CADTH

CADTH Drug Implementation Advice

Tixagevimab and Cilgavimab (Evusheld)

Sponsor: AstraZeneca Canada

Indication: 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 an individual infected with severe acute respiratory syndrome coronavirus 2

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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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What is the Unmet Need for Prophylaxis 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 preventing transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, ultimately protecting against symptomatic COVID-19 illness, and COVID-19–related hospitalization and death. However, some individuals remain unvaccinated due to contraindications and certain risk groups may have reduced protection following vaccination, such those who are immunocompromised. Seropositivity rates after COVID-19 vaccine in patients who are immunocompromised are known to be significantly lower than those of healthy health care workers,[1] meaning vaccines provide a reduced efficacy against SARS-CoV-2 illness in those who are immunocompromised when compared to the overall population.[2]

What is Evusheld?

Tixagevimab and cilgavimab (Evusheld) is a combination of long-acting monoclonal antibodies for intramuscular administration (IM) providing pre-exposure prophylaxis against COVID-19 for people at risk of SARS-CoV-2 infection. Tixagevimab and cilgavimab bind to non-overlapping epitopes of the spike protein receptor binding domain and block its interaction with the host cellular receptor, thus blocking virus entry and neutralizing it.[3] Tixagevimab and cilgavimab (Evusheld) should be administered at the dosage recommended in the Health Canada product monograph. Tixagevimab and cilgavimab (Evusheld) is indicated for the 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 an individual infected with SARS-CoV-2 and:

- who are immunocompromised and unlikely to mount an adequate immune response to COVID-19 vaccination, **or**
- for whom COVID-19 vaccination is not recommended.

Pre-exposure prophylaxis with tixagevimab and cilgavimab (Evusheld) is not a substitute for vaccination in individuals for whom COVID-19 vaccination is recommended.

How Did CADTH Approach This Review?

The aim of this CADTH review was to inform decision-making on the appropriate use of tixagevimab and cilgavimab (Evusheld) for the 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 an individual infected with SARS-CoV-2. CADTH convened an implementation advice panel (the “panel”) that spanned various disciplines and clinical settings with geographical representation across Canada. The panel captured expert advice through consensus and prioritized patient populations that were most likely to benefit from pre-exposure prophylaxis treatment in a tiered risk group approach.

What is the Implementation Advice?

The panel suggests prioritizing patients with a high likelihood of having an inadequate antibody response to vaccination (i.e., individuals with primary or secondary immunodeficiency), as well as individuals who are unvaccinated against SARS-CoV-2 infection due to contraindications to a COVID-19 vaccine(s), into 2 groups based on those with the highest risk of symptomatic illness and those who could benefit most from the drug, dependent on availability of supply (Table 1).

What Are the Limitations of the Review?

Important gaps in the available evidence include the lack of efficacy and safety data in pediatric patients, in individuals vaccinated against SARS-CoV-2, on the reduction of progression to severe COVID-19, and clade efficacy on existing dominant variants of concern. Further information is required with regards to appropriateness and timing of repeat doses. There is also a scarcity of efficacy and safety data in a large patient population of patients who are immunocompromised and mount a reduced response to vaccine.

Table 1: Prioritization of Pre-exposure Prophylaxis for Patients at Risk of COVID-19 With Tixagevimab and Cilgavimab (Evusheld) Based on a Tiered Risk Group Approach

Tier	Risk group
1	Individuals (≥ 12 years of age and weighing at least 40 kg) who are immunocompromised[a] and not expected to mount an adequate immune response to SARS-CoV-2 infection
2	Individuals (≥ 12 years of age and weighing at least 40 kg) with contraindications to Health Canada–approved SARS-CoV-2 vaccines

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

[a] Definition from COVID-19 vaccine – Canadian Immunization Guide: "Moderately to severely immunocompromised includes individuals 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 transplantation 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/day or 20 mg/day if weight > 10 kg, for ≥ 14 days), alkylating agents, antimetabolites, or tumor-necrosis factor (TNF) inhibitors and other biologic agents that are significantly immunosuppressive."[4]

Rationale for Decision

Results from the PROVENT double-blind randomized controlled trial demonstrated that the use of tixagevimab and cilgavimab was associated with a reduction of 77% in the risk of experiencing a SARS-CoV-2–positive symptomatic illness compared with placebo in adult patients who were unvaccinated and considered candidates to benefit from passive immunization with antibodies. Based on the evidence available at the time of the review, the panel suggested prioritizing patient populations for the appropriate use of tixagevimab and cilgavimab, in the context of limited supply. However, important gaps in the available evidence led the panel to also use expert opinion to inform decision-making.

Tier 1: Individuals (≥ 12 years of age and weighing at least 40 kg) who are immunocompromised and not expected to mount an adequate immune response to SARS-CoV-2 infection

In the PROVENT trial, 7% of patients presented with what was overall labelled as an immunocompromised state. The scarcity of efficacy and safety data in a large patient population of adequately identified patients who are 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 therefore been identified as a patient population with an unmet need. Evidence used to support the advice included results of the subgroup analyses from the PROVENT trial, which estimated a relative risk reduction of 74% (95% confidence interval [CI], 34.4 to 89.6) in patients with an increased risk of inadequate response to immunization, which was consistent with the results observed in the overall population. These results should be interpreted with caution, considering the wide range of criteria used in the study for inadequate response to immunization, and considering the limitations inherent to subgroup analyses mentioned in the Summary of Evidence section of the report.

Tier 2: Individuals (≥ 12 years of age and weighing at least 40 kg) with contraindications to Health Canada–approved SARS-CoV-2 vaccines

The inclusion criteria in the PROVENT trial stated that patients were not vaccinated for COVID-19 and did not have a previous or current SARS-CoV-2 infection. Therefore, the study results are generalizable in a clinical setting to individuals who are unvaccinated due to contraindications and who have been identified as having an unmet need at the time of the review. Based on expert opinion, the panel members agreed that tixagevimab and cilgavimab should not be viewed as a replacement to vaccines, and its use should only be limited to the very small number of individuals who have a true contraindication to any of the Health Canada–approved SARS-CoV-2 vaccines.

Panel Deliberation

The panel, comprising 9 members representing primary care and family medicine, infectious diseases, emergency medicine, pediatrics, geriatrics, clinical immunology and allergy, ethics, pharmacy, and nursing from urban and rural clinical settings across Canada, met on March 15, 2022. The aim was to inform decision-making on the appropriate use of tixagevimab and cilgavimab for the pre-exposure prophylaxis of COVID-19. Particularly, CADTH was seeking feedback from the panel regarding the prioritization of patient populations to receive pre-exposure prophylaxis in situations when supply is limited. These would include:

- patient populations that demonstrate the greatest unmet need
- patient populations that are most likely to achieve benefit from the drug
- patient populations that are less likely to benefit from the drug and not achieve treatment goals due to uncertainty in efficacy and/or safety.

The clinical value of tixagevimab and cilgavimab was deliberated in the context of the ongoing public health emergency of the COVID-19 pandemic. The advice reflects the panel's consensus based on the best available evidence for the pre-exposure prophylaxis of COVID-19 with tixagevimab and cilgavimab and is 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. Drug costs or a health economic analysis were not considered.

Place in Therapy

Goals of Treatment

The specific goal of treatment with tixagevimab and cilgavimab, which is a pre-exposure COVID-19 preventing product, is to reduce symptomatic illness for individuals at risk of SARS-CoV-2 infection.

Unmet Needs

The panel members agreed that the greatest unmet needs are in patients who are immunocompromised and may have an inadequate antibody response to vaccinations. This includes patients with primary immunodeficiency or secondary immunodeficiency, such as, but not limited to, solid organ transplant, stem cell transplant, and hematological malignancies, as well as those on B-cell–depleting drugs and those receiving CAR-T cell therapy.

The panel also identified an unmet need in patients who are unvaccinated due to contraindications to receiving a Health Canada–approved COVID-19 vaccine. Vaccination is the only COVID-19–preventing product with proven beneficial impact on hospitalizations and deaths.

The panel noted that individuals who are immune competent with passive and/or active immunization are least likely to benefit from the drug and not achieve treatment goals.

Prescribing Advice

- The panel advised that the initiation of therapy with tixagevimab and cilgavimab should be as soon as appropriate in accordance with the product monograph.
- At the time of this review, there is no evidence regarding repeat doses of tixagevimab and cilgavimab. The panel agreed that administration for subsequent doses should follow tixagevimab and cilgavimab's product monograph.
- 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 patient, regardless of baseline risk factors.

Other Discussion Points

The panel noted the following:

- Treatment with tixagevimab and cilgavimab should not be viewed as an alternative to immunization. Vaccination is recognized as a highly efficacious measure in preventing SARS-CoV-2 infection, 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 that the combination of tixagevimab and cilgavimab has any impact on outcomes such as hospitalizations. Administration in individuals who are unvaccinated should be in those who have a documented or true contraindication to immunization with a Health Canada–approved COVID-19 vaccine, which is expected to be in a small and very specific population.

- The use of antibody testing was discussed as a potential strategy to identify patients who were most likely to benefit from therapy; however, this was deemed not feasible and would reduce access to treatment overall.
- Pre-exposure prophylaxis with tixagevimab and cilgavimab should be initiated early in relation to timing of outbreaks and height of SARS-CoV-2 circulation in the community, taking into consideration local epidemiology.
- Individuals that remain unvaccinated and are at high risk of exposure to SARS-CoV-2, specifically those living or working in congregate settings, were included in the PROVENT trial as a subgroup analysis and discussed by the panel. These individuals may benefit from pre-exposure prophylaxis with tixagevimab and cilgavimab; however, this was not considered in the implementation advice as this population was not approved within the product monograph.
- As noted in the product monograph, a higher proportion of patients in PROVENT who received tixagevimab and cilgavimab versus placebo reported serious cardiovascular events (0.7% versus 0.3%), notably myocardial infarction and cardiac failure. A smaller imbalance was observed for serious thromboembolic events (0.5% versus 0.2%).[3] Most subjects had cardiac risk factors and/or a prior history of cardiovascular disease.[3]

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); solution for injection, intramuscular. Tixagevimab and cilgavimab (Evusheld) should be administered at the dosage recommended in the Health Canada product monograph.
Indication	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 an individual infected with SARS-CoV-2 and: • who are immunocompromised and unlikely to mount an adequate immune response to COVID-19 vaccination, **or** • for whom COVID-19 vaccination is not recommended. Pre-exposure prophylaxis with tixagevimab and cilgavimab (Evusheld) is not a substitute for vaccination in individuals for whom COVID-19 vaccination is recommended.
Health Canada approval status	Approved
NOC date	April 14, 2022
Sponsor	AstraZeneca

NOC = Notice of Compliance; SARS-CoV-2= severe acute respiratory syndrome coronavirus 2.

COVID-19

As of March 4, 2022, Canada has published case report data on 3,219,741 SARS-CoV-2 infections, including 134,279 hospitalizations and 36,326 deaths, since the beginning of the COVID-19 pandemic.[6] The main goal of COVID-19–related treatments and measures is to prevent hospitalizations and deaths, which, based on the current evidence, appear to be directly related to age and are more common in patients with comorbidities.[6] During the second wave of the pandemic in Canada, the most common comorbidities in hospitalized patients 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]

Throughout the pandemic, various domestic and international groups have examined risk factors for hospitalization and death related to COVID-19. In British Colombia, age has shown to be the largest risk factor for COVID-19 hospitalization.[8] The presence of at-risk conditions, in addition to advancing age, increases the risk of COVID-19 hospitalization, as outlined in Figure 1.[8]

Figure 1: Risk of COVID-19 Hospitalization

Model estimates* of the proportion of cases that would result in hospitalization by demographic group and vaccine status

# of at-risk conditions	Age group	Female				Male			
		0 Doses	1 Dose	2 Doses	3 Doses	0 Doses	1 Dose	2 Doses	3 Doses
0 at-risk conditions	<20	0.3%	0.1%	0.1%	0.0%	0.4%	0.2%	0.1%	0.0%
	20-39	1.5%	0.5%	0.4%	0.2%	1.8%	0.7%	0.4%	0.2%
	40-49	1.9%	0.7%	0.4%	0.2%	2.3%	0.8%	0.5%	0.3%
	50-59	2.7%	1.0%	0.6%	0.3%	3.2%	1.2%	0.8%	0.4%
	60-69	2.9%	1.1%	0.7%	0.3%	3.6%	1.3%	0.8%	0.4%
	70-79	5.2%	1.8%	1.2%	0.6%	6.3%	2.2%	1.5%	0.7%
	80+	9.5%	3.3%	2.2%	1.1%	11.8%	4.0%	2.7%	1.3%
1-2 at-risk conditions	<20	0.9%	0.3%	0.2%	0.1%	1.2%	0.4%	0.3%	0.1%
	20-39	4.5%	1.7%	1.1%	0.5%	4.7%	1.8%	1.1%	0.6%
	40-49	5.2%	1.9%	1.2%	0.6%	5.9%	2.2%	1.3%	0.7%
	50-59	6.8%	2.6%	1.6%	0.8%	8.3%	3.2%	1.9%	1.0%
	60-69	7.5%	3.0%	1.8%	0.9%	9.5%	3.6%	2.2%	1.1%
	70-79	13.9%	5.4%	3.3%	1.6%	17.2%	6.9%	4.2%	2.0%
	80+	26.2%	9.7%	6.2%	2.9%	33.9%	13.1%	8.1%	3.9%
3+ at-risk conditions	<20	5.5%	1.8%	1.3%	0.5%	7.3%	1.8%	1.4%	1.4%
	20-39	23.0%	10.6%	5.1%	2.9%	25.2%	11.0%	6.6%	3.6%
	40-49	26.2%	10.6%	5.8%	3.6%	35.6%	8.3%	6.5%	4.0%
	50-59	36.0%	13.2%	7.7%	4.3%	37.0%	12.3%	8.9%	5.1%
	60-69	33.2%	14.8%	7.6%	3.9%	40.3%	16.2%	9.4%	5.0%
	70-79	50.1%	23.2%	12.8%	5.9%	59.6%	26.6%	15.9%	7.5%
	80+	71.9%	31.8%	20.7%	9.4%	83.7%	43.8%	26.3%	12.7%

Hospitalization risk for younger people with two or more doses approaches zero

Even with 3 doses, substantial risk observed for those over 80+ (over 10%) when multiple risk conditions present

*Point estimates expected to change as more data becomes available. Differences between same-colored cells may not be statistically significant.

Source: COVID-19 in BC Preliminary Analysis of Cases Dec 14 – Jan 6 (Hospitalizations up to Jan 10).[8]

Vaccination is recognized as a highly efficacious measure in protecting against SARS-CoV-2 infection, symptomatic COVID-19 illness, and COVID-19–related hospitalization and death. More than 32 million Canadians have had at least 1 dose of the vaccine as of February 27, 2022;[9] however, some individuals remain unvaccinated and certain risk groups may have reduced protection following vaccination, such as those who are immunocompromised. Patients who are immunocompromised remain at high risk of contracting a SARS-CoV-2 infection despite a full course of vaccination. Indeed, it has been shown that, after COVID-19 vaccination, seropositivity rates in patients who are immunocompromised are lower than in healthy health care workers.[1] In this study, the seropositivity rates were as low as 37% in patients with solid organ transplant and 55% in patients with hematological malignancies.[1] In addition, a recent systematic review that included 3 cohort studies evaluating 7,283,329 patients, as well as 2 case-control studies evaluating 498,204 negative and 15,994 positive SARS-CoV-2 cases, concluded that COVID-19 vaccines may provide a 79% efficacy protection against SARS-CoV-2 infection in cohort studies of patients who are immunocompromised and an 88% efficacy protection for those in case-control studies, which

constitutes a reduced protection compared to the overall general population.[2] It is also expected that individuals with an impaired immune response take longer to fight the infection, increasing the probability of mutations in the SARS-CoV-2 spike protein and, as a result, the development and emergence of new viral variants of concern.[3] Therefore, some individuals may benefit from the use of pre-exposure prophylaxis treatment, including individuals who are unvaccinated or those who are at risk of inadequate response to vaccination. This highlights a potential benefit for the use of pre-exposure prophylaxis treatment, which may be beneficial in special populations where an increased risk of COVID-19 hospitalization has been identified and for those who lack adequate vaccine protection.

As of March 20, 2022, the main SARS-CoV-2 variant of concern in Canada with active cases was Omicron (95.1%), with the Omicron subvariant BA.2 as the dominant variant (39.4%), followed by BA.1.1 (28.3%), other Omicron (24.9%), non-Omicron variants (5%), and BA.1 (2.5%).[6]

On February 23, 2022, Public Services and Procurement Canada announced signed agreements for access to novel antibody therapies for COVID-19 prophylaxis.[10] In preparation of this regulatory approval, CADTH developed interim procedures to review therapeutics related to drugs for COVID-19 to help identify patient populations that may gain the most benefit from these treatments.[11]

Tixagevimab and Cilgavimab (Evusheld)

Tixagevimab and cilgavimab (Evusheld) is a combination of long-acting monoclonal antibodies for IM that provides immediate and sustained pre-exposure prophylaxis against COVID-19 for people at risk of SARS-CoV-2 infection. 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 angiotensin-converting enzyme-2 receptors on human cells and, therefore, stop infection.[3]

The indication for tixagevimab and cilgavimab is for the 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 an individual infected with SARS-CoV-2 and who are immunocompromised and unlikely to mount an adequate immune response to COVID-19 vaccination or for whom COVID-19 vaccination is not recommended. Pre-exposure prophylaxis with tixagevimab and cilgavimab is not a substitute for vaccination in individuals for whom COVID-19 vaccination is recommended. As outlined in the product monograph, the recommended dose is 300 mg, administered as 2 separate 1.5 mL, sequential, injections of 150 mg of tixagevimab and 150 mg of cilgavimab. Due to the decreased in vitro neutralization activity of tixagevimab and cilgavimab against the Omicron subvariants BA.1 (12- to 183-fold) and BA.1.1 (176- to 424-fold) compared to the reference strain, it is unknown whether the 300 mg dose is protective against these subvariants clinically. Consideration should be given to increase the dose to 600 mg in regions where BA.1 and BA.1.1 are circulating.

Tixagevimab and cilgavimab (Evusheld) has been authorized for emergency use in the US as pre-exposure prophylaxis of COVID-19 in certain adults and pediatric individuals with no SARS-CoV-2 infection who have moderate to severe immune compromise and may not mount an adequate immune response to COVID-19 vaccination, or for whom vaccination is not recommended.[12] Since then, the approved dosage has been increased to 300 mg of tixagevimab and 300 mg of cilgavimab based on the fact that the drug may be less active

against certain Omicron subvariants.[13] The combination of tixagevimab and cilgavimab has also been granted approval in this indication in several other jurisdictions, such as conditional marketing authorization in the UK, marketing authorization in the European Union, and provisional approval in Australia.

Summary of Evidence

Description of Studies

One ongoing manufacturer-sponsored, multi-centre, phase III, double-blind randomized controlled trial was the primary source of evidence for the efficacy and safety of tixagevimab and cilgavimab. The PROVENT trial (N = 5,254) evaluated the superiority of the combination of tixagevimab and cilgavimab compared with placebo for the prevention of COVID-19 in adult patients who were considered candidates to benefit from passive immunization with antibodies, defined as having increased risk for inadequate response to active immunization (predicted poor responders to vaccines or being intolerant of vaccine) or having increased risk for SARS-CoV-2 infection (locations or circumstances putting an individual at appreciable risk of exposure to SARS-CoV-2).

Medications were administered as 1 single dose of 300 mg made up of tixagevimab 150 mg and cilgavimab 150 mg through IM administration. No concomitant therapy was prohibited during the study.

The primary outcome of the PROVENT trial was the relative risk reduction in the first case of SARS-CoV-2–positive symptomatic illness occurring post-dose of study drug and prior to day 183. In order to be included in the primary end point, patients needed to have confirmed SARS-CoV-2 infection and meet at least 1 of the qualifying symptoms:

- no minimum duration: fever, shortness of breath, difficulty breathing
- present for 2 or more days: chills, cough, fatigue, muscle aches, body aches, headache, new loss of taste or smell, sore throat, congestion, runny nose, nausea, vomiting, diarrhea.

The duration of efficacy follow-up of 182 days was based on the expected duration of protection by tixagevimab and cilgavimab. The safety follow-up duration was 15 months.

Patients were eligible for the trial if they were at least 18 years old and were a candidate for benefit from passive immunization with antibodies, either because they were at increased risk for inadequate response to active immunization or because they were at increased risk of contracting SARS-CoV-2 infection. Additional details and definitions regarding the PROVENT trial and included patient population are provided in Table 3. Inclusion criteria specified that patients were not vaccinated against COVID-19 and did not have a prior or current SARS-CoV-2 infection. All patients needed to have a negative SARS-CoV-2 serology testing at screening. Key exclusion criteria included pregnancy and breastfeeding; concomitant significant infection or other acute illness; history of infection with severe acute respiratory syndrome or Middle East respiratory syndrome; clinically significant bleeding disorder; previous hypersensitivity, infusion-related reaction, or severe adverse reaction following administration of a monoclonal antibody; any prior receipt of vaccine or other monoclonal antibody or biologic drug indicated for the prevention of SARS-CoV-2 or COVID-19.

Once patients became eligible for vaccines, they could request unblinding and, where necessary, vaccination against COVID-19. Unblinding was necessary because different advice was provided to patients based on whether they had received the active study treatment or placebo. There was no study-associated contraindication to receiving a vaccine in patients who received placebo. Patients who received tixagevimab and cilgavimab were advised that the 300 mg dose may provide 6 to 9 months of protection, but that this had not yet been demonstrated. In these patients, there would be little or no urgency to receive a vaccine. In addition, in the predicted presence of adequate neutralizing antibody titers, an appropriate and effective response to the vaccine could be impaired. Such patients were advised to consider waiting an appropriate length of time (6 to 9 months) before receiving an anti-SARS-CoV-2 vaccine. Patient-level unblinding information was restricted to key personnel at the study site, and the rationale was documented. Patients were allowed to continue in the study; however, they would be censored at the date of unblinding and/or receipt of a COVID-19 vaccine or other preventive product if either happened before having met the criteria for the primary efficacy end point.

Table 3: Details of PROVENT Trial

Study details	Description
Designs and populations	
Study design	Phase III DB RCT (placebo-controlled)
Locations	Multicenter study (87 study centres): US, UK, Belgium, France, Spain

Patient enrolment dates	21 November 2020 — ongoing (anticipated study completion June 2022)
	Data cut-off dates:
	• 05 May 2021
	  ○ Primary efficacy analysis
	  ○ Planned after approximately 24 primary end point events had been confirmed across the active and control groups, or 30% of study participants had become unblinded, whichever occurred first[a]
	• 29 June 2021
	  ○ Safety
	  ○ Minimum of 3 months' data on all participants
	  ○ Not prespecified, decided before study unblinding
	• 29 August 2021
	  ○ Key efficacy and safety with increased duration of follow-up
	  ○ Median 6 months analysis; minimum of 5 months' data in all ongoing participants
	  ○ Not prespecified, decided after study unblinding

Randomized (N)	N = 5,254 patients randomized in a 2:1 ratio (5,197 patients treated: n = 3,460 in the Evusheld group and n = 1,737 in the placebo group)

Inclusion criteria	• At least 18 years of age
	• Candidate for benefit from passive immunization with antibodies:
	  ○ Patients at increased risk for inadequate response to active immunization (predicted poor responders to vaccines), defined as:
	  ▪ elderly (≥ 60 years old)
	  ▪ obese (BMI ≥ 30)
	  ▪ congestive heart failure
	  ▪ chronic obstructive pulmonary disease
	  ▪ chronic kidney disease (GFR < 30 mL/min)
	  ▪ chronic liver disease

Study details	Description
	▪ immunocompromised state from solid organ transplant, blood or bone marrow transplant, immune deficiencies, HIV, use of corticosteroids, or use of other immunosuppressive medicines ▪ intolerant of vaccine (previous history of severe adverse event or serious adverse event after receiving any approved vaccine) ○ Increased risk for SARS-CoV-2 infection, defined as those whose locations or circumstances put them at appreciable risk of exposure to SARS-CoV-2 and COVID-19, based on available risk assessment at time of enrolment, including: ▪ health care workers, including staff of long-term care facilities ▪ workers in industrial settings shown to have been at high risk for SARS-COV-2 transmission ▪ military personnel residing or working in high-density settings ▪ students living in dormitory settings ▪ others living in settings of similar close or high-density proximity • Medically stable (disease not requiring significant change in therapy or hospitalization for worsening disease during the one month prior to enrolment, with no acute change in condition at the time of study enrolment) • Negative result from point of care SARS-CoV-2 serology testing at screening
Exclusion criteria	• Significant infection or other acute illness upon randomization • Prior laboratory-confirmed SARS-CoV-2 infection or positive SARS-CoV-2 result at screening • History of infection with SARS or MERS • Known history of allergy or reaction to any component of study drug • Previous hypersensitivity, infusion-related reaction, or severe adverse reaction following administration of a monoclonal antibody • Any receipt of investigational or licensed vaccine or other monoclonal antibody or biologic drug indicated for the prevention of SARS-CoV-2 or COVID-19 • Clinically significant bleeding disorder (factor deficiency, coagulopathy, or platelet disorder), or prior history of significant bleeding or bruising following IM event • Pregnancy or breastfeeding
Drugs	
Intervention	One single dose of Evusheld 300 mg: administered as 2 sequential IM injections of tixagevimab 150 mg and cilgavimab 150 mg
Comparators	One single dose of placebo: administered as 2 sequential IM injections
Duration	
Efficacy follow-up	182 days (26 weeks; 6 months)
Safety follow-up	15 months
Outcomes	
Primary end point	Efficacy: Relative risk reduction in the first case of SARS-CoV-2–positive symptomatic illness occurring post-dose of study drug and prior to day 183 in the full pre-exposure analysis set, confirmed by a SARS-CoV-2–positive result based on a RT-PCR testing and meeting the qualifying symptoms: • fever, shortness of breath or difficulty breathing (no minimum duration) • chills, cough, fatigue, muscle aches, body aches, headache, new loss of taste, new loss of smell, sore throat, congestion, runny nose, nausea, vomiting or diarrhea present for ≥ 2 days Safety: AEs, SAEs, AEs of special interest
Key secondary end point	Incidence of participants who have a post-treatment response for SARS-CoV-2 nucleocapsid antibodies (i.e., going from negative at baseline to positive at any time post-baseline)

Study details	Description
Other secondary end points	• Incidence of SARS-CoV-2 RT-PCR–positive severe or critical symptomatic illness • Incidence of COVID-19–related emergency department visits

AE = adverse event; BMI = body mass index; DB = double-blind; IM = intramuscular; GFR = glomerular filtration rate; MERS = Middle East respiratory syndrome; RCT = randomized controlled trial; RT-PCR = reverse transcriptase polymerase chain reaction; SAE = serious adverse event; SARS = severe acute respiratory syndrome; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

[a]The high pace of vaccination against SARS-CoV-2 in some countries, and the rapid rate at which study participants chose to be unblinded and vaccinated, necessitated amendments to the PROVENT study design. A protocol amendment modified the primary analysis to reduce the potential impact of unblinding and/or COVID-19 vaccination on the study's ability to robustly quantify placebo-controlled efficacy. The primary analysis was originally scheduled to occur after 183 days but was amended to take place either after the earlier of 24 primary end point events or when the study reached an unblinding rate of 30%.

Source: Clinical Study Report.[3]

Statistical Analyses

A hierarchical approach was used to control for multiplicity of the primary, key supportive, and key secondary analyses. The primary efficacy outcome was based on patients in the full pre-exposure analysis set, defined as all randomized patients who received at least one dose of the study drug without having had a prior SARS-CoV-2 confirmed COVID-19 infection, analyzed according to their randomized treatment. For patients with multiple events, only the first occurrence was used for the primary efficacy end point analysis. The set of intercurrent events consisted of patients who became unblinded to treatment assignment and/or took a COVID-19 vaccine or other COVID-19 preventive product, in both cases prior to having met the primary efficacy end point. The intercurrent events were handled using a while on treatment strategy, where patients who experienced an intercurrent event were censored at the date of unblinding or receipt of first dose of COVID-19 product, whichever was earlier. Absence of data following patient withdrawal prior to having met the primary efficacy end point was treated as missing and patients were considered as not having the event through the time of last observation. Deaths that were caused by COVID-19 and all hospitalizations due to COVID-19 were also considered as primary efficacy end points.

Two key supportive analyses were also performed. In the first key supportive analysis, patients who became unblinded to treatment assignment were included and analyzed regardless of unblinding or receipt of a COVID-19 preventive product. In the second key supportive analysis, the end point was defined as first case of SARS-CoV-2 RT-PCR–positive symptomatic illness or death from any cause. The primary efficacy was calculated as relative risk reduction. Efficacy summaries are presented with a 2-sided 95% CI. Statistical significance was achieved if the 2-sided P value was lower than 0.05. A Poisson regression model with robust variance adjusting for follow-up time was used as the primary efficacy analysis model to estimate the risk reduction on the incidence of SARS-CoV-2 RT-PCR–positive symptomatic illness. The model contained the planned treatment group and age group (≥ 60 years and < 60 years) as a covariate. The logarithm of a participant's corresponding follow-up time at risk starting from dose up to the study day 183 visit was used as an offset variable in the model to adjust for participants having different exposure times during which the events occurred.

Subgroup analyses were reported for some populations of patients, estimates were based on Poisson regression with robust variance using full model or reduced model. The full model for the subgroup analyses included covariates for treatment group, and age (≥ 60 years versus < 60 years) subgroup and treatment subgroup interaction. In addition, the log of the follow-up time was included as an offset.

Study Population

Overall, 5,254 patients were randomized in a 2:1 ratio; of these, 97% of patients were still in the ongoing trial at the time of data cut-off (May 2021); no patient had yet completed the study. The proportions of patients who discontinued the study were similar between treatment groups. The most frequent reason for discontinuation was withdrawal by patient.

Table 4: Patients Disposition in the PROVENT Trial (May 2021)

Category	TIXA and CILGA	Placebo
Participants screened, N	5,973	
Participants randomized, n (%)	3,500 (100.0)	1,754 (100.0)
Participants randomized but not dosed,[a] n (%)	40 (1.1)	17 (1.0)
Participants ongoing in study, n (%)	3,409 (97.4)	1,700 (96.9)
Participants who discontinued from study, n (%)	91 (2.6)	54 (3.1)
• Death, n	4	4
• Lost to follow-up, n	11	8
• Protocol deviation, n	1	0
• Physician decision, n	1	0
• Withdrawal by participant, n	56	32
• Other,[b] n	18	10
ITT,[c] N	3,460	1,737
Full pre-exposure analysis set,[d] N	3,441	1,731
Safety analysis set,[e] N	3,461	1,736

CILGA = cilgavimab; RT-PCR = reverse transcriptase polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndromecoronavirus-2; FAS = full analysis set; ITT = intention to treat; TIXA = tixagevimab.

[a] Most patients who were not dosed were randomized in error.

[b] In the "Other" category, 4 patients received TIXA and CILGA (reasons given were withdrew consent, subject received vaccine and no longer wanted to continue, subject was moving, or incarcerated) and 2 received placebo (reason given was subject decision). All other patients in this category did not receive the study drug due to screen failure.

[c] Randomized and received study drug, FAS.

[d] Subset of patients from the FAS who did not have a prior SARS-CoV-2 RT-PCR–positive confirmed COVID-19 infection (ITT), primary analysis set.

[e] All patients who received study drug.

Source: Clinical Study Report.[3]

Baseline characteristics were generally comparable between treatment groups (refer to Table 5). Among patients included in the trial, 57% were between the ages of 18 and younger than 60 years. The proportion of patients 75 years or older reached 4%. Most of the trial population was White. The mean body mass index was 29, at the upper limit of the overweight body mass index category. Inclusion criteria stated that patients were not vaccinated for COVID-19 and did not have a prior or current SARS-CoV-2 infection; as such, patients needed to have a negative SARS-CoV-2 serology test at baseline.

Table 5: Baseline Characteristics in the PROVENT Trial (May 2021)

Patient characteristic	TIXA and CILGA (N = 3,460)	Placebo (N = 1,737)
Age, mean (SD), years	53.6 (14.99)	53.3 (14.97)
Age group, n (%)		
≥ 18 to < 60 years	1,960 (56.6)	980 (56.4)
≥ 60 years	1,500 (43.4)	757 (43.6)
≥ 65 years	817 (23.6)	409 (23.5)
≥ 75 years	148 (4.3)	70 (4.0)
Sex, n (%)		
Female	1,595 (46.1)	802 (46.2)
Male	1,865 (53.9)	935 (53.8)
Race, n (%)		
White	2,545 (73.6)	1,249 (71.9)
Black or African American	597 (17.3)	302 (17.4)
Asian	110 (3.2)	60 (3.5)
American Indian or Alaska Native	19 (0.5)	10 (0.6)
Native Hawaiian or other Pacific Islander	4 (0.1)	4 (0.2)
Not reported	89 (2.6)	56 (3.2)
Unknown	79 (2.3)	42 (2.4)
Other	15 (0.4)	12 (0.7)
Missing	2 (0.1)	2 (0.1)
Ethnicity, n (%)		
Hispanic or Latino	539 (15.6)	215 (12.4)
Not Hispanic or Latino	2,731 (78.9)	1,412 (81.3)
Not reported	116 (3.4)	72 (4.1)
Unknown	74 (2.1)	38 (2.2)
BMI, mean (SD), kg/m^2	29.6 (6.9)	29.6 (7.0)
SARS-CoV-2 RT-PCR status at baseline, n (%)		
Positive	19 (0.5)	6 (0.3)
Negative	3,334 (96.4)	1,672 (96.3)
Missing	107 (3.1)	59 (3.4)

BMI = body mass index; CILGA = cilgavimab; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SD = standard deviation; RT-PCR = reverse transcriptase polymerase chain reaction; TIXA = tixagevimab.

Source: Clinical Study Report.[3]

A total of 78% of patients presented with at least one risk factor for severe COVID-19. The most common comorbidities for severe illness included history of obesity (42%), obesity (42%), hypertension (36%), smoking (21%), diabetes mellitus (14%), and asthma (11%).

Table 6: COVID-19 Baseline Comorbidities in the PROVENT Trial (May 2021)

Characteristic, n (%)	TIXA and CILGA (N = 3,460)	Placebo (N = 1,737)
Any high-risk for severe COVID-19 at baseline	2,666 (77.1)	1,362 (78.4)
History of obesity (> 30 kg/m^2)	1,474 (42.6)	729 (42.0)
Obesity (≥ 30 kg/m^2)	1,456 (42.1)	712 (41.0)
Morbid obesity (≥ 40 kg/m^2)	269 (7.8)	141 (8.1)
Chronic kidney disease	184 (5.3)	86 (5.0)
Diabetes	492 (14.2)	242 (13.9)
Immunosuppressive disease	15 (0.4)	9 (0.5)
Immunosuppressive treatment	109 (3.2)	63 (3.6)
Cardiovascular disease	272 (7.9)	151 (8.7)
COPD	179 (5.2)	95 (5.5)
Chronic liver disease	149 (4.3)	91 (5.2)
Hypertension	1,229 (35.5)	637 (36.7)
Asthma	378 (10.9)	198 (11.4)
Cancer	250 (7.2)	133 (7.7)
Smoking	720 (20.8)	370 (21.3)
Sickle cell disease	1 (0.0)	1 (0.1)

CILGA = cilgavimab; COPD = chronic obstructive pulmonary disease; TIXA = tixagevimab.

Source: Clinical Study Report.[3]

A total of 73% of patients in the study presented with an increased risk for inadequate response to active immunization. The most common risk factors included age of 60 years or older (42%) and obesity (43%). A total of 7% of patients presented with what was labelled as an immunocompromised state. A total of 53% of patients had an increased risk of exposure to infection with SARS-CoV-2. The most common risk factors included living in high-density proximity other than the pre-specified settings (20%) and living in industrial setting with high risk (14%). A total of 9% of patients were in the health care workers category that included staff for long-term care facilities.

Table 7: COVID-19 Baseline Risk Assessment in the PROVENT Trial (May 2021)

COVID-19 risk	TIXA and CILGA (N = 3,460)	Placebo (N = 1,737)
Increased risk for inadequate response to active immunization, n (%)	2,546 (73.6)	1,264 (72.8)
Elderly (≥ 60 years)	1,470 (42.5)	719 (41.4)
Obese (> 30 kg/m^2)	1,486 (42.9)	731 (42.1)
Congestive heart failure	63 (1.8)	35 (2.0)
COPD	145 (4.2)	67 (3.9)
Chronic kidney disease	128 (3.7)	55 (3.2)
Chronic liver disease	30 (0.9)	25 (1.4)
Immunocompromised state	257 (7.4)	113 (6.5)
Intolerant of vaccine	15 (0.4)	9 (0.5)
Increased risk of exposure to infection with SARS-CoV-2, n (%)	1,820 (52.6)	909 (52.3)

COVID-19 risk	TIXA and CILGA (N = 3,460)	Placebo (N = 1,737)
Health care work (including staff for long-term care facilities)	295 (8.5)	143 (8.2)
Industrial setting with high risk	490 (14.2)	233 (13.4)
Military personnel	30 (0.9)	19 (1.1)
Student in dormitory	48 (1.4)	20 (1.2)
Other living with high-density proximity	668 (19.3)	341 (19.6)
Other	361 (10.4)	186 (10.7)

CILGA = cilgavimab; COPD = chronic obstructive pulmonary disease; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; TIXA = tixagevimab.

Source: Clinical Study Report.[3]

There was a notable difference between groups in terms of post-randomization vaccination against COVID-19 during the study, which was less frequent in the active treatment group than in the placebo group (12% versus 31% of patients, respectively). All patients were COVID-19 vaccine naive when the study began, per the inclusion criteria; however, the protocol was amended as the study was ongoing to permit unblinding if patients wished to consider receiving a COVID-19 vaccination. At the primary analyses data cut-off date of May 2021, the proportion of patients who elected to become unblinded was 29% in the active treatment group and 31% in the placebo group. The smaller proportion of participants who were vaccinated against COVID-19 in the tixagevimab and cilgavimab treatment group is consistent with the advice provided to patients who considered vaccination against SARS-CoV-2.

Table 8: Study Unblinding and COVID-19 Vaccination in the PROVENT Trial (May 2021)

Category	TIXA and CILGA (N = 3,441)	Placebo (N = 1,731)
Any unblinding or COVID-19 vaccination, n (%)	1,248 (36.3)	677 (39.1)
Any unblinding	**1,008 (29.3)**	**540 (31.2)**
Any COVID-19 vaccination	**424 (12.3)**	**537 (31.0)**
Any unblinding and vaccination	184 (5.3)	400 (23.1)
Any unblinding without vaccination	824 (23.9)	140 (8.1)
Any vaccination without unblinding	240 (7.0)	137 (7.9)

CILGA = cilgavimab; COPD = chronic obstructive pulmonary disease; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; TIXA = tixagevimab.

Source: Clinical Study Report.[3]

Efficacy Results

The use of tixagevimab and cilgavimab in the PROVENT trial was associated with a reduction of 77% in the risk of experiencing SARS-CoV-2–positive symptomatic illness compared with placebo, as of the data cut-off date of May 2021, in adult patients who were candidates for benefit from passive immunization with antibodies, either because they were at increased risk for inadequate response to active immunization or because they were at increased risk of contracting SARS-CoV-2 infection (relative risk reduction = 77%; 95% CI, 46.1 to 90.0; $P < 0.001$). However, the number of events that occurred and were included in the analysis was low considering the overall size of the trial population. In this primary analysis, the data cut-off date was May 5, 2021, and data were censored at unblinding of

treatment allocation or when patients received a COVID-19 preventive product other than the study drug, all leading to a short duration of treatment follow-up for event observation.

Results of the supportive analyses performed for the primary outcome were consistent with those obtained from the primary analysis. These include a longer follow-up duration for the data cut-off date of August 2021. In addition, one of the analyses included events regardless of unblinding of treatment allocation or when patients received a COVID-19 preventive product other than the study drug. The total number of events contributing to the analysis went from 25 events in the primary analysis to 64 events in this particular case, with a similar statistically significant relative risk reduction.

Table 9: Key Efficacy Results for the PROVENT Trial (Full Pre-Exposure Population)

Primary outcome in the trial	TIXA and CILGA (N = 3,441)	Placebo (N = 1,731)
Primary analysis: DCO of May 2021 (Data censored at unblinding or receipt of COVID-19 preventive product)		
First SARS-CoV-2 RT-PCR–positive symptomatic illness, n (%)	**8 (0.2)**	**17 (1.0)**
RRR (95% CI)	**76.7 (46.05 to 89.96)**	
P value	**< 0.001**	
Key supportive analysis (Regardless of unblinding or receipt of COVID-19 preventive product)		
First SARS-CoV-2 RT-PCR-positive symptomatic illness, n (%)	10 (0.3)	22 (1.3)
RRR (95% CI)	77.3 (52.0 to 89.3)	
P value	< 0.001	
Key supportive analysis (While on treatment with all-cause mortality)		
First SARS-CoV-2 RT-PCR–positive symptomatic illness or death from any cause, n (%)	12 (0.3)	19 (1.1)
RRR (95% CI)	68.78 (35.6 to 84.9)	
P value	0.002	
DCO of August 2021		
Data censored at unblinding or receipt of COVID-19 preventive product		
First SARS-CoV-2 RT-PCR–positive symptomatic illness, n (%)	11 (0.3)	31 (1.8)
RRR (95% CI)	82.8 (65.8 to 91.4)	
P value	< 0.001	
Regardless of unblinding or receipt of COVID-19 preventive product		
First SARS-CoV-2 RT-PCR–positive symptomatic illness, n (%)	20 (0.6)	44 (2.5)
RRR (95% CI)	77.4 (61.7 to 86.7)	
P value	< 0.001	
Key supportive analysis (While on treatment with all-cause mortality)		
First SARS-CoV-2 RT-PCR–positive symptomatic illness or death from any cause, n (%)	18 (0.5)	36 (2.1)

Primary outcome in the trial	TIXA and CILGA (N = 3,441)	Placebo (N = 1,731)
RRR (95% CI)	75.77 (57.3 to 86.2)	
P value	< 0.001	

CI = confidence interval; CILGA = cilgavimab; DCO = data cut-off; ITT = intent to treat; RRR = relative risk reduction; RT-PCR = reverse transcriptase polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; TIXA = tixagevimab.

Note: Estimates are based on a Poisson regression with robust variance. The model includes covariate for treatment (Evusheld versus placebo) and age (≥ 60 years versus < 60 years), with the log of the follow-up time as an offset. Estimated RRR greater than 0% provides evidence in favour of Evusheld with P values less than 0.05 indicating statistical significance. All key analyses were controlled for multiple comparisons.

Source: Clinical Study Report.[3]

Among patients who experienced a primary outcome event of SARS-CoV-2 RT-PCR-positive symptomatic illness, the proportions of patients experiencing individual symptoms were typically higher in patients who received placebo than in patients who received tixagevimab and cilgavimab. No comparative statistical analyses were performed between treatment groups to quantify this numerically observed difference.

Table 10: Results for Qualifying Symptoms (Full Pre-Exposure Population; May 2021)

Proportion	TIXA and CILGA (N = 3,441)	Placebo (N = 1,731)
DCO May 2021: Regardless of unblinding or receipt of COVID-19 preventive product		
All patients with SARS-CoV-2 RT-PCR-positive symptomatic illness, n (%)	10 (0.3)	20 (1.2)
Events with no minimum duration, n (% of patients with primary outcome event)		
Fever	0	9 (45)
Shortness of breath	2 (20)	6 (30)
Difficulty breathing	0	3 (15)
Present for ≥ 2 days, n (% of patients with primary outcome event)		
Chills	2 (20)	9 (45)
Cough	4 (40)	15 (75)
Fatigue	5 (50)	16 (80)
Muscle aches	3 (30)	9 (45)
Body aches	1 (10)	7 (35)
Headache	4 (40)	9 (45)
New loss of taste	1 (10)	6 (30)
New loss of smell	1 (10)	8 (40)
Sore throat	5 (50)	4 (20)
Congestion	7 (70)	7 (35)
Runny nose	3 (30)	11 (55)
Nausea	3 (30)	3 (15)
Vomiting	0	1 (5)
Diarrhea	0	3 (15)

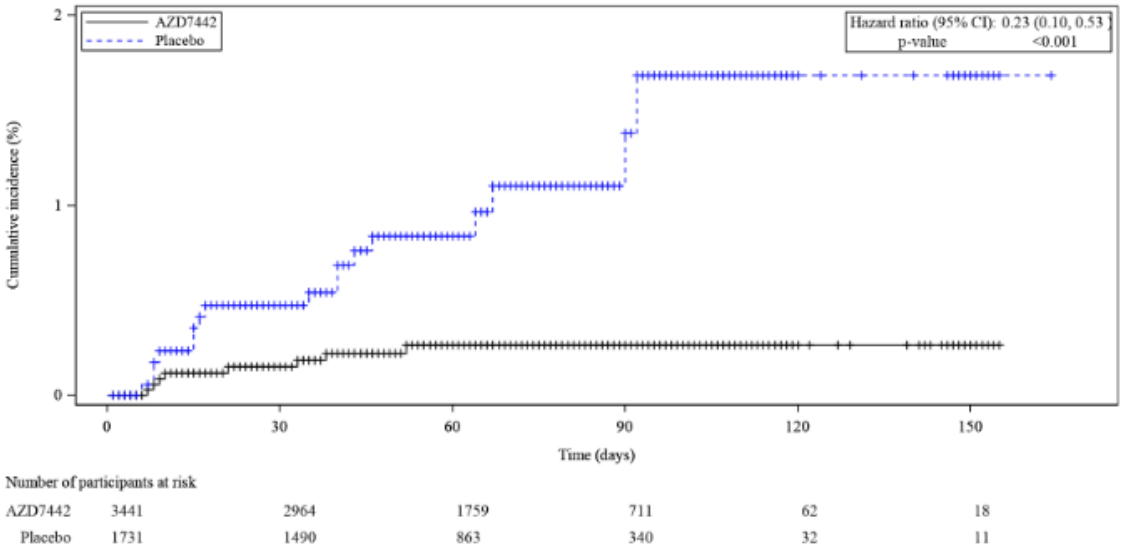
COVID-19 = coronavirus disease 2019; CILGA = cilgavimab; DCO = data cut-off; ITT = intent to treat; RT-PCR = reverse transcriptase polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; TIXA = tixagevimab.

Note: Presented event categories are mutually exclusive and participants are only counted once across the event categories.

Source: Clinical Study Report.[3]

Figure 2 provides the results of time-to-event analyses for the primary outcome in the PROVENT trial according to the data cut-off date of May 2021. Corresponding results for the analysis performed at data cut-off date of August 2021 is presented in Appendix 1 (Figure 4).

Figure 2: Time to First SARS-CoV-2 RT-PCR–Positive Symptomatic Illness Kaplan-Meier Curves by Arm (ITT; Full Pre-exposure Population; May 2021)



ITT = intent to treat; RT-PCR = reverse transcriptase polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

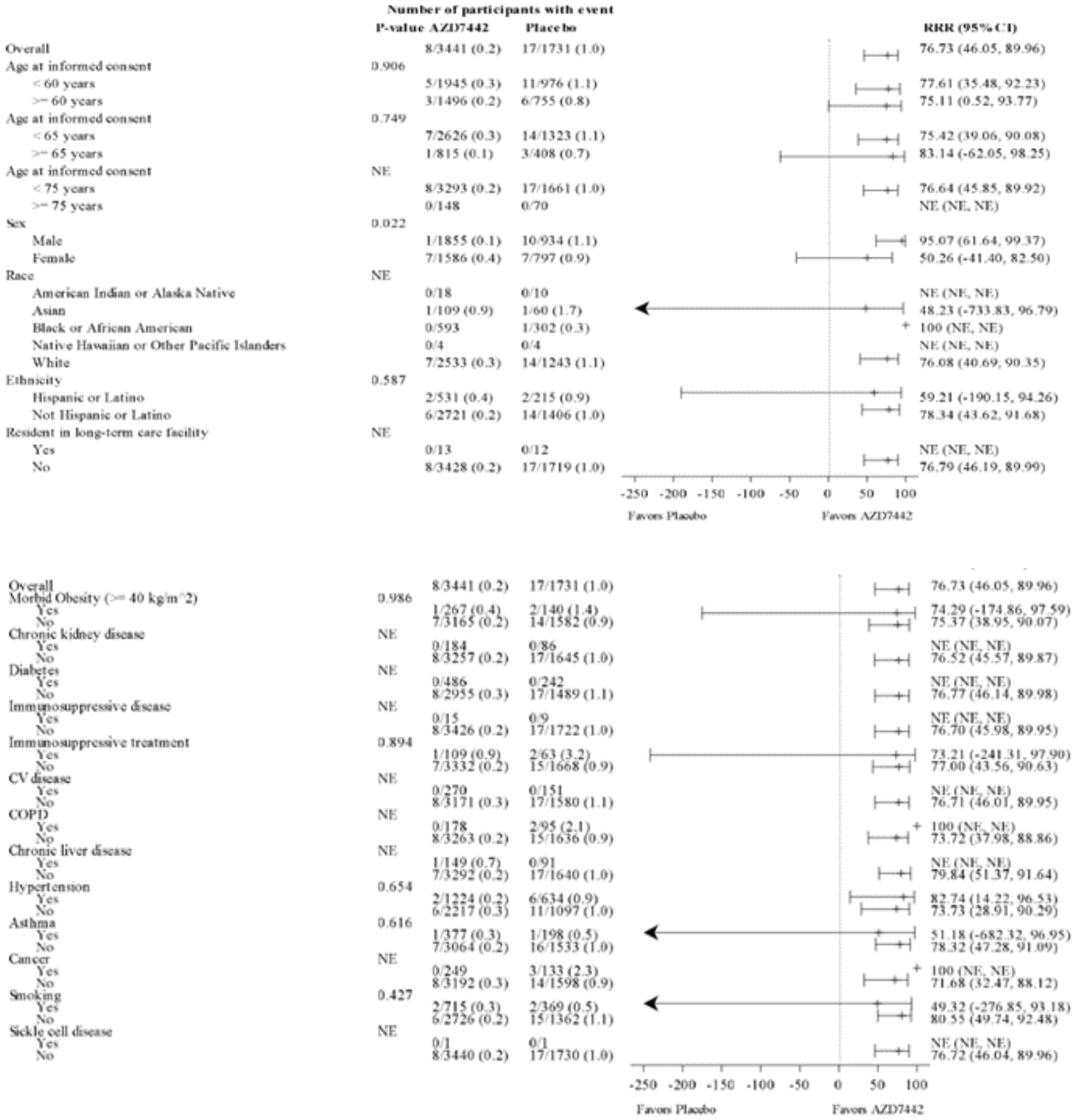
Source: Clinical Study Report.[3]

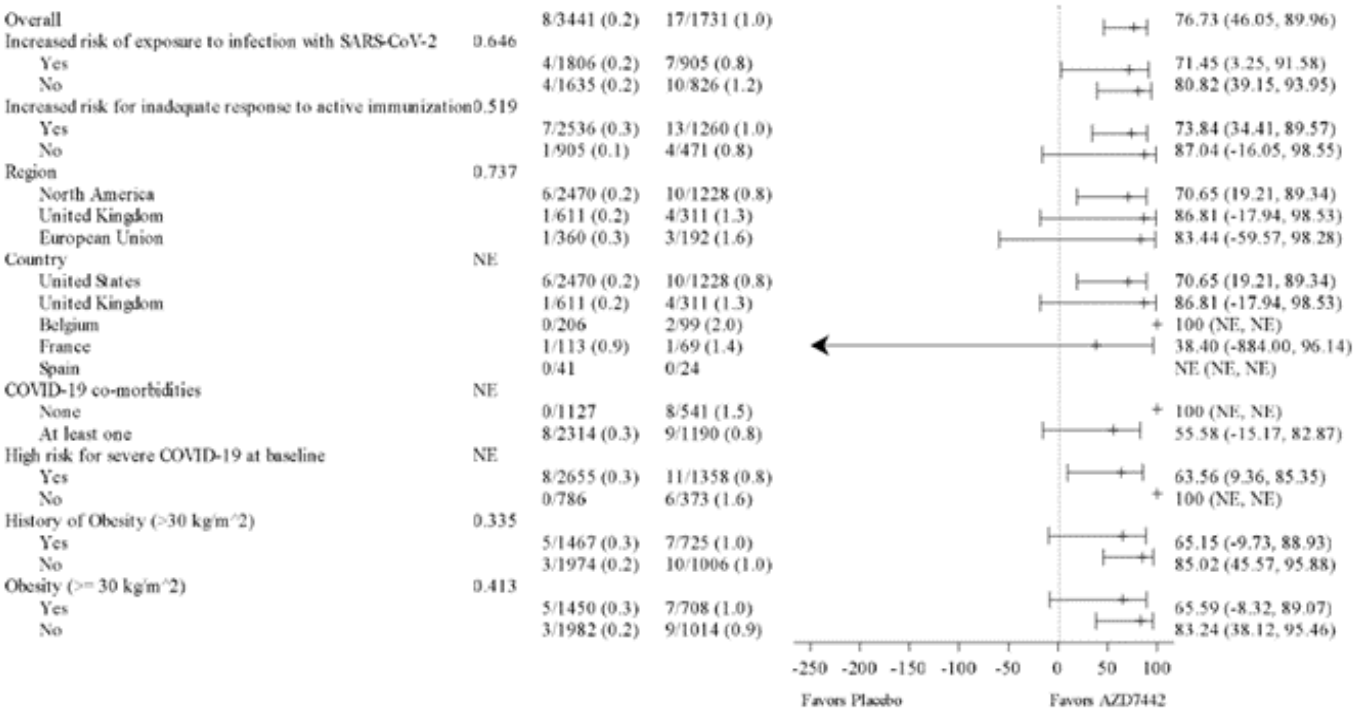
Selected subgroup analyses were reported for the primary outcome in the PROVENT trial and results are presented in (data cut-off date of May 2021). Limited conclusions can be drawn from these analyses because the study was not designed to show a treatment difference between subgroups. As was the case for the primary outcome in the overall population, the number of events that occurred and were included in the analyses was low.

Results for the analyses performed in these subpopulations were consistent with those obtained for the overall population. Among these are a few subgroups of particular interest for the CADTH review. The results of the subgroup analyses in patients with an increased risk of inadequate response to immunization estimated a relative risk reduction that was consistent with the results observed in the overall population (relative risk reduction of 74%; 95% CI, 34.4 to 89.6).

There was no evidence to suggest the magnitude of the benefit differed between patients 60 years of age and older and patients younger than 60 years of age, nor in patients with an increased risk of exposure to infection with SARS-CoV-2 or in those who do not. In patients receiving immunosuppressive treatment, the point estimate is consistent with that of the overall population. No events were observed in the randomized patients residing in long-term care facilities (N = 25) or in those with immunosuppressive disease (N = 24). Results should be interpreted in light of the previously mentioned limitations.

Figure 3: Incidence of First SARS-CoV-2 Symptomatic Illness in the PROVENT Trial — Subgroup Results (Full Pre-Exposure Population; May 2021)





COPD = chronic obstructive pulmonary disease; COVID-19 = coronavirus disease 2019; ITT = intent to treat; RT-PCR = reverse transcriptase polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Source: Clinical Study Report.[3]

Results from supportive subgroup analyses for the primary outcome in the PROVENT trial and performed at the data cut-off date of August 2021 are presented in Appendix 1 (Figure 5). They provide a longer duration of follow-up and were consistent with those obtained at the data cut-off date of May 2021.

Harms Results

The safety analyses data cut-off date was June 2021, providing a median duration of follow-up of 137 days in the active group and 135 days in the placebo group (i.e., the safety population).

A total of 41% of patients experienced adverse events (AEs) throughout the trial until data cut-off. The most common AEs reported included headache and fatigue. The proportions of patients experiencing serious AEs were small and occurred in similar proportions of patients in each treatment group. Discontinuations due to AEs were low. A total of 0.2% of patients who received tixagevimab and cilgavimab died during the available study follow-up; there were no COVID-19–related deaths in this treatment arm. A similar proportion of 0.3% of patients who received placebo died; the cause of death was reported as COVID-19–related in 2 patients in this group.

Among harms of special interest, it should be noted that only small proportions of patients reported visits to the emergency room (2.5% of patients in the active treatment group and 2.0% of patients in the placebo group). This was considered as a safety outcome; therefore, no comparative statistical analyses were reported between treatment groups. These

emergency room visits were considered COVID-19–related in 6 patients (0.2%) who received tixagevimab and cilgavimab and in 3 patients (0.2%) who received placebo.

Results from supportive safety analyses for key harms outcomes were performed at the data cut-off date of August 2021, providing a longer duration of follow-up. Overall, these results were consistent with those obtained from the analyses performed at the data cut-off date of June 2021.

Table 11: Key Harms Results in the PROVENT Trial (Safety Population; June 2021)

Harms	TIXA and CILGA (N = 3,461)	Placebo (N = 1,736)
AEs, n (%)	**1,417 (40.9)**	**698 (40.2)**
Most common events, n (%)		
Headache	227 (6.6)	112 (6.5)
Fatigue	163 (4.7)	76 (4.4)
Cough	120 (3.5)	63 (3.6)
Oropharyngeal pain	109 (3.1)	42 (2.4)
Diarrhea	105 (3.0)	42 (2.4)
Rhinorrhea	106 (3.1)	41 (2.4)
Nausea	87 (2.5)	37 (2.1)
Myalgia	83 (2.4)	35 (2.0)
Nasal congestion	86 (2.5)	28 (1.6)
Urinary tract infection	70 (2.0)	33 (1.9)
Arthralgia	66 (1.9)	26 (1.5)
Pain	64 (1.8)	23 (1.3)
Back pain	50 (1.4)	34 (2.0)
Chills	54 (1.6)	30 (1.7)
Hypertension	53 (1.5)	26 (1.5)
Dyspnea	54 (1.6)	24 (1.4)
Vaccination complication	43 (1.2)	32 (1.8)
Pyrexia	37 (1.1)	31 (1.8)
Vomiting	35 (1.0)	20 (1.2)
COVID-19	15 (0.4)	27 (1.6)
Pain in extremity	20 (0.6)	19 (1.1)
SAEs, n (%)	**92 (2.7)**	**42 (2.4)**
WDAEs, n (%)	**4 (0.1)**	**1 (0.1)**
Deaths, n (%)	**7 (0.2)**	**5 (0.3)**
Related to COVID-19, n (%)	0	2 (0.1)
Harms of special interest — AEs, n (%)		
Anaphylaxis	1	0
Injection site reaction	82 (2.4)	36 (2.1)
Emergency room visits	85 (2.5)	35 (2.0)
COVID-19–related emergency room visits	6 (0.2)	3 (0.2)

Harms	TIXA and CILGA (N = 3,461)	Placebo (N = 1,736)
Supportive data — key harms outcomes, n (%) — Data cut-off: August 2021		
AEs	1,579 (45.6)	790 (45.5)
SAEs	130 (3.8)	58 (3.3)
WDAEs	2 (0.1)	1 (0.1)
Deaths	9 (0.3)	7 (0.4)

AEs = adverse events; CILGA = cilgavimab; COVID-19 = coronavirus disease 2019; SAEs = serious adverse events; TIXA = tixagevimab; WDAEs = withdrawal (study discontinuation) due to adverse events.

Source: Clinical Study Report.[3]

Critical Appraisal

Overall, the PROVENT 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 PROVENT trial was still ongoing and the results reported were based on analyses performed at data cut-off. No patient had yet completed the study. The main findings appeared credible and were supported by results from the longer follow-up duration of the August 2021 data cut-off. Nevertheless, the follow-up duration remains limited in time and no data are available to inform on the efficacy and safety of tixagevimab and cilgavimab beyond 6 months after initial administration or after a second dose of the monoclonal antibodies' combination.

In real life, uncertainty regarding treatment benefit cannot be excluded considering the wide interindividual variations observed in the SARS-CoV-2 infections, as well as the possible widespread use of the drug. Results of the subgroup analyses were aligned with those of the total population; however, the study was not designed for drawing conclusions for any subgroups. The drug was well-tolerated, with few patients discontinuing the study. Exposure and follow-up in larger patient populations may be required to fully characterize the safety profile.

In the PROVENT trial, the combination of tixagevimab and cilgavimab was associated with a statistically significant reduction of 77% (95% CI, 46.1 to 90.0; $P < 0.001$) in the risk of experiencing a SARS-CoV-2–positive symptomatic illness compared with placebo; however, the number of events that occurred and were included in the analysis was low considering the overall size of the trial population. This suggests that several individuals in a real clinical setting would need to receive treatment with tixagevimab and cilgavimab in order to prevent one single event; however, this could also be a result of the short follow-up duration. Indeed, the total number of events contributing to the analysis went from 25 events in the primary analysis to 64 events in the August 2021 data cut-off analyses, with a similar reduction in relative risk.

All patients were COVID-19 vaccine naive when the study began, per the inclusion criteria. As the study was ongoing, the protocol was amended to permit unblinding if patients wished to consider receiving a COVID-19 vaccination. Patient-level unblinding information was documented and restricted to key personnel at the study site. At the primary analyses data cut-off date of May 2021, 30% of patients had become unblinded; however, vaccination

against COVID-19 was notably less frequent in the active treatment group than in the placebo group, which was consistent with the advice provided to patients according to treatment group. Patients who received a COVID-19 vaccine were allowed to continue in the study; however, they were censored at the date of unblinding or receipt of COVID-19 preventive product. Considering the measures taken to handle both unblinding and higher vaccination rate in the placebo group, it is not expected that this situation would produce a significant bias in favour of any of the 2 treatment groups in the primary analysis. However, bias against active treatment may be observed in the supportive analysis at data cut-off date of August 2021, where the magnitude of the relative risk reduction is lower in uncensored data, when all events were included regardless of unblinding or receipt of COVID-19 preventive product.

Generalizability

A wide range of interindividual variations have been observed in SARS-CoV-2 infections, including COVID-19 disease characteristics and response to prophylaxis or post-infection treatment. These include individual risk factors for insufficient immunoprotection and sustained disease progression, as well as rapid apparition of several mutations in coronavirus genotypes (variants).

In terms of populational generalizability, a total of 4% of patients included in the PROVENT trial were 75 years of age or older; this limits conclusions on the efficacy and safety of the combination of tixagevimab and cilgavimab in an elderly population, which is important given the significant mortality risk in this population.[14] A total of 78% of patients presented with at least 1 of the various risk factors for severe illness from COVID-19, as seen in routine clinical settings. Inclusion criteria stated that patients were not vaccinated for COVID-19 and did not have a prior or current SARS-CoV-2 infection. As such, the vast majority of patients were found to have a negative SARS-CoV-2 baseline antibody status; however, most of the Canadian population is vaccinated against COVID-19. Although 53% of patients had an increased risk of exposure to infection with SARS-CoV-2, the study results were not informative regarding the efficacy of tixagevimab and cilgavimab in specific subpopulations, such as health care workers or in residents of long-term care facilities, mainly due to the small number of patients in these subgroups.

The definition of increased risk for inadequate response to active immunization included a wide range of risk factors, the most frequently reported in the PROVENT trial being age of 60 years or older and obesity. However, the study provided limited data regarding patients who are immunocompromised (which has been considered a population at high risk of severe illness in previous panel discussions),[15] as only 7% of patients presented with what was labelled as an immunocompromised state.

While infection with SARS-CoV-2 results in mild disease in some individuals, it can also lead to severe disease in others, requiring hospitalization and various resources from a health care system perspective. Preventing these serious patient outcomes and health care utilization outcomes is considered the main treatment goal of COVID-19. In the PROVENT trial, the primary outcome could not provide information specific to severe COVID-19 cases, as it captured all levels of disease severity. Therefore, no comparative analysis was reported for the outcomes of severe or critical symptomatic COVID-19, deaths, or hospitalizations, which were all experienced by only small proportions of patients in the PROVENT trial. Therefore, it is not possible, based on the data available at this time, to conclude that the combination of tixagevimab and cilgavimab has any impact on outcomes such as hospitalizations.

The PROVENT 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 the SARS-CoV-2 Omicron variant and its 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 such as BA.1 and BA.2.[16] In addition, the PROVENT trial does not inform on the efficacy and safety of a repeat dosing schedule every 6 months.

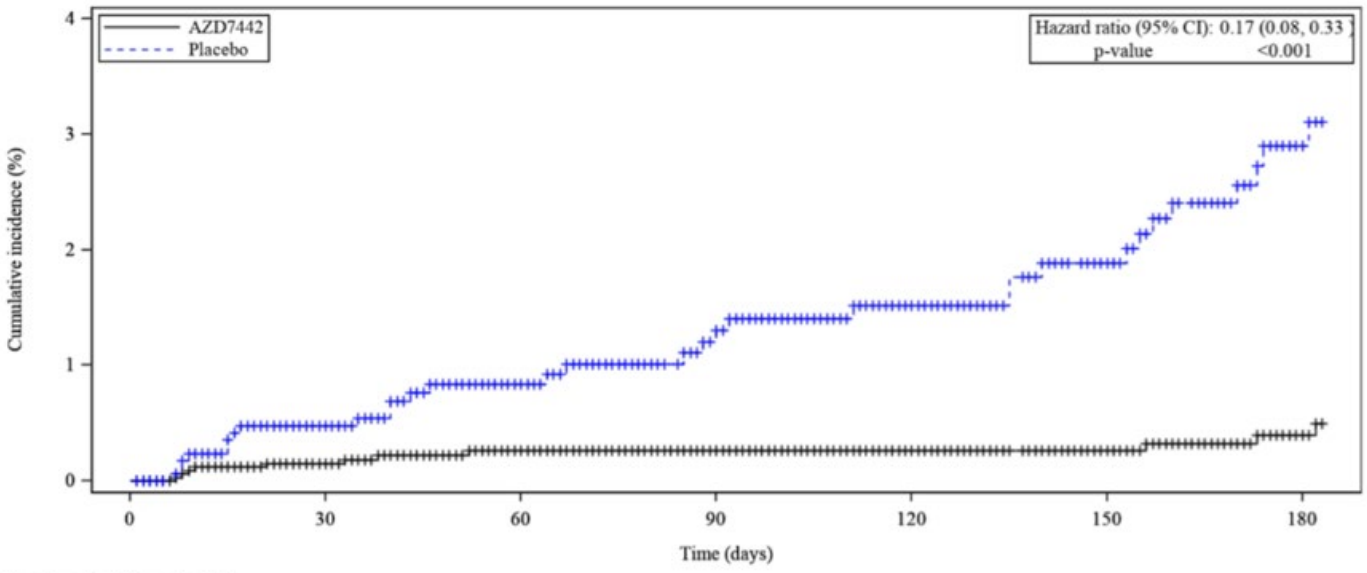
As a result, the real-world effectiveness of tixagevimab and cilgavimab in patients in Canada may vary from what was observed in the PROVENT study. Important gaps in the available evidence include the lack of data in patients fully vaccinated with an additional booster dose against SARS-CoV-2, data on the outcomes of severe COVID-19 illnesses and hospitalizations, clinical data regarding the efficacy of tixagevimab and cilgavimab against the Omicron variant and subvariants, and exposure and follow-up data in larger patient populations to fully characterize the dosing schedule and safety profile.

Appendix 1: Follow-Up Data in the PROVENT Trial (August 2021)

Note that this appendix has not been copy-edited.

Figure 4 provides the results of time-to-event analyses for the primary outcome in the PROVENT trial according to the data cut-off date of August 2021. A statistically significant difference was observed between treatment arms in both the May 2021 data cut-off and August 2021 data cut-off.

Figure 4: Time to First SARS-CoV-2 RT-PCR–Positive Symptomatic Illness Kaplan-Meier Curves by Arm (ITT; Full Pre-exposure Population; Data Cut-Off of August 2021)

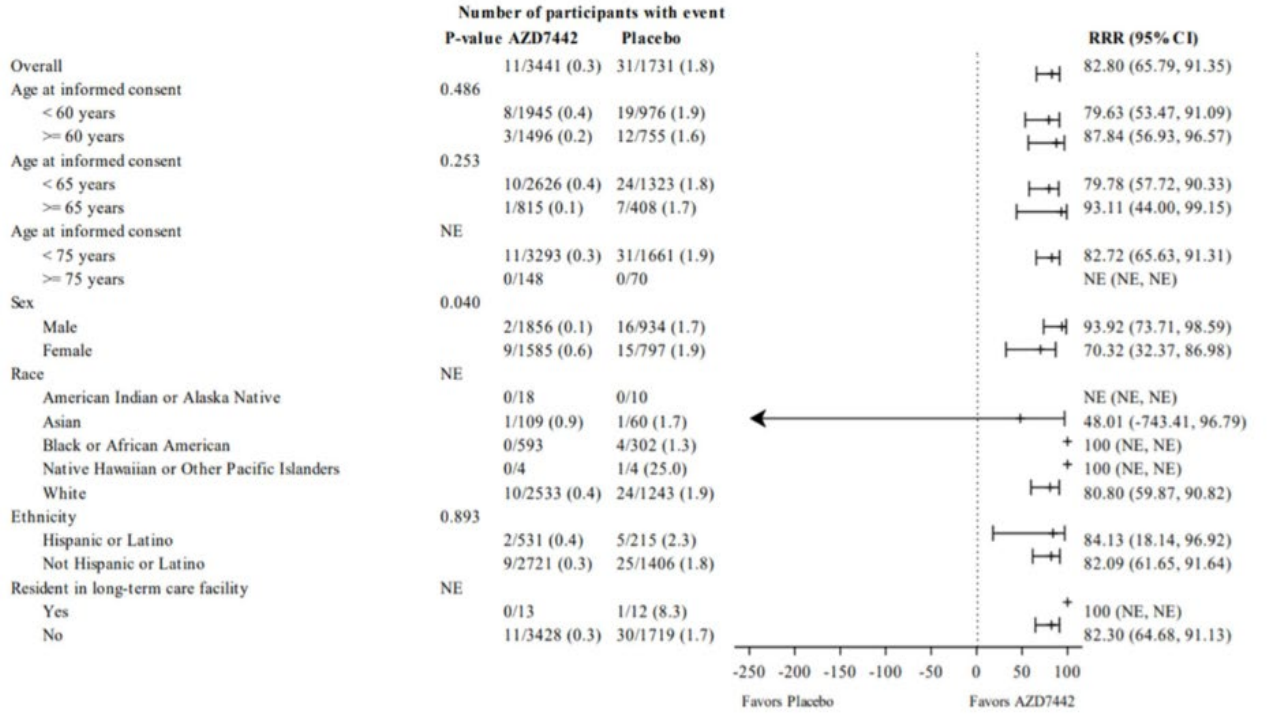


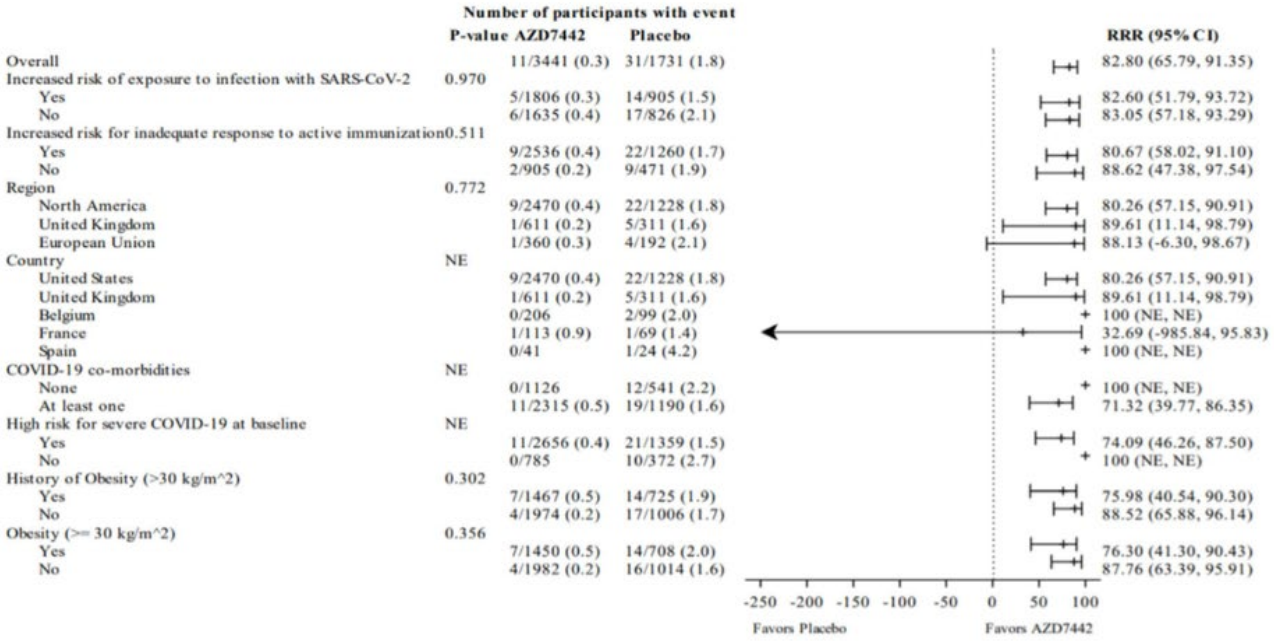
ITT = intent to treat; RT-PCR = reverse transcriptase polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

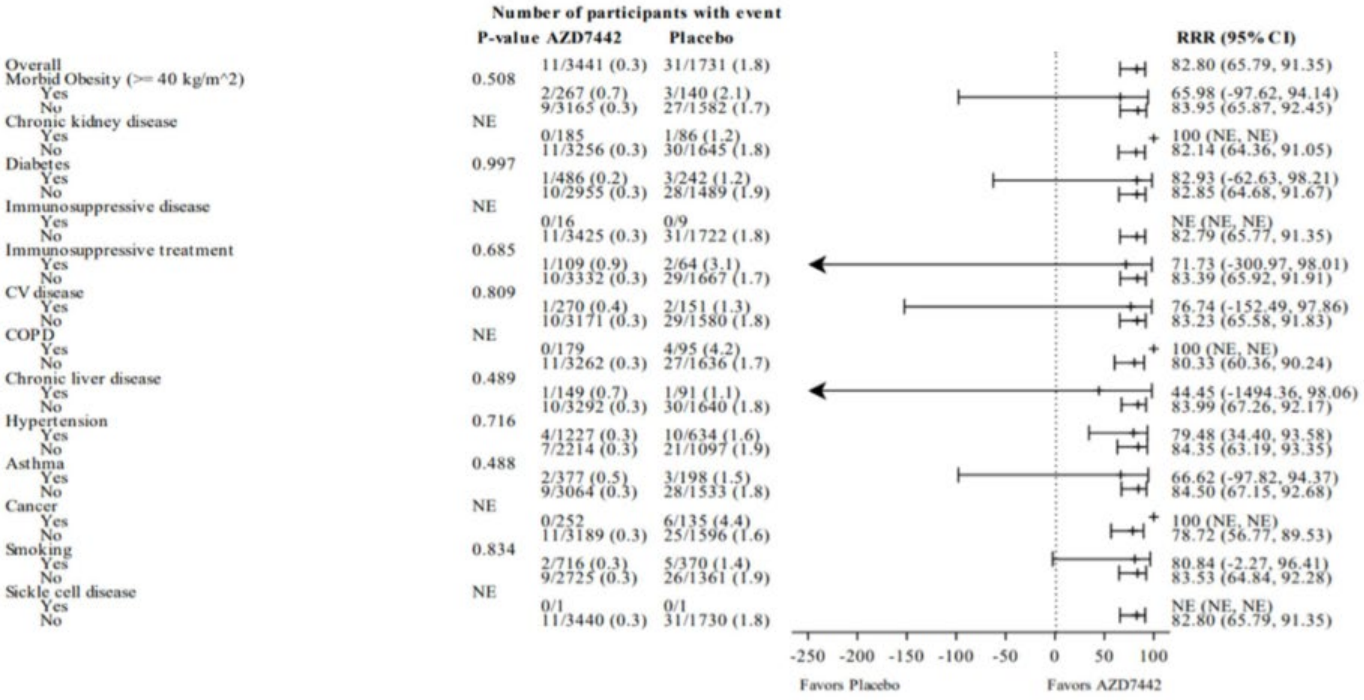
Source: Clinical Study Report.[3]

Results from supportive subgroup analyses for the primary outcome in the PROVENT trial, performed at DCO of August 2021 are presented in Figure 5. They provide a longer duration of follow-up. Overall, these results were consistent with those obtained from the analyses performed at DCO of May 2021.

Figure 5: Primary Efficacy Outcomes in the PROVENT Trial — Incidence of First SARS-CoV-2 Symptomatic Illness, Subgroup Results (ITT; Full Pre-Exposure Population; Data Cut-Off of August 2021)







COPD = chronic obstructive pulmonary disease; COVID-19 = coronavirus disease 2019; ITT = intent to treat; RT-PCR = reverse transcriptase polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Source: Clinical Study Report.[3]

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