EVIDENCE SUMMARY

RESEARCH QUESTION: Among COVID-19 patients, should tixagevimab-cilgavimab be used for treatment?

Review by: Liza Marie P. Bejemino, MD, Natasha Ann R. Esteban-Ipac, MD, Mario M. Panaligan, MD, Ivan N. Villespin, MD, Arnel Gerald Q. Jiao, MD, Marissa M. Alejandria, MD, MSc

RECOMMENDATIONS

Recommendations	Certainty of Evidence	Strength of Recommendation
We suggest the use of tixagevimab-cilgavimab as treatment for unvaccinated non-hospitalized patients with mild to moderate COVID-19 with at least 1 risk factor* for progression to severe disease. *Risk factors for severe COVID-19: age ≥65 years, body-mass index ≥35kg/m^2, cardiovascular disease (including hypertension), chronic lung disease (including asthma), chronic metabolic disease (including diabetes), chronic kidney disease (including receipt of dialysis), chronic liver disease, and immunocompromised conditions	Very low	Weak
We suggest the use of tixagevimab-cilgavimab as treatment for unvaccinated hospitalized COVID-19 patients in addition to standard of care.	Low	Weak
We suggest against the use of tixagevimab-cilgavimab among children with COVID-19.	Very low	Weak

Consensus Issues

The consensus panel gave a weak recommendation supporting the use of tixagevimab-cilgavimab among unvaccinated, non-hospitalized and hospitalized adult patients with COVID-19 due to low certainty of evidence, applicability issues, and the drug's prohibitive cost. The panel emphasized that both trials on tixagevimab-cilgavimab were done at a time when Delta was the predominant variant, hence the results may have limited applicability because Omicron is now the predominant variant locally. The panel also highlighted the fact that the benefits are among the unvaccinated patients, while most of the patients in our country are already vaccinated. The cost of a full treatment course consisting of one (1) intravenous dose of tixagevimab-cilgavimab was estimated at around ₱28,000 based on an international report. The panel saw that there are more cost-effective treatment options presently available in the local market. Clinicians are advised to ensure due diligence in discussing with their patients the drug's perceived benefits in light of the low certainty of evidence and the trials' applicability issues.

Since there are no available studies of use of tixagevimab cilgavimab among children, and no FDA approval has been granted, suggesting against the use of the drug among children will be more beneficial.

KEY FINDINGS

- There were two randomized controlled trials that compared tixagevimab-cilgavimab against placebo as treatment for COVID-19 infection.
- Tixagevimab-cilgavimab significantly reduced death (all-cause mortality) at day 28 (RR of 0.65, 95% CI 0.46-0.93) and day 90 (RR of 0.72, 95% CI 0.53-0.97) compared to those given placebo.
- There was no significant difference in the risk of adverse events (RR 0.91, 95% CI 0.74-1.11) and serious adverse events among those given tixagevimab-cilgavimab compared to the placebo group (RR 0.72, 95% CI 0.50-1.04).
- The overall certainty of evidence was rated very low due to serious risk of bias downgraded for indirectness, attrition bias, inconsistency, and imprecision in one critical outcomes (all-cause mortality) among non-hospitalized patients.
- No available studies are available for children and adolescents.

INTRODUCTION

While the nationwide roll-out of COVID-19 vaccination reduced hospitalizations and death from COVID-19, SARS-CoV-2 infection continues to spread, as variants continue to emerge putting individuals at risk of COVID-19 particularly unvaccinated individuals and individuals with the inability to mount an adequate immune response following vaccination [1-4].Thus the need for new therapies that serve as alternative options for the treatment of COVID-19 infection particularly for those at increased risk of severe or critical disease.

Tixagevimab-cilgavimab is a combination of two fully human, long-acting SARS-CoV-2-neutralizing monoclonal antibodies (mAbs) namely tixagevimab (AZD8895) and cilgavimab (AZD1061) [5-8]. Individually, they prevent the spike protein from binding to angiotensin-converting enzyme 2 (ACE2) receptor and block cell entry of the virus [5-8]. These two potent neutralizing antibodies against SARS-CoV-2 were isolated from the B cells of individuals with prior SARS-CoV-2 infection and bind simultaneously to distinct non-overlapping epitopes on the spike protein receptor binding (RBD) which provides protection against symptomatic infection and have also been shown to limit the progression of SARS-CoV-2 infection [5-8]. Collectively, they build a higher barrier to viral escape and a larger extent of coverage, resulting to neutralization of all known SARS-CoV-2 variants of concern (Alpha, Beta, Gamma, and Delta) [7]. SARS-CoV-2 neutralizing antibody titers in sera conferred by AZD7442 were considerably higher than titers associated with convalescent plasma [9-11]. In a non-human primate model of SARS-CoV-2 infection, therapeutic AZD7442 administration accelerated viral clearance from the lungs [12].

REVIEW METHODS

A systematic search was done on Pubmed (Medline), Cochrane Library (CENTRAL), Google Scholar until September 16, 2022 with a combined MeSH and free text search using the terms coronavirus infections, COVID-19, severe acute respiratory syndrome coronavirus 2 or SARS-CoV-2, and AZD7442 or "tixagevimab-cilgavimab" OR "cilgavimab and tixagevimab drug combination" OR "cilgavimab and tixagevimab drug combination". The COVID-NMA Living Data was also checked and a search for ongoing studies in the NIH clinicaltrials.gov and various trial registries was done. Preprints using medrxiv, chinaxiv and biorxiv were also searched. There were no limits used in the search. Only 2 randomized controlled trials that compared tixagevimab-cilgavimab against placebo or standard of care for treatment of COVID-19 were included in this review. A search for studies in children was also done but there were no studies found.

RESULTS

Characteristics of included studies

There were two randomized controlled trials that compared tixagevimab-cilgavimab against placebo as treatment for COVID-19. One trial assessed non-hospitalized patients (outpatients) while the other assessed hospitalized patients. The study on non-hospitalized patients is an ongoing, phase 3 multicenter, double-blind, randomized, placebo-controlled trial, assessing the safety and efficacy of a single dose tixagevimab-cilgavimab given as two consecutive intramuscular injections (one containing tixagevimab 300mg and the other containing cilgavimab 300mg) among unvaccinated patients with mild to moderate COVID-19. The trial is being conducted at 95 sites in United States, Latin America, Japan, and United Kingdom. The primary endpoints were severe COVID-19 or death from any cause through day 29 and safety [13].

The study on hospitalized patients is a randomized, double-blind, phase 3, placebo-controlled trial of adults with symptoms for up to 12 days and hospitalized for COVID-19 at 81 sites in the USA, Europe, Uganda, and Singapore. Patients received intravenous tixagevimab 300mg-cilgavimab300mg or placebo, in addition to remdesivir and other standard care such as corticosteroid [14].

Certainty of evidence

The overall certainty of evidence was rated very low due to indirectness and serious risk of bias downgraded for attrition bias and inconsistency in critical outcomes of all-cause mortality among non-hospitalized patients. The risk of bias summary is in Appendix 4. The GRADE evidence profile is in Appendix 5.

Effectiveness outcomes

Mortality
Tixagevimab-cilgavimab significantly reduced all-cause mortality at day 28 (RR of 0.65, 95% CI 0.46-0.93, I^2=0%) and at day 90 (RR of 0.72, 95% CI 0.53-0.97, I^2=0%) compared to those given placebo. Subgroup analysis based on hospital status show that mortality is significantly reduced among those hospitalized patients given intravenous tixagevimab-cilgavimab at day 28 (RR 0.62, 95% CI 0.43-0.91) and at day 90 (RR 0.70, 95% CI 0.51-0.96) but not among those given intramuscularly in the outpatient (RR 1.00, 95% CI 0.32-3.06).

OUTPATIENTS
Composite outcome of severe COVID-19 or death
Among outpatients with mild to moderate COVID-19, tixagevimab-cilgavimab significantly reduced the composite outcome of severe COVID-19 or death by day 28 (RR 0.58, 95% CI 0.36-0.95, 1 study, n=910) compared to placebo. A subgroup analysis based on age show that tixagevimab-cilgavimab had significant reduction in the composite outcome of severe COVID-19 or death among those less than 65 years old (RR 0.35, 95% CI 0.17-0.71) but not among those 65 years and above (RR 1.06, 95% CI 0.43-2.61). Another subgroup analysis based on risk group shows that tixagevimab-cilgavimab reduces severe COVID-19 or death among high-risk patients (RR 0.53, 95% CI 0.30-0.93) and not among low-risk patients (RR 0.26, 95% CI 0.03-2.20). A subgroup analysis also shows that tixagevimab-cilgavimab reduced severe COVID-19 or death among those with at least one COVID-19 comorbidity (RR 0.46, 99% CI 0.25-0.83) but not among those without any comorbidities (RR 0.80, 95%CI 0.19-3.38).

Other outcomes
Among outpatients with mild to moderate COVID-19, tixagevimab-cilgavimab significantly prevented respiratory failure (RR 0.28, 95% CI 0.08-0.99) and hospitalization for COVID-19 including its complications (RR 0.43, 95% CI 0.25-0.75). However, there was no significant difference in viral negative conversion by day 7 among those given tixagevimab-cilgavimab and placebo (RR=1.38, 95% CI 0.92-2.07).

HOSPITALIZED PATIENTS

Among hospitalized patients given tixagevimab-cilgavimab in addition to standard of care, there is significant reduction of all-cause mortality at day 28 (RR 0.62, 95% CI 0.43-0.91) and at day 90 (RR 0.70, 95% CI 0.51-0.96) compared to those given placebo in addition to standard of care.

Subgroup analysis based on vaccination status showed statistically significant reduction of all-cause mortality at day 28 (RR 0.54, 95% CI 0.33-0.87) among unvaccinated hospitalized patients given tixagevimab-cilgavimab in addition to standard of care but showed no significant effect for mortality at day 28 among fully vaccinated (RR 0.98, 95% CI 0.48-2.01) and partially vaccinated (RR 0.55, 95% CI 0.17-1.75) hospitalized patients. Another subgroup analysis done for mortality at day 90 showed no significant effect for among fully vaccinated (RR 0.75, 95% CI 0.38-1.46), partially vaccinated (RR 0.55, 95% CI 0.20-1.54) nor unvaccinated (RR 0.72, 95% CI 0.49-1.04) hospitalized patients given tixagevimab-cilgavimab in addition to standard of care.

Likewise, there is no significant difference in sustained recovery or clinical improvement at day 28 among hospitalized patients given tixagevimab-cilgavimab in addition to standard of care (RR 1.02, 95% CI 0.96-1.08) nor sustained recovery up to day 90 (RR 1.02, 95% CI 0.98-1.07). A subgroup analysis by age, baseline pulmonary category/oxygen status, immunosuppression status and COVID-19 vaccination status, all show that tixagevimab-cilgavimab has no significant effect on sustained recovery or clinical improvement up to 90 days.

Tixagevimab-cilgavimab also did not have significant benefit in improving the pulmonary ordinal scale or WHO progression score level 7 or above at day 28 among hospitalized patients (RR 0.80, 95% CI 0.60-1.07).

Safety

There was no significant difference in the tixagevimab-cilgavimab group compared to the placebo group for adverse events (RR 0.91, 95% CI 0.74-1.11, I^2=72%) but with significant heterogeneity. Subgroup analysis show that outpatients or those given the drug via intramuscular route had significantly less adverse events reported (RR 0.81, 95% CI 0.67-0.97) while those hospitalized and received the drug via IV route had no significant difference with the placebo (RR 0.99, 95% CI 0.89-1.11). Most of the adverse events were mild or moderate in intensity. The most common adverse event reported was injection-site reaction among the outpatient, while most of the adverse events reported among the hospitalized patients were related to respiratory-thoracic-mediastinal, GI, and nervous system.

Patients given tixagevimab-cilgavimab had no significant difference for serious adverse events compared to patients given placebo (RR 0.72, 95% CI 0.50-1.04, I^2=30%). A subgroup analysis shows that outpatients or those given via intramuscular route had significantly less serious adverse events reported (RR 0.61, 95% CI 0.40-0.92) while those hospitalized or given intravenously had no significant difference with those given placebo (RR 0.88, 95% CI 0.56-1.39). Serious adverse events reported were pneumonia, cardiac disorders, other infections, and death. No deaths were considered to be related to tixagevimab-cilgavimab.

For hospitalized patients, there was statistically significant benefit for composite safety outcome (composite of death, serious adverse events, incident organ failure, and serious co-infection) up to day 90 (RR 0.83, 95% CI 0.70-0.98) but there was no statistically significant difference for composite safety outcome up to day 28 (RR 0.90, 95% CI 0.77-1.04).

RECOMMENDATIONS FROM OTHER GROUPS

The US NIH Panel recommends the use of anti-SARS-CoV-2 mAbs for patients with high-risk conditions that have been represented in clinical trials evaluating anti-SARS-CoV-2 mAbs and for patients with conditions that have had limited representation in clinical trials but are considered a high risk for progression to severe COVID-19 [19]. The Australian Living Guidelines consider (conditional recommendation) using tixagevimab plus cilgavimab within 5 days of symptom onset in unvaccinated adults with COVID-19 who do not require oxygen and who have one or more risk factors for disease progression [20]. The American Academy of Pediatrics (AAP), Infectious Diseases Society of America (IDSA), National Comprehensive Cancer Network (NCCN), American College of Rheumatology (ACR), and American Society of Transplantation (AST) has no recommendation for treatment but suggest pre-exposure prophylaxis with tixagevimab/cilgavimab rather than no tixagevimab-cilgavimab, when predominant regional variants are susceptible to the agent in moderately or severely immunocompromised individuals at increased risk for inadequate immune response to COVID-19 vaccine or for persons for whom COVID-19 vaccine is not recommended due to a documented serious adverse reaction to the vaccine (Conditional recommendation, Low certainty of evidence) [21-28]. The WHO, Surviving Sepsis Campaign Guidelines, American Thoracic Society/European Respiratory Society has no recommendation on the use of AZD7442 as treatment or as pre-exposure prophylaxis for COVID-19 infection.

Table 1. Recommendations on the Use of AZD7442 as Treatment for COVID 19 Infection

Group / Agency	Recommendation	Strength of Recommendation / Quality of Evidence
Australian Living Guidelines	Treatment Consider using tixagevimab plus cilgavimab within 5 days of symptom onset in unvaccinated* adults with COVID-19 who do not require oxygen and who have one or more risk factors for disease progression. In addition to at-risk unvaccinated adults, also consider using tixagevimab plus cilgavimab within 5 days of symptom onset in adults with COVID-19 who do not require oxygen and are immunocompromised; or are at particularly high risk of severe disease on the basis of advanced age and multiple risk factors. Do not use tixagevimab plus cilgavimab for the treatment of COVID-19 in pregnant or breastfeeding women outside of randomized trials with appropriate ethical approval.	Conditional recommendation (UPDATED 27 July 2022)
US NIH Guidelines	**Recommends AZD7442 as SARS-CoV-2 Post-exposure Prophylaxis for Certain Adults and Adolescents**	(UPDATED 10 November 2022)
	Post-Exposure Prophylaxis For people exposed to individuals with SARS-CoV-2 infection, do not use tixagevimab plus cilgavimab for post-exposure prophylaxis outside of randomized trials with appropriate ethical approval.	
Infectious Diseases Society of America (IDSA) (Updated November 21, 2022), American Academy of Pediatrics (AAP) National	No Recommendation on treatment but with recommendation on pre-exposure prophylaxis aligned with the US FDA EUA (Updated October 2022): PRE-EXPOSURE PROPHYLAXIS For pre-exposure prophylaxis of COVID-19 in adults and pediatric individuals (≥12 years of age and weighing ≥40):	

Comprehensive Cancer Network (NCCN), American College of Rheumatology (ACR), American Society of Transplantation (AST), European Medicines Agency EMA's Human Medicines Committee (CHMP:Committee for Medicinal Products for Human Use), French National Authority for Health (HAS), UK Medicines and Healthcare products Regulatory Agency (MHRA), Singapore National Center for Infectious Disease (NCID) guidelines on pre-exposure prophylaxis for COVID-19, Malaysia Interim guidelines for AZD7442 as pre-exposure prophylaxis in COVID-19, Department of Disease Control Thailand	Who are not currently infected with SARS-CoV-2 and who have not had a known recent exposure to an individual infected with SARS-CoV-2 AND Who have moderate to severe immune compromise due to a medical condition or receipt of immunosuppressive medications or treatments and may not mount an adequate immune response to COVID-19 vaccination OR For whom vaccination with any available COVID-19 vaccine, according to the approved or authorized schedule, is not recommended due to a history of severe adverse reaction (e.g., severe allergic reaction) to a COVID-19 vaccine(s) and/or COVID-19 vaccine component(s) **Additional Warning:** Risk for COVID-19 Due to SARS-CoV-2 Viral Variants Not Neutralized by EVUSHELD Certain SARS-CoV-2 viral variants may not be neutralized by monoclonal antibodies such as tixagevimab and cilgavimab, the components of EVUSHELD. EVUSHELD may not be effective at preventing COVID-19 caused by these SARS-CoV-2 viral variants.
WHO, Surviving Sepsis Campaign Guidelines, American Thoracic Society/European Respiratory Society	No Recommendation

ONGOING TRIALS

There are currently 8 ongoing randomized clinical trials on tixagevimab-cilgavimab evaluating the efficacy and safety of the drug when used as treatment for COVID-19 (Appendix 7). One of these studies include adolescents 16 years old and above.

ADDITIONAL CONSIDERATIONS FOR EVIDENCE TO DECISION (ETD) PHASE

COST

US purchased a total of 1.7 million doses from Astrazeneca for a total cost of $855 million, making the individual cost of Evusheld at approximately $502 (₱28,614) per dose. The cost of tixagevimab-cilgavimab is being subsidized by the US government and distributed to eligible individuals [17]. As of writing, pharmaceutical company has not yet released or published a cost for AZD7442 or tixagevimab-cilgavimab.

PATIENT'S VALUES AND PREFERENCE, EQUITY, ACCEPTABILITY, AND FEASIBILITY

Both trials were conducted prior to the emergence of the omicron variant hence efficacy against the omicron variant cannot be derived from these trials. However, tixagevimab-cilgavimab has been shown to retain neutralizing activity against omicron in in vitro studies. The major variant of concern during the study period of the trials was delta.

The US FDA issued an emergency use authorization (EUA) last December 8, 2021 to tixagevimab-cilgavimab (AstraZeneca's Evusheld) for pre-exposure prophylaxis of individuals aged ≥12 years (weighing at least 40kg) who have moderate to severe immune compromise due to a medical condition or receipt of immunosuppressive medications or treatments and may not mount an adequate immune response to COVID-19 vaccination, or have a history of severe adverse reactions to a COVID-19 vaccine and/or its component. Furthermore, the product is authorized for emergency use for individuals who are not currently infected with SARS-CoV-2 and who have not had a known recent exposure to an individual infected with

SARS-CoV-2. However, US FDA has not yet authorized the use of tixagevimab-cilgavimab (AstraZeneca's Evusheld) in individuals as treatment for COVID-19 infection [15].

The US FDA last June 29, 2022 revised its dosing guidelines recommending repeat dosing with 300mg of tixagevimab and 300mg cilgavimab in cases where patients require ongoing protection from COVID-19. EUA was updated on February 24, 2022. The dosing regimen was revised because available data indicate that a higher dose of Evusheld may be more likely to prevent infection by the COVID-19 Omicron subvariants BA.1 and BA.1.1 than the originally authorized dose. EUA was updated on October 3, 2022 and they added a warning namely the risk for COVID-19 due to SARS-CoV-2 viral variants were not neutralized by EVUSHELD [16].

As of writing, the drug is not available and has no emergency use authorization from the Philippine FDA.

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Appendix 1: Preliminary Evidence to Decision

Table 1. Summary of initial judgements prior to the panel discussion (N=10/10)

FACTORS	JUDGEMENT					RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No	Yes				COVID-19 has affected millions of people worldwide and has caused substantial mortality and morbidity. While the nationwide rollout of COVID-19 vaccination reduced hospitalizations and death from COVID-19, SARS-CoV-2 infection continues to spread, as variants continue to emerge putting individuals at risk of COVID-19
Benefits	Large	Moderate	Small	Uncertain		Pooling the studies for treatment showed statistically significant benefit for those given tixagevimab-cilgavimab combination therapy compared to those given placebo for death (all-cause mortality) at D28 (RR of 0.65, 95% CI 0.46-0.93) and at D90 (RR of 0.72, 95% CI 0.53-0.97). Subgroup analysis of hospitalized patients given tixagevimab-cilgavimab as treatment in addition to standard of care showed statistically significant benefit for death (all-cause mortality) at D28 (RR 0.62, 95% 0.43-0.91) and at D90 (RR 0.70, 95% CI 0.51-0.96). The results showed statistically significant benefit for outpatients given AZD7442 (tixagevimab-cilgavimab) compared to those given placebo for severe COVID 19 or death at D28 (RR 0.58, 95% CI 0.36-0.95); prevention of respiratory failure (RR 0.28, 95% CI 0.08-0.99) and hospitalization including complications (RR 0.43, 95% CI 0.25-0.75). A subgroup analysis based on age show that tixagevimab-cilgavimab had significant reduction in the composite outcome of severe COVID-19 or death among those less than 65 years old (RR 0.35, 95% CI 0.17-0.71); high-risk patients (RR 0.53, 95% CI 0.30-0.93) and among those with at least one COVID-19 comorbidity (RR 0.46, 99% CI 0.25-0.83)
Harm	Large	Small	Uncertain			Pooling the studies showed no statistically no significant difference in the risk of serious adverse events among those given tixagevimab-cilgavimab compared to the placebo group (RR 0.91, 95% CI 0.74-1.11).

Certainty of Evidence	High	Moderate	Low	Very low			The overall certainty of evidence for the pooled studies was rated low due to serious risk of bias downgraded for attrition bias and inconsistency in one critical outcome (adverse events) and attrition bias and imprecision in another critical outcome (negative viral conversion at D7) .
Balance of effects	Favors drug (9)	Does not favor drug (1)	Uncertain				There is net potential benefit in terms of death (all-cause mortality) at D28 for both outpatient and hospitalized patients and severe COVID 19 or death at D28 (RR 0.58, 95% CI 0.36-0.95); prevention of respiratory failure (RR 0.28, 95% CI 0.08-0.99) and hospitalization & complications (RR 0.43, 95% CI 0.25-0.75) for outpatients.with no significant difference on adverse events and serious adverse events.
Values	Important uncertainty or variability (2)	Possibly important uncertainty or variability (3)	Possibly NO important uncertainty or variability (5)	No important uncertainty or variability			
Resources Required	Uncertain	Large cost (10)	Moderate Cost	Negligible cost	Moderate savings	Large savings	US purchased a total of 1.7 million doses from Astrazeneca for a total cost of $855 million, making the individual cost of Evusheld at approximately $502 (₱28,614) per dose. Proper storage conditions indicate that they must be stored in their original packaging to remain protected from light, and must remain at temperatures between 36° and 48° F, or 2° to 8° C.

Certainty of evidence of required resources	No included studies (1)	Very low	Low (7)	Moderate	High (2)		• There is low certainty of evidence on the cost of tixagevimab-cilgavimab treatment. • The cost was derived from Fierce Pharma News Report. • At present, the pharma company (Astrazeneca) has not yet issued a cost.

Cost effectiveness	No included studies (6)	Favors the comparison	Does not favor either the intervention or the comparison (1)	Favors the intervention (3)		● The trial did not assess cost effectiveness.
Equity	Uncertain (3)	Reduced (3)	Probably no impact	Increased (4)		
Acceptability	Uncertain (7)	No	Yes (3)			
Feasibility	Uncertain (6)	No (1)	Yes (3)			

Additional Considerations / Comments:

- The drug currently has no emergency use authorization from the Philippine FDA, thus may only be used in the context of clinical trials.
- There is need for more data on the drug's effectivity against variants.

Appendix 2: Search Strategy

DATABASE	SEARCH STRATEGY / SEARCH TERMS	DATE AND TIME OF SEARCH	RESULTS	
			Yield	Eligible
Medline	((“coronavirus”[MeSH Terms] OR “coronavirus”[All Fields] OR “coronaviruses”[All Fields] OR (“covid 19”[All Fields] OR “covid 19”[MeSH Terms] OR “covid 19 vaccines”[All Fields] OR “covid 19 vaccines”[MeSH Terms] OR “covid 19 serotherapy”[All Fields] OR “covid 19 serotherapy”[Supplementary Concept] OR “covid 19 nucleic acid testing”[All Fields] OR “covid 19 nucleic acid testing”[MeSH Terms] OR “covid 19 serological testing”[All Fields] OR “covid 19 serological testing”[MeSH Terms] OR “covid 19 testing”[All Fields] OR “covid 19 testing”[MeSH Terms] OR “sars cov 2”[All Fields] OR “sars cov 2”[MeSH Terms] OR “severe acute respiratory syndrome coronavirus 2”[All Fields] OR “ncov”[All Fields] OR “2019 ncov”[All Fields] OR ((“coronavirus”[MeSH Terms] OR “coronavirus”[All Fields] OR “cov”[All Fields]) AND 2019/11/01:3000/12/31[Date – Publication])) OR (“sars cov 2”[MeSH Terms] OR “sars cov 2”[All Fields] OR “sars cov 2”[All Fields]) OR (“sars cov 2”[MeSH Terms] OR “sars cov 2”[All Fields] OR “ncov”[All Fields])) AND “tixagevimab-cilgavimab”[All Fields]) OR (“cilgavimab and tixagevimab drug combination”[Supplementary Concept] OR “cilgavimab and tixagevimab drug combination”[All Fields] OR “azd7442”[All Fields])	9/16/22	42	3 (2 on treatment ; 1 on prophylaxis)
CENTRAL	(Coronaviridae Infections OR Coronavirus OR coronavirus OR novel coronavirus OR NCOV OR covid19 OR covid 19 OR covid-19 OR severe acute respiratory syndrome coronavirus 2 OR SARS2 OR SARS 2 OR SARS COV2 OR SARS COV 2 OR SARS-COV-20 AND “tixagevimab-cilgavimab” OR (“cilgavimab and tixagevimab drug combination” OR “cilgavimab and tixagevimab drug combination” OR “azd7442”	9/16/22	13,169	3 (2 on treatment ; 1 on prophylaxis)
COVID-NMA Initiative	{“tixagevimab-cilgavimab” OR (“cilgavimab and tixagevimab drug combination” OR “cilgavimab and tixagevimab drug combination” OR “azd7442”}	9/16/22	2	2
Google Scholar	{Coronavirus OR novel coronavirus OR NCOV OR covid19 OR covid 19 OR covid-19 OR severe acute respiratory syndrome coronavirus 2 OR SARS2 OR SARS 2 OR SARS COV2 OR SARS COV 2 OR SARS-COV-2} AND {“tixagevimab-cilgavimab” OR (“cilgavimab and tixagevimab drug combination” OR “cilgavimab and tixagevimab drug combination” OR “azd7442”} AND {Randomized trial}	9/16/22	330	2
ClinicalTrials.gov	Coronavirus AND {“tixagevimab-cilgavimab” OR (“cilgavimab and tixagevimab drug combination” OR “cilgavimab and tixagevimab drug combination” OR “azd7442”}	9/16/22	13	2

Chinese Clinical Trial Registry	{Coronavirus OR novel coronavirus OR NCOV OR covid19 OR covid 19 OR covid-19 OR severe acute respiratory syndrome coronavirus 2 OR SARS2 OR SARS 2 OR SARS COV2 OR SARS COV 2 OR SARS-COV-2} AND {"tixagevimab-cilgavimab" OR ("cilgavimab and tixagevimab drug combination" OR "cilgavimab and tixagevimab drug combination" OR "azd7442"}	9/16/22	1	0
EU Clinical Trials Register	Coronavirus AND {"tixagevimab-cilgavimab" OR ("cilgavimab and tixagevimab drug combination" OR "cilgavimab and tixagevimab drug combination" OR "azd7442"}	9/16/22	16	1
Republic of Korea – Clinical Research Information Service	Coronavirus AND {"tixagevimab-cilgavimab" OR ("cilgavimab and tixagevimab drug combination" OR "cilgavimab and tixagevimab drug combination" OR "azd7442"}	9/16/22	1	0
Japan Primary Registries Network/ NIPH Clinical Trials Search	Coronavirus AND {"tixagevimab-cilgavimab" OR ("cilgavimab and tixagevimab drug combination" OR "cilgavimab and tixagevimab drug combination" OR "azd7442"}	9/16/22	2	0
CenterWatch	Coronavirus AND {"tixagevimab-cilgavimab" OR ("cilgavimab and tixagevimab drug combination" OR "cilgavimab and tixagevimab drug combination" OR "azd7442"}	9/16/22	216	2
WHO database COVID-19 studies	{"tixagevimab-cilgavimab" OR ("cilgavimab and tixagevimab drug combination" OR "cilgavimab and tixagevimab drug combination" OR "azd7442"}	9/16/22	26	2
chinaxiv.org	Coronavirus AND {"tixagevimab-cilgavimab" OR ("cilgavimab and tixagevimab drug combination" OR "cilgavimab and tixagevimab drug combination" OR "azd7442"}	9/16/22	0	0
Medrxiv.org	Coronavirus AND {"tixagevimab-cilgavimab" OR "cilgavimab and tixagevimab drug combination" OR "cilgavimab and tixagevimab drug combination" OR "azd7442"}	9/16/22	14	1
Biorxiv.org	Coronavirus AND {"tixagevimab-cilgavimab" OR "cilgavimab and tixagevimab drug combination" OR "cilgavimab and tixagevimab drug combination" OR "azd7442"}	9/16/22	5	0

Appendix 3: Characteristics of Included Studies

Study ID	Patients (n) & Duration of Follow-Up	Interventions	Outcomes	Study Design
Efficacy and safety of intramuscular administration of tixagevimab–cilgavimab for early outpatient treatment of COVID-19 (TACKLE): a phase 3, andomized, double-blind, placebo-controlled trial *Montgomery et al., Multicenter*	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. ** 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 ormeasured fever.* (N =910)* Duration of follow-up: 457 days	EXPERIMENTAL: single 600 mg dose (two consecutive 3 mL intramuscular injections, one each of 300 mg tixagevimab and 300 mg cilgavimab) CONTROL: saline placebo (0·9% NaCl; two consecutive 3 mL intramuscular injections)	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 dyspnea, and lung infiltrates) or hypoxemia (oxygen saturation <90% in room air, severe respiratory distress, or both), plus a WHO Clinical Progression Scale score of 5 or more. The primary safety endpoints were adverse events, serious adverse events, and adverse events of special interest throughout the study. 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. The key secondary endpoint was a composite of death from any cause or for COVID-19 complications or sequalae to day 169.	Randomized, double-blind, placebo-controlled

			** Respiratory failure was defined as a requirement for mechanical ventilation, extracorporeal membrane oxygenation, non-invasive ventilation, or high-flow nasal cannula oxygen delivery.*	
Tixagevimab–cilgavimab for treatment of patients andomizedg with COVID-19: a randomized, double-blind, phase 3 trial ACTIV-3–Therapeutics for Inpatients with COVID-19 (TICO) Study Group *Holland et al., Multicenter* NCT04501978	Adults with symptoms for up to 12 days and andomizedg for COVID-19 at 81 sites in the USA, Europe, Uganda, and Singapore Patients were excluded if they had acute organ failure including receipt of invasive mechanical ventilation, extracorporeal membrane oxygenation, vasopressor therapy, mechanical circulatory support, or new renal replacement therapy. 1417 in the primary modified intention-to-treat population were infused with tixagevimab–cilgavimab (n=710) or placebo (n=707). The participant follow-up is ongoing.	EXPERIMENTAL: Intravenous tixagevimab 300 mg–cilgavimab 300 mg in addition to remdesivir and other standard care. CONTROL: Placebo, in addition to remdesivir and other standard care.	The primary outcome was time to sustained recovery up to day 90, defined as 14 consecutive days at home after hospital discharge, with co-primary analyses for the full cohort and for participants who were antibody-negative at baseline. Efficacy and safety analyses were done in the modified intention-to-treat population, defined as participants who received a complete or partial infusion of tixagevimab–cilgavimab or placebo.	Randomized, double-blind, phase 3, placebo-controlled trial,

Appendix 4: Study Appraisal

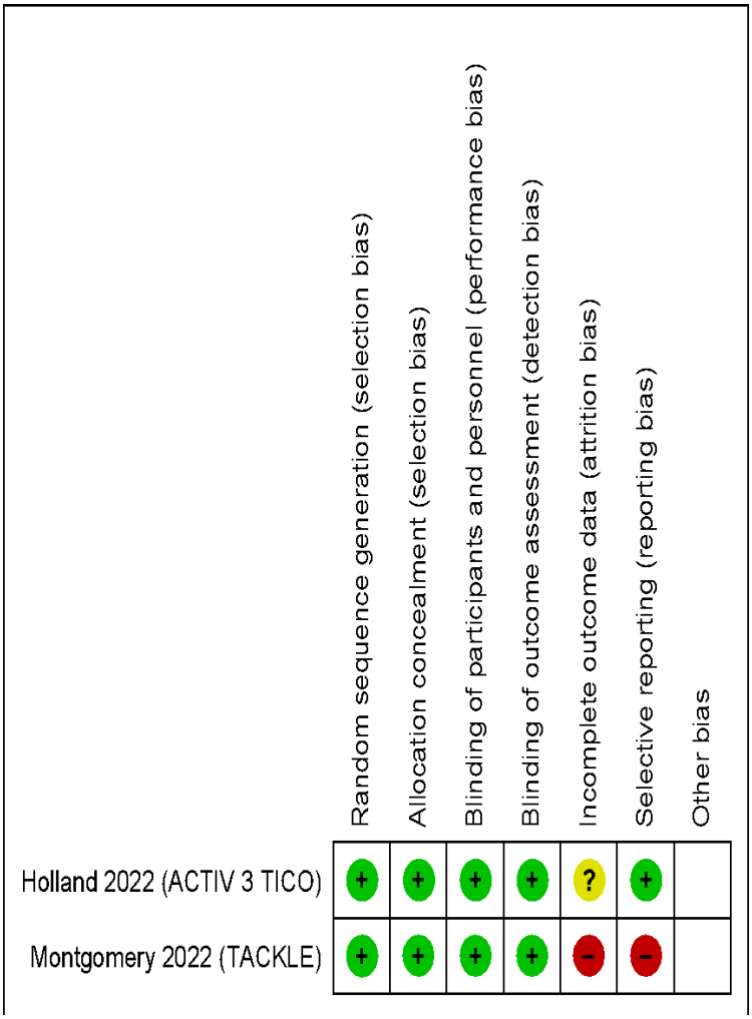

Figure 1. Risk of bias summary table

Appendix 5: GRADE Evidence Profile

Author(s): Liza Marie Bejemino, MD
Question: Tixagevimab-Cilgavimab compared to Placebo for COVID-19 treatment (2 studies)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	AZD7442	Placebo	Relative (95% CI)	Absolute (95% CI)		
All-cause Mortality D28												
2	randomized trials	serious[a]	not serious	serious[b]	not serious	none	47/1188 (4.0%)	71/1177 (6.0%)	**RR 0.65** (0.46 to 0.93)	**21 fewer per 1,000** (from 33 fewer to 4 fewer)	⨁⨁◯◯ Low	CRITICAL
All-cause Mortality D28 - All-cause Mortality At D28 among hospitalized patients												
1	randomized trials	not serious	not serious	serious[b]	not serious	none	41/732 (5.6%)	65/723 (9.0%)	**RR 0.62** (0.43 to 0.91)	**34 fewer per 1,000** (from 51 fewer to 8 fewer)	⨁⨁⨁◯ Moderate	CRITICAL
All-cause Mortality D28 - All-cause Mortality at D28 among outpatient												
1	randomized trials	serious[a]	not serious	serious[b]	serious[c]	none	6/456 (1.3%)	6/454 (1.3%)	**RR 1.00** (0.32 to 3.06)	**0 fewer per 1,000** (from 9 fewer to 27 more)	⨁◯◯◯ Very Low	CRITICAL
All-cause Mortality D90												
2	randomized trials	serious[a]	not serious	serious[b]	not serious	none	67/1188 (5.6%)	92/1177 (7.8%)	**RR 0.72** (0.53 to 0.97)	**22 fewer per 1,000** (from 37 fewer to 2 fewer)	⨁⨁◯◯ Low	CRITICAL
All-cause mortality at D90 (hospitalized patients)												
1	randomized trials	not serious	not serious	serious[b]	not serious	none	61/732 (8.3%)	86/723 (11.9%)	**RR 0.70** (0.51 to 0.96)	**36 fewer per 1,000** (from 58 fewer to 5 fewer)	⨁⨁⨁◯ Moderate	CRITICAL
All-cause Mortality at D90 among outpatient												
1	randomized trials	serious[a]	not serious	serious[b]	serious[c]	none	6/456 (1.3%)	6/454 (1.3%)	**RR 1.00** (0.32 to 3.06)	**0 fewer per 1,000** (from 9 fewer to 27 more)	⨁◯◯◯ Very Low	CRITICAL
Severe COVID 19 or Death at D28 (Outpatient)												

	Certainty assessment							№ of patients		Effect		Certainty	Importance
	№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	AZD7442	Placebo	Relative (95% CI)	Absolute (95% CI)		
	1	randomized trials	serious[a]	not serious	serious[b]	not serious	none	24/456 (5.3%)	41/454 (9.0%)	**RR 0.58** (0.36 to 0.95)	**38 fewer per 1,000** (from 58 fewer to 5 fewer)	⨁⨁◯◯ Low	CRITICAL
	Prevention of Respiratory Failure (Outpatient)												
	1	randomized trials	serious[a]	not serious	serious[b]	not serious	none	3/405 (0.7%)	11/412 (2.7%)	**RR 0.28** (0.08 to 0.99)	**19 fewer per 1,000** (from 25 fewer to 0 fewer)	⨁⨁◯◯ Low	
	Hospitalization for COVID 19 including hospitalization (Outpatient)												
	1	randomized trials	serious[a]	not serious	serious[b]	not serious	none	17/413 (4.1%)	40/421 (9.5%)	**RR 0.43** (0.25 to 0.75)	**54 fewer per 1,000** (from 71 fewer to 24 fewer)	⨁⨁◯◯ Low	
	Viral Negative Conversion D7 (Outpatient)												
	1	randomized trials	serious[a]	not serious	serious[b]	serious[c]	none	46/162 (28.4%)	30/146 (20.5%)	**RR 1.38** (0.92 to 2.07)	**78 more per 1,000** (from 16 fewer to 220 more)	⨁◯◯◯ Very Low	
	Pulmonary Ordinal Scale OR WHO Progression Score Level 7 or above at D28 (Hospitalized Patients)												
	1	randomized trials	not serious	not serious	serious[b]	not serious	none	72/732 (9.8%)	89/723 (12.3%)	**RR 0.80** (0.60 to 1.07)	**25 fewer per 1,000** (from 49 fewer to 9 more)	⨁⨁⨁◯ Moderate	
	Sustained Recovery OR Clinical Improvement at D28 (Hospitalized Patients)												
	1	randomized trials	not serious	not serious	serious[b]	not serious	none	554/732 (75.7%)	538/723 (74.4%)	**RR 1.02** (0.96 to 1.08)	**15 more per 1,000** (from 30 fewer to 60 more)	⨁⨁⨁◯ Moderate	
	Sustained Recovery OR Clinical Improvement at D90 (Hospitalized Patients)												
	1	randomized trials	not serious	not serious	serious[b]	not serious	none	617/732 (84.3%)	595/723 (82.3%)	**RR 1.02** (0.98 to 1.07)	**16 more per 1,000** (from 16 fewer to 58 more)	⨁⨁⨁◯ Moderate	
	Adverse Events												
	2	randomized trials	serious[a]	serious[d]	serious[b]	not serious	none	469/1188 (39.5%)	498/1177 (42.3%)	**RR 0.91** (0.74 to 1.11)	**38 fewer per 1,000** (from 110 fewer to 47 more)	⨁◯◯◯ Very Low	

	Certainty assessment							№ of patients		Effect		Certainty	Importance
	№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	AZD7442	Placebo	Relative (95% CI)	Absolute (95% CI)		
	Adverse Events - Adverse Events (Outpatient) (IM route)												
	1	randomized trials	serious[a]	not serious	serious[b]	not serious	none	132/456 (28.9%)	163/454 (35.9%)	**RR 0.81** (0.67 to 0.97)	**68 fewer per 1,000** (from 118 fewer to 11 fewer)	⨁⨁◯◯ Low	
	Adverse Events - Adverse Events (Hospitalized Patients) (IV route)												
	1	randomized trials	not serious	not serious	serious[b]	not serious	none	337/732 (46.0%)	335/723 (46.3%)	**RR 0.99** (0.89 to 1.11)	**5 fewer per 1,000** (from 51 fewer to 51 more)	⨁⨁⨁◯ Moderate	
	Serious Adverse Events												
	2	randomized trials	serious[a]	not serious	serious[b]	not serious	none	67/1188 (5.6%)	92/1177 (7.8%)	**RR 0.72** (0.50 to 1.04)	**22 fewer per 1,000** (from 39 fewer to 3 more)	⨁⨁◯◯ Low	CRITICAL
	Serious Adverse Events - Serious Adverse Events (Outpatient) (IM route)												
	1	randomized trials	serious[a]	not serious	serious[b]	not serious	none	33/456 (7.2%)	54/454 (11.9%)	**RR 0.61** (0.40 to 0.92)	**46 fewer per 1,000** (from 71 fewer to 10 fewer)	⨁⨁◯◯ Low	
	Serious Adverse Events - Serious Adverse Events (Hospitalized Patients) (IV route)												
	1	randomized trials	not serious	not serious	serious[b]	serious[c]	none	34/732 (4.6%)	38/723 (5.3%)	**RR 0.88** (0.56 to 1.39)	**6 fewer per 1,000** (from 23 fewer to 20 more)	⨁⨁◯◯ Low	
	Composite Safety Outcome at D28 (hospitalized patients)												
	1	randomized trials	not serious	not serious	serious[b]	not serious	none	225/732 (30.7%)	248/723 (34.3%)	**RR 0.90** (0.77 to 1.04)	**34 fewer per 1,000** (from 79 fewer to 14 more)	⨁⨁⨁◯ Moderate	
	Composite Safety Outcome at D90 (hospitalized patients)												
	1	randomized trials	not serious	not serious	serious[b]	not serious	none	178/732 (24.3%)	212/723 (29.3%)	**RR 0.83** (0.70 to 0.98)	**50 fewer per 1,000** (from 88 fewer to 6 fewer)	⨁⨁⨁◯ Moderate	
All-cause Mortality D28 based on vaccination Status (hospitalized patients)													
1	randomized trials	not serious	not serious	serious[b]	not serious	none		41/710 (5.8%)	65/707 (9.2%)	**RR 0.64** (0.44 to 0.93)	**33 fewer per 1,000** (from 51 fewer to 6 fewer)	⨁⨁⨁◯ Moderate	

Certainty assessment								№ of patients		Effect		Certainty	Importance
№ of studies		Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	AZD7442	Placebo	Relative (95% CI)	Absolute (95% CI)		
All-cause Mortality D28 based on vaccination Status (hospitalized patients) - Fully Vaccinated													
1	randomized trials	not serious	not serious	serious[b]	serious[c]	none	13/103 (12.6%)	13/101 (12.9%)	**RR 0.98** (0.48 to 2.01)	**3 fewer per 1,000** (from 67 fewer to 130 more)	⨁⨁◯◯ Low		
All-cause Mortality D28 based on vaccination Status (hospitalized patients) - Partially Vaccinated													
1	randomized trials	not serious	not serious	serious[b]	serious[c]	none	4/82 (4.9%)	8/90 (8.9%)	**RR 0.55** (0.17 to 1.75)	**40 fewer per 1,000** (from 74 fewer to 67 more)	⨁⨁◯◯ Low		
All-cause Mortality D28 based on vaccination Status (hospitalized patients) - Not Vaccinated													
1	randomized trials	not serious	not serious	serious[b]	not serious	none	24/525 (4.6%)	44/516 (8.5%)	**RR 0.54** (0.33 to 0.87)	**39 fewer per 1,000** (from 57 fewer to 11 fewer)	⨁⨁⨁◯ Moderate		
All-cause Mortality D90 based on vaccination Status (hospitalized patients)													
1	randomized trials	not serious	not serious	serious[b]	not serious	none	61/710 (8.6%)	86/707 (12.2%)	**RR 0.71** (0.52 to 0.96)	**35 fewer per 1,000** (from 58 fewer to 5 fewer)	⨁⨁⨁◯ Moderate		
All-cause Mortality D90 based on vaccination Status (hospitalized patients) - Fully Vaccinated													
1	randomized trials	not serious	not serious	serious[b]	not serious	none	13/103 (12.6%)	17/101 (16.8%)	**RR 0.75** (0.38 to 1.46)	**42 fewer per 1,000** (from 104 fewer to 77 more)	⨁⨁⨁◯ Moderate		
All-cause Mortality D90 based on vaccination Status (hospitalized patients) - Partially Vaccinated													
1	randomized trials	not serious	not serious	serious[b]	serious[c]	none	5/82 (6.1%)	10/90 (11.1%)	**RR 0.55** (0.20 to 1.54)	**50 fewer per 1,000** (from 89 fewer to 60 more)	⨁⨁◯◯ Low		
All-cause Mortality D90 based on vaccination Status (hospitalized patients) - Not Vaccinated													
1	randomized trials	not serious	not serious	serious[b]	not serious	none	43/525 (8.2%)	59/516 (11.4%)	**RR 0.72** (0.49 to 1.04)	**32 fewer per 1,000** (from 58 fewer to 5 more)	⨁⨁⨁◯ Moderate		

CI: confidence interval; **RR:** risk ratio

Explanations

a. downgraded for attrition bias
b. when the trial was conducted, the major variant of concern is not omicron
c. wide confidence interval
d. substantial heterogeneity

Appendix 6: Forest Plots

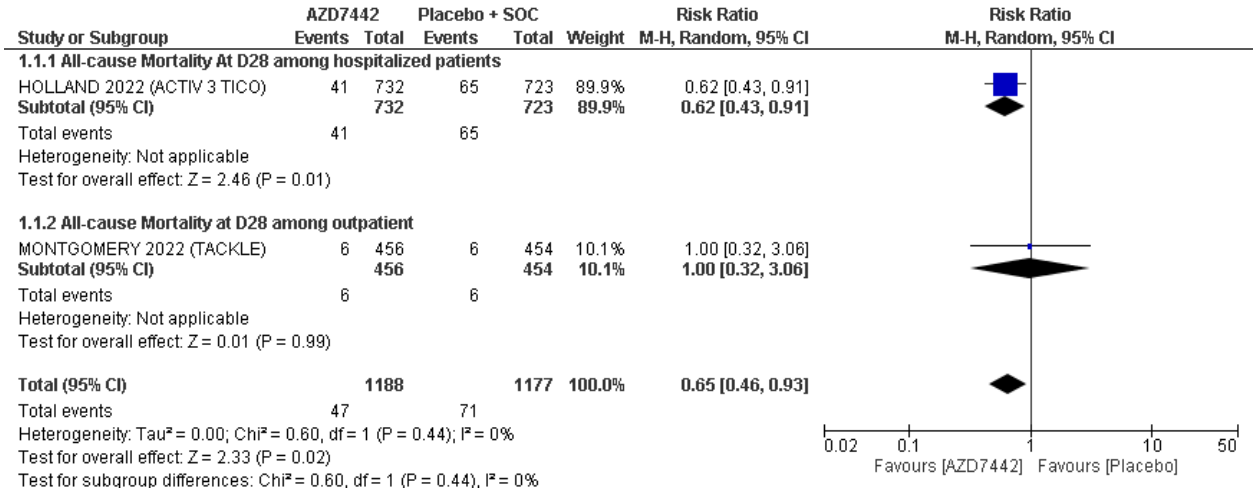

Figure 2. All-cause mortality (Day 28).

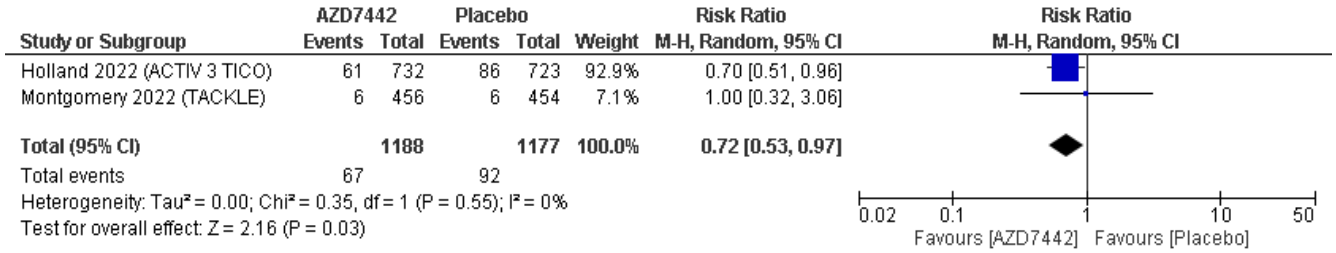

Figure 3. All-cause mortality (Day 90).

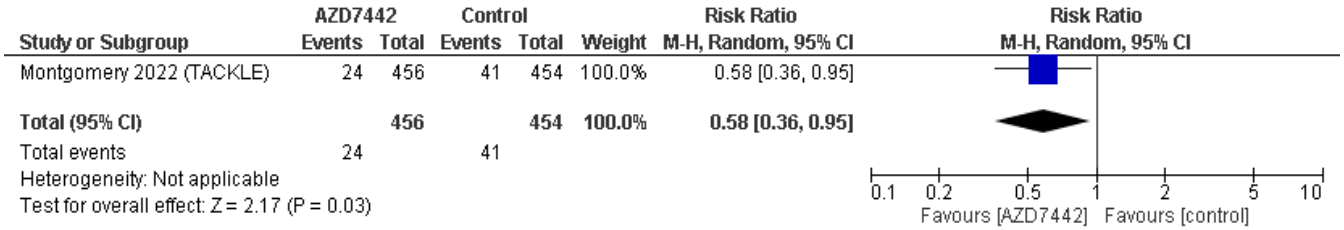

Figure 4. Composite outcome of Severe COVID 19 or Death at D28 (OUTPATIENT)

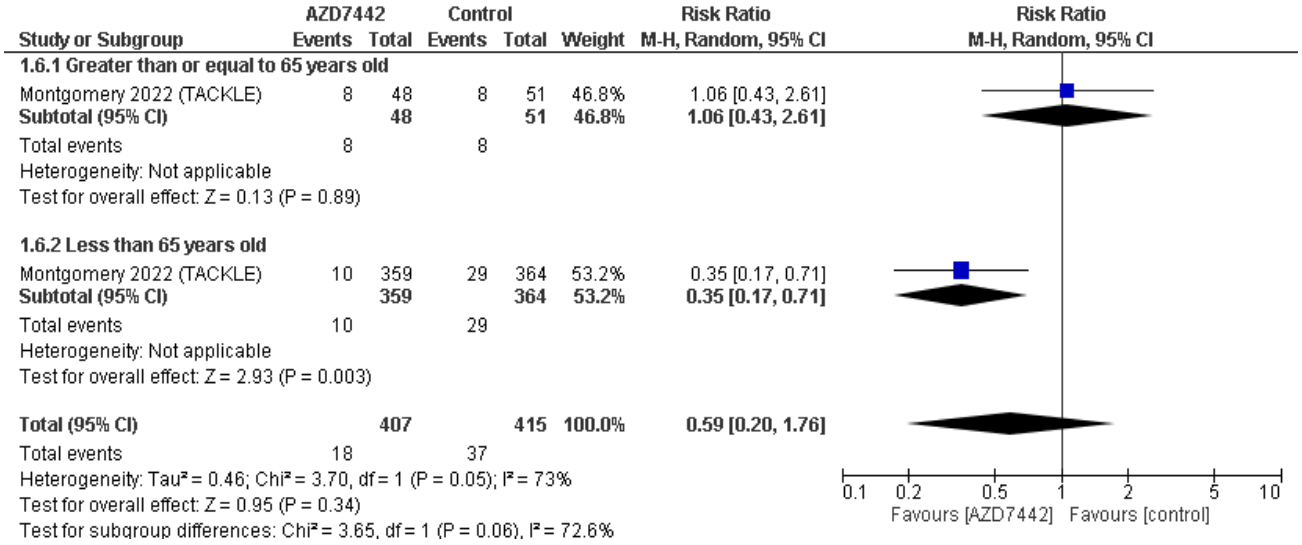

Figure 5. Composite outcome of Severe COVID 19 or Death at D28 (OUTPATIENT)_Subgroup analysis based on age

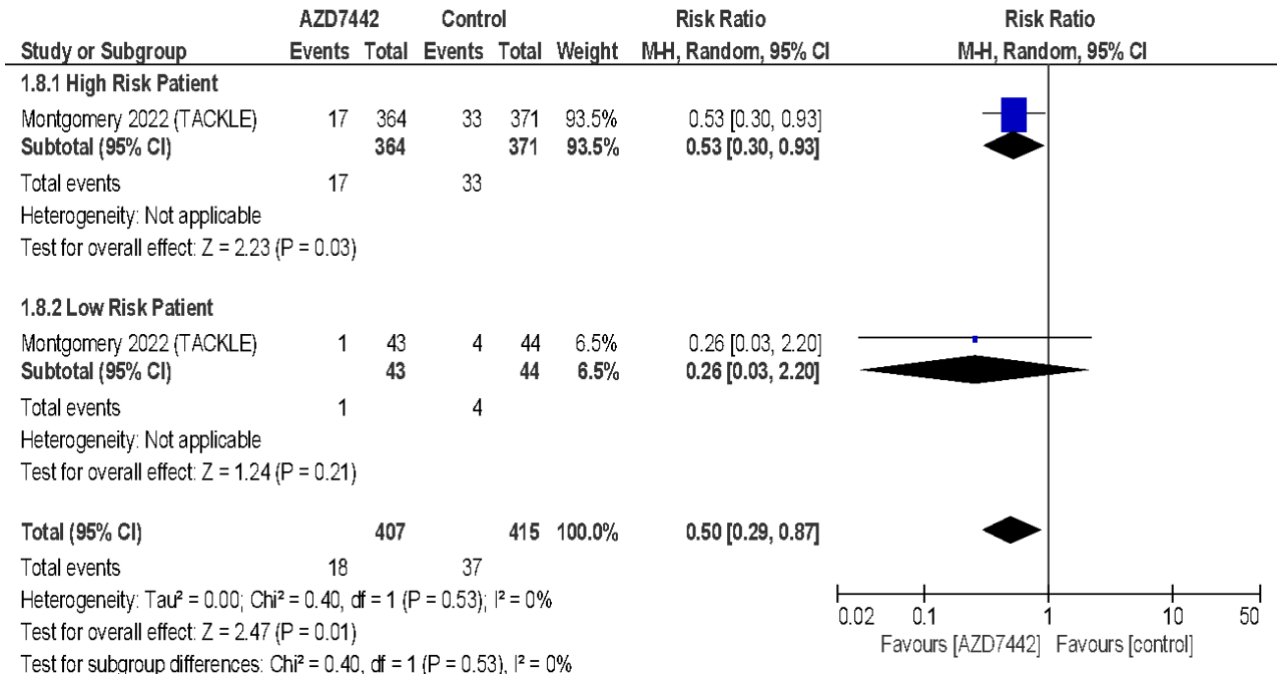

Figure 6. Composite outcome of Severe COVID 19 or Death at D28 (OUTPATIENT)_Subgroup analysis based on risk group

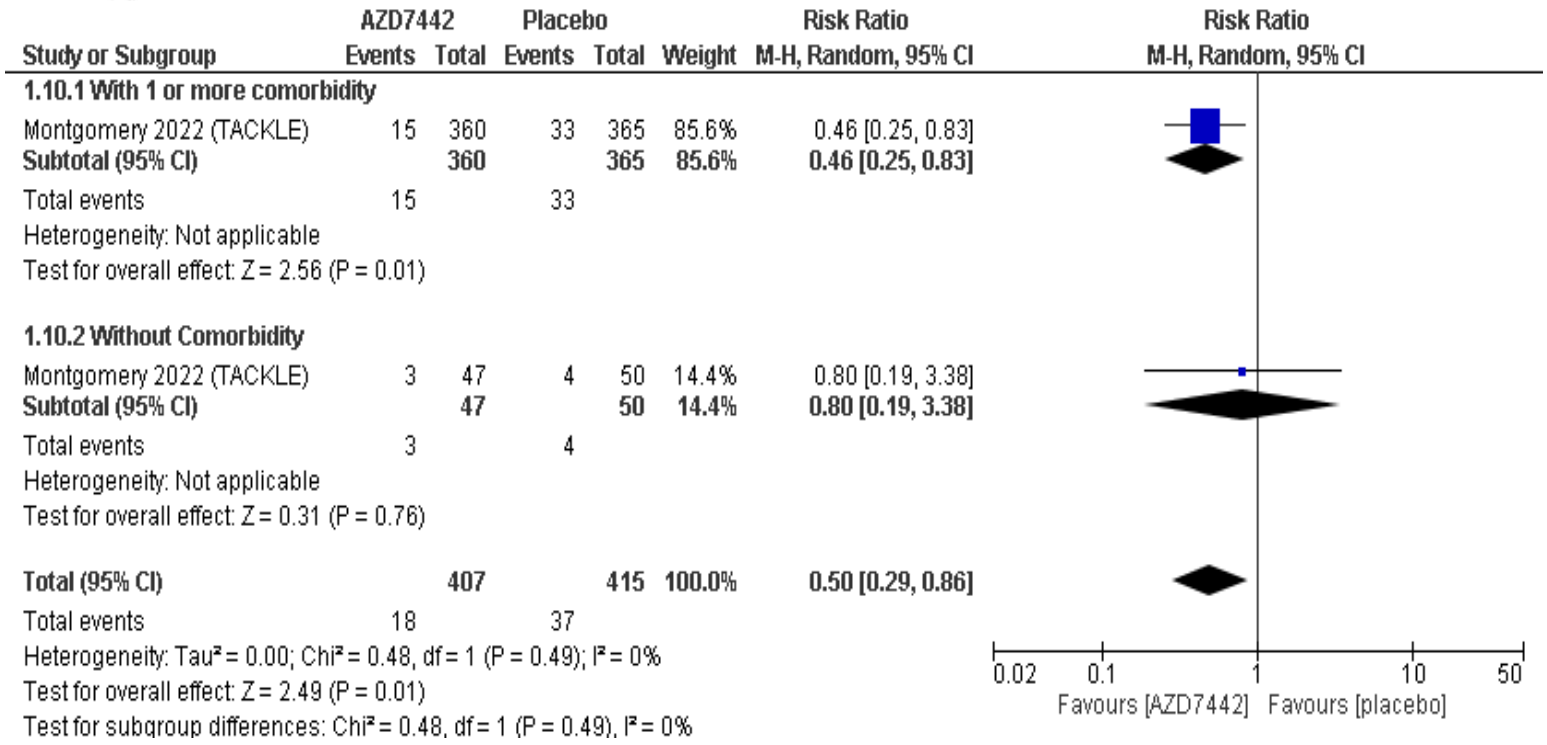

Figure 7. Composite outcome of severe COVID 19 or Death at D28 (OUTPATIENT)_Subgroup analysis based on COVID-19 comorbidity

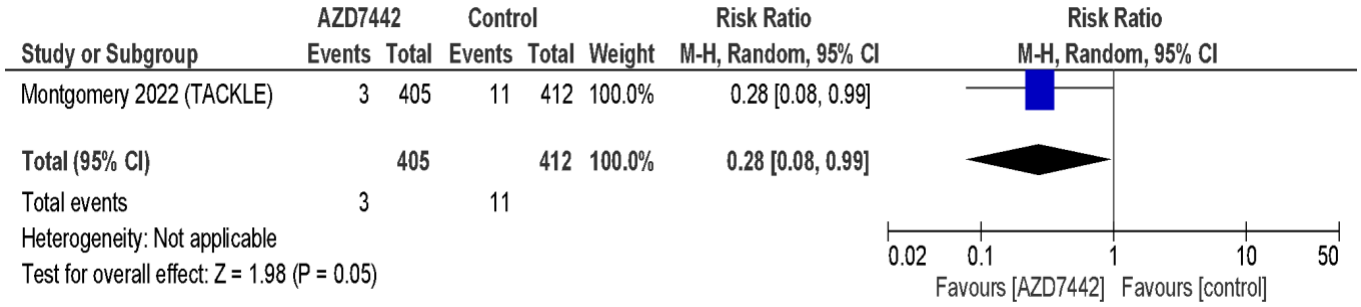

Figure 8. Prevention of respiratory failure (OUTPATIENT).

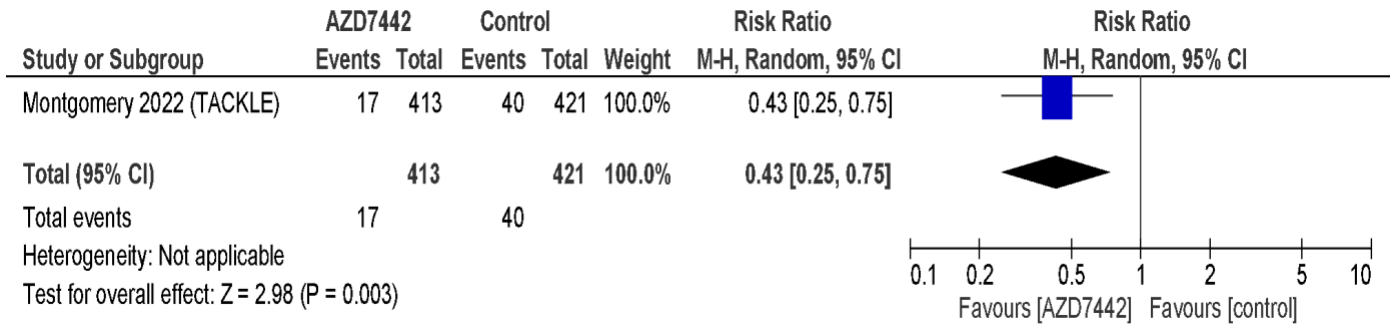

Figure 9. Hospitalization for COVID-19 including complications (OUTPATIENT)

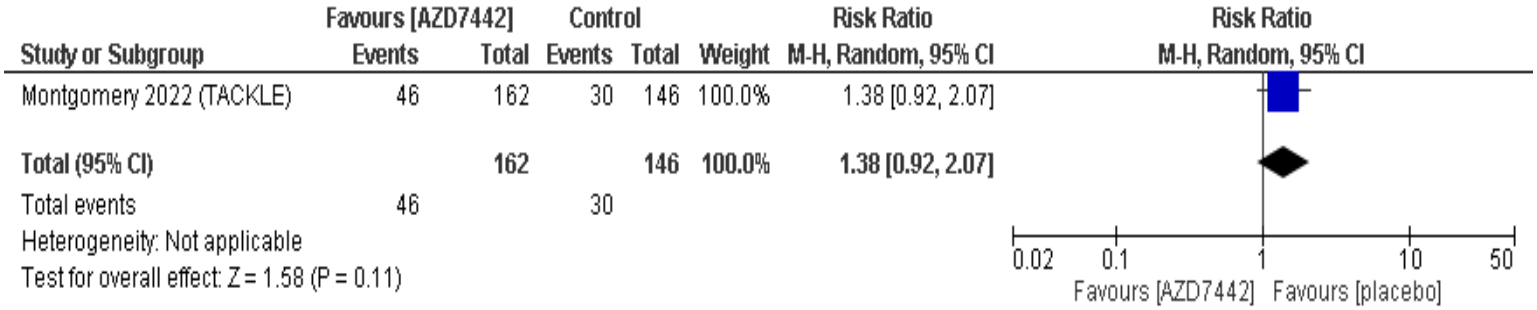

Figure 10. Viral negative conversion day 7 (OUTPATIENT)

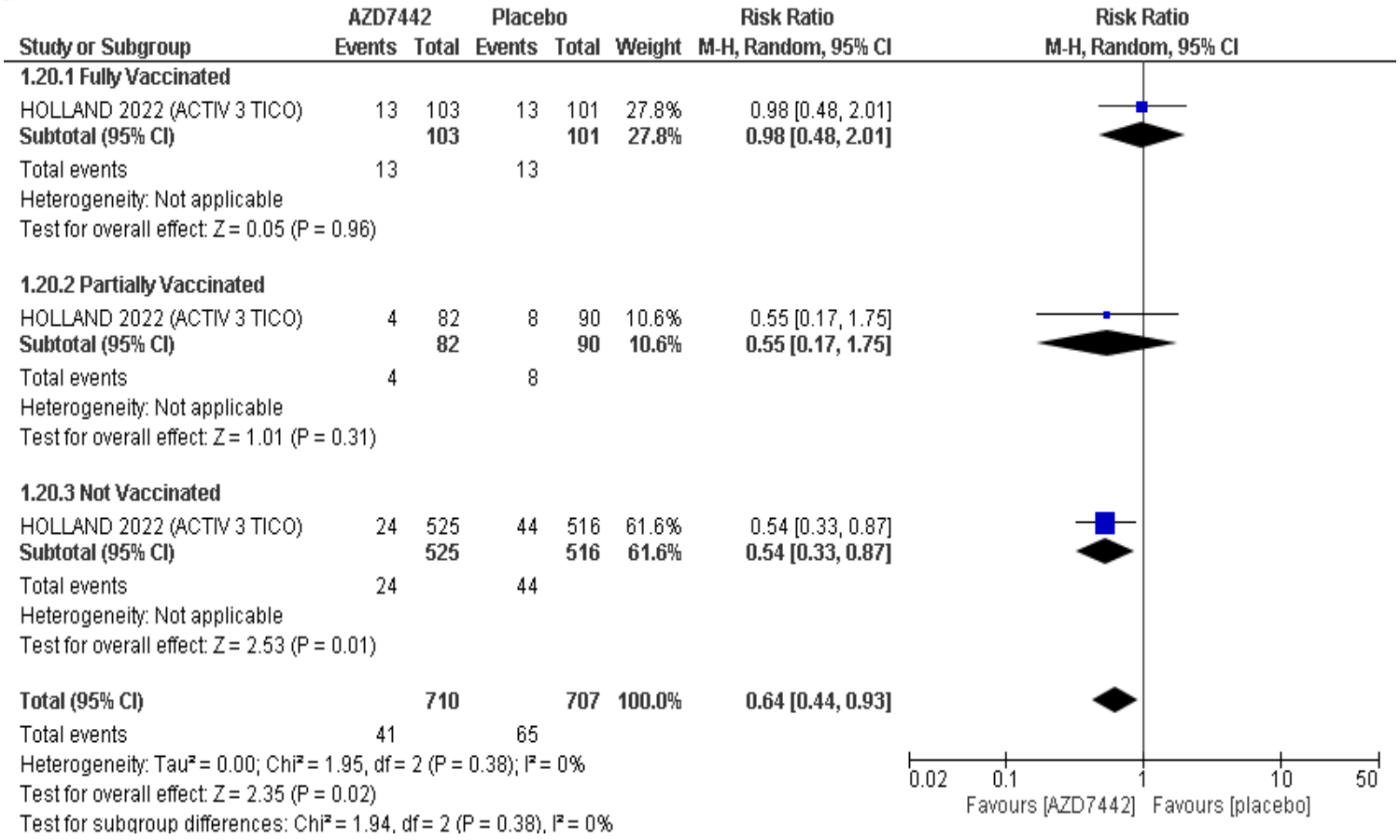

Figure 11. All-cause mortality D28 based on vaccination status (hospitalized patients).

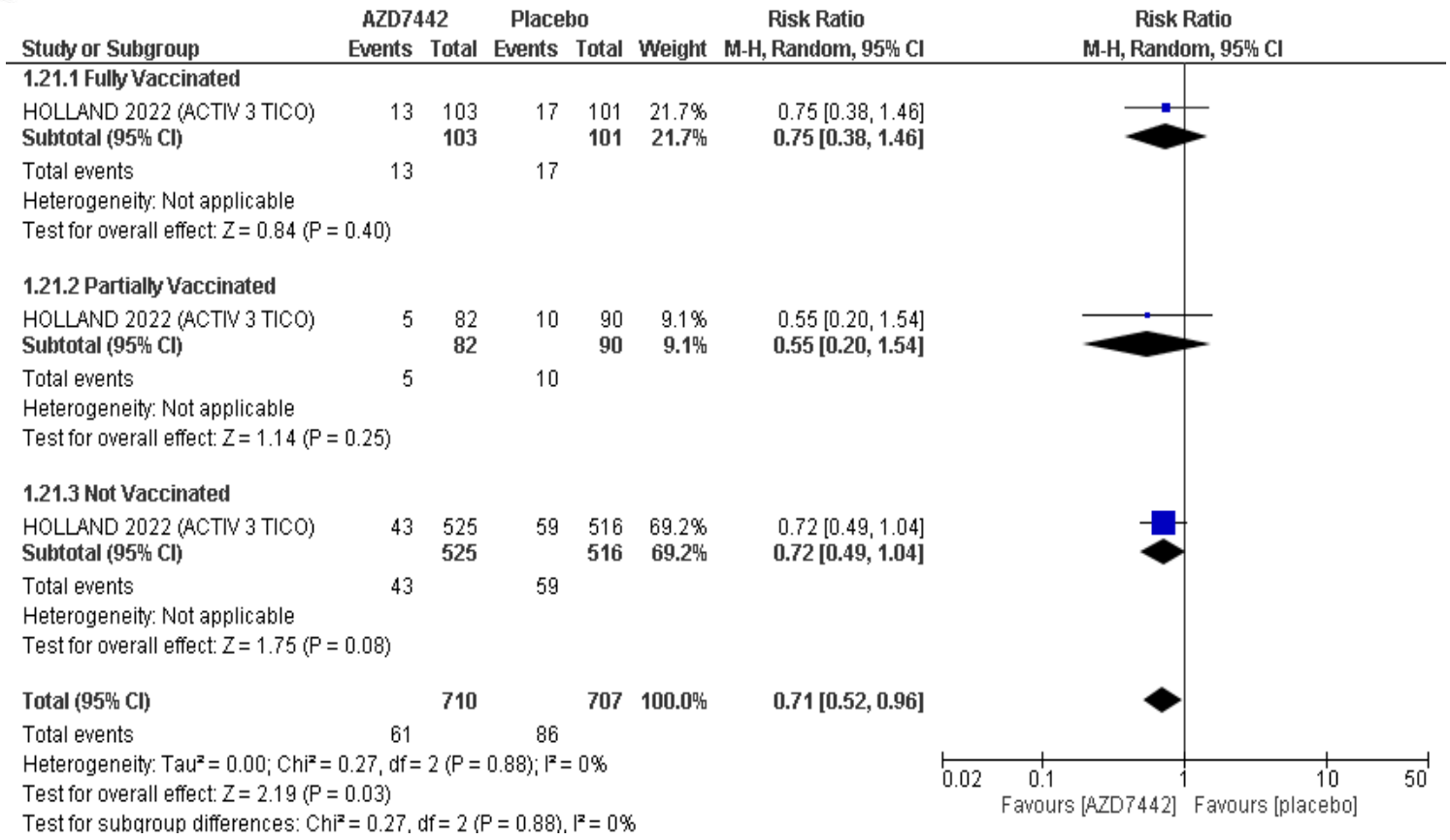

Figure 12. All-cause mortality D90 based on vaccination status (hospitalized patients)

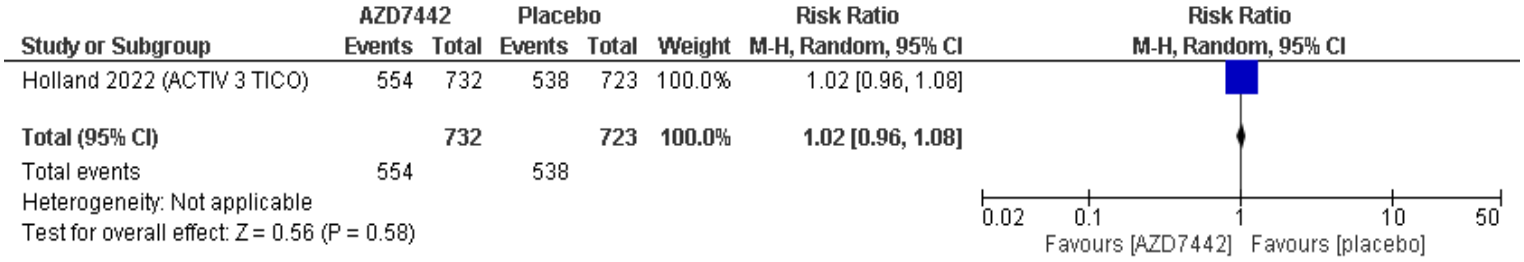

Figure 13. Sustained Recovery up to D28 OR Clinical Improvement at D28 (HOSPITALIZED PATIENTS)

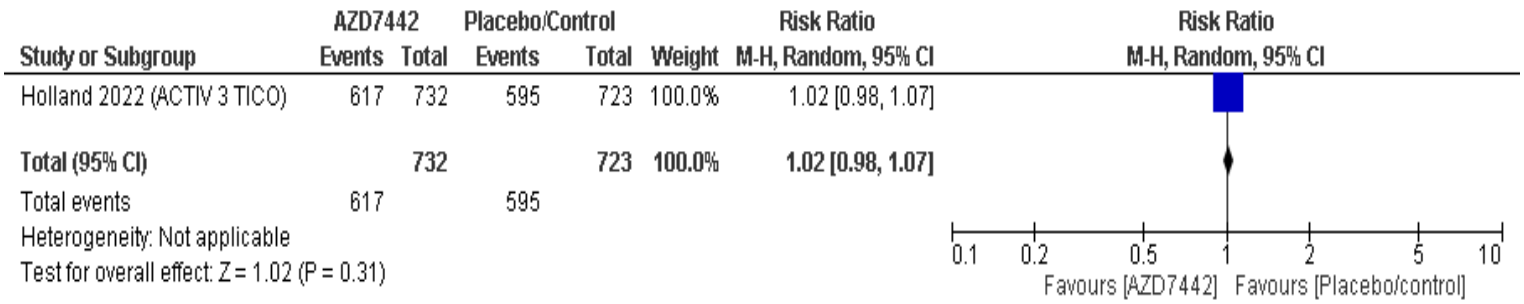

Figure 14. Sustained Recovery up to D90 OR Clinical Improvement at day 90 (HOSPITALIZED PATIENTS)

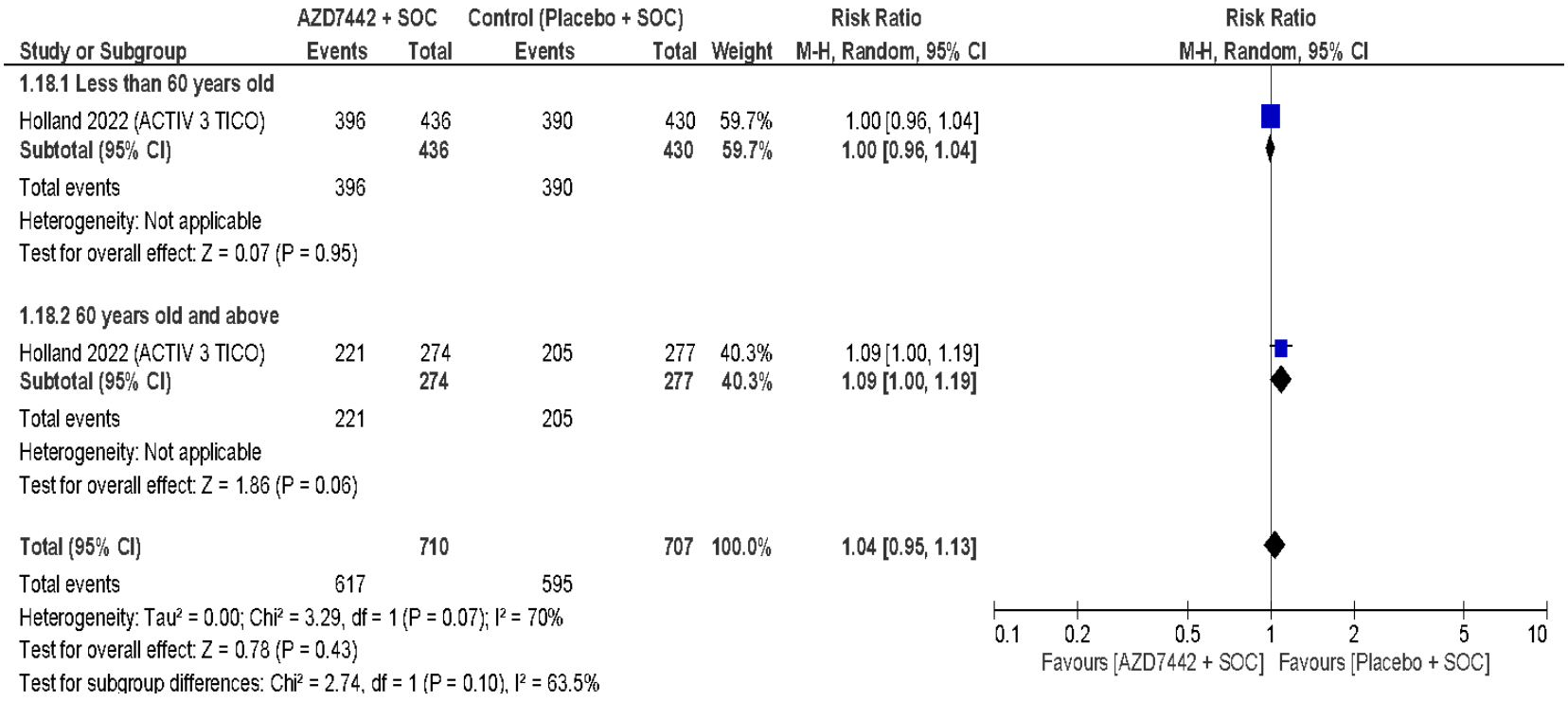

Figure 15. Sustained Recovery up to D90 (HOSPITALIZED PATIENTS)_Subgroup analysis by age

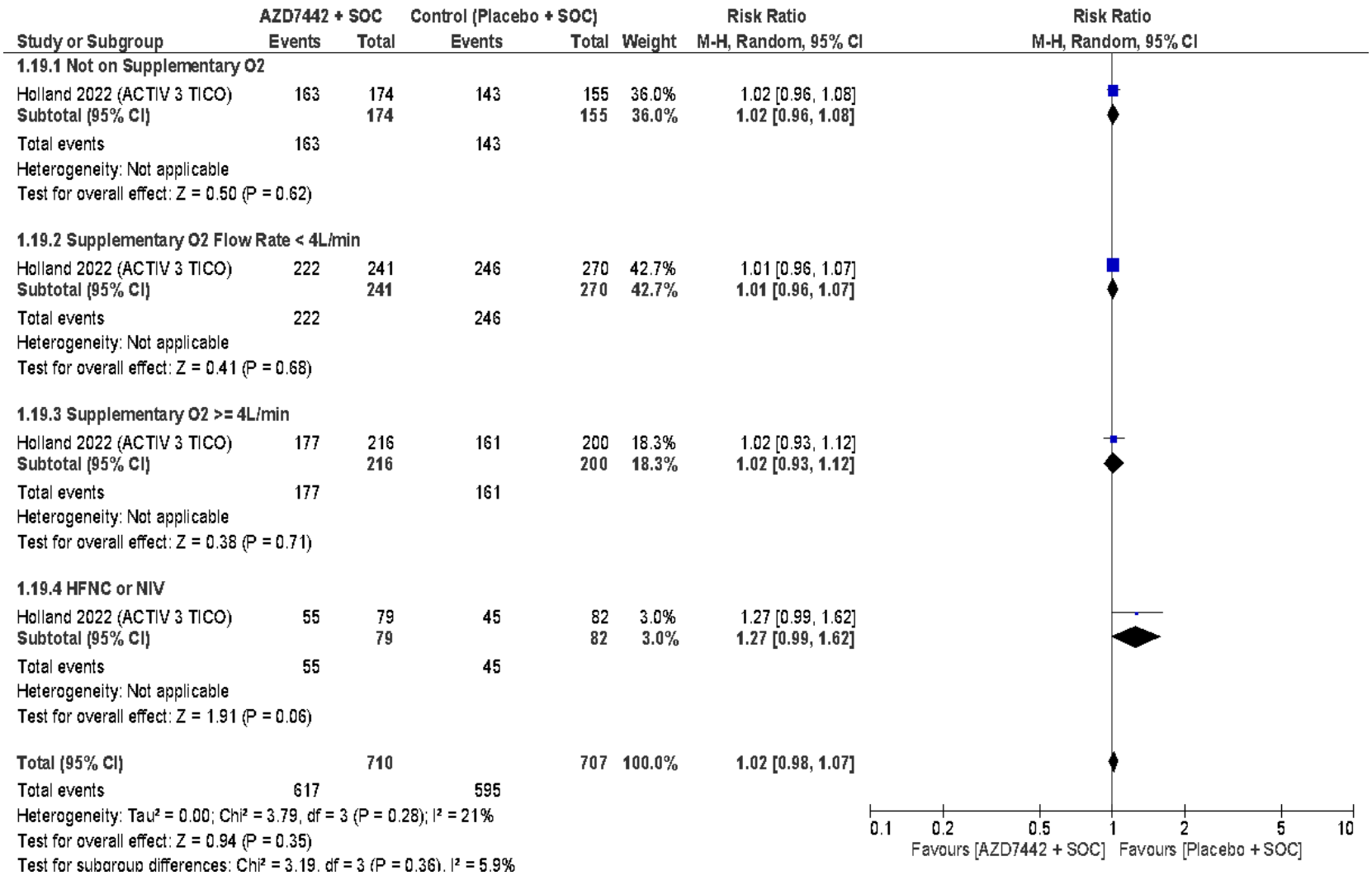

Figure 16. Sustained Recovery up to D90 (HOSPITALIZED PATIENTS)_Subgroup analysis by Baseline Pulmonary Category

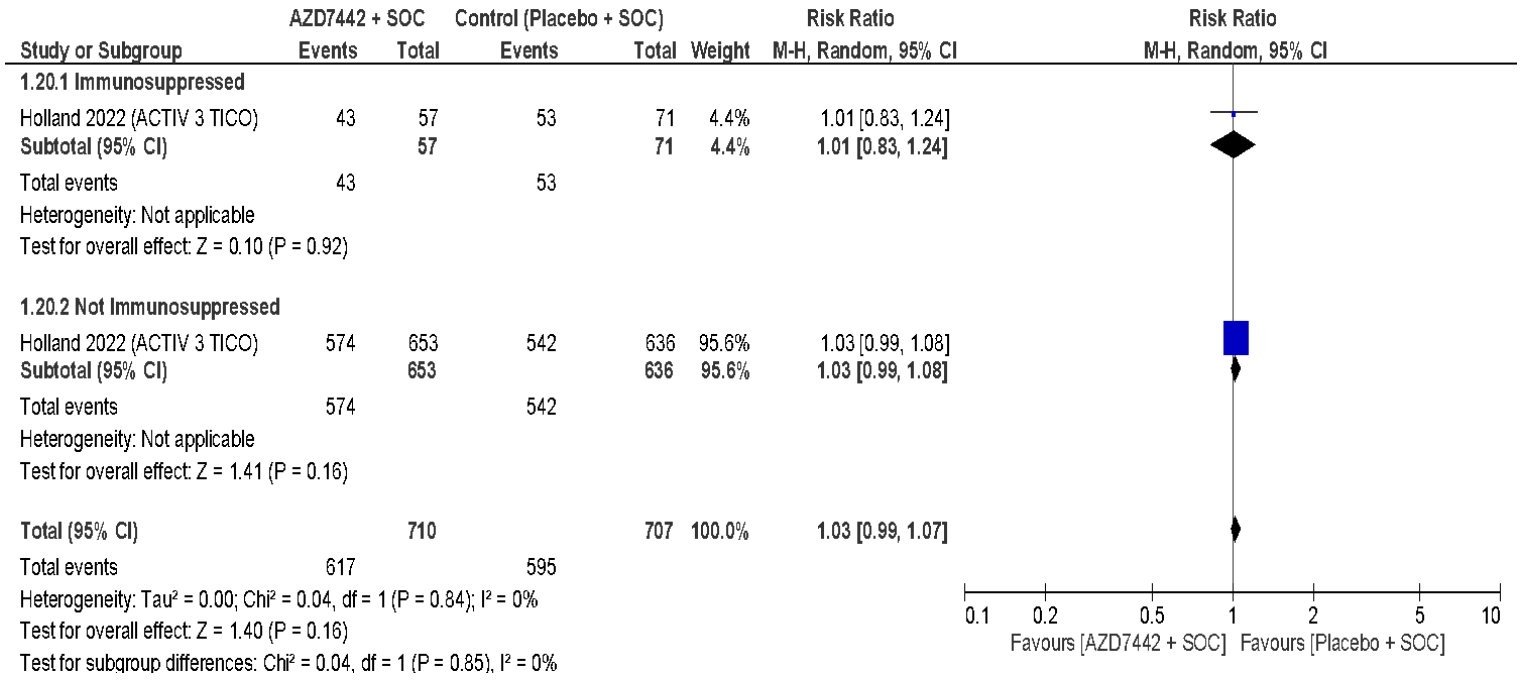

Figure 17. Sustained Recovery up to D90 (HOSPITALIZED PATIENTS)_Subgroup analysis by Immunosuppression Status

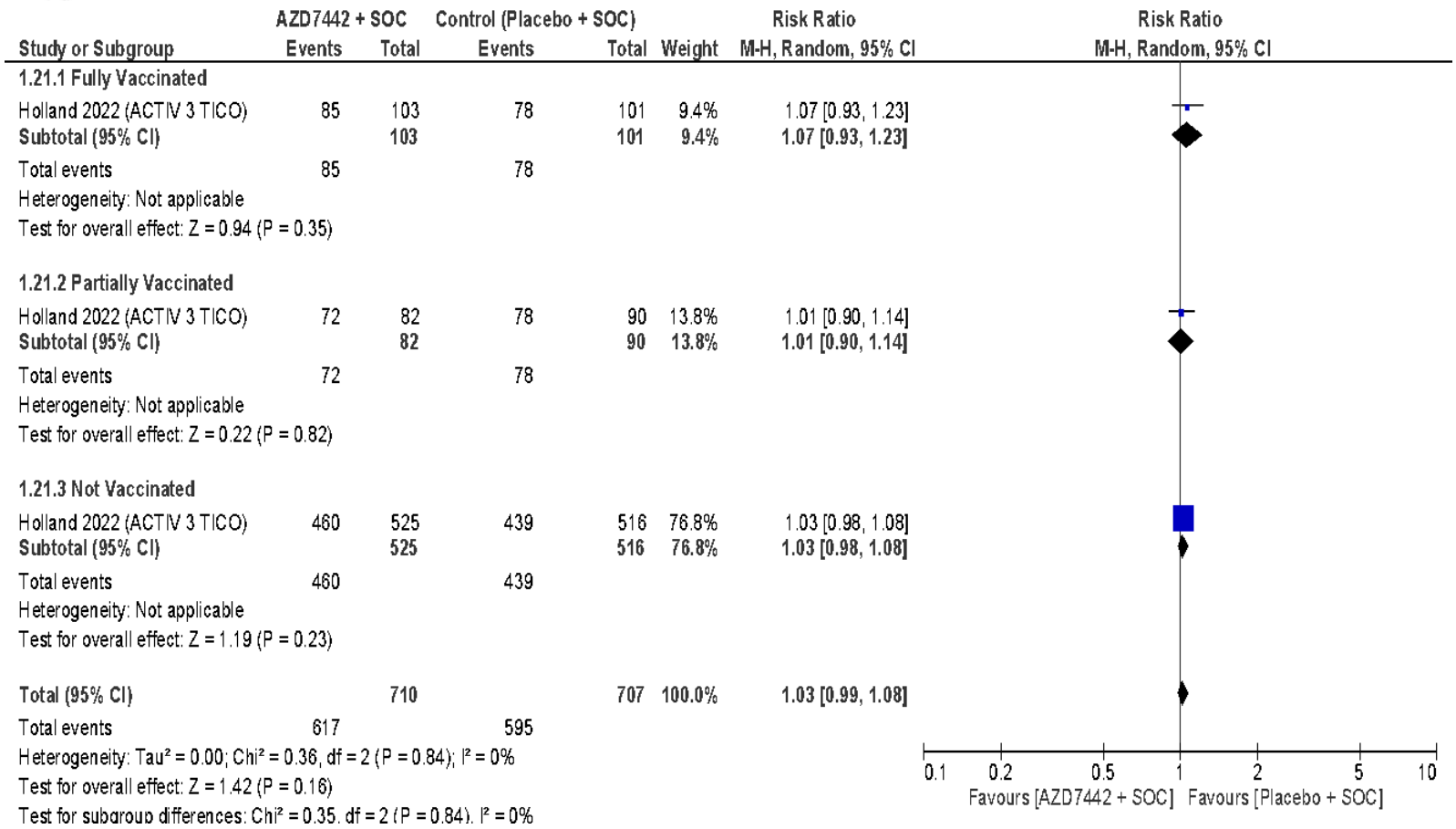

Figure 18. Sustained Recovery up to D90 (HOSPITALIZED PATIENTS)_Subgroup analysis by SARS COV 2 Vaccination Status

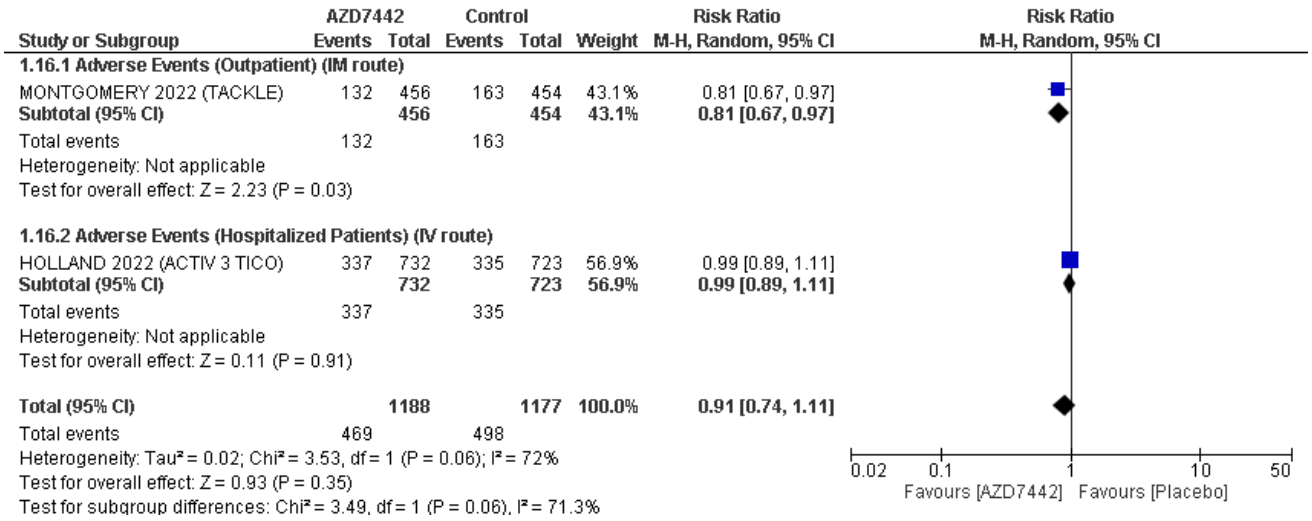

Figure 19. Adverse events

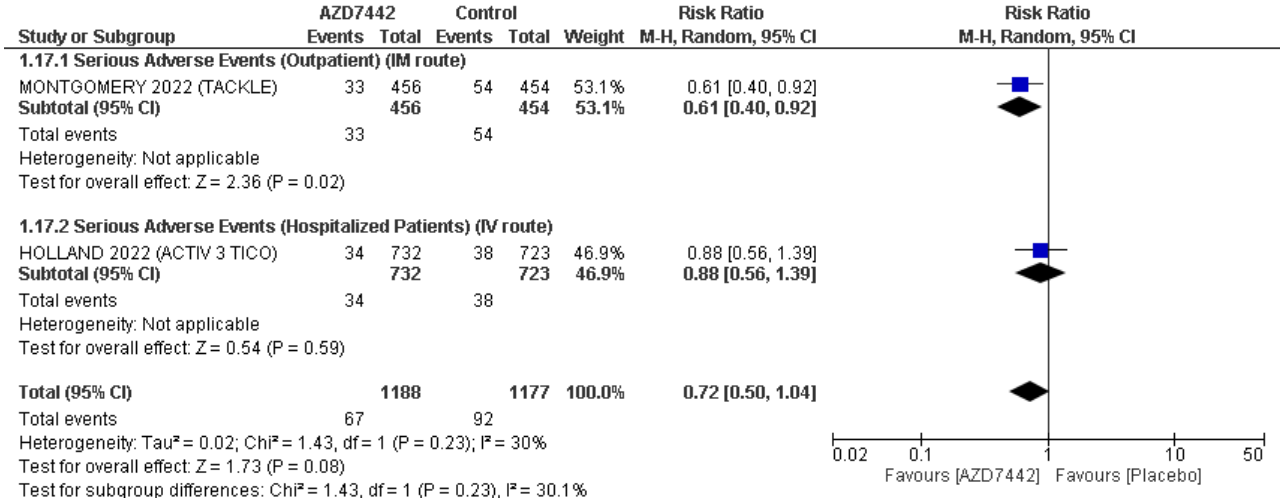

Figure 20. Serious adverse events

Appendix 7: Ongoing Studies

Clinical Trial Identifier/Title	Study Design	Country	Population	Intervention	Outcome	Estimated Date of Completion
NCT05587894 **Optimization of Antiviral Therapy in Immunocompromised COVID-19 Patients: a Randomized Factorial Controlled Strategy Trial (OPTICOV)**	Randomized	US	16 Years and older (Child, Adult, Older Adult)	•Drug: Paxlovid 5 days •Drug: Paxlovid 10 days •Drug: Tixagevimab and Cilgavimab	•Measure of SARS-CoV-2 viral load (threshold cycle (Ct) Sustained resolution or abatement or absence of signs or symptoms defined as a FLU-PRO-Plus score #1 at Day5, Day10, Day14, Day21 and Day28 •All-cause hospitalization and/ or death at Day28 •Hospitalization at Day28	January 2025

NCT04518410 **ACTIV-2: A Study for Outpatients With COVID-19**	Randomized controlled trial	US	18 Years and older (Adult, Older Adult)	• Biological: bamlanivimab • Drug: Placebo (IV) • Biological: BRII-196/BRII-198 • Biological: AZD7442 (IV) • Biological: AZD7442 (IM) • Drug: SNG001 • Drug: Camostat • Drug: Placebo (IM) • Drug: Placebo (Inhaled solution) • Drug: Placebo (oral tablet) • and 5 more	• COVID-19 symptom duration (Phase 2) • Quantification of SARS- CoV-2 RNA (Phase 2) • Proportion of participants with new adverse event (AE) # Grade 3 (Phase 2) • Cumulative incidence of death due to any cause or hospitalization due to any cause (Phase 3) • Proportion of participants with new adverse event (AE) # Grade 3 (Phase 3) • COVID-19 symptom duration (Phase 3) • Quantification of SARS- CoV-2 RNA (Phase 3) • Cumulative incidence of death from any cause or hospitalization due to any cause (Phase 2) • Cumulative incidence of death from any cause, or hospitalization due to any cause related to COVID-19 (Phase 3) • Level of SARS-CoV-2 RNA from NP swabs (Phase 2) • and 11 more	June 22, 2023

NCT04315948 **Trial of Treatments for** **COVID-19 in Hospitalized Adults** **(Discovery)**	Randomized controlled trial	Austria	18 Years and older (Adult, Older Adult)	• Drug: Remdesivir • Drug: Lopinavir/ ritonavir • Drug: Interferon Beta-1A • Drug: Hydroxychloroquine • Other: Standard of care • Drug: AZD7442 • Other: Placebo	• Percentage of subjects reporting each severity rating on a 7-point ordinal scale • Status on an ordinal scale • National Early Warning Score 2 (NEWS-2 score) • Number of oxygenation free days in the first 28 days • Incidence of new oxygen use, non-invasive ventilation or high flow oxygen devices during the trial. • Ventilator free days in the first 28 days • Incidence of new mechanical ventilation use during the trial. • Need for mechanical ventilation or death by Day 15 • Hospitalization • Mortality • and 7 more	October 2023
NCT04507256 **AZD7442 - a Potential Combination Therapy for the Prevention and Treatment of COVID-19**	Randomized controlled trial	UK	18 Years to 55 Years (Adult)	• Combination Product: AZD7442 • Other: Placebo	• Number of participants with adverse events (AEs) and serious AEs • Observed maximum concentration (Cmax) (IV infusion) • Time to reach maximum concentration (Tmax) (IV infusion) • Terminal elimination half-life, estimated as (ln2)/#z (t½#z) (IV infusion) • Area under the concentration curve from time	Completed but no results posted yet

					zero to the time of last quantifiable concentration (AUClast) (IV infusion) • Area under the concentration time curve from time zero extrapolated to infinity (AUCinf) (IV infusion) • Volume of distribution at steady state (Vss) (IV infusion) • Volume of distribution at terminal phase (Vz) (IV infusion) • Systemic clearance (CL) (IV infusion) • Cmax (IM injection) • and 8 more	
NCT05321394 **Non-inferiority Trial on Treatments in Early COVID-19**	Randomized controlled trial	Italy	50 Years and older (Adult, Older Adult)	• Drug: Sotrovimab • Drug: Tixagevimab Cilgavimab • Drug: Nirmatrelvir Ritonavir	• COVID-19 progression • Visits to the Emergency Room • Duration of supplemental oxygen therapy • Duration of hospitalization • Non-invasive ventilation • Duration of non-invasive ventilation • Mechanical ventilation • Duration of mechanical ventilation • 28-day mortality • 90-day mortality • Duration of symptoms	October 30, 2022

NCT04507256 **AZD7442 - a Potential Combination Therapy for the Prevention and Treatment of COVID-19**	Randomized controlled trial	UK	18 Years to 55 Years (Adult)	•Combination Product: AZD7442 •Other: Placebo	•Number of participants with adverse events (AEs) and serious AEs •Observed maximum concentration (Cmax) (IV infusion) •Time to reach maximum concentration (Tmax) (IV infusion) •Terminal elimination half-life, estimated as (ln2)/#z (t½#z) (IV infusion) •Area under the concentration curve from time zero to the time of last quantifiable concentration (AUClast) (IV infusion) •Area under the concentration time curve from time zero extrapolated to infinity (AUCinf) (IV infusion) •Volume of distribution at steady state (Vss) (IV infusion) •Volume of distribution at terminal phase (Vz) (IV infusion) •Systemic clearance (CL) (IV infusion)	October 19, 2021(no results posted)

NCT04723394 **Phase III Study of AZD7442 for Treatment of COVID-19 in Outpatient Adults** **(TACKLE)**	Randomized controlled trial	US	18 Years and older (Adult, Older Adult)	• Drug: AZD7442 • Drug: Placebo	• A composite of either severe COVID-19 or death from any cause through Day 29. • AEs, SAEs, and AESIs through end of study. • A composite of either death from any cause or hospitalization for COVID-19 complications or sequelae during the 168- day post-dose period (Day 1 to Day 169). • The incidence of participants with respiratory failure, defined as requirement for mechanical ventilation, ECMO, non-invasive ventilation, or high-flow nasal cannula oxygen delivery. • COVID-19 symptom severity assessments based on symptom severity scores over time during the 28-day period from and including the day of the dose of AZD7442 or placebo. • Progression through Day 29 of one or more COVID-19-associated symptoms to a worse status than recorded in the participant-reported symptom diary at study entry, prior to start of AZD7442 or placebo. • Detection (detectable versus undetectable) from baseline of SARS-CoV-2 11RofN1A3 f-rom nasal swabs through Day 29. • Level of SARS-CoV-2	October 28, 2022

					RNA	
NCT04501978 **ACTIV-3: Therapeutics for Inpatients With COVID-19** **(TICO)**	Randomized controlled trial	US	18 Years and older (Adult, Older Adult)	• Biological: LY3819253 • Drug: Placebo • Biological: Remdesivir • Biological: VIR-7831 • Biological: BRII-196/BRII-198 • Biological: **AZD7442** • Drug: MP0420 • Drug: PF-07304814	• Time from randomization to sustained recovery • All-cause mortality • Composite of time to sustained recovery and mortality • Days alive outside short-term acute care hospital • Pulmonary ordinal outcome • Pulmonary+ ordinal outcome • Incidence of clinical organ failure • Composite of death or serious clinical COVID-19 related events • Composite of cardiovascular events and thromboembolic events • Composite of grade 3 and 4 clinical adverse events, serious adverse events (SAEs) or death • and 7 more	July 2022 (with initial results)