

## **Neutralizing Antibodies for Pre-exposure and Post-exposure Prophylaxis**

*Section last reviewed and updated 12/23/2021*

*Last literature search conducted 11/30/2021*

### **Resources:**

- [CDC: SARS-CoV-2 variants](#)
- [FDA: Qualifications for SARS-CoV-2 exposure](#)
- [FDA: EUA for Evusheld™ \(tixagevimab co-packaged with cilgavimab\)](#)
- [NIH: National Center for Advancing Translational Science](#)

**Recommendation 1 (NEW):** In moderately or severely immunocompromised individuals\* at increased risk for inadequate immune response to COVID-19 vaccine or for whom COVID-19 vaccine is not recommended due to a documented serious adverse reaction to the vaccine, the IDSA guideline panel suggests pre-exposure prophylaxis with tixagevimab/cilgavimab rather than no tixagevimab/cilgavimab. (Conditional recommendation, Low certainty of evidence)

### **Remarks:**

- Dosing for tixagevimab/cilgavimab is 150 mg of tixagevimab & 150 mg of cilgavimab administered as two separate consecutive intramuscular injections once.
- Local SARS-CoV-2 variant susceptibility should be considered.

\*See [Figure 1](#) below

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**Figure 1.** FDA EUA criteria for the use of tixagevimab/cilgavimab for pre-exposure prophylaxis of COVID-19 in moderately or severely immunocompromised patients<sup>1</sup>

According to the FDA Emergency Use Authorization of Evusheld, medical conditions or treatments that may result in moderate to severe immune compromise include but are not limited to:

- Active treatment for solid tumor and hematologic malignancies
- Receipt of solid-organ transplant and taking immunosuppressive therapy
- Receipt of chimeric antigen receptor (CAR)-T-cell or hematopoietic stem cell transplant (within 2 years of transplantation or taking immunosuppression therapy)
- Moderate or severe primary immunodeficiency (e.g., DiGeorge syndrome, Wiskott-Aldrich syndrome)
- Advanced or untreated HIV infection (people with HIV and CD4 cell counts <200mm<sup>3</sup>, history of an AIDS-defining illness without immune reconstitution, or clinical manifestations of symptomatic HIV)
- Active treatment with high-dose corticosteroids (i.e., ≥20 mg prednisone or equivalent per day when administered for ≥2 weeks), alkylating agents, antimetabolites, transplant-related immunosuppressive drugs, cancer chemotherapeutic agents classified as severely immunosuppressive, tumor-necrosis (TNF) blockers, and other biologic agents that are immunosuppressive or immunomodulatory (e.g., B-cell depleting agents)

#### Reference

1. U.S. Food and Drug Administration. Fact Sheet for Healthcare Providers: Emergency Use Authorization of Evusheld™. Available at: <https://www.fda.gov/media/154701/download>. Accessed 22 December 2021.

**Figure 2.** FDA EUA criteria for the use of tixagevimab/cilgavimab for pre-exposure prophylaxis of COVID-19<sup>1</sup>

This EUA for the use of the unapproved products tixagevimab and cilgavimab for pre-exposure prophylaxis in adults and pediatric individuals (12 years of age and older weighing at least 40 kg) who are:

- Not currently infected with SARS-CoV-2 and who have not had a known recent exposure to an individual infected with SARS-CoV-2 **AND**:
  - have moderate to severe immune compromise due to a medical condition **OR** receipt of immunosuppressive medications or treatments **AND** may not mount an adequate immune response to COVID-19 vaccination **OR**
  - For whom vaccination with any available COVID-19 vaccine, according to the approved or authorized schedule, is not recommended due to a history of severe adverse reaction (e.g., severe allergic reaction) to a COVID-19 vaccine(s) and/or a COVID-19 vaccine component(s).

#### Reference

1. U.S. Food and Drug Administration. Fact Sheet for Healthcare Providers: Emergency Use Authorization of Evusheld™. Available at: <https://www.fda.gov/media/154701/download>. Accessed 22 December 2021.

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**Recommendation 2: In persons exposed to COVID-19 who are at high risk of progression to severe COVID-19, the IDSA guideline panel suggests post-exposure casirivimab/imdevimab rather than no casirivimab/imdevimab. (Conditional recommendation, Low certainty of evidence)**

#### **Remarks:**

- Dosing for casirivimab/imdevimab is casirivimab 600 mg & imdevimab 600 mg IV or SC once.
- In the trial considered for this recommendation, participants were enrolled within 96 hours after a household contact received a diagnosis of SARS-CoV-2 infection.
- Local SARS-CoV-2 variant susceptibility should be considered.

**Figure 3.** FDA EUA criteria for the use of casirivimab/imdevimab for post-exposure prophylaxis of COVID-19<sup>1</sup>

**This EUA is for the use of the unapproved products casirivimab and imdevimab for post-exposure prophylaxis of COVID-19 in adult and pediatric individuals (12 years of age and older weighing at least 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 (e.g., 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 criteria **OR**
  - Who are at high risk of exposure to an individual infected with SARS-CoV-2 because of occurrence of SARS-CoV-2 infection in other individuals in the same institutional setting (e.g., nursing homes, prisons).

#### **Reference**

1. U.S. Food and Drug Administration. Fact Sheet for Health Care Providers: Emergency Use Authorization (EUA) of Regen-CoV™ (casirivimab with imdevimab). Available at: <https://www.fda.gov/media/145611/download>. Accessed 9 April 2021.

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#### ***Why are neutralizing antibodies considered for prophylaxis?***

Neutralizing antibodies directed at the receptor-binding domain of SARS-CoV-2 spike protein have been evaluated as prophylactic agents for COVID-19. In animal models there is evidence that antibody therapy may more rapidly reduce viral load in the upper and lower airways of infected animals resulting in reduced viral-induced pathology, demonstrating in vivo prophylactic and treatment efficacy [1, 2]. Additionally, antibody mediated enhancement of disease has not been detected in animal models [2] but this potential phenomenon should be closely monitored in the future studies. In a large, randomized study of unvaccinated nursing home patients and staff where there was at least one confirmed case of COVID-19 at the facility, a single dose of either bamlanivimab appeared to significantly reduce the incidence of “mild or worse” COVID-19 amongst the nursing home residents [3].

Potential advantages of neutralizing antibodies include the ability to standardize the amount of neutralizing activity and the possibility of conferring protection more rapidly than with vaccine-induced immune responses (which generally take several weeks).

#### ***Summary of the evidence***

##### Tixagevimab/cilgavimab

Our search identified one RCT reporting on pre-exposure prophylaxis (PrEP) with a single dose of intramuscular tixagevimab/cilgavimab administration in adults  $\geq 18$  years of age who are at increased risk of inadequate response to COVID-19 vaccination or SARS-CoV-2 infection [4, 5]. Patients included were those that were either age  $\geq 60$  years, immunocompromised, had severe renal or liver impairment, COPD, or those who had an increased risk of exposure including those working in healthcare or living in congregate living settings. All participants had a negative SARS-CoV-2 serology test result at screening, had no history of SARS-CoV-2 infection, and had not received vaccine or biologic indicated for prevention of SARS-CoV-2 or COVID-19. Study participants received a single combined 300 mg intramuscular dose of the combination of tixagevimab (150 mg) /cilgavimab (150 mg).

##### Casirivimab/imdevimab

Our search identified one RCT reporting on post-exposure prophylaxis (PEP) with neutralizing antibodies (combination of casirivimab/imdevimab) for patients exposed to COVID-19 who are at high risk of progression to severe disease [6] ([Table 2](#)).

One RCT reported on 1,505 persons testing negative for SARS-CoV-2 infection (by reverse-transcriptase-quantitative polymerase-chain-reaction assay [RT-qPCR]) within 96 hours following household contact with a diagnosis of SARS-CoV-2 infection [6]. Of those included in the trial, 30.5% participants were categorized as having a high risk of COVID-19 (e.g.,  $\geq 65$  years of age, body mass index [BMI]  $\geq 35$ , chronic kidney disease, etc.). Participants in the treatment group received a total dose of 1200 mg of casirivimab/imdevimab subcutaneously.

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#### **Benefits**

##### Tixagevimab/cilgavimab

PrEP with tixagevimab/cilgavimab appears to have little or no effect on mortality through a median of 6 months (RR: 0.50; 95% CI: 0.13, 2.0; absolute risk reduction: 1 fewer per 1,000 [from 2 fewer to 2 more]; moderate CoE). Symptomatic COVID-19 infection within six months after administration was reduced in those who received tixagevimab/cilgavimab compared to placebo (RR: 0.18; 95% CI: 0.09, 0.35; moderate CoE).

##### Casirivimab/imdevimab

Persons receiving PEP with casirivimab/imdevimab demonstrated an 81% relative risk reduction in development of symptomatic SARS-CoV-2 infection (RR: 0.19; 95% CI: 0.10, 0.35; moderate CoE). Of the 70 persons who developed symptomatic infection, those who received casirivimab/imdevimab rather than placebo experienced a shorter duration of symptoms (mean difference [MD]: -2.0 weeks; 95% CI: -2.91, -1.09; low CoE).

#### **Harms**

##### Tixagevimab/cilgavimab

Serious adverse events were not meaningfully different in those that received PrEP with tixagevimab/cilgavimab compared to placebo (RR: 1.09; 95% CI: 0.67, 1.78; moderate CoE).

##### Casirivimab/imdevimab

Serious treatment-emergent adverse events may be less frequent among persons receiving casirivimab/imdevimab compared to those receiving placebo; however, this may not be meaningfully different from those receiving placebo (RR: 0.66; 95% CI: 0.30, 1.47; low CoE).

#### **Other considerations**

##### Tixagevimab/cilgavimab

The panel agreed that the overall certainty of evidence for PrEP with tixagevimab/cilgavimab was low due to concerns with the generalizability of the trial population to the FDA-authorized indications (e.g., immunocompromised persons) and low number of events (fragility of results). The panel noted concerns with feasibility at different centers given the large number of potentially eligible individuals and supply constraints.

##### Casirivimab/imdevimab

The panel agreed that the overall certainty of evidence for post-exposure prophylaxis with casirivimab/imdevimab was low due to low number of events (fragility of results). The panel notes some indirectness between the trial participants (30.5% with any high-risk factor for COVID) and the current approved indications for post-exposure prophylaxis within the EUA.

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#### ***Conclusions and research needs for this recommendation***

##### Tixagevimab/cilgavimab

The guideline panel suggests PrEP with tixagevimab/cilgavimab in moderately or severely immunocompromised individuals at increased risk for inadequate immune response to COVID-19 vaccine or for whom COVID-19 vaccine is not recommended due to documented severe reactions to the COVID-19 vaccine. Data on the efficacy of pre-exposure prophylaxis specifically in immunocompromised individuals who have received COVID-19 vaccines are needed.

##### Casirivimab/imdevimab

The guideline panel suggests PEP using casirivimab/imdevimab in persons exposed to COVID-19, who are at high risk of progression.

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**Table 1.** GRADE evidence profile, Recommendation 1

**Question:** Tixagevimab/cilgavimab compared to no tixagevimab/cilgavimab for pre-exposure prophylaxis in adults at increased risk for inadequate immune response to COVID-19 vaccine or for whom COVID-19 vaccine is not recommended

*New evidence profile developed 12/23/2021*

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	tixagevimab/cilgavimab	no tixagevimab/cilgavimab	Relative (95% CI)	Absolute (95% CI)		
<b>All-cause mortality (follow-up: median 6 months)</b>												
1 <sup>1,2</sup>	randomized trials	not serious <sup>a</sup>	not serious	serious <sup>b,c</sup>	serious <sup>d</sup>	none	4/3461 (0.1%)	4/1736 (0.2%)	<b>RR 0.50</b> (0.13 to 2.00)	<b>1 fewer per 1,000</b> (from 2 fewer to 2 more)	⊕⊕○○ LOW	CRITICAL
<b>Symptomatic COVID-19 (follow-up: median 6 months; assessed with: RT-PCR-positive symptomatic illness)</b>												
1 <sup>1,2</sup>	randomized trials	not serious	not serious	serious <sup>c</sup>	serious <sup>d</sup>	none	11/3441 (0.3%)	31/1731 (1.8%)	<b>HR 0.17</b> (0.08 to 0.33)	<b>15 fewer per 1,000</b> (from 16 fewer to 12 fewer)	⊕⊕○○ LOW	CRITICAL
<b>Serious adverse events (follow-up: median 83 days)</b>												
1 <sup>1,2</sup>	randomized trials	not serious	not serious	serious <sup>c</sup>	serious <sup>d</sup>	none	50/3461 (1.4%)	23/1736 (1.3%)	<b>RR 1.09</b> (0.67 to 1.78)	<b>1 more per 1,000</b> (from 4 fewer to 10 more)	⊕⊕○○ LOW	CRITICAL
<b>GRADE Working Group grades of evidence</b>												
<p><b>High certainty:</b> We are very confident that the true effect lies close to that of the estimate of the effect</p> <p><b>Moderate certainty:</b> We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different</p> <p><b>Low certainty:</b> Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect</p> <p><b>Very low certainty:</b> We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect</p>												
<p><b>Risk of bias:</b> Study limitations</p> <p><b>Inconsistency:</b> Unexplained heterogeneity across study findings</p> <p><b>Indirectness:</b> Applicability or generalizability to the research question</p> <p><b>Imprecision:</b> The confidence in the estimate of an effect to support a particular decision</p> <p><b>Publication bias:</b> Selective publication of studies</p>												

*NB: Certainty ratings may be derived from evidence that includes pre-print articles, which have not been peer reviewed or published.*

**CI:** Confidence interval; **HR:** Hazard ratio; **RR:** Risk ratio

**Explanations**

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- a. Possible misclassification bias due to unequal rate of drop-outs after unblinding.
- b. 2 deaths in the control arm were attributed to COVID-19.
- c. Trial population indirect to the population indicated within the FDA EUA (e.g., immunocompromised).
- d. Small number of events; fragility present.

#### **References**

1. U.S. Food and Drug Administration. FACT SHEET FOR HEALTHCARE PROVIDERS: EMERGENCY USE AUTHORIZATION FOR EVUSHELD™ (tixagevimab co-packaged with cilgavimab). Available at: <https://www.fda.gov/media/154701/download>. Accessed 22 December 2021.
2. Levin M, Ustianowski A, De Wit S, et al. Intramuscular AZD7442 (tixagevimab/cilgavimab) for prevention of COVID-19. **2021**: [Under review].



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**Table 2.** GRADE evidence profile, Recommendation 2

**Question:** Prophylactic casirivimab/imdevimab compared to no prophylactic casirivimab/imdevimab for persons exposed to COVID-19 at high risk for progression to severe disease  
*Developed 8/17/2021; last reviewed 9/19/2021*

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	prophylactic casirivimab/imdevimab	no prophylactic casirivimab/imdevimab	Relative (95% CI)	Absolute (95% CI)		
<b>Symptomatic SARS-CoV-2 infection (1200 mg SC) (follow-up: 28 days; assessed with: RT-qPCR plus broad-term definition)</b>												
1 <sup>1</sup>	randomized trials	not serious	not serious	not serious	serious <sup>a</sup>	none	11/753 (1.5%)	59/752 (7.8%)	<b>RR 0.19</b> (0.10 to 0.35)	<b>64 fewer per 1,000</b> (from 71 fewer to 51 fewer)	⊕⊕⊕○ MODERATE	CRITICAL
<b>Duration of symptomatic infection (1200 mg SC)</b>												
1 <sup>1</sup>	randomized trials	not serious	not serious	not serious	very serious <sup>a</sup>	none	11	59	-	<b>MD 2 weeks fewer</b> (2.91 fewer to 1.09 fewer)	⊕⊕○○ LOW	CRITICAL
<b>COVID-19 related hospitalizations or ER visits (1200 mg SC) (follow-up: 28 days)</b>												
1 <sup>1</sup>	randomized trials	not serious	not serious	not serious <sup>b</sup>	very serious <sup>a,c</sup>	none	0/753 (0.0%)	4/752 (0.5%)	<b>RR 0.11</b> (0.01 to 2.06)	<b>5 fewer per 1,000</b> (from 5 fewer to 6 more)	⊕⊕○○ LOW	CRITICAL
<b>Serious treatment-emergent adverse events (1200 mg SC) (follow-up: 28 days)</b>												
1 <sup>1</sup>	randomized trials	not serious	not serious	serious <sup>d</sup>	serious <sup>a,c</sup>	none	10/1311 (0.8%)	15/1306 (1.1%)	<b>RR 0.66</b> (0.30 to 1.47)	<b>4 fewer per 1,000</b> (from 8 fewer to 5 more)	⊕⊕○○ LOW	CRITICAL
<b>GRADE Working Group grades of evidence</b>												
<p><b>High certainty:</b> We are very confident that the true effect lies close to that of the estimate of the effect</p> <p><b>Moderate certainty:</b> We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different</p> <p><b>Low certainty:</b> Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect</p> <p><b>Very low certainty:</b> We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect</p>												
<p><b>Risk of bias:</b> Study limitations</p> <p><b>Inconsistency:</b> Unexplained heterogeneity across study findings</p> <p><b>Indirectness:</b> Applicability or generalizability to the research question</p> <p><b>Imprecision:</b> The confidence in the estimate of an effect to support a particular decision</p> <p><b>Publication bias:</b> Selective publication of studies</p>												

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*NB: Certainty ratings may be derived from evidence that includes pre-print articles, which have not been peer reviewed or published.*

**CI:** Confidence interval; **MD:** Mean difference; **RR:** Risk ratio

#### **Explanations**

- a. Small number of events; fragility present
- b. COVID-19 related hospitalizations is a surrogate for ICU admission, mechanical ventilation and death. Not rated down.
- c. 95% CI cannot exclude meaningful harm
- d. Serious treatment emergent adverse events reported for entire study population (including symptomatic and asymptomatic) and may not be generalizable to seronegative population.

#### **Reference**

1. O'Brien MP, Forleo-Neto E, Musser BJ, et al. Subcutaneous REGEN-COV Antibody Combination to Prevent Covid-19. *N Engl J Med* **2021**; 385: 1184-95.

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#### **References**

1. Jones BE, Brown-Augsburger PL, Corbett KS, et al. LY-CoV555, a rapidly isolated potent neutralizing antibody, provides protection in a non-human primate model of SARS-CoV-2 infection. *bioRxiv* **2020**: Available at: <https://doi.org/10.1101/2020.09.30.318972> [Preprint 9 October 2020].
2. Baum A, Ajithdoss D, Copin R, et al. REGN-COV2 antibodies prevent and treat SARS-CoV-2 infection in rhesus macaques and hamsters. *Science* **2020**; 370(6520): 1110-5.
3. Cohen MS, Nirula A, Mulligan MJ, et al. Effect of Bamlanivimab vs Placebo on Incidence of COVID-19 Among Residents and Staff of Skilled Nursing and Assisted Living Facilities: A Randomized Clinical Trial. *JAMA* **2021**; 326(1): 46-55.
4. U.S. Food and Drug Administration. FACT SHEET FOR HEALTHCARE PROVIDERS: EMERGENCY USE AUTHORIZATION FOR EVUSHELD™ (tixagevimab co-packaged with cilgavimab). Available at: <https://www.fda.gov/media/154701/download>. Accessed 22 December 2021.
5. Levin M, Ustianowski A, De Wit S, et al. Intramuscular AZD7442 (tixagevimab/cilgavimab) for prevention of COVID-19. **2021**: [Under review].
6. O'Brien MP, Forleo-Neto E, Musser BJ, et al. Subcutaneous REGEN-COV Antibody Combination to Prevent Covid-19. *N Engl J Med* **2021**; 385: 1184-95.

## **Supplementary Materials**

### **Study characteristics**

- **Table s1.** Pre-exposure prophylactic tixagevimab/cilgavimab vs. no tixagevimab/cilgavimab in adults at risk for inadequate immune response to COVID-19 vaccine or for whom COVID-19 vaccine is not recommended
- **Table s2.** Post-exposure prophylactic casirivimab/imdevimab vs. no casirivimab/imdevimab for persons exposed to COVID-19 at high risk of progression to severe disease

### **Risk of bias**

- **Table s3.** Randomized controlled studies, pre-exposure prophylaxis (tixagevimab/cilgavimab vs. no tixagevimab/cilgavimab)
- **Table s4.** Randomized controlled studies, post-exposure prophylaxis (casirivimab/imdevimab vs. no casirivimab/imdevimab)

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**Table s1.** Should tixagevimab/cilgavimab vs. no tixagevimab/cilgavimab be used for pre-exposure prophylaxis in adults at risk for inadequate immune response to COVID-19 vaccine or for whom COVID-19 vaccine is not recommended?

Study/ year	Country/ hospital	Study design	N subjects (intervention /comparator)	% female	Age mean (SD)/ median (IQR)	Severity of disease	Intervention (study arms)	Comparator	Co- interventions	Outcomes reported	Funding source
Levin/2021 <sup>1</sup>	87 sites in Belgium, France, Spain, UK and US	RCT	5197 (3461/1736)	46.1	53.5 (15.0)	Adult patients at increased risk for inadequate COVID-19 vaccine response or increased risk of SARS-CoV-2 infection with negative SARS-CoV-2 serology	Tixagevimab/cilgavimab 300 mg x 1 dose	Placebo	None	Mortality  PCR positive symptomatic illness occurring post dose through day 183  Serious adverse events	AstraZeneca  US Department of Health and Human Services  US Biomedical Research and Development Authority

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**Table s2.** Should persons exposed to COVID-19 who are at high risk of progression to severe disease receive post-exposure casirivimab/imdevimab vs. no casirivimab/imdevimab?

Study/year	Country/Hospital	Study design	N subjects (intervention/comparator)	% female	Age mean (SD) / Median (IQR)	Severity of disease	Intervention (study arms)	Comparator	Co-interventions	Outcomes reported	Funding source
O'Brien/2021 <sup>2</sup> Part A	United States (110 sites) Romania (1 site) Moldova (1 site)	RCT	1505 (753/752)	54.1	Mean: 42.9 (range of 12-92)	Previously and currently uninfected (RT-PCR negative) household contacts of persons with SARS CoV-2 infection	REGEN-COV 1200 mg (casirivimab 600 mg /imdevimab 600 mg) x 1 subcutaneous injection	Placebo	None	Symptomatic RT-PCR confirmed SARS-CoV-2 infection within 28 days  Symptomatic and asymptomatic RT-PCR confirmed infection within 28 days  Number of weeks of symptoms present  Number of weeks of high viral load  COVID-19 related hospitalization or ER visit  Safety	Regeneron Pharmaceuticals  F. Hoffman-La Roche  COVID-19 Prevention Network grant, which is funded by cooperative awards from National Institute of Allergy and Infectious Diseases and National Institutes of Health
O'Brien/2021 <sup>3</sup> Part B	United States (110 sites) Romania (1 site) Moldova (1 site)	RCT	314 (155/156)	55	Mean: 40.9 (18)	RT-PCR positive for SARS CoV-2 and asymptomatic	REGEN-COV 1200 mg (casirivimab 600 mg /imdevimab 600 mg) x 1 subcutaneous injection	Placebo	None	Proportion of patients who developed signs and symptoms of COVID-19 within 14 days of positive RT-PCR  Number of weeks of symptomatic	Regeneron Pharmaceuticals  F. Hoffman-La Roche  COVID-19 Prevention Network grant, which is funded

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Study/ year	Country/ Hospital	Study design	N subjects (intervention/ comparator)	% female	Age mean (SD) / Median (IQR)	Severity of disease	Intervention (study arms)	Comparator	Co- interventions	Outcomes reported	Funding source
										SARS CoV-2 infection  Number of weeks of high viral load over 28 days  COVID-19 related hospitalization or ER visit  Safety	by cooperative awards from National Institute of Allergy and Infectious Diseases and National Institutes of Health

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**Table s3.** Risk of bias for randomized controlled studies (pre-exposure tixagevimab/cilgavimab vs. no tixagevimab/cilgavimab in adults at risk for inadequate immune response to COVID-19 vaccine or for whom COVID-19 vaccine is not recommended)

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Levin 2021 <sup>1</sup>							

Low	High	Unclear
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**Table s4.** Risk of bias for randomized controlled studies (post-exposure casirivimab/imdevimab vs. no casirivimab/imdevimab for persons exposed to COVID-19 at risk of progression to severe disease)

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
O'Brien 2021 (Part A) <sup>2</sup>							
O'Brien 2021 (Part B) <sup>3</sup>							

Low	High	Unclear
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#### **References for Supplementary Materials**

1. Levin M, Ustianowski A, De Wit S, et al. Intramuscular AZD7442 (tixagevimab/cilgavimab) for prevention of COVID-19. **2021**: [Under review].
2. O'Brien MP, Forleo-Neto E, Musser BJ, et al. Subcutaneous REGEN-COV Antibody Combination to Prevent Covid-19. *N Engl J Med* 2021; 385: 1184-95
3. O'Brien MP, Eduardo Forleo-Nato, Sarkar N, et al. Subcutaneous REGEN-COV antibody combination in early SARS-CoV-2 infection. medRxiv **2021**. Available at: <https://doi.org/10.1101/2021.06.14.21258569> [Preprint 14 June 2021].