Decline to Issue COVID-19 Emergency Use Authorization (EUA) for Pemgarda (Pemivibart)

Center for Drug Evaluation and Research (CDER) Review

Application Type (EUA or Pre-EUA) If EUA, designate whether for incident preparedness (pre-event) or response (intra-event).	Request for EUA
EUA Number	EUA 000122
Sponsor (entity requesting EUA), point of contact, address, phone number, fax number, email address	Invivyd, Inc. Rachael Gerlach PhD, MPH VP, Regulatory Affairs 1601 Trapelo Road, Suite 178 Waltham, MA 02451 (P) (b) (6) (F) (b) (6) (b) (6)
Manufacturer, if different from Sponsor	
Submission Date(s)	July 18, 2024
Receipt Date(s)	July 18, 2024
OND Division / Office	Division of Antivirals / Office of Infectious Diseases
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 Mario Sampson, Clinical Pharmacology Reviewer Su-Young Choi, Clinical Pharmacology Team Lead Chunfeng Ren, Statistical Reviewer Wen Zeng, Statistical Team Lead Yodit Belew, Associate Director for Therapeutic Review Wendy Carter, Division Director, DAV Adam Sherwat, Deputy Office Director, OID John Farley, Office Director, OID
Review Completion Date	February 20, 2025
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	Treatment of mild to moderate COVID-19
Intended Population(s)	Adults and pediatric patients (12 years of age and older weighing at least 40 kg) who: • have moderate-to-severe immune compromise due to a medical condition or receipt of immunosuppressive medications or treatments **and** • for whom alternative COVID-19 treatment options approved by FDA are not accessible or clinically appropriate
Product in the Strategic National Stockpile (SNS)	No
Product for DoD force protection	No
Distributor, if other than Sponsor (e.g., SNS)	Invivyd, Inc.

I. Executive Summary

Recommendation to Decline Request for Emergency Use Authorization

On July 18, 2024, the Sponsor, INVYVID, submitted a request to authorize under Emergency Use Authorization (EUA) the use of pemivibart for the treatment of mild to moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) who:

- have moderate-to-severe immune compromise due to a medical condition or receipt of immunosuppressive medications or treatments **and**

- for whom alternative COVID-19 treatment options approved by FDA are not accessible or clinically appropriate.

The statutory criteria for issuing an EUA are set forth in Section 564(c) of the Federal Food, Drug and Cosmetic Act (FD&C Act). Specifically, the FDA must determine, among other things, that "based on the totality of scientific information available to [FDA], including data from adequate and well-controlled clinical trials, if available," it is reasonable to believe that the product may be effective in diagnosing, treating, or preventing a serious or life-threatening disease or condition caused by the chemical, biological, radiological, or nuclear agent; that the known and potential benefits, when used to diagnose, prevent, or treat such disease or condition, outweigh the known and potential risks of the product; and that there are no adequate, approved, and available alternatives.

CDER scientific review staff have reviewed the available information, including the Sponsor's analyses providing a direct comparison of pemivibart to its prototype monoclonal antibody (mAb), adintrevimab (referred to as Method 1 in the Sponsor's request). CDER scientific review staff have also reviewed two additional meta-analyses comparing the range of pemivibart neutralization titers with those associated with other Receptor Binding Domain (RBD) targeting monoclonal antibody products (referred to as Methods 2 and 3 in the Sponsor's request).

Based on the totality of scientific evidence available, we are unable to reasonably conclude that the known and potential benefits of pemivibart, when used for the treatment of COVID-19 as described above, outweigh the known and potential risks for the product. As such, we recommend declining to issue an EUA at this time.

A summary of the review includes the following:

- When comparing the calculated serum neutralization titer (abbreviated as titer throughout this review document) values for pemivibart against KP.3.1.1 and XEC versus adintrevimab against Delta, the pemivibart titer is similar to or higher than the adintrevimab titer only during the first 3 days after administration. After this initial 3-day period, the titer for pemivibart against KP 3.1.1 and XEC is less than the titer for adintrevimab against Delta. Although the optimal duration of

adequate mAb titers is unknown, it is the CDER scientific team's assessment that ensuring adequate titers for a duration longer than 3 days is clinically important for the treatment of COVID-19 in immunocompromised patients given the potential for prolonged disease and viral shedding in this population.

- When comparing pemivibart with the range of neutralization titer values of other RBD-targeting mAbs, the latter having randomized, controlled clinical data supporting their efficacy as a COVID-19 treatment, titers for pemivibart against relevant SARS-CoV-2 variants are lower than those generated for most of the mAbs included in the meta-analysis. The CDER scientific team has concluded that in order to address the uncertainties and limitations associated with immunobridging, the titer of a new mAb (pemivibart) should be comparable to the titers of the majority of products with clinical efficacy data to support its use as a COVID-19 treatment.

Additional areas of uncertainty for all three methods that reduce the confidence in extrapolating efficacy for treatment based on an immunobridging approach include:

- Optimal drug concentrations/titers for successful treatment in immunocompetent individuals may differ substantially from those required in severely immunocompromised individuals who lack an adequate immunological response after infection is established.

- Variability in antibody-mediated activities other than neutralization may contribute to differences in treatment effects between antibodies and may not be readily normalizable, thus limiting the ability to conclude comparable effectiveness based upon similar neutralization titers.

We also note the potential risks of pemivibart for COVID-19 treatment can be largely extrapolated from the CANOPY trial, which was discussed in detail in the pemivibart EUA review for pre-exposure prophylaxis (PrEP). The risks include a Box Warning for anaphylaxis which was observed in 0.6% (4/623) of participants in the CANOPY trial. Additional Warnings and Precautions include hypersensitivity and infusion-related reactions occurring during the infusion and up to 24 hours after the infusion and that may be severe or life-threatening.

Importantly, and consistent with FDA policy, FDA may take into account a variety of considerations in exercising its authorities to authorize a product for emergency use under an EUA.[1] This includes the extent to which the product would serve a significant unmet medical need in the context of available countermeasures and FDA's overall

[1] See Guidance for Industry and Other Stakeholders "Emergency Use Authorization of Medical Products and Related Authorities" (January 2017).

understanding of COVID-19, which has and may continue to evolve over time.[2,3] These considerations, among others, also inform FDA's determination on the sufficiency of evidence necessary to support the issuance of an EUA.

II. EUA Determination/Declaration

There is currently an outbreak of Coronavirus Disease 2019 (COVID 19) caused by SARS-CoV-2, a novel coronavirus. The Secretary of the U.S. Department of Health and Human Services (HHS) has:

- Determined that there is a public health emergency, or significant potential for a public health emergency.[4]

- Declared that circumstances exist justifying the authorization of emergency use of drugs and biological products for the prevention or treatment of COVID-19.[5]

III. Eligibility of the Product for an EUA

In issuing an EUA in the context of the COVID-19 Public Health Emergency, the Agency must determine the following:

- Based on the totality of the scientific evidence available to FDA, including data from adequate and well-controlled clinical trials, if available, it is reasonable to believe that the

    - product may be effective in (1) diagnosing, treating, or preventing COVID-19, or (2) diagnosing, treating, or preventing a serious or life-threatening

---

[2] Id.

[3] At the time of this declination, there are multiple FDA-approved and authorized therapeutics intended for the treatment of COVID-19, including mild-to-moderate COVID-19 disease with clinical data supporting their use.

[4] See U.S. Department of Health and Human Services, Determination of a Public Health Emergency and Declaration that Circumstances Exist Justifying Authorizations Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3. February 4, 2020; https://www.federalregister.gov/documents/2020/02/07/2020-02496/determination-of-public-health-emergency. See also U.S. Department of Health and Human Services, Amended Determination of a Public Health Emergency or Significant Potential for a Public Health Emergency Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3(b). March 15, 2023 ("Amended Determination"); https://www.federalregister.gov/documents/2023/03/20/2023-05609/covid-19-emergency-use-authorization-declaration.

[5] See U.S. Department of Health and Human Services, Declaration that Circumstances Exist Justifying Authorizations Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3, 85 FR 18250 (April 1, 2020); https://www.federalregister.gov/documents/2020/04/01/2020-06905/emergency-use-authorization-declaration. See also Amended Determination ("The declarations issued pursuant to section 564(b)(1) of the FD&C Act that circumstances exist justifying the authorization of emergency use of certain in vitro diagnostics, personal respiratory protective devices, other medical devices and drugs and biological products, as set forth in those declarations, and that are based on the February 4, 2020 determination, remain in effect until those declarations are terminated in accordance with section 564 of the FD&C Act.").

disease or condition caused by an EUA product or an FDA approved product used to diagnose, treat, or prevent COVID-19; and

- that the known and potential benefits of the product, when used to diagnose, treat, or prevent such serious or life-threatening disease or condition, outweigh the known and potential risks of such product; and that

- There are no adequate, approved, and available alternatives to the product for diagnosing, treating, or preventing the serious or life-threatening disease or condition.

IV. Proposed Use and Dosing of the Product Under the EUA

The proposed use of pemivibart is for the treatment of mild to moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) who:

- have moderate-to-severe immune compromise due to a medical condition or receipt of immunosuppressive medications or treatments **and**

- for whom alternative COVID-19 treatment options approved by FDA are not accessible or clinically appropriate.

The proposed treatment dose of pemivibart is a single 4500 mg IV infusion.

V. Background Information on the Disease/Condition and Available Therapeutic Alternatives

COVID-19, a disease caused by the SARS-CoV-2 virus, can be serious or life-threatening. The first COVID-19 vaccination was authorized for emergency use by FDA in December 2020, and updated COVID-19 vaccines are currently available. However, some individuals with moderate or severe immune compromise are unlikely to mount an adequate immune response to vaccination, which potentially increases the risk of hospitalization or death due to COVID-19. Even though the immune response to vaccination may be blunted, COVID-19 vaccination is still recommended for immunocompromised individuals.

The following therapeutic alternatives to pemivibart are available for the treatment of mild-to-moderate COVID-19 in individuals at high risk for progression to severe COVID-19, which includes those with moderate-to-severe immune compromise.

- Nirmatrelvir and ritonavir (Paxlovid) is FDA-approved for the treatment of COVID-19 in certain adults with mild to moderate disease. Nirmatrelvir and ritonavir (Paxlovid) also remains authorized for emergency use for the treatment of COVID-19 in certain pediatric patients (12 years of age and older weighing at least 40 kg) with mild to moderate COVID-19. Nirmatrelvir, a SARS-CoV-2 main

protease (Mpro: also referred to as 3CLpro or nsp5 protease) inhibitor, is coadministered with ritonavir, an HIV-1 protease inhibitor and potent inhibitor of the CYP3A4 enzyme, resulting in increased plasma levels of nirmatrelvir for desired therapeutic effect. Nirmatrelvir and ritonavir are administered orally twice daily for 5 days. The efficacy and safety of nirmatrelvir and ritonavir was demonstrated in a randomized, double-blind, placebo-controlled trial with a primary endpoint of COVID-19 related hospitalization or all-cause mortality through Day 28.

- Remdesivir (Veklury), a SARS-CoV-2 nucleotide analog RNA polymerase inhibitor, is FDA-approved for the treatment of COVID-19 in certain adults and pediatric patients (birth to less than 18 years of age weighing at least 1.5 kg) with mild to moderate COVID-19. For this particular use, remdesivir is administered via IV infusion over 30-120 minutes once daily for 3 days. The efficacy and safety of remdesivir for the relevant indication was demonstrated in a randomized, double-blind, placebo-controlled trial with a primary endpoint of COVID-19 related hospitalization or all-cause mortality through Day 28.

- Molnupiravir (Lagevrio) is currently authorized for emergency use in adults for whom alternative COVID-19 treatment options approved or authorized by FDA are not accessible or clinically appropriate. Molnupiravir is administered orally every 12 hours for 5 days. Clinical data supporting the EUA for molnupiravir are based on a randomized, double-blind, placebo-controlled trial with a primary endpoint of all-cause hospitalization or all-cause mortality through Day 29.

VI. Assessment of EUA Request

This section describes the CDER scientific team's assessment of the information included in Invivyd's request to authorize pemivibart for the treatment of COVID-19 in certain adults and pediatric patients.

FDA's authorization of products under an EUA rests upon an understanding of the potential effectiveness of the product for its intended use, such as treatment of COVID-19, as well as the risks of the product. At this time, FDA has concluded that the known and potential benefits of pemivibart, when used for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) as proposed, do not outweigh the known and potential risks of the product.

We acknowledge that circulating SARS-CoV-2 variants are continually changing. Therefore, our assessment is based on the totality of the scientific evidence available to FDA and the predominant circulating SARS-CoV-2 variants as of February 15, 2025.

No clinical efficacy data from adequate and well-controlled trials with pemivibart for the treatment of COVID-19 are available at this time. Previously, an immunobridging approach was used to support the issuance of the pemivibart EUA for use as PrEP of

COVID-19 in certain adults and pediatric individuals[6]. The definition and description of the immunobridging approach and general considerations and limitations are described in detail in the previous EUA122 review for PrEP. This review will primarily discuss the assessments and considerations specific to Invivyd's request to authorize pemivibart for the treatment of COVID-19.

The immunobridging approach used for the pemivibart EUA for PrEP was based on a comparison of neutralization titers of pemivibart versus other neutralizing antibodies, including adintrevimab. However, there is significantly greater uncertainty associated with this type of immunobridging approach, when applied to treatment of COVID-19 with monoclonal antibodies, for reasons including the following:

a. Point estimates of antibody neutralization titers appear to be correlated with prevention of infection; however, thresholds for the titer level and duration required to successfully treat an established infection in immunocompromised patients have not been adequately established. It is the CDER scientific team's assessment that the lack of an adequate immune response and prolonged duration of viral shedding and disease observed in severely immunocompromised patients (Aydillo et al., 2020; Dioverti et al., 2022; Li et al., 2023; Li et al., 2024; Raglow et al., 2024) indicate that adequate antibody titers should be sustained for a longer duration compared to patients with fully functional immune responses. This further reduces confidence in the immunobridging approach for treatment when extrapolating efficacy from immunocompetent to immunocompromised patients.

b. Antibody titer based on neutralization activity in cell culture may be an adequate correlate for prevention of infection, regardless of mAb Fc functionality (Stadler et al., 2023a); however, additional activities of mAbs such as Fc-mediated effector functions can play a more significant role in the effectiveness of treatment compared to prevention of infection (e.g., Winkler et al., 2021), and antibodies often differ in Fc-mediated activities (reviewed in Zhang et al., 2023). While data submitted by the Sponsor appear to demonstrate that both pemivibart and adintrevimab have the capacity to mediate Fc-effector functions, uncertainty remains regarding the magnitude of the relative Fc-mediated activities of these mAbs against different SARS-CoV-2 spike variants, and comparisons of these functions to those of unrelated mAbs included in the meta-analysis may not be feasible. In general, relative activities of Fc effector functions and their contribution to product efficacy can be difficult to quantify and normalize for the purpose of extrapolating treatment efficacy from other monoclonal antibodies.

As previously described in the pemivibart EUA review for PrEP, there are two possible approaches for conducting immunobridging analyses. The first approach is a direct comparison of the titer of a new mAb to that of a similar mAb with clinical efficacy data. The second approach is to compare the titer of a new mAb to that of all mAbs targeting the RBD of the SARS-CoV-2 spike protein for which clinical efficacy data are available, regardless of inherent differences among these mAbs. A critical assumption for the

[6] See FDA's Summary Review at: https://www.fda.gov/media/177333/download?attachment

prototype-based direct immunobridging is that the products are highly similar. As noted in the PrEP EUA review, differences between adintrevimab and pemivibart exist beyond the eight amino acid changes in the Fab region; specifically, differences in half-life values (approximately 140 days for adintrevimab versus 45 days for pemivibart) were observed. Like the situation for PrEP, this issue raises uncertainty in the reliability of a direct immunobridging approach between pemivibart and adintrevimab in the setting of treatment.

To support an EUA for treatment, the Sponsor submitted analyses for both the direct comparison to the prototype (referred to as Method 1 in the Sponsor's submission) and meta-analysis (referred to as Methods 2 and 3 in the Sponsor's submission) approaches. Notably, the Sponsor's initial analyses (submitted 7/18/2024) were based on the EC_{50} values of pemivibart against variants that are no longer circulating. The Sponsor subsequently submitted updated analyses (11/22/24 and 1/23/25) with the addition of KP.3.1.1 and XEC data, respectively.

Immunobridging Based on a Prototype Comparison

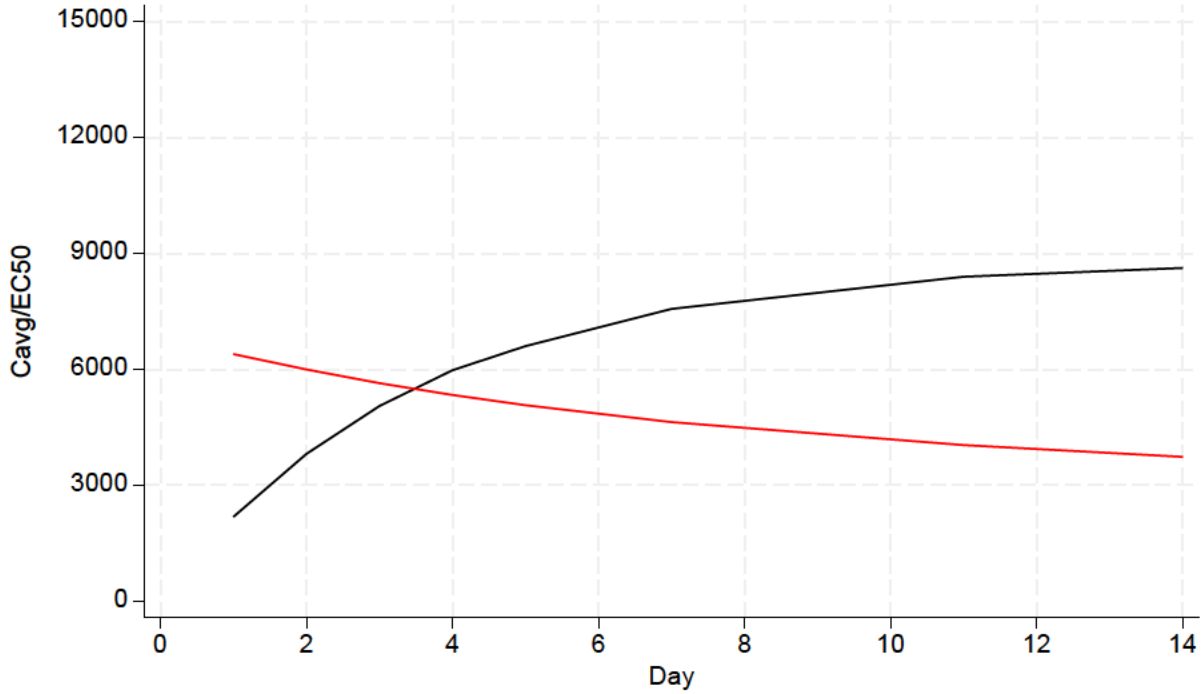
As previously described in the pemivibart EUA review for PrEP, adintrevimab is considered the parental benchmark mAb of pemivibart. The efficacy of adintrevimab for the treatment of COVID-19 was evaluated in the STAMP trial. Briefly, STAMP was a Phase 2/3, randomized, placebo-controlled trial that evaluated the efficacy and safety of adintrevimab for treatment of mild to moderate COVID-19 in unvaccinated patients at high risk for progression to severe COVID-19 when the Delta variant was dominant. The most common pre-defined risk factors for progression of COVID-19 in the Delta variant analysis population were obesity (58%), age > 55 (49%), cardiac disease (14%), and Type 1 or 2 diabetes (14%). Four percent of participants had immunodeficiency due to underlying illness or immunosuppressant medications. In this trial, the proportion of participants in the Delta variant analysis population with COVID-19-related hospitalization or all-cause death (primary efficacy endpoint) was 4.7% (8/169) in the adintrevimab arm compared with 13.8% (23/167) in the placebo arm. The standardized risk difference (primary estimand) was -8.7% (95% CI: -14.71, -2.67; p=0.0047), demonstrating a 64.4% standardized relative risk reduction (RRR) in favor of adintrevimab. Of note, FDA reviewed the trial results as presented in the clinical study report synopsis but did not conduct an independent analysis of the trial using datasets.

To bridge the efficacy of pemivibart against the currently circulating variant(s) to the efficacy of adintrevimab against Delta, the titer values between the two products were compared (described as Method 1 in the EUA request). While the overall approach—utilizing calculated titer values (exposure metrics over EC_{50} values derived from an identical cell-based assay; the currently established assay for determining EC_{50} values used to derive mAb titers for pemivibart is the Monogram pseudotyped lentivirus virus-like particle [VLP] neutralization assay) to establish a bridge—is the same as that used for the PrEP indication, it differs in terms of duration/timing of treatment and titer value calculations. For the PrEP indication, the treatment duration is defined as the entire dosing interval, and the trough titer values (Day 90 titer of pemivibart) were primarily

used to support immunobridging. Although, the optimal duration or exposure metrics of adequate mAb titers (e.g., an acceptable timepoint for immunobridging between mAbs) for treatment is unknown, the CDER scientific team's assessment is that it is clinically important to maintain a longer duration of adequate titers for effective treatment in a moderately to severely immunocompromised population as compared to the duration of treatment needed for immunocompetent patients. Of note, only 4% of participants in the STAMP trial had immunodeficiency due to an underlying illness or immunosuppressant medications at baseline; therefore, the efficacy of adintrevimab in the intended population for the treatment EUA is unknown. We recognize that uncertainty related to efficacy in the immunocompromised population also existed in the EVADE trial that supported the PrEP EUA.

Differences in titer values between pemivibart and adintrevimab at various time points were evaluated to determine whether this approach would support the requested treatment EUA. As shown in Figure 1, the titer for pemivibart against XEC is similar to or higher than the titer for adintrevimab against Delta only during the first 3 days after pemivibart administration. After this initial 3-day period, the titer for pemivibart against XEC is less than the titer for adintrevimab against Delta. Since the EC_{50} value of pemivibart against KP 3.1.1 is nearly identical to that against XEC, the same conclusion is made for KP 3.1.1. As the duration of symptomatic disease and viral shedding in severely immunocompromised patients infected with SARS-CoV-2 may be prolonged compared to immunocompetent patients, it is the CDER scientific team's assessment that it is clinically important to maintain pemivibart titers against currently circulating SARS-CoV-2 variants (e.g., XEC or KP 3.1.1) at levels greater than or equal to the titer for adintrevimab against Delta for longer than 3 days. Notably, the immunobridging approach also includes extrapolating efficacy from immunocompetent participants in the STAMP trial to the intended treatment EUA immunocompromised population. Adintrevimab efficacy in an immunocompromised population could not be estimated in the STAMP trial because only 4% of the participants were immunocompromised, and there are uncertainties in extrapolating efficacy between different patient populations.

Figure 1. Titer-time profile of pemivibart for XEC and adintrevimab for Delta through Day 14 after dosing



Red: pemivibart for XEC; Black: adintrevimab for Delta Source: FDA reviewer (based on the sponsor's submission dated 1/23/2025)

In summary, we conclude that the direct comparison to adintrevimab alone does not support the EUA of pemivibart for treatment of COVID-19. The Sponsor also made the following assertions to support their claim that pemivibart provides sufficiently higher titer values for treatment. First, when using authentic virus neutralization assay (AVNA) results for adintrevimab against Delta (7 ng/mL) and using the lower bound of 90% of the estimated geometric mean ratio of titers at least 0.8 or higher, immunobridging was nominally established through at least Day 14. However, as has been consistently communicated to the Sponsor (communications sent May 19, 2023; January 5, 2024; and April 24, 2024), antibody titer normalization for a direct comparison to a prototype should be based on EC_{50} values obtained using the same assay, and the currently available EC_{50} value data for pemivibart neutralization of emerging variants are derived from the Monogram pseudotyped VLP neutralization assay; EC_{50} values determined in different cell culture assays for a given variant can vary due to differences in assay methodology and endpoints (e.g., virus entry, virus spread, or cytopathic effect), therefore, normalization of titers between prototype and new antibodies should be based on EC_{50} values determined in the same assay. The Sponsor also asserted that pemivibart titers remain at high geometric mean titers of 3731 (XEC) and 3662 (KP.3.1.1) through 14 days. However, there is no data supporting that this titer level is high enough to ensure adequate treatment effects. Another point that the Sponsor made was that "evolution of acceptable lower bounds of defined thresholds has continued to uphold the clinical efficacy of pemivibart in the setting of COVID-19 prevention," and

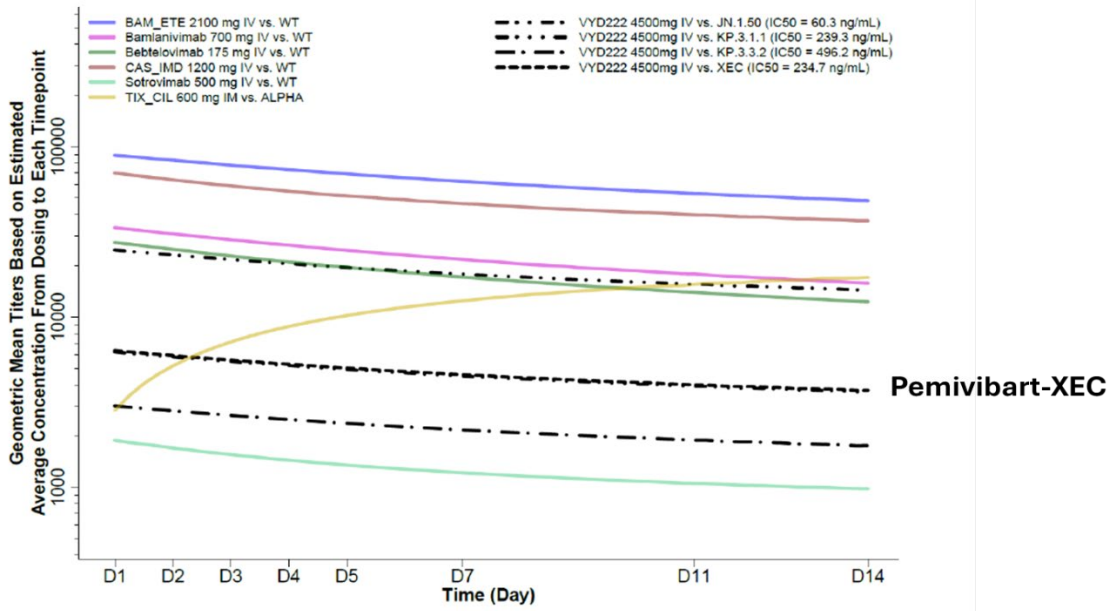
cited the revised EUA factsheet of pemivibart for prevention in September 2024. It appears that the Sponsor refers to our decision to maintain the EUA of pemivibart for PrEP despite the emergence of variants with higher EC_{50} values as compared to JN.1, the relevant variant for the initial authorization. However, available data supporting the initial EUA and the continuation of the EUA for COVID-19 PrEP differ from those for treatment, and considerations made for the PrEP indication may not be relevant to the treatment indication.

Finally, the Sponsor stated that pemivibart IV administration may offer an advantage over adintrevimab IM dosing by providing immediate drug exposure and stated that receiving treatment with sufficient antiviral activity as soon as possible after symptom onset has been shown to have greater clinical efficacy in other clinical studies for both anti-SARS-CoV-2 mAbs and small molecules. While we acknowledge that the current immunobridging approach does not account for the potential benefit of achieving higher titer levels within the first few days after administration, there are no data supporting the position that higher titer levels (compared to the prototype) in this initial brief period are clinically relevant, particularly when the lower titer levels for the remaining longer time period do not support immunobridging. Therefore, this assertion does not alter our conclusion.

Immunobridging Based on a Meta-Analysis Comparison

The Sponsor submitted two analyses comparing the range of pemivibart titers with those associated with other RBD-targeting mAbs, most of which have supportive efficacy data from randomized controlled clinical trials. The first analysis (Method 2 in the EUA request) compares the time-titer profile of pemivibart to other mAbs based on popPK modeling available in the public domain. Of note, the Sponsor provided limited details on their approach to extracting PK data for other mAbs from publications. According to the Sponsor's analysis, titers for pemivibart against XEC are consistently lower than those generated from other mAbs, except sotrovimab (Figure 2). When compared to EVUSHELD, titers for pemivibart against XEC are higher than the titers for EVUSHELD against ancestral variants only for two days.

Figure 2. Pemivibart titer over time and comparator mAbs based on estimated average concentrations



AUC=area under the concentration-time curve; BAM_ETE=bamlanivimab and etesevimab; CAS_IMD=casirivimab and imdevimab; IC_{50}=half-maximal inhibitory concentration; IM=intramuscular; IV=intravenous; mAb=monoclonal antibody; PK=pharmacokinetic; sVNA=serum virus neutralizing antibody; TIX_CIL=tixagevimab and cilgavimab; VYD222=pemivibart; WT=wild-type virus.
The PK profiles for comparators were simulated using population PK parameters available in the public domain. PK profiles for pemivibart are based on the pemivibart popPK model.

Source: Sponsor's submission, EUA122, dated 1/23/2025 (link)

A similar conclusion was reached using another method based on a published meta-analysis (Method 3 in the EUA request, Stadler et al., 2023b). In this meta-analysis, data were extracted from published randomized controlled trials of passive antibody treatment. To compare the efficacy of passive antibody treatments with different administered antibody doses, the authors first calculated the neutralizing (normalized) dose (the administrated mAb dose (in mg) per plasma volume (L) divided by the EC_{50} (mg/L) value of the mAb measured in cell culture as a multiple of the average convalescent neutralization titer). It is noted that the EC_{50} values used to normalize the

dose were predicted values from a linear mixed model. Then the authors fitted a nonlinear logistic regression model to investigate the relationship between the neutralizing dose (fold-convalescent) and efficacy (RRR). The Sponsor compared the neutralizing dose of pemivibart (4500 mg IV) for SARS-CoV-2 variants JN.1, KP.3, KP.3.1.1, LB.1, and JN.1.50 (light green shaded area, Figure 3).

These results were consistent with those from Method 2. For the currently circulating variant (XEC), the neutralizing dose of pemivibart (11.2) is higher than one previously authorized mAb (i.e., sotrovimab) but falls below the other RBD-targeting mAbs included in the analysis with clinical efficacy data for treatment of COVID-19 (see Figure 3). It should also be noted that neutralizing dose calculations do not account for differences in non-neutralizing activities of mAbs (e.g., Fc-mediated effector functions), which may significantly contribute to efficacy, particularly with respect to treatment.

In this analysis, the Sponsor's assertion significantly relies on the comparison to various trials conducted with convalescent plasma (green bars in Figure 3). However, we do not consider convalescent plasma data adequate as a benchmark for immunobridging of mAbs because of inherent differences between a mAb and convalescent plasma, including the polyclonal nature and heterogeneity in neutralizing activity of convalescent plasma and potential differences in the non-neutralizing functions of convalescent plasma relative to a mAb. The Sponsor also stated that the range of pemivibart neutralizing dose is on the plateau of the dose-response curve. However, due to the limitations of the analysis (described further below) including the fitted-curve, a reliable determination cannot be made based on the comparison between pemivibart titer against XEC and the dose-response curve.

Additional limitations of this Method 3 meta-analysis approach include the following:

- For the exposure-response model, the authors used the neutralizing (normalized) dose as the exposure parameter instead of the neutralized antibody titer in serum. This approach does not account for the potential impact of the pharmacokinetic profile of each mAb on efficacy.

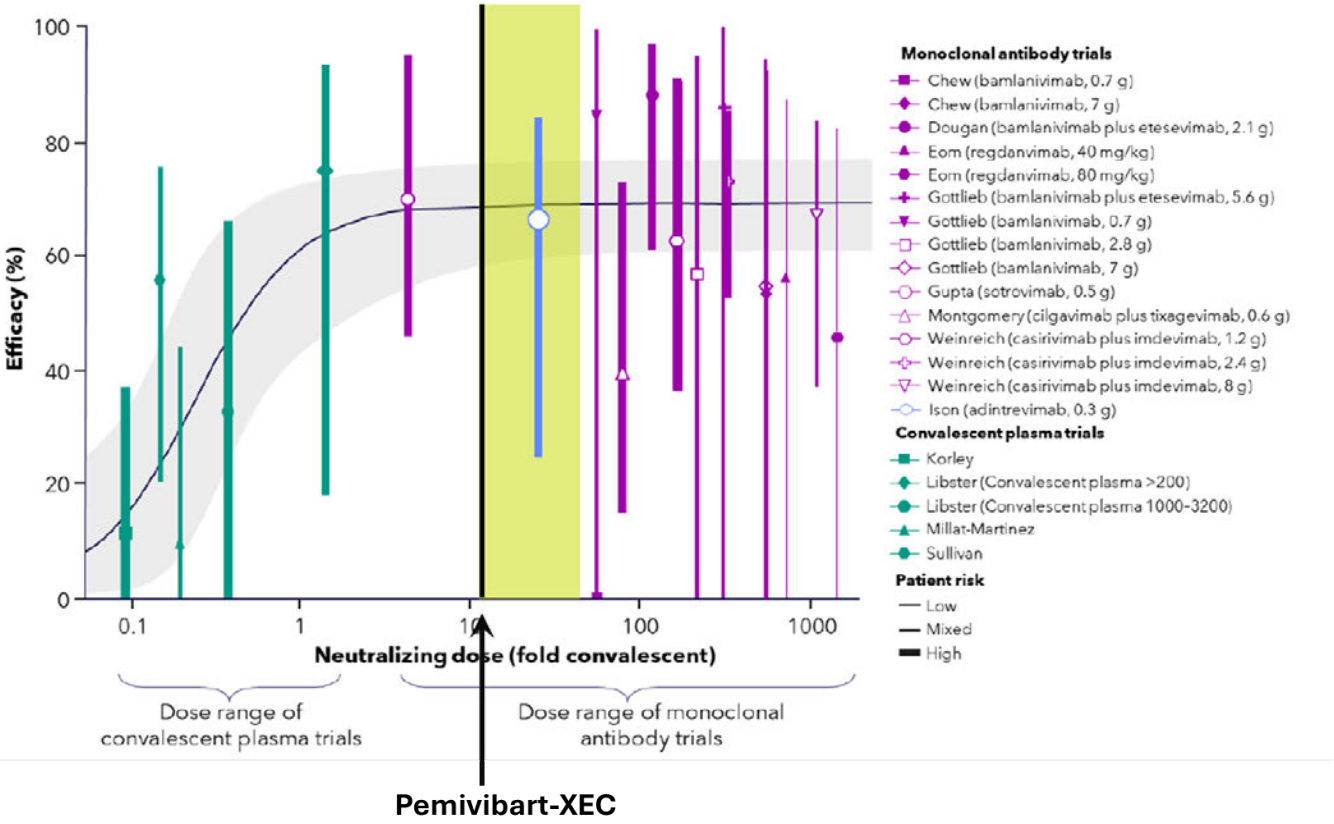
- Only one logistic model was fitted to the limited data to construct the exposure-response curve. Additional models may be needed to verify the goodness-of-fit of the model presented.

- Limited data (only 19 data points) were used to fit the model, including 5 data points for the lower neutralizing doses, which predominately come from the 4 convalescent plasma trials.

- Some efficacy data from the prior RBD mAb trials are based on small sample sizes, which contribute to the wide confidence intervals in the estimated relationship between dose and efficacy (i.e., exposure-response curve). Additionally, few trials were powered to demonstrate efficacy based on the preferred primary endpoint of hospitalization or all-cause death.

- Clinical efficacy data supporting the other comparator mAbs were based on different populations and SARS-CoV-2 variants that are no longer circulating. Additionally, the variability associated with cell culture-based EC_{50} value estimates, along with limitations related to PK data and efficacy estimates for the mAbs in prior clinical trials, impact the ability to precisely estimate titer ranges for treatment efficacy.

Figure 3. Neutralizing dose-response curve for pemivibart versus other mAbs previously evaluated for treatment of COVID-19



Source: Sponsor's submission, EUA122, dated 1/23/2025 (link). The lowest neutralizing dose of pemivibart (11.2, indicated with a black arrow) is against XEC and the highest neutralizing dose of pemivibart is against JN.1.50 (44.3).

In conclusion, based on Methods 2 and 3, the titer range for pemivibart against relevant SARS-CoV-2 variants is consistently lower than the titers observed for the majority of other RBD-targeting mAbs, except sotrovimab, that have evidence of clinical efficacy from prior trials. As stated in the PrEP review, to support immunobridging, the neutralization titer of a new mAb should be similar to or higher than the majority of products with efficacy data due to the uncertainties and limitations associated with immunobridging and a meta-analytic approach.

VII. Risk-Benefit Assessment and Recommendation for Emergency Use

Based on the totality of scientific evidence, the CDER scientific team has concluded that the known and potential benefits of pemivibart for the treatment of mild-to-moderate COVID-19 in the proposed population do not outweigh the known and potential risks of the product, and that the criteria for issuance of an EUA are not met at this time.

Pemivibart did not meet the direct immunobridging endpoint beyond Day 3 and it is the CDER scientific team's assessment that a longer duration is clinically important, particularly for those who are severely immunocompromised, given the potential for prolonged disease and viral shedding in this population. In the meta-analysis approach, the range of titers for pemivibart against currently or recently circulating variant(s) falls below the range of titers for most other RBD-targeting mAbs, for which evidence of efficacy is available from prior clinical trials. To support immunobridging, the neutralization titer of a new mAb should be comparable to the majority of products with efficacy data due to the uncertainties and limitations associated with immunobridging.

FDA's safety assessment of pemivibart was based on data from the CANOPY trial, which was discussed in detail in the pemivibart EUA review for PrEP. The potential risks of pemivibart for COVID-19 treatment can be largely extrapolated from the CANOPY trial. The risks include a Box Warning for anaphylaxis which was observed in 0.6% (4/623) of participants in the CANOPY trial. Additional Warnings and Precautions include hypersensitivity and infusion-related reactions occurring during the infusion and up to 24 hours after the infusion and may be severe or life-threatening.

Importantly, and consistent with FDA policy, FDA may take into account a variety of considerations in exercising its authorities to authorize a product for emergency use under an EUA.[7] This includes the extent to which the product would serve a significant unmet medical need in the context of available countermeasures and FDA's overall understanding of COVID-19, which has and may continue to evolve over time.[8,9] These considerations, among others, also inform FDA's determination on the sufficiency of evidence necessary to support the issuance of an EUA.

[7] See Guidance for Industry and Other Stakeholders "Emergency Use Authorization of Medical Products and Related Authorities" (January 2017).
[8] Id.
[9] At the time of this declination, there are multiple FDA-approved and authorized therapeutics intended for the treatment of COVID-19, including mild-to-moderate COVID-19 disease with clinical data supporting their use.

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
02/20/2025 12:02:52 PM

WILLIAM L INCE
02/20/2025 12:25:19 PM

SU-YOUNG CHOI
02/20/2025 12:26:23 PM

CHUNFENG REN
02/20/2025 12:28:29 PM

JULIAN J O REAR
02/20/2025 12:36:34 PM

WEN ZENG
02/20/2025 12:54:30 PM

KIMBERLY A STRUBLE
02/20/2025 12:58:14 PM

WENDY W CARTER
02/20/2025 05:25:01 PM

ADAM I SHERWAT
02/21/2025 06:42:58 AM