Monoclonal Antibody Emergency Use Authorization – Review of Clinical Indications and Allocation in California

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Many slides adapted from Operation Warp Speed Monoclonal Antibody Playbook

https://www.phe.gov/emergency/events/COVID19/investigation-MCM/Bamlanivimab/Documents/OWS_MAB_%20playbook_10Nov20-508.pdf

About Monoclonal Antibodies

Monoclonal antibodies (mAbs) directly neutralize the COVID-19 virus and are intended to **prevent progression of disease**

mAbs likely to be most effective when **given early in infection**

Product delivered via **single administration (e.g., IV infusion)**

Early evidence suggested promise of mAb products in outpatient settings

Emergency Use Authorizations (EUAs) for bamlanivimab and casirivimab/imdevimab

1. Positive direct SARS-CoV-2 test (e.g., PCR, rapid antigen test)
2. As soon as possible after positive test, within 10 days of symptom onset
3. In patients at high risk
4. Provider reviews EUA fact sheet; patient/caregiver provided with EUA fact sheet
5. Administered in a setting where HCPs have direct access to medications to manage severe reactions

mAb Clinical Indications

- Mild to moderate outpatient treatment
  - **Not asymptomatic, not hospitalized and not requiring O2 (or increased baseline O2) due to COVID**
  - High risk for severe illness including BMI ≥ 35, chronic kidney disease, diabetes, immunosuppression, or age ≥ 65 years. Additional criteria for ≥ 55 years and for people 12 – 17 years
- **Treat early** – within 10 days of symptom onset (median 4 days from symptom onset in clinical trial)
- Administered by intravenous (IV) infusion over 60 minutes
- Mandatory FDA MedWatch reporting of all medication errors and serious adverse events or deaths

https://www.cdph.ca.gov/Programs/CID/DCDC/Pages/COVID-19/Bamlanivimab-Fact-Sheet.aspx

Emergency Use Authorizations
High-Risk Criteria

- All Patients (who meet at least 1 of the following criteria):
  - BMI ≥35
  - Chronic kidney disease
  - Diabetes
  - Immunosuppressive disease
  - Receiving immunosuppressive treatment
  - Age ≥ 65 years
  - Age ≥ 55 years AND have any of the following
    - Cardiovascular disease
    - Hypertension
    - COPD/other chronic respiratory disease
- Adolescents (Age 12-17 years) who meet at least 1 of the following criteria:
  - BMI ≥85th percentile for age/gender
  - Sickle cell disease
  - Congenital or acquired heart disease
  - Neurodevelopmental disorders (e.g., cerebral palsy)
  - Medical-related technological dependence [e.g., tracheostomy, gastrostomy, or positive pressure ventilation (not related to COVID-19)]
  - Asthma, reactive airway, or other chronic respiratory disease that requires daily medication for control

Casirivimab / Imdevimab Clinical Trials Data

BLAZE-1 clinical trial [1] : 465 non-hospitalized adults, mild-mod COVID-19

- Secondary analysis of hospitalization or ER visit:
  - Bamlanivimab: 1.6% (4.2% age ≥ 65 or BMI ≥ 35)
  - Placebo: 6.3% (14.6% age ≥ 65 or BMI ≥ 35)

ACTIV-3 clinical trial [2]: 326 hospitalized participants

- Bamlanivimab was discontinued as not beneficial

[1] Chen P, Nirula A, Heller B, et al. SARS-CoV-2 Neutralizing Antibody LY-CoV555 in Outpatients with Covid-19. NEJM. Electronically published: October 28, 2020. DOI: 10.1056/NEJMoa2029849
[2] NIH Press Release. Statement—NIH-Sponsored ACTIV-3 Trial Closes LY-CoV555 Sub-Study. October 26, 2020

Casirivimab / Imdevimab Clinical Trials Data

Outpatient 2067 clinical trial - 799 non-hospitalized adults, mild-mod COVID-19

- Primary study outcome: decline in viral load was larger at day 7 with treatment.
- Secondary analysis of hospitalizations or ER visit
  - Casirivimab/imdevimab: 1.8% (2.6% with risk factor for severe illness)
  - Placebo: 4.3% (9.0% with risk factor for severe illness)

- Hospitalized patient trial: Based on a potential safety signal and an unfavorable risk/benefit profile, enrollment of hospitalized patients requiring high-flow oxygen or mechanical ventilation was suspended. **Hospitalized patients who require no or low-flow oxygen can continue to enroll in the trial.**

[1] Fact Sheet for Health Care Providers - Emergency Use Authorization (EUA) of Casirivimab and Imdevimab. Available at: https://www.fda.gov/media/143892/download

[2] Regeneron Press Release. REGN-COV2 Independent Data Monitoring Committee Recommends Holding Enrollment in Hospitalized Patients with High Oxygen Requirements and Continuing Enrollment in Patients with Low or No Oxygen Requirements. October 30, 2020.

Overall Safety Summary

Bamlanivimab

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

Preferred term	Placebo N=156 %	Bamlanivimab			
		700 mg N=101 %	2,800 mg N=107 %	7,000 mg N=101 %	Total N=309 %
Nausea	4%	3%	4%	5%	4%
Diarrhea	5%	1%	2%	7%	3%
Dizziness	2%	3%	3%	3%	3%
Headache	2%	3%	2%	0%	2%
Pruritus	1%	2%	3%	0%	2%
Vomiting	3%	1%	3%	1%	2%

Casirivimab / Imdevimab

Infusion-related reactions of grade 2 or higher severity were reported in **1.5% of patients** and included pyrexia, chills, urticaria, pruritus, abdominal pain, and flushing.

One anaphylactic reaction has been observed with casirivimab/imdevimab. It resolved with treatment including epinephrine.

Monoclonal Products: Two Phases of Allocation

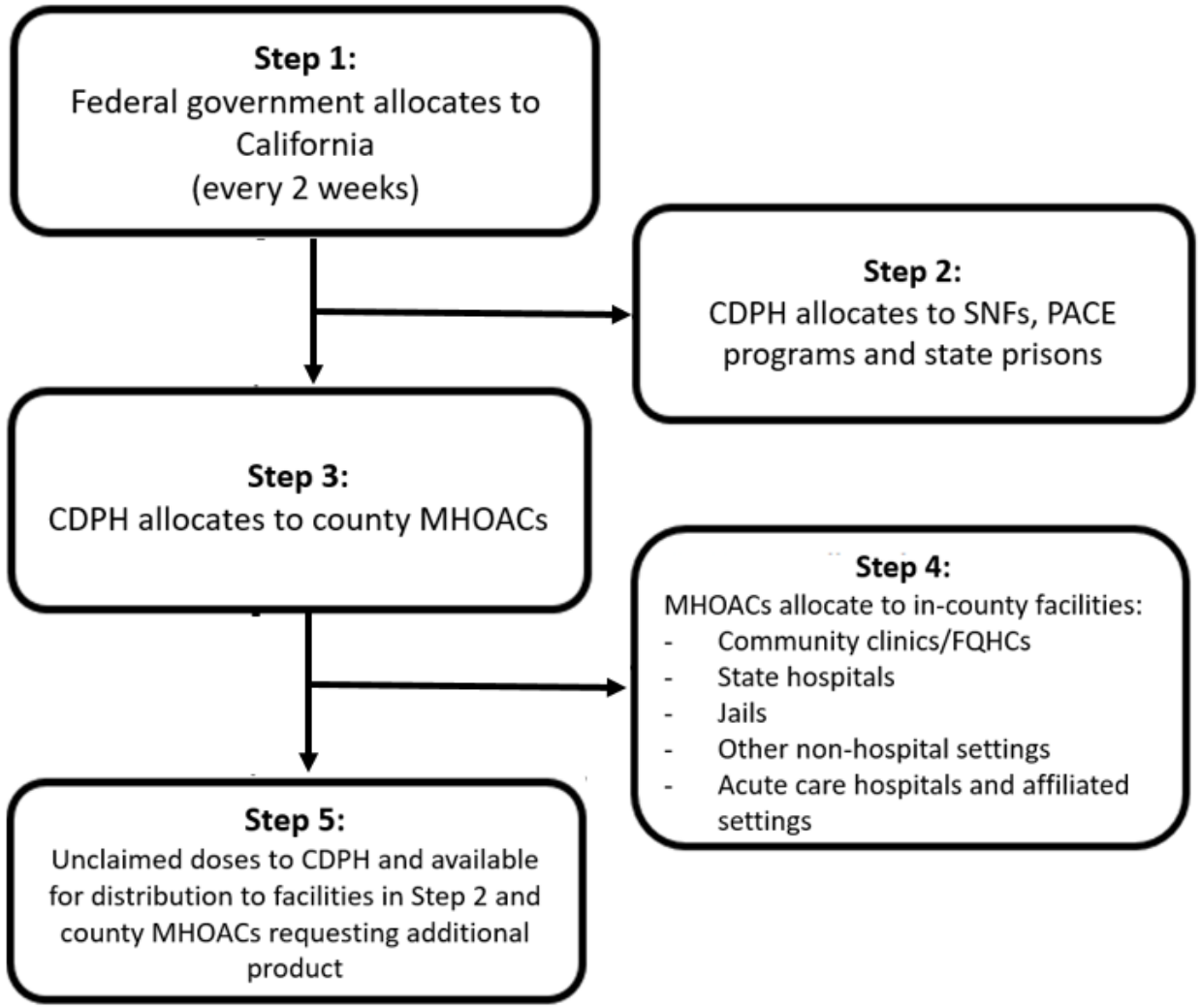
- **Phase 1:** states and territories allocate these products to hospitals and hospital-affiliated locations only
- **Phase 2:** states and territories allocate to outpatient facilities
  - Skilled Nursing Facilities and the PACE program
  - Urgent care clinics
  - State hospitals
  - State prisons
  - Community sites / temporary tents

Alternate site of care will need same core capabilities and supplies as typical site of administration

https://www.phe.gov/emergency/events/COVID19/investigation-MCM/Bamlanivimab/Documents/OWS_MAB_%20playbook_10Nov20-508.pdf

1/12/21: Currently, California has a sufficient supply of monoclonal antibodies for all providers who request them

Should any facilities in California need more monoclonal product, they should contact as soon as possible their county's Medical and Health Operational Area Coordinators (MHOACs) according to local policies and procedures.


Step 1:
Federal government allocates to California
(every 2 weeks)
Step 2:
CDPH allocates to SNFs, PACE programs and state prisons
Step 3:
CDPH allocates to county MHOACs
Step 4:
MHOACs allocate to in-county facilities:
- Community clinics/FQHCs
- State hospitals
- Jails
- Other non-hospital settings
- Acute care hospitals and affiliated settings
Step 5:
Unclaimed doses to CDPH and available for distribution to facilities in Step 2 and county MHOACs requesting additional product

Skilled Nursing Facilities (SNFs), PACE programs and State Prisons Prioritized

SNFs, PACE programs and state prisons are potentially optimal non-hospital settings for bamlanivimab treatment as the vast majority of residents are:

- in the age group and/or with high-risk medical conditions with the highest potential benefit
- tested frequently, resulting in early diagnoses
- physically residing at or close to a location that can potentially provide an immediate infusion

mAb Allocations for California

- Week 1: 4,040 vials Bamlanivimab
- Week 2: 2,250 vials Bamlanivimab
- Week 3: 3,230 vials Bamlanivimab
  - And 2,328 courses Casirivimab/Imdevimab
- Week 4: 3,040 vials Bamlanivimab
  - And 2,160 courses Casirivimab/Imdevimab
- Week 5: 4,450 vials Bamlanivimab
  - And 1,240 courses Casirivimab/Imdevimab
- Week 6: 6,420 vials of Bamlanivimab
  - And 1,380 courses Casirivimab/Imdevimab
- Weeks 7-8*: 14,020 vials of Bamlanivimab
  - And 4,080 courses Casirivimab/Imdevimab
- Weeks 9-10: 14,420 vials of Bamlanivimab
  - And 1,570 courses of Casirivimab/Imdevimab

* Federal allocation changed from weekly to once-every-two-weeks starting in Week 7.

1 vial = 1 dose = 1 treatment course

California Monoclonal Antibody Allocation (excel) - Guidance Documents (ca.gov) – under the “Other” section – updated weekly

Adverse Event Mandatory Reporting

- Clinical trials evaluating the safety of these mAbs are ongoing
- Completion of **FDA MedWatch Form** to report all medication errors and serious adverse events occurring during use of bamlanivimab and considered to be potentially related to bamlanivimab is mandatory and must be done by the prescribing healthcare provider and/or the provider's designee. These adverse events **must be reported within 7 calendar days from the onset of the event**
- Serious Adverse Events are defined as:
  - death;
  - a life-threatening adverse event;
  - inpatient hospitalization or prolongation of existing hospitalization;
  - a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
  - a congenital anomaly/birth defect;
  - a medical or surgical intervention to prevent death, a life-threatening event, hospitalization, disability, or congenital anomaly

Readiness Checklist: Administration of Outpatient mAbs under EUA

Allocate **dedicated space** and develop plan to **manage patient flow**

- ❑ Clear process for patients that are coming to clinical site including scheduling requirements
- ❑ Admission process for COVID-19 positive patients designed to minimize risk of spread per facility requirements / directions / guidelines'
- ❑ Dedicated room available for treatment

Ensure **dedicated source of supplies;** which may be difficult to procure

- ❑ Needed infusion components obtained
  - ❑ Example: IV kits, infusion chair, IV pole, vital sign monitoring equipment, emergency medications

Assign **sufficient personnel** to meet expected demand

- ❑ Sufficient staffing plans in place for Nurse/IV tech, Physician, Pharmacist
  - Likely need dedicated team to treat patients

Prepare for **drug administration** process

- ❑ Pre–visit: Clear treatment and monitoring plan developed for during infusion
- ❑ Treatment: 1-hour treatment and up 1-hour post-treatment observation
  - ❑ Emergency protocol defined for addressing potential infusion reactions or complications
- ❑ Post-treatment: Clear process for patient follow-up defined using telemedicine as possible

Ensure **process for reimbursement** in place (non-drug administrative costs)

Prepare for **reporting needs** for adverse events and record keeping

Resources (1)

California SARS-CoV-2 Crisis Care Guidelines

NIH COVID-19 Treatment Guidelines: https://www.covid19treatmentguidelines.nih.gov/.

IDSA Treatment Guidelines: https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/#toc-10.

MedWatch

- Complete and submit the report online: www.fda.gov/medwatch/report.htm, or
- Use a postage-paid Form FDA 3500 (available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM163919.pdf) and returning by mail (MedWatch, 5600 Fishers Lane, Rockville, MD 20852-9787), or by fax (1-800-FDA-0178), or
- Call 1-800-FDA-1088 to request a reporting form

Operation Warp Speed Monoclonal Antibody Playbook: https://www.phe.gov/emergency/events/COVID19/investigation-MCM/Bamlanivimab/Documents/OWS_MAB_%20playbook_10Nov20-508.pdf

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MHOAC Contact Information: https://emsa.ca.gov/medical-health-operational-area-coordinator/

Resources (2)

Bamlanivimab

- EUA Letter of Authorization, FDA. Available at https://www.fda.gov/media/143602/download
- FAQ on Bamlanivimab EUA, FDA. Available at https://www.fda.gov/media/143605/download
- Fact Sheet for Health Care Providers Emergency use Authorization (EUA) of Bamlanivimab. U.S. Food and Drug Administration
- Eli Lilly video for bamlanivimab preparation/administration: https://www.kaltura.com/index.php/extwidget/preview/partner_id/1759891/uiconf_id/30232671/entry_id/1_i3nkvs7k/embed/dynamic?
    - Complete video transcript and more info: https://www.covid19.lilly.com/bamlanivimab/hcp/dosing-administration#dosing-and-administration

Casirivimab / Imdevimab

- EUA Letter of Authorization., FDA. Available at https://www.fda.gov/media/143891/download
- FAQ on Casirivimab/Imdevimab EUA. Available at https://www.fda.gov/media/143894/download
- Fact Sheet for Heatlh Care Providers: Emergency Use Authorization (EUA) of Casirivimab and Emdevimab (fda.gov)

Thank you

Questions?

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