

RAPID C-19 Oversight Group

Briefing:

Tixagevimab and cilgavimab (AZD7442, EVUSHELD; AstraZeneca) **[C19-053]**

For administrative purposes only:

Version	Section	Date	Initial
0.1	1-5	01.02.2021	■
0.2	1-5	01.02.2021	■
1.0	1-5	01.02.2021	■
1.1	1-5	12.10.2021	■
1.2	1-5	13.10.2021	■
1.3	1-5	13.10.2021	■
1.4	1-5	15.10.2021	■
1.5	1-5	23.11.2021	■
1.6	1-5	23.11.2021	■
1.7	1-5	23.11.2021	■
1.8	1-5	06.12.2021	■
1.9	1-5	06.12.2021	■
1.10	1-5	07.12.2021	■
1.11	1-5	04.02.2022	■
1.12	1-5	08.02.2022	■
1.13	1-5	16.05.2022	■
1.14	1-5	18.05.2022	■
2.0	1-5	18.05.2022	■
2.1	1-5	13.06.2022	■
2.2	1-5	13.06.2022	■
2.3	1-5	14.06.2022	■
3.0	1-5	14.06.2022	■
3.1	1-5	02.08.2022	■
3.2	1-5	16.08.2022	■
3.3	1-5	16.08.2022	■
4.0	1-5	16.08.2022	■
4.1	1-5	22.08.2022	■

Key:

NEW	New evidence
NEW	New evidence of high interest
UPDATED	Updated section

1. Key considerations

Question	Response	Section
<p>1.</p> <p>a) Where does tixagevimab and cilgavimab sit in the treatment pathway?</p> <p>b) Are there other treatments sitting in this place in the pathway?</p> <p>c) What is the mechanism of action of tixagevimab and cilgavimab that explains why it is being investigated as a potential treatment for COVID-19, and its particular place in the treatment pathway?</p> <p>d) Are there other treatments in this class (i.e with the same or similar mechanism of action) that have been considered by the Oversight Group and if so, what are these?</p>	<p>Prevention / mild / moderate / severe / critical / rehabilitation</p> <p>Y / N</p> <p>Tixagevimab and cilgavimab is a combination of 2 monoclonal antibodies (AZD8895 and AZD1061) derived from convalescent patients after SARS-CoV-2 infection. By targeting the virus's receptor-binding domain on the SARS-CoV-2 spike protein, tixagevimab and cilgavimab can block viral attachment to human cells, and therefore block infection. Tixagevimab and cilgavimab is a Long-Acting AntiBody (LAAB), as amino acid substitutions introduced into the antibodies extend its half-life - prolonging potential prophylactic benefit for 6-12 months following single administration. Amino acid substitutions also decrease Fc effector function, and potential antibody-dependent enhancement of disease. For this reason, tixagevimab and cilgavimab is being evaluated for prevention and treatment of COVID-19.^{a b}</p> <p>The Oversight Group has considered other neutralising antibodies directed against the spike protein of SARS-CoV-2:</p> <ul style="list-style-type: none"> • Bamlanivimab • Etesevimab • Regdanvimab • Sotrovimab • VIR-7832 • Amubarvimab and romlusevimab • DZIF-10c • BGB-DXP593 • BGB-DXP604 • Casirivimab and imdevimab • Bebtelovimab • Adintrevimab 	<p>5.2, appendix 2</p>

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e) Are there other treatments in this class that are currently in clinical trials for COVID-19 and if so, what are they?	There are other neutralising antibodies in clinical trials for the treatment and prevention of COVID-19. These will be scheduled for briefing development when appropriate.	
2. Is the evidence base sufficient to allow further action to be taken at this stage? <i>Sufficient evidence base should take into account the amount of evidence (number of trials and total number of participants) as well as robustness of the trials.</i>	Y / N Published results from the PROVENT RCT investigating tixagevimab and cilgavimab for pre-exposure prophylaxis are available (Levin et al. 2022). Published results from the TACKLE RCT investigating tixagevimab and cilgavimab for the treatment of COVID-19 in outpatients are available (Montgomery et al. 2022). Published results from the ACTIV-3 RCT investigating tixagevimab and cilgavimab for the treatment of COVID-19 in hospitalised patients are available (Holland et al. 2022). Top-line results reported in the press are available for STORM CHASER; a phase 3 RCT investigating tixagevimab and cilgavimab for post-exposure prophylaxis.	5.1 , appendix 1
3. Is there a positive signal of efficacy across the outcomes?	Y / N / Unknown Results suggest that tixagevimab and cilgavimab is beneficial for pre-exposure prophylaxis , with a 77% relative risk reduction of developing symptomatic COVID-19 at 6 months. Results suggest that tixagevimab and cilgavimab is beneficial for the treatment of COVID-19 in outpatients , with a 51% relative risk reduction of severe COVID-19 or death from any cause. Tixagevimab and cilgavimab treatment did not meet the primary endpoint of sustained clinical recovery in the ACTIV-3 trial in hospitalised patients, though there was a significant mortality benefit (secondary endpoint).	5.1 , appendix 1

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	Tixagevimab and cilgavimab did not meet the primary endpoint of preventing the development of symptomatic COVID-19 in the STORM CHASER, post-exposure prophylaxis , trial.	
4. Is there a specific population where there could be significant benefit?	<p>Y / N / Unknown</p> <p>Most participants in the TACKLE trial were at high risk of progression to severe COVID-19 (90%). Many participants in the trial were seronegative (84%).</p> <p>The PROVENT trial included people considered at risk of inadequate response to vaccination and people at higher risk of exposure to infection. More than 75% of participants had comorbidities that put them at high risk for severe COVID-19 if they were to become infected, including people who are immunocompromised and may have a reduced immune response to vaccination.</p>	5.1 , appendix 1
5. Is there a signal of harm (including unfavourable effects and adverse events)?	<p>Y / N / Unknown</p> <p>Tixagevimab and cilgavimab was well tolerated in the TACKLE and ACTIV-3 treatment trials and PROVENT pre-exposure prophylaxis trial.</p> <p>The NIH COVID-19 treatment guidelines include a warning about the potential risk of cross-hypersensitivity between COVID-19 vaccines and tixagevimab plus cilgavimab.</p>	5.1 , appendix 1
6. Are there other relevant issues for consideration (e.g. combination therapies, special populations of interest, regulatory issues, potential supply issues, service delivery or technology delivery challenges)?	<p>Y / N / Unknown</p> <p><u>Variants</u></p> <p>In vitro evidence suggests that tixagevimab and cilgavimab is active against Alpha, Beta and Gamma variants.^{c,d} A company press-release states that preliminary in vitro findings demonstrate that tixagevimab and cilgavimab demonstrates broad anti-COVID activity, and in particular neutralises the Delta variant.</p>	

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	<ul style="list-style-type: none"> Monitor for full published results from ongoing key trials. <p>Oversight Group 18/05/2022</p> <ul style="list-style-type: none"> Consider updated advice to CMO in light of new information about efficacy against the Omicron BA.2 variant. Monitor for full published results from ongoing key trials. <p>Oversight Group 08/12/2021</p> <ul style="list-style-type: none"> Consider preparing advice to the CMO in light of results from the pre-exposure prophylaxis, PROVENT, trial. Monitor for full published results from ongoing key trials. <p>Oversight Group 24/11/2021 Stand down / monitor / progress</p> <ul style="list-style-type: none"> Monitor for full results from ongoing key trials. <p>Oversight Group 13/10/2021 Stand down / monitor / progress</p> <ul style="list-style-type: none"> Monitor for full results from ongoing key trials. <p>Oversight Group 03/02/2021 Stand down / monitor / progress</p> <ul style="list-style-type: none"> Also monitor for effect against E484K mutation in the SARS-COV-2 spike protein. Begin playbook for group of neutralising antibodies in COVID-19.
<p>Progress: Oversight Group to take action (e.g. commission an evidence summary, begin regulatory discussions).</p> <p>Monitor: Oversight Group to reconsider topic at a later date (e.g. after trial results have published).</p> <p>Stand down: Oversight Group considers there is not, and is not likely to be, any positive signal that warrants further consideration of this topic.</p>	
<p>Source: ^a NCT04625972, ^b AstraZeneca press release (09/10/2020), ^c Wang et al. 2021, ^d Dejinrattisai et al. 2021</p>	

2. Treatment

Treatment	Tixagevimab and cilgavimab (AZD7442: AZD8895 + AZD1061; EVUSHELD) also known as a Long-Acting AntiBody (LAAB)
Type	Antiviral
Mechanism of action	Monoclonal antibody combination, targeting virus spike protein and blocking virus attachment to human cells. ^a
Administration	Intramuscular or intravenous injection ^a

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Dose and schedule	Single dose of 300 mg or 600 mg
Cost	Unknown
Existing guidance/information	The NIH COVID-19 treatment guidelines recommend using tixagevimab and cilgavimab for the pre-exposure prophylaxis of SARS-CoV-2 in adults and adolescents (≥12 years and ≥40 kg). The guideline recommends using tixagevimab 300 mg plus cilgavimab 300 mg administered as 2 consecutive intramuscular injections. The guidelines were updated 8 August 2022 and include a new recommendation for repeat dosing of tixagevimab 300 mg and cilgavimab 300 mg every 6 months. The update includes a warning about the potential risk of cross-hypersensitivity between COVID-19 vaccines and tixagevimab plus cilgavimab.
Source: ^a AstraZeneca press release (09/10/2020)	

3. Regulatory status

Commercial sponsor	Tixagevimab and cilgavimab is developed by AstraZeneca. Tixagevimab and cilgavimab was discovered by Vanderbilt University Medical Center and licensed to AstraZeneca in June 2020. ^a
New or repurposed	New
Branded or generic	Branded
Regulatory status/plans	<p>COVID-19</p> <p>Tixagevimab and cilgavimab (EVUSHELD) has a conditional marketing authorisation 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:</p> <ul style="list-style-type: none"> • who are unlikely to mount an adequate immune response to COVID-19 vaccination or • for whom COVID-19 vaccination is not recommended. <p>The recommended dosage is 300 mg of Evusheld: 150 mg of each antibody administered as separate sequential intramuscular injections. The summary of product characteristics notes that a higher dose of 600 mg of Evusheld, 300 mg of each antibody, may be more appropriate for some SARS-CoV-2 variants (e.g. Omicron BA.1, Omicron BA.1.1.) based on in vitro neutralisation susceptibility data which show reduced susceptibility for Evusheld.</p> <p>Tixagevimab and cilgavimab (EVUSHELD) is authorised by the European Medicines Agency for the pre-exposure prophylaxis of COVID-19 in adults and adolescents aged 12 years and older weighing at least 40 kg.</p> <p>Tixagevimab and cilgavimab is authorised by Health Canada for preventing COVID-19 in adults and adolescents (≥12 years of age, weighing at least 40 kg) who have not had a</p>

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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.

The FDA issued [EUA](#) for tixagevimab and cilgavimab for the pre-exposure prophylaxis of COVID-19 in adults and adolescents (≥ 12 years and ≥ 40 kg) who either have moderate to severely compromised immune systems or in whom a COVID-19 vaccine is not recommended. The [FDA increased the initial dose](#) from 150 mg of each antibody to 300 mg of each antibody. This is because a higher dose may be more likely to prevent infection by the Omicron subvariants BA.1 and BA.1.1 than the originally authorised dose; the antibody combination is expected to have greater neutralising activity of the BA.2 subvariant. The FDA has [revised the EUA](#) for tixagevimab and cilgavimab to recommend repeat dosing every 6 months with a dose of 300 mg of each antibody if patients need ongoing protection. This revision is in light of the Omicron variants (BA.2, BA.2.12.1, BA.4 and BA.5) currently circulating in the United States and nonclinical data and pharmacokinetic modelling suggesting that activity against these subvariants may be retained for 6 months with 300 mg dose of each antibody.

Other existing indications in the UK

None.

Source: ^a [Precision vaccinations \(31.12.2020\)](#)

4. Supply activities

Supply	<p>AstraZeneca has agreed to supply the US Government with 700,000 doses of tixagevimab and cilgavimab if granted an Emergency Use Authorisation by the FDA and has agreements to supply to other countries.^c</p> <p>AstraZeneca has contracted Lonza to manufacture tixagevimab and cilgavimab. The Swiss pharmaceutical services firm will produce the antibodies in a new facility at its Portsmouth, New Hampshire, biologics complex in the first half of 2021.^a</p> <p>AstraZeneca has received support of around \$486m from the US Government for the development and supply of tixagevimab and cilgavimab under an agreement with the Biomedical Advanced Research and Development Authority (BARDA).</p> <p>AstraZeneca plans to supply up to 100,000 doses starting towards the end of 2020 and the US Government can acquire up to an additional one million doses in 2021 under a separate agreement.^b</p>
Source: ^a C&EN Global Enterprise; 2020 , ^b AstraZeneca press release (09/10/2020) , ^c AstraZeneca press release (18/11/2021)	

5. Evidence

5.1 Published evidence

The table below highlights the signals from the main published evidence and the strength of these signals, taking into account the magnitude of effect shown and the quality of the evidence. Any published studies not reporting key outcomes of interest or case studies are briefly summarised at the end of the table. Detailed information on all published studies are in [appendix 1](#).

Study description	Population	Outcomes and results (intervention vs. comparator)	Evidence assessment*
Treatment			
TACKLE NCT04723394 Montgomery et al. 2022 , published interim results. <i>Earlier results:</i> AstraZeneca press-release 11/10/2021 ; AstraZeneca press-release 18/11/2021 Ongoing phase 3, double-blind RCT	Adult (≥18 years) outpatients with: <ul style="list-style-type: none"> laboratory-confirmed SARS-CoV-2 infection ≤3 days before enrolment WHO Clinical Progression Scale score >1 to <4, Participants had to receive the study drug ≤7 days from self-reported onset of	Primary outcome: composite of either severe COVID-19 or death from any cause through day 29 <i>Severe COVID-19 was defined as a minimum of either pneumonia or hypoxaemia, plus a WHO Clinical Progression Scale score of ≥5 (i.e. hospitalised and requiring oxygen therapy).</i> 18/407 (4%) events in the treatment arm and 37/415 (9%)	Precision Moderate Robustness Information reported in a peer-reviewed published manuscript; a robustly conducted trial and large sample size.

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<p>n=910, the primary analysis was based on 822 participants</p> <p>95 sites in the USA, Latin America, Europe, UK and Japan</p> <p>Between January 2021 and July 2021</p> <p>Study has a follow-up period of 457 days. The interim results are from the primary data cutoff (August 21, 2021) at which time all ongoing study participants had completed at least 29 days of study follow-up. Median safety follow-up was 84 days.</p> <p>Intervention: single tixagevimab/cilgavimab 600 mg dose (2 consecutive 3 ml intramuscular injections, 1 each of 300 mg tixagevimab and 300 mg cilgavimab; n=456)</p> <p>Comparator: placebo (n=454)</p>	<p>mild to moderate COVID-19 symptoms or measured fever.</p> <p>Peripheral oxygen saturation of $\geq 92\%$ at rest within 24 hours before enrolment was required.</p> <p>Exclusion criteria included, but were not limited to:</p> <ul style="list-style-type: none"> history of hospitalisation for COVID-19, or current need for hospitalisation or immediate medical attention previously received an investigational or licensed vaccine or other monoclonal antibody or biologic indication for the prevention of COVID-19 <p>Due to local public health guidelines, some sites in Japan and Russia were required to hospitalise participants for isolation purposes; these participants were excluded from the primary analysis but were included in the full analysis set.</p> <p>Baseline characteristics were similar between the groups. Mean age was 46.1 years; 13% of participants were ≥ 65 years.</p> <p>The majority of participants (84%) were seronegative.</p> <p>90% were at high risk of progression to severe COVID-19 (defined as at least 1</p>	<p>in the placebo arm; 50.5% relative risk reduction (95% CI 14.6 to 71.3; $p=0.0096$); absolute risk reduction 4.5% (95% CI 1.1 to 8.0; $p<0.0001$), NNT 22.</p> <p>There were 6 (1%) deaths due to any cause in each arm.</p> <p>Most events were in participants at high risk of progression to severe COVID-19 (17/364 in the treatment arm and 33/371 in the placebo arm).</p> <p>In prespecified analysis of participants who received treatment within 5 days of symptom onset (n=504): 9/253 (4%) in the treatment arm and 27/251 (11%) in the placebo arm; 67% relative risk reduction (95% CI 31.1 to 84.1, $n=0.0017$); absolute risk reduction 7.2%, NNT 14.</p> <p>Secondary endpoints at day 29:</p> <p>Incidence of respiratory failure 3/405 (1%) events in the treatment arm and 11/412 (3%) in the placebo arm; 72% relative risk reduction (95% CI 0.3 to 92.1), $p=0.036$</p> <p>Incidence of antidrug antibodies to tixagevimab/cilgavimab in serum Antidrug antibodies occurred in 6/134 (5%) participants. They were at a low median titre which was very close to the lower limit of quantification of the assay.</p> <p>Viral sequencing (prespecified exploratory analysis): The alpha SARS-CoV-2 variant was the most prevalent through to day 29 (258/834 sequenced samples, 60%), followed by gamma (20%) and delta (15%).</p> <p>Primary safety endpoints:</p> <p>Adverse events 132/452 (29%) in the treatment arm and 163/451 (36%) in the</p>	<p>Certainty of effect: moderate</p>
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	<p>risk factor including age ≥ 65 years or having at least 1 comorbidity (e.g. cancer, diabetes, obesity, chronic lung disease and cardiovascular disease, immuno-compromised)</p>	<p>placebo arm. The most common adverse event in both arms was COVID-19 pneumonia.</p> <p>Serious adverse events 33/452 (7%) in the treatment arm and 54/451 (12%) in the placebo arm. The most common event was COVID-19 pneumonia.</p>	
<p>ACTIV-3 NCT04501978</p> <p>Holland et al. 2022; results published in peer-reviewed journal</p> <p>Phase 3, multi-arm, double blind RCT</p> <p>n=1,417</p> <p>81 sites in the USA, Europe, Uganda and Singapore</p> <p>Intervention: tixagevimab 300 mg and cilgavimab 300 mg single IV infusion over a 30-minute period (n=710)</p> <p>Comparator: placebo (n=707)</p> <p>Between 10 February and 30 September 2021</p>	<p>Hospitalised adults with confirmed SARS-CoV-2 infection and symptoms for up to 12 days</p> <p>At the beginning of the trial, patients on high-flow nasal oxygen or non-invasive ventilation were excluded. On 19 July 2021, after 743 patients were enrolled, eligibility was expanded at the recommendation of the US FDA and data and safety monitoring board to include these patients.</p> <p>Patients were excluded if they had acute organ failure including receipt of invasive mechanical ventilation, ECMO, vasopressor therapy, mechanical circulatory support, or new renal replacement therapy.</p> <p>Remdesivir was provided to all study participants unless contraindicated. Corticosteroids were encouraged for participants with hypoxaemia.</p> <p>Baseline characteristics were balanced between</p>	<p>Primary outcome: time from randomisation to sustained clinical recovery up to day 90, defined as return to home for 14 consecutive days</p> <p>Estimated cumulative incidence of sustained recovery was 78% for the treatment group and 76% for the placebo group at day 28, and 89% and 86%, respectively, at day 90 (recovery rate ratio 1.08; 95% CI 0.97 to 1.20; p=0.21).</p> <p>Results were similar in the seronegative subgroup (recovery rate ratio 1.14; 95% CI 0.97 to 1.34; p=0.13).</p> <p>Secondary outcomes All-cause mortality up to day 90 61/710 (9%) in the treatment group vs. 86/707 (12%) in the placebo group (HR 0.70; 95% CI 0.50 to 0.97; p=0.032; absolute risk reduction 3.6%, NNT 28)</p> <p>Composite of sustained recovery and mortality up to day 90 No significant difference between the groups (p=0.33; win ratio 1.08; 95% CI 0.92 to 1.27)</p> <p>Safety Composite of death, serious adverse events, incident organ failure and serious co-infection through day 90 178 (25%) in the treatment group vs. 212 (30%) in the placebo group (HR 0.83; 95% CI 0.68 to 1.01; p=0.059)</p> <p>Serious adverse events occurred in 34 (5%) of</p>	<p>Precision Moderate</p> <p>Robustness Results published in a peer-reviewed journal; a robustly conducted trial and large sample size.</p> <p>Certainty of effect: moderate</p>

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	<p>groups. The median duration of symptoms at enrolment was 8 days, 1,041 (73%) were unvaccinated, and 128 (9%) were immunocompromised including 56 (4%) taking anti-rejection medications.</p> <p>687 (51%) of 1,347 were infected with the delta SARS-CoV-2 variant.</p>	<p>participants in the treatment group and 38 (5%) in the placebo group. Most safety events were classified as respiratory-thoracic-mediastinal, gastrointestinal, nervous system or general system organ classification.</p>	
Prophylaxis			
<p>PROVENT NCT04625725, 2020-004356-16</p> <p>Pre-exposure prophylaxis</p> <p>Levin et al. 2022 and pre-publication manuscript shared in confidence by the company</p> <p><i>Earlier results:</i> AstraZeneca press-release 20/08/2021 and press-release 18/11/2021</p> <p>Ongoing, phase 3, randomised, double-blind trial</p> <p>n=5,197</p> <p>UK, US, Spain, France and Belgium</p> <p>Intervention: tixagevimab and cilgavimab 300 mg single dose administered in 2 separate, sequential IM injections</p> <p>Comparator: placebo</p> <p>Patients were randomised to receive treatment or placebo between 21 November 2020 and 22 March</p>	<p>Adults (≥18 years) at increased risk for either inadequate response to COVID-19 vaccination, or increased risk of SARS-CoV-2 infection owing to location or circumstance. All patients had a negative SARS-CoV-2 serology test result at screening.</p> <p>Excluded participants who had a history of SARS-CoV-2 infection, a positive SARS-CoV-2 result, or prior vaccine or biologic indication for prevention of SARS-CoV-2 or COVID-19.</p> <p>Mean age was 53.5 years, 43.4% were aged ≥60 years, 46.1% were female, 14.5% identified as Hispanic or Latinx, 73.0% were white, and 17.3% were black.</p> <p>73.3% of participants were considered to be at increased risk of inadequate response to vaccination, 52.5% at increased risk of exposure to SARS-</p>	<p>Primary efficacy endpoint: first case of any SARS-CoV-2 RT-PCR positive symptomatic illness occurring post dose before day 183</p> <p>8/3,441 (0.2%) treatment arm and 17/1,731 (1.0%) placebo arm; 76.7% (95% CI 46 to 90) relative risk reduction; p<0.001 Absolute risk reduction: 0.8%; NNT 125</p> <p>There was no one with severe or critical symptomatic COVID-19 in the treatment arm and 1 in the placebo arm.</p> <p>6 participants in the treatment group visited the emergency room for symptoms consistent with COVID-19, versus 0 in the placebo group. These participants were not hospitalised and 3/6 subsequently tested positive for COVID-19.</p> <p>Tixagevimab and cilgavimab efficacy was consistent across participants subgroups (baseline demographic and comorbidity) where evaluable. It was not possible to assess efficacy in smaller but important participant subgroups, such as immunosuppressed individuals, due to a low number of events.</p> <p>Median 6-month follow up</p> <p>11/3,441 (0.3%) treatment arm and 31/1,731 (1.8%) placebo arm; 82.8% (95% CI 65.8 to 91.4) relative risk reduction.</p>	<p>Precision Moderate</p> <p>Robustness Information reported in a peer-reviewed published manuscript; a robustly conducted trial and large sample size.</p> <p>Certainty of effect: moderate</p>

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<p>2021. Data cut-off for the primary analysis was 5 May 2021, an extended follow-up data cut-off occurred on 29 August 2021. The estimated study completion date is 29 June 2022.</p> <p>Median follow-up times from dosing to the primary analysis was 83 days and median follow up for the extended follow-up analysis was 196 days.</p> <p>Participants will be followed for up to 15 months.</p> <p>The trial was ongoing when the Alpha variant was predominant in participating countries, with the primary data cut-off occurring as the Delta variant began to spread.</p> 	<p>CoV-2, and 77.5% were at high risk for severe COVID-19 disease.</p>	<p>Absolute risk reduction: 1.5%; NNT 67</p> <p>There were an additional 4 people with severe or critical COVID-19, all in the placebo group.</p> <p>Safety Primary safety endpoint: adverse events (AEs), serious AEs, medically attended AEs, and AEs of special interest All events occurred at similar rates in the treatment and placebo groups: AEs: 1,221/3,461 (35.3%) treatment arm and 593/1,736 (34.2%) placebo arm. Most events were of mild or moderate severity. Serious AEs: 50/3,461 (1.4%) treatment arm and 23/1,736 (1.3%) placebo arm Medically attended AEs: 360/3,461 (10.4%) treatment arm and 157/1,736 (9.0%) placebo arm AEs of special interest: 93/3,461 (2.7%) treatment arm and 37/1,736 (2.1%) placebo arm</p> <p>8 deaths occurred, 4 in each arm. 2 were COVID-19 related, both in the placebo group. All deaths were unrelated to study drug.</p> <p>Median 6-month follow up No additional AEs of special interest and no unexpected longer-term safety signals were identified. 16 deaths occurred (9 in the treatment group and 7 in the placebo group); none were intervention related. There were no additional COVID-19-related deaths.</p> <p>SARS-CoV-2 variants detected in symptomatic participants Illness visit viral genotypic data were available for 7/11 participants in the treatment group and 13/31 participants in the placebo group. 11 were</p>	
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		infected with currently designated variants of concern: 1 in the treatment group (Beta variant) and 10 in the placebo group (5 instances each of the Alpha and Delta variants).	
<p><u>STORM CHASER</u> NCT04625972</p> <p>Post-exposure prophylaxis</p> <p>AstraZeneca press-release and slides 15/06/2021</p> <p>Phase 3, randomised, double-blind trial</p> <p>n=1,121</p> <p>59 sites in the UK and US</p> <p>Intervention: tixagevimab and cilgavimab 300 mg single dose (n=749) administered in 2 separate, sequential IM injections</p> <p>Comparator: placebo (n=372)</p>	<p>Unvaccinated adults (≥18 years) with potential exposure, within 8 days, to a specific identified individual with laboratory-confirmed SARS-CoV-2 virus, symptomatic or asymptomatic, and who were therefore assessed at the time of enrolment to be at appreciable risk of imminently developing COVID-19. Such individuals included, but were not limited to, those who shared a household, those living in institutional residence, healthcare workers and long-term care facility workers.</p> <p>All participants had a negative SARS-CoV-2 antibody test on the day of dosing to exclude prior infection, and a nasopharyngeal swab was collected and subsequently analysed for SARS-CoV-2 by RT-PCR to detect virus.</p>	<p>Primary endpoint: first case of any SARS-CoV-2 RT-PCR positive symptomatic illness occurring post dose before day 183 23/749 (3.1%) in the treatment group and 17/372 (4.6%) in the placebo group; 33% relative risk reduction; 95% CI -26 to 65; not statistically significant</p> <p>Pre-planned analysis of SARS-CoV-2 negative participants at time of dosing: 6/715 (0.8%) in the treatment group and 11/358 (3.1%) in the placebo group; 73% relative risk reduction; 95% CI 27 to 90</p> <p>Post-hoc analysis of participants who were PCR negative at baseline: Risk of developing symptomatic COVID-19 within 7 days of dosing: 5/715 (0.7%) in the treatment group and 5/358 (1.4%) in the placebo group; 51% relative risk reduction; 95% CI -71 to 86</p> <p>Risk of developing symptomatic COVID-19 more than 7 days after dosing: 1/710 (0.1%) in the treatment group and 6/353 (1.7%) in the placebo group; 92% relative risk reduction; 95% CI 32 to 99</p> <p>Tixagevimab and cilgavimab was well tolerated; preliminary analyses show similar adverse events in the placebo and treatment arms.</p> <p><i>The primary analysis was to be conducted 30 days after 25 events meeting the primary efficacy endpoint definition had occurred. This primary analysis includes data and additional events accumulated up to 7 April 2021, 30 days after the symptom assessment date of the 25th</i></p>	<p>Precision Low</p> <p>Robustness Limited information reported via company press release.</p> <p>Certainty of effect: low</p>

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		<i>event; participants will continue to be followed for 15 months.</i>	
Safety			
NCT04507256 Pre-print 08/09/2021 Phase 1, randomised, double-blind, placebo-controlled study n=60 UK Tixagevimab and cilgavimab dose: • 300 mg IM, 2 injections of each mAb administered sequentially • 300 mg, 1,000 mg or 3,000 mg IV, 2 infusions of each mAb administered sequentially • 3,000 mg co-administered by IV n=10 in all groups	Healthy adults	Preliminary results showed that 300 mg IM tixagevimab and cilgavimab provided SARS-CoV-2 serum geometric mean neutralising titres >10-fold higher than those of convalescent sera for ≥3 months. These remained 3-fold higher than those of convalescent sera 9 months post-administration, suggesting that 300 mg IM tixagevimab and cilgavimab could provide protection against COVID-19 for up to 12 months.	Precision N/A Robustness N/A Certainty of effect: N/A
<p>*Explanation of the certainty of the effect based on the precision of the estimates and the robustness of the evidence</p> <p>High certainty Very confident that the true effect lies close to that of the estimate of the effect</p> <p>Moderate certainty Moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different</p> <p>Low certainty Confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect</p> <p>Very low certainty Very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.</p>			

5.2 Ongoing trials

- Tixagevimab and cilgavimab has been investigated as a therapy for prophylaxis (pre- and post-exposure) of COVID-19 and treatment of COVID-19 in patients in the community and hospital settings.
- A phase 1 study in healthy volunteers in Japan (n=40) investigating the safety and pharmacokinetics of tixagevimab and cilgavimab has completed but results are not yet available.
- There are 5 ongoing trials that have stopped recruiting:
 - phase 2/3 trial (ACTIV-2) investigating tixagevimab and cilgavimab and other interventions as treatments for COVID-19 in outpatients
 - phase 3 trial (DisCoVeRy) investigating tixagevimab and cilgavimab and other interventions as treatments for COVID-19 in hospitalised patients
 - phase 1 and phase 2 trials investigating the safety and pharmacokinetics of tixagevimab and cilgavimab in healthy adults in China

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- a phase 1 trial investigating the safety and pharmacokinetics of tixagevimab and cilgavimab in healthy adults in Japan.
- There are 4 ongoing trials currently recruiting:
 - phase 3, open-label, non-inferiority trial investigating tixagevimab and cilgavimab versus sotrovimab as treatment for outpatients in Italy
 - phase 2 open-label study in the US investigating the safety of tixagevimab and cilgavimab prophylaxis in adults and adolescents
 - real world evaluation in the US of tixagevimab and cilgavimab prophylaxis in patients with cancer
 - phase 1 single-arm trial investigating safety and pharmacokinetics of tixagevimab and cilgavimab treatment and prophylaxis in babies, children, and adolescents from ≥ 29 weeks gestational age to <18 years
- A phase 2 single-arm trial in Canada investigating tixagevimab and cilgavimab prophylaxis in adults with chronic lymphocytic leukaemia is not yet recruiting.
- There are 3 observational studies ongoing in France evaluating:
 - monoclonal antibodies, including tixagevimab and cilgavimab, as treatment or prophylaxis in patients at high risk of severe COVID-19 ([NCT05439044](#))
 - tixagevimab and cilgavimab prophylaxis in immunocompromised patients ([NCT05216588](#))
 - tixagevimab and cilgavimab prophylaxis in solid organ transplant patients ([NCT05234398](#))

5.2.1 Key trials

The table below shows the key trials (in UK and NIHR-prioritised if applicable) that are likely to impact on decision-making (because of robust trial design and reporting of key outcomes):

Treatment
<p>ACTIV-2/ NCT04518410 (<i>National Institute of Allergy and Infectious Diseases sponsored RCT</i>)</p> <ul style="list-style-type: none"> • Actual enrolment for all interventions: 4,044 • Location: United States, South America, South Africa, Canada, Philippines • Setting/population: Adult outpatients with laboratory-confirmed SARS-CoV-2 and symptoms • Primary outcomes: COVID-19 symptom duration, death or hospitalisation, viral load and safety • Actual PCD: 1 March 2022. <i>Active, not recruiting.</i>
<p>DisCoVeRy/ NCT04315948 (<i>Institut National de la Santé Et de la Recherche Médicale, France sponsored RCT</i>)</p> <ul style="list-style-type: none"> • Estimated enrolment for all interventions: 2,416, n=620 for tixagevimab and cilgavimab • Location: Austria, Belgium, Luxembourg, Norway, France, Greece and Portugal • Setting/population: Hospitalised adults with COVID-19 and presence of pulmonary rales/crackles, SpO₂ $\leq 94\%$ on room air or requirement of supplementary oxygen including high flow oxygen devices or non-invasive ventilation • Primary outcomes: severity rating on 7-point ordinal scale (includes hospitalisation, oxygen requirement and death) • Estimated PCD: July 2022. <i>Active, not recruiting.</i>

Further details of these trials are presented in [appendix 2](#).

5.2.2 Trials with the earliest completion dates

The table below shows the trials due to report soon that are reasonably well designed and powered and/or investigating relevant clinical outcomes of interest:

Design	Size	Location	Primary outcome(s)	Estimated PCD
Treatment				
RCT, NCT04518410 (ACTIV-2) Key trial Adult outpatients	4,044 (for all interventions)	US, South America, South Africa, Canada, Philippines	COVID-19 symptom duration, death or hospitalisation, viral load and safety	01/03/2022 (actual PCD)
RCT NCT04315948 (DisCoVeRy) Key trial Hospitalised adults	2,416 (for all interventions; 620 for tixagevimab and cilgavimab)	Austria, Belgium, Luxembourg, Norway, France, Greece and Portugal	Severity rating on 7-point ordinal scale (includes hospitalisation, oxygen requirement and death)	July 2022 <i>Registry last updated 05/07/2022</i>
Open label, randomised, non-inferiority trial versus sotrovimab NCT05321394 Outpatients	1,095 (for all interventions)	Italy	Hospitalisation or need of supplemental oxygen therapy at home or death	30/09/2022

Further details of these trials are presented in [appendix 2](#).

Appendix 1: Published evidence

A. Systematic reviews/evidence summaries

Reference	Results
<p>Susceptibility of SARS-CoV-2 Omicron variants to therapeutic monoclonal antibodies: systematic review and meta-analysis</p> <p>Tao et al. 2022 pre-print</p>	<ul style="list-style-type: none"> A systematic review, last updated 22 February 2022, of the in vitro activity of monoclonal antibodies against the Omicron variants. In 18 studies, cilgavimab and tixagevimab independently displayed median reductions in activity of >300-fold against Omicron BA.1, while in ten studies, cilgavimab and tixagevimab displayed a median 63-fold (IQR: 26-145) reduced activity against Omicron BA.1. In two studies, cilgavimab was approximately 100-fold more susceptible to BA.2 than to BA.1.
Source: NICE Information Services literature search (12.08.2022)	

B. Trials and studies

Reference	Design and location of study	Population	Results
Treatment			
<p>TACKLE NCT04723394</p> <p>Montgomery et al. 2022 published interim results.</p> <p>Earlier results: AstraZeneca press-release 11/10/2021; AstraZeneca</p>	<p>Ongoing phase 3, double-blind RCT</p> <p>n=910, the primary analysis was based on 822 participants</p> <p>95 sites in the USA, Latin America, Europe, UK and Japan</p> <p>Between January 2021 and July 2021</p> <p>Study has a follow-up period of 457 days. The interim results are</p>	<p>Adult (≥18 years) outpatients with:</p> <ul style="list-style-type: none"> laboratory-confirmed SARS-CoV-2 infection ≤3 days before enrolment WHO Clinical Progression Scale score >1 to <4, <p>Participants had to receive the study drug ≤7 days from self-reported onset of mild to moderate COVID-19 symptoms or measured fever.</p>	<p>Primary outcome: composite of either severe COVID-19 or death from any cause through day 29</p> <p>Severe COVID-19 was defined as a minimum of either pneumonia or hypoxaemia, plus a WHO Clinical Progression Scale score of ≥5 (i.e. hospitalised and requiring oxygen therapy).</p> <p>18/407 (4%) events in the treatment arm and 37/415 (9%) in the placebo arm; 50.5% relative risk reduction (95% CI 14.6 to 71.3; p=0.0096); absolute risk reduction 4.5% (95% CI 1.1 to 8.0; p<0.0001), NNT 22.</p> <p>There were 6 (1%) deaths due to any cause in each arm.</p>

Reference	Design and location of study	Population	Results
press-release 18/11/2021	<p>from the primary data cutoff (August 21, 2021) at which time all ongoing study participants had completed at least 29 days of study follow-up. Median safety follow-up was 84 days.</p> <p>Intervention: single tixagevimab/cilgavimab 600 mg dose (2 consecutive 3 ml intramuscular injections, 1 each of 300 mg tixagevimab and 300 mg cilgavimab; n=456)</p> <p>Comparator: placebo (n=454)</p>	<p>Peripheral oxygen saturation of $\geq 92\%$ at rest within 24 hours before enrolment was required.</p> <p>Exclusion criteria included, but were not limited to:</p> <ul style="list-style-type: none"> history of hospitalisation for COVID-19, or current need for hospitalisation or immediate medical attention previously received an investigational or licensed vaccine or other monoclonal antibody or biologic indication for the prevention of COVID-19 <p>Due to local public health guidelines, some sites in Japan and Russia were required to hospitalise participants for isolation purposes; these participants were excluded from the primary analysis but were included in the full analysis set.</p> <p>Baseline characteristics were similar between the groups. Mean age was 46.1 years; 13% of participants were ≥ 65 years.</p> <p>The majority of participants (84%) were seronegative.</p> <p>90% were at high risk of progression to severe COVID-19 (defined as at least 1 risk factor</p>	<p>Most events were in participants at high risk of progression to severe COVID-19 (17/364 in the treatment arm and 33/371 in the placebo arm).</p> <p>In prespecified analysis of participants who received treatment within 5 days of symptom onset (n=504): 9/253 (4%) in the treatment arm and 27/251 (11%) in the placebo arm; 67% relative risk reduction (95% CI 31.1 to 84.1, n=0.0017); absolute risk reduction 7.2%, NNT 14.</p> <p>Secondary endpoints at day 29:</p> <p>Incidence of respiratory failure 3/405 (1%) events in the treatment arm and 11/412 (3%) in the placebo arm; 72% relative risk reduction (95% CI 0.3 to 92.1), p=0.036</p> <p>Incidence of antidrug antibodies to tixagevimab/cilgavimab in serum Antidrug antibodies occurred in 6/134 (5%) participants. They were at a low median titre which was very close to the lower limit of quantification of the assay.</p> <p>Viral sequencing (prespecified exploratory analysis): The alpha SARS-CoV-2 variant was the most prevalent through to day 29 (258/834 sequenced samples, 60%), followed by gamma (20%) and delta (15%).</p> <p>Primary safety endpoints:</p> <p>Adverse events 132/452 (29%) in the treatment arm and 163/451 (36%) in the placebo arm. The most common adverse event in both arms was COVID-19 pneumonia.</p> <p>Serious adverse events</p>

Reference	Design and location of study	Population	Results
		including age ≥ 65 years or having at least 1 comorbidity (e.g. cancer, diabetes, obesity, chronic lung disease and cardiovascular disease, immune-compromised)	33/452 (7%) in the treatment arm and 54/451 (12%) in the placebo arm. The most common event was COVID-19 pneumonia.
ACTIV-3 NCT04501978 Holland et al. 2022 ; results published in peer-reviewed journal	Phase 3, multi-arm, double blind RCT n=1,417 81 sites in the USA, Europe, Uganda and Singapore Intervention: tixagevimab 300 mg and cilgavimab 300 mg single IV infusion over a 30-minute period (n=710) Comparator: placebo (n=707) Between 10 February and 30 September 2021	Hospitalised adults with confirmed SARS-CoV-2 infection and symptoms for up to 12 days At the beginning of the trial, patients on high-flow nasal oxygen or non-invasive ventilation were excluded. On 19 July 2021, after 743 patients were enrolled, eligibility was expanded at the recommendation of the US FDA and data and safety monitoring board to include these patients. Patients were excluded if they had acute organ failure including receipt of invasive mechanical ventilation, ECMO, vasopressor therapy, mechanical circulatory support, or new renal replacement therapy. Remdesivir was provided to all study participants unless contraindicated. Corticosteroids were encouraged for participants with hypoxaemia.	Primary outcome: time from randomisation to sustained clinical recovery up to day 90, defined as return to home for 14 consecutive days Estimated cumulative incidence of sustained recovery was 78% for the treatment group and 76% for the placebo group at day 28, and 89% and 86%, respectively, at day 90 (recovery rate ratio 1.08; 95% CI 0.97 to 1.20; p=0.21). Results were similar in the seronegative subgroup (recovery rate ratio 1.14; 95% CI 0.97 to 1.34; p=0.13). Secondary outcomes All-cause mortality up to day 90 61/710 (9%) in the treatment group vs. 86/707 (12%) in the placebo group (HR 0.70; 95% CI 0.50 to 0.97; p=0.032; absolute risk reduction 3.6%, NNT 28) Composite of sustained recovery and mortality up to day 90 No significant difference between the groups (p=0.33; win ratio 1.08; 95% CI 0.92 to 1.27) Safety Composite of death, serious adverse events, incident organ failure and serious co-infection through day 90 178 (25%) in the treatment group vs. 212 (30%) in the placebo group (HR 0.83; 95% CI 0.68 to 1.01; p=0.059)

Reference	Design and location of study	Population	Results
		<p>Baseline characteristics were balanced between groups. The median duration of symptoms at enrolment was 8 days, 1,041 (73%) were unvaccinated, and 128 (9%) were immunocompromised including 56 (4%) taking anti-rejection medications.</p> <p>687 (51%) of 1,347 were infected with the delta SARS-CoV-2 variant.</p>	<p>Serious adverse events occurred in 34 (5%) of participants in the treatment group and 38 (5%) in the placebo group. Most safety events were classified as respiratory-thoracic-mediastinal, gastrointestinal, nervous system or general system organ classification.</p>
Prevention			
<p>PROVENT NCT04625725, 2020-004356-16</p> <p>Pre-exposure prophylaxis</p> <p>Levin et al. 2022 and pre-publication manuscript shared in confidence by the company</p>	<p>Ongoing, phase 3, randomised, double-blind trial</p> <p>n=5,197 UK, US, Spain, France and Belgium</p> <p>Intervention: tixagevimab and cilgavimab 300 mg single dose administered in 2 separate, sequential IM injections</p> <p>Comparator: placebo</p> <p>Patients were randomised to receive treatment or placebo between 21 November 2020 and 22 March 2021. Data cut-off for the primary analysis was 5 May 2021, an extended follow-up data cut-off occurred on 29 August 2021. The estimated study completion date is 29 June 2022. Median follow-up</p>	<p>Adults (≥18 years) at increased risk for either inadequate response to COVID-19 vaccination, or increased risk of SARS-CoV-2 infection owing to location or circumstance. All patients had a negative SARS-CoV-2 serology test result at screening.</p> <p>Excluded participants who had a history of SARS-CoV-2 infection, a positive SARS-CoV-2 result, or prior vaccine or biologic indication for prevention of SARS-CoV-2 or COVID-19.</p> <p>Mean age was 53.5 years, 43.4% were aged ≥60 years, 46.1% were female, 14.5% identified as Hispanic or Latinx, 73.0% were white, and 17.3% were black.</p>	<p>Primary efficacy endpoint: first case of any SARS-CoV-2 RT-PCR positive symptomatic illness occurring post dose before day 183 8/3,441 (0.2%) treatment arm and 17/1,731 (1.0%) placebo arm; 76.7% (95% CI 46 to 90) relative risk reduction; $p<0.001$</p> <p>There was no one with severe or critical symptomatic COVID-19 in the treatment arm and 1 in the placebo arm.</p> <p>Median 6-month follow up 11/3,441 (0.3%) treatment arm and 31/1,731 (1.8%) placebo arm; 82.8% (95% CI 65.8 to 91.4) relative risk reduction.</p> <p>There were an additional 4 people with severe or critical COVID-19, all in the placebo group.</p> <p>Safety Primary safety endpoint: adverse events (AEs), serious AEs, medically attended AEs, and AEs of special interest All events occurred at similar rates in the treatment and placebo groups:</p>

Reference	Design and location of study	Population	Results
	<p>times from dosing to the primary analysis was 83 days and median 6-month follow up was 196 days.</p> <p>Participants will continue to be followed for up to 15 months.</p> <p>The trial was ongoing when the Alpha variant was predominant in participating countries, with the primary data cut-off occurring as the Delta variant began to spread.</p>	<p>73.3% of participants were considered to be at increased risk of inadequate response to vaccination, 52.5% at increased risk of exposure to SARS-CoV-2, and 77.5% were at high risk for severe COVID-19 disease.</p>	<p>AEs: 1,221/3,461 (35.3%) treatment arm and 593/1,736 (34.2%) placebo arm. Most events were of mild or moderate severity.</p> <p>Serious AEs: 50/3,461 (1.4%) treatment arm and 23/1,736 (1.3%) placebo arm</p> <p>Medically attended AEs: 360/3,461 (10.4%) treatment arm and 157/1,736 (9.0%) placebo arm</p> <p>AEs of special interest: 93/3,461 (2.7%) treatment arm and 37/1,736 (2.1%) placebo arm</p> <p>8 deaths occurred, 4 in each arm. 2 were COVID-19 related, both in the placebo group. All deaths were unrelated to study drug.</p> <p>Median 6-month follow up No additional AEs of special interest and no unexpected longer-term safety signals were identified. 16 deaths occurred (9 in the treatment group and 7 in the placebo group); none were intervention related. There were no additional COVID-19-related deaths.</p> <p>SARS-CoV-2 variants detected in symptomatic participants Illness visit viral genotypic data were available for 7/11 participants in the treatment group and 13/31 participants in the placebo group. 11 were infected with currently designated variants of concern: 1 in the AZD442 group (Beta variant) and 10 in the placebo group (5 instances each of the Alpha and Delta variants).</p>
<p>PROVENT NCT04625725, 2020-004356-16</p> <p>Pre-exposure prophylaxis</p>	<p>Phase 3, randomised, double-blind trial</p> <p>n=5,197</p> <p>UK, US, Spain, France and Belgium</p>	<p>Adults (≥18 years) who would benefit from prevention with tixagevimab and cilgavimab (long-acting antibodies), defined as having increased risk for inadequate response to active immunisation (predicted poor responders to vaccines or</p>	<p>Primary endpoint: first case of any SARS-CoV-2 RT-PCR positive symptomatic illness occurring post dose before day 182</p> <p>8/3,460 (0.2%) treatment arm and 17/1,737 (1%) placebo arm; 77% (95% CI 46 to 90) relative risk reduction; p<0.001</p> <p>There were 25 people with symptomatic COVID-19 at the primary analysis.</p>

Reference	Design and location of study	Population	Results
<p>AstraZeneca press-release 20/08/2021 and press-release 18/11/2021</p> <p>Note: peer-reviewed results available, see above</p>	<p>Intervention: tixagevimab and cilgavimab 300 mg single dose (n=3,460) administered in 2 separate, sequential IM injections</p> <p>Comparator: placebo (n=1,737)</p> <p>The primary analysis is based on 5,172 participants, with data cut-off 9 May 2021. The primary efficacy endpoint was the first case of SARS-CoV-2 PCR positive symptomatic illness occurring post dose before day 183. The 6-month analysis based on 4,991 participants, data cut-off 29 August 2021. Participants will continue to be followed for 15 months.</p>	<p>intolerant of vaccine) or having increased risk for SARS-CoV-2 infection, including those whose locations or circumstances put them at appreciable risk of exposure to the SARS-CoV-2 virus.</p> <p>Participants at time of screening were unvaccinated and had a negative point-of-care SARS-CoV-2 serology test.</p> <p>Approximately 43% of participants were ≥60 years. More than 75% had baseline comorbidities and other characteristics associated with an increased risk for severe COVID-19 should they become infected, including those with immunosuppressive disease or taking immunosuppressive medications, diabetes, severe obesity or cardiac disease, COPD, chronic kidney and chronic liver disease.</p>	<p>The primary analysis was based on 5,172 participants who did not have SARS-CoV-2 infection at baseline.</p> <p>There was no one with severe COVID-19 and no COVID-19-related deaths in the treatment arm. In the placebo arm, there were 3 people with severe COVID-19, which included 2 deaths.</p> <p>Tixagevimab and cilgavimab was well tolerated and preliminary analyses show adverse events were balanced between the treatment and placebo groups.</p> <p>UPDATE: median of 6 months of participant follow up Tixagevimab and cilgavimab reduced the risk of developing symptomatic COVID-19 compared with placebo by 83%.</p> <p>Safety</p> <p>There was no one with severe COVID-19 and no COVID-19-related deaths in those who had tixagevimab and cilgavimab at the 6-month analyses. In the placebo arm, there were 2 additional people with severe COVID-19 at the 6-month assessment, for a total of 5 people with severe COVID-19 and 2 COVID-related deaths.</p> <p>Tixagevimab and cilgavimab was generally well tolerated; no new safety issues were identified in the 6-month analysis.</p>
<p>STORM CHASER NCT04625972</p> <p>Post-exposure prophylaxis</p>	<p>Phase 3, randomised, double-blind trial</p> <p>n=1,121</p> <p>59 sites in the UK and US</p>	<p>Unvaccinated adults (≥18 years) with potential exposure, within 8 days, to a specific identified individual with laboratory-confirmed SARS-CoV-2 virus, symptomatic or asymptomatic, and who were therefore assessed at the time of</p>	<p>Primary endpoint: first case of any SARS-CoV-2 RT-PCR positive symptomatic illness occurring post dose before day 183 23/749 in the treatment group and 17/372 in the placebo group; 33% relative risk reduction; 95% CI -26 to 65; not statistically significant</p>

Reference	Design and location of study	Population	Results
<p>AstraZeneca press-release and slides 15/06/2021</p>	<p>Intervention: tixagevimab and cilgavimab 300 mg single dose (n=749) administered in 2 separate, sequential IM injections</p> <p>Comparator: placebo (n=372)</p>	<p>enrolment to be at appreciable risk of imminently developing COVID-19. Such individuals included, but were not limited to, those who shared a household, those living in institutional residence, healthcare workers and long-term care facility workers.</p> <p>All participants had a negative SARS-CoV-2 antibody test on the day of dosing to exclude prior infection, and a nasopharyngeal swab was collected and subsequently analysed for SARS-CoV-2 by RT-PCR to detect virus.</p>	<p>Pre-planned analysis of SARS-CoV-2 negative participants at time of dosing: 6/715 in the treatment group and 11/358 in the placebo group; 73% relative risk reduction; 95% CI 27 to 90</p> <p>Post-hoc analysis of participants who were PCR negative at baseline: Risk of developing symptomatic COVID-19 within 7 days of dosing: 5/715 in the treatment group and 5/358 in the placebo group; 51% relative risk reduction; 95% CI -71 to 86</p> <p>Risk of developing symptomatic COVID-19 more than 7 days after dosing: 1/710 in the treatment group and 6/353 in the placebo group; 92% relative risk reduction; 95% CI 32 to 99</p> <p>Tixagevimab and cilgavimab was well tolerated; preliminary analyses show similar adverse events in the placebo and treatment arms.</p> <p><i>The primary analysis was to be conducted 30 days after 25 events meeting the primary efficacy endpoint definition had occurred. This primary analysis includes data and additional events accumulated up to 7 April 2021, 30 days after the symptom assessment date of the 25th event; participants will continue to be followed for 15 months.</i></p>
Safety			
<p>NCT04507256</p> <p>Pre-print 08/09/2021</p>	<p>Phase 1, randomised, double-blind, placebo-controlled study</p> <p>n=60</p> <p>UK</p>	<p>Healthy adults</p>	<p>Preliminary results showed that 300 mg IM tixagevimab and cilgavimab provided SARS-CoV-2 serum geometric mean neutralising titres >10-fold higher than those of convalescent sera for ≥3 months. These remained 3-fold higher than those of convalescent sera 9 months post-administration, suggesting that 300 mg IM tixagevimab and cilgavimab could provide protection against COVID-19 for up to 12 months.</p>

Reference	Design and location of study	Population	Results
	<p>Tixagevimab and cilgavimab dose:</p> <ul style="list-style-type: none"> • 300 mg IM, 2 injections of each mAb administered sequentially • 300 mg, 1,000 mg or 3,000 mg IV, 2 infusions of each mAb administered sequentially • 3,000 mg co-administered by IV <p>n=10 in all groups</p>		
Source: NICE Information Services literature search (12.08.2022)			
Abbreviations: COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; ECMO: extracorporeal membrane oxygenation; RT-PCR, reverse transcriptase polymerase chain reaction; IM, intramuscular; CI, confidence interval; NNT, number needed to treat; mAb, monoclonal antibody			

C. Real-world evidence: comparative studies

UPDATED

Study description	Population	Outcomes and results
Prophylaxis		
<p>Young-Xu et al. 2022, pre-print (May 2022): Tixagevimab/Cilgavimab for Prevention of COVID-19 during the Omicron Surge: Retrospective Analysis of National VA Electronic Data</p> <p>Retrospective cohort study in the US</p> <p>First dose of Evusheld administered 13 January 2022 and patients followed-up through 30 April 2022; coincided with the Omicron BA.1 surge across the US</p>	<ul style="list-style-type: none"> • US veterans (≥ 18 years as of 1 Jan 2022) who received healthcare from the US Department of Veterans Affairs (VA) • Assumed that the eligibility criteria for Evusheld treatment were in line with the EUA. The control group included immunocompromised or other high-risk patients who did not receive Evusheld. • Immunocompromised status defined as receipt of an immunosuppressive medication ≤ 30 days before index date or presence of immunocompromising condition during the 2 years before index date. Severely immunocompromised was those who had a solid organ transplant or 	<p>Primary outcome: composite of SARS-CoV-2 infection confirmed by RT-PCR or antigen testing, COVID-19 hospitalisation (defined as having both an admission and discharge diagnosis for COVID-19 from a hospital or within 30 days of positive SARS-CoV-2 test), and all-cause mortality</p> <p>17/1,733 (1.0%) treatment group vs. 206/6,354 (3.2%) control group; HR 0.31, 95% CI 0.18 to 0.53</p> <p>Individual outcomes of the primary composite endpoint SARS-CoV-2 positive RT-PCR or antigen test</p> <p>$<0.5\%$ 'numbers not shown to protect patient information' in the treatment group vs. 69/6,354 (1%) in the control group; HR 0.34, 95% CI 0.13 to 0.87</p>

Study description	Population	Outcomes and results
<p>Initially 150 mg/150 mg administered until the FDA revised the EUA to increase the dose to 300 mg/300 mg on 24 February 2022. Patients who received the lower dose were advised to receive an additional dose. The analysis includes any patient who received ≥ 1 dose of Evusheld.</p> <p>Electronic health records which contain patient-level information on all patient encounters in the Department of Veterans Affairs medical facilities were analysed.</p>	<p>received anti-rejection medication or chemotherapy in the prior month.</p> <ul style="list-style-type: none"> Patients who were diagnosed with SARS-CoV-2 infection by RT-PCR or antigen test within 3 months of the date or pseudo-date of Evusheld administration were excluded. After propensity-score matching: n=1,733 treatment group and n=6,354 control group. After propensity-score matching 74% of population had received 3 doses of vaccine. 	<p>COVID-19 hospitalisation $<0.5\%$ 'numbers not shown to protect patient information' in the treatment group vs. 38/6,354 (0.5%) in the control group; HR 0.13, 95% CI 0.02 to 0.99</p> <p>All-cause mortality $<0.5\%$ 'numbers not shown to protect patient information' in the treatment group vs. 99/6,354 (2%) in the control group; HR 0.36, 95% CI 0.18 to 0.73</p> <p>Outcomes by vaccination status COVID-19 infection or related hospitalisation in fully vaccinated (≥ 3 doses of any vaccine or 2 doses of Ad26.COV2) population 0.85% in the treatment group vs. 2.8% in the control group</p> <p>COVID-19 infection or related hospitalisation in unvaccinated population 1.35% in the treatment group vs. 3.7% in the control group</p> <p>Safety and adverse events not reported</p>
<p>Kertes et al. 2022 Published: Association between AZD7442 (tixagevimab-cilgavimab) administration and SARS-CoV-2 infection, hospitalization and mortality</p> <p>Retrospective observational study in Israel</p> <p>People invited to receive Evusheld between 23 February and 2 May 2022; coincided with predominantly Omicron BA.1 variant between February and March 2022, with BA.2 becoming the most prevalent from April 2022</p>	<ul style="list-style-type: none"> Members of Maccabi Health Care Services aged ≥ 12 years and ≥ 40 kg who did not have a positive PCR or antigen COVID-19 test in the last month, were not vaccinated against COVID-19 in the last 2 weeks and had evidence of severe immunosuppression were offered Evusheld treatment. Severe immunosuppression defined as: hypogammaglobulinemia; CLL; anti-CD20 therapy; bone marrow transplant; CAR-T therapy; solid organ transplant; aggressive lymphoma; multiple myeloma. 	<p>Primary outcome: SARS-CoV-2 infection, defined as any person with a recorded positive PCR or antigen test in the follow-up period 29/825 (3.5%) treatment group vs. 308/4,299 (7.2%) control group; $p < 0.001$, OR after adjustment 0.51, 95% CI 0.30 to 0.84</p> <p>In univariate analyses, age, number of doses of COVID-19 vaccine received, prior COVID-19 illness, socioeconomic status and CKD were found associated with SARS-CoV-2 infection. Gender and all other comorbidities were not found to be associated with SARS-CoV-2 infection in the univariate analyses.</p>

Study description	Population	Outcomes and results
<p>Evusheld 300 mg total dose</p> <p>Data were extracted from the Maccabi HealthCare Services database</p> <p>Median follow-up 53 days in treatment group and 73 days in control group</p>	<ul style="list-style-type: none"> 825 people received Evusheld and 4,299 people did not receive Evusheld There were statistically significant differences in the baseline characteristics for age, gender, vaccination, and comorbidities. 91.3% of people in the treatment group had 3-4 COVID-19 vaccines vs. 76.3% in the control group. 	<p>Secondary outcome: severe COVID-19 disease, defined as either COVID-19-related hospitalisation and/or all-cause mortality</p> <p>COVID-19-related hospitalisation 1/825 (0.1%) treatment group vs. 27/4,299 (0.6%) control group; p=0.05</p> <p>All-cause mortality 0/825 treatment group vs. 40/4,299 (0.9%) control group; p=0.005</p> <p>Severe COVID-19 disease 0.1% treatment group vs. 1.5% control group; p=0.001</p> <p>Safety and adverse events not reported</p>
<p>Jurdi et al. 2022 Published and pre-print: Tixagevimab/cilgavimab pre-exposure prophylaxis is associated with lower breakthrough infection risk in vaccinated solid organ transplant recipients during the omicron wave</p> <p>Retrospective multicentre observational study in the US</p> <p>Between 28 December 2021 and 13 April 2022, during the Omicron wave</p> <p>40.5% received 300 mg total dose, 59% received 600 mg dose and 0.5% received 900 mg dose The Mass General Brigham Research Patient Data Registry was used to identify a control group of age-matched vaccinated solid organ</p>	<ul style="list-style-type: none"> Solid organ transplant (kidney, liver and lung) recipients who received Evusheld for prophylaxis 222 patients received Evusheld and 222 vaccine-matched solid organ transplant recipients who did not receive Evusheld Median age 65 years (IQR 55-72), 39% were female 25% had a history of coronary artery disease and 23% had a history of heart failure 7% had a history of prior SARS-CoV-2 infection and 99% had received ≥1 dose of SARS-CoV-2 vaccine Median time from transplantation to Evusheld administration was 3.8 years (IQR 1.9-8.2) 	<p>Primary outcome: breakthrough SARS-CoV-2 infection, defined as newly positive PCR or antigen test 4 patients (1.8%) developed breakthrough infections. Kaplan-Meier estimates of 60-day breakthrough infection rates were 1.8% in the Evusheld group and 4.7% in the age-matched vaccinated control group (p = 0.045). In the Evusheld group, 1 subject was hospitalised and there were no deaths. In the control group, 5 were hospitalised and 4 died.</p> <p>Safety 9 patients (4%) experienced an adverse event at a median of 15 days (IQR 5- 22) after Evusheld administration. The most common adverse events were nausea, vomiting or diarrhoea (n=4, 1.8%), headache (n=3, 1.4%) and abdominal pain (n=2, 0.9%). 2 patients (0.9%) developed new lung infiltrates with negative infectious evaluation, thought to be pneumonitis; 1 patient (0.5%) developed a mild heart failure exacerbation and 1 (0.5%) developed new atrial fibrillation requiring cardioversion.</p>

Study description	Population	Outcomes and results
<p>transplant recipients who did not receive Evusheld for comparison.</p> <p>Follow-up for each patient in the control group was started on the same day that their age-matched counterpart in the treatment group receive Evusheld to control for the variation in disease incidence</p> <p>Mean 67 ± 18 days follow up</p> <p>Source: NICE Information Services literature search (12.08.2022)</p>		

D. Real-world evidence: non-comparative studies

Reference	Results
Prophylaxis	
Nguyen et al. 2022 publication: Pre-exposure prophylaxis with tixagevimab and cilgavimab (Evusheld®) for COVID-19 among 1112 severely immunocompromised patients	<ul style="list-style-type: none"> Observational multicentre cohort study of immunocompromised patients with impaired response to COVID-19 vaccine (≥3 doses) who received tixagevimab (150 mg) and cilgavimab (150 mg) as pre-exposure prophylaxis between 28 December 2021 and 31 March 2022 during the Omicron wave in France (n=1,112). After a median follow-up of 6 days, COVID-19 was confirmed in 49/1,112 (4.4%) at least 5 days following treatment. 43/49 had mild to moderate COVID-19 and 6/49 had moderate to severe COVID-19. 29/49 (59%) were infected with Omicron. During the study period, mean weekly incidence rate was 1,669 in 100,000 inhabitants in Ile-de-France and 530 in 100,000 among patients who received tixagevimab and cilgavimab prophylaxis.
Ordway et al. 2022 Publication: Characterization of Early-Onset Severe Acute Respiratory Syndrome Coronavirus 2 Infection in Immunocompromised	<ul style="list-style-type: none"> A descriptive analysis of immunocompromised patients who received tixagevimab and cilgavimab (300 mg) for pre-exposure prophylaxis in line with the FDA EUA during the first 2 months of the programme at a clinic in the US. Of the 674 immunocompromised patients who received tixagevimab and cilgavimab, 8 were subsequently diagnosed with SARS-CoV-2 infection within 2 weeks of treatment: of these patients 6 had received 3 doses of COVID-19 vaccine, 1 had 2 doses and 1 had not received any COVID-19 vaccine due to ongoing chemotherapy and then stem cell transplant. 2 patients required hospitalisation; no patients died. Only 1 sample was available for genomic analysis, and it was Omicron BA.1. Omicron BA.1 was the most common circulating variant at the time of the study.

Reference	Results
Patients Who Received Tixagevimab-Cilgavimab Prophylaxis	
Benotmane et al. 2022 Published brief communication: Breakthrough COVID-19 cases despite prophylaxis with 150 mg of tixagevimab and 150 mg of cilgavimab in kidney transplant recipients	<ul style="list-style-type: none"> A case series of kidney transplant recipients (n=416) who showed a weak serological response to SARS-CoV-2 mRNA vaccines and received pre-exposure prophylaxis cilgavimab and tixagevimab (300 mg total dose) in France (December 2021 to March 2022). Of the 416 patients who received tixagevimab plus, 39 (9.4%) developed COVID-19, 14 (35.9%) required hospitalisation and 3 (7.7%) were admitted to an intensive care unit; 2 patients died of COVID-19-related acute respiratory distress syndrome. SARS-CoV-2 sequencing was carried out in 15 cases (BA.1 n=5; BA.1.1 n=9; BA.2 n=1). The authors concluded that pre-exposure prophylaxis with 300 mg dose of cilgavimab and tixagevimab does not adequately protect kidney transplant recipients against omicron.
Goulenok et al. 2022 Publication: Pre-exposure anti-SARS-CoV-2 monoclonal antibodies in severely immunocompromised patients with immune-mediated inflammatory diseases	<ul style="list-style-type: none"> A real-world study in France on the clinical use of prophylactic tixagevimab and cilgavimab (dose not reported) in patients with immune-mediated inflammatory diseases who are severely immunocompromised and do not generate an adequate humoral response to vaccination. Of all outpatients with immune-mediated inflammatory disease (n=219) who were fully vaccinated (4 doses of vaccine) between March and May 2021, 17 were considered to mount an inadequate humoral response to vaccination and were eligible for pre-exposure prophylaxis with tixagevimab and cilgavimab. Only 10 of the 17 eligible patients received treatment. COVID-19 occurred in 8 of the 27 patients, with all but 1 infection due to the Omicron variant. 5/8 patients required hospitalisation; 1 patient died. Only 1 of the 8 patients received prophylactic tixagevimab and cilgavimab; they developed mild COVID-19 and did not require hospital admission.
Benotmane et al. 2022 Pre-print: research letter: Pre-exposure prophylaxis with Evusheld™ elicits limited neutralizing activity against the omicron variant in kidney transplant patients	<ul style="list-style-type: none"> Serum samples from 63 adult kidney transplant recipients who received prophylactic tixagevimab/cilgavimab (300 mg total dose) in the Lyon and Strasbourg University Hospitals were collected to assess for neutralising activity against Omicron BA.1. After a median interval from injection of 29 days, only 9.5% (6/63) of patients who received tixagevimab/cilgavimab were able to neutralise Omicron BA.1 variant compared to 71% (10/14) of patients who were infected with SARS-CoV-2 (positive control) and 2.6% (1/39) of those who received prophylactic casirivimab and imdevimab (negative control).
Source: NICE Information Services literature search (12.08.2022)	

Appendix 2: Ongoing trials

A. Completed, no results

Reference	Sponsor	Design	Location	Population	Primary endpoints	Actual PCD*
NCT04896541	AstraZeneca	Phase 1, double-blind, RCT Tixagevimab and cilgavimab single doses: - 300 mg IM (male) - 600 mg IM (male) - 300 mg IV (male and female) - 1,000 mg IV (male) Comparator: placebo	Japan	<ul style="list-style-type: none"> Healthy Japanese adults (18 to 55 years of age) Negative results from both SARS-CoV-2 RT-PCR and serology tests <p>Actual enrolment: 40</p>	Adverse events and pharmacokinetics through day 361	14/06/2022
Source: National Institute for Health Research Innovation Observatory (scan 04.08.2022)						
*PCD (Primary Completion Date) defined on clinicaltrials.gov as the date on which the last participant in a clinical study was examined or received an intervention to collect final data for the primary outcome measure. The "estimated" primary completion date is the date that the researchers think will be the primary completion date for the study.						

B. Active, not recruiting

Reference	Sponsor	Design	Location	Population	Primary endpoints	Actual PCD*
Treatment						
TACKLE NCT04723394	AstraZeneca	Phase 3, double blind RCT Intervention: 600 mg tixagevimab and cilgavimab IM Comparator: placebo	United Kingdom, United States, Argentina, Brazil, Bulgaria, Czechia, Germany, Hungary, Italy, Japan, Mexico, Peru, Poland,	<ul style="list-style-type: none"> Adults (≥18 years) Laboratory-confirmed SARS-CoV-2 infection WHO Clinical Progression Scale score > 1 and < 4 Dosed with trial treatment ≤7 days from onset of 	Severe COVID-19 or death from any cause through day 29 Safety and tolerability through day 457	21/08/2021 <i>Interim results published – see Section 5.1, follow-up ongoing</i>

Reference	Sponsor	Design	Location	Population	Primary endpoints	Actual PCD*
			Russian Federation, Spain and Ukraine	<p>mild to moderate symptoms</p> <ul style="list-style-type: none"> • ≥ 1 signs/symptoms within 24 hours before day 1: cough, sore throat, shortness of breath or difficulty breathing, body pain or muscle aches, fatigue, headache, chills, nasal congestion or discharge, nausea or vomiting, diarrhoea, new loss of taste or smell. • Oxygenation saturation of $\geq 92\%$ • Using contraception/ not of childbearing potential <p>Exclusion criteria include, but are not limited to, history or current hospitalisation for COVID-19 and receipt of any investigational or licensed vaccine for prevention of COVID-19</p> <p>Actual enrolment: 910</p>		
ACTIV-2 NCT04518410	National Institute of Allergy and Infectious Diseases	Phase 2/3 randomised, triple blind, placebo-controlled, adaptive trial Investigating several interventions	United States, South America, South Africa, Canada, Philippines	<ul style="list-style-type: none"> • Adults (≥ 18 years) • Outpatient • Laboratory-confirmed SARS-CoV-2 infection • Able to begin study treatment ≤ 7 days from self-reported onset of COVID-19-related 	<ul style="list-style-type: none"> • COVID-19 symptom duration through day 28 • Quantification of SARS-CoV-2 RNA at day 3, day 7 and day 14 • Adverse events \geq Grade 3 	1 March 2022 (actual PCD)

Reference	Sponsor	Design	Location	Population	Primary endpoints	Actual PCD*
		<p>Tixagevimab and cilgavimab 300 mg by single IV infusion</p> <p><i>Participants are no longer being randomised to tixagevimab and cilgavimab.</i></p>		<p>symptoms or measured fever</p> <ul style="list-style-type: none"> ≥ 1 sign/symptom within 24 hours of participating in the study, including but not limited to, cough, fever, shortness of breath, sore throat, body pain, fatigue, nausea or vomiting Oxygen levels ≥ 92% at rest <p>Actual enrolment for all interventions: 4,044</p>	<ul style="list-style-type: none"> Death or hospitalisation due to any cause through day 28 	
<p>DisCoVeRy</p> <p>NCT04315948</p>	<p>Institut National de la Santé Et de la Recherche Médicale, France</p>	<p>Phase 3, triple blind RCT</p> <p>Investigating several interventions; all treatment arms apart from tixagevimab and cilgavimab have been ceased</p> <p>600 mg tixagevimab and cilgavimab single IV infusion</p> <p>Comparator: standard of care with placebo</p> <p>The number of patients with vaccination (partly or fully) will be limited to 20% of all participants</p>	<p>Austria, Belgium, Luxembourg, Norway, Portugal, France, Greece, Portugal</p>	<ul style="list-style-type: none"> Adults (≥ 18 years) Hospitalised with any of the following: presence or pulmonary rales/crackles, SpO2 ≤ 94% on room air or requirement of supplementary oxygen including high flow oxygen devices or non-invasive ventilation Time between onset of symptoms and randomisation < 11 days Positive SARS-CoV-2 PCR performed on a NP swab within 5 days preceding randomisation Contraceptive use <p>Exclusion criteria includes, but not limited to: need for</p>	<p>Percentage of subjects reporting each severity rating on a 7-point ordinal scale: a) not hospitalised, no limitations on activities; b) not hospitalised, limitation on activities; c) hospitalised, not requiring supplemental oxygen; d) hospitalised, requiring supplemental oxygen; e) hospitalised, on non-invasive ventilation or high flow oxygen; f) hospitalised, on invasive mechanical ventilation or ECMO; g) death. Time frame day 15.</p>	<p>Estimated PCD July 2022</p> <p><i>Registry last updated 05/07/2022</i></p>

Reference	Sponsor	Design	Location	Population	Primary endpoints	Actual PCD*
				<p>invasive mechanical ventilation and/or ECMO at time of enrolment and any prior receipt of investigational or licensed other mAb/biologic indicated for the prevention of SARS-CoV-2 infection or COVID-19, and for those not vaccinated, expected receipt of vaccine in the 30 days following hospital discharge</p> <p>Estimated enrolment for all interventions: 2,416, n=620 for tixagevimab and cilgavimab</p>		
Prevention						
<p>PROVENT NCT04625725 / 2020-004356-16</p> <p>Pre-exposure prophylaxis</p>	AstraZeneca	<p>Phase 3, double blind RCT</p> <p>Intervention: 300 mg IM tixagevimab and cilgavimab single dose (n~3,433)</p> <p>Comparator: placebo (n~1,717)</p> <p>Sub-study of approximately 500 participants will receive a second dose of tixagevimab and cilgavimab 300 mg IM at approximately 12 months after first dose (12 month repeat dose interval; Arm 1) and approximately 500</p>	United Kingdom, Belgium, France, Spain, United States	<ul style="list-style-type: none"> Adult (≥ 18 years) Can benefit from passive immunisation with antibodies Negative SARS-CoV-2 serology at screening Using contraception/ not of childbearing potential <p>Excludes patients who have previously received an investigational or licensed vaccine or other mAb or biologic indicated for the prevention of SARS-CoV-2 or COVID-19 or expected to receive during the period of study follow up.</p>	<p>The incidence of the first case of SARS-CoV-2 RT-PCR positive symptomatic illness through day 183.</p> <p>Safety and tolerability through day 457</p> <p>Sub-study primary endpoint: safety and tolerability through day 639</p>	<p>05/05/2021</p> <p><i>Interim results published – see Section 5.1, follow-up ongoing</i></p>

Reference	Sponsor	Design	Location	Population	Primary endpoints	Actual PCD*
		participants will receive a second dose approximately 6 months after first dose (6 month repeat dose interval; Arm 2)		<p>Sub-study inclusion criteria which are additional to those in parent study:</p> <ul style="list-style-type: none"> Participant has been randomised, dosed and is ongoing in the parent study and is 12±2 months post first dose ≥1 of the following: immunocompromised and/or may be at increased risk of an inadequate response to a COVID-19 vaccine or in the opinion of the investigator, are at increased risk and would benefit from a repeat dose of tixagevimab and cilgavimab Negative SARS-CoV-2 RT-PCR test collected ≤3 days before sub-study day 1 or negative rapid SARS-CoV-2-antigen test at screening <p>Sub-study exclusion criteria include, but are not limited to: patients who have received a COVID-19 vaccination ≤14 days before sub-study day 1 or plan to receive a COVID-19 vaccination ≤14 days after sub-study day 1. (Such</p>		

Reference	Sponsor	Design	Location	Population	Primary endpoints	Actual PCD*
				<p>participants can be included in the study once they have reached >14 days after their last dose of vaccine).</p> <p>Actual enrolment: 5,197</p>		
Safety						
NCT05184062	AstraZeneca	<p>Phase 2, double-blind RCT</p> <p>Treatment: 600 mg tixagevimab and cilgavimab by single IV infusion</p> <p>Comparator: placebo</p>	China	<ul style="list-style-type: none"> Adults (≥ 18 years) Negative for SARS-CoV-2 confirmed by RT-PCR Healthy or medical stable <p>Exclusion criteria includes, but is not limited to, COVID-19 infection history or any receipt of monoclonal antibody indicated for COVID-19</p> <p>Estimated enrolment: 272</p>	Safety, including, but not limited to: incidence of adverse events, serious adverse events, abnormality in haematology and vital signs	<p>13 August 2022</p> <p><i>Registry last updated 14 July 2022</i></p>
NCT05437289	AstraZeneca	<p>Phase 1, double-blind RCT</p> <p>Interventions:</p> <ul style="list-style-type: none"> Tixagevimab (150 mg) and cilgavimab (150 mg) IM Tixagevimab (300 mg) and cilgavimab (300 mg) IM Tixagevimab (150 mg) and cilgavimab (150 mg) IV Tixagevimab (300 mg) and cilgavimab (300 mg) IV 	China	<p>Healthy Chinese adults (18 to 55 years of age) with negative SARS-CoV-2 RT-PCR and serology tests within 14 days prior to randomisation</p> <p>Actual enrolment: 61</p>	Safety, tolerability, pharmacokinetics and pharmacodynamics	27/11/2021

Reference	Sponsor	Design	Location	Population	Primary endpoints	Actual PCD*
		Comparator: placebo				
NCT05406375	MedImmune LLC	Phase 1, double-blind RCT Interventions: single dose of tixagevimab and cilgavimab: <ul style="list-style-type: none"> • 300 mg IM (male) • 600 mg IM (male) • 300 mg IV (male and female) • 1,000 mg IV (male) Comparator: placebo	Japan	Healthy Japanese adults aged 18 to 55 years of age with negative SARS-CoV-2 RT-PCR and serology tests Actual enrolment: 40	Safety and pharmacokinetics	Estimated PCD 24.06/2022

Source: National Institute for Health Research Innovation Observatory (scan 04.08.2022)

Abbreviations: RT-PCR, reverse transcriptase polymerase chain reaction; ECMO, extracorporeal membrane oxygenation; IM, intramuscular; IV, intravenous

*PCD (Primary Completion Date) defined on clinicaltrials.gov as the date on which the last participant in a clinical study was examined or received an intervention to collect final data for the primary outcome measure. The "estimated" primary completion date is the date that the researchers think will be the primary completion date for the study.

C. Recruiting

Reference	Sponsor	Design	Location	Population	Primary endpoints	Estimated PCD*
Pre-exposure prophylaxis, treatment						
TRUST NCT05281601	AstraZeneca	Phase 1, open-label study of tixagevimab and cilgavimab in babies, children and young people from 29 weeks gestational age to younger than 18 years.	US, Belgium, Brazil, Germany, Mexico, Spain, Ukraine, UK	<ul style="list-style-type: none"> • ≥ 29 weeks gestational age to <18 years. • Minimum 1.5 kg bodyweight. COHORT 1 (pre-exposure prophylaxis)	Pharmacokinetic parameters, adverse events	28 July 2022 <i>Registry last updated 26 July 2022</i>

Reference	Sponsor	Design	Location	Population	Primary endpoints	Estimated PCD*
		Single dose of tixagevimab and cilgavimab, either IM or IV		<ul style="list-style-type: none"> Increased risk of severe COVID-19 because immunocompromised or with 1 or more comorbid conditions. Increased risk for SARS-CoV-2. Medically stable. A negative RT-PCR test ≤ 3 days before day 1 or a negative rapid SARS-CoV-2 antigen test at screening. No COVID-19 symptoms before enrolment within 10 days of dosing. <p>COHORT 2 (treatment)</p> <ul style="list-style-type: none"> Increased risk of severe COVID-19 because immunocompromised or with 1 or more comorbid conditions. Medically stable. Positive RT-PCR test ≤ 3 days before day 1 or positive rapid SARS-CoV-2 antigen test at screening. People with symptoms must have tixagevimab and cilgavimab no more than 7 days from the self-reported date of first reported sign/symptom. 		

Reference	Sponsor	Design	Location	Population	Primary endpoints	Estimated PCD*
				<ul style="list-style-type: none"> Oxygen saturation $\geq 92\%$ at rest, within 24 hours before day 1 unless the person regularly has chronic supplementary oxygen for an underlying lung condition. <p>COHORT 3 (treatment)</p> <ul style="list-style-type: none"> Hospitalised with COVID-19 and ≤ 7 days between onset of symptoms and tixagevimab and cilgavimab dose. Positive RT-PCR test ≤ 3 days before day 1 or positive rapid SARS-CoV-2 antigen test at screening. Spontaneous blood ALT/AST levels ≤ 5 times the ULN. GFR ≥ 30 mL/min. <p>Participants will have IM tixagevimab and cilgavimab unless they have severe COVID-19, or it is contraindicated, or they have a central IV line and the physician considers IV appropriate.</p> <p>Estimated enrolment: 100</p>		

Reference	Sponsor	Design	Location	Population	Primary endpoints	Estimated PCD*
Treatment						
NCT05321394	Azienda Ospedaliera Universitaria Integrata Verona	<p>Phase 3, open label, randomised non-inferiority trial of tixagevimab plus cilgavimab and nirmatrelvir plus ritonavir versus sotrovimab</p> <p>Interventions: 300 mg tixagevimab and 300 mg cilgavimab IM</p> <p>300 mg nirmatrelvir and 100 mg ritonavir twice daily for 5 days</p> <p>Comparator: 500 mg sotrovimab IV</p>	Italy	<ul style="list-style-type: none"> Age ≥ 50 years Laboratory-confirmed SARS-CoV-2 infection, no more than 4 days prior to the study drug administration Peripheral oxygen saturation $\geq 94\%$ on room air and not requiring supplemental oxygen Onset of symptoms no more than 4 days prior to study drug administration <p>Exclusion criteria include, but are not limited to, previously or currently hospitalised or requiring hospitalisation, history of a positive SARS-CoV-2 test prior to the one serving as eligibility for this study, previous treatment with a SARS-CoV-2 specific monoclonal antibody.</p> <p>Estimated enrolment: 1,095</p>	COVID-19 progression: hospitalisation or need of supplemental oxygen therapy at home or death within 14 days of randomisation	30/09/2022
Prophylaxis						
ENDURE NCT05375760	AstraZeneca	<p>Phase 2, open-label study</p> <p>Interventions: 600 mg tixagevimab and cilgavimab followed by 300 mg tixagevimab and</p>	US	<p>Adults or paediatric patients (≥ 12 years)</p> <p>Excludes patients with symptoms consistent with COVID-19 or confirmed COVID-19</p>	Safety	15 November 2023

Reference	Sponsor	Design	Location	Population	Primary endpoints	Estimated PCD*
		<p>cilgavimab every 3 months (5 doses in total) IM</p> <p>1,200 mg IV tixagevimab and cilgavimab followed by 600 mg tixagevimab and cilgavimab IM every 6 months (3 doses in total)</p>		Estimated enrolment: 200		
NCT05438498	MediMergent, LLC	<p>Real world evaluation</p> <p>Intervention: tixagevimab (300 mg) and cilgavimab (300 mg) IV or IM, one dose</p>	US	<ul style="list-style-type: none"> Adults (≥ 18 years) Diagnosis of either haematologic malignancy or solid tumour Patients on active treatment for solid tumour or haematologic malignancies may be included Patients up to 12 months post-treatment of haematologic malignancy and either in remission, stable or progressing may be included Patients up to 6 months post treatment of solid tumours may be included Cancer is progressing Vaccinated with at least 1 dose of COVID-19 vaccine 	Serum concentration of tixagevimab and cilgavimab from day 30 to day 360	03/09/2023

Reference	Sponsor	Design	Location	Population	Primary endpoints	Estimated PCD*
				<ul style="list-style-type: none"> Negative SARS-CoV-2 antigen test at screening <p>Estimated enrolment: 1,500</p>		
Source: National Institute for Health Research Innovation Observatory (scan 04.08.2022) and NICE Information Services literature search (12.08.2022)						
Abbreviations: RT-PCR, reverse transcriptase polymerase chain reaction; IM, intramuscular; IV, intravenous						
*PCD (Primary Completion Date) defined on clinicaltrials.gov as the date on which the last participant in a clinical study was examined or received an intervention to collect final data for the primary outcome measure. The "estimated" primary completion date is the date that the researchers think will be the primary completion date for the study.						

D. Not yet recruiting

Reference	Sponsor	Design	Location	Population	Primary endpoints	Estimated PCD*
Prophylaxis						
PACE-CLL NCT05465876	Sunnybrook Health Sciences Centre Collaborator: AstraZeneca	Phase 2, open-label single-arm Intervention: tixagevimab and cilgavimab	Canada	<p>Adults (≥ 18 years) with a diagnosis of CLL who have received at least 2 standard of care SAR-CoV-2 vaccines within the last 18 months prior to enrolment.</p> <p>Participants must have a demonstrated absent or suboptimal response to standard of care SARS-CoV-2 vaccinations.</p> <p>Participants must have a life expectancy >6 months.</p>	Passive immunity measured by the proportion of participants with anti-spike antibodies (time frame 12 months)	September 2024

Reference	Sponsor	Design	Location	Population	Primary endpoints	Estimated PCD*
				<p>Exclusion criteria includes but is not limited to, signs and symptoms consistent with symptomatic COVID-19 illness within 30 days of consent.</p> <p>Estimated enrolment: 200</p>		

Source: National Institute for Health Research Innovation Observatory (scan 04.08.2022)

Abbreviations: CLL: chronic lymphocytic leukaemia

*PCD (Primary Completion Date) defined on clinicaltrials.gov as the date on which the last participant in a clinical study was examined or received an intervention to collect final data for the primary outcome measure. The "estimated" primary completion date is the date that the researchers think will be the primary completion date for the study.

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