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ADISINSIGHT REPORT

Tixagevimab + Cilgavimab: First Approval

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Abstract
Tixagevimab 150 mg and cilgavimab 150 mg (EVUSHELD™ 150 mg + 150 mg solution for injection; tixagevimab + cilgavimab) is an intramuscular (IM) long-acting monoclonal antibody combination developed by AstraZeneca for the prevention and treatment of COVID-19. In March 2022, tixagevimab + cilgavimab was approved in the UK for pre-exposure prophylaxis of COVID-19 in adults who are not currently infected with SARS-CoV-2 and who have not had a known recent exposure to an individual infected with SARS-CoV-2 and who are unlikely to mount an adequate immune response to COVID-19 vaccination or for whom COVID-19 vaccination is not recommended, and in the EU for the prevention of COVID-19 in adults and adolescents aged ≥ 12 years and weighing ≥40 kg. In December 2021, tixagevimab + cilgavimab was granted Emergency Use Authorization by the US FDA for the pre-exposure prophylaxis of COVID-19 in adults and paediatric individuals (≥ 12 years of age and weighing ≥ 40 kg). This article summarizes the milestones in the development of tixagevimab + cilgavimab leading to this first approval for pre-exposure prophylaxis of COVID-19 in individuals who are not currently infected with SARS-CoV-2.

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Tixagevimab + Cilgavimab (EVUSHELD™): Key points

An IM long-acting monoclonal antibody combination developed by AstraZeneca for the prevention and treatment of COVID-19

Received its first approval on 17 March 2022 in the UK and on 25 March 2022 in the EU

Approved in the UK for pre-exposure prophylaxis of COVID-19 in adults who are not currently infected with SARS-CoV-2 and who have not had a known recent exposure to an individual infected with SARS-CoV-2 and who are unlikely to mount an adequate immune response to COVID-19 vaccination or for whom COVID-19 vaccination is not recommended. Approved in the EU for the prevention of COVID-19 in adults and adolescents aged ≥ 12 years and weighing ≥40 kg

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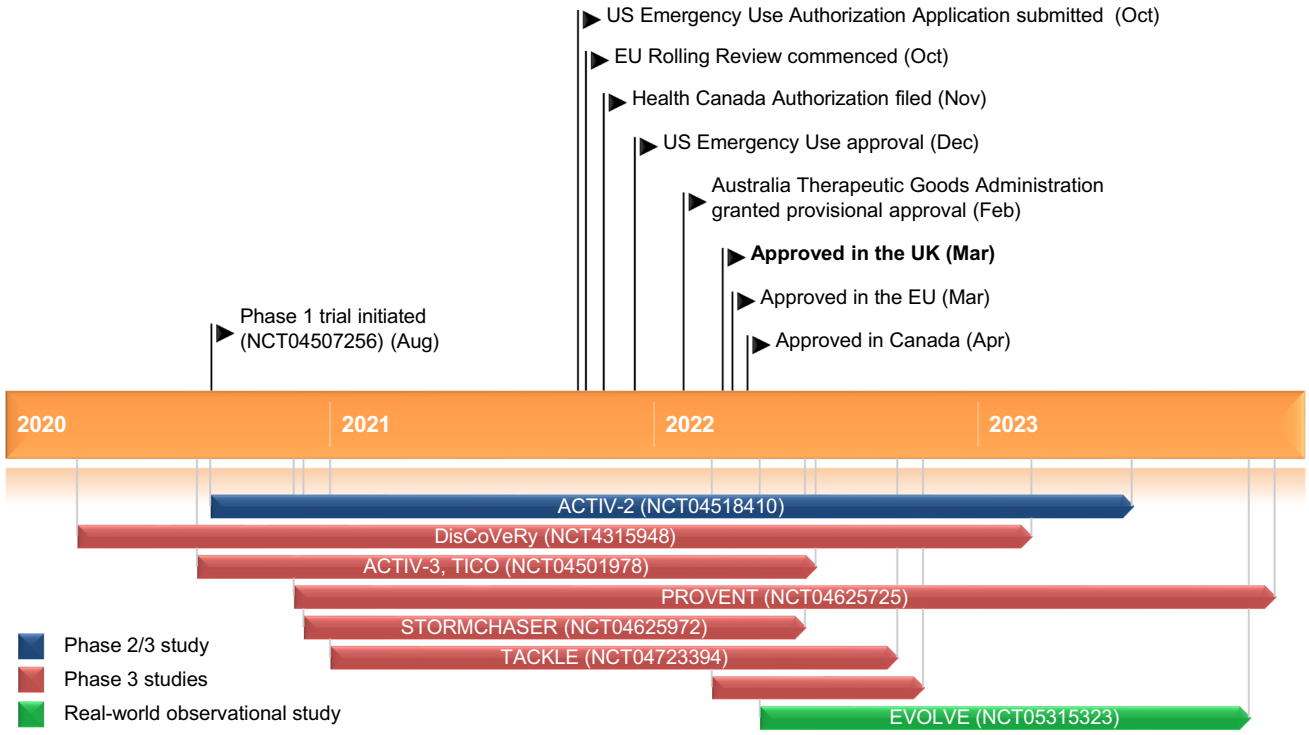
1 Introduction

The management of COVID-19 has continued to evolve since the infection was first identified in December 2019. While vaccination has been the mainstay of infection prevention and mitigation, individuals who are at higher risk of severe disease require additional therapeutic support [1–3]. SARS-CoV-2-neutralizing monoclonal antibodies derived from convalescent plasma are an option for the prevention and treatment of COVID-19 in at-risk individuals [4]; concurrent administration of monoclonal antibodies that bind to different sites on the SARS-CoV-2 spike protein may help to overcome the immune evasion and maintain susceptibility of more recent SARS-CoV-2 variants [2, 5].

Tixagevimab and cilgavimab are long-acting monoclonal antibodies derived from B-cells donated by convalescent patients after infection with SARS-CoV-2 virus. They bind to distinct sites on the SARS-CoV-2 spike protein and when administered concurrently, show synergistic activity against SARS-CoV-2 [2, 6–8].

Co-packaged and concurrently administered tixagevimab 150 mg and cilgavimab 150 mg (EVUSHELD™ 150 mg + 150 mg solution for injection; tixagevimab + cilgavimab) received its first approval on 17 March 2022 in the UK for the pre-exposure prophylaxis of COVID-19 in adults who are not currently infected with SARS-CoV-2 and who have not had a known recent exposure to an individual infected with SARS-CoV-2 and who are unlikely to mount an adequate immune response to COVID-19 vaccination or for



Key milestones in the development tixagevimab + cilgavimab in the prevention and treatment of COVID-19

whom COVID-19 vaccination is not recommended [1, 9]. The recommended dose is 300 mg, consisting of 150 mg of tixagevimab and 150 mg of cilgavimab administered as separate sequential intramuscular (IM) injections at different injection sites in two different muscles, preferably in the gluteal muscles. A higher 600 mg dose, consisting of 300 mg of tixagevimab and 300 mg of cilgavimab, may be more appropriate for some SARS-CoV-2 variants (for example, Omicron BA.1, Omicron BA.1.1), based on in vitro neutralisation susceptibility data which show reduced susceptibility for tixagevimab + cilgavimab [9, 10]. Tixagevimab + cilgavimab was approved on 25 March 2022 in the EU for the prevention of COVID-19 in adults and adolescents aged ≥ 12 years and weighing ≥ 40 kg [11, 12]. The recommended dose is 150 mg of tixagevimab and 150 mg of cilgavimab, administered as two separate sequential IM injections at different injection sites in two different muscles, preferably in the gluteal muscles [11, 12]. Tixagevimab + cilgavimab was approved on 14 April 2022 in Canada for the pre-exposure prophylaxis of COVID-19 in adults and adolescents aged ≥ 12 years and weighing ≥ 40 kg who have not had a known recent exposure to an individual infected with SARS-CoV-2 and who are immune compromised and unlikely to mount an adequate immune response to COVID-19 vaccination or for whom COVID-19 vaccination is not recommended [13]. The recommended dose is 300 mg of tixagevimab + cilgavimab administered as two separate sequential IM injections of 150 mg of tixagevimab and 150 mg of cilgavimab at different injection sites in two different muscles, preferably in the gluteal muscles. Consideration should be given to increase the dose to 600 mg in regions where Omicron BA.1 and BA.1.1 are circulating [13].

In December 2021, tixagevimab + cilgavimab was granted Emergency Use Authorization (EUA) by the US FDA for the pre-exposure prophylaxis of COVID-19 in adults and paediatric individuals (≥ 12 years of age weighing ≥ 40 kg) who are not currently infected with SARS-CoV-2 and who have not had a known recent exposure to an individual infected with SARS-CoV-2 and who have moderate to severe immune compromise due to a medical condition or receipt of immunosuppressive medications or treatments and may not mount an adequate immune response to COVID-19 vaccination or for whom vaccination with any available COVID-19 vaccine, according to the approved or authorized schedule, is not recommended due to a history of severe adverse reaction (e.g., severe allergic reaction) to a COVID-19 vaccine(s) and/or COVID19 vaccine component(s). The authorized dose was 150 mg of tixagevimab and 150 mg of cilgavimab [10]. In February 2022, the EUA for tixagevimab + cilgavimab was revised by the US FDA to change the dosing regimen because of in vitro neutralization of tixagevimab + cilgavimab against the Omicron subvariants BA.1 and BA.1.1 (BA.1+R346K). The initial

dosing regimen is tixagevimab 300 mg and cilgavimab 300 mg administered as two separate consecutive IM injections, preferably in each of the gluteal muscles; individuals who have already received the previously authorized initial dose should receive an additional dose as soon as possible, with the dosing regimen based when the initial regimen was administered [10]. Tixagevimab + cilgavimab was also granted EUA in the United Arab Emirates in late 2021 [14] and provisional use in Australia in early 2022 [15].

1.1 Company Agreements

In December 2021, Samsung Biologics and AstraZeneca extended the long-term strategic manufacturing collaboration agreement in which Samsung Biologics manufactures tixagevimab + cilgavimab for COVID-19 infection. The original agreement was signed in September 2020 and the partnership was expanded in May 2021 [16].

In November 2020, Lonza entered an agreement with AstraZeneca for manufacturing of tixagevimab + cilgavimab. Under the agreement, AstraZeneca will leverage Lonza's extensive antibody manufacturing expertise, quality control testing, regulatory competence and experience with accelerated manufacturing campaigns [17].

In June 2020, AstraZeneca licensed coronavirus-neutralizing monoclonal antibodies from Vanderbilt University with a plan to advance a pair of these monoclonal antibodies into clinical development as a potential combination therapy for the prevention and treatment of COVID-19. The agreement was based on an earlier April 2020 collaboration agreement with Vanderbilt [18].

In April 2020, AstraZeneca entered a research and development agreement with the United States Army Medical Research Institute of Infectious Diseases (USAMRIID) and the University of Maryland School of Medicine to conduct preclinical safety and efficacy of antibodies discovered by AstraZeneca against COVID-19 [19].

2 Scientific Summary

2.1 Pharmacodynamics

Tixagevimab and cilgavimab are recombinant human IgG1κ monoclonal antibodies that contain substitutions in the Fc regions [9, 12], the M252Y/S254T/T256E (YTE) modification (extends the half-life of monoclonal antibodies [9, 20, 21]) and the L234F/L235E/P331S (TM) modification (decreases binding of the Fc receptor and complement component C1q, reducing antibody effector function and the potential risk of antibody-dependent disease enhancement [9, 21, 22]). Tixagevimab and cilgavimab simultaneously bind to distinct, nonoverlapping epitopes on the spike protein receptor binding domain (RBD) to neutralize SARS-CoV-2 [9, 12, 21, 23]; tixagevimab binds to the back of the left shoulder epitope and cilgavimab binds to the front of the right shoulder epitope [24]. Tixagevimab, cilgavimab and tixagevimab + cilgavimab bind to the spike protein receptor binding domain with equilibrium dissociation constants (KD) of 2.76 pM, 13.0 pM and 13.7 pM, respectively; binding blocks interaction with the human ACE2 receptor, which is required for SARS-CoV-2 virus attachment. Tixagevimab, cilgavimab and tixagevimab + cilgavimab blocked RBD binding to the human ACE2 receptor with IC_{50} values of 0.32 nM (48 ng/mL), 0.53 nM (80 ng/mL) and 0.43 nM (65 ng/mL), respectively [9, 12, 21]. In cell culture studies, tixagevimab, cilgavimab and tixagevimab + cilgavimab showed reduced or no antibody-dependent cell-mediated cytotoxicity, antibody-dependent cellular phagocytosis or antibody-dependent natural killer cell activation and did not mediate antibody-dependent complement deposition activity with guinea pig complement proteins [10].

Tixagevimab + cilgavimab potently and synergistically neutralizes SARS-CoV-2 in vitro and provides protection in animal models of SARS-CoV-2 infection [8, 9]. In a SARS-CoV-2 virus neutralization assay on Vero E6 cells, tixagevimab, cilgavimab and tixagevimab + cilgavimab neutralized SARS-CoV-2 (USA-WA1/2020 isolate) with EC_{50} values of 60.7 pM (9 ng/mL), 211.5 pM (32 ng/mL) and 65.9 pM (10 ng/mL), respectively [9], values that correlated with in vivo clinically effective tixagevimab + cilgavimab serum concentrations of 2.2 μg/mL [12].

Following 10 serial passages in a cell culture of SARS-CoV-2 or 2 serial passages in a replication competent vesicular stomatitis virus encoding SARS-CoV-2 spike protein (pseudovirus) in the presence of tixagevimab, cilgavimab and tixagevimab + cilgavimab, escape variants with reduced susceptibility to cilgavimab (all > 200-fold increase in IC_{50}) included spike protein amino acid substitutions R346I, K444E and K444R. No escape variants to tixagevimab or tixagevimab + cilgavimab were selected [9, 12]. In in vitro neutralization assays that used recombinant SARS-CoV-2 pseudoviruses with individual spike substitutions that have been identified in circulating SARS-CoV-2, variants with reduced susceptibility to cilgavimab (all > 200-fold) included spike protein amino acid substitutions R346I, K444E, K444Q and K444R. Variants with reduced susceptibility to tixagevimab included spike protein amino acid substitutions F486S (> 600-fold) and F486V (121- to 149-fold) [9]. In vitro, tixagevimab

+ cilgavimab retained activity against pseudoviruses harbouring individual SARS-CoV-2 spike substitutions (E484D/K/Q, F490S, Q493R, S494P, K417E/N, D420N, K444Q, V445A, Y453F, L455F, N460K/S/T, F486V, and Q493K) that were associated with reduced susceptibility to other monoclonal antibodies targeting the RBD of SARS-CoV-2 spike protein [12].

Although the neutralizing activity of tixagevimab + cilgavimab against more recent SARS-CoV-2 strains is reduced compared with activity against earlier strains [25], IC_{50} values against numerous pseudovirus and/or live virus SARS-CoV-2 variants tested [9, 12, 24, 26–29] (including SARS-CoV-2 B.1.1.529 Omicron, BA.1 [live virus IC_{50} 147–278 ng/mL [9, 12, 24, 26–29]; fold reduction in susceptibility 12–30 [9, 12, 29]] and Omicron BA.2 [pseudovirus and live virus IC_{50} 9.8–35 ng/mL; fold reduction in susceptibility 5.4 [9, 12, 29]]) are within the range of neutralising antibody titres in individuals who have recovered naturally from COVID-19 infection [30]. Omicron BA.1.1 showed a 176-fold reduction in susceptibility to tixagevimab + cilgavimab (live virus IC_{50} 1147 ng/mL) [9, 12, 29]. Tixagevimab + cilgavimab when used as pre-exposure prophylaxis in a hamster model had inhibitory activity in vivo against Omicron BA.1, although activity was less than against an earlier variant (SARS-CoV-2 B.1 G614) [31]; the plasma EC_{90} value estimated in hamsters infected by SARS-CoV-2 B.1 G614 (1.2 µg/mL) [31] was below the mean serum concentrations of tixagevimab + cilgavimab in humans after an IM 300 mg dose [9, 10, 12] whereas the plasma EC_{90} value in hamsters infected with Omicron BA.1 was ≈22-fold higher (27.0 µg/mL) [31].

After administration of a single dose of tixagevimab + cilgavimab in the phase 3 PROVENT trial (NCT04625725), neutralizing antibody geometric mean titres (GMT) at days 7 (n = 891), 28 (n = 954) and 57 (n = 43) post-dose were similar to those observed in a phase 1 trial in healthy volunteers (NCT04507256 [21]) and were 16-, 22-, and 17-fold higher than the GMT (30.8) in convalescent plasma from patients with COVID-19 [12].

In rhesus macaque and cynomolgus macaque models of SARS-CoV-2 infection, prophylaxis with tixagevimab + cilgavimab 3 days prior to exposure to SARS-CoV-2 virus dose-dependently prevented upper and lower respiratory tract infection and compared with placebo, reduced lung injury (pulmonary inflammation and alveolar damage) associated with COVID-19 infection [10, 21].

The potential of tixagevimab and cilgavimab to mediate antibody-dependent viral entry was assessed in FcγRII-expressing Raji cells co-incubated with recombinant virus pseudotyped with SARS-CoV-2 spike protein. Over an antibody concentration range of 6.6 nM (1 µg/mL) to 824 pM (125 ng/mL), tixagevimab, cilgavimab and tixagevimab + cilgavimab did not mediate entry of pseudovirus into these cells [12]. The potential for antibody-dependent enhancement of infection mediated by tixagevimab and cilgavimab was evaluated in a primate model of SARS-CoV-2. Intravascular administration of tixagevimab + cilgavimab before virus inoculation was associated with a dose-dependent improvement in measured outcomes (total viral RNA in the lungs or nasal mucosae, infectious virus levels in the lungs based on $TCID_{50}$ measurements, and lung injury and pathology based on histology measurements). Disease enhancement was not observed at any dose, including at sub-neutralizing doses as low as 0.04 mg/kg [12].

2.2 Pharmacokinetics

The pharmacokinetics of tixagevimab and cilgavimab are comparable, linear and dose-proportional [9] after a single intravenous (IV) administration of tixagevimab 150 mg and cilgavimab 150 mg to tixagevimab 1500 mg and cilgavimab 1500 mg [9, 12] or after a single IM administration of tixagevimab 150 mg and cilgavimab 150 mg to tixagevimab 300 mg and cilgavimab 300 mg [9, 12]. After a single IM administration of tixagevimab 150 mg and cilgavimab 150 mg in a phase 1 trial in healthy volunteers (NCT04507256), the mean maximum concentrations (C_{max}) of tixagevimab and cilgavimab (16.5 and 15.3 µg/mL) were reached at a median T_{max} of 14 days [9, 12, 21]. Estimated absolute bioavailability was 68.5% for tixagevimab and 65.8% for cilgavimab after a single 150 mg IM dose. According to pharmacokinetic modelling, the central volume of distribution for tixagevimab and cilgavimab was 2.72 and 2.48 L, respectively, and the peripheral volume of distribution was 2.64 L and 2.57 L [9, 12]. Based on pharmacokinetic/pharmacodynamic modelling, the estimated time to reach the minimum protective serum concentration of 2.2 µg/mL after IM administration of tixagevimab 150 mg and cilgavimab 150 mg in the gluteal region is 6 h [9, 12].

After a single IM dose of tixagevimab 150 mg and cilgavimab 150 mg in the phase 3 PROVENT trial (NCT04625725) in individuals considered to be at increased risk for inadequate response to active immunisation, the tixagevimab and cilgavimab C_{max} values were 13.1 and 11.7 µg/mL and median T_{max} was 20 days based on pharmacokinetic modelling; the estimated absolute bioavailability was 62% for tixagevimab and 59% for cilgavimab [9]. In PROVENT, the mean serum concentration of tixagevimab + cilgavimab was 18.9 µg/mL at day 8 and 24.0 µg/mL at day 29, which translated to a SARS-CoV-2 mean neutralizing antibody titre of 493.1 and 677.3 at the respective timepoints in an 80% plaque-reduction neutralization test that used wild-type virus (16- and 22-fold higher

than titres from samples of convalescent plasma following COVID-19 infection) [2]. The median serum concentration of tixagevimab + cilgavimab at day 183 in the PROVENT trial was 8.3 μg/mL (range 1.3–19.5 μg/mL) [12].

Tixagevimab and cilgavimab are expected to be degraded into small peptides and component amino acids via catabolic pathways in the same manner as endogenous IgG antibodies and are not expected to undergo metabolism by hepatic enzymes [including cytochrome P450 (CYP) enzymes] or renal excretion; consequently, interactions with medicinal products that are substrates, inducers, or inhibitors of CYP enzymes or are renally excreted are unlikely [9, 12]. The clearance for tixagevimab and for cilgavimab was 0.041 L/day for each, with interindividual variability of 21% and 29%, respectively. The estimated population median terminal elimination half-lives for tixagevimab and cilgavimab were 89 and 84 days, respectively [9, 12].

No studies have been conducted to evaluate the effects of renal or hepatic impairment on the pharmacokinetics of tixagevimab and cilgavimab. As tixagevimab and cilgavimab are not eliminated intact in the urine, renal impairment is not expected to significantly affect the exposure of tixagevimab and cilgavimab and dialysis is not expected to impact the pharmacokinetics of tixagevimab and cilgavimab. A population pharmacokinetic analysis found no difference in the clearance of tixagevimab and cilgavimab in patients with mild or moderate renal impairment compared with those with normal renal function. The impact of hepatic impairment on the pharmacokinetics of tixagevimab and cilgavimab is also expected to be low [9, 12].

There was no clinically meaningful difference in the pharmacokinetics of tixagevimab and cilgavimab in individuals aged ≥ 65 years or < 65 years in a pooled pharmacokinetic analysis ($n = 2560$; 21% were aged ≥ 65 years) [9, 12]. According to population pharmacokinetic modelling, tixagevimab and cilgavimab exposures in adolescents aged ≥ 12 years who weight ≥ 40 kg are expected to be comparable to those in adults after administration of the recommended dosing regimen of tixagevimab + cilgavimab [12]. Population pharmacokinetic modelling also indicated that increasing body weight is associated with a decrease in serum concentrations of tixagevimab + cilgavimab; after administration of the recommended dosing regimen, the average serum concentration of tixagevimab + cilgavimab in an adult weighing > 95 kg was predicted to be ≈ 37% lower than that in an adult weighing 65 kg [12]. Pharmacokinetic modelling showed that COVID-19 vaccination following tixagevimab + cilgavimab administration or administration of tixagevimab + cilgavimab to an immunocompromised individual had no clinically relevant impact on tixagevimab + cilgavimab clearance [9, 12].

Features and properties of tixagevimab + cilgavimab

Alternative names	AZD 8895 + AZD 1061; EVUSHELD
Class	Antivirals, monoclonal antibodies
Mechanism of action	Virus internalisation inhibitors; targets coronavirus spike glycoprotein
Route of administration	Intramuscular injection
Pharmacodynamics	Recombinant human IgG1κ monoclonal antibodies that contain substitutions in the Fc regions to extend the half-life and reduce antibody effector function and the potential risk of antibody-dependent disease enhancement. Simultaneously bind to distinct, nonoverlapping epitopes on the spike protein receptor binding domain to neutralize SARS-CoV-2 by blocking interaction with the human ACE2 receptor, which is required for SARS-CoV-2 virus attachment Live virus IC_{50} values against more recent variants, including Omicron BA.1 and Omicron BA.2, are reduced compared with earlier variants, but are within the range of neutralising antibody titres in individuals who have recovered naturally from COVID-19 infection
Pharmacokinetics (from PROVENT)	C_{max} 13.1 μg/mL(tixagevimab), 11.7 μg/mL (cilgavimab); T_{max} 20 days, estimated absolute bioavailability 62% (tixagevimab), 59% (cilgavimab). CL 0.041 L/day (tixagevimab and cilgavimab), median $t_{1/2}$ 89 days (tixagevimab), 84 days (cilgavimab) Tixagevimab + cilgavimab C_{mean} 18.9 μg/mL at day 8, 24.0 μg/mL at day 29, C_{median} 8.3 μg/mL at day 183
Adverse events (all grades, regardless of causality)	
Most frequent	Headache, fatigue, cough (incidence ≤ 6%)
Adverse reactions	Injection-site reactions, hypersensitivity reactions (both incidence < 2%)
ATC codes	
WHO ATC code	J05A-X (other antivirals)
EphMRA ATC code	J5 (antivirals for systemic use)
Chemical name	Immunoglobulin G1 [248-threonine,249-methionine,316-tyrosine,318-threonine,320-glutamic acid], anti-(severe acute respiratory syndrome coronavirus 2 spike glycoprotein receptor-binding domain) (human monoclonal AZD1061 γ1-chain), disulfide with human monoclonal AZD1061 κ-chain, dimer/Immunoglobulin G1 [240-threonine,241-methionine,308-tyrosine,310-threonine,312-glutamic acid], anti-(severe acute respiratory syndrome coronavirus 2 spike glycoprotein receptor-binding domain) (human monoclonal AZD8895 γ1-chain), disulfide with human monoclonal AZD8895 κ-chain, dimer

2.3 Therapeutic Trials

2.3.1 PROVENT

A single 300 mg IM dose of tixagevimab + cilgavimab administered as pre-exposure prophylaxis significantly reduced the risk of symptomatic COVID-19 infection compared with placebo in adults with an increased risk of an inadequate response to vaccination against COVID-19 and/or an increased risk of exposure to SARS-CoV-2 in the phase 3 PROVENT trial (NCT04625725) [2]. Patients were randomized to receive a single administration of tixagevimab + cilgavimab 300 mg (n = 3441) or placebo (1731) and were followed for up to 183 days in the primary efficacy analysis. At data cut-off, symptomatic SARS-CoV-2 RT-PCR–positive illness occurred in significantly fewer tixagevimab + cilgavimab than placebo recipients [8 (0.2%) vs 17 (1.0%) patients; relative risk reduction (RRR) 76.7% (95% CI 46.0–90.0); $p < 0.001$]. SARS-CoV-2 RT-PCR–positive severe or critical illness occurred in none of the tixagevimab + cilgavimab recipients and in 1 (0.1%) placebo recipient; two COVID-19 deaths occurred in the placebo group [2]. The benefit of pre-exposure prophylaxis with tixagevimab + cilgavimab was still evident at a median 6.5-month follow-up post-hoc assessment: symptomatic SARS-CoV-2 RT-PCR–positive illness occurred in 0.3% (11/3441) of tixagevimab + cilgavimab recipients compared with 1.8% (31/1731) of placebo recipients [RRR 82.8% (95% CI 65.8–91.4)]; an additional four cases of severe or critical COVID-19 were reported in placebo group [2, 9, 10, 12].

Sequencing data collected at illness visits was available for 21 participants with COVID-19 infection in PROVENT (6 tixagevimab + cilgavimab and 15 placebo recipients) [9, 10, 12]. At an allele fraction ≥ 25%, 14 participants were infected with variants of concern/of interest, including 8 placebo recipients with Alpha (B.1.1.7), 1 tixagevimab + cilgavimab recipient with Beta (B.1.351), 3 placebo recipients with Delta (B.1.617.2) and 2 tixagevimab + cilgavimab recipients with Epsilon (B.1.429) [10, 12]. One tixagevimab + cilgavimab recipient was infected with B.1.375 and 3 tixagevimab + cilgavimab and 3 placebo recipients were infected with the A_1 set of lineages containing a constellation of spike protein substitutions including D614G and P681H or Q677P [10]. Additional spike protein RBD substitutions detected at an allele fraction ≥ 3% in tixagevimab + cilgavimab recipients included V503F [9, 12]; the significance of this substitution in relation to tixagevimab + cilgavimab efficacy is being investigated [9].

At baseline in PROVENT, the median age was 53.5 years and 77.5% of participants had high-risk factors for severe COVID-19, including obesity (41.7%), hypertension (35.9%), smoking (21.0%), diabetes (14.1%), asthma (11.1%), cardiovascular disease (8.1%), cancer (7.4%) and immunosuppression (3.8%) [2]. The primary efficacy end point was the first episode of symptomatic COVID-19, confirmed by positive results on reverse-transcriptase–polymerase-chain-reaction (RT-PCR) testing, with an onset after the administration of tixagevimab + cilgavimab or placebo and on or before day183. Individuals who had a history of COVID-19 infection, a positive SARS-CoV-2 result at screening or who had previously received a vaccine or biologic agent indicated for the prevention of SARS-CoV-2 infection or COVID-19 were excluded from the trial [2].

2.3.2 STORM CHASER

Tixagevimab + cilgavimab as post-exposure prophylaxis did not meet the primary endpoint in the phase 3 double-blind, placebo-controlled STORM CHASER trial (NCT04625972) in unvaccinated adult participants who had been exposed to the SARS-CoV-2 virus within the 8 days prior to treatment [10, 32]. Participants (n = 1121) were randomized to receive a single 300 mg IM dose of tixagevimab + cilgavimab (n = 749) or placebo (372). At the time of the efficacy analysis (median follow-up post-administration of 49 days), 3.1% (23/749) of tixagevimab + cilgavimab recipients compared with 4.6% (17/372) of placebo recipients had symptomatic COVID-19 infection (RRR 33%; 95% CI − 26 to 65) [10, 32]. However, 48 of subjects who were randomized and received tixagevimab + cilgavimab or placebo were found to be positive for SARS-CoV-2 (RT-PCR analysis of nasopharyngeal swabs) at baseline [10]. In the subgroup of patients who were RT-PCR-negative at the time of treatment administration (n = 1073), 0.8% (6/715) of tixagevimab + cilgavimab recipients and 3.1% (11/358) of placebo recipients had symptomatic COVID-19 infection (RRR 73%; 95% CI 27–90) [10, 32].

Sequencing data collected at illness visits was available for 19 participants with COVID-19 infection in STORM CHASER (12 tixagevimab + cilgavimab and 7 placebo recipients) [10]. At an allele fraction ≥ 25%, 12 participants were infected with variants of concern/of interest, including 5 tixagevimab + cilgavimab and 4 placebo recipients with Alpha (B.1.1.7) and 2 tixagevimab + cilgavimab and 1 placebo recipients with Epsilon (B.1.427/B.1.429). One tixagevimab + cilgavimab and 7 placebo recipients were infected with B.1.1.519 and 4 tixagevimab + cilgavimab and 2 placebo recipients were infected with the A_1 set of lineages containing a constellation of spike protein substitutions including D614G and

D138H, Q675H, Q677H, or V1176F. Additional spike protein RBD substitutions detected at an allele fraction ≥ 3% in tixagevimab + cilgavimab recipients included S325P, Del342, C361W, Del428, F429V, and F515C [10].

The primary efficacy endpoint in STORM CHASER was the first case of SARS-CoV-2 RT-PCR-positive symptomatic illness occurring post dose and before Day 183; the primary analysis was conducted 30 days after 25 events meeting the primary efficacy endpoint definition had occurred [32]. Individuals with a history of laboratory-confirmed SARS-CoV-2 infection or SARS-CoV-2 antibody positivity at screening were excluded [10].

2.3.3 TACKLE

Treatment with a 600 mg IM dose of tixagevimab + cilgavimab significantly reduced the risk of severe COVID-19 infection or death compared with placebo in non-hospitalised adult patients with mild-to-moderate symptomatic COVID-19 infection who had been symptomatic for ≤ 7 days ($n = 903$) in the randomized, double-blind, placebo-controlled, phase 3 TACKLE trial (NCT04723394) [33]. Severe COVID-19 or death from any cause through day 29 (primary efficacy endpoint) occurred in significantly fewer tixagevimab + cilgavimab recipients than placebo recipients [18/407 (4%) vs 37/415 (9%) patients; RRR 50.5% (95% CI 14.6–71.3); $p = 0.0096$]. In the subgroup of participants who received treatment within 5 days of developing symptoms, the risk reduction was greater (67%), with 4% (9/253) of tixagevimab + cilgavimab recipients compared with 11% (27/251) of placebo recipients developing severe COVID-19 infection or dying through day 29. At baseline, 90% of patients enrolled in TACKLE were at high-risk of progression to severe COVID-19 [33].

2.3.4 ACTIV-3 (TICO)

The addition of IV tixagevimab + cilgavimab to standard-of-care treatment (including remdesivir), did not significantly improve the time to sustained recovery in adult patients hospitalized for COVID-19 infection in the phase 3, adaptive, randomized, blinded ACTIV-3/Therapeutics for Inpatients with COVID-19 (TICO) Study (NCT04501978) [34]. Patients ($n = 1417$) in the primary modified intention-to-treat population were administered a 600 mg IV dose of tixagevimab + cilgavimab ($n = 710$) or placebo ($n = 707$) as an infusion. By day 90, similar proportions of tixagevimab + cilgavimab and placebo recipients in the full cohort had achieved sustained recovery (87% vs 84%); a similar outcome was seen in the subgroup of patients who were seronegative at baseline. However, 90-day mortality was significantly lower in the tixagevimab + cilgavimab group [8.6% vs 12.2%; hazard ratio 0.70 (95% CI 0.50–0.97; $p = 0.03$)] The primary outcome was time to sustained recovery through day 90, defined as 14 consecutive days at home after hospital discharge, with co-primary analyses for the full cohort and for participants who were neutralizing antibody-negative at baseline [34].

2.4 Adverse Events

IM tixagevimab + cilgavimab was generally well tolerated in individuals participating in pre- or post-exposure prophylaxis clinical trials and in non-hospitalized patients with COVID-19 [9, 10, 12]. Injection-site reactions (1.3%) and hypersensitivity (1.0%) were the most common adverse reactions reported in pooled data from the placebo-controlled, phase 3 PROVENT (NCT04625725; pre-exposure prophylaxis) and STORM CHASER (NCT04625972; post-exposure prophylaxis) trials. In these trials, 4210 adult participants received a 300 mg IM dose of tixagevimab + cilgavimab and the median safety follow-up duration for the primary safety analysis was 83 days in PROVENT and 49 days in STORM CHASER; updated analyses were conducted at a median 6.5 and 6 months, respectively [9, 10, 12].

Similar (35.3% and 34.2%) proportions of tixagevimab + cilgavimab ($n = 3461$) and placebo ($n = 1736$) recipients reported an adverse event in the PROVENT trial (primary safety analysis) [2]. Most were mild (73%) or moderate (24%) in severity. The most frequent adverse events (all grades, regardless of causality) were headache (6% vs 5%), fatigue (4% vs 3%) and cough (3% vs 3%). Serious adverse events were reported in 1% of individuals in either treatment arm [10]. The adverse event profile of tixagevimab + cilgavimab at the updated safety follow-up data cut-off was consistent with that seen in the earlier analysis [10]. More tixagevimab + cilgavimab than placebo recipients experienced serious cardiovascular adverse events in the PROVENT trial (including myocardial infarction and cardiac failure) [0.7% vs 0.3%]; serious thrombo-embolic events (including pulmonary embolus) were reported in 0.8% and 0.6% of participants, respectively. Most participants experiencing these adverse events had cardiovascular risk factors and/or a history of cardiovascular disease that could explain the occurrence of these events and a causal relationship with tixagevimab + cilgavimab has not been established [12].

Key clinical trials of tixagevimab + cilgavimab in COVID-19

Drug(s)	Indication/ Patient group	Phase	Status	Location(s)	Sponsor	Identifier
Tixagevimab + cilgavimab, placebo	Pre-exposure prophylaxis	3	Ongoing	Global	AstraZeneca	NCT04625725; PROVENT; EudraCT2020-004356-16
Tixagevimab + cilgavimab, placebo	Post-exposure prophylaxis	3	Ongoing	USA, UK	AstraZeneca	NCT04625972; STORM CHASER; EudraCT2020-004719-28
Tixagevimab + cilgavimab, placebo	Outpatients with COVID-19	3	Ongoing	Global	AstraZeneca	NCT04723394; TACKLE; EudraCT2020-005315-44
Tixagevimab + cilgavimab, sotrovimab, nirmatrelvir + ritonavir	Outpatients with COVID-19	3	Recruiting	Italy	AOUI Verona	NCT05321394; MANTICO 2; EudraCT 2021-002612-31
Tixagevimab + cilgavimab, remdesivir, interferon beta-1A, lopinavir/ritonavir, hydroxychloroquine, placebo	Hospitalized with COVID-19	3	Recruiting	Global	INSERM, France	NCT04315948, DisCoVeRY; EudraCT2020-000936-23
Tixagevimab + cilgavimab, bamlanivimab, remdesivir, sotrovimab, ensovibep, amubarvimab + romlusevimab, lufotrelvir, placebo	Hospitalized with COVID-19	3	Active	Global	University of Minnesota	NCT04501978; ACTIV-3 (TICO); EudraCT2020-003278-37
Tixagevimab + cilgavimab, bamlanivimab, SNG001, amubarvimab + romlusevimab, camostat, SAB-185, BMS-986414 + BMS-986413, casirivimab + imdevimab placebo	Outpatients with COVID-19	2/3	Active	Global	NIAID	NCT04518410; ACTIV-2
Tixagevimab + cil gavimab, placebo	Healthy participants	2	Ongoing	China	AstraZeneca	NCT05184062
Tixagevimab + cilgavimab	Paediatric participants	1	Recruiting	Global	AstraZeneca	NCT05281601; TRUST; EudraCT2021-006056-13
Tixagevimab + cilgavimab	Healthy participants	1	Ongoing	Japan	AstraZeneca	NCT04896541
Tixagevimab + cilgavimab	Healthy participants	1	Recruiting	USA	AstraZeneca	NCT05166421
Tixagevimab + cilgavimab, placebo	Healthy participants	1	Completed	UK	AstraZeneca	NCT04507256
Tixagevimab + cilgavimab	Pre-exposure prophylaxis		Recruiting	GCC countries	AstraZeneca	NCT05315323; EVOLVE

AOUI Azienda Ospedaliera Universitaria Integrata Verona, *GCC* Gulf Cooperation Council, *INSERM* Institut National de la Sante et de la Recherche Medicale, *NIAID* National Institute of Allergy and Infectious Diseases

In the STORM CHASER trial, 22% of tixagevimab + cilgavimab (162/749 participants) and 30% of placebo (111/372) recipients reported an adverse event. Serious adverse events were reported in < 1% of participants in either treatment arm and no cardiac serious adverse events occurred [10].

The adverse events profile of 600 mg IM tixagevimab + cilgavimab in non-hospitalized patients with mild-to-moderate COVID-19 in the phase 3 placebo-controlled TACKLE trial (NCT04723394) was generally comparable to that in the PROVENT and STORM CHASER trials [9]. 29% of tixagevimab + cilgavimab and 36% of placebo recipients reported adverse events, of which most were mild (56%) or moderate (27%) in severity. Serious adverse events occurred in 7% of tixagevimab + cilgavimab and 12% of placebo recipients. The most common adverse reaction was injection-site reaction (2.4%). Anaphylaxis or serious hypersensitivity reactions were nor reported. Three tixagevimab + cilgavimab recipients and one placebo recipient, all of whom had cardiac risk factors and/or a prior history of cardiovascular disease at baseline, experienced a cardiac serious adverse event. In TACKLE, 452 patients received tixagevimab + cilgavimab and the median safety follow-up duration was 84 days [9].

Through day 183 after tixagevimab + cilgavimab administration in the PROVENT trial, treatment-emergent anti-tixagevimab, anti-cilgavimab and anti-tixagevimab + cilgavimab antibodies were detected in 0.8% (6/716), 1.1% (7/644) and 1.3% (10/743) evaluable participants. Anti-drug antibodies do not appear to have any impact on the efficacy or safety of tixagevimab + cilgavimab [12].

2.5 Ongoing Clinical Trials

As well as the phase 3 PROVENT (NCT04625725; pre-exposure prophylaxis) and STORM CHASER (NCT04625972; post-exposure prophylaxis) trials of tixagevimab + cilgavimab, the phase 3 TACKLE trial (NCT04723394; non-hospitalized patients with COVID-19) is ongoing. Several large adaptive trials that include a tixagevimab + cilgavimab arm are recruiting [the phase 3 MANTICO 2 noninferiority trial in outpatients with mild or moderate COVID-19 (NCT05321394)] or ongoing [the phase 3 DisCoVeRY in hospitalized patients with COVID-19 (NCT04315948); the phase 2/3 ACTIV-2 in outpatients with COVID-19 (NCT04518410); the phase 3 ACTIV-3 in hospitalized patients with COVID-19 (TICO; NCT04501978)]. A phase 2, placebo-controlled safety and tolerability trial of IV tixagevimab + cilgavimab in Chinese adult participants (NCT05184062) and phase 1 studies of IM or IV tixagevimab + cilgavimab in paediatric participants aged ≥ 29 weeks gestational age to < 18 years (TRUST; NCT05281601) and healthy Japanese volunteers (NCT04896541) are underway, as is a phase 1 study of IM tixagevimab + cilgavimab in healthy volunteers (NCT05166421). A prospective, observational, real-world study to determine utilization of and clinical outcomes with tixagevimab + cilgavimab as pre-exposure prophylaxis in Gulf Cooperation Council countries (NCT05315323) is recruiting.

3 Current Status

Tixagevimab + cilgavimab received its first approval on 17 March 2022 in the UK for the pre-exposure prophylaxis of COVID-19 in adults who are not currently infected with SARS-CoV-2 and who have not had a known recent exposure to an individual infected with SARS-CoV-2 and who are unlikely to mount an adequate immune response to COVID-19 vaccination or for whom COVID-19 vaccination is not recommended [1] and was also approved on 25 March 2022 in the EU for the pre-exposure prophylaxis of COVID-19 in adults and adolescents aged ≥ 12 years and weighing ≥ 40 kg [11].

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