Emergency Use Authorization (EUA) for EVUSHELD

Center for Drug Evaluation and Research Review Memorandum

Identifying Information

Application Type (EUA or Pre-EUA)	EUA
EUA Application Number(s)	000104
Date of Memorandum	June 29, 2022
Sponsor (entity requesting EUA or pre-EUA consideration), point of contact, address, phone number, fax number, email address	AstraZeneca Pharmaceuticals LP Stacey Cromer Berman, PhD Senior Regulatory Affairs, Director and Team Lead One MedImmune Way Gaithersburg, MD 20878 Phone: (b) (6) Email: (b) (6)
Original Authorization	December 8, 2021
OND Division / Office	Division of Antivirals (DAV)/Office of Infectious Diseases (OID)
Proprietary Name	EVUSHELD
Established Name/Other names used during development	AZD7442 (tixagevimab, AZD8895) injection; (cilgavimab, AZD1061) injection, co-packaged for intramuscular use
Dosage Forms/Strengths	Tixagevimab 300 mg/3 mL (100 mg/mL) IM Cilgavimab 300 mg/3 mL (100 mg/mL) IM
Therapeutic Class	SARS-CoV-2 spike protein-directed attachment inhibitor
Intended Use or Need for EUA	Pre-exposure prophylaxis of COVID-19

Intended Population(s)	Adults and pediatric individuals (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** may not mount an adequate immune response to COVID-19 vaccination **or**
	  • For whom vaccination with any available COVID-19 vaccine, according to the approved or authorized schedule, is not recommended due to a history of severe adverse reaction to a COVID-19 vaccine(s) and/or COVID-19 vaccine component(s).

Abbreviations: DAV, Division of Antivirals; EUA, emergency use authorization; OID, Office of Infectious Diseases; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Rationale for Revisions to EUA Fact Sheets

The EVUSHELD EUA Fact Sheet for Healthcare Providers, and Patient Fact Sheet are being revised at this time, and a Dear Healthcare Provider Letter communicating these changes is being issued, to provide recommendations on repeat EVUSHELD dosing.

Background on Regulatory History

On December 8, 2021, EVUSHELD (tixagevimab co-packaged with cilgavimab) received an emergency use authorization (EUA) for the pre-exposure prophylaxis (PrEP) of coronavirus disease 2019 (COVID-19) in certain adults and pediatric individuals. The authorized dose was EVUSHELD 300 mg (150 mg of tixagevimab and 150 mg of cilgavimab) administered as consecutive intramuscular (IM) injections, which was the dose evaluated in the Phase 3 trial PROVENT in which EVUSHELD used as PrEP demonstrated a relative risk reduction of SARS-CoV-2 RT-PCR-positive symptomatic illness of 77% compared to placebo. During the primary analysis period of PROVENT when these efficacy analyses took place, predominant SARS-CoV-2 variants were Alpha (B.1.1.7), Beta (B.1.351), Delta (B.1.617.2), and Epsilon (B.1.429). Although no safety or efficacy data with repeat dosing were available at the time of the authorization, the totality of the scientific evidence at that time suggested that the EVUSHELD 300 mg IM (150 mg of tixagevimab and 150 mg of cilgavimab) dose may be effective for PrEP for 6 months post-administration and supported a dosing interval of every 6 months.

At the time of the original authorization, the Omicron variant (B.1.1.529 [BA.1]) had just emerged and neutralization activity of EVUSHELD against Omicron BA.1 was unknown. In the subsequent weeks, in vitro neutralization assays demonstrated reduced activity of EVUSHELD against Omicron subvariants BA.1 and BA.1.1 (BA.1+R346K) compared to wild type reference strain. In addition, by the end of December 2021, the Omicron BA.1 subvariant was increasing in prevalence in the United States (U.S.). Consequently, in a revised authorization on February 24, 2022, using pharmacokinetic (PK) modeling assessments to predict an adequate dose for PrEP, the originally authorized EVUSHELD IM dose of 300 mg (150 mg tixagevimab and 150 mg cilgavimab) was increased to 600 mg EVUSHELD (300 mg tixagevimab and 300 mg cilgavimab) for PrEP to increase the likelihood of attainment of a minimum protective concentration based on in vitro neutralization activities of EVUSHELD against the circulating Omicron subvariants. In addition, the originally recommended timing (6 months) for repeat dosing of the original EVUSHELD 300 mg (150 mg tixagevimab and 150 mg cilgavimab) dose was removed because PK assessments no longer supported a 6-month duration of protection against the Omicron subvariants circulating at that time, despite the increased EVUSHELD 600 mg (300 mg tixagevimab and 300 mg cilgavimab) dose and because it was unclear which SARS-CoV-2 variant or Omicron subvariant would become dominant in the U.S. over those next few months (see CDER memorandum of revised authorization on 02/24/2022).

Assessments to Support Current EVUSHELD EUA Fact Sheet Revisions

Repeat Dosing

EVUSHELD Activity against Current Circulating SARS-COV-2 Variants

As of June 18, 2022, the dominant SARS-CoV-2 variants circulating in the U.S. are the Omicron subvariants BA.2.12.1 (56%), BA.5 (24%), BA.4 (11%), and BA.2 (9%)[1]. Increasing proportions of BA.5 and BA.4 over time have been observed. However, at this time, it remains unknown whether BA.5 and BA.4 will outcompete BA.2.12.1 as the major circulating SARS-CoV-2 subvariants. We note that Omicron subvariants BA.1 and BA.1.1 are no longer circulating in the U.S. at detectable levels.

EVUSHELD susceptibility data against authentic virus or virus-like particles (VLPs) pseudotyped with the spike proteins of currently circulating Omicron subvariants are available (Table 1); susceptibility data for BA.1 and BA.1.1 are provided for comparison when available from the same source. EVUSHELD neutralized authentic Omicron BA.2 with EC_{50} values ranging from 14.5 to 52 ng/mL, corresponding to 4.2- to 8.8-fold reductions in susceptibility compared to pre-Omicron reference SARS-CoV-2. No susceptibility data for authentic BA.2.12.1, BA.4, or BA.5 subvariants are available.

[1]Centers for Disease Control and Prevention. COVID Data Tracker. Atlanta, GA: US Department of Health and Human Services, CDC; accessed 2022, June 24. https://covid.cdc.gov/covid-data-tracker

EVUSHELD neutralized VLPs pseudotyped with the spike proteins of Omicron subvariants BA.2, BA.2.12.1, and BA.4/BA.5 with EC_{50} values of 3.6 to 4,608 ng/mL, 10.7 to 135 ng/mL, and 40 to 609 ng/mL, respectively, corresponding to 1.6- to 1900-fold, 5- to 33-fold, and 19- to 149-fold reductions relative to reference VLPs, respectively.

Notably, the VLP susceptibility data reported by Yamasoba et al., 2022 and Zhou H. et al., 2022 do not appear to be consistent with data reported by other labs, presumably due to methodological differences, and were not included in the pharmacokinetic modeling described below.

Table 1. EVUSHELD susceptibility data against previous and current Omicron subvariants

			EC_{50} (ng/mL) [Fold-Change from Reference][3]				
Data Source	**Target[1]**	**mAb[2]**	**BA.1**	**BA.1.1**	**BA.2**	**BA.2.12.1**	**BA.4/BA.5**
Bruel et al., 2022	Virus	EVU	715 [275]		23 [8.8]		
Case et al., 2022	Virus	EVU	167 [26]	1147 [176]	35.4 [5.4]		
Nutalai et al., 2022	Virus	EVU	273 [30]	3816 [424]	52 [6]		
Takashita et al., 2022	Virus	pmAbs	256 [75]	1375 [402]	14.48 [4.2]		
AZ (Monogram/FDA)	VLP	EVU	171 [132]	466 [424]	9.8 [3.2]	10.7 [5]	69.4 [33]
Tuekprakhon et al., 2022	VLP	EVU	232 [232]	806 [806]	8 [8]		65 [65]
Yamasoba et al., 2022	VLP	EVU			33 [8]	135 [33]	609 [149]
Zhou H. et al., 2022	VLP	EVU	862 [360]		4608 [1900]		
Cao et al., 2022	VLP	pmAbs	491 [230]	8090 [3900]	8.2 [3.9]	18 [8.6]	40 [19]
Zhou T. et al., 2022	VLP	pmAbs	51 [23]		3.6 [1.6]		

[1] Neutralization assay conducted using authentic virus (Virus) or virus-like particles pseudotyped with the S protein of the indicated Omicron subvariant (VLP)
[2] Monoclonal antibodies (mAb) used in the assay. EVUSHELD (EVU; tixagevimab and cilgavimab) or its parental monoclonal antibodies (pmAbs), COV2-2196 and COV2-2130.
[3] Reference virus/VLP were pre-Omicron variants suscept ble to both tixagevimab and cilgavimab

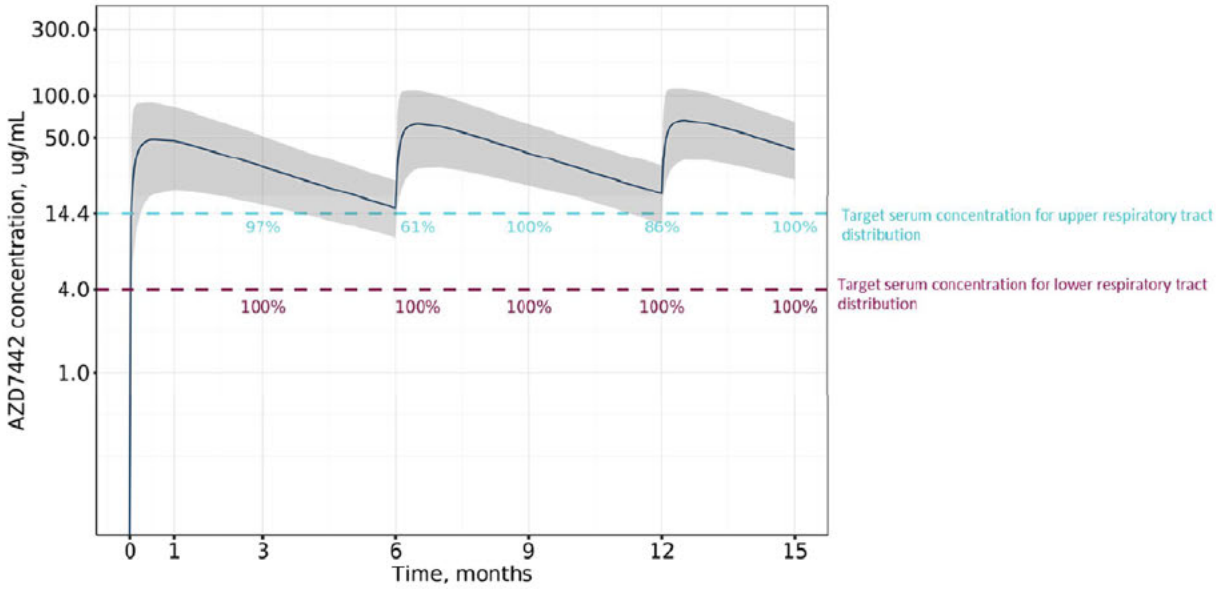
Pharmacokinetic (PK) Modeling to Predict an Adequate Dose for PrEP

In vitro neutralization activity of EVUSHELD against Omicron subvariant BA.4/BA.5 is lower than original SARS-CoV-2 variants, as well as against Omicron subvariants BA.2 and BA.2.12.1 (the other circulating subvariants currently detected in U.S.); therefore, PK modeling-based assessments against only the Omicron subvariants BA.4/BA.5 are shown because doses adequate for BA.4/BA.5 will also be adequate for the other currently circulating variants.

Figure 1 shows the predicted serum EVUSHELD concentration over a 15-month period for the proposed repeat dosing regimen against the BA.4 and BA.5 subvariants. Using a target-site penetration ratio of 1.8% (human nasal lining fluid to serum ratio of EVUSHELD concentrations, D8850C00001 trial), and a minimum protective EVUSHELD concentration against BA.4 and BA.5 of 260 ng/mL (in vitro EC_{80} assuming a hill slope of 1 and EC_{50} of 65 ng/mL, see **Table 1**), a target-site adjusted serum minimum protective EVUSHELD concentration for the upper respiratory track can be

estimated (blue dotted line). Following 600 mg EVUSHELD (300 mg tixagevimab and 300 mg cilgavimab) administered IM every 6 months, the probability of target attainment (PTA) or percent of individuals at or above this threshold at 3, 6, 12 months is projected to be 97%, 61%, and 86% respectively. Moreover, using less conservative modeling assumptions with a target-site penetration ratio of 6.5% (bronchoalveolar lung epithelial lining fluid or lung interstitial fluid, literature assumption, See CDER memorandum of revised authorization on 02/24/2022), and a minimum protective EVUSHELD concentration against BA.4 and BA.5 of 260 ng/mL (in vitro EC_{80} assuming a hill slope of 1 and EC_{50} of 65 ng/mL, see **Table 1**), a target-site adjusted serum minimum protective EVUSHELD concentration for the lower respiratory track can be estimated (red dotted line). Following 600 mg EVUSHELD (300 mg tixagevimab and 300 mg cilgavimab) administered IM every 6 months, the percent of individuals at or above this threshold is projected to be 100% at all time points.

Figure 1: Predicted Serum EVUSHELD Concentration over Time and Predicted % of Individuals That Will Have AZD7442 Concentrations ≥ a Target-Site Adjusted Minimum Protective Concentration (PTA) Using the In Vitro EC_{80} for AZD7442 Against SARS-CoV-2 Omicron Subvariants BA.4 and BA.5 and either 1.8% or 6.5% target-site drug penetration ratios for the 600 mg Initial Dose and 600 mg IM Maintenance Dose Every 6 Months for BA.4 and BA.5 Subvariants



Note: For 6-month repeat EVUSHELD 600 mg (300 mg tixagevimab and 300 mg cilgavimab) dosing, PTA results were not significantly different when considering the higher EC_{50} value of 69 ng/mL (Table 1, PTA data not shown).

Source: Response to Information Request Dated 01NOV2021, Figure 1 (pg.5), EUA 000104 SN76

Model predictions at 6 months are sensitive to underlying assumptions and a range of model predictions can be observed. Changing target-site adjusted penetration from 1.8% to 2% or 2.5% (within the 90% confidence interval of the geometric mean), but keeping all other assumptions and inputs (e.g., dosing regimen) unchanged, results in a PTA of 71% or 90%, respectively. Moreover, changing the in vitro EC_{50} used to define

the minimum effective EVUSHELD concentration to 40 ng/mL (minimum value in **Table 1**), but keeping all other assumptions and inputs unchanged, results in a PTA of 96%. Notably, changing the in vitro EC_{50} used to define the minimum effective EVUSHELD concentration to 69 ng/mL (maximum value in **Table 1** after excluding outlier), but keeping all other assumptions and inputs unchanged, did not significantly change the PTA from that reported in **Figure 1**.

The originally authorized EVUSHELD IM dose [300 mg (150 mg tixagevimab and 150 mg cilgavimab] was also considered since in vitro neutralization activity of EVUSHELD against Omicron subvariant BA.4/BA.5 is reduced to a smaller degree than against Omicron subvariant BA.1 or BA1.1 compared to SARS-CoV-2 variants present during the PROVENT trial. Following a single EVUSHELD 300 mg IM dose, PTA is approximately 50% at 3 months and <1% at 6-months- assuming 1.8% target-site penetration and a minimum effective EVUSHELD concentration against BA.4 and BA.5 of 260 ng/mL (in vitro EC_{80} assuming a hill slope of 1 and EC_{50} of 65 ng/mL). Thus, less than desired in vivo drug activity is projected following administration of the originally authorized dose of EVUSHELD 300 mg (150 mg tixagevimab and 150 mg cilgavimab) IM considering current circulating and potentially future dominant SARS-CoV-2 variants. This assessment using the originally authorized EVUSHELD 300 mg dose supports continuing with the higher EVUSHELD 600 mg dose.

We acknowledge that this approach, using a lower target site penetration ratio (i.e., 1.8%), was not supportive for BA.1 dosing given available data, thus we made the assessment using published lung (target-site) penetration ratios (i.e., 6.5% and 12%), focusing on achieving adequate lower respiratory tract concentrations (See CDER memorandum of revised authorization on 02/24/2022). However, this approach used for BA.1 should not be viewed as an optimal approach for all situations, particularly for the PrEP authorized use in immunocompromised patients. When feasible and supported by safety data, it is prudent to select a dosing regimen that is expected to provide therapeutic concentrations supported by more conservative assumptions. Of note, a 1.8% target-site penetration ratio (in combination with EC_{80} values) appears to reasonably explain the observed clinical data from the PROVENT trial (i.e., maintaining efficacy up to 6 months but not beyond after 6 months; see 'Other Clinical Data Supporting Repeat Dosing' section). However, it should be acknowledged that there are still uncertainties as to whether 1.8% in combination with EC_{80} is the best predictor for efficacy; the follow up efficacy data are limited in terms of number of subjects, impact of vaccination, and variant /susceptibility data for individual patients infected.

No clinical PK-PD relationships or thresholds of protection have been established to date for EVUSHELD or other mAbs targeting SARS-CoV-2. The predictive accuracy of this translational PK-PD modeling approach is not established. Limitations of the above evidence include but are not limited to: (i) uncertainty in the in vivo validity of using in vitro EC_{80} or EC_{90} values from a microneutralization assay, for which results are likely dependent on specific conditions and platform, as the PD metric associated with clinical protection, (ii) uncertainty regarding the relevant respiratory tract site(s) of drug action

(e.g., nasal or bronchoalveolar epithelial lining fluid, interstitial compartment), (iii) uncertainty regarding the specific and accurate measurement of drug(s) at these principal sites of drug action.

In summary, PK modeling assessments of the available data to date predict that 6-month repeat EVUSHELD 600 mg (300 mg of tixagevimab and 300 mg of cilgavimab) IM dosing may be effective in providing long-term PrEP from symptomatic SARS-CoV-2 infection in the authorized patient population.

Safety Data Supporting Repeat Dosing

Currently, the highest single dose that can be supported by clinical data is 600 mg EVUSHELD (300 mg of tixagevimab and 300 mg of cilgavimab) (See CDER memorandum of revised authorization on 02/24/2022).

No safety or immunogenicity data are available with the proposed recommended 6-month repeat 600 mg IM EVUSHELD (300 mg of tixagevimab and 300 mg of cilgavimab) dosing regimen. However, based on modeling predictions, the exposures expected with 600 mg IM EVUSHELD (300 mg of tixagevimab and 300 mg of cilgavimab) administered every 6 months would be similar to the exposures in the six months following a single 600 mg EVUSHELD (300 mg of tixagevimab and 300 mg of cilgavimab) dose administered IM or administered intravenously, for which supportive safety data are available from the clinical trials TACKLE and ACTIV-3, respectively. In addition, preliminary data are available with repeat dosing of 300 mg IM EVUSHELD (150 mg of tixagevimab and 150 mg of cilgavimab) administered 10 – 14 months after an initial 300 mg IM EVUSHELD (150 mg of tixagevimab and 150 mg of cilgavimab) dose, as described below. The Sponsor is conducting clinical trials to evaluate safety, PK and immunogenicity with various repeat dosing strategies including repeat doses of 600 mg IM every 6 months.

Preliminary interim safety, PK, and immunogenicity data are available with repeat 300 mg IM EVUSHELD (150 mg of tixagevimab and 150 mg of cilgavimab) dosing administered to subjects from PROVENT 10 - 14 months after their initial 300 mg IM EVUSHELD (150 mg of tixagevimab and 150 mg of cilgavimab) dose from the PROVENT repeat-dose sub-study. Safety data are available from 305 subjects with a median (min, max) follow-up duration of 8 days (1, 33 days) between the repeat dose and the last safety assessment. Overall, 44 subjects (14%) reported any adverse events. The only adverse events reported by more than 2 subjects were headache (n=8), asymptomatic COVID-19 (n=7), fatigue (n=7), oropharyngeal pain (n=5), cough (n=4), and COVID-19 (n=4); notably, for the interim analysis, dosing took place during the Omicron BA.1/BA.1.1 wave, during which the 300 mg dose would not be anticipated to be effective due to decreased neutralization activity of EVUSHELD against these subvariants (see the rationale for the increased dose in the background section above). One subject reported a serious adverse event (moderate migraine headache 2 days after receiving EVUSHELD, for which she was evaluated with a CT scan of the head

that showed no acute changes and recovered after receiving codeine). Two subjects reported injection site pain. Although these data are quite limited, there were no apparent safety signals with a repeat 300 mg EVUSHELD dose 10 – 14 months after the initial dose.

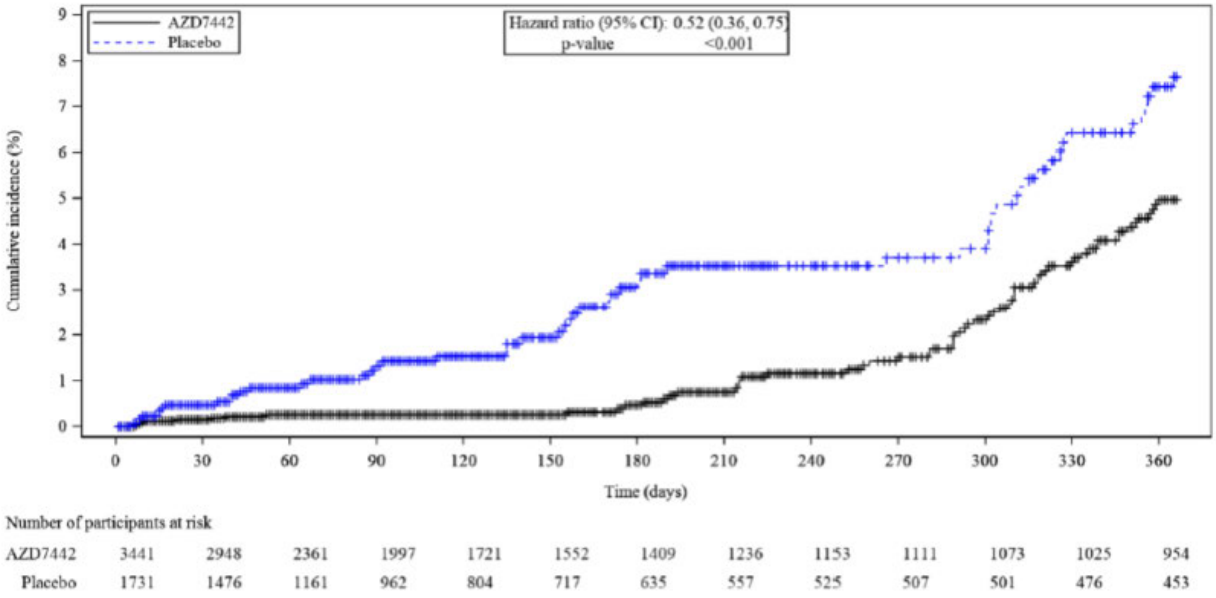
With respect to anti-drug antibody (ADA) effects on serum EVUSHELD drug concentrations, treatment-emergent anti-tixagevimab, anti-cilgavimab and anti-EVUSHELD antibodies (TE-ADA) were detected in 3% (101/3152), 4% (113/3068) and 5% (156/3158) ADA-evaluable subjects, respectively, in the PROVENT parent study following a single IM EVUSHELD (150 mg of tixagevimab and 150 mg of cilgavimab) dose. The percent difference in drug concentration between treatment-emergent positive ADA (TE-ADA+) subjects and negative ADA (ADA-) subjects was 0.0% (Day 8), -12% (Day 29), and -26% (Day 183). This difference in serum concentrations of EVUSHELD increased over time between subjects with TE-ADA+ compared to ADA- subjects. However, given the between subject variability of the PK data in ADA- subjects (%CV of the geometric mean serum AZD7442 concentrations ranged from 63.059% to 90.809%), differences are not statistically significant, and the clinical significance of this observation is unknown.

Treatment-emergent anti-tixagevimab, anti-cilgavimab and anti-EVUSHELD antibodies (TE-ADA) were detected in 0% (0/49), 10% (5/49) and 10% (5/49), of ADA-evaluable subjects, respectively, through sub-study Day 29, in the PROVENT repeat dose sub-study following a subsequent single IM dose of EVUSHELD (150 mg of tixagevimab and 150 mg cilgavimab) administered 10 to 14 months after the initial dose in the PROVENT parent study. The percent difference in drug concentration between TE-ADA+ subjects and ADA- subjects after the subsequent second EVUSHELD dose was -14%.

Other Clinical Data Supporting Repeat Dosing

Longer term PROVENT data with an April 13, 2022, data cut-off indicated that a single 300 mg IM EVUSHELD dose (150 mg tixagevimab and 150 mg cilgavimab) provided no protective efficacy after 6 months. From Day 184 to Day 366, in the full pre-exposure analysis set in which subjects were censored for either COVID-19 vaccination or unblinding, 49/3441 (1.4%) EVUSHELD recipients versus 22/1731 (1.3%) placebo recipients had their first SARS-CoV-2 RT-PCR-positive symptomatic illness (see **Figure 2** below for a Kaplan-Meier Curve provided by the Sponsor). From Day 184 to Day 365, in the full pre-exposure analysis in which subjects were included regardless of unblinding or receipt of a COVID-19 vaccination, 260/3441 (7.6%) EVUSHELD recipients versus 118/1731 (6.8%) placebo recipients had their first SARS-CoV-2 RT-PCR-positive symptomatic illness. Most of the days between Day 184 to 365 were in time periods when Delta and other pre-Omicron variants were dominant; PROVENT enrolled subjects between November 21, 2020, and March 29, 2021, and 68% of subjects (3508/5172) were at least 9 months past dosing by December 2021 when Omicron emerged in the U.S.

Figure 2: Time to First SARS-CoV-2 RT-PCR-positive Symptomatic Illness Occurring Post Dose of Investigational Product by Day 366 in the Full Pre-Exposure Analysis Set (subjects were censored at the time of unblinding or COVID-19 vaccination) in PROVENT (April 13, 2022, Data Cut-off)



This lack of protection beyond 6 months, even in the setting of variants against which EVUSHELD does not have reduced neutralization activity compared to the reference strain, supports a decision that repeat dosing with a dose higher than 300 mg or with a dosing interval less than 6 months is needed to offer long-term protection while the Omicron subvariants are circulating.

Overall Assessment

The totality of data support changing the EVUSHELD dosing regimen to include a recommendation for 6-month repeat dosing of 600 mg IM EVUSHELD (300 mg tixagevimab and 300 mg cilgavimab). Pharmacokinetic and pharmacodynamic modeling using the EVUSHELD neutralization data against the Omicron subvariants BA.4 and BA.5 suggest that the single EVUSHELD 600 mg (300 mg tixagevimab and 300 mg cilgavimab) IM dose currently authorized may not be sufficient to provide protection beyond 6-months against currently circulating SARS-CoV-2 Omicron subvariants; however, the modeling suggests in vivo activity against these subvariants may be retained if 6-month repeat dosing of EVUSHELD 600 mg IM (300 mg tixagevimab and 300 mg cilgavimab) is initiated. Supporting the PK conclusions are long-term clinical data from PROVENT that showed the efficacy of EVUSHELD 300 mg IM (150 mg tixagevimab and 150 mg cilgavimab) as pre-exposure prophylaxis did not extend beyond 6 months. Finally, the safety data with redosing, while limited, do not raise safety concerns. In summary, the known and potential benefits of the product with the proposed recommended 6-month repeat 600 mg IM EVUSHELD (300 mg of tixagevimab and 300 mg of cilgavimab) dosing regimen are considered to outweigh the known and potential risks of the product with repeat dosing, at this time and may be

effective in providing long-term PrEP from symptomatic SARS-CoV-2 infection in the authorized patient population.

Summary of Fact Sheet Revisions:

Section 2.1 (Dosage for Emergency Use of EVUSHELD) of the Fact Sheet for Healthcare Providers was revised to add the repeat dosing recommendations.

Section 12.3 (Pharmacokinetics) of the Fact Sheet for Healthcare Providers was updated to:

- Add pharmacokinetic data from the PROVENT repeat dose sub-study: "*In the PROVENT repeat dose sub-study, following a second IM dose of EVUSHELD (150 mg of tixagevimab and 150 mg of cilgavimab) administered 10 to 14 months after the initial IM dose of EVUSHELD (150 mg of tixagevimab and 150 mg of cilgavimab) (N= 53), the geometric mean serum concentration was 26.4 µg/mL on post-administration Day 29. This serum concentration was similar to the geometric mean drug concentration on post-administration Day 29 (23.3 µg/mL) following the initial IM EVUSHELD dose (150 mg of tixagevimab and 150 mg of cilgavimab) in the PROVENT parent study.*"
- Align the language in the paragraph on pharmacokinetic and pharmacodynamic modeling to describe the current dosing recommendations for the currently circulating SARS-CoV-2 variants.

Section 12.4 (Microbiology) of the Fact Sheet for Healthcare Providers was updated to add neutralization data of cilgavimab, tixagevimab, and tixagevimab and cilgavimab in combination against more recent Omicron subvariants including BA.2.12.1, BA.3, and BA.4/BA.5.

Section 12.6 (Immunogenicity) of the Fact Sheet for Healthcare Providers was added to provide available data on the development of anti-EVUSHELD antibodies (ADA) in the parent PROVENT study and the PROVENT repeat dose sub-study, as well the impact of ADA on the serum concentrations of EVUSHELD.

In addition, edits were made to the patient Fact Sheet to be consistent with these changes. A Dear Health Care Provider Letter communicating the repeat dosing recommendations is also being issued.

Regulatory Conclusion and Associated Actions:

The Division of Antivirals and Office of Infectious Diseases recommends revisions to EUA 104 as outlined above in order to best protect public health and to provide health care providers with the most current recommendations about EVUSHELD.

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/

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