COVID-19 Pharmacotherapy

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LT, USPHS

Disclosure

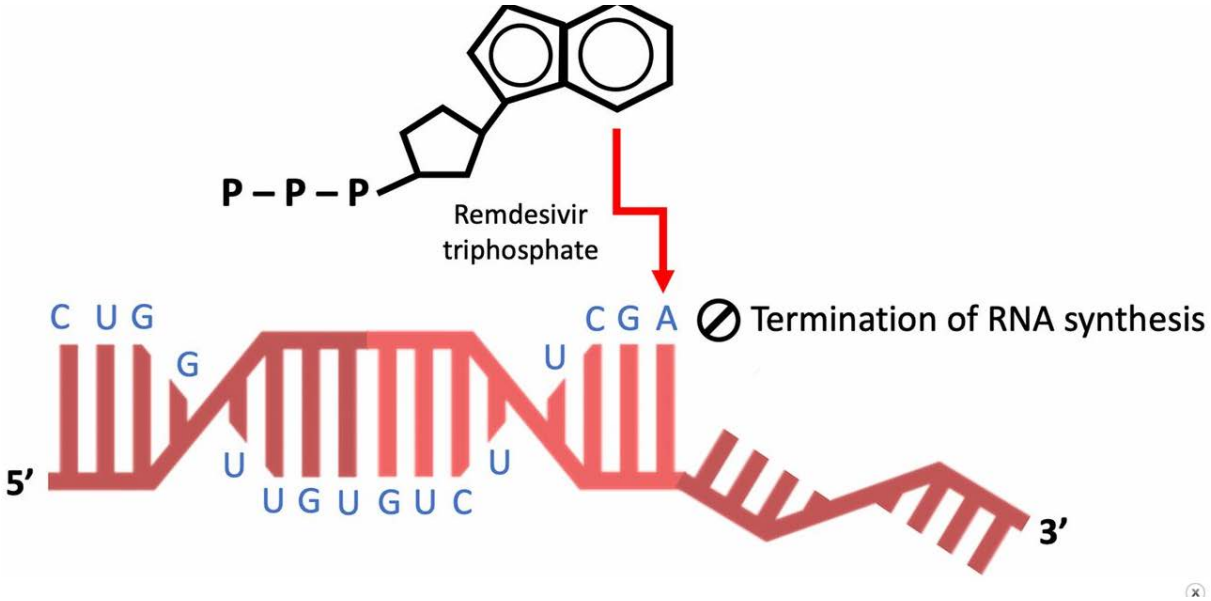
- No conflicts of interest to disclose
- Recommendations to follow primarily from Alaska Native Medical Center's Policy and Procedures
- Clinical questions regarding specific patients should be deferred to ANMC Infectious Disease Department
- Rapidly evolving FDA EUA and approved indications

Objectives

- Understanding inclusion and exclusion criteria for COVID-19 pharmacotherapies
- Mechanism of action (MOA), pharmacokinetics, and pharmacodynamics for various therapies
- Monitoring parameters for pharmacotherapies
- Regulatory requirements for emergency use authorization therapies

Remdesivir (Veklury®)

- Adenosine nucleotide analog prodrug that is metabolized intracellularly to a nucleoside monophosphate intermediate
- The nucleoside monophosphate is phosphorylated to active compound nucleoside triphosphate metabolite
- The remdesivir- triphosphate (RDV TP) competes with ATP for incorporation into nascent RNA chains by SARS-CoV-2 RNA Dependent RNA Polymerase (RdRp)
- Inhibits RNA chain termination

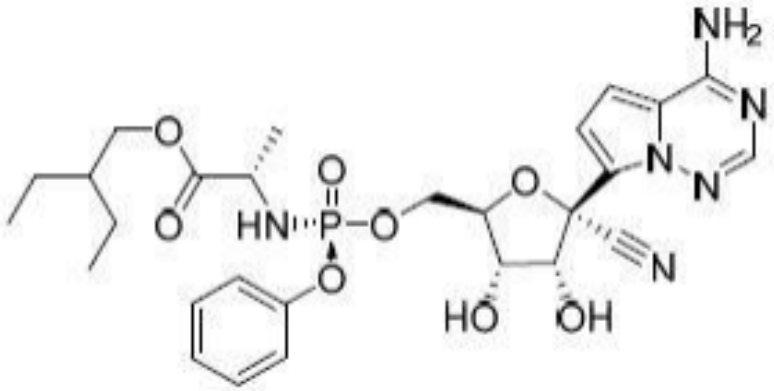


Adamsick ML, et al. JASN. 2020:31(7):1384 - 1386

Remdesivir [package insert]. Foster City, CA. Gilead Sciences Inc. 2020.

Road To Approval

- FDA released on Emergency Use Authorization (EUA) May 1, 2020
- FDA approval on October 22, 2020 for adult patients and pediatric patients 12 years of age or older weighing at least 88 lbs (40kg) for the treatment of hospitalized COVID-19 patients
- No longer need to follow EUA requirements for the approved patient population
- Three Clinical Trials
  1. NIAID ACTT-1: Mild/moderate and Severe COVID-19
  2. GS-US-540-5774: Moderate COVID-19
  3. GS-US-540-5773: Severe COVID-19



Remdesivir [package insert]. Foster City, CA. Gilead Sciences Inc. 2020.

Spinner CD, et al. JAMA. 2020;324(11):1048-1057

Beigel JH, et al. N Engl J Med. 2020; 383:1813-1826

Remdesivir (Veklury®)

- NIAID ACTT-1: Mild/moderate and Severe COVID-19
  - Randomized, double-blind, placebo-controlled, phase 3 clinical trial enrolling 1048 patients
  - Hospitalized patients with mild, moderate, or severe COVID-19 infection
- GS-US-540-5774: Moderate COVID-19
  - Randomized, open-label, phase 3 clinical trial enrolling 584 patients
  - Hospitalized patients with moderate COVID-19 infection
  - 5 day vs. 10 days treatment
- GS-US-540-5773: Severe COVID-19
  - Randomized, open-label, phase 3 clinical trail enrolling 397 patients
  - Hospitalized patients with severe COVID-19 infection
  - 5 day vs. 10 days treatment

Remdesivir [package insert]. Foster City, CA. Gilead Sciences Inc. 2020.

Spinner CD, et al. JAMA. 2020;324(11):1048-1057

Beigel JH, et al. N Engl J Med. 2020; 383:1813-1826

WHO recommends against the use of remdesivir in COVID-19 patients

WHO has issued a conditional recommendation against the use of remdesivir in hospitalized patients, regardless of disease severity, as there is currently no evidence that remdesivir improves survival and other outcomes in these patients.

This recommendation, released on 20 November, is part of a living guideline on clinical care for COVID-19. It was developed by an international guideline development group, which includes 28 clinical care experts, 4 patient-partners and one ethicist.

The guidelines were developed in collaboration with the non-profit Magic Evidence Ecosystem Foundation (MAGIC), which provided methodologic support. The guidelines are an innovation, matching scientific standards with the speed required to respond to an ongoing pandemic.

Work on this began on 15 October when the WHO Solidarity Trial published its interim results. Data reviewed by the panel included results from this trial, as well as 3 other randomized controlled trials. In all, data from over 7000 patients across the 4 trials were considered.

The evidence suggested no important effect on mortality, need for mechanical ventilation, time to clinical improvement, and other patient-important outcomes.

http://www.who.int/

Remdesivir (Veklury®)

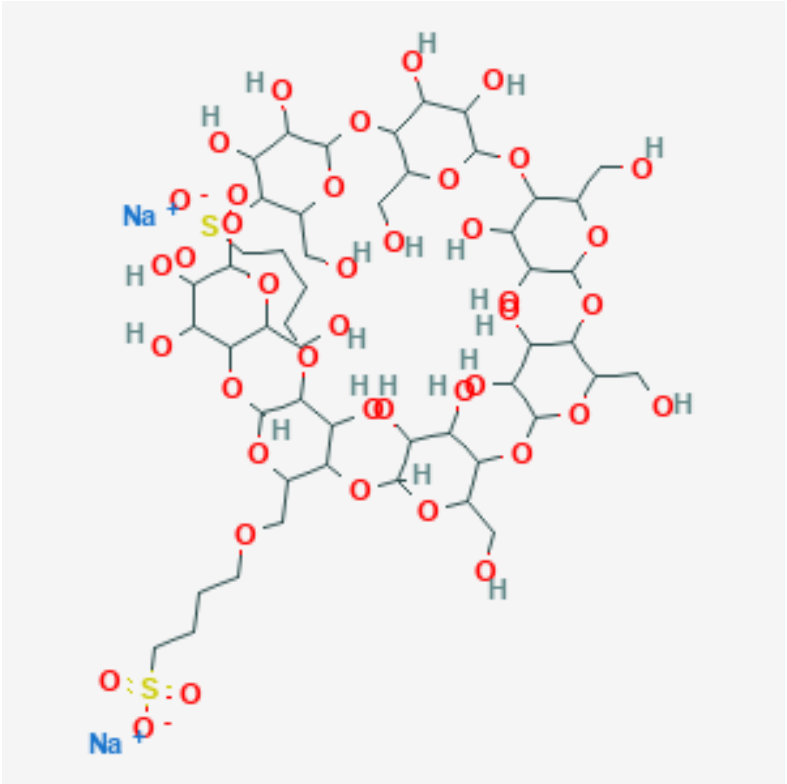
- Dosing
  - Adults and pediatric patients 12 years of age or older and weighing >40 kg: 200mg IV on day followed by 100mg IV daily for 5 – 10 days
  - Duration based on need for mechanical ventilation and/or extracorporeal membrane oxygenation (ECMO)
  - Plan for discharge prior to 5 days of therapy medication can be discontinued early
- Use lyophilized powder for pediatric patients NOT solution for injection

https://abc7chicago.com

Remdesivir [package insert]. Foster City, CA. Gilead Sciences Inc. 2020.

Contraindications?

- Hypersensitivity
- eGFR < 30 mL/min
  - excipient betadex sulfobutyl ether sodium
- ALT > 10 x ULN
  - EUA was 5 x ULN
- Co-administration with chloroquine phosphate or hydroxychloroquine sulfate
  - In vitro antagonism in cell culture

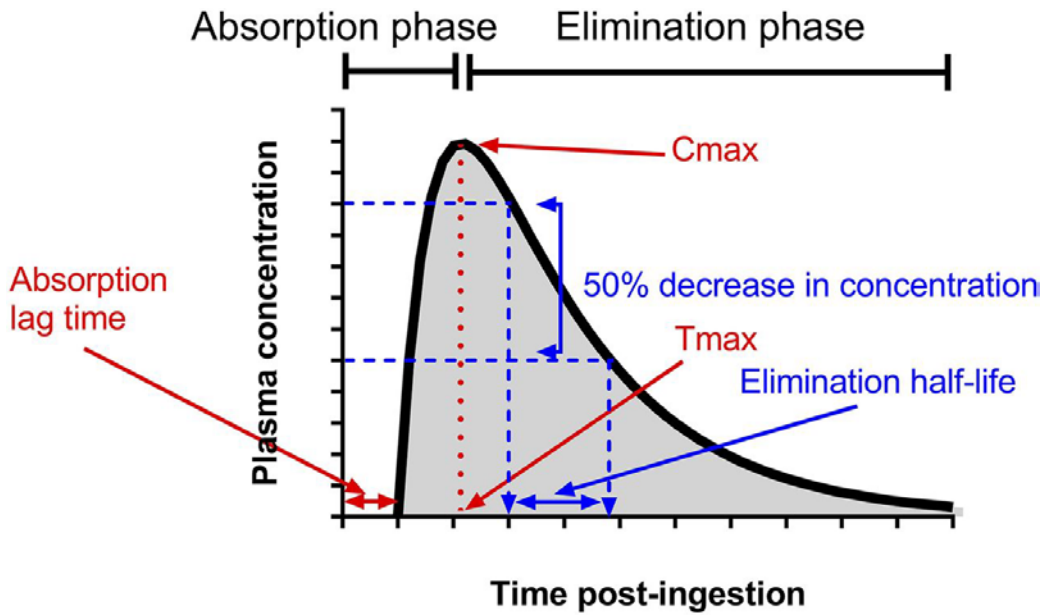


https://pubchem.ncbi.nlm.nih.gov

Remdesivir [package insert]. Foster City, CA. Gilead Sciences Inc. 2020.

Pharmacokinetics

- Tmax: 0.67 – 0.68 hr
- Percent plasma bound: 88 - 93.6%
- T1/2: 1 hr
- Metabolism: CES1 (80%), Cathepsin A (10%), CYP3A (10%)
- Urine elimination: 10%
- Feces elimination: not detected



Lea-Henry TN, et al. CJASN. 2018; 13(7): 1085-1095

Remdesivir [package insert]. Foster City, CA. Gilead Sciences Inc. 2020.

What to do with eGFR < 30 mL/min?

Remdesivir in Patients with Acute or Chronic Kidney Disease and COVID-19

Meagan L. Adamsick,[1] Ronak G. Gandhi,[1] Monique R. Bidell,[1] Ramy H. Elshaboury,[1] Roby P. Bhattacharyya,[2] Arthur Y. Kim,[2] Sagar Nigwekar,[3] Eugene P. Rhee,[3] and Meghan E. Sise[3]

[1]Department of Pharmacy, Massachusetts General Hospital, Boston, Massachusetts
[2]Division of Infectious Diseases, Department of Medicine, Massachusetts General Hospital, Boston, Massachusetts
[3]Division of Nephrology, Department of Medicine, Massachusetts General Hospital, Boston, Massachusetts

JASN 31: 1384–1386, 2020. doi: https://doi.org/10.1681/ASN.2020050589

Monitoring Parameters & Administration

- Monitoring Parameters
  - Start of therapy and as clinically indicated
    - SCr
    - LFT's
    - Prothrombin time
- Administration
  - Administer ONLY in normal saline
  - Infuse over 30 – 120 minutes

Remdesivir [package insert]. Foster City, CA. Gilead Sciences Inc. 2020.

Special Populations

- Pregnancy: data inconclusive
  - data in animal subjects
- Lactation: no available data for remdesivir in breast milk
- Renal impairment: not studied in eGFR <30 mL/min
- Hepatic impairment: not been evaluated

Remdesivir [package insert]. Foster City, CA. Gilead Sciences Inc. 2020.

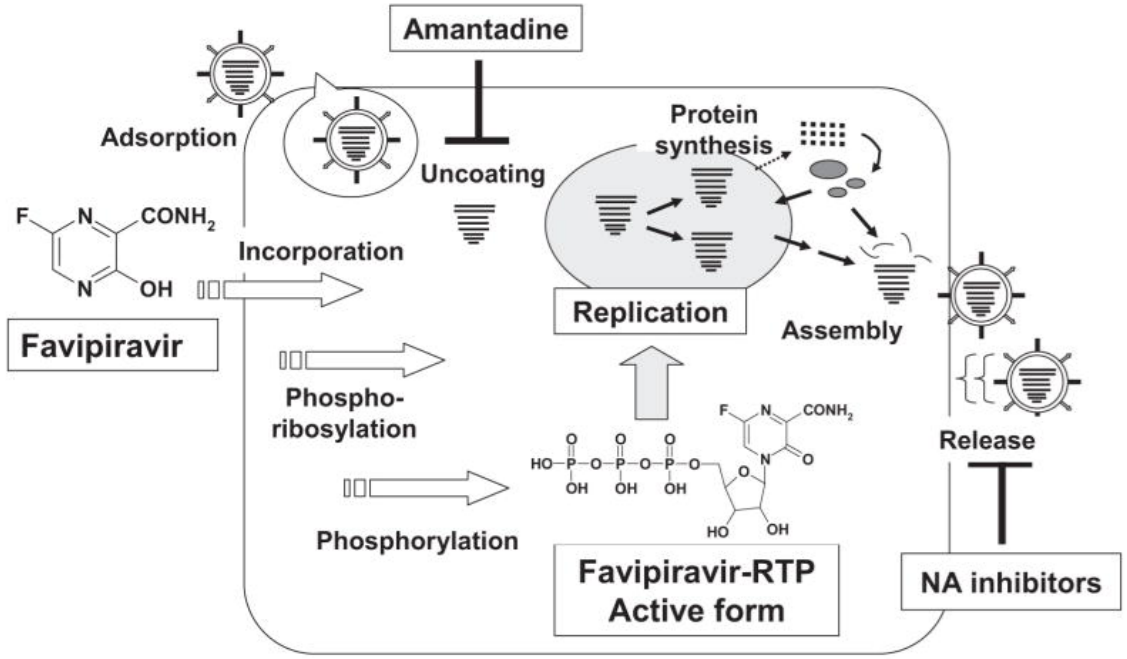
Adverse Reactions

- Disclaimer: Clinical trials conducted under varying conditions adverse rates cannot accurately be determined
- Nausea
- ALT increase
- AST increase
- Hypersensitivity reactions
- Generalized seizure
- Rash

Remdesivir [package insert]. Foster City, CA. Gilead Sciences Inc. 2020.

Favipiravir?

- Pyrazine carboxamide derivative which selectively inhibits influenza viral RNA-dependent RNA polymerase
- Favipiravir is phosphorylated into its active form
- Viral RNA polymerase mistakenly recognizes Favipiravir-RTP as purine nucleotide acting as competitive inhibitor
- Approved in Japan and France for influenza treatment



Furata Y, et al. Antiviral Res. 2013:100(2):456 -54

Favipiravir

Trial record **11 of 76** for: favipiravir

◂ Previous Study | Return to List | Next Study ▸

Study of the Use of Favipiravir in Hospitalized Subjects With COVID-19

Trial record **23 of 76** for: favipiravir

◂ Previous Study | Return to List | Next Study ▸

Oral Favipiravir Compared to Placebo in Subjects With Mild COVID-19

https://clinicalstudies.info.nih.gov/

Favipiravir

Experimental Treatment with Favipiravir for COVID-19: An Open-Label Control Study☆

Qingxian Cai,[a,#] Minghui Yang,[a,#] Dongjing Liu,[a,#] Jun Chen,[a,#] Dan Shu,[a] Junxia Xia,[a] Xuejiao Liao,[a] Yuanbo Gu,[a] Qiue Cai,[a] Yang Yang,[a] Chenguang Shen,[a] Xiaohe Li,[a] Ling Peng,[a] Deliang Huang,[a] Jing Zhang,[a] Shurong Zhang,[a] Fuxiang Wang,[a] Jiaye Liu,[a] Li Chen,[a] Shuyan Chen,[a] Zhaoqin Wang,[a] Zheng Zhang,[a] Ruiyuan Cao,[b] Wu Zhong,[b,*] Yingxia Liu,[a,*] and Lei Liu[a,*]

Favipiravir

- Open-label, nonrandomized, before-after controlled study enrolling 35 patient in study arm and 45 for control arm
- Inclusion criteria
  - 16 – 75 years old
  - Diagnosis less than 7 days
  - Required to take contraceptive measures
- Exclusion criteria
  - Severe clinical condition
  - Respiratory failure
  - Shock
  - Chronic liver or kidney disease

Qingxian C, et al. Engineering. 2020

Favipiravir

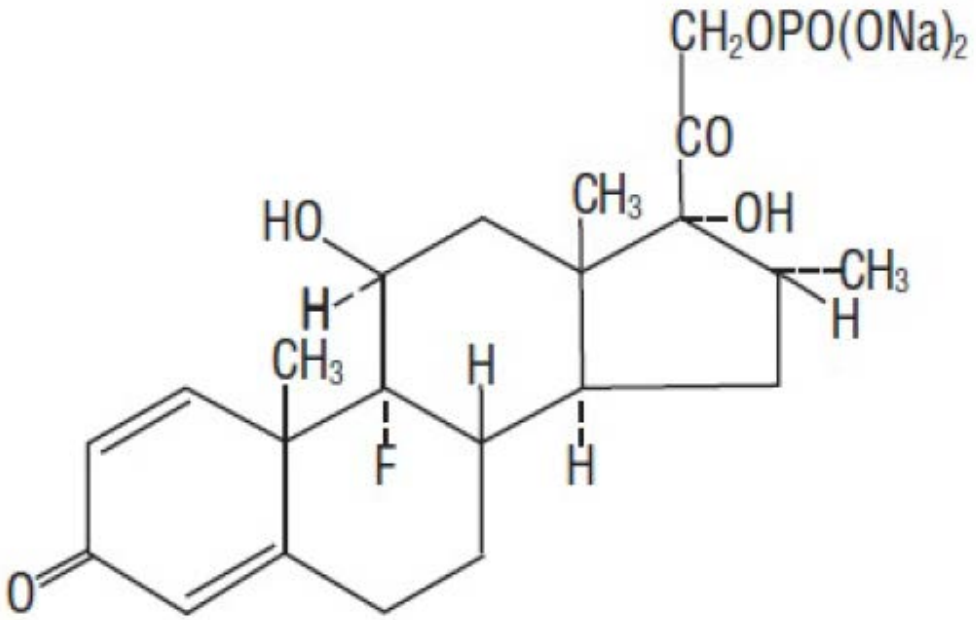
- Study arm
  - Favipiravir 1600mg BID on day one, followed by 600mg BID days 2-14
- Control arm
  - Lopinavir 400mg + ritonavir 100mg BID
- Results
  - Favipiravir patients had viral clearance at 4 days (IQR: 2.5 – 9) and the control arm had viral clearance at day 11 (IQR: 8-13)($P<0.001$)
  - No statistically different appearance in CT scans at days 4 and 9, but a significant difference at day 14 (91.4% vs. 62.2%; $P= 0.004$)
- Concerns for internal and external validity of study based on design

Qingxian C, et al. Engineering. 2020

Dexamethasone

Dexamethasone

- MOA: Long-acting corticosteroid with almost exclusive glucocorticoid activity and negligible mineralocorticoid effect.
- 6mg IV or PO for up to 10 days
- RECOVERY trial
- PK/PD of IV vs. PO
- Theoretical benefit later in Illness because disease progression thought to be immunopathological processes



RECOVERY collaborative group. N Enj J Med. 2020
Shaikh S, et. Al. ISRN Anesthesiology. 2012

Table 1

Classification and comparison of systemic steroids [1, 7].

Glucocorticoid	Anti-inflammatory potency	Na-retaining potency	Duration of action	Equivalent dose
Cortisol	1	1	Short (<12 hrs)	20
Cortisone	0.8	0.8		25
Prednisone	4	0.8		5
Prednisolone (P)	4	0.8	Intermediate (12–36 hrs)	5
6 methyl P	5	0.5		4
Triamcinolone	5	0		4
Dexamethasone	25	0	Large (>36 hrs)	0.75
Betamethasone	25	0		0.75

Shaikh S, et. Al. ISRN Anesthesiology. 2012

ORIGINAL ARTICLE

Dexamethasone in Hospitalized Patients with Covid-19 — Preliminary Report

The RECOVERY Collaborative Group*

RECOVERY Trial

- Controlled, open-label, and conducted at 176 National Health Service organizations
- Inclusion criteria:
  - Hospitalized patient with suspected COVID-19 infection and no medical history that was an exclusion at opinion of treating physician
  - > 18 years of age (changed midway through trial)
  - Pregnant and breastfeeding patients included
- Treatments
  - Dexamethasone 6mg IV or PO
  - Azithromycin/tocilizumab/hydroxychloroquine/lopinavir-ritonavir/convalescent plasma
- Results
  - 2104 patients received dexamethasone
  - Mortality at 28 days was significantly lower in the dexamethasone group than in the usual care group
  - Dexamethasone group deaths of 482 of 2104 patients (22.9%) and in 1110 of 4321 patients (25.7%) in control group
  - RR: 0.83; 95% confidence interval (0.75 to 0.93; P<0.001)

RECOVERY collaborative group. N Enj J Med. 2020

Baricitinib (Olumiant®) & Remdesivir

FDA NEWS RELEASE

Coronavirus (COVID-19) Update: FDA Authorizes Drug Combination for Treatment of COVID-19

Share | Tweet | Linkedin | Email | Print

For Immediate Release: November 19, 2020

Español

Today, the U.S. Food and Drug Administration issued an emergency use authorization (EUA) for the drug baricitinib, in combination with remdesivir, for the treatment of suspected or laboratory confirmed COVID-19 in hospitalized adults and pediatric patients two years of age or older requiring supplemental oxygen, invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).

EUA Approval

- Baricitinib in combination with remdesivir for treatment of suspected or confirmed COVID-19 infection in hospitalized adults and pediatric patients 2 years of age or older requiring supplemental oxygen therapy, invasive mechanical ventilation, or extracorporeal membrane oxygenation
- Optimal treatment duration undetermined but current recommendation is 14 days or until hospital discharge
- Dosing
  - Adult and pediatric patients 9 years of age or older: 4mg PO once daily
  - Pediatric patients between 2 – 9 years of age: 2mg PO once daily
- Not recommended for patients with ESRD, AKI, dialysis, known active tuberculosis
- Limited data on use with systemic corticosteroids but EUA approves use with steroids

https://www.covid19.lilly.com/baricitinib

Mandatory EUA Requirements

- Counsel patient and provide “Fact Sheet for Patients, Parents and Caregivers”
- Inform patients of alternatives
- Inform patients that medication is not approved and is being used in EUA
- Laboratory Studies:
  - eGFR
  - Aminotransferases
  - CBC with differential
- Mandatory reporting of adverse drug reactions

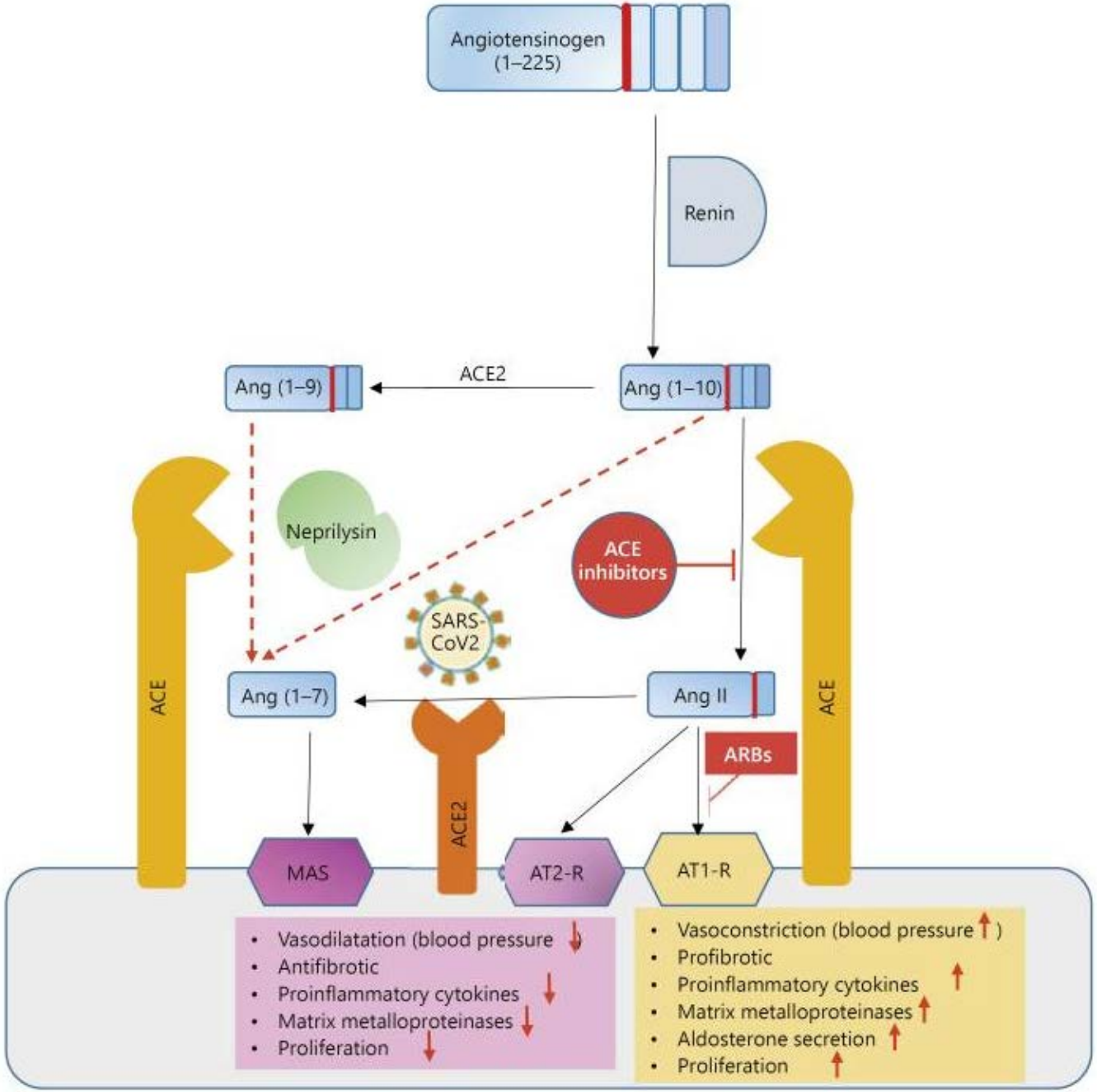
https://www.covid19.lilly.com/baricitinib

Baricitinib (Olumiant®)

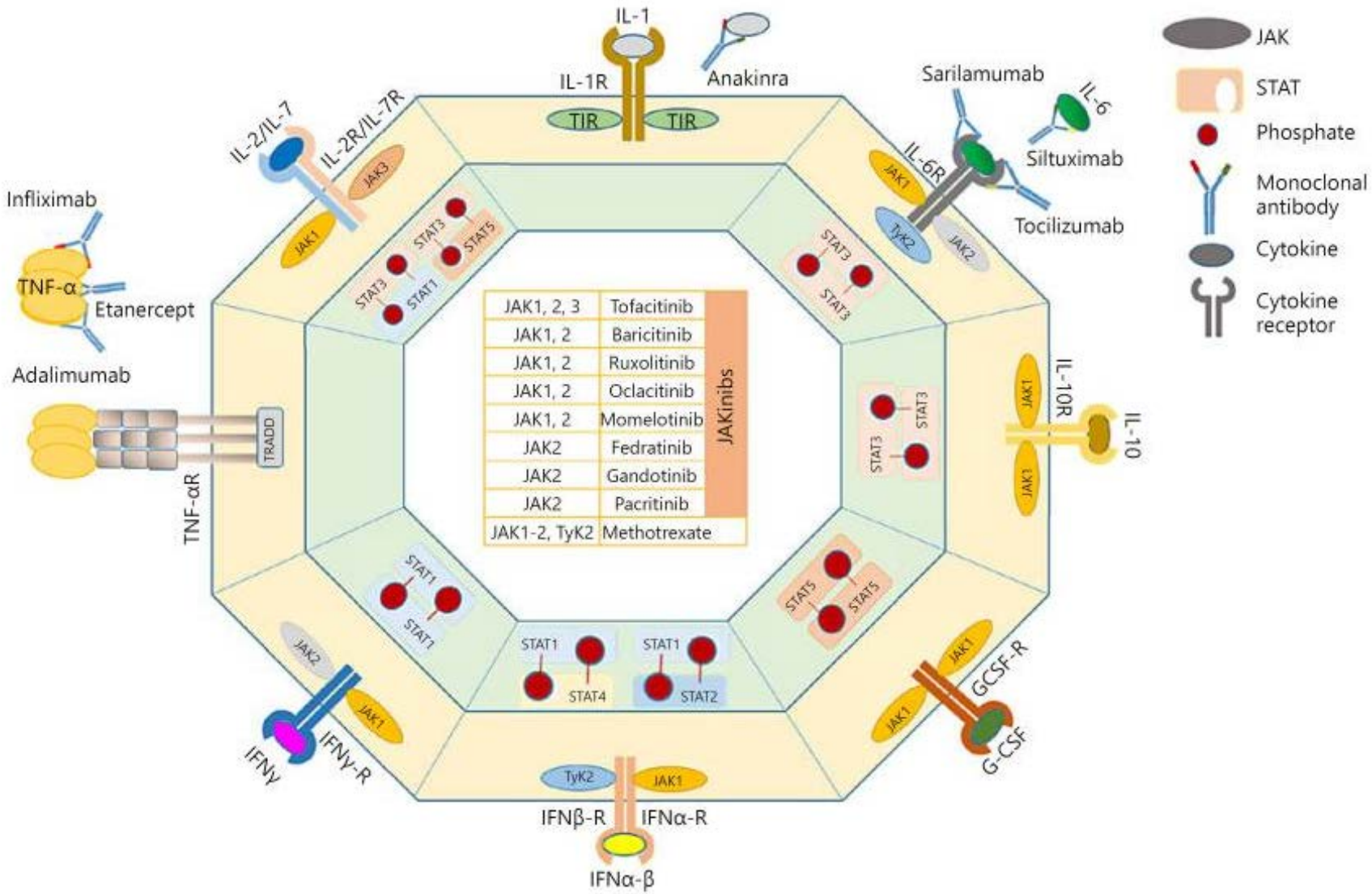
- ClATP competitive kinase inhibitor that selectively and reversible inhibits Janus kinases JAK1 and JAK2
- Classified as disease-modifying antirheumatic drugs (DMARD)
- Administered orally
- May be crushed for administration

www.olumiant.com

Taylor PC, et al. N Enj J Med. 2017; 376(7):652-662
Seif F, et al. Int Arch Allergy Immunology. 2020:181(6):467-475.



Seif F, et al. Int Arch Allergy Immunology. 2020:181(6):467-475.



Seif F, et al. Int Arch Allergy Immunology. 2020:181(6):467-475.

Baricitinib (Olumiant®)

Table 1: Dosage Adjustments for Patients with Abnormal Laboratory Values[a,b]

Laboratory Analyte	Laboratory Analyte Value	Recommendation
eGFR	≥60 mL/min/1.73 m^2	• Adults and pediatric patients 9 years of age and older: No dosage adjustment • Pediatric patients 2 years to less than 9 years of age: 2 mg once daily
	30 to <60 mL/min/1.73 m^2	• Adults and pediatric patients 9 years of age and older: 2 mg once daily • Pediatric patients 2 years to less than 9 years of age: 1 mg once daily
	15 to <30 mL/min/1.73 m^2	• Adults and pediatric patients 9 years of age and older: 1 mg once daily • Pediatric patients 2 years to less than 9 years of age: Not recommended
	<15 mL/min/1.73 m^2	Not recommended
Absolute Lymphocyte Count (ALC)	≥200 cells/μL	Maintain dose
	<200 cells/μL	Consider interruption until ALC is ≥200 cells/μL
Absolute Neutrophil Count (ANC)	≥500 cells/μL	Maintain dose
	<500 cells/μL	Consider interruption until ANC is ≥500 cells/μL
Aminotransferases	If increases in ALT or AST are observed and drug-induced liver injury (DILI) is suspected	Interrupt baricitinib until the diagnosis of DILI is excluded

[a] Abbreviations: ALC = absolute lymphocyte count, ALT = alanine transaminase, ANC = absolute neutrophil count, AST = aspartate transaminase, DILI = drug induced liver injury, eGFR = estimated glomerular filtration rate, hrs = hours.

[b] If a laboratory abnormality is likely due to the underlying disease state, consider the risks and benefits of continuing baricitinib at the same or a reduced dose.

https://www.covid19.lilly.com/baricitinib

Baricitinib (Olumiant®)

- Black Box Warnings
  - At high risk for developing serious infections that may lead to hospitalization and death
  - Lymphoma and other malignancies have been reported
  - DVT and PE occur at increased incidence in patients on baricitinib vs. placebo
- Averse Reactions:
  - COVID-19 Treatment:
    - **Thrombosis have been observed in COVID-19 patients treated with baricitinib vs. placebo

Uptodate.com
https://www.covid19.lilly.com/baricitinib

Baricitinib (Olumiant®)

- Rheumatoid arthritis treatment
  - >10%
    - Infection
    - Upper respiratory tract infection
  - 1 – 10%
    - Nausea (3%)
    - Herpes Zoster Infection (1%)
    - ↑ AST, ↑ ALT
  - <1%
    - Arterial Thrombus
    - Acne Vulgaris
    - Malignant lymphoma, malignant neoplasm, neutropenia

Uptodate.com

Adaptive COVID-19 Treatment Trial 2 (ACTT-2)

ACTT-2 Study in Hospitalized Patients

- Adaptive randomized double-blind placebo-controlled trial comparing remdesivir vs. remdesivir + baricitinib
- Enrolled 1034 patients
- Treatments
  - Experimental: remdesivir 200mgIV day 1, followed by remdesivir 100mg daily for up to 10 days and 4mg oral baricitinib daily while hospitalized not to exceed 14 days
  - Control: remdesivir 200mg IV day 1, followed by remdesivir 100mg daily for up to 10 days
- Primary Outcome: Time to recovery (Day 1 – Day 29)
- Secondary Outcomes: Many
- Data not released

https://clinicaltrials.gov/ct2/show/NCT04401579

Inclusion Criteria

- Hospitalized
- Male or non-pregnant females >18 years of age
- Illness of any duration and one of the following
  - Radiographic infiltrates on chest X-ray OR
  - Sp02</= 94% on room air OR
  - Requiring supplemental 02 OR
  - Requiring mechanical ventilation of ECMO
  - Female participants must agree to abstinence or primary means of birth control

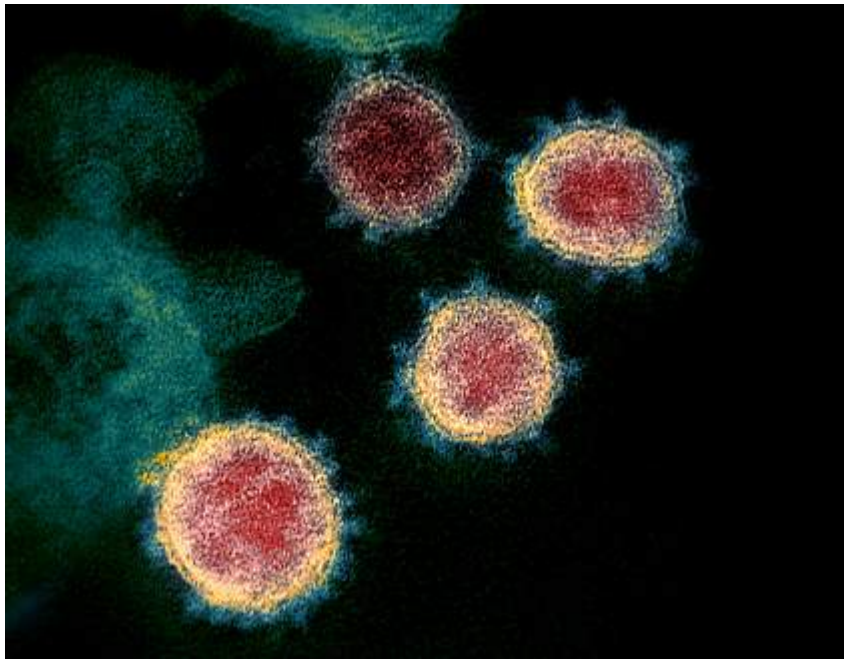
https://clinicaltrials.gov/ct2/show/NCT04401579

Exclusion Criteria

- AST/ALT > 5 x UNL
- eGFR< 30mL/min or HD
- Neutropenia (ANC <1000 cells/microliter)
- Lymphopenia (absolute lymphocyte count <200 cells/microliter)
- Pregnant or breast feeding
- Anticipated discharge from hospital within 72 hrs
- Received 3 or more doses of remdesivir prior to enrollment
- Received convalescent plasma, IVIG, other immunosuppressants, probenecid that cannot be discontinued
- History of VTE within 12 weeks of enrollment or history of recurrent VTE (> 1 VTE)
- Suspected serious infections (TB)

https://clinicaltrials.gov/ct2/show/NCT04401579

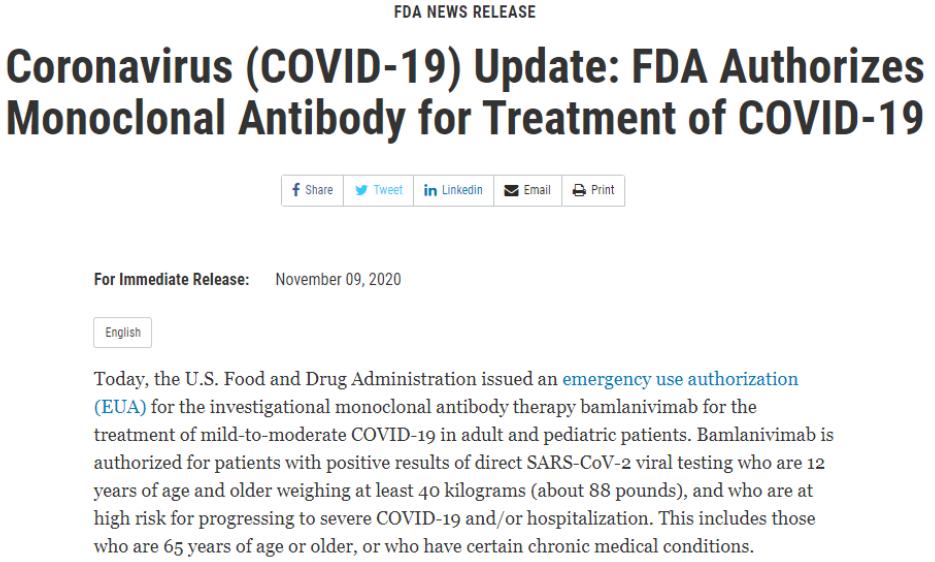
Enter the Monoclonal Antibodies…



https://www.nih.gov/news-events/nih-research-matters/novel-coronavirus-structure-reveals-targets-vaccines-treatments

Bamlanivimab (LY-CoV555)

- November 9, 2020 FDA released an emergency use authorization (EUA)
- Treatment of mild to moderate COVID-19 in adults and pediatric (12 years of age or older weighing at least 40kg) patients who are at high risk for progressing to severe COVID-19 and/or hospitalization
- Released by Eli Lilly and AbCellera™



FDA NEWS RELEASE

Coronavirus (COVID-19) Update: FDA Authorizes Monoclonal Antibody for Treatment of COVID-19

Share Tweet Linkedin Email Print

For Immediate Release: November 09, 2020

English

Today, the U.S. Food and Drug Administration issued an emergency use authorization (EUA) for the investigational monoclonal antibody therapy bamlanivimab for the treatment of mild-to-moderate COVID-19 in adult and pediatric patients. Bamlanivimab is authorized for patients with positive results of direct SARS-CoV-2 viral testing who are 12 years of age and older weighing at least 40 kilograms (about 88 pounds), and who are at high risk for progressing to severe COVID-19 and/or hospitalization. This includes those who are 65 years of age or older, or who have certain chronic medical conditions.

Bamlanivimab. Eli Lilly. https://www.covid19.lilly.com/bamlanivimab/hcp

How Does FDA EUA Define "High Risk"?

- Must meet at least one:
  - BMI ≥35
  - CKD
  - Diabetes
  - Immunosuppressive disease
  - Currently receiving immunosuppressant treatment
  - ≥65 years of age
  - ≥55 years of age
    - Cardiovascular disease OR
    - HTN OR
    - COPD/ other chronic respiratory disease

- Are 12 – 17 years of age AND have
  - BMI ≥85th percentile for their age and gender based on CDC growth charts, OR
  - Sickle cell disease, OR
  - Congenital or acquired heart disease, OR
  - Neurodevelopmental disorders, for example, cerebral palsy, OR
  - Medical-related technological dependence (tracheostomy, gastrostomy, or positive pressure ventilation (not related to COVID-19)) OR
  - Asthma, reactive airway or other chronic respiratory disease that requires daily medication control

Bamlanivimab. Eli Lilly. https://www.covid19.lilly.com/bamlanivimab/hcp

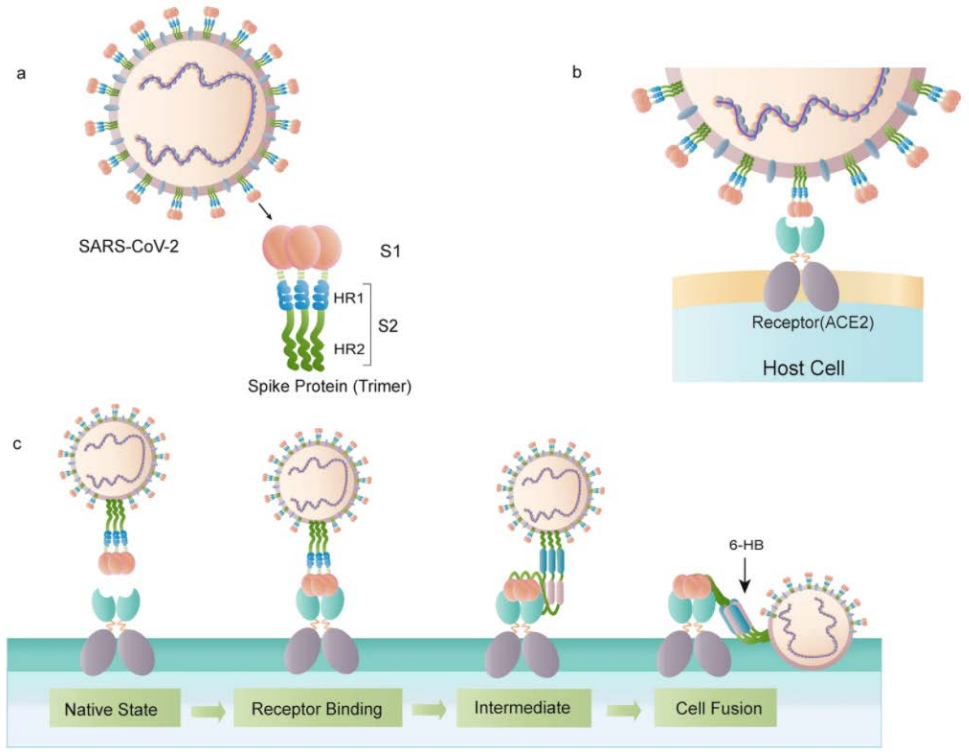
Contraindications

- Hospitalization due to COVID-19 OR
- Require oxygen therapy due to COVID-19 OR
- Require and increase in baseline oxygen flow rate due to COVID-19 in those chronic oxygen therapy due to other comorbidity

Bamlanivimab. Eli Lilly. https://www.covid19.lilly.com/bamlanivimab/hcp

Mechanism of Action

- Recombinant neutralizing human IgG1κ monoclonal antibody (mAb) to spike protein of SARS-CoV-2
- Binding to spike protein of SARS-CoV-2 prevents attachment to ACE2 receptor
- Inhibits viral invasion into host cell



Huang Y, et al. Acta Pharmacologica Sinica. 2020 41:1141-1149

Bamlanivimab. Eli Lilly. https://www.covid19.lilly.com/bamlanivimab/hcp

BLAZE-1 Clinical Trial

› N Engl J Med. 2020 Oct 28;NEJMoa2029849. doi: 10.1056/NEJMoa2029849. Online ahead of print.

SARS-CoV-2 Neutralizing Antibody LY-CoV555 in Outpatients with Covid-19

Peter Chen [1], Ajay Nirula [1], Barry Heller [1], Robert L Gottlieb [1], Joseph Boscia [1], Jason Morris [1], Gregory Huhn [1], Jose Cardona [1], Bharat Mocherla [1], Valentina Stosor [1], Imad Shawa [1], Andrew C Adams [1], Jacob Van Naarden [1], Kenneth L Custer [1], Lei Shen [1], Michael Durante [1], Gerard Oakley [1], Andrew E Schade [1], Janelle Sabo [1], Dipak R Patel [1], Paul Klekotka [1], Daniel M Skovronsky [1], BLAZE-1 Investigators

BLAZE-1 Clinical Trial

- Ongoing phase 2, randomized, double-blind, placebo-controlled, single dose trial conducted at 41 sites in U.S.
- Enrolled 452 patients with positive SARS-CoV-2 and mild-moderate symptoms treated outpatient
- Treatment arms
  - LY-CoV555 (700mg or 2800mg or 7000mg)
  - Placebo
- Primary Outcome:
  - Change in baseline viral load at day 11

Chen P, e al. N Engl J Med. 2020

BLAZE-1 Clinical Trial

Table 2

Change from Baseline in Viral Load.

Variable	LY-CoV555 (N=309)	Placebo (N=143)	Difference (95% CI)
Primary outcome			
Mean change from baseline in viral load at day 11		−3.47	
	700 mg, −3.67		−0.20 (−0.66 to 0.25)
	2800 mg, −4.00		−0.53 (−0.98 to −0.08)
	7000 mg, −3.38		0.09 (−0.37 to 0.55)
	Pooled doses, −3.70		−0.22 (−0.60 to 0.15)
Secondary outcomes*			
Mean change from baseline in viral load at day 3		−0.85	
	700 mg, −1.27		−0.42 (−0.89 to 0.06)
	2800 mg, −1.50		−0.64 (−1.11 to −0.17)
	7000 mg, −1.27		−0.42 (−0.90 to 0.06)
	Pooled doses, −1.35		−0.49 (−0.87 to −0.11)
Mean change from baseline in viral load at day 7		−2.56	
	700 mg, −2.82		−0.25 (−0.73 to 0.23)
	2800 mg, −3.01		−0.45 (−0.92 to 0.03)
	7000 mg, −2.85		−0.28 (−0.77 to 0.20)
	Pooled doses, −2.90		−0.33 (−0.72 to 0.06)

Chen P, e al. N Engl J Med. 2020

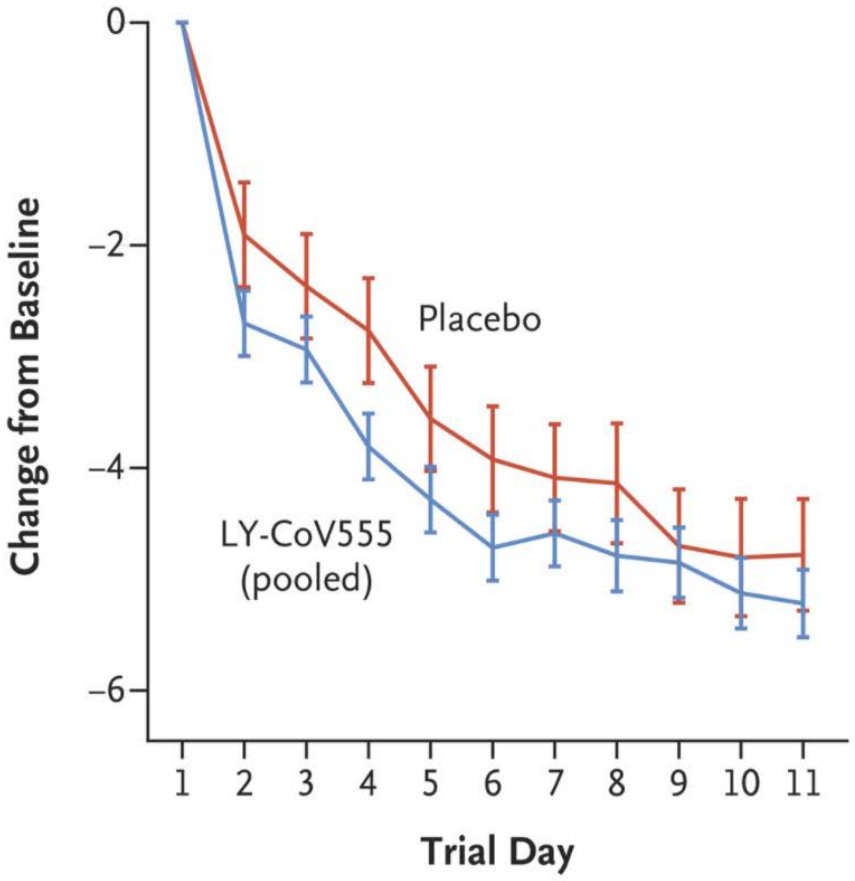
BLAZE-1 Clinical Trial

Hospitalization.

Key Secondary Outcome	LY-CoV555	Placebo	Incidence
	no. of patients/total no.		%
Hospitalization		9/143	6.3
	700 mg, 1/101		1.0
	2800 mg, 2/107		1.9
	7000 mg, 2/101		2.0
	Pooled doses, 5/309		1.6

Chen P, e al. N Engl J Med. 2020

BLAZE-1 Clinical Trial



	Delta Value (95% CI)
Day 2	−0.79 (−1.35 to −0.24)
Day 3	−0.57 (−1.12 to −0.01)
Day 4	−1.04 (−1.60 to −0.49)
Day 5	−0.73 (−1.28 to −0.17)
Day 6	−0.79 (−1.35 to −0.23)
Day 7	−0.50 (−1.06 to 0.07)
Day 8	−0.65 (−1.28 to −0.02)
Day 9	−0.15 (−0.75 to 0.45)
Day 10	−0.32 (−0.94 to 0.29)
Day 11	−0.44 (−1.02 to 0.15)

Chen P, e al. N Engl J Med. 2020

BLAZE-1 Trial

Adverse Event	Bamlanivimab Pooled Doses	Placebo
Nausea	3.5%	3.5%
Diarrhea	4.9%	4.9%
Dizziness	2.1%	2.1%
Headache	2.1%	2.1%
Pruritus	0.7%	0.7%
Vomiting	2.8%	2.8%

Chen P, e al. N Engl J Med. 2020

Casirivimab (REGN10933) & Imdevimab (REGN10987)

FDA NEWS RELEASE

Coronavirus (COVID-19) Update: FDA Authorizes Monoclonal Antibodies for Treatment of COVID-19

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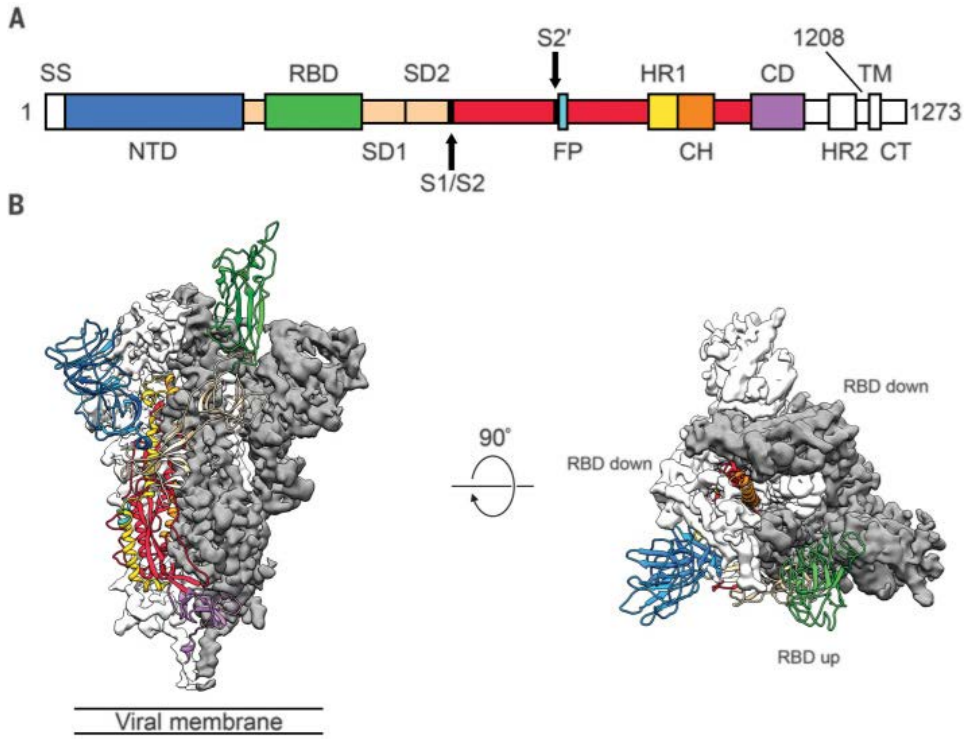
For Immediate Release: November 21, 2020

Español

Casirivimab & Imdevimab (REGN-COV2)

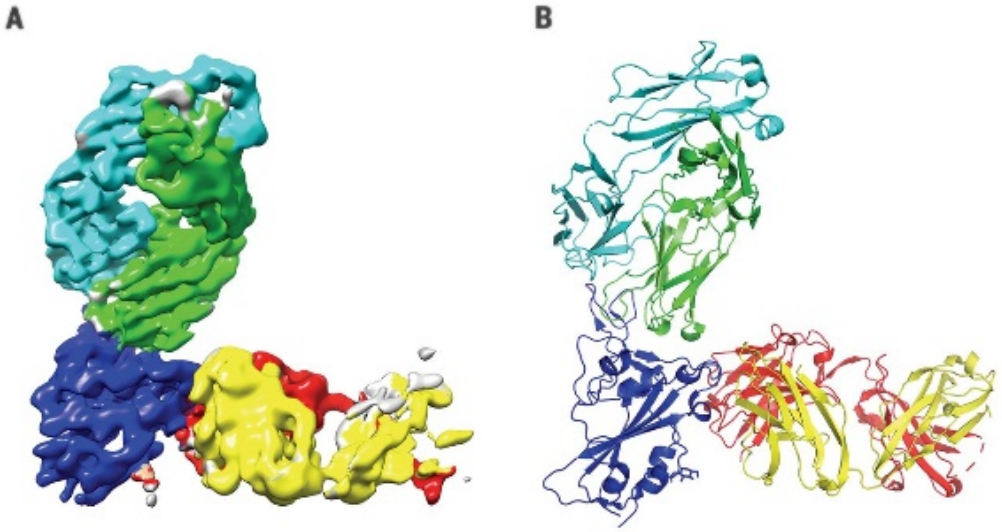
- Casirivimab (IgG1κ) and imdevimab (IgG1λ) recombinant monoclonal antibodies that bind to overlapping epitopes of the SARS-CoV-2 spike protein receptor binding domain (RBD) blocking binding to ACE2 receptor and viral invasion



Wrapp D, et al. Science. 2020; 13:367(6483):1260-1263

Casirivimab & Imdevimab (REGN-COV2)

- Anti-SARS-CoV-2 spike antibodies generated:
  1. VI mice immunized with DNA plasmid expressing spike protein
  2. Antibodies isolated from peripheral blood mononuclear cells (PBMCs)
- Selected antibodies that could be paired to account for decreased efficacy from:
  - Genetic variation from infections
  - Selective pressure by single antibody in treatment of large numbers of patients



Hansen J, et al. Science. 2020;369(6506):1010-1014

Casirivimab & Imdevimab (REGN-COV2) EUA

- Casirivimab & imdevimab to be administered together for treatment of mild to moderate COVID-19 in adult and pediatric patients (12 years of age and older weighing at least 40kg) who are at high risk for progression to severe COVID-19 and/or hospitalization
- Inclusion criteria:
  - See high risk definition for bamlanivimab
  - ASAP from diagnosis
  - Within 10 days of diagnosis
- Exclusion criteria:
  - See exclusions for bamlanivimab
- Dose: Single IV infusion of 1,200mg casirivimab and 1,200mg of imdevimab administered together as a single infusion

https://www.regeneron.com/casirivimab-imdevimab

Casirivimab & Imdevimab (REGN-COV2) EUA

- Safety/ Adverse Events
  - No severe reactions reported
  - Infusion related reactions:
    - Fever
    - Chills
    - Urticaria
    - Pruritus
    - Abdominal pain
    - Flushing
  - If infusion reaction occurs consider slowing or stopping infusion and administering appropriate medications
  - Must administer in a location that has appropriate staff to address an anaphylactic reaction

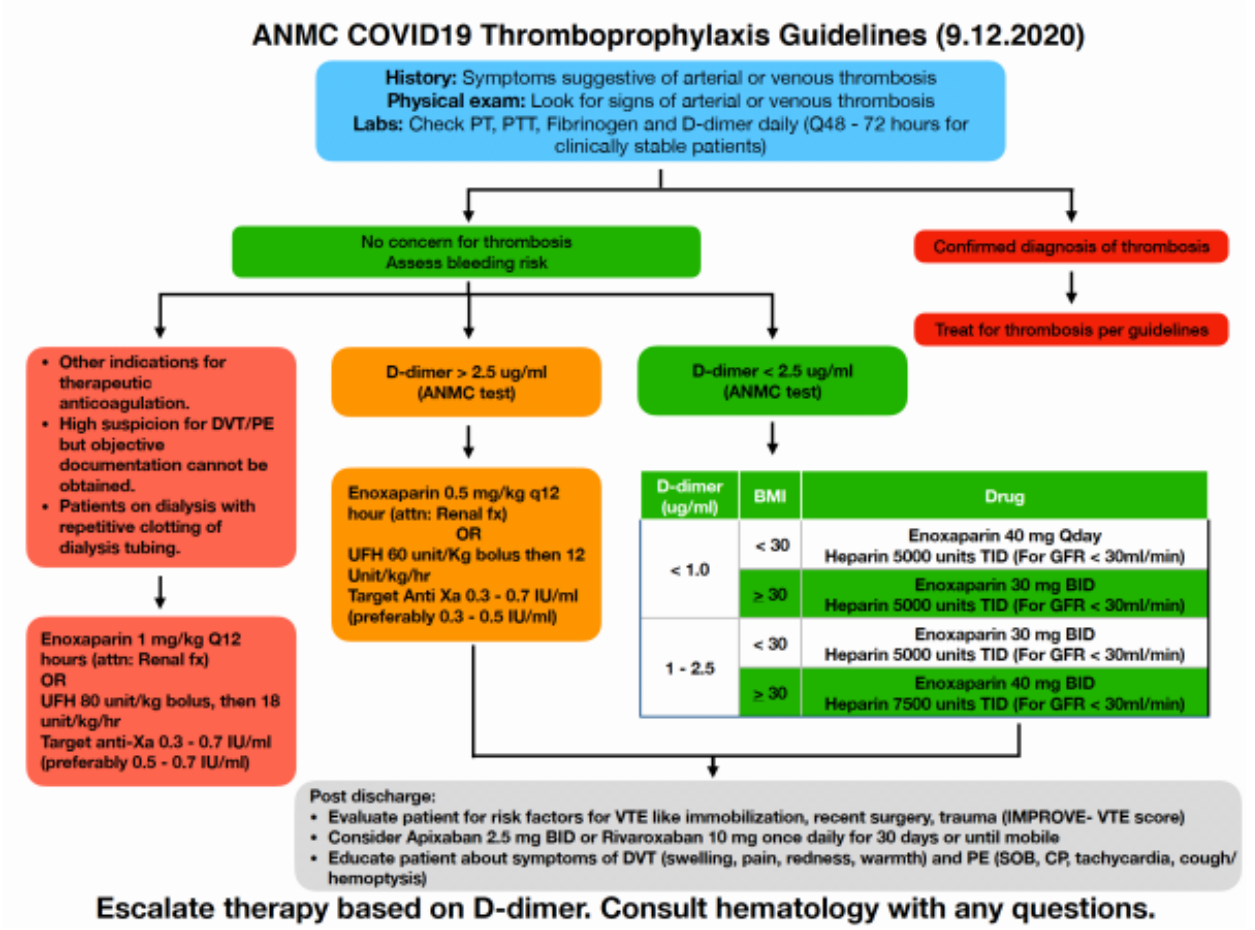
https://www.regeneron.com/casirivimab-imdevimab

"Safety, Tolerability, & Efficacy of Anti-Spike SARS-CoV-2 Monoclonal Antibodies for the Treatment of Ambulatory Adult Patients with COVID-19"

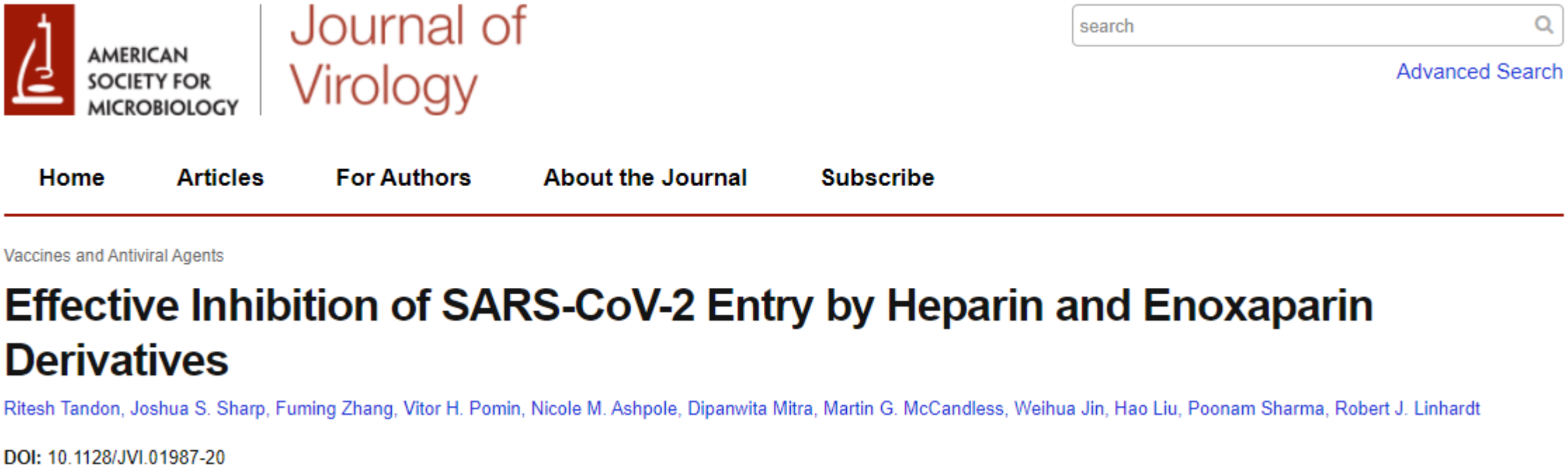
- Interim analysis
- Double-blind randomized clinical trial carsirivimab/imdevimab 2400mg (N=238), 8000mg (n=267), or placebo (n=262)
- Enrolled OUTPATIENTS with recently diagnosed mild-moderate COVID-19 infection in U.S. and Romania
- Primary endpoint: reduction in viral load at baseline and day 7
  - $P<0.0001$
- Secondary endpoint: reduction in medically attended visits @ 28 days
  - Both doses (2.8%) vs. placebo (6.5%)

https://www.regeneron.com/casirivimab-imdevimab

Thromboembolic prophylaxis in COVID-19



Old Treatments New Indications?



DOAC's?

TH Open. 2020 Oct; 4(4): e376–e382.
Published online 2020 Nov 23. doi: 10.1055/s-0040-1720962

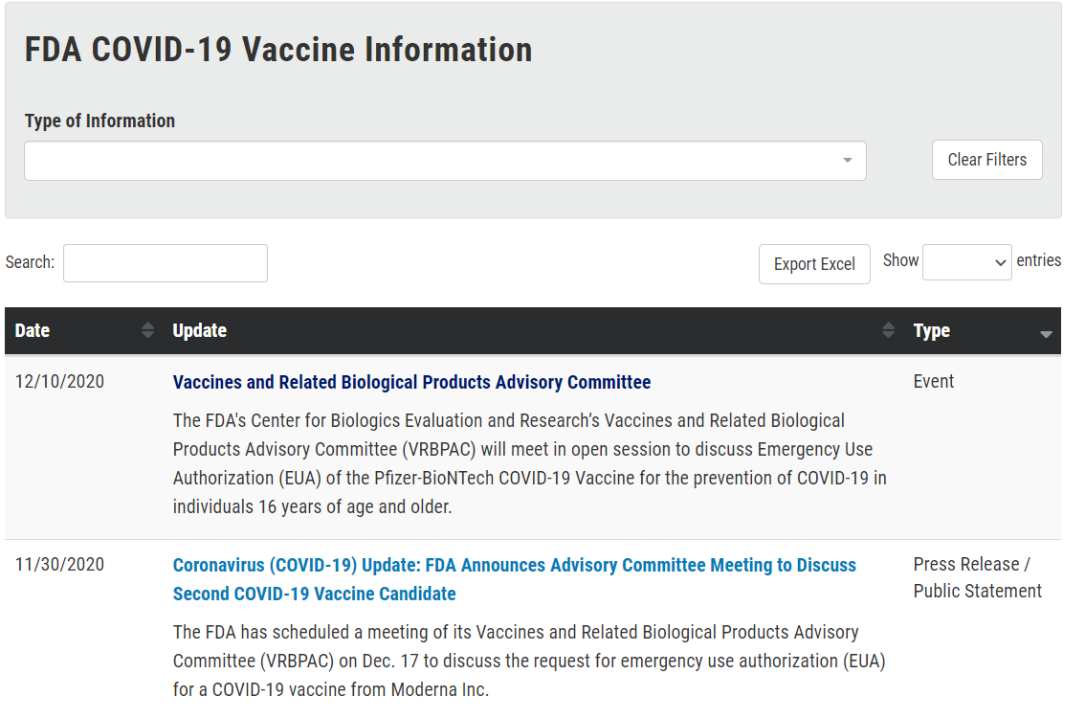
PMCID: PMC7685067
PMID: 33244512

Safety and Efficacy of Apixaban For Therapeutic Anticoagulation in Critically Ill ICU Patients with Severe COVID-19 Respiratory Disease

Eric Wenzler,[1] Monaz H. Engineer,[1] Maidah Yaqoob,[2] and Scott T. Benken[1]

Vaccine(s)?

- 58 vaccines in clinical trials
- 87 preclinical vaccines are under investigation
- 2 vaccines applying for Emergency Use Authorization both mRNA vaccines and 2 doses
  - mRNA-1273 (Moderna)
  - BNT162b2 (Pfizer and BioNTech)



FDA COVID-19 Vaccine Information

Type of Information

Clear Filters

Search:

Export Excel

Show entries

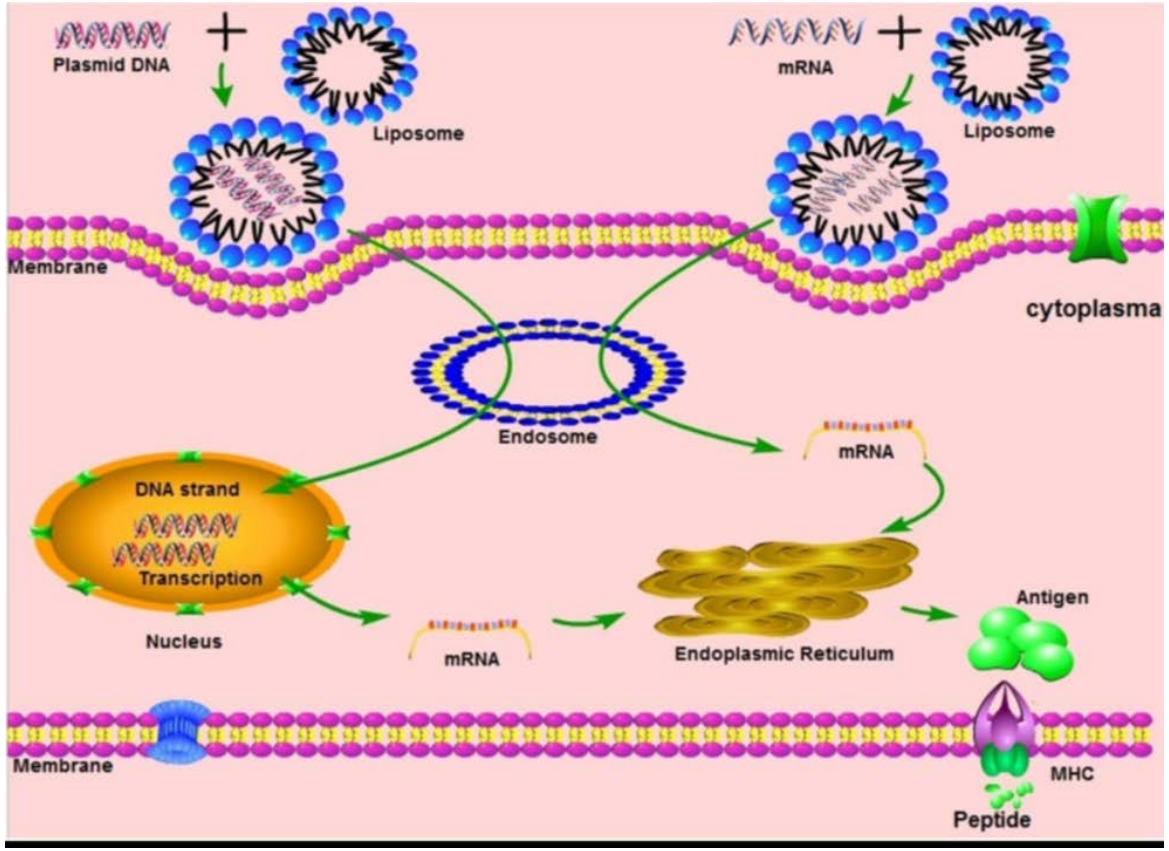
Date	Update	Type
12/10/2020	**Vaccines and Related Biological Products Advisory Committee** The FDA's Center for Biologics Evaluation and Research's Vaccines and Related Biological Products Advisory Committee (VRBPAC) will meet in open session to discuss Emergency Use Authorization (EUA) of the Pfizer-BioNTech COVID-19 Vaccine for the prevention of COVID-19 in individuals 16 years of age and older.	Event
11/30/2020	**Coronavirus (COVID-19) Update: FDA Announces Advisory Committee Meeting to Discuss Second COVID-19 Vaccine Candidate** The FDA has scheduled a meeting of its Vaccines and Related Biological Products Advisory Committee (VRBPAC) on Dec. 17 to discuss the request for emergency use authorization (EUA) for a COVID-19 vaccine from Moderna Inc.	Press Release / Public Statement

https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/covid-19-vaccines

Covid-19 Vaccine Tracker: Latest Updates - The New York Times (nytimes.com)

mRNA Vaccine

- Nucleic acid vaccines are essentially a viral infection
- Result in production of viral protein *in situ* BUT do not produce viable viral particles or integrate into host cell genome
  - Do not cross nuclear membrane like DNA based vaccines
- Do not need adjuvants because readily recognized by conserved pattern recognition receptors (PRR)
- Concerns for stability (SS)
  - Delivery on nanoparticles (Rnases)

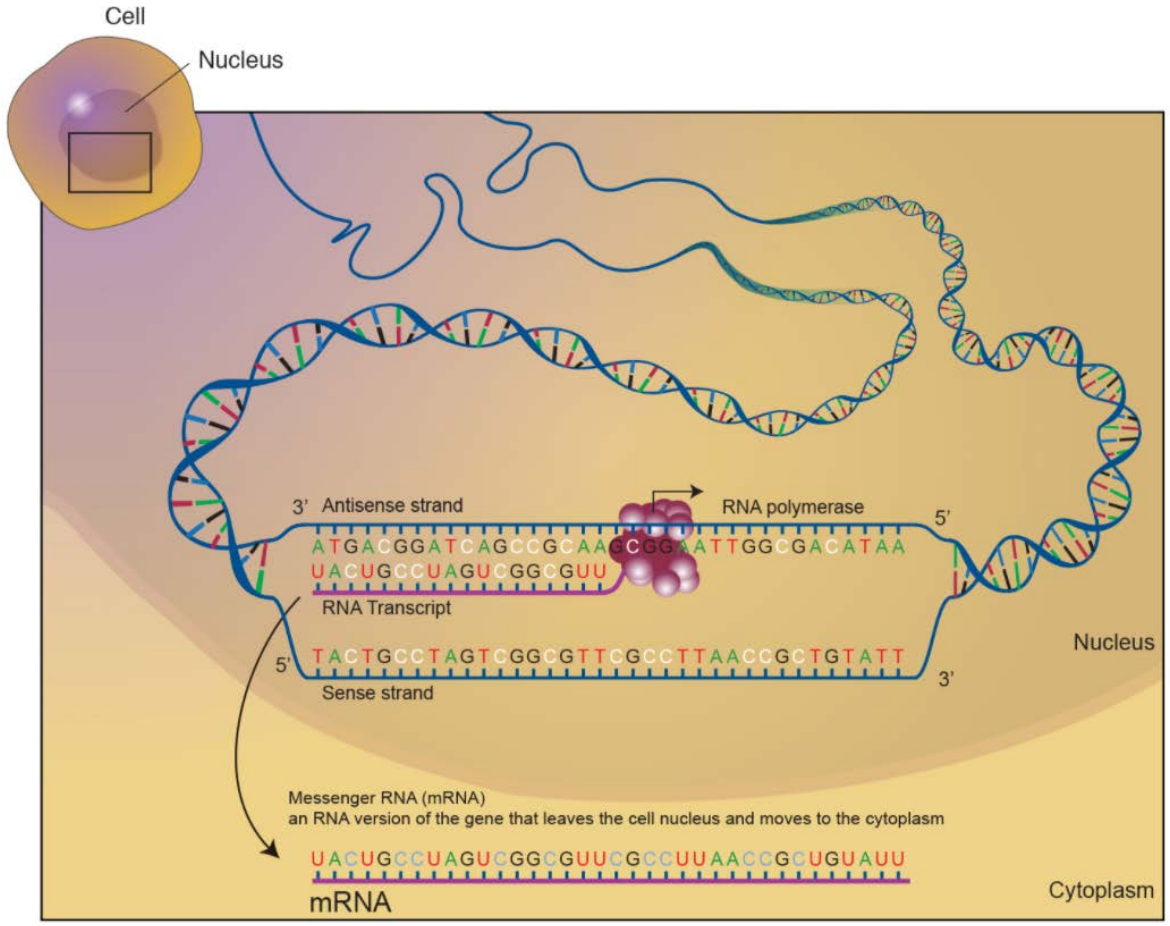


Zhang C, et al. Front Immuno. 2019:10:594.

Maruggi g, et al. 2019:27(4):757-772.

mRNA

- Messenger RNA
- Single stranded molecule of complementary DNA strand
- Intermediate molecule in protein translation
- Carries code from DNA to ribosomes

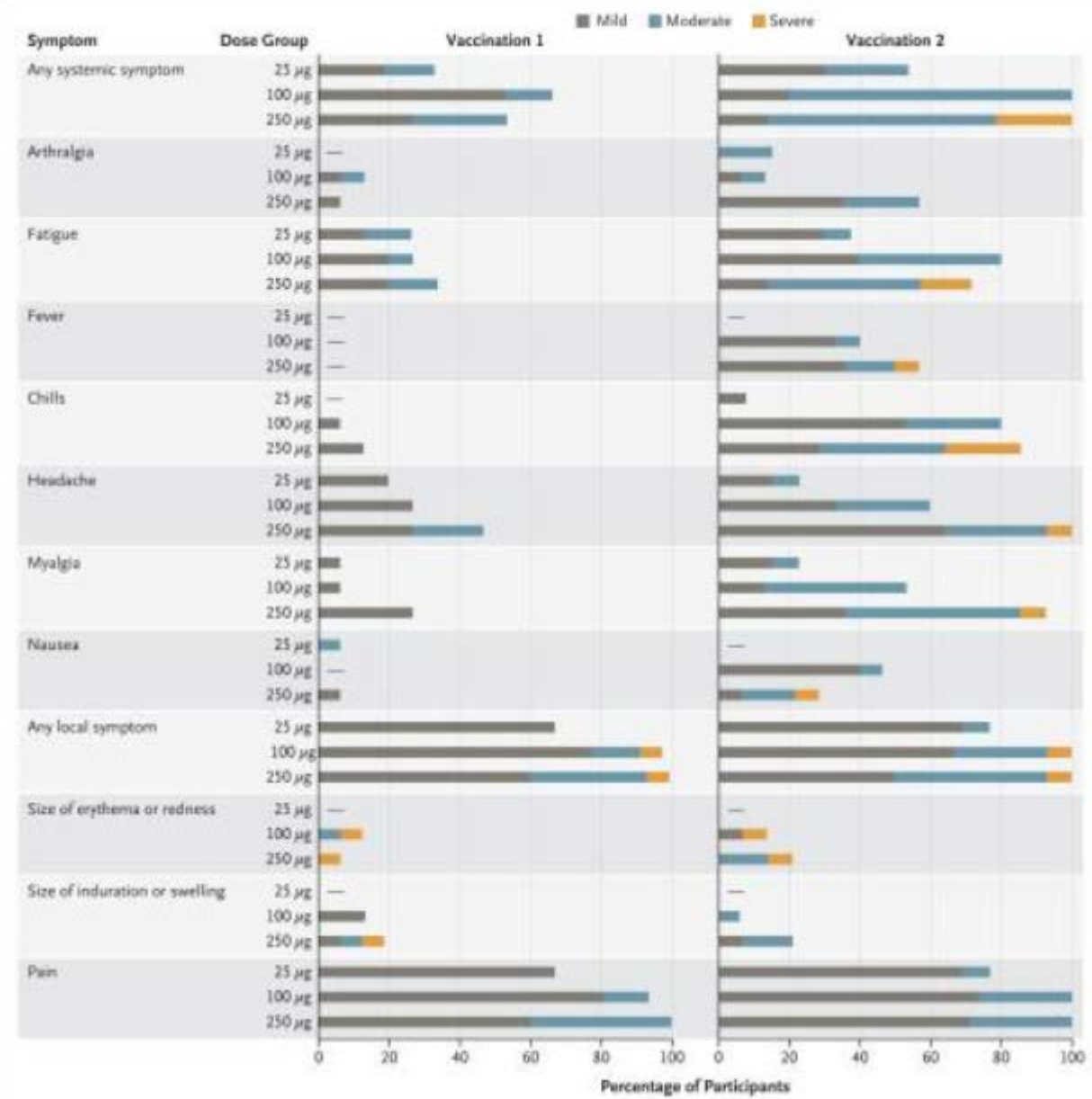


www.genome.gov

mRNA-1273 (Moderna)

- COVE Phase 3 study
  - Enrolled 30,000 patients
  - 25,654 patients received second dose
- Moderna reported on November 16, 2020 they met primary endpoint of vaccine efficacy for symptomatic COVID-19 infection of 94.5%
- This data has not been released so it can not be evaluated

https://www.modernatx.com/cove-study



https://www.modernatx.com/cove-study

Vaccine Production During a Pandemic

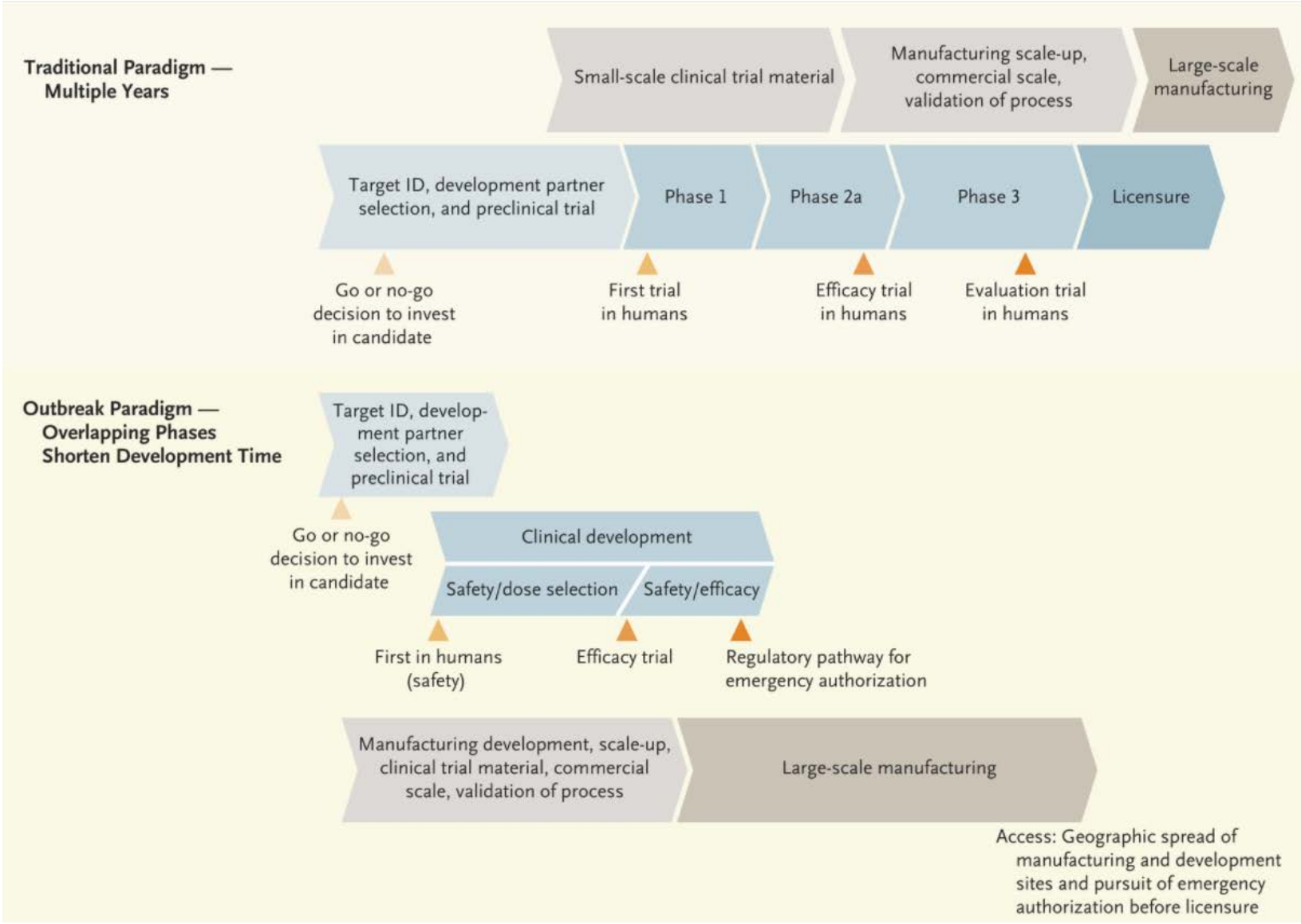
The NEW ENGLAND JOURNAL of MEDICINE

Perspective

MAY 21, 2020

Developing Covid-19 Vaccines at Pandemic Speed

Nicole Lurie, M.D., M.S.P.H., Melanie Saville, M.D., Richard Hatchett, M.D., and Jane Halton, A.O., P.S.M.



Lurie N, et. al. N Engl J Med. 2020;382:1969 - 1973

Questions?