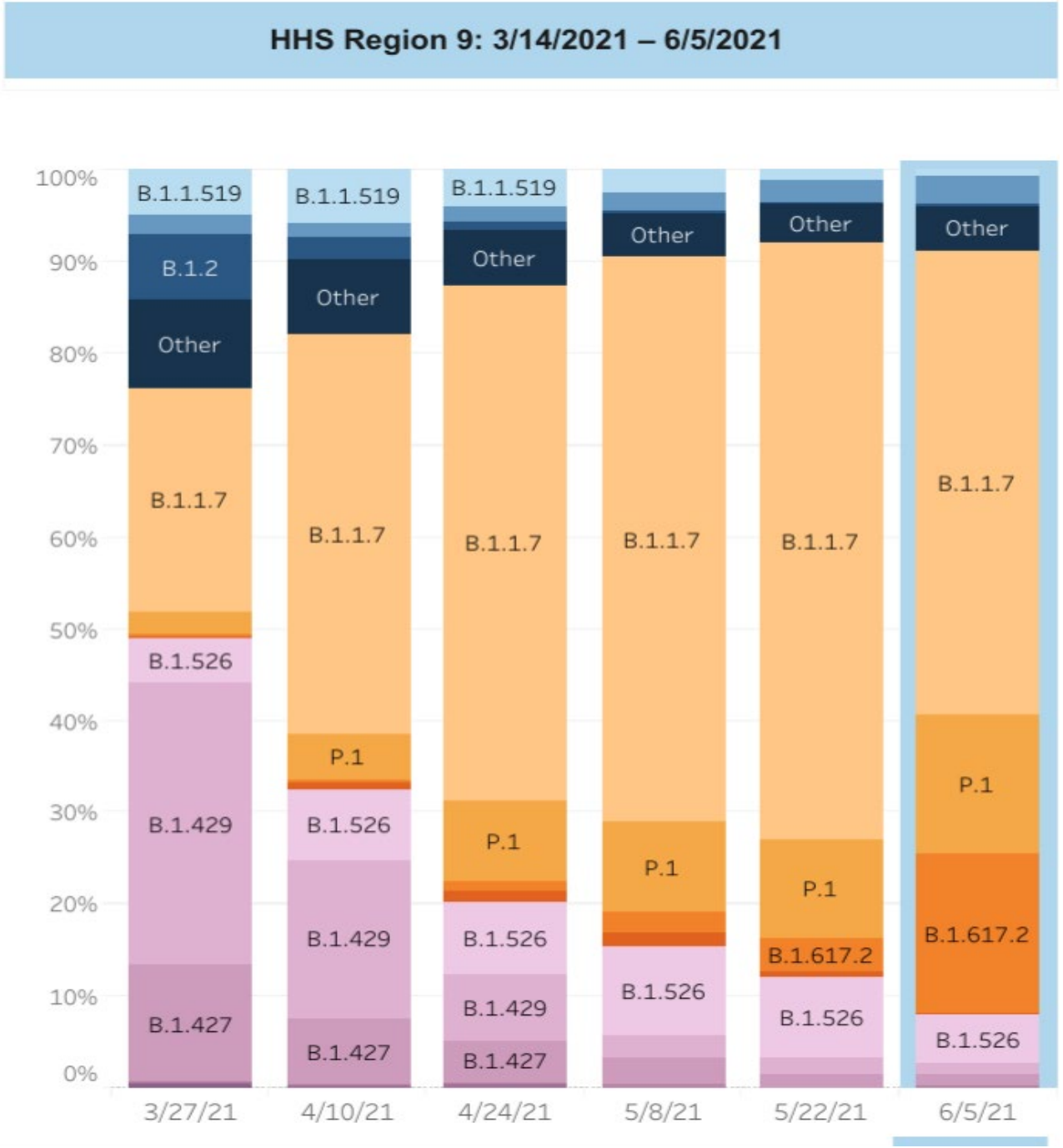
RBM (within 4Å)

Contacts

Variants

Centers for Disease Control and Prevention
CDC 24/7: Saving Lives, Protecting People™

CDC – COVID Data Tracker - Variant Proportions Region 9 3/14/2021 to 6/5/2021



Regeneron Pharmaceutical – News release June 16, 2021

"Multiple analyses, including a recent publication in *Cell*, have shown that REGEN-COV retains potency against the main variants of concern circulating within the U.S.; consequently, REGEN-COV remains available for use in all 50 states. REGEN-COV retains potency against variants including P.1 (first identified in Brazil, now classified by the World Health Organization [WHO] as Gamma), B.1.351 (first identified in South Africa, now classified by the WHO as Beta) and B.1.162.2 (first identified in India, now classified by the WHO as Delta). The combined frequency of the P.1 and B.1.351 variants now exceeds 10% of new COVID-19 diagnoses across eight states (Arizona, California, Florida, Illinois, Indiana, Massachusetts, Oregon and Wa shington), and the prevalence of these and other variants continues to be closely monitored."

NIH COVID-19 Treatment Guidelines Update - June 17, 2021

- The COVID-19 Treatment Guidelines Panel recommends using anti-SARS-CoV2 monoclonal antibodies to treat non-hospitalized patients with mild to moderate COVID-19 who are at high risk of clinical progression

https://www.covid19treatmentguidelines.nih.gov/

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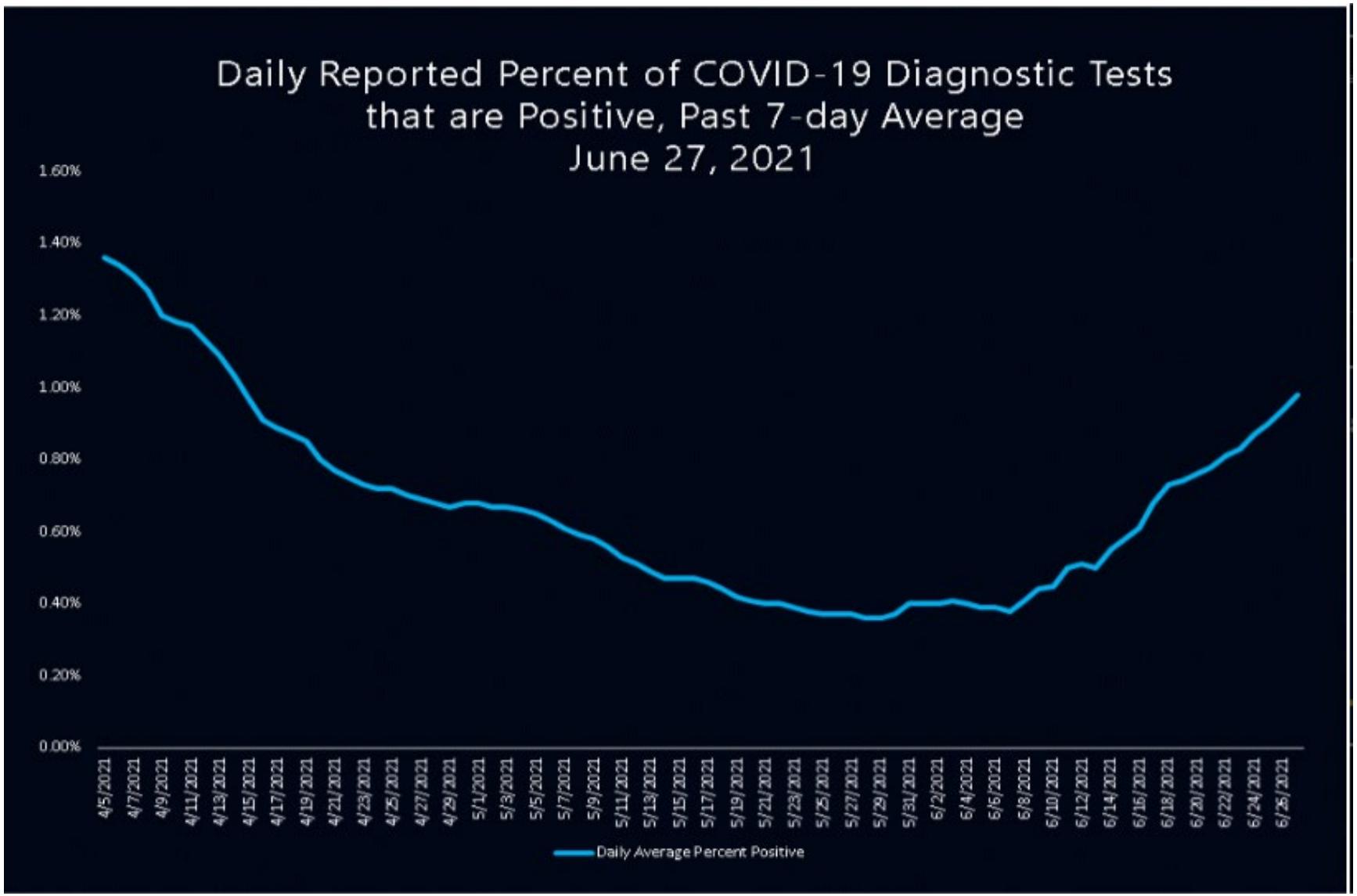
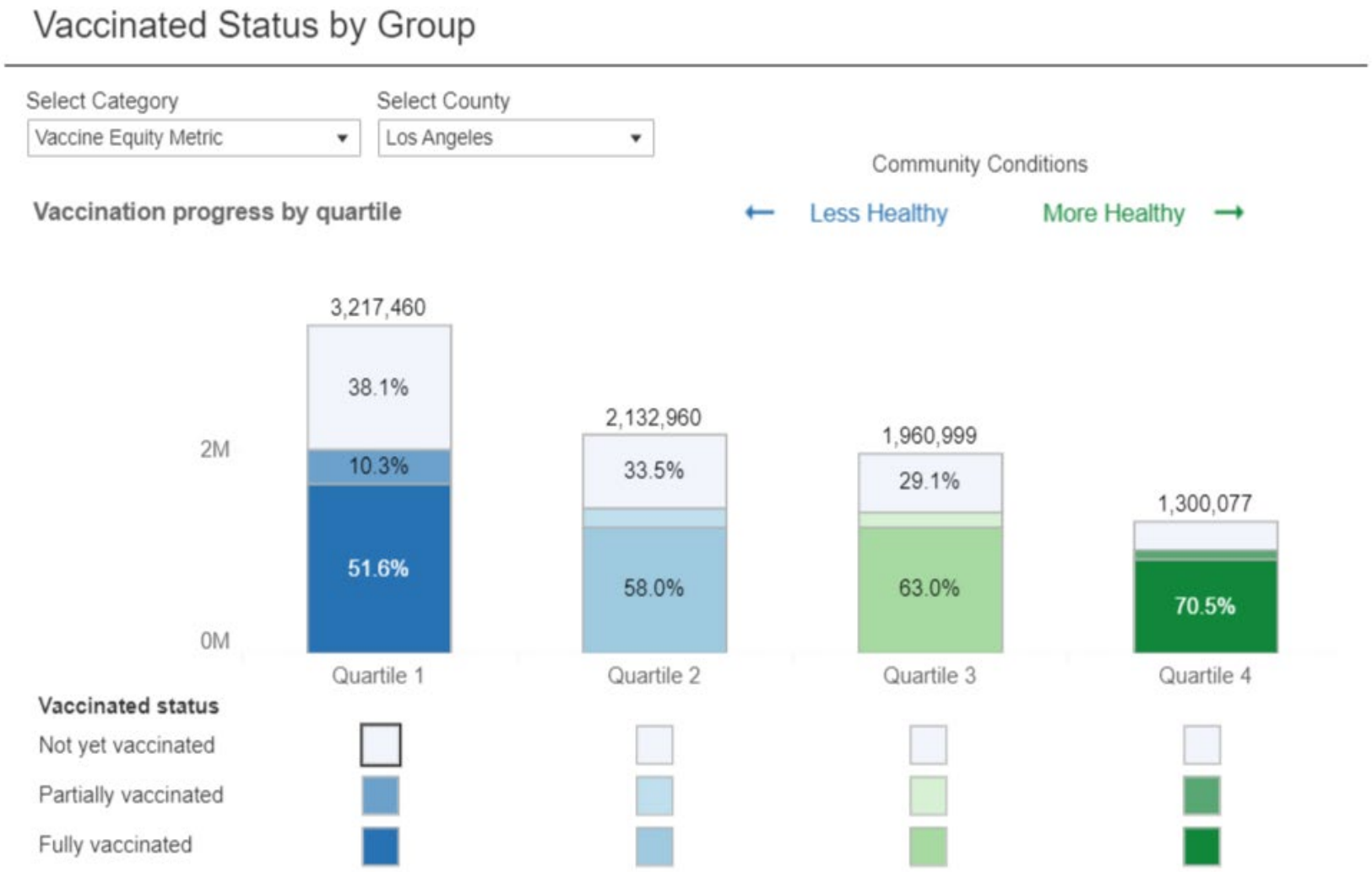
Why Treatment with Monoclonal Antibodies when the Rates of Infection are Low?

LA County DPH- Testing Positivity Rate



Vaccination Completion in California – by quartile

https://covid19.ca.gov/vaccination-progress-data/



The HPI quartiles are the total state population divided into 25% segments based on conditions that shape health, including housing, transportation, and education

Vaccine Breakthrough COVID-19 infections

CDC: On fully vaccinated people > 2% of break-through infections result in death

- Total breakthrough infections 10,262
- 995 hospitalized (10%)
- 160 deaths (2%)

- MMWR CDC: COVID-19 Vaccine Infections Reported to the CDC- United States , January 1- April 30 2021 (Release 5/25/2021)

The Fall/Winter – Season

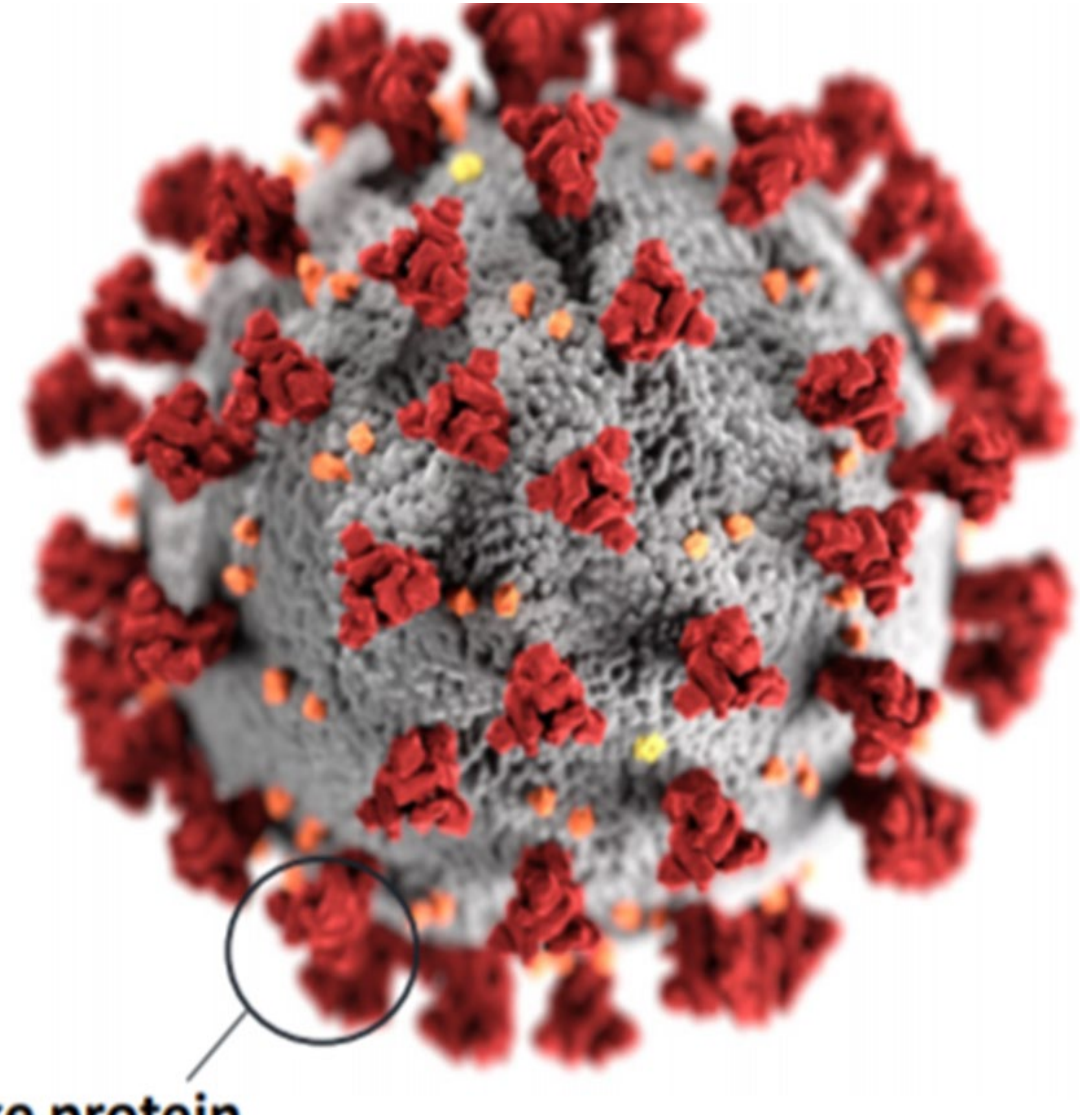
Booster vaccines

New variants

Control of Pandemic- other countries

Travel

Mask and distancing restrictions



Future of Monoclonal Antibodies

- More pharmaceuticals producing more choices
  - New product: Sotrovimab (not available)
- More data
- Full FDA approval
- Now free→ pricing

Resources and Data

- https://covid19.ca.gov/vaccination-progress-data/
- https://www.idsociety.org/multimedia/clinician-calls/cdcidsa-covid-19-clinician-call-covid-19-treatment-updates-focus-on-monoclonal-antibodies-and-tocilizumab/
- https://covid.cdc.gov/covid-data-tracker
- https://combatcovid.hhs.gov/i-have-covid-19-now/monoclonal-antibodies-high-risk-covid-19-positive-patients?msclkid=2cbb420d51b715f3b52622a3016fb1a5
- https://www.covid19treatmentguidelines.nih.gov/outpatient-management/

Inclusion Criteria

- Inclusion criteria:
  - 12 or older age group
  - Weigh at least 40 kg
  - Positive COVID-19
  - Within 10 days of symptom onset
  - Meets **high risk criteria**

Citations

- COVID-19 Treatment Guidelines Panel, Coronavirus Disease 2019 (COVID-19) Treatment Guidelines, National Institutes of Health, Available at https://covid19treamentguidelines.nih.gov (06/30/2021)

Demonstration by Dr. Marco Angulo Ordering Casirivimab + Imdevimab

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Post-treatment

Isolation after M-Ab treatment

It's important to know discuss with patients that even if they start feeling better, they can still spread the virus for a while. They will need to isolate until all of these things happen:

- At least 10 days have passed since the first symptoms of COVID-19
- No fever for at least 24 hours, without taking any medicine that reduces fever
- Other symptoms of COVID-19 are improving

Hypersensitivity Reactions

- Hypersensitivity Including Anaphylaxis and Infusion-Related Reactions
- Serious hypersensitivity reactions, including anaphylaxis, have been observed with administration of bamlanivimab with and without etesevimab. 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 and etesevimab together. These reactions may be severe or life threatening.
- Signs and symptoms of infusion related reactions may include:
- fever, difficulty breathing, reduced oxygen saturation, chills, fatigue, arrhythmia (e.g., atrial fibrillation, sinus tachycardia, bradycardia), chest pain or discomfort, weakness, altered mental status, nausea, headache, bronchospasm, hypotension, hypertension, angioedema, throat irritation, rash including urticaria, pruritus, myalgia, dizziness and diaphoresis.

- If an infusion-related reaction occurs, consider slowing or stopping