When the Pandemic Ends and the Endemic Continues: The Evolving Role of mAbs Against COVID-19

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Unclassified/For Public Use

Agenda

1. Introduction to monoclonal antibody (mAb) therapies
2. mAbs for post-exposure prophylaxis use case updates
3. mAbs for treatment use case updates
4. Variants of concern
5. Clinical data
6. Strategies to increase uptake
7. Resources

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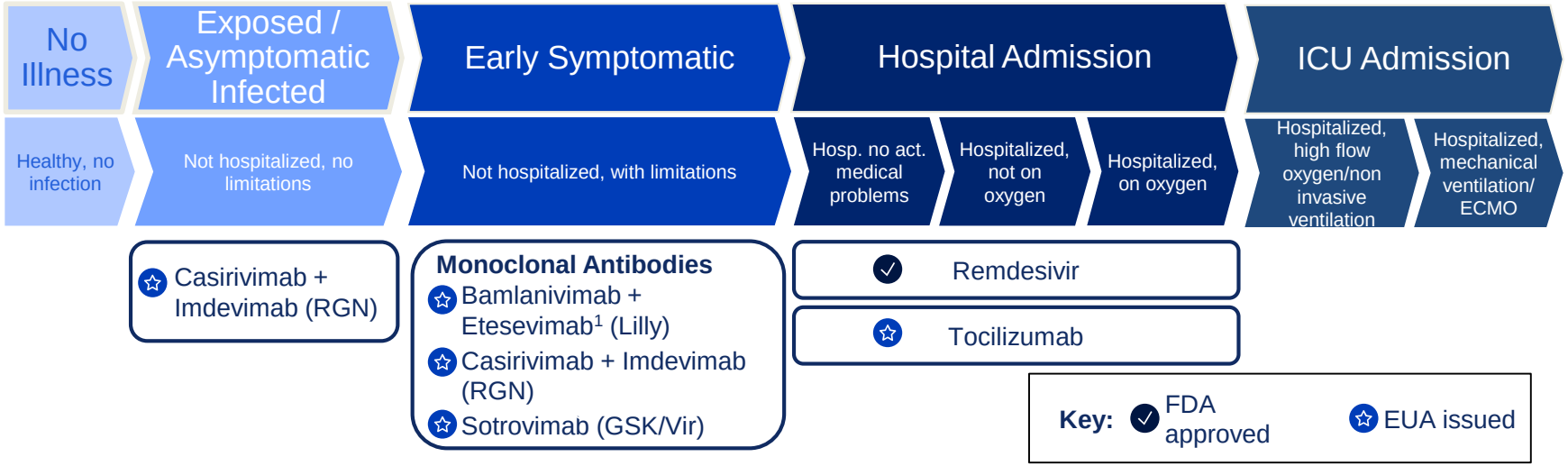
Introduction to mAb therapies

Summary of COVID-19 Therapeutics



1. National shipment pause due to variants, as of 06/25/2021

Bottom Line: monoclonal antibodies for treatment reduce relative risk of hospitalization

- COVID-19 monoclonal antibodies (mAbs) are intended for patients with **mild to moderate COVID-19 who are at high risk of developing severe disease**
- mAbs are likely to be most effective when **given early in disease course**
- Early evidence appears to suggest promise of mAb products in outpatient settings; products (bamlanivimab/etesevimab[1] and REGEN-COV(casirivimab/imdevimab)) **reduce the relative risk of hospitalizations by up to 70% in high-risk patients**

1. National shipment pause due to variants, as of 06/25/2021

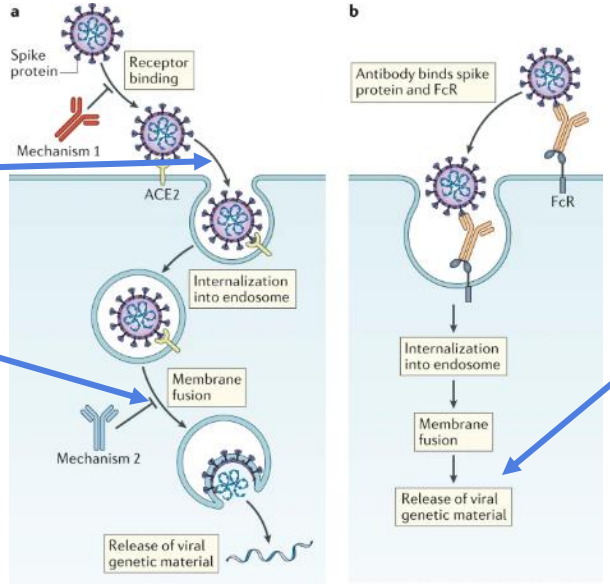
Potential mechanisms for the clinical effects of monoclonals

a) Bind to Virus

1) Block cell uptake

2) Block membrane fusion

Impede ability to replicate



b) Bind to Virus

3) Deliver to immune

Destruction

Source: Nature

USG role in distribution of COVID-19 mAbs

Our goal: Facilitate the effective use of monoclonal antibody therapeutics to reduce COVID-19 hospitalizations

Three outpatient mAbs have been granted EUA for the treatment of COVID-19 based on their potential to reduce progression to severe disease and hospitalization in high-risk patients:

- Post-exposure prophylaxis
  - REGEN-COV (casirivimab and imdevimab)

- Active COVID-19 infection in high-risk individuals with mild to moderate symptoms
  - REGEN-COV (casirivimab and imdevimab)
  - Bamlanivimab/Etesevimab (currently paused[1])
  - Sotrovimab (commercially available)

HHS/ASPR has oversight responsibility for the fair and transparent allocation and distribution of REGEN-COV and bamlanivimab/etesevimab

1. National shipment pause of bam / ete and ete alone due to variants, as of 06/25/2021

EUA Updates

Therapy	EUA Issuance	EUA revisions	USG procured?
Bamlanivimab *(Eli Lilly & Co.)*	Nov. 9, 2020	EUA revoked – April 16, 2021 • Due to sustained increase of viral variants resistant to bam alone	Yes
Casirivimab /Imdevimab *(Regeneron)*	Nov. 21, 2020 (treatment) Jul. 30, 2021 (post-exposure prophylaxis)	EUA revised – 03/2021 • Antiviral resistance EUA revised – 05/2021 • **Updated high risk criteria** for patient selection EUA revised – 06/2021 • Updated w/ coformulation • Updated w/ **subcutaneous RoA** as an alt. to IV • Updated authorized dosage EUA revised – 07/2021 • Updated authorized **use for post-exposure prophylaxis**	Yes
Bamlanivimab /Etesevimab[1] *(Eli Lilly & Co.)*	Feb. 9, 2021	EUA revised – 05/2021 • Updated high risk criteria for patient selection • Antiviral resistance	Yes
Sotrovimab *(GSK / Vir Biotechnology)*	May 26, 2021	N/A	No, commercially available

1. National shipment pause due to variants, as of 06/25/2021

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mAbs for post-exposure prophylaxis use-case updates

REGEN-COV Emergency Use Authorization(EUA) expanded to include post-exposure prophylaxis

- As of July 30, 2021, **FDA has authorized post-exposure prophylaxis use of the COVID-19 monoclonal antibody therapeutic REGEN-COV (casirivimab and imdevimab)**
- REGEN-COV is expected to be effective against circulating variants, including the Delta variant. Please refer to the following for more information:
  - FDA fact sheet and EUA Letter of authorization
  - Regeneron press release
- For additional information and approved materials, including information about ordering, please refer to the REGEN-COV webpage
- Should you have any questions regarding the expanded indication for REGEN-COV, please contact us at COVID19therapeutics@hhs.gov

REGEN-COV post-exposure prophylaxis treatment eligibility

REGEN-COV (casirivimab and imdevimab) is authorized for post-exposure prophylaxis of COVID-19:

- ***in adult and pediatric individuals*** (≥12 yrs+, weighing ≥40 kg) who are at ***high risk for progression to severe COVID-19***, including hospitalization or death, ***and*** are:
- ***Not fully vaccinated or who are not expected to mount an adequate immune response*** to complete SARS-CoV-2 vaccination (for example, individuals with immunocompromising conditions including those taking immunosuppressive medications) ***and***
  - Have been exposed to an individual infected with SARS-CoV-2 consistent with close contact criteria per CDC ***or***
  - Who are at high risk of exposure to an individual infected with SARS-CoV-2 because of occurrence of COVID-19 infection in other individuals in the same institutional setting (for example, nursing homes or prisons)

New authorized use is in addition to the prior authorization of REGEN-COV to treat

- **non-hospitalized patients w/ mild to moderate COVID-19** in adult and pediatric patients, aged 12 and older, w/ **positive results** of direct SARS-CoV-2 viral testing, and who are **at high risk** for progression to severe COVID-19

Limitations of authorized use:

- *Post-exposure prophylaxis w/ REGEN-COV is not a substitute for vaccination against COVID-19*
- *REGEN-COV is not authorized for pre-exposure prophylaxis for prevention of COVID-19*

Guidelines for REGEN-COV repeat dosing for post-exposure prophylaxis

- For individuals whom repeat dosing is determined to be appropriate for ongoing exposure to SARS-CoV-2 for longer than 4 weeks and who are not expected to mount an adequate immune response to complete SARS-CoV-2 vaccination
- Initial dose is 600 mg of casirivimab + 600 mg of imdevimab by subcutaneous injection or intravenous infusion
- Followed by subsequent repeat dosing of 300 mg of casirivimab and 300 mg of imdevimab by subcutaneous injection or intravenous infusion **once every 4 weeks** for the duration of ongoing exposure

mAbs for treatment use-case updates

1) mAb treatment eligibility

- May be eligible to receive treatment if the patient (12 years of age or older and weighing at least 40 kg):
  - Has mild to moderate COVID-19 that has tested positive with direct viral testing,
  - Is within 10 days of symptom onset, **and**
  - Is at high risk of progression to severe COVID-19 including hospitalization or death

- Please reference EUA factsheets for specific treatment guidelines and detailed definitions of high-risk patients
  - Bamlanivimab /Etesevimab[1]
  - Casirivimab /Imdevimab

1. National shipment pause due to variants, as of 06/25/2021

2) EUA for REGEN-COV™ (casirivimab and imdevimab) treatment

- Effective June 3, 2021, the FDA has authorized under emergency use a **lower dose** of REGEN-COV (600mg casirivimab and 600mg imdevimab), which is half the dose originally authorized
- REGEN-COV should be administered by intravenous (IV) infusion; subcutaneous injections are an **alternative when IV infusion is not feasible** and would lead to a delay in treatment
- **Single vial of co-formulated product now available to order via AmerisourceBergen (as of June 10, 2021)**
  - Single vial represents one full, complete treatment at the lower authorized dose

Please contact Regeneron Medical Affairs with any questions about using **existing** inventory to treat patients at 1-844-734-6643

3) FDA authorizes Sotrovimab for treatment of COVID-19

- Effective May 26, 2021**, Sotrovimab (GSK / Vir Biotechnology) authorized for the treatment of mild to moderate COVID-19**
- Commercially available therapy
- Please refer to the following for more information:
  - FDA fact sheet and EUA Letter of authorization
  - FDA press release
  - COMET-ICE clinical trial
- For additional information and approved materials, **including information about ordering**, please refer to the Sotrovimab webpage

Please contact the GSK COVID Contact Center if you have further questions: 1-866-GSK-COVID (1-866-475-2684)

4) COVID-19 treatment guidelines

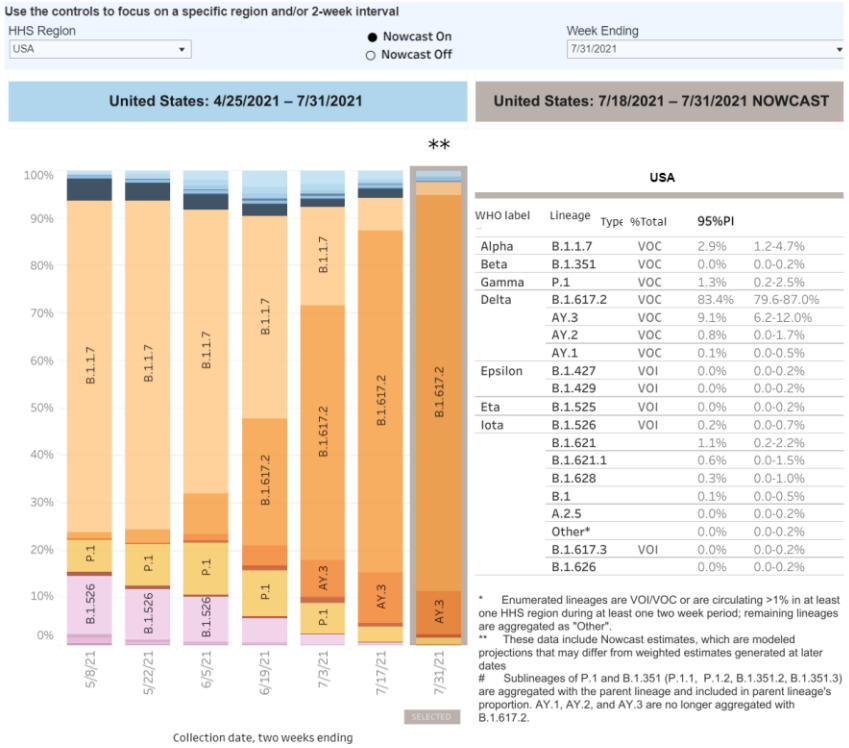
- The NIH has **strongly recommended (AIIa)** the following for use in non-hospitalized COVID-19 patients:
  - **Casirivimab + imdevimab (Regeneron)**
  - **Bamlanivimab + etesevimab (Eli Lilly)[1]**
- Updated NIH COVID-19 guidelines can be found at: https://www.covid19treatmentguidelines.nih.gov/statement-on-anti-sars-cov-2-monoclonal-antibodies-eua/

1. National shipment pause due to variants, as of 06/25/2021

Ratings of NIH treatment guidelines recommendations:
Rating of Recommendations: A = strong; B = moderate; C = optional
Rating of Evidence: I = one or more randomized trials without major limitations; IIa = other randomized trials or subgroup analyses of randomized trials; IIb = nonrandomized trials or observational cohort studies; III = expert opinion

Variants

Presence of Delta variant nationally



USA

WHO label	Lineage	Type	%Total	95%PI	
Alpha	B.1.1.7	VOC	2.9%	1.2-4.7%	
Beta	B.1.351	VOC	0.0%	0.0-0.2%	
Gamma	P.1	VOC	1.3%	0.2-2.5%	
Delta	B.1.617.2	VOC	83.4%	79.6-87.0%	
	AY.3	VOC	9.1%	6.2-12.0%	
	AY.2	VOC	0.8%	0.0-1.7%	
	AY.1	VOC	0.1%	0.0-0.5%	
Epsilon	B.1.427	VOI	0.0%	0.0-0.2%	
	B.1.429	VOI	0.0%	0.0-0.2%	
Eta	B.1.525	VOI	0.0%	0.0-0.2%	
Iota	B.1.526	VOI	0.2%	0.0-0.7%	
	B.1.621		1.1%	0.2-2.2%	
	B.1.621.1		0.6%	0.0-1.5%	
	B.1.628		0.3%	0.0-1.0%	
	B.1		0.1%	0.0-0.5%	
	A.2.5		0.0%	0.0-0.2%	
	Other*		0.0%	0.0-0.2%	
	B.1.617.3	VOI	0.0%	0.0-0.2%	
	B.1.626		0.0%	0.0-0.2%	

* Enumerated lineages are VOI/VOC or are circulating >1% in at least one HHS region during at least one two week period; remaining lineages are aggregated as "Other".
** These data include Nowcast estimates, which are modeled projections that may differ from weighted estimates generated at later dates
# Sublineages of P.1 and B.1.351 (P.1.1, P.1.2, B.1.351.2, B.1.351.3) are aggregated with the parent lineage and included in parent lineage's proportion. AY.1, AY.2, and AY.3 are no longer aggregated with B.1.617.2.

- B.1.617.2 (Delta) variant was at 31% nationally as of 6/19 and is **83.4% nationally as of 7/31** (pending data via Nowcast)
- States/territories encouraged to reach out with questions/concerns

National shipment pause of bam/ete and ete alone due to Beta (B.1.351) and Gamma (P.1) variant prevalence

Presence of variants

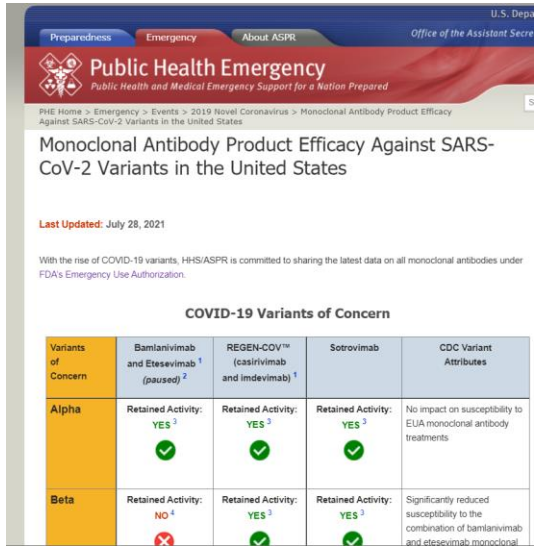
- CDC has identified the **combined frequencies of Beta variant (B.1.351,** first identified in South Africa) and **Gamma variant** (**P.1,** first identified in Brazil) **throughout the U.S. has been trending upward**
- Results from in vitro studies suggest that:
  - Bam / ete administered together **are not active against** either Beta (B.1.351) or Gamma (P.1) variants
  - REGEN-COV and sotrovimab **are likely to retain activity** against Beta (B.1.351) and Gamma (P.1) variants

Impact on providers

- Effective as of 06/25/2021, **distribution of bam / ete together and etesevimab alone have been paused on a national basis until further notice**
- **FDA recommends health care providers use alternative authorized mAb therapies** (REGEN-COV / Sotrovimab) until further notice
  - REGEN-COV can be ordered directly from Amerisource Bergen
  - Sotrovimab can be ordered via GlaxoSmithKline's website

Please contact **COVID19Therapeutics@hhs.gov** with any questions

mAb product efficacy against variants of concern



- mAb product efficacy against SARS-CoV-2 variants in the U.S. available on [phe.gov](phe.gov)
- Includes product activity against variants for the following:
  - Bam/Ete
  - REGEN-COV
  - Sotrovimab

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Clinical Data

Review of clinical data

Date	Source	Trial design / patients	Reported outcomes	Notes
Jan ’21	JAMA	RCT, n = 577	▪ 70% reduction in hospitalization for high-risk patients	Lillly trial (Ph 2)
Feb ’21	Website	Observational	▪ 50% decrease in hospitalizations, 40% decrease in emergency department visits	St. Luke's
Mar ’21	Lily	RCT, n = 769	▪ 87% relative reduction vs. placebo in hospitalizations / death	Lilly trial (Ph 3)
Mar ’21	Regeneron	RCT, n = 4,567	▪ 70% relative reduction vs. placebo in hospitalizations / death	Regen. trial (Ph 3)
Mar ’21	NEJM	Observational, n not listed	▪ 4.2% hospitalization rate for those treated with mAbs vs. 9-14.6% reported for untreated high-risk ▪ Only 13% felt symptoms progressed after therapy	Houston Methodist
Mar ’21	Medrxiv	Observational, n = 234 matched,	▪ Patients receiving mAb had 69% lower odds of hospitalization or mortality, and 50% lower odds of hospitalization or ED visit without hospitalization ▪ 6% hospitalization in treated vs. 16.2% untreated,	UPMC
Apr ’21	Medrxiv	Observational, n = 270 treated, 328 untreated	▪ 1.9% of treated patients presented to E.D. / required hospitalization vs. 12% of untreated	ASPR
Apr ’21	Medrxiv	Observational, n = 2,818	▪ Hospitalization rate was 4.4% for patients who received MAB therapy w/in 0-4 days, 5% w/in 5-7 days, and 6.1% w/in ≥8 days of symptom onset (p = 0.15)	Northwell Health
May ‘21	Medrxiv *(preprint)*	RCT, n = 4,057	▪ 2400mg & 1200mg drugs sig. reduced hospitalization or all-cause death compared to placebo (71.3% reduction [1.3% vs 4.6%; p<0.0001] and 70.4% reduction [1.0% vs 3.2%; p=0.0024], respectively	Regen. trial
Jun ‘21	JAMA	RCT, n = 1175	▪ Bam significantly reduced the incidence of COVID-19 in the prevention population compared with placebo (p<.001) at skilled nursing/assisted living facilities	Lilly trial (Ph 3)
Jun ‘21	Medrxiv *(preprint)*	RCT, n = 2,475	▪ Subcutaneous REGEN-COV significantly prevented symptomatic SARS-CoV-2 infection compared with placebo (p<0.0001)	Regen. trial

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Bamlanivimab plus Etesevimab in Mild or Moderate Covid-19

M. Dougan, A. Nirula, M. Azizad, B. Mocherla, R.L. Gottlieb, P. Chen, C. Hebert, R. Perry, J. Boscia, B. Heller, J. Morris, C. Crystal, A. Igbinadolor, G. Huhn, J. Cardona, I. Shawa, P. Kumar, A.C. Adams, J. Van Naarden, K.L. Custer, M. Durante, G. Oakley, A.E. Schade, T.R. Holzer, P.J. Ebert, R.E. Higgs, N.L. Kallewaard, J. Sabo, D.R. Patel, M.C. Dabora, P. Klekotka, L. Shen, and D.M. Skovronsky, for the BLAZE-1 Investigators*

ABSTRACT

BACKGROUND

Patients with underlying medical conditions are at increased risk for severe coronavirus disease 2019 (Covid-19). Whereas vaccine-derived immunity develops over time, neutralizing monoclonal-antibody treatment provides immediate, passive immunity and may limit disease progression and complications.

METHODS

In this phase 3 trial, we randomly assigned, in a 1:1 ratio, a cohort of ambulatory patients with mild or moderate Covid-19 who were at high risk for progression to severe disease to receive a single intravenous infusion of either a neutralizing monoclonal-antibody combination agent (2800 mg of bamlanivimab and 2800 mg of etesevimab, administered together) or placebo within 3 days after a laboratory diagnosis of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. The primary outcome was the overall clinical status of the patients, defined as Covid-19–related hospitalization or death from any cause by day 29.

RESULTS

A total of 1035 patients underwent randomization and received an infusion of bamlanivimab–etesevimab or placebo. The mean (±SD) age of the patients was 53.8±16.8 years, and 52.0% were adolescent girls or women. By day 29, a total of 11 of 518 patients (2.1%) in the bamlanivimab–etesevimab group had a Covid-19–related hospitalization or death from any cause, as compared with 36 of 517 patients (7.0%) in the placebo group (absolute risk difference, −4.8 percentage points; 95% confidence interval [CI], −7.4 to −2.3; relative risk difference, 70%; P<0.001). No deaths occurred in the bamlanivimab–etesevimab group; in the placebo group, 10 deaths occurred, 9 of which were designated by the trial investigators as Covid-19–related. At day 7, a greater reduction from baseline in the log viral load was observed among patients who received bamlanivimab plus etesevimab than among those who received placebo (difference from placebo in the change from baseline, −1.20; 95% CI, −1.46 to −0.94; P<0.001).

CONCLUSIONS

Among high-risk ambulatory patients, bamlanivimab plus etesevimab led to a lower incidence of Covid-19–related hospitalization and death than did placebo and accelerated the decline in the SARS-CoV-2 viral load. (Funded by Eli Lilly; BLAZE-1 ClinicalTrials.gov number, NCT04427501.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Skovronsky at Eli Lilly, 893 Delaware St., Indianapolis, IN 46225, or at skovronsky_daniel@lilly.com.

*A list of the BLAZE-1 investigators is provided in the Supplementary Appendix, available at NEJM.org.

Drs. Dougan and Nirula contributed equally to this article.

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COVID-19 Monoclonal Antibody (mAb) Therapy Real-World Effectiveness and Implementation

Date	Source	Article	Description
Mar '21	NEJM	*Rapid operationalization of COVID-19 mAb infusion clinics at Houston Methodist*	• Established six clinics in <6 weeks across Houston region - Treated 2,500+ high-risk patients w/ mAb Tx - Avoided ~250 COVID-19–related hospitalizations • Patient experience: - Nearly 99% of patients would recommend the treatment - 95% of patients confident in comms b/w providers
May '21	UPMC	*UPMC and HHS Leaders Discuss Expanded Eligibility Guidelines for Life-Saving COVID-19 Treatment*	• UPMC saw a 25-fold inc. in the administration of mAb treatments since March

Strategies to increase uptake

USG-procured therapies are provided at no-cost

- Health care providers can order product directly through the distributor AmerisourceBergen at no cost; information on ordering available at phe.gov
- CMS reimbursement rates have recently been increased to $450 for most outpatient settings; and $750 when administered in a patient's home
- Additional information on reimbursement can be found at Monoclonal Antibody COVID-19 Infusion | CMS
- Treatment options for uninsured available through HRSA

USG activities to support administration of mAbs

1. **Build product understanding and awareness** – Ensure **providers are up-to-date** on the **latest EUA therapies** (and eligible patient populations), and **patients are aware of treatment options**

2. **Provide information on product location** – Ensure providers have the information to **direct patients to a place to receive treatment**

3. **Facilitate product administration** – Ensure providers can **safely administer current products** (drug on hand, material, directions, etc.)

4. **Track utilization** – **Understand utilization of product** across localities and populations

Administration can occur across a wide variety of models

Hospital

- Hospital-based infusion centers
- Emergency departments
- Converted space within hospital for COVID infusion
- Alternate care sites

Ambulatory center

- Infusion centers
- Urgent care clinics
- Dialysis centers
- Alternate care sites

Nursing homes

- Skilled nursing facilities
- Long-term care facilities

Mobile sites

- Bus/trailer
- Other mobile sites

Home

- At patient's home

Information support via https://CombatCOVID.hhs.gov/
Materials include links to EUA criteria, consolidated playbooks & educational materials

mAb expansion efforts

- **Expansion of capacity** in existing care sites with or without current infusion capabilities
- Setup of **new temporary capacity** (e.g., “pop-up” centers, mobile units, tents, etc.)
- Setup of **new “semi-permanent” capacity** (e.g., new brick & mortar locations)
- **Virtual support** for existing / new centers (e.g., IT support, administrative support, education & training for staff, telemedicine screeners and follow-up, etc.)
- **Staff support** for infusions in congregate settings (e.g., long-term care facilities)
- **Infusion site access** to not just the general public, but to military and their dependents
- **Increased provider and patient awareness** about mAbs and opportunities for use

Resources

Best practices and resources

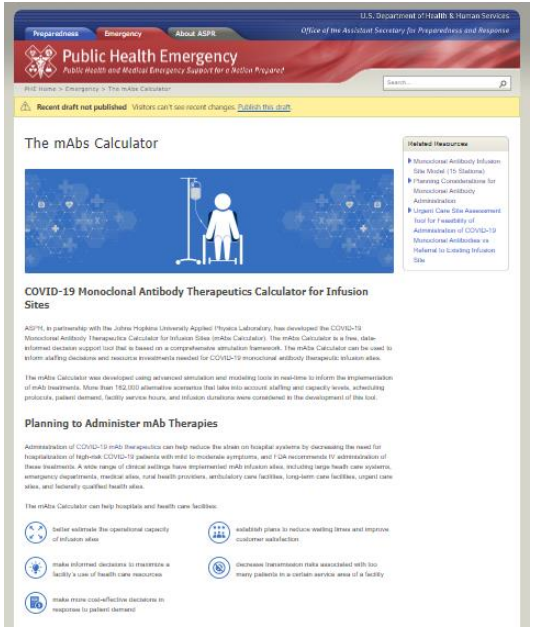
- USG engages with medical and professional societies to share best practices
- Best practices and testimonials available at https://combatcovid.hhs.gov/hcp/videos-monoclonal-antibodies
- Additional information and resources available at combatcovid.hhs.gov / phe.gov/mAbs

mAb calculator live on phe.gov

COVID-19 monoclonal antibody therapeutics calculator for infusion sites

mAbs calculator can help hospitals and health care facilities:

- Better estimate the **operational capacity of infusion sites**
- Make informed decisions to **maximize a facility's use of health care resources**
- Make more **cost-effective decisions in response to patient demand**
- **Establish plans to reduce waiting times** and **improve customer satisfaction**
- **Decrease transmission risks** associated with too many patients in a certain service area of a facility



Learn more at www.PHE.gov/mAbs-calculator

Weekly office call sessions

Weekly mAbs Administration Sites and Stakeholders Call Sessions

- **State, Local, Tribal, and Territorial Public Health Officials**:
  Wednesdays (2:00-2:45PM ET)
- **Healthcare Systems and State Hospital Associations**
  Wednesdays (3:15-4:00PM ET)
- **Office Call Sessions**: **HHS / ASPR Allocation, Distribution, Administration of COVID-19 Therapeutics**
  Thursdays (2:00-2:30PM ET)

Please email COVID19Therapeutics@hhs.gov to request Zoom links for these calls

Asks for community leaders

Promote the awareness of therapies in your local communities

- Share information in local community outlets
- Post information online for individuals to understand that mAbs are available treatment options (neighborhood apps, social media, etc)
- Host outreach events

Understand where administration locations are in your local community and encourage individuals to seek out mAb treatment

Share experiences to support others in pursuing treatment

- Post information online (blogs, social media, etc)
- Share your experience with HHS/ASPR at COVID19Therapeutics@hhs.gov