Emergency Use Authorization (EUA) for PEMGARDA
Center for Drug Evaluation and Research (CDER) Review Memorandum

Identifying Information

Application Type (EUA or Pre-EUA)	EUA
EUA Application Number(s)	000122
Date of Memorandum	September 25, 2024
Sponsor (entity requesting EUA or pre-EUA consideration), point of contact, address, phone number, fax number, email address	Invivyd, Inc. Timothy Kachmar, MS, Regulatory Affairs 1601 Trapelo Road, Suite 178 Waltham, MA 02451 P: (b) (6) F: (b) (6) (b) (6)
Manufacturer	Invivyd, Inc.
Original Authorization	March 22, 2024
OND Division / Office	Division of Antivirals (DAV)/Office of Infectious Diseases (OID)
Reviewer Name(s)/ Discipline(s)	Sarita Boyd, Clinical Reviewer Kimberly Struble, Clinical Team Lead Will Ince, Clinical Virology Reviewer Jules O'Rear, Clinical Virology Team Lead Su-Young Choi, Clinical Pharmacology Team Lead Yodit Belew, Associate Director for Therapeutic Review Wendy Carter, Division Director (Acting), DAV Adam Sherwat, Deputy Office Director, OID John Farley, Office Director, OID
Proprietary Name	Pemgarda
Established Name/Other names used during development	Pemivibart (VYD222)
Dosage Forms/Strengths	Injection: 500 mg/4 mL (125 mg/mL)
Therapeutic Class	SARS-CoV-2 spike protein-directed human IgG1λ monoclonal antibody (mAb)
Intended Use or Need for EUA	Pre-exposure prophylaxis of coronavirus disease 2019 (COVID-19)
Intended Population(s)	Adults and adolescents (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** • 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.

Background on Regulatory History

PEMGARDA (pemivibart) is a recombinant human monoclonal IgG1λ antibody that targets the SARS-CoV-2 spike protein receptor binding domain (RBD). PEMGARDA received Emergency Use Authorization on March 22, 2024 for pre-exposure prophylaxis of COVID-19 in adults and adolescents (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 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 (see EUA122 Summary Review [March 22, 2024]).

Rationale for Revisions to EUA and Fact Sheets

The PEMGARDA EUA Fact Sheet for Healthcare Providers is being revised at this time to:

1. Include updated information on PEMGARDA pseudotyped lentivirus virus-like particle (VLP) neutralization activity data against recently circulating SARS-CoV-2 variant JN.1.50 and currently circulating SARS-CoV-2 variants KP.3.1.1 and LB.1.
2. Clarify the risk for COVID-19 due to SARS-CoV-2 viral variants with substantially reduced susceptibility to PEMGARDA.

The rationale for the revisions is as follows:

1. **To include updated information on PEMGARDA pseudotyped lentivirus VLP neutralization activity data against recently circulating SARS-CoV-2 variant JN.1.50 and currently circulating SARS-CoV-2 variants KP.3.1.1 and LB.1.**

   At the time of the March 22, 2024 Emergency Use Authorization, the dominant circulating SARS-CoV-2 variant in the U.S. was JN.1. Calculated serum neutralization titer values of the monoclonal antibody (mAb) pemivibart (active ingredient in PEMGARDA) against JN.1, derived from serum mAb concentrations divided by the neutralization EC_{50} value of the mAb in cell culture, were comparable to calculated titer values of previously evaluated mAbs associated with clinical efficacy for the pre-exposure prophylaxis of COVID-19 (see EUA122 Summary Review [August 23, 2024]). However, SARS-CoV-2 is continually evolving, and emerging subvariants are routinely monitored for their susceptibility to pemivibart in comparison to JN.1. At the time of this revision, the JN.1-lineage variants KP.3.1.1, KP.2.3, and LB.1 are the top 3 most abundant variants circulating in the U.S., comprising approximately 52.7%, 12.2%, and 10.9% of infections, respectively, based on the September 14, 2024 CDC Nowcast estimate.

   This revision to Section 12.4 (Microbiology) of the Fact Sheet for Healthcare Providers includes updated pemivibart neutralization EC_{50} values for currently and recently circulating SARS-CoV-2 variants determined in the Monogram Biosciences PhenoSense® Anti-SARS-CoV-2 Neutralizing Antibody Assay (Monogram Biosciences/LabCorp). This pseudotyped lentivirus VLP assay has served as the basis of the immunobridging approach for evaluating whether SARS-CoV-2 variants may be susceptible to pemivibart. Results for pemivibart neutralization activity against pseudotyped lentivirus VLPs representing currently circulating variants KP.3.1.1 (JN.1 + S31del, F456L, Q493E, V1104L) and LB.1 (JN.1 + S31del, Q183H, R346T, F456L), along with recently circulating variant JN.1.50 (JN.1 + A67V,

L249F, R346T, H445P, F456L) (substitutions relative to JN.1; RBD substitutions are underlined) are shown in Table 1 below. In the Monogram pseudotyped VLP assay, KP.3.1.1 and LB.1 exhibit EC_{50} values that are 3.2- to 2.4-fold higher than that of JN.1, respectively, indicating that pemivibart is likely to retain adequate neutralization activity against KP.3.1.1 and LB.1 based on this assay. KP.2.3 and other untested variants are likely to exhibit similar susceptibilities to pemivibart as tested variants that share the same RBD amino acid sequences and convergent S31 deletion in the Monogram pseudotyped VLP assay. JN.1.50 exhibits adequate susceptibility to pemivibart but is no longer circulating at a monitorable frequency in the U.S.

The determination of whether pemivibart may be active against emerging variants has been based on neutralization data obtained in the Monogram Biosciences PhenoSense® Anti-SARS-CoV-2 Neutralizing Antibody Assay (Huang et al., 2021). In this assay, neutralization activity of pemivibart is assessed against single-cycle spike-pseudotyped lentivirus VLPs in HEK293 cells expressing human ACE2 and TMPRSS2. EC_{50} values derived from this assay have been used for immunobridging, by comparing estimated pemivibart serum antibody titers (mAb concentration / EC_{50} value) against emerging variants to monoclonal antibody titers shown clinically to be effective against previous variants (EUA Summary Review [March 22, 2024]).

EC_{50} values and fold-changes from references for certain SARS-CoV-2 variants reported by other laboratories using pemivibart-like monoclonal antibodies (e.g., Wang et al., 2024 [preprint]; Planas et al., 2024 [preprint]) may differ from, and could be higher than, those measured in the Monogram Biosciences PhenoSense® Anti-SARS-CoV-2 Neutralizing Antibody Assay using pemivibart. Reported EC_{50} values from other sources may differ due to assay differences, including the specific pseudotyped VLP vector, use of live virus, target cell type, incubation times and temperatures, and other assay methodologies. The antibody tested by other labs may differ from pemivibart in sequence (e.g., pemivibart-like antibodies may share the same VH and VL amino acid sequences but differ in other domains), antibody expression methods and expression cell lines, and antibody purification methods. Publicly available neutralization data against emerging SARS-CoV-2 variants are reviewed by the FDA and may be factored into the totality of evidence when considering the potential for adequate activity of PEMGARDA to support continued emergency use authorization. These data are evaluated considering their differences in experimental methodologies, availability of methodological and assay performance details, data consistency and quality, and the applicability of the data to PEMGARDA and to the immunobridging analyses. A determination that PEMGARDA may be effective against emerging variants is primarily guided by data obtained in the Monogram Biosciences PhenoSense® Anti-SARS-CoV-2 Neutralizing Antibody Assay using pemivibart, because of the importance of maintaining assay and analyte continuity when comparing the susceptibility of emerging variants to those against which the initial immunobridging analysis was conducted. Furthermore, the Monogram assay is well-characterized, and assay details and results are available for FDA review in the context of an emergency use authorization.

Table 1: Pemivibart Pseudotyped Lentivirus Virus-Like Particle Neutralization Data for SARS-CoV-2 Variants

Pango Lineage	Substitutions, Deletions, and/or Insertions Present in Pseudotyped Lentivirus VLP Spike Proteins relative to Ancestral SARS-CoV-2 [a]	Pemivibart Mean EC_{50} Values in ng/mL (SD / range) [b]	EC_{50} Value Fold-Change from the Mean B.1 EC_{50} Value [c]	EC_{50} Value Fold-Change from the Mean JN.1 EC_{50} Value [d]
JN.1.50	Ins16MPLF, T19I, R21T, L24-P26del, A27S, S50L, A67V, H69del, V70del, V127F, G142D, Y144del, F157S, R158G, N211del, L212I, V213G, L216F, H245N, L249F, A264D, I332V, G339H, R346T, K356T, S371F, S373P, S375F, T376A, R403K, D405N, R408S, K417N, N440K, V445P, G446S, N450D, L452W, L455S, F456L, N460K, S477N, T478K, N481K, del483, E484K, F486P, Q498R, N501Y, Y505H, E554K, A570V, D614G, P621S, H655Y, N679K, P681R, N764K, D796Y, S939F, Q954H, N969K, P1143L	60.3 (17.8)	7.2	0.8
KP.3.1.1	Ins16MPLF, T19I, R21T, L24-P26del, A27S, S31del, S50L, H69del, V70del, V127F, G142D, Y144del, F157S, R158G, N211del, L212I, V213G, L216F, H245N, A264D, I332V, G339H, K356T, S371F, S373P, S375F, T376A, R403K, D405N, R408S, K417N, N440K, V445H, G446S, N450D, L452W, L455S, F456L, N460K, S477N, T478K, N481K, V483del, E484K, F486P, Q493E, Q498R, N501Y, Y505H, E554K, A570V, D614G, P621S, H655Y, N679K, P681R, N764K, D796Y, S939F, Q954H, N969K, V1104L, P1143L	239.3 (141.4)	28.5	3.2
LB.1	Ins16MPLF, T19I, R21T, L24-P26del, A27S, S31del, S50L, H69del, V70del, V127F, G142D, Y144del, F157S, R158G, Q183H, N211del, L212I, V213G, L216F, H245N, A264D, I332V, G339H, R346T, K356T, S371F, S373P, S375F, T376A, R403K, D405N, R408S, K417N, N440K, V445H, G446S, N450D, L452W, L455S, F456L, N460K, S477N, T478K, N481K, V483del, E484K, F486P, Q498R, N501Y, Y505H, E554K, A570V, D614G, P621S, H655Y, N679K, P681R, N764K, D796Y, S939F, Q954H, N969K, P1143L	178.7 (114.1)	21.3	2.4

Source: For JN.1, data are derived from study report NVD200-NC-003-R8, for JN.1.50, KP.3.1.1, and LB.1, data are derived from study report VYD222-NC-014-R6

a. Substitutions in the spike protein of the tested pseudotyped lentivirus VLP relative to the ancestral wild-type SARS-CoV-2 spike reference sequence (NCBI accession number NC_045512.2).
b. EC_{50} values for pemivibart neutralization of SARS-CoV-2 variants were determined in the PhenoSense® Anti-SARS-CoV-2 Neutralizing Antibody Assay (Monogram Biosciences/LabCorp). In this assay, neutralization activity of the pemivibart drug product is assessed against single-cycle spike-pseudotyped lentivirus virus-like particles (VLPs) in HEK293 cells expressing human ACE2 and TMPRSS2 (EUA122 Summary Review [March 22, 2024]). EC_{50} values are the mean of at least 3 replicates.
c. Fold-change in EC_{50} value for a given variant was calculated by dividing the observed EC_{50} value by the average observed EC_{50} value for WT D614G (B.1) of 8.4 ng/mL (SD: ±3 ng/mL) obtained from 30 replicates across 13 previous experiments performed using the PhenoSense® Anti-SARS-CoV-2 Neutralizing Antibody Assay.
d. Fold-change in EC_{50} value for a given variant was calculated by dividing the observed EC_{50} value by the average observed EC_{50} value for JN.1 of 74.6 ng/mL obtained from a previous experiment performed using the PhenoSense® Anti-SARS-CoV-2 Neutralizing Antibody Assay.

2. To clarify the risk for COVID-19 due to SARS-CoV-2 viral variants with substantially reduced susceptibility to PEMGARDA.

At the time of this memorandum, PEMGARDA likely retains adequate neutralization activity against circulating SARS-CoV-2 variants in the U.S., based on (1) pemivibart EC_{50} values determined in the Monogram Biosciences PhenoSense® Anti-SARS-CoV-2 Neutralizing Antibody Assay against KP.3.1.1, LB.1, KP.3, and KP.2, which comprise more than 75% of currently circulating variants, and (2) spike RBD similarity of untested, circulating variants compared to variants that have been shown to be susceptible in the Monogram assay. However, the Warnings and Precautions section in the Factsheet for Healthcare Providers is being updated to clarify that certain SARS-CoV-2 viral variants may emerge that have

substantially reduced susceptibility to PEMGARDA. The instructions to advise individuals to test for COVID-19 and seek medical attention, including starting treatment for COVID-19 as appropriate, if signs or symptoms of COVID-19 occur remain a part of the Warnings and Precautions section.

Summary of Fact Sheet Revisions

The Warnings and Precautions in Section 5.4 of the Fact Sheet for Healthcare Providers was edited to state that certain SARS-CoV-2 viral variants may emerge that have substantially reduced susceptibility to PEMGARDA.

Section 12.4 (Microbiology) of the Fact Sheet for Healthcare Providers was updated to:

- Remove the "pending" status of pseudotyped lentivirus VLP neutralization data against KP.3.1.1 in Table 2.
- Add pseudotyped lentivirus VLP neutralization data against KP.3.1.1, LB.1, and JN.1.50 in Table 2.
- Add a footnote to Table 2 specifying that EC_{50} values for pemivibart neutralization of SARS-CoV-2 variants were determined in the Monogram Biosciences PhenoSense® Anti-SARS-CoV-2 Neutralizing Antibody Assay (Monogram Biosciences/LabCorp).
- Remove text stating that preliminary, non-peer-reviewed data in the public domain indicate that KP.3.1.1 may have substantially reduced susceptibility to pemivibart.
- Add a footnote to Table 2 indicating that EC_{50} values for certain SARS-CoV-2 variants in this table may differ from those reported by other labs and obtained under different assay conditions.
- Amend a footnote in Table 2 to clarify that the deletion at S31 (observed in KP.3.1.1 and LB.1) is in the N-terminal domain (NTD) and is distal to the receptor-binding domain (RBD).

The following text was added to Section 14.3 of the Fact Sheet for Healthcare Providers to provide additional context to the changes in Section 12.4 pertaining to the overall benefit-risk assessment of PEMGARDA at this time.

> The totality of scientific evidence including the available clinical and pharmacokinetic data along with the nonclinical viral neutralization data provided from Monogram in *Microbiology (12.4)* support the potential benefit of PEMGARDA in the authorized patient population.

Section 15 was added to the Fact Sheet for Healthcare Providers to include a reference to the Monogram Biosciences PhenoSense® Anti-SARS-CoV-2 Neutralizing Antibody Assay (Huang et al., 2021).

Regulatory Conclusion and Associated Actions

The totality of scientific evidence including the available clinical and pharmacokinetic data along with the nonclinical viral neutralization data obtained in the Monogram Biosciences PhenoSense® Anti-SARS-CoV-2 Neutralizing Antibody Assay indicate that pemivibart is likely to have adequate neutralization activity against currently circulating variants relative to JN.1 and support the potential benefit of PEMGARDA in the authorized patient population.

The Division of Antivirals and the Office of Infectious Diseases recommend revisions to EUA 122 as outlined above in order to best protect public health and to provide health care providers with the most current recommendations about PEMGARDA. Based on the totality of the data, the Division of Antivirals and the Office of Infectious Diseases have determined that the known and potential benefits of PEMGARDA outweigh the known and potential risks.

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