Tixagevimab–Cilgavimab EVUSHELD Intramuscular for Early Outpatient Treatment in COVID-19 Patients at High Risk of Progression (The TACKLE RCT) [1]

SUMMARY

n=910 mild-moderate, unvaccinated COVID-19 +'ve, outpatients at high-risk of progression

EVUSHELD 600 mg IM 2 consecutive IM injections, 300mg each of tixagevimab and cilgavimab given within 7 days symptom onset

vs

Placebo (normal saline solution)

Primary Endpoint Result:		
Severe COVID-19 or any cause death (favours EVUSHELD) ↓**RR ~50%; NNT≈23** /29 day follow-up	**At 89 days, the EVUSHELD group had less adverse events and serious adverse events compared to placebo.** There were 6 deaths in both groups (2 of which were CV related, both in the **EVUSHELD** group).	**Serious AEs: 7.3% vs 12.0%** (more common in placebo group) **Concerns related to: efficacy against current variants, lack of long-term safety data, cardiac adverse events.**

Bottom line: In mostly younger, mild-moderate COVID-19 patients who are unvaccinated, treatment with intramuscular **EVUSHELD** within 7 days of symptoms significantly reduced progression to severe COVID-19 or death from any cause by 29 days. Earlier treatment was better. **EVUSHELD** was well tolerated with less adverse events compared to placebo. Long-term follow-up is ongoing and will provide insights on overall safety, including cardiovascular safety.

TRIAL BACKGROUND

DESIGN: randomized (stratified by high-risk vs low-risk, days since symptom onset, and risk of progression), multinational (95 sites, 4 countries), double-blind (participants, investigators, sponsor staff were blinded; pharmacist on site was unmasked to open-label product prior to syringe masking); sponsor involvement in trial design, data collection, analysis, & writing. Trial enrollment occurred between Jan 28 and July 22, 2021. The most prominent variants during the trial were Alpha 60%, Gamma 20%, Delta 15%, other <7%); primary efficacy follow-up at 29 days; overall follow-up ongoing over 457 days. Modified ITT analysis for efficacy; per protocol analysis for safety. Funding was by AstraZeneca.

INTERVENTION: Tixagevimab 300mg + cilgavimab 300mg **EVUSHELD IM x1** vs **placebo** in mild-mod COVID-19 patients at high-risk of progression.

INCLUSION, select: ≥18 yrs of age, non-hospitalized, unvaccinated, COVID-19 positive patients (antigen or RT-PCR from respiratory tract, collected within 3 days of enrollment), with a WHO Clinical Progression Scale score of >1 to <4; receiving study drug within 7 days of mild-moderate symptom onset; a peripheral O_2 saturation of 92% or more within 24hrs of enrollment; not involved in other clinical trials for COVID-19.

EXCLUSION, select: hospitalization, history of, or current hospitalization for COVID-19 (other than for mandatory public health isolation purposes); history of severe reactions to a mAb; previous receipt of, or expected to receive a vaccine or mAb indicated for COVID-19.

POPULATION: n=910; mean age ≈ 46yrs (13% of the participants were ≥65yrs), 50% ♀; 62% White (52% Hispanic/Latinx), American Indian or Alaska Native 24%, Asian 6%, 4% Black, 5% unknown. BMI=29, time from symptom onset ~5 days, serology COVID positive 14%; **unvaccinated**, **at high-risk for progression to severe COVID-19 =89%**. **Risk factors for progression**: BMI>30 43%, smoking 40%, hypertension 28%, diabetes 12%, chronic lung or asthma 12%, CVD 9%, immunocompromised state 5%, cancer 4%, CKD 2%, chronic liver 2%. Baseline demographics: fairly well-balanced groups, however more variants of concern in placebo group e.g. Delta (**Evusheld** 3% vs Placebo 12%).

RESULTS

Follow-up @ 29days post-dose

Outcome	EVUSHELD n=407	Placebo n=415	Difference % 95% CI	NNT 95% CI	Observations and Comments
Primary Severe COVID-19* or any cause death at 29 days	18 (4.4%)	37 (8.9%)	ARR ≈ 4.5% 95% CI 1.1-8.0	**NNT≈23** 95% CI 13-91	↓ RR ≈50.5% RR 95% CI 14.6-71.3; p=0.0096 Kaplan Meier curve separates ~7 days (HR=0.49, p=0.01) Those treated sooner post symptom onset did better Subgroups: older less likely to benefit; negative baseline antibody more likely to benefit Current applicability uncertain (Omicron strain, vaccinated).
Secondary**	-	-	-	-	Trial ongoing for secondary and safety outcomes. Day 29: **Hospitalization**: 4.1% vs 9.5%; **ICU**: 0.7% vs 2.6%

* Severe COVID-19 defined as **pneumonia** (fever, cough, tachypnea/dyspnea and lung infiltrates), **or hypoxemia** (O2 saturation <90% in room air, and/or severe respiratory distress), **PLUS a WHO Clinical Progression scale score ≥5**.

**Key secondary endpoint is a composite of death from any cause or hospitalisation for COVID-19 complications or sequelae during the 169-day post-dose period.

RESULTS

Safety Analysis	EVUSHELD N=452	Placebo* N=451	Difference %	Comments (Median initial safety follow-up ~84 days)
Any Adverse Event (AE)	132 (29%)	163 (36%)	-7%	Evusheld well tolerated: both AEs and SAEs were less in the treatment group compared to placebo control.* There were 6 deaths in each group in longer follow-up period. - In the Evusheld group, 2 deaths were cardiac related (compared to 0; of some interest given PROVENT data). - Placebo group, all 6 COVID-19 related e.g. pneumonia, other infection, compared to 3 in the Evusheld group. Long term efficacy/safety follow-up ongoing (169/456 days).
Any AE leading to study withdrawal	5 (1%)	7 (2%)	-1%	
COVID-19 pneumonia	26 (6%)	49 (11%)	-5%	
Headache	5 (1.1%)	2 (0.4%)	0.7%	
Any Serious Adverse Event (SAE)	33 (7.3%)	54 (11.9%)	-4.6% **NNT≈22** 95% CI 13-26	
Death from any cause (per Table 3)	6 (1%)	6 (1%)	-	

***Note:** higher rate of AEs, and serious AEs in placebo group relate largely to the group having more COVID-19 related symptoms.

STRENGTHS, LIMITATIONS, & UNCERTAINTIES

STRENGTHS:

- There was a large proportion of representation from Hispanic and American Indian and Alaska Native participants.
- Trial had global representation

LIMITATIONS:

- Protocol amended to allow for lower power, less precision (wider confidence intervals) in results.
- Primary analysis ensured that assessment of efficacy was only in non-hospitalized patients. This, in combination with the slightly longer time since symptom onset in the placebo group, could bias the results in favour of the treatment group.
- Short duration of follow-up for efficacy, and interim results for safety (especially given long half-life of ~90 days).
- Older adults, and those with impaired immune systems, were not well represented. These are the groups that are most vulnerable.
- Benefit predominantly driven by Hispanic or Latino ethnicity in Latin America where baseline balance appears to be off (larger representation in placebo group vs treatment group)?
- Low representation of Black and African American populations (of note given their increased risk)
- Sponsor blinded but had the right to break the code for unexpected SAEs.
- There has been controversy/uncertainty around pre-exposure prophylaxis dosing/changes & susceptibilities (e.g. per updates from manufacturer and FDA)[4]

UNCERTAINTIES

- Did the higher percentage of the Delta variant in the placebo group (12%) vs treatment group (3%) bias the results in favour of the drug?
- Trial data represents a window of time where variants other than Omicron would have been most prevalent. Is **EVUSHELD** effective against currently circulating COVID-19 subvariants for e.g., Omicron? (Some recent data with drugs with similar mechanism suggest fall in efficacy.)
  (Dose used in this trial for treatment was double that of the **PROVENT** prevention trial. The optimal dose needed is uncertain and may vary.)
  How does efficacy and safety compare to alternative antiviral treatments (e.g. **PAXLOVID**)?
  Do the 2 cardiovascular related deaths (in the longer follow-up safety data), both in the **EVUSHELD** group, further substantiate the concern for potential cardiovascular harm as raised in the **PROVENT** trial?
- Given a relatively younger (mean age 46), population, would cardiovascular concerns be more evident in an older, higher risk group?
- What is the impact of treatment emergent antidrug antibodies as seen in 5% of those who received **EVUSHELD** up to 84 days?
- What is the quality and duration of the immune response to vaccination after receiving **EVUSHELD**?
- Did access to COVID-19 vaccines change during the trial reflecting participants' desire to get vaccinated?
- Would **EVUSHELD** still be effective in patients with a higher likelihood of past history of COVID-19 infection (now the case for many Canadians)?
- Would **EVUSHELD** still be effective in vaccinated individuals?
- How does **EVUSHELD** compare to alternate therapy options? (Lack head-to-head trials, but some suggestion of less relative effectiveness.)
- Does **EVUSHELD** affect the efficacy or safety of other COVID-19 therapeutics such as **nirmatrelvir-ritonavir PAXLOVID** or **remdesivir VEKLURY**? e.g. What is the impact on other COVID-19 therapies?

INSIGHTS FROM PRELIMINARY REAL-WORLD EVUSHELD PREVENTION DATA (RETROSPECTIVE COHORT STUDY, US DEPT VA)[2]

- Although this study is an observational, retrospective, evaluation of **EVUSHELD** as a *preventative* treatment option, it offers some preliminary (pre-print) insights that await peer review and full publication. 1) Demonstrated preventative effectiveness after the emergence of Omicron variants, 2) inclusion of a high number of immunocompromised patients, 3) inclusion of predominantly vaccinated individuals (73% had 3+ mRNA doses, or 2 doses of Ad26COV2). Pre-print results suggest that in this high-risk group, preventative administration of **EVUSHELD** resulted in a benefit on both COVID-19 hospitalization (HR 0.13, 95% CI = 0.02-0.99) and all-cause mortality (HR 0.36, 95% CI = 0.18-0.73). Funding was from the VA, independent of the manufacturer. Due to the pre-print nature of publication, caution is warranted in interpreting the results.

SHARED DECISION MAKING

- Patient values, risk of COVID-19, risk of progressing to severe outcomes, potential to benefit vs harm, degree of certainty vs uncertainty.

ACKNOWLEDGEMENTS: Written by Loren D Regier. Thanks to our Trial Summary Reviewers: A Crawley, M LeBras, T McLeer, C Bell, K Boechler, Dr. S Lee.

Abbreviations, select: AE=adverse events DI=drug interaction CI=confidence interval **NNT**=number needed to treat **RCT**=randomized controlled trial RR=relative risk, SAE=serious adverse events

References:

1) Montgomery H, Hobbs FDR, Padilla F, et al. **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.** *Lancet Respir Med.* 2022; (published online June 7.) Accessed 10 Jun 2022 at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9173721

2) Young-Xu Y, Epstein L, Marconi VC, Davey V, Zwain G, Smith G, et al. **Tixagevimab/Cilgavimab for Prevention of COVID-19 during the Omicron Surge: Retrospective Analysis of National VA Electronic Data** medRxiv 2022.05.28.22275716; doi: https://doi.org/10.1101/2022.05.28.22275716

3) **FDA. FACT SHEET FOR HEALTHCARE PROVIDERS**: EMERGENCY USE AUTHORIZATION FOR EVUSHELD (tixagevimab co-packaged with cilgavimab). 2022. https://www.fda.gov/media/154701/download

4) **Links re dosing updates from manufacturer and FDA (pre-exposure prophylaxis).** 1) Update on FDA adjustment to Evusheld dosage regimen in US (astrazeneca.com) ; 2) FDA authorizes revisions to Evusheld dosing | FDA

Additional info:

Full inclusion criteria

Participants were eligible for trial inclusion only if all the below criteria were met:

• Aged ≥18 years.

• Documented laboratory-confirmed SARS-CoV-2 infection, as determined by molecular test (antigen or nucleic acid) from any respiratory tract specimen collected ≤3 days prior to day 1. The antigen tests were validated SARS-CoV-2 nucleocapsid antigen assays operated by an authorised laboratory.

• World Health Organisation (WHO) Clinical Progression Scale score >1 and <4. In response to health authority feedback recommending that a minimum score of <0 on the Clinical Progression Scale is not appropriate, the criteria for inclusion was changed from score >0 and <4 to >1.

• Participant must be dosed with investigational medicinal product (IMP) ≤7 days from self-reported onset of COVID-19–related symptoms (mild to moderate COVID) or measured fever, defined as the self-reported date of first reported sign/symptom from the following:

- Subjective fever or feeling feverish
- Cough
- Shortness of breath or difficulty breathing at rest or with activity
- Sore throat
- Myalgia
- Fatigue
- Headache
- Chills
- Nasal obstruction or congestion
- Nasal discharge
- New loss of taste or smell
- Nausea or vomiting
- Diarrhoea
- Documented temperature >37·8°C
- New onset confusion (only for patients ≥60 years old)
- Appetite loss or decreased food intake (only for patients ≥60 years old)
- Increased supplemental oxygen requirement (only for patients on baseline supplemental oxygen)

• ≥1 of the following signs/symptoms must be present within 24 h prior to day 1:

- Cough
- Sore throat
- Shortness of breath or difficulty breathing at rest or with activity
- Myalgia
- Fatigue
- Headache
- Chills
- Nasal obstruction or congestion
- Nasal discharge
- Nausea or vomiting
- Diarrhoea
- New loss of taste or smell

• Oxygen saturation of ≥ 92% obtained at rest by study staff within 24 h prior to day 1, unless the potential patient regularly receives chronic supplementary oxygen for an underlying lung condition.

• Agreement not to participate 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 entry, whichever is earliest.

• Male participants must use a condom from day 1 and agree to continue through 90 days following administration of IMP.

• Female participants of childbearing potential must use one highly effective form of birth control, defined as one that can achieve a failure rate of <1% per year when used consistently and correctly. All women of childbearing age must have a negative pregnancy test result at visit 1 and during the study.

• Participants must be able to understand and comply with study requirements/procedures (if applicable, with assistance by caregiver, surrogate, or legally authorised representative) based on the assessment of the investigator.

• All participants must provide signed informed consent, if able. Participants considered clinically unable to consent at screening and who are entered by consent of a legally acceptable representative must show evidence of assent, as applicable, in accordance with local regulations.

Full exclusion criteria

Participants were excluded from the study if any of the below criteria applied:

• History of or current hospitalisation for COVID-19. Hospitalisation is defined as ≥24 h of acute care, in a hospital or similar acute care facility, including emergency rooms, temporary facilities, and hospital care at home. Sites that allowed patients to be admitted for isolation/public health purposes did not meet the protocol definition of hospitalised.

• Current need for hospitalisation or immediate medical attention in a clinic or emergency room service in the clinical opinion of the site investigator.

• Previous hypersensitivity, infusion-related reaction, or severe adverse reaction following administration of a monoclonal antibody.

• Any prior receipt of investigational or licensed vaccine or other monoclonal antibody/biologic indicated for the prevention of SARS-CoV-2 or COVID-19 prior to study entry or expected administration immediately after enrolment.

• Requirement for mechanical ventilation or anticipated impending need.

• Clinically significant bleeding disorder, or prior history of significant bleeding or bruising following intramuscular (IM) injections or venipuncture.

• Any other significant disease, disorder, or finding that may significantly increase the risk to the participant because of participation in the study, affect the ability of the participant to participate, or impair interpretation of the study data.

• Known allergy/sensitivity or any hypersensitivity to components of the IMP or placebo.

• Any comorbidity requiring surgery within 7 days prior to study entry, or that is considered life-threatening in the opinion of the site investigator within 30 days prior to study entry.

• Use of any prohibited medication within 30 days or five half-lives, whichever is longer, prior to study entry.

• Receipt of convalescent COVID-19 plasma treatment at any time prior to study entry.

• Receipt of systemic steroids or inhaled steroids within 30 days prior to study entry unless a stable dose is used for chronic condition.

• Receipt of any IMP in the preceding 90 days or five half-lives, whichever is longer, or expected receipt of IMP during study follow-up, or concurrent participation in another interventional study.

• Judgement by investigator that the participant should not participate as they are unlikely to comply with study procedures, restrictions, and requirements.

• Previous randomisation in the present study.

• Pregnancy or breastfeeding in female participants.

• Blood drawn in excess of a total of 450 mL (1 unit) for any reason within 30 days prior to randomisation.

• Employees of the sponsor involved in planning, executing, supervising, or reviewing the AZD7442 program, clinical study site staff, or any other individuals involved with the conduct of the study, or immediate family members of such individuals.

• In nations, states, or other jurisdictions that, for legal or ethical reasons, bar the enrolment of participants who lack capacity to provide their own informed consent, such participants were excluded.

Definition of being at high-risk of progression to severe COVID-19

Persons aged ≥65 years at randomisation.

Persons aged <65 years and having ≥1 of the following conditions:

- Cancer
- Chronic lung disease or moderate to severe asthma
- Obesity (body mass index ≥30; may be based on self-report of recent height and weight measurement)
- Hypertension
- Cardiovascular disease (including history of smoke)
- Diabetes
- Chronic kidney disease
- Chronic liver disease
- Immunocompromised state from solid organ transplant, blood or bone marrow transplant, immune deficiencies, human immunodeficiency virus, use of corticosteroids, or use of other immunosuppressive medicines
- Sickle cell disease
- Smoking (current or former)