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Figure 1. FDA Emergency Use Authorization (EUA) criteria for the use of pemivibart for pre-exposure prophylaxis of COVID-19 in moderately or severely immunocompromised patients [pemivibart EUA]

According to the FDA Emergency Use Authorization of pemivibart, 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
- Hematologic malignancies associated with poor responses to COVID-19 vaccines regardless of current treatment status (e.g., chronic lymphocytic leukemia, non-Hodgkin lymphoma, multiple myeloma, acute leukemia)
- Receipt of solid-organ transplant or an islet 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 immunosuppressive therapy)
- Moderate or severe primary immunodeficiency (e.g., common variable immunodeficiency disease, severe combined immunodeficiency, DiGeorge syndrome, Wiskott-Aldrich syndrome)
- Advanced or untreated HIV infection (people with HIV and CD4 cell counts <200/mm3, 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, and biologic agents that are immunosuppressive or immunomodulatory (e.g., B-cell depleting agents)

Figure 2. FDA EUA criteria for the use of pemivibart for pre-exposure prophylaxis of COVID-19 [pemivibart EUA]

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

- 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
- Who have moderate-to-severe immune compromise due to a medical condition or receipt of immunosuppressive medications or treatments and are unlikely to mount an adequate response to COVID-19 vaccination.

Table 1. Broad categorization of example immunocompromised status based on medical condition or immunosuppressive treatment. Thresholds by which this categorization has been determined have been derived from cohort studies beginning in the Omicron era of COVID-19; however, this may not be representative of currently evolving variants.

The risk of progression to severe COVID-19 is a continuum influenced by various factors, including the degree of immunosuppression. The categorization of risk and the examples provided in the table below are illustrative, based on a few studies, and are not exhaustive or a thorough list of all conditions [Evans 2023, Solera 2024].

Risk category	Example health condition	Example therapeutics
Higher risk immunocompromised patients	• Stem cell transplant <2 years • Graft versus host disease, grade 3 or 4 • Hematological malignancy on therapy • Lung transplant • Fewer than 1% peripheral B-cells assessed in past 6 months	• B-cell depleting agents in past 12 months (e.g., rituximab, ofatumumab, ocrelizumab, others) • CAR-T therapy in past 12 months • Abatacept
Moderate risk immunocompromised patients	• Solid organ transplant other than lung • Solid tumor on treatment • Congenital agammaglobulinemia • Graft versus host disease, grade 1 or 2 • HIV infection with CD4 <200 • Other severe primary immunodeficiency	• Tyrosine kinase inhibitor (e.g., ibrutinib, acalabrutinib, others) • High-dose corticosteroids (>20 mg prednisone or equivalent for >4 weeks) • Anthracycline derivates
Lower risk immunocompromised patients	• HIV infection with CD4 >200 • Inflammatory bowel disease • Cirrhosis • ESRD • Solid tumor (treatment >12 month prior)	• Anti-TNF • Anti-IL-6 • Anti-IL12 and 23 • Corticosteroids ≤10 mg long-term, or <20 mg for <4 weeks • Intra-articular steroids

Table 2. GRADE Evidence Profile: In moderately or severely immunocompromised persons 12 years or older, should pemivibart compared to no pemivibart be used for pre-exposure prophylaxis?

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pemivibart	No pemivibart	Relative (95% CI)	Absolute (95% CI)		
All-cause mortality												
No data												
Symptomatic infections (as inferred by immunobridging neutralization study of pemivibart 4,500 mg IV based on titers against JN.1 at day 28)												
1[CANOPY, pemivibart EUA]	non-randomised studies	serious[a]	not serious	serious[b]	not serious	none	Immunobridging is established if the lower limit of the 2-sided 90% CI of the ratio of the geometric mean titer value is greater than 0.8. Results: the geometric mean ratio between the calculated titer for pemivibart against JN.1 (based on an authentic virus neutralization assay EC50 value of 63.6 ng/mL) and the calculated titer for adintrevimab against Delta (based on a similar authentic virus neutralization assay EC50 value of 7 ng/mL) was 0.82 (90% CI: 0.80-0.85). The authors conclude that the calculated pemivibart serum neutralizing antibody titers were consistent with the titer levels associated with efficacy in prior clinical trials of adintrevimab and certain other monoclonal antibody products previously authorized for the prevention of COVID-19.				⨁◯◯◯Very low	IMPORTANT
Symptomatic infections (as inferred by indirect evidence from adintrevimab 300 mg PrEP cohort) (follow-up: 3 months)[c]												
1[Ison 2023]	randomised trial	not serious	not serious	serious[d]	serious[e]	none	12/752 (1.6%)	40/728 (5.5%)	**RR 0.29** (0.15 to 0.55)	**39 fewer per 1,000** (from 47 fewer to	⨁⨁◯◯ Low	CRITICAL

										25 fewer)		

Anaphylaxis

1[CANOPY, pemivibart EUA]	non-randomised studies	not serious	not serious	not serious	not serious	none	4/623 (0.6%)	0/162 (0.0%)	not estimable	**6 more per 1,000** (from 0 more to 12 more)[f]	⨁⨁◯◯ Low	CRITICAL

CI: confidence interval; **RR:** risk ratio

Explanations

a. No control group comparison (see Supplementary Table 2)

b. Not based on patient-important outcomes. Neutralizing activity only.

c. Adintrevimab is the ancestral neutralizing antibody which is no longer active against circulating virus but was used to create pemivibart

d. Several layers of indirectness are present: 1) Indirect data from parent monoclonal antibody against SARS CoV-2 variant that is no longer in circulation; 2) indirectness whether JN.1 will be susceptible to pemivibart to the same degree, i.e. uncertainty of remaining effect estimate at currently circulating variants; 3) uncertainty of baseline risk: over time, the proportion of symptomatic infections have declined and whether the historical 5.5% symptomatic infection rate seen with adintrevimab (enrollment in 2021) within 3 months is still applicable is unknown. With declining baseline risk for symptomatic infections, the absolute risk difference of downstream patient important outcomes (hospital admission, severe COVID etc.) resulting from pemivibart declines as well and may become less clinically relevant over time.

e. Fragility present; low number of events

f. Anaphylaxis was observed in 4/263 (0.6%) participants receiving pemivibart, 2 of which were described as life-threatening.