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	August 23, 2024
Sponsor (entity requesting EUA or pre-EUA consideration), point of contact, address, phone number, fax number, email address	Invivyd, Inc. Barry Sickels, PhD, Senior Vice President, 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 Chungfen Ren, Statistical Reviewer Wen Zeng, Statistical 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).

Rationale for Revisions to EUA and Fact Sheets

The Letter of Authorization for PEMGARDA (LOA) is being revised to add a limitation of authorized use (LOAU) regarding SARS-CoV-2 variants with substantially reduced susceptibility to PEMGARDA. The PEMGARDA EUA Fact Sheet for Healthcare Providers and Fact Sheet for Patients, Parents, and Caregivers are being revised at this time to:

(1) include PEMGARDA pseudotyped virus-like particle (VLP) neutralization activity data against recently and currently circulating SARS-CoV-2 variants including GE.1.2.1, JN.1.13.1, KQ.1, KP.1.1, KP.2, and KP.3, and, to note recent preliminary, non-peer-reviewed data in the public domain indicating that KP.3.1.1 may have substantially reduced susceptibility to pemivibart.
(2) indicate the risk of COVID-19 due to SARS-CoV-2 viral variants with substantially reduced susceptibility to PEMGARDA
(3) Add a LOAU for SARS-CoV-2 variants with substantially reduced susceptibility to PEMGARDA
(4) remove specific authentic virus neutralization data deemed no longer reliable based on new information obtained from the Sponsor
(5) update immunobridging results
(6) add exploratory clinical efficacy results from the CANOPY trial

The rationale for each revision is as follows:

1. **To include PEMGARDA pseudotyped lentivirus VLP neutralization activity data against recently and currently circulating SARS-CoV-2 variants including GE.1.2.1, JN.1.13.1, KQ.1, KP.1.1, KP.2, and KP.3, and, to note recent preliminary, non-peer-reviewed data in the public domain indicating that KP.3.1.1 may have substantially reduced susceptibility to pemivibart.**

   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. Serum neutralization titers of pemivibart against JN.1 based on pseudotyped lentivirus VLP and authentic virus neutralization assays were comparable to calculated titer values of previously evaluated monoclonal antibodies associated with clinical efficacy for the pre-exposure prophylaxis of COVID-19 (see EUA122 Summary Review). Subvariants have subsequently emerged with amino acid substitutions in the spike protein RBD that have been evaluated in pseudotyped lentivirus VLP assays.

This update to Section 12.4 (Microbiology) of the Factsheet for Healthcare Providers includes updated pseudotyped lentivirus VLP neutralization data against currently circulating variants. Results for pemivibart neutralization activity against pseudotyped lentivirus VLPs representing the following variants containing spike protein substitutions relative to XBB.2.3 or JN.1 consensus sequences as indicated (RBD substitutions are underlined) were included in Table 1: GE.1.2.1 (XBB.2.3 + K77R, N148T, N185del, F186I, A376S, K478T), JN.1.13.1 (JN.1 + F59S, R346T, A1087S), KQ.1 (JN.1 + R346T, T572I), KP.1.1 (JN.1 + R346T, F456L, K1086R, V1104L), KP.2 (JN.1 + R346T, F456L, V1104L, P1143L), and KP.3 (JN.1 + F456L, Q493E, V1104L).

At the time of this revision, the JN.1-lineage variants KP.3 and KP.3.1.1 are the most abundant variants circulating in the U.S. (approximately 17% and 37% of circulating variants, respectively, based on the August 17, 2024 CDC Nowcast estimate). KP.3 exhibits an EC_{50} value that is 3-fold higher than that of JN.1, and PEMGARDA is likely to retain adequate neutralization activity against KP.3. However, collection and evaluation of KP.3.1.1 neutralization data is ongoing. Of note, preliminary, non-peer-reviewed data in the public domain indicate that pemivibart may have substantially reduced activity against KP.3.1.1 (Wang et al., 2024). Wang et al. produced their own monoclonal antibody stated to contain the same heavy chain variable (VH) and light chain variable (VL) domains as pemivibart. The Division independently verified that the VH and VL amino acid sequences provided by the authors were identical to those of pemivibart based on publicly available information (EUA122 Summary Review). Wang et al. report a 33-fold increase in the EC_{50} value for their antibody against KP.3.1.1 relative to JN.1 in a pseudotyped vesicular stomatitis virus (VSV) VLP assay.

The data presented by Wang et al., indicate that currently circulating KP.3.1.1 spike variants may have substantially reduced susceptibility to pemivibart. EC_{50} values for the antibody produced by Wang et al. against pseudotyped VSV VLPs representing historic SARS-CoV-2 variants exhibited similar fold-changes relative to reference compared to fold-changes for pemivibart against the same variants in the pseudotyped lentivirus VLP assay. However, there are several limitations that affect the interpretation of the data with respect to the potential impact on pemivibart activity against KP.3.1.1, which include differences in the antibody product evaluated by Wang et al. and pemivibart, differences between the pseudotyped VSV VLP assay carried out by Wang et al., and the pseudotyped lentivirus VLP assay carried out by the sponsor to support immunobridging for pemivibart, including potential differences in the specific spike sequences of the variants used in respective assays. The posted preprint by Wang et al., has not been peer-reviewed, and data may be subject to change by the authors.

Evaluations of pemivibart neutralization activity against pseudotyped lentivirus VLPs representing other emerging variants, including KP.3.1.1, are ongoing and will be included in future Fact Sheet updates (see Revision Rationale 2 below).

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 ng/mL (SD / range)	EC_{50} Value Fold-Change from the Mean B.1 EC_{50} Value [b]	EC_{50} Value Fold-Change from the JN.1 EC_{50} Value [c]
GE.1.2.1	T19I, L24-P26del, A27S, K77R, V83A, G142D, Y144del, H146Q, N148T, Q183E, N185del, F186I, V213E, D253G, G339H, R346T, L368I, S371F, S373P, S375F, T376S, D405N, R408S, K417N, N440K, V445P, G446S, N460K, S477N, E484A, F486P, F490S, Q498R, N501Y, Y505H, P521S, D614G, H655Y, N679K, P681H, N764K, D796Y, Q954H, N969K	72.1 (14.8)	8.6	1.0
JN.1.13.1	Ins16MPLF, T19I, R21T, L24-P26del, A27S, S50L, F59S, H69-V70del, V127F, G142D, Y144del, F157S, R158G, N211del, L212I, V213G, L216F, H245N, A264D, I332V, G339H, R346T, K356T, S371F, S373P, S375F, T376A, R403K, D405N, R408S, K417N, N440K, V445H, G446S, N450D, L452W, L455S, N460K, S477N, T478K, N481K, V483del, E484K, F486P, Q498R, N501Y, Y505H, E554K, A570V, D614G, P621S, H655Y, N679K, P681R, N764K, D796Y, S939F, Q954H, N969K, A1087S, P1143L	220.3 (32.5)	26.2	2.9
KQ.1	Ins16MPLF, T19I, R21T, L24-P26del, A27S, S50L, H69-V70del, V127F, G142D, Y144del, F157S, R158G, N211del, L212I, V213G, L216F, H245N, A264D, I332V, G339H, R346T, K356T, S371F, S373P, S375F, T376A, R403K, D405N, R408S, K417N, N440K, V445H, G446S, N450D, L452W, L455S, N460K, S477N, T478K, N481K, V483del, E484K, F486P, Q498R, N501Y, Y505H, E554K, A570V, T572I, D614G, P621S, H655Y, N679K, P681R, N764K, D796Y, S939F, Q954H, N969K, P1143L	208.5 (30.3)	24.8	2.8
KP.1.1	Ins16MPLF, T19I, R21T, L24-P26del, A27S, S50L, H69-V70del, V127F, G142D, Y144del, F157S, R158G, 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, K1086R, V1104L, P1143L	174.2 (28.7)	21.1	2.3
KP.2	Ins16MPLF, T19I, R21T, L24-P26del, A27S, S50L, H69-V70del, V127F, G142D, Y144del, F157S, R158G, 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, V1104L, P1143L	154.1 (29.4)	18.3	2.1
KP.3	Ins16MPLF, T19I, R21T, L24-P26del, A27S, S50L, H69-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	223.0 (62.6)	25.1	3.0

Source: For JN.1, data are derived from study report NVD200-NC-003-R8, for GE.1.2.1, JN.1.13.1, KQ.1, KP.1.1, KP.2, KP.3, data are derived from study report VYD222-NC-014-R5; EC_{50} values were determined in the Monogram Biosciences PhenoSense® Anti-SARS-CoV-2 Neutralizing Antibody Assay (Monogram Biosciences/LabCore) as described in EUA122 Summary Review.

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. 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 obtained across 30 replicates from 13 previous experiments performed using the same pseudotyped lentivirus VLP neutralization assay platform.
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 JN.1 of 74.6 ng/mL obtained from a previous experiment performed using the same pseudotyped lentivirus VLP neutralization assay platform.

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

At the time of this memorandum, PEMGARDA retains adequate neutralization activity against a majority of circulating variants based on the pseudotyped lentivirus VLP EC_{50} values determined against representative spike variants (KP.1.1, KP.2, and KP.3; see Table 1) and the August 17, 2024 CDC Nowcast data. However, pseudotyped lentivirus VLP neutralization data are pending for some variants that are increasing in frequency, which may have substantially reduced susceptibility to PEMGARDA, including KP.3.1.1 (see

Revision Rationale 1). The authorized PEMGARDA Fact Sheets will be updated as more data become available.

PEMGARDA is currently the only authorized or approved product in the U.S. for pre-exposure prophylaxis of COVID-19 in individuals who have moderate to severe immune compromise and are unlikely to mount an adequate immune response to COVID-19 vaccination. As a prophylactic product with a half-life of around 45 days, PEMGARDA is intended to protect against both current and future variants. It is unknown at this time whether the KP.3.1.1 variant will continue to outcompete the currently PEMGARDA-susceptible variants, or whether PEMGARDA will retain neutralization activity against novel variants that become dominant in the future.

Because PEMGARDA may not provide adequate protection against all currently circulating variants, the Warnings and Precautions section in the Factsheet for Healthcare Providers is being updated to indicate the increased risk for COVID-19 due to exposure to SARS-CoV-2 viral variants with substantially reduced susceptibility to PEMGARDA, compared to variants that are anticipated to remain susceptible to PEMGARDA. 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. This risk is also being updated in the Factsheet for Patients, Parents, and Caregivers.

3. **To add a LOAU for SARS-CoV-2 variants with substantially reduced susceptibility to PEMGARDA to the LOA and Fact Sheet for Healthcare Providers**

A LOAU is being added to the PEMGARDA LOA and Fact Sheet for Healthcare Providers. The LOAU will ensure that, based on available information including variant susceptibility to PEMGARDA and national variant frequency, any patient receiving PEMGARDA consistent with the terms and conditions of the authorization will likely benefit from the therapy and avoid exposure to the risk of adverse events from specific treatment agents that are not expected to provide benefit. This LOAU is consistent with another LOAU used for a different SARS CoV-2 monoclonal antibody product previously authorized for pre-exposure prophylaxis in a similar patient population.

For the PEMGARDA authorized population, we have determined that benefit-risk will no longer be favorable for use when the combined frequency of variants with substantially reduced susceptibility to PEMGARDA is greater than 90%, based on available information including variant susceptibility to PEMGARDA and national variant frequencies. In our assessment, at that time, the risk of exposing patients to possible side effects of PEMGARDA such as anaphylaxis and other hypersensitivity reactions, which can be serious or life-threatening, is likely to outweigh the anticipated benefit of the product in reducing the risk of COVID-19.

4. **To remove specific authentic virus neutralization data for JN.1 deemed unreliable and no longer informative based on new information obtained from the Sponsor**.

At the time of the initial authorization, authentic virus neutralization data were reported in Section 12.4 of the Fact Sheet for Healthcare Providers that were derived from study report VYD222-ND-013-R0. While the report stated that "*each authentic virus isolate was amplified directly from clinical swabs in a single passage over the course of 3-4 days in Vero E6-*

TMPRSS2 cells, the genomic sequence was determined, the variant profile confirmed, and the sequence deposited into GISAID with the identifiers noted…", information recently obtained from the Sponsor indicated that upon re-sequencing of the virus stock used for neutralization assays, it was determined that the stock contained a SARS-CoV-2 variant unrelated to JN.1. Therefore, the authentic virus neutralization EC_{50} value of 63.6 ng/mL reported for JN.1 is no longer considered informative for regulatory purposes and will be removed from Sections 12.2, 12.4, and 14 of the Fact Sheet for Healthcare Providers. Further discussion of the impact of removal of the reported JN.1 authentic virus neutralization EC_{50} value on titer comparison evaluations is provided in Revision Rationale 5 below.

5. To update the immunobridging results

Briefly, potential clinical efficacy of pemivibart was initially supported by antibody titer values calculated from EC_{50} values obtained for pemivibart against JN.1 in an authentic virus neutralization assay (63.6 ng/mL) and in a pseudotyped lentivirus VLP neutralization assay (74.6 ng/mL). The Sponsor recently provided information indicating that the previously reported authentic virus neutralization EC_{50} value for pemivibart against JN.1 (63.6 ng/mL) is unreliable and no longer informative (see Revision Rationale 4). As such, a re-assessment of the calculated titer for pemivibart against JN.1 was done based only on the JN.1 pseudotyped lentivirus VLP neutralization assay EC_{50} value of 74.6 ng/mL. Because the difference between the two EC_{50} values was minimal (less than 20%), the overall conclusion, that pemivibart may be effective for pre-exposure prophylaxis against COVID-19 caused by JN.1 based on the serum neutralization titer-efficacy relationships identified with other neutralizing human monoclonal antibodies against SARS-CoV-2, remains the same. Additional clinical exploratory efficacy data also support that conclusion (See Revision Rationale 6).

Of note, when using the protocol-defined immunobridging endpoint, the revised calculated titer value did not meet the endpoint [geometric mean ratio between the calculated titer for pemivibart against JN.1 and the calculated titer for adintrevimab against Delta was 0.7 (90% CI: 0.68-0.72)]. However, as noted in the original EUA review, the limitations and considerations of the primary immunobridging endpoint should be recognized in interpreting the results. Based on the comparison between the titer for pemivibart against JN.1 and the titer-response trend based on a meta-analysis, our determination that pemivibart may be effective for the authorized use remains unchanged**.**

6. To add exploratory clinical efficacy results from the CANOPY trial

Planned exploratory clinical efficacy results from the CANOPY trial recently became available. The CANOPY trial was a clinical trial intended to generate data to support immunobridging and safety of PEMGARDA and also collect data on rates of RT-PCR-confirmed COVID-19 in participants. Please refer to the original EUA122 Summary Review for additional details about endpoints in the CANOPY trial and the rationale for why the clinical efficacy endpoints are considered exploratory. During the trial, participants were instructed per protocol to monitor for and report any symptoms of COVID-19-like illness (CLI) to the sites. If CLI symptoms were reported and met criteria for a CLI visit, participants would have the first CLI visit (CLI Day 1) within 2 days for RT-PCR testing for SARS-CoV-2 and other respiratory pathogens. Participants with a positive SARS-CoV-2 test result would subsequently have virtual visits 27 days (CLI Day 28) and 3 months (CLI Month 3) later for self-assessment of disease severity. The proportion of RT-PCR-confirmed symptomatic

COVID-19, COVID-19-related hospitalization, or all-cause death through Month 3 and through Month 6 for each cohort is described below.

Cohort B

An exploratory objective of Cohort B in the CANOPY trial was to evaluate clinical efficacy of PEMGARDA compared to placebo in the prevention of RT-PCR-confirmed COVID-19 in randomized participants without current SARS-CoV-2 infection at baseline. Cohort B consisted of adults without moderate-to-severe immune compromise who were at risk of acquiring SARS-CoV-2 due to regular unmasked face-to-face interactions in indoor settings. A full description of Cohort B is available in the original EUA122 Summary Review.

Participants in Cohort B received the initial dose of study treatment between September 8, 2023, and October 2, 2023, with 50% having received the initial dose by September 15, 2023. Redosing of the same study treatment at Month 3 occurred between November 27, 2023, and January 19, 2024, with 50% having received the initial dose by December 14, 2023. Two participants with RT-PCR-confirmed COVID-19 in the placebo arm through Month 6 were excluded from the exploratory efficacy analysis because they had SARS-CoV-2 infection at baseline as measured by RT-PCR. Of the initial 484 randomized participants, 163 participants reported CLI symptoms and met the criteria for at least one CLI visit.

The exploratory endpoints of proportion of RT-PCR-confirmed symptomatic COVID-19, COVID-19-related hospitalization, or all-cause death through Month 3 (after the initial dose), from Month 3 through Month 6 (after redosing), and cumulatively through Month 6 are displayed in Table 2. No COVID-19-related hospitalizations or all-cause deaths occurred in either treatment arm of Cohort B through Month 6.

Seventeen of the 25 cumulative participants who met the endpoint had RT-PCR-confirmed symptomatic COVID-19 during a period of time when JN.1 was dominant, ranging from 40% to 80% of the circulating variants; 8 participants met the endpoint during a period of time when variants with similar susceptibilities to PEMGARDA as JN.1 were dominant (EG.5 or HV.1) (CDC Nowcast). Confirmation of the SARS-CoV-2 variant identity of subjects who were RT-PCR-positive is ongoing. Overall, the exploratory clinical efficacy results provide additional support that PEMGARDA may be effective for pre-exposure prophylaxis against COVID-19 caused by the JN.1 variant, the dominant circulating variant at the time of the initial EUA, and other currently circulating variants with similar neutralizing susceptibilities as JN.1. Therefore, this information will be included in Section 14 of the Fact Sheet for Healthcare Providers with a statement that PEMGARDA is not authorized for use in individuals who do not have moderate-to-severe immune compromise. Section 12.4 (Microbiology) will be referenced for the fold-change in EC_{50} values for currently circulating variants compared to JN.1.

Table 2. Exploratory Clinical Efficacy Results in Randomized Participants without SARS-CoV-2 Infection at Baseline in CANOPY Cohort B (Adults who do not have Moderate-to-Severe Immune Compromise)

	PEMGARDA N=317	**Placebo N=160**
RT-PCR-confirmed symptomatic COVID-19, COVID-19-related hospitalization, or all-cause death[a] through Month 3[b]		
Proportion: n (%)	1 (0.3)	8 (5.0)

	PEMGARDA N=317	Placebo N=160
Standardized Relative Risk Reduction (95% confidence interval [CI])	94% (50%, 99%)	
RT-PCR-confirmed symptomatic COVID-19, COVID-19-related hospitalization, or all-cause death[a] from Month 3 through Month 6[c]		
Proportion: n (%)	5 (1.6)	11 (7.2)
Standardized Relative Risk Reduction (95% CI)	78% (38%, 92%)	
RT-PCR-confirmed symptomatic COVID-19, COVID-19-related hospitalization, or all-cause death[a] through Month 6[d]		
Proportion: n (%)	6 (1.9)	19 (11.9)
Standardized Relative Risk Reduction (95% CI)	84% (61%, 94%)	

Source: Sponsor's Clinical Information Amendment – Exploratory CANOPY Analyses, VYD222-PREV-001 Cohort A CLI Visit Dataset, VYD222-PREV-001 Cohort B CLI Visit Dataset, and VYD222-PREV-001 CIOMS Cohort A All-Cause Deaths submitted on 07-Aug-2024.

[a] No COVID-19-related hospitalizations or all-cause deaths occurred in either treatment arm of Cohort B through Month 6.

[b] Following the initial dosing period of the trial

[c] Following the redosing period of the trial

[d] Cumulative following the initial dosing period and the redosing period of the trial

Cohort A

In Cohort A, an open-label cohort of patients with moderate-to-severe immune compromise, data were also collected on the prevention of RT-PCR-confirmed COVID-19, COVID-19-related hospitalization, or all-cause death in participants who received a full initial dose of the study drug. A full description of Cohort A is available in the original EUA122 Summary Review.

Participants in Cohort A received the initial dose of PEMGARDA between September 15, 2023, and November 8, 2023, with 50% having received the initial dose by October 18, 2023. Redosing of PEMGARDA at Month 3 occurred between December 5, 2023, and February 19, 2024, with 50% having received the initial dose by January 16, 2024. Of the initial 306 participants who received at least a partial dose of PEMGARDA, 100 participants reported CLI symptoms and met the criteria for at least one CLI visit, and 8 participants were excluded from the analysis because they did not receive the full initial dose of PEMGARDA.

The pre-specified endpoint of proportion of RT-PCR-confirmed symptomatic COVID-19, COVID-19-related hospitalization, or all-cause death in Cohort A (N=298) was as follows:

- n=3 (1.0%) through Month 3, after the initial dose
- n=8 (2.7%) from Month 3 through Month 6, after redosing
- n=11 (3.7%) cumulatively through Month 6

Nine of the 11 cumulative participants who met the endpoint through Month 6 had RT-PCR-confirmed symptomatic COVID-19 with none resulting in COVID-19-related hospitalization or all-cause death. The remaining 2 participants who met the endpoint through Month 6 died without RT-PCR-confirmed COVID-19 or any CLI visits (all-cause death). One of the all-cause deaths (Participant 151-190) occurred approximately 92 days after the initial dose of PEMGARDA and was included in the original EUA122 Summary Review; the cause of death

remains unknown. The second all-cause death (Participant 126-044) occurred 92 days after the initial dose of PEMGARDA and was caused by suicide.

Eight of the 9 participants met this endpoint during a period of time when JN.1 was dominant, ranging from 30% to 80% of the circulating variants, and 1 participant met the endpoint during a period of time when a variant with similar susceptibility to PEMGARDA as JN.1 was dominant (HV.1) (CDC Nowcast). The SARS-CoV-2 variant was identified in 6 participants; 5 were infected with JN.1 and 1 was infected with EG.10.1. While the clinical efficacy results in Cohort A are difficult to interpret without a comparator arm, the data will be included in the Fact Sheet for Healthcare Providers for completeness and because the cohort consisted of a population similar to the authorized use population.

Summary of Authorization and Fact Sheet Revisions

The PEMGARDA EUA Fact Sheet for Healthcare Provides; Fact Sheet for Patients, Parents, and Caregivers; and Letter of Authorization are being revised at this time to add the following LOAU:

- *PEMGARDA is authorized for use only when the combined national frequency of variants with substantially reduced susceptibility to PEMGARDA is less than or equal to 90%, based on available information including variant susceptibility to PEMGARDA and national variant frequencies.*
- *Footnote: FDA will monitor conditions to determine whether use is consistent with the scope of authorization, referring to available information, including information on variant susceptibility (e.g., Section 12.4 of the authorized Fact Sheet for Healthcare Providers) and CDC variant frequency data available at: https://covid.cdc.gov/covid-data-tracker/#variant-proportions.*

The Warnings and Precautions in Section 5.4 of the Fact Sheet for Healthcare Providers was edited to indicate the risk for COVID-19 due to SARS-CoV-2 viral variants with substantially reduced susceptibility to PEMGARDA – instead of viral variants not neutralized by PEMGARDA. A cross-reference to Section 12.4 (Microbiology) was added for cell culture neutralization activity of PEMGARDA against recently and currently circulating SARS-CoV-2 viral variants.

Section 12.2 (Pharmacodynamics) of the Fact Sheet for Healthcare Provider was updated to revise the range of calculated geometric mean titer values based on the pseudotyped lentivirus VLP neutralization assay EC_{50} value against JN.1

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

- Remove the authentic virus neutralization data reported for JN.1.
- Add pseudotyped lentivirus VLP neutralization data against GE.1.2.1, JN.1.13.1, KQ.1, KP.1.1, KP.2, and KP.3.
- To note recent preliminary, non-peer-reviewed data in the public domain indicating that KP.3.1.1 may have substantially reduced susceptibility to pemivibart.
- Replace pseudotyped lentivirus VLP EC_{50} value fold-changes relative to B.1 with EC_{50} value fold changes relative to JN.1, the dominant variant circulating at the time of the initial emergency use authorization.

The immunobridging results in Section 14 (CLINICAL STUDIES) of the Fact Sheet for Healthcare Providers was updated to:

- Replace the authentic virus neutralization data for pemivibart reported for JN.1 (EC_{50} value of 63.6 ng/mL) with pseudotyped lentivirus VLP neutralization data for pemivibart against JN.1 (EC_{50} value of 74.6 ng/mL)
- Update the geometric mean ratio and 90% confidence interval (CI) between the calculated titer for pemivibart against JN.1 (based on pseudotyped lentivirus VLP neutralization data instead of authentic virus neutralization data) and the calculated titer for adintrevimab against Delta (based on authentic virus neutralization data) to 0.70 (90% CI: 0.68-0.72).

Section 14 (CLINICAL STUDIES) of the Fact Sheet for Healthcare Providers was also updated to add exploratory clinical efficacy results from the CANOPY trial, including RT-PCR-confirmed symptomatic COVID-19, COVID-19-related hospitalization, or all-cause death through Month 3 and through Month 6 in Cohort B (PEMGARDA vs. placebo in adults without moderate-to-severe immune compromise) and in Cohort A (open-label PEMGARDA in adults with moderate-to-severe immune compromise).

Section 17 (PATIENT COUNSELING INFORMATION) of the Fact Sheet for Healthcare Providers was updated to add information on the risk for COVID-19 due to SARS-CoV-2 viral variants with substantially reduced susceptibility to PEMGARDA.

In addition, edits were made to the patient Fact Sheet to be consistent with these changes.

Regulatory Conclusion and Associated Actions:

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 conclude that the known and potential benefits of pemivibart outweigh the known and potential risks and no change in the authorization status is warranted at this time.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SARITA D BOYD
08/23/2024 02:23:22 PM

KIMBERLY A STRUBLE
08/23/2024 02:59:04 PM

WENDY W CARTER
08/23/2024 03:05:54 PM

ADAM I SHERWAT
08/26/2024 06:15:36 AM