Monoclonal Antibody Therapy Webinar

August 26, 2021

While we wait to get started…

- **We are recording this webinar**. The slides and recording will be sent to all registrants.
- We have disabled participant microphones and video for this webinar.
- **Live captioning can be enabled**. Click the ellipses at the top of your Teams window to view the menu of actions available.
- **To submit a question to the panelists, please use the link pasted in the chat.**
- For webinar issues, email Tom Cogswell (thomas.cogswell@dhsoha.state.or.us)

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Monoclonal Antibody Therapies to Treat COVID-19

Shimi Sharief MD MPH
Senior Health Advisor, COVID-19 Response
Ariel Smits MD, MPH
Health Evidence Review Commission (HERC) Medical Director, Senior Health Advisor, COVID-19 Response
Dawn Mautner MD, MS
Medicaid Medical Director, Senior Health Advisor, COVID-19 Response

Acknowledgements:
Melissa Sutton MD MPH
Medical Director of Respiratory Pathogens

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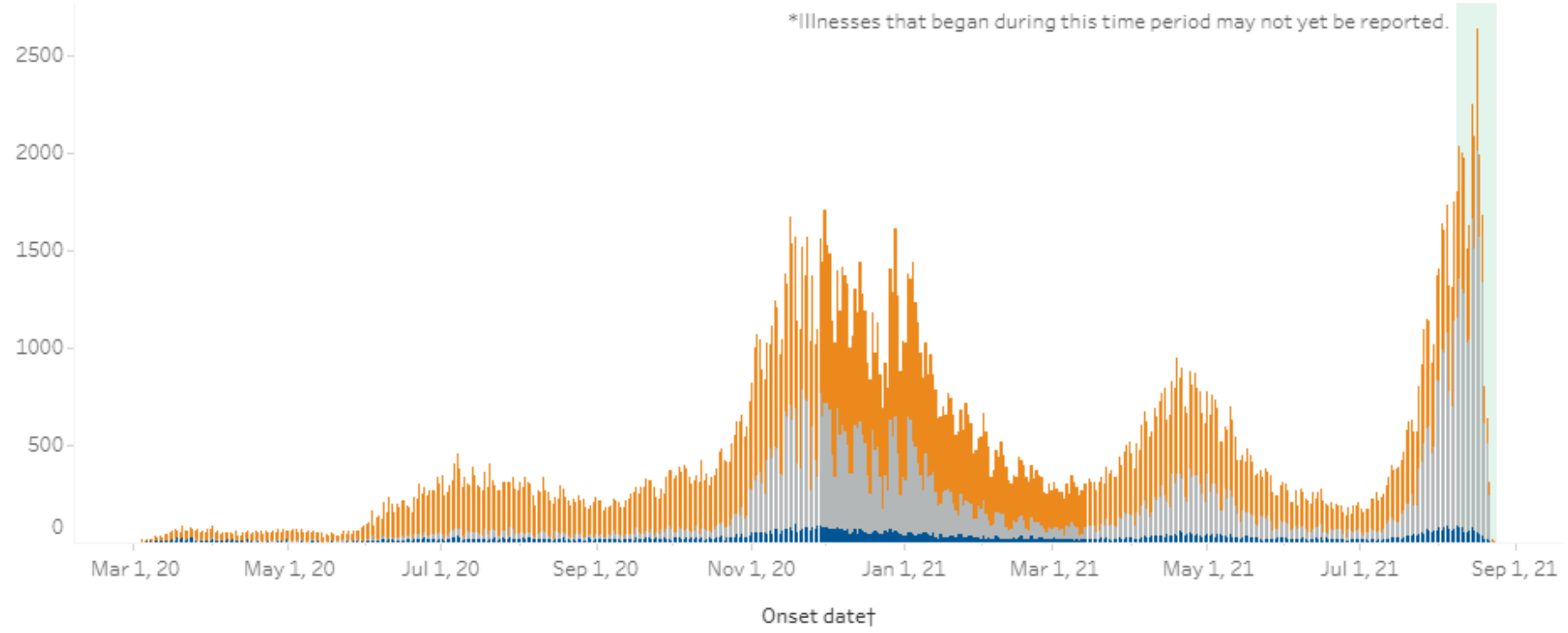
COVID-19 Positive Patients

View on web

Oregon's Epi Curve: COVID-19 cases

This chart shows the number of Oregonians who have been identified as COVID-19 cases and whether they were ever hospitalized for their illness.‡

Total Cases	Hospitalized	Not Hospitalized	Hospitalization Status Unknown
260,425	14,053	162,432	83,940



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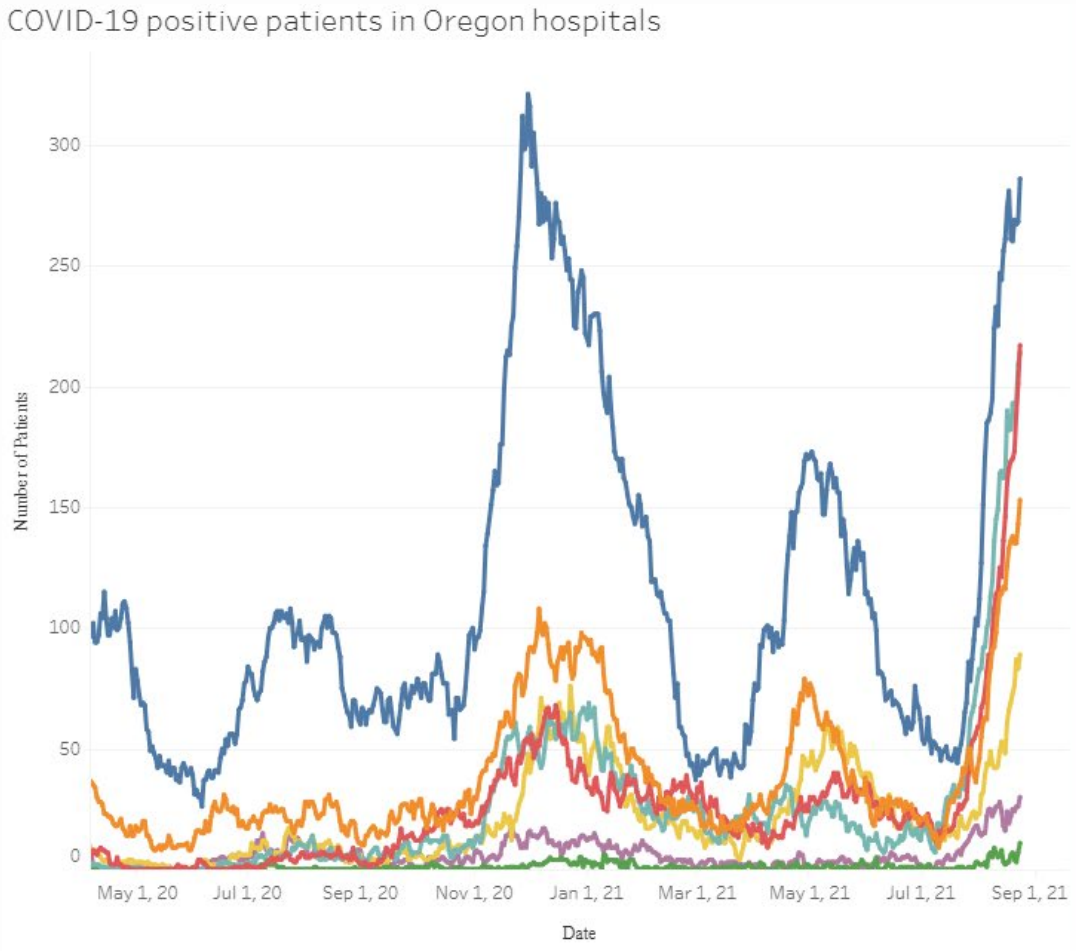
COVID-19 Positive Patients by Region

View on web



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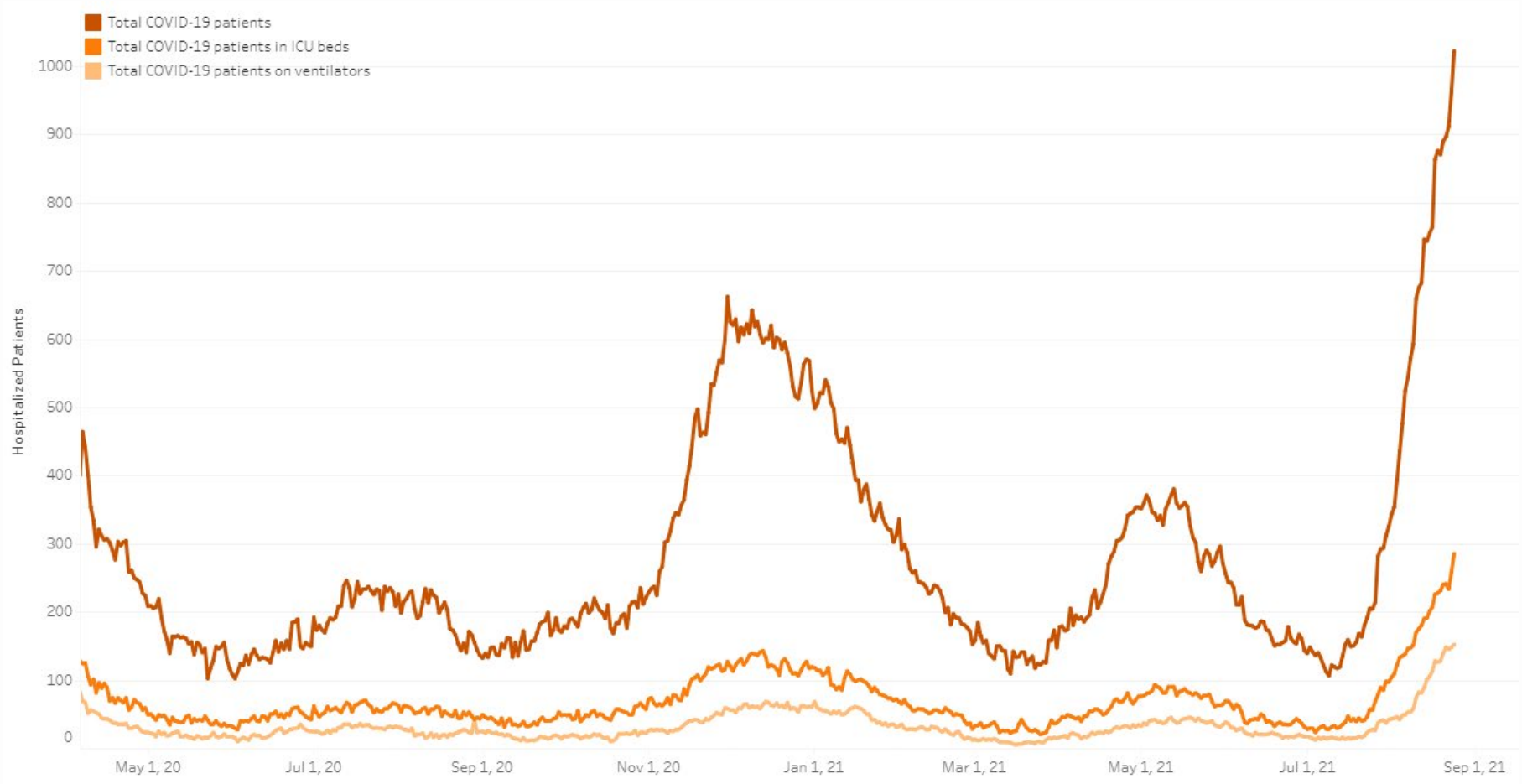
Hospitalizations by Severity

View on web



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Hospital Capacity

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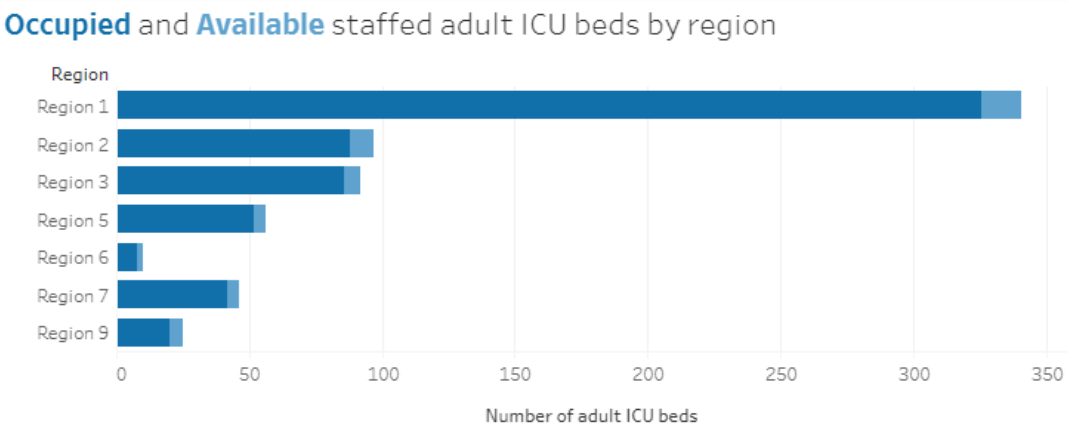

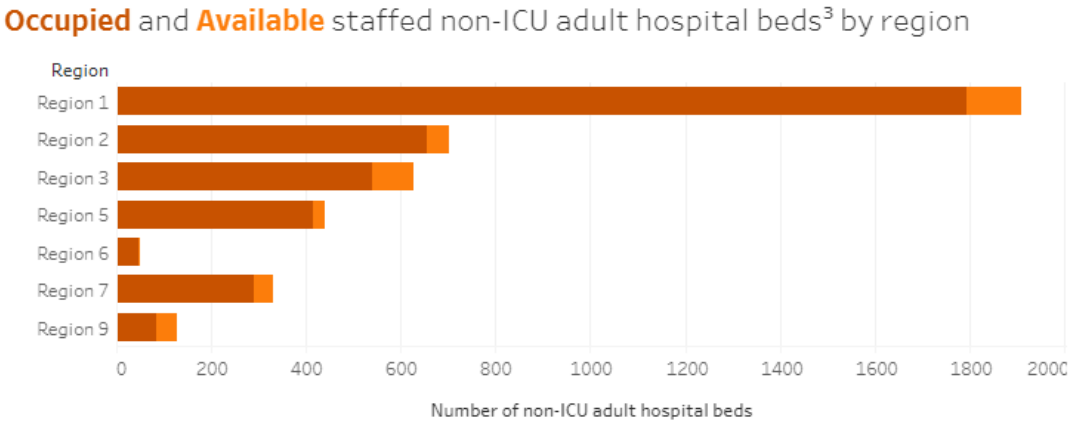

Variants of concern in Oregon

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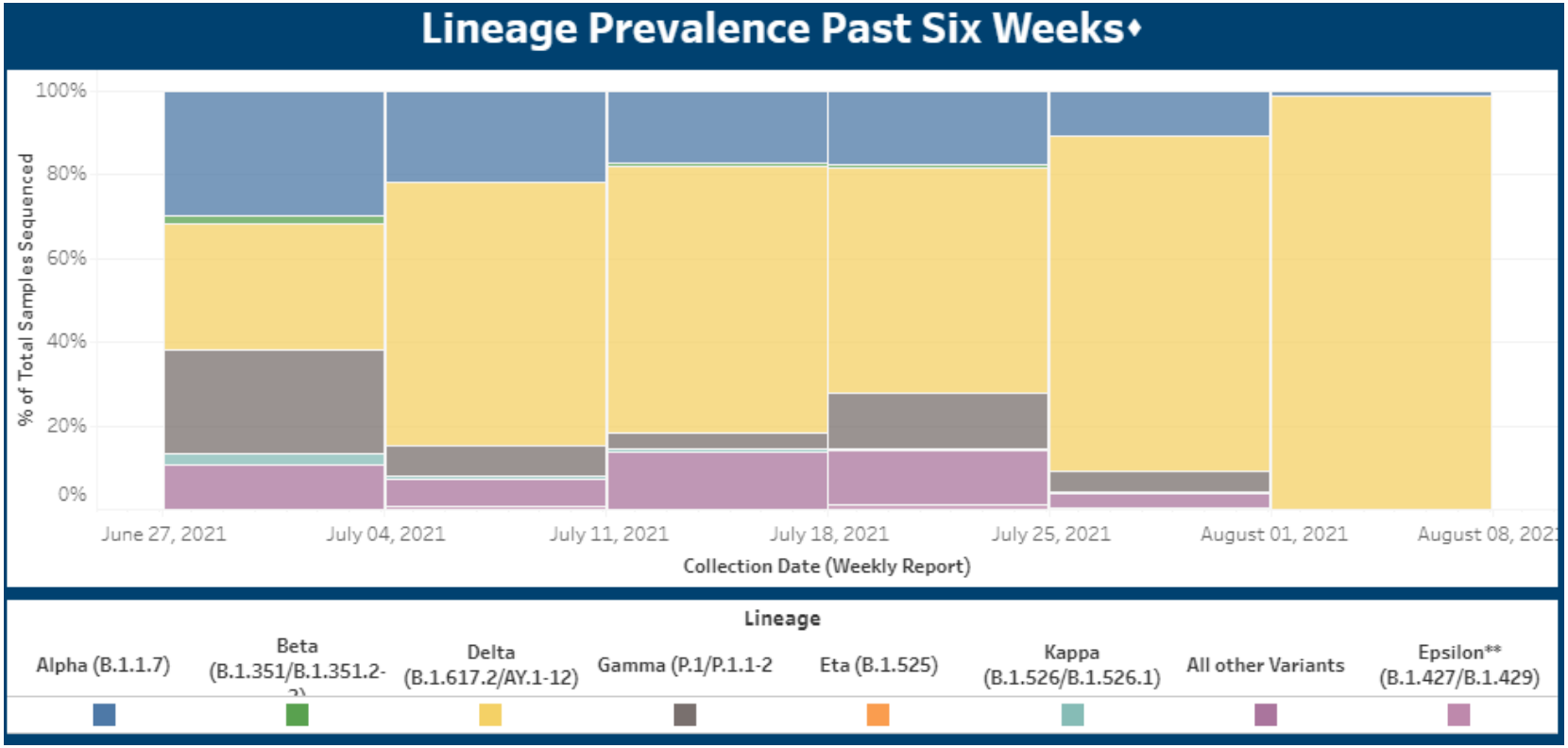

- **B.1.617.2** is now dominant 98.8% of cases sequenced in the last week
  - 2-3x more transmissible
  - Lower VE against symptomatic infection

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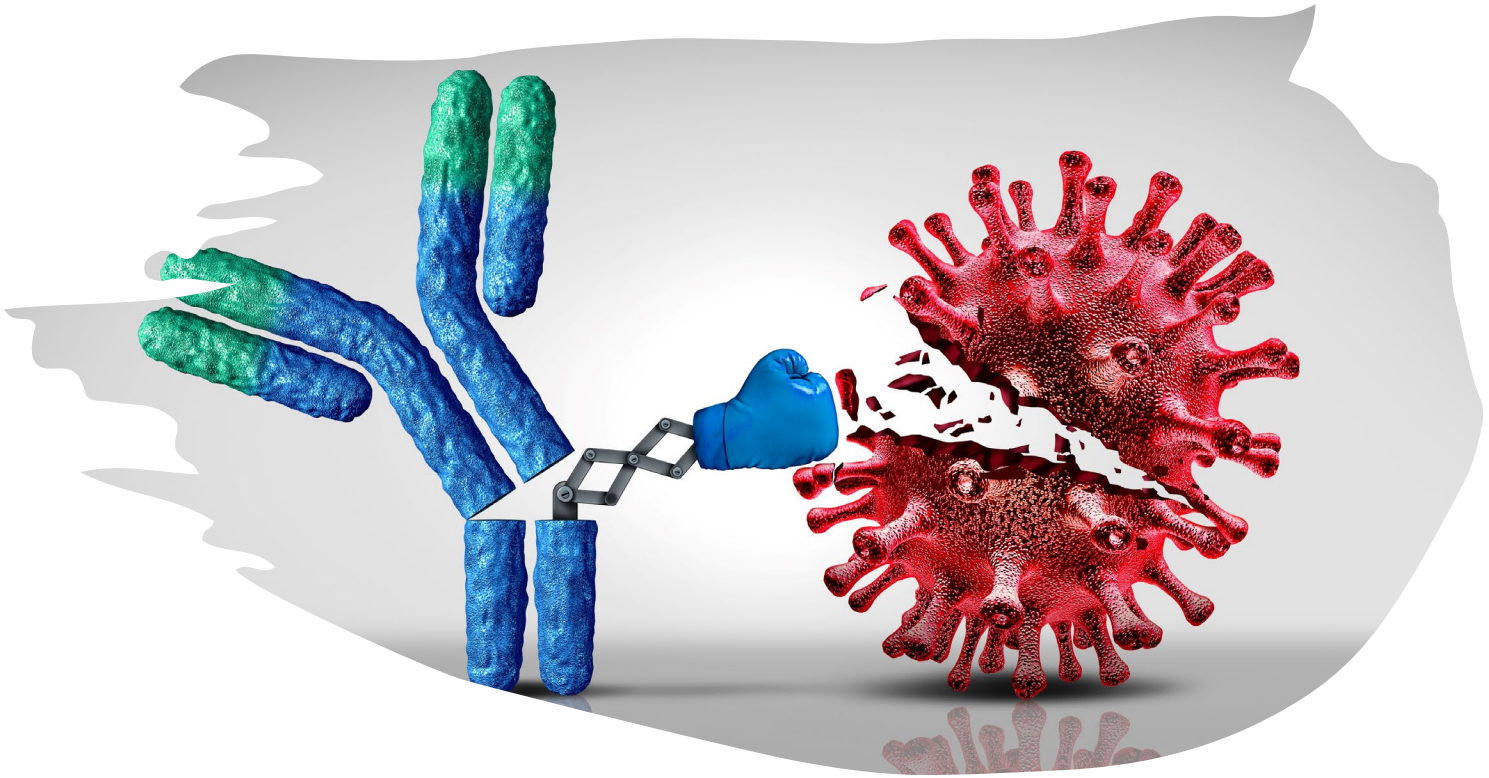

Monoclonal Antibodies

Monoclonal Antibodies
Outpatient Therapy – Eligibility Criteria

Authorized under EUA to treat patients to prevent hospitalization due to COVID-19.

- Eligible adults and children > 12 (and >40kg) who are outpatients, with mild to moderate illness, and who have test confirmed COVID-19 (PCR and antigen both ok) and are*:
  - Diabetic
  - BMI > 25
  - CKD or require dialysis
  - > 65 years old
  - > 55 years old with certain conditions (HTN, CVD, COPD)
  - > 12 years old with certain conditions

* **Not an exhaustive list**

Monoclonal Antibodies
Outpatient Therapy – Eligibility Criteria

Eligibility is not limited to the conditions listed on prior slide. Other factors, such as **race or ethnicity**, are associated with increased risk for progression to severe COVID-19.

For example, data show that patients of color or from Tribal communities are most harmed by health inequities and the risks of hospitalization and death for these groups are greater than those of white patients. These patients may face higher risk than white patients, due to longstanding societal injustices including racism, discrimination, colonization, etc., which have and continue to negatively impact health outcomes.

FDA EUA Fact Sheet for Healthcare providers

Monoclonal Antibodies
Outpatient Therapy – Exclusion Criteria

- Excluded for patients who:
  - Require hospitalization for 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 due to COVID-19 or other comorbidity

- For full EUA language, click here.

COVID-19 Monoclonal Antibody Therapy

Drug	Setting		Route		Indications	
	Out pt	In pt	IV	Sub-Q	Mild to moderate COVID-19 in high-risk pts	Post-exposure prophylaxis
Sotrovimab[1]	X		X		X	
Casirivimab and imdevimab	X		X	X	X	X
Bamlanivimab & etesevimab[2]	X		X		X	
Tocilizumab[3]		X	X		X	

[1] FDA EUA 5/26/21
[2] Distribution paused 6/25/21
[3] FDA EUA 6/24/21; reports of supply shortages as of 8/20/2021

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Casirivimab/Imdevimab: Post-Exposure Prophylaxis

- Authorized for post-exposure prophylaxis in exposed eligible children (12+) and adults.
  - **Exposed to a case of SARS-CoV-2, or**
  - At **high risk of exposure to infection/cases in institutional setting** (ex. nursing homes, prisons).

- In those unvaccinated, incompletely vaccinated or those completely vaccinated and expected to have suboptimal response

- Can be used for repeat dosing for those with ongoing exposure > 4 weeks (especially in large household or facility-wide outbreaks).

For full EUA language, click here.

Updated Dosing of Casirivimab/Imdevimab

- Was previously authorized at 1200mg of each product which needed to combined into one patient dose
- EUA was **changed recently** to make the authorized dose **600mg of each product**
- Facilities who were in receipt of the older vials now have **twice as many doses** on stock
  - The doses should be utilized within 3 hours of vial puncture

Summary of Evidence - Treatment

- Reduced viral load
- 50-70% reduction in medically attended visits/hospitalizations
  - NNT = 33-50

- References:
  - David M. Weinreich M.D., Sumathi Sivapalasingam M.D., Thomas Norton M.D., et al. (2021). REGN-COV2, a Neutralizing Antibody Cocktail, in Outpatients with Covid-19. *The New England Journal of Medicine*, 384:238-251, DOI:10.1056/NEJMoa2035002 https://www.nejm.org/doi/full/10.1056/NEJMoa2035002

  - *Fact Sheet for Health Care Providers Emergency Use Authorization of Regen-COV™*. (n.d.). Regeneron. Retrieved August 23, 2021, pages 44-47 from https://www.regeneron.com/downloads/treatment-covid19-eua-fact-sheet-for-hcp.pdf

Summary of evidence – Post-exposure prophylaxis

- There was an 81% risk reduction in the development of **symptomatic** test-confirmed COVID-19 between treated and untreated group.
  - NNT= 15.8

- There was a 66% reduction in development of **any** test confirmed disease in the treated vs. untreated group.
  - NNT = 10

- A sub analysis of only **those patients at high risk for progression**, this efficacy came out to 74% reduction to developing **symptomatic** COVID-19 in treated group compared to placebo.
  - NNT = 20

Current distribution pathways

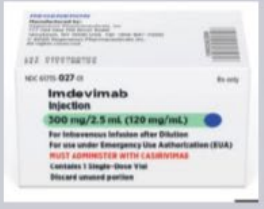
- Casirivimab/Imdevimab (Regeneron)
  - Available at no cost to providers and pre-purchased and shipped from federal government HHS
  - OHA not involved in allocation but involved with outreach/education and as liaison for questions.

- Bamlanivimab/Etesivimab – *Currently on pause due to high numbers of beta and gamma variants nationwide.*

- Sotrovimab and Tocilizumab – Available through commercial purchase (GSK and Genentech respectively). Active against gamma and beta.

Dosing for treatment and post-exposure prophylaxis

Casirivimab and imdevimab formulations and dose preparation
Authorized dose: REGEN-COV (casirivimab 600mg and imdevimab 600mg)

Administration Route	Single Product Vials	REGEN-COV
Intravenous **(Mixed and administered per EUA instructions)** Intravenous infusion is strongly recommended. Subcutaneous injection is an alternative route of administration when intravenous infusion is not feasible and would lead to delay in treatment. https://www.regeneron.com/downloads/treatment-covid19-eua-fact-sheet-for-hcp.pdf	casirivimab (REGN10933) **5mL total** (from 2.5- or 11.1-mL vials)   imdevimab (REGN10987) **5mL total** (from 2.5- or 11.1-mL vials)  	**10mL total** 
Subcutaneous	Two syringes with 2.5mL each of casirivimab (REGN10933) (**total of 5mL casirivimab**) Two syringes with 2.5mL each of imdevimab (REGN10987) (**total of 5mL imdevimab**)	Four syringes each containing 2.5mL REGEN-COV for a **total of 10mL**

REGEN-COV (casirivimab 1200mg and imdevimab 1200mg) dosing no longer authorized under EUA

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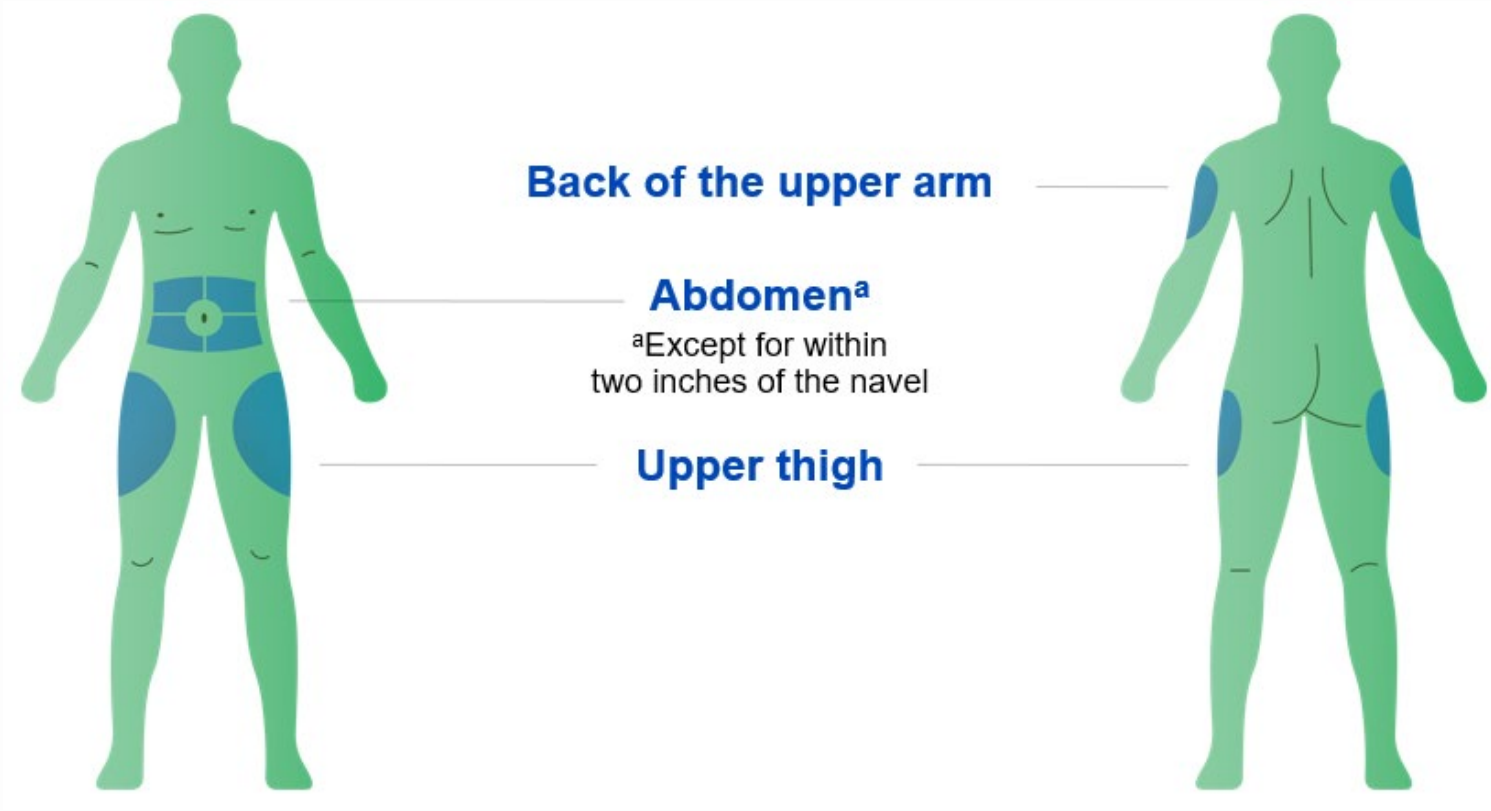
Subcutaneous injection sites



Additional instructions found at Regen-Cov.com

Common Barriers

- Provider issues:
  - Lack of provider awareness
  - Perceived effectiveness/appropriate indications
  - Training/staffing/personnel/workflow
- Patient issues:
  - Lack of willingness to undergo treatment
  - Waiting too long to get COVID tested
- Drug issues
  - Trouble obtaining or storing drug
- Administration issues
  - Ability to bring in COVID positive patients to infusion center
- System issues
  - Difficulty obtaining COVID test results in timely manner
  - Difficulty with scheduling patients/coordinating testing and care

Provider Eligibility

- Any outpatient facility is eligible to administer these products provided they are able to store and handle and administer them with qualified personnel
  - Potential of expansion to include pharmacists/pharmacies

- No need for pharmacy affiliation to be enrolled as an administering provider.
  - OHA can help you create an LOA to get enrolled in lieu of a pharmacy NCPDP or NPI number.

- OHA can also help you setup a login with Amerisource Bergen.

- If you have any questions regarding enrolling newly as a provider please contact OHA:
  - ORESF8.LogisticsChiefs@dhsoha.state.or.us

LOGISTICS – IV Infusion

- Previously the recommendation was for a standard 250 ml saline bag for dilution of the IV product.
- That has since been updated with the following guidelines for time of administration based on the size of bag used:

Table 2: Recommended Administration Rate for Casirivimab and Imdevimab for Intravenous Infusion.

Size of Prefilled 0.9% Sodium Chloride Infusion Bag used	Maximum Infusion Rate	Minimum Infusion Time
50 mL[a]	180 mL/hr	20 minutes
100 mL	310 mL/hr	21 minutes
150 mL	310 mL/hr	31 minutes
250 mL	310 mL/hr	50 minutes

[a] The minimum infusion time for patients administered casirivimab and imdevimab together using the 50 mL prefilled 0.9% Sodium Chloride infusion bag must be at least 20 minutes to ensure safe use.

LOGISTICS – Subcutaneous (SQ) Injection

- Recommend prioritizing SQ when:
  - Access to IV infusion is limited/impossible; or
  - Would lead to delays in treatment while waiting for IV product.

- Broadens accessibility of settings:
  - Shorter time for administration and monitoring.
  - Broader scope of personnel (ex. MAs, CNAs) to administer and monitor post administration.
  - Broader settings (e.g. tents, cars)

SQ Considerations

- Storage
  - Regular refrigerator temperatures for both (2-8C)
  - Pharmacy or other staff at facility who can store/receive product

- Handling:
  - Prepared SQ doses sit:
    - Refrigerator for 4 hours at most
    - Room temp for 4 hours at most

- Personnel for administration
  - Medical assistants, nurses and other qualified staff
  - Monitoring for anaphylaxis and ability to give epi/Benadryl just as with vaccination clinics – require 60 mins.
  - Healthcare provider for questions/respond for emergency (telehealth ok)

Reimbursement

- No cost to provider to order Casirivimab/Imdevimab.
  - Costs associated with other products.

- CMS and commercial rates:
  - $450 per administration in any outpatient facility regardless of formulation.
  - $750 per administration in the patient's home.

Multnomah County Pilot

Amy Henninger, MD; Primary Care Medical Director
Multnomah County Health Department

Questions?

- Concerns?
- Barriers?
- How can we help?

Panelists

Shimi Sharief, MD, MPH; OHA

Ariel Smits MD, MPH; OHA

Dawn Mautner MD, MS; OHA

Amy Henninger, MD; Multnomah County

James Lapkoff, MD; Acting Supervisory Medical Officer, IMT Program; Health and Human Services

Morgan Hakki, MD; Associate Professor of Medicine, Interim Division Head, Division of Infectious Diseases, Vice Chair of Clinical Programs, Department of Medicine; OHSU

Jamie Osbourne, MD; Chief Medical Officer for Operations & Outcomes; La Clinica

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Thank you!

Contacts:

- Enrollment/ordering/logistics:

  ORESF8.LogisticsChiefs@dhsoha.state.or.us

- All other questions:

  Katelyn.niel@dhsoha.state.or.us

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Resources

- EUA fact sheet:
  - https://www.regeneron.com/downloads/treatment-covid19-eua-fact-sheet-for-hcp.pdf
- Referral locations:
  - https://protect-public.hhs.gov/pages/therapeutics-distribution
  - https://infusioncenter.org/infusion_resources/covid-19-antibody-treatment-resource-center/
- Outpatient therapy playbook
  - https://www.phe.gov/emergency/events/COVID19/investigation-MCM/Documents/USG-COVID19-Tx-Playbook.pdf

Studies/References

- Treatment: https://www.nejm.org/doi/full/10.1056/NEJMoa2035002
- Prophylaxis: https://www.nejm.org/doi/full/10.1056/NEJMoa2109682
- Also reference pages 40-48 EUA fact sheet: https://www.regeneron.com/downloads/treatment-covid19-eua-fact-sheet-for-hcp.pdf
- Reference Regeneron clinical resources for healthcare providers: https://www.regencov.com/hcp/dosing/dosing-administration

Appendix

Neutralizing activity against variants

Table 9: Pseudotyped Virus-Like Particle Neutralization Data for SARS-CoV-2 Variant Substitutions with Casirivimab and Imdevimab Together

Lineage with Spike Protein Substitution	Country First Identified	WHO Nomenclature	Key Substitutions Tested	Fold Reduction in Susceptibility
B.1.1.7	UK	Alpha	N501Y[a]	no change[d]
B.1.351	South Africa	Beta	K417N, E484K, N501Y[b]	no change[d]
P.1	Brazil	Gamma	K417T, E484K, N501Y[c]	no change[d]
B.1.427/B.1.429	USA (California)	Epsilon	L452R	no change[d]
B.1.526[e]	USA (New York)	Iota	E484K	no change[d]
B.1.617.1/B.1.617.3	India	Kappa/no designation	L452R+E484Q	no change[d]
B.1.617.2	India	Delta	L452R+T478K	no change[d]

[a] Pseudotyped VLP expressing the entire variant spike protein was tested. The following changes from wild-type spike protein are found in the variant: del69-70, del145, N501Y, A570D, D614G, P681H, T716I, S982A, D1118H.

[b] Pseudotyped VLP expressing the entire variant spike protein was tested. The following changes from wild-type spike protein are found in the variant: D80Y, D215Y, del241-243, K417N, E484K, N501Y, D614G, A701V.

[c] Pseudotyped VLP expressing the entire variant spike protein was tested. The following changes from wild-type spike protein are found in the variant: L18F, T20N, P26S, D138Y, R190S, K417T, E484K, N501Y, D614G, H655Y, T1027I, V1176F

[d] No change: ≤2-fold reduction in susceptibility.

[e] Not all isolates of the New York lineage harbor the E484K substitution (as of February 2021).

Delta variant considerations

- **All three products – Bamlanivimab/Etesivimab, Casirivimab/Imdevimab and Sotrovimab are ALL effective against the Delta variant.**

- Pause occurred on Bamlanivimab/Etesivimab when gamma and beta exceeded >10% of all specimens nationally. NOT due to Delta.

- We advise facilities that have previous stock of Bamlanivimab/Imdevimab to hold onto to those unexpired doses in the event that the variant distributions change again especially with ongoing rise of Delta nationwide. That is starting to happen now but awaiting HHS guidance to be able to switch.

Post-Exposure Prophylaxis Commonly Asked Questions

Question 1: Is there a recommended time window from exposure to post-exposure dose?

Answer: There is no specific timeframe, but EUA states the drug should be administered as soon as possible. Clinical study references patients were randomized within 96 hours of a household member receiving a positive PCR test. See Section 18 of the Fact Sheet.

Question 2: How should we interpret "not likely to mount an adequate immune response" as outlined in the Regeneron EUA with post exposure prophylaxis?

Answer: Data on COVID-19 vaccine protection in people who are immunocompromised are limited. Additional information on vaccine protection in immunocompromised individuals is here. Healthcare providers and their patients should discuss whether their clinical condition makes vaccine protection unlikely enough to warrant PEP.

Question 3: Would hospital medical staff providing care to COVID patients fall in the criteria for post-exposure treatment?

Answer: If the medical staff are determined by their health care provider to be high risk for severe illness or hospitalization if infected, then yes, they can be candidates for the treatment.

Question 4: If a patient receives REGEN-COV for post-exposure prophylaxis and then tests positive for COVID at a later date, may the patient then be treated with REGEN-COV

Answer: There is no restriction in the EUA that prevents a patient who received REGEN-COV for post exposure prophylaxis (PEP) from being treated later if they test positive for COVID-19. Clinical judgment by the health care provider should be used in such cases based on time of PEP dose versus treatment dose. Half-life is approximately 1 month

Repeat dosing in those exposed > 4 weeks

Prepare 300 mg of Casirivimab and 300 mg of Imdevimab	Preparation of 2 Syringes
Using Casirivimab and Imdevimab Co-formulated Vial	Withdraw 2.5 mL solution per syringe into TWO separate syringes.
Using Casirivimab and Imdevimab Individual Vials	• **Casirivimab:** Withdraw 2.5 mL solution into ONE syringe. • **Imdevimab:** Withdraw 2.5 mL solution into ONE syringe. For total of 2 syringes.

[a] Subsequent repeat dosing every 4 weeks after initial 600 mg casirivimab and 600 mg imdevimab dosing for the duration of ongoing exposure.

General Guidelines for REGEN-COV Intravenous Dosing, Dilution

Dilution Instructions for REGEN-COV (600 mg Casirivimab and 600mg Imdevimab) for intravenous infusion

Size of Prefilled 0.9% Sodium Chloride Infusion Bag	Preparing Using Co-Formulated Casirivimab and Imdevimab Vial	Preparing Casirivimab and Imdevimab Using Individual Vials[a]
50 mL 20 min minimum	Add 10 mL of co-formulated casirivimab and imdevimab (1 vial) into a prefilled 0.9% sodium chloride infusion bag and administer as instructed below	Add: • 5 mL of casirivimab (may use 2 vials of 2.5 ml OR 5 mL from 1 vial of 11.1 mL) • 5 mL of imdevimab (may use 2 vials of 2.5 ml OR 5 mL from 1 vial of 11.1 mL) and inject into a prefilled 0.9% sodium chloride infusion bag and administer as instructed below
100 mL 21 min minimum		
150 mL 31 min minimum		
250 mL 50 min minimum		

[a] 600 mg of casirivimab and 600 mg of imdevimab are added to the same infusion bag and administered together as a single intravenous infusion.

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General Guidelines for REGEN-COV Subcutaneous Dosing and Administration

Administration Instructions for REGEN-COV (600 mg Casirivimab and 600mg Imdevimab) for subcutaneous injection[1]

Prepare 600 mg of Casirivimab and 600 mg of Imdevimab	Preparation of 4 Syringes
Using Casirivimab and Imdevimab Co-formulated Vial	Withdraw 2.5 mL solution per syringe into FOUR separate syringes. Administer the subcutaneous injections consecutively, **each at a different injection site**, into the thigh, back of the upper arm, or abdomen, except for 2 inches (5 cm) around the navel. The waistline should be avoided.
Using Casirivimab and Imdevimab Individual Vials	• **Casirivimab:** Withdraw 2.5 mL solution per syringe into TWO separate syringes. • **Imdevimab:** Withdraw 2.5 mL solution per syringe into TWO separate syringes. For total of 4 syringes.

Intravenous infusion is strongly recommended. Subcutaneous injection is an alternative route of administration when intravenous infusion is not feasible and would lead to delay in treatment.

EUA Fact Sheet for HCP: https://www.regeneron.com/downloads/treatment-covid19-eua-fact-