Canada's Drug and
Health Technology Agency

CADTH Drug Implementation Advice

Tixagevimab and Cilgavimab (Evusheld)

Sponsor: AstraZeneca Canada

Proposed indication: Treatment of mild to moderate COVID-19 in adults and adolescents (≥ 12 years of age weighing at least 40 kg)

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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Implementation Advice

What Is the Unmet Need for the Treatment of COVID-19?

COVID-19 is a major public health burden associated with substantial numbers of infections, deaths, and hospitalizations. Vaccination is recognized as a highly efficacious measure in protecting against severe infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). However, certain risk groups may have a reduced protective response after vaccination, such as those who are immunocompromised. Also, the effectiveness of current vaccines may change in the absence of additional doses, as the protective effects wane over time, and with the emergence of new variants. This may lead to breakthrough infections in those who are vaccinated. In individuals with advanced age and medical comorbidities, there remains a risk of progressing to severe COVID-19, even in spite of vaccination.

Various medications are now available for the outpatient treatment of mild to moderate COVID-19, with the goal being to reduce the risk of progression to severe disease, hospitalization, and death. For this indication, treatments recommended in Canada that retain activity against the latest SARS-CoV-2 variants include nirmatrelvir and ritonavir (Paxlovid) and remdesivir; however, there are potential challenges with these options, such as drug interactions and mode of administration.

What Is Evusheld?

Evusheld (tixagevimab and cilgavimab) is a combination of long-acting monoclonal antibodies for intramuscular administration (IM). Tixagevimab and cilgavimab bind to non-overlapping epitopes of the SARS-COV-2 spike protein receptor–binding domain and block its interaction with the host cellular receptor, thus blocking virus entry and neutralizing it.[2] This mechanism of action leads to reduced infection severity. It is also variant-specific, with activity depending on the ability of the monoclonal antibodies to bind to the spike protein of circulating variants.

Evusheld currently has a Health Canada indication for the treatment of mild to moderate COVID-19 in adults and adolescents (≥ 12 years of age and weighing at least 40 kg). The recommended dosage for the treatment of mild to moderate COVID-19 is 600 mg (tixagevimab 300 mg and cilgavimab 300 mg) through IM administration. This indication is also under review in other jurisdictions, including the US, Australia, and the UK, and has been approved in the European Union and Japan.

Evusheld was approved by Health Canada in April 2022 for pre-exposure prophylaxis of COVID-19 in adults and adolescents (≥ 12 years of age and weighing at least 40 kg), who have not had a known recent exposure to SARS-CoV-2, who are immunocompromised and unlikely to mount an adequate immune response to COVID-19 vaccination, or for whom COVID-19 vaccination is not recommended. Since then, the sponsor submitted a request for an increase in the recommended dosage, which is currently under review by Health Canada (600 mg Evusheld through IM administration every 6 months). This

comes as a result of additional data, including the expected level of neutralization activity against the Omicron BA.2, BA.4, and BA.5 variants.[1] The use of tixagevimab and cilgavimab for pre-exposure prophylaxis of COVID-19 has been reviewed by CADTH in a separate guidance document.[2]

How Did CADTH Approach This Review?

The aim of this CADTH review was to inform decision-making on the optimal use of tixagevimab and cilgavimab (Evusheld) for the treatment of mild to moderate COVID-19, especially in the context of a potential limited supply. In line with the *Procedures for CADTH Review of Nationally Procured Drug Products*,[3] an implementation advice panel (the "panel") was convened, which spanned various disciplines and clinical settings with geographically diverse representation from across Canada. The panel captured expert advice through consensus and prioritized patient populations that were most likely to benefit from treatment in a tiered risk group approach. Drug costs or a health economic analysis were out of scope, as is the case for all CADTH reviews of nationally procured drug products.

What Is the Implementation Advice?

The panel suggests prioritizing adult patients with confirmed SARS-CoV-2 infection and symptoms of mild to moderate COVID-19 into 3 groups (Table 1). The tiered risk groups are based on patients who are considered to have the highest risk of progressing to severe disease, and patients who are expected to benefit most from the drug. This guidance aims to prioritize patients in clinical practice, and in the case where supply may need to be prioritized.

The risk groups were identified based on the evidence available at the time of the review. As important gaps in the available evidence remained, the panel also used expert opinion to inform the advice.

What Are the Limitations of the Review?

Important gaps in the evidence included the lack of efficacy and safety data of tixagevimab and cilgavimab in individuals vaccinated against SARS-CoV-2, and in special populations such as pediatric or older patients. In addition, the evidence could not inform on the clinical effectiveness of tixagevimab and cilgavimab for current variants of concern such as Omicron, as the main variants in the trial were Alpha, Gamma, and Delta. There is also a scarcity of exposure and safety data overall in large patient populations to fully characterize the safety profile of tixagevimab and cilgavimab, especially regarding potential cardiovascular harms.

With a rapidly changing landscape and evolving virus characteristics, the real-world effectiveness of medications being reviewed at one point during the pandemic may change over time. At the time of this review, the dominant SARS-CoV-2 variant of concern in Canada is BA 5.1,[1] against which tixagevimab and cilgavimab may retain a reduced but significant neutralizing activity based on in vitro assessments.[1,2] However,

changes in virus structure with the emergence of new variants of concern may impact the expected efficacy of therapeutic monoclonal antibody preparations for COVID-19. Emerging data on clinical effectiveness should be followed closely.

Table 1: Prioritization of Patient Treatment With Mild to Moderate COVID-19 With Tixagevimab and Cilgavimab (Evusheld) Based on a Tiered Risk Group Approach

Tier	Risk group
1	Immunocompromised[a] individuals (≥ 12 years of age weighing at least 40 kg) who are not expected to mount an adequate immune response to SARS-CoV-2 infection.
2	Individuals who are at increased risk for progression to severe disease, which includes individuals with **all** the following risk factors: • age ≥ 70 years • presence of ≥ 2 comorbidities[b] • ≥ 12 weeks since the most recent of SARS-CoV-2 vaccine doses[c] or SARS-CoV-2 infection.
3	Individuals who are at increased risk for progression to severe disease, which includes individuals with **at least 1** of the following risk factors: • age ≥ 70 years • presence of ≥ 2 comorbidities[b] • ≥ 12 weeks since the most recent of SARS-CoV-2 vaccine doses[c] or SARS-CoV-2 infection.

SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

[a] Individuals who were moderately to severely immunocompromised included those with the following conditions: active treatment for solid tumour or hematologic malignancies; receipt of solid-organ transplant and taking immunosuppressive therapy; receipt of hematopoietic stem cell transplant (within 2 years of transplant or taking immunosuppression therapy); receipt of chimeric antigen receptor (CAR) T-cell therapy; moderate to severe primary immunodeficiency with associated humoral and/or cell-mediated immunodeficiency or immune dysregulation; HIV with AIDS-defining illness or tuberculosis diagnosis in last 12 months before starting vaccine series, or severe immune compromise with CD4 < 200 cells/uL or CD4% < 15%, or without HIV viral suppression; active treatment with the following categories of immunosuppressive therapies: anti-B cell therapies (monoclonal antibodies targeting CD19, CD20, and CD22), high-dose systemic corticosteroids (prednisone equivalent of ≥ 2 mg/kg per day or 20 mg per day if weighing > 10 kg, for ≥ 14 days), alkylating agents, antimetabolites, or tumor-necrosis factor inhibitors and other biologic agents that are significantly immunosuppressive.[4]

[b] Comorbidities may include obesity (i.e., body mass index ≥ 30), current smoking status, chronic kidney disease, diabetes, immunosuppressive disease or immunosuppressive treatment, cardiovascular disease (including congenital heart disease) or hypertension, chronic lung disease (including chronic obstructive pulmonary disease, moderate to severe asthma, interstitial lung disease, cystic fibrosis, and pulmonary hypertension), sickle cell disease, neurodevelopmental disorders (including cerebral palsy, Down syndrome), genetic or metabolic syndromes and severe congenital anomalies, injection drug use, problematic alcohol use, severe mental illness, and medical-related technological dependence not related to COVID-19 (including tracheostomy, gastrostomy, or positive pressure ventilation).[2-6]

[c] In individuals who have had a primary series of vaccination.

Rationale for Decision

Results from the TACKLE double-blind randomized controlled trial demonstrated that the use of tixagevimab and cilgavimab was associated with a reduction of 50% in the risk of experiencing severe COVID-19 or death from any cause through day 29 compared with placebo. These results were obtained in a population of adults with confirmed SARS-CoV-2 infection and mild to moderate COVID-19 symptoms, who received treatment within 7 days of symptom onset. Individuals were unvaccinated against SARS-CoV-2 and treated as outpatients during a period of variant dominance.

Based on the findings from this study available at the time of the review, the panel suggested prioritization of patient populations for the appropriate use of tixagevimab

and cilgavimab in the context of a potential limited supply. Other evidence considered included findings from epidemiological studies identifying factors that are likely to put an individual at risk of progression to severe disease, as well as pan-Canadian data on the prevalence of variants of concern for SARS-CoV-2. Important gaps in the available evidence led the panel to also use expert opinion to inform the advice.

Tier 1: Individuals who are immunocompromised and not expected to mount an adequate immune response to SARS-CoV-2 infection

In the TACKLE trial, 5% of patients presented with what was described as an immunocompromised state. The scarcity of efficacy and safety data in a large patient population of patients adequately identified as immunocompromised is an evidence gap leading the panel to use expert opinion to formulate advice within this tier. Individuals who are immunocompromised are not expected to mount an adequate immune response to SARS-CoV-2 infection and have a higher risk of severe infection; therefore, they have been identified as a patient population at highest risk of progression to severe COVID-19.

Tier 2 and 3: Individuals who are at increased risk for progression to severe disease, which includes individuals with all and/or at least 1 of the following risk factors: 70 years or older; presence of 2 or more comorbidities; and/or 12 or more weeks since the most recent of either a SARS-CoV-2 vaccine dose or a SARS-CoV-2 infection

Gaps in the available evidence from the TACKLE trial led the panel to use additional available evidence, as well as expert opinion. The Public Health Agency of Canada published reports on the high risk of hospitalizations and deaths, which appear to be directly related to age and more common in patients with comorbidities.[4] Similarly, data analyses available from COVID-19 cases in British Columbia showed an increase in hospitalization rate that was proportional with age and a higher number of comorbidities.[5] Hospitalizations were also more frequent in patients with reduced numbers of vaccine doses.[5]

Overall, 89% of patients in TACKLE had at least 1 comorbidity. The trial did not specifically report on patients presenting with more than 1 comorbidity. A total of 9% of the patient population was between 65 and 74 years of age, 2% of patients were between 75 and 79 years of age, and 1.5% of patients were 80 years or older. Subgroup results were reported for the primary outcome of severe COVID-19 or death from any cause through day 29. Findings for subpopulations of patients with advanced age did not consistently demonstrate benefits similar to those reported in the overall population. However, conclusions should not be drawn from these findings, as results were associated with wide confidence intervals (CIs) and suffered from imprecision due to the small proportions of patients, and subsequently low number of events, that could be included in the analyses. Limitations inherent to subgroup analyses are discussed in the Summary of Evidence section of this report.

Selection criteria in the TACKLE trial stated that patients were not vaccinated for COVID-19 and did not receive other monoclonal antibody or biologic drugs indicated for the prevention of SARS-CoV-2 infection. Therefore, the real-world effectiveness of

tixagevimab and cilgavimab in individuals who are vaccinated against COVID-19 remains an evidence gap. Based on expert opinion, the panel concluded that there is a risk for disease progression that is related to the number of SARS-CoV-2 vaccine doses received, and whether it has been more than 12 weeks since the most recent SARS-CoV-2 vaccine dose or infection, as per National Advisory Committee on Immunization (NACI) guidance for heightened epidemiological risks.[6] Patients not expected to have adequate immune protection against SARS-CoV-2 due to the waning effectiveness of vaccination, which puts them at risk of disease progression, were therefore identified by the panel as those who are more likely to benefit from treatment.

Panel Deliberation

The panel, comprising 9 members representing primary care and family medicine, infectious disease, emergency medicine, internal and critical care medicine, pediatrics, geriatrics, clinical immunology and allergy, ethics, pharmacy and nursing from academic, community, and rural clinical settings across Canada met on September 22, 2022. The aim was to inform decision-making on the appropriate use of tixagevimab and cilgavimab for the treatment of mild to moderate COVID-19. Particularly, CADTH was seeking feedback from the panel regarding the prioritization of patient populations to receive treatment in situations when supply is limited. These would include:

- patient populations that demonstrate the greatest unmet need for a treatment to avoid progression to severe COVID-19
- patient populations that are most likely to achieve benefit from the drug and achieve treatment goals of preventing hospitalizations and/or death
- patient populations that are less likely to benefit from the drug and not achieve treatment goals due to uncertainty in efficacy and/or safety.

Considerations for special populations, as well as considerations associated with administration and treatment course (i.e., prescribing advice), were discussed.

The clinical value of tixagevimab and cilgavimab was deliberated on in the context of the ongoing COVID-19 public health emergency. The advice reflects the panel's consensus based on the best available evidence for the treatment of COVID-19 with tixagevimab and cilgavimab and based on their clinical expertise in the diagnosis and management of COVID-19. The panel also discussed ethical considerations for the judicious use of tixagevimab and cilgavimab, particularly in scenarios of high demand for treatment.

Place in Therapy

Goals of Treatment

The panel concluded that the primary goal of treatment is the reduction of hospitalizations and deaths in patients who are symptomatic and at high risk for progression to severe COVID-19.

As the COVID-19 pandemic evolves, additional treatment goals may be considered. The panel felt that these may include the reduction in the number of days of symptomatic illness and sick leave, as well as the reduction in COVID-19–related complications such as long COVID. Further efficacy and safety data are required to inform these goals of therapy.

Unmet Needs

The panel members agreed that the greatest unmet needs are in patients who are immunocompromised, who are at highest risk for progression to severe COVID-19 and have the highest risk of severe infection, as they are not expected to mount an adequate immune response to SARS-CoV-2 infection. Individuals with advanced age or multiple comorbidities were also considered at higher risk of progression to severe disease by the panel based on findings from epidemiological studies identifying factors that are likely to put an individual at risk of progression to severe disease. The third group of patients identified were individuals who are not expected to have an adequate immune protection at the time of SARS-CoV-2 infection due to the waning effectiveness of vaccination or prior infection.

Prescribing Advice

- The panel advised that the initiation of therapy with tixagevimab and cilgavimab should be as soon as possible, optimally within 5 days, but up to a maximum of 7 days, after symptom onset, notwithstanding the date of diagnostic testing. This is based on a supportive analysis from the TACKLE trial suggesting that, when treatment was received within 5 days of symptom onset, the use of tixagevimab and cilgavimab was associated with a reduction of 67% in the risk of experiencing severe COVID-19 or death from any cause through day 29 compared with placebo.
- The panel stressed that the real-world effectiveness of medications being reviewed at one point during the pandemic may change over time, especially considering the emergence of new variants and their impact on disease severity. The panel advised prescribers to seek up-to-date knowledge of the clinical effectiveness of tixagevimab and cilgavimab, and to assess the balance between effectiveness and potential harms for each individual patient in relation to the risk of progressing to severe disease.
- The panel advised that tixagevimab and cilgavimab not be used in patients with a previous history of myocardial infarction, unstable coronary artery disease, heart failure, coronary artery bypass graft, arrhythmia, cardiomegaly, cardiomyopathy, cardio-respiratory arrest, or any other unstable cardiac condition. Furthermore, the panel advised that a patient-centred care discussion be held to discuss risks and benefits before prescribing tixagevimab and cilgavimab to any patients, regardless of baseline risk factors.
- The panel affirms that there is a need to confirm the SARS-CoV-2 infection through a diagnostic test; furthermore, there is consensus that the use of either a rapid antigen test (RAT) supervised by a health care professional, or polymerase chain reaction (PCR) test is acceptable.
- An evidence gap exists for repeat doses of treatment with tixagevimab and cilgavimab in those with a confirmed diagnosis of COVID-19, or in those who

previously received tixagevimab and cilgavimab for pre-exposure prophylaxis of COVID-19. As such, this should be administered per the product monograph and evaluated on a case-by-case basis in consultation with a specialist.

Other Discussion Points

- The panel appreciates that the evidence available for tixagevimab and cilgavimab is in the unvaccinated adult patient population. However, the panel members unanimously agreed that treatment with tixagevimab and cilgavimab should not be viewed as an alternative to up-to-date immunization through vaccination against COVID-19. The panel members strongly support vaccination as the primary prevention modality against SARS-CoV-2 infection. Vaccination is widely recognized as a highly efficacious measure in preventing severe disease, ultimately protecting against the most serious COVID-19–related outcomes of hospitalization and death.
- It is not possible, based on the data available at this time, to conclude with certainty that the real-world effectiveness of tixagevimab and cilgavimab in patients living in Canada would be similar to what was observed in the TACKLE study. A wide range of interindividual variations have been observed in SARS-CoV-2 infections, including individual response factors to treatment (such as advanced age, comorbidities, and vaccination status) that may differ from that of the population included in the trial. There is also a rapid evolution in the SARS-CoV-2 characteristics. These include virus virulence, as evolution of new variants may change the risk associated with COVID-19, making it more or less likely to progress to hospitalizations and deaths. Epidemiological data will be needed to assess the risk of progressing to severe disease associated with future variants. Evolution of virus mutations in the coronavirus proteins, to which monoclonal antibodies bind, may also affect the ability of the therapy to neutralize the virus, therefore impacting clinical effectiveness of treatments.
- Various options are available for the treatment of mild to moderate COVID-19, including oral medication and parenteral drugs administered intravenously. At this time, no direct treatment comparison is available to inform on the comparative effectiveness of any medication over another. However, consideration for choice in therapy may be given to the mode of administration, drug-drug interactions, adherence or compliance with treatment course, as well as availability of products and accessibility. The balance between expected benefits and potential harms should be assessed for each individual patient by the treating specialist.

Background

An overview of the details for the drug under review is provided in Table 2.

Table 2: Review Details

Item	Description
Drug product	Tixagevimab 150 mg and cilgavimab 150 mg (Evusheld 300 mg); solution for injection, intramuscular
Proposed indication	For the treatment of mild to moderate COVID-19 in adults and adolescents (≥ 12 years of age weighing at least 40 kg)
Health Canada approval status	NOC
NOC date	October 18, 2022
Sponsor	AstraZeneca

NOC = Notice of Compliance.

COVID-19

As of September 9, 2022, Canada has published case report data on 4,197,701 SARS-CoV-2 infections, including 44,437 deaths, since the beginning of the COVID-19 pandemic. [4] The main goal of COVID-19 related measures and treatments is to prevent hospitalizations and deaths that appear to be directly related to age and are more common in patients with comorbidities.[4]

Throughout the pandemic, various domestic and international groups have examined risk factors for hospitalization and death related to COVID-19. In Canada, the most common comorbidities in patients who were hospitalized during the second wave of the pandemic were hypertension (27.6%), diabetes (15.9%), asthma (7.0%), coronary artery disease (6.0%), chronic lung disease (5.2%), congestive heart failure (3.5%), active cancer (3.2%), and obesity (1.9%). [7] Certain populations may also be at increased risk of worse outcomes, including those in long-term care settings[7] and those from Indigenous populations.[8] In an analysis from cases in British Columbia, age has been shown to be the largest risk factor for COVID-19 hospitalization.[5] The presence of at-risk conditions, in addition to advancing age, also led to increased risk of COVID-19 hospitalization.[5]

The pathogenesis is understood to be related to 2 main processes:[9] the replication of SARS-CoV-2 during mild to moderate disease and the dysregulation of the immune and inflammatory response as the disease progresses, which is responsible for tissue damage and other complications. The treatment strategy for the mild to moderate stage aims to prevent or minimize replication of the virus by means of antiviral treatments, with the ultimate goals of stopping disease progression to severe COVID-19 and avoiding hospitalization and death. For this indication, treatments recommended in Canada that retain activity against the latest SARS-CoV-2 variants include the oral medication nirmatrelvir and ritonavir (Paxlovid), which is associated with serious drug interactions that may not be suitable for specific patients, and with reports of COVID-19 rebound.[10]

Another treatment option is IV remdesivir; however, IV administration is associated with an additional burden for both the patients and the health care system.

As of August 21, 2022, the main SARS-CoV-2 variant of concern in Canada with active cases was Omicron (90.1%), with the following distribution of Omicron subvariants (BA 5.1 = 13.8%; BA.5.2 = 23.2%, BA5.2.1 = 26.5%, and other BA.5 = 26.6%).[4]

In order to facilitate timely access to novel COVID-19 therapies, CADTH has developed procedures to perform its review simultaneously with Health Canada's regulatory approval process for nationally procured drug products. The aim of this CADTH review was to inform decision-making on the optimal use of tixagevimab and cilgavimab (Evusheld) for the treatment of mild to moderate COVID-19, especially in the context of a potential limited supply, in line with the *Procedures for CADTH Review of Nationally Procured Drug Products*.[3]

Tixagevimab and Cilgavimab (Evusheld)

Tixagevimab and cilgavimab (Evusheld) is a combination of long-acting monoclonal antibodies for IM providing an immediate and sustained antiviral effect. Tixagevimab and cilgavimab are 2 separate SARS-CoV-2–specific neutralizing monoclonal antibodies that bind to distinct, non-overlapping epitopes of the spike protein receptor–binding domain. By targeting either of these regions of the spike protein on the virus, antibodies can block the virus's attachment to ACE2 receptors on human cells and, therefore, neutralize it.[11] This mechanism of action leads to reduced infection severity. It is also variant-specific, with activity depending on the ability of the monoclonal antibodies to bind to the spike protein of circulating variants.

Evusheld currently has a Health Canada indication for the treatment of mild to moderate COVID-19 in adults and adolescents (≥ 12 years of age and weighing at least 40 kg). The recommended dosage for the treatment of mild to moderate COVID-19 is 600 mg (tixagevimab 300 mg and cilgavimab 300 mg) through IM administration. This indication is also under review in other jurisdictions, including the US, Australia, and the UK, and has been approved in the European Union and Japan.

Evusheld was approved by Health Canada in April 2022 for pre-exposure prophylaxis of COVID-19 in adults and adolescents (≥12 years of age and weighing at least 40 kg), who have not had a known recent exposure to SARS-CoV-2, who are immunocompromised and unlikely to mount an adequate immune response to COVID-19 vaccination, or for whom COVID-19 vaccination is not recommended. Since then, the sponsor submitted a request for an increase in the recommended dosage, which is currently under review by Health Canada (600 mg Evusheld through IM administration every 6 months). This comes as a result of additional data, including the expected level of neutralization activity against the Omicron BA.2, BA.4, and BA.5 variants.[10] The use of tixagevimab and cilgavimab for pre-exposure prophylaxis of COVID-19 has been reviewed by CADTH in a separate guidance document.[2]

Summary of Evidence

Description of Studies

One ongoing manufacturer-sponsored, multicentre, phase III, double-blind, randomized controlled trial was the primary source of evidence for the efficacy and safety of tixagevimab and cilgavimab. The TACKLE trial (n = 1,014)[11] evaluated the superiority of the combination of tixagevimab and cilgavimab against with placebo for the treatment of mild to moderate COVID-19. Medications were administered at the dosage recommended in the product monograph (i.e., one single dose of 600 mg [tixagevimab 300 mg and cilgavimab 300 mg administered as 2 separate sequential injections]) through IM administration. All patients, no matter treatment allocation, were allowed to receive concomitant standard of care therapy based on local guidelines.

The primary outcome of the TACKLE study was the relative risk reduction in the composite outcome of severe COVID-19 or death from any cause through day 29. Severe COVID-19 was characterized in the trial by a minimum of either pneumonia (fever, cough, tachypnea, or dyspnea, **and** lung infiltrates) or hypoxemia (oxygen saturation of < 90% in room air and/or severe respiratory distress) and a WHO Clinical Progression Scale score of 5 or higher.[12]

Patients were eligible for the trial if they were at least 18 years old with a laboratory-confirmed SARS-CoV-2 infection, a WHO Clinical Progression Scale score higher than 1 but lower than 4, and an oxygenation saturation level of no less than 92% at rest. Allocated treatment needed to be administered within 7 days of self-reported symptom onset. Additional details and definitions regarding the TACKLE trial and patient population are provided in Table 3, including a detailed list of COVID-19–related symptoms for inclusion purposes. Key exclusion criteria also included prior or current hospitalization for COVID-19; current or expected need for mechanical ventilation; clinically significant bleeding disorder; any other significant and relevant disease, disorder, or serious comorbidity; as well as previous hypersensitivity, infusion-related reaction, or severe adverse reaction following administration of a monoclonal antibody.

The selection criteria specified that upon study entry, patients were not vaccinated against COVID-19 and did not receive a prior monoclonal antibody or biologic drug indicated for the prevention of SARS-CoV-2 or COVID-19. Patients who became hospitalized with COVID-19 were allowed to receive approved treatment options, including investigational drugs under emergency use authorization, and they were to be treated according to local standard of care. COVID-19 vaccination was not allowed during acute illness. Patients who became eligible for access to a SARS-CoV-2 vaccine could do so after day 30. They were then unblinded as to their allocated study treatment and were encouraged to remain in the study.

Table 3: Details of TACKLE Trial

Study details	Detail
Designs and populations	
Study design	Phase III DB RCT (placebo-controlled)
Locations	Multicenter study (95 study centres in 14 countries): US, UK, Europe, South America, Japan

Patient enrolment dates	29 January 2021 — ongoing (anticipated study completion 2022)
	
	Data cut-off dates:
	• August 21, 2021
	  ○ Primary efficacy analysis
	  ○ Conducted 30 days after 43 primary end point events had occurred
	  ○ Median on-study follow-up time of 84 days
	• January 14, 2022
	  ○ Key secondary efficacy analyses, PK, PD, safety
	  ○ Declared when all patients reached their day 169 visit
	  ○ Median on-study follow-up time of 170 days

Randomized (N)	N = 1,014 patients randomized in a 1:1 ratio 903 patients treated: N = 456 in the Evusheld group and n = 454 in the placebo group

Inclusion criteria	• At least 18 years of age
	• Laboratory-confirmed SARS-CoV-2 infection
	• WHO Clinical Progression Scale Score > 1 and < 4
	• Patients to receive allocated treatment ≤ 7 days from self-reported onset of the following COVID-19 related symptoms:
	  ○ subjective fever or feeling feverish, chills, documented temperature > 37.8°C (100°F)
	  ○ sore throat, cough, shortness of breath or difficulty breathing at rest or with activity
	  ○ body pain or muscle pain or aches, fatigue, headache, nausea or vomiting, diarrhea
	  ○ nasal obstruction or congestion, nasal discharge
	  ○ new loss of taste or smell
	  ○ new onset confusion (in patients ≥ 60 years old)
	  ○ appetite loss or decreased food intake (≥ 60 years old)
	  ○ increased supplemental oxygen requirement (only for patients on baseline supplemental oxygen)
	• Oxygenation saturation ≥ 92% at rest (if no regular chronic supplementary oxygen for an underlying lung condition)
	• No participation in another clinical trial for the treatment of COVID-19 or SARS-CoV-2 during the study period

Exclusion criteria	• History or current hospitalization for COVID-19 • Need for hospitalization or immediate medical attention in a clinic or emergency room service • Previous hypersensitivity, infusion-related reaction, or severe adverse reaction to administration of a monoclonal antibody • Any prior or expected receipt of investigational or licensed vaccine or other monoclonal antibody or biologic drug indicated for the prevention of SARS-CoV-2 or COVID-19 • Requirement for mechanical ventilation or anticipated impending need for mechanical ventilation • Clinically significant bleeding disorder (factor deficiency, coagulopathy, platelet disorder) or significant bleeding or bruising following IM injection or venepuncture

Study details	Detail
	• Any other significant disease, disorder, or finding significantly increasing risk to patient, affecting ability to participate or impairing interpretation of data • Any recent life-threatening comorbidity, or requiring surgery within last 7 days • Any receipt of convalescent COVID-19 plasma treatment • Systemic or inhaled steroids within 30 days prior to study entry (except stable dose for chronic condition) • Pregnancy or breastfeeding
Drugs	
Intervention	One single dose of Evusheld 600 mg administered as 2 sequential IM injections of tixagevimab 300 mg and cilgavimab 300 mg
Comparator	One single dose of placebo administered as 2 sequential IM injections
Concomitant intervention(s)	Background local standard of care therapy
Duration	
Efficacy follow-up	456 days
Safety follow-up	456 days
Outcomes	
Primary end point	**Efficacy:** Relative risk reduction in the composite outcome of severe COVID-19 or death from any cause through day 29 • Severe COVID-19: minimum of either pneumonia (fever, cough, tachypnea, or dyspnea AND lung infiltrates) or hypoxemia (SpO2 < 90% in room air and/or severe respiratory distress) and a WHO Clinical Progression Scale score ≥ 5 **Safety:** AEs, SAEs, AEs of special interest
Key secondary end point	Composite of death from any cause or hospitalization for COVID-19 complications or sequalae through day 169
Other main secondary end points	• Incidence of patients with respiratory failure • COVID-19 symptom severity assessments • Progression of COVID-19–associated symptoms • Detection level and change from baseline of SARS-CoV-2 RNA • Time to return to pre-COVID-19 health • Duration of fever • Serum concentration and PK parameters • Incidence of serum antidrug antibodies

AE = adverse event; DB = double blind; IM = intramuscular; PD = pharmacodynamics; PK = pharmacokinetics; RCT = randomized controlled trial; RNA = ribonucleic acid; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndromecoronavirus-2.

Source: Interim Clinical Study Report.[11]

Statistical Analyses

The primary, key supportive, and key secondary analyses were statistically tested as part of the overall hierarchical testing strategy used to control for multiplicity and type I error inflation. The primary efficacy outcome was based on patients in the modified full analysis set, defined as all patients who received treatment 7 days or fewer from symptom onset and were not hospitalized at baseline for isolation purposes. The set of intercurrent events consisted of patients who received COVID-19 treatment product(s) prior to day 29 without already having met the primary efficacy end point. The intercurrent events were to be handled following the treatment policy strategy. Absence of data following patient withdrawal before having met the primary efficacy end point was treated as a missing primary end point.

Four alternative analyses were also performed for the primary efficacy population and included in the hierarchical testing methodology. The first supportive analysis was conducted in patients who received early intervention (i.e., who received treatment allocated within 5 days of symptom onset). The second supportive analysis was conducted only considering events occurring from day 4 through day 29 (patients with events occurring prior to day 4 were considered as not experiencing an event). The third supportive analysis was conducted in the full analysis set, defined as all randomized patients who received treatment. The fourth supportive analysis was conducted in patients who were seronegative at baseline.

The primary efficacy was calculated as relative risk reduction (RRR). Efficacy summaries were presented with a 2-sided 95% CI. Statistical significance was achieved if the 2-sided P value was lower than 0.05. The primary efficacy analysis model estimated the risk reduction in the incidence of severe COVID-19 or death from any cause using the stratified Cochran-Mantel Haenszel method. Kaplan-Meier curves for time to severe COVID-19 or death from any cause also supported the primary analysis. The Kaplan-Meier cumulative incidences were reported. A stratified log-rank test was conducted to assess the difference between the curves. A Cox proportional hazards model was conducted to obtain hazard ratios and their respective 95% CIs. The stratification factors were included as covariates in the Cox model.

The study had 90% power to detect a relative reduction of 65% in the incidence of severe COVID-19 or death between the study groups, assuming the incidence of severe COVID-19 or death in the placebo group was 4.6%.

Study Population

Overall, 1,014 patients were randomized in a 1:1 ratio. At the time of key secondary data cut-off (January 14, 2022), no patient had yet completed the study. Details on patients' disposition in the TACKLE study are presented in Table 4. The proportions of patients who discontinued the study at the secondary data cut-off were similar between treatment groups (5.0% in the active treatment group and 7.5% in the placebo group). The most frequent reason for discontinuation was withdrawal by patient.

Table 4: Patients Disposition in the TACKLE Trial

Category, n (%)	TIXA-CILGA	Placebo
Patients enrolled, N	1,014	
Patients randomized	456 (100.0)	454 (100.0)
Patients randomized but not dosed	4 (0.9)	3 (0.7)
Patients who received treatment	452 (99.1)	451 (99.3)
Patients who discontinued from study at primary DCO	**16 (3.5)**	**19 (4.2)**
Death	6 (1.3)	5 (1.1)
Adverse event	0	2 (0.4)
Lost to follow-up	2 (0.4)	2 (0.4)
Physician decision	1 (0.2)	0
Withdrawal by patient	7 (1.5)	7 (1.5)
Other	0	3 (0.7)
Patients who discontinued from study at key secondary DCO	**23 (5.0)**	**34 (7.5)**
Death	7 (1.5)	6 (1.3)
Adverse event	0	2 (0.4)
Lost to follow-up	3 (0.7)	7 (1.5)
Physician decision	1 (0.2)	0
Withdrawal by patient	12 (2.6)	16 (3.5)
Other	0	3 (0.7)
ITT, N Randomized and received study drug, FAS	452	451
mFAS, N Randomized and received study drug ≤ 7 days from symptom onset and were not hospitalized at baseline for isolation purposes	413	421
Safety analysis set, N All patients who received study drug	452	451

DCO = data cut-off; FAS = full analysis set; ITT = intent to treat; mFAS = modified full analysis set; TIXA-CILGA = tixagevimab and cilgavimab.

Source: Interim Clinical Study Report.[11]

Details on patient characteristics in the TACKLE study are presented in Table 5. Baseline characteristics were overall comparable between treatment groups. Among patients included in the trial, 87% were between the ages of 18 years and younger than 65 years. The proportion of patients between the ages of 75 years and younger than 80 years was 2%, with an additional 1.4% of patients 80 years or older. Most of the trial population was White, followed by American Indian or Alaska Native. The mean body mass index was 29, at the upper limit of the overweight body mass index category. Selection criteria stated that patients were not vaccinated against COVID-19 and did not receive a prior monoclonal antibody or biologic drug indicated for the prevention of SARS-CoV-2 or COVID-19; however, there was no restriction related to prior outpatient SARS-CoV-2

infection or COVID-19. This explains the SARS-CoV-2 baseline antibody status profile of the included population reported in Table 5.

The mean time from symptom onset was 5 days; 41% of patients received allocated treatment on day 6 or day 7 from reported symptom onset. A total of 88% of patients had a WHO Clinical Progression Scale score of 2 (symptomatic and independent). The vast majority of patients (90%) had a high risk of progression to severe COVID-19, which was defined as either being 65 years or older or being younger than 65 years and having at least 1 of the high-risk comorbidities for progression to severe COVID-19 or death. Among those, the most common comorbidities for progression to severe illness included obesity (43%), smoking (41%), hypertension (29%), chronic lung disease or asthma (12%), diabetes (12%), and cardiovascular disease (9%).

Sequencing data were available for 834 patients and showed that the main SARS-CoV-2 variants at baseline were Alpha, Gamma, and Delta. The Omicron variant was not reported for any patient in the trial.

The proportions of patients who were vaccinated against COVID-19 during the study after day 29 were 28% in the active treatment group and 36% in the placebo group. These patients were unblinded as to their allocated study treatment and were encouraged to remain in the study. This is not expected to have any impact on the primary outcome measurement, which was assessed in the study through day 29.

Of note, a significant proportion of patients (45.7% of randomized patients) had important protocol deviations at the key secondary data cut-off, which was balanced between treatment groups. The most frequent protocol deviations reported were related to e-diary non-compliance. Important protocol deviations related to eligibility criteria, use of prohibited medications, and study treatment or procedures were few. Therefore, it is not expected that this situation would produce a significant bias in favour of any of the 2 treatment groups.

Table 5: Baseline Characteristics in the TACKLE Trial at Key Secondary Data Cut-Off

Patient characteristic	TIXA-CILGA (N = 452)	Placebo (N = 451)
Age, mean (SD), years	46.3 (15.42)	45.9 (14.99)
Age group, n (%)		
≥ 18 to < 65 years	393 (86.9)	394 (87.4)
≥ 65 to < 75 years	38 (8.4)	46 (10.2)
≥ 75 to < 80 years	12 (2.7)	6 (1.3)
≥ 80 years	9 (2.0)	5 (1.1)
Sex, n (%)		
Female	239 (52.9)	216 (47.9)
Male	213 (47.1)	235 (52.1)
Race, n (%)		
White	285 (63.1)	274 (60.8)

Patient characteristic	TIXA-CILGA (N = 452)	Placebo (N = 451)
Black or African American	16 (3.5)	20 (4.4)
Asian	30 (6.6)	21 (4.7)
American Indian or Alaska Native	100 (22.1)	115 (25.5)
Not reported	21 (4.6)	21 (4.7)
Ethnicity, n (%)		
Hispanic or Latino	230 (50.9)	238 (52.8)
Not Hispanic or Latino	222 (49.1)	213 (47.2)
BMI, mean (SD), kg/m^2	29 (5.5)	29 (6.6)
Serum for SARS-CoV-2 serology, n (%)		
Positive	60 (13.3)	68 (15.1)
Negative	383 (84.7)	376 (83.4)
Missing	9 (2.0)	7 (1.6)
Time from symptom onset, mean (SD), days	4.9 (1.61)	5.0 (1.59)
Time from symptom onset group, n (%)		
≤ 5 days	268 (59.3)	265 (58.8)
> 5 days	184 (40.7)	186 (41.2)
WHO clinical progression scale score, n (%)		
2 – symptomatic; independent	396 (87.6)	398 (88.2)
3 – symptomatic; assistance needed	56 (12.4)	53 (11.8)
Risk group,[a] n (%)		
High	405 (89.6)	406 (90.0)
Low	47 (10.4)	45 (10.0)
Presence of COVID-19 comorbidities, n (%)		
≥ 1 comorbidity	401 (88.7)	400 (88.7)
No comorbidity	51 (11.3)	51 (11.3)
High-risk comorbidities for progression to severe COVID-19 or death, n (%)		
Obesity	195 (43.1)	193 (42.8)
Smoking	180 (39.8)	184 (40.8)
Hypertension	137 (30.3)	121 (26.8)
Chronic lung disease or asthma	58 (12.8)	50 (11.1)
Diabetes	53 (11.7)	56 (12.4)
Cardiovascular disease	42 (9.3)	38 (8.4)
Immunocompromised state	22 (4.9)	24 (5.3)
Cancer	19 (4.2)	15 (3.3)
Chronic kidney disease	10 (2.2)	9 (2.0)
Chronic liver disease	7 (1.5)	14 (3.1)

Patient characteristic	TIXA-CILGA (N = 452)	Placebo (N = 451)
Sickle cell disease	0	0
SARS-CoV-2 variant, n		
Number of patients with data	413	421
Alpha	139	119
Gamma	37	46
Delta	33	33
Lambda	11	9
Mu	0	2
Beta	0	1

BMI = body mass index; SARS-CoV-2 = severe acute respiratory syndromecoronavirus-2; SD = standard deviation; TIXA-CILGA = tixagevimab and cilgavimab.

[a] The protocol definition for being at high risk of progression to severe COVID-19 was defined as either being ≥ 65 years of age, or being < 65 years and having at least one of the high-risk comorbidities for progression to severe COVID-19 or death.

Source: Interim Clinical Study Report.[11]

Efficacy Results

The use of tixagevimab and cilgavimab in the TACKLE trial was associated with a reduction of 50% in the risk of experiencing severe COVID-19 or death from any cause through day 29 compared with placebo in adult patients who are not in hospitalized but have confirmed SARS-CoV-2 infection and mild to moderate COVID-19 symptoms based on the WHO Clinical Progression Scale, and who received treatment within 7 days of symptom onset (RRR of 50%; 95% CI, 14.4 to 71.3; P = 0.010).

The primary efficacy analysis was conducted 30 days after 43 primary end point events occurred (primary data cut-off date of August 21, 2021). Enrolment of patients in the trial stopped after 43 events occurred. The key secondary data cut-off was declared when all patients reached their day 169 visit (key secondary data cut-off date of January 14, 2022). The small numerical changes observed in the primary outcome results between the primary and key secondary data cut-off analyses were attributable to updates to the database as some patients completed their day 29 visit after the primary data cut-off.

Results of the supportive analyses performed for the primary outcome are shown in Table 6. The first supportive analysis suggests that the use of tixagevimab and cilgavimab was associated with a reduction of 67% in the risk of experiencing severe COVID-19 or death from any cause through day 29 compared with placebo when treatment was received within 5 days of symptom onset (RRR of 67%; 95% CI, 31.1 to 84.1; P = 0.002). In the second supportive analysis that included only primary outcome events occurring from day 4 through day 29, the use of tixagevimab and cilgavimab was associated with a risk reduction of 66% compared to placebo (RRR of 66%; 95% CI, 33.9 to 82.6; P < 0.001). The third supportive analysis that included all randomized patients yielded a reduction of 41% in the risk of experiencing a primary outcome event with tixagevimab and cilgavimab versus placebo (RRR of 41%; 95% CI, 4.8 to 64.0; P = 0.028). The fourth supportive analysis performed in patients seronegative at baseline led to a

risk reduction of 61% for the primary outcome with tixagevimab and cilgavimab versus placebo (RRR of 61%; 95% CI, 28.9 to 78.4; P = 0.001).

Results of supplementary time-to-event analyses for the primary outcome are shown in Table 6. Figure 2 also provides the results of time-to-event analyses for the primary outcome in the TACKLE trial. Secondary outcome results also included data on respiratory failure, the incidence of which was reduced by 72% with active treatment versus placebo through day 29 (95% CI, 0.25 to 92.06). Additional data on symptom progression and resolution were reported and details are presented in Appendix 2. However, these were not part of the main analyses and the strength of evidence associated with these findings does not allow for definite conclusions as to the efficacy of tixagevimab and cilgavimab on these outcomes.

Table 6: Key Efficacy Results for the TACKLE Trial

Outcomes	TIXA-CILGA	Placebo
Primary outcome in the trial: severe COVID-19 or death from any cause through day 29		
Primary analysis at primary DCO	N = 407	N = 415
n (%)	18 (4.4)	37 (8.9)
RRR (95% CI); P value	**50.49% (14.56 to 71.31); P = 0.010**	
Primary analysis at key secondary DCO	N = 410	N = 419
n (%)	18 (4.4)	37 (8.8)
Event type, n (%):		
Severe COVID-19	16 (3.9)	37 (8.8)
Death	2 (0.5)	0
RRR (95% CI); P value	50.38% (14.38 to 71.25); P = 0.010	
Supportive analyses for the primary outcome at key secondary DCO		
1. First supportive analysis Allocated treatment received ≤ 5 days from symptom onset	N = 254	N = 252
n (%)	9 (3.5)	27 (10.7)
RRR (95% CI); P value	66.93% (31.10, 84.13); p = 0.002	
2. Second supportive analysis Primary outcome event from day 4 through day 29	N = 410	N = 419
n (%)	11 (2.7)	33 (7.9)
RRR (95% CI); P value	66.04% (33.85 to 82.57); P < 0.001	
3. Third supportive analysis All randomized patients	N = 449	N = 448
n (%)	24 (5.3)	41 (9.2)
RRR (95% CI); P value	41.47% (4.82 to 64.00); P = 0.028	
4. Fourth supportive analysis Patients seronegative at baseline	N = 349	N = 350

Outcomes	TIXA-CILGA	Placebo
n (%)	14/347 (4.0)	36/345 (10.4)
RRR (95% CI); P value	60.80% (28.87 to 78.40); P = 0.001	
Secondary outcome in the trial: respiratory failure through day 29 at key secondary DCO		
Cox regression of time to first primary outcome event through day 29	N = 413	N = 421
n (%)	18 (4.4)	37 (8.8)
RRR (95% CI); P value	71.77% (0.28 to 0.85); P = 0.012[a]	
Supplementary time-to-event analysis for the primary outcome at key secondary DCO		
Cox regression of time to first primary outcome event through day 29	N = 413	N = 421
n (%)	18 (4.4)	37 (8.8)
HR (95% CI); P value	0.49 (0.28, 0.85); P = 0.012[a]	

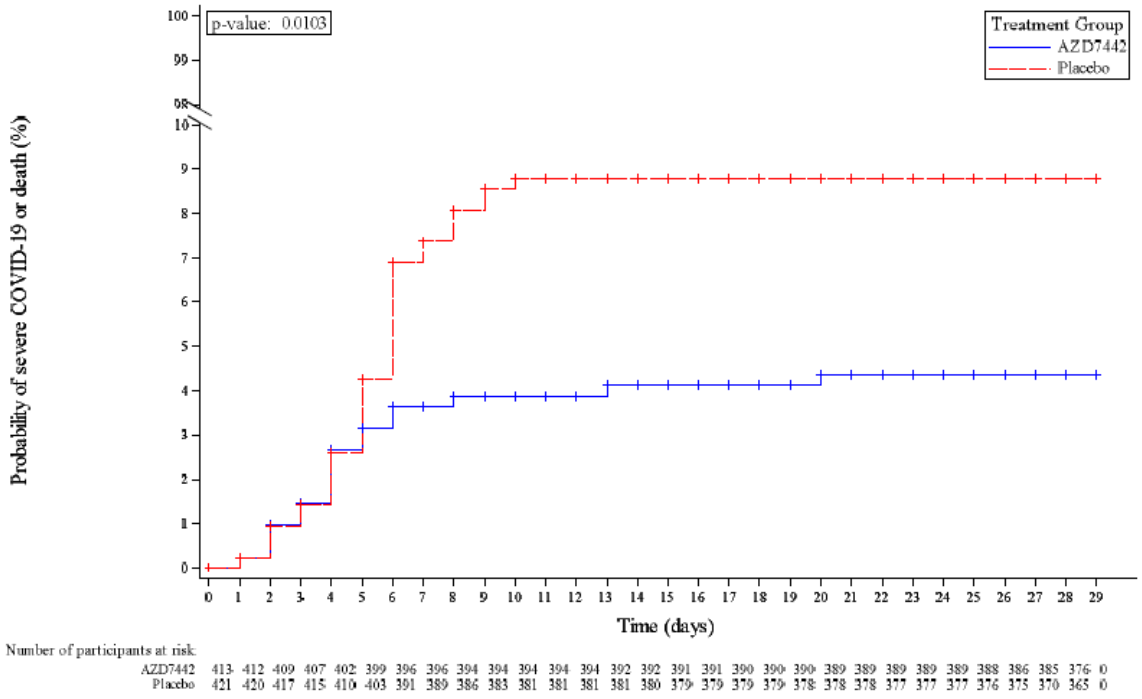
CI = confidence interval; DCO = data cut-off; HR = hazard ratio; RRR = relative risk reduction; TIXA-CILGA = tixagevimab and cilgavimab.

Note: Primary DCO was August 21, 2021. Key secondary DCO was January 14, 2022.

[a] Not controlled for multiple comparisons.

Source: Interim Clinical Study Report.[11]

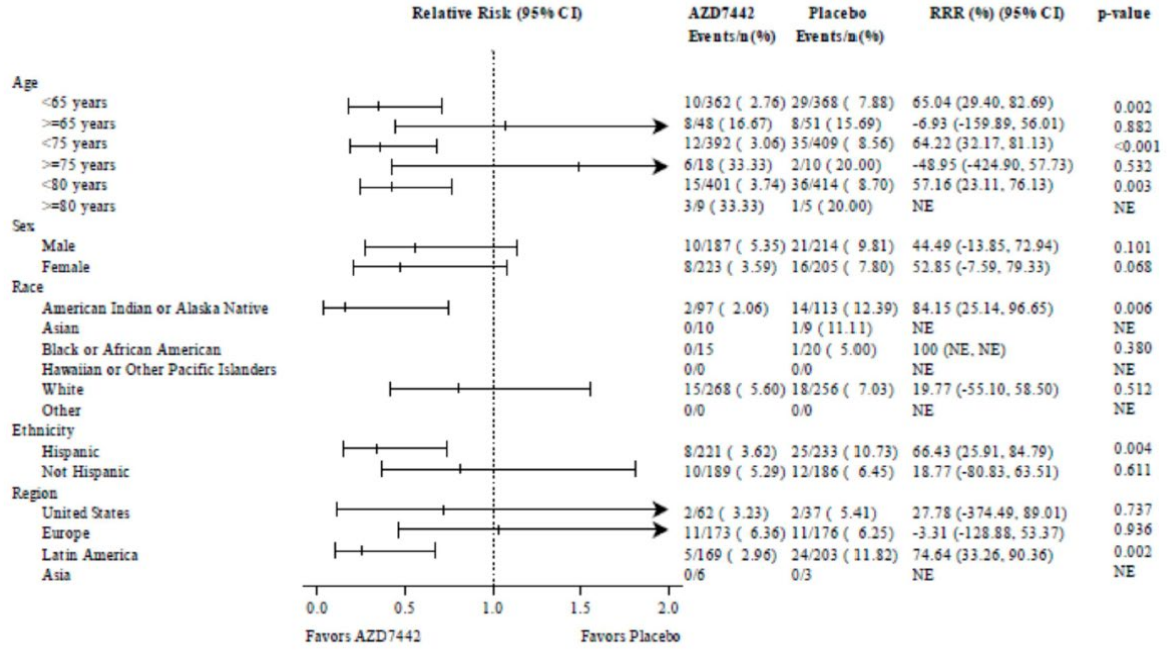
Figure 1: Supplementary Analysis of the Primary End Point — Time to Severe COVID-19 or Death From Any Cause Through Day 29



Source: Clinical Study Report.[11]

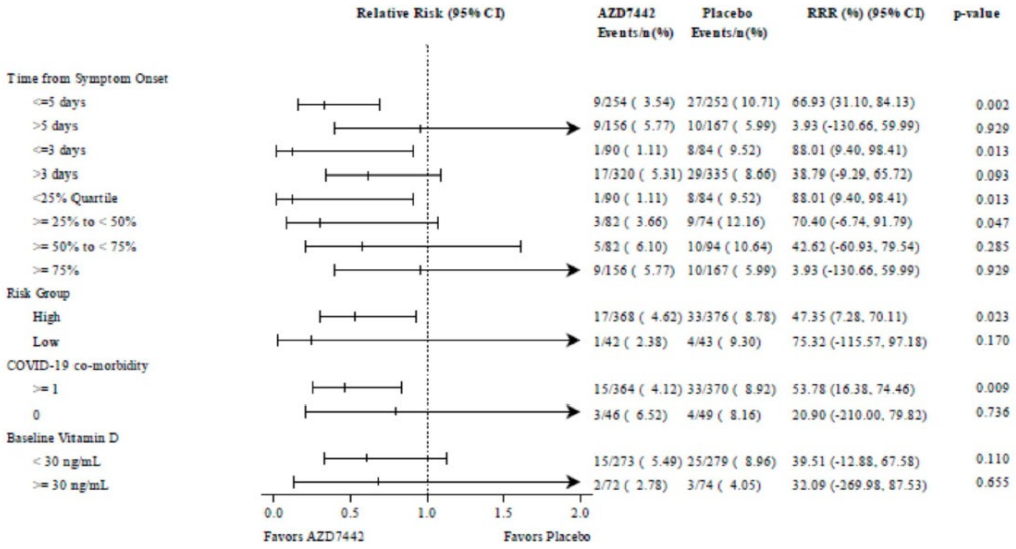
Selected subgroup analyses were reported for the primary outcome in the TACKLE trial and results are presented in Figure 3. Limited conclusions can be drawn from these analyses because the study was not designed to show a treatment difference between subgroups. The point estimates for most subpopulations were consistent with that of the overall population; however, they were often associated with a wide CI that could overlap the null hypothesis. It should be noted that for some subgroups, the number of events that occurred was very low; therefore, subgroup results should be interpreted carefully, in light of the limitations previously mentioned.

Figure 2: Forest Plot for the Subgroup Analysis of the Primary End Point — Severe COVID-19 or Death From Any Cause Through Day 29 for Age, Sex, Race, Ethnicity, and Region



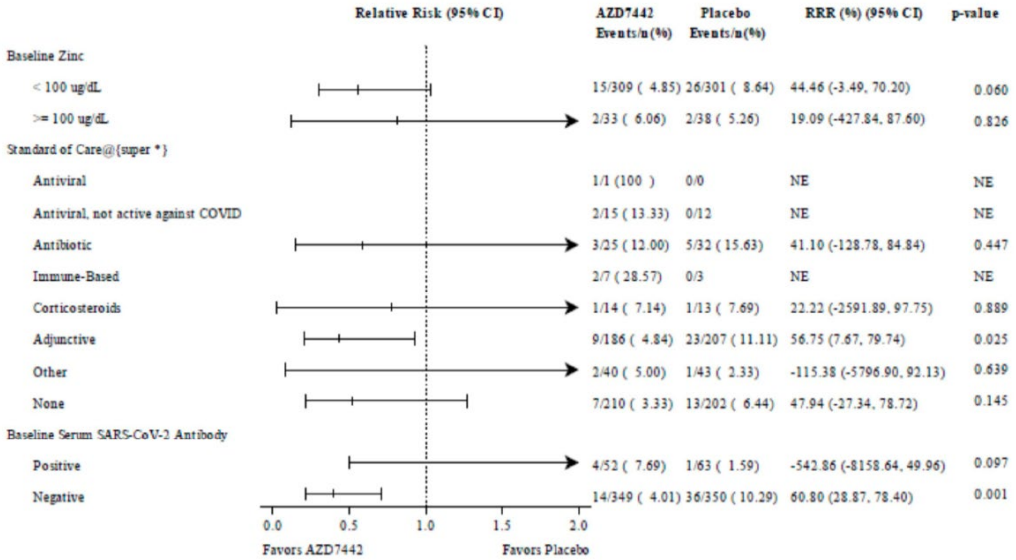
Source: Interim Clinical Study Report.[11]

Figure 3: Forest Plot for the Subgroup Analysis of the Primary End Point — Severe COVID-19 or Death From Any Cause Through Day 29 for Time From Symptom Onset, Risk Group, Covid-19 Comorbidity, and Baseline Vitamin D



Source: Interim Clinical Study Report.[11]

Figure 4: Forest Plot for the Subgroup Analysis of the Primary End Point — Severe COVID-19 or Death From Any Cause Through Day 29 for Baseline Zinc, Standard of Care, Baseline Serum SARS-CoV-2 Antibody



Source: Interim Clinical Study Report.[11]

Harms Results

The safety analyses are described for the key secondary data cut-off (January 14, 2022), providing a median duration of follow-up of 170 days (safety population).

A total of 38.5% of patients who received tixagevimab and cilgavimab experienced adverse events (AEs) throughout the trial until data cut-off; the proportion was numerically higher in patients who received placebo (43.5%). The most common AE reported was COVID-19 pneumonia, which was reported by a higher proportion of patients in the placebo group. Other frequently reported AEs included injection site pain, diarrhea, and type 2 diabetes mellitus. The proportions of patients experiencing serious AEs were 8.8% in the active treatment group and 13.5% in the placebo group. Discontinuations due to AEs were low. Among harms of special interest, it should be noted that only small proportions of patients reported administration site conditions and skin tissue disorders.

A total of 1.5% of patients who received tixagevimab and cilgavimab died during the available study follow-up; in this treatment arm, there were 3 COVID-19–related deaths, 2 cardiac-related deaths, and 2 cancer-related deaths. No deaths were considered related to study treatment. A total of 1.3% of patients who received placebo died; all causes of death were reported as COVID-19–related, with the exception of 1 patient who died of septic shock. Therefore, although the proportions of patients who died were similar between treatment arms, it is noteworthy that the causes of death differed.

Table 7: Key Harms Results in TACKLE — Key Secondary DCO (Safety Analysis Set)

Preferred term	TIXA-CILGA (N = 452)	Placebo (N = 451)
AEs, n (%)	**174 (38.5)**	**196 (43.5)**
Most common events, n (%)		
COVID-19 pneumonia	26 (5.8)	49 (10.9)
COVID-19	7 (1.5)	15 (3.3)
Injection site pain	8 (1.8)	11 (2.4)
Vaccination complication	7 (1.5)	9 (2.0)
Urinary tract infection	6 (1.3)	9 (2.0)
Hypertension	5 (1.1)	10 (2.2)
Diarrhea	8 (1.8)	5 (1.1)
Type 2 diabetes mellitus	8 (1.8)	5 (1.1)
Diabetes mellitus inadequate control	7 (1.5)	4 (0.9)
Headache	7 (1.5)	4 (0.9)
Back pain	6 (1.3)	5 (1.1)
Nasopharyngitis	4 (0.9)	5 (1.1)
Insomnia	6 (1.3)	1 (0.2)
Dizziness	5 (1.1)	1 (0.2)
Myalgia	5 (1.1)	0
Nausea	5 (1.1)	1 (0.2)

Preferred term	TIXA-CILGA (N = 452)	Placebo (N = 451)
Asthenia	1 (0.2)	6 (1.3)
SAEs, n (%)	**40 (8.8)**	**61 (13.5)**
Most common events (experienced by > 1 patient), n (%)		
COVID-19 pneumonia	23 (5.1)	37 (8.2)
Acute myocardial infarction	2 (0.4)	0
Cholecystitis chronic	2 (0.4)	0
COVID-19	1 (0.2)	9 (2.0)
Arrythmia	0	2 (0.4)
WDAEs, n (%)	**5 (1.1)**	**7 (1.6)**
Event listing, n (%)		
Death	5 (1.1)	5 (1.1)
COVID-19 pneumonia	0	1 (0.2)
Asthenia	0	1 (0.2)
Deaths, n (%)	**7 (1.5)**	**6 (1.3)**
Causes of death, n (%)		
Acute left ventricular failure	1 (0.2)	0
Sudden cardiac death	1 (0.2)	0
COVID-19 pneumonia	2 (0.4)	4 (0.9)
COVID-19	1 (0.2)	1 (0.2)
Septic shock	0	1 (0.2)
Colorectal cancer metastatic	1 (0.2)	0
Gastric cancer	1 (0.2)	0
Harms of special interest — AEs, n (%)		
General disorders and administration site conditions	14 (3.1)	13 (2.9)
Skin and subcutaneous tissue disorders	1 (0.2)	2 (0.4)

AE = adverse event; DCO = data cut-off; SAE = serious adverse event; TIXA-CILGA = tixagevimab and cilgavimab; WDAE = withdrawal due to adverse event.

Source: Clinical Study Report.[11]

Critical Appraisal

Overall, the TACKLE trial was methodologically rigorous. Some issues have been identified, however, regarding the generalizability of the findings, especially to the current situation and characteristics of COVID-19 in Canada.

Internal Validity

At the time of the CADTH review, the TACKLE trial was still ongoing and results reported were based on analyses performed at data cut-off. No patient had yet completed the study. Although the follow-up duration remains limited in time, the main efficacy findings assessed through day 29 appeared credible and were reinforced by the supportive analyses for the primary outcome that were included in the hierarchical testing structure,

which suggested that the efficacy of tixagevimab and cilgavimab may be stronger if some particular conditions are met (e.g., if administered within 5 days of symptom onset). The efficacy findings were also supported by results from a longer follow-up duration (up to 170 days at the key secondary data cut-off). However, no data are available to inform on the safety of tixagevimab and cilgavimab beyond 6 months after the initial administration of the monoclonal antibodies' combination.

Results of the subgroup analyses were mostly aligned with those of the total population; however, the study was not designed for drawing conclusions for any subgroups and as such, CIs were wide and often overlapped the null hypothesis. The drug appeared well-tolerated, with higher proportions of patients reporting AEs and serious AEs in the placebo groups, and few patients overall discontinuing the study. Exposure and follow-up in larger patient populations may be required to fully characterize the safety profile.

Generalizability

In terms of populational generalizability, a total of 3.4% of patients included in the TACKLE trial were 75 years or older; this limits conclusions on the efficacy and safety of the combination of tixagevimab and cilgavimab in an older population, which is important given the significant mortality risk in this population. A total of 90% of patients had a high risk of progression to severe COVID-19 based on age alone or on the presence of high-risk comorbidities, as seen in the routine clinical setting. Selection criteria stated that patients were not vaccinated against COVID-19 and did not receive a prior monoclonal antibody or biologic drug indicated for the prevention of SARS-CoV-2 or COVID-19; however, most of the Canadian population is vaccinated against COVID-19.

Findings from the trial are based on a sample size of 1,014 patients, which is adequate for demonstrating statistical superiority in a clinical trial. In real life, uncertainty surrounding treatment benefit cannot be excluded considering the wide interindividual variations observed in SARS-CoV-2 infections, as well as the possible widespread use of the drug.

The TACKLE trial did not provide information on the efficacy of tixagevimab and cilgavimab against the newest variants of concern that are now prevalent or emerging in Canada. At the time of this review, no clinical data are available regarding the activity of the drug under review against any of the SARS-CoV-2 Omicron variant and subvariants. However, it has been reported that the combination of tixagevimab and cilgavimab may retain a reduced but significant neutralizing activity against certain Omicron variants at the recommended dose of 600 mg (tixagevimab 300 mg and cilgavimab 300 mg).[13]

In addition, the TACKLE trial does not inform on the efficacy and safety of repeat dosing in patients who already received the treatment in the pre-exposure prophylaxis indication, as no patient had received prophylaxis with tixagevimab and cilgavimab before entering the TACKLE study.

Theoretically, there is potential risk for developing antidrug antibody with repeat dosing of monoclonal antibody. In the TACKLE study, the antidrug antibody data were analyzed for a subset of participants up to 84 days from receiving tixagevimab and cilgavimab.

Among 134 participants, 5% (6 participants) had detectable lower limit quantification of antidrug antibody assay (3.348 log 10 copies per mL).[11] This data may signal a need to cautiously monitor for the safety and the development of antidrug antibody as the practice of repeat dosing of tixagevimab and cilgavimab for prophylactic use or related to treatment is encouraged.

One multicentre, phase III, double-blind, randomized controlled trial evaluated the efficacy and safety of Evusheld 600 mg (tixagevimab 300 mg and cilgavimab 300 mg) administered by IV compared to placebo in patients who were hospitalized with COVID-19 symptoms for up to 12 days and who were also treated with remdesivir and other standard care. In the ACTIVE-3 trial (n = 1,455),[14] the estimated cumulative incidence of sustained recovery, defined in the trial as 14 consecutive days at home after hospital discharge, did not differ between treatment groups (recovery rate ratio = 1.08; 95% CI, 0.97 to 1.20; P = 0.21).

A wide range of interindividual variations have been observed in SARS-CoV-2 infections, including COVID-19 disease characteristics and response to both prophylaxis and post-infection treatment. These include, but are not limited to, individual risk factors for insufficient immunoprotection and sustained disease progression, as well as rapid apparition of several mutations in coronavirus genotypes (variants). As a result, the real-world effectiveness of tixagevimab and cilgavimab in patients in Canada may vary from what was observed in the TACKLE study.

Important gaps in the evidence included the lack of efficacy and safety data of tixagevimab and cilgavimab in individuals vaccinated against SARS-CoV-2, and in special populations such as pediatric or older patients. In addition, the evidence could not inform on the clinical effectiveness of tixagevimab and cilgavimab for current variants of concern such as Omicron, as the main variants in the trial were Alpha, Gamma, and Delta. There is also a scarcity of exposure and safety data overall in large patient populations to fully characterize the safety profile of tixagevimab and cilgavimab.

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Appendix 1: Therapeutics for COVID-19 Infection

Table 8: Therapeutics for Mild to Moderate COVID-19 Infection

Criteria	Nirmatrelvir-Ritonavir	Remdesivir	Tixagevimab-cilgavimab
Brand Name	Paxlovid	Veklury	Evusheld
Mechanism of Action	Viral protease inhibitor that halts viral replication	Nucleotide analog ribonucleic acid (RNA) polymerase inhibitor that halts viral replication	mAB against conserved epitope of spike protein; blocks viral entry.
Relevant Indication(s)	Treatment of mild to moderate COVID-19 in adults with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death	Non-hospitalized adults with positive results of direct severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death	*Proposed Indication*: For the treatment of mild to moderate COVID-19 in adults and adolescents (≥12 years of age weighing at least 40 kg).
Sponsor	Pfizer Canada ULC	Gilead Sciences Inc.	AstraZeneca Canada Inc.
Dosage	Nirmatrelvir 150mg x 2 and ritonavir 100mg x 1 taken orally twice daily for 5 days	Remdesivir 200mg IV on day 1, then 100mg IV daily for 2 days	600 mg (tixagevimab 300 mg and cilgavimab 300 mg) through IM administration x 1
Prescribing Window	Within 5 days of Symptom Onset	Within 7 days of Symptom Onset	Within 7 days of Symptom Onset
Administration Route	Oral	Intravenous	Intramuscular
Key Concerns	Drug interactions	Require IV administration	Requires IM injection
Landmark trial	EPIC-HR	PINETREE	TACKLE
Patient Population	Non-hospitalized, symptomatic adults with COVID-19 who were at high risk for progression to severe disease, excluded vaccinated individuals	Non-hospitalized patients with COVID-19 with at least one risk factor for disease progression (age ≥ 60 years, obesity, or certain coexisting medical conditions), excluded vaccinated individuals	Non-hospitalized adults aged 18 years or older with a laboratory-confirmed SARS-CoV-2 infection, Excluded vaccinated individuals
Primary Outcomes	The incidence of COVID-19 related hospitalization or death by day 28	Composite of COVID-19 related hospitalization or death from any cause by day 28.	Composite of either severe COVID-19 or death from any cause through to day 29.

Criteria	Nirmatrelvir-Ritonavir	Remdesivir	Tixagevimab-cilgavimab
Key Results	The incidence of COVID-19 related hospitalization or death by day 28 was lower in the nirmatrelvir group than in the placebo group by 6.32 percentage points (95% confidence interval [CI], -9.04 to -3.59; p< 0.001; relative risk reduction, 89.1%)	COVID 19-related hospitalization or death from any cause occurred in 2 patients (0.7%) in the remdesivir group and in 15 (5.3%) in the placebo group (hazard ratio, 0.13; 95% CI, 0.03-0.59; p=0.008).	Severe COVID-19 or death occurred in 18 (4%) of 407 participants in the tixagevimab-cilgavimab group versus 37 (9%) of the 415 participants in the placebo group (relative risk reduction 50.5% [95% IC 14.6-71.3]; p=0.0096). The absolute risk reduction was 4.5% (95% CI 1.1-8.0; p<0.0001)
Authors' Conclusions	Treatment of symptomatic COVID-19 with nirmatrelvir plus ritonavir resulted in a risk of progression to severe COVID-19 that was 89% lower than the risk with placebo.	Remdesivir resulted in an 87% lower risk of hospitalization or death compared with placebo.	A single intramuscular tixagevimab-cilgavimab dose provided statistically and clinically significant protection against progression to severe COVID-19 or death verse placebo in unvaccinated individuals.

Note: This table has not been copy-edited.

Appendix 2: Secondary Outcomes on Symptoms Progression and Resolution

Note that this appendix has not been copy-edited.

Figure 5: COVID-19 Symptom Severity Overall Change From Baseline Through Day 29

Symptom	Primary DCO		Key Secondary DCO	
	LS Mean Difference (95% CI) [a,b]	p-value	LS Mean Difference (95% CI) [a,b]	p-value
Shortness of breath	0.03 (-0.01, 0.06)	0.106	0.03 (-0.01, 0.06)	**0.107**
Difficulty breathing	0.02 (-0.01, 0.05)	0.258	0.02 (-0.01, 0.05)	**0.260**
Chills	-0.01 (-0.03, 0.01)	0.483	-0.01 (-0.03, 0.01)	**0.477**
Cough	-0.05 (-0.10, -0.01)	0.024	-0.05 (-0.10, -0.01)	0.024
Fatigue	-0.03 (-0.08, 0.02)	0.253	-0.03 (-0.08, 0.02)	**0.248**
Muscle aches	-0.05 (-0.09, -0.01)	0.018	-0.05 (-0.09, -0.01)	0.018
Body aches	-0.02 (-0.06, 0.02)	0.342	-0.02 (-0.06, 0.02)	**0.341**
Headache	0.02 (-0.02, 0.05)	0.378	0.02 (-0.02, 0.05)	**0.380**
New loss of taste	0.04 (-0.01, 0.08)	0.127	0.04 (-0.01, 0.08)	0.127
New loss of smell	0.04 (-0.01, 0.09)	0.141	0.04 (-0.01, 0.09)	0.141
Sore throat	0.02 (-0.01, 0.05)	0.208	0.02 (-0.01, 0.05)	**0.210**
Congestion	0.02 (-0.01, 0.05)	0.238	0.02 (-0.01, 0.05)	**0.240**
Runny nose	0.01 (-0.02, 0.04)	0.510	0.01 (-0.02, 0.04)	**0.512**
Nausea	-0.01 (-0.04, 0.01)	0.289	-0.01 (-0.04, 0.01)	**0.287**
Vomiting	-0.00 (-0.01, 0.01)	0.523	-0.00 (-0.01, 0.01)	**0.520**
Diarrhea	0.00 (-0.02, 0.02)	0.881	0.00 (-0.02, 0.02)	**0.884**

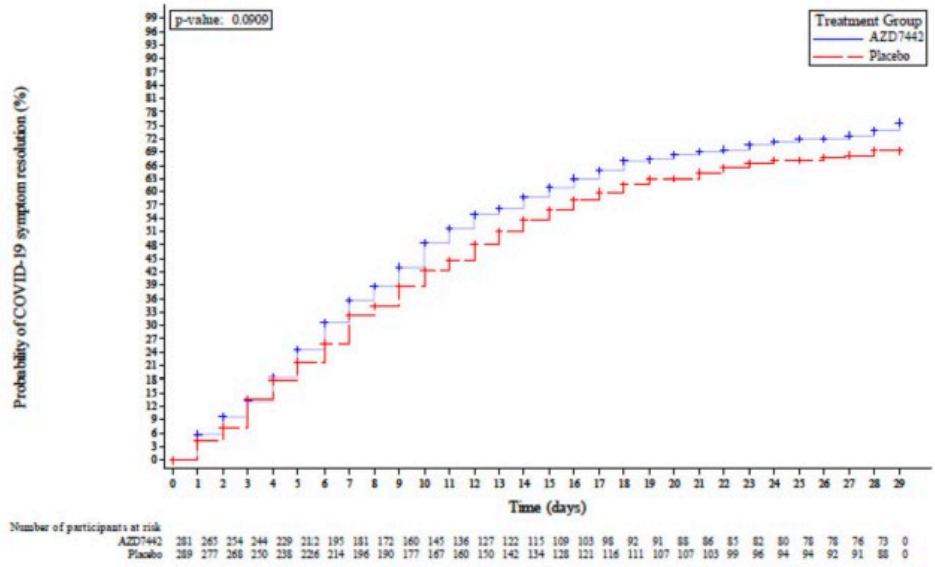
[a] Results from a Mixed Model for Repeated Measures, including terms for baseline value, time from symptom onset (≤ 5 versus > 5 days), risk of progression to severe COVID-19 (high versus low), treatment, visit, and treatment by visit interaction. An autoregressive covariance structure of order 1 was used. P-values are nominal.

[b] Average LS mean difference in symptom severity through 29 days.

Text in bold indicates change from the Primary DCO to Key Secondary DCO.
Missing response data were not imputed.
CI, confidence interval, COVID-19, coronavirus disease 2019; DCO, data cut-off; LS, least squares; mFAS, modified full analysis set.

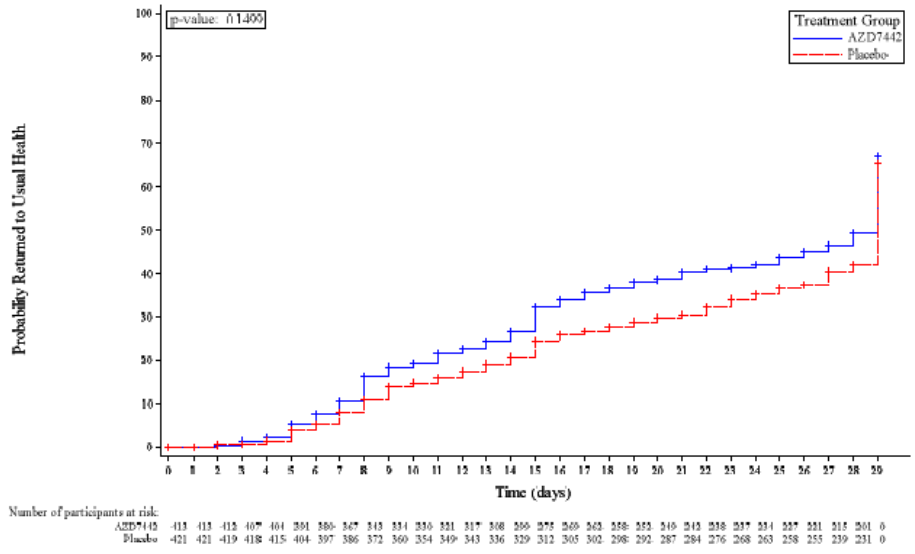
Source: Interim Clinical Study Report.[11]

Figure 6: Time to COVID-19 Symptom Resolution Through Day 29 (Post-Hoc Kaplan-Meier Analysis)



Source: Interim Clinical Study Report.[11]

Figure 7: Time to Return to Pre–COVID-19 Health Through Day 29



P-value is based on log-rank test stratified by time from symptom onset (≤ 5 versus > 5 days) and risk of progression to severe COVID-19 (high versus low).
COVID-19, coronavirus disease 2019; DCO, data cut-off; mFAS, modified full analysis set.
Source: Figure 14.2.2.4

Source: Interim Clinical Study Report.[11]

Appendix 3: WHO Clinical Progression Scale[12]

Figure 8: WHO Clinical Progression Scale

Patient State	Descriptor	Score
Uninfected	Uninfected; no viral RNA detected	0
Ambulatory mild disease	Asymptomatic; viral RNA detected	1
	Symptomatic; independent	2
	Symptomatic; assistance needed	3
Hospitalised: moderate disease	Hospitalised; no oxygen therapy*	4
	Hospitalised; oxygen by mask or nasal prongs	5
Hospitalised: severe diseases	Hospitalised; oxygen by NIV or high flow	6
	Intubation and mechanical ventilation, $pO_2/FiO_2 \geq 150$ or $SpO_2/FiO_2 \geq 200$	7
	Mechanical ventilation $pO_2/FIO_2 < 150$ ($SpO_2/FiO_2 < 200$) or vasopressors	8
	Mechanical ventilation $pO_2/FiO_2 < 150$ and vasopressors, dialysis, or ECMO	9
Dead	Dead	10

ECMO = extracorporeal membrane oxygenation; FiO2 = fraction of inspired oxygen; NIV = non-invasive ventilation; pO2 = partial pressure of oxygen; SpO2 = oxygen saturation.

*If hospitalised for isolation only, record status as for ambulatory patient.