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Efficacy and safety of intramuscular administration of tixagevimab–cilgavimab for early outpatient treatment of COVID-19 (TACKLE): a phase 3, randomised, double-blind, placebo-controlled trial

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Summary

Background Early intramuscular administration of SARS-CoV-2-neutralising monoclonal antibody combination, tixagevimab–cilgavimab, to non-hospitalised adults with mild to moderate COVID-19 has potential to prevent disease progression. We aimed to evaluate the safety and efficacy of tixagevimab–cilgavimab in preventing progression to severe COVID-19 or death.

Methods TACKLE is an ongoing, phase 3, randomised, double-blind, placebo-controlled study conducted at 95 sites in the USA, Latin America, Europe, and Japan. Eligible participants were non-hospitalised adults aged 18 years or older with a laboratory-confirmed SARS-CoV-2 infection (determined by RT-PCR or an antigen test) from any respiratory tract specimen collected 3 days or less before enrolment and who had not received a COVID-19 vaccination. A WHO Clinical Progression Scale score from more than 1 to less than 4 was required for inclusion and participants had to receive the study drug 7 days or less from self-reported onset of mild to moderate COVID-19 symptoms or measured fever. Participants were randomly assigned (1:1) to receive either a single tixagevimab–cilgavimab 600 mg dose (two consecutive 3 mL intramuscular injections, one each of 300 mg tixagevimab and 300 mg cilgavimab) or placebo. Randomisation was stratified (using central blocked randomisation with randomly varying block sizes) by time from symptom onset, and high-risk versus low-risk of progression to severe COVID-19. Participants, investigators, and sponsor staff involved in the treatment or clinical evaluation and monitoring of the participants were masked to treatment-group assignments. The primary endpoints were severe COVID-19 or death from any cause through to day 29, and safety. This study is registered with ClinicalTrials.gov, NCT04723394.

Findings Between Jan 28, 2021, and July 22, 2021, 1014 participants were enrolled, of whom 910 were randomly assigned to a treatment group (456 to receive tixagevimab–cilgavimab and 454 to receive placebo). The mean age of participants was 46-1 years (SD 15-2). Severe COVID-19 or death occurred in 18 (4%) of 407 participants in the tixagevimab–cilgavimab group versus 37 (9%) of 415 participants in the placebo group (relative risk reduction 50-5% [95% CI 14-6–71-3]; p=0-0096). The absolute risk reduction was 4-5% (95% CI 1-1–8-0; p=0-0001). Adverse events occurred in 132 (29%) of 452 participants in the tixagevimab–cilgavimab group and 163 (36%) of 451 participants in the placebo group, and were mostly of mild or moderate severity. There were three COVID-19-reported deaths in the tixagevimab–cilgavimab group and six in the placebo group.

Interpretation A single intramuscular tixagevimab–cilgavimab dose provided statistically and clinically significant protection against progression to severe COVID-19 or death versus placebo in unvaccinated individuals and safety was favourable. Treating mild to moderate COVID-19 earlier in the disease course with tixagevimab–cilgavimab might lead to more favourable outcomes.

Funding AstraZeneca.

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Research in context

Evidence before this study
Before the TACKLE study began (January, 2021), monoclonal antibodies for the prevention and treatment of COVID-19 were in early stages of development and, as a consequence, there were few published clinical trials. Since then, randomised, placebo-controlled, phase 3 clinical trials have been published for different monoclonal antibodies. A literature search of PubMed from date of inception to Jan 11, 2022, using the terms “SARS-CoV-2” or “COVID-19” and “monoclonal antibodies” or “mAbs” with the filters of “randomised controlled trial” and “clinical trial, phase 3”, and no language restrictions, identified 117 peer-reviewed publications related to the efficacy and safety of monoclonal antibodies in patients with COVID-19. Of these, only five reported on use in the outpatient treatment setting, and none reported on monoclonal antibodies using an intramuscular route of administration.

Added value of this study
This study provides evidence of the efficacy and safety of a single 600 mg intramuscular dose of tixagevimab–cilgavimab for the treatment of COVID-19 in non-hospitalised adults with mild to moderate COVID-19 at high risk of progression to severe disease, who had not received a COVID-19 vaccine. Tixagevimab-cilgavimab is a long-acting antibody, with longer half-life compared with other monoclonal antibodies published so far. Tixagevimab-cilgavimab was the first monoclonal antibody combination to receive US Food and Drug Administration authorisation for use in COVID-19 prevention, providing extended protection from a single intramuscular dose. Other authorised anti-SARS-CoV-2 monoclonal antibodies are indicated to be administered intravenously and subcutaneously. It is therefore of interest to evaluate the efficacy of intramuscular tixagevimab-cilgavimab in treating mild to moderate COVID-19.

Implications of all the available evidence
The TACKLE results add to the growing evidence supporting tixagevimab–cilgavimab use as treatment against SARS-CoV-2 in different settings and provide additional support beyond the emergency use authorisation for prevention of COVID-19. Further studies of tixagevimab–cilgavimab treatment are needed among individuals who have received COVID-19 vaccination.

Methods

Study design
TACKLE is an ongoing, phase 3, randomised, double-blind, placebo-controlled, multicentre study. The trial is being conducted at 95 sites in the USA, Latin America, Europe, and Japan. The proportion of hospital versus non-hospital study sites is included in the appendix (p 7). The study was conducted in accordance with the Good Clinical Practice guidelines and the Declaration of Helsinki, Council for International Organizations of Medical Sciences International Ethical guidelines, applicable International Conference on Harmonisation Good Clinical Practice guidelines, and all applicable laws and regulations. The protocol, protocol amendments, and all other relevant documentation were reviewed and approved by an institutional review board or ethics committee. The protocol (including amendments) and statistical analysis plan are in the appendix (pp 21–205).

Participants
Eligible participants were non-hospitalised adults (definition of hospitalisation in the appendix p 9) aged 18 years or older with a documented laboratory-confirmed SARS-CoV-2 infection, as determined by RT-PCR (testing for viral RNA) or an antigen test (testing for presence of SARS-CoV-2 proteins) from any respiratory tract specimen collected 3 days or less before enrolment (day 1). A WHO Clinical Progression Scale score of more than 1 to less than 4 (appendix p 15) was required for inclusion. Participants had to receive study drug 7 days or less (inclusive; day 1 symptom count started from the first day of symptoms) from self-reported onset of mild to

administration of SARS-CoV-2-neutralising monoclonal antibodies and antivirals leads to more favourable clinical outcomes.1,5 However, effectiveness of some SARS-CoV-2-neutralising monoclonal antibodies might be limited by the emergence of new SARS-CoV-2 variants.6,8,9 Therefore, additional COVID-19 treatment options are needed in populations at increased risk of severe disease to mitigate the risk for severe outcomes and reduce the burden on health-care systems, and in preparation for the possible emergence of more malign variants of concern.

Tixagevimab–cilgavimab (AZD7442, Catalent, Bloomington, IN, USA) is a combination of two fully human, extended half-life SARS-CoV-2-neutralising monoclonal antibodies that simultaneously bind to distinct, non-overlapping epitopes of the viral spike protein receptor-binding domain.10 Tixagevimab–cilgavimab has been shown to have neutralisation activity in vitro against the original SARS-CoV-2 and variants of concern.11 Tixagevimab–cilgavimab can be administered by intramuscular injection and has received authorisation in various countries, including US Food and Drug Administration emergency use authorisation for the prevention of COVID-19 in specific adults and children (aged 12 years and older weighing at least 40 kg).12

This ongoing phase 3 trial (TACKLE) aims to evaluate the safety and efficacy of a single 600-mg intramuscular dose of tixagevimab–cilgavimab for the treatment of COVID-19 in non-hospitalised adults (≥18 years) with mild to moderate COVID-19 to prevent progression to severe COVID-19 or death.
moderate COVID-19 symptoms or measured fever. Peripheral saturation of arterial blood with oxygen (oxygen saturation) of 92% or more obtained at rest by study staff within 24 h before enrolment (day 1) was required. Participants could not be involved in another clinical trial for the treatment of COVID-19 or SARS-CoV-2 during the study period until reaching hospitalisation or 28 days after study entry, whichever was earliest.

Participants were excluded if they had a history of hospitalisation or were currently hospitalised for COVID-19, or if they had a current need for hospitalisation or immediate medical attention in a clinic or emergency room service in the clinical opinion of the site investigator. Due to local public health guidelines, some sites in Japan and Russia were required to hospitalise participants for isolation purposes upon testing positive for COVID-19; these participants were excluded from the primary analysis, but were included in the full analysis set (all randomised assigned participants who received study drug) and the third supportive estimand of the primary analysis. Participants could be enrolled if the only reason for hospitalisation related to a local policy-driven need for isolation. Participants were excluded if they had a history of hypersensitivity, infusion-related reaction, or severe adverse reaction following administration of a monoclonal antibody, or if they had previously received an investigational or licensed vaccine or other monoclonal antibody or biologic indicated for the prevention of SARS-CoV-2 or COVID-19 before study entry, or if administration of these products was expected immediately after enrolment. Full inclusion and exclusion criteria are provided in the appendix (pp 7–11). All participants provided written informed consent.

Randomisation and masking
All participants were centrally randomly assigned (1:1) to receive either tixagevimab–cilgavimab or placebo using interactive response technology. Randomisation was stratified (using central blocked randomisation) by time from symptom onset (≤5 days vs >5 days), and high-risk versus low-risk of progression to severe COVID-19 (including those aged ≥65 years, immunocompromised individuals, and those with comorbidities, such as cancer and chronic diseases). At least 60% of enrolled participants were required to meet the protocol definition of being at high risk. Full definition of individuals at high risk are included in the appendix (p 11). An external third-party vendor (Signant Health; Blue Bell, PA, USA) was responsible for creating and housing the randomisation scheme. A method of randomly varying block sizes with 1:1 randomisation of treatment within each block of cells was used. The participants, investigators, and sponsor staff involved in the treatment or clinical evaluation and monitoring of the participants were masked to treatment-group assignments. Masked study site staff could enrol participants. Study drug containers were not numbered before sending to the study sites; tixagevimab–cilgavimab was distributed as an open-label product vial, and placebo was normal saline solution provided by the site. Both were handled by an unmasked pharmacist at the study site who received a notification on what treatment to assign for each participant. Syringe masking was done to maintain masking.

Procedures
On day 1, participants were given either tixagevimab–cilgavimab as a single 600 mg dose (two consecutive 3 mL intramuscular injections, one each of 300 mg tixagevimab and 300 mg cilgavimab) or saline placebo (0·9% NaCl; two consecutive 3 mL intramuscular injections).

The first 20 participants who received the study drug (approximately ten allocated to tixagevimab–cilgavimab and approximately ten allocated to placebo) formed a sentinel group (randomly assigned 1:1 without stratification) and underwent safety monitoring for 4 h post-dose and daily follow-up for the first 4 days after receiving the study drug. An independent Data Safety Monitoring Board reviewed safety data through to day 8 and provided a recommendation to continue or to halt dosing of additional participants. The next 80 participants received the study drug with safety monitoring for 2 h post-dose. Subsequent participants received the study drug with safety monitoring for 1 h post-dose. Further details on study drug allocation, post-dose follow-up, and criteria for study suspension are provided in the appendix (pp 11–12).

Participants will be monitored for safety purposes for 456 days after receiving the study drug, to allow assessment of safety over 5 half-lives for tixagevimab–cilgavimab (approximately 450 days). The primary analysis was conducted 30 days after approximately 43 primary endpoint events had been observed, and additional analysis will be conducted after all participants have been followed up through to day 169. A final analysis will be conducted once all participants have completed the study at day 457. The Data Safety Monitoring Board will continue to monitor safety throughout the study.

Participants were recruited into one of two independent cohorts: cohort 1 (approximately 300 participants) and cohort 2 (up to approximately 1400 participants. Clinical assessments included supplemental oxygen use recorded at screening and at each in-person visit. Clinical assessment at in-person follow-up visits was done at days 1, 3, 6, 15, 29, 85, 169, and 366 for cohort 1, and days 1, 6, 29, 85, 169, and 366 for cohort 2. At study entry, if peripheral oxygen saturation was less than 92% on usual supplemental oxygen requirements, the participant was referred for emergency department evaluation and did not receive the study drug, and after day 1 to day 29, peripheral oxygen saturation measurements of less than 96% were reviewed and referred for medical attention. Severe COVID-19 was assessed for each participant.

For safety assessments, a complete physical examination was done at screening and at day 366. Adverse
events were reported by the participant; the investigator and any designees were responsible for detecting, documenting, and recording events that met the definition of an adverse event. Non-serious adverse events were collected from receipt of the study drug throughout the study, up to and including the last visit. Serious adverse events and adverse events of special interest were (and will continue to be) recorded from the time of signing of the informed consent form throughout the study, up to and including the last visit.

Full methods for complete physical examinations, virological, and antidrug antibody assessments are provided in the appendix (pp 12–13). Targeted physical examination was done at each in-person visit (days 1, 3, 6, 15, 29, 85, and 169 for cohort 1, days 1, 6, 29, 85, and 169 for cohort 2). A complete physical examination was done at day 366 and included, but was not limited to, assessment of height, bodyweight, general appearance, head, ears, eyes, nose, throat, neck, skin, in addition to cardiovascular, respiratory, abdominal, and nervous systems. For virological assessments including viral sequencing, mid-turbinate nasal swabs and plasma were collected on days 1, 3, 6, 15, and 29 for cohort 1 and days 1, 6, 29, and 29 for cohort 2 for qualitative and quantitative SARS-CoV-2 RNA assessment.

Clinical samples were screened for antidrug antibody assessment (at days 1, 29, 85, 169, 366, and optional at day 457) against tixagevimab and cilgavimab separately using an enhanced chemiluminescence solution-phase bridging method. Samples were reported screen positive for antidrug antibody in the screening assay if the mean enhanced chemiluminescence value was at or above the value of the plate-specific cut point factor.

**Outcomes**

The primary efficacy endpoint was a composite of either severe COVID-19 or death from any cause through to day 29, with severe COVID-19 being defined as a minimum of either pneumonia (fever, cough, tachypnoea or dyspnoea, and lung infiltrates) or hypoxaemia (oxygen saturation <90% in room air, severe respiratory distress, or both), plus a WHO Clinical Progression Scale score of 5 or more. The treating principal investigators were responsible for determining whether participants met the criteria of severe COVID-19 based on specific clinical parameters. Each reported event was reviewed by the masked AstraZeneca Global Study Team to confirm the principal investigator’s classification of a participant as having severe COVID-19, as well as confirming participant hospitalisations where severe COVID-19 was not reported. Independent adjudication of these results was deemed unnecessary since misclassification of events was unlikely based on the defined clinical criteria, the clinical experience of the treating principal investigators, and masked oversight from the Global Study Team.

The primary safety endpoints were adverse events, serious adverse events, and adverse events of special interest throughout the study. Adverse events of special interest included anaphylaxis and other serious hypersensitivity reactions, including immune complex disease and injection site reactions.

Secondary endpoints at day 29 included the incidence of respiratory failure, levels of SARS-CoV-2 RNA in nasal swabs, and incidence of antidrug antibodies to tixagevimab–cilgavimab in serum. Respiratory failure was defined as a requirement for mechanical ventilation, extracorporeal membrane oxygenation, non-invasive ventilation, or high-flow nasal cannula oxygen delivery. The key secondary endpoint was a composite of death from any cause or hospitalisation for COVID-19 complications or sequelae to day 169. Other secondary endpoints were whether tixagevimab–cilgavimab reduces the progression of participant-reported COVID-19-associated symptoms to day 29, the differences in symptom duration between tixagevimab–cilgavimab and placebo to day 29, and the single-dose pharmacokinetics of tixagevimab–cilgavimab. See appendix p 12 for full details of secondary endpoints.
The study has a follow-up period of 457 days. Here, we report data from the primary data cutoff (Aug 21, 2021), at which time all ongoing study participants had completed at least 29 days of study follow-up. The key secondary endpoint of a composite of death from any cause or hospitalisation for COVID-19 complications or sequelae to day 169 is not yet available and will be analysed using a later data cutoff and reported elsewhere. Analyses of other secondary endpoints including the progression of participant-reported COVID-19-associated symptoms and differences in symptom duration will also be reported elsewhere. Analyses through to the end of the study (day 457) will be done after the final database lock after the last patient last visit.

Statistical analysis
For the sample size, up to approximately 1700 participants were planned to be randomly assigned to receive a single 600-mg dose of tixagevimab–cilgavimab administered intramuscularly (up to approximately 850 participants) or placebo (up to approximately 850 participants). Enrolment was planned to stop once approximately 43 primary events had been observed in the primary analysis population. This is an event-driven study with a primary analysis initiated 30 days after approximately 43 primary endpoints had been confirmed in the primary analysis population. The study had 90% or more power to detect a relative risk (RR) reduction of 65% in the analysis population. This is an event-driven study with a primary analysis initiated 30 days after approximately 43 primary endpoints had been confirmed in the primary analysis population. The study had 90% or more power to detect a relative risk (RR) reduction of 65% in the incidence of severe COVID-19 or death between the study groups, based on the assumption that severe COVID-19 or death in the placebo group would be 4·6%.

Table 1: Participant demographics and baseline clinical characteristics in the full analysis set

| Age, years | Tixagevimab–cilgavimab (n=452) | Placebo (n=451) | Total (N=903) |
|------------|--------------------------------|----------------|--------------|
| Age group, years |                                |                |              |
| <18         | 10 (2%)                        | 8 (2%)         | 18 (2%)      |
| 18 to <65   | 219 (48%)                      | 239 (52%)      | 458 (50%)    |
| ≥65         | 21 (5%)                        | 11 (2%)        | 32 (4%)      |
| Sex         |                                |                |              |
| Female      | 239 (53%)                      | 216 (48%)      | 455 (50%)    |
| Male        | 213 (47%)                      | 235 (52%)      | 448 (50%)    |
| Ethnicity   |                                |                |              |
| Hispanic or Latino | 230 (51%) | 238 (53%) | 468 (52%) |
| Not Hispanic or Latino | 222 (49%) | 213 (47%) | 435 (48%) |
| Race        |                                |                |              |
| White       | 285 (63%)                      | 274 (61%)      | 559 (62%)    |
| American Indian or Alaska Native | 100 (22%) | 115 (26%) | 215 (24%) |
| Asian       | 30 (7%)                        | 21 (5%)        | 51 (6%)      |
| Black or African American | 16 (4%) | 20 (4%) | 36 (4%) |
| Unknown, not reported, multiple, or missing data | 21 (5%) | 21 (5%) | 42 (5%) |
| Body-mass index, kg/m² | 28.9 (5.5) | 29.2 (6.6) | 29.0 (6.0) |
| Time from symptom onset, days | 4.9 (1.6) | 5.0 (1.6) | 5.0 (1.6) |
| Serum for SARS-CoV-2 serology |                |                |              |
| Positive    | 60 (13%)                       | 67 (15%)       | 127 (14%)    |
| Negative    | 384 (85%)                      | 374 (83%)      | 758 (84%)    |
| Missing data | 8 (2%)                         | 10 (2%)        | 18 (2%)      |
| At high risk of progression to severe COVID-19* | 404 (89%) | 405 (90%) | 809 (90%) |

Risk factors for severe COVID-19

- One or more risk factor: 400 (89%) vs 399 (89%) vs 799 (89%)
- Obesity, body mass-index >30 kg/m²: 195 (43%) vs 193 (43%) vs 388 (43%)
- Smoking: 180 (40%) vs 184 (41%) vs 364 (40%)
- Hypertension: 125 (30%) vs 121 (27%) vs 256 (28%)
- Diabetes: 53 (12%) vs 55 (12%) vs 108 (12%)
- Chronic lung disease or asthma: 58 (13%) vs 50 (11%) vs 108 (12%)
- Cardiovascular disease: 42 (9%) vs 38 (8%) vs 80 (9%)
- Cancer: 18 (4%) vs 15 (3%) vs 33 (4%)
- Chronic kidney disease: 10 (2%) vs 9 (2%) vs 19 (2%)
- Chronic liver disease: 7 (2%) vs 13 (3%) vs 20 (2%)
- Immunocompromised state: 22 (5%) vs 23 (5%) vs 45 (5%)

Data are mean (SD) or n (%). *High risk of progression defined as at least one risk factor, including age (>65 years old) or having at least one comorbidity (cancer, chronic lung disease, obesity, hypertension, cardiovascular disease, diabetes, chronic kidney disease, chronic liver disease, immunocompromised state, sickle cell disease, or smoking).

The primary efficacy endpoint was calculated for the modified full analysis set, which comprised all participants in the full analysis set (all randomly assigned participants who received study drug) who received study drug 7 days or less from symptom onset and were not hospitalised at baseline (up to and including day 1) for isolation purposes. Data collected following an intercurrent event (receipt of COVID-19 treatment product before day 29) were not included.
Primary efficacy endpoints and supportive estimands

| Estimand Description | Analysis Set | Tixagevimab-cilgavimab | Placebo | RR Reduction (95% CI) | p Value |
|----------------------|--------------|-------------------------|---------|----------------------|---------|
| Primary endpoint: severe COVID-19 or death from any cause through to day 29 | Modified full analysis set* | 18/407 (4%) | 37/415 (9%) | 50·5% (14·6–71·3) | 0·0096 |
| First supportive estimand: severe COVID-19 or death from any cause through to day 29 | Non-hospitalised participants who received study drug ≤5 days from symptom onset (early intervention analysis set) | 9/253 (4%) | 27/251 (11%) | 66·9% (31·1–84·1) | 0·0017 |
| Second supportive estimand: severe COVID-19 or death from any cause from day 4 through to day 29 | Modified full analysis set* | 12/407 (3%) | 33/415 (8%) | 63·0% (29·4–80·6) | 0·0015 |
| Third supportive estimand: severe COVID-19 or death from any cause through to day 29 | Full analysis set† | 24/446 (5%) | 44/444 (9%) | 41·6% (5·0–64·1) | 0·028 |
| Fourth supportive estimand: severe COVID-19 or death from any cause through to day 29 | Non-hospitalised participants, who were seronegative at baseline and received study drug ≥7 days from symptom onset (seronegative analysis set) | 14/247 (4%) | 36/345 (10%) | 61·3% (29·7–78·7) | 0·0011 |

Secondary and exploratory endpoints

| Endpoint Description | Analysis Set | Tixagevimab-cilgavimab | Placebo | RR Reduction (95% CI) | p Value |
|----------------------|--------------|-------------------------|---------|----------------------|---------|
| Secondary endpoint: prevention of respiratory failure | Modified full analysis set | 3/405 (1%) | 11/412 (3%) | 71·9% (0·3–92·1) | 0·036 |
| Exploratory: hospitalisation for COVID-19 including complications through day 29 | Modified full analysis set | 17/413 (4%) | 40/421 (10%) | -- | -- |

Data are n/N (%). RR=relative risk. Results from a Cochran-Mantel-Haenszel test stratified by time from symptom onset (≤5 days vs >5 days) and risk of progression to severe COVID-19 (high risk vs low risk). RR reduction represents the percentage reduction in incidence of severe COVID-19 or death from any cause in the tixagevimab-cilgavimab group relative to the placebo group. A RR reduction >0 represents favourable efficacy in the tixagevimab-cilgavimab group. For the primary outcome and supportive estimands, p<0·05 indicates a statistically significant result; missing response data were not imputed. For the secondary outcome, p<0·05 indicates a nominally statistically significant result, as this analysis was not included in the multiple testing hierarchy. *Six patients from each group had missing data and were not included in this analysis.  †Six patients in the tixagevimab-cilgavimab group and seven patients in the placebo group had missing data and were not included in this analysis.

Table 2: Primary efficacy endpoints and supportive analyses, and secondary efficacy endpoints

primary efficacy endpoint) were analysed using an intention-to-treat strategy, therefore, no censoring was done for the intercurrent event.

To support the primary endpoint, Kaplan-Meier curves were used to summarise time to severe COVID-19 or death from any cause during the first 28 days post-dose for each randomly assigned group. A stratified log-rank test was conducted to assess the difference between groups. A Cox proportional hazards model was used to obtain a hazard ratio (HR) and respective 95% CIs, with statistical testing done for the safety endpoints. SAS (version 9.4) was used for all statistical analysis. This trial is registered with ClinicalTrials.gov, NCT04723394.

The safety analysis was done in the safety analysis set, which included all participants who received the study drug. erroneously treated participants were analysed according to the treatment they actually received. No statistical testing was done for the safety endpoints. SAS (version 9.4) was used for all statistical analysis. This trial is registered with ClinicalTrials.gov, NCT04723394.
Role of the funding source
The funder of the study was responsible for manufacturing tixagevimab–cilgavimab, for designing the study, for acquiring, analysing, and interpreting the data, for writing the report, and reviewing the manuscript.

Results
Between Jan 28, 2021, and July 22, 2021, 1014 participants were enrolled, of whom 910 were randomly assigned to a treatment group (456 to receive tixagevimab–cilgavimab and 454 to receive placebo). 413 participants in the tixagevimab–cilgavimab group and 421 in the placebo group were included in the modified full analysis set (figure 1). 43 participants in the tixagevimab–cilgavimab group and 33 in the placebo group were excluded from the primary analysis because they were either hospitalised at baseline for isolation purposes (in Japan and Russia), or were randomly assigned after 7 days of symptom onset. Median safety follow-up was 84·0 days (tixagevimab–cilgavimab IQR 31·0–86·0, placebo IQR 30·0–86·0) in both treatment groups.

Baseline clinical characteristics were similar between the groups (table 1). Mean age was 46·1 years (SD 15·2) and 116 (13%) of 903 participants were aged 65 years or older. 455 (50%) participants were female, 448 (50%) were male, and 559 (62%) were White.

In the primary efficacy analysis, severe COVID-19 or death occurred in 18 (4%) of 407 participants in the tixagevimab–cilgavimab group versus 37 (9%) of 415 participants in the placebo group (RR reduction 50·5% [95% CI 14·6–71·3]; p=0·0096; table 2). Six participants from each group were not included in the primary analysis due to missing data (ie, 407 and 415 were included rather than 413 and 421). The absolute risk reduction was 4·5% (95% CI 1·1–8·0; p<0·0001). The four supportive analyses of the primary efficacy endpoint also showed significant reductions in the development of severe COVID-19 or death with tixagevimab–cilgavimab versus placebo (table 2). Kaplan-Meier probability of severe COVID-19 or death from any cause occurring up to day 29 is summarised in figure 2A. The supplementary Cox Regression analysis showed a 51% reduction in the risk for severe COVID-19 or death from any cause for tixagevimab–cilgavimab versus placebo (figure 2A). Additional supportive analysis of the primary efficacy endpoint by time from symptom onset showed reduction in severe COVID-19 or death with tixagevimab–cilgavimab compared with
Figure 2: Analysis of the composite primary endpoint of severe COVID-19 or death from any cause up to day 29 after receiving study drug (A) Kaplan–Meier plot of time to severe COVID-19 or death from any cause through to day 29 in the modified full analysis set. p value is based on log-rank test stratified by time from symptom onset (≤5 days vs >5 days), when applicable, and risk of progression to severe COVID-19 (high risk vs low risk). Total number of patients censored: tixagevimab–cilgavimab group n=389, placebo group n=378. (B) Forest plot of RR reduction estimates for severe COVID-19 or death from any cause through to day 29 by time from symptom onset at random assignment. Day 1 symptom count started from the first day of symptoms. RR reductions represent the percentage reduction in incidence of severe COVID-19 or death in the tixagevimab–cilgavimab group relative to placebo. A RR reduction >0 represents favourable efficacy in the tixagevimab–cilgavimab group. (C) Forest plot of RR reduction estimates for severe COVID-19 or death from any cause through to day 29 by participant subgroup in the modified full analysis set. Arrows denote 95% CI bounds that are lower than the scale shown. Results in panel C were from a Cochran–Mantel-Haenszel test with stratification factors used in the primary analysis. For the subgroups of age, risk of progression was not a stratification factor. If there was no stratification factor, a χ² test was used. HR=hazard ratio. NE=not evaluable. RR=relative risk.

| Number of participants with event | RR reduction (95% CI) |
|----------------------------------|-----------------------|
| Tixagevimab–cilgavimab, n/N (%)  | Placibo, n/N (%)       |
| Age                              |                       |
| <65 years                        | 10/359 (3%)           | 29/364 (8%)              | 65·1% (79·6 to 82·7)                |
| ≥65 years                        | 8/41 (17%)            | 8/51 (16%)               | -9·9% (-159·9 to 56·0)              |
| <75 years                        | 12/389 (3%)           | 35/405 (9%)              | 64·3% (32·3 to 81·2)                |
| ≥75 years                        | 6/18 (33%)            | 2/10 (20%)               | -43·0% (-424·9 to 57·7)             |
| <80 years                        | 15/398 (4%)           | 36/410 (9%)              | 57·2% (23·2 to 76·2)                |
| ≥80 years                        | 3/9 (33%)             | 1/5 (20%)                | NE (NE)                              |
| Sex                              |                       |
| Male                             | 10/186 (5%)           | 21/211 (10%)             | 44·9% (-12·8 to 73·1)               |
| Female                           | 8/221 (4%)            | 16/204 (8%)              | 52·9% (-7·5 to 79·4)                |
| Race                             |                       |
| American Indian or Alaskan Native| 2/97 (2%)             | 14/113 (12%)             | 84·3% (25·0 to 96·7)                |
| Asian                            | 0/10                  | 1/9 (11%)                | NE (NE)                              |
| Black or African American        | 0/15                  | 1/10 (5%)                | 100 (NE)                             |
| Hawaiian or other Pacific Islanders| 0/0                  | 0/0                      | NE (NE)                              |
| White                            | 15/265 (6%)           | 18/253 (7%)              | 19·4% (-55·7 to 58·3)               |
| Other                            | 0/0                   | 0/0                      | NE (NE)                              |
| Ethnicity                        |                       |
| Hispanic or Latino               | 8/218 (4%)            | 25/230 (11%)             | 66·5% (26·0 to 84·9)                |
| Not Hispanic or Latino           | 10/189 (5%)           | 12/185 (7%)              | 18·7% (-81·0 to 63·5)               |
| Region                           |                       |
| USA                              | 2/62 (3%)             | 2/36 (6%)                | 30·3% (-359·7 to 89·4)              |
| Europe                           | 11/123 (6%)           | 12/125 (6%)              | -3·5% (-129·0 to 5·3)               |
| Latin America                    | 3/166 (2%)            | 4/212 (1%)               | 74·5% (32·8 to 93·0)                |
| Asia                             | 0/0                   | 0/0                      | NE (NE)                              |
| Risk group                       |                       |
| High                             | 17/364 (5%)           | 33/371 (9%)              | 47·5% (7·5 to 70·2)                 |
| Low                              | 1/44 (2%)             | 4/44 (9%)                | 75·4% (-115·1 to 97·2)              |
| COVID-19 comorbidity             |                       |
| ≥1                               | 15/360 (4%)           | 33/365 (9%)              | 53·9% (16·6 to 74·5)                |
| 0                                | 3/47 (6%)             | 4/50 (8%)                | 21·0% (-209·4 to 79·8)              |
| Baseline vitamin D               |                       |
| <30 ng/mL                        | 15/270 (6%)           | 25/276 (9%)              | 39·5% (-12·8 to 67·6)               |
| ≥30 ng/mL                        | 2/72 (3%)             | 3/74 (4%)                | 32·1% (-270·0 to 87·5)              |
| Baseline zinc                    |                       |
| <100 µg/dL                       | 15/301 (5%)           | 26/296 (9%)              | 44·1% (-4·3 to 70·0)                |
| ≥100 µg/dL                       | 2/33 (6%)             | 2/38 (5%)                | 19·1% (-42·8 to 87·6)               |
| Standard of care                 |                       |
| Antiviral                        | 0/0                   | 0/0                      | NE (NE)                              |
| Antiviral, not active against COVID-19 | 2/15 (13%)     | 0/2                     | NE (NE)                              |
| Antibiotic                       | 2/24 (8%)             | 5/32 (16%)               | 65·5% (-99·6 to 94·0)               |
| Immune-based                     | 2/7 (29%)             | 0/3                     | NE (NE)                              |
| Corticosteroids                  | 1/11 (9%)             | 1/14 (7%)                | -18·2% (-298·8 to 95·5)             |
| Adjunctive                       | 8/183 (4%)            | 23/206 (11%)             | 61·2% (14·4 to 82·4)                |
| Other                            | 1/36 (3%)             | 0/4                    | NE (NE)                              |
| None                             | 7/209 (3%)            | 13/189 (7%)              | 49·0% (-25·1 to 79·2)               |
| Baseline serum SARS-CoV-2 antibody|                     |                       | -136·2% (-551·5 to 42·8)            |
| Positive                         | 4/52 (8%)             | 1/62 (2%)                | 61·3% (29·7 to 78·7)                |
| Negative                         | 14/347 (4%)           | 36/345 (10%)             | NE (NE)                              |
placebo in the 7 days after symptom onset. The greatest reductions in development of severe COVID-19 or death were observed when tixagevimab–cilgavimab was administered as early as possible after symptom onset, as shown by the RR reductions at 3 days or less (prespecified subgroup), 5 days or less and, at 7 days or less (prespecified subgroup) from symptom onset (figure 2B).

For most participant subgroups, reductions in the risk of developing severe COVID-19 or death with tixagevimab–cilgavimab were consistent with the primary analysis (figure 2C). Most events were observed in participants at high risk of progression to severe COVID-19 (figure 2C). Although the number of events was low in participants at low risk of progression to severe COVID-19, a large but not statistically significant RR reduction with tixagevimab–cilgavimab was observed in this group. There was a low proportion of seropositive participants, those aged 75 years or older, and those on corticosteroids at baseline (table 1, figure 2C) and concomitantly a small number of events in these subgroups, resulting in low RR reductions with wide 95% CIs.

There was a significant reduction in respiratory failure in participants in the tixagevimab–cilgavimab group compared with the placebo group (table 2).

Antidrug antibody data were available in a subset of participants up to 84 days after receiving the study drug. Treatment-emergent antidrug antibodies to tixagevimab–cilgavimab occurred in six (5%) of 134 participants, with a low median titre of 120, which was very close to the lower limit of quantification of the antidrug antibody assay of 3.348 log_{10} copies per mL, which was very close to the lower limit of quantification of the antidrug antibody assay of 3.348 log_{10} copies per mL. Further details on the antidrug antibody assay are shown in the appendix (p 13).

There was a greater reduction in viral shedding for tixagevimab–cilgavimab versus placebo between baseline and day 6 (appendix p 19), with mean change in log_{10} viral RNA from baseline to day 6 of −1.9 (95% CI −1.7 to −2.1) in the tixagevimab–cilgavimab groups versus −1.5 (−1.3 to −1.7) in the placebo group.

Adverse events were reported by 132 (29%) of 452 participants in the tixagevimab–cilgavimab group and 163 (36%) of 451 in the placebo group. The most common adverse event in both groups was COVID-19 pneumonia (table 3). Serious adverse events were reported by 33 (7%) participants in the tixagevimab–cilgavimab group and 54 (12%) in the placebo group. The most common serious adverse event was COVID-19 pneumonia (appendix p 18). Most adverse events were mild or moderate in severity (table 3). The most common adverse event of special interest was injection site pain (table 3). Investigators reported three (1%) COVID-19 deaths in the tixagevimab–cilgavimab group compared with six (1%) in the placebo group; deaths due to any cause were reported for six (1%) participants in each treatment group (table 3).

In prespecified exploratory analysis, viral sequencing in 413 tixagevimab–cilgavimab participants, and 421 placebo participants, indicated that the alpha (B.1.1.7) SARS-CoV-2 variant was the most prevalent through to day 29 (238 [60%] of 394 sequenced samples), followed by gamma (P.1; 84 [20%]), delta (B.1.617.2; 66 [15%]), lambda (C.37; 20 [5%]), mu (B.1.621; two [1%]), and beta (B.1.51; one [<1%]; appendix p 17).

In the post-hoc exploratory analysis, fewer participants were hospitalised for COVID-19 in the tixagevimab–cilgavimab group versus the placebo group across all reported hospital settings (table 2; appendix p 16). Fewer participants in the tixagevimab–cilgavimab group compared with the placebo group were admitted to the
intensive care unit due to COVID-19, required admission to an inpatient hospital setting, required acute hospital care at home (acute hospital care at home occurred if physician determines condition is appropriate for acute in-patient hospitalisation, and if patients were evaluated daily), or were admitted to the emergency department for longer than 24 h (appendix p 16).

Discussion
Findings from the TACKLE study suggest that a single, intramuscular, 600 mg dose of tixagevimab–cilgavimab was associated with statistically and clinically significant protection against the development of severe COVID-19 or death in non-hospitalised unvaccinated adults with mild to moderate COVID-19. Additional prespecified analyses showed that earlier treatment with tixagevimab–cilgavimab led to more favourable outcomes (reduced risk for progression to severe COVID-19 and death). Tixagevimab–cilgavimab had a favourable safety profile and was well tolerated.

Treatments are needed for individuals who develop SARS-CoV-2 breakthrough infections and are at high risk for severe disease, hospitalisation, and death, such as older adults, those with multiple comorbidities, and individuals with impaired immune systems. Additionally, cases of prolonged and unresolved SARS-CoV-2 infection have been reported in immunocompromised individuals, which might result in the emergence of new variants. Furthermore, a substantial proportion of the global population remain unvaccinated and are at increased risk for progression to severe COVID-19 and death. Tixagevimab–cilgavimab had a favourable safety profile and was well tolerated.

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participants, there was a small number of events for several findings, resulting in wide 95% CIs. Other limitations include the absence of formal and specific assessment for COVID-19 deaths beyond investigator decision. The duration of available data limited interpretation of safety (median follow up 84–0 days) and some secondary endpoints. Although this study did not measure T cells or assess antibody-dependent cellular cytotoxicity, previous evidence suggests that antibodies against tixagevimab–cilgavimab show little to no antibody-dependent cellular cytotoxicity activity. Efficacy against the omicron (B.1.1.529) SARS-CoV-2 variant cannot be derived from this study given the study period reported; however, tixagevimab–cilgavimab has been shown to retain neutralising activity against omicron in vitro. Despite reduction in neutralisation against the omicron BA.1 subvariant, the half maximal inhibitory concentration values ranged from 51 to 277 ng/mL. Other SARS-CoV-2 neutralising monoclonal antibodies have been shown to differ in neutralising abilities for variants of concern such as omicron. Further in-vitro studies showed minimal loss of neutralising activity against the (now dominant) omicron BA.2 subvariant compared with wild-type SARS-CoV-2 (5-fold reduction in live virus assays and 3-fold reduction in pseudovirus assays). Further evidence is expected from planned real-world studies that will assess the effects of tixagevimab–cilgavimab with COVID-19 vaccination, including its use, effectiveness, and acceptability in clinical practice, in immunocompromised individuals with breakthrough infections, and against omicron. To our knowledge, data from TACKLE are the first from an outpatient treatment study of a long-acting monoclonal antibody combination with intramuscular administration for treating mild to moderate COVID-19. These results show that tixagevimab–cilgavimab provided statistically and clinically significant protection against the development of severe COVID-19 or death in unvaccinated individuals and was well tolerated. Tixagevimab-cilgavimab administered intramuscularly presents a potential additional option for treating mild to moderate COVID-19 in individuals at high risk, and contributes to the armamentarium against COVID-19, which is crucial for reducing the burden on health-care systems.

**Contributors**

All authors contributed to data interpretation, writing, and editing of the manuscript, and all reviewed and approved the manuscript for submission. All authors had access to the raw study data. Data in the manuscript were verified by DA, SS, AT, RHA, KS, RMG, VA, WKP, GCKWK, BHB, and MTE. HM was International co-ordinator for the TACKLE trial and contributed to the data interpretation and writing of the manuscript. FDRH contributed to study design, study permissions, interpretation of the data, drafting and editing of the manuscript, and operationalisation of TACKLE in the UK. FP contributed to the supervision, validation, and visualisation of the data. DA, AT, and SS contributed to the study design concept, statistical analysis plan, and the interpretation of results. KK contributed to the group discussion of the manuscript. JASC contributed intellectual participation in the structure of the manuscript, reviewing of literature, revision of statistical analysis, data interpretation, the selection of the graphic information, the group discussion of the manuscript, and the form of the presentation. RHA contributed to the dose selection, pharmacokinetics, and antidrug antibody analyses. BHB contributed to project delivery and administration, and resources. DB contributed to the data analysis, interpretation, and study design. PG contributed to data analysis, interpretation, project administration, and supervision. J] contributed to the study design and data collection and quality. GCKWK contributed to the review and agreement of the statistical analysis plan, the review of study results, and agreement on interpretation, including additional analyses required and key conclusions. KWP was directly involved in data curation, investigation, methodology (of amendments), project administration, and as the clinical scientist for TACKLE, directly assessed and verified the quality of the data (in a masked fashion). KS contributed to the conceptualisation of the study, investigation, and validation of the data. RMV was involved in the study design, collection and interpretation of data, and data checking of information. VA contributed to the study design, study execution, data collection, data analysis, and interpretation of the manuscript. MNP contributed to study conceptualisation and design, data analysis and interpretation, funding acquisition, project administration, and resourcing. MTE was involved in the study design, collection, analysis, and interpretation of data, as well as conceptualisation, formal analysis, methodology, project administration, supervision, and data checking of information provided in the manuscript. Ultimate responsibility for opinions, conclusions, and data interpretation lies with the authors. All authors were involved in the drafting and critical revision of the manuscript. All authors approved the final version of the manuscript and were responsible for the final decision to submit for publication.

**Declaration of interests**

HM has received consultation fees from AstraZeneca and is supported by the UK National Institute for Health Research’s Comprehensive Biomedical Research Centre at University College London Hospitals. He has consulted for Millfield Medical Ltd on the development of a new continuous positive airway pressure machine. JASC reports serving on advisory boards for Pfizer and Eli Lilly; and serving on advisory boards and as a speaker for AstraZeneca and Roche. FDRH reports funding from AstraZeneca to cover meeting attendance and operationalisation of TACKLE in the UK as UK principal investigator. He has received funding by UK Research and Innovation and National Institute for Health and Care Research (NIHR) for national Urgent Public Health COVID-19 trials, and as Director of the NIHR Applied Research Collaboration, Oxford Thames Valley, and investigator on the Oxford Biomedical Research Centre and NIHR MedTech. FP has received personal fees and grants from Amgen, AstraZeneca, Boehringer Ingelheim, Ferrer, Kowa, Medix, Merck, Merck Sharp and Dohme, Novartis, Pfizer, Sanofi, Servier, and Silanes. KK has received research grants for the conduct of the TACKLE trial, reports funding from Regeneron, Eli Lilly, Merck, Pfizer, and Adagio, and serves as a speaker for Regeneron. DA, AT, SS, RHA, BHB, DB, PG, JJ, GCKWK, WKP, RMV, KS, VA, MNP, and MTE are employees of, and hold or may hold stock in, AstraZeneca. Data sharing

Data underlying the findings described in this manuscript may be requested in accordance with AstraZeneca’s data sharing policy described at https://astrazeneca-trialstrial.pharmac.m.com/ST/ Submission/Disclosure. AstraZeneca Group of Companies allows researchers to submit a request to access anonymised participant-level clinical data, aggregate clinical or genomics data (when available), and anonymised clinical study reports through the Vivli web-based data request platform.

**Acknowledgements**

We thank the trial participants, their families, and all investigators involved in this study. Yee-Man Ching, of AstraZeneca facilitated author discussions, coordinated manuscript preparation and critically reviewed the manuscript. Marius Albucescu and Karen Near of AstraZeneca were involved in the study design of TACKLE. Medical writing support was provided by Sharrin Saleque, Joe Alling, Celian Ellis, and Matthew Stone, all of Core Medica, London, UK, supported by AstraZeneca according to Good Publication Practice guidelines.
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