

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

Identifying Information

Application type (EUA or pre-EUA) If EUA, designate whether prevent or intra-event EUA request.	EUA	
EUA application number(s)	000122	
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)	
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Integrated review completion date	March 22, 2024	
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 IgG1 λ 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): <ul style="list-style-type: none"> • 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. 	
Product in the Strategic National Stockpile (SNS)	No	
Distributor	Invivyd, Inc.	

Abbreviations: COVID-19, coronavirus disease 2019; CPMS, chief project management staff; DMEPA, Division of Medication Error Prevention Analysis; DPACC, Division of Pulmonology, Allergy, and Critical Care; DPV II, Division of Pharmacovigilance II; EUA, emergency use authorization; IgG, immunoglobulin G; OBP, Office of Biotechnology Products; OND, Office of New Drugs; OPDP, Office of Prescription Drug Promotion; OPE, Office of Pharmacovigilance and Epidemiology; OPMA, Office of Pharmaceutical Manufacturing Assessment; RPM, regulatory project manager; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TL, team lead

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I. 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.¹
- Declared that circumstances exist justifying the authorization of emergency use of drugs and biological products for the prevention or treatment of COVID-19.²

II. Recommendations

A. Recommend EUA Issuance

The Division of Antivirals (DAV), Office of Infectious Diseases (OID), Office of New Drugs (OND), CDER recommends EUA issuance.

The EUA will authorize pemivibart for the pre-exposure prophylaxis of coronavirus disease 2019 (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.

¹ 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>.

² 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.”).

B. Eligibility of the Product for an EUA

- COVID-19 is a serious or life-threatening disease or condition caused by SARS-CoV-2, as specified in the declaration of emergency.
- Based on the totality of the scientific evidence available to FDA, it is reasonable to believe that pemivibart (PEMGARDA) may be effective 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, who have not had a known recent exposure to an individual infected with SARS-CoV-2, and who have moderate-to-severe immune compromise and are unlikely to mount an adequate immune response to COVID-19 vaccination. When used under such conditions, it is reasonable to believe that the known and potential benefits outweigh the known and potential risks of the product.
- There is no adequate, approved, and available alternative to the emergency use of pemivibart 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.

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

Proposed Use(s) Under EUA

Pemivibart for the pre-exposure prophylaxis of coronavirus disease 2019 (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.

Medical conditions or treatments that may result in moderate to severe immune compromise and an inadequate immune response to COVID-19 vaccination include:

- 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)

Limitations of Authorized Use

- Pemivibart is not authorized for use in individuals:
 - For treatment of COVID-19, **or**
 - For post-exposure prophylaxis of COVID-19 in individuals who have been exposed to someone infected with SARS-CoV-2.
- Pre-exposure prophylaxis with pemivibart is not a substitute for vaccination in individuals for whom COVID-19 vaccination is recommended. Individuals for whom COVID-19 vaccination is recommended, including individuals with moderate-to-severe immune compromise who may derive benefit from COVID-19 vaccination, should receive COVID-19 vaccination.
- In individuals who have recently received a COVID-19 vaccine, pemivibart should be administered at least 2 weeks after vaccination.

Recommended Dosage for Use Under EUA

- Adults and adolescents (12 years of age and older weighing at least 40 kg)
 - Initial Dosing
 - The initial dosage of pemivibart is 4500 mg administered as a single intravenous (IV) infusion.
 - Repeat Dose
 - The repeat dosage is 4500 mg of pemivibart administered as a single IV infusion every 3 months. Repeat dosing should be timed from the date of the most recent pemivibart dose.
- Pregnant or lactating patients
 - No dosage adjustment is recommended in pregnant or lactating women. Pemivibart has not been studied in pregnant or lactating women. Pemivibart

should only be used during pregnancy if the potential benefit outweighs the potential risk for the mother and the fetus.

- Other specific populations (e.g., geriatric patients, patients with renal or hepatic impairment)
 - No dosage adjustment is recommended in geriatric patients. Clinical trials of pemivibart have included individuals over age 65, including those over 75 years of age. Based on population pharmacokinetic (PK) analyses, there was no clinically meaningful difference in PK of pemivibart based on age.
 - No dosage adjustment is recommended in patients with renal impairment. Pemivibart is not eliminated intact in the urine, thus renal impairment is not expected to affect the exposure of pemivibart. Similarly, dialysis is not expected to impact the PK of pemivibart.
 - No clinical trials have been conducted to evaluate the effects of hepatic impairment on the PK of pemivibart. The effect of hepatic impairment on the PK of pemivibart is unknown.

Rationale for the Recommended Dosage

The recommended dosage is pemivibart 4500 mg IV every 3 months. The safety, PK, and serum neutralization titer (abbreviated as titer throughout the document) of the recommended dosage was evaluated in the CANOPY trial. Following single dose administration of pemivibart 4500 mg IV, calculated geometric mean titer values [pemivibart serum concentration divided by the neutralization EC₅₀ value of pemivibart against JN.1 determined in an authentic virus neutralization assay ([Table 18](#))] ranged from 3451 (on Day 90) to 22552 (end of infusion on Day 1). When compared to the titers associated with efficacy of three other SARS-CoV-2-targeting mAbs (including adintrevimab, the parent mAb of pemivibart) in prior clinical trials, the range of titers achieved with pemivibart for 3 months following administration of 4500 mg IV were consistent with the titer levels associated with efficacy of the other mAbs in their respective prior clinical trials.

IV. Product Information (Dose Preparation and Administration)

Pemivibart is supplied in a single-dose vial at a concentration of 125 mg/mL. Each pemivibart carton contains nine vials of pemivibart. Each vial contains an overfill to allow the withdrawal of 500 mg (4.0 mL) of pemivibart.

Preparation

- Remove pemivibart vials from refrigerated storage and allow to equilibrate to room temperature (18°C to 26°C [64°F to 79°F]) for 10 minutes before preparation. **Do not expose to direct heat. Do not shake vials.**

- Visually inspect the vials for particulate matter and discoloration. Pemivibart is a clear to slightly opalescent, colorless to yellow solution. Discard the vial if the solution is cloudy, discolored, or if visible particles are observed.
- Prepare IV bag by removing and discarding 36 mL from a 50 mL prefilled bag of 0.9% sodium chloride for IV injection.
- Withdraw 36 mL of pemivibart from nine vials into appropriately sized polypropylene syringe(s) (e.g., one 40 mL syringe or two 20 mL syringes) and inject into prepared 0.9% sodium chloride IV bag.
- The final product for administration will contain 50 mL: 36 mL of pemivibart and 14 mL of 0.9% sodium chloride.
- This product is preservative-free and therefore should be administered immediately.
- If immediate administration is not possible, the diluted solution may be stored at room temperature under ambient light for up to 4 hours. Do not shake the diluted solution.

Administration

- Pemivibart should be prepared and administered by a qualified healthcare provider using aseptic technique.
- Pemivibart should only be administered in settings in which healthcare providers have immediate access to medications to treat a severe hypersensitivity reaction, such as anaphylaxis, and the ability to activate the emergency medical system (EMS), as necessary.
- Attach infusion set including inline 0.2-micron filter to prepared IV bag, then prime the infusion set.
- Administer the entire 50 mL infusion using infusion pump or gravity infusion set over a minimum of 60 minutes. Due to potential overfill, the entire contents of prepared IV bag should be administered to avoid underdosing.
- Once infusion is complete, flush line with 0.9% sodium chloride.
- Clinically monitor patients during infusion and observe patients for at least 2 hours after infusion is complete.

Storage

- Store unopened vials in a refrigerator at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Discard any unused portion.
- **Do not freeze. Do not shake.**

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. Since January 2020, over 1.1 million deaths and over 6.8 million hospitalizations due to COVID-19 have been reported in the U.S. according to the Centers for Disease Control and Prevention (CDC).

The first COVID-19 vaccination was authorized for emergency use by FDA in December 2020, and currently, three vaccines are approved or authorized by FDA. Vaccination is the most effective way to prevent serious outcomes and death. 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.

There is no adequate, approved, and available alternative to the emergency use of pemivibart administered as pre-exposure prophylaxis of COVID-19 in individuals who have moderate-to-severe immune compromise and are unlikely to mount an adequate response to COVID-19 vaccination.

Even though the immune response to vaccination may be blunted, COVID-19 vaccination is still recommended for immunocompromised individuals. Based on the safety and efficacy demonstrated and the widespread availability of COVID-19 vaccines in the U.S., a Limitation of Authorized Use stating that administration of pemivibart is not a substitute for vaccination against COVID-19 will be included in the Fact Sheet for Health Care Providers. This information will also be included in the scope of the authorization (section II) of the Letter of Authorization. In addition, recommendations on the timing of pemivibart in relation to vaccine receipt for immunocompromised individuals will be included in the Fact Sheet for Health Care Providers. Similar messaging will be provided in the Fact Sheet for Patients, Parents and Caregivers.

VI. Related Regulatory Submission(s)

Pemivibart has been studied under IND 165736 (Sponsor: Invivyd, Inc.) in a Phase 1 trial of single ascending doses ranging from 1500-4500 mg via IV push and in an ongoing Phase 3 trial consisting of 4500 mg via IV infusion, followed 3 months later by a second dose of 4500 mg via IV infusion.

Adintrevimab, the parent mAb of pemivibart, was studied under IND 152327 in a Phase 2/3 prophylaxis trial using 300 mg IM administered as a single dose. The Sponsor was Adagio Therapeutics, Inc., which underwent a name change to Invivyd, Inc., on September 13, 2022. Please refer to section VIII Human Clinical Efficacy and Immunobridging for further details.

In addition to the above-mentioned cross-referenced submissions, a master file, MAF# 026457, is referenced for pemivibart. This master file is for the SARS-CoV-2

pseudotyped virus-like particle neutralization assay. The holder of this master file is Monogram Biosciences, Inc.

The initial request for an EUA for pemivibart was submitted on December 27, 2023. Safety data for pemivibart through Day 28 following dosing in all participants in the Phase 3 trial CANOPY were submitted on January 8, 2024. Safety data following the second dose of pemivibart for all participants in CANOPY was submitted on February 23, 2024. Interim PK data through Day 28 from Cohort A (n=98) and B (n=286) were submitted on December 27, 2023. The complete PK data from Cohort A through Day 28 (n=293) and additional data at Day 90 [pre- and post-dose, n=58 and 62, respectively] were submitted on March 1, 2024. Interim population PK reports containing PK data from CANOPY and VYD222-1-001 were submitted on February 8, 2024 and March 8, 2024.

VII. Summary of Clinical Data

The safety and PK data to support the authorization of pemivibart were generated from the ongoing Phase 3 trial CANOPY. Additional data from the Phase 1 trial VYD-222-1-001 and the Phase 3 trial EVADE also support the authorization ([Table 1](#)).

Table 1. All Clinical Trials

Study Number	IND, NDA, BLA, or Literature Reference	Type of Study (PK, BE, Efficacy, Safety)	Population (N)	Study Design and Type of Control	Test Product(s); Dosing Regimens; Dosage Forms; Routes of Administration; Duration	Study Status
VYD222-PREV-001 (CANOPY) NCT06039449	IND 165736	Immuno-bridging/PK, safety	Cohort A: adults who have moderate-to-severe immune compromise (n=300 planned) Cohort B: adults who do not have moderate-to-severe immune compromise, but who are at risk of SARS-CoV-2 infection (n=450 planned)	Phase 3 study to evaluate pemivibart for protection against COVID-19 based on calculated serum viral neutralizing antibody (sVNA) titers against relevant SARS-CoV-2 variants Cohort A: Open-label, single-arm Cohort B: Randomized (2:1), double-blind, placebo-controlled	Single dose on Day 1. Redose with same assigned study drug at Month 3. Administered by IV infusion over 30 min. Cohort A: Pemivibart 4500 mg Cohort B: Pemivibart 4500 mg or placebo	Enrollment complete Cohort A: Pemivibart (n=306) Cohort B: Pemivibart (n=322) Placebo (n=162) Follow-up ongoing
VYD222-1-001 NCT05791318	IND 165736	Safety, PK	Healthy adults (n=30 planned)	Phase 1, randomized (8:2), double-blind, placebo-controlled, single-ascending dose study	Single dose administered as IV push over 4-5 min Pemivibart 1500 mg or placebo; Pemivibart 2500 mg or placebo; Pemivibart 4500 mg or placebo	Enrollment complete Pemivibart (n=24) Placebo (n=6) Follow-up ongoing

Study Number	IND, NDA, BLA, or Literature Reference	Type of Study (PK, BE, Efficacy, Safety)	Population (N)	Study Design and Type of Control	Test Product(s); Dosing Regimens; Dosage Forms; Routes of Administration; Duration	Study Status
ADG20-PREV-001 (EVADE) NCT04859517	IND 152327	Efficacy, safety	Cohort B (PrEP): Adults and adolescents with no known history of or recent exposure to SARS-CoV-2 infection; no prior SARS-CoV-2 vaccine; but whose circumstances put them at increased risk of exposure (n=5142 planned)	Phase 2/3, randomized (1:1), double-blind, placebo-controlled study to evaluate efficacy of adintrevimab in the prevention of RT-PCR-confirmed COVID-19 through 3 months	Single dose administered as IM injection Adintrevimab 300 mg or placebo	Enrollment paused on 11-Jan-2022 due to emergence of the Omicron variant Terminated early on 26-Oct-2022 Adintrevimab (n=1048) Placebo (n=1047)

Source: FDA Review Team

Abbreviations: PK, pharmacokinetics; IND, investigational new drug application; NDA, new drug application; BLA, biologics license application; BE, bioequivalence; PrEP, pre-exposure prophylaxis; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; IM, intramuscular injection; RT-PCR, reverse transcription polymerase chain reaction; COVID-19, coronavirus disease 2019

VIII. Human Clinical Efficacy and Immunobridging

A. Overview of Immunobridging Approach

An immunobridging approach was used to support the “may be effective” standard for this EUA. The immunobridging approach bridges from a new monoclonal antibody (mAb) to a similar mAb for which there are clinical efficacy data (hereafter referred to as the prototype mAb), by comparing the serum neutralization titer between the new mAb and the prototype mAb with clinical efficacy data. SEE ATTACHED ADDENDUM

While actionable results from a controlled clinical trial with clinically meaningful endpoints would be ideal to evaluate the efficacy of a new mAb like pemivibart, completing such a trial for a mAb targeting the receptor-binding domain (RBD) of the SARS-CoV-2 spike protein has been challenging due to the rapid antigenic evolution of SARS-CoV-2; RBD-targeting mAbs are often specific for certain variants and may not be active against antigenically distinct variants that periodically emerge and become dominant.

Extensive internal and external discussions with stakeholders, including the Joint EMA-FDA workshop, Efficacy of Monoclonal Antibodies in the Context of Rapidly Evolving SARS-CoV-2 Variants (15th December 2022), were held to address this issue. As stated in the workshop summary ([EMA and FDA 2023](#)), there was overall agreement among the stakeholders on the need to expedite the development of new mAbs for the pre-exposure prophylaxis of immunocompromised patients using a biomarker approach based on immunobridging (e.g., geometric mean titer of neutralizing antibodies). Based on the workshop and follow-up discussions, the Agency concluded that immunobridging could be an acceptable approach to support an EUA for new mAbs for pre-exposure prophylaxis of immunocompromised patients.

A titer is a commonly used endpoint to support the development of products for which neutralization activity against a pathogen, measured in cell culture-based assays, is considered the key mechanism of action, and where there is biological plausibility in the correlation between the titer and the degree of protection. In addition, for COVID-19, several studies have indicated a correlation between antibody titer level and protection from symptomatic SARS-CoV-2 infection following the administration of monoclonal antibodies ([Follmann et al. 2023](#); [Schmidt et al. 2023](#); [Stadler et al. 2023](#)). In summary, the use of titer as a surrogate endpoint to determine whether a new mAb may be effective for an EUA is supported by the mAb’s purported mechanism of action as well as available data indicating the correlation between the titer and the protection from symptomatic SARS-CoV-2.

The Agency also determined that a calculated titer based on PK can be used in lieu of a measured titer for immunobridging. A calculated titer is defined as the serum mAb concentration, at a specific time point following the administration of a mAb, divided by a cell culture-based EC₅₀ value of the mAb against a specific SARS-CoV-2 variant. Titer

can be calculated for any SARS-CoV-2 variant using the same PK information as long as a cell culture EC₅₀ value of the mAb against the variant has been determined. In contrast, a measured titer is determined in a cell culture-based neutralization assay using serum collected from individuals who received the mAb.

A calculated titer does not account for pre-existing cellular or humoral immunity against SARS-CoV-2 (i.e., the neutralizing activity in serum is attributed only to the administered mAb) and would be expected to approximate the change from baseline in measured titer in individuals with some baseline immunity. In contrast, measured titers would not distinguish between the neutralizing activities of the administered mAb and baseline neutralizing activity or added neutralizing activity during the study (i.e., neutralizing antibodies induced by vaccination or infection). A benefit of the calculated titer approach over the measured titer approach is the ability to promptly estimate titer values against any emerging variants and compare the titer values across multiple products and multiple variants at the same time.

Of note, the conclusion drawn from the immunobridging approach is limited to a specific variant for which a cell culture-based EC₅₀ value is available. In this review, all assessments were performed based on the EC₅₀ value of pemivibart against JN.1 determined in a pseudotyped VLP assay (PVNA) or an authentic virus neutralization assay (AVNA). Therefore, the Agency's conclusion is only applicable to JN.1 or variants with very similar EC₅₀ values determined in the same or similar assays (see Section [XIII](#)).

There are two possible approaches for conducting immunobridging analyses using calculated titers to support authorization of a new mAb for the pre-exposure prophylaxis of COVID-19. The first approach is a direct comparison of the titer of a new mAb to that of a similar mAb with clinical efficacy data (prototype mAb). The direct comparison of titers between a prototype mAb and a new mAb is contingent on the similarities between the prototype and new mAb. Both mAbs will have used the same manufacturing platform, and the two mAbs should have similar analytical (manufacturing), safety, and PK characteristics, and similar mechanism of action (e.g., competitive inhibition of ACE2 binding to the RBD), and non-neutralizing functions (e.g., predicted Fc-mediated effector functions). The differences between the prototype and new mAb are limited to the Fab regions and their specific structural epitopes.

The potential strength of this approach is the ability to use the efficacy data of a similar mAb (prototype) to provide a higher degree of certainty in bridging available evidence associated with efficacy between products. However, the strength of a direct titer comparison approach is dependent on the amount and quality of the efficacy data of a prototype.

The second approach uses data from a meta-analysis that compares the new mAb to 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. This approach assumes that, despite notable differences in manufacturing, PK, and Fc functions among these mAbs, the efficacy of the mAbs is primarily driven by the

neutralization activity of the mAb. With this assumption, an exposure (titer)-response (efficacy) relationship from prior clinical studies of several mAbs can provide a range of titer values associated with efficacy.

For this approach, the Agency utilized a published meta-analysis ([Stadler et al. 2023](#)). Briefly, this study was conducted to model the titer-response relationship for mAbs evaluated for the pre-exposure prophylaxis of COVID-19 using published efficacy data of three mAbs (casirivimab/imdevimab, cilgavimab/tixagevimab, and adintrevimab, see [Figure 1](#)). The Agency critically reviewed the methodology and results described in the publication and the study design and results of individual studies contributing to the analyses. Overall, the Agency concluded it is reasonable to believe that a new mAb may be effective if the range of titer values is consistent with the titer values associated with efficacy in prior clinical trials, and a new mAb may be effective if the titer range for the new mAb falls where the majority of the observed data provided evidence of efficacy in prior trials.

While a meta-analytic approach may be able to support an EUA for the pre-exposure prophylaxis of COVID-19, it is important to acknowledge the limitations and uncertainties of this approach ([Appendix 4](#)). Specifically, limitations regarding the fitted curve of the titer-response relationship include variability and heterogeneity of the EC₅₀ values used to calculate titers, the high variability in the estimated efficacy (relative risk reduction), the limited data points, especially in the lower calculated titer range, and the fact that the dependence among the data points was not accounted for in the analysis.

There are also general limitations related to either immunobridging approach that should be considered. The immunobridging analysis and conclusion are significantly dependent on the EC₅₀ value used to derive calculated titer values. EC₅₀ values determined in cell culture assays can vary due to differences in assay methodology and endpoints (e.g., virus entry, virus spread, or cytopathic effect) and inherent variability within assay types. While we considered the most robust comparison of titers between prototype and new antibodies to be based on EC₅₀ values determined in the same well-characterized assay, anticipated cross-assay variability (e.g., ≥2 fold differences) may result in a different immunobridging conclusion. Thus, we also considered a range of reported EC₅₀ values and fold-differences when conducting analyses.

Additionally, the efficacy data from prior clinical trials with other neutralizing human monoclonal antibodies against SARS-CoV-2 was based on different populations and pre-Omicron SARS-CoV-2 variants that are no longer circulating. Along with the limitations stated in [Appendix 4](#), these inherent limitations of the immunobridging approach do not allow for an accurate prediction of efficacy (such as specific relative risk reduction as compared to placebo) of a new product based on data generated in prior clinical trials.

Despite these limitations, the Agency concluded that an immunobridging approach may be able to support the emergency use authorization of a new mAb for the prevention of COVID-19. Of note, an immunobridging approach would not provide substantial evidence of effectiveness to support a BLA.

Description of the EVADE Trial: Study Design and Efficacy Results

EVADE Trial Design

Please refer to [Appendix 3](#) for further details.

The source of clinical efficacy data for adintrevimab (the parent mAb; see Section XIII) to support the pre-specified immunobridging approach for pemivibart is the EVADE trial (ADG20-PREV-001). EVADE was a Phase 2/3, multicenter, double-blind, placebo-controlled, randomized study that evaluated the safety and efficacy of adintrevimab in the prevention of symptomatic COVID-19 in adults and adolescents with no known history of SARS-CoV-2 infection but whose circumstances placed them at increased risk of acquiring SARS-CoV-2 infection and developing symptomatic COVID-19. Two independent cohorts were included in this trial. Cohort A evaluated post-exposure prophylaxis, and therefore, the efficacy results from this cohort are not relevant to the EUA request for pemivibart. Cohort B in EVADE evaluated pre-exposure prophylaxis (PrEP), which is relevant to the EUA request for pemivibart.

Cohort B enrolled participants with no known history of SARS-CoV-2 infection and no known recent exposure but whose circumstances put them at increased risk of exposure to SARS-CoV-2 and symptomatic COVID-19. Participants were randomized 1:1 to receive a single IM dose of 300 mg adintrevimab or placebo. The primary endpoint was the proportion of participants with RT-PCR–confirmed symptomatic COVID-19 through 3 months.

EVADE Results

Note, FDA reviewed the trial results as presented in the clinical study report but did not conduct an independent analysis of the trial using datasets.

In the pre-Omicron analysis population, the proportion of participants with RT-PCR–confirmed symptomatic COVID-19 through 3 months or emergence of Omicron (primary efficacy endpoint) was 1.6% in the adintrevimab arm compared with 5.5% in the placebo arm, a 71.0% relative risk reduction. The standardized risk difference (primary estimand) was -3.9% (95% CI: -5.75, -2.01; $p < 0.0001$), demonstrating a 70.8% standardized relative risk reduction in favor of adintrevimab through 3 months.

Description of the CANOPY Trial (VYD222-PREV-001): Study Design and Key Results

To support immunobridging, the Sponsor conducted CANOPY Part A. The trial was designed to support the first approach of immunobridging, which involves a direct comparison between the parent mAb (adintrevimab) and pemivibart (Section [XIII](#)).

Trial Design and Primary Endpoints

CANOPY is an ongoing Phase 3 multicenter trial evaluating pemivibart in adults who test negative for current SARS-CoV-2 infection in two distinct cohorts. While adolescents aged 12 to <18 years and weighing at least 40 kg were eligible for

enrollment, no adolescents were enrolled. In both cohorts, the dosing schedule was an IV infusion of study treatment on Day 1 followed by redosing with the same study treatment at Month 3.

Cohort A is a single-arm, open-label study of pemivibart 4500 mg adults with moderate-to-severe immune compromise designed to evaluate (1) the safety and tolerability of pemivibart and (2) protection against symptomatic COVID-19 based on titers against SARS-CoV-2 following pemivibart administration (immunobridging). Cohort B is a randomized, double-blind, placebo-controlled comparison of pemivibart 4500 mg vs. placebo designed to evaluate the safety and tolerability of pemivibart. Blinding in Cohort B was maintained through approximately Day 28, after which blinding was compromised.

The primary efficacy objective of Cohort A was to evaluate protection against symptomatic COVID-19 based on titers against SARS-CoV-2 following pemivibart administration by immunobridging to historical data from the EVADE study, which provided data of clinical efficacy for adintrevimab, the parent mAb of pemivibart.

The primary immunobridging endpoint for Cohort A compared the ratio of the geometric mean titers between pemivibart against the relevant variant (JN.1) at Day 28 to the reference titer at Day 28. The reference titer at Day 28 was the extrapolated titer from the Day 90 adintrevimab titer (which was calculated based on Day 90 concentration of adintrevimab and the EC₅₀ value against the B.1.617.2 (Delta) variant using AVNA) using the half-life of pemivibart. Immunobridging would be established if the lower limit of the 2-sided 90% CI of the ratio of the geometric mean titer value is greater than 0.8.³

Eligibility Criteria

Cohort A participants were required to meet one of the following criteria for moderate-to-severe immune compromise:

- Actively treated for solid tumor or hematologic malignancies
- Acute leukemia, chronic lymphocytic leukemia, non-Hodgkin lymphoma, or multiple myeloma (regardless of treatment)
- Solid organ transplant recipient taking immunosuppressive therapy

³ The geometric mean titer associated with adintrevimab efficacy is 3514, which was calculated based on the adintrevimab concentration on Day 90 and adintrevimab AVNA EC₅₀ value against Delta (7 ng/mL). This titer value is the efficacy benchmark for the immunobridging approach. In CANOPY Cohort A, the primary endpoint is designed to determine whether the geometric mean titer of pemivibart on Day 90 would be similar or higher than 3514 (the efficacy benchmark titer). The reference titer in the primary endpoint is the Day 28 titer of pemivibart that would yield a titer of 3514 on Day 90 based on the half-life of pemivibart (i.e., back-calculated based on the half-life of pemivibart). The titer value of 8944 of pemivibart against JN.1 on Day 28 is anticipated to result in a titer similar to or higher than 3514 on Day 90 based on the half-life of pemivibart. Therefore, 8944 was used as the reference titer to be compared to pemivibart titer on Day 28 against JN.1.

- Chimeric antigen receptor (CAR)-T-cell therapy or hematopoietic stem cell transplant (within 2 years of transplantation or taking immunosuppressive therapy)
- Moderate or severe primary immunodeficiency
- Advanced HIV infection (CD4⁺ cell count <350 cells/mm³)
- Taking high-dose corticosteroids (≥20 mg of prednisone or equivalent per day when administered for at least 2 weeks), B-cell-depleting agents (within the past year), alkylating agents, antimetabolites, transplant-related immunosuppressive drugs, TNF blockers, or other immunosuppressive or immunomodulatory biologic agents for rheumatic diseases

Cohort B participants were required to be at risk of acquiring SARS-CoV-2 due to regular unmasked face-to-face interactions in indoor settings (e.g., workplace, gym facility, public transportation, etc.) but without meeting any of the above criteria for immune compromise.

Eligibility criteria for both cohorts (unless otherwise specified) included:

- Tests negative for current SARS-CoV-2 infection by local antigen test or RT-PCR at the time of screening
- Agrees to defer receipt of any COVID-19 vaccination or booster for a minimum of 28 days after dosing on Day 1
- Has not received a COVID-19 vaccine or booster within 120 days before randomization (Cohort B only)
- Has not received convalescent plasma or a mAb to SARS-CoV-2 active against currently circulating variants, including in the setting of a clinical trial, within 120 days before randomization
- Has no known or suspected SARS-CoV-2 infection within 120 days before randomization
- Has not been exposed to someone with known or suspected SARS-CoV-2 infection in the 5 days before randomization
- For participants assigned female sex at birth:
 - Is not of childbearing potential, OR
 - Is of childbearing potential and practicing adequate contraception for at least 28 days before dosing on Day 1 through 6 months after any dosing and has a negative pregnancy test result on Day 1.
 - NOTE: Pregnant participants will be eligible for enrollment after iDMC review of safety lead-in data only upon Sponsor communication to sites and only in regions permitted by local health authorities and local ethics committees. If pregnant participants are eligible for enrollment, this criterion is no longer applicable.

Analysis Populations

The analysis data sets are defined in [Table 2](#).

Table 2. Analysis Sets, CANOPY

Defined Analysis Data Sets	Description
Full Analysis Set (FAS)	Cohort A: Includes all participants who received a full dose of study drug at the initial dosing. Cohort B: Includes all randomized participants regardless of whether the participant received study drug. Participants will be analyzed based on the treatment they are randomized to, irrespective of what they actually might have received.
Pharmacokinetic Full Analysis Set (PK FAS)	Includes all participants who received a full dose of study drug at the initial dosing and who have a quantifiable serum concentration result (\geq LLOQ) at Day 28.
Modified Full Analysis Set (mFAS)	Cohort A: Includes all FAS participants with measured Day 1 sVNA titers against a relevant variant below the minimum Protection Titer Threshold without current SARS-CoV-2 infection at baseline as measured by central lab RT-PCR. Cohort B: Includes all FAS participants without current SARS-CoV-2 infection at baseline as measured by central lab RT-PCR. Participants will be analyzed based on the treatment they are randomized to, irrespective of what they actually might have received.
Safety Analysis Set	Includes all participants who have received any amount of study drug. Participants will be analyzed based on the actual treatment they received.
Safety Redosing Set	Includes all participants who received any amount of study drug at the initial dosing (Day 1) and the redosing (Month 3).
PK Analysis Set	Includes all participants who received any amount of pemivibart during the study and have at least one quantifiable serum concentration (\geq LLOQ) postdose.

LLOQ=lower limit of quantification; PK=pharmacokinetic; RT-PCR=reverse transcription polymerase chain reaction;
sVNA=serum virus neutralizing antibody
Source: EUA Summary Report v2.0, 05-Jan-2024

Participant Disposition

Disposition for Cohort A participants is presented in [Table 3](#).

Table 3. Participant Disposition, CANOPY, Cohort A

Disposition	Cohort A, Pemivibart (n=306) n (%)
Discontinued from study	6 (2)
Reason for discontinuation	
Death	1 (<1)
Lost to follow-up	1 (<1)
Physician decision	0
Participant request	1 (<1)
Withdrawal of consent	3 (1)

	Cohort A, Pemivibart (n=306) n (%)
Disposition	
Duration of total follow-up	
Mean (SD), days	122 (19)
Median (Min, Max), days	122 (1, 155)
≥28 days	304 (99)
≥91 days (3 months)	302 (99)
≥183 days (6 months)	0
Duration of follow-up following redosing	
3-28 days	295 (96)
29-90 days	181 (59)
≥91 days	0

Source: Derived from the EUA Summary Report v3.0, 19-Feb-2024, Table 6
Abbreviations: SD, standard deviation

Baseline Demographics and Characteristics

Baseline demographics and characteristics for the full analysis set are displayed in [Table 4](#). Cohort A enrolled older participants and more female participants compared to Cohort B. Cohort B enrolled a larger percentage of Black/African American participants compared to Cohort A. No other differences are notable.

Table 4. Baseline Demographics and Characteristics, CANOPY, Full Analysis Set

Characteristic	Cohort A Pemivibart N=306	Cohort B Pemivibart N=322	Cohort B Placebo N=162
Sex, n (%)			
Male	119 (39)	156 (48)	71 (44)
Female	187 (61)	166 (52)	91 (56)
Age, years			
Mean (SD)	56 (13)	48 (15)	48 (15)
Median (min, max)	59 (22, 83)	48 (18, 84)	48 (19, 78)
Age groups (years), n (%)			
18-<55	127 (42)	204 (63)	102 (63)
≥55	179 (59)	118 (37)	60 (37)
≥65	95 (43)	61 (19)	27 (17)
≥75	22 (7)	9 (3)	1 (<1)
Race, n (%)			
White	262 (86)	201 (62)	108 (67)
Black/African American	37 (12)	94 (29)	48 (30)
Asian	6 (2)	15 (5)	7 (4)
American Indian or Alaska Native	4 (1)	3 (1)	1 (<1)
Native Hawaiian or Pacific Islander	0 (0)	3 (1)	0 (0)
Other, multiple, not reported	8 (3)	11 (4)	4 (2)
Ethnicity, n (%)			
Hispanic	17 (6)	87 (27)	56 (35)
Non-Hispanic	286 (94)	231 (72)	103 (64)
Not reported	3 (1)	4 (1)	3 (2)

Characteristic	Cohort A Pemivibart N=306	Cohort B Pemivibart N=322	Cohort B Placebo N=162
Weight, kg			
Mean (SD)	84 (23)	85 (20)	84 (21)
Median (min, max)	79 (43, 191)	83 (47, 166)	81 (43, 163)
BMI, kg/m ²			
Mean (SD)	30 (8)	30 (7)	30 (7)
Median (min, max)	28 (17, 61)	28 (18, 56)	29 (17, 57)
Region, n (%)			
United States	306 (100)	322 (100)	162 (100)

Source: Derived from the EUA Summary Report v2.0, 05-Jan-2024

Abbreviations: BMI, body mass index; SD, standard deviations

In Cohort A, the most common immunocompromising condition was receipt of high-dose corticosteroids or other immunosuppressive medications ([Table 5](#)).

Table 5. Baseline Immunocompromising Conditions, CANOPY, Cohort A, Safety Analysis Set

Parameter	Cohort A Pemivibart N=306 n (%)
Actively treated for solid tumor or hematologic malignancies	20 (6.5)
Acute leukemia, chronic lymphocytic leukemia, non-Hodgkin lymphoma, or multiple myeloma (regardless of treatment)	40 (13.1)
Solid organ transplant recipient taking immunosuppressive therapy	33 (10.8)
CAR-T-cell therapy or hematopoietic stem cell transplant (within 2 years of transplantation or taking immunosuppressive therapy)	2 (0.7)
Moderate or severe primary immunodeficiency	37 (12.1)
Advanced HIV infection (CD4 ⁺ cell count less than 350 cells/mm ³)	27 (8.8)
Taking other immunosuppressive medications	200 (65.4)

Source: Derived from the EUA Summary Report v2.0, 05-Jan-2024

Abbreviations: CAR, chimeric antigen receptor; CD4, clusters of differentiation 4; HIV, human immunodeficiency virus

CANOPY Results

Results of the Immunobridging Endpoint Specified In Protocol

At the time the protocol was designed, EC₅₀ values for pemivibart and the parent antibody (adintrevimab) against a relevant variant (XBB.1.5) and Delta, respectively, were determined using different assays [a pseudotyped virus-like particle (VLP) assay (PVNA) for pemivibart and an authentic virus neutralization assay (AVNA) for adintrevimab; see assay descriptions in Section [XIII](#)]. Because JN.1 was the dominant circulating SARS-CoV-2 variant when the CANOPY results became available, the analyses were updated to include the EC₅₀ value for JN.1 (using AVNA and PVNA) instead of XBB.1.5 (using PVNA).

The primary immunobridging results are as follows: The geometric mean ratio between the calculated titer for pemivibart against JN.1 (based on an AVNA EC₅₀ value of 63.6 ng/mL) and the calculated titer for adintrevimab against Delta (based on an AVNA EC₅₀

value of 7 ng/mL), was 0.82 (90% CI: 0.80-0.85).⁴ While the results met the protocol-specified endpoint, there are limitations of this analysis, including differences in the methodologies of the respective AVNA assays used to determine the EC₅₀ values for pemivibart and adintrevimab against the respective variants (see Section XIII).

Given the limitations of the primary immunobridging results, a key sensitivity analysis was performed using EC₅₀ values derived from an identical cell-based assay (PVNA). When using the calculated titer of pemivibart against JN.1 and the calculated titer of adintrevimab against Delta based on EC₅₀ values derived from the same PVNA (74.6 ng/mL and 3.5 ng/mL, respectively), the geometric mean ratio between the two values was 0.35 (90% CI: 0.34-0.36). This sensitivity analysis highlights the impact of even modest differences in EC₅₀ values on the results of the primary immunobridging endpoint.

While the results of the key sensitivity analysis did not meet the protocol-specified endpoint, assumptions and limitations of the protocol-specified endpoint should be recognized in interpreting the results. This endpoint is based on a lower limit of commonly used bioequivalence criteria (80%), not based on a noninferiority margin derived from prior clinical trial data. The bioequivalence criteria are commonly used to demonstrate the lack of a significant difference in the rate and extent of absorption between two products without considering other factors (e.g., exposure-response relationship for efficacy or safety or any other information supporting the range of exposures associated with clinical benefit). Therefore, while the results of the sensitivity analysis did not meet the protocol-specified endpoint, this does not necessarily indicate a low or an unacceptable level of efficacy is anticipated with the product.

Moreover, the benchmark (comparator) is the titer of adintrevimab against the Delta variant at Month 3. While the exact duration of efficacy of adintrevimab is unknown, limited follow-up data beyond Month 3 in the EVADE trial suggests potentially longer duration of protection of adintrevimab, thus the Month 3 comparison is considered a conservative benchmark.

In addition, differences beyond the eight amino acid changes in the Fab between adintrevimab and pemivibart were noted; specifically, differences in half-life values (approximately 140 days for adintrevimab versus 45 days for pemivibart) were observed. This raises a concern that the two products may not be highly similar, which is a critical assumption for the prototype-based direct immunobridging.

⁴ Based on the geometric mean titer of pemivibart at Day 28 against JN.1 (7377, 90%CI: 7159-7902) using PK Full Analysis Set (PK FAS) includes all participants who received a full dose of study drug (pemivibart) at the initial dosing and have a quantifiable serum concentration result at Day 28 (n=287); when calculating geometric mean titers and associated statistics, the EC₅₀ value was treated as a constant (e.g., variability and ranges of EC₅₀ values for pemivibart against JN.1 in the cell-based assays were not factored in when generating 90% CIs of geometric mean titer values). When geometric mean titer values and associated 90% CIs were calculated by treating the EC₅₀ values as variable, the results were very similar to those calculated when treating EC₅₀ values as a constant. As the two approaches yield very similar results, the EC₅₀ value was consistently treated as a constant throughout the review.

Given the aforementioned limitations with the direct titer comparison between pemivibart and adintrevimab, the review team decided to include in the overall analysis a comparison between the titer of pemivibart against JN.1 to the titer-response trend based on a meta-analysis to further support our determination as to whether the product may be effective.

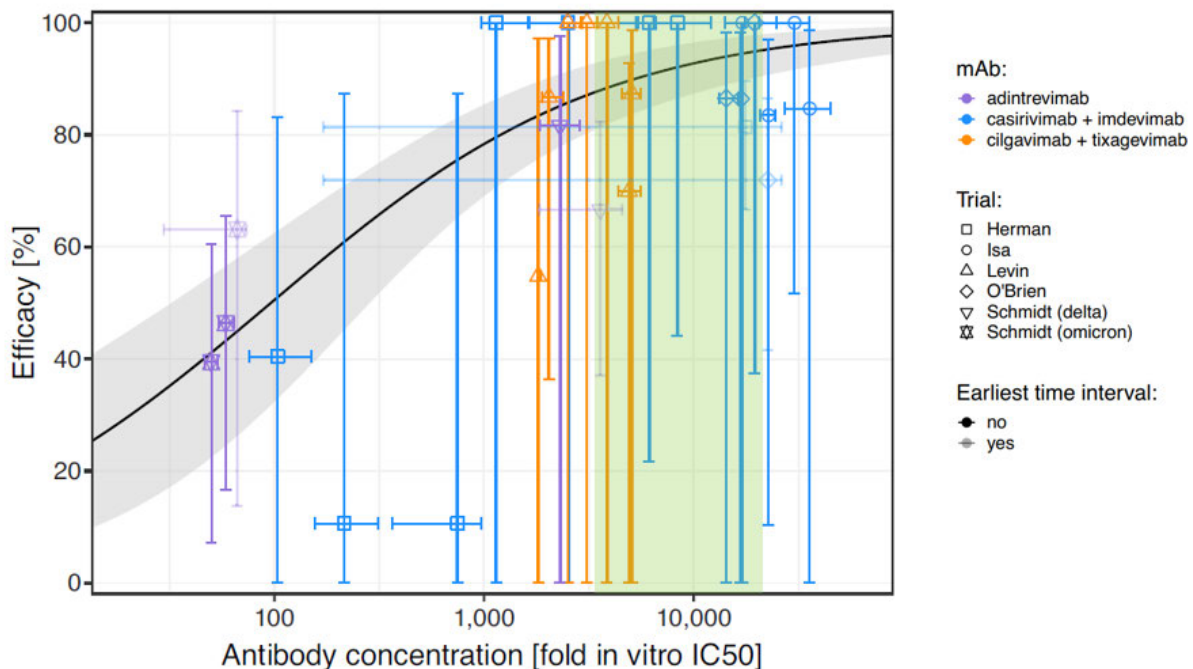
Comparison of the Range of Titers of Pemivibart 4500 mg IV and Those Associated With Other mAbs With Efficacy (Meta-Analysis)

Following a single dose administration of pemivibart 4500 mg, the geometric mean titers at the end of infusion on Day 1, at Month 1, and at Month 3 are 22552 (%CV:123.42), 7204 (%CV:37), and 3451 (%CV:39) respectively⁵. The range of titers achieved with pemivibart for 3 months following administration of 4500 mg IV were consistent with the titer levels associated with efficacy in prior clinical trials with other mAbs ([Figure 1](#)). This supplementary analysis further supports the Agency's conclusion that pemivibart may be effective with dosing every 3 months. The accumulation ratio with every 3-month dosing is approximately 1.3, thus significant accumulation is not anticipated upon repeat dosing.

As stated in [Appendix 4](#), it should be noted that the estimates of predicted efficacy cannot be inferred based on the comparison of the ranges of pemivibart titer values and the curve depicted in [Figure 1](#).

⁵ Calculated based on observed pemivibart geometric mean concentrations on Day 1 [1434.3 mcg/mL (%CV: 123.4, n=295)], Day 28 [458.2 mcg/mL (%CV: 37.0, n=293)] and Day 90 [219.5 mcg/mL, (%CV: 38.9, n=58)] using the AVNA EC₅₀ value of 63.6 ng/mL

Figure 1. Comparison Between Titer-Response Relationship Based on a Meta-Analysis and the Range of Titer Following the Administration of Pemivibart 4500 mg IV (Green Box)



Source: modified from Fig 2 of [Stadler et al. 2023](#)

This graph illustrates calculated titers (antibody concentration fold in vitro IC_{50} [cell culture EC_{50} value] of each antibody) and protective efficacy in the matching trial and time interval for three mAbs. For full details, refer to [Stadler et al. 2023](#). The green box indicates the range of titer values of pemivibart against JN.1 at the recommended dosing regimen

Abbreviations: EC_{50} , half-maximal effective concentration; IC_{50} , half-maximal inhibitory concentration; IV, intravenous; mAb, monoclonal antibody

B. Secondary Clinical Efficacy Endpoint

A secondary endpoint of CANOPY was RT-PCR-confirmed symptomatic COVID-19 through 3, 6, and 12 months. Participants were instructed per protocol to monitor for and report any symptoms of COVID-19-like illness (CLI) to the site; in addition, sites contacted participants weekly in between visits through Month 3 to remind participants to monitor for and report CLI symptoms. 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 and presence of long COVID symptoms, respectively.

Cohort A

Limited data are available for the secondary endpoint of RT-PCR-confirmed symptomatic COVID-19 in Cohort A. The interpretation of this endpoint is challenging because of the single-arm, open-label design. Based on available information, 2 of 306 (0.7%) participants in Cohort A met the protocol-defined criteria for COVID-19 through Month 3. A third participant met criteria for COVID-19 the day after Month 3 redosing of pemivibart. A brief description of the three cases is as follows.

Participant (b) (6) (RT-PCR-Confirmed COVID-19 Through Month 3)

A 34-year-old White female taking adalimumab for treatment of ankylosing spondylitis received the full dose of pemivibart 4500 mg on Day 1 and had CLI symptom onset on Day 68. The CLI Day 1 visit occurred 9 days after symptom onset, and a positive RT-PCR test from a nasal swab confirmed SARS-CoV-2 infection. COVID-19 treatment included nirmatrelvir/ritonavir and prednisone. Symptoms resolved 21 days after onset. The overall severity was moderate, and variant testing indicated that the infection was with JN.1.4.

Participant (b) (6) (RT-PCR-Confirmed COVID-19 Through Month 3)

A 53-year-old White female taking ocrelizumab for treatment of multiple sclerosis received the full dose of pemivibart 4500 mg on Day 1 and had CLI symptom onset at Day 62. The CLI Day 1 visit occurred 4 days after symptom onset, and a positive RT-PCR test from a saliva sample confirmed SARS-CoV-2 infection. Reported treatment included ibuprofen as needed. Symptoms resolved 7 days after onset. The overall severity was mild. No variant information is available.

Participant (b) (6) (RT-PCR-Confirmed COVID-19 After Month 3)

A 24-year-old White female taking abatacept for treatment of psoriatic arthritis received the full dose of pemivibart 4500 mg on Day 1 and again at Month 3. CLI symptom onset occurred 1 day after the Month 3 dose. The CLI Day 1 visit occurred 5 days after symptom onset, and a positive RT-PCR test from a nasal swab confirmed SARS-CoV-2 infection. No additional information is available. Follow-up is ongoing, and the CLI Day 28 visit had not occurred at the time of this review.

Cohort B

On March 18, 2024, the Sponsor submitted unblinded topline results of the secondary clinical efficacy endpoint from Cohort B through Month 3. Per the Sponsor's submission, the proportion of participants with RT-PCR-confirmed symptomatic COVID-19 through 3 months was 0.3% (1/314) in the pemivibart arm and 5% (8/159) in the placebo arm. Of note, the protocol specified that no formal statistical testing would be conducted for Cohort B and secondary and exploratory efficacy endpoints would be analyzed descriptively only.

Prior to the Sponsor's submission of March 18, 2024, the Agency expressed concerns related to the trial integrity of Cohort B, as detailed in Information Requests dated January 5, 2024, and January 19, 2024. Although there was no planned interim analysis for efficacy for Cohort B, an "administrative" interim analysis was conducted, and on January 11, 2024, the Sponsor submitted an unplanned unblinded efficacy analysis from Cohort B through approximately Day 28 with statistical testing (reporting observed risk difference and relative risk reduction with associated 95% confidence intervals and p-values). Notably, there was no planned multiplicity adjustment in the protocol.

The Agency consider the rates of RT-PCR-confirmed symptomatic COVID-19 in Cohort B to be of only exploratory value.

IX. Human Clinical Safety

For the proposed EUA, the total safety database consists of 631 participants who received pemivibart 4500 mg IV (partial or full dose) in either the CANOPY study (n=623) or the Phase 1 study (n=8) with follow-up safety data to at least Month 3. The CANOPY protocol included redosing of pemivibart 4500 mg IV at Month 3. Of the 623 participants who received the first dose of pemivibart, approximately 596 participants received the second dose (partial or full dose) with follow-up safety data through at least 24 hours after redosing. An additional 16 participants in the Phase 1 study received a single dose of pemivibart IV at doses lower than 4500 mg.

Both planned doses in CANOPY are complete, and the collection of follow-up safety data is ongoing. The CANOPY study population includes adults with moderate-to-severe immune compromise (Cohort A) and adults without moderate-to-severe immune compromise who are at risk for acquiring SARS-CoV-2 infection (Cohort B). While Cohort A (n=306) comprises the most relevant population for the proposed EUA, Cohort B offers additional safety information for pemivibart at the intended dose (n=317) compared to placebo (n=162). For Cohort B, the Sponsor provided unblinded safety data through Day 28 and blinded safety data after Day 28. Overall, the available safety database is sufficient to assess the potential risks associated with pemivibart 4500 mg IV.

A. VYD222-PREV-001 (CANOPY)

Analysis Sets

The safety analysis set and safety redosing set are the most relevant analysis sets for the safety review ([Table 2](#)).

Participant Disposition and Exposure for Safety Analysis

The safety analysis set for Cohort A includes a total of 306 participants, of whom 296 are included in the safety redosing set with follow-up data to at least 24 hours after redosing. The safety analysis set for Cohort B includes a total of 479 participants, of whom 450 are included in the safety redosing set with follow-up data to at least 28 days after redosing ([Table 6](#)). Because the initial safety data for Cohort B was received in an unblinded manner, it is known that 317 participants are in the pemivibart arm and 162 participants are in the placebo arm for the Cohort B safety analysis set. Because subsequent safety data were received in a blinded manner, the treatment arm is unknown for the 450 participants in the Cohort B safety redosing set. Note, unblinded safety data were not provided in the Sponsor's submission on March 18, 2024, which contained unblinded topline results of the secondary clinical efficacy endpoint through Month 3.

Table 6. Participant Disposition, CANOPY, Safety Analysis Set

Participant Disposition	Cohort A Pemivibart (N306) n (%)	Cohort B Pemivibart or Placebo (N=479) n (%)
Safety analysis set	306 (100)	479 (100)
Safety redosing set	296 (97)	450 (93)
Discontinued from study	6 (2)	24 (5)
Reason for discontinuation		
Death	1 (<1)	0
Lost to follow-up	1 (<1)	13 (3)
Physician decision	0	0
Participant request	1 (<1)	5 (1)
Withdrawal of consent	3 (1)	6 (1)
Duration of total follow-up		
Mean (SD), days	122 (19)	150 (19)
Median (Min, Max), days	122 (1, 155)	152 (9, 162)
1-2 days	306 (100)	479 (100)
≥28 days	304 (99)	478 (99.8)
≥91 days (3 months)	302 (99)	468 (98)
≥183 days (6 months)	0	0
Duration of follow-up following redosing		
1-2 days	296 (97)	450 (94)
3-28 days	295 (96)	450 (94)
29-90 days	181 (59)	450 (94)
>90 days	0	0

Source: Derived from the EUA Summary Report v3.0 dated 19-Feb-2024, and 23-Feb-2024 Response to FDA Information Request
Abbreviations: SD, standard deviation

Safety Results

Overview

The DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, version 2.1 (July 2017) was used to grade AEs and laboratory abnormalities per protocol. The first case of symptomatic COVID-19, including worsening or sequelae, was not captured as an AE unless SAE criteria were met. Likewise, solicited COVID-19-like illness (CLI) symptoms (per protocol) were not captured as AEs unless the participant entered a CLI reporting period and tested negative for SARS-CoV-2.

As shown in [Table 7](#), AEs through Day 28 were reported more frequently with pemivibart (Cohort A+B) compared to placebo. While more participants in Cohort A reported an AE through Day 28, most events were considered unrelated to study drug. Nonetheless, drug-related AEs through Day 28 were more frequently reported in Cohort A compared to Cohort B/pemivibart, while no drug-related AEs were reported with placebo.

All 25 drug-related AEs in Cohort A through Day 28 were reported on study Days 1-2 and were either mild (n=19) or moderate (n=6). Similarly, seven of eight drug-related AEs in Cohort B/pemivibart through Day 28 were reported on study Days 1-2, and all eight were mild (n=6) or moderate (n=2). Most drug-related events and all AEs leading to permanent discontinuation of study drug consisted of hypersensitivity reactions

(HSRs), infusion related reactions (IRRs), or injection site reactions (ISRs), which are discussed in the Adverse Events of Special Interest section of the review. SAEs through Day 28 were uncommon and none were related to study drug.

Table 7. Safety Through Day 28, First Dose, CANOPY, Safety Analysis Set

AE Type	Cohort A	Cohort B	Cohort B	Cohort A+B
	Pemivibart (N=306)	Pemivibart (N=317)	Placebo (N=162)	Pemivibart (N=623)
	n (%)	n (%)	n (%)	n (%)
Any AE	93 (30)	25 (8)	7 (4)	118 (19)
AE related to study treatment	25 (8)	8 (3)	0	33 (5)
AE ^a leading to permanent d/c of treatment	4 (1)	1 (<1)	0	5 (1)
AE ^a leading to dose interruption/slowing	16 (5)	3 (1)	0	19 (3)
Nonserious Grade 3 or 4 AEs	0	0	0	0
Any SAE	3 (1)	0	0	3 (<1)
SAE related to study treatment	0	0	0	0
Fatal SAE	0	0	0	0
Fatal SAE related to study treatment	0	0	0	0

Source: Derived from the 23-Feb-2024 Response to FDA Information Request

^a Infusion site extravasation/infiltration events are included even if not reported as an AE

Abbreviations: AE, adverse event; d/c, discontinuation; SAE, serious adverse event

[Table 8](#) displays the safety summary covering the period of the first dose (+3 months) followed by the second dose (+2 days). Safety data from Cohort A comprise the most relevant data for this time period because Cohort B safety data for this time period was received in a blinded manner at the time of this review. The table includes the total number of blinded events for Cohort B but a percentage cannot be accurately calculated. Unblinded Cohort B safety data are expected in the coming months.

Safety data from Day 29 to Month 3, following the first dose, are discussed under other sections in this review, including Deaths, SAEs, and Common AEs.

Following the second dose at Month 3 (+2 days), drug-related AEs were reported in 11 Cohort A participants, which includes some participants who also reported a drug-related AE following the first dose. Cumulatively, from Day 1 to Month 3 (+2 days), drug-related AEs were reported in a total of 32 (11%) Cohort A participants. Three additional Cohort A participants experienced an AE leading to permanent discontinuation of pemivibart during the second dose, for a total of seven (2%) cumulative participants who discontinued pemivibart due to AEs during the first or second dose.

Cumulatively, most drug-related events, AEs leading to permanent discontinuation of study drug, and AEs leading to dose interruption or slowing of the infusion were related to hypersensitivity reactions (HSRs), infusion related reactions (IRRs), injection site reactions (ISRs) or procedure-related events (e.g., infusion site extravasation), all of which are discussed in the Adverse Events of Special Interest section of the review.

Table 8. Cumulative Safety, Day 1 Through Month 3 (+2 Days), First and Second Dose, CANOPY, Safety Analysis Set

AE Type	Cohort A	Cohort B
	Pemivibart (N=306) n (%)	Pemivibart or Placebo (N=479) n ^a
Any AE	145 (47)	97
AE related to study treatment	32 (11)	15
AE ^b leading to permanent d/c of treatment	7 (2)	7
AE ^b leading to dose interruption/slowng	30 (10)	6
Nonserious Grade 3 or 4 AEs	0	1
Any SAE	14 (5)	4
SAE related to study treatment	2 (1)	0
Fatal SAE	1 (<1)	0
Fatal SAE related to study treatment	0	0

Source: Derived from the 23-Feb-2024 Response to FDA Information Request

^a Percentage is not shown for Cohort B because unblinded data were not available.

^b Infusion site extravasation/infiltration events are included even if not reported as an AE

Abbreviations: AE, adverse event; d/c, discontinuation; SAE, serious adverse event

Deaths

One death has been reported across both cohorts as of as of February 16, 2024. Participant (b) (6) in Cohort A was found dead by police during a wellness check on approximately Day 92 after the first dose of pemivibart, prior to redosing. The cause of death is unknown at this time, and follow-up is ongoing. Pertinent medical history included advanced HIV, non-Hodgkin's lymphoma, coronary artery disease, type 2 diabetes mellitus, hypercholesterolemia, COPD, asthma, obesity, pulmonary embolism, transient ischemia attack, and anaphylaxis to aspirin and penicillin.

Serious Adverse Events

A total of 18 participants experienced an SAE through Month 3 (+2 days) ([Table 9](#)). With a longer duration of follow-up data cut through February 16, 2024 (beyond Month 3 for many participants), a total of 26 nonfatal SAEs have been reported in 20 participants, 18 events in 15 participants in Cohort A and 8 events in 5 participants in Cohort B ([Table 9](#)). The higher rate of SAEs in Cohort A is not unexpected given the number and types of underlying conditions in participants in this cohort.

The narratives for all reported SAEs, irrespective of causality, were reviewed. Two SAEs were related to pemivibart, both of which were anaphylactic reactions that occurred during the second IV infusion at Month 3. Note: Two additional participants had anaphylaxis (per FDA adjudication) during the first IV infusion but are not included in [Table 9](#) because they were not reported as serious events. All events of anaphylaxis are discussed in detail in the Adverse Events of Special Interest section of the review. The assessment that none of the other SAEs were related to pemivibart is reasonable based on the available information provided to date. Follow-up is ongoing for many SAEs.

Table 9. Nonfatal SAEs, CANOPY, Safety Analysis Set

Participant#/ Age (y)/ Sex/Race	~Days to SAE Onset^a	SAE PT (Severity)	Related to Study Drug	Cause or Contributing Factor(s)	Relevant Medical History^b
Cohort A					
(b) (6) 47/M/White	135 d	Pneumonia ^c (G3)	N	Not provided	HIV, HTN, BPH, GERD, iron deficiency anemia, cholecystectomy, laminectomy
(b) (6) 65/F/White	35 d	Cholangitis infective (G4), Cholangitis (G4)	N	Pre-existing condition	Liver transplant, cholangitis following liver transplant, type 2 diabetes, arthritis, HTN, asthma, fatty liver disease
(b) (6) 35/M/White	115 d 32 d	Kidney infection (G4) Basilar artery aneurysm (G4)	N N	Not provided Not provided	Non-Hodkin's lymphoma, cancer-CNS, iliotal band syndrome, HTN, deviated septum, femoral impingement, use of port catheter
(b) (6) 47/M/White	72 d	Immune thrombocytopenia (G4)	N	Underlying disease	Immunodeficiency common variable, immune thrombocytopenia, CKD
(b) (6) 60/M/White	During redose	Anaphylactic reaction (G4)	Y	Pemivibart 2 nd dose	Crohn's disease, alcoholism, bowel resection, kidney stones, depression
(b) (6) 46/F/White	During redose	Anaphylactic reaction (G4)	Y	Pemivibart 2 nd dose	Psoriatic arthritis, ADHD, depression
(b) (6) 54/M/Black	76 d	Pneumonia ^c (G3)	N	Underlying HIV	HIV, DVT, anal and rectal cancers s/p chemotherapy, chronic ear infection, chronic sinus infection
(b) (6) 65/F/White	59 d 80 d	Influenza (G2) UTI (G2)	N	Concurrent condition	Secondary progressive MS, GERD, intermittent SVT, depression, PTSD, HTN, obesity, asthma
(b) (6) 33/F/White	75 d	Hypotension (G2)	N	Concurrent conditions	Ulcerative colitis, ileostomy, ILD, Stage 3b kidney failure, HTN, ADHD, macrocytosis, depression
(b) (6) 59/M/White	27 d	Anal cancer (G3)	N	Concurrent conditions	Anal squamous cell cancer, anal intraepithelial neoplasia, colostomy, HIV, HPV
(b) (6) 61/F/White	86 d	Pyelonephritis (G3)	N	UTI	Chronic inflammatory demyelinating polyneuropathy, HTN, diabetes, hyperlipidemia, atrial fibrillation
(b) (6) 58/F/White	33 d	Cellulitis (G3)	N	Surgical site	Trigger finger (surgery), papillary thyroid carcinoma, Ehlers-Danlos syndrome, systemic lupus, acinic cell tumor, parotid gland cancer
(b) (6) 45/M/White	69 d	Prostatic abscess (G3)	N	Not provided	Advanced HIV, oral candidiasis, hypokalemia
(b) (6) 69/F/White	115 d	Cholecystitis (G3)	N	Not provided	Slow growth B-cell lymphoma, chronic mononucleosis, common variable immunodeficiency, GERD, asthma, ADHD, obesity, asthma

Participant#/ Age (y)/ Sex/Race	~Days to SAE Onset^a	SAE PT (Severity)	Related to Study Drug	Cause or Contributing Factor(s)	Relevant Medical History^b
Cohort B / Pemivibart or Placebo (Blinded)					
(b) (6) 35/M/Black	39 d	Ankle fracture (G3)	N	Bike fall	Bilateral finger amputation, skin graft, depression, type 2 diabetes, obesity
(b) (6) 68/M/White	78 d	Ventricular fibrillation (G3)	N	Concurrent CHF	CHF, HTN, hyperlipidemia, CKD, coronary artery disease, cardioverter defibrillator implant, prosthetic heart valve, mitral valve clip, aneurysm, atrial fibrillation, non-ischemic cardiomyopathy
(b) (6) 49/M/White	112 d	Cardiac failure acute (G1)	N	Underlying conditions	
(b) (6) 49/M/White	67 d	Bursitis (G2), subcutaneous abscess (G2)	N	Vehicle accident	HTN, hyperlipidemia, GERD, BPH
(b) (6) 53/M/White	80 d	Pneumothorax (G4)	N	Inguinal hernia repair	GERD, BPH
(b) (6) 64/F/White	72 d	Crohn's disease (G2), Atypical pneumonia ^c (G2)	N	Not provided	Crohn's disease, degenerative joint disease, decreased GFR, HTN, hyperlipidemia

Source: Derived from the EUA Summary Report v3.0 dated 19-Feb-2024, and 23-Feb-2024 Response to FDA Information Request

^a The number of days is approximated (+/-3-5 days) based on the date of the first dose and the date of onset of the SAE.

^b Additional medical conditions were reported for most participants.

^c SARS-CoV-2 testing was negative in all three participants with serious pneumonia at the time of each event.

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; B, Black or African American; BPH, benign prostatic hyperplasia; CHF, congestive heart failure; CKD, chronic kidney disease; CNS, central nervous system; d, day(s); DVT, deep vein thrombosis; F, female; G, grade; GERD, gastroesophageal reflux disease; GFR, glomerular filtration rate; HIV, human immunodeficiency virus; HPV, human papillomavirus; HTN, hypertension; ILD, interstitial lung disease; M, male; MS, multiple sclerosis; PT, preferred term; PTSD, post-traumatic stress disorder; SAE, serious adverse event; SVT, supraventricular tachycardia; s/p, status post; UTI, urinary tract infection; W, White

Common Adverse Events

[Table 10](#) and [Table 11](#) display AEs reported by system organ class (SOC) and preferred term (PT), respectively, in at least 2% of participants in any treatment arm through Day 28, irrespective of causality. PTs residing within the SOC infections and infestations were most commonly reported across treatment arms; none of these AEs were considered related to study drug. In participants who received pemivibart in Cohorts A and B, upper respiratory tract infection and viral infection were the most commonly reported PTs through Day 28, both of which were reported at a similar rate with placebo. AEs within the SOC general disorders and administration site were also frequently reported in Cohort A; drug-related PTs within this SOC consisted of fatigue and infusion site reactions (infusion site bruising, infusion site erythema, and infusion site extravasation). These events are discussed in the Adverse Events of Special Interest section of the review. All nonserious AEs were mild or moderate in severity.

Table 10. Adverse Events by System Organ Class $\geq 2\%$ in Any Treatment Arm Through Day 28, CANOPY, Safety Analysis Set

System Organ Class	Cohort A Pemivibart (N=306) n (%)	Cohort B Pemivibart (N=317) n (%)	Cohort B Placebo (N=162) n (%)	Cohort A+B Pemivibart (N=623) n (%)
General disorders and administration site conditions	24 (8)	3 (1)	0	27 (4)
Infections and infestations	24 (8)	10 (3)	6 (4)	34 (5)
Gastrointestinal disorders	15 (5)	0	0	15 (2)
Nervous system disorders	13 (4)	0	0	13 (2)
Respiratory, thoracic and mediastinal disorders	7 (2)	3 (1)	0	10 (2)
Skin and subcutaneous tissue disorders	6 (2)	0	0	6 (1)

Source: Derived from the Feb-2024 Response to FDA Information Request

Table 11. Adverse Events by Preferred Term $\geq 2\%$ in Any Treatment Arm Through Day 28, CANOPY, Safety Analysis Set

Preferred Term	Cohort A Pemivibart (N=306) n (%)	Cohort B Pemivibart (N=317) n (%)	Cohort B Placebo (N=162) n (%)	Cohort A+B Pemivibart (N=623) n (%)
Fatigue	9 (3)	0	0	9 (1)
Infusion related reaction ^a	7 (2)	1 (<1)	0	8 (1)
Viral infection	7 (2)	4 (1)	3 (2)	11 (2)
Upper respiratory tract infection ^b	6 (2)	6 (2)	3 (2)	12 (2)
Influenza like illness	5 (2)	0	0	5 (1)
Nausea	5 (2)	0	0	5 (1)
Headache	6 (2)	1 (<1)	1 (1)	7 (1)

Source: Derived from the Feb-2024 Response to FDA Information Request

^a Includes only events reported specifically as an AE of infusion related reaction

^b Combined terms: viral upper respiratory tract infection and upper respiratory tract infection

Abbreviations: AE, adverse event

Drug-related AEs reported from Day 29 through Month 3 following the first dose were also reviewed across cohorts. No new safety concerns were identified. The safety of

pemivibart following the second dose (+2 days) is limited to HSRs, including anaphylaxis, and IRRs. Refer to the Adverse Events of Interest section for this analysis.

Laboratory Findings and Vital Signs

Chemistry and CBC laboratory assessments were scheduled for collection on Day 1 (predose), Day 28, Month 3 (predose), Month 6, and Month 12. Potentially clinically significant laboratory abnormalities, defined as any Grade 4 change or any postbaseline increase of two or more grades, were available at Day 28 and Month 3 (or any time postbaseline) for review.

Increased serum creatinine (Grade 2-4) was observed in 6% (17/306) of Cohort A participants and 12% (57/479) of Cohort B participants (blinded) any time postbaseline. The higher rate of elevated serum creatinine in Cohort B cannot be interpreted until unblinded data are provided for Cohort B. Decreased creatinine clearance (Grade 3-4) was observed in 5% (16/306) of Cohort A participants and 6% (27/479) of Cohort B participants (blinded) any time postbaseline. Of the participants with kidney-related laboratory abnormalities, only three participants, two in Cohort A and one in Cohort B, had changes considered clinically significant by the investigator. Clinically significant AEs reported in the three participants, respectively, were kidney stone with infection (moderate), worsening of chronic kidney disease (mild), and abnormal renal function test (moderate).

All other reported changes in renal function were not considered clinically relevant by the Investigator. Of note, 10 of the participants in Cohort A with reported changes in renal function had a medical history of chronic kidney disease or kidney transplant. Given the background comorbidities of participants in both Cohort A and Cohort B, along with very few clinical AEs reported with kidney-related laboratory abnormalities, the results do not indicate a serious safety concern at this time. However, the final results for all participants in both cohorts, including unblinded data from Cohort B, will be evaluated when available.

No other trends in laboratory abnormalities were noted. Grade 3 or 4 changes in glucose, hemoglobin, or ALT/AST were relatively infrequent, and none were considered clinically significant by the Investigator.

Vital signs were collected predose and postdose at Day 1 and Month 3. Changes in SpO₂ ($\leq 93\%$ and decrease $\geq 3\%$) were observed in approximately 3% of participants in each cohort any time postbaseline (8/306 in Cohort A; 13/479 in Cohort B). These changes were observed at predose and postdose timepoints as well as CLI visits. None were considered clinically relevant by the Investigator.

Overall, no safety signals are apparent based on an assessment of available laboratory results and vital signs.

ECG Findings

ECG assessments were not performed in the CANOPY trial. In addition, no formal (thorough) QTc studies have been performed in humans because monoclonal antibodies, such as pemivibart, have a low likelihood of direct ion channel interactions.

Immunogenicity

The incidence and impact of anti-drug antibodies (ADA) following pemivibart administration are currently unknown. An ADA assay method validation report for anti-pemivibart antibodies was submitted but is being used to test ADA samples only in the FIH study at pemivibart doses of 1500 mg and 2500 mg. No ADA neutralizing antibody assays have been used to test samples from CANOPY due to the need for a different format of the ADA assay for a pemivibart dose of 4500 mg. This assay is currently being validated, and the ADA method validation report will be submitted to the Agency once available. The ADA results will be submitted thereafter.

Adverse Events of Special Interest

Anaphylaxis

Anaphylaxis was observed in 4 of 623 (0.6%) participants in the pemivibart safety analysis set across cohorts in CANOPY. All four were in Cohort A. In two participants, anaphylactic reaction was reported as an SAE during the second infusion at Month 3. In the other two participants, nonserious AEs of infusion related hypersensitivity reaction and infusion related reaction, respectively, were reported during the first infusion; both of these reactions were re-adjudicated by the Agency as anaphylaxis based on Sampson's criteria #1 noted in [Figure 2 \(Sampson et al. 2006\)](#). The decision to reclassify both events as anaphylaxis was based on input from allergy and immunology experts in the Agency. Please refer to [Appendix 5](#) for the full consult review.

Figure 2. Sampson's Criteria #1 for Anaphylaxis

Table I. Clinical criteria for diagnosing anaphylaxis

Anaphylaxis is highly likely when any one of the following 3 criteria are fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula)

AND AT LEAST ONE OF THE FOLLOWING

a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)

b. Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)

Source: Sampson HA, Munoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: Summary report – Second National Institute of Allergy and Infectious Disease/ Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol 2006; 117:391-7. <https://www.sciencedirect.com/science/article/pii/S0091674905027235?via%3Dihub>
Abbreviations: BP, blood pressure; PEF, peak expiratory flow

The four cases of anaphylaxis are summarized below.

Participant (b) (6)

A 60-year-old White male weighing 84 kg and taking adalimumab for treatment of Crohn's disease was enrolled in Cohort A. During the first dose of pemivibart 4500 mg, he experienced mild, transient paresthesia but completed the infusion without interruption. One month later, he received both the Pfizer COVID-19 vaccine and an influenza vaccine. At Month 3, approximately 20 minutes into the planned 30-minute infusion of the second pemivibart dose, the participant experienced Grade 4 anaphylaxis. Symptoms began as itchiness as well as erythema and urticaria spreading from the IV site to his chest, trunk, neck, and upper and lower extremities. Pemivibart administration was discontinued (total of 4050 mg was infused), and the participant received oral diphenhydramine 50 mg. Within 15 minutes of pemivibart discontinuation, the participant experienced angioedema of the tongue and lips and slurring of words, and he received a dose of epinephrine. Additional symptoms thereafter included difficulty breathing and increased salivation. Emergency medical services (EMS) transported the participant to the hospital. Physical examination in the emergency department (ED) showed minimal tongue swelling, no posterior pharyngeal swelling, no respiratory distress, normal breath sounds, and "normal" voice. Diffuse trunk and back erythema was observed but no edema or urticaria was present. During observation in the ED for 6 hours, no rebound symptoms occurred, and other than IV famotidine to complete the histamine blockade, no additional treatment or interventions were necessary. The discharge diagnosis was acute anaphylaxis.

Participant (b) (6)

A 46-year-old White female weighing 72 kg and taking certolizumab and methotrexate for treatment of psoriatic arthritis was enrolled in Cohort A. The first dose of pemivibart 4500 mg was administered without any reported adverse reactions. She received an influenza vaccine 2 days prior to the first dose and the Moderna COVID-19 vaccine 1 month after the first dose. At Month 3, approximately 20 minutes into the planned 30-minute infusion of the second pemivibart dose, the participant experienced Grade 4 anaphylaxis. Symptoms began as itchiness around her feet, arms, and neck along with flushing of the face and hives on her arms and neck. Pemivibart administration was discontinued, and IV diphenhydramine 50 mg was administered. She developed anxiety, difficulty breathing, and swelling of the lips, face, and eyelids, and a dose of epinephrine was administered. Thereafter, her throat felt tight, and her tongue felt big. She had a severe headache and felt faint but did not lose consciousness. EMS transported her to the hospital. In the ED, she received another dose of epinephrine for a rebound allergic reaction consisting of itchiness and redness, especially on the neck and face, chest pain, and left arm tingling. During overnight observation, a third event of itching and hives occurred, for which she received another dose of diphenhydramine. She also received metoclopramide and tramadol for headache. The next day, anaphylaxis was considered resolved but with sequelae related to a flare of her underlying psoriatic

arthritis. She was sent home with medications, including prednisone 40 mg for 4 days. A week later, an ongoing reaction was reported, with symptoms of myalgia, arthralgia, fatigue, sharp chest pain, and tachycardia. An ECG was performed at an urgent care facility where it was determined that tachycardia was related to an inflammatory reaction due to the study drug and that a flare of her pre-existing psoriatic arthritis was likely due to the recent anaphylactic event. She was prescribed prednisone and metoprolol. The event was ongoing at the time of this review.

Participant (b) (6)

A 44-year-old White male weighing 104 kg and taking prednisone for exacerbation of chronic obstructive lung disease was enrolled in Cohort A. Immediately during the first dose of pemivibart, the participant experienced an anaphylactic reaction that was initially reported as an infusion-related reaction consisting of dyspnea, diaphoresis, red face, chest tightness, and tachycardia. Pemivibart was permanently discontinued (total of 9 mg was infused), and the participant received one dose each of oral diphenhydramine 25 mg and albuterol 180 mcg inhalation. Symptoms resolved within 3 hours.

Participant (b) (6)

A 64-year-old White female weighing 74 kg and taking mycophenolate mofetil and prednisone for Churg Strauss syndrome was enrolled in Cohort A. Within 4 minutes of the first dose of pemivibart, the participant experienced an anaphylactic reaction initially reported as a hypersensitivity reaction consisting of flushing, dizziness, ringing in ears, and wheezing. Pemivibart was permanently discontinued (total of 630 mg was infused), and the participant received one dose of oral diphenhydramine 25 mg. Symptoms were considered mild and resolved within 10 minutes. Approximately 10 hours later, the participant experienced mild nausea and moderate diarrhea. Symptoms resolved the next day without treatment.

There is known risk of cross-hypersensitivity between products containing the structurally similar ingredients polysorbate or polysorbate 80 and polyethylene glycol (PEG). Pemivibart and adalimumab contain polysorbate 80, certolizumab contains polysorbate, and the Pfizer and Moderna COVID-19 vaccines contain PEG. Two participants with serious anaphylactic reactions were chronically receiving adalimumab or certolizumab. However, both of these products are frequently administered (e.g., every 2 weeks), and cross-reactivity was not apparent with the first pemivibart dose in either participant. In addition, based on the SAE narratives received as of February 22, 2024, no serious reactions have been reported with continued administration of adalimumab or certolizumab in either participant after resolution of anaphylaxis with pemivibart. In Cohort A, 140 participants have received at least 1 of 34 different immunomodulatory agents, including adalimumab or other products that contain polysorbate 80 (e.g., infliximab, rituximab). Similarly, the COVID-19 vaccines administered between pemivibart infusions would not have been the first introduction of vaccines in these participants, although sensitization could occur at any time. In the overall safety population of the trial, 79 total participants received a COVID-19 vaccine

between the first and second dose of pemivibart, and most if not all participants likely had a history of COVID-19 vaccination prior to trial entry. Cross-reactivity between products containing polysorbate 80 and PEG does not appear to explain the anaphylactic reactions observed in the trial. However, it remains a risk that is adequately described as a Warning and Precaution in the proposed EUA FS.

A subject matter expert in therapeutic antibodies in the Agency's Division of Product Quality Research was consulted to compare the sequences between pemivibart, adintrevimab, adalimumab, and certolizumab and provide an assessment on whether cross-reactivity between mAbs may have contributed to increased immunogenicity in the two participants who experienced serious anaphylactic reactions. The consult review is included in [Appendix 6](#). In summary, no final conclusions can be drawn without any ADA data from these participants or an in silico prediction of immunogenicity. However, despite all four mAbs using a heavy-chain variable region (VH) gene from the same family, it is unlikely that pre-existing ADA, if present in the two participants, cross-reacted with pemivibart.

History of anaphylaxis to any substance was also explored as a possible risk factor for anaphylaxis to pemivibart. Neither participant with serious anaphylactic reactions had a history anaphylaxis or any known drug or environmental allergies prior to trial entry. In the overall safety population, 10 participants reported a history of anaphylaxis, all in Cohort A. The available information supports maintaining the proposed Contraindication in the EUA FS for individuals with previous severe hypersensitivity reactions, including anaphylaxis, to any component of pemivibart but not expanding it to include such previous reactions to any substance.

In summary, the rate of anaphylaxis observed in the trial is relatively high, which raises concern as anaphylaxis can be life-threatening. While anaphylaxis has been reported with other SARS-CoV-2 mAbs, the most relevant comparator is tixagevimab/cilgavimab (Evusheld) because of the similar benefit-risk considerations for pre-exposure prophylaxis of COVID-19. In the PROVENT trial, the rate of anaphylaxis with tixagevimab/cilgavimab was 0.03% (1/3,461) ([AstraZeneca 2023](#)), which is much lower than the rate of 0.6% (4/623) observed with pemivibart in CANOPY. To highlight this important risk, the Agency will include a Boxed Warning for anaphylaxis in the EUA FS. The Warning and Precaution section will contain a separate subsection for anaphylaxis and a separate subsection for other hypersensitivity reactions and infusion-related reactions to allow for an emphasis on the risk of anaphylaxis and a more accurate differentiation between the types of reactions. The Boxed Warning will include the following:

- Anaphylaxis has been observed with pemivibart in 0.6% (4/623) of participants in a clinical trial.
- Anaphylaxis was reported during the first and second infusion of pemivibart.
- Anaphylaxis can be life-threatening.

- Prior to administering pemivibart, consider the potential benefit of COVID-19 prevention along with the risk of anaphylaxis.
- Administer pemivibart only in settings in which healthcare providers have immediate access to medications to treat anaphylaxis and the ability to activate the emergency medical system (EMS), as necessary.
- Clinically monitor individuals during the infusion and for at least two hours after completion of the infusion.
- Discontinue pemivibart immediately if signs or symptoms of anaphylaxis or any severe systemic reaction are observed and initiate appropriate medications and/or supportive therapy.

Systemic Infusion-Related Reactions and Hypersensitivity Reactions

Hypersensitivity reactions (HSRs) and infusion-related reactions (IRRs) are defined in this review as any of the following reported events within 24 hours of study treatment and assessed as related to study treatment. The signs and symptoms listed in the second bullet are derived from the EUA FS for SARS-CoV-2 mAbs, including the proposed EUA FS for pemivibart. Note, systemic IRR/HSRs in this section include all four anaphylaxis cases discussed in the Anaphylaxis section above.

- AE reported as HSR or IRR
- AEs including, at minimum, fever, difficulty breathing, reduced oxygen saturation, chills, fatigue, arrhythmia (e.g., atrial fibrillation, sinus tachycardia, bradycardia), chest pain or discomfort, weakness, altered mental status, nausea, headache, bronchospasm, hypotension, hypertension, angioedema, throat irritation, rash including urticaria, pruritus, myalgia, vaso-vagal reactions (e.g., presyncope, syncope), dizziness, and diaphoresis

Local injection site reactions are not included in the analysis of HSRs or IRRs and are presented separately.

Brief narratives were reviewed for nonserious IRR/HSRs reported in CANOPY. None of the narratives indicated that premedication, which was at the discretion of the investigator, was administered prior to either the first dose or second dose in participants who experienced an IRR/HSR with either or both doses. The Sponsor confirmed that four participants in the trial received premedication, all prior to the second dose; none of these four participants had an IRR/HSR with the first dose. Note, in the CANOPY trial, pemivibart 4500 mg was administered via IV infusion over 30 minutes.

First Dose IRR/HSR Assessment

Within 24 hours of the first dose, IRR/HSRs related to study treatment were reported in 24 (4%) participants in the combined pemivibart arms (Cohort A+B) compared to none in the placebo arm ([Table 12](#)). The incidence of IRR/HSRs with pemivibart was notably higher in Cohort A (7%) compared to Cohort B/pemivibart (1%). The main difference

between Cohort A and Cohort B is that the population in Cohort A has moderate-to-severe immune compromise. It is possible that moderate-to-severe immune compromise is causing or contributing to the higher incidence of IRR/HSRs, but the specific mechanism is unknown and may vary based on the type or degree of immune compromise caused by different underlying conditions or medications. No trends were apparent in reviewing the types of baseline immunocompromising conditions in Cohort A participants who experienced an IRR/HSR with pemivibart.

All IRR/HSRs reported with the first dose were mild (17/24; 71%) or moderate (7/24; 29%), and all participants recovered with or without intervention. Two of the moderate IRR/HSRs were adjudicated by FDA as anaphylaxis. Time to resolution of symptoms in most participants ranged from within minutes to 1 week; but one participant with hypersensitivity recovered after 2 weeks, and one participant with dermatitis recovered after 7 weeks. Interventions included discontinuation of study drug, temporary interruption of study drug, and/or treatment with supportive medications.

Six participants in the combined pemivibart arms (Cohort A+B) discontinued the first infusion (i.e., did not complete the 4500 mg dose) due to an IRR/HSR, including two participants who experienced moderate IRR/HSRs that were adjudicated by FDA as anaphylaxis. Refer to the Anaphylaxis subsection for additional details. The other four participants discontinued the first infusion due to an IRR/HSR reported as either infusion related reaction (n=2), hypersensitivity (n=1), or tachycardia and tremor (n=1). Five of the six participants had permanent discontinuation of study drug (i.e., were not redosed at Month 3). One participant was redosed.

Four participants, all in Cohort A, had the infusion temporarily interrupted but subsequently completed the full dose.

In addition to the two participants who had anaphylaxis during the first infusion, three participants received medications to treat the IRR/HSR. All three participants received diphenhydramine (IV, oral, or topical), and one also received corticosteroids (IV methylprednisolone, followed by oral prednisone for 5 days). One event occurred after completion of the infusion, and the other two occurred during the infusion and led to discontinuation of the infusion.

Table 12. IRR/HSR^a Summary, First Dose, CANOPY, Safety Analysis Set

	Cohort A Pemivibart (N=306) n (%)	Cohort B Pemivibart (N=317) n (%)	Cohort B Placebo (N=162) n (%)	Cohort A+B Pemivibart (N=623) n (%)
IRR/HSR Category				
IRR/HSR related to study treatment	20 (7)	4 (1)	0	24 (4)
IRR/HSR leading to discontinuation of treatment	4 (1)	2 (1)	0	6 (1)
IRR/HSR leading to dose interruption/slowing	4 (1)	0	0	4 (1)
Onset of IRR/HSR				
During infusion	10 (3)	2 (1)		12 (2)
Within 1 hour after infusion	1 (<1)	0		1 (<1)
>1 hour to <24 hours after infusion	9 (3)	2(1)		11 (2)

IRR/HSR Category	Cohort A Pemivibart (N=306) n (%)	Cohort B Pemivibart (N=317) n (%)	Cohort B Placebo (N=162) n (%)	Cohort A+B Pemivibart (N=623) n (%)
Severity of IRR/HSR				
Mild	14	3		17 (3)
Moderate	6	1		7 (1)
Severe	0	0		0
Life-threatening	0	0		0
PTs^b reported in ≥2 participants				
Infusion related reaction ^c	7 (2)	1 (<1)		2 (<1)
Hypersensitivity or infusion related HSR ^c	1 (<1)	1 (<1)		8 (1)
Fatigue	4 (1)	-		4 (1)
Headache	4 (1)	-		4 (1)
Tachycardia	2 (1)	-		2 (<1)

Source: Derived from the EUA Summary Report v3.0 dated 19-Feb-2024 and 23-Feb-2024 Response to FDA Information Request

^a IRR/HSR includes reports of an infusion related reaction, hypersensitivity reaction, or AE in the specified definition of an IRR or HSR within 24 hours of the infusion.

^b Multiple PTs may have been reported in an individual participant. PTs reported in one participant each in either Cohort A or Cohort B/pemivibart included brain fog, dermatitis, diarrhea, myalgia, nausea, parasthesia, presyncope, and tremor.

^c Includes both IRR/HSRs adjudicated by FDA as anaphylaxis.

Abbreviations: HSR, hypersensitivity reaction; IRR, infusion-related reaction; PT, preferred term

First and Second Dose, Cumulative IRR/HSR Assessment

The assessment of cumulative IRR/HSRs following the first and second dose of study drug focuses more on Cohort A because unblinded data were not available for all Cohort B participants for the second dose. Cumulatively, IRR/HSRs related to study treatment were reported in 25/306 (8%) Cohort A participants ([Table 13](#)); 52% (13/25) of IRR/HSRs were mild, 40% (10/25) of IRR/HSRs were moderate (including two events adjudicated by FDA as anaphylaxis), and two IRR/HSRs were life-threatening anaphylaxis. All participants recovered from the initial reaction with or without intervention.

Three participants in Cohort A discontinued the second infusion due to an IRR/HSR, two due to serious anaphylactic reactions and one due to a moderate hypersensitivity reaction. One participant in Cohort B (with known randomization to the pemivibart arm) discontinued the infusion due to a mild hypersensitivity reaction. One Cohort B/pemivibart participant received the second dose even though the first infusion was discontinued due to a mild infusion infusion related reaction; during the second dose a mild infusion related reaction also occurred, but the infusion was completed.

Three participants, all in Cohort A, had the second infusion temporarily interrupted but subsequently completed the full dose. One of these participants had both doses temporarily interrupted.

In addition to the two participants who had anaphylaxis during the second dose, two participants in Cohort A received medications to treat the IRR/HSR. One participant received diphenhydramine (oral and IM) and methylprednisolone (IM) for hypersensitivity that occurred immediately after completion of the infusion. One participant, who discontinued study infusion, received diphenhydramine (oral) and famotidine (oral).

Table 13. IRR/HSR^a Summary, First and Second Dose, CANOPY, Safety Analysis Set

IRR/HSR Category	Cohort A	Cohort B
	Pemivibart (N=306) n (%)	Pemivibart or Placebo (N=479) n ^b
IRR/HSR related to study treatment	25 (8)	11
IRR/HSR leading to discontinuation of treatment	7 (2)	3
IRR/HSR leading to dose interruption/delay	6 (1)	0
Severity of IRR/HSR, worst grade		
Mild	13	9
Moderate	10	2
Severe	0	0
Life-threatening	2	0
PTs ^c reported in ≥2 participants		
Anaphylactic reaction	2 (1)	-
Hypersensitivity or infusion related HSR	3 (1)	2
Infusion related reaction	11 (4)	7
Fatigue	4 (1)	-
Headache	4 (1)	-
Tachycardia	2 (1)	-

Source: Derived from the EUA Summary Report v3.0 dated 19-Feb-2024 and 23-Feb-2024 Response to FDA Information Request

^a IRR/HSR includes reports of an infusion related reaction, hypersensitivity reaction, or AE in the specified definition of an IRR or HSR within 24 hours of the infusion.

^b Percentage is not shown for Cohort B because complete unblinded data beyond Day 28 were not available.

^c Multiple PTs may have been reported in an individual participant. PTs reported in one participant each in either Cohort A or Cohort B included brain fog, dermatitis, diarrhea, myalgia, nausea, parasthesia, presyncope, and tremor.

Abbreviations: HSR, hypersensitivity reaction; IRR, infusion related reaction; PT, preferred term

Of the 296 participants in Cohort A who received both doses, 10 participants experienced an IRR/HSR with the second dose. Of the 10 participants, 5 had an IRR/HSR with the first dose ([Table 14](#)), and 5 had no reported IRR/HSRs with the first dose. An additional 10 participants had an IRR/HSR with the first dose but not with the second dose.

The treatment arms are unknown for all 450 Cohort B participants who received both doses. Because the participant number and treatment arm are known for participants who experienced an IRR/HSR with the first dose, whether an IRR/HSR occurred with the second dose in these participants is also known. Of the four participants in the pemivibart arm who had an IRR/HSR with the first dose, one participant also had an IRR/HSR with the second dose ([Table 14](#)). While it is known that an additional seven participants in Cohort B had an IRR/HSR with only the second dose, the treatment arm (pemivibart vs. placebo) remains blinded for three of these participants (the other four participants were randomized to the pemivibart arm).

Overall across cohorts, 18 participants experienced an IRR/HSR with the first dose and subsequently received the second dose, of whom 6 experienced another IRR/HSR with the second dose and 12 reported no IRR/HSRs with the second dose. Six participants who had an IRR/HSR with the first dose were not redosed, five due to permanent discontinuation of study drug and one due to death before the second dose. Of the 16 participants who had no IRR/HSR with the first dose but subsequently experienced an

IRR/HSR with the second dose, 10 were in Cohort A, and 6 were in Cohort B; however, the treatment arm is not known for all 6 participants in Cohort B.

Participants in CANOPY received pemivibart over a 30-minute infusion time, with the exception of the last 31 Cohort A participants who received a second infusion over a 60-minute infusion time. No IRR/HSRs were reported in these 31 participants.

Table 14. IRR/HSRs^a Occurring After Both the First and Second Dose

Participant Number	First Dose: PT	Second Dose: PT
Cohort A		
(b) (6)	Parasthesia (mild)	Anaphylactic reaction (LT)
	Fatigue (mild)	Infusion related reaction (mild)
	Infusion related reaction (mild)	Infusion related reaction (mild)
	Infusion related reaction (mild)	Infusion related reaction (mild)
	Presyncope (mild), headache (mild)	Infusion related reaction (moderate)
Cohort B / Pemivibart^b		
(b) (6)	Infusion related reaction (mild)	Infusion related reaction (mild)

Source: Derived from the 23-Feb-2024 and 09-Feb-2024 Responses to FDA Information Requests

^a IRR/HSR includes reports of an infusion related reaction, hypersensitivity reaction, or AE in the specified definition of an IRR or HSR within 24 hours of the infusion.

^b The treatment arm is known for the second dose for this participant because an IRR was reported with the first dose. Abbreviations: HSR, hypersensitivity reaction; IRR, infusion related reaction; LT, life-threatening; PT, preferred term

HSRs and IRRs are a known safety risk with SARS-CoV-2 mAbs. The rate of IRR/HSRs with pemivibart in Cohort A, the intended population, is relatively high compared to the rate observed with other SARS-CoV-2 mAbs in clinical trials in other patient populations. However, this risk can be adequately described in the EUA FS, and IRR/HSRs can reasonably be monitored and treated. The proposed Boxed Warning (see Anaphylaxis subsection) addresses serious and severe HSRs. For other systemic reactions, a separate Warning and Precaution will inform prescribers about IRR/HSRs, similar to the information in the EUA FS for other SARS-CoV-2 mAbs.

In addition, the main risk mitigation strategy for IRR/HSRs for the EUA is the extension of the infusion time from 30 minutes to 60 minutes. While extension of the infusion time may reduce the incidence and severity of IRR/HSRs, this strategy is not expected to impact the risk of IgE-mediated anaphylaxis. Premedication for pemivibart recipients will not be recommended in the EUA FS because (1) there is no evidence that premedication will reduce the risk of IRR/HSRs with pemivibart, and (2) there is a possibility that premedication may mask or delay serious or severe IRR/HSRs.

Local Infusion Site Reactions

Cumulatively in Cohort A of CANOPY, local infusion site reactions (ISRs) occurred in 7/306 (2%) participants, six with the first dose only and one with the second dose only. ISRs were reported as infusion site bruising (3), infusion site erythema (3), infusion site rash (1), and injection site reaction (1). All ISRs were mild in severity, and most occurred as early as immediately after initiation of the infusion to the day after the infusion. One participant reported injection site reaction (itching and bleeding at the

infusion site) 4 days after the infusion; this participant also experienced anaphylaxis. No ISRs were reported in Cohort B. ISRs will be included in the Adverse Reactions section of the EUA FS.

Other localized infusion site events included IV infiltration, extravasation, or vein rupture, which were noted in 11/623 (2%) participants during the first dose. The frequency was higher in Cohort A (n=9) compared to Cohort B (n=2). Four participants were unable to complete the first dose. Cumulatively in Cohort A, these events were reported in 14/306 (5%) participants, eight with the first dose only, five with the second dose only, and one with both doses.

Delayed Hypersensitivity Reactions

Drug-related AEs reported from Day 3 to Month 3 were reviewed for signals of delayed hypersensitivity reactions after the first dose. One report each of night sweats and urticaria was reported in Cohort A. Both reactions were mild in severity. One drug-related event of moderate eye pain was reported in a Cohort B/pemivibart participant beginning 3 days after the first dose. The participant was referred for an MRI but opted instead to receive acupuncture. The reaction subsided after 45 days. During the second infusion, moderate eye pain recurred, and the infusion was discontinued. Based on the available data, it is unclear whether these events represent a hypersensitivity reaction, but the events were attributed to study drug by the investigator. The following statement will be included in the EUA FS for pemivibart: Hypersensitivity reactions occurring more than 24 hours after the infusion have also been reported with the use of SARS-CoV-2 monoclonal antibodies under EUA.

X. Specific Populations

Dosing Considerations for Special Populations

- No dosage adjustment is recommended in pediatric individuals who weigh at least 40 kg and are 12 years of age and older. Because data are not currently available to inform dosing, pemivibart will not be recommended for pediatric individuals weighing less than 40 kg or those less than 12 years of age.
- Safety and PK data of pemivibart are not available in pediatrics, pregnant women, lactating women, or patients with renal or hepatic insufficiency. No dosage adjustment is recommended based on age, sex, race, body weight, renal impairment, during pregnancy, or while lactating (Section [XI](#)).
- Nonclinical reproductive toxicology studies with pemivibart have not been conducted.
- No binding of clinical concern was seen with pemivibart in a tissue cross-reactivity study in select human fetal tissues.
- No specific risks to pregnant or lactating women have been identified based on the nonclinical safety data.

XI. Human Clinical Pharmacology

Pemivibart

Interim PK data are available from single ascending dose study VYD222-1-001 (Study 001) in healthy adults (n=24) and Phase 3 study VYD222-PREV-001 (CANOPY) in adults with moderate to severe immune compromise (Cohort A, n=303) and adults without moderate to severe immune compromise (Cohort B, n=314) ([Table 15](#), [Table 16](#)). In both studies, pemivibart was measured in human serum using a validated electrochemiluminescence method.

Table 15. Pemivibart Clinical Trials

Study Number	Dose(s) and Route	No.	
		Adults	PK Sampling Times
Study 001	1500 mg IV	8	Predose, end of infusion, Days 2, 7, 14, 21, and 45, and Months 3, 6, and 12
	2500 mg IV	8	
	4500 mg IV	8	
CANOPY, Cohort A	4500 mg IV on Day 1 and 4500 mg IV on Day 90 (approximately)	303	End of infusion (Day 1), Day 14, Day 28, and Month 3 (predose and end of infusion), 6, and 12.
CANOPY, Cohort B		314	End of infusion (Day 1), Day 10 (n=~75), Day 28, and Month 3 (predose and end of infusion), 6, and 12.

Source: Pemivibart popPK report dated 3/8/2024, p16.
Abbreviations: IV, intravenous; PK, pharmacokinetic

Table 16. Summary Statistics of Population PK Parameters of Pemivibart Following a Single 4500 mg Intravenous Dose to Adults, CANOPY, Pooled Cohort A and Cohort B

Parameter	Pemivibart
C _{max} (µg/mL)	1750 (38.2)
C _{Day28} (µg/mL)	460 (40.7)
C _{Day90} (µg/mL)	175 (44.4)
AUC _{0-3 months} (day×µg/mL)	36600 (40.4)
T _{1/2} (days)	44.6 (28.1-64.6)
Accumulation ratio	1.33
CL (L/d)	0.0909 (23.3)
V _{ss} (L)	5.54 (17.0)
Metabolism	Catabolic pathways; Same manner as endogenous IgG
Excretion	Not likely to undergo renal excretion

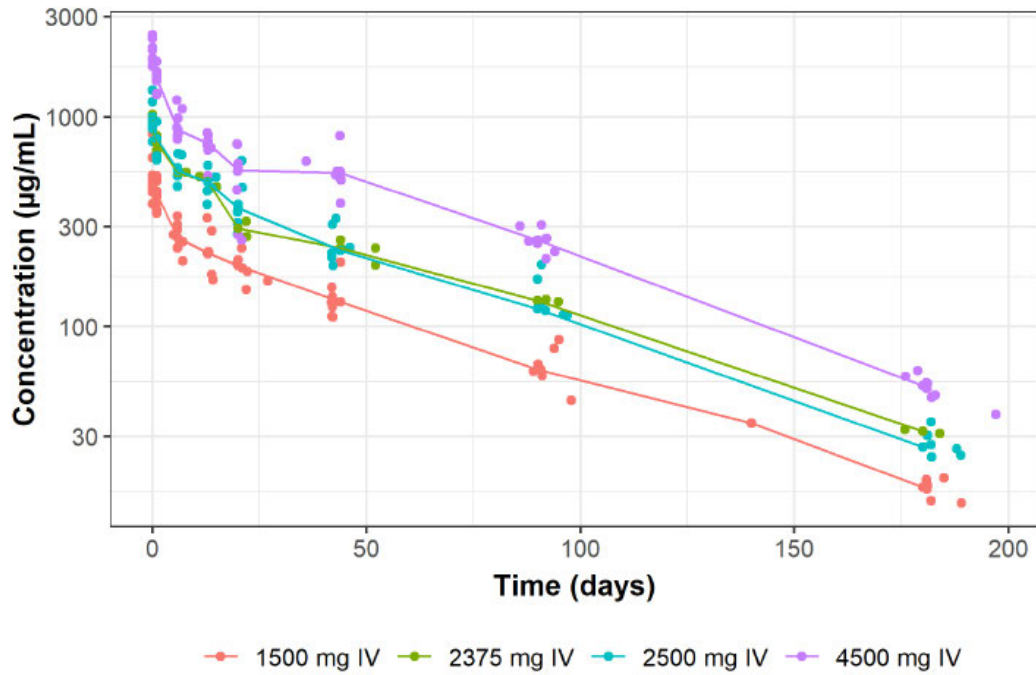
Source: Pemivibart popPK report dated 3/8/2024, p49. Accumulation ratio calculated from half-life.

Note: All values presented as geometric mean (%covariance), except for T_{1/2}, which is presented as median (min, max).

Abbreviations: AUC_{0-6 months}, area under the serum concentration-time curve from Day 0 to Month 6; C_{Day28}, day 28 pemivibart concentration; C_{Day90}, day 90 pemivibart concentration; CL, renal clearance; C_{max}, maximum concentration; PK, pharmacokinetic; T_{1/2}, half-life; V_{ss}, steady state volume of distribution

PK data are available through Month 6 for Study 001 ([Figure 3](#)) and through Month 3 for CANOPY ([Figure 4](#)). Note the two clusters of CANOPY concentrations at Month 3 represent the pre-dose and end of infusion timepoints.

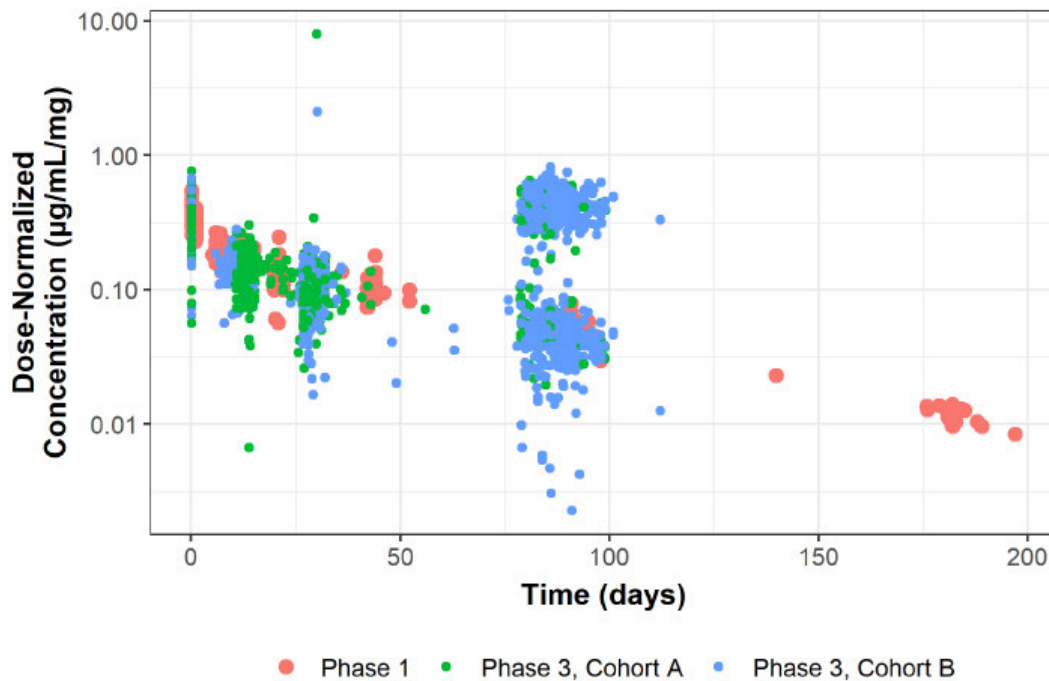
Figure 3. Pemivibart Concentrations Over Time by Treatment Regimen, Study 001



Note: Two subjects from Cohort 2 did not receive the full 2500 mg dose but the dose received was only 5% lower (2375 mg). The colored lines represent the mean VYD222 concentrations by nominal PK sampling time. Abbreviations are provided in the [Abbreviation Listing](#).

Source: Pemivibart popPK report dated 3/8/2024, p30.
Abbreviations: IV, intravenous; PK pharmacokinetic; VYD222, pemivibart

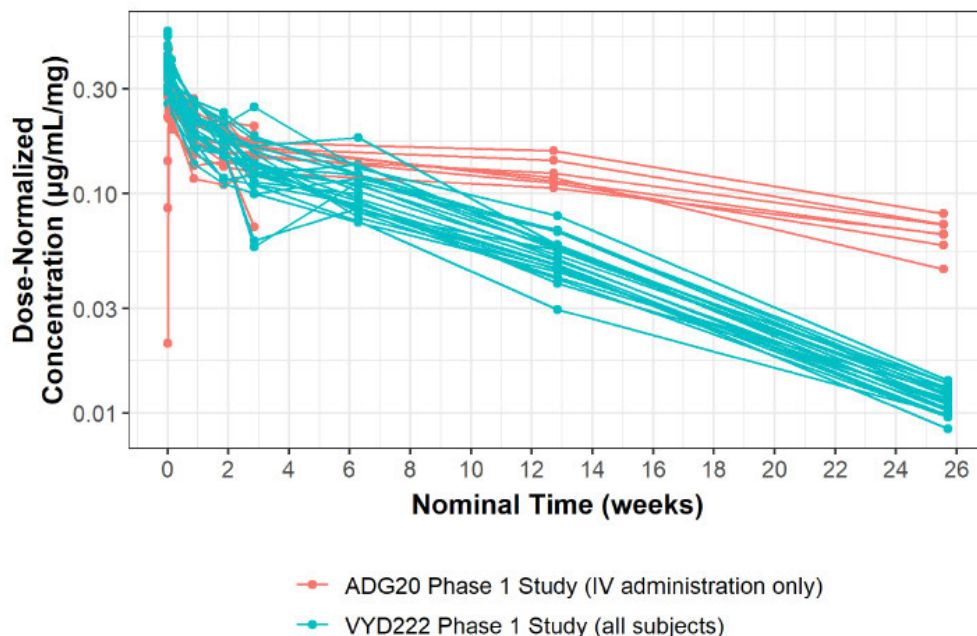
Figure 4. Dose-Normalized Pemivibart Concentrations Over Time, Study 001 and CANOPY



Source: Pemivibart popPK report dated 3/8/2024, p31.

It is noted that the half life of pemivibart is shorter than the half-life of adintrevimab ([Figure 5](#)), which was not anticipated. The reason for the difference is not known.

Figure 5. Dose-Normalized Pemivibart (VYD222) and Adintrevimab (ADG20) Concentrations Over Time



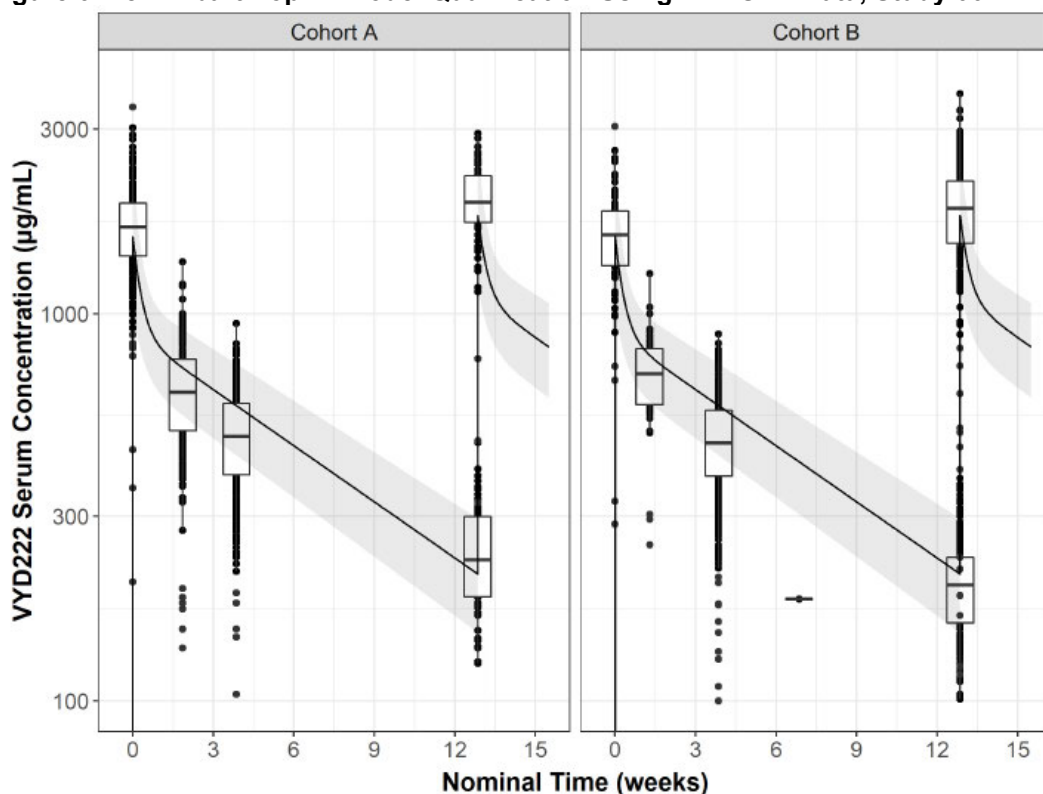
Note: Note that only those subjects enrolled in Cohort 2 (500 mg IV) of Study ADG20-1-001 are included in the above plot. Abbreviations are provided in the [Abbreviation Listing](#).

Source: Pemivibart popPK report dated 3/8/2024, p31.
Abbreviations: ADG20, adintrevimab; IV, intravenous; VYD222, pemivibart

The model developed using Study 001 data overpredicted concentrations in CANOPY at the Week 2 and Week 4 timepoints; Week 12 CANOPY concentrations were predicted well. ([Figure 6](#)). The popPK model for the pooled dataset contains a covariates to account for 11% higher clearance and 30% higher peripheral volume of distribution in the CANOPY study vs Study 001. Half-life is nearly identical (45 days) in both studies.

There are no physiological explanations for the observed differences in clearance and peripheral volume of distribution between studies. Of note, there was no PK difference between Cohort A (moderately or severely immunocompromised) and Cohort B (not moderately or severely immunocompromised) of the CANOPY trial. Therefore, the difference in the immunocompromised status between the Phase 1 study (healthy participants) and CANOPY A (moderately or severely immunocompromised) does not explain this observation.

Figure 6. Pemivibart PopPK Model Qualification Using CANOPY Data, Study 001



Note: Box-and-whisker plots show the distribution of serum concentrations at nominal time points for subjects enrolled in the Phase 3 study. The black lines and grey shaded regions show the median and 5th – 95th percentiles of the simulated concentrations using the Phase 1 Population PK Model and the demographics of the Phase 3 subjects. Abbreviations are provided in the [Abbreviation Listing](#).

Source: Pemivibart popPK report dated 3/8/2024, p38.
Abbreviations: popPK, population pharmacokinetic; VYD222, pemivibart

Dosing Recommendation Rationale for Pediatric Patients and Other Specific Populations

In the pooled Phase 1/3 population PK analysis, the PK profile of pemivibart was not affected by sex, age (18 to 84 years of age), race or ethnicity. While increased body weight (43 to 190 kg) was associated with decreased exposures, this is not anticipated to be clinically relevant.

Pediatrics

The PK, safety, and effectiveness of pemivibart has not been studied in any pediatric population. The recommended dosing regimen is expected to result in comparable serum exposures of pemivibart between pediatric patients 12 years of age and older and weighing at least 40 kg and adults. PK data are available for seven adults weighing 43-50 kg in CANOPY.

Renal Impairment

No dedicated studies have been conducted to examine the effects of renal impairment on the PK of pemivibart. Renal impairment is not expected to impact the PK of

pemivibart, since mAbs with molecular weight >69 kDa are known not to undergo renal elimination. Similarly, dialysis is not expected to impact the PK of pemivibart.

Hepatic Impairment

No dedicated studies have been conducted to examine the effects of hepatic impairment on the PK of pemivibart. The impact of hepatic impairment on the PK of pemivibart is unknown.

Drug-Drug Interactions

Drug-drug interaction studies have not been performed. Pemivibart interactions with concomitant medications that are renally excreted or that are substrates, inducers, or inhibitors of CYP enzymes are unlikely.

XII. Nonclinical Data To Support Safety

- Pemivibart was evaluated in a GLP 22-day intravenous repeat-dose toxicology study in Sprague-Dawley rats with a 21-day recovery period. No adverse, drug-related findings were observed in this study up to the highest dose tested (302 mg/kg/dose). The safety factor at the NOAEL of 302 mg/kg is 4 relative to the proposed human dose of 4500 mg in a 60-kg adult.
- GLP tissue cross-reactivity studies were also conducted in normal adult and select fetal human tissues. No binding of clinical concern was observed with pemivibart in these studies.

XIII. Nonclinical Data To Support Efficacy

Pemivibart (VYD222) is a recombinant human monoclonal IgG1 λ antibody that was directly derived from adintrevimab (parent mAb), and has a similar Fab sequence and identical Fc domain. It binds to the SARS-CoV-2 spike protein receptor binding domain (RBD) and inhibits ACE2 binding. Summaries of the key findings from the study reports describing pemivibart derivation, mechanism of action, structural analyses, antiviral activity, and resistance are presented below.

Monoclonal Antibody Derivation

Pemivibart was generated from [REDACTED] (b) (4) [REDACTED] from the parental IgG1 λ clone, ADI-55688, which was isolated from a survivor of the 2003 SARS-CoV outbreak ([CDC 2017](#)). ADI-55688 was selected based on broad neutralizing activity against SARS-CoV-2 and SARS-CoV. [REDACTED] (b) (4) [REDACTED] modified by introducing half-life-extending M435L and N441A substitutions (“LA” modification) into the fragment crystallizable (Fc) region to form

adintrevimab (ADG20) ([Deveau 2020](#)). ADG-2/adintrevimab was shown to target an epitope overlapping the receptor binding motif (RBM) in the SARS-CoV-2 spike protein ([Brown 2020a](#); [Rappazzo 2020](#)).

(b) (4)

Pemivibart differs by eight amino acid substitutions from the parental benchmark monoclonal antibody adintrevimab with changes in the heavy chain CDRs 1 (two substitutions) and 3 (three substitutions), and light chain CDRs 2 (one substitution) and 3 (two substitutions) ([Doyle 2022b](#)). Pemivibart maintains the same Fc region of adintrevimab, including a “LA” modification (M435L/N441A) to extend serum half-life.

Mechanism of Action

Antibody Binding Affinity

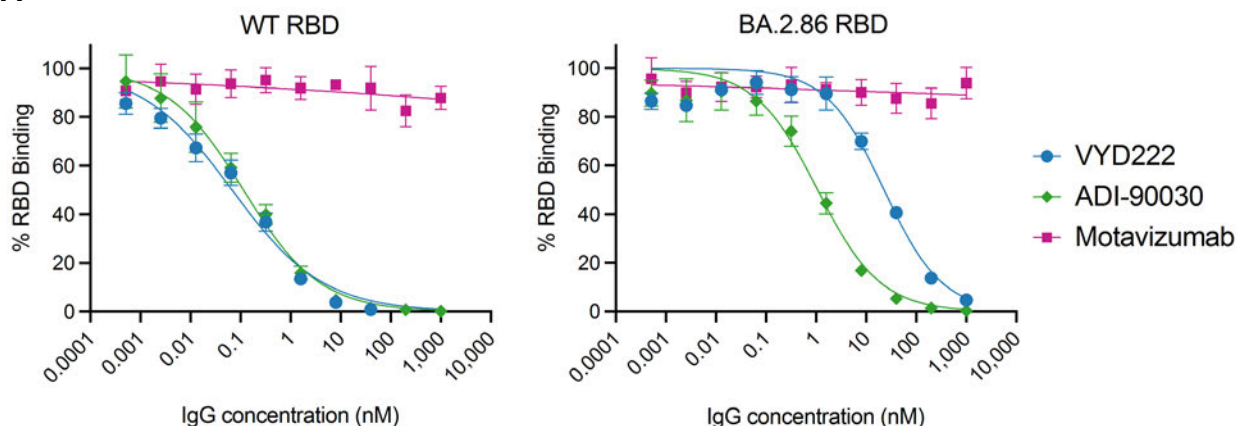
The pemivibart fragment antigen-binding (Fab) domain bound to recombinant biotinylated SARS-CoV-2 RBD proteins representing B.1 (ancestral SARS-CoV-2 with spike substitution D614G), Beta, Delta, BA.1, BA.2, and BA.4/5, SARS-CoV-2 variants with KD values of 2.1 nM, 1.7 nM, 3.5 nM, 18 nM, 13.5 nM, and 15.9 nM, respectively, as measured by biolayer interferometry ([Doyle 2022b](#)).

Inhibition of ACE2 Binding

Pemivibart blocks ACE2 binding to the SARS-CoV-2 RBD. Recombinant human ACE2 protein failed to bind to pemivibart-bound recombinant ancestral SARS-CoV-2 RBD as determined by biolayer interferometry ([Doyle 2022a](#)). In an ELISA, pemivibart inhibited binding of biotinylated SARS-CoV-2 S RBD protein representing B.1 and BA.2.86 SARS-CoV-2 variants to plate-bound recombinant human ACE2 protein with IC50 values of 0.068 and 23 nM (0.010 and 3.37 µg/mL), respectively; an anti-RSV F protein mAb failed to prevent RBD binding to ACE2 ([Figure 7](#)) ([West and Chupp 2024](#)).

Figure 7. Pemivibart (VYD222)-Mediated Inhibition of SARS-CoV-2 Spike RBD Binding to Human ACE2

A



B

Variant	hACE2 IC ₅₀ (µg/mL)		
	VYD222	ADI-90030	Motavizumab
WT RBD	0.010	0.016	n.d.
BA.2.86 RBD	3.365	0.155	n.d.

Source: [VYD222-NC-012](#) p. 6

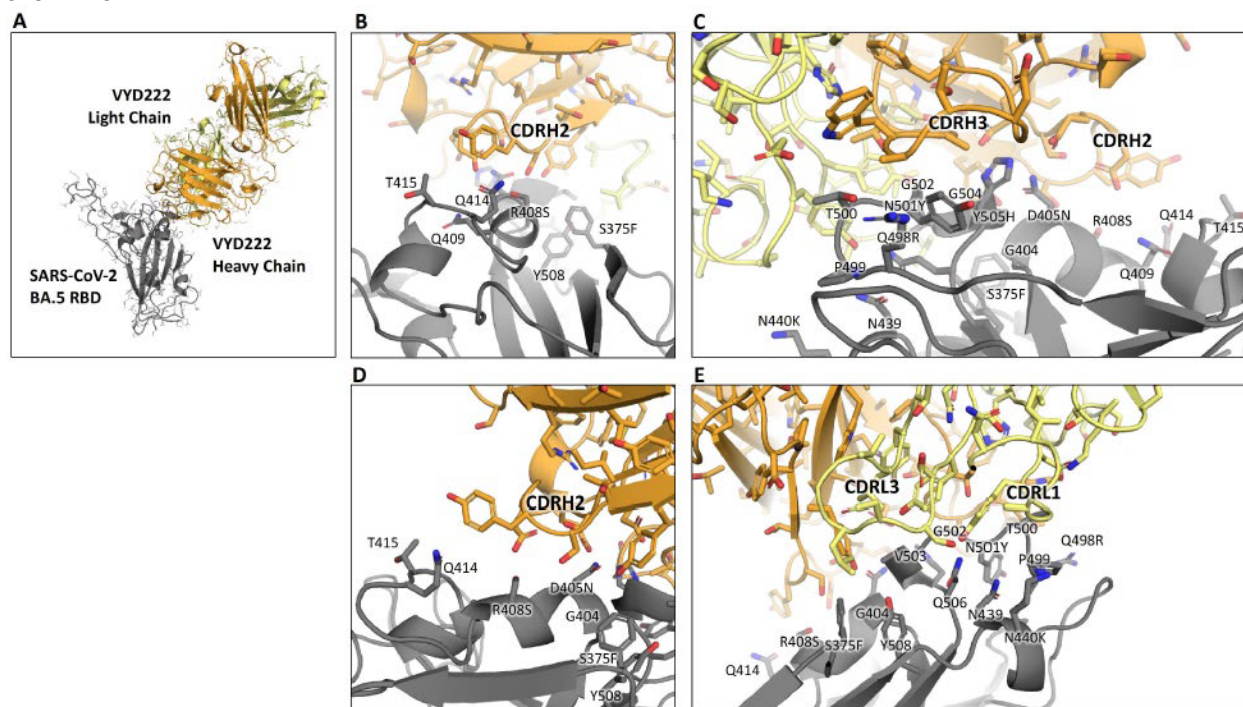
Shown are concentration-response curves (A) and IC₅₀ values for ACE2 binding inhibition (B) as measured in an ELISA.

Abbreviations: ACE2, angiotensin-converting enzyme 2; IgG, immunoglobulin G; RBD, receptor binding domain; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; WT, wild-type

Structural Epitope Determination

The pemivibart epitope in the SARS-CoV-2 RBD overlaps with the ACE2 binding motif [spike residues 438-506 ([Lan et al. 2020](#))], as determined by X-ray crystallographic analysis, consistent with the mechanism of action of prevention of ACE2 binding ([Figure 8](#)). The structures of pemivibart Fabs bound to recombinant ancestral and BA.5 SARS-CoV-2 RBDs were solved to 3 Å and 2.7 Å, respectively. Residues within 5 Å of the bound Fab in the BA.5 RBD were F375, G404, N405, S408, Q409, Q414, T415, N439, K440, R498, P499, T500, Y501, G502, V503, G504, H505, Q506, and Y508 [ACE2 contact residues are in bold ([Lan et al. 2020](#))] ([West 2023b](#)).

Figure 8. Representation of the X-Ray Crystal Structure of the Pemivibart Fab Domain Bound to the BA.5 RBD



Source: Study report [VYD222-NC-011-R0](#), Figure 2

Shown are an overview of the structure of the pemivibart Fab with the BA.5 RBD (A) and various views of the binding interface, with the interacting complementarity determining regions labeled along with the SARS-CoV-2 residues within 5 Å of bound pemivibart Fab; substitutions in BA.5 relative to B.1 are indicated (B-E). Heavy chains are indicated in orange and light chains in yellow. Abbreviations: CDR, complementarity determining region; RBD, receptor binding domain; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; VYD222, pemivibart

Fc-Mediated Functions

Fc-mediated effector functions were determined for the parent mAb (adintrevimab), which shares an identical Fc domain and overlapping epitope with pemivibart. Adintrevimab was shown to bind to Fc gamma receptors (FcγRs) FcγRI, FcγRIIa, FcγRIIb, and FcγRIIIa and complement component C1q based on surface plasmon resonance analysis ([Brown 2020b](#)). Adintrevimab triggered FcγRIIIa-mediated transgene activation in Jurkat-Lucia reporter cells when bound to immobilized recombinant spike or RBD proteins, and mediated THP-1 cell antibody-dependent cellular phagocytosis (ADCP) of antibody-bound RBD-conjugated FITC-labeled microspheres ([Narayan 2020a](#)).

Adintrevimab also mediated antibody-dependent complement deposition (ADCD) when bound to RBD-conjugated microspheres ([Narayan 2020a](#)); however, adintrevimab failed to demonstrate complement-mediated cytotoxicity (CDC) against HEK293T or CHO-K1 cells expressing SARS-CoV-2 spike protein, compared to convalescent plasma positive controls ([Craig 2021](#)). Antibody-dependent enhancement (ADE) of infection by adintrevimab was not apparent over a mAb concentration range of 100 to 0.032 ng/mL when assessed by uptake of SARS-CoV-2 spike-pseudotyped VLPs expressing luciferase in THP-1 cells, compared to a positive control antibody targeting a distinct epitope ([Narayan 2020b](#)).

Antiviral Activity

Antiviral activity data supporting this EUA include neutralization activity of pemivibart against current and historical SARS-CoV-2 variants determined in authentic virus neutralization assays and pseudotyped VLP neutralization assays. Serum virus neutralizing antibody titers were based on EC₅₀ values for pemivibart and the parent antibody adintrevimab derived from these assays against the relevant current and benchmark SARS-CoV-2 variants.

Authentic Virus Neutralization Assays

Neutralization of authentic SARS-CoV-2 variants by pemivibart and adintrevimab was evaluated in several different types of assays that differed in key attributes as indicated in [Table 4](#). In these assays, antibodies were pre-incubated with virus followed by infection of cells. After an incubation period sufficient to allow detection of virus foci formation or virus spread, immunostaining was performed to determine expression of viral NP or spike proteins in infected cells to quantify infectivity, from which a concentration-response curve and EC₅₀ value was derived. Authentic virus neutralization assays (AVNA) are dependent on multiple rounds of virus replication, and results may be influenced by assay-specific differences, such as the replication kinetics of different cell culture-adapted isolates representing a particular variant, ACE2 and TMPRSS2 expression in target cells, incubation times, and other conditions that may differ between assays. While attempts were made to optimize assay conditions to reduce the impact of these differences on estimated EC₅₀ values, results may be variable within and across AVNA types.

Pemivibart AVNA EC₅₀ values ranged from 0.039 nM (5.8 ng/mL) against Omicron BA.2 to 9.8 nM (1,445 ng/mL) against Omicron EG.5.1, and were within 1- to 13-fold of EC₅₀ values obtained in the pseudotyped VLP neutralization assays (PVNA) ([Table 17](#)). Against Omicron JN.1, pemivibart exhibited an AVNA EC₅₀ value of 0.431 nM (63.6 ng/mL), which was 0.85-fold the EC₅₀ value obtained in the PVNA (74.6 ng/mL).

Adintrevimab exhibited AVNA EC₅₀ values ranging from 0.006 nM (0.91 ng/mL) to 0.342 (50.4 ng/mL) against pre-Omicron variants; however, EC₅₀ values for adintrevimab were highly variable across AVNA assays for the same variant, with values varying by approximately 6-fold (0.047 nM vs 0.281 nM) against Delta and up to 8.5-fold against B.1 (0.041 nM vs 0.342 nM), depending on the assay ([Table 17](#)). Epitope sequence differences were not the source of variability, as reported RBD sequences for Delta and B.1 were identical between isolates used in the different assays ([Table 17](#)). Assays that produced results that were consistent between assay types were considered more reliable, and the more conservative AVNA EC₅₀ value for adintrevimab against Delta [0.047 nM (7 ng/mL)] was used to calculate titers.

Table 17. Authentic Virus Neutralization EC₅₀ Values and Assay Characteristics

mAb	Variant	AVNA EC ₅₀ Value in ng/mL	SD or Run %CV* (ng/mL)	AVNA EC ₅₀ Value in nM	Cell Type	Incub. Time (hrs)	Detection	Readout	Study Report ^a	PVNA EC ₅₀ Value (ng/mL)	Fold Change AVNA/ PVNA
Pemivibart	B.1	34	33	0.23	Vero E6/ TMPRSS2	18	Anti-NP mAb	Foci count (chromogen)	VYD222-NC- 009-R1	8.4	4
Pemivibart	B.1 ^b	31.7 ^c	5.8*	0.215	Vero E6	48	Anti-NP mAb	ELISA (chromogen)	NVD200-NC- 002-R0	8.4	3.77
Pemivibart	B.1	24.3	8.4*	0.165	Vero E6/ TMPRSS2	48	Anti-NP mAb	ELISA (chromogen)	VYD222-ND- 013-R0	8.4	2.89
Pemivibart ^d	B.1.617.2 ^e	11 ^c	15.5*	0.075	Vero E6	48	Anti-NP mAb	ELISA (chromogen)	NVD200-NC- 002-R0	5.2	2.1
Pemivibart ^d	BA.1 ^f	14.2 ^c	8.3*	0.096	Vero E6	48	Anti-NP mAb	ELISA (chromogen)	NVD200-NC- 002-R0	121	0.12
Pemivibart ^d	BA.2	5.8 ^c	9.2*	0.039	Vero E6	48	Anti-NP mAb	ELISA (chromogen)	NVD200-NC- 002-R0	44.6	0.13
Pemivibart ^d	BA.4.1 ^g	25.8 ^c	3.9*	0.175	Vero E6	48	Anti-NP mAb	ELISA (chromogen)	NVD200-NC- 002-R0	47.9	0.54
Pemivibart	XBB.1.5	290	341	1.966	Vero E6/ TMPRSS2	18	Anti-NP mAb	Foci count (chromogen)	VYD222-NC- 009-R1	104.3	2.8
Pemivibart	XBB.1.5 ^h	479.9	4.5	3.253	Vero E6/	48	Anti-NP mAb	ELISA (chromogen)	VYD222-ND- 013-R0	104.3	4.6
Pemivibart	XBB.1.16	118	81	0.8	Vero E6/ TMPRSS2	18	Anti-NP mAb	Foci count (chromogen)	VYD222-NC- 009-R1	77.6	1.5
Pemivibart	XBB.1.16 ⁱ	661.2	9.6*	4.482	Vero E6/ TMPRSS2	48	Anti-NP mAb	ELISA (chromogen)	VYD222-ND- 013-R0	77.6	8.5
Pemivibart	EG.5.1 ^j	1,445	7.2*	9.796	Vero E6/ TMPRSS2	48	Anti-NP mAb	ELISA (chromogen)	VYD222-ND- 013-R0	NA	NA
Pemivibart	HV.1	529.4	4.8*	3.589	Vero E6/ TMPRSS2	48	Anti-NP mAb	ELISA (chromogen)	VYD222-ND- 013-R0	41.2	12.8
Pemivibart	JN.1	63.6 [†]	10.5*	0.431	Vero E6/ TMPRSS2	48	Anti-NP mAb	ELISA (chromogen)	VYD222-ND- 013-R0	74.6	0.85
Adintrevimab	A (USA- Wal/2020)	1.3	NA	0.009	HeLa-ACE2	24	Anti-spike mAb cocktail	ELISA (luminescence)	ADG20-NC-015	3.9	0.3
Adintrevimab	A (USA- Wal/2020)	0.91	NA	0.006	Vero E6	24	Anti-spike mAb cocktail	ELISA (luminescence)	ADG20-NC-015	3.9	0.2
Adintrevimab	AUS/VIC01/ 2020 (WT)	4	NA	0.027	Vero	NR	Anti-NP mAb	Foci count (chromogen)	ADG20-NC-030- R4	NA	NA
Adintrevimab	B.1	6	NA	0.041	Vero E6	15-24	Anti-NP mAb	Foci count (chromogen)	ADG20-NC-038	3.9	1.6
Adintrevimab	B.1 ^b	50.4 ^c	5.8*	0.342	Vero E6	48	Anti-NP mAb	ELISA (chromogen)	NVD200-NC- 002-R0	3.9	13.1

mAb	Variant	AVNA EC₅₀ Value in ng/mL	SD or Run %CV* (ng/mL)	AVNA EC₅₀ Value in nM	Cell Type	Incub. Time (hrs)	Detection	Readout	Study Report^a	PVNA EC₅₀ Value (ng/mL)	Fold Change AVNA/ PVNA
Adintrevimab	B.1	11.6	8.4*	0.079	Vero E6/ TMPRSS2	48	Anti-NP mAb	ELISA (chromogen)	VYD222-ND- 013-R0	3.9	3
Adintrevimab	B.1.1.7	7	NA	0.047	Vero	NR	Anti-NP mAb	Foci count (chromogen)	ADG20-NC-030- R4	NA	NA
Adintrevimab	B.1.1.7	4	NA	0.027	Vero E6	15-24	Anti-NP mAb	Foci count (chromogen)	ADG20-NC-038	NA	NA
Adintrevimab	B.1.351	5	NA	0.034	Vero E6	15-24	Anti-NP mAb	Foci count (chromogen)	ADG20-NC-038	4.4	1.1
Adintrevimab	B.1.351	13	NA	0.088	Vero	NR	Anti-NP mAb	Foci count (chromogen)	ADG20-NC-030- R4	4.4	3
Adintrevimab	B.1.617.2 ^e	7 [†]	NA	0.047	Vero	NR	Anti-NP mAb	Foci count (chromogen)	ADG20-NC-030- R4	3.5	2
Adintrevimab	B.1.617.2 ^e	41.5 ^c	15.5*	0.281	Vero E6	48	Anti-NP mAb	ELISA (chromogen)	NVD200-NC- 002-R0	3.5	11.8
Adintrevimab	P.1	8	NA	0.054	Vero	NR	Anti-NP mAb	Foci count (chromogen)	ADG20-NC-030- R4	NA	NA
Adintrevimab	BA.1 ^k	1029	NA	6.976	Vero	NR	Anti-NP mAb	Foci count (chromogen)	ADG20-NC-030- R4	1035	1
Adintrevimab	BA.1 ^f	62 ^c	8.3*	0.42	Vero E6	48	Anti-NP mAb	ELISA (chromogen)	NVD200-NC- 002-R0	1035	0.06
Adintrevimab	BA.1.1	756	NA	5.125	Vero	NR	Anti-NP mAb	Foci count (chromogen)	ADG20-NC-030- R4	1035	0.7
Adintrevimab	BA.2	>10000	NA	>68	Vero	NR	Anti-NP mAb	Foci count (chromogen)	ADG20-NC-030- R4	>5000	NA
Adintrevimab	BA.2	>5000 ^c	9.2*	>34	Vero E6	48	Anti-NP mAb	ELISA (chromogen)	NVD200-NC- 002-R0	>5000	NA
Adintrevimab	BA.4.1 ^g	>5000 ^c	3.9*	>34	Vero E6	48	Anti-NP mAb	ELISA (chromogen)	NVD200-NC- 002-R0	>5000	NA
Adintrevimab	XBB.1.5 ^h	>50000	4.5*	>338	Vero E6/ TMPRSS2	48	Anti-NP mAb	ELISA (chromogen)	VYD222-ND- 013-R0	>5000	NA
Adintrevimab	XBB.1.16 ⁱ	>50000	9.6*	>338	Vero E6/ TMPRSS2	48	Anti-NP mAb	ELISA (chromogen)	VYD222-ND- 013-R0	>5,000	NA
Adintrevimab	EG.5.1 ^j	>50000	7.2*	>338	Vero E6/ TMPRSS2	48	Anti-NP mAb	ELISA (chromogen)	VYD222-ND- 013-R0	NA	NA
Adintrevimab	HV.1	>50000	4.8*	>338	Vero E6/ TMPRSS2	48	Anti-NP mAb	ELISA (chromogen)	VYD222-ND- 013-R0	NA	NA

mAb	Variant	AVNA EC ₅₀ Value in ng/mL	SD or Run %CV* (ng/mL)	AVNA EC ₅₀ Value in nM	Cell Type	Incub. Time (hrs)	Detection	Readout	Study Report ^a	PVNA EC ₅₀ Value (ng/mL)	Fold Change AVNA/ PVNA
Adintrevimab	JN.1	53.8	10.5*	0.365	Vero E6/ TMPRSS2	48	Anti-NP mAb	ELISA (chromogen)	VYD222-ND- 013-R0	NA	NA

Source: Source data are derived from the indicated Study Report.

* Indicates % CV.

[†] AVNA EC₅₀ values used for titer calculations.

^a In foci count assays, infectivity was quantified by counting individual foci in each well detected by immunostaining; in ELISA assays, infectivity was quantified by total absorbance in each well after immunostaining.

^b Isolate spike sequence deviation from B.1 consensus (relative to B.1): +F157L

^c The results from this assay were internally inconsistent when compared with other assays.

^d Evaluations were carried out with a precursor version of pemivibart lacking the "LN" Fc modification.

^e Isolate spike sequence deviation from B.1.617.2 consensus (relative to B.1): +A222V.

^f Isolate spike sequence deviation from BA.1 consensus (relative to B.1): -D215EPED.

^g Isolate spike sequence deviation from BA.4.1 consensus (relative to B.1): -G142D.

^h Isolate spike sequence deviation from XBB.1.5 consensus (relative to B.1): +H146K, +K304Q.

ⁱ Isolate spike sequence deviation from XBB.1.16 consensus (relative to B.1): +A890V, +G1219C.

^j Isolate spike sequence deviation from EG.5.1 consensus (relative to B.1): +V213Q.

^k Isolate spike sequence deviation from BA.1 consensus (relative to B.1): +A701V

Abbreviations: Adi., adintrevimab; Anti-NP, anti-nucleoprotein; AVNA, authentic virus neutralization assays; CV, coefficient of variation; EC₅₀, half-maximal effective concentration; ELISA, enzyme linked immunosorbent assay; hrs, hours; Incub., incubation; mAb, monoclonal antibody; NA, not available; NR, not reported; Pem., pemivibart; PVNA, pseudotyped virus-like particle neutralization assay

Pseudotyped Virus-Like Particle Neutralization Assays

Pemivibart and adintrevimab were evaluated in a SARS-CoV-2 spike-pseudotyped virus-like particle (VLPs) neutralization assay (PVNA) [Monogram Biosciences PhenoSense® Anti-SARS-CoV-2 Neutralizing Antibody Assay (Monogram Biosciences/LabCore) (CBER Master File [026457](#))] ([West 2024](#)) ([Table 18](#)). This assay utilizes a lentiviral vector, containing a firefly luciferase reporter gene, that is pseudotyped with the full-length spike of the respective SARS-CoV-2 variant. Neutralization of the resulting pseudotyped VLPs was evaluated in HEK293T cells transiently transfected to express human ACE2 and TMPRSS2. This assay is a single-cycle assay that measures the inhibition of pseudotyped VLP entry and reporter gene expression in the target cell and does not involve virus spread. Reported neutralization EC₅₀ values were provided by Monogram Biosciences and were determined using an in-house data analysis program ([Huang et al. 2021](#)).

The Sponsor generated dose-response curves for display ([Figure 9](#)) by fitting the neutralization data to a four-parameter logistic nonlinear regression model (GraphPad Prism Version 9.5.1); these curves were not used to calculate EC₅₀ values. The RBD sequences for pseudotyped VLPs differed from variant consensus RBD sequences, based on available global sequence data, for BQ.1 (-N460K), XBB (+Q493R), and XBB.1 (+Q493R). The spike sequences of the BA.2.86- and JN.1-pseudotyped VLPs tested for susceptibility to pemivibart differed from the global consensus sequences for each of these variants at a position outside of the RBD (+I670V); however, this position is distant from the pemivibart epitope, represents a conservative amino acid change, and is therefore not expected to significantly impact pemivibart neutralization activity.

In the PVNA, pemivibart exhibited EC₅₀ values ranging from 0.02 to 14.3 nM (3.2 to 2,112 ng/mL) against VLPs representing previously circulating SARS-CoV-2 variants, and an EC₅₀ value of 0.51 nM (74.6 ng/mL) against the currently dominant JN.1 variant ([Table 18](#)). Adintrevimab exhibited EC₅₀ values ranging from 0.02 to 0.04 nM (2.3 to 5.7 ng/mL) against pre-Omicron variants, but exhibited significantly reduced activity against evaluated Omicron-lineage variants ([Table 18](#)).

Table 18. Cumulative PVNA Antiviral Activity for Pemivibart and Adintrevimab Against the Indicated Variants

Pango Lineage	RBD Substitutions Relative to B.1 Present in Monogram Pseudotyped VLPs	Pemivibart (VYD222)				Adintrevimab (ADG20)			
		Mean EC ₅₀ Values in ng/mL (SD / Range) ^a	EC ₅₀ Values in nM	N	Fold-Change from B.1	Mean EC ₅₀ Values in ng/mL (SD / Range) ^a	Mean EC ₅₀ Values in nM	N	Fold-Change from B.1
B.1		8.4 (3)	0.06	30	1.0	3.85 (1.52)	0.03	11	1
B.1.1.7	N501Y	11.4	0.08	1	1.4	3.8	0.03	1	0.99
B.1.351	K417N, E484K, N501Y	9	0.06	1	1.1	4.4	0.03	1	1.14
P.1	K417T, E484K, N501Y	12.2	0.08	1	1.5	7	0.05	1	1.82
B.1.617.2	L452R, T478K	5.2 (4.2-6.2)	0.04	2	0.6	3.53 (0.93)	0.02	5	0.92
B.1.427	L452R	3.2	0.02	1	0.4	2.3	0.02	1	0.6
P.2	E484K	9.3	0.06	1	1.1	6.3	0.04	1	1.64
B.1.526	E484K	8.6	0.06	1	1.0	4.5	0.03	1	1.17
B.1.621	R346K, E484K, N501Y	9.5	0.06	1	1.1	5.7	0.04	1	1.48
BA.1	G339D, S371L, S373P, S375F, K417N, N440K, G446S, S477N, T478K, E484A, Q493R, G496S, Q498R, N501Y, Y505H	121.4	0.82	1	14.5	1035.15 (809.81)	7.02	4	268.87
BA.2	G339D, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, S477N, T478K, E484A, Q493R, Q498R, N501Y, Y505H	44.6 (6.5)	0.30	3	5.3	>5,000	>33.9	3	>1000
BA.4/BA.5	G339D, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, L452R, S477N, T478K, E484A, F486V, Q498R, N501Y, Y505H	47.9 (29.7-66.2)	0.33	2	5.7	>5,000	>33.9	5	>1000
BA.4.6	G339D, R346T, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, L452R, S477N, T478K, E484A, F486V, Q498R, N501Y, Y505H	29.2	0.2	1	3.5	>5,000	>33.9	1	>1000
BF.7	G339D, R346T, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, L452R, S477N, T478K, E484A, F486V, Q498R, N501Y, Y505H	72.7	0.49	1	8.7	>5,000	>33.9	1	>1000
BQ.1 ^b	G339D, R346T, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, K444T, L452R, S477N, T478K, E484A, F486V, Q498R, N501Y, Y505H	164.6	1.12	1	19.6	>50,000	>339	1	>10,000
BQ.1.1	G339D, R346T, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, K444T, L452R, N460K, S477N, T478K, E484A, F486V, Q498R, N501Y, Y505H	102.1	0.69	1	12.2	>5,000	>33.9	5	>1000

Pango Lineage	RBD Substitutions Relative to B.1 Present in Monogram Pseudotyped VLPs	Pemivibart (VYD222)				Adintrevimab (ADG20)			
		Mean EC ₅₀ Values in ng/mL (SD / Range) ^a	EC ₅₀ Values in nM	N	Fold-Change from B.1	Mean EC ₅₀ Values in ng/mL (SD / Range) ^a	Mean EC ₅₀ Values in nM	N	Fold-Change from B.1
BA.2.75 ^c	G339H, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, G446S, N460K, S477N, T478K, E484A, Q498R, N501Y, Y505H	1,364.6	9.25	1	162.5	>5,000	>33.9	2	>1000
BN.1	G339H, R346T, K356T, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, G446S, N460K, S477N, T478K, E484A, F490S, Q498R, N501Y, Y505H	2,112	14.32	1	251.4	>50,000	>339	1	>10,000
XBB ^d	G339H, R346T, L368I, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, V445P, G446S, N460K, S477N, T478K, E484A, F486S, F490S, Q493R, Q498R, N501Y, Y505H	152.2	1.03	1	18.1	>50,000	>339	1	>10,000
XBB.1 ^e	G339H, R346T, L368I, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, V445P, G446S, N460K, S477N, T478K, E484A, F486S, F490S, Q493R, Q498R, N501Y, Y505H	121.1	0.82	1	14.4	>5,000	>33.9	2	>1000
XBB.1.5	G339H, R346T, L368I, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, V445P, G446S, N460K, S477N, T478K, E484A, F486P, F490S, Q498R, N501Y, Y505H	104.3	0.71	1	12.4	>5,000	>33.9	5	>1000
XBB.1.16	G339H, R346T, L368I, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, V445P, G446S, N460K, S477N, T478K, E484A, F486P, F490S, Q498R, N501Y, Y505H	77.6 (18.1)	0.53	3	9.2	>5,000	>33.9	3	>1000
XBB.1.5.10	G339H, R346T, L368I, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, V445P, G446S, F456L, N460K, S477N, T478K, E484A, F486P, F490S, Q498R, N501Y, Y505H	108.1 (35.5)	0.73	3	12.9				
XBB.1.5.1	G339H, R346T, L368I, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, V445P, G446S, N460K, S477N, T478K, E484A, F486P, F490S, Q498R, N501Y, Y505H	80 (8.9)	0.54	3	9.5				
XBB.2.3	G339H, R346T, L368I, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, V445P, G446S, N460K, S477N, T478K, E484A, F486P, F490S, Q498R, N501Y, Y505H, P521S	87 (15.5)	0.59	3	10.4				

Pango Lineage	RBD Substitutions Relative to B.1 Present in Monogram Pseudotyped VLPs	Pemivibart (VYD222)				Adintrevimab (ADG20)			
		Mean EC ₅₀ Values in ng/mL (SD / Range) ^a	EC ₅₀ Values in nM	N	Fold-Change from B.1	Mean EC ₅₀ Values in ng/mL (SD / Range) ^a	Mean EC ₅₀ Values in nM	N	Fold-Change from B.1
EU.1.1	G339H, R346T, L368I, S371F, S373P, S375F, T376A, D405N, R408S, I410V, K417N, N440K, V445P, G446S, N460K, S477N, T478K, E484A, F486P, F490S, Q498R, N501Y, Y505H, P521S	52.1 (10.6)	0.35	3	6.2				
FL.1.5.1	G339H, R346T, L368I, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, V445P, G446S, F456L, N460K, S477N, T478R, E484A, F486P, F490S, Q498R, N501Y, Y505H	102.1 (8.8)	0.69	3	12.2				
XBB.1.5.CON-V0817 ^f	G339H, R346T, L368I, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, V445P, G446S, L452R, L455F, F456L, N460K, S477N, T478R, E484A, F486P, F490S, Q498R, N501Y, Y505H	157.2 (86.6)	1.07	6	18.7				
HV.1	G339H, R346T, L368I, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, V445P, G446S, L452R, F456L, N460K, S477N, T478K, E484A, F486P, F490S, Q498R, N501Y, Y505H	41.2 (9.2)	0.28	3	4.9				
HK.3	G339H, R346T, L368I, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, V445P, G446S, L455F, F456L, N460K, S477N, T478K, E484A, F486P, F490S, Q498R, N501Y, Y505H	72.3 (7.7)	0.49	3	8.6				
JD.1.1	G339H, R346T, L368I, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, V445P, G446S, L455F, F456L, N460K, A475V, S477N, T478K, E484A, F486P, F490S, Q498R, N501Y, Y505H	101.9 (4.9)	0.691	3	12.3				
BA.2.86 ^g	I332V, G339H, K356T, S371F, S373P, S375F, T376A, R403K, D405N, R408S, K417N, N440K, V445H, G446S, N450D, L452W, N460K, S477N, T478K, N481K, del483, E484K, F486P, Q498R, N501Y, Y505H	167.7 (4.4)	1.14	6	20.0				

Pango Lineage	RBD Substitutions Relative to B.1 Present in Monogram Pseudotyped VLPs	Pemivibart (VYD222)				Adintrevimab (ADG20)			
		Mean EC ₅₀ Values in ng/mL (SD / Range) ^a	EC ₅₀ Values in nM	N	Fold-Change from B.1	Mean EC ₅₀ Values in ng/mL (SD / Range) ^a	Mean EC ₅₀ Values in nM	N	Fold-Change from B.1
JN.1 ^h	I332V, G339H, K356T, S371F, S373P, S375F, T376A, R403K, D405N, R408S, K417N, N440K, V445H, G446S, N450D, L452W, L455S, N460K, S477N, T478K, N481K, del483, E484K, F486P, Q498R, N501Y, Y505H	74.6 (5.8)	0.51	3	8.9				

Source: Derived from study reports NVD200-NC-003-R8 and VYD222-NC-014-R0

All data were generated using the PhenoSense SARS-CoV-2 Neutralizing Antibody Assay (Monogram Biosciences, Inc).

Fold-changes of >10 are highlighted in orange, fold-changes >100 are highlighted in red. Grey shading: Not determined.

^a Mean EC₅₀ values are reported along with a range when data were obtained from two independent experiments or as mean ± standard deviation when data were obtained from three or more independent experiments.

^b Spike sequence deviation from BQ.1 consensus (relative to B.1): -N460K.

^c Spike sequence deviation from BA.2.75 consensus (relative to B.1): -LPPA24S.

^d Spike sequence deviation from XBB consensus (relative to B.1): +Q493R.

^e Spike sequence deviation from XBB.1 consensus (relative to B.1): +Q493R.

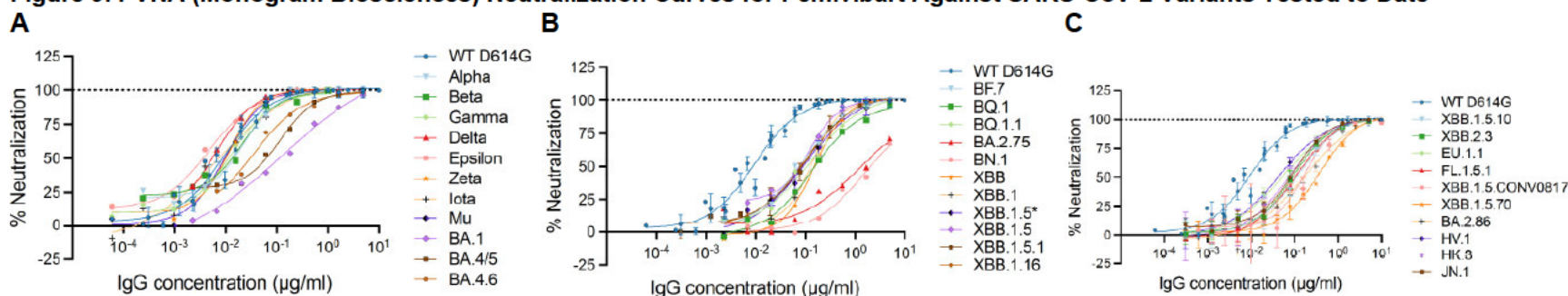
^f Spike-pseudotyped VLP containing L452R, L455F, F456L, and K478R relative to XBB.1.5.

^g Spike sequence deviation from BA.2.86 consensus (relative to B.1): +I670V.

^h Spike sequence deviation from JN.1 consensus (relative to B.1): +I670V.

Abbreviations: EC₅₀, half-maximal effective concentration PVNA, pseudotyped virus-like particle neutralization assays; RBD, receptor binding domain; SD, standard deviation; VLP, virus-like particle

Figure 9. PVNA (Monogram Biosciences) Neutralization Curves for Pemivibart Against SARS-CoV-2 Variants Tested to Date



Source: Derived from study report [NVD200-NC-003-R5](#) p. 9

Variants were plotted in three separate groups (A-C) for clarity.

Abbreviations: IgG, immunoglobulin G; PVNA, pseudotyped virus-like particle neutralization assay; SARS-CoV-2, severe acute respiratory; WT, wild-type

Resistance

Limited attempts have been made to select for SARS-CoV-2 variants with reduced susceptibility to pemivibart in cell culture. In one experiment, a SARS-CoV-2 variant, XBB.1.5.6, which shares an identical RBD sequence with XBB.1.5, against which pemivibart exhibited an EC₅₀ value of 290 ng/mL in Vero E6/TMPRSS2 cells, was passaged 3 times in Vero E6 cells in the presence of a range of pemivibart concentrations (156.25 – 10,000 ng/mL). A T500N substitution emerged at passage 2 and was associated with reduced susceptibility based on an increase in the 100% inhibitory concentration of pemivibart ([West 2023a](#)). T500 is within the structurally determined epitope for pemivibart and is a key ACE2 contact residue in the RBM. Additional spike substitutions, R489Q, Y501N, and H505Y, also emerged together in virus passaged both in the presence and absence of pemivibart and were likely associated with cell culture adaptation to Vero E6 cells; however, virus expressing these three substitutions in the absence of T500N grew in the presence of 10,000 ng/mL of pemivibart, indicating a potential role in antibody escape. These viruses were not tested individually for their impact on pemivibart susceptibility. R489Q, Y501N, and H505Y are reversions to wild type amino acids, and like T500, these positions are key ACE2 receptor binding domain residues and are within 5 Å of the pemivibart binding interface.

Cross-Resistance

Cross-resistance is not expected between pemivibart and remdesivir (Veklury® ([Gilead Sciences 2020](#))), nirmatrelvir (Paxlovid® ([Pfizer 2023](#))), or molnupiravir (Lagevrio™ ([Merck 2023](#))), since pemivibart has a distinct mechanism of action and targets a different viral protein than those targeted by currently approved or authorized drugs.

XIV. Supply Information

One treatment course of pemivibart per individual for the proposed EUA consists of nine single-dose vials of pemivibart (500 mg/4 mL).

In a correspondence dated February 23, 2024, the Sponsor stated that (b) (4) doses will be ready for distribution on February 28, 2024 to support initial launch supply (b) (4)

(b) (4) These projections are subject to revision based on FDA authorization, manufacturing performance, and activities supporting clinical development and other activities.

XV. Chemistry, Manufacturing, and Controls Information

Pemivibart is a recombinant human IgG1κ monoclonal antibody produced in Chinese Hamster Ovary (CHO) cells. It was generated from its parent SARS-CoV-2 antibody adintrevimab (b) (4)

(b) (4) It is composed of two identical heavy chains and two identical lambda light chains. The primary structure of pemivibart has eight amino acid changes

compared to adintrevimab, five in the VH region and three in the VL region. It retains the LA modification (M435L/N441A), confirmed by NGS, designed to extend serum half-life. Pemivibart does not contain modification(s) intended to reduce Fc-mediated effector functions and has a single N-glycosylation site at N304 of each heavy chains. The predominant glycan is a biantennary, fucosylated structure with no terminal galactose.

Pemivibart is supplied as sterile, preservative-free liquid in single-dose vials. Each vial contains 4 mL of solution composed of 500 mg pemivibart (at 125 mg/mL concentration), 33.03 mg glycine, 63.2 mg L-arginine hydrochloride, 3.67 mg L-histidine, 3.43 mg L-histidine hydrochloride monohydrate, 5.97 mg L-methionine, 1.2 mg polysorbate 80, sterile water for injection, pH 6.2.

The manufacturing processes of pemivibart are adequately controlled to support consistent production of materials for EUA that are safe, pure, potent and of consistent quality. The overall control strategy for drug substance (DS) and drug product (DP) is comprehensive for control of raw materials, process performance, and product quality attributes of DS and DP. (b) (4)

[Redacted text block]

The DS manufacturing process (b) (4)

[Redacted text block]

[Redacted text block]

[Redacted text block]

The MCB was tested in accordance with ICH Q5A and Q5D which demonstrated its safety and identity for use in pemivibart production. Process and product controls including, but not limited to, raw material controls, unprocessed bulk testing, viral clearance study results for downstream purification processes, analytical methods, DS and DP release and stability specifications, are acceptable to support the safety, quality, and potency of materials to be used under the EUA. Detailed characterization data, including primary, secondary, and high order structure, established and/or potential mechanisms of actions, product- and process related impurities were provided.

Data from in-use compatibility study demonstrate that the product is compatible with administration components and that its quality is maintained under the handling, preparation, and administration conditions proposed for pemivibart at hospital/clinic setting. Comparability data provided, including process performance data, release data, extended-characterization data, and comparative stability data, support that the quality of materials to be distributed under the EUA is comparable to that of materials used in clinical studies to support the EUA.

The proposed expiries for pemivibart DS and DP are (b) (4) months and 24 months, respectively, when stored at their respective long-term storage condition (i.e., (b) (4) for DS and 2-8°C for DP). The proposed DS and DP expiry is supported by the totality of stability results provided including, but not limited to, the available stability data under the long term, accelerated and stressed storage conditions, stability results from representative lots and comparative stability data. The stability protocols provided are adequate to detect potential changes in critical quality attributes during storage. The Sponsor was advised to update IND 165736 with stability data from ongoing studies as they become available to further support the proposed shelf life.

XVI. Manufacturing Site Inspections

It was determined that the HPRA inspection carried out (b) (4), had adequate inspectional coverage of the manufacturing areas proposed for EUA-000122 drug substance and drug product. An inspection waiver was recommended for (b) (4) for EUA-000122 by OPMA in a TB-EER form that was archived in DARRTS.

Table 19. Manufacturing Sites

Manufacturing Site Identifier	Drug Substances/ Intermediates/ Drug Product/Testing/Labeler/ Packager	Location (US and Non-U.S.)	Inspectional History of the Manufacturing Sites			
			Associated NDA, BLA, or IND	Commercial Sponsor/ Applicant of the Associated Submissions	Inspection Dates	GMP Status (If Known)
(b) (4)	Drug substance and drug product	(b) (4)	(b) (4)	(b) (4)	HPRA inspection (b) (4)	GMP compliant
(b) (4)	MCB testing (except sterility), Bulk harvest testing (except for bioburden)				704(a) document review, (b) (4)	GMP compliant

Source: HPRA GMP inspection report (b) (4), CMS work activity (b) (4)
 Abbreviations: BLA, biologics license application; GMP, good manufacturing practice; HPRA, Health Products Regulatory Authority; IND, investigational new drug; MCB, master cell bank; NDA, new drug application; US, United States.

Based on FDA's evaluation of the manufacturing process and control strategy, and the listed facilities, FDA considers the following conditions to the authorization as necessary to protect the public health⁶:

- Invivyd will manufacture PEMGARDA Injection (pemivibart) to meet all quality standards and per the manufacturing process and control strategy as detailed in Invivyd's EUA request. Invivyd will not implement any changes to the description of the product, manufacturing process, facilities and equipment, and elements of the associated control strategy that assure process performance and quality of the authorized product, without notification to and concurrence by the Agency as described under condition D
- All manufacturing, packaging, and testing sites for both drug substance and drug product used for EUA supply will comply with current good manufacturing practice requirements of the Federal Food, Drug, and Cosmetic Act Section 501(a)(2)(B).
- Invivyd will submit information to the Agency within three working days of receipt concerning significant quality problems with distributed drug product of PEMGARDA (Pemivibart) Injection, 500 mg/4 mL that includes the following:
 - Information concerning any incident that causes the drug product or its labeling to be mistaken for, or applied to, another article; or
 - Information concerning any microbiological contamination, or any significant chemical, physical, or other change or deterioration in the distributed drug product, or any failure of one or more distributed batches of the drug product to meet established specifications.

If a significant quality problem affects unreleased product and may also impact product(s) previously released and distributed, then information. should be submitted for all potentially impacted lots.

Invivyd will include in its notification to the Agency whether the batch, or batches, in question will be recalled. If FDA requests that these, or any other batches, at any time, be recalled, Invivyd must recall them.

If not included in its initial notification, Invivyd must submit information confirming that Invivyd has identified the root cause of the significant quality problems, taken corrective action, and provide a justification confirming that the corrective action is appropriate and effective. Invivyd must submit this information as soon as possible but no later than 45 calendar days from the initial notification.

- Invivyd will list PEMGARDA (Pemivibart) Injection, 500 mg/4 mL with a unique product NDC under the marketing category of Emergency Use Authorization.

⁶ See the evaluation documented in OMQ's Authorization Recommendation Memo for Emergency Use Authorization in CMS Case #679502, as well as OPQ's Chemistry, Manufacturing, and Controls EUA Assessment Memo, dated March 22, 2024, associated with EUA 122.

Further, the listing will include each establishment where manufacturing is performed for the drug and the type of operation performed at each such establishment

XVII. Clinical Trial Site Inspections

Clinical site inspections were not conducted for this EUA.

XVIII. Animal Study Site Inspections (Efficacy and PK/PD)

Nonclinical site inspections were not conducted for this EUA.

XIX. Recommendations From Treatment Guidelines and Other Sources

For pre-exposure prophylaxis of COVID-19 in adults and pediatric patients 12 years of age and older who are moderately or severely immunocompromised, COVID-19 vaccination is recommended by the following consensus panels and expert guidelines:

- The Center for Disease Control (CDC), in conjunction with the Advisory Committee on Immunization Practices ([CDC 2023](#)).
 - The CDC also provides COVID-19 vaccination guidance specifically for people who are moderately or severely immunocompromised.
- The National Institutes of Health (NIH) COVID-19 Treatment Guidelines ([NIH 2024](#)). The rating of the recommendation is AI, which indicates a strong recommendation based on one or more randomized trials without major limitations.
 - The NIH COVID-19 treatment guidelines also states that vaccine response rates may be lower in patients who are moderately or severely immunocompromised.
 - The NIH COVID-19 treatment guidelines also recognizes that no biomedical intervention other than vaccines prevents COVID-19.
 - Pemivibart is not included in COVID-19 treatment or prevention guidelines as it is currently not approved nor authorized for emergency use in the U.S.

XX. Risk-Benefit Assessment and Recommendations for Emergency Use

Pemivibart is a recombinant human monoclonal IgG1 λ antibody that binds to the SARS-CoV-2 spike protein receptor binding domain and inhibits ACE2 binding. Pemivibart differs by eight amino acid substitutions from the parental benchmark monoclonal antibody adintrevimab but maintains the same Fc region of adintrevimab, including a “LA” modification (M435L/N441A) to extend serum half-life. Pemivibart has

demonstrated activity in cell culture against SARS-CoV-2 and is currently being evaluated in the clinical trial VYD222-PREV-001, also called CANOPY (NCT06039449).

Based on the FDA's review of the totality of scientific evidence available, including data from CANOPY, a Phase 3 trial evaluating pemivibart for protection against COVID-19 based on an immunobridging approach, it is reasonable to believe that pemivibart, at a dose of 4500 mg IV every 3 months, may be effective for pre-exposure prophylaxis against 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.

FDA has also determined that the known and potential benefits of pemivibart, when used for the pre-exposure prophylaxis of COVID-19 as described in this memorandum, outweigh the known and potential risks of the product.

The primary efficacy objective of Cohort A of CANOPY, which consisted of adults who have moderate-to-severe immune compromise, was to evaluate protection against symptomatic COVID-19 based on titers against SARS-CoV-2 following pemivibart administration by immunobridging to historical data from the EVADE study, which provided evidence of clinical efficacy of adintrevimab, the parent mAb of pemivibart. The primary immunobridging endpoint for Cohort A compared the ratio of the geometric mean titers between pemivibart against the relevant variant JN.1 at Day 28 to the reference titer at Day 28. The reference titer at Day 28 was the extrapolated titer from the Day 90 adintrevimab titer [which was calculated based on the Day 90 concentration of adintrevimab divided by the EC₅₀ value against the B.1.617.2 (Delta) variant determined in an AVNA] using the half-life of pemivibart. Immunobridging would be 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.

The primary immunobridging results are as follows: 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). However, there are limitations of this analysis, including differences in the methodologies of assays used to determine the EC₅₀ values for pemivibart and adintrevimab against the respective variants. In a sensitivity analysis using an identical cell-based assay (a pseudotyped VLP neutralization assay), for the calculated titer comparison between pemivibart against JN.1 (based on an EC₅₀ value of 74.6 ng/mL) and adintrevimab against Delta (based on an EC₅₀ value of 3.5 ng/mL), the geometric mean ratio was 0.35 (90% CI: 0.34-0.36). This sensitivity analysis highlights the impact of even modest differences in EC₅₀ values on the results of the primary endpoint.

Given the limitations of the protocol-specified immunobridging endpoint, a supplementary analysis was performed comparing the titer values of pemivibart against JN.1, using published literature, to the titers associated with clinical efficacy of three other SARS-CoV-2 targeting mAbs in prior clinical trials. The range of titers achieved with pemivibart for 3 months following administration of 4500 mg IV were consistent with the titer levels associated with clinical efficacy in prior clinical trials evaluating certain monoclonal antibodies for the prevention of COVID-19. Following single dose administration of pemivibart 4500 mg IV, calculated geometric mean titer values (pemivibart concentration divided by the PVNA AVNA EC₅₀ value against JN.1) range from 3451 (on Day 90) to 22552 (end of infusion on Day 1). After the repeat dose of pemivibart 4500 mg IV every 3 months, it is anticipated that the range of titers at steady-state will be approximately 33% higher than those observed following the first dose administration.

Based on the totality of scientific evidence available, it is reasonable to believe that pemivibart may be effective for pre-exposure prophylaxis of COVID-19 in the authorized population.

There are limitations of the data supporting the benefits of pemivibart. 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 EC₅₀ 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 protective titer ranges.

Regarding an assessment of the known and potential risks, the overall safety database for pemivibart is comprised of over 620 adult participants who have received at least one dose of pemivibart 4500 mg with follow-up safety for at least 3 months. Approximately 296 participants have received a second dose of pemivibart 4500 mg 3 months after the first dose, and an additional 450 participants have received a second dose of either pemivibart 4500 mg or placebo (2:1 randomization to pemivibart:placebo). Notably, approximately half of all pemivibart recipients are enrolled in Cohort A (i.e., moderately to severely immunocompromised), which is the intended population for the EUA. Cohort B of CANOPY enrolled participants who are not moderately or severely immunocompromised.

The most serious adverse reaction was anaphylaxis, observed in 0.6% (4/623) of CANOPY participants who received pemivibart across cohorts. All four participants were enrolled in Cohort A. Anaphylaxis occurred either during the first or second infusion and was life-threatening in two participants. While anaphylaxis has been reported with other SARS-CoV-2 mAbs, the incidence of anaphylaxis was higher in the clinical trial of pemivibart compared to the clinical trial of tixagevimab/cilgavimab (Evusheld), the only other monoclonal antibody product previously authorized for the prevention of COVID-19. To highlight this important risk, anaphylaxis is included as a Boxed Warning in the EUA FS, along with a separate subsection within the Warnings and Precautions section.

Because no strategies are available to predict who may have an anaphylactic reaction to pemivibart, healthcare providers are advised to consider the potential benefit of COVID-19 prevention along with the risk of anaphylaxis prior to administering pemivibart. To mitigate the risk of serious outcomes due to anaphylaxis, pemivibart should be administered only in settings in which healthcare providers have immediate access to medications to treat anaphylaxis and the ability to activate the emergency medical system (EMS), as necessary; and pemivibart should be discontinued immediately if signs or symptoms of anaphylaxis or any severe systemic reaction are observed. In addition, the recommended monitoring period is at least 2 hours after the end of the infusion, which is longer than the postinfusion monitoring period for previously authorized SARS-CoV-2 mAbs.

Additional adverse events of concern included systemic hypersensitivity reactions (other than anaphylaxis) and infusion-related reactions as well as local infusion site reactions. Aside from the two life-threatening anaphylactic reactions, all other systemic reactions observed in CANOPY with the first or second dose of pemivibart were mild or moderate in severity. All local infusion site reactions observed in CANOPY were mild. To mitigate the risk of serious systemic infusion-related reactions and local injection site reactions, the recommended infusion time for pemivibart is at least 60 minutes, which is longer than the 30-minute infusion time for most participants in CANOPY. The risk mitigation strategies described for anaphylaxis also apply to other systemic hypersensitivity reactions and infusion-related reactions. In addition, a separate Warning and Precaution in the EUA FS for hypersensitivity reactions and infusion-related reactions is included.

Because the available data do not support a potential benefit of pemivibart for post-exposure prophylaxis or treatment of COVID-19, limitations for authorized use in the Fact Sheet specify that pemivibart is not authorized for post-exposure prophylaxis or treatment of COVID-19. In addition, as there are vaccines FDA approved for the prevention of COVID-19, the authorization will be limited to individuals who have moderate-to-severe immune compromise and are unlikely to mount an adequate response to COVID-19 vaccination.

The benefit-risk assessment for pemivibart is not favorable for individuals in whom COVID-19 vaccination is not recommended due to history of severe adverse reaction to a COVID-19 vaccine(s) because this population, in the absence of moderate-to-severe immune compromise, is likely to have some degree of pre-existing immunity from prior vaccination and/or prior infection and is unlikely to have the same degree of risk for serious outcomes related to COVID-19 compared to a moderately to severely immunocompromised population. Excluding this population would not preclude individuals who have a history of a severe adverse reaction to COVID-19 vaccination and who are moderately or severely immunocompromised from receiving the product, if they meet the terms and conditions of the authorization.

Based on the totality of scientific evidence available, pemivibart, at a dose of 4500 mg every 3 months, may be effective for pre-exposure prophylaxis against 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. Furthermore, when used for pre-exposure prophylaxis of COVID-19 as described in this memorandum (i.e., in individuals 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), the known and potential benefits of pemivibart outweigh the known and potential risks of the product. Therefore, the Review Division and the Office of Infectious Diseases conclude that the statutory criteria under Section 564(c) of the Federal Food, Drug, and Cosmetic Act are met and recommend authorization of an EUA for pemivibart, at a dose of 4500 mg IV every 3 months, for pre-exposure prophylaxis of COVID-19 as described above.

XXI. Considerations for Adverse Event Monitoring

This product will be used either in clinical trials under IND or in clinical practice under EUA. In clinical trials, FDA IND safety reporting regulations will apply.

The prescribing health care provider and/or the provider's designee will be responsible for mandatory reporting of all medication errors and all serious adverse events occurring during pemivibart use and considered potentially related to pemivibart within 7 calendar days from the healthcare provider's awareness of the event. The reports should include unique identifiers and the words "PEMGARDA use for the pre-exposure prophylaxis of COVID-19 under Emergency Use Authorization (EUA)"

XXII. Mandatory and Discretionary Requirements for Use of the Product Under the EUA

Refer to the Letter of Authorization and the authorized Fact Sheets for Health Care Providers.

XXIII. Information To Be Conveyed to Health Care Providers and Recipients of the Product

Fact sheets will be available to health care providers and patients through electronic links.

- The URL is www.pemgarda.com.

FDA agrees with the plan for implementation and dissemination of the Fact Sheets.

- Fact Sheet for Health Care Providers (Section [XXVI](#))
- Fact Sheet for Patients and Parents/Caregivers (Section [XXVI](#))

XXIV. Outstanding Issues/Data Gaps

The EUA for pemivibart is primarily based on safety and PK data through Month 3 (+2 days) in CANOPY. While all participants in the trial have completed both planned doses of pemivibart or placebo, follow-up is ongoing, and additional data are expected. Final results from CANOPY remain critical to confirm the initial benefit-risk assessment. Pending results from CANOPY include safety and PK data through Month 12 (9 months after the second dose, which exceeds five half-lives) and ADA assessments for all participants at the protocol-defined time points (Days 1 and 28; and Months 3, 6, and 12). In addition, unblinded Cohort B safety data beyond Day 28 has not been provided for most participants. As such, we are requiring that the Sponsor submit the following information as conditions of authorization:

- Anti-drug antibody (ADA) assessments for all participants from the CANOPY clinical trial on Days 1 and 28 by May 31, 2024; Month 3 by June 30, 2024; and Month 6 by July 31, 2024.
- A topline safety summary for all participants (Cohorts A and B) through Month 6 (last patient last visit) from the CANOPY clinical trial by June 30, 2024.
- An interim clinical study report for the CANOPY clinical trial with PK, safety, and efficacy data for all participants (Cohorts A and B) through Month 6 (last patient last visit) by October 31, 2024.
- All pharmacokinetic data and the bioanalytical report for all participants through Month 12 from the CANOPY clinical trial by March 31, 2025.
- The final clinical study report for the clinical trial CANOPY by March 31, 2025.
- Bimonthly (every 2 months) aggregate of post-EUA reports of severe or serious hypersensitivity reactions, including anaphylaxis. Sampson's criteria should be used to appropriately classify reported hypersensitivity reactions as anaphylaxis. In the bimonthly aggregate reports, include the following information at minimum.
 - Specific symptoms (preferred terms)
 - Severity of symptoms (for descriptive purposes)
 - Onset of event in relation to the infusion
 - Total dosage of pemivibart infused
 - Interventions taken (medications, hospitalization, etc.)
 - Duration of event
 - Outcome of event
- All genotypic and phenotypic resistance analysis data for subjects failing pemivibart prophylaxis in the CANOPY clinical trial by April 30, 2024 (first batch of phenotypic data), March 31, 2025 (complete whole-genome sequence analysis data for Cohorts A and B), and April 30, 2025 (complete viral phenotypic data for Cohorts A and B).

- Spike sequence data for each treatment failure identified in the CANOPY trial as soon as practicable, but no later than 6 weeks after failure determination. Phenotypic data for spike variants with substitutions in the PEMGARDA epitope at contact and adjacent residues should be obtained and submitted within 2 calendar days from receipt from the contractor.

Additional Virology Conditions of Authorization

- Invivyd will establish a process for monitoring genomic database(s) for the emergence of global viral variants of SARS-CoV-2. A summary of Invivyd's process should be submitted to the Agency as soon as practicable, but no later than 30 calendar days of the issuance of this letter, and within 30 calendar days of any material changes to such process. Invivyd will provide reports to the Agency on a monthly basis summarizing any findings as a result of its monitoring activities and, as needed, any follow-up assessments planned or conducted.
- FDA may require Invivyd to assess the activity of the authorized pemivibart against any global SARS-CoV-2 variant(s) of interest (e.g., variants that are prevalent or becoming prevalent that harbor substitutions in the target protein). Invivyd will perform the required assessment in a manner and timeframe agreed upon by Invivyd and the Agency. Invivyd will submit to FDA a preliminary summary report immediately upon completion of its assessment followed by a detailed study report within 30 calendar days of study completion. Invivyd will submit any relevant proposal(s) to revise the authorized labeling based on the results of its assessment, as may be necessary or appropriate based on the foregoing assessment.
- Invivyd shall provide samples as requested of the authorized pemivibart to the HHS for evaluation of activity against emerging global viral variants of SARS-CoV-2, including specific amino acid substitution(s) of interest (e.g., variants that are highly prevalent or that harbor substitutions in the target protein) within 5 business days of any request made by HHS. Analyses performed with the supplied quantity of authorized pemivibart may include, but are not limited to, cell culture potency assays, protein binding assays, cell culture variant assays (pseudotyped virus-like particles and/or authentic virus), and in vivo activity assays.
- Invivyd must conduct additional studies selecting SARS-CoV-2 with reduced susceptibility to pemivibart in cell culture. Such studies must employ strategies as agreed upon between Invivyd and the Agency, and Invivyd must provide a protocol within 30 calendar days of the issuance of this letter.

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XXVI. Appendices

Appendix 1. Fact Sheet for Health Care Providers

See next page.

FACT SHEET FOR HEALTHCARE PROVIDERS: EMERGENCY USE AUTHORIZATION OF PEMGARDA (PEMIVIBART)

HIGHLIGHTS OF EMERGENCY USE AUTHORIZATION (EUA)

These highlights of the EUA do not include all the information needed to use PEMGARDA under the EUA. See the FULL FACT SHEET FOR HEALTHCARE PROVIDERS for PEMGARDA.

PEMGARDA (pemivibart) injection, for intravenous use
Original EUA Authorized Date: mm/yyyy

WARNING: ANAPHYLAXIS

See Full Fact Sheet for Healthcare Providers for the complete boxed warning.

- Anaphylaxis has been observed with PEMGARDA in 0.6% (4/623) of participants in a clinical trial.
- Anaphylaxis was reported during the first and second infusion of PEMGARDA. (5.1, 6.1)
- Anaphylaxis can be life-threatening.
- Prior to administering PEMGARDA, consider the potential benefit of COVID-19 prevention along with the risk of anaphylaxis. (5.1, 6.1, 14)
- Administer PEMGARDA only in settings in which healthcare providers have immediate access to medications to treat anaphylaxis and the ability to activate the emergency medical system (EMS), as necessary.
- Clinically monitor individuals during the infusion and for at least two hours after completion of the infusion.
- Discontinue PEMGARDA immediately if signs or symptoms of anaphylaxis or any severe systemic reaction are observed and initiate appropriate medications and/or supportive therapy.

EUA FOR PEMGARDA

The U.S. FDA has issued an EUA for the emergency use of the unapproved product PEMGARDA (pemivibart), a SARS-CoV-2 spike protein-directed attachment inhibitor, for the pre-exposure prophylaxis of coronavirus disease 2019 (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 immune response to COVID-19 vaccination.

PEMGARDA has been authorized by FDA for the emergency use described above. PEMGARDA is not FDA-approved for any use, including use for pre-exposure prophylaxis of COVID-19. (1)

LIMITATIONS OF AUTHORIZED USE

- PEMGARDA is not authorized for use:
 - For treatment of COVID-19, or:
 - For post-exposure prophylaxis of COVID-19 in individuals who have been exposed to someone infected with SARS-CoV-2.
- Pre-exposure prophylaxis with PEMGARDA is not a substitute for vaccination in individuals for whom COVID-19 vaccination is recommended. Individuals for whom COVID-19 vaccination is recommended, including individuals with moderate-to-severe immune compromise who may derive benefit from COVID-19 vaccination, should receive COVID-19 vaccination.
- In individuals who have recently received a COVID-19 vaccine, PEMGARDA should be administered at least 2 weeks after vaccination.
- PEMGARDA may only be prescribed for an individual patient by physicians, advanced practice registered nurses, and physician assistants who are licensed or authorized under State law to prescribe drugs.
- PEMGARDA is authorized only for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of PEMGARDA under section 564(b)(1) of the Act, 21 U.S.C. § 360bbb 3(b)(1), unless the authorization is terminated or revoked sooner.

See Full Fact Sheet for Healthcare Providers for examples of medical conditions or treatments that may result in moderate to severe immune compromise and an inadequate immune response to COVID-19 vaccination, the justification for emergency use of drugs during the COVID-19 pandemic, information on available alternatives, and additional information on COVID-19.

DOSAGE AND ADMINISTRATION

PEMGARDA must be infused over a minimum of 60 minutes. (2.3) The dosage of PEMGARDA for emergency use in adults and adolescents (12 years of age and older weighing at least 40 kg) is:

Initial Dose: 4500 mg administered as a single intravenous infusion. (2.1)

Repeat Dose: 4500 mg administered as a single intravenous infusion approximately every 3 months. Repeat dosing should be timed from the date of the most recent PEMGARDA dose. (2.1)

See Full Fact Sheet for Healthcare Providers for details on preparation and administration. (2.3)

DOSAGE FORMS AND STRENGTHS

Injection: PEMGARDA 500 mg/4 mL (125 mg/mL) in a single-dose vial. (3)

CONTRAINDICATIONS

PEMGARDA is contraindicated in individuals with previous severe hypersensitivity reactions, including anaphylaxis, to any component of PEMGARDA. (4)

WARNINGS AND PRECAUTIONS

- Anaphylaxis: Anaphylaxis has been observed with PEMGARDA in 4 of 623 (0.6%) participants in a clinical trial. Administer PEMGARDA only in settings in which healthcare providers have immediate access to medications to treat anaphylaxis and the ability to activate the emergency medical system (EMS), as necessary. If signs or symptoms of an anaphylactic reaction occur, immediately discontinue administration, and initiate appropriate medications and/or supportive therapy. Discontinue PEMGARDA use permanently in individuals who experience signs or symptoms of anaphylaxis. (5.1)
- Hypersensitivity and Infusion-Related Reactions: Hypersensitivity and infusion-related reactions occurring during the infusion and up to 24 hours after the infusion have been observed with PEMGARDA and may be severe or life-threatening. If signs or symptoms of a clinically significant hypersensitivity reaction or infusion-related reaction occur, immediately discontinue administration, and initiate appropriate medications and/or supportive therapy. Clinically monitor individuals during infusion and for at least 2 hours after infusion is complete. (5.2)
- Risk of Cross-Hypersensitivity with COVID-19 Vaccines: PEMGARDA contains polysorbate 80, which is in some COVID-19 vaccines and is structurally similar to polyethylene glycol (PEG), an ingredient in other COVID-19 vaccines. For individuals with a history of severe hypersensitivity reaction to a COVID-19 vaccine, consider consultation with an allergist-immunologist prior to PEMGARDA administration. (5.3)
- Risk for COVID-19 Due to SARS-CoV-2 Viral Variants Not Neutralized by PEMGARDA: Certain SARS-CoV-2 viral variants may emerge that are not neutralized by monoclonal antibodies such as PEMGARDA. PEMGARDA may not be effective at preventing COVID-19 caused by these SARS-CoV-2 viral variants. Inform individuals of the increased risk, compared to other variants, for COVID-19 due to SARS-CoV-2 viral variants not neutralized by PEMGARDA. If signs and symptoms of COVID-19 occur, advise individuals to test for COVID-19 and seek medical attention, including starting treatment for COVID-19 as appropriate. (5.4)

ADVERSE REACTIONS

The most common adverse events (all grades, incidence $\geq 2\%$) observed in participants who have moderate-to-severe immune compromise treated with PEMGARDA included systemic and local infusion-related or hypersensitivity reactions, upper respiratory tract infection, viral infection, influenza-like illness, fatigue, headache, and nausea.

You or your designee must report all SERIOUS ADVERSE EVENTS or MEDICATION ERRORS potentially related to PEMGARDA (1) by submitting FDA Form 3500 [online](#), (2) by [downloading this form](#), and then submitting it by mail or fax, or (3) by contacting the FDA at 1-800-FDA-1088 to request this form. Please also provide a copy of this form to Invivyd, Inc. by email at: pv@invivyd.com or call 1-800-890-3385 to report adverse events. (6.4)
See PATIENT AND PARENTS/CAREGIVER FACT SHEET

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FULL FACT SHEET FOR HEALTHCARE PROVIDERS

WARNING: ANAPHYLAXIS

- **Anaphylaxis has been observed with PEMGARDA in 0.6% (4/623) of participants in a clinical trial.**
- **Anaphylaxis was reported during the first and second infusion of PEMGARDA [see *Warnings and Precautions (5.1)*, *Adverse Reactions (6.1)*].**
- **Anaphylaxis can be life-threatening.**
- **Prior to administering PEMGARDA, consider the potential benefit of COVID-19 prevention along with the risk of anaphylaxis [see *Warnings and Precautions (5.1)*, *Adverse Reactions (6.1)*, and *Clinical Studies (14)*].**
- **Administer PEMGARDA only in settings in which healthcare providers have immediate access to medications to treat anaphylaxis and the ability to activate the emergency medical system (EMS), as necessary.**
- **Clinically monitor individuals during the infusion and for at least two hours after completion of the infusion.**
- **Discontinue PEMGARDA immediately if signs or symptoms of anaphylaxis or any severe systemic reaction are observed and initiate appropriate medications and/or supportive therapy.**

1 EMERGENCY USE AUTHORIZATION FOR PEMGARDA

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) for the emergency use of the unapproved product PEMGARDA (pemivibart) for the pre-exposure prophylaxis of coronavirus disease 2019 (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.

Medical conditions or treatments that may result in moderate to severe immune compromise and an inadequate immune response to COVID-19 vaccination include:

- 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)

Limitations of Authorized Use

- PEMGARDA is not authorized for use:
 - For treatment of COVID-19, or
 - For post-exposure prophylaxis of COVID-19 in individuals who have been exposed to someone infected with SARS-CoV-2.
- Pre-exposure prophylaxis with PEMGARDA is not a substitute for vaccination in individuals for whom COVID-19 vaccination is recommended. Individuals for whom COVID-19 vaccination is recommended, including individuals with moderate-to-severe immune compromise who may derive benefit from COVID-19 vaccination, should receive COVID-19 vaccination.
- In individuals who have recently received a COVID-19 vaccine, PEMGARDA should be administered at least 2 weeks after vaccination.

PEMGARDA may only be prescribed for an individual patient by physicians, advanced practice registered nurses, and physician assistants that are licensed or authorized under State law to prescribe drugs .

PEMGARDA has been authorized by FDA for the emergency use described above.

PEMGARDA is not FDA-approved for any use, including use for pre-exposure prophylaxis of COVID-19.

PEMGARDA is authorized only for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of PEMGARDA under section 564(b)(1) of the FD&C Act, 21 U.S.C. § 360bbb-3(b)(1), unless the authorization is terminated or revoked sooner.

Justification for Emergency Use of Drugs During the COVID-19 Pandemic:

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 emergency¹.
- Declared that circumstances exist justifying the authorization of emergency use of drugs and biological products for the prevention or treatment of COVID-19².

An EUA is an FDA authorization for the emergency use of an unapproved product or unapproved use of an approved product (i.e., drug, biological product, or device) in the United States under certain circumstances including, but not limited to, when the Secretary of HHS declares that there is a public health emergency that affects the national security or the health and security of United States citizens living abroad, and that involves biological agent(s) or a disease or condition that may be attributable to such agent(s). Criteria for issuing an EUA include:

- The biological agent(s) can cause a serious or life-threatening disease or condition.
- Based on the totality of the available scientific evidence (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 the serious or life-threatening disease or condition; and
 - the known and potential benefits of the product - when used to diagnose, prevent, or treat such disease or condition - outweigh the known and potential risks of the product, taking into consideration the material threat posed by the biological agent(s).
- There is no adequate, approved, and available alternative to the product for diagnosing, preventing, or treating the serious or life-threatening disease or condition.

Information Regarding Available Alternatives for the EUA Authorized Use

There are no adequate, approved, and available alternatives to PEMGARDA for the pre-exposure prophylaxis of COVID-19 in individuals who are unlikely to mount an adequate immune response to COVID-19 vaccination.

For information on clinical studies of PEMGARDA and other therapies for the pre-exposure prophylaxis of COVID-19, see www.clinicaltrials.gov.

¹ 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>.

² 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.”).

2 DOSAGE AND ADMINISTRATION

2.1 Dosage for Emergency Use of PEMGARDA

Initial Dosing:

The initial dosage of PEMGARDA in adults and adolescents (12 years of age and older weighing at least 40 kg) is 4500 mg administered as a single intravenous (IV) infusion [see *Clinical Pharmacology* ([12.3](#))].

Repeat Dose:

The repeat dosage is 4500 mg of PEMGARDA administered as a single IV infusion every 3 months. Repeat dosing should be timed from the date of the most recent PEMGARDA dose.

The recommendations for dosing are based on the totality of the scientific evidence including clinical pharmacology data, antiviral activity data, and clinical study data [see *Clinical Pharmacology* ([12.3](#)), *Microbiology* ([12.4](#)), and *Clinical Studies* ([14](#))].

2.2 Dosage Adjustment in Specific Populations

No dosage adjustment is recommended in pregnant or lactating individuals, in geriatrics, or in individuals with renal or hepatic impairment [see *Use in Specific Populations* ([8](#))].

2.3 Dose Preparation and Administration

General Information:

- PEMGARDA should be prepared and administered by a qualified healthcare provider using aseptic technique.
- Vials of PEMGARDA are for one-time use only.
- Visually inspect the vials for particulate matter and discoloration. PEMGARDA is a clear to slightly opalescent, colorless to yellow solution. Discard the vial if the solution is cloudy, discolored, or if visible particles are observed.
- PEMGARDA should be administered as an IV infusion diluted with 0.9% sodium chloride.

Materials Needed:

- 9 single-dose vials of PEMGARDA (125 mg/mL)
- 50 mL prefilled bag of 0.9% sodium chloride (normal saline) for IV injection
- IV extension set with inline 0.2-micron filter
- Infusion pump or gravity infusion set
- 0.9% sodium chloride injection for flushing

Preparation:

- Remove PEMGARDA vials from refrigerated storage and allow to equilibrate to room temperature (18°C to 26°C [64°F to 79°F]) for 10 minutes before preparation. **Do not expose to direct heat. Do not shake vials. Inspect the vials.**

- Prepare IV bag by removing and discarding 36 mL from a 50 mL prefilled bag of 0.9% sodium chloride for IV injection.
- Withdraw 36 mL of PEMGARDA from nine (9) vials into appropriately sized polypropylene syringe(s) (e.g., one 40 mL syringe or two 20 mL syringes) and inject into prepared 0.9% sodium chloride IV bag.
- The final product for administration will contain 50 mL: 36 mL of PEMGARDA and 14 mL of 0.9% sodium chloride.
- This product is preservative-free and therefore should be administered immediately.
- If immediate administration is not possible, the diluted solution may be stored at room temperature under ambient light for up to 4 hours. Do not shake the diluted solution.

Administration:

- PEMGARDA should only be administered in settings in which healthcare providers have immediate access to medications to treat a severe hypersensitivity reaction, such as anaphylaxis, and the ability to activate the emergency medical system (EMS), as necessary [*see Warnings and Precautions (5.1)*].
- Attach infusion set including inline 0.2-micron filter to prepared IV bag, then prime the infusion set.
- Administer the entire 50 mL infusion using infusion pump or gravity infusion set over a minimum of 60 minutes. Due to potential overflow, the entire contents of prepared IV bag should be administered to avoid underdosing.
- Once infusion is complete, flush line with 0.9% sodium chloride.
- Clinically monitor patients during infusion and observe patients for at least 2 hours after infusion is complete [*see Warnings and Precautions (5.1)*].

3 DOSAGE FORMS AND STRENGTHS

PEMGARDA is a sterile, preservative-free, clear to slightly opalescent, colorless to yellow solution available as:

- Injection: 500 mg/4 mL (125 mg/mL) in a single-dose vial

4 CONTRAINDICATIONS

PEMGARDA is contraindicated in individuals with previous severe hypersensitivity reactions, including anaphylaxis, to any component of PEMGARDA.

5 WARNINGS AND PRECAUTIONS

5.1 Anaphylaxis

Anaphylaxis has been observed with PEMGARDA in 4 of 623 (0.6%) participants in a clinical trial [see *Adverse Reactions (6.1)*]. Two participants had anaphylaxis during the first infusion, and two participants had anaphylaxis during the second infusion. Anaphylaxis can be life-threatening, and two of the anaphylactic reactions in the clinical trial were reported as life-threatening. Manifestations included pruritus, flushing, urticaria, erythema, angioedema, diaphoresis, dizziness, tinnitus, wheezing, dyspnea, chest discomfort, and tachycardia. In all 4 cases, PEMGARDA was permanently discontinued.

Prior to administering PEMGARDA, consider the potential benefit of COVID-19 prevention along with the risk of anaphylaxis [*Adverse Reactions (6.1)*, and *Clinical Studies (14)*].

Administer PEMGARDA only in settings in which healthcare providers have immediate access to medications to treat anaphylaxis and the ability to activate the emergency medical system (EMS), as necessary.

Clinically monitor individuals during the 60-minute infusion and for at least two hours after completion of the infusion. If signs or symptoms of an anaphylactic reaction occur, immediately discontinue administration, and initiate appropriate medications and/or supportive therapy. Discontinue PEMGARDA use permanently in individuals who experience signs or symptoms of anaphylaxis [see *Contraindications (4)*].

5.2 Hypersensitivity and Infusion-Related Reactions

Hypersensitivity and infusion-related reactions occurring during the infusion and up to 24 hours after the infusion have been observed with administration of PEMGARDA. Hypersensitivity or infusion-related reactions may be severe or life threatening. If signs or symptoms of a clinically significant hypersensitivity or infusion-related reaction occur, immediately discontinue administration, and initiate appropriate medications and/or supportive therapy. Signs and symptoms of hypersensitivity or infusion-related reactions may include:

- Fever, difficulty breathing, reduced oxygen saturation, chills, fatigue, arrhythmia (e.g., atrial fibrillation, sinus tachycardia, bradycardia), chest pain or discomfort, weakness, altered mental status, nausea, headache, bronchospasm, hypotension, hypertension, angioedema, throat irritation, rash including urticaria, pruritus, myalgia, vasovagal reactions (e.g., pre-syncope, syncope), dizziness, and diaphoresis.

If a mild infusion-related reaction occurs, consider slowing or stopping the infusion and administer appropriate medications and/or supportive care. Clinically monitor individuals during infusion and for at least two hours after completion of the infusion for signs and symptoms of hypersensitivity.

Hypersensitivity reactions occurring more than 24 hours after the infusion have also been reported with the use of SARS-CoV-2 monoclonal antibodies under Emergency Use Authorization.

5.3 Risk of Cross-Hypersensitivity With COVID-19 Vaccines

PEMGARDA contains polysorbate 80, which is in some COVID-19 vaccines and is structurally similar to polyethylene glycol (PEG), an ingredient in other COVID-19 vaccines [*see Description (11)*]. For individuals with a history of a severe hypersensitivity reaction to a COVID-19 vaccine, consider consultation with an allergist-immunologist prior to PEMGARDA administration.

Administration of PEMGARDA should be done under the supervision of a healthcare provider with appropriate medical support to manage severe hypersensitivity reactions. If signs and symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur during administration of PEMGARDA, immediately discontinue administration and initiate appropriate medications and/or supportive care. Clinically monitor individuals after infusion and observe for at least two hours.

5.4 Risk for COVID-19 Due to SARS-CoV-2 Viral Variants Not Neutralized by PEMGARDA

Certain SARS-CoV-2 viral variants may emerge that are not neutralized by monoclonal antibodies such as PEMGARDA. PEMGARDA may not be effective at preventing COVID-19 caused by these SARS-CoV-2 viral variants.

Inform individuals of the increased risk, compared to other variants, for COVID-19 due to emergent SARS-CoV-2 viral variants not neutralized by PEMGARDA. If signs or symptoms of COVID-19 occur, advise individuals to test for COVID-19 and seek medical attention, including starting treatment for COVID-19 as appropriate. Symptoms of COVID-19 may include fever or chills, cough, shortness of breath or difficulty breathing, fatigue, muscle or body aches, headache, new loss of taste or smell, sore throat, congestion or runny nose, nausea or vomiting, or diarrhea³.

6 ADVERSE REACTIONS

6.1 Adverse Reactions from Clinical Studies

The following adverse reactions have been observed in the clinical study of PEMGARDA that supported the EUA [*see Clinical Studies (14)*]. The adverse reaction rates observed in the clinical study cannot be directly compared to rates in the clinical studies of other products and may not reflect the rates observed in clinical practice. Additional adverse reactions associated with PEMGARDA may become apparent with more widespread use.

The safety of PEMGARDA is based on exposure of 623 participants who received at least one dose of PEMGARDA 4500 mg IV in one of two cohorts in the ongoing CANOPY trial. Cohort A is a single-arm, open-label trial in adults who have moderate-to-severe immune compromise (n=306), while Cohort B is a randomized, placebo-controlled trial in which adults who do not have moderate-to-severe immune compromise received PEMGARDA (n=317) or placebo (n=162). In Cohort A, 296 participants received a second dose of PEMGARDA 4500 mg IV

³ For additional information on the symptoms of COVID-19, please see <https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html>.

three months after the initial dose. In Cohort B, 450 participants received a second dose of PEMGARDA 4500 mg IV or placebo three months after the initial dose. Cumulative safety with the first two doses of PEMGARDA is assessed only in Cohort A because unblinded safety data in Cohort B were not available after Day 28.

Anaphylaxis

Anaphylaxis was observed in 4 of 623 (0.6%) participants in CANOPY, all in Cohort A.

Two participants had anaphylaxis during the first infusion, and two participants had anaphylaxis during the second infusion. All four reactions led to permanent discontinuation of PEMGARDA. Three participants had complete resolution, and one participant had acute resolution with sequelae related to a flare of an underlying condition.

Symptoms of anaphylaxis during the first dose included dyspnea, diaphoresis, erythema (face), chest discomfort, and tachycardia in one participant, and flushing, dizziness, tinnitus, and wheezing in one participant. Treatment for both included diphenhydramine.

Both instances of anaphylaxis with the second dose were reported as life-threatening. Symptoms during the second infusion and following discontinuation of the infusion in both participants included pruritus, urticaria, angioedema, dyspnea, and either erythema or flushing. One participant also experienced headache, dizziness, and chest pain; additionally, pruritus, erythema, and urticaria reoccurred in this participant within 24 hours of the initial onset of anaphylaxis. Both participants were treated with diphenhydramine and epinephrine, and one participant also received oral prednisone and metoprolol for an associated flare of an underlying condition.

Systemic Infusion-Related Reactions and Hypersensitivity Reactions

First Dose

Systemic infusion-related reactions and hypersensitivity reactions (i.e., adverse events assessed as causally related) were observed with the first dose in CANOPY in 4% (24/623) of participants who received PEMGARDA across cohorts, including:

- 7% (20/306) of participants who have moderate-to-severe immune compromise (Cohort A), and
- 1% (4/317) of participants who received PEMGARDA in Cohort B

Infusion-related reactions and hypersensitivity reactions were not observed in any participants who received placebo in Cohort B.

Systemic infusion-related or hypersensitivity reactions that started within 24 hours of the first dose of PEMGARDA treatment were reported as infusion-related reaction, infusion-related hypersensitivity, hypersensitivity, fatigue, headache, tachycardia, brain fog, dermatitis, diarrhea, myalgia, nausea, paresthesia, presyncope, and tremor. All reactions were mild or moderate, but two reactions were anaphylaxis [see *Box Warnings, and Warnings and Precautions (5.1, 5.2)*]. Infusion-related reactions or hypersensitivity reactions led to discontinuation of the first infusion in 1% (6/623) of participants who received PEMGARDA.

First and Second Dose, Cumulative – Moderately to Severely Immunocompromised Population

Cumulatively, infusion-related reactions and hypersensitivity reactions were observed in 9% (27/306) of participants who have moderate-to-severe immune compromise, who received

PEMGARDA in Cohort A of CANOPY. The severity of the reactions was generally mild (17/27) or moderate (8/27), but two reactions were life-threatening [see *Boxed Warnings and Warnings and Precautions* (5.1, 5.2)]. Infusion-related reactions or hypersensitivity reactions led to discontinuation of the first or second infusion in 2% (7/306) of Cohort A participants.

Two percent (5/306) of participants who have moderate-to-severe immune compromise (Cohort A) had an infusion-related reaction or hypersensitivity reaction with both the first and second dose of PEMGARDA.

Local Infusion Site Reactions

First and Second Dose, Cumulative

Cumulatively, local infusion site reactions were observed in 2% (6/306) of participants who have moderate-to-severe immune compromise (Cohort A) with either the first or second dose. No local infusion site reactions were observed in Cohort B. Local reactions were reported as infusion site bruising, infusion site erythema, infusion site rash, and injection site reaction. All local reactions were mild, and none led to treatment discontinuation.

Cumulatively, infusion site infiltration, extravasation, or vein rupture was noted in 5% (14/306) of participants who have moderate-to-severe immune compromise (Cohort A) with either the first or second dose.

Other Common Adverse Events

First and Second Dose, Cumulative – Moderately to Severely Immunocompromised Population

In addition to systemic and local infusion-related/hypersensitivity reactions described above, the most common ($\geq 2\%$) treatment-emergent adverse events, irrespective of causality, observed with PEMGARDA in participants who have moderate-to-severe immune compromise (Cohort A) in CANOPY were upper respiratory tract infection (6%), viral infection (4%), influenza-like illness (3%), fatigue (3%), headache (2%), and nausea (2%).

6.4 Required Reporting for Serious Adverse Events and Medication Errors

The prescribing healthcare provider and/or the provider's designee is/are responsible for mandatory reporting of all serious adverse events* and medication errors potentially related to PEMGARDA within 7 calendar days from the healthcare provider's awareness of the event, using FDA Form 3500 (for information on how to access this form, see below). The FDA requires that such reports, using FDA Form 3500, include the following:

- Patient demographics and baseline characteristics (e.g., patient identifier, age or date of birth, sex, weight, ethnicity, and race).
- A statement "PEMGARDA use for the pre-exposure prophylaxis of COVID-19 under Emergency Use Authorization (EUA)" under the "**Describe Event, Problem, or Product Use/Medication Error**" heading.
- Information about the serious adverse event or medication error (e.g., signs and symptoms, test/laboratory data, complications, timing of drug initiation in relation to the occurrence of the event, duration of the event, treatment required to mitigate the event, evidence of event improvement/disappearance after stopping or reducing the dosage, evidence of event reappearance after reintroduction, clinical outcomes).

- Patient's preexisting medical conditions and use of concomitant products.
- Information about the product (e.g., dosage, route of administration, NDC #).

Submit serious adverse event and medication error reports using FDA Form 3500 to FDA MedWatch using one of the following methods:

- Complete and submit the report online: www.fda.gov/medwatch/report.htm.
- Complete and submit a postage-paid FDA Form 3500 (<https://www.fda.gov/media/76299/download>) and return by:
 - Mail to MedWatch, 5600 Fishers Lane, Rockville, MD 20852-9787, or
 - Fax to 1-800-FDA (332)-0178, or
- Call 1-800-FDA (332)-1088 to request a reporting form.

In addition, please provide a copy of all FDA MedWatch forms to:

Invivyd, Inc.

Email: pv@invivyd.com

Or call Invivyd, Inc. at 1-800-890-3385 to report serious adverse events.

The prescribing healthcare provider and/or the provider's designee is/are responsible for mandatory responses to requests from FDA for information about serious adverse events and medication errors following receipt of PEMGARDA.

*Serious adverse events are defined as:

- Death
- A life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Other important medical events, which may require a medical or surgical intervention to prevent death, a life-threatening event, hospitalization, disability, or congenital anomaly

7 DRUG INTERACTIONS

Drug-drug interaction studies have not been performed. PEMGARDA is not renally excreted or metabolized by cytochrome P450 enzymes; therefore, interactions with concomitant medications that are renally excreted or that are substrates, inducers, or inhibitors of cytochrome P450 enzymes are unlikely [*see Clinical Pharmacology (12.3)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary:

There are insufficient data to evaluate a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. PEMGARDA should only be used during pregnancy if the potential benefit outweighs the potential risk for the mother and the fetus.

Nonclinical reproductive toxicity studies have not been performed with pemivibart. In tissue cross-reactivity studies using human fetal tissues, no off-target binding was detected for pemivibart. Human immunoglobulin G1 (IgG1) antibodies are known to cross the placental barrier; therefore, pemivibart has the potential to be transferred from the mother to the developing fetus. It is unknown whether the potential transfer of pemivibart provides any treatment benefit or risk to the developing fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the US general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

8.2 Lactation

Risk Summary:

There are no available data on the presence of PEMGARDA in human or animal milk, the effects on the breastfed infant, or the effects on milk production. Maternal IgG is known to be present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for PEMGARDA and any potential adverse effects on the breastfed infant from PEMGARDA.

8.4 Pediatric Use

PEMGARDA is not authorized for use in pediatrics less than 12 years of age or weighing less than 40 kg. The safety and effectiveness of PEMGARDA has not been established in pediatrics.

The recommended dosing regimen is expected to result in comparable serum exposures of pemivibart in adolescents 12 years of age and older and weighing at least 40 kg as observed in adults, since adults with similar body weight have been included in the CANOPY study [*see Adverse Reactions (6.1) and Clinical Studies (14)*].

8.5 Geriatric Use

Of the 623 participants who received PEMGARDA in the CANOPY trial, 156 (25%) were aged ≥ 65 years and 31 (5%) were aged ≥ 75 years. Based on population pharmacokinetic (PK) analyses, there was no clinically meaningful difference of age on the PK of pemivibart.

8.6 Renal Impairment

PEMGARDA is not eliminated intact in the urine, thus renal impairment is not expected to affect the exposure of pemivibart. Similarly, dialysis is not expected to impact the PK of pemivibart.

8.7 Hepatic Impairment

The effect of hepatic impairment on the PK of pemivibart is unknown.

10 OVERDOSAGE

Doses above 4500 mg PEMGARDA (the authorized dose of pemivibart) were not administered in clinical studies. There is no specific treatment for overdose with PEMGARDA.

11 DESCRIPTION

Pemivibart is a human IgG1 mAb produced by a Chinese Hamster Ovary cell line and has a molecular weight of 147.51 kDa.

PEMGARDA (pemivibart) injection is a sterile, preservative-free, clear to slightly opalescent, colorless to yellow solution for intravenous infusion after dilution. Each 4 mL of solution contains 500 mg of pemivibart, glycine (33.03 mg), L-arginine hydrochloride (63.2 mg), L-histidine (3.67 mg), L-histidine hydrochloride monohydrate (3.43 mg), L-methionine (5.97 mg), polysorbate 80 (1.2 mg), sterile water for injection (USP). The pH is 6.2.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Pemivibart is a SARS-CoV-2 antiviral drug [*see Microbiology (12.4)*].

12.2 Pharmacodynamics

Available data suggest a positive relationship between serum neutralizing antibody titers and COVID-19 pre-exposure-prophylactic efficacy using clinical data (completed prior to the emergence of Omicron and Omicron lineage VOCs) and drug concentration data of neutralizing human monoclonal antibodies against SARS-CoV-2.

Following single-dose administration of pemivibart 4500 mg IV, calculated geometric mean titer values (pemivibart concentration divided by the authentic virus neutralization assay EC₅₀ value against JN.1) [*see Microbiology (12.4)*] range from 3451 (on Day 90) to 22552 (end of infusion on Day 1). After the repeat dose of pemivibart 4500 mg IV every 3 months, it is anticipated that the range of titers at steady-state will be approximately 33% higher than those observed following the first dose administration.

12.3 Pharmacokinetics

A summary of PK parameters of pemivibart following administration of a single 4500 IV dose of pemivibart to adults based on population PK modeling is provided in [Table 1](#).

Table 1: Summary Statistics of Population PK Parameters of Pemivibart Following a Single 4500 mg Intravenous Dose in Adults

Parameter	Pemivibart
C _{max} (µg/mL)	1750 (38.2)
C _{Day 28} (µg/mL)	460 (40.7)
C _{Day 90}	175 (44.4)
AUC _{0-3 months}	36600 (40.4)
T _{1/2} (days)	44.8 (28.1-64.6)
Accumulation ratio	1.33
CL (L/d)	0.0909 (23.3)
V _{ss} (L)	5.54 (17.0)
Metabolism	Catabolic pathways; same manner as endogenous IgG
Excretion	Not likely to undergo renal excretion

AUC_{0-3 months}= area under the serum concentration-time curve from Day 0 to Month 3; CL=renal clearance; C_{max}=maximum concentration; PK=pharmacokinetic; T_{1/2}=half-life; V_{ss}=steady state volume of distribution.

Note: All values presented as geometric mean (% covariance), except for T_{1/2}, which is presented as median (min, max). Numerical values are post-hoc PK parameter estimates for subjects enrolled in Phase 3 CANOPY.

Specific Populations:

The PK of pemivibart was not substantially affected by age, sex, or race based on a population PK analysis to the pooled data from VYD222-1-001 and Phase 3 CANOPY. Body weight is not expected to have a clinically relevant effect on the PK of pemivibart in individuals with body weights ranging from 43 to 190 kg through 3 months postdose.

Patients with Immune Compromise

Population PK analysis showed immune compromise status had no clinically relevant effect on the PK of pemivibart.

Pediatric Patients

The PK of pemivibart in pediatric individuals has not been evaluated. The dosing regimen is expected to result in comparable plasma exposures of pemivibart in pediatric individuals 12 years of age or older who weigh at least 40 kg as observed in adult individuals [see *Use in Specific Populations (8.4)*].

Patients with Renal Impairment

Renal impairment is not expected to impact the PK of pemivibart since mAbs with molecular weight >69 kDa are known not to undergo renal elimination. Similarly, dialysis is not expected to impact the PK of pemivibart.

Patients with hepatic impairment

Pemivibart is not anticipated to be impacted by hepatic impairment. Pemivibart is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as other IgG mAbs and human endogenous IgG antibodies.

12.4 Microbiology

Mechanism of Action:

Pemivibart is a recombinant human monoclonal IgG1 λ antibody that targets the SARS-CoV-2 spike protein receptor binding domain (RBD), thereby inhibiting virus attachment to the human ACE2 receptor on host cells. Amino acid substitutions in the Fc region (M435L/N441A) of pemivibart extend serum half-life. Pemivibart binds the spike RBD proteins of ancestral SARS-CoV-2 B.1 (D614G) and Omicron variants BA.1, BA.2, and BA.4/5 with equilibrium dissociation constants (K_D) of 2.1 nM, 18 nM, 13.5 nM, and 15.9 nM, respectively, and blocks attachment of ancestral SARS-CoV-2 and BA.2.86 variant RBD proteins to the human ACE2 receptor with IC_{50} values of 0.068 nM (10 ng/mL) and 23 nM (3370 ng/mL), respectively.

Antiviral Activity:

Pemivibart neutralized authentic SARS-CoV-2 isolates in Vero E6 or Vero E6-TMPRSS2 cells with EC_{50} values of 0.165-0.230 nM (24.3-34 ng/mL) against B.1, and 0.075 nM (11 ng/mL) against B.1.617.2 (Delta). For Omicron variants, EC_{50} values were 0.096 nM (14.2 ng/mL) against BA.1, 0.039 nM (5.8 ng/mL) against BA.2, 0.175 nM (25.8 ng/mL) against BA.4.1, 0.80-4.48 nM (118-661.2 ng/mL) against XBB.1.16, 1.97-3.25 nM (290-479.9 ng/mL) against XBB.1.5, 9.8 nM (1,445 ng/mL) against EG.5.1, 3.59 nM (529.4 ng/mL) against HV.1, and 0.43 nM (63.6 ng/mL) against JN.1.

Pemivibart has not been directly evaluated for Fc-mediated effector functions or antibody-dependent enhancement (ADE) of infection. The parent antibody of pemivibart, which contains an identical Fc region and targets an overlapping epitope, exhibited antibody-dependent cellular phagocytosis (ADCP) and antibody-dependent complement deposition (ADCD), but failed to exhibit detectable ADE in cell culture.

Antiviral Resistance:

There is a potential risk of prophylaxis failure due to the emergence of a pemivibart-resistant SARS-CoV-2 variant. Prescribing healthcare providers should consider the prevalence of SARS-CoV-2 variants in their area, where data are available, when considering prophylactic treatment options.

Data are limited regarding the scope of spike substitutions in Omicron-lineage variants that may confer significantly reduced susceptibility to pemivibart. Escape variants were identified following serial passage of SARS-CoV-2 (Omicron XBB.1.5.6) in cell culture in the presence of pemivibart that contained a T500N spike substitution or a combination of Q489R, N501Y, and Y505H spike substitutions. Each of these substitutions is within 5 Å of the pemivibart binding interface.

Pemivibart neutralization susceptibility of recent and historic SARS-CoV-2 variants was evaluated using a pseudotyped, luciferase-expressing, lentivirus virus-like particle (VLP) assay. Pemivibart neutralized SARS-CoV-2 spike protein-pseudotyped VLPs representing B.1 and pre-Omicron variants with EC_{50} values ranging from 0.022 to 0.083 nM (3.2 to 12.2 ng/mL), and Omicron-lineage variants with EC_{50} values ranging from 0.198 to 14.3 nM (29.2 to 2,112 ng/mL) ([Table 2](#)).

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

Pango lineage	RBD substitutions relative to B.1 present in pseudotyped VLPs	Pemivibart	
		Mean EC ₅₀ values ng/mL (SD / range) ^a	Fold-change from B.1
B.1		8.4 (3)	1.0
B.1.1.7	N501Y	11.4	1.4
B.1.351	K417N, E484K, N501Y	9	1.1
P.1	K417T, E484K, N501Y	12.2	1.5
B.1.617.2	L452R, T478K	5.2 (4.2-6.2)	0.6
B.1.427	L452R	3.2	0.4
P.2	E484K	9.3	1.1
B.1.526	E484K	8.6	1.0
B.1.621	R346K, E484K, N501Y	9.5	1.1
BA.1	G339D, S371L, S373P, S375F, K417N, N440K, G446S, S477N, T478K, E484A, Q493R, G496S, Q498R, N501Y, Y505H	121.4	14.5
BA.2	G339D, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, S477N, T478K, E484A, Q493R, Q498R, N501Y, Y505H	44.6 (6.5)	5.3
BA.4/BA.5	G339D, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, L452R, S477N, T478K, E484A, F486V, Q498R, N501Y, Y505H	47.9 (29.7-66.2)	5.7
BA.4.6	G339D, R346T, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, L452R, S477N, T478K, E484A, F486V, Q498R, N501Y, Y505H	29.2	3.5
BF.7	G339D, R346T, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, L452R, S477N, T478K, E484A, F486V, Q498R, N501Y, Y505H	72.7	8.7
BQ.1	G339D, R346T, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, K444T, L452R, S477N, T478K, E484A, F486V, Q498R, N501Y, Y505H	164.6	19.6
BQ.1.1	G339D, R346T, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, K444T, L452R, N460K, S477N, T478K, E484A, F486V, Q498R, N501Y, Y505H	102.1	12.2
BA.2.75	G339H, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, G446S, N460K, S477N, T478K, E484A, Q498R, N501Y, Y505H	1,364.6	162.5
BN.1	G339H, R346T, K356T, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, G446S, N460K, S477N, T478K, E484A, F490S, Q498R, N501Y, Y505H	2,112	251.4
XBB	G339H, R346T, L368I, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, V445P, G446S, N460K, S477N, T478K, E484A, F486S, F490S, Q493R, Q498R, N501Y, Y505H	152.2	18.1

Pango lineage	RBD substitutions relative to B.1 present in pseudotyped VLPs	Pemivibart	
		Mean EC ₅₀ values ng/mL (SD / range) ^a	Fold-change from B.1
XBB.1	G339H, R346T, L368I, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, V445P, G446S, N460K, S477N, T478K, E484A, F486S, F490S, Q493R, Q498R, N501Y, Y505H	121.1	14.4
XBB.1.5	G339H, R346T, L368I, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, V445P, G446S, N460K, S477N, T478K, E484A, F486P, F490S, Q498R, N501Y, Y505H	104.3	12.4
XBB.1.16	G339H, R346T, L368I, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, V445P, G446S, N460K, S477N, T478R, E484A, F486P, F490S, Q498R, N501Y, Y505H	77.6 (18.1)	9.2
XBB.1.5.10	G339H, R346T, L368I, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, V445P, G446S, F456L, N460K, S477N, T478K, E484A, F486P, F490S, Q498R, N501Y, Y505H	108.1 (35.5)	12.9
XBB.1.5.1	G339H, R346T, L368I, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, V445P, G446S, N460K, S477N, T478K, E484A, F486P, F490S, Q498R, N501Y, Y505H	80 (8.9)	9.5
XBB.2.3	G339H, R346T, L368I, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, V445P, G446S, N460K, S477N, T478K, E484A, F486P, F490S, Q498R, N501Y, Y505H, P521S	87 (15.5)	10.4
EU.1.1	G339H, R346T, L368I, S371F, S373P, S375F, T376A, D405N, R408S, I410V, K417N, N440K, V445P, G446S, N460K, S477N, T478K, E484A, F486P, F490S, Q498R, N501Y, Y505H, P521S	52.1 (10.6)	6.2
FL.1.5.1	G339H, R346T, L368I, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, V445P, G446S, F456L, N460K, S477N, T478R, E484A, F486P, F490S, Q498R, N501Y, Y505H	102.1 (8.8)	12.2
HV.1	G339H, R346T, L368I, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, V445P, G446S, L452R, F456L, N460K, S477N, T478K, E484A, F486P, F490S, Q498R, N501Y, Y505H	41.2 (9.2)	4.9
HK.3	G339H, R346T, L368I, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, V445P, G446S, L455F, F456L, N460K, S477N, T478K, E484A, F486P, F490S, Q498R, N501Y, Y505H	72.3 (7.7)	8.6
JD.1.1	G339H, R346T, L368I, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, V445P, G446S, L455F, F456L, N460K, A475V, S477N, T478K, E484A, F486P, F490S, Q498R, N501Y, Y505H	101.9 (4.9)	12.3

Pango lineage	RBD substitutions relative to B.1 present in pseudotyped VLPs	Pemivibart	
		Mean EC ₅₀ values ng/mL (SD / range) ^a	Fold-change from B.1
BA.2.86	I332V, G339H, K356T, S371F, S373P, S375F, T376A, R403K, D405N, R408S, K417N, N440K, V445H, G446S, N450D, L452W, N460K, S477N, T478K, N481K, del483, E484K, F486P, Q498R, N501Y, Y505H	167.7 (4.4)	20.0
JN.1	I332V, G339H, K356T, S371F, S373P, S375F, T376A, R403K, D405N, R408S, K417N, N440K, V445H, G446S, N450D, L452W, L455S, N460K, S477N, T478K, N481K, del483, E484K, F486P, Q498R, N501Y, Y505H	74.6 (5.8)	8.9

EC₅₀=half-maximal inhibitory concentration; Pango=Phylogenetic Assignment of Named Global Outbreak; RBD=receptor binding domain; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; WT=wild-type.

- a. EC₅₀ values are reported as the mean along with range when data were obtained from 2 independent experiments or as mean and standard deviation when data were obtained from 3 or more independent experiments. 5,000 ng/mL was the upper concentration tested.

Evaluations are ongoing of the pemivibart neutralization susceptibility of variants that have been identified through global surveillance.

Cross-resistance:

Cross-resistance is not expected between pemivibart and currently approved/authorized COVID-19 therapies, including remdesivir, nirmatrelvir, or molnupiravir, since pemivibart has a distinct mechanism of action and targets a different viral protein than these drugs.

12.6 Immunogenicity

There are no immunogenicity data available for the currently authorized dosing regimen of PEMGARDA 4500 mg IV administered every 3 months.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity, mutagenicity, and reproductive toxicology studies have not been conducted with pemivibart.

13.2 Animal Toxicology and/or Pharmacology

In a toxicology study in rats, pemivibart had no adverse effects when administered intravenously.

In tissue cross-reactivity studies with pemivibart using human adult and fetal tissues, no off-target binding was detected.

14 CLINICAL STUDIES

14.1 Overview of Immunobridging Approach

SEE ATTACHED ADDENDUM

. To support this EUA, an immunobridging

approach was used to determine if PEMGARDA may be effective for pre-exposure prophylaxis of COVID-19. Immunobridging is based on the serum neutralization titer-efficacy relationships identified with other neutralizing human monoclonal antibodies against SARS-CoV-2. This includes adintrevimab, the parent mAb of pemivibart, and other mAbs that were previously authorized for EUA. To support immunobridging, serum neutralization titer was utilized to compare PEMGARDA to previous mAbs [see *Clinical Pharmacology* (12.2)].

14.2 Pre-exposure Prophylaxis of COVID-19 (VYD222-PREV-001 [CANOPY])

CANOPY [NCT06039449] is an ongoing clinical trial evaluating PEMGARDA for the pre-exposure prophylaxis of COVID-19 in adults ≥ 18 years of age in two cohorts.

- Cohort A: single-arm, open-label trial in adults who have moderate-to-severe immune compromise.
- Cohort B: placebo-controlled, randomized trial in adults who do not have moderate-to-severe immune compromise.

A total of 623 participants, 306 in Cohort A and 317 in Cohort B, received at least one dose of PEMGARDA 4500 mg in the trial. In Cohort A, 296 participants received a second dose of PEMGARDA 4500 mg at Month 3. In Cohort B, 162 participants received at least one dose of placebo, and a total of 450 participants received a second dose of either PEMGARDA 4500 mg or placebo (blinded) at Month 3. The trial excluded participants with known or suspected SARS-CoV-2 infection within 120 days before randomization or a positive SARS-CoV-2 antigen test or RT-PCR at the time of screening. The primary data to support this EUA comes from Cohort A and is summarized below.

Participants in Cohort A were mostly female (61%), White (86%) or Black/African American (12%), and not Hispanic or Latino (94%). The median age was 59 years, with 31% aged 65 years or older. All participants had underlying moderate-to-severe immune compromise, including:

- 65% taking high-dose corticosteroids/other immunosuppressive medications
- 13% acute leukemia, chronic lymphocytic leukemia, non-Hodgkin, lymphoma, or multiple myeloma (regardless of treatment)
- 12% primary immunodeficiency
- 11% solid organ transplant recipient
- 9% advanced HIV infection
- 7% actively treated for solid tumor or hematologic malignancies

Results:

The primary efficacy objective of Cohort A was to evaluate protection against symptomatic COVID-19 based on calculated titers against SARS-CoV-2 following PEMGARDA administration by immunobridging to historical data from the EVADE study, which provided evidence of clinical efficacy of adintrevimab, the parent mAb of pemivibart. The primary immunobridging endpoint for Cohort A compared the ratio of the geometric mean titers between pemivibart against the relevant variant (JN.1) at Day 28 to the reference titer at Day 28. The reference titer at Day 28 was the extrapolated titer from the Day 90 adintrevimab titer [which

was calculated based on Day 90 concentration of adintrevimab divided by the EC₅₀ value against the B.1.617.2 (Delta) variant determined in an authentic virus neutralization assay] using the half-life of pemivibart. Immunobridging would be 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.

The primary immunobridging results are as follows: 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). However, there are limitations of this analysis, including differences in the methodologies of the assays used to determine the EC₅₀ values for pemivibart and adintrevimab against the respective variants. In a sensitivity analysis using an identical cell-based assay (a pseudotyped VLP neutralization assay), for the calculated titer comparison between pemivibart against JN.1 (based on an EC₅₀ value of 74.6 ng/mL) and adintrevimab against Delta (based on an EC₅₀ value of 3.5 ng/mL), the geometric mean ratio was 0.35 (90% CI: 0.34-0.36). This sensitivity analysis highlights the impact of even modest differences in EC₅₀ values on the results of the primary endpoint.

As a supplementary analysis, the titer values of pemivibart against JN.1 [see *Clinical Pharmacology* (12.2)] were compared, using published literature, to the titers associated with efficacy of three other SARS-CoV-2 targeting mAbs in prior clinical trials. The range of titers achieved with pemivibart for 3 months following administration of 4500 mg IV were consistent with the titer levels associated with clinical efficacy in prior clinical trials evaluating certain monoclonal antibodies for the prevention of COVID-19.

14.3 Overall Benefit-Risk Assessment and Limitations of Data Supporting the Benefits of the Product

Based on the totality of scientific evidence available, it is reasonable to believe that PEMGARDA may be effective for pre-exposure prophylaxis of COVID-19 in the authorized population. 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.

There are limitations of the data supporting the benefits of PEMGARDA. Evidence of clinical efficacy for other neutralizing human monoclonal antibodies against SARS-CoV-2 was based on different populations and SARS-CoV-2 variants that are no longer circulating. Additionally, the variability associated with cell-based EC₅₀ value determinations, along with limitations related to PK data and efficacy estimates for the mAbs in prior clinical trials, impact the ability to precisely estimate protective titer ranges.

16 HOW SUPPLIED/STORAGE AND HANDLING

PEMGARDA injection is a sterile, preservative-free, clear to slightly opalescent, colorless to yellow solution supplied in a single-dose 6R vial intended for intravenous infusion only.

Antibody	Concentration	Package Size	NDC
Pemivibart	500 mg/4 mL vial (125 mg/mL)	Nine vials per carton	81960-031-03

Refrigerate unopened vials at 2 °C to 8 °C (36 °F to 46 °F) in the original carton to protect from light.

Do not freeze or shake. Do not use if seal is broken or missing.

17 PATIENT COUNSELING INFORMATION

As a prescribing healthcare practitioner, you must communicate to the patient, parent, and caregiver information consistent with the “FACT SHEET FOR PATIENTS, PARENTS OR CAREGIVERS” and provide them with a copy of this Fact Sheet prior to administration of PEMGARDA.

Anaphylaxis

Inform individuals that anaphylaxis has been observed with PEMGARDA. Advise individuals that they will be monitored during and for at least two hours after completion of the infusion. In those who experience signs or symptoms of anaphylaxis, PEMGARDA use will be discontinued permanently [see *Boxed Warnings, and Warnings and Precautions (5.1)*].

Hypersensitivity and Infusion-Related Reactions

Inform individuals that hypersensitivity and infusion-related reactions have occurred during the infusion and up to 24 hours after the infusion with PEMGARDA. These hypersensitivity or infusion-related reactions may be severe or life threatening. Inform individuals that they will be monitored during and for at least two hours after completion of the infusion for signs and symptoms of hypersensitivity [see *Warnings and Precautions (5.2)*].

Dosing

Inform individuals that they may need to receive additional doses of PEMGARDA every 3 months if ongoing protection is needed [see *Dosage and Administration (2) and Clinical Pharmacology (12)*].

Risk for COVID-19 Due to SARS-CoV-2 Viral Variants Not Neutralized by PEMGARDA

Certain SARS-CoV-2 viral variants may emerge that are not neutralized by monoclonal antibodies such as PEMGARDA. PEMGARDA may not be effective at preventing COVID-19 caused by these SARS-CoV-2 viral variants. Inform individuals of the increased risk, compared to other variants, for COVID-19 due to SARS-CoV-2 viral variants not neutralized by PEMGARDA. If signs or symptoms of COVID-19 occur, advise individuals to test for COVID-19 and seek medical attention, including starting treatment for COVID-19 as appropriate [see *Warnings and Precautions (5.4)*].

18 MANUFACTURER INFORMATION

For additional information, visit: www.Pemgarda.com or scan the code below:



Manufactured and distributed by:
Invivyd, Inc.
1601 Trapelo Road, Suite 178
Waltham, MA 02451

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Appendix 2. Fact Sheet for Patients and Parent/Caregivers

See next page.

Fact Sheet for Patients, Parents, and Caregivers Emergency Use Authorization (EUA) of PEMGARDA (pemivibart) for Coronavirus Disease 2019 (COVID-19)

What is the most important information I should know about PEMGARDA?

PEMGARDA may cause serious side effects, including:

- **A serious allergic reaction called anaphylaxis.** Anaphylaxis can be life-threatening and can happen during or after your infusion of PEMGARDA. In case you have a severe allergic reaction to PEMGARDA and need medical help right away, you will receive PEMGARDA in a healthcare setting. Your healthcare provider will monitor you for allergic reactions during your infusion and for at least 2 hours after you are finished receiving PEMGARDA. Your healthcare provider will stop PEMGARDA right away if you develop signs or symptoms of anaphylaxis or severe allergic reaction. **Tell your healthcare provider right away if you get any of the following signs or symptoms of anaphylaxis during or after your infusion of PEMGARDA:**
 - itching
 - flushing
 - hives
 - skin redness
 - swelling of your face, lips, mouth, tongue, throat, hands, or feet
 - sweating
 - dizziness
 - ringing in the ears
 - wheezing
 - trouble breathing
 - chest discomfort
 - fast heartbeat
- See **“What are the important possible side effects of PEMGARDA?”** for more information about side effects.

You are being given this Fact Sheet because your healthcare provider believes it is necessary to provide you or your child with PEMGARDA for pre-exposure prophylaxis to help prevent coronavirus disease 2019 (COVID-19) caused by the SARS-CoV-2 virus.

This Fact Sheet contains information to help you understand the potential risks and the potential benefits of receiving PEMGARDA, which you, or your child, have received or may receive.

The United States (US) Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) to make PEMGARDA available during the COVID-19 pandemic (for more details about an EUA please see **“What is an Emergency Use Authorization (EUA)?”** at the end of this document). PEMGARDA is not an FDA-approved medicine in the US.

Read this Fact Sheet for information about PEMGARDA. Talk to your healthcare provider about your options or if you have any questions. It is your choice for you or your child to receive PEMGARDA or stop at any time.

What is COVID-19?

COVID-19 is caused by a virus called a coronavirus (SARS-CoV-2). You can get COVID-19 through contact with another person who has the virus.

COVID-19 illnesses have ranged from very mild (including some with no reported symptoms) to severe, including illness resulting in death. While information so far suggests that most COVID-19 illnesses are mild, serious illness can happen and may cause some of your other medical conditions to become worse. Older people and people of all ages with severe, long lasting (chronic) medical conditions like immune compromise, heart disease, lung disease, diabetes, and obesity, for example, seem to be at higher risk of being hospitalized for COVID-19.

What is PEMGARDA?

PEMGARDA is an investigational medicine that is authorized for use for pre-exposure prophylaxis to help prevent COVID-19 in adults and children 12 years of age and older who weigh at least 88 pounds (40 kg) who:

- are **not** currently infected with SARS-CoV-2 and who have **not** been known to be exposed to someone who is infected with SARS-CoV-2 **and**
- have moderate-to-severe immune compromise because of a medical condition or because they receive medicines or treatments that suppress the immune system **and** they are unlikely to have an adequate response to COVID-19 vaccination.

PEMGARDA is investigational because it is still being studied. There is limited information about the safety and effectiveness of using PEMGARDA for prevention of COVID-19. The FDA has authorized the emergency use of PEMGARDA for pre-exposure prophylaxis to help prevent COVID-19 under an EUA. For more information on EUA, see the “**What is an Emergency Use Authorization (EUA)?**” section at the end of this Fact Sheet.

PEMGARDA is **not** authorized:

- to treat COVID-19
- to prevent COVID-19 after being around someone infected with SARS-CoV-2 (post-exposure prophylaxis)
- for use in children under 12 years of age or weighing less than 88 pounds (40 kg)

Pre-exposure prophylaxis to help prevent COVID-19 with PEMGARDA does not take the place of receiving COVID-19 vaccination in people who can be vaccinated for COVID-19. If your healthcare provider recommends it, you should receive a COVID-19 vaccination.

If you have received a COVID-19 vaccine, you should wait at least 2 weeks after vaccination to receive PEMGARDA.

What should I tell my healthcare provider before I receive PEMGARDA?

Tell your healthcare provider about all of your medical conditions, including if you:

- have any allergies, including if you have had a severe allergic reaction to a COVID-19 vaccine or to PEMGARDA.
- are pregnant or plan to become pregnant. It is not known if PEMGARDA can harm your unborn baby.

- are breastfeeding or plan to breastfeed. It is not known if PEMGARDA can pass into your breast milk. Talk to your healthcare provider about the best way to feed your baby if you receive PEMGARDA.
- have any serious illnesses.
- take any medicines including prescription, over-the-counter, vitamins, and herbal products.

How will I receive PEMGARDA?

- You will receive 1 dose of PEMGARDA.
- PEMGARDA will be given to you through an infusion in a vein (intravenous [IV] infusion). It will take about 60 minutes to finish the infusion.
- You will receive PEMGARDA in a healthcare setting.
- You will be observed by a healthcare provider during your infusion and for at least 2 hours after your infusion is finished.

You may need to receive additional doses of PEMGARDA for ongoing protection from COVID-19. Viruses can change over time (mutate) and develop into a slightly different form of the virus, called a variant. Based on what we know about current SARS-CoV-2 variants, you may need to receive additional doses of PEMGARDA every 3 months.

Who should generally not take PEMGARDA?

Do not take PEMGARDA if you have had a severe allergic reaction to PEMGARDA or any ingredient in PEMGARDA. See the end of this Fact Sheet for a complete list of ingredients in PEMGARDA.

What are the important possible side effects of PEMGARDA?

- See **“What is the most important information I should know about PEMGARDA?”**
- **Allergic and infusion-related reactions.** Allergic and infusion-related reactions are common and can sometimes be severe or life-threatening. Allergic and infusion-related reactions can happen during and after your infusion of PEMGARDA. You may have an increased risk of allergic reaction with PEMGARDA if you have had a severe allergic reaction to a COVID19 vaccine. PEMGARDA contains polysorbate 80, an ingredient in some COVID19 vaccines. Also, polysorbate 80 is similar to polyethylene glycol (PEG), an ingredient in other COVID19 vaccines. Your healthcare provider may consult with a healthcare provider who specializes in allergy and immunology before giving you PEMGARDA if you have had a serious allergic reaction to a COVID-19 vaccine. Your healthcare provider will monitor you for allergic reactions during the infusion and for at least 2 hours after you receive PEMGARDA. **Tell your healthcare provider right away if you get any of the following signs or symptoms of an allergic or infusion-related reaction during or after your infusion of PEMGARDA:**
 - fever
 - headache
 - trouble breathing or shortness of breath
 - throat tightness or irritation

- chills
- tiredness
- fast or slow heart rate
- chest pain or discomfort
- weakness
- confusion
- nausea
- high or low blood pressure
- swelling of your face, lips, mouth, tongue, throat, hands, or feet
- rash, including hives
- itching
- muscle aches
- feeling lightheaded, faint, or dizzy
- sweating

The side effects of receiving any medicine by vein (IV) may include pain, redness, bleeding, bruising of the skin, soreness, swelling, and possible infection at the infusion site.

The most common side effects in people treated with PEMGARDA who have moderate-to-severe immune compromise include allergic and infusion-related reactions, infusion site reactions, common cold, viral infection, flu-like illness, tiredness, headache and nausea.

These are not all the possible side effects of PEMGARDA. Not a lot of people have been given PEMGARDA. Serious and unexpected side effects may happen. PEMGARDA is still being studied, so it is possible that all of the risks are not known at this time.

What other important information do I need to know when receiving PEMGARDA?

Risk of COVID-19 caused by certain SARS-CoV-2 variants: Viruses can change over time (mutate) and develop into a slightly different form of the virus, called a variant. PEMGARDA may not be effective at preventing COVID-19 caused by certain SARSCoV-2 variants. If you are exposed to these variants, your chance of developing COVID-19 is higher than from other variants. Tell your healthcare provider right away, and test for COVID-19, if you develop any symptoms of COVID-19, including:

- fever or chills
- cough
- shortness of breath or difficulty breathing
- congestion or runny nose
- nausea or vomiting
- diarrhea
- headache
- sore throat
- new loss of taste or smell
- feeling tired (fatigue)
- muscle or body aches

For more information about the symptoms of COVID-19, go to <https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html>.

If you develop COVID-19, your healthcare provider may recommend one of the available COVID-19 treatments.

What other prevention choices are there?

Vaccines to help prevent COVID-19 are approved or available under Emergency Use Authorization. Use of PEMGARDA does not replace vaccination against COVID-19. For

information on clinical studies of PEMGARDA and other therapies for the pre-exposure prophylaxis of COVID-19, see www.clinicaltrials.gov.

It is your choice to receive or not receive PEMGARDA for pre-exposure prophylaxis to help prevent COVID-19. Should you decide not to receive PEMGARDA, it will not change your standard medical care.

PEMGARDA is not authorized to treat COVID-19 or for post-exposure prophylaxis of COVID-19.

What if I am pregnant or breastfeeding?


There is no experience using PEMGARDA in women who are pregnant or breastfeeding. For a mother and unborn baby, the benefit of receiving PEMGARDA may be greater than the risk of using the product. If you are pregnant or breastfeeding, discuss your options and specific situation with your healthcare provider.

How do I report side effects with PEMGARDA?

Tell your healthcare provider right away if you have any side effect that bothers you or does not go away. Report side effects to FDA MedWatch at www.fda.gov/medwatch, or call 1800FDA1088, or call Invivyd at 1-800-890-3385.

How can I learn more about PEMGARDA?

If you have questions, visit the website, or call the telephone number provided below. To access the most recent PEMGARDA Fact Sheet, please scan the QR code provided below.

Website	Telephone Number
<p data-bbox="354 1136 646 1171">www.Pemgarda.com</p> 	<p data-bbox="1008 1136 1235 1171">1-800-890-3385</p>

How can I learn more about COVID-19?

- Ask your healthcare provider.
- Visit <https://www.cdc.gov/COVID19>.
- Contact your local or state public health department.

What is an Emergency Use Authorization?

The United States FDA has made PEMGARDA available under an emergency access mechanism called an Emergency Use Authorization (EUA). The EUA is supported by a Secretary of Health and Human Services (HHS) declaration that circumstances exist to justify the emergency use of drugs and biological products during the COVID-19 pandemic.

PEMGARDA for pre-exposure prophylaxis to help prevent COVID-19 has not undergone the same type of review as an FDA-approved product. In issuing an EUA under the relevant COVID-19 declaration, the FDA has determined, among other things, that based on the total amount of scientific evidence available, including data from adequate and well-controlled clinical trials, it is reasonable to believe that the product may be effective for diagnosing, treating, or preventing COVID-19; that the known and potential benefits of the product, when used to diagnose, treat, or prevent such disease or condition, outweigh the known and potential risks of such product; and that there are no adequate, approved, and available alternatives.

All of these criteria must be met to allow the product to be used during the COVID-19 pandemic. The EUA for PEMGARDA is in effect for the duration of the COVID-19 declaration justifying emergency use of PEMGARDA, unless terminated or revoked (after which PEMGARDA may no longer be used under the EUA).

What are the ingredients in PEMGARDA?

Active ingredient: pemivibart

Inactive ingredients: glycine, L-arginine hydrochloride, L-histidine, L-histidine hydrochloride monohydrate, L-methionine, polysorbate 80, and sterile water for injection.



Manufactured and distributed by: Invivyd, Inc., 1601 Trapelo Road, Suite 178, Waltham, MA 02451

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Issued: March 2024

Appendix 3. ADG20-PREV-001 (EVADE) Trial

The source of clinical efficacy data for adintrevimab to support the immunobridging approach for pemivibart is the EVADE trial (ADG20-PREV-001). Two independent cohorts were included in this trial. Cohort A evaluated postexposure prophylaxis, and therefore, the efficacy results from this cohort is not relevant to the EUA request for pemivibart. Cohort B in EVADE evaluated pre-exposure prophylaxis (PrEP), which is relevant to the EUA request for pemivibart.

Relevant excerpts from the Sponsor's Clinical Study Report for EVADE (Cohort B) are copied below. The efficacy results largely focus on Cohort B, the relevant population for this EUA request. Note, FDA reviewed the trial results but did not conduct an independent analysis using datasets from the trial.

1. STUDY CONDUCT

This study was conducted at 87 centers in 8 countries.

Enrollment in EVADE was suspended on 11-Jan-2022 after the emergence and global spread of the Omicron variant in December 2021, because Invivyd considered that the 300 mg IM dose of adintrevimab would not provide durable protection against COVID-19 due to this variant. The study was terminated early on 26-Oct-2022 due to the Sponsor's decision to discontinue further clinical development of adintrevimab. At the time of study termination, all participants had been followed for at least 6 months postdose.

Table 20. Study Conduct, ADG20-PREV-001 (EVADE)

First Participant, First Visit	Last Participant, Last Visit	Database Lock Date
27-Apr-2021	07-Nov-2022	30-Nov-2022

2. METHODOLOGY

2.1. Study Design

EVADE was a Phase 2/3, multicenter, double-blind, placebo-controlled, randomized study evaluating the safety and efficacy of adintrevimab in the prevention of symptomatic COVID-19 in adults and adolescents with no known history of SARS-CoV-2 infection but whose circumstances placed them at increased risk of acquiring SARS-CoV-2 infection and developing symptomatic COVID-19.

- **Cohort A (PEP):** Participants with reported recent exposure to an individual testing positive for SARS-CoV-2 (index case), randomized 1:1 to receive a single IM dose of 300 mg adintrevimab or placebo
- **Cohort B (PrEP):** Participants with no known history of SARS-CoV-2 infection and no known recent exposure but whose circumstances put them at increased risk of

exposure to SARS-CoV-2 and symptomatic COVID-19, randomized 1:1 to receive a single IM dose of 300 mg adintrevimab or placebo

These cohorts included participants whose age (≥ 55 years) or health status placed them at risk for severe COVID-19 or COVID-19 complications. Randomization was stratified by geographical region (United States/Western Europe vs Central/Eastern Europe vs rest of world) and age/risk for severe/critical COVID-19 (aged 12 to < 55 years and low risk for severe/critical COVID-19 vs aged 12 to < 55 years and high risk for severe/critical COVID-19 vs aged ≥ 55 years).

The study enrolled in two parts: a Phase 2 safety lead-in consisting of 200 adult participants enrolled across Cohorts A and B and a separate Phase 3 expansion to enroll the remainder of participants in each cohort.

Participants received a single IM dose of study drug on Day 1 ([Table 21](#)). Participants recorded any ISRs using an e-Diary (or paper back-up diary) daily on Day 1 postdose through Day 4. Samples for PK, ADA, and serology were collected at various timepoints throughout the study.

Surveillance for symptomatic COVID-19 was performed up to the Month 12 Visit by participant completion of an e-Diary, participant reporting of symptoms in their e-Diary or by phone call to the site, and regular site phone calls to the participant. Participants with confirmed CLI symptoms entered the CLI Period and were to have an initial CLI visit within 48 hours of symptom onset. During the initial CLI Visit (CLI Day 1), a nasopharyngeal (NP) swab for RT-PCR testing for SARS-CoV-2 and a saliva sample for assessing viral RNA shedding were collected for processing by a central laboratory; additional assessments were performed as described in the protocol. For the remainder of the CLI Period, vital signs and symptom severity, duration, and outcome of the CLI, as well Investigator assessment of overall CLI severity, were collected via daily telemedicine visits (on CLI Days 2 to 21) and in-person at the final visit on CLI Day 28.

Participants continued in the CLI Period unless a negative result on the CLI Day 1 central NP RT-PCR test was reported. These participants stopped CLI assessments and continued the study following the main SoA.

Table 21. Study Treatments Administered

Treatment	Dose	Route of Administration	Dose Regimen	Use
Adintrevimab	300 mg	IM	Single dose on Day 1	Experimental
Normal saline	N/A	IM	Single dose on Day 1	Placebo

Abbreviations: N/A, not applicable; IM, intramuscular

2.2. Eligibility Criteria

This study enrolled adult and adolescent (aged 12 to < 18 years) participants whose circumstances placed them at increased risk of acquiring SARS-CoV-2 infection and/or developing symptomatic COVID-19. Participants in Cohort A were enrolled within 5 days of exposure to an individual with a diagnosis of SARS-CoV-2. Participants in

Cohort B had occupational, housing, recreational, or social conditions that were likely to increase their risk of exposure to SARS-CoV-2. Participants tested negative for current or previous SARS-CoV-2 infection by RT-PCR and serology at the time of Screening, except that participants in Cohort A could be randomized without RT-PCR results, if they were asymptomatic and these results were not available by Day 5 of Screening. Approximately 20% of the study population was anticipated to comprise individuals at increased risk for severe COVID-19 or COVID-19 complications due to their age or underlying medical conditions.

Participants were not enrolled if they had received a prior SARS-CoV-2 vaccine, convalescent plasma, or monoclonal antibody, or if they intended to receive a COVID-19 vaccine within 6 months after randomization.

2.3. Study Objectives and Endpoints

The primary and secondary objectives and endpoints for Cohort B are provided in [Table 22](#).

Table 22. Objectives and Endpoints, Cohort B (PrEP)

Objectives	Endpoints
Primary (Cohort B [PrEP])	
<p>To evaluate the efficacy of adintrevimab compared with placebo in the prevention of RT-PCR–confirmed symptomatic COVID-19 through 3 months in all randomized participants without prior or current SARS-CoV-2 infection at baseline.</p>	<p>Proportion of participants with RT-PCR–confirmed symptomatic COVID-19 through 3 months.</p> <p><u>Supplementary:</u></p> <ul style="list-style-type: none"> • Time from randomization to first RT-PCR–confirmed symptomatic COVID-19. • Probability of RT-PCR–confirmed symptomatic COVID-19 through 3 months.
<p>To evaluate the safety and tolerability of adintrevimab compared with placebo following intramuscular administration.</p>	<p>Assessment of safety based on:</p> <ul style="list-style-type: none"> • Incidence of treatment-emergent adverse events. • Incidence of solicited injection site reactions through Day 4. • Changes from baseline in clinical laboratory tests (ie, complete blood count with differential and serum chemistry). • Changes from baseline in vital signs (body temperature, heart rate, respiration rate, and systolic and diastolic blood pressure).
Secondary (Cohort B [PrEP])	
<p><u>Key Secondary Objective:</u> To evaluate the efficacy of adintrevimab compared with placebo in the prevention of RT-PCR–confirmed symptomatic COVID-19 through 3 months in all randomized participants without current SARS-CoV-2 infection at baseline.</p>	<p>Proportion of participants with RT-PCR–confirmed symptomatic COVID-19 through 3 months.</p> <p><u>Supplementary:</u></p> <ul style="list-style-type: none"> • Time from randomization to first RT-PCR–confirmed symptomatic COVID-19. • Probability of RT-PCR–confirmed symptomatic COVID-19 through 3 months.
<p><u>Key Secondary Objective:</u> To evaluate the efficacy of adintrevimab compared with placebo in the prevention of SARS-CoV-2 infection (based on RT-PCR or serology) regardless of symptoms through 3 months, in each of the following populations:</p> <ul style="list-style-type: none"> • All randomized participants without prior or current SARS-CoV-2 infection at baseline. • All randomized participants without current SARS-CoV-2 infection at baseline. 	<p>Proportion of participants with SARS-CoV-2 infection regardless of symptoms through 3 months.</p> <p><u>Supplementary:</u></p> <ul style="list-style-type: none"> • Time from randomization to first SARS-CoV-2 infection. • Probability of SARS-CoV-2 infection through 3 months.
<p>To evaluate the efficacy of adintrevimab compared with placebo in the prevention of RT-PCR–confirmed symptomatic COVID-19 through 3 months in all randomized participants.</p>	<p>Proportion of participants with RT-PCR–confirmed symptomatic COVID-19 through 3 months.</p>

Objectives and Endpoints, Cohort B (PrEP) (continued)

Objectives	Endpoints
To evaluate the efficacy of adintrevimab compared with placebo in the prevention of SARS-CoV-2 infection (based on RT-PCR or serology) regardless of symptoms through 3 months in all randomized participants.	Proportion of participants with SARS-CoV-2 infection regardless of symptoms through 3 months.
To evaluate the efficacy of adintrevimab compared with placebo in the prevention of asymptomatic SARS-CoV-2 infection (based on serology) in all randomized participants without prior or current SARS-CoV-2 infection at baseline.	Proportion of participants with asymptomatic SARS-CoV-2 infection as determined by serology at Month 6.
To evaluate the effect of adintrevimab on the following clinical and virologic parameters in all randomized participants with laboratory confirmed symptomatic COVID-19 through CLI Day 28:	
Severity of COVID-19.	Proportion of participants with RT-PCR-confirmed mild, moderate, or severe/critical COVID-19 through CLI Day 28.
Duration of COVID-19.	Time to sustained resolution of COVID-19 symptoms through CLI Day 28.
COVID-19–related medically attended outpatient visits.	Proportion of participants with at least 1 COVID-19–related medically attended outpatient visit (physician’s office, telemedicine, emergency rooms, or urgent care centers) through CLI Day 28.
COVID-19–related hospitalization.	Proportion of participants with a COVID-19–related hospitalization through CLI Day 28.
COVID-19–related mortality.	COVID-19–related mortality through CLI Day 28.
All-cause mortality.	All-cause mortality through CLI Day 28.
SARS-CoV-2 viral load.	Viral load from CLI Day 1 sample assessed by RT-qPCR.
To evaluate the pharmacokinetics of adintrevimab in serum.	PK parameters of ADG20 including but not limited to: AUC_{0-inf} , AUC_{0-last} , C_{max} , T_{max} , CL , $t_{1/2}$, and V_{ss} .
To evaluate the immunogenicity of adintrevimab.	Incidence of ADAs against adintrevimab.

ADA=antidrug antibody; AUC =area under the plasma concentration–time curve; AUC_{0-inf} : AUC extrapolated to infinite time; AUC_{0-last} =AUC from zero up to the last concentration \geq lower limit of quantification; CL=clearance; CLI=COVID-19-like illness; C_{max} =maximum plasma concentration; PrEP=pre-exposure prophylaxis; PK=pharmacokinetic; RT-(q)PCR=(quantitative) reverse transcription polymerase chain reaction; $t_{1/2}$ =plasma concentration half-life; T_{max} =time to reach C_{max} ; V_{ss} =apparent volume of distribution at steady state.

2.4. Number of Participants (Planned and Analyzed)

The planned enrollment was 5142 participants in Cohort B; however, enrollment was suspended in January 2022 and the study was terminated early on 26-Oct-2022. At the time of enrollment pause, 2095 participants (adintrevimab: 1048; placebo: 1047) were randomized in Cohort B.

2.5. Statistical and Analytical Methods

A summary of the statistical analysis methods is provided in Version 6 of the study protocol, with details provided in Version 1.0 of the Statistical Analysis Plan. The data in this report represent the final results of the study. Definitions for the analysis sets used for the analyses of disposition, safety, and efficacy provided in this report are summarized in [Table 23](#).

Table 23. Defined Analysis Sets and Descriptions

Analysis Dataset (in-text abbreviation)	Description
Full Analysis Set (FAS)	Includes all randomized participants regardless of whether the participant received study drug.
Pre-emergence of Omicron Analysis Set (pre-Omicron)	Includes all participants randomized on or prior to 30-Nov-2021, allowing participants to be followed a minimum of 2 weeks through 15-Dec-2021 when Omicron became the predominant variant.
Modified Full Analysis Set: RT-PCR negative and seronegative (mFAS)	Includes all participants without prior or current SARS-CoV-2 infection at baseline based on central tests (RT-PCR negative and seronegative). If either central RT-PCR or central serology is missing at baseline, a negative baseline status can be imputed for a participant if there is a post-baseline negative central serology sample collected at least 14 days from Day 1 and prior to any positive local/central RT-PCR.
Modified Full Analysis Set 1: RT-PCR-negative (mFAS-1)	Includes all randomized participants without current SARS-CoV-2 infection at baseline based on central tests (RT-PCR-negative regardless of serology status). If central RT-PCR is missing at baseline, a negative baseline status can be imputed for a participant if there is a post-baseline negative central serology sample collected at least 14 days from Day 1 and prior to any positive local/central RT-PCR.
Modified Full Analysis Set 2: RT-PCR-negative and seropositive (mFAS-2)	Includes all randomized participants with prior infection but without current SARS-CoV-2 infection at baseline based on central tests (RT-PCR-negative and seropositive). No imputation is performed if any baseline test is missing.
Safety	Includes all participants who received study drug.

Abbreviations: FAS, full analysis set; RT-PCR, reverse transcription polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; mFAS, modified FAS

2.5.1. Efficacy Analyses

The primary efficacy analysis was focused on evaluating adintrevimab in the population randomized prior to the emergence of the Omicron variant, termed the pre-Omicron analysis set. The pre-Omicron analysis set includes all participants randomized on or prior to 30-Nov-2021, allowing participants to be followed a minimum of 2 weeks through 15-Dec-2021 when Omicron became the predominant variant in the United States. Thus, the data cutoff date for the primary and secondary efficacy endpoints was 15-Dec-2021. The primary efficacy population is as follows:

- Cohort B: Pre-Omicron mFAS, comprising participants who met criteria in both the pre-Omicron analysis set and the mFAS.

2.5.2. Safety Analyses

An interim analysis of safety was performed after all participants had the opportunity to be followed for 6 months post dose. Vital signs, laboratory tests, and solicited AE (ISR) data were summarized at this 6-month interim analysis (data cutoff: 25-Jul-2022). A final safety analysis was performed when all participants had completed or discontinued the study. All TEAEs, including deaths and SAEs, were summarized for the final analysis (data cutoff: 07-Nov-2022).

ISRs through Day 4 were solicited from participants through an e-Diary and/or contacts with site personnel. All other AEs were unsolicited, including ISRs reported after Day 4. Hypersensitivity reactions occurring through Day 4 were considered AEs of special interest; hypersensitivity reactions occurring after Day 4 were captured as TEAEs. Solicited CLI symptoms (as listed in the protocol) collected through participant e-Diaries or via site contact with participants throughout the study were not to be captured as AEs unless the participant entered a CLI Period, ultimately tested negative for SARS-CoV-2, and the symptoms met the AE criteria outlined in the protocol. However, some sites reported these symptoms (eg, flu-like illness, headache, nausea) as unsolicited AEs.

For the purposes of this study, the first case of COVID-19 or SARS-CoV-2 infection, including worsening or sequelae, was not recorded as an AE, unless it met SAE criteria. Subsequent episodes of COVID-19 in the same participant were captured according to standard AE reporting processes.

3. RESULTS: COHORT A (POST-EXPOSURE PROPHYLAXIS)

This section is purposely omitted for the purpose of this review.

4. RESULTS: COHORT B (PRE-EXPOSURE PROPHYLAXIS)

4.1. Cohort B: Study Participants

4.1.1. Disposition of Participants

At the time of the enrollment pause, 2095 participants were randomized into Cohort B (the FAS) of which 1480 (70.6%) were included in the pre-Omicron mFAS, the primary efficacy population for this analysis. In the FAS, a total of 93 participants did not receive study drug (adintrevimab: n=49; placebo: n=44) and were not included in the Safety Set. One participant randomized to placebo was treated with adintrevimab in error and is therefore included in the adintrevimab arm for analyses of safety.

In the FAS, 77.9% of participants discontinued the study, primarily due to study termination by the Sponsor ([Table 24](#)). Besides study termination, the most common reason for study discontinuation was participant lost to follow-up (10.0%). The overall discontinuation rate was similar between the treatment arms. The median duration of follow-up was 54 weeks (range: 1 to 79), with 88.5% of participants followed through at least 24 weeks (≈6 months) and 67.4% followed for >48 weeks.

Table 24. Participant Disposition, Cohort B, Full Analysis Set

Parameter	Statistic	ADG20 (N=1048)	Placebo (N=1047)	Total (N=2095)
Received study treatment	Yes	n(%)	999 (95.3)	1003 (95.8)
	No	n(%)	49 (4.7)	44 (4.2)
Completed treatment [a]	Yes	n(%)	999 (95.3)	1003 (95.8)
Duration of follow-up after randomization (weeks) [b]	n	1048	1047	2095
	Mean (SD)	48.9(16.31)	47.9(17.31)	48.4 (16.82)
	Median	54.0	53.0	54.0
	Q1, Q3	47.0, 59.0	46.0, 59.0	46.0, 59.0
	Min, Max	1, 79	1, 78	1, 79
<= 4 weeks	n(%)	49 (4.7)	59 (5.6)	108 (5.2)
> 4 weeks	n(%)	999 (95.3)	988 (94.4)	1987 (94.8)
> 12 weeks	n(%)	968 (92.4)	943 (90.1)	1911 (91.2)
> 24 weeks	n(%)	938 (89.5)	916 (87.5)	1854 (88.5)
> 36 weeks	n(%)	894 (85.3)	873 (83.4)	1767 (84.3)
> 48 weeks	n(%)	717 (68.4)	696 (66.5)	1413 (67.4)
Study discontinuation [c]	Yes	n(%)	822 (78.4)	811 (77.5)
	No	n(%)	226 (21.6)	236 (22.5)
Primary reason for study discontinuation	DEATH	n(%)	3 (0.3)	6 (0.6)
	LOST TO FOLLOW-UP	n(%)	110 (10.5)	100 (9.6)
	OTHER	n(%)	68 (6.5)	77 (7.4)
	STUDY TERMINATED BY SPONSOR	n(%)	579 (55.2)	549 (52.4)
	WITHDRAWAL BY PARENT/GUARDIAN	n(%)	0	1 (0.1)
	WITHDRAWAL BY SUBJECT	n(%)	62 (5.9)	78 (7.4)
				140 (6.7)

n=number of participants in each category; N=total number of participants in the relevant analysis set; %=percentage of participants in each category relative to the total number of participants in the relevant analysis set with data

[a] Received full dose.

[b] Ongoing participants: data cut-off date - randomization date + 1; discontinued or completed study participants: end of study date - randomization date + 1.

[c] No=completed study.

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4.1.2. Demographics and Baseline Characteristics

Overall, demographics and baseline characteristics in the Cohort B FAS were well-balanced between treatment arms. Most participants in Cohort B were enrolled in the United States (83.0%) or Eastern Europe (16.4%). In the FAS, 50.8% were female, 77.5% were white, and 22.2% were Hispanic or Latino. The median age was 47.0 years, with 2.1% of participants aged 75 years or older. Nine (0.4%) adolescents were enrolled, with seven (0.7%) in the adintrevimab arm. Median BMI was 28.1 kg/m² (range: 15.7 to 73.4).

Baseline SARS-CoV-2 RT-PCR and serology results were balanced between treatment arms. A small number of participants (1.8%) had a positive SARS-CoV-2 RT-PCR test at baseline as assessed by NP sample. Positive baseline serology results were observed in 4.8% of participants, including 4.1% with antibodies to N protein.

Risk factors for severe/critical COVID-19 were well-balanced across treatment arms. Overall, 59.9% of participants were considered high risk. In adult participants, the most common risk factors were age ≥ 55 years (31.0%), obesity (22.4%), cardiac disease (17.0%), diabetes (8.1%), and substance use disorder (6.9%).

4.1.3. Extent of Exposure

In Cohort B, 1001 participants received adintrevimab and 1001 received placebo. All participants treated with adintrevimab received the full dose (300 mg IM) as planned.

4.2. Cohort B: Efficacy Evaluation

4.2.1. Prevention of SARS-CoV-2 Infection Through Month 3

4.2.1.1. Proportion of Participants With RT-PCR–Confirmed Symptomatic COVID-19 Through Month 3

In the primary efficacy population (pre-Omicron mFAS), treatment with adintrevimab provided a clinically meaningful reduction in the risk of developing symptomatic COVID-19 through 3 months compared with placebo in adult and adolescent participants with no current or prior SARS-CoV-2 infection who were at high risk for acquiring SARS-CoV-2.

The proportion of participants with RT-PCR–confirmed symptomatic COVID-19 through 3 months after randomization or emergence of Omicron (primary efficacy endpoint) was 1.6% in the adintrevimab arm compared with 5.5% in the placebo arm, a 71.0% relative risk reduction ([Table 25](#)). The standardized risk difference (primary estimand) was -3.9% (95% CI: -5.75, -2.01; $p < 0.0001$), demonstrating a 70.8% standardized relative risk reduction in favor of adintrevimab. The favorable treatment effect for adintrevimab was observed across key subgroups, including participants at high risk for disease progression.

The proportion of participants with RT-PCR–confirmed symptomatic COVID-19 through Month 3 or emergence of Omicron was also analyzed in other study populations as secondary endpoints in the study. The treatment effect was similar to the primary efficacy population:

- In participants with no current infection regardless of serostatus (pre-Omicron mFAS-1), 12 (1.5%) participants in the adintrevimab arm versus 40 (5.1%) in the placebo arm had events. The standardized risk difference was -3.6% (95% CI: -5.38, -1.87; $p < 0.0001$), demonstrating a 70.6% standardized relative risk reduction in favor of adintrevimab.
- In all randomized participants (pre-Omicron FAS), 14 (1.7%) versus 45 (5.5%) of participants had events in the adintrevimab and placebo arms, respectively, a standardized relative risk reduction of 69.0%.

Table 25. Proportion of Participants With RT-PCR-Confirmed Symptomatic COVID-19 Through Month 3 or Emergence of Omicron, Cohort B, Pre-Omicron Modified Full Analysis Set

		ADG20 (N = 752)	Placebo (N = 728)	ADG20 vs. Placebo
RT-PCR-confirmed symptomatic COVID-19 through Month 3 or emergence of Omicron	n(%)	12 (1.6)	40 (5.5)	
Symptomatic COVID-19	n(%)	12 (1.6)	39 (5.4)	
COVID-19-related hospitalization	n(%)	1 (0.1)	6 (0.8)	
All-cause death	n(%)	0	1 (0.1)	
Risk difference ^[a]				-3.9%
95% CI				(-5.94, -2.09)
Relative risk reduction				71.0%
Standardized risk ^[b]		1.6%	5.5%	
Standardized risk difference ^[b]				-3.9%
95% CI				(-5.75, -2.01)
2-sided p-value				<0.0001
Standardized relative risk reduction ^[b]				70.8%
95% CI				(44.83, 84.52)
No RT-PCR-confirmed symptomatic COVID-19 through Month 3 or emergence of Omicron	n(%)	740 (98.4)	688 (94.5)	
≥ 90 Days follow-up to study discontinuation or emergence of Omicron	n(%)	343 (45.6)	296 (40.7)	
< 90 Days follow-up to study discontinuation or emergence of Omicron	n(%)	397 (52.8)	392 (53.8)	

pre-Omicron=randomized on or before 30NOV2021

CI=confidence interval; RT-PCR=reverse transcription-polymerase chain reaction

RT-PCR-confirmed symptomatic COVID-19 events through Month 3 (90 days from randomization) or the emergence of Omicron (15DEC2021), whichever is earlier, are included in this analysis. An RT-PCR-confirmed symptomatic COVID-19 event is defined as having a central RT-PCR-confirmed SARS-CoV-2 infection with COVID-19 symptoms occurring within 14 days from the positive RT-PCR test sample collection (nasopharyngeal, saliva, or nasal sample) or COVID-19-related hospitalization with a positive local or central SARS-CoV-2 test within 14 days, or all-cause death.

The treatment policy strategy is used for handling intercurrent events. Participants with < 90 days follow-up to study discontinuation and no reported outcome are imputed as not having the outcome through Month 3.

[a] Estimate and 95% CI expressed in percentage. The 95% CI is calculated from the Miettinen-Nurminen method.

[b] Estimate and 95% CI expressed in percentage. The population-level standardized estimator is derived from a logistic regression model fitted to the binary outcome predicted by treatment and randomization stratification factors: geography and age/risk category.

The standardized estimator's standard error and associated CI are calculated using the delta method based on the algorithm of Ge et al. (2011).

Source: Table 14.2.7.1, Listing 16.2.7.1

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4.2.1.2. Time From Randomization to First RT-PCR-Confirmed Symptomatic COVID-19 and Probability Through Month 3

In the primary efficacy population (pre-Omicron mFAS), the probability of RT-PCR-confirmed symptomatic COVID-19 was significantly lower for adintrevimab compared with placebo ($p < 0.0001$), with an HR of 0.27 (95% CI: 0.14, 0.49), translating into 73% efficacy favoring adintrevimab. The curves on the KM plot separated early and remained separated throughout the observation period in favor of adintrevimab, suggesting durable protection beyond 3 months.

The treatment effect favoring adintrevimab was similar for participants in the pre-Omicron mFAS-1 (HR: 0.27 [95% CI: 0.15, 0.50]; $p < 0.0001$), and the pre-Omicron FAS population (HR: 0.29 [95% CI: 0.16, 0.52]).

4.2.1.3. Proportion of Participants With SARS-CoV-2 Infection (Asymptomatic or Symptomatic) Through Month 3

The proportion of participants with an RT-PCR– or serology-confirmed asymptomatic or symptomatic SARS-CoV-2 infection through Month 3 or the emergence of Omicron was lower for adintrevimab versus placebo across all populations. In the primary efficacy population (pre-Omicron mFAS), 22 (2.9%) participants in the adintrevimab arm versus 53 (7.3%) in the placebo arm had events. The standardized risk difference was -4.3% (-6.54, -2.10; $p = 0.0001$), demonstrating a 59.5% standardized relative risk reduction. Similar results were observed in the pre-Omicron mFAS-1 (standardized relative risk reduction of 59.3%; $p = 0.0001$) and in the pre-Omicron FAS (58.2%; nominal $p < 0.0001$).

4.2.2. Clinical Outcomes in Participants With RT-PCR–Confirmed COVID-19 Through Month 3

4.2.2.1. Maximum Severity of COVID-19 Through CLI Day 28

In participants who developed symptomatic COVID-19 in the primary efficacy population (pre-Omicron mFAS), treatment with adintrevimab was associated with a reduction in severity of disease through Day 28 post-diagnosis compared with placebo. Severe/critical disease through CLI Day 28 was reported in 1 of 12 (8.3%) participants who received adintrevimab and subsequently developed symptomatic COVID-19, whereas 7 of 40 (17.5%) participants with symptomatic COVID-19 in the placebo arm had severe/critical disease through CLI Day 28.

4.2.2.2. All-Cause Mortality and COVID-19-Related Mortality Through CLI Day 28

In participants who developed RT-PCR–confirmed symptomatic COVID-19 in the primary efficacy population (pre-Omicron mFAS), no deaths were reported in the adintrevimab arm through CLI Day 28. One COVID-19–related death was observed in the placebo arm.

4.2.2.3. COVID-19-Related Medically Attended Outpatient Visits and COVID-19–Related Hospitalization Through CLI Day 28

In the pre-Omicron mFAS, a COVID-19–related medically attended visit (hospitalization >24 hours) was reported for 1 of 12 (8.3%) participants who received adintrevimab and subsequently developed symptomatic COVID-19. In the placebo arm, 6 of 40 (15.0%) participants with confirmed COVID-19 had a COVID-19–related medically attended visit through CLI Day 28, all of which were hospitalizations >24 hours.

4.2.2.4. Time to Sustained Resolution of COVID-19 Symptoms Through CLI Day 28

In the pre-Omicron mFAS, the median time from reported symptom onset to sustained resolution of RT-PCR–confirmed COVID-19 symptoms through CLI Day 28 was numerically less in the adintrevimab arm (16.5 days) compared with the placebo arm (21.0 days).

4.2.2.5. CLI Day 1 Viral Load

In participants with RT-PCR-confirmed symptomatic COVID-19, the viral RNA shedding on CLI Day 1 was lower for participants treated with adintrevimab compared with placebo. The mean (SD) CLI Day 1 viral RNA was 3.26 (2.997) versus 5.36 (1.751) log₁₀ copies/mL in saliva and 5.91 (1.788) and 7.15 (1.591) log₁₀ copies/mL in NP sample in the adintrevimab and placebo arms, respectively.

4.2.3. Prevention of Asymptomatic SARS-CoV-2 Infection Through Month 6

In participants with no prior or current infection at baseline (pre-Omicron mFAS), fewer asymptomatic SARS-CoV-2 infections were detected in those who received adintrevimab (10 [1.3%] participants) compared with placebo (18 [2.5%] participants).

4.3. Cohort B: Safety Evaluation

4.3.1. Adverse Events

Adintrevimab was safe and well-tolerated in adult and adolescent participants in the pre-exposure prophylaxis setting. In the Cohort B safety set, the incidence of TEAEs was similar for adintrevimab (42.1%) compared with placebo (39.3%) ([Table 26](#)). Most TEAEs in the adintrevimab arm were mild or moderate in severity. There were three (0.3%) deaths due to AEs in the adintrevimab arm, compared with six (0.6%) in the placebo arm. SAEs occurred with the same incidence in each treatment arm (4.6%). All deaths and other SAEs were considered unrelated to the study drug. One (0.1%) mild hypersensitivity reaction was reported in each treatment arm; both events occurred within 4 days of dosing and resolved without treatment.

The most frequently reported TEAEs were solicited ISRs, which occurred with a similar incidence in the adintrevimab (9.0%) and placebo (9.5%) arms ([Table 26](#)). The most frequently reported (≥2%) TEAEs by PT in each treatment arm were:

- Adintrevimab: injection site pain (7.6%), influenza like illness (5.5%), and upper respiratory tract infection (3.4%)
- Placebo: injection site pain (8.4%), influenza like illness (4.4%), and upper respiratory tract infection (2.5%)

Table 26. Adverse Events, Cohort B

Adverse event category (participants)	ADG20 (N=1001) n (%)	Placebo (N=1001) n (%)	Total (N=2002) n (%)
Any TEAEs	421 (42.1)	393 (39.3)	814 (40.7)
Any unsolicited TEAEs	369 (36.9)	340 (34.0)	709 (35.4)
Any solicited TEAEs	90 (9.0)	95 (9.5)	185 (9.2)
Any study drug-related TEAEs [a]	100 (10.0)	102 (10.2)	202 (10.1)
Any unsolicited study drug-related TEAEs	12 (1.2)	11 (1.1)	23 (1.1)
Any solicited study drug-related TEAEs	90 (9.0)	95 (9.5)	185 (9.2)
Any TEAEs ≥ Grade 3	50 (5.0)	53 (5.3)	103 (5.1)
Any serious TEAEs	46 (4.6)	46 (4.6)	92 (4.6)
Any TEAEs leading to death	3 (0.3)	6 (0.6)	9 (0.4)
Any treatment-emergent medically attended adverse events	185 (18.5)	180 (18.0)	365 (18.2)
Any study drug-related serious TEAEs [a]	0	0	0
Any study drug-related TEAEs leading to death [a]	0	0	0
Any treatment-emergent hypersensitivity reactions [b]	1 (0.1)	1 (0.1)	2 (0.1)
Any treatment-emergent hypersensitivity reactions through Day 4 [b]	1 (0.1)	1 (0.1)	2 (0.1)

TEAE=treatment-emergent adverse event

%=percentage of participants with at least one AE in each category relative to the total number of participants in the relevant analysis set. Participants with multiple AEs in each category are counted only once. Treatment-emergent AEs are those that occurred after dosing and existing AEs that worsened during the study. Solicited AEs do not have seriousness assigned.

[a] A missing relationship to study drug is imputed as 'Related', and all solicited AEs are assumed to be 'Related'.

[b] Hypersensitivity reactions are determined by medical adjudication based on the narrow and broad terms of the three Standardized MedDRA Queries (SMQs) hypersensitivity, anaphylactic reaction, and angioedema. Hypersensitivity reactions occurring through Day 4 are considered AEs of special interest.

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4.3.2. Deaths and Serious Adverse Events

Three (0.3%) deaths were reported in the adintrevimab arm compared with six (0.6%) in the placebo arm. In the adintrevimab arm, two deaths were due to COVID-19 compared with three deaths due to COVID-19 pneumonia in the placebo arm. The remaining death in the adintrevimab arm was due to atrial fibrillation in a participant with a history of cardiac disease. All deaths were considered not related to study drug ([Table 26](#)).

A total of 46 (4.6%) participants experienced SAEs in each treatment arm; all SAEs were considered not related to the study drug ([Table 26](#)). The most frequently reported SAEs were infections and infestations, occurring in 1.5% of participants treated with adintrevimab and 2.1% of participants receiving placebo. The most frequent PTs in the adintrevimab arm were pneumonia (4 [0.4%]) and COVID-19 (3 [0.3%]); of note, COVID-19 pneumonia was also reported by 1 (0.1%) participant. By comparison, in the placebo arm there were 9 (0.9%) participants with COVID-19 pneumonia, 6 (0.6%) with COVID-19, and 2 (0.2%) with pneumonia. All other SAEs in the adintrevimab arm were reported by 1 or 2 participants (≤0.2%) each.

4.3.3. Clinical Laboratory Evaluation

There were no trends in the types or timing of potentially clinically significant serum chemistry, hematology, or coagulation value changes from baseline indicative of a

specific safety risk for adintrevimab based on results reported through the 6-month interim analysis.

4.3.4. Vital Signs Evaluation

There were no trends in the types or timing of potentially clinically significant vital sign value changes from baseline indicative of a specific safety risk for adintrevimab based on results reported through the 6-month interim analysis.

5. PHARMACOKINETICS RESULTS

Because the Sponsor terminated the study early, PK samples were not analyzed for all participants at all timepoints planned in the protocol. Based on the available PK results, adintrevimab was well absorbed following a single 300 mg IM injection. In both cohorts, the median serum concentration was similar at Day 8 and Day 28 at 36.6 and 33.7 µg/mL, respectively, in Cohort A and 37.5 and 32.5 µg/mL, respectively, in Cohort B. At Month 6, the median concentration was 19.4 µg/mL based on available samples from five participants in Cohort B. Due to sparse sampling, other PK parameters cannot be calculated. Estimations based on population PK modeling are reported separately.

6. IMMUNOGENICITY RESULTS

Because the Sponsor terminated the study early, ADA samples were not analyzed for all participants at all timepoints planned in the protocol. All available immunogenicity results are reported separately. Briefly, of the 1239 participants who received adintrevimab in this study, samples were tested for ADA from 750 participants. The majority of tested samples were collected for the predose and/or Day 28 timepoints. In the screening assay for ADAs, 34 (4.5%) participants tested potentially positive at a postdose timepoint and 52 (6.9%) tested potentially positive at predose. None of the potentially positive postdose samples were tested for confirmation because the Sponsor terminated the study early. Therefore, the incidence of treatment-emergent ADAs could not be assessed. Potentially positive predose samples from 22 participants were tested for confirmation, of which 5 were confirmed positive.

7. CONCLUSIONS

7.1. Efficacy

Pre-Exposure Prophylaxis (Cohort B)

Pre-exposure prophylaxis with adintrevimab provides a statistically significant and clinically meaningful reduction in the risk of developing symptomatic COVID-19 compared with placebo in adults with no current or prior SARS-CoV-2 infection who are at high risk for acquiring SARS-CoV-2 infection.

The following key efficacy results were observed:

- In the pre-Omicron analysis population, the proportion of participants with RT-PCR–confirmed symptomatic COVID-19 through 3 months or emergence of Omicron

(primary efficacy endpoint) was 1.6% in the adintrevimab arm compared with 5.5% in the placebo arm, a 71.0% relative risk reduction. The standardized risk difference (primary estimand) was -3.9% (95% CI: -5.75, -2.01; $p < 0.0001$), demonstrating a 70.8% standardized relative risk reduction in favor of adintrevimab through 3 months.

- The favorable treatment effect for adintrevimab was observed across key subgroups, including participants at high risk for disease progression.
- The supplementary analysis of time to RT-PCR–confirmed symptomatic COVID-19 confirmed the primary findings, with an HR of 0.27 (95% CI: 0.14, 0.49), translating into 73% efficacy favoring adintrevimab.

7.2. Safety

Adintrevimab is safe and well-tolerated in adults and adolescents with no current SARS-CoV-2 infection who are at high risk for acquiring SARS-CoV-2. No unexpected safety signals were observed. The following key safety results were observed.

- The incidence of TEAEs was similar between adintrevimab and placebo. The most frequently reported TEAEs attributed to adintrevimab were ISRs, which occurred in less than 10% of participants. Most TEAEs were mild or moderate in severity.
- No deaths or SAEs attributable to adintrevimab were reported.
- No safety concerns for adintrevimab based on clinical laboratory or vital sign abnormalities were identified.

Appendix 4. Assessment and Limitations of the Meta-Analysis for the Immunobridging Approach

For this meta-analysis approach, the Agency utilized a published meta-analysis ([Stadler et al. 2023](#)). The authors fit a titer-response curve between the calculated mAbs titers and the efficacy estimate (the relative risk reduction [RRR] of mAb to placebo) for the pre-exposure prophylaxis of COVID-19 using published efficacy data of three mAbs (i.e., casirivimab/imdevimab, cilgavimab/tixagevimab, and adintrevimab) from four clinical trials.

Below is a brief description of the data used for fitting the curve in the paper. Please refer to the publication for additional details.

The original subject-level data are not available, and two independent scientists used the digital data extraction approach to estimate the geometric means at different timepoints (visits) of all four trials from the published papers. To match with the efficacy data, the geometric mean for a time interval between two adjacent visits was estimated by linearly interpolating the (log) geometric means of two adjacent visits. The calculated titer was calculated using the geometric mean for each time interval divided by the EC_{50} value for the dominant variant circulating during the respective trials.

The EC₅₀ values for variants were estimated by a linear mixed effect model with a random effect to account for study/assay differences using the EC₅₀ value data from the Stanford database.

The RRR for a time interval was estimated by the numbers of subjects at risk and the numbers of infection events that occurred within the time interval in both treatment and placebo arms. Due to the different visit schedule among trials, different lengths of the time interval in days among these data points were used. The paper stated that “the efficacy data reported early after treatment (i.e., in the first time point reported in the study) were excluded from the model fitting (low opacity data points in the figure), since antibody concentration changed rapidly over this time interval and to ensure exclusion of unidentified infections that might have occurred before treatment.” The final data points (observations) used to fit the curve were 24 data points from the four trials.

The following limitations regarding the fitted curve of the titer response relationship were identified.

EC₅₀ Values Used for the Calculated Titer

Estimated EC₅₀ values used to obtain the calculated titers for each antibody against a specific variant were derived from summary statistics of highly variable individual EC₅₀ values extracted from the Stanford University Coronavirus Antiviral and Resistance Database and curated by Stadler et al. (2023) (Figure S1). EC₅₀ values used in the meta-analysis were determined in a number of independent laboratories utilizing diverse types of authentic virus and pseudotyped virus-like particle (VLP) neutralization assays carried out in a variety of cell lines. Authentic virus neutralization assays employed various neutralization quantitation methods, including cytopathic effect reduction and immunofocus reduction. Pseudotyped VLP assays included different reporter vector backbones, including lentivirus, murine leukemia virus, and vesicular stomatitis virus. The diversity of assays and data analysis methodologies, along with potential differences in the specific genotypes of variants evaluated in individual assays, likely contributed to the variability in EC₅₀ values used to calculate neutralization titers. Furthermore, individual EC₅₀ values contributing to the central estimate EC₅₀ value used to derive calculated titers in the meta-analysis were derived from publication tables and figures and could not be independently verified in all cases.

Given that the EC₅₀ values derived from the Stanford Database represent summary statistics rather than the original, individual replicate EC₅₀ values, and that values were obtained from a variety of assay types, a linear mixed model with study/assay as random effect was employed to estimate a final EC₅₀ value used to derive titers for each mAb product against a particular SARS-CoV-2 variant. The authors acknowledge that “this means that the results of any particular study or assay may vary quite considerably from the central estimate of the EC₅₀ for analysis” For example, the final estimated EC₅₀ value for adintrevimab against the Delta variant was 8.02 ng/mL, while the individual EC₅₀ values used to derive the final estimated EC₅₀ value ranged from 1 to 14 ng/mL. As a result, the calculated titer values could vary by a few folds.

Dependence Among Data Points (Observations)

A total of 24 data points from these four trials were used to fit the curve. Within the same trial, subjects must not have been infected in the previous time interval(s) in order to be included in the analyses for later time intervals. This dependency among these 24 data points was not accounted for in the model fitting.

High Variability in the Estimated Efficacy (RRR)

The time intervals used for generating 24 data points were relatively short from about 25 days to approximately 90 days, except for one data point with a time interval of only a few days. There was substantial variation in the number of events within the short time intervals, which likely was responsible for part of the high variability seen in the RRR estimates. Also, because the numbers of infection events in each interval are all relatively low, the 95% confidence intervals of estimated RRR were all very wide as shown in the figure. Some of time intervals were excluded from the model fitting because the RRR could not be calculated without an event.

Limited Data Points Especially in the Lower Calculated Titer Range

Only 24 data points were available for the model fitting and the data points in the lower calculated titer range are very limited. One potential reason is that all four trials used here are positive trials, which have shown higher efficacy in terms of the RRR and had calculated titers that generally fell in the upper end of the range. This causes uncertainty in the shape of the fitted curve, especially in the lower calculated titer range, where the shape of the curve was primarily determined by the assumed model, rather than observed data. The authors tried six different models and demonstrated comparable performance in fitting the data based on having similar Akaike information criterion (AIC) values.

General limitations Related to the Study Design

Of the four clinical trials utilized for this meta-analysis, only one trial was designed and powered to demonstrate the efficacy for PrEP and completed as planned. One trial did not complete planned enrollment due to changes in variants. The other two trials were not designed to demonstrate efficacy for PrEP as the primary endpoint. Additionally, there were some differences among those studies regarding the methodology used to define symptomatic infection and how the data from vaccinated subjects were factored into the analyses. These differences potentially contributed to the variability and uncertainty of each data point in the meta-analysis in addition to the aforementioned limitations.

Considering the above, we found that there is major uncertainty in the shape of the fitted curve, especially in the lower calculated titer range. Thus, we recommend not using the curve to calculate estimates of the predicted efficacy in terms of RRR based on the calculated titer values, especially in the lower calculated titer range. However, there is a positive correlation between the calculated titer and the drug efficacy as shown in the figure. The calculated titer values for pemivibart at the recommended dose

lies within the range of data points with higher efficacy observed in the right side of the figure.

Despite the limitations mentioned above, the calculated serum neutralizing antibody titers with pemivibart were in the general range where efficacy was seen with other mAbs; therefore, it is reasonable to believe pemivibart may be effective for pre-exposure prophylaxis of COVID-19.

Appendix 5. Allergy and Immunology Consult Review

DPACC – CONSULT REVIEW

Sponsor: Invivyd

Name of product: Pemivibart (VYD222)

Consulting Division: Division of Antivirals (DAV)

Consulting Reviewer: Sarita Boyd, PharmD, (DAV)

Medical Officer: Jennifer Lan, MD, Division of Pulmonology, Allergy, and Critical Care (DPACC)

Team Lead: Miya Paterniti, MD, DPACC

Associate Director for Therapeutic Review: Kelly Stone, MD, PhD, DPACC

Review Due Date: March 4, 2024

Submission Type: Emergency Use Authorization 122 for COVID-19

I. Executive Summary

This is a Medical Officer response to the request for consultation from the Division of Antivirals (DAV) regarding the Emergency Use Authorization (EUA) application 122 for pemivibart, an anti-SARS-CoV-2 monoclonal antibody proposed for pre-exposure prophylaxis of COVID-19 in moderate to severe immunocompromised patients. Efficacy and safety are assessed in one phase 3 clinical trial that is composed of an open-label cohort in moderate-to-severe immunocompromised patients and a triple-blind, randomized, placebo-controlled cohort in subjects who are at risk of contracting COVID-19. Safety review of the EUA submission noted a high rate of infusion-related reactions and hypersensitivity adverse events (see DAV review), including anaphylaxis. DAV is requesting input from the Division of Pulmonology, Allergy, and Critical Care (DPACC) regarding assessing the incidence of anaphylaxis in the trial along with potential mitigation strategies for the infusion reactions and anaphylaxis risk.

We reviewed the narratives and agreed with the Sponsor's identification of two anaphylaxis cases and identified two additional cases of anaphylaxis, which the Sponsor determined to be a hypersensitivity reaction and an infusion-related reaction. Based on our adjudication, the anaphylaxis rate of pemivibart is 0.64% (4 events /623 subjects who received pemivibart) in the clinical trial. Adjudication of anaphylaxis is based on the National Institute of Allergy and Infectious Disease and Food Allergy and Anaphylaxis Network (NIAID/FAAN) criterion number 1 (see [Table 1. Clinical Criteria for Diagnosing Anaphylaxis](#) below). The mechanism of the observed hypersensitivity reactions, including anaphylaxis, is unknown. Risk can be mitigated by contraindicating use for patients with severe hypersensitivity reactions to any component of pemivibart. As pemivibart will be administered in a medical setting, labeling to ensure providers are aware of the need to monitor patients for reactions, with immediate availability of trained personnel with emergency resuscitation drugs and equipment necessary for the management of serious hypersensitivity reactions, including anaphylaxis, is an additional risk mitigation strategy.

II. Background


1. Drug

Pemivibart is an anti-SARS-CoV-2 monoclonal antibody currently proposed for an EUA for the following indication:

For the pre-exposure prophylaxis of COVID-19 in adults and pediatric individuals (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 may not mount an adequate immune response to COVID-19 vaccination, or

-  (b) (4)

The proposed dosing schedule is an initial dosage of pemivibart 4500 mg administered as a single intravenous (IV) infusion followed by a repeat dose of 4500 mg as a single IV infusion approximately every  months.

2. CANOPY Trial Synopsis

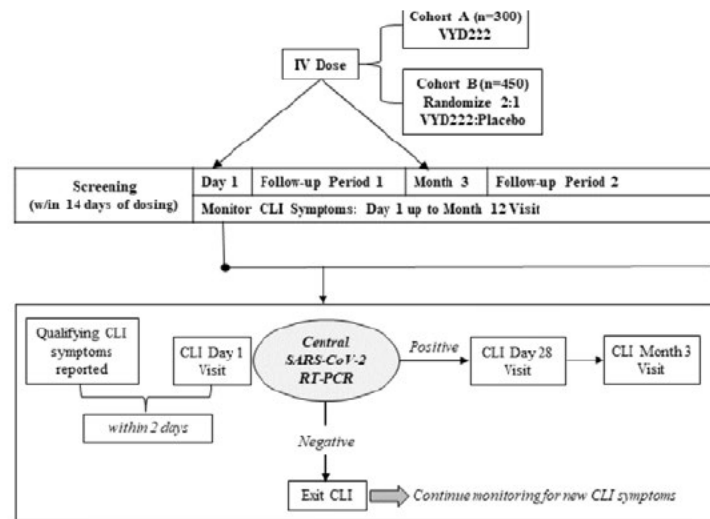
Study Design

The data supporting this EUA relies on one phase 3 trial, CANOPY, which is an ongoing clinical trial assessing pemivibart for the pre-exposure prophylaxis of COVID-19 in adults >18 years of age in two cohorts (Figure 1):

Cohort A: A single-arm, open-label study in adults with significant immune compromise (n = 306)

Cohort B: A triple-blind, placebo-controlled, randomized study in adults whose circumstances places them at risk of acquiring SARS-CoV-2 infection (n =484, 322 to pemivibart, 162 to placebo)

Figure 1. Study Design Schematic



IV=intravenous; CLI=COVID-19-like illness; RT-PCR=reverse transcription polymerase chain reaction; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2.

Each Cohort is dosed with pemivibart twice, three months apart. As of February 21, 2024, Cohort B has completed Month 3 repeat infusion. Cohort A is ongoing. The total number of subjects treated with pemivibart is 623 subjects as 5 participants randomized in Cohort B were never dosed.

Primary Endpoint

Effectiveness of pemivibart was based on assessment of serum virus neutralizing antibody titers. Clinical efficacy is anticipated to be sustained if the titers stay above the protection titer threshold on Day 28.

Key Inclusion Criteria

1. Adults ≥ 18 years for Cohort B only; Adolescents aged 12 to <18 years old weighing at least 40 kg at time of screening.
2. Cohort A: Varying response of COVID-19 vaccine booster based on titer levels.
3. Has significant immune compromise OR is at risk of SARS-COV-2

Cohort A: significant immune compromise defined as:

- Actively treated for solid tumor or hematologic malignancies
- Solid organ transplant recipient taking immunosuppressants.
- CAR-T-cell therapy or stem cell transplant (within 2 years)
- Moderate or severe primary immunodeficiency
- Advanced HIV infection (CD4 cell count <350 cells/mm³)
- Taking high dose corticosteroids (≥ 20 mg prednisone or equivalent per day when administered for at least 2 weeks), B cell depleting agents

within the past year, alkylating agents, antimetabolites, transplant-related immunosuppressive drugs, TNF blockers, or other immunosuppressive agents.

Cohort B: at risk of acquiring SARS-Cov-2 due to regular unmasked face to face interaction in indoor settings.

4. Agrees to defer COVID-19 vaccination or booster for minimum of 28 days after dosing on Day 1

Key Exclusion Criteria

1. For Cohort B: Prior receipt of a COVID-19 vaccine or booster within 120 days before randomization.
2. Prior receipt of convalescent plasma or a mAb to SARS-CoV-2 active against currently circulating variants, including in the setting of a clinical trial, within 120 days before randomization.
3. Prior known or suspected SARS-CoV-2 infection within 120 days before randomization.
4. Exposure to someone with known or suspected SARS-CoV-2 infection in the 5 days before randomization.
5. Was acutely ill with any of the following symptoms: fever ≥ 38 °C (≥ 100.4 °F), shortness of breath/difficulty breathing, chills (shivering), cough, fatigue (low energy or tiredness), muscle or body aches, headache, loss of taste or smell, sore throat, congestion (stuffy or runny nose), nausea, vomiting, diarrhea.
6. Known allergy/sensitivity or hypersensitivity to the study drug, including excipients.

Safety

All subjects were monitored closely for signs and symptoms of systemic hypersensitivity reactions for at least 1 hour post dose. Narratives were obtained for all adverse events that occurred within an hour of infusion. Hypersensitivity reactions were recorded as adverse events and assessed for intensity. Anaphylaxis was not an adverse event of special interest and there was no independent adjudication committee.

Use of premedication was not required in this study, but could be used at the discretion of the Investigator. In the event infusion reactions were observed in subjects, the Investigator could decide to premedicate later subjects or premedicate at redosing with aspirin, acetaminophen, antihistamines, or other appropriate medications prior to start of study drug infusion. According to the Sponsor, no premedication was given to any of the subjects that were included in the trial at the time of application submission. As the trial is still ongoing, four subjects have since been premedicated, all on February 4, 2024, after the anaphylaxis events were reported.

3. Narratives of Anaphylaxis

Two MedWatch reports for anaphylaxis were submitted by the Sponsor. Both reports of anaphylaxis occurred in Cohort A and occurred on second infusion of pemivibart. We reviewed the two MedWatch narratives that were considered by the Sponsor to be anaphylaxis and agreed

with the Sponsor that these case met criteria for anaphylaxis. When adjudicating, FDA applied the National Institute of Allergy and Infectious Disease and Food Allergy and Anaphylaxis Network (NIAID/FAAN) criterion number 1 (see [Table 1. Clinical Criteria for Diagnosing Anaphylaxis](#) below) as pemivibart is not a known allergen for the subjects. The NIAID/FAAN framework does not grade the severity of a reaction, as anaphylactic reactions are, by definition, systemic, and unpredictable; as such, they are considered potentially life-threatening. DPACC also reviewed the narratives that were required for all study drug related adverse events occurring 1-hour post-dose monitoring period. Review of the narratives resulted in identification of two anaphylaxis cases which the Sponsor determined to be a hypersensitivity reaction and an infusion-related reaction. The four narratives which met criteria for anaphylaxis are summarized below.

Two cases of anaphylaxis reported via MedWatch with Preferred Term of anaphylactic reaction:

- Subject (b) (6) (Cohort A)

Subject (b) (6) is a 60-year-old male with a history of Crohn's disease, alcoholism, kidney stones, depression, and anxiety. He has known drug allergies to metronidazole and metoclopramide. Concomitant medications include citalopram, lorazepam, and adalimumab. The subject received the first dose of pemivibart on (b) (6). The subject reported feeling some "tingling," but otherwise received the full infusion.

One month later, on (b) (6), the subject received both the Pfizer COVID-19 vaccine and the influenza vaccine.

On (b) (6), the subject arrived for his 3-month visit for his second dose of pemivibart. Baseline vitals prior to infusion were heart rate (HR) 46 beats per minute (bpm), blood pressure (BP) 120/80, temperature 97.7 F, respiratory rate (RR) 14 breaths per minute (brpm). Approximately 20 minutes into the infusion, the subject experienced itchiness and was noted to have **urticaria** spreading from the IV site to the rest of his body. Infusion was stopped and the IV line was flushed with normal saline. The subject was given 50 mg of oral diphenhydramine. Vitals remained stable (HR 56 bpm, O2 saturation 97%, BP 140/80, temperature 97.8, RR 20 brpm). Approximately 15 minutes after symptoms began, **angioedema of the tongue and lips** were observed, and the subject began slurring words. The subject was placed in a supine position on the table and was given 0.3 mL of epinephrine intramuscularly. Vitals remained stable with no drop in blood pressure (BP 142/84, SpO2 99%, HR 56 bpm). However, approximately 20 minutes since symptoms began, the subject noted to have **difficulty breathing** with increased secretions around his mouth. He was transported via emergency medical services to the emergency department where vital signs remained stable (BP 119/73, HR 59 bpm, RR 12 brpm, SpO2 98%). The emergency department exam showed diffused erythema, but no edema or urticaria or respiratory distress was noted. Subject received IV famotidine and was observed for 6 hours. All symptoms resolved by the time of discharge.

Reviewer comment: Subject (b) (6) met the criteria of anaphylaxis (defined by NIAID/FAAN criterion number 1) as the subject experienced an acute onset of symptoms involving the skin and mucosal tissue (urticaria, angioedema) along with respiratory compromise (difficulty breathing).

- Subject (b) (6) (Cohort A)

Subject (b) (6) is a 46-year-old female with a past medical history of psoriatic arthritis, attention deficit hyperactivity disorder (ADHD), and depression with no known drug allergies. Relevant concomitant medications include amphetamine, certolizumab, methotrexate, vitamin D, bupropion, and levonorgestrel. The subject received her first dose of pemivibart on (b) (6), with no adverse events reported.

One month later, the subject received the Moderna COVID-19 vaccine.

On January (b) (6), the subject received her month 3 dose of pemivibart. Pre-infusion vitals include HR 110 bpm, BP 130/80, SpO2 99%, temperature 97.6 F, and RR 18 brpm. Approximately 20 minutes into the infusion, the subject complained of itching, **flushing, and hives** around extremities and neck. Vitals remained stable (BP 140/80, SpO2 100%, HR 84 bpm). The infusion was stopped and the subject was given a dose of IV diphenhydramine 12 minutes after symptoms began. The subject then noted **swelling in lips, face and eyelids** and relayed “I don’t feel good” and “**I can’t breathe**”. A dose of 0.3 mL IV epinephrine was given 15 minutes after symptoms began. IV epinephrine was accidentally given instead of intramuscularly. 911 was called. The subject noted an extreme headache after IV administration of epinephrine and the subject reported “you’re going to lose me; I feel like I’m going to faint,” but the subject never lost consciousness. The subject also mentioned throat tightness and tongue swelling. Emergency medical services arrived 16 minutes after start of symptoms, and she was transferred to the emergency department. In the emergency department, she had rebound symptoms of itchiness and redness on neck and face along with continued headache, chest pain, and left arm tingling. Another intramuscular 0.3 mL of epinephrine was given. The subject was observed overnight and had a third round of itching and hives but did not require epinephrine. By next day, symptoms had resolved. A week later, subject noted myalgia, arthralgia, fatigue, chest pain and tachycardia and was started on prednisone and a beta blocker.

Reviewer comment: Subject (b) (6) met the criteria of anaphylaxis (defined by NIAID/FAAN criterion number 1) as the subject experienced an acute onset of symptoms involving the skin and mucosal tissue (flushing, hives, swelling in lips, face and eyelids) along with respiratory compromise (I can’t breathe).

Review of narratives from the adverse events occurring 1 hour post-dose identified two events meeting criteria for anaphylaxis:

- Subject (b) (6) (Cohort A)

Subject (b) (6) is a 64-year-old female with history of Churg Strauss syndrome on prednisone and mycophenolate mofetil who developed **flushing**, dizziness, ringing in ears, and **wheezing** within 4 minutes of infusion of her first dose of pemivibart on (b) (6). Infusion was stopped and symptoms resolved within 10 minutes and subject was given one dose 25 mg of oral diphenhydramine. That evening approximately 11 hours after dosing, subject experienced nausea and diarrhea. The subject withdrew from the study and was not re-dosed at Month 3. This adverse event was labeled as infusion related hypersensitivity reaction, nausea and diarrhea.

Reviewer comment: Subject (b) (6) met the criteria of anaphylaxis (defined by NIAID/FAAN criterion number 1) as the subject experienced an acute onset of symptoms involving the skin and mucosal tissue (flushing) along with respiratory compromise (wheezing). The subject has Churg Strauss syndrome, placing her at greater risk for respiratory symptoms during anaphylaxis, but does not discount the respiratory symptoms as a symptom of anaphylaxis. The subject did experience nausea and diarrhea 11 hours after dosing, which is the median duration for a biphasic reaction¹. The potential biphasic reaction does not change the classification of the event, but may be clinically relevant to support the adjudication of anaphylaxis.

- Subject (b) (6) (Cohort A)

Subject (b) (6) is a 44-year-old male with a history of chronic obstructive lung disease on prednisone who developed immediate **dyspnea**, diaphoresis, **red face**, **chest tightness**, and tachycardia on first infusion of pemivibart. Infusion was immediately stopped and resolved within 3 hours after dosing with 25 mg oral diphenhydramine and 180 ug **albuterol inhalation**. Study drug was discontinued and the subject was not re-dosed at Month 3. This adverse event was labeled as infusion related reaction.

Reviewer comment: Subject (b) (6) met the criteria of anaphylaxis (defined by NIAID/FAAN criterion number 1) as the subject experienced an acute onset of symptoms involving the skin and mucosal tissue (red face) along with respiratory compromise (dyspnea, requiring albuterol). The subject has chronic obstructive lung disease, placing him at greater risk for respiratory symptoms during anaphylaxis, but does not discount the respiratory symptoms as a symptom of anaphylaxis.

III. Questions

¹ Golden DBK, et al. Anaphylaxis: A 2023 practice parameter update. Ann Allergy Asthma Immunol. 2024 Feb;132(2):124-176. doi: 10.1016/j.anai.2023.09.015. Epub 2023 Dec 18. PMID: 38108678.

1. Please review and provide your overall assessment of two anaphylactic reactions occurring in a relatively small population of 261, which results in a relatively high and concerning rate (0.8%).

DPACC agrees with the two cases identified by the Sponsor as anaphylaxis (subjects (b) (6)). After review of the narratives provided for all adverse events that occurred within one hour of infusion, two additional anaphylaxis events were adjudicated as they met NIAID/FAAN criterion 1. Considering the 4 anaphylaxis events and the total number of subjects who received any dose of pemivibart in Cohort A and Cohort B, the anaphylaxis rate for pemivibart would be 0.64 % (4 events /623 subjects who received pemivibart) in the trial.

a. Comment on the potential mechanism for anaphylaxis.

Anaphylaxis is a severe, potentially fatal, systemic allergic reaction which can include a range of clinical signs and symptoms, including urticaria, angioedema, nausea, vomiting, diarrhea, abdominal pain, bronchospasm, hypotension, and loss of consciousness.² Anaphylaxis can occur via two mechanisms: IgE-mediated or non-IgE-mediated reactions. IgE-mediated reactions occur when there is development of allergen-specific IgE that is bound to IgE receptors (FcεR1) on the surface of basophils and tissue mast cells; subsequent exposure to the allergen cross-links receptors with release of mediators of the allergic immune response, such as histamine, cytokines, prostaglandins. Non-IgE-mediated reactions occur through direct activation of mast cells and/or basophils, resulting in the release of the same mediators; this mechanism does not involve prior sensitization. IgE-mediated and non-IgE-mediated reactions are often clinically indistinguishable. The mechanism of the observed hypersensitivity reaction, including anaphylaxis, for pemivibart is unknown.

b. Comment on excipients (e.g., polysorbate80) in pemivibart and vaccines (e.g., COVID-19 and influenza) and/or biologics (e.g., adalimumab or certolizumab) that were administered around the time of administration of pemivibart (before or after) and whether this may have contributed to anaphylaxis.

Pemivibart, the two mRNA COVID-19 vaccines, and influenza vaccine described in the narratives contain polyethylene glycol (PEG) or a derivative of PEG. Current guidelines recommend exclusion from the mRNA vaccination of any person with a history of allergic reaction associated with any of the vaccine components, including polyethylene glycol (PEG) and PEG derivatives, such as polysorbates³. Polysorbate 80, a derivative of PEG, is also found in adalimumab and certolizumab, which are two concomitant medications for Subjects (b) (6).

² Golden DBK, et al. Anaphylaxis: A 2023 practice parameter update. *Ann Allergy Asthma Immunol.* 2024 Feb;132(2):124-176. doi: 10.1016/j.anai.2023.09.015. Epub 2023 Dec 18. PMID: 38108678.

³ Castells, MC, Phillips EJ. Maintaining Safety with SARS-CoV-2 Vaccines. *N Engl J Med* 2021; 284:642-649.

Theoretically, the same excipients that are used in vaccines and other biologics can sensitize a patient prior to pemivibart dosing. However, in the two cases of anaphylaxis for subjects (b) (6), both were previously exposed to polysorbate 80 (as derivative of PEG) as their concomitant medications included polysorbate 80 (adalimumab or certolizumab). They did not react to their first dose of pemivibart, nor to the COVID-19 vaccination and/or influenza vaccination one month after their first infusion of pemivibart. If the two subjects were allergic to polysorbate 80 or PEG, the subject should have reacted to the first dose of pemivibart and to the vaccinations. As such, it is unlikely that PEG or polysorbate 80 was the cause of anaphylaxis. As for the two subjects who experienced anaphylaxis with the first dose of pemivibart (Subjects (b) (6)), based on the limited event details, it is unclear if PEG played a role in these reactions.

c. Comment on any potential mitigation strategies (e.g., scratch test or any other options).

There are no mitigation strategies to predict who may react to pemivibart. Testing for IgE mediated reactions generally involve either skin testing to the allergen or serological testing to assess presence of IgE antibody to the allergen. These tests are usually performed retrospectively to confirm IgE mediated reactions after a detailed history suggests an IgE mediated reaction. Serological testing has limited availability. In addition, both serological and skin testing are not adequately validated with unclear specificity and sensitivity and lack internal positive controls; therefore, their utility in confirming IgE mediated reactions are low.

d. Comment on the utility of restricting the EUA to a single dose given the more severe reactions with the second dose, including anaphylaxis. Is there a higher risk for anaphylaxis with the second dose compared to the first dose?

Generally, IgE-mediated reactions result from IgE antibody development after sensitization to an antigen, triggering an allergic reaction upon second or later doses. Theoretically, there would be a higher risk of a reaction on second dose. However, as it is unknown if the pemivibart reactions are IgE-mediated or non-IgE-mediated, there is insufficient evidence to determine a risk difference between the first and second dose.

2. **Please provide your overall assessment of the other IRR/HSRs that occurred with either the first and/or second dose**
 - a. **Comment on risk mitigation strategies, such as premedication prior to the infusion including specific medications, dosage, and continuation of medication for at least 24 hours (or longer) in case delayed reactions are a concern. Patients will be monitored in clinic for 1h post infusion. Most reactions in the trial occurred during the infusion or within 1h of the infusion, otherwise at least 6h later.**

Although infusion reactions and hypersensitivity reactions, including anaphylaxis, are often discussed together, their mechanism of action differ and should be considered separate entities with different risk and mitigation strategies. The exact mechanisms of infusion reactions are unknown, but it is suspected to be a result of various types of antibody-antigen interactions resulting in cytokine release⁴. Infusion reactions typically develop from the time of infusion to 2 hours after the initiation of infusion, although symptoms may be delayed up to 24 hours. The most common symptoms include fever, chills, flushing, itching, alterations of heart rate and blood pressure, chest discomfort, dyspnea, myalgias, abdominal pain, nausea, vomiting, diarrhea, and rashes⁵. Many of the infusion reaction symptoms overlap with symptoms seen in hypersensitivity reactions and anaphylaxis, making them clinically indistinguishable.

Prophylaxis with antihistamines, acetaminophen, and/or glucocorticoids is recommended for certain drugs with a high incidence of infusion related reactions as standard of care practice. However, these regimens have been empirically derived rather than established through randomized controlled trials, so the true effectiveness of these medications in preventing infusion reactions is unknown. By contrast, anaphylaxis is generally not prevented by premedication, although the severity of the reaction may be reduced by use of antihistamines and glucocorticoids. The major concern with pre-medication is the risk of masking early signs of anaphylaxis, leading to delayed administration of epinephrine and poorer clinical outcomes.⁶ For pemivibart, DPACC considers the use of premedication to mitigate risk of infusion reactions to be the practice of medicine and does not warrant inclusion in labeling. Providers can choose whether premedication is warranted for their individual patient. Labeling to recommend premedication for all patients in the EUA factsheet is not recommended.

⁴Picard M, Galvao VR. Current Knowledge and Management of Hypersensitivity Reactions to Monoclonal Antibodies. *J Allergy Clin Immunol Pract.* 2017; 5(3):600

⁵ Isabwe GAC et al. Hypersensitivity reactions to therapeutic monoclonal antibodies: Phenotypes and endotypes. *J Allergy Clin Immunol.* 2018; 142(1): 159.

⁶ Shaker MS et al. Anaphylaxis- a 2020 practice parameter update, systematic review, and Grading of Recommendations, Assessment, Development and Evaluation (GRADE) analysis. *J Allergy Clin Immunol.* 2020 Apr; 145(4): 1082-1123.

b. Comment on lengthening the infusion time from 30 min to 60 min. Should patients be observed in the clinic for more than 1h after the infusion?

Lengthening the infusion time is a frequently implemented mitigation strategy to decrease the incidence of infusion reactions. Lengthening the infusion time will not mitigate anaphylaxis or hypersensitivity reactions. If efficacy is not affected, lengthening the infusion time is a reasonable mitigation strategy for infusion reactions.

While all four cases of anaphylaxis occurred immediately, generally, anaphylaxis occurs within the first 2 hours of antigen exposure. Therefore, increasing the observation time for 1 hour to 2 hours is a reasonable mitigation strategy.

Infusions reactions generally also occur within 30 minutes, but can be delayed up to 24 hours post infusion, so increasing observation time would not aid in monitoring infusion reactions.

3. Please provide any thoughts on whether the authorized patient population should be further restricted to only those with severe immunocompromise given the risks.

DPACC defers to DAV to determine whether the benefit-risk is favorable for both proposed indicated populations. While the clinical trials to support an EUA for pemivibart identified a high incidence of anaphylaxis, pemivibart is administered in a medical setting, allowing for monitoring and immediate access to medical care if serious hypersensitivity reactions such as anaphylaxis occur. Labeling should clearly communicate the anaphylaxis risk and necessary mitigations strategies, including the need to monitor patients and to have appropriate personnel, medications, and equipment immediately available. Given the 0.6% rate identified in clinical trials, labeling should be fully leveraged as anaphylaxis is a serious adverse reaction that requires immediate treatment to reduce morbidity and mortality. DPACC recommends a boxed warning to highlight the anaphylaxis risk.

DPACC does not recommend additional labeling, such as contraindicating use in individuals with a prior history of anaphylaxis to other agents including drugs and biologics, as there is no data to support this contraindication for pemivibart.

IV. Table 1. Clinical Criteria for Diagnosing Anaphylaxis

Table I. Clinical criteria for diagnosing anaphylaxis

Anaphylaxis is highly likely when any one of the following 3 criteria are fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula)

AND AT LEAST ONE OF THE FOLLOWING

a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)

b. Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)

2. Two or more of the following that occur rapidly after exposure to a *likely allergen for that patient* (minutes to several hours):

a. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)

b. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)

c. Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)

d. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)

3. Reduced BP after exposure to *known allergen for that patient* (minutes to several hours):

a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP*

b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

Source: Sampson et al. Second Symposium on the Definition and Management of Anaphylaxis: Summary report-Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network Symposium JACI 2006

Appendix 6. Subject Matter Expert Review (Marjorie Shapiro, PhD) of Monoclonal Antibody Sequences To Further Assess Potential Causes of Anaphylaxis

Sequence Comparison Between Pemivibart, Adintrevimab, Adalimumab, and Certolizumab Pegol

Summary and Conclusion

- There are eight amino acid differences between pemivibart and adintrevimab, five in the VH region and three in the VL region. It is not clear if the pemivibart sequence would be more immunogenic than the ADG20 sequence.
- Adalimumab and certolizumab use VH genes from the same VH family as pemivibart/adintrevimab but different VL isotypes.
- Since the VH genes are from the same family (V genes with $\geq 80\%$ homology at the DNA level), there is sequence similarity in the framework regions of the VH. The CDR regions are different between pemivibart/adintrevimab, adalimumab and certolizumab.
- The TNF antagonists have variable, but generally high rates of ADA across several autoimmune indications. However, in general, when given in combination with MTX, the ADA rates are lower.
- A recent publication in Journal of Immunology ([Rispens et al. 2023](#)) showed that ADA to rituximab did not cross-react with two other anti-CD20 mAbs (ofatumumab and obinutuzumab), but some ADA cross-reacted with ocrelizumab, which is not clonally related to rituximab, but has stretches of similar sequences in VH CDR1 and CDR2 and VL CDR1 and CDR3. However, the authors didn't identify the epitopes recognized by the ADA.
- It is possible that ADA directed against public idiotopes (common immunogenic sequences on different abs) generated against an anti-TNF mAb could cross react with a different mAb binding a different target, but there is currently no literature to support this.
- However, it is unlikely that ADA would be generated against common sequences in framework regions of closely related mAbs. Similar sequences in germline framework regions should be tolerizing. Homology between V genes is lowest in the CDRs and if ADAs are raised against a public epitope in humans, there is a higher chance that they are directed against a CDR.
- Without ADA data from the two patients who had the anaphylactic reactions or an in-silico analysis of potential immunogenic epitopes in pemivibart and adintrevimab, it is not possible to determine that (1) ADA due to the sequence differences between pemivibart and adintrevimab or (2) pre-existing ADA against adalimumab or certolizumab cross that react with VYD222 could be responsible for the anaphylactic reactions. The latter possibility seems very unlikely.

Background

Two patients who are immunocompromised due to being on adalimumab or certolizumab pegol + MTX for CD and PsA, respectively, had hypersensitivity reactions upon redosing of pemivibart. This rate of hypersensitivity upon redosing was not seen with the parental adintrevimab mAb. It is not clear if the sequence difference between the two mAbs would result in this difference or if treatment with anti-TNF mAbs may play a role. The sequences of all four mAbs were compared to look for similarities and differences in the CDRs.

An IR was sent to Invivyd asking if an in-silico analysis to predict antigenic epitopes was performed on both mAbs. Invivyd replied that they had not. In addition, the ADA status of patients in the clinical trial supporting the EUA is currently unknown. The ADA assay they have used patients treated with 1500 mg and 2500 mg doses, not the 4500 mg. They are currently developing an assay to detect ADA in the presence of higher levels of VYD222.

Origin of mAbs

ADG20 was isolated from a 2003 SARS survivor 13 years postinfection and selected for its ability to bind a common RBD epitope on SARS, SARS-CoV-2 and the bat corona virus WIV-1-CoV. However, prior to submission of an EUA, in 2022, it was shown to have reduced in vitro potency against Omicron B.1.1.529. VYD222 was derived from ADG20 by in vitro re-engineering and affinity maturation to select Fabs that bind current Omicron variants.

Adalimumab and certolizumab pegol are anti-TNF mAbs approved for a variety of autoimmune diseases including, but not limited to, RA, Crohn's Disease, PsA, AS, Plaque Psoriasis. Adalimumab was isolated from a human phage display library using guided selection based on a murine anti-TNF mAb. Certolizumab pegol is a humanized version of a murine mAb.

Gene Usage Summary

[Table 27](#) lists the human germline genes with the highest homology to each mAb (percent homology to the human germline gene is in parentheses). VYD222 and ADG20 use a lambda light chain while adalimumab and certolizumab use a kappa light chain. Therefore, comparisons between anti-SARS-CoV-2 and anti-TNF VL sequences would not be informative. The VH genes from all four mAbs use different members of the VH3 family.

Table 27. Human Germline Gene Use by and Percentage Homology to VYD222, ADG20, and Anti-TNF mAbs

mAb	VH (%)	CDR3	JH (%)	VL (%)	JL (%)
VYD222	IGHV3-21*07 (88.8)	ARDFGGDTAWAGTGFTY	IGHJ4 (92.9)	IGLV1-40*01 (83.8)	IGLJ1*01 (91.7)
ADG20	IGHV3-21*07 (89.8)	ARDFSGHTAWAGTGFEY	IGHJ4 (92.9)	IGLV1-40*01 (95.9)	IGLJ1*01 (91.7)
Adalimumab	IGHV3-9*01 (93.9)	AKVSYLSTASSLDY	IGHJ4 (92.9)	IGKV1-27*01 (95.8)	IGKJ1/J2 (91.7)
Certolizumab	IGHV3-23*04 (77.6)	ARGYRS..YAMDY	IGHJ4 (100.0)	IGKV1-16*01 (85.3)	IGLJ1*01 (100.0)

Source: Sequence analysis performed using IMGT/DomainGapAlign Tool [IMGT/DomainGapAlign](#)

Ehrenmann F., Kaas Q. and Lefranc M.-P. Nucleic Acids Res., 38:D301-D307 (2010).

Ehrenmann, F., Lefranc, M.-P. Cold Spring Harbor Protoc., 6:737-749 (2011).

Abbreviations: ADG20, adintrevimab; CDR, complementarity determining region; mAb, monoclonal antibody; TNF, tumor necrosis factor; VYD222, pemivibart

In the sequence comparison below, the alignments are based on analysis using IMGT. Amino acids in **bold red** show differences between VYD222 and ADG20, sequences in **bold black** show the same residues in the VH CDRs among all four mAbs. Underlined sequences represent CDRs as determined by Kabat rather than IMGT.

VL

	CDR1				CDR2			
VYD:	QSVLTQPPS.VSGAP	QQRITISCTGS	<u>SSNIG...AGYD</u>	<u>VHWYQQLP</u>	GTAPKLLIY	<u>GS.....S</u>	<u>SRNYGVP.D</u>	RFSGSK..SG
ADG:	QSVLTQPPS.VSGAP	QQRITISCTGS	<u>SSNIG...AGYD</u>	<u>VHWYQQLP</u>	GTAPKLLIY	<u>GS.....S</u>	<u>SRNSGVP.D</u>	RFSGSK..SG.
ADA:	DIQMTQSPSSLSASV	GDRVTITCRAS	<u>QGI.....RNY</u>	<u>LAWYQQKP</u>	GKAPKLLIY	<u>AA.....S</u>	<u>TLQSGVP.S</u>	RFSGSG..SG
CER:	DIQMTQSPSSLSASV	GDRVTITCKAS	<u>QNV.....GTN.</u>	<u>VAWYQQKP</u>	GKAPKALIY	<u>SA.....S</u>	<u>FLYSGVP.Y</u>	RFSGSG..SG

	CDR3			
VYD:	TSASLAITGLQA	EDEADYYC	<u>QSYDSD.LGVLYT</u>	FGTGTKVTVL GQPKAAPSV
ADG:	TSASLAITGLQA	EDEADYYC	<u>QSYDSS.LSVLYT</u>	FGTGTKVTVL GQPKAAPSV
ADA:	TDFTLTISLQP	EDVATYYC	<u>QRYNR....APYT</u>	FGQGTKVEIK RTV
CER:	TDFTLTISLQP	EDFATYYC	<u>QQYNI....YPLT</u>	FGQGTKVEIK RTV

VH

	CDR1				CDR2			
VYD:	EVQLVESGG.GLVKP	GGSLRLSCAAS	<u>GFTF....GSYE</u>	<u>MNWVRQAP</u>	GKGLEWVSS	<u>ISED..GYST</u>	<u>YYPDSLK.G</u>	RFTISRDSAK
ADG:	EVQLVESGG.GLVKP	GGSLRLSCAAS	<u>GFTF....SSYY</u>	<u>MNWVRQAP</u>	GKGLEWVSS	<u>ISED..GYST</u>	<u>YYPDSLK.G</u>	RFTISRDSAK
ADA:	EVQLVESGG.GLVQP	GRSLRLSCAAS	<u>GFTF....DDYA</u>	<u>MHWVRQAP</u>	GKGLEWVSA	<u>ITWN..SGHI</u>	<u>DYADSV.E.G</u>	RFTISRDNAK
CER:	EVQLVESGG.GLVQP	GGSLRLSCAAS	<u>GYVF....TDYG</u>	<u>MNWVRQAP</u>	GKGLEWMGW	<u>INTY..IGEP</u>	<u>IYADSVK.G</u>	RFTFSLDTSK

	CDR3			
VYD:	NSLYLQMNSLRA	DDTAVYYC	<u>ARDFGDTAWAGTGFTY</u>	WGQGTTLVTVSS
ADG:	NSLYLQMNSLRA	DDTAVYYC	<u>ARDFSGHTAWAGTGFEY</u>	WGQGTTLVTVSS
ADA:	NSLYLQMNSLRA	EDTAVYYC	<u>AKVSYLSTASSL...DY</u>	WGQGTTLVTVSS ASTKGP
CER:	STAYLQMNSLRA	EDTAVYYC	<u>ARGYRS..YAM...DY</u>	WGQGTTLVTVSS

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
03/22/2024 09:59:53 AM

KIMBERLY A STRUBLE
03/22/2024 10:00:46 AM

WENDY W CARTER
03/22/2024 10:05:38 AM

ADAM I SHERWAT
03/22/2024 10:15:56 AM

**Emergency Use Authorization (EUA) for Pemivibart (PEMGARDA)
Center for Drug Evaluation and Research (CDER) Review Addendum**

Identifying Information

Application type (EUA or pre-EUA) If EUA, designate whether prevent or intra-event EUA request.	EUA																																										
EUA application number(s)	000122																																										
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.																																										
Submission date(s)	Initial submission: December 27, 2023																																										
Receipt date(s)	Initial submission: December 27, 2023																																										
OND Division / Office	Division of Antivirals/Office of Infectious Diseases																																										
Reviewer name(s)/ Discipline(s)	<table border="1"> <thead> <tr> <th>Discipline/Reviewer</th> <th>Team Lead</th> </tr> </thead> <tbody> <tr> <td>Clinical: Sarita Boyd</td> <td>Kimberly Struble</td> </tr> <tr> <td>Non-Clinical: David McMillan</td> <td>Christopher Ellis</td> </tr> <tr> <td>Clinical Virology: William Ince</td> <td>Julian O'Rear</td> </tr> <tr> <td>Clinical Pharmacology: Mario Sampson</td> <td>Su-Young Choi</td> </tr> <tr> <td>Director, Division of Infectious Diseases Pharmacology</td> <td>Kellie Reynolds</td> </tr> <tr> <td>Biometrics: Wen Zeng</td> <td>Hengrui Sun, Scott Komo</td> </tr> <tr> <td>Science Policy Analyst</td> <td>Andrew LeBoeuf</td> </tr> <tr> <td>Associate Director of Labeling</td> <td>Stacey Min</td> </tr> <tr> <td>Regulatory Project Manager: Talia Lindheimer</td> <td>CPMS: Linda Akunne</td> </tr> <tr> <td align="center" colspan="2">Office of Surveillance and Epidemiology</td> </tr> <tr> <td>DMEPA: Melina Fanari/ Yevegenia (Jen) Kogan</td> <td>RPM: Danyal Chaudhry</td> </tr> <tr> <td>OPE: Neha Gada</td> <td>DPV II: Rachna Kapoor, Kimberly Swank, Ida-Lina Diak</td> </tr> <tr> <td align="center" colspan="2">Office of Product Quality: OBP Review Team</td> </tr> <tr> <td>Regulatory Business Process Manager</td> <td>Andrew Shiber</td> </tr> <tr> <td>OBP Labeling Reviewer: Liming Lu</td> <td>Vicky Borders-Hemphill</td> </tr> <tr> <td>Product Quality: Chringma Sherpa</td> <td>Anshu Rastogi (TL), Rachel Novak (Supervisor)</td> </tr> <tr> <td>OPMA: Jeanne Fringer</td> <td>Maxwell Van Tassell (Microbiology), Zhong Li (Facilities)</td> </tr> <tr> <td align="center" colspan="2">Other Consults</td> </tr> <tr> <td>OPDP: Wendy Lubarsky, Sam Skariah</td> <td>PLT: Laurie Buonaccorsi, Barbara Fuller</td> </tr> <tr> <td>DPACC: Jennifer Lan, Miya Paterniti, Kelly Stone</td> <td>Medical Editors: Katharine Bradley, Hyo Sook Song</td> </tr> </tbody> </table>	Discipline/Reviewer	Team Lead	Clinical: Sarita Boyd	Kimberly Struble	Non-Clinical: David McMillan	Christopher Ellis	Clinical Virology: William Ince	Julian O'Rear	Clinical Pharmacology: Mario Sampson	Su-Young Choi	Director, Division of Infectious Diseases Pharmacology	Kellie Reynolds	Biometrics: Wen Zeng	Hengrui Sun, Scott Komo	Science Policy Analyst	Andrew LeBoeuf	Associate Director of Labeling	Stacey Min	Regulatory Project Manager: Talia Lindheimer	CPMS: Linda Akunne	Office of Surveillance and Epidemiology		DMEPA: Melina Fanari/ Yevegenia (Jen) Kogan	RPM: Danyal Chaudhry	OPE: Neha Gada	DPV II: Rachna Kapoor, Kimberly Swank, Ida-Lina Diak	Office of Product Quality: OBP Review Team		Regulatory Business Process Manager	Andrew Shiber	OBP Labeling Reviewer: Liming Lu	Vicky Borders-Hemphill	Product Quality: Chringma Sherpa	Anshu Rastogi (TL), Rachel Novak (Supervisor)	OPMA: Jeanne Fringer	Maxwell Van Tassell (Microbiology), Zhong Li (Facilities)	Other Consults		OPDP: Wendy Lubarsky, Sam Skariah	PLT: Laurie Buonaccorsi, Barbara Fuller	DPACC: Jennifer Lan, Miya Paterniti, Kelly Stone	Medical Editors: Katharine Bradley, Hyo Sook Song
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	Division of Product Quality Research: Marjorie Shapiro
Integrated review completion date	March 22, 2024
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 IgG1 λ 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.
Product in the Strategic National Stockpile (SNS)	No
Distributor	Invivyd, Inc.

Abbreviations: COVID-19, coronavirus disease 2019; CPMS, chief project management staff; DMEPA, Division of Medication Error Prevention Analysis; DPACC, Division of Pulmonology, Allergy, and Critical Care; DPV II, Division of Pharmacovigilance II; EUA, emergency use authorization; IgG, immunoglobulin G; OBP, Office of Biotechnology Products; OND, Office of New Drugs; OPDP, Office of Prescription Drug Promotion; OPE, Office of Pharmacovigilance and Epidemiology; OPMA, Office of Pharmaceutical Manufacturing Assessment; RPM, regulatory project manager; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TL, team lead

This addendum references the EUA summary review for pemivibart dated March 22, 2024.

The Agency is removing the following sentence in the EUA summary review on page 16 in the Overview of Immunobridging Approach subsection within Section VIII. Human Clinical Efficacy and Immunobridging.

No clinical efficacy data from adequate and well-controlled trials with pemivibart for the pre-exposure prophylaxis of COVID-19 are available at this time.

The rationale for removing this text is based on information received from the Sponsor on March 18, 2024, and is further explained on pages 28-29 of the EUA summary review in the Secondary Clinical Efficacy Endpoint subsection within Section VIII. Human Clinical Efficacy and Immunobridging.

The following statement in Section 14 of the Fact Sheet for Health Care Providers has also been removed. The corrected Fact Sheet for Health Care Providers is attached to this addendum.

No clinical efficacy data from adequate and well controlled trials with PEMGARDA for pre-exposure prophylaxis of COVID-19 are available.

This correction does not alter the conclusion of the review or alter the information presented in the authorized Facts Sheet for Patients, Providers, and Caregivers.

FACT SHEET FOR HEALTHCARE PROVIDERS: EMERGENCY USE AUTHORIZATION OF PEMGARDA (PEMIVIBART)

HIGHLIGHTS OF EMERGENCY USE AUTHORIZATION (EUA)

These highlights of the EUA do not include all the information needed to use PEMGARDA under the EUA. See the FULL FACT SHEET FOR HEALTHCARE PROVIDERS for PEMGARDA.

PEMGARDA (pemivibart) injection, for intravenous use
Original EUA Authorized Date: 03/2024

WARNING: ANAPHYLAXIS

See Full Fact Sheet for Healthcare Providers for the complete boxed warning.

- Anaphylaxis has been observed with PEMGARDA in 0.6% (4/623) of participants in a clinical trial.
- Anaphylaxis was reported during the first and second infusion of PEMGARDA. (5.1, 6.1)
- Anaphylaxis can be life-threatening.
- Prior to administering PEMGARDA, consider the potential benefit of COVID-19 prevention along with the risk of anaphylaxis. (5.1, 6.1, 14)
- Administer PEMGARDA only in settings in which healthcare providers have immediate access to medications to treat anaphylaxis and the ability to activate the emergency medical system (EMS), as necessary.
- Clinically monitor individuals during the infusion and for at least two hours after completion of the infusion.
- Discontinue PEMGARDA immediately if signs or symptoms of anaphylaxis or any severe systemic reaction are observed and initiate appropriate medications and/or supportive therapy.

EUA FOR PEMGARDA

The U.S. FDA has issued an EUA for the emergency use of the unapproved product PEMGARDA (pemivibart), a SARS-CoV-2 spike protein-directed attachment inhibitor, for the pre-exposure prophylaxis of coronavirus disease 2019 (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 immune response to COVID-19 vaccination.

PEMGARDA has been authorized by FDA for the emergency use described above. PEMGARDA is not FDA-approved for any use, including use for pre-exposure prophylaxis of COVID-19. (1)

LIMITATIONS OF AUTHORIZED USE

PEMGARDA is not authorized for use:

- For treatment of COVID-19, or:
- For post-exposure prophylaxis of COVID-19 in individuals who have been exposed to someone infected with SARS-CoV-2.

Pre-exposure prophylaxis with PEMGARDA is not a substitute for vaccination in individuals for whom COVID-19 vaccination is recommended.

Individuals for whom COVID-19 vaccination is recommended, including individuals with moderate-to-severe immune compromise who may derive benefit from COVID-19 vaccination, should receive COVID-19 vaccination. In individuals who have recently received a COVID-19 vaccine, PEMGARDA should be administered at least 2 weeks after vaccination.

PEMGARDA may only be prescribed for an individual patient by physicians, advanced practice registered nurses, and physician assistants who are licensed or authorized under State law to prescribe drugs.

PEMGARDA is authorized only for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of PEMGARDA under section 564(b)(1) of the Act, 21 U.S.C. § 360bbb 3(b)(1), unless the authorization is terminated or revoked sooner.

See Full Fact Sheet for Healthcare Providers for examples of medical conditions or treatments that may result in moderate to severe immune compromise and an inadequate immune response to COVID-19 vaccination, the justification for emergency use of drugs during the COVID-19 pandemic, information on available alternatives, and additional information on COVID-19.

DOSAGE AND ADMINISTRATION

PEMGARDA must be infused over a minimum of 60 minutes. (2.3) The dosage of PEMGARDA for emergency use in adults and adolescents (12 years of age and older weighing at least 40 kg) is:

Initial Dose: 4500 mg administered as a single intravenous infusion. (2.1)

Repeat Dose: 4500 mg administered as a single intravenous infusion approximately every 3 months. Repeat dosing should be timed from the date of the most recent PEMGARDA dose. (2.1)

See Full Fact Sheet for Healthcare Providers for details on preparation and administration. (2.3)

DOSAGE FORMS AND STRENGTHS

Injection: PEMGARDA 500 mg/4 mL (125 mg/mL) in a single-dose vial. (3)

CONTRAINDICATIONS

PEMGARDA is contraindicated in individuals with previous severe hypersensitivity reactions, including anaphylaxis, to any component of PEMGARDA. (4)

WARNINGS AND PRECAUTIONS

Anaphylaxis: Anaphylaxis has been observed with PEMGARDA in 4 of 623 (0.6%) participants in a clinical trial. Administer PEMGARDA only in settings in which healthcare providers have immediate access to medications to treat anaphylaxis and the ability to activate the emergency medical system (EMS), as necessary. If signs or symptoms of an anaphylactic reaction occur, immediately discontinue administration, and initiate appropriate medications and/or supportive therapy. Discontinue PEMGARDA use permanently in individuals who experience signs or symptoms of anaphylaxis. (5.1)

Hypersensitivity and Infusion-Related Reactions: Hypersensitivity and infusion-related reactions occurring during the infusion and up to 24 hours after the infusion have been observed with PEMGARDA and may be severe or life-threatening. If signs or symptoms of a clinically significant hypersensitivity reaction or infusion-related reaction occur, immediately discontinue administration, and initiate appropriate medications and/or supportive therapy. Clinically monitor individuals during infusion and for at least 2 hours after infusion is complete. (5.2)

Risk of Cross-Hypersensitivity with COVID-19 Vaccines: PEMGARDA contains polysorbate 80, which is in some COVID-19 vaccines and is structurally similar to polyethylene glycol (PEG), an ingredient in other COVID-19 vaccines. For individuals with a history of severe hypersensitivity reaction to a COVID-19 vaccine, consider consultation with an allergist-immunologist prior to PEMGARDA administration. (5.3)

Risk for COVID-19 Due to SARS-CoV-2 Viral Variants Not Neutralized by PEMGARDA: Certain SARS-CoV-2 viral variants may emerge that are not neutralized by monoclonal antibodies such as PEMGARDA. PEMGARDA may not be effective at preventing COVID-19 caused by these SARS-CoV-2 viral variants. Inform individuals of the increased risk, compared to other variants, for COVID-19 due to SARS-CoV-2 viral variants not neutralized by PEMGARDA. If signs and symptoms of COVID-19 occur, advise individuals to test for COVID-19 and seek medical attention, including starting treatment for COVID-19 as appropriate. (5.4)

ADVERSE REACTIONS

The most common adverse events (all grades, incidence $\geq 2\%$) observed in participants who have moderate-to-severe immune compromise treated with PEMGARDA included systemic and local infusion-related or hypersensitivity reactions, upper respiratory tract infection, viral infection, influenza-like illness, fatigue, headache, and nausea.

You or your designee must report all SERIOUS ADVERSE EVENTS or MEDICATION ERRORS potentially related to PEMGARDA (1) by submitting FDA Form 3500 [online](#), (2) by [downloading](#) this form, and then submitting it by mail or fax, or (3) by contacting the FDA at 1-800-FDA-1088 to request this form. Please also provide a copy of this form to Invivyd, Inc. by email at: pv@invivyd.com or call 1-800-890-3385 to report adverse events. (6.4)

See PATIENT AND PARENTS/CAREGIVER FACT SHEET

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FULL FACT SHEET FOR HEALTHCARE PROVIDERS

WARNING: ANAPHYLAXIS

Anaphylaxis has been observed with PEMGARDA in 0.6% (4/623) of participants in a clinical trial.

Anaphylaxis was reported during the first and second infusion of PEMGARDA [see *Warnings and Precautions (5.1)*, *Adverse Reactions (6.1)*].

Anaphylaxis can be life-threatening.

Prior to administering PEMGARDA, consider the potential benefit of COVID-19 prevention along with the risk of anaphylaxis [see *Warnings and Precautions (5.1)*, *Adverse Reactions (6.1)*, and *Clinical Studies (14)*].

Administer PEMGARDA only in settings in which healthcare providers have immediate access to medications to treat anaphylaxis and the ability to activate the emergency medical system (EMS), as necessary.

Clinically monitor individuals during the infusion and for at least two hours after completion of the infusion.

Discontinue PEMGARDA immediately if signs or symptoms of anaphylaxis or any severe systemic reaction are observed and initiate appropriate medications and/or supportive therapy.

1 EMERGENCY USE AUTHORIZATION FOR PEMGARDA

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) for the emergency use of the unapproved product PEMGARDA (pemivibart) for the pre-exposure prophylaxis of coronavirus disease 2019 (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.

Medical conditions or treatments that may result in moderate to severe immune compromise and an inadequate immune response to COVID-19 vaccination include:

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 $<200/\text{mm}^3$, 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)

Limitations of Authorized Use

PEMGARDA is not authorized for use:

- For treatment of COVID-19, or
- For post-exposure prophylaxis of COVID-19 in individuals who have been exposed to someone infected with SARS-CoV-2.

Pre-exposure prophylaxis with PEMGARDA is not a substitute for vaccination in individuals for whom COVID-19 vaccination is recommended. Individuals for whom COVID-19 vaccination is recommended, including individuals with moderate-to-severe immune compromise who may derive benefit from COVID-19 vaccination, should receive COVID-19 vaccination.

In individuals who have recently received a COVID-19 vaccine, PEMGARDA should be administered at least 2 weeks after vaccination.

PEMGARDA may only be prescribed for an individual patient by physicians, advanced practice registered nurses, and physician assistants that are licensed or authorized under State law to prescribe drugs .

PEMGARDA has been authorized by FDA for the emergency use described above.

PEMGARDA is not FDA-approved for any use, including use for pre-exposure prophylaxis of COVID-19.

PEMGARDA is authorized only for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of PEMGARDA under section 564(b)(1) of the FD&C Act, 21 U.S.C. § 360bbb-3(b)(1), unless the authorization is terminated or revoked sooner.

Justification for Emergency Use of Drugs During the COVID-19 Pandemic:

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 emergency¹.

Declared that circumstances exist justifying the authorization of emergency use of drugs and biological products for the prevention or treatment of COVID-19².

An EUA is an FDA authorization for the emergency use of an unapproved product or unapproved use of an approved product (i.e., drug, biological product, or device) in the United States under certain circumstances including, but not limited to, when the Secretary of HHS declares that there is a public health emergency that affects the national security or the health and security of United States citizens living abroad, and that involves biological agent(s) or a disease or condition that may be attributable to such agent(s). Criteria for issuing an EUA include:

The biological agent(s) can cause a serious or life-threatening disease or condition.

Based on the totality of the available scientific evidence (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 the serious or life-threatening disease or condition; and
- the known and potential benefits of the product - when used to diagnose, prevent, or treat such disease or condition - outweigh the known and potential risks of the product, taking into consideration the material threat posed by the biological agent(s).

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

Information Regarding Available Alternatives for the EUA Authorized Use

There are no adequate, approved, and available alternatives to PEMGARDA for the pre-exposure prophylaxis of COVID-19 in individuals who are unlikely to mount an adequate immune response to COVID-19 vaccination.

For information on clinical studies of PEMGARDA and other therapies for the pre-exposure prophylaxis of COVID-19, see www.clinicaltrials.gov.

¹ 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>.

² 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.”).

2 DOSAGE AND ADMINISTRATION

2.1 Dosage for Emergency Use of PEMGARDA

Initial Dosing:

The initial dosage of PEMGARDA in adults and adolescents (12 years of age and older weighing at least 40 kg) is 4500 mg administered as a single intravenous (IV) infusion [see *Clinical Pharmacology (12.3)*].

Repeat Dose:

The repeat dosage is 4500 mg of PEMGARDA administered as a single IV infusion every 3 months. Repeat dosing should be timed from the date of the most recent PEMGARDA dose.

The recommendations for dosing are based on the totality of the scientific evidence including clinical pharmacology data, antiviral activity data, and clinical study data [see *Clinical Pharmacology (12.3)*, *Microbiology (12.4)*, and *Clinical Studies (14)*].

2.2 Dosage Adjustment in Specific Populations

No dosage adjustment is recommended in pregnant or lactating individuals, in geriatrics, or in individuals with renal or hepatic impairment [see *Use in Specific Populations (8)*].

2.3 Dose Preparation and Administration

General Information:

PEMGARDA should be prepared and administered by a qualified healthcare provider using aseptic technique.

Vials of PEMGARDA are for one-time use only.

Visually inspect the vials for particulate matter and discoloration. PEMGARDA is a clear to slightly opalescent, colorless to yellow solution. Discard the vial if the solution is cloudy, discolored, or if visible particles are observed.

PEMGARDA should be administered as an IV infusion diluted with 0.9% sodium chloride.

Materials Needed:

9 single-dose vials of PEMGARDA (125 mg/mL)

50 mL prefilled bag of 0.9% sodium chloride (normal saline) for IV injection

IV extension set with inline 0.2-micron filter

Infusion pump or gravity infusion set

0.9% sodium chloride injection for flushing

Preparation:

Remove PEMGARDA vials from refrigerated storage and allow to equilibrate to room temperature (18°C to 26°C [64°F to 79°F]) for 10 minutes before preparation. **Do not expose to direct heat. Do not shake vials. Inspect the vials.**

Prepare IV bag by removing and discarding 36 mL from a 50 mL prefilled bag of 0.9% sodium chloride for IV injection.

Withdraw 36 mL of PEMGARDA from nine (9) vials into appropriately sized polypropylene syringe(s) (e.g., one 40 mL syringe or two 20 mL syringes) and inject into prepared 0.9% sodium chloride IV bag.

The final product for administration will contain 50 mL: 36 mL of PEMGARDA and 14 mL of 0.9% sodium chloride.

This product is preservative-free and therefore should be administered immediately.

If immediate administration is not possible, the diluted solution may be stored at room temperature under ambient light for up to 4 hours. Do not shake the diluted solution.

Administration:

PEMGARDA should only be administered in settings in which healthcare providers have immediate access to medications to treat a severe hypersensitivity reaction, such as anaphylaxis, and the ability to activate the emergency medical system (EMS), as necessary [see *Warnings and Precautions (5.1)*].

Attach infusion set including inline 0.2-micron filter to prepared IV bag, then prime the infusion set.

Administer the entire 50 mL infusion using infusion pump or gravity infusion set over a minimum of 60 minutes. Due to potential overflow, the entire contents of prepared IV bag should be administered to avoid underdosing.

Once infusion is complete, flush line with 0.9% sodium chloride.

Clinically monitor patients during infusion and observe patients for at least 2 hours after infusion is complete [see *Warnings and Precautions (5.1)*].

3 DOSAGE FORMS AND STRENGTHS

PEMGARDA is a sterile, preservative-free, clear to slightly opalescent, colorless to yellow solution available as:

Injection: 500 mg/4 mL (125 mg/mL) in a single-dose vial

4 CONTRAINDICATIONS

PEMGARDA is contraindicated in individuals with previous severe hypersensitivity reactions, including anaphylaxis, to any component of PEMGARDA.

5 WARNINGS AND PRECAUTIONS

5.1 Anaphylaxis

Anaphylaxis has been observed with PEMGARDA in 4 of 623 (0.6%) participants in a clinical trial [see *Adverse Reactions (6.1)*]. Two participants had anaphylaxis during the first infusion,

and two participants had anaphylaxis during the second infusion. Anaphylaxis can be life-threatening, and two of the anaphylactic reactions in the clinical trial were reported as life-threatening. Manifestations included pruritus, flushing, urticaria, erythema, angioedema, diaphoresis, dizziness, tinnitus, wheezing, dyspnea, chest discomfort, and tachycardia. In all 4 cases, PEMGARDA was permanently discontinued.

Prior to administering PEMGARDA, consider the potential benefit of COVID-19 prevention along with the risk of anaphylaxis [*Adverse Reactions (6.1)*, and *Clinical Studies (14)*].

Administer PEMGARDA only in settings in which healthcare providers have immediate access to medications to treat anaphylaxis and the ability to activate the emergency medical system (EMS), as necessary.

Clinically monitor individuals during the 60-minute infusion and for at least two hours after completion of the infusion. If signs or symptoms of an anaphylactic reaction occur, immediately discontinue administration, and initiate appropriate medications and/or supportive therapy. Discontinue PEMGARDA use permanently in individuals who experience signs or symptoms of anaphylaxis [*see Contraindications (4)*].

5.2 Hypersensitivity and Infusion-Related Reactions

Hypersensitivity and infusion-related reactions occurring during the infusion and up to 24 hours after the infusion have been observed with administration of PEMGARDA. Hypersensitivity or infusion-related reactions may be severe or life threatening. If signs or symptoms of a clinically significant hypersensitivity or infusion-related reaction occur, immediately discontinue administration, and initiate appropriate medications and/or supportive therapy. Signs and symptoms of hypersensitivity or infusion-related reactions may include:

Fever, difficulty breathing, reduced oxygen saturation, chills, fatigue, arrhythmia (e.g., atrial fibrillation, sinus tachycardia, bradycardia), chest pain or discomfort, weakness, altered mental status, nausea, headache, bronchospasm, hypotension, hypertension, angioedema, throat irritation, rash including urticaria, pruritus, myalgia, vasovagal reactions (e.g., pre-syncope, syncope), dizziness, and diaphoresis.

If a mild infusion-related reaction occurs, consider slowing or stopping the infusion and administer appropriate medications and/or supportive care. Clinically monitor individuals during infusion and for at least two hours after completion of the infusion for signs and symptoms of hypersensitivity.

Hypersensitivity reactions occurring more than 24 hours after the infusion have also been reported with the use of SARS-CoV-2 monoclonal antibodies under Emergency Use Authorization.

5.3 Risk of Cross-Hypersensitivity With COVID-19 Vaccines

PEMGARDA contains polysorbate 80, which is in some COVID-19 vaccines and is structurally similar to polyethylene glycol (PEG), an ingredient in other COVID-19 vaccines [*see Description (11)*]. For individuals with a history of a severe hypersensitivity reaction to a COVID-19 vaccine, consider consultation with an allergist-immunologist prior to PEMGARDA administration.

Administration of PEMGARDA should be done under the supervision of a healthcare provider with appropriate medical support to manage severe hypersensitivity reactions. If signs and symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur during administration of PEMGARDA, immediately discontinue administration and initiate appropriate medications and/or supportive care. Clinically monitor individuals after infusion and observe for at least two hours.

5.4 Risk for COVID-19 Due to SARS-CoV-2 Viral Variants Not Neutralized by PEMGARDA

Certain SARS-CoV-2 viral variants may emerge that are not neutralized by monoclonal antibodies such as PEMGARDA. PEMGARDA may not be effective at preventing COVID-19 caused by these SARS-CoV-2 viral variants.

Inform individuals of the increased risk, compared to other variants, for COVID-19 due to emergent SARS-CoV-2 viral variants not neutralized by PEMGARDA. If signs or symptoms of COVID-19 occur, advise individuals to test for COVID-19 and seek medical attention, including starting treatment for COVID-19 as appropriate. Symptoms of COVID-19 may include fever or chills, cough, shortness of breath or difficulty breathing, fatigue, muscle or body aches, headache, new loss of taste or smell, sore throat, congestion or runny nose, nausea or vomiting, or diarrhea³.

6 ADVERSE REACTIONS

6.1 Adverse Reactions from Clinical Studies

The following adverse reactions have been observed in the clinical study of PEMGARDA that supported the EUA [see *Clinical Studies (14)*]. The adverse reaction rates observed in the clinical study cannot be directly compared to rates in the clinical studies of other products and may not reflect the rates observed in clinical practice. Additional adverse reactions associated with PEMGARDA may become apparent with more widespread use.

The safety of PEMGARDA is based on exposure of 623 participants who received at least one dose of PEMGARDA 4500 mg IV in one of two cohorts in the ongoing CANOPY trial. Cohort A is a single-arm, open-label trial in adults who have moderate-to-severe immune compromise (n=306), while Cohort B is a randomized, placebo-controlled trial in which adults who do not have moderate-to-severe immune compromise received PEMGARDA (n=317) or placebo (n=162). In Cohort A, 296 participants received a second dose of PEMGARDA 4500 mg IV three months after the initial dose. In Cohort B, 450 participants received a second dose of PEMGARDA 4500 mg IV or placebo three months after the initial dose. Cumulative safety with the first two doses of PEMGARDA is assessed only in Cohort A because unblinded safety data in Cohort B were not available after Day 28.

Anaphylaxis

Anaphylaxis was observed in 4 of 623 (0.6%) participants in CANOPY, all in Cohort A.

³ For additional information on the symptoms of COVID-19, please see <https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html>.

Two participants had anaphylaxis during the first infusion, and two participants had anaphylaxis during the second infusion. All four reactions led to permanent discontinuation of PEMGARDA. Three participants had complete resolution, and one participant had acute resolution with sequelae related to a flare of an underlying condition.

Symptoms of anaphylaxis during the first dose included dyspnea, diaphoresis, erythema (face), chest discomfort, and tachycardia in one participant, and flushing, dizziness, tinnitus, and wheezing in one participant. Treatment for both included diphenhydramine.

Both instances of anaphylaxis with the second dose were reported as life-threatening. Symptoms during the second infusion and following discontinuation of the infusion in both participants included pruritus, urticaria, angioedema, dyspnea, and either erythema or flushing. One participant also experienced headache, dizziness, and chest pain; additionally, pruritus, erythema, and urticaria reoccurred in this participant within 24 hours of the initial onset of anaphylaxis. Both participants were treated with diphenhydramine and epinephrine, and one participant also received oral prednisone and metoprolol for an associated flare of an underlying condition.

Systemic Infusion-Related Reactions and Hypersensitivity Reactions

First Dose

Systemic infusion-related reactions and hypersensitivity reactions (i.e., adverse events assessed as causally related) were observed with the first dose in CANOPY in 4% (24/623) of participants who received PEMGARDA across cohorts, including:

7% (20/306) of participants who have moderate-to-severe immune compromise (Cohort A), and 1% (4/317) of participants who received PEMGARDA in Cohort B

Infusion-related reactions and hypersensitivity reactions were not observed in any participants who received placebo in Cohort B.

Systemic infusion-related or hypersensitivity reactions that started within 24 hours of the first dose of PEMGARDA treatment were reported as infusion-related reaction, infusion-related hypersensitivity, hypersensitivity, fatigue, headache, tachycardia, brain fog, dermatitis, diarrhea, myalgia, nausea, paresthesia, presyncope, and tremor. All reactions were mild or moderate, but two reactions were anaphylaxis [see *Box Warnings, and Warnings and Precautions (5.1, 5.2)*]. Infusion-related reactions or hypersensitivity reactions led to discontinuation of the first infusion in 1% (6/623) of participants who received PEMGARDA.

First and Second Dose, Cumulative – Moderately to Severely Immunocompromised Population

Cumulatively, infusion-related reactions and hypersensitivity reactions were observed in 9% (27/306) of participants who have moderate-to-severe immune compromise, who received PEMGARDA in Cohort A of CANOPY. The severity of the reactions was generally mild (17/27) or moderate (8/27), but two reactions were life-threatening [see *Boxed Warnings and Warnings and Precautions (5.1, 5.2)*]. Infusion-related reactions or hypersensitivity reactions led to discontinuation of the first or second infusion in 2% (7/306) of Cohort A participants.

Two percent (5/306) of participants who have moderate-to-severe immune compromise (Cohort A) had an infusion-related reaction or hypersensitivity reaction with both the first and second dose of PEMGARDA.

Local Infusion Site Reactions

First and Second Dose, Cumulative

Cumulatively, local infusion site reactions were observed in 2% (6/306) of participants who have moderate-to-severe immune compromise (Cohort A) with either the first or second dose. No local infusion site reactions were observed in Cohort B. Local reactions were reported as infusion site bruising, infusion site erythema, infusion site rash, and injection site reaction. All local reactions were mild, and none led to treatment discontinuation.

Cumulatively, infusion site infiltration, extravasation, or vein rupture was noted in 5% (14/306) of participants who have moderate-to-severe immune compromise (Cohort A) with either the first or second dose.

Other Common Adverse Events

First and Second Dose, Cumulative – Moderately to Severely Immunocompromised Population

In addition to systemic and local infusion-related/hypersensitivity reactions described above, the most common ($\geq 2\%$) treatment-emergent adverse events, irrespective of causality, observed with PEMGARDA in participants who have moderate-to-severe immune compromise (Cohort A) in CANOPY were upper respiratory tract infection (6%), viral infection (4%), influenza-like illness (3%), fatigue (3%), headache (2%), and nausea (2%).

6.4 Required Reporting for Serious Adverse Events and Medication Errors

The prescribing healthcare provider and/or the provider's designee is/are responsible for mandatory reporting of all serious adverse events* and medication errors potentially related to PEMGARDA within 7 calendar days from the healthcare provider's awareness of the event, using FDA Form 3500 (for information on how to access this form, see below). The FDA requires that such reports, using FDA Form 3500, include the following:

Patient demographics and baseline characteristics (e.g., patient identifier, age or date of birth, sex, weight, ethnicity, and race).

A statement "PEMGARDA use for the pre-exposure prophylaxis of COVID-19 under Emergency Use Authorization (EUA)" under the "**Describe Event, Problem, or Product Use/Medication Error**" heading.

Information about the serious adverse event or medication error (e.g., signs and symptoms, test/laboratory data, complications, timing of drug initiation in relation to the occurrence of the event, duration of the event, treatment required to mitigate the event, evidence of event improvement/disappearance after stopping or reducing the dosage, evidence of event reappearance after reintroduction, clinical outcomes).

Patient's preexisting medical conditions and use of concomitant products.

Information about the product (e.g., dosage, route of administration, NDC #).

Submit serious adverse event and medication error reports using FDA Form 3500 to FDA MedWatch using one of the following methods:

Complete and submit the report online: www.fda.gov/medwatch/report.htm.

Complete and submit a postage-paid FDA Form 3500 (<https://www.fda.gov/media/76299/download>) and return by:

- Mail to MedWatch, 5600 Fishers Lane, Rockville, MD 20852-9787, or
- Fax to 1-800-FDA (332)-0178, or

Call 1-800-FDA (332)-1088 to request a reporting form.

In addition, please provide a copy of all FDA MedWatch forms to:

Invivyd, Inc.

Email: pv@invivyd.com

Or call Invivyd, Inc. at 1-800-890-3385 to report serious adverse events.

The prescribing healthcare provider and/or the provider's designee is/are responsible for mandatory responses to requests from FDA for information about serious adverse events and medication errors following receipt of PEMGARDA.

*Serious adverse events are defined as:

Death

A life-threatening adverse event

Inpatient hospitalization or prolongation of existing hospitalization

A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions

A congenital anomaly/birth defect

Other important medical events, which may require a medical or surgical intervention to prevent death, a life-threatening event, hospitalization, disability, or congenital anomaly

7 DRUG INTERACTIONS

Drug-drug interaction studies have not been performed. PEMGARDA is not renally excreted or metabolized by cytochrome P450 enzymes; therefore, interactions with concomitant medications that are renally excreted or that are substrates, inducers, or inhibitors of cytochrome P450 enzymes are unlikely [see *Clinical Pharmacology* (12.3)].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary:

There are insufficient data to evaluate a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. PEMGARDA should only be used during pregnancy if the potential benefit outweighs the potential risk for the mother and the fetus.

Nonclinical reproductive toxicity studies have not been performed with pemivibart. In tissue cross-reactivity studies using human fetal tissues, no off-target binding was detected for

pemivibart. Human immunoglobulin G1 (IgG1) antibodies are known to cross the placental barrier; therefore, pemivibart has the potential to be transferred from the mother to the developing fetus. It is unknown whether the potential transfer of pemivibart provides any treatment benefit or risk to the developing fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the US general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

8.2 Lactation

Risk Summary:

There are no available data on the presence of PEMGARDA in human or animal milk, the effects on the breastfed infant, or the effects on milk production. Maternal IgG is known to be present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for PEMGARDA and any potential adverse effects on the breastfed infant from PEMGARDA.

Pediatric Use

PEMGARDA is not authorized for use in pediatrics less than 12 years of age or weighing less than 40 kg. The safety and effectiveness of PEMGARDA has not been established in pediatrics.

The recommended dosing regimen is expected to result in comparable serum exposures of pemivibart in adolescents 12 years of age and older and weighing at least 40 kg as observed in adults, since adults with similar body weight have been included in the CANOPY study [*see Adverse Reactions (6.1) and Clinical Studies (14)*].

8.5 Geriatric Use

Of the 623 participants who received PEMGARDA in the CANOPY trial, 156 (25%) were aged ≥ 65 years and 31 (5%) were aged ≥ 75 years. Based on population pharmacokinetic (PK) analyses, there was no clinically meaningful difference of age on the PK of pemivibart.

8.6 Renal Impairment

PEMGARDA is not eliminated intact in the urine, thus renal impairment is not expected to affect the exposure of pemivibart. Similarly, dialysis is not expected to impact the PK of pemivibart.

8.7 Hepatic Impairment

The effect of hepatic impairment on the PK of pemivibart is unknown.

10 OVERDOSAGE

Doses above 4500 mg PEMGARDA (the authorized dose of pemivibart) were not administered in clinical studies. There is no specific treatment for overdose with PEMGARDA.

11 DESCRIPTION

Pemivibart is a human IgG1 mAb produced by a Chinese Hamster Ovary cell line and has a molecular weight of 147.51 kDa.

PEMGARDA (pemivibart) injection is a sterile, preservative-free, clear to slightly opalescent, colorless to yellow solution for intravenous infusion after dilution. Each 4 mL of solution contains 500 mg of pemivibart, glycine (33.03 mg), L-arginine hydrochloride (63.2 mg), L-histidine (3.67 mg), L-histidine hydrochloride monohydrate (3.43 mg), L-methionine (5.97 mg), polysorbate 80 (1.2 mg), sterile water for injection (USP). The pH is 6.2.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Pemivibart is a SARS-CoV-2 antiviral drug [see *Microbiology (12.4)*].

12.2 Pharmacodynamics

Available data suggest a positive relationship between serum neutralizing antibody titers and COVID-19 pre-exposure-prophylactic efficacy using clinical data (completed prior to the emergence of Omicron and Omicron lineage VOCs) and drug concentration data of neutralizing human monoclonal antibodies against SARS-CoV-2.

Following single-dose administration of pemivibart 4500 mg IV, calculated geometric mean titer values (pemivibart concentration divided by the authentic virus neutralization assay EC₅₀ value against JN.1) [see *Microbiology (12.4)*] range from 3451 (on Day 90) to 22552 (end of infusion on Day 1). After the repeat dose of pemivibart 4500 mg IV every 3 months, it is anticipated that the range of titers at steady-state will be approximately 33% higher than those observed following the first dose administration.

12.3 Pharmacokinetics

A summary of PK parameters of pemivibart following administration of a single 4500 IV dose of pemivibart to adults based on population PK modeling is provided in [Table 1](#).

Table 1: Summary Statistics of Population PK Parameters of Pemivibart Following a Single 4500 mg Intravenous Dose in Adults

Parameter	Pemivibart
C _{max} (µg/mL)	1750 (38.2)
C _{Day 28} (µg/mL)	460 (40.7)
C _{Day 90}	175 (44.4)
AUC _{0-3 months}	36600 (40.4)
T _{1/2} (days)	44.8 (28.1-64.6)
Accumulation ratio	1.33
CL (L/d)	0.0909 (23.3)
V _{ss} (L)	5.54 (17.0)
Metabolism	Catabolic pathways; same manner as endogenous IgG

Parameter	Pemivibart
Excretion	Not likely to undergo renal excretion

AUC_{0-3 months}= area under the serum concentration-time curve from Day 0 to Month 3; CL=renal clearance; C_{max}=maximum concentration; PK=pharmacokinetic; T_{1/2}=half-life; V_{ss}=steady state volume of distribution.

Note: All values presented as geometric mean (% covariance), except for T_{1/2}, which is presented as median (min, max). Numerical values are post-hoc PK parameter estimates for subjects enrolled in Phase 3 CANOPY.

Specific Populations:

The PK of pemivibart was not substantially affected by age, sex, or race based on a population PK analysis to the pooled data from VYD222-1-001 and Phase 3 CANOPY. Body weight is not expected to have a clinically relevant effect on the PK of pemivibart in individuals with body weights ranging from 43 to 190 kg through 3 months postdose.

Patients with Immune Compromise

Population PK analysis showed immune compromise status had no clinically relevant effect on the PK of pemivibart.

Pediatric Patients

The PK of pemivibart in pediatric individuals has not been evaluated. The dosing regimen is expected to result in comparable plasma exposures of pemivibart in pediatric individuals 12 years of age or older who weigh at least 40 kg as observed in adult individuals [see *Use in Specific Populations (8.4)*].

Patients with Renal Impairment

Renal impairment is not expected to impact the PK of pemivibart since mAbs with molecular weight >69 kDa are known not to undergo renal elimination. Similarly, dialysis is not expected to impact the PK of pemivibart.

Patients with hepatic impairment

Pemivibart is not anticipated to be impacted by hepatic impairment. Pemivibart is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as other IgG mAbs and human endogenous IgG antibodies.

12.4 Microbiology

Mechanism of Action:

Pemivibart is a recombinant human monoclonal IgG1 λ antibody that targets the SARS-CoV-2 spike protein receptor binding domain (RBD), thereby inhibiting virus attachment to the human ACE2 receptor on host cells. Amino acid substitutions in the Fc region (M435L/N441A) of pemivibart extend serum half-life. Pemivibart binds the spike RBD proteins of ancestral SARS-CoV-2 B.1 (D614G) and Omicron variants BA.1, BA.2, and BA.4/5 with equilibrium dissociation constants (K_D) of 2.1 nM, 18 nM, 13.5 nM, and 15.9 nM, respectively, and blocks attachment of ancestral SARS-CoV-2 and BA.2.86 variant RBD proteins to the human ACE2 receptor with IC₅₀ values of 0.068 nM (10 ng/mL) and 23 nM (3370 ng/mL), respectively.

Antiviral Activity:

Pemivibart neutralized authentic SARS-CoV-2 isolates in Vero E6 or Vero E6-TMPRSS2 cells with EC₅₀ values of 0.165-0.230 nM (24.3-34 ng/mL) against B.1, and 0.075 nM (11 ng/mL)

against B.1.617.2 (Delta). For Omicron variants, EC₅₀ values were 0.096 nM (14.2 ng/mL) against BA.1, 0.039 nM (5.8 ng/mL) against BA.2, 0.175 nM (25.8 ng/mL) against BA.4.1, 0.80-4.48 nM (118-661.2 ng/mL) against XBB.1.16, 1.97-3.25 nM (290-479.9 ng/mL) against XBB.1.5, 9.8 nM (1,445 ng/mL) against EG.5.1, 3.59 nM (529.4 ng/mL) against HV.1, and 0.43 nM (63.6 ng/mL) against JN.1.

Pemivibart has not been directly evaluated for Fc-mediated effector functions or antibody-dependent enhancement (ADE) of infection. The parent antibody of pemivibart, which contains an identical Fc region and targets an overlapping epitope, exhibited antibody-dependent cellular phagocytosis (ADCP) and antibody-dependent complement deposition (ADCD), but failed to exhibit detectable ADE in cell culture.

Antiviral Resistance:

There is a potential risk of prophylaxis failure due to the emergence of a pemivibart-resistant SARS-CoV-2 variant. Prescribing healthcare providers should consider the prevalence of SARS-CoV-2 variants in their area, where data are available, when considering prophylactic treatment options.

Data are limited regarding the scope of spike substitutions in Omicron-lineage variants that may confer significantly reduced susceptibility to pemivibart. Escape variants were identified following serial passage of SARS-CoV-2 (Omicron XBB.1.5.6) in cell culture in the presence of pemivibart that contained a T500N spike substitution or a combination of Q489R, N501Y, and Y505H spike substitutions. Each of these substitutions is within 5 Å of the pemivibart binding interface.

Pemivibart neutralization susceptibility of recent and historic SARS-CoV-2 variants was evaluated using a pseudotyped, luciferase-expressing, lentivirus virus-like particle (VLP) assay. Pemivibart neutralized SARS-CoV-2 spike protein-pseudotyped VLPs representing B.1 and pre-Omicron variants with EC₅₀ values ranging from 0.022 to 0.083 nM (3.2 to 12.2 ng/mL), and Omicron-lineage variants with EC₅₀ values ranging from 0.198 to 14.3 nM (29.2 to 2,112 ng/mL) (Table 2).

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

Pango lineage	RBD substitutions relative to B.1 present in pseudotyped VLPs	Pemivibart	
		Mean EC ₅₀ values ng/mL (SD / range) ^a	Fold-change from B.1
B.1		8.4 (3)	1.0
B.1.1.7	N501Y	11.4	1.4
B.1.351	K417N, E484K, N501Y	9	1.1
P.1	K417T, E484K, N501Y	12.2	1.5
B.1.617.2	L452R, T478K	5.2 (4.2-6.2)	0.6
B.1.427	L452R	3.2	0.4
P.2	E484K	9.3	1.1
B.1.526	E484K	8.6	1.0
B.1.621	R346K, E484K, N501Y	9.5	1.1

Pango lineage	RBD substitutions relative to B.1 present in pseudotyped VLPs	Pemivibart	
		Mean EC ₅₀ values ng/mL (SD / range) ^a	Fold-change from B.1
BA.1	G339D, S371L, S373P, S375F, K417N, N440K, G446S, S477N, T478K, E484A, Q493R, G496S, Q498R, N501Y, Y505H	121.4	14.5
BA.2	G339D, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, S477N, T478K, E484A, Q493R, Q498R, N501Y, Y505H	44.6 (6.5)	5.3
BA.4/BA.5	G339D, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, L452R, S477N, T478K, E484A, F486V, Q498R, N501Y, Y505H	47.9 (29.7-66.2)	5.7
BA.4.6	G339D, R346T, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, L452R, S477N, T478K, E484A, F486V, Q498R, N501Y, Y505H	29.2	3.5
BF.7	G339D, R346T, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, L452R, S477N, T478K, E484A, F486V, Q498R, N501Y, Y505H	72.7	8.7
BQ.1	G339D, R346T, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, K444T, L452R, S477N, T478K, E484A, F486V, Q498R, N501Y, Y505H	164.6	19.6
BQ.1.1	G339D, R346T, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, K444T, L452R, N460K, S477N, T478K, E484A, F486V, Q498R, N501Y, Y505H	102.1	12.2
BA.2.75	G339H, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, G446S, N460K, S477N, T478K, E484A, Q498R, N501Y, Y505H	1,364.6	162.5
BN.1	G339H, R346T, K356T, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, G446S, N460K, S477N, T478K, E484A, F490S, Q498R, N501Y, Y505H	2,112	251.4
XBB	G339H, R346T, L368I, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, V445P, G446S, N460K, S477N, T478K, E484A, F486S, F490S, Q493R, Q498R, N501Y, Y505H	152.2	18.1
XBB.1	G339H, R346T, L368I, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, V445P, G446S, N460K, S477N, T478K, E484A, F486S, F490S, Q493R, Q498R, N501Y, Y505H	121.1	14.4
XBB.1.5	G339H, R346T, L368I, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, V445P, G446S, N460K, S477N, T478K, E484A, F486P, F490S, Q498R, N501Y, Y505H	104.3	12.4
XBB.1.16	G339H, R346T, L368I, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, V445P, G446S, N460K, S477N, T478R, E484A, F486P, F490S, Q498R, N501Y, Y505H	77.6 (18.1)	9.2
XBB.1.5.10	G339H, R346T, L368I, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, V445P, G446S, F456L, N460K, S477N, T478K, E484A, F486P, F490S, Q498R, N501Y, Y505H	108.1 (35.5)	12.9

Pango lineage	RBD substitutions relative to B.1 present in pseudotyped VLPs	Pemivibart	
		Mean EC ₅₀ values ng/mL (SD / range) ^a	Fold-change from B.1
XBB.1.5.1	G339H, R346T, L368I, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, V445P, G446S, N460K, S477N, T478K, E484A, F486P, F490S, Q498R, N501Y, Y505H	80 (8.9)	9.5
XBB.2.3	G339H, R346T, L368I, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, V445P, G446S, N460K, S477N, T478K, E484A, F486P, F490S, Q498R, N501Y, Y505H, P521S	87 (15.5)	10.4
EU.1.1	G339H, R346T, L368I, S371F, S373P, S375F, T376A, D405N, R408S, I410V, K417N, N440K, V445P, G446S, N460K, S477N, T478K, E484A, F486P, F490S, Q498R, N501Y, Y505H, P521S	52.1 (10.6)	6.2
FL.1.5.1	G339H, R346T, L368I, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, V445P, G446S, F456L, N460K, S477N, T478R, E484A, F486P, F490S, Q498R, N501Y, Y505H	102.1 (8.8)	12.2
HV.1	G339H, R346T, L368I, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, V445P, G446S, L452R, F456L, N460K, S477N, T478K, E484A, F486P, F490S, Q498R, N501Y, Y505H	41.2 (9.2)	4.9
HK.3	G339H, R346T, L368I, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, V445P, G446S, L455F, F456L, N460K, S477N, T478K, E484A, F486P, F490S, Q498R, N501Y, Y505H	72.3 (7.7)	8.6
JD.1.1	G339H, R346T, L368I, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, V445P, G446S, L455F, F456L, N460K, A475V, S477N, T478K, E484A, F486P, F490S, Q498R, N501Y, Y505H	101.9 (4.9)	12.3
BA.2.86	I332V, G339H, K356T, S371F, S373P, S375F, T376A, R403K, D405N, R408S, K417N, N440K, V445H, G446S, N450D, L452W, N460K, S477N, T478K, N481K, del483, E484K, F486P, Q498R, N501Y, Y505H	167.7 (4.4)	20.0
JN.1	I332V, G339H, K356T, S371F, S373P, S375F, T376A, R403K, D405N, R408S, K417N, N440K, V445H, G446S, N450D, L452W, L455S, N460K, S477N, T478K, N481K, del483, E484K, F486P, Q498R, N501Y, Y505H	74.6 (5.8)	8.9

EC₅₀=half-maximal inhibitory concentration; Pango=Phylogenetic Assignment of Named Global Outbreak; RBD=receptor binding domain; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; WT=wild-type.

- a. EC₅₀ values are reported as the mean along with range when data were obtained from 2 independent experiments or as mean and standard deviation when data were obtained from 3 or more independent experiments. 5,000 ng/mL was the upper concentration tested.

Evaluations are ongoing of the pemivibart neutralization susceptibility of variants that have been identified through global surveillance.

Cross-resistance:

Cross-resistance is not expected between pemivibart and currently approved/authorized COVID-19 therapies, including remdesivir, nirmatrelvir, or molnupiravir, since pemivibart has a distinct mechanism of action and targets a different viral protein than these drugs.

12.6 Immunogenicity

There are no immunogenicity data available for the currently authorized dosing regimen of PEMGARDA 4500 mg IV administered every 3 months.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity, mutagenicity, and reproductive toxicology studies have not been conducted with pemivibart.

13.2 Animal Toxicology and/or Pharmacology

In a toxicology study in rats, pemivibart had no adverse effects when administered intravenously. In tissue cross-reactivity studies with pemivibart using human adult and fetal tissues, no off-target binding was detected.

14 CLINICAL STUDIES

14.1 Overview of Immunobridging Approach

To support this EUA, an immunobridging approach was used to determine if PEMGARDA may be effective for pre-exposure prophylaxis of COVID-19. Immunobridging is based on the serum neutralization titer-efficacy relationships identified with other neutralizing human monoclonal antibodies against SARS-CoV-2. This includes adintrevimab, the parent mAb of pemivibart, and other mAbs that were previously authorized for EUA. To support immunobridging, serum neutralization titer was utilized to compare PEMGARDA to previous mAbs [see *Clinical Pharmacology (12.2)*].

14.2 Pre-exposure Prophylaxis of COVID-19 (VYD222-PREV-001 [CANOPY])

CANOPY [NCT06039449] is an ongoing clinical trial evaluating PEMGARDA for the pre-exposure prophylaxis of COVID-19 in adults ≥ 18 years of age in two cohorts.

Cohort A: single-arm, open-label trial in adults who have moderate-to-severe immune compromise.

Cohort B: placebo-controlled, randomized trial in adults who do not have moderate-to-severe immune compromise.

A total of 623 participants, 306 in Cohort A and 317 in Cohort B, received at least one dose of PEMGARDA 4500 mg in the trial. In Cohort A, 296 participants received a second dose of PEMGARDA 4500 mg at Month 3. In Cohort B, 162 participants received at least one dose of placebo, and a total of 450 participants received a second dose of either PEMGARDA 4500 mg

or placebo (blinded) at Month 3. The trial excluded participants with known or suspected SARS-CoV-2 infection within 120 days before randomization or a positive SARS-CoV-2 antigen test or RT-PCR at the time of screening. The primary data to support this EUA comes from Cohort A and is summarized below.

Participants in Cohort A were mostly female (61%), White (86%) or Black/African American (12%), and not Hispanic or Latino (94%). The median age was 59 years, with 31% aged 65 years or older. All participants had underlying moderate-to-severe immune compromise, including:

65% taking high-dose corticosteroids/other immunosuppressive medications

13% acute leukemia, chronic lymphocytic leukemia, non-Hodgkin, lymphoma, or multiple myeloma (regardless of treatment)

12% primary immunodeficiency

11% solid organ transplant recipient

9% advanced HIV infection

7% actively treated for solid tumor or hematologic malignancies

Results:

The primary efficacy objective of Cohort A was to evaluate protection against symptomatic COVID-19 based on calculated titers against SARS-CoV-2 following PEMGARDA administration by immunobridging to historical data from the EVADE study, which provided evidence of clinical efficacy of adintrevimab, the parent mAb of pemivibart. The primary immunobridging endpoint for Cohort A compared the ratio of the geometric mean titers between pemivibart against the relevant variant (JN.1) at Day 28 to the reference titer at Day 28. The reference titer at Day 28 was the extrapolated titer from the Day 90 adintrevimab titer [which was calculated based on Day 90 concentration of adintrevimab divided by the EC₅₀ value against the B.1.617.2 (Delta) variant determined in an authentic virus neutralization assay] using the half-life of pemivibart. Immunobridging would be 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.

The primary immunobridging results are as follows: 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). However, there are limitations of this analysis, including differences in the methodologies of the assays used to determine the EC₅₀ values for pemivibart and adintrevimab against the respective variants. In a sensitivity analysis using an identical cell-based assay (a pseudotyped VLP neutralization assay), for the calculated titer comparison between pemivibart against JN.1 (based on an EC₅₀ value of 74.6 ng/mL) and adintrevimab against Delta (based on an EC₅₀ value of 3.5 ng/mL), the geometric mean ratio was 0.35 (90% CI: 0.34-0.36). This sensitivity analysis highlights the impact of even modest differences in EC₅₀ values on the results of the primary endpoint.

As a supplementary analysis, the titer values of pemivibart against JN.1 [see *Clinical Pharmacology (12.2)*] were compared, using published literature, to the titers associated with efficacy of three other SARS-CoV-2 targeting mAbs in prior clinical trials. The range of titers

achieved with pemivibart for 3 months following administration of 4500 mg IV were consistent with the titer levels associated with clinical efficacy in prior clinical trials evaluating certain monoclonal antibodies for the prevention of COVID-19.

14.3 Overall Benefit-Risk Assessment and Limitations of Data Supporting the Benefits of the Product

Based on the totality of scientific evidence available, it is reasonable to believe that PEMGARDA may be effective for pre-exposure prophylaxis of COVID-19 in the authorized population. 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.

There are limitations of the data supporting the benefits of PEMGARDA. Evidence of clinical efficacy for other neutralizing human monoclonal antibodies against SARS-CoV-2 was based on different populations and SARS-CoV-2 variants that are no longer circulating. Additionally, the variability associated with cell-based EC₅₀ value determinations, along with limitations related to PK data and efficacy estimates for the mAbs in prior clinical trials, impact the ability to precisely estimate protective titer ranges.

16 HOW SUPPLIED/STORAGE AND HANDLING

PEMGARDA injection is a sterile, preservative-free, clear to slightly opalescent, colorless to yellow solution supplied in a single-dose 6R vial intended for intravenous infusion only.

Antibody	Concentration	Package Size	NDC
Pemivibart	500 mg/4 mL vial (125 mg/mL)	Nine vials per carton	81960-031-03

Refrigerate unopened vials at 2 °C to 8 °C (36 °F to 46 °F) in the original carton to protect from light.

Do not freeze or shake. Do not use if seal is broken or missing.

17 PATIENT COUNSELING INFORMATION

As a prescribing healthcare practitioner, you must communicate to the patient, parent, and caregiver information consistent with the “FACT SHEET FOR PATIENTS, PARENTS OR CAREGIVERS” and provide them with a copy of this Fact Sheet prior to administration of PEMGARDA.

Anaphylaxis

Inform individuals that anaphylaxis has been observed with PEMGARDA. Advise individuals that they will be monitored during and for at least two hours after completion of the infusion. In

those who experience signs or symptoms of anaphylaxis, PEMGARDA use will be discontinued permanently [see *Boxed Warnings, and Warnings and Precautions (5.1)*].

Hypersensitivity and Infusion-Related Reactions

Inform individuals that hypersensitivity and infusion-related reactions have occurred during the infusion and up to 24 hours after the infusion with PEMGARDA. These hypersensitivity or infusion-related reactions may be severe or life threatening. Inform individuals that they will be monitored during and for at least two hours after completion of the infusion for signs and symptoms of hypersensitivity [see *Warnings and Precautions (5.2)*].

Dosing

Inform individuals that they may need to receive additional doses of PEMGARDA every 3 months if ongoing protection is needed [see *Dosage and Administration (2) and Clinical Pharmacology (12)*].

Risk for COVID-19 Due to SARS-CoV-2 Viral Variants Not Neutralized by PEMGARDA

Certain SARS-CoV-2 viral variants may emerge that are not neutralized by monoclonal antibodies such as PEMGARDA. PEMGARDA may not be effective at preventing COVID-19 caused by these SARS-CoV-2 viral variants. Inform individuals of the increased risk, compared to other variants, for COVID-19 due to SARS-CoV-2 viral variants not neutralized by PEMGARDA. If signs or symptoms of COVID-19 occur, advise individuals to test for COVID-19 and seek medical attention, including starting treatment for COVID-19 as appropriate [see *Warnings and Precautions (5.4)*].

18 MANUFACTURER INFORMATION

For additional information, visit: www.Pemgarda.com or scan the code below:



Manufactured and distributed by:
Invivyd, Inc.
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Waltham, MA 02451

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