Philippine COVID-19 Living Clinical Practice Guidelines
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In cooperation with the Philippine Society for Microbiology and Infectious Diseases
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EVIDENCE SUMMARY

RESEARCH QUESTION: **Among close contacts of COVID-19 patients, should AZD7422 (Tixagevimab-Cilgavimab) be used as prophylaxis for COVID-19 infection?**

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RECOMMENDATIONS

Recommendations	Certainty of Evidence	Strength of Recommendation
Pre-exposure Prophylaxis We suggest against the use of AZD7442 (tixagevimab-cilgavimab) as pre-exposure prophylaxis against COVID-19.	Very low	Weak
Post-exposure Prophylaxis We suggest against the use of AZD7442 (tixagevimab-cilgavimab) as post-exposure prophylaxis against COVID-19.	Very low	Weak

Consensus Issues
Following the presentation on the latest findings on post-exposure prophylaxis using AZD7442 (tixagevimab-cilgavimab), the panel notes that there are not enough high-quality studies that support the effectiveness against prevailing variants. The study presented was conducted prior to the emergence of the omicron variant.

KEY FINDINGS

- Two randomized controlled trials investigated the efficacy and safety of tixagevimab-cilgavimab (AZD7442) as prophylaxis for COVID-19 infection: one as pre-exposure prophylaxis, and the other as post-exposure prophylaxis.
- **As pre-exposure prophylaxis.** Those given AZD7442 showed significant reduction in the development of symptomatic COVID-19 infection and severe/critical COVID-19 infection in all participants as well as in individuals with increased risk of inadequate response to COVID-19 vaccine, individuals with high risk of exposure, individuals with comorbidities and individuals with high risk of severe COVID, compared to those given placebo. There was no significant difference in adverse events and serious adverse events between the AZD7442 (tixagevimab-cilgavimab) group and the placebo group. The overall quality of evidence was rated very low due to serious risk of bias (downgraded for attrition bias, indirectness, and imprecision in two critical outcomes, namely, mortality and emergency department visit). However, recently US FDA withdraw its emergency use authorization (EUA) for AZD7442 as pre-exposure prophylaxis since the predominant and emerging omicron subvariants are not susceptible to AZD7442.
- **As post-exposure prophylaxis.** Results showed inconclusive results for the following outcomes: RT-PCR positive symptomatic COVID-19 infection, severe or critical COVID-19 infection, and emergency department visit. The subset of participants with negative or missing SARS-CoV-2 RT-PCR result at baseline who were given AZD7442 showed statistically significant reduction in the development of RT-PCR positive symptomatic COVID-19 infection. Individuals given AZD7442 showed statistically significant reduction in the development of adverse events, but no significant difference in serious

adverse events when compared to placebo. The overall quality of evidence was rated very low due to serious risk of bias (downgraded for attrition bias, indirectness, and imprecision for four critical outcomes, namely, RT-PCR positive symptomatic COVID-19 infection, severe or critical COVID-19 infection, emergency department visit and serious adverse events).

INTRODUCTION

While the nationwide rollout of COVID-19 vaccination starting in March 2021 reduced hospitalizations and death from COVID-19, SARS-CoV-2 infection continues to spread, as variants continue to emerge - putting individuals at risk of COVID-19, particularly unvaccinated individuals and individuals with the inability to mount an adequate immune response following vaccination [1-4]. Furthermore, the waning immunity from vaccines continues to pose a risk even among fully vaccinated individuals, thus the need for new therapies that can provide or augment protection from COVID-19 infection.

AZD7442 is a combination of two fully human, long-acting SARS-CoV-2-neutralizing monoclonal antibodies (mAbs) namely tixagevimab (AZD8895) and cilgavimab (AZD1061) [5-8]. Individually, they prevent the spike protein from binding to angiotensin-converting enzyme 2 (ACE2) receptor and block cell entry of the virus [5-8]. These two potent neutralizing antibodies against SARS-CoV-2 were isolated from the B-cells of individuals with prior SARS-CoV-2 infection, and they bind simultaneously to distinct non-overlapping epitopes on the spike protein receptor binding (RBD) which provides protection against symptomatic infection and have also been shown to limit the progression of SARS-CoV-2 infection [5-8]. Collectively, they build a higher barrier to viral escape and a larger extent of coverage, resulting in neutralization of all known SARS-CoV-2 variants of concern (Alpha, Beta, Gamma, and Delta) [7]. Although efficacy of AZD7442 against Omicron could not be assessed in the trials retrieved, it has been shown in in vitro studies that AZD7442 has neutralizing activity against the BA.1, BA.1.1, BA.2, BA.2.12.1, BA.3, BA.4, and BA.5 Omicron subvariants [8-10]. AZD7442 exhibits extended half-life and provides high anti-SARS-CoV-2 neutralizing antibody levels in healthy adult participants [9-11]. SARS-CoV-2 neutralizing antibody titers in sera conferred by AZD7442 were considerably higher than titers associated with convalescent plasma [9-11]. Extrapolation of the time course of serum AZD7442 concentrations suggests that AZD7442 may provide up to 12 months of protection and benefit individuals at high-risk of COVID-19 [12]. In a non-human primate model of SARS-CoV-2 infection, prophylactic AZD7442 administration prevented infection and therapeutic administration accelerated viral clearance from the lungs [12].

At present, the predominant variant of concern for COVID infection worldwide and in the Philippines is the omicron variant. Therefore, it is essential to consider interventions that can offer protection from this particular variant of concern.

REVIEW METHODS

A systematic search was done on Pubmed (Medline), Cochrane Library (CENTRAL), Google Scholar until January 25, 2022 with a combined MeSH and free text search using the terms coronavirus infections, COVID-19, severe acute respiratory syndrome coronavirus 2 or SARS-CoV-2, and AZD7442 or tixagevimab-cilgavimab. The COVID-NMA Living Data was also checked and a search for ongoing studies in the NIH *clinicaltrials.gov* and various trial registries was done. Preprints using medrxiv, chinaxiv and biorxiv were also searched. Only randomized controlled trials that compared AZD7442 OR "tixagevimab-cilgavimab" OR "cilgavimab and tixagevimab drug combination" OR "cilgavimab and tixagevimab drug combination" against placebo or standard of care for pre-exposure prophylaxis or prevention of COVID-19 were included in this review. There were no limits used in the search.

RESULTS

There were two randomized controlled trials found that compared AZD7442 against placebo as prophylaxis. One study used AZD7442 as pre-exposure prophylaxis while another study used it as post-exposure prophylaxis.

The study on pre-exposure prophylaxis is an ongoing, multicenter, double-blind, parallel-group, randomized, placebo-controlled trial, that assessed the safety and efficacy of a single dose of AZD7442 (two consecutive intramuscular injections; one each of tixagevimab and cilgavimab) for pre-exposure prophylaxis against COVID-19 in adults who had an increased risk of inadequate response to COVID-19 vaccination, an increased risk of exposure to SARS-CoV-2, or both [13]. Increased risk for SARS-CoV-2 infection is defined

as individuals whose locations or circumstances put them at appreciable risk of exposure to SARS-CoV-2 and COVID-19, such as health care workers, workers in industrial settings, military personnel residing or working in high-density settings, students living in dormitory settings and others living in settings of similar close or high-density proximity. The trial is being conducted at 87 sites in Belgium, France, Spain, the United Kingdom, and the United States. The primary safety end point was the incidence of adverse events after a single dose of AZD7442. The primary efficacy end point was symptomatic RT-PCR positive COVID-19 infection occurring after administration of AZD7442 or placebo and on or before day 183 [13]. The viral genotypic data collected from some of the participants were alpha, beta and delta.

Another trial is a phase 3 COVID-19 Study to Optimally Reduce Morbidity in Care Homes and Sites with Enhanced Risk (STORM CHASER) conducted to assess AZD7442 for post-exposure prevention of symptomatic COVID-19 in adults within 8 days of exposure to an individual with laboratory-confirmed SARS-CoV-2 infection. The STORM CHASER trial is an ongoing, 15-month, phase 3, randomized, double-blind, placebo-controlled, multicenter study, conducted in 59 sites across the United States and the United Kingdom. The primary safety endpoint was safety and tolerability of a single intramuscular dose of AZD7442 compared to placebo while the primary efficacy endpoint was incidence of post-dose SARS-CoV-2 RT-PCR–positive symptomatic COVID-19 infection occurring before day 183. SARS-CoV-2 sequencing data of some participants indicated that they were infected with the alpha variant and there were few cases with the delta variant [14].

The overall certainty of evidence for the pre-exposure prophylaxis study was rated very low; it was downgraded due to serious risk of bias (i.e., attrition bias), indirectness (i.e. the study was conducted prior to the emergence of the omicron variant), and imprecision for two critical outcomes (i.e., mortality and emergency department visit). The overall quality of evidence for the post-exposure prophylaxis study was rated very low due to downgrading for serious risk of bias (specifically attrition bias), indirectness (i.e. the study was conducted prior to the emergence of the omicron variant), and imprecision in four critical outcomes (RT-PCR positive symptomatic COVID-19 infection, severe or critical COVID-19 infection, emergency department visit and serious adverse events).The risk of bias summary is in Appendix 3. The GRADE evidence profile is in Appendix 4.

Efficacy

Pre-exposure Prophylaxis

On primary analysis, individuals given AZD7442 showed statistically significant reduction in the development of symptomatic COVID-19 infection (RR 0.24, 95% CI 0.10-0.55) but inconclusive results in the development of severe/critical COVID-19 infection (RR 0.17, 95% CI 0.01-4.12) compared to those given placebo. At median six-month follow-up, individuals given AZD7442 showed statistically significant reduction in the development of symptomatic COVID-19 infection (RR 0.18, 95% CI 0.09-0.35) and in the development of severe/critical COVID-19 infection (RR 0.05, 95% CI 0.00-0.83) compared to those given placebo. Severe COVID-19 was characterized by a minimum of either pneumonia (fever, cough, tachypnea or dyspnea, and lung infiltrates) or hypoxemia (oxygen saturation [SpO2] <90% in room air or severe respiratory distress) and a World Health Organization (WHO) Clinical Progression Scale score of 5 or higher. At median six month follow-up, there was also statistically significant benefit in the AZD7442ab group compared to the placebo group in developing symptomatic COVID-19 infection in individuals with increased risk of inadequate response (RR 0.20, 95% CI 0.09-0.44), individuals with high risk of exposure (RR 0.18, 95% CI 0.06-0.50), individuals with comorbidities (RR 0.30, 95% CI 0.14-0.62) and individuals with high risk of severe COVID (RR 0.27, 95% CI 0.13-0.55) but no significant difference in individuals with immunosuppressive disease and immunosuppressive treatment (RR 0.29, 95% CI 0.03-3.17). There was no significant difference in mortality (RR 0.65, 95% CI 0.24-1.73) and emergency department visit (RR 6.54, 95% CI 0.37-116.05) between the tixagevimab-cilgavimab group and the placebo group.

Post-exposure Prophylaxis

Individuals given AZD7442 showed inconclusive results in the development of RT-PCR positive symptomatic COVID-19 infection (RR 0.67, 95% CI 0.36-1.24). Subgroup analysis of participants aged 60 years old and above (RR 0.50, 95% CI 0.13-1.96), participants with comorbidities (RR 0.59, 95% CI 0.22-1.57) and

participants with high risk for severe COVID-19 (RR 0.50, 95% CI 0.22-1.13) also showed no statistically significant results. In a subset of individuals with negative or missing SARS-CoV-2 RT-PCR result at baseline who were given AZD7442, there was statistically significant reduction in the development of RT-PCR positive symptomatic COVID-19 infection (RR 0.27, 95% CI 0.10-0.73). Results were also inconclusive for the outcomes: development of severe or critical COVID-19 infection (RR 0.17, 95% CI 0.01-4.06) and emergency department visit (RR 0.25, 95% CI 0.02-2.73).

Safety

Pre-exposure Prophylaxis

There was no statistically significant difference in adverse events (RR 1.03, 95% CI 0.95-1.12) and serious adverse events (RR 1.09, 95% CI 0.67-1.78) in the AZD7442 group and the placebo group. Most of the adverse events were mild or moderate in intensity. The most common adverse event reported was injection-site reaction. Serious adverse events reported were nervous system disorders, cardiac disorders, gastrointestinal disorders and other infections. There were 87 adverse events and 1 serious adverse event related to AZD7442 but there was no death considered by the investigators to be related to AZD7442.

Post-exposure Prophylaxis

Individuals given AZD7442 showed statistically significant reduction in the development of adverse events (RR 0.72, 95% CI 0.59-0.89) compared to the placebo group but no significant difference in serious adverse events (RR 0.83, 95% CI 0.20-3.45) between the AZD7442 (tixagevimab-cilgavimab) group and the placebo group. The most common adverse events were headache, fatigue, and cough. Serious adverse events (infection, psychiatric disorders & nervous system disorders) were reported both by participants in the AZD7442 and placebo groups but none were considered related to study intervention. There were three deaths in the study: two participants from the AZD7442 group (metastatic lung cancer, cerebral ischemia) and one participant from the placebo group (unexplained death). None of the deaths were considered related to the study intervention.

EVIDENCE TO DECISION

The US FDA issued an emergency use authorization (EUA) last December 8, 2021 for pre-exposure prophylaxis of individuals aged ≥12 years (weighing at least 40kg) 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 have a history of severe adverse reactions to a COVID-19 vaccine and/or its component. Furthermore, the product was authorized for emergency use for individuals who were not currently infected with SARS-CoV-2 and who have not had a known recent exposure to an individual infected with SARS-CoV-2 [14].

Tixagevimab and cilgavimab are two separate injections that come packaged together. One vial contains 150mg of tixagevimab and the other contains 150mg of cilgavimab. It is given as a single dose. Each injection is given back-to-back into a muscle and it is recommended that each should be given into a separate buttock muscle, one after the other. Proper storage conditions indicate that they must be stored in their original packaging to remain protected from light, and must remain at temperatures between 36° and 48°F, or 2°-8°C [14].

The US FDA guidance recommended an initial dose of 300mg of tixagevimab and 300mg of cilgavimab administered as two separate consecutive intramuscular injections and a repeat dose of 300mg of tixagevimab and 300mg of cilgavimab every 6 months timed from the date of the most recent dose. EUA was updated on October 3, 2022. The dosing regimen was revised because available data indicate that a higher dose of Evusheld may be more likely to prevent infection by the COVID-19 Omicron subvariants BA.1 and BA.1.1 than the originally authorized dose [15]. They also added a warning namely the risk for COVID-19 due to SARS-CoV-2 viral variants not neutralized by EVUSHELD.

The United States purchased a total of 1.7 million doses from Astrazeneca for a total cost of $855 million, making the individual cost of Evusheld at approximately $502 (₱28, 164) per dose. The cost of tixagevimab-cilgavimab is being subsidized by the US government and distributed to eligible individuals [16].

While US FDA has issued an EUA for tixagevimab-cilgavimab (EVUSHELD) as pre-exposure prophylaxis for certain individuals previously, it did not issue an EUA for the use of EVUSHELD as post exposure prophylaxis.

However, on January 26, 2023, US FDA announced that Evusheld is not currently authorized for pre-exposure prophylaxis against SARS-CoV-2 infection in the United States since more than 90% of the circulating SARS-CoV-2 variants specifically Omicron BQ.1, BQ.1.1, XBB, and XBB.1.5 sublineages are unlikely to be susceptible to tixagevimab-cilgavimab as pre-exposure prophylaxis against SARS-CoV-2 infection [17].

RECOMMENDATIONS FROM OTHER GROUPS

The US FDA announced on January 26, 2023 that AZD7442 (Evusheld) is not currently authorized for pre-exposure prophylaxis against SARS-CoV-2 infection in the United States [17]. In line with this announcement, the US NIH Panel, American Academy of Pediatrics (AAP), Infectious Diseases Society of America (IDSA) and American Society of Transplantation (AST) also withdraw their recommendation on the use of AZD7442 as pre-exposure prophylaxis against SARS-CoV-2 infection [19-22]. The Australian Living Guidelines do not routinely use tixagevimab plus cilgavimab as pre-exposure prophylaxis, however use may be considered in exceptional circumstances, in individuals who are severely immunocompromised [23]. The National Comprehensive Cancer Network (NCCN) and American College of Rheumatology (ACR) has not yet updated their recommendation and still suggest pre-exposure prophylaxis with tixagevimab/cilgavimab rather than no tixagevimab-cilgavimab, when predominant regional variants are susceptible to the agent in moderately or severely immunocompromised individuals at increased risk for inadequate immune response to COVID-19 vaccine or for persons for whom COVID-19 vaccine is not recommended due to a documented serious adverse reaction to the vaccine [24-28]. The WHO, Surviving Sepsis Campaign Guidelines, American Thoracic Society/European Respiratory Society has no recommendation on the use of AZD7442 as pre-exposure prophylaxis for COVID-19 infection. The Australian Living Guidelines and the US NIH Panel do not recommend the use of tixagevimab plus cilgavimab for post-exposure prophylaxis outside of randomized trials with appropriate ethical approval [23]. The American Academy of Pediatrics (AAP), Infectious Diseases Society of America (IDSA), National Comprehensive Cancer Network (NCCN), American College of Rheumatology (ACR), American Society of Transplantation (AST), WHO, Surviving Sepsis Campaign Guidelines, American Thoracic Society/European Respiratory Society has no recommendation on the use of AZD7442 as post-exposure prophylaxis for COVID-19 infection.

Table 1. Recommendations on the Use of AZD7442 as Pre-exposure or Post-exposure Prophylaxis for COVID 19 Infection

CPGs/ Expert Group	**Recommendation**	**CPGs/ Expert Group**
US FDA EUA	**Evusheld is not currently authorized for pre-exposure prophylaxis against SARS-CoV-2 infection in the United States** EVUSHELD 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	(UPDATED 1/ 26/ 2023)

	exposed to someone infected with SARS-CoV-2.	
US NIH GUIDELINE	**Pre-Exposure Prophylaxis** **The Panel now recommends against the use of tixagevimab plus cilgavimab as PrEP of COVID-19 (IIIA)*** **On January 26, 2023, the Food and Drug Administration (FDA) updated the Emergency Use Authorization (EUA) for tixagevimab plus cilgavimab to limit its use.1 Tixagevimab plus cilgavimab is authorized for use as pre-exposure prophylaxis (PrEP) of COVID-19 when the combined frequency of nonsusceptible subvariants in the United States is ≤90%.2 Because the overall prevalence of these subvariants is now >97%, tixagevimab plus cilgavimab is not currently authorized for use in the United States. To address the revised EUA, the COVID-19 Treatment Guidelines Panel (the Panel) has changed its recommendation for tixagevimab plus cilgavimab.* **Post-Exposure Prophylaxis** For people exposed to individuals with SARS-CoV-2 infection, do not use tixagevimab plus cilgavimab for post-exposure prophylaxis outside of randomized trials with appropriate ethical approval.	(UPDATED 1/30/2023)
Infectious Diseases Society of America (IDSA)	As of 1/26/2023, based on CDC Nowcast data, fewer than 10% of circulating variants in the US are susceptible to tixagevimab/cilgavimab (Evusheld), the sole product that has been available for pre-exposure prophylaxis. **Tixagevimab/cilgavimab is therefore no longer authorized for use in the US until further notice by FDA***. **SARS-CoV-2 is expected to continue to evolve. Although the general trend has been towards increasing resistance to neutralizing monoclonal antibodies, there have been instances in which new variants became more susceptible to existing anti-SARS-CoV-2 neutralizing antibodies. Should this occur again, or should newly developed, more active neutralizing antibodies be authorized for prophylaxis, the panel will offer recommendations regarding use.*	UPDATED (1/27/2023)

American Academy of Pediatrics (AAP)	Given dominant SARS-CoV-2 variants circulating in the United States, no monoclonal antibody (mAb) product is currently authorized for the treatment or pre-exposure prophylaxis of COVID-19. As of November 30, 2022, the mAb bebtelovimab is no longer authorized for treatment in any region in the United States because of lack of efficacy against circulating SARS-CoV-2 variants. As of January 26, 2023, the mAb tixagevimab copackaged with cilgavimab (Evusheld) is no longer authorized for pre-exposure prophylaxis in the United States because of lack of efficacy against circulating SARS-CoV-2 variants. Retained product can be appropriately held for possible future use in the event that SARS-CoV-2 variants that are neutralized by Evusheld become more prevalent in the future. No COVID-19 mAb product or antiviral medication is authorized for use as postexposure prophylaxis.	UPDATED (02/08/2023)
American Society of Transplantation (AST)	Many of the Omicron subvariants, beginning with BA.4.6, BA.5, BQ.1 and BQ.1.1, were found to be significantly less susceptible to tixagevimab/cilgavimab (Evusheld). Based on this, the US FDA also removed authorization of Evusheld for pre-exposure prophylaxis on 1/26/2023.	UPDATED (2/1/2023)
Australian Living Guidelines	**Pre-Exposure Prophylaxis** Do not routinely use tixagevimab plus cilgavimab as pre-exposure prophylaxis, however use may be considered in exceptional circumstances, in individuals who are severely immunocompromised. **Post-Exposure Prophylaxis** For people exposed to individuals with SARS-CoV-2 infection, do not use tixagevimab plus cilgavimab for post-exposure prophylaxis outside of randomized trials with appropriate ethical approval. **Treatment** Consider using tixagevimab plus cilgavimab within 5 days of symptom onset in unvaccinated*	UPDATED (2/24/2023)

	adults with COVID-19 who do not require oxygen and who have one or more risk factors for disease progression. In addition to at-risk unvaccinated adults, also consider using tixagevimab plus cilgavimab within 5 days of symptom onset in adults with COVID-19 who do not require oxygen and are immunocompromised; or are at particularly high risk of severe disease on the basis of advanced age and multiple risk factors. Do not use tixagevimab plus cilgavimab for the treatment of COVID-19 in pregnant or breastfeeding women outside of randomized trials with appropriate ethical approval.	
National Comprehensive Cancer Network (NCCN)	For pre-exposure prophylaxis of COVID-19 in adults and pediatric individuals (≥12 years of age and weighing ≥40kg): Who are moderately to severely immunocompromised and may have an inadequate immune response to COVID-19 vaccination (including all persons undergoing active cancer therapy)	July 21, 2022
American College of Rheumatology (ACR)	Moderately to severely immunocompromised patients are candidates for LAAB and should be actively considered for pre-exposure prophylaxis For high-risk AIIRD patients, pre-exposure prophylaxis monoclonal antibody treatment (tixagevimab co-packaged with cilgavimab) is recommended (Moderate Task Force consensus) High risk is defined as moderate to severely compromised immune systems who may not mount an adequate immune response to COVID-19 vaccination when available, if licensed or approved under FDA EUA. AIIRD = autoimmune and inflammatory rheumatic disease	July 21, 2022
European Medicines Agency EMA's Human Medicines Committee (CHMP: Committee for Medicinal Products for Human Use)	Indicated for the pre-exposure prophylaxis of COVID-19 In adults and adolescents aged 12 years and older weighing at least 40kg	July 21, 2022
French National Authority for Health (HAS)	Indicated for PrEP in adult and adolescent patients (aged 12 years and over weighing at least 40kg): Having an immunity deficiency linked to a pathology or treatment	March 18, 2022

	AND who are weakly or non-responsive after a complete vaccination schedule OR Not eligible for vaccination AND who are at high risk of severe COVID-19	
UK Medicines and Healthcare products Regulatory Agency (MHRA)	Indicated for the pre-exposure prophylaxis of COVID-19 in adults: 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 are unlikely to mount an adequate immune response to COVID-19 vaccination OR For whom COVID-19 vaccination is not recommended	March 17, 2022
Singapore National Center for Infectious Disease (NCID) guidelines on pre-exposure prophylaxis for COVID-19	The role of monoclonal antibodies in prevention (pre- or post-exposure prophylaxis) of COVID-19 are limited: active immunity via an effective SARS-CoV-2 primary vaccine series and boosters as required is clearly preferable. Based on the findings of the PROVENT trial, tixagevimab-cilgavimab may be considered (Ungraded), via the Special Access Route (SAR), for preexposure prophylaxis of COVID-19 in adults and pediatric (12 years of age and older weighing at least 40kg) 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 who: 1) 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 (as evidenced by low/absent Anti-S antibody or neutralizing antibody levels) OR	(Version 9.0, dated 28 April 2022)

	2) Are not recommended for vaccination with any available COVID-19 vaccine, according to the approved or authorized schedule, due to a history of severe adverse reaction (e.g. severe allergic reaction) to a COVID-19 vaccine(s) and/or COVID-19 vaccine components(s).	
Malaysia Interim guidelines for AZD7442 as pre-exposure prophylaxis in COVID-19	Tixagevimab plus Cilgavimab (LAAB) can be used as PrEP for adults and adolescents (aged ≥12 years and weighing ≥40kg) who do not have COVID-19 infection, who have not been recently exposed to an individual with COVID-19 infection, AND who: • Are moderately to severely immunocompromised and may have an inadequate immune response to COVID-19 vaccination; OR • Are not able to be fully vaccinated with any available COVID-19 vaccines due to a documented history of severe adverse reactions to a COVID-19 vaccine or any of its components.	March 2022
Department of Disease Control Thailand	Recommends AZD7442 as SARS CoV-2 PrEP for prioritized risk groups Tixagevimab plus Cilgavimab (LAAB) can be used as PrEP for adults and adolescents (aged ≥12 years and weighting ≥40kg) LAAB is prioritized for individuals with following conditions: • End stage renal disease with Kidney transplant receiving immunosuppressive drugs • End stage renal disease on hemodialysis • End stage renal disease on peritoneal dialysis • Organ transplant recipients receiving immunosuppressive drugs • Bone marrow transplant recipients receiving immunosuppressive drugs	July 2022
WHO, Surviving Sepsis Campaign Guidelines, American	No recommendation	

Thoracic Society/European Respiratory Society	

ONGOING STUDIES AND RESEARCH GAPS

There are currently 11 ongoing clinical trials on tixagevimab-cilgavimab evaluating the efficacy and safety of the drug when used as prophylaxis for COVID-19 (Appendix 5).

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Appendix 1: Preliminary Evidence to Decision

Table 1. Summary of initial judgements prior to the panel discussion (N=7/9)

FACTORS	JUDGEMENT						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No	Yes (N=7)					
Benefits	Large (N=1)	Moderate (N=4)	Small (N=1)	Varies (N=1)			Individuals given tixagevimab-cilgavimab as pre-exposure prophylaxis showed statistically significant reduction in the development of symptomatic COVID-19 infection (RR 0.24, 95% CI 0.10-0.55) and in the development of severe/critical COVID-19 infection (RR 0.05, 95% CI 0.00-0.83) but there was no significant difference in mortality (RR 0.70, 95% CI 0.22-2.22) and emergency department visit (RR 6.54, 95% CI 0.37-116.05). There was also statistically significant benefit in developing symptomatic COVID-19 infection in individuals with increased risk of inadequate response to vaccination (RR 0.20, 95% CI 0.09 to 0.44), individuals with high risk of exposure (RR 0.18, 95% CI 0.06-0.50), individuals with comorbidities (RR 0.30, 95% CI 0.14-0.62) and individuals with high risk of severe COVID (RR 0.27, 95% CI 0.13-0.55) but no significant difference in individuals with immunosuppressive disease and immunosuppressive treatment (RR 0.29, 95% CI 0.03-3.17).
Harms	Large	Moderate (N=1)	Small (N=5)	Trivial (N=1)			There was no significant difference in adverse events (RR 1.03, 95% CI 0.95-1.12) and serious adverse events (RR 1.09, 95% CI 0.67-1.78) in the AZD7442 (tixagevimab-cilgavimab) group and the placebo group. Most of the adverse events were mild or moderate in intensity and there was no death considered by the investigators to be related to AZD7442 (tixagevimab-cilgavimab).

Balance of Benefits and Harms	Favors the use of intervention	Probably favors the use of intervention (N=6)	Varies (N=1)				The results showed statistically significant reduction in the development of symptomatic COVID-19 infection and severe/critical COVID-19 infection compared to those given placebo in all participants as well as in individuals with increased risk of inadequate response to COVID-19 vaccine, individuals with high risk of exposure, individuals with comorbidities and individuals with high risk of severe COVID but did not reach statistical significance for mortality and ED visit. There was no significant difference in adverse events and serious adverse events between the AZD7442 (tixagevimab-cilgavimab) group and the placebo group. Overall, AZD7442 (tixagevimab-cilgavimab) showed net potential benefit [significantly beneficial] for the prevention of development of symptomatic COVID-19 infection and severe/critical COVID-19 infection with no significant adverse events and serious adverse events reported.
Certainty of Evidence	High	Moderate (N=2)	Low (N=1)	Very low (N=4)			The overall quality of evidence was rated very low due to serious risk of bias downgraded for attrition bias and downgraded twice for imprecision in 1 critical outcome (emergency department visit)
Values	Important uncertainty or variability (N=2)	Possibly important uncertainty or variability (N=3)	Possibly NO important uncertainty or variability (N=2)	No important uncertainty or variability			· No research evidence found
Resources Required	Uncertain (N=1)	Large cost (N=4)	Moderate Cost (N=1)	Negligible cost	Moderate savings (N=1)	Large savings	
Certainty of evidence of required resources	No included studies (N=1)	Very low (N=1)	Low (N=1)	Moderate (N=3)	High (N=1)		The US FDA guidance recommended an initial dose of 300mg of tixagevimab and 300mg of cilgavimab administered as two separate consecutive intramuscular injections.

Cost effectiveness	No included studies (N=5)	Favors the comparator (N=1)	Does not favor either criteria or the comparator	Probably favors the intervention	Favors criteria	Varies (N=1)	Proper storage conditions indicate that they must be stored in their original packaging to remain protected from light, and must remain at temperatures between 36° and 48° F, or 2°-8° C. US purchased a total of 1.7 million doses from Astrazeneca for a total cost of $855 million, making the individual cost of Evusheld at approximately $502 (₱28,164) per dose.
Equity	Uncertain (N=2)	Probably Reduced (N=3)	Reduced (N=1)	Probably No Impact (N=1)	Increased	Varies	
Acceptability	Uncertain (N=4)	No (N=1)	Probably No (N=1)	Yes	Probably yes (N=1)	Varies	
Feasibility	Uncertain (N=3)	No (N=1)	Probably No (N=1)	Yes	Probably yes (N=1)	Varies (N=1)	

Appendix 2: Search Yield and Results

DATABASE	SEARCH STRATEGY / SEARCH TERMS	DATE AND TIME OF SEARCH	RESULTS	
			Yield	Eligible
Medline	(("coronavirus"[MeSH Terms] OR "coronavirus"[All Fields] OR "coronaviruses"[All Fields] OR ("covid 19"[All Fields] OR "covid 19"[MeSH Terms] OR "covid 19 vaccines"[All Fields] OR "covid 19 vaccines"[MeSH Terms] OR "covid 19 serotherapy"[All Fields] OR "covid 19 serotherapy"[Supplementary Concept] OR "covid 19 nucleic acid testing"[All Fields] OR "covid 19 nucleic acid testing"[MeSH Terms] OR "covid 19 serological testing"[All Fields] OR "covid 19 serological testing"[MeSH Terms] OR "covid 19 testing"[All Fields] OR "covid 19 testing"[MeSH Terms] OR "sars cov 2"[All Fields] OR "sars cov 2"[MeSH Terms] OR "severe acute respiratory syndrome coronavirus 2"[All Fields] OR "ncov"[All Fields] OR "2019 ncov"[All Fields] OR (("coronavirus"[MeSH Terms] OR "coronavirus"[All Fields] OR "cov"[All Fields]) AND 2019/11/01:3000/12/31[Date - Publication])) OR ("sars cov 2"[MeSH Terms] OR "sars cov 2"[All Fields] OR "sars cov 2"[All Fields]) OR ("sars cov 2"[MeSH Terms] OR "sars cov 2"[All Fields] OR "ncov"[All Fields])) AND "tixagevimab-cilgavimab"[All Fields]) OR ("cilgavimab and tixagevimab drug combination"[Supplementary Concept] OR "cilgavimab and tixagevimab drug combination"[All Fields] OR "azd7442"[All Fields])	1/25//23	72	4 (2 on prophylaxis & 2 on treatment)
CENTRAL	(Coronaviridae Infections OR Coronavirus OR coronavirus OR novel coronavirus OR NCOV OR covid19 OR covid 19 OR covid-19 OR severe acute respiratory syndrome coronavirus 2 OR SARS2 OR SARS 2 OR SARS COV2 OR SARS COV 2 OR SARS-COV-20 AND "tixagevimab-cilgavimab" OR ("cilgavimab and tixagevimab drug combination" OR "cilgavimab and tixagevimab drug combination" OR "azd7442"	1/25//23	22	4 (2 on prophylaxis & 2 on treatment)
COVID-NMA Initiative	{"tixagevimab-cilgavimab" OR ("cilgavimab and tixagevimab drug combination" OR "cilgavimab and tixagevimab drug combination" OR "azd7442"}	1/25//23	2	2
Google Scholar	{Coronavirus OR novel coronavirus OR NCOV OR covid19 OR covid 19 OR covid-19 OR severe acute respiratory syndrome coronavirus 2 OR SARS2 OR SARS 2 OR SARS COV2 OR SARS COV 2 OR SARS-COV-2} AND {"tixagevimab-cilgavimab" OR ("cilgavimab and tixagevimab drug combination" OR "cilgavimab and tixagevimab drug combination" OR "azd7442"} AND {Randomized trial}	1/25//23	604	4 (2 on prophylaxis & 2 on treatment)
ClinicalTrials.gov	Coronavirus AND {"tixagevimab-cilgavimab" OR ("cilgavimab and tixagevimab drug combination" OR "cilgavimab and tixagevimab drug combination" OR "azd7442"}	1/25//23	21	4 (2 on prophylaxis & 2 on treatment)
Chinese Clinical Trial Registry	{Coronavirus OR novel coronavirus OR NCOV OR covid19 OR covid 19 OR covid-19 OR	1/25//23	2	0

	severe acute respiratory syndrome coronavirus 2 OR SARS2 OR SARS 2 OR SARS COV2 OR SARS COV 2 OR SARS-COV-2} AND {"tixagevimab-cilgavimab" OR ("cilgavimab and tixagevimab drug combination" OR "cilgavimab and tixagevimab drug combination" OR "azd7442"}			
EU Clinical Trials Register	Coronavirus AND {"tixagevimab-cilgavimab" OR ("cilgavimab and tixagevimab drug combination" OR "cilgavimab and tixagevimab drug combination" OR "azd7442"}	1/25//23	21	2
Republic of Korea - Clinical Research Information Service	Coronavirus AND {"tixagevimab-cilgavimab" OR ("cilgavimab and tixagevimab drug combination" OR "cilgavimab and tixagevimab drug combination" OR "azd7442"}	1/25//23	1	0
Japan Primary Registries Network/ NIPH Clinical Trials Search	Coronavirus AND {"tixagevimab-cilgavimab" OR ("cilgavimab and tixagevimab drug combination" OR "cilgavimab and tixagevimab drug combination" OR "azd7442"}	1/25//23	2	0
CenterWatch	Coronavirus AND {"tixagevimab-cilgavimab" OR ("cilgavimab and tixagevimab drug combination" OR "cilgavimab and tixagevimab drug combination" OR "azd7442"}	1/25//23	893	4 (2 on prophylaxis & 2 on treatment)
WHO database COVID-19 studies	{"tixagevimab-cilgavimab" OR ("cilgavimab and tixagevimab drug combination" OR "cilgavimab and tixagevimab drug combination" OR "azd7442"}	1/25//23	36	4 (2 on prophylaxis & 2 on treatment)
chinaxiv.org	Coronavirus AND {"tixagevimab-cilgavimab" OR ("cilgavimab and tixagevimab drug combination" OR "cilgavimab and tixagevimab drug combination" OR "azd7442"}	1/25//23	0	0
Medrxiv.org	Coronavirus AND {"tixagevimab-cilgavimab" OR "cilgavimab and tixagevimab drug combination" OR "cilgavimab and tixagevimab drug combination" OR "azd7442"}	1/25//23	24	1
Biorxiv.org	Coronavirus AND {"tixagevimab-cilgavimab" OR "cilgavimab and tixagevimab drug combination" OR "cilgavimab and tixagevimab drug combination" OR "azd7442"}	1/25//23	14	0

Appendix 3: Characteristics of Included Studies

Study ID	Patients (n) & Duration of Follow-Up	Interventions	Outcomes	Study Design
Intramuscular AZD7442 (Tixagevimab-Cilgavimab) for Prevention of COVID-19 *M.J.Levin et al. (Belgium, France, Spain, UK,USA)*	Adults (≥18 years of age) who had an increased risk of an inadequate response to vaccination against coronavirus disease 2019 (Covid-19), an increased risk of exposure to SARS-CoV-2, or both. A total of 5197 participants underwent randomization and received one dose of AZD7442 or placebo (3460 in the AZD7442 group and 1737 in the placebo group). <u>Duration of follow-up:</u> up to 183 days in the primary analysis	EXPERIMENTAL: single dose (two consecutive intramuscular injections, one containing tixagevimab and the other containing cilgavimab) of either 300mg of AZD7442 CONTROL: Placebo	PRIMARY: Incidence of adverse events after a single dose of AZD7442. Symptomatic Covid-19 (SARS-CoV-2 infection confirmed by means of reverse transcriptase–polymerase-chain-reaction assay) occurring after administration of AZD7442 or placebo and on or before day 183	Randomized, double-blind, placebo-controlled

NCT04625972 **Phase III Double-blind, Placebo-controlled Study of AZD7442 for Post- Exposure Prophylaxis of COVID-19 in Adults (STORM CHASER)** *M.J.Levin et al. (USA & UK)*	Adults (18 Years to 120 Years) without prior severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection or COVID-19 vaccination were enrolled within 8 days of exposure to a SARS-CoV-2–infected individual	• Drug: AZD7442 • Drug: Placebo (randomized 2:1 to a single 300-mg AZD7442 dose (one 1.5-mL intramuscular injection each of tixagevimab and cilgavimab) or placebo)	Primary end points were safety and first post-dose SARS-CoV-2 reverse-transcription polymerase chain reaction (RT-PCR)–positive symptomatic COVID-19 event before day 183	Randomized controlled trial

Appendix 4: Study Appraisal

Figure 1. *Risk of bias summary table*

Appendix 5a: GRADE Evidence Profile

Question: AZD7442 compared to Placebo for COVID-19 Pre-exposure Prophylaxis
Bibliography: . AZD7442 versus Placebo for COVID-19. Cochrane Database of Systematic Reviews [Year], Issue [Issue].

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	AZD7442	Placebo	Relative (95% CI)	Absolute (95% CI)		
Symptomatic COVID-19 (RT-PCR Positive) (Primary Analysis)												
1	randomised trials	serious[a]	not serious	serious[d]	not serious	None	8/3441 (0.2%)	17/1731 (1.0%)	**RR 0.24** (0.10 to 0.55)	**7 fewer per 1,000** (from 9 fewer to 4 fewer)	⨁⨁◯◯ Low	
Symptomatic COVID-19 (RT-PCR Positive)												
1	randomised trials	serious[a]	not serious	serious[d]	not serious	None	11/3441 (0.3%)	31/1731 (1.8%)	**RR 0.18** (0.09 to 0.36)	**15 fewer per 1,000** (from 16 fewer to 11 fewer)	⨁⨁◯◯ Low	
Symptomatic COVID-19 (RT-PCR Positive) - below 60 years old												
1	randomised trials	serious[a]	not serious	serious[d]	not serious	None	8/1945 (0.4%)	19/976 (1.9%)	**RR 0.21** (0.09 to 0.48)	**15 fewer per 1,000** (from 18 fewer to 10 fewer)	⨁⨁◯◯ Low	
Symptomatic COVID-19 (RT-PCR Positive) - 60 years old and above												
1	randomised trials	serious[a]	not serious	serious[d]	not serious	None	3/1496 (0.2%)	12/755 (1.6%)	**RR 0.13** (0.04 to 0.45)	**14 fewer per 1,000** (from 15 fewer to 9 fewer)	⨁⨁◯◯ Low	
Severe or Critical COVID-19 Infection (Median at 6 mos followup)												
1	randomised trials	serious[a]	not serious	serious[d]	not serious	None	0/3441 (0.0%)	5/1731 (0.3%)	**RR 0.05** (0.00 to 0.83)	**3 fewer per 1,000** (from 0 fewer to --)	⨁⨁◯◯ Low	
Mortality(Median at 6 mos followup)												
1	randomised trials	serious[a]	not serious	serious[d]	serious[b]	None	9/3441 (0.2%)	7/1731 (0.3%)	**RR 0.65** (0.24 to 1.73)	**1 fewer per 1,000** (from 2 fewer to 4 more)	⨁◯◯◯ Very low	
Symptomatic Confirmed COVID-19 Infection based on Risk of Inadequate Response to COVID-19 Vaccination												
1	randomised trials	serious[a]	not serious	serious[d]	not serious	None	11/3441 (0.3%)	31/1731 (1.8%)	**RR 0.18** (0.09 to 0.35)	**15 fewer per 1,000** (from 16 fewer to 12 fewer)	⨁⨁◯◯ Low	
Symptomatic Confirmed COVID-19 Infection based on Risk of Inadequate Response to COVID-19 Vaccination - Increased Risk of Inadequate Response to COVID-19 Vaccination												
1	randomised trials	serious[a]	not serious	serious[d]	not serious	None	9/2536 (0.4%)	22/1260 (1.7%)	**RR 0.20** (0.09 to 0.44)	**14 fewer per 1,000** (from 16 fewer to 10 fewer)	⨁⨁◯◯ Low	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	AZD7442	Placebo	Relative (95% CI)	Absolute (95% CI)		
Symptomatic Confirmed COVID-19 Infection based on Risk of Inadequate Response to COVID-19 Vaccination - Low Risk of Inadequate Response to COVID-19 Vaccination												
1	randomised trials	serious[a]	not serious	serious[d]	not serious	None	2/905 (0.2%)	9/471 (1.9%)	**RR 0.12** (0.03 to 0.53)	**17 fewer per 1,000** (from 19 fewer to 9 fewer)	⨁⨁◯◯ Low	
Symptomatic Confirmed COVID-19 Infection based on Risk of Exposure to SARS COV-2												
1	randomised trials	serious[a]	not serious	serious[d]	not serious	None	11/3441 (0.3%)	31/1731 (1.8%)	**RR 0.18** (0.09 to 0.35)	**15 fewer per 1,000** (from 16 fewer to 12 fewer)	⨁⨁◯◯ Low	
Symptomatic Confirmed COVID-19 Infection based on Risk of Exposure to SARS COV-2 - Increased Risk of Exposure to SARS COV-2												
1	randomised trials	serious[a]	not serious	serious[d]	not serious	None	5/1806 (0.3%)	14/905 (1.5%)	**RR 0.18** (0.06 to 0.50)	**13 fewer per 1,000** (from 15 fewer to 8 fewer)	⨁⨁◯◯ Low	
Symptomatic Confirmed COVID-19 Infection based on Risk of Exposure to SARS COV-2 - Low Risk of Exposure to SARS COV-2												
1	randomised trials	serious[a]	not serious	serious[d]	not serious	None	6/1635 (0.4%)	17/826 (2.1%)	**RR 0.18** (0.07 to 0.45)	**17 fewer per 1,000** (from 19 fewer to 11 fewer)	⨁⨁◯◯ Low	
Symptomatic Confirmed COVID-19 Infection based on Presence of Comorbidities												
1	randomised trials	serious[a]	not serious	serious[d]	serious[b]	none	11/3441 (0.3%)	31/1731 (1.8%)	**RR 0.10** (0.01 to 1.78)	**16 fewer per 1,000** (from 18 fewer to 14 more)	⨁◯◯◯ Very low	
Symptomatic Confirmed COVID-19 Infection based on Presence of Comorbidities - With Comorbidities												
1	randomised trials	serious[a]	not serious	serious[d]	not serious	none	11/2315 (0.5%)	19/1190 (1.6%)	**RR 0.30** (0.14 to 0.62)	**11 fewer per 1,000** (from 14 fewer to 6 fewer)	⨁⨁◯◯ Low	
Symptomatic Confirmed COVID-19 Infection based on Presence of Comorbidities - Without Comorbidities												
1	randomised trials	serious[a]	not serious	serious[d]	not serious	none	0/1126 (0.0%)	12/541 (2.2%)	**RR 0.02** (0.00 to 0.32)	**22 fewer per 1,000** (from 15 fewer to --)	⨁⨁◯◯ Low	
Symptomatic Confirmed COVID-19 Infection based on Risk of Severe COVID-19												
1	randomised trials	serious[a]	not serious	serious[d]	serious[b]	none	11/3441 (0.3%)	31/1731 (1.8%)	**RR 0.11** (0.01 to 1.31)	**16 fewer per 1,000** (from 18 fewer to 6 more)	⨁◯◯◯ Very low	
Symptomatic Confirmed COVID-19 Infection based on Risk of Severe COVID-19 - High Risk of Severe COVID-19												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	AZD7442	Placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious[a]	not serious	serious[d]	not serious	none	11/2656 (0.4%)	21/1359 (1.5%)	**RR 0.27** (0.13 to 0.55)	**11 fewer per 1,000** (from 13 fewer to 7 fewer)	⨁⨁◯◯ Low	
Symptomatic Confirmed COVID-19 Infection based on Risk of Severe COVID-19 - Low Risk of Severe COVID-19												
1	randomised trials	serious[a]	not serious	serious[d]	not serious	none	0/785 (0.0%)	10/372 (2.7%)	**RR 0.02** (0.00 to 0.38)	**26 fewer per 1,000** (from 17 fewer to --)	⨁⨁◯◯ Low	
Symptomatic Confirmed COVID-19 Infection based on presence of immunosuppresive disease												
1	randomised trials	serious[a]	not serious	serious[d]	not serious	none	11/3441 (0.3%)	31/1731 (1.8%)	**RR 0.18** (0.09 to 0.35)	**15 fewer per 1,000** (from 16 fewer to 12 fewer)	⨁⨁◯◯ Low	
Symptomatic Confirmed COVID-19 Infection based on presence of immunosuppresive disease - With immunosuppressive disease												
1	randomised trials	serious[a]	not serious	serious[d]	not serious	none	0/16 (0.0%)	0/9 (0.0%)	not estimable		⨁⨁◯◯ Low	
Symptomatic Confirmed COVID-19 Infection based on presence of immunosuppresive disease - Without Immunosupressive Disease												
1	randomised trials	serious[a]	not serious	serious[d]	not serious	none	11/3425 (0.3%)	31/1722 (1.8%)	**RR 0.18** (0.09 to 0.35)	**15 fewer per 1,000** (from 16 fewer to 12 fewer)	⨁⨁◯◯ Low	
Symptomatic Confirmed COVID-19 Infection based on presence of Immunosuppressive treatment												
1	randomised trials	serious[a]	not serious	serious[d]	not serious	none	11/3441 (0.3%)	31/1731 (1.8%)	**RR 0.18** (0.09 to 0.36)	**15 fewer per 1,000** (from 16 fewer to 11 fewer)	⨁⨁◯◯ Low	
Symptomatic Confirmed COVID-19 Infection based on presence of Immunosuppressive treatment - With Immunosuppressive treatment												
1	randomised trials	serious[a]	not serious	serious[d]	serious[b]	none	1/109 (0.9%)	2/64 (3.1%)	**RR 0.29** (0.03 to 3.17)	**22 fewer per 1,000** (from 30 fewer to 68 more)	⨁◯◯◯ Very low	
Symptomatic Confirmed COVID-19 Infection based on presence of Immunosuppressive treatment - Without Immunosuppressive treatment												
1	randomised trials	serious[a]	not serious	serious[d]	not serious	none	10/3332 (0.3%)	29/1667 (1.7%)	**RR 0.17** (0.08 to 0.35)	**14 fewer per 1,000** (from 16 fewer to 11 fewer)	⨁⨁◯◯ Low	
Emergency Department Visit												
1	randomised trials	serious[a]	not serious	serious[d]	extremely serious[c]	none	6/3441 (0.2%)	0/1731 (0.0%)	**RR 6.54** (0.37 to 116.05)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁◯◯◯ Very low	
Adverse Events												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	AZD7442	Placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious[a]	not serious	serious[d]	not serious	none	1221/3461 (35.3%)	593/1736 (34.2%)	**RR 1.03** (0.95 to 1.12)	**10 more per 1,000** (from 17 fewer to 41 more)	⨁⨁◯◯ Low	
Serious Adverse Events												
1	randomised trials	serious[a]	not serious	serious[d]	not serious	none	50/3461 (1.4%)	23/1736 (1.3%)	**RR 1.09** (0.67 to 1.78)	**1 more per 1,000** (from 4 fewer to 10 more)	⨁⨁◯◯ Low	

CI: confidence interval; **RR:** risk ratio

Explanations

a. Downgraded for serious risk of bias due to performance and attrition bias
b. Wide Confidence Interval
c. very wide confidence interval
d. the trial was conducted prior to the emergence of the omicron variant which is the predominant variant as present; the variants identified in the trial were alpha, beta and delta

Appendix 5b: GRADE Evidence Profile

Question: AZD7442 compared to Placebo for Post-exposure Prophylaxis of Symptomatic COVID-19
Bibliography: . AZD7442 for Post-exposure Prophylaxis of Symptomatic COVID-19. Cochrane Database of Systematic Reviews [Year], Issue [Issue].

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	AZD7442	Placebo	Relative (95% CI)	Absolute (95% CI)		
RT-PCR Positive Symptomatic COVID-19												
1	randomised trials	serious[a]	not serious	serious[b]	not serious	none	23/749 (3.1%)	17/372 (4.6%)	**RR 0.67** (0.36 to 1.24)	**15 fewer per 1,000** (from 29 fewer to 11 more)	⨁⨁◯◯ Low	
RT-PCR Positive Symptomatic COVID-19 (Based on Age)												
1	randomised trials	serious[a]	not serious	serious[b]	not serious	none	23/749 (3.1%)	17/372 (4.6%)	**RR 0.67** (0.36 to 1.24)	**15 fewer per 1,000** (from 29 fewer to 11 more)	⨁⨁◯◯ Low	
RT-PCR Positive Symptomatic COVID-19 (Based on Age) - Less than 60 years old												
1	randomised trials	serious[a]	not serious	serious[b]	not serious	none	19/600 (3.2%)	13/297 (4.4%)	**RR 0.72** (0.36 to 1.44)	**12 fewer per 1,000** (from 28 fewer to 19 more)	⨁⨁◯◯ Low	
RT-PCR Positive Symptomatic COVID-19 (Based on Age) - 60 years old and above												
1	randomised trials	serious[a]	not serious	serious[b]	serious[c]	none	4/149 (2.7%)	4/75 (5.3%)	**RR 0.50** (0.13 to 1.96)	**27 fewer per 1,000** (from 46 fewer to 51 more)	⨁◯◯◯ Very low	
RT-PCR Positive Symptomatic COVID-19 (Based on presence of co-morbidities)												
1	randomised trials	serious[a]	not serious	serious[b]	not serious	none	23/749 (3.1%)	17/372 (4.6%)	**RR 0.68** (0.37 to 1.26)	**15 fewer per 1,000** (from 29 fewer to 12 more)	⨁⨁◯◯ Low	
RT-PCR Positive Symptomatic COVID-19 (Based on presence of co-morbidities) - No comorbidities												
1	randomised trials	very serious[a]	not serious	serious[b]	serious[c]	none	14/374 (3.7%)	10/199 (5.0%)	**RR 0.74** (0.34 to 1.65)	**13 fewer per 1,000** (from 33 fewer to 33 more)	⨁◯◯◯ Very low	
RT-PCR Positive Symptomatic COVID-19 (Based on presence of co-morbidities) - One or more comorbidities												
1	randomised trials	serious[a]	not serious	serious[b]	serious[c]	none	9/375 (2.4%)	7/173 (4.0%)	**RR 0.59** (0.22 to 1.57)	**17 fewer per 1,000** (from 32 fewer to 23 more)	⨁◯◯◯ Very low	
RT-PCR Positive Symptomatic COVID-19 (Based on Risk for Severe COVID-19)												
1	randomised trials	serious[a]	not serious	serious[b]	not serious	none	23/749 (3.1%)	17/372 (4.6%)	**RR 0.67** (0.34 to 1.32)	**15 fewer per 1,000** (from 30 fewer to 15 more)	⨁⨁◯◯ Low	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	AZD7442	Placebo	Relative (95% CI)	Absolute (95% CI)		
RT-PCR Positive Symptomatic COVID-19 (Based on Risk for Severe COVID-19) - High Risk for Severe COVID												
1	randomised trials	serious[a]	not serious	serious[b]	not serious	none	11/492 (2.2%)	11/244 (4.5%)	**RR 0.50** (0.22 to 1.13)	**23 fewer per 1,000** (from 35 fewer to 6 more)	⨁⨁◯◯ Low	
RT-PCR Positive Symptomatic COVID-19 (Based on Risk for Severe COVID-19) - Low Risk for Severe COVID												
1	randomised trials	serious[a]	not serious	serious[b]	serious[c]	none	12/257 (4.7%)	6/128 (4.7%)	**RR 1.00** (0.38 to 2.59)	**0 fewer per 1,000** (from 29 fewer to 75 more)	⨁◯◯◯ Very low	
RT-PCR Positive Symptomatic COVID-19 (Based on SARS COV 2 RT-PCR Status at Baseline)												
1	randomised trials	serious[a]	not serious	serious[b]	serious[c]	none	23/749 (3.1%)	17/372 (4.6%)	**RR 0.59** (0.14 to 2.56)	**19 fewer per 1,000** (from 39 fewer to 71 more)	⨁◯◯◯ Very low	
RT-PCR Positive Symptomatic COVID-19 (Based on SARS COV 2 RT-PCR Status at Baseline) - Negative/Missing SARS COV 2 RT-PCR result												
1	randomised trials	serious[a]	not serious	serious[b]	not serious	none	6/715 (0.8%)	11/358 (3.1%)	**RR 0.27** (0.10 to 0.73)	**22 fewer per 1,000** (from 28 fewer to 8 fewer)	⨁⨁◯◯ Low	
RT-PCR Positive Symptomatic COVID-19 (Based on SARS COV 2 RT-PCR Status at Baseline) - Positive SARS COV 2 RT-PCR result												
1	randomised trials	serious[a]	not serious	serious[b]	not serious	none	17/34 (50.0%)	6/14 (42.9%)	**RR 1.17** (0.58 to 2.33)	**73 more per 1,000** (from 180 fewer to 570 more)	⨁⨁◯◯ Low	
RT-PCR Positive Symptomatic COVID-19 (Based on Presence of Obesity)												
1	randomised trials	serious[a]	not serious	serious[b]	not serious	none	23/746 (3.1%)	17/372 (4.6%)	**RR 0.65** (0.31 to 1.35)	**16 fewer per 1,000** (from 32 fewer to 16 more)	⨁⨁◯◯ Low	
RT-PCR Positive Symptomatic COVID-19 (Based on Presence of Obesity) – Obese												
1	randomised trials	serious[a]	not serious	serious[b]	not serious	none	6/295 (2.0%)	8/162 (4.9%)	**RR 0.41** (0.15 to 1.17)	**29 fewer per 1,000** (from 42 fewer to 8 more)	⨁⨁◯◯ Low	
RT-PCR Positive Symptomatic COVID-19 (Based on Presence of Obesity) - Not Obese												
1	randomised trials	serious[a]	not serious	serious[b]	serious[c]	none	17/451 (3.8%)	9/210 (4.3%)	**RR 0.88** (0.40 to 1.94)	**5 fewer per 1,000** (from 26 fewer to 40 more)	⨁◯◯◯ Very low	
Severe or Critical COVID-19 Infection												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	AZD7442	Placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious[a]	not serious	serious[b]	serious[c]	none	0/749 (0.0%)	1/372 (0.3%)	**RR 0.17** (0.01 to 4.06)	**2 fewer per 1,000** (from 3 fewer to 8 more)	⨁◯◯◯ Very low	
Emergency Department Visit												
1	randomised trials	serious[a]	not serious	serious[b]	serious[c]	none	1/749 (0.1%)	2/372 (0.5%)	**RR 0.25** (0.02 to 2.73)	**4 fewer per 1,000** (from 5 fewer to 9 more)	⨁◯◯◯ Very low	
Adverse Events												
1	randomised trials	serious[a]	not serious	serious[b]	not serious	none	162/749 (21.6%)	111/372 (29.8%)	**RR 0.72** (0.59 to 0.89)	**84 fewer per 1,000** (from 122 fewer to 33 fewer)	⨁⨁◯◯ Low	
Serious Adverse Events												
1	randomised trials	serious[a]	not serious	serious[b]	serious[c]	none	5/749 (0.7%)	3/372 (0.8%)	**RR 0.83** (0.20 to 3.45)	**1 fewer per 1,000** (from 6 fewer to 20 more)	⨁◯◯◯ Very low	

CI: confidence interval; **RR:** risk ratio

Explanations

a. downgraded for attrition bias and some unblinded participants
b. the trial was conducted prior to the emergence of the omicron variant
c. wide confidence interval

Appendix 6: Table of Ongoing Studies

Clinical Trial Identifier/Title	Study Design	Country	Population	Intervention	Outcome	Estimated Date of Completion
NCT05375760 **A Randomized, Open-label, Dose-ranging Study in Adults and Pediatric Individuals 12 Years of Age to Assess the Safety, Immunogenicity, Pharmacokinetics and Pharmacodynamics of AZD7442, for Pre-exposure Prophylaxis of COVID-19**	Randomized controlled trial	USA	Age: 12 Years to 99 Years (Child, Adult, Older Adult)	• Biological: AZD7442 (tixagevimab [AZD8895] + cilgavimab [AZD1061])	• Adverse Events • Serious Adverse Events • Adverse Events of Special Interest • Incidence of ADA in serum • Serum AZD7442 concentrations • Changes from baseline in GMTs and GMFRs values in SARS-CoV-2 nAbs	July 17, 2024

NCT05184062 **A Study to Evaluate the Safety and Tolerability of AZD7442 in Chinese Adults**	Randomized controlled trial	USA	18 Years and older (Adult, Older Adult)	AZD7442 vs placebo • Drug: 600mg AZD7442 IV • Drug: 600mg placebo I	• Incidence of adverse events (AEs) • Incidence of serious adverse events (SAEs) • Incidence of adverse event of special interests (AESIs) • Safety as determined by abnormality in haematology • Safety as determined by abnormality in clinical chemistry • Safety as determined by abnormality in urinalysis • Safety as determined by abnormality in Coagulation. • Incidence of abnormal 12- lead electrocardiogram (ECG) • Safety as determined by abnormal vital signs (blood pressure, pulse rate, body temperature, and respiratory rate)	June 30, 2023

NCT05437289 **A Study to Evaluate the Safety and Tolerability of AZD7442 in Healthy Chinese Adults**	Randomized controlled trial	USA	18 Years to 55 Years (Adult)	AZD7442 vs placebo • Drug: AZD7442 IM • Drug: Placebo IM • Drug: AZD7442 IV • Drug: Placebo IV	• Incidence of adverse events (AEs) • Incidence of serious adverse events (SAEs) • Incidence of adverse event of special interests (AESIs) • Number of participants with abnormal laboratory test results • Number of participants with abnormal Coagulation test results • Number of participants with abnormal urinalysis • Number of participants with abnormal ECG readings • Number of participants with abnormal vital signs	February 10, 2023

NCT04507256 **AZD7442 - a Potential Combination Therapy for the Prevention and Treatment of COVID-19**	Randomized controlled trial	UK	18 Years to 55 Years (Adult)	• Combination Product: AZD7442 • Other: Placebo	• Number of participants with adverse events (AEs) and serious AEs • Observed maximum concentration (Cmax) (IV infusion) • Time to reach maximum concentration (Tmax) (IV infusion) • Terminal elimination half life, estimated as (ln2)/#z (t½#z) (IV infusion) • Area under the concentration curve from time zero to the time of last quantifiable concentration (AUClast) (IV infusion) • Area under the concentration time curve from time zero extrapolated to infinity (AUCinf) (IV infusion) • Volume of distribution at steady state (Vss) (IV infusion) • Volume of distribution at terminal phase (Vz) (IV infusion) • Systemic clearance (CL) (IV infusion) • Cmax (IM injection) • and 8 more	Completed but no results posted yet
NCT04625725 **Phase III Double-blind, Placebo-**	Randomized controlled trial	US	18 Years to 120 Years (Adult, Older Adult)	• Drug: AZD7442 • Drug: Placebo	• The incidence of the first case of SARS-CoV-2 RT PCR positive symptomatic illness	November 30, 2023

controlled Study of AZD7442 for Pre-exposure Prophylaxis of COVID-19 in Adult (PROVENT)					• AEs, SAEs, MAAEs, and AESIs post dose of IMP • The incidence of participants who have a post-treatment response (negative at baseline to positive at any time post-baseline) for SARS-CoV-2 nucleocapsid antibodies. • The incidence of SARS-CoV-2 RT-PCR-positive severe or critical symptomatic illness occurring after dosing with IMP • The incidence of COVID-19-related Emergency Department visits occurring after dosing with IMP • Serum AZD7442 concentrations, PK parameters if data permit. • Incidence of ADA to AZD7442 in serum.	
NCT05438498 **Real World Evaluation of the Effectiveness of AZD7442 for Prevention of SARS-CoV-2**	Non-randomized	US	18 Years to 100 Years (Adult, Older Adult)	• Drug: Evusheld (tixagevimab +cilgavimab) IM or IV	• AZD7442 Serum Concentration • Cancer Group and Treatment Group Comparison • SARS-CoV-2 Infection	December 3, 2023

NCT05315323 **Clinical Use of EVUSHELD as Pre-exposure Prophylaxis in Real-world Setting in Gulf Cooperation Council Countries** **(EVOLVE)**	Observational (Prospective Cohort)	worldwide	12 Years and older (Child, Adult, Older Adult)	AZD7442	• Demographics • clinical characteristics • baseline and repeat administration • Incidence of SARS-CoV-2 infection • Incidence of all-cause hospitalization and mortality • COVID-19 risk behavior at time of AZD7442 • Describe health-related quality of life • Describe COVID-19-related healthcare resource utilization	November 30, 2023
NCT05461378 **PREP (Pre-Exposure Prophylaxis) of COVID-19** **(PrEP)**	Observational Cohort: Prospective	US	12 Years and older (Child, Adult, Older Adult)	•Drug: Evusheld	Outcome Measures: • Concentration of AZD7442 in serum over time [ENROLLMENT, 6 MONTHS, 12 MONTHS] Concentration of AZD7442 in serum over time [ENROLLMENT, 6 MONTHS, 12 MONTHS] Concentration of AZD7442 in serum over time [ENROLLMENT, 6 MONTHS, 12 MONTHS] • Concentration of AZD7442 in serum • Assessment of SARS-CoV-2 Spike IgG levels using Bioplex/Biorad assays, viral	February 28, 2024

					neutralization assay using competitive ACE2 EIA, and pseudovirus neutralization titers • Assessment of T-cell responses using an ELISPOT assay • Determining SARS-CoV-2 variant type using whole genome sequencing • Determining Concentration of AZD7442 in serum, SARS-CoV-2 Spike IgG levels using Bioplex/Biorad assays, viral neutralization assay using competitive ACE2 EIA, and pseudovirus neutralization titers • Proportion of participants with #1 COVID-19-related medically-attended visit • Proportion of participants who die by the end of the study • Lifestyle Modification Questionnaire	

NCT05569408 **eVusheld Assessment reaL wORld Effectiveness in DoD Health System** **(VALOR DoD)**	Observational Cohort: Retrospective	worldwide	12 Years and older (Child, Adult, Older Adult)	•Drug: EVUSHELD	Outcome Measures: • COVID-19 Hospitalisation • All-cause mortality • Documented SARS-CoV-2 infection • Medically attended COVID-19 • COVID-19 hospitalisation • COVID-19 Intensive Care Unit (ICU) admisssion • COVID-19 related mortality	October 15, 2023
NCT05375760 **A Randomized, Open-label, Dose-ranging Study in Adults and Pediatric Individuals # 12 Years of Age to Assess the Safety, Immunogenicity, Pharmacokinetics, and Pharmacodynamics of AZD7442, for Pre-exposure Prophylaxis of COVID-19** **(ENDURE)**	Randomized	US	12 Years to 99 Years (Child, Adult, Older Adult)	• Biological: AZD7442 (tixagevimab [AZD8895] + cilgavimab [AZD1061])	Outcome Measures: • Adverse Events • Serious Adverse Events • Adverse Events of Special Interest • Incidence of ADA in serum • Serum AZD7442 concentrations • Changes from baseline in GMTs and GMFRs values in SARS-CoV-2 nAbs	July 24, 2024