Efficacy and safety of intramuscular administration of AZD7442 (tixagevimab/cilgavimab) for early outpatient treatment of COVID-19: the TACKLE phase 3 randomised controlled trial

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Summary

Background Early intramuscular (IM) administration of SARS-CoV-2–neutralising monoclonal antibody combination, AZD7442 (tixagevimab/cilgavimab), to non-hospitalised adults with mild to moderate COVID-19 has potential to prevent disease progression.

Methods TACKLE is an ongoing phase 3, 1:1 randomised, double-blind, placebo-controlled study of a single AZD7442 600-mg dose (two consecutive IM injections) for treatment of non-hospitalised adults with mild to moderate COVID-19, who had not received a COVID-19 vaccine, who were dosed ≤7 days with AZD7442 or placebo from symptom onset. Primary study endpoints were severe COVID-19 or death from any cause through day 29, and safety.

Findings Overall, 910 participants were randomised, 903 of whom were treated (AZD7442, n=452; placebo, n=451). Severe COVID-19 or death occurred in 18/407 (4·4%) *vs* 37/415 (8·9%) of participants with AZD7442 *vs* placebo, a relative risk reduction of 50·5% (95% confidence interval [CI] 14·6–71·3) (p=0·010). The absolute risk reduction was 4·5% (95% CI 1·1–8·0; p<0·001). Adverse events occurred in 29% (132/452) and 36% (163/451) of participants administered AZD7442 and placebo, respectively, and were mostly of mild or moderate severity. There were three COVID-19-reported deaths in the AZD7442 group and six in the placebo group.

Interpretation A single AZD7442 IM dose provided statistically and clinically significant protection against progression to severe COVID-19 or death *vs* placebo in unvaccinated individuals and safety was favourable. Treating mild to moderate COVID-19 earlier in the disease course with AZD7442 lead to more favourable outcomes.

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Research in context

Evidence before this study

Before the TACKLE study began (January 2021), monoclonal antibodies (mAbs) 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 mAbs. A literature search of PubMed on January 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", identified 117 peer-reviewed publications related to the efficacy and safety of mAbs. Of these, only 5 reported on use in the outpatient treatment setting, and none reported on mAbs 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 AZD7442 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. AZD7442 is a long-acting antibody, with longer half-life compared with other mAbs published so far.[1,2] AZD7442 was the first mAb to receive United States 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 mAbs are indicated to be administered intravenously and subcutaneously. It is therefore of interest to evaluate the efficacy of intramuscular AZD7442 in treating mild to moderate COVID-19.

Implications of all the available evidence

TACKLE demonstrated that a single intramuscular dose of 600 mg AZD7442 significantly reduced the development of severe COVID-19 or death in those with mild to moderate COVID-19. These results add to the growing evidence supporting AZD7442 use against SARS-CoV-2 in different settings and provide additional support beyond the emergency use authorisation for prevention of COVID-19. Further studies of AZD7442 treatment are needed among individuals who have received COVID-19 vaccination.

Introduction

COVID-19 vaccines are effective at preventing symptomatic and severe COVID-19;[3] however, some populations remain at risk as SARS-CoV-2 continues to circulate.[4] Older adults, individuals with multiple comorbidities, and those who are immunocompromised remain at risk of severe COVID-19 outcomes from breakthrough infections, especially as new variants emerge that may confer decreased vaccine effectiveness.[3,5,6]

SARS-CoV-2–neutralising monoclonal antibodies (mAbs) and antiviral therapies have been shown to be effective in the treatment of non-hospitalised adults with COVID-19 who are at high risk of progression to severe COVID-19 and death.[7-11] Further evidence suggests that earlier administration of SARS-CoV-2–neutralising mAbs and antivirals leads to more favourable clinical outcomes.[8,11] However, effectiveness of some SARS-CoV-2–neutralising mAbs may be limited by the emergence of new SARS-CoV-2 variants.[10,12,13] Additional COVID-19 treatment options are therefore needed in populations at increased risk of severe disease, to mitigate the risk for severe outcomes and reduce the burden on healthcare systems, and in preparation for the possible emergence of more malign variants of concern.

AZD7442 is a combination of two fully human, extended–half-life SARS-CoV-2–neutralising monoclonal antibodies mAbs—tixagevimab and cilgavimab—that simultaneously bind to distinct nonoverlapping epitopes of the viral spike protein receptor-binding domain.[14] AZD7442 has been shown to have neutralisation activity in vitro against the original SARS-CoV-2 and variants of concern.[14] AZD7442 can be administered by intramuscular (IM) injection and has received authorisation in various countries, including United States Food and Drug Administration emergency use authorisation for the prevention of COVID-19 in certain adults and paediatric individuals (12 years of age and older weighing at least 40 kg).[15]

This ongoing phase 3 trial (TACKLE) is evaluating the safety and efficacy of a single 600-mg IM dose of AZD7442 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.

Methods

Study design

TACKLE is an ongoing phase 3, randomised, double-blind, placebo-controlled multicentre study (NCT04723394). The trial is being conducted at 95 sites in the United States, Latin America, Europe, and Japan, and in accordance with the Good Clinical Practice (GCP) guidelines and the Declaration of Helsinki, Council for International Organizations of Medical Sciences International Ethical guidelines, applicable International Conference on Harmonisation GCP guidelines, and all applicable laws and regulations. The proportion of hospital *vs* non-hospital study sites is included in the **supplementary appendix.** The protocol, protocol amendments, and all other relevant documentation were reviewed and approved by an institutional review board or ethics committee. All participants provided written informed consent. The study has a follow-up period of 457 days. Here, we report data 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. The key secondary endpoint of a composite of death from any cause or hospitalisation for COVID-19 complications or sequalae through day 169, is not yet available and will be analysed using a later data cut-off. Analyses through to the end of the study (day 457) will be conducted after the final database lock after the last patient last visit. The protocol (including amendments) and statistical analysis plan are available online at thelancet.com.

Participants

Eligible participants were non-hospitalised adults (definition of hospitalisation in **supplementary appendix**) aged ≥18 years with a documented laboratory-confirmed SARS-CoV-2 infection, as determined by a reverse transcription polymerase chain reaction (RT-PCR) (testing for viral RNA) or antigen test (testing for presence of SARS-CoV-2 proteins) from any respiratory tract specimen collected ≤3 days prior to enrolment (day 1). A World Health Organisation (WHO) Clinical Progression Scale score between >1 and <4 (**supplementary table 1**) was required for inclusion. Participants had to be dosed ≤7 days (inclusive; day 1 symptom count started from the first day of symptoms) from self-reported onset of mild to moderate COVID-19 symptoms or measured fever. Peripheral saturation of arterial blood with oxygen ('oxygen saturation') of ≥92% obtained at rest by study staff within 24 h prior to 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 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 participants who received study drug) and the third supportive estimand of the primary analysis. Participants were allowed to be enroled if the only reason for hospitalisation related to a local policy-driven need for isolation. Participants were excluded if they had history of hypersensitivity, infusion-related reaction, or severe adverse reaction following administration of a mAb, or previously received an investigational or licensed vaccine or other mAb/biologic indicated for the prevention of SARS-CoV-2 or COVID-19 prior to study entry, or if administration of these products was expected immediately after enrolment.

Full inclusion and exclusion criteria are provided in the **supplementary appendix**.

Randomisation and masking

All participants were centrally assigned to a randomised treatment (1:1 to AZD7442 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 *vs* 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). Full definition of high risk individuals are included in the **supplementary appendix**). 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 blinded to treatment-group assignments. Blinded study site staff could enrol participants. Study drug containers were not numbered before sending to the study

sites; AZD7442 was distributed as an open-label product vial, and placebo was normal saline solution provided by the site. Both were handled by an unblinded pharmacist at the study site who received a notification on what treatment to assign for each participant. Syringe masking was performed in order to maintain blinding.

Procedures

Participants were randomised to a single 600-mg dose of AZD7442 (two consecutive 3-mL IM injections, one each of 300 mg tixagevimab and 300 mg cilgavimab) or saline (0·9% NaCL) placebo IM (two consecutive 3-mL IM injections) on day 1.

The first 20 participants dosed (n= ~10 allocated to AZD7442; n= ~10 allocated to placebo) formed a sentinel group (randomised 1:1 without stratification) and underwent safety monitoring for 4 h post-dose and daily follow-up for the first 4 days after dosing. An independent Data Safety Monitoring Board (DSMB) reviewed safety data through to day 8 and provided a recommendation to continue or to halt dosing of additional participants. The next 80 participants were dosed with safety monitoring for 2 h post-dose. Subsequent participants were dosed 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 **supplementary appendix**.

Participants will be monitored for safety purposes for 456 days after dosing, to allow assessment of safety over 5 half-lives for AZD7442 (~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 through day 169. A final analysis will be conducted once all participants have completed the study at day 457. The DSMB will continue to monitor safety throughout the study.

Outcomes

The primary efficacy endpoint was a composite of either severe COVID-19 or death from any cause through 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 and/or severe respiratory distress), plus a WHO Clinical Progression Scale score of ≥5.[16] The treating principal investigators (PI's) 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 blinded AstraZeneca Global Study Team to confirm the PI'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 PI's, and blinded oversight from the Global Study Team.

The primary safety endpoints were adverse events (AEs), serious AEs (SAEs), and AEs of special interest (AESIs) throughout the study. AESIs 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 through study day 29, levels of RNA in nasal swabs through day 29, and incidence of antidrug antibodies (ADAs) to AZD7442 in serum. Respiratory failure was defined as a requirement for mechanical ventilation, extracorporeal membrane oxygenation, noninvasive ventilation, or high-flow nasal cannula oxygen delivery. Exploratory endpoints (post hoc) included hospitalisation for COVID-19 disease or its complications through day 29, and baseline and emergent viral resistance to AZD7442 per viral genotypic analysis. See **supplementary appendix** for full list of secondary endpoints.

Assessments

Clinical assessments included supplemental oxygen use recorded at screening and each in-person visit. At study entry, if peripheral oxygen saturation was <92% on usual supplemental oxygen requirements, the participant was referred for emergency department evaluation and was not dosed, and after day 1 to day 29, peripheral oxygen saturation measurements of <96% were reviewed and referred for medical attention. Severe COVID-19 was assessed for each participant.

For safety assessments, a complete physical examination was to be performed at screening and then at day 366. AEs were reported by the participant; the investigator and any designees were responsible for

detecting, documenting, and recording events that met the definition of an AE. Nonserious AEs were collected from dosing throughout the study, up to and including the last visit. SAEs and AESIs 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 methodology for complete physical examinations, virologic, and ADA assessments are provided in the **supplementary appendix.**

Statistical analysis

For sample size, up to ~1700 participants were planned to be randomised to receive a single 600-mg dose of AZD7442 administered intramuscularly (n= up to ~850) or placebo (n= up to ~850). 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% power to detect a relative risk reduction (RRR) of 65% in the incidence of severe COVID-19 or death between the study groups (AZD7442 or placebo), based on the assumption that severe COVID-19 or death in the placebo group would be 4·6%. These assumptions reflected a protocol amendment (version 7·0, 5 July 2021), following observed event rates of 4.6% to 5.8% in control arms from published studies.[7,9] Accordingly, statistical power was reduced from 95% to 90% to accommodate the decrease in expected event rate while maintaining a reasonable sample size and required number of events for analysis. Further details on protocol amendments, in addition to protocol deviations, are provided in the **supplementary appendix**.

For the primary efficacy endpoint, the RRR in incidence of severe COVID-19 or death from any cause in the AZD7442 group relative to the placebo group was calculated using a Cochran-Mantel-Haenszel (CMH) test. The primary efficacy endpoint was a binary response, and the CMH test was used to investigate treatment effect stratified by the two stratification factors at randomisation. Efficacy was estimated by the common relative risk or risk ratio from the CMH test. The RRR = 100 × (1 – relative risk) represented the percent reduction in incidence of severe COVID-19 or death from any cause in the AZD7442 group relative to the placebo group.

The primary efficacy endpoint was calculated for the modified full analysis set (mFAS), which comprised all participants in the FAS (all randomised participants who received study drug) who received dosing ≤7 days from symptom onset and were not hospitalised at baseline (≤day 1) for isolation purposes. Data collected following an intercurrent event (receipt of COVID-19 treatment product prior to day 29 without already having met the primary efficacy endpoint) were analysed using an intent-to-treat strategy, therefore, no censoring was performed 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 randomised 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 and respective 95% confidence intervals (CIs), with the stratification factors included as covariates.

Supportive analyses of the primary endpoint (supportive estimands) were performed using the same statistical methodology as described for the primary efficacy endpoint. First supportive estimand (early intervention) analysis included all participants in the mFAS who received dosing ≤5 days from symptom onset. Second supportive estimand analysis was conducted in the mFAS and only considered events occurring from day 4 through day 29. Third supportive estimand analysis was conducted in the FAS (i.e., including participants who may have been excluded from the primary analysis due to being hospitalised for isolation purposes). Fourth supportive estimand analysis was conducted in participants in the mFAS who were seronegative for SARS-CoV-2 at baseline.

The primary endpoint and supportive estimands 1 to 4 were tested sequentially in a hierarchical order to control for multiplicity; p-values for secondary endpoint analyses should be considered nominal. Analyses used for all secondary endpoints reported in this manuscript and further information on the supportive estimands are shown in the **supplementary appendix.**

The safety analysis utilised the safety analysis set (SAS), which included all participants who received

dosing. Erroneously treated participants were assigned to the treatment they actually received. No statistical testing was performed for the safety endpoints.

Role of the funding source

AstraZeneca was responsible for manufacturing AZD7442, designing and funding the study, acquiring and analysing the data, and review of the manuscript. ClinicalTrials.gov number NCT04723394.

Results

Between January 28, 2021 and July 22, 2021, TACKLE screened 1014 participants, of whom 910 were randomised, with 452 and 451 receiving AZD7442 and placebo, respectively. A total of 413 AZD7442 and 421 placebo participants were included in the primary efficacy analysis (mFAS), and 452 AZD7442 and 451 placebo participants were included in the FAS and SAS (**figure 1**). A total of 43 and 33 participants in the AZD7442 and placebo groups, respectively, were excluded from the primary analysis mFAS population as they were either hospitalised at baseline for isolation purposes (in Japan and Russia), or were randomised after 7 days of symptom onset. Median safety follow-up was 84·0 days in both treatment groups.

Baseline clinical characteristics were similar between the groups (**table 1**). Mean age was 46·1 years (standard deviation: 15·2) and 12·8% (116/903) of participants were aged ≥65 years, 50·4% (455/903) were female, and 61·9% (559/903) were White. There was a high proportion of participants identifying as Hispanic (468/903; 51·8 %) or as American Indian/Alaska Native (215/903; 23·8%). Most participants (758/903; 83·9%) had negative serum SARS-CoV-2 serology at baseline. Most participants (809/903; 89·6%) were considered to be at high risk of progression to severe COVID-19 (defined in the **supplementary appendix**), with the most common risk factors being obesity, (388/903; 43·0%), smoking (364/903; 40·3%), and hypertension (256/903; 28·3%).

In the primary efficacy analysis (mFAS population), severe COVID-19 or death occurred in 18/407 (4·4%) participants who received AZD7442 *vs* 37/415 (8.9%) with placebo for a RRR of 50·5% (95% CI 14·6–71·3, p=0·010) (**table 2**). The absolute risk reduction was 4·5% (95% CI 1·1–8.0; p<0·001). The four supportive analyses of the primary efficacy endpoint also demonstrated statistically significant reductions in the development of severe COVID-19 or death with AZD7442 *vs* placebo (**table 2**).

Respiratory failure (secondary endpoint; mFAS population) occurred in 3/405 (0·7%) AZD7442 *vs* 11/412 (2·7%) placebo participants, a reduction of 71·9% with AZD7442 *vs* placebo (95% CI 0·3–92·1, nominal p=0·036) (**table 2**). Hospitalisation for COVID-19 or its complications occurred in 17/413 (4·1%) and 40/421 (9·5%) of AZD7442 and placebo participants (mFAS population), respectively (**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 AZD7442 *vs* placebo (hazard ratio=0·49, 95% CI 0·28–0·86; p=0·0103; **figure 2a)**.

Additional supportive analysis of the primary efficacy endpoint by time from symptom onset showed reduction in severe COVID-19 or death with AZD7442 compared with placebo in the 7 days post-symptom onset. Highest reductions in development of severe COVID-19 or death were observed when AZD7442 was administered as early as possible after symptom onset, as shown by the RRR of 88·0% at ≤3 days (pre-specified subgroup) compared with 66·9% at ≤5 days and 50·5% at ≤7 days (pre-specified subgroup) (**figure 2b**).

For most participant subgroups, reductions in the risk of developing severe COVID-19 or death with AZD7442 were consistent with the primary analysis (**figure 2c**). Most events were observed in participants at high risk of progression to severe COVID-19 (17/364 [4·7%] *vs* 33/371 [8·9%] for AZD7442 *vs* placebo; RRR: 47.5% [95% CI: 7.5–70.2]). Although the number of events was low in participants at low risk of progression to severe COVID-19 (1/43 [2.3%] *vs* 4/44 [9.1%] for AZD7442 *vs* placebo), a RRR of 75·4% (95% CI -115·1–97·2) following AZD7442 was observed in this group. There was a low proportion of seropositive participants, those aged ≥75 years, and those on corticosteroids at baseline (**table 1**) and concomitantly a small number of events in these subgroups, resulting in low RRRs with wide CIs.

A greater proportion of participants was hospitalised for COVID-19 in the placebo group (40/421; 9·5%) *vs* the AZD7442 group (17/413; 4·1%) *vs* across all reported hospital settings; 11/421 (2·6%) *vs* 3/413 (0·7%) were admitted to the intensive care unit due to COVID-19, 24/421 (5·7%) *vs* 12/413 (2·9%) required admission to an inpatient hospital setting, 7/421 (1·7%) *vs* 1/413 (0·2%) 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), and 3/421 (0·7%) *vs* 1/413 (0·2%) were admitted to the emergency department for >24 hours, for placebo *vs* AZD7442, respectively (**supplementary table 2**).

ADA data were available in a subset of participants up to 84 days post-dose. Treatment-emergent ADAs (TE-ADAs) to AZD7442 occurred in 6/134 (4·5%) of participants, with a low median titre of 120 which was very close to the lower limit of quantification of the ADA assay of 3.348 Log10 copies/mL (2228 copies/mL). Further details on the ADA assay are provided in the **supplementary appendix**.

There was a greater reduction in viral shedding for AZD7442 *vs* placebo between baseline and day 6 (**supplementary figure 1**), with mean (95% CI) changes in Log_{10} viral RNA from baseline to day 6 of –1·9 (–1·7, –2·1) vs –1·5 (–1·3, –1·7) with AZD7442 vs placebo.

Viral sequencing in 413 AZD7442 participants, and 421 placebo participants, indicated that the Alpha variant was the most prevalent through day 29 (59·9% of sequenced samples [258/834]), followed by Gamma at 19·5% (84/834), Delta at 15·3% (66/834), Lambda at 4·6% (20/834), Mu at 0·5% (2/834), and Beta at 0·2% (1/834) (**supplementary table 3**).

AEs were reported by 132/452 (29·2%) and 163/451 (36·1%) AZD7442 and placebo participants, respectively. The most common AE was COVID-19 pneumonia, occurring in 26/452 (5·8%) and 49/451 (10·9%) AZD7442 and placebo participants, respectively (**table 3**). SAEs were reported by 33/452 (7·3%) and 54/451 (12·0%) AZD7442 and placebo participants, respectively. The most common SAE was COVID-19 pneumonia occurring in 23/452 (5·1%) and 49/451 (10·9%) AZD7442 and placebo participants, respectively (**supplementary table 4**). Most AEs were mild or moderate in severity (**table 3**). The most common AESI was injection site pain, and this occurred in 8/452 (1·8%) and 10/451 (2·2%) participants receiving AZD7442 and placebo, respectively (**table 3**). Investigators reported 3/452 (0·7%) COVID-19 deaths in the AZD7442 group compared with 6/451 (1·3%) in the placebo group; deaths due to any cause were reported for six (1·3%) participants in each treatment group (6/452 for AZD7442 and 6/451 for placebo) (**table 3**).

Discussion

TACKLE demonstrated that a single IM 600-mg dose of AZD7442 was associated with statistically and clinically significant protection against the development of severe COVID-19 or death in non-hospitalised adults with mild to moderate COVID-19. Additional pre-specified analyses showed that earlier treatment with AZD7442 led to more favourable outcomes (reduced risk for progression to severe COVID-19 and death), with 88·0% and 66·9% RRRs observed when participants were treated within 3 and 5 days of symptom onset, respectively, and 50·5% when treated within 7 days of symptom onset. AZD7442 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, hospitalization, and death, such as older adults, those with multiple comorbidities, and individuals with impaired immune systems.[17-21] In addition, cases of prolonged and unresolved SARS-CoV-2 infection have been reported in immunocompromised individuals, which may result in the emergence of new variants.[22] Furthermore, a substantial proportion of the global population remain unvaccinated[23] and remain at increased risk of hospitalisation and mortality from COVID-19 compared with vaccinated individuals.[21,24,25] This study showed a reduced risk of progression to severe COVID-19 or death with AZD7442 in a population where approximately 90% of participants were at high risk of severe COVID-19, including older adults, those with comorbidities such as hypertension, diabetes, chronic lung disease, cardiovascular disease, and cancer, or individuals who were immunocompromised. As such, these data support the potential of AZD7442 to provide a new treatment option for individuals who require protection from severe COVID-19 outcomes.

The incidence of AEs was similar in the AZD7442 and placebo groups, with most being mild or moderate in severity. Specifically, the incidence of injection site pain was similar in both groups. While all-cause mortality was balanced between groups, there were fewer COVID-19-reported deaths in the AZD7442 group (3/452; 0.7%) compared with the placebo group (6/451; 1.3%). Overall, these safety results are consistent with the phase 3 PROVENT and STORM CHASER trials of AZD7442.[15,26] Safety monitoring for AZD7442 will continue in the ongoing sponsor-funded TACKLE, PROVENT (NCT04625725), and STORM CHASER (NCT04625972) trials, as well as the collaborative ACTIV-2 (NCT04518410), ACTIV-3 (NCT04501978), and DisCoVeRy (NCT04315948) trials.

While other SARS-CoV-2–neutralising mAbs have shown effectiveness against COVID-19 in the treatment setting,[7,8] AZD7442's IM administration route may offer clinical advantages, especially in outpatient and primary care settings. AZD7442 was specifically formulated for IM administration, which allows for early intervention and ease of access, facilitating its use in the real-world. The extended half-life of 90 days of AZD7442 (compared with the shorter half-lives of 18–32 days of other SARS-CoV-2–neutralising mAbs[1,2]), resulting from specific 'YTE' genetic modifications (M252Y/S254T/T256E),[14] could potentially also confer long-term protection against symptomatic COVID-19, as demonstrated in the PROVENT study.[26] Although antiviral therapies are effective in the treatment of COVID-19,[10,11] multiple treatment options are needed in the armamentarium against COVID-19 due to the risk of resistance occurring against any specific drug.[27]

In addition to the YTE modifications, AZD7442 component mAbs, tixagevimab and cilgavimab, also include triple amino acid modifications (TM) designed to reduce both Fc receptor interactions and the theoretical risk of antibody-enhanced disease. Indeed, non-human primate studies of AZD7442 confirmed that the TM modification ablates all downstream Fc-effector functions (cellular responses and complement cascade), with no impact on neutralisation activity or clearance of SARS-CoV-2.[14] This is supported by the faster reductions in SARS-CoV-2 viral RNA from nasal swabs with AZD7442 *vs* placebo shown in TACKLE.

Study strengths include a population with high prevalence of comorbidities considered to be risk factors for progression of COVID-19. The diversity of the study population is shown by the large proportion of Hispanic and American Indian/Alaska Native participants, reflecting the large contribution to the study population from Latin America, including Mexico. These data consistently showed that more hospitalisations occurred in the placebo arm compared with the AZD7442 arm, regardless of hospital setting (which ranged from the emergency room to intensive care units), supporting AZD7442 utility across a variety of healthcare settings.

Study limitations include a limited representation of Black/African American and Asian participants, especially given the disproportionate impact of COVID-19 among these populations[28]; exclusion of individuals

previously vaccinated against COVID-19; and a limited number of immunocompromised individuals, and older adults. Although increased age is a major risk factor for severe COVID-19, recruitment of those aged >65 years was limited mainly due to prioritisation of older adults for vaccination when the study was enrolling. Other limitations include the lack 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 days) and some secondary endpoints. Although this study did not measure T cells or assess antibody-dependent cellular cytotoxicity, previous evidence suggests that AZD7442 antibodies display little to no antibody-dependent cellular cytotoxicity activity.[14] Efficacy against Omicron cannot be derived from this study given the study period reported, however, AZD7442 has been shown to retain neutralising activity against Omicron in vitro. Despite reduction in neutralisation against the Omicron BA.1 subvariant, IC50 values ranged from 51 to 277 ng/mL.[12-14] Other SARS-CoV-2 neutralising mAbs have been shown to differ in neutralising abilities for variants of concern such as Omicron.[12,13] 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 and 3-fold reduction in live virus and pseudovirus assays, respectively).[29] Further evidence is expected from planned real-world studies that will assess the effects of AZD7442 with COVID-19 vaccination, including its use, effectiveness, and acceptability in clinical practice, in immunocompromised individuals with breakthrough infections, and against Omicron.

Data from TACKLE are the first from an outpatient treatment study of a long-acting mAb combination with IM administration for treating mild to moderate COVID-19. These results show that AZD7442 provided statistically and clinically significant protection against the development of severe COVID-19 or death and was well tolerated. AZD7442 administered intramuscularly presents a potential additional option for treating mild to moderate COVID-19 in high risk individuals, and contribute to the armamentarium against COVID-19, which is critical for reducing the burden on healthcare 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 Douglas Arbetter, Seth Seegobin, Alison Templeton, Rosalin Arends, Katie Streicher, Rolando Viani, Pedro Garbes, Vijay Alagappan, Kelly Padilla, Gavin Koh, Bryan Brodek, and Mark Esser. 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. DA, AT, and SS contributed to the study design concept, statistical analysis plan, and the interpretations 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. RA contributed to the dose selection, pharmacokinetics, and ADA 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. JJ contributed to the study design and data collection/quality. GK 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. KP 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 blinded fashion). KS contributed to the conceptualisation, investigation, and validation. 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. MP contributed to study conceptualisation and design, data analysis and interpretation, funding acquisition, project administration and resourcing. ME 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.

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 CPAP 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 attendances and operationalisation of TACKLE in the UK as UK principal investigator. He has received funding by the UKRI and NIHR for national UPH COVID trials, and as Director of the NIHR Applied Research Collaboration, Oxford Thames Valley, and investigator on the Oxford BRC 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, KWP, 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://astrazenecagrouptrials.pharmacm.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.

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Table 1: **Participant demographics and baseline clinical characteristics (FAS)**

Characteristic	**AZD7442 (n=452)**	**Placebo (n=451)**	**Total (N=903)**
Age, mean (SD), years	46·3 (15·4)	45·9 (15·0)	46·1 (15·2)
Age group, n (%), years			
≥18 to <65	393 (86·9)	394 (87·4)	787 (87·2)
≥65 to <75	38 (8·4)	46 (10·2)	84 (9·3)
≥75	21 (4·6)	11 (2·4)	32 (3·5)
Sex, female, n (%)	239 (52·9)	216 (47·9)	455 (50·4)
Ethnicity, n (%)			
Hispanic/Latino	230 (50·9)	238 (52·8)	468 (51·8)
Race, n (%)			
White	285 (63·1)	274 (60·8)	559 (61·9)
American Indian/Alaska Native	100 (22·1)	115 (25·5)	215 (23·8)
Asian	30 (6·6)	21 (4·7)	51 (5·6)
Black or African American	16 (3·5)	20 (4·4)	36 (4·0)
Unknown/Not reported/Multiple/Missing	21 (4·6)	21 (4·7)	42 (4·7)
BMI, mean (SD), kg/m^2	28·9 (5·5)	29·2 (6·6)	29·0 (6·0)
Time from symptom onset, mean (SD), day	4·9 (1·6)	5·0 (1·6)	5·0 (1·6)
Serum for SARS-CoV-2 serology, n (%)			
Positive	60 (13·3)	67 (14·9)	127 (14·1)
Negative	384 (85·0)	374 (82·9)	758 (83·9)
Missing data	8 (1·8)	10 (2·2)	18 (2·0)
At high risk of progression to severe COVID-19*, n (%)	404 (89·4)	405 (89·8)	809 (89·6)
Risk factors for severe COVID-19 ≥1, n (%)	400 (88·5)	399 (88·5)	799 (88·5)
Obesity (BMI >30 kg/m^2)	195 (43·1)	193 (42·8)	388 (43·0)
Smoking	180 (39·8)	184 (40·8)	364 (40·3)
Hypertension	135 (29·9)	121 (26·8)	256 (28·3)
Diabetes	53 (11·7)	55 (12·2)	108 (12·0)
Chronic lung disease/Asthma	58 (12·8)	50 (11·1)	108 (12·0)

Cardiovascular disease	42 (9·3)	38 (8·4)	80 (8·9)
Cancer	18 (4·0)	15 (3·3)	33 (3·7)
Chronic kidney disease	10 (2·2)	9 (2·0)	19 (2·1)
Chronic liver disease	7 (1·5)	13 (2·9)	20 (2·2)
Immunocompromised state	22 (4·9)	23 (5·1)	45 (5·0)

BMI=body mass index. COVID-19=coronavirus disease 2019. FAS=full analysis set. SD=standard deviation. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2.

*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).

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

Primary efficacy endpoints and supportive estimands					
Estimand	**Population**	**AZD7442 n/N (%)**	**Placebo n/N (%)**	**RRR (95% CI)**	**p value***
Primary: severe COVID-19 or death from any cause through day 29	Non-hospitalised participants dosed ≤7 days from symptom onset (mFAS)	18/407 (4·4)	37/415 (8·9)	50·5 (14·6, 71·3)	0·010
First supportive: severe COVID-19 or death from any cause through day 29	Non-hospitalised participants dosed ≤5 days from symptom onset (EIAS)	9/253 (3·6)	27/251 (10·8)	66·9 (31·1, 84·1)	0·002
Second supportive: severe COVID-19 or death from any cause from day 4 through day 29	Non-hospitalised participants dosed ≤7 days from symptom onset (mFAS)	12/407 (2·9)	33/415 (8·0)	63·0 (29·4, 80·6)	0·002
Third supportive: severe COVID-19 or death from any cause through day 29	All randomised participants (FAS)	24/446 (5·4)	41/444 (9·2)	41·6 (5·0, 64·1)	0·028
Fourth supportive: severe COVID-19 or death from any cause through day 29	Non-hospitalised participants, who are seronegative at baseline, dosed ≤7 days from symptom onset (SNAS)	14/347 (4·0)	36/345 (10·4)	61·3 (29·7, 78·7)	0·001

Secondary efficacy endpoints		
	AZD7442	**Placebo**
Secondary: prevention of respiratory failure (mFAS)		
Participants with event, n (%)	3 (0·7)	11 (2·7)
RRR (95% CI)	71·9 (0·3, 92·1)	
Nominal p value†	0·036	
Exploratory: hospitalisation for COVID-19 including complications through day 29 (mFAS)		
Participants with event, n (%)	17 (4·1)	40 (9·5)

CI=confidence interval. CMH=Cochran-Mantel-Haenszel. COVID-19=coronavirus disease 2019. EIAS=early intervention analysis set. FAS=full analysis set. mFAS=modified full analysis set. RRR=relative risk reduction. SNAS=seronegative analysis set.

*Results from a CMH 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). RRR represents the percent reduction in incidence of severe COVID-19 or death from any cause in the AZD7442 group relative to the placebo group. A RRR >0 represents

favourable efficacy in the AZD7442 group. p<0·05 indicates a statistically significant result. Missing response data were not imputed. †p<0·05 indicates a nominally statistically significant result, as this analysis was not included in the multiple testing hierarchy.

Table 3: **Comparable safety profile between AZD7442 and placebo (SAS)**

Event	**AZD7442 (n=452)**	**Placebo (n=451)**
Any AE, n (%)*	132 (29·2)	163 (36·1)
Mild AEs	67 (14·8)	65 (14·4)
Moderate AEs	34 (7·5)	50 (11·1)
Severe AEs	22 (4·9)	30 (6·7)
Total deaths, n (%)	6 (1·3)	6 (1·3)†
Acute myocardial infarction/Acute left ventricular failure	1 (0·2)	0
Sudden cardiac death	1 (0·2)	0
COVID-19 pneumonia with outcome of death	2 (0·4)	4 (0·9)
COVID-19 with outcome of death	1 (0·2)	1 (0·2)
COVID-19 pneumonia, superinfection bacterial, septic shock	0	1 (0·2)
Malignant disease progression	1 (0·2)	0
Any SAE (including death), n (%)	33 (7·3)	54 (12·0)
Any treatment-related AE‡, n (%)	23 (5·1)	21 (4·7)
Any AE leading to study withdrawal§, n (%)	5 (1·1)	7 (1·6)
Common AEs, n (%)		
COVID-19 pneumonia	26 (5·8)	49 (10·9)
Headache	5 (1·1)	2 (0·4)
Any AESI, n (%)	15 (3·3)	15 (3·3)
Injection site pain	8 (1·8)	10 (2·2)
Injection site erythema	2 (0·4)	2 (0·4)
Injection site discomfort	2 (0·4)	1 (0·2)
Injection site bruising	1 (0·2)	1 (0·2)
Injection site haematoma	1 (0·2)	1 (0·2)
Injection site induration	1 (0·2)	0
Injection site inflammation	1 (0·2)	0
Injection site nodule	1 (0·2)	0
Injection site warmth	0	1 (0·2)

AE=adverse event. AESI=adverse event of special interest. COVID-19=coronavirus disease 2019. SAE=serious adverse event. SAS=safety analysis set. SOC=system organ class.

*Each participant is counted only once (based on their maximum reported intensity) within a treatment group. †This differs from the initial number of deaths shown in supplementary figure 1 because one death occurred after the data cutoff, but the AE began prior to the data cutoff, thus the outcome was recorded. This death is excluded from the disposition because the record itself is post data cutoff. ‡Possibly related, as assessed by the investigator. Includes AEs that occurred through end of study. §Two participants in the placebo arm discontinued from the study due to AEs. Percentages are based on the total numbers of participants in the treatment group (n). Participants with multiple events of the same preferred term are counted only once in that preferred term. Participants with events in >1 preferred term within the same SOC are counted only once in that SOC row. Includes AEs that occurred through end of study. AESIs include injection site reactions, and anaphylaxis and other serious hypersensitivity reactions, including immune complex disease. See details in protocol section 8·3·4, available as Supplementary Material.

Figure 1: Participant disposition (CONSORT flow diagram)

COVID-19=coronavirus disease 2019. FAS=full analysis set. mFAS=modified full analysis set. SAS=safety analysis set.

*Informed consent received. †This differs from the initial number of deaths shown in table 3 because one death occurred after the data cutoff, but the AE began prior to the data cutoff, thus the outcome was recorded. This death is excluded from the disposition because the record itself is post data cutoff. ‡Participants excluded from the primary analysis mFAS population comprised those hospitalised at baseline for isolation purposes (in Japan and Russia) or those randomised after 7 days of symptom onset.

Figure 2: (a) Time to severe COVID-19 or death from any cause through day 29 (mFAS), (b) Severe COVID-19 or death through day 29 by time from symptom onset to randomisation and (c) severe COVID -19 or death through day 29 by subgroups (mFAS)

CI=confidence interval. COVID-19=coronavirus disease 2019. HR=hazard ratio. mFAS=modified full analysis set. NE=not evaluable. RRR=relative risk reduction.
For panel a, 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). In panel b, day 1 symptom count started from the first day of symptoms. RRR represents the percent reduction in incidence of severe COVID-19 or death from any cause in the AZD7442 group relative to placebo. A RRR >0 represents favourable efficacy in the AZD7442 group. For panel c, arrows denote lower 95% CIs 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 chi-square test was used.