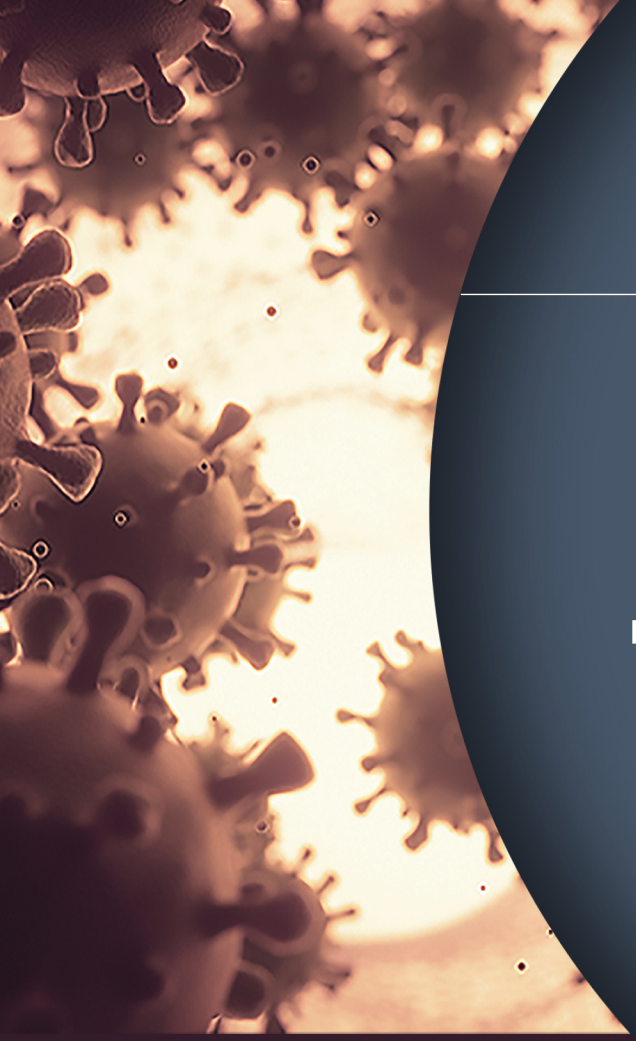

Project ECHO®

COVID-19 FRONTLINE THERAPIES:

Navigating Through This Health Crisis and Optimizing Patient Care

MEETING INFO
Monday, September 13, 2021

FACULTY
William A. Fischer II, MD
Associate Professor of Medicine
Pulmonary and Critical Care Medicine
Director of Emerging Pathogens
Institute for Global Health and Infectious Diseases
The University of North Carolina
Chapel Hill, NC

This activity is provided by Med Learning Group.
This activity is co-provided by Ultimate Medical Academy/Complete Conference Management (CCM) .
This activity is supported by an independent medical education grant from Regeneron Pharmaceuticals, Inc.

AGENDA

1. **Rationale for the Use of New Virus-neutralizing Monoclonal Antibodies**
    a. High mutation rate of RNA viruses
    b. The risk of viral mutations leading to therapy resistance
    c. Mechanism of action of new virus-neutralizing monoclonal antibodies in mitigating the risk of viral resistance to therapy
2. **Therapies Granted Emergency Use Authorization for Patients with COVID-19**
    a. Symptoms of mild-to-moderate COVID-19
    b. Recommended treatment for hospitalized patients
    c. Animation of the mechanism of action of monoclonal antibody therapies with emergency use authorization
    d. What is emergency use authorization?
    e. Clinical trial data on the efficacy and safety of new virus-neutralizing monoclonal antibodies patients who test positive for COVID-19
    f. Guidance of the development of in-clinic infusion capability to deliver new virus-neutralizing monoclonal antibodies at the point-of-care
3. **Updates on COVID-19 Vaccine Development**
    a. COVID-19 vaccines with emergency use authorization
    b. Animation of the mechanisms of new vaccine technologies
    c. Efficacy and safety of vaccination against COVID-19
4. **Resources for Providers and Their Patients with COVID-19**
5. **Case studies**
6. **Conclusions**

COVID-19 Frontline Therapies: Navigating Through This Health Crisis and Optimizing Patient Care

FACULTY

PROGRAM CHAIR

Shyam Kottilil, MD, PhD
Professor of Medicine
Chief, Division of Infectious Diseases
Institute of Human Virology
University of Maryland
Baltimore, MD

FACULTY PRESENTERS

William A. Fischer II, MD
Associate Professor of Medicine, Pulmonary and Critical Care Medicine
Director of Emerging Pathogens
Institute for Global Health and Infectious Diseases
The University of North Carolina
Chapel Hill, NC

Michael G. Ison, MD, MS, FIDSA, FAST
Professor
Northwestern University Feinberg School of Medicine
Chicago, IL

Christopher Palma, MD, ScM
Assistant Professor of Medicine
University of Rochester
Rochester, NY

PROGRAM OVERVIEW

The COVID-19 FRONTLINE TeleECHO series provides a comprehensive and up-to-date perspective on the ever-changing management of patients with COVID-19. Each TeleECHO session features in-depth case studies to encourage retention of the lessons and provide new perspectives on the management of patients during the COVID-19 pandemic. The case studies will focus on different issues facing clinicians, such as identifying patients who would benefit from monoclonal antibody therapy and best practices for incorporating agents authorized for emergency use into the care of hospitalized and non-hospitalized patients with COVID-19. Strategies for administering neutralizing monoclonal antibodies, such as referral to local infusion centers or developing in-clinic infusion capabilities, will also be discussed.

TARGET AUDIENCE

This CME initiative is designed for HCPs who are involved in the care and treatment of patients with COVID-19, including physicians, NPs, PAs, nurses, and pharmacists across emergency medicine, primary care, family medicine, infusion centers, and the Department of Veteran Affairs.

LEARNING OBJECTIVES

Upon the completion of this program, attendees should be able to:

- Assess the rationale for the use of new virus-neutralizing monoclonal antibodies to mitigate the risk of viral resistance to therapy
- Critique the efficacy and safety of new virus-neutralizing monoclonal antibody therapies and other therapies approved for emergency use in all patients who test positive for COVID-19
- Develop in-clinic infusion capability in order to administer new virus-neutralizing monoclonal antibodies to patients with COVID-19 at the point-of-care
- Use guidance and resources developed to promote safe and responsible use of infusion therapies for treating patients with COVID-19

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This CME activity was planned and produced in accordance with the ACCME Essentials.

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Med Learning Group designates this live virtual activity for a maximum of 1.0 *AMA Category 1 Credit*™. Physicians should claim only the credit commensurate with the extent of their participation in the live virtual activity.

NURSING CREDIT INFORMATION

Purpose: This program would be beneficial for nurses involved in the treatment of patients with COVID-19.
Credits: 1.0 ANCC Contact Hour.

CNE Accreditation Statement: Ultimate Medical Academy/CCM is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation. Awarded 1.0 contact hour of continuing nursing education of RNs and APNs.

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DISCLOSURE OF CONFLICTS OF INTEREST

Faculty Member	Disclosures
Shyama Kottilil, MD, PhD	Discloses that the University of Maryland has received funds to participate in trials, as well he has received research funds paid to the university from Merck Inc, Gilead Sciences and Arbutus Pharmaceuticals. He has also provided contracted research for Regeneron, Eli Lilly, and air Pharmaceuticals, as well as serving on the advisory board for Hepatitis B Functional Cure program at Merck Inc.
William A. Fischer II, MD	Discloses that he has been contracted for research for Ridgeback Biopharmaceuticals for COVID-19 research, as well as worked as Consulted for Merck and Roche. He also worked for Syneos and Janssen for adjudication of AE in RSV and Influenza studies respectively, and served as the site PI for the Phase I Lilly study of - Bamlanivimab and for the Phase II study of Casirivimab/Imdevimab at University of North Carolina.
Michael G. Ison, MD, MS, FIDSA, FAST	Discloses that he has received royalty from UpToDate. Dr. Ison has received consulting fees from Roche, Janssen and Celltrion.
Christopher Palma, MD, ScM	Discloses that he has been contracted for research for Regeneron.

CME Content Review

The content of this activity was independently peer reviewed.
The reviewer of this activity has nothing to disclose.

CNE Content Review

The content of this activity was peer reviewed by a nurse reviewer.
The reviewer of this activity has nothing to disclose.

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Christina Gallo, SVP, Educational Development for Med Learning Group, has nothing to disclose.

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There are no fees for participating and receiving CME credit for this live virtual activity. To receive CME/CNE credit participants must:

1. Read the CME/CNE information and faculty disclosures.
2. Participate in the web-based live activity.
3. Submit the evaluation form to Med Learning Group.

You will receive your certificate upon completion.

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COVID-19 FRONTLINE Therapies

Navigating Through This Health Crisis and Optimizing Patient Care

William A. Fischer II, MD
Associate Professor of Medicine, Pulmonary and Critical Care Medicine
Director of Emerging Pathogens
Institute for Global Health and Infectious Diseases
The University of North Carolina
Chapel Hill, NC

1

Disclosures

- Dr. Fischer discloses that he has been contracted for research for Ridgeback Biopharmaceuticals for COVID-19 research, as well as worked as Consulted for Merck and Roche. He also worked for Syneos and Janssen for adjudication of AE in RSV and Influenza studies respectively and served as the site PI for the Phase I Lilly study of - Bamlanivimab and for the Phase II study of Casirivimab/Imdevimab at University of North Carolina.

- During this lecture, Dr. Fischer may mention the use of medications for both FDA-approved and nonapproved indications.

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2

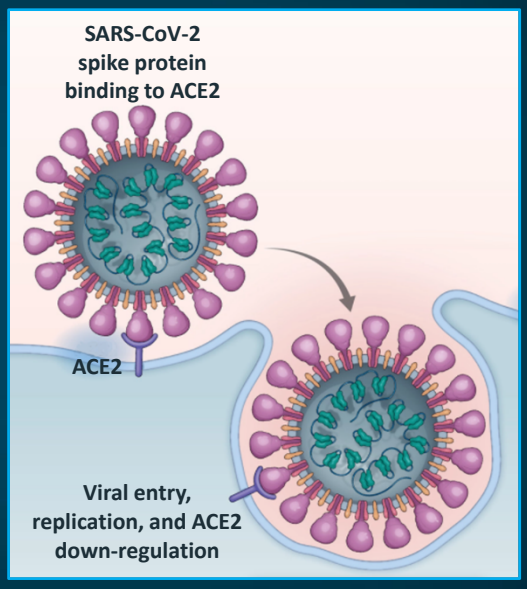
Learning Objectives

- Assess the rationale for the use of new virus-neutralizing monoclonal antibodies to mitigate the risk of viral resistance to therapy
- Critique the efficacy and safety of new virus-neutralizing monoclonal antibody therapies and other therapies approved for emergency use in all patients who test positive for COVID-19
- Develop in-clinic infusion capability in order to administer new virus-neutralizing monoclonal antibodies to patients with COVID-19 at the point-of-care
- Use guidance and resources developed to promote safe and responsible use of infusion therapies for treating patients with COVID-19

3

SARS-CoV-2

- COVID-19 is caused by the SARS-CoV-2 virus[1–3]
- The virus is spread primarily via respiratory droplets during face-to-face contact[2]
- Spike protein on viral surface binds to ACE2 receptor on target cells, facilitating viral entry into host cells[2,3]



SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; COVID-19 = coronavirus disease 2019; ACE = angiotensin-converting enzyme.

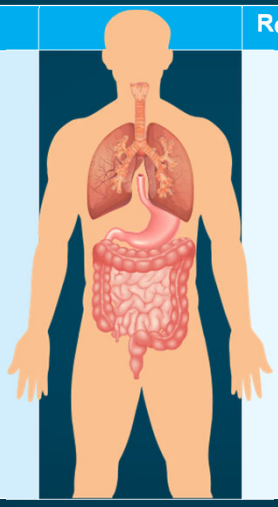
1. Adapted from Vaduganathan M, et al. *N Engl J Med*. 2020;382:1653-1659. 2. Wiersinga WJ, et al. *JAMA*. 324:782-793. 3. Baum A, et al. *Science*. 2020;369:1014-1018.

4

Clinical Presentation of COVID-19

Systemic and respiratory disorders caused by COVID-19

Systemic Disorders	Respiratory Disorders
Fever, fatigue, headache	Rhinorrhea, sneezing, sore throat
Acute cardiac injury	Cough, sputum production, Hemoptysis
Viremia	Pneumonia
Hypoxemia	Ground-glass opacities
Dyspnea	Acute respiratory distress syndrome
Lymphopenia	
Diarrhea	



Most common symptoms of COVID-19 at presentation

Symptom	Patients Presenting with Symptom (N = 1420)
Headache	70.3%
Loss of smell	70.2%
Nasal obstruction	67.8%
Asthenia	63.3%
Cough	63.2%
Myalgia	62.5%
Rhinorrhea	60.1%
Taste dysfunction	54.2%
Sore throat	52.9%
Fever (>38°C)	45.4%

C = Celsius.

Guan WJ, et al. *N Engl J Med*. 2020;382:1708-1720. Rothan HA, Byrareddy SN. *J Autoimmun*. 2020;109:102433. Lechien JR , et al. *J Intern Med*. 2020;288:335-344. Wang W, et al. *J Med Virol*. 2020;92:441-447.

5

COVID-19 Disease Severity

A large study of 44,672 confirmed COVID-19 cases identified by the Chinese Center for Disease Control and Prevention found that 81% of cases were classified as mild to moderate, 14% were severe, and 5% were critical

	Disease Characteristics—NIH
Asymptomatic or Presymptomatic	Individuals who test positive using a virologic test but who have no symptoms that are consistent with COVID-19
Mild illness	Various symptoms (eg, fever, cough, sore throat, headache, malaise, muscle pain, etc.) without shortness of breath, dyspnea, or abnormal chest imaging
Moderate illness	SpO_2 ≥94% on room air and lower respiratory disease evidenced by clinical assessment or imaging
Severe illness	SpO_2 <94% on room air, PaO_2/FiO_2 <300, respiratory rate >30 breaths/min, or lung infiltrates >50%
Critical illness	Respiratory failure, septic shock, and/or multiorgan dysfunction

NIH = National Institutes of Health; SpO_2 = oxygen saturation; PaO_2 = arterial oxygen partial pressure; FiO_2 = fraction of inspired oxygen.

Wu Z, McGoogan JM. *JAMA*. 2020;323:1239-1242. NIH. COVID-19 treatment guidelines (https://files.covid19treatmentguidelines.nih.gov/guidelines/covid19treatmentguidelines.pdf). NIH. Clinical spectrum of SARS-CoV-2 infection (www.covid19treatmentguidelines.nih.gov/overview/clinical-spectrum/). URLs accessed 3/18/2021.

6

Risk Factors for Severe COVID-19

- Cancer
- Cardiovascular disease
- Chronic kidney disease
- Chronic lung diseases
- Dementia or other neurological conditions
- Diabetes
- Down syndrome
- HIV infection
- Immunocompromised state
- Liver disease
- Overweight and obesity
- Older age (≥65 years of age)
- People from racial and ethnic minority groups
- People with disabilities
- Pregnancy
- Sickle cell disease or thalassemia
- Smoking, current or former
- Solid organ or blood stem cell transplant
- Stroke or cerebrovascular disease
- Substance use disorders

CDC. Medical Conditions (https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html). Accessed May 21, 2021.

7

Association Between Pre-existing Characteristics and COVID-19 Survival

- Prospective cohort study of 20,133 patients in UK hospitalized with COVID-19
- Increasing age, male sex, and chronic comorbidities, including obesity, were identified as independent risk factors for mortality

		HR (95% CI)	*P*- value
Age on admission (years)	<50		
	50–59	2.63 (2.06–3.35)	<.001
	60–69	4.99 (3.99–6.25)	<.001
	70–79	8.51 (6.85–10.57)	<.001
	≥80	11.09 (8.93–13.77)	<.001
Sex at birth	Female	0.81 (0.75–0.86)	<.001
Chronic cardiac disease	Yes	1.16 (1.08–1.24)	<.001
Chronic pulmonary disease	Yes	1.17 (1.09–1.27)	<.001
Chronic kidney disease	Yes	1.28 (1.18–1.39)	<.001
Diabetes	Yes	1.06 (0.99–1.14)	.087
Obesity	Yes	1.33 (1.19–1.49)	<.001
Chronic neurological disorder	Yes	1.17 (1.06–1.29)	.001
Dementia	Yes	1.40 (1.28–1.52)	<.001
Malignancy	Yes	1.13 (1.02–1.24)	.017
Moderate/severe liver disease	Yes	1.51 (1.21–1.88)	<.001

UK = United Kingdom; HR = hazard ratio; CI = confidence interval.

Docherty AB, et al. *BMJ*. 2020;369:m1985.

8

Therapies Granted Emergency Use Authorization for Patients With COVID-19

9

Antibody Therapy in Mild-to-Moderate COVID-19

	Asymptomatic or presymptomatic	Mild illness	Moderate illness	Severe illness	Critical illness
Features	Positive SARS-CoV-2 test; no symptoms	Mild symptoms (eg, fever, cough, or change in taste or smell); no dyspnea	Clinical or radiographic evidence of lower respiratory tract disease; oxygen saturation ≥94%	Oxygen saturation <94% respiratory rate ≥30 breaths/min; lung infiltrates >50%	Respiratory failure, shock, and multiorgan dysfunction or failure
Testing	Screening testing; if patient has known exposure, diagnostic testing	Diagnostic testing	Diagnostic testing	Diagnostic testing	Diagnostic testing
Isolation	Yes	Yes	Yes	Yes	Yes
Proposed disease pathogenesis	Viral replication; Inflammation				
Potential treatment	Antiviral therapy; Antibody therapy; Anti-inflammatory therapy				
Management considerations	Monitoring for symptoms	Clinical monitoring and supportive care	Clinical monitoring; if patient hospitalized and at high risk for deterioration, possibly remdesivir	Hospitalization, oxygen therapy, and specific therapy (remdesivir, dexamethasone)	Critical care and specific therapy (dexamethasone, possibly remdesivir)

According to the Centers for Disease Control and Prevention (CDC), diagnostic testing for SARS-CoV-2 is intended to identify current infection in individuals and is performed when a person has signs or symptoms consistent with Covid-19 or when a person is asymptomatic but has recent known or suspected exposure to SARS-CoV-2. Screening testing for SARS-CoV-2 is intended to identify infected persons who are asymptomatic and without known or suspected exposure to SARS-CoV-2. Screening testing is performed to identify persons who may be contagious so that measures can be taken to prevent further transmission.

Adapted from Gandhi RT, et al. *N Engl J Med*. 2020;383:1757-1766

10

IDSA: Recommended Treatment Options for Hospitalized Patients

Treatment	Guidance
Remdesivir	• Recommended for hospitalized patients with COVID-19 (EUA May 1, 2020) • Most benefit seen in those with severe COVID-19 on supplemental oxygen rather than patients on mechanical ventilation or ECMO • 5 days of treatment recommended for patients on supplemental oxygen • 10 days of treatment recommended for patients on mechanical ventilation or ECMO
Glucocorticoids	• Recommended for hospitalized patients with severe COVID-19 • Dexamethasone 6 mg IV or PO for 10 days or equivalent • Not recommended for hospitalized patients without hypoxemia (SpO_2 >94%) requiring supplemental oxygen
Baricitinib	• Baricitinib recommended for hospitalized patients requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO; no longer required to be administered with remdesivir (EUA updated July 28, 2021)
Tocilizumab	• Recommended for hospitalized patients who are receiving corticosteroids and require supplemental oxygen, mechanical ventilation, or extracorporeal membrane oxygenation (ECMO) (EUA June 24, 2021)

IDSA = Infectious Diseases Society of America; ECMO = extracorporeal membrane oxygenation; PO = by mouth.

Bhimraj A, et al. IDSA Guidelines. V3.9.0. (www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/).

11

mAb Therapies With Emergency Use Authorization (EUA)

These therapies must be given as soon as possible and within 10 days of symptom onset

Bamlanivimab 700 mg AND Etesevimab 1400 mg

EUA reissued August 27, 2021, in certain states

‡Casirivimab *600 mg AND Imdevimab *600 mg

Administer together as single IV infusion over 20–50 minutes ***OR*** as *SC injection when IV infusion is not feasible or would delay treatment

Sotrovimab 500 mg (monotherapy)

Administered as IV infusion over 30 minutes

IV = intravenous, SC = subcutaneous.

‡Casirivimab plus imdevimab approved in Japan for COVID-19 on July 20, 2021

*EUA for casirivimab and imdevimab lowered to 1,200 mg and includes SC injection.

Bamlanivimab and etesevimab EUA, Rev 8/2021 (https://www.fda.gov/media/145801/download). URL accessed 9/7/2021. Casirivimab and imdevimab EUA, Rev 6/2021. (www.fda.gov/media/ 143892/download). Sotrovimab EUA (ww.fda.gov/media/149534/download). FDA. Bamlanivimab EUA revoked. (www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-revokes-emergency-use-authorization-monoclonal-antibody-bamlanivimab). URLs accessed 2/12/2021.

12

A brief animation exploring the mechanism of action of monoclonal antibody therapy

13

Emergency Use Authorization of COVID-19 mAb Therapy

- EUA for the treatment of mild-to-moderate COVID-19 in patients:
  - Who are at least 12 years of age and weigh at least 40 kg
  - Have positive results of direct SARS-CoV-2 viral testing and **within 10 days of symptom onset**
  - Who have mild-to-moderate symptoms
  - Who are at high risk of progressing to severe COVID-19 or hospitalization
- No benefit in patients hospitalized due to COVID-19
  - May be associated with worse clinical outcomes in hospitalized COVID-19 patients requiring high-flow oxygen or mechanical ventilation

Casirivimab and imdevimab EUA. (www.fda.gov/media/143892/download). Bamlanivimab and etesevimab EUA. (https://www.fda.gov/media/145802/download). URLs accessed 3/26/2021.

14

Updates to Emergency Use Authorization of COVID-19 mAb Therapies

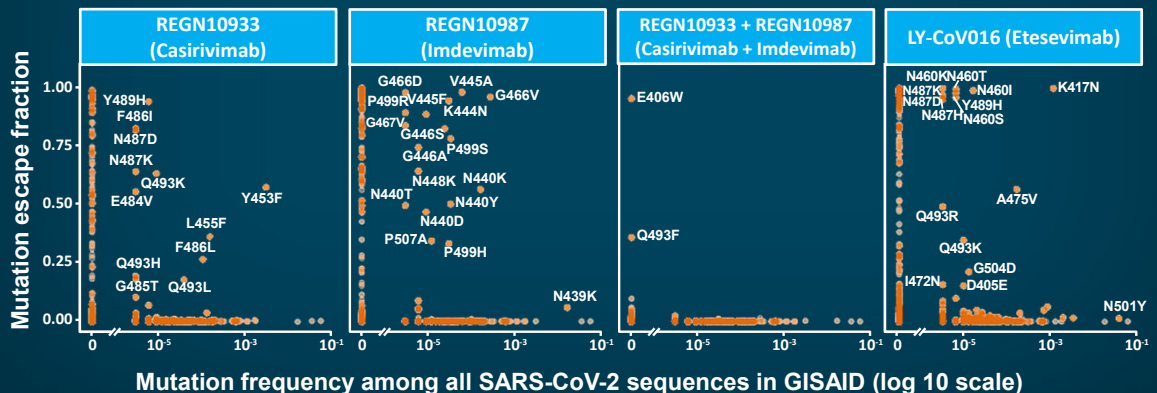
- Bamlanivimab plus etesevimab
  - EUA reissued on August 27, 2021, in certain states where combined frequency of variant resistance is ≤5% as determined by the FDA
- Casirivimab plus imdevimab
  - Fully approved in Japan on July 20, 2021
  - EUA expanded for post-exposure prophylaxis in certain people at high risk of severe COVID-19 after being exposed to the virus:
    - Immunocompromised people and those taking immunosuppressive medicines who may not adequately respond to vaccination
    - People in an institutionalized setting

Casirivimab and imdevimab EUA. (www.fda.gov/media/143892/download). Bamlanivimab and etesevimab EUA. (https://www.fda.gov/media/145802/download). URLs accessed 3/26/2021. Bamlanivimab and etesevimab EUA, Rev 8/2021 (https://www.fda.gov/media/145801/download). Bamlanivimab and Etesevimab Authorized States, Territories, and U.S. Jurisdictions (https://www.fda.gov/media/151719/download) URLs accessed 9/7/2021.

15

Antibody Escape Mutations in Circulating SARS-CoV-2

- Very few variants can escape dual monoclonal-antibody therapies
  - Data suggests that bamlanivimab plus etesevimab are not active against either SARS-CoV-2 P.1/Gamma variant (first identified in Brazil) and B.1.351/Beta variant (first identified in South Africa)
  - Reports indicate that casirivimab plus imdevimab are active against P.1/Gamma, B.1.351/Beta, and B.1.617.2 (first idenfitied in India)



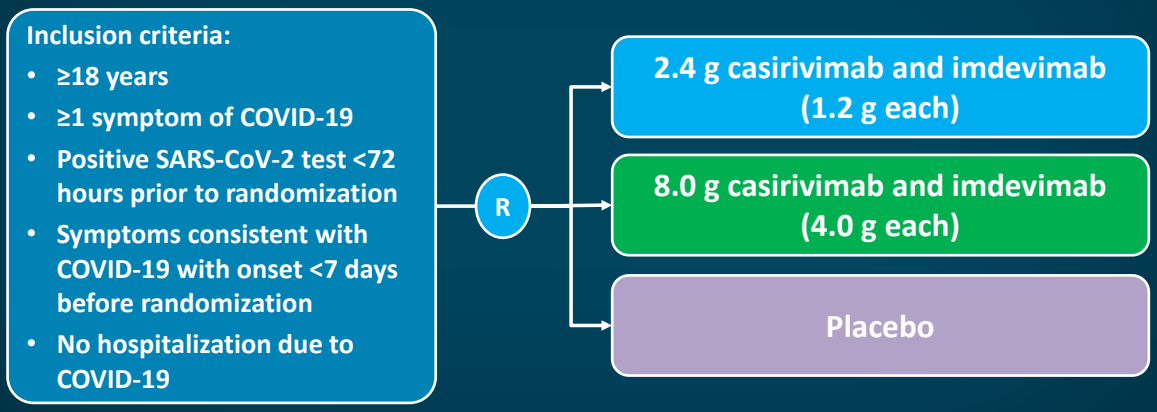
GISAID = Global Initiative on Sharing Avian Influenza Data.

Starr TN, et al. *Science*. 2021;371:850-854. Copin R, et al. *Cell*. 2021;184(15):3949-3961.

16

Casirivimab and Imdevimab (REGN-COV2)

Phase 1–3 trial of casirivimab and imdevimab in nonhospitalized adults with mild-to-moderate COVID-19



Casirivimab and imdevimab EUA. (www.fda.gov/media/143892/download). Accessed 1/7/2021.

17

Casirivimab and Imdevimab: Interim Results

Interim analysis of 275 nonhospitalized patients with mild-to-moderate COVID-19

At Least 1 COVID-19-Related Medical Visit Within 29 Days		
Treatment	**Events/Total Patients**	**Incidence**
All patients		
Placebo	6/93	6%
Casirivimab and imdevimab 2.4 g	3/92	3%
Casirivimab and imdevimab 8.0 g	3/90	3%
All doses casirivimab and imdevimab	6/182	3%
Seronegative patients*		
Placebo	5/33	15%
Casirivimab and imdevimab 2.4 g	2/41	5%
Casirivimab and imdevimab 8.0 g	3/39	8%
All doses casirivimab and imdevimab	5/80	6%

*Seronegative patients: Those who did not have natural antibodies against SARS-CoV-2 at the time of randomization

Weinreich DM, et al. *N Engl J Med*. 2021;384:238-251.

18

Casirivimab/Imdevimab: Efficacy by Baseline Viral Load

Casirivimab/imdevimab (REGN-COV2) provided greater reduction in viral load in those patients with higher viral load at baseline

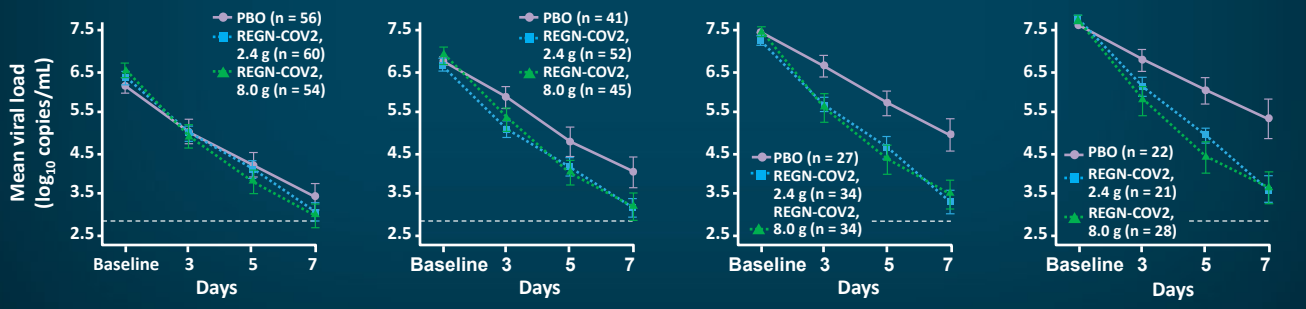
Viral load over time according to baseline viral-load category

	>10^4 copies/mL	
	Difference in Change from Baseline, Day 7	
	TWA LS mean	Mean
2.4 g vs PBO	–0.36	–0.64
8.0 g vs PBO	–0.59	–0.90

	>10^5 copies/mL	
	Difference in Change from Baseline, Day 7	
	TWA LS mean	Mean
2.4 g vs PBO	–0.59	–0.83
8.0 g vs PBO	–0.75	–1.12

	>10^6 copies/mL	
	Difference in Change from Baseline, Day 7	
	TWA LS mean	Mean
2.4 g vs PBO	–0.81	–1.46
8.0 g vs PBO	–1.14	–1.54

	>10^7 copies/mL	
	Difference in Change from Baseline, Day 7	
	TWA LS mean	Mean
2.4 g vs PBO	–1.03	–1.84
8.0 g vs PBO	–1.32	–1.75



TWA = time-weighted average; LS = least-squares; PBO = placebo.

Weinreich DM, et al. *N Engl J Med*. 2021;384:238-251.

19

Casirivimab/Imdevimab Safety

Event	REGN-COV2 2.4 g (n = 88)	REGN-COV2 8.0 g (n = 88)	REGN-COV2 Combined (n = 176)	Placebo (n = 93)
	Number of patients (%)			
Any serious adverse event	1 (1)	0	1 (1)	2 (2)
Any adverse event of special interest* (Grade 2 or higher hypersensitivity or infusion-related reactions)	0	2 (2)	2 (1)	2 (2)
Any serious adverse event of special interest*	0	0	0	0
Grade ≥2 infusion-related reaction within 4 days	0	2 (2)	2 (1)	1 (1)
Grade ≥2 hypersensitivity reaction within 29 days	0	1 (1)	1 (1)	2 (2)
Adverse events that occurred or worsened during the observation period†				
Grade 3 or 4 event	1 (1)	0	1 (1)	1 (1)
Event that led to death	0	0	0	0
Event that led to withdrawal from the trial	0	0	0	0
Event that led to infusion interruption*	0	1 (1)	1 (1)	1 (1)

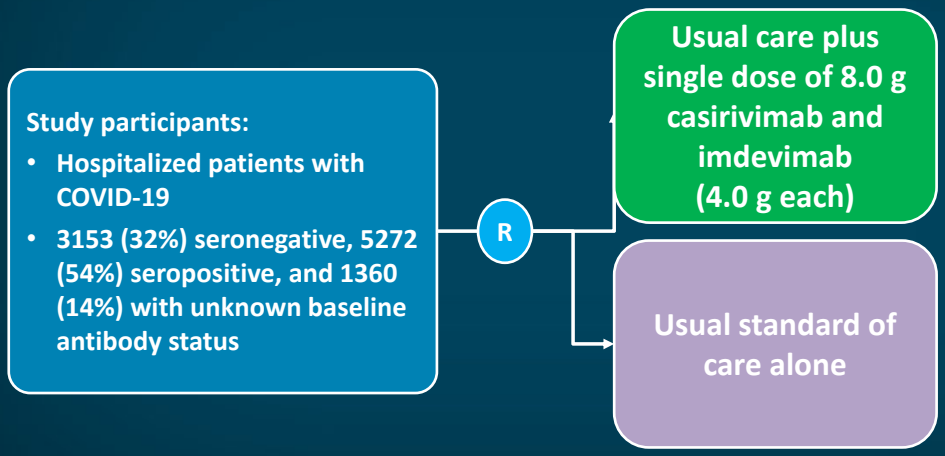
*Events were grade 2 or higher hypersensitivity reactions or infusion-related reactions.
†Events listed here were not present at baseline or were an exacerbation of a preexisting condition that occurred during the observation period, which is defined as the time from administration of REGN-COV2 or placebo to the last study visit.

Weinreich DM, et al. *N Engl J Med*. 2021;384:238-251.

20

UK RECOVERY Trial

Phase 3 trial of casirivimab and imdevimab in hospitalized adults who were seronegative at baseline only



20% reduced risk of death in patients (24% vs 30%) hospitalized with COVID-19 who were seronegative at baseline

Reduction in progression to respiratory failure from 37% to 30% in non intubated patients

Horby PW, et al. *medRxiv*. 2021.06.15.21258542.

21

Sotrovimab (VIR-7831)

- Recombinant human IgG1κ monoclonal antibody
- Binds to a conserved epitope on the spike-protein receptor-binding domain; does not compete with human ACE2 receptor binding

COMET-ICE: 583 nonhospitalized adults with mild to moderate COVID-19	Sotrovimab n = 291	Placebo n = 292
Hospitalization or death	3 (1%)	21 (7%)
COVID-19-related hospitalizations or ED visits	1.0%	5.8%

- Sotrovimab retains activity against currently circulating variants
- Administered as a 500 mg single dose
- Potential side effects: anaphylaxis, infusion-related reactions, rash, diarrhea

ED = emergency department.

Sotrovimab EUA. (www.fda.gov/media/149534/download). Accessed 6/2/2021.

22

Ongoing Clinical Trials of EUA Monoclonal Antibodies

Agent	Indication	Clinical Data
Intravenous bamlanivimab[1]	• Prophylaxis	• Incidence of infection with bamlanivimab monotherapy was **8.5%** compared with **15.2%** of placebo group, *P*< .001[1]

Subcutaneous casirivimab with imdevimab[2,3]	• Reducing progression of asymptomatic to symptomatic infection
	• Prophylaxis for household contacts
		• Preliminary data show:
		  • Reduced risk of progressing to symptomatic COVID-19, shortened symptom duration, and markedly reduced viral levels[2]
		  • Reduced risk of symptomatic infections by **81%**[3]

Intramuscular sotrovimab	• Low risk adults • Early treatment in high-risk adults • Prophylaxis for high-risk adults	• Data pending

1. Cohen MS, et al. JAMA. 2021;June 03;Epub ahead of print. 2. Regeneron press release, 4/12/2021. (https://investor.regeneron.com/news-releases/news-release-details/phase-3-treatment-trial-recently-infected-asymptomatic-patients). 3. Regeneron press release, 4/12/2021. (https://investor.regeneron.com/news-releases/news-release/news-release-details/phase-3-prevention-trial-showed-81-reduced-risk-symptomatic-sars). 4. GSK press release, 3/10/2021. (www.gsk.com/en-gb/media/press-releases/vir-biotechnology-and-gsk-announce-vir-7831-reduces-hospitalisation-and-risk-of-death-in-early-treatment-of-adults-with-covid-19). 5. NCT04779879 (COMET-PEAK), updated 3/3/2021. (https://clinicaltrials.gov/ct2/show/NCT04779879). URLs accessed 6/7/2021.

23

Other Neutralizing Monoclonal Antibodies for SARS-CoV-2 Currently in Development

Agent	Status	Identifier	Actual Start Date
TY027	Phase 3, Recruiting	NCT04649515	December 4, 2020
ABBV-47D11/ABV-2B04	Phase 1, Recruiting	NCT04644120	December 10, 2020
MW33	Phase 1, Completed	NCT04533048	August 7, 2020
HFB30132A	Phase 1, Active, not recruiting	NCT04590430	October 20, 2020
ADM03820	Phase 1, Recruiting	NCT04592549	December 4, 2020
HLX70	Phase 1, Not yet recruiting	NCT04561076	December 9, 2020
DZIF-10c	Phase 1/2, Recruiting	NCT04631705 NCT04631666	December 14, 2020 December 8, 2020
BGB DXP593	Phase 1, Recruiting Phase 2, Completed	NCT04532294 NCT04551898	September 8, 2020 December 2, 2020
SCTA01	Phase 1, Competed Phase 2/3, Recruiting	NCT04483375 NCT04644185	July 24, 2020 February 10, 2021
CT-P59	Phase 1, Recruiting Phase 1, Active, not recruiting	NCT04525079 NCT04593641	July 18, 2020 September 4, 2020

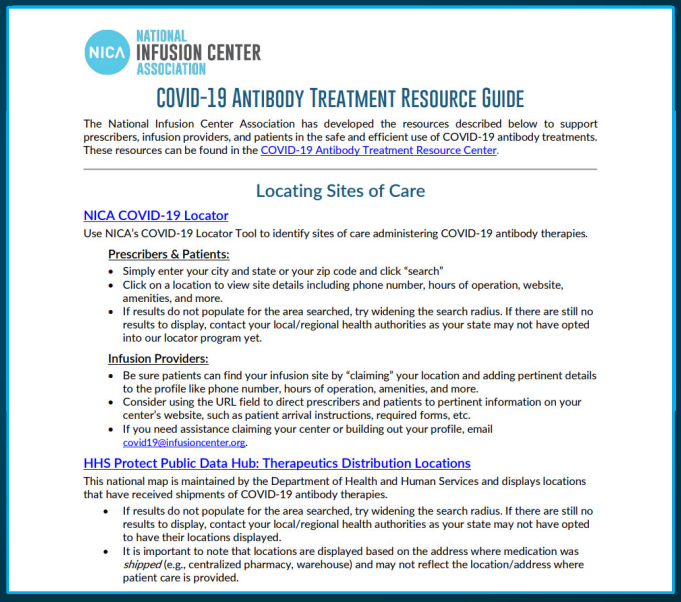
Table adapted from Taylor PC, et al. *Nat Rev*. (https://doi.org/10.1038/s41577-021-00542-x).

24

COVID-19 Antibody Treatment Resource Guide

National Infusion Center Association

- Infusion center locator
- Resources for providers
  - Bamlanivimab + etesevimab guidebook
  - Casirivimab + imdevimab guidebook
- Patient education resources
- Treatment indication checklist
- Plus, other resources



NATIONAL INFUSION CENTER ASSOCIATION

COVID-19 ANTIBODY TREATMENT RESOURCE GUIDE

The National Infusion Center Association has developed the resources described below to support prescribers, infusion providers, and patients in the safe and efficient use of COVID-19 antibody treatments. These resources can be found in the COVID-19 Antibody Treatment Resource Center.

Locating Sites of Care

NICA COVID-19 Locator

Use NICA's COVID-19 Locator Tool to identify sites of care administering COVID-19 antibody therapies.

Prescribers & Patients:

- Simply enter your city and state or your zip code and click "search"
- Click on a location to view site details including phone number, hours of operation, website, amenities, and more.
- If results do not populate for the area searched, try widening the search radius. If there are still no results to display, contact your local/regional health authorities as your state may not have opted into our locator program yet.

Infusion Providers:

- Be sure patients can find your infusion site by "claiming" your location and adding pertinent details to the profile like phone number, hours of operation, amenities, and more.
- Consider using the URL field to direct prescribers and patients to pertinent information on your center's website, such as patient arrival instructions, required forms, etc.
- If you need assistance claiming your center or building out your profile, email covid19@infusioncenter.org.

HHS Protect Public Data Hub: Therapeutics Distribution Locations

This national map is maintained by the Department of Health and Human Services and displays locations that have received shipments of COVID-19 antibody therapies.

- If results do not populate for the area searched, try widening the search radius. If there are still no results to display, contact your local/regional health authorities as your state may not have opted to have their locations displayed.
- It is important to note that locations are displayed based on the address where medication was *shipped* (e.g., centralized pharmacy, warehouse) and may not reflect the location/address where patient care is provided.

National Infusion Center Association (https://infusioncenter.org/infusion_resources/covid-19-antibody-treatment-resource-center/). Accessed 1/18/2021.

25

COVID-19 Toolkits for Clinicians and Patients

COVID Frontline

- COVID Frontline
  - https://covid-frontline.com
  - Antibody resources, podcasts, blog, poster portal, and animations
- Clinician Toolkit
  - Prevention and diagnosis, management strategies, literature highlights, and additional resources
- Patient Toolkit
  - Resources for people with COVID or those who are interested in learning more about it

COVID Frontline (https://covid-frontline.com/) Accessed 4/13/2021.

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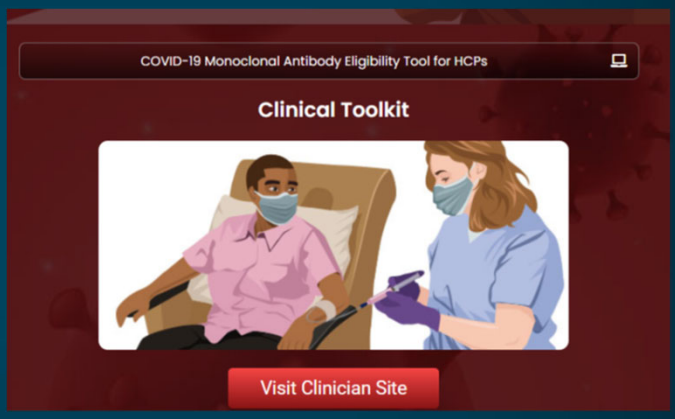
COVID-19 Monoclonal Antibody Eligibility Tool for HCPs

- Decision aid to help HCPs determine if a patient is eligible for monoclonal antibody cocktails
  - https://hcps.covid-frontline.com/
- Asks important questions about patient signs, symptoms, age, and medical histories at critical decision points in the pathway
- Provides resources for administering monoclonal antibodies, or for locating a medical facility with infusion capabilities, as well as other resources



COVID Frontline. (https://hcps.covid-frontline.com/). Accessed 5/19/2021

27

Updates On COVID-19 Vaccine Development

28

FDA Approved COVID-19 Vaccines

FDA approved on August 23, 2021

Pfizer-BioNTech COVID-19 vaccine[1]

For individuals 16 years of age and older; requires 2 doses

1. US Food and Drug Administration (FDA). First COVID-19 vaccine, 12/11/2020 (www.fda.gov/news-events/press-announcements/fda-takes-key-action-fight-against-covid-19-issuing-emergency-use-authorization-first-covid-19). 2. FDA. Second COVID-19 vaccine, 12/18/2020 (www.fda.gov/news-events/press-announcements/fda-issues-emergency-use-authorization-third-covid-19-vaccine, 2/27/2021). 3. FDA. Third COVID-19 vaccine (www.fda.gov/news-events/press-announcements/fda-issues-emergency-use-authorization-third-covid-19-vaccine). All URLs accessed 3/18/2021.

29

COVID-19 Vaccines With Emergency Use Authorization (EUA)

Pfizer-BioNTech COVID-19 vaccine[1]

For individuals 12 years of age and older; requires 2 doses

3 doses for certain immunocompromised individuals

Moderna COVID-19 vaccine[2]

For individuals 18 years of age and older; requires 2 doses

Janssen COVID-19 vaccine[3]

For individuals 18 years of age and older; requires 1 dose

1. US Food and Drug Administration (FDA). First COVID-19 vaccine, 12/11/2020 (www.fda.gov/news-events/press-announcements/fda-takes-key-action-fight-against-covid-19-issuing-emergency-use-authorization-first-covid-19). 2. FDA. Second COVID-19 vaccine, 12/18/2020 (www.fda.gov/news-events/press-announcements/fda-issues-emergency-use-authorization-third-covid-19-vaccine, 2/27/2021). 3. FDA. Third COVID-19 vaccine (www.fda.gov/news-events/press-announcements/fda-issues-emergency-use-authorization-third-covid-19-vaccine). All URLs accessed 3/18/2021.

30

A brief animation exploring the mechanisms of action of vaccines

31

Pfizer BioNTech COVID-19 Vaccine Receives FDA Approval

Contains messenger RNA (mRNA) to make the spike protein of the virus

- Administered as a series of 2 doses, 3 weeks apart
- Participants ≥ 16 years of age
- Followed for at least 4 months after second dose
- Approximately 12,000 recipients followed for at least 6 months

R

N = ~40,000

Vaccine (n = ~20,000)

Placebo (n = ~20,000)

91% effective in preventing symptomatic COVID-19

Commonly reported side effects: pain, redness, and swelling at injection site, fatigue, headache, muscle or joint pain, chills, and fever

RNA = ribonucleic acid.

FDA. FDA Approves First COVID-19 Vaccine, 8/23/2021 (https://www.fda.gov/news-events/press-announcements/fda-approves-first-covid-19-vaccine). Accessed 8/26/2021.

32

Pfizer BioNTech COVID-19 Vaccine

- Administered as a series of 2 doses, 3 weeks apart
- Majority of participants from US
- Followed for a median of 2 months after receiving second dose

R

N = 37,586

Vaccine (n = 18,801)

Placebo (n = 18,785)

Data available from ongoing study

- 95% effective in preventing symptomatic COVID-19
- 170 cases of COVID-19
  - 8 in vaccine group (1 severe)
  - 162 in placebo group (3 severe)

Commonly reported side effects: pain at injection site, headache, chills, fever, tiredness, muscle pain, joint pain; more people experience side effects after second dose versus first dose

RNA = ribonucleic acid.

FDA. First COVID-19 vaccine, 12/11/2020 (www.fda.gov/news-events/press-announcements/fda-takes-key-action-fight-against-covid-19-issuing-emergency-use-authorization-first-covid-19). Accessed 4/25/2021.

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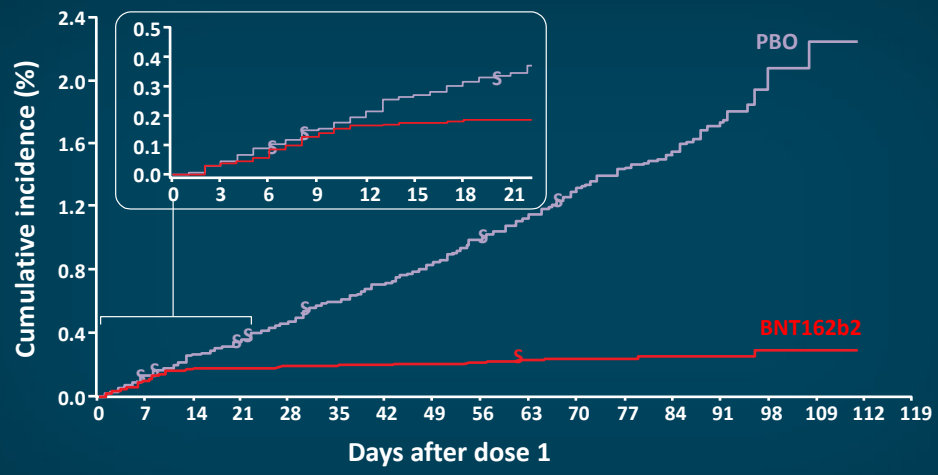
Protective Timeline of mRNA Vaccines



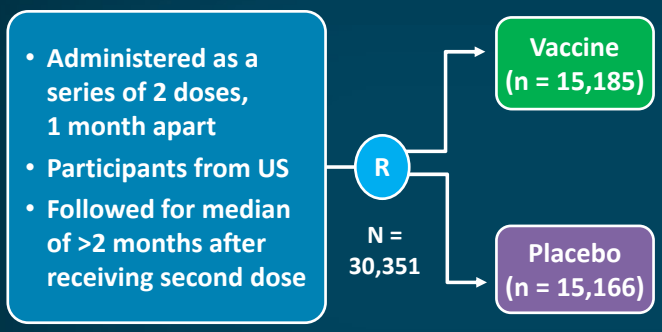
Most cases in the vaccine group occurred within 14 days after first dose

Polack FP, et al. *N Engl J Med*. 2020;383:2603-2615.

34

Moderna COVID-19 Vaccine

Contains messenger RNA (mRNA) to make the spike protein of the virus



FDA evaluation of available data

- 94.1% effective in preventing symptomatic COVID-19
- 196 cases of COVID-19
  - 11 in vaccine group (0 severe)
  - 185 in placebo group (30 severe)

Commonly reported side effects: pain at injection site, headache, chills, fever, swollen lymph nodes (injection arm), tiredness, muscle pain, joint pain, nausea/vomiting; more people experience side effects after second dose versus first dose

FDA. Second COVID-19 vaccine, 12/18/2020 (www.fda.gov/news-events/press-announcements/fda-takes-additional-action-fight-against-covid-19-issuing-emergency-use-authorization-second-covid). Accessed 4/25/2021.

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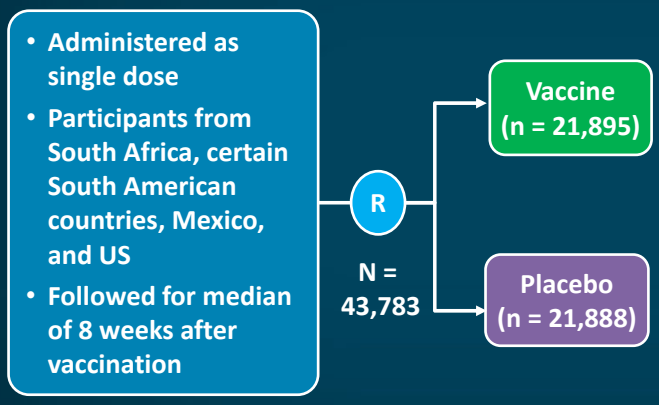
Janssen COVID-19 Vaccine

Uses adenovirus type 26 (Ad26) to deliver DNA to make spike protein of SARS-CoV-2 virus



Outcomes in per-protocol population

- At least 14 days after vaccination
  - 67% effective in preventing moderate-to-severe/critical disease
  - 77% effective in preventing severe/critical disease
- At least 28 days after vaccination
  - 66% effective in preventing moderate-to-severe/critical disease
  - 85% effective in preventing severe/critical disease

Commonly reported side effects: pain at injection site, fatigue, nausea, headache, muscle aches; most side effects were mild to moderate and lasted 1-2 days.

FDA. Third COVID-19 vaccine, 2/27/2021 (www.fda.gov/news-events/press-announcements/fda-issues-emergency-use-authorization-third-covid-19-vaccine). Accessed 4/25/2021.

36

Summary

Casirivimab plus imdevimab (includes SC injection) and sotrovimab have EUA for mild-to-moderate COVID-19 in patients ≥12 years (and ≥40 kg) who are at high risk of progressing to severe COVID-19 or hospitalization and for post-exposure prophylaxis for certain individuals at high risk

- mAbs against SARS-CoV-2 reduced the risk of COVID-19-related hospitalization
- These therapies may be associated with worse clinical outcomes in hospitalized COVID-19 patients requiring high-flow oxygen or mechanical ventilation
- Therapy should be provided as soon as possible and within 10 days of symptoms onset

Pfizer BioNTech receives full FDA approval for people 16 years of age and older

Pfizer BioNTech, Moderna, and Janssen COVID-19 vaccines have EUA for prevention of SARS-CoV-2 infections

- Side effects are generally mild and are most common after the second dose of vaccine
- Pfizer BioNTech authorized for 3 doses

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Case Study

Immunodeficiency and COVID-19

38

History of Present Illness

- CL is a 44-year-old female:
  - History of rheumatoid arthritis, hypertension and bipolar disorder
  - Presents for an appointment to receive COVID-19 vaccine
- She complaints of no symptoms, no exposure or recent travel
- She works from home as a high school biology teacher
- Her medications include amlodipine, lamotrigine, clonazepam, aspirin, ibuprofen and adalimumab, last dose was 2 weeks ago.
- She has no reported allergies to previous vaccinations or drugs

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Laboratory Results

Lab	Value	Normal range
WBC	2,500 /mL	4000-10,000/ mL
Hemoglobin	10.4 g/dL	12-15 g/dL
Glucose	120 mg/dL	65-110 mg/dL
ALT	31 U/L	5-30 U/L
AST	34 U/L	5-30 U/L
BUN	12 mg/dL	8-21 mg/dL
Creatinine	0.9 mg/dL	0.8-1.3 mg/dL
D-dimer	110 ng/L	<500 ng/mL
CRP	<5 mg/L	<5 mg/L
LDH	150 U/L	5—150 U/L
ESR	12 mm/hr	<2 mm/hr
Ferritin	350 ng/mL	12-300 ng/mL
Prothrombin time	13 sec	11-14 sec
SpO2	99% RA	>96% RA

Should CL receive COVID vaccine today?

WBC = white blood cell count, ALT = alanine aminotransferase, AST = aspartate aminotransferase, BUN = blood urea nitrogen, CRP = c-reactive protein, LDH = lactate dehydrogenase, ESR = erythrocyte sedimentation rate, SpO_2 = oxygen saturation

40

Clinical Course

- She received first dose of Pfizer COVID vaccine without any complications
- A second dose was given three weeks later
  - Patient had increased soreness, mild fever, and nausea after the second dose

When can she resume adalimumab therapy?

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American College of Rheumatology Guidelines

•Methotrexate**:** Skip for 1 week after each vaccine dose

•JAK inhibitors (ie, tofacitinib, baricitinib, upadacitinib): Skip for 1 week after each vaccine dose

•Abatacept, injectable form**:** Skip one week before and after the first vaccine dose only

•Abatacept, IV form**:** Get COVID-19 vaccine 4 weeks after your last infusion, then skip a week and get next infusion

•Rituximab: Get COVID-19 vaccine approximately 4 weeks before next infusion, then delay next infusion by 2-4 weeks after second vaccine dose — if possible

•Cyclophosphamide infusion: Time administration so it's one week after each COVID-19 vaccine dose

American College of Rheumatology. COVID-19 Vaccine Clinical Guidance Summary for Patients with Rheumatic and Musculoskeletal Diseases. American College of Rheumatology. February 8, 2021. Available at https://www.rheumatology.org/Portals/0/Files/COVID-19-Vaccine-Clinical-Guidance-Rheumatic-Diseases-Summary.pdf. Accessed April 9, 2021.

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Case Study

Pregnancy and COVID-19

43

History of Present Illness

- AD is a 22-year-old female:
  - 34 weeks pregnant with significant gestational diabetes and medical history of obesity
  - Presents with fever, shortness of breath, cough, hemoptysis of 4 days duration after attending a baby shower party one week ago
- She tests positive for SARS-CoV-2
- Her SpO2 is 97% on room air and her BP is 150/90 mmHg

Is AD a candidate for monoclonal antibody therapy?

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Laboratory Results

Lab	Value	Normal range
WBC	7,500 /mL	4000-10,000/ mL
Hemoglobin	15.1 g/dL	12-15 g/dL
Glucose	145 mg/dL	65-110 mg/dL
ALT	41 U/L	5-30 U/L
AST	53 U/L	5-30 U/L
BUN	28 mg/dL	8-21 mg/dL
Creatinine	1.0 mg/dL	0.8-1.3 mg/dL
D-dimer	750 ng/L	<500 ng/mL
CRP	9.8 mg/L	<5 mg/L
LDH	170 U/L	5—150 U/L
ESR	38 mm/hr	<2 mm/hr
Ferritin	411 ng/mL	12-300 ng/mL
Prothrombin time	12 sec	11-14 sec
SpO2	97% RA	>96% RA

WBC = white blood cell count, ALT = alanine aminotransferase, AST = aspartate aminotransferase, BUN = blood urea nitrogen, CRP = c-reactive protein, LDH = lactate dehydrogenase, ESR = erythrocyte sedimentation rate, SpO_2 = oxygen saturation

45

Hospital Course

- She received monoclonal antibody therapy as part of a clinical trial
- She also received betamethasone in anticipation of preterm labor
- SpO2 remained >95% and was discharged home from ED
- She went into preterm labor and was subsequently hospitalized for bed rest
- Patient recovered completely within one week and had a normal vaginal delivery in 3 weeks

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Thank you!

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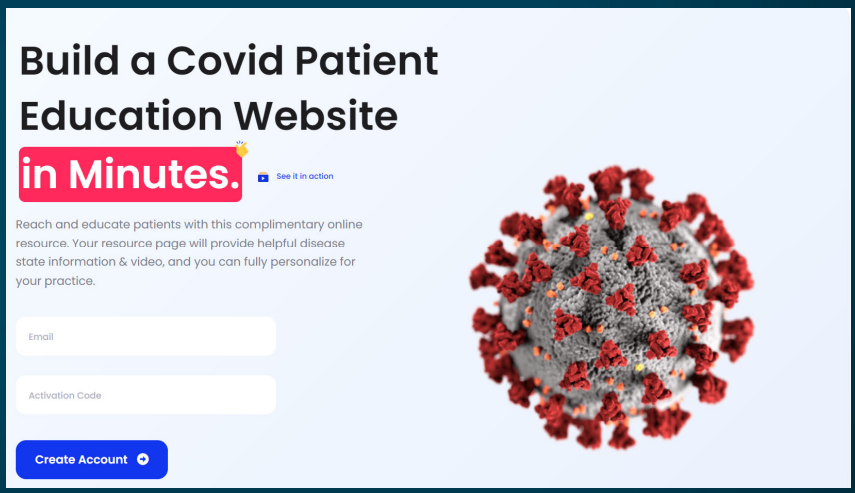
COVID Frontline Patient Resource Portal

- Customizable
- Information geared toward patients regarding signs and symptoms of COVID-19 and treatment for hospitalized and non-hospitalized patients
- Videos, downloadable patient guides, Monoclonal Antibody Eligibility Tool for patients

- Activation page: http://covidfrontlineresource.com/activation
  - Activation code: **MLGCFL1**



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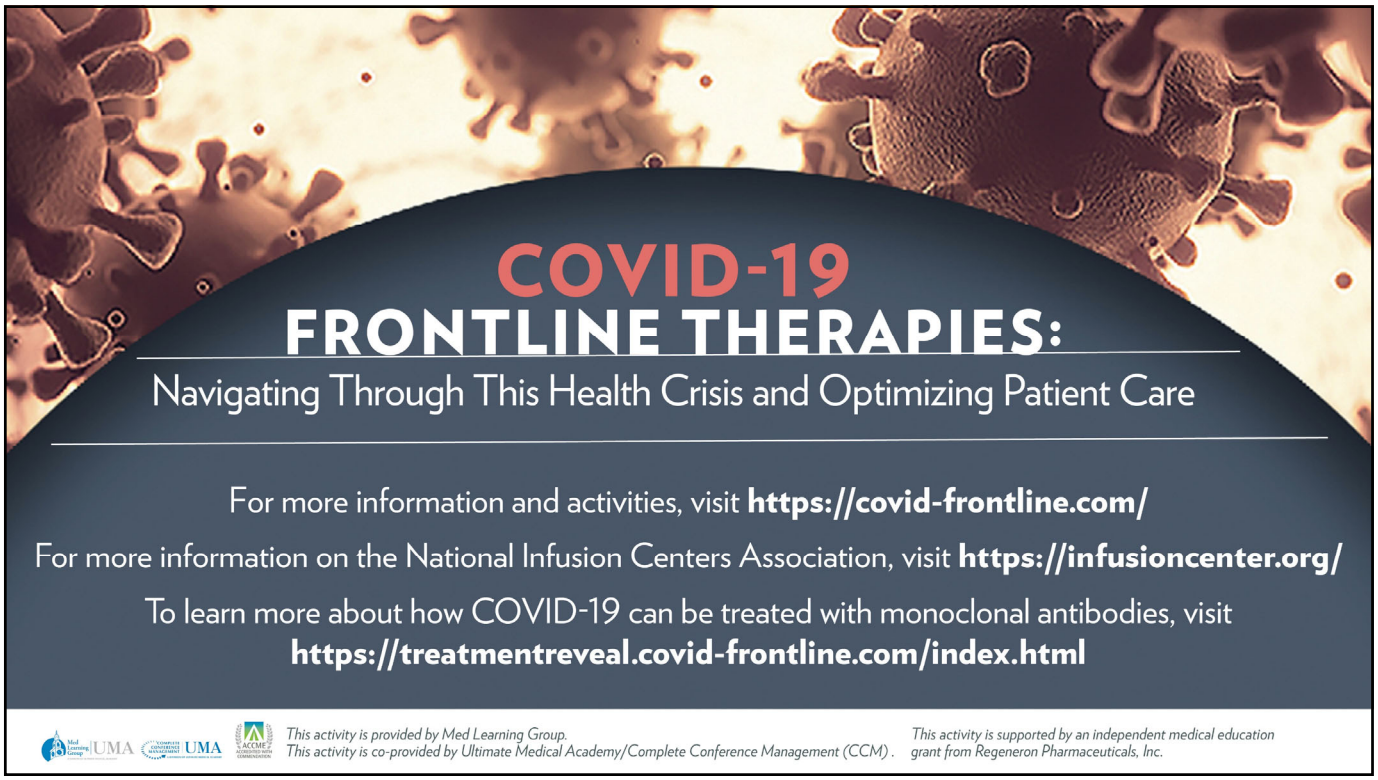
COVID-19
FRONTLINE THERAPIES:
Navigating Through This Health Crisis and Optimizing Patient Care
For more information and activities, visit https://covid-frontline.com/
For more information on the National Infusion Centers Association, visit https://infusioncenter.org/
To learn more about how COVID-19 can be treated with monoclonal antibodies, visit
https://treatmentreveal.covid-frontline.com/index.html
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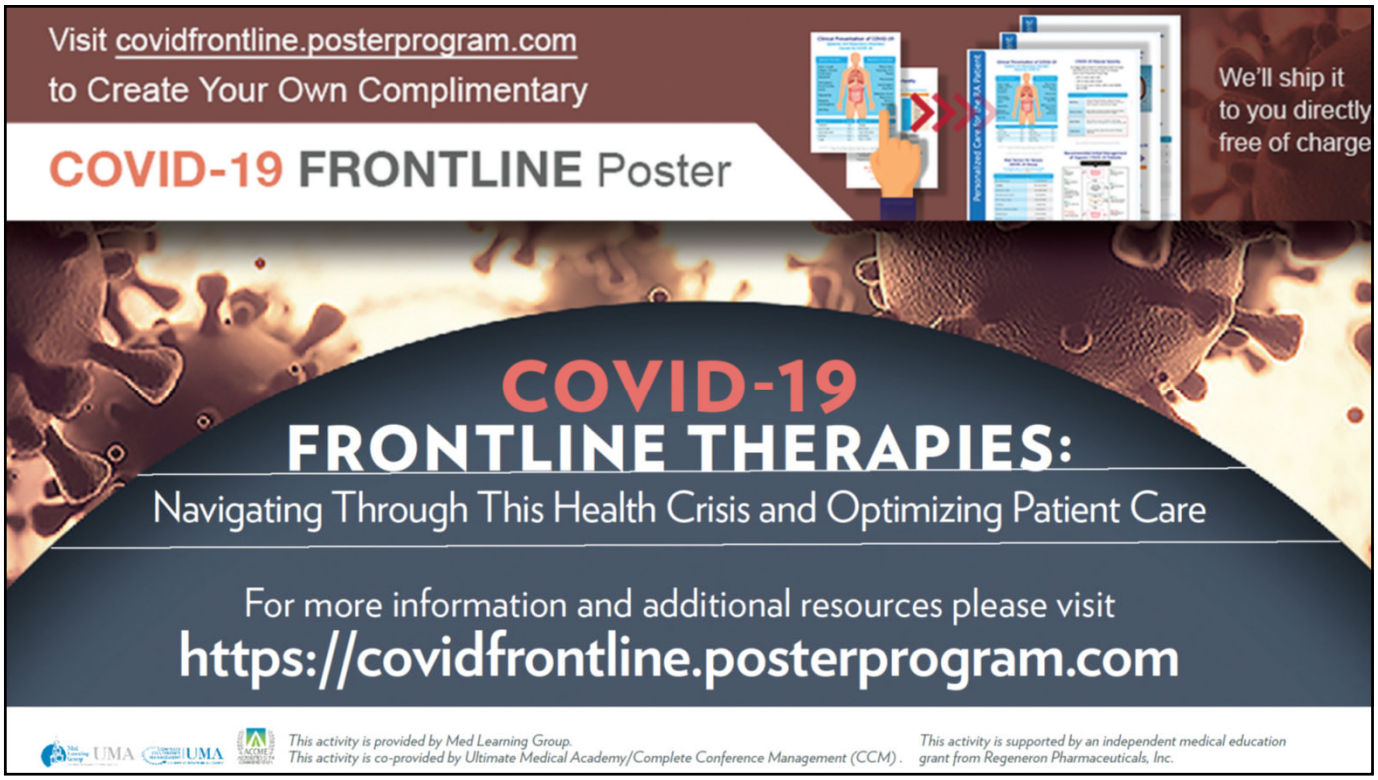
Visit covidfrontline.posterprogram.com
to Create Your Own Complimentary
COVID-19 FRONTLINE Poster
We'll ship it
to you directly
free of charge
COVID-19
FRONTLINE THERAPIES:
Navigating Through This Health Crisis and Optimizing Patient Care
For more information and additional resources please visit
https://covidfrontline.posterprogram.com
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This activity is supported by an independent medical education grant from Regeneron Pharmaceuticals, Inc.

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COVID-19 Frontline Therapies:
Navigating Through This Health Crisis and Optimizing Patient Care

Overview of SARS-CoV-2

Resource	Address
Baum A, Fulton BO, Wloga E, et al. Antibody cocktail to SARS-CoV-2 spike protein prevents rapid mutational escape seen with individual antibodies. *Science*. 2020;369:1014-1018.	https://science.sciencemag.org/content/369/6506/1014
Docherty AB, Harrison EM, Green CA, et al. Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: Prospective observational cohort study. *BMJ*. 2020;369:m1985.	https://www.bmj.com/content/369/bmj.m1985
Guan W, Ni ZY, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med*. 2020;382:1708-1720.	https://www.nejm.org/doi/full/10.1056/NEJMoa2002032
Lechien JR, Chiesa-Estomba CM, Place S, et al. Clinical and epidemiological characteristics of 1420 European patients with mild-to-moderate coronavirus disease 2019. *J Intern Med*. 2020;288:335-344.	https://pubmed.ncbi.nlm.nih.gov/32352202/
National Institutes of Health (NIH). COVID-19 Treatment Guidelines. Clinical Spectrum of SARS-CoV-2 Infection. Updated April 21, 2021. Accessed May 1, 2021.	https://www.covid19treatmentguidelines.nih.gov/overview/clinical-spectrum
National Institutes of Health (NIH). COVID-19 Treatment Guidelines. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. Updated April 21, 2021. Accessed May 1, 2021.	https://files.covid19treatmentguidelines.nih.gov/guidelines/covid19treatmentguidelines.pdf
Richardson S, Hirsch JS, Narasimhan M, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. *JAMA*. 2020;323:2052-2059.	https://jamanetwork.com/journals/jama/fullarticle/2765184
Rothan HA, Byrareddy SN. The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. *J Autoimmun*.	https://pubmed.ncbi.nlm.nih.gov/32113704/

2020;109:102433.	
Siddiqi HK, Mehra MR. COVID-19 illness in native and immunosuppressed states: A clinical-therapeutic staging proposal. *J Heart Lung Transplant*. 2020;39:405-407.	https://pubmed.ncbi.nlm.nih.gov/32362390/
Vaduganathan M, Vardeny O, Michel T, McMurray JJV, Pfeffer MA, Solomon SD. Renin-angiotensin-aldosterone system inhibitors in patients with COVID-19. *N Engl J Med*. 2020;382:1653-1659.	https://www.nejm.org/doi/full/10.1056/NEJMsr2005760
Wang W, Tang J, Wei F. Updated understanding of the outbreak of 2019 novel coronavirus (2019-nCoV) in Wuhan, China. *J Med Virol*. 2020;92:441-447.	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7167192/
Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott HC. Pathophysiology, transmission, diagnosis, and treatment of coronavirus disease 2019 (COVID-19): A review. *JAMA*. 2020;324:782-793.	https://jamanetwork.com/journals/jama/fullarticle/2768391

Antibody Therapies for the Management of COVID-19

Resource	Address
ACTIV-3/TICO LY-CoV555 Study Group, Lundgren JD, Grund B, et al. A neutralizing monoclonal antibody for hospitalized patients with COVID-19. *N Engl J Med*. 2021;384:905-914.	https://www.nejm.org/doi/full/10.1056/NEJMoa2033130
Chen P, Nirula A, Heller B, et al. SARS-CoV-2 neutralizing antibody LY-CoV555 in outpatients with COVID-19. *N Engl J Med*. 2021;384:229-237.	https://www.nejm.org/doi/full/10.1056/NEJMoa2029849
Gandhi RT, Lynch JB, del Rio C. Mild or moderate COVID-19. *N Engl J Med*. 2020;383:1757-1766.	https://www.nejm.org/doi/full/10.1056/NEJMcp2009249
Gottlieb RL, Nirula A, Chen P, et al. Effect of bamlanivimab as monotherapy or in combination with etesevimab on viral load in patients with mild to moderate COVID-19: A randomized clinical trial. *JAMA*. 2021;325:632-644.	https://jamanetwork.com/journals/jama/fullarticle/2775647

Hansen J, Baum A, Pascal KE, et al. Studies in humanized mice and convalescent humans yield a SARS-CoV-2 antibody cocktail. *Science*. 2020;369:1010-1014.	https://science.sciencemag.org/content/369/6506/1010
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Updates on COVID-19 Vaccine Development

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