EVIDENCE SUMMARY

RESEARCH QUESTION: **Among COVID-19 patients, should bamlanivimab in combination with etesevimab be used for treatment?**

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RECOMMENDATION

Recommendation	Certainty of Evidence	Strength of Recommendation
We suggest against the use of bamlanivimab and etesevimab combination therapy as treatment COVID-19 patients	Low	Weak

Consensus Issues
Although available evidence showed net benefit in terms of all-cause mortality, COVID-19-related hospitalizations and emergency department visits,and need for oxygen supplementation with the use of bamlanivimab and etesevimab combination therapy, there were concerns on its activity against the omicron variant, which is the predominant circulating variant at the time this recommendation was made. Studies showed that omicron variant can be resistant to this combination therapy; hence, the panel decided to reverse the previous recommendation regarding its use.

KEY FINDINGS

- The evidence on the use of bamlanivimab + etesevimab combination therapy was based on four randomized controlled trials (RCT) among non-hospitalized patients with COVID-19.
- The combination of bamlanivimab and etesevimab compared to placebo showed significant benefit in primary composite outcome of need for hospitalization, emergency room visit, and death. It also showed significant reduction in the all-cause mortality, need for hospitalization, duration of hospitalization, need for oxygenation, symptom resolution at day 15, and mean reduction in viral load compared to placebo.
- There was no significant difference in need for mechanical ventilation, intensive care unit (ICU) admission, symptom resolution at day 7, symptom resolution at day 11, and viral clearance.
- There was no significant difference in adverse events and serious adverse events between the two groups.

WHAT'S NEW IN THIS VERSION?

This version includes two new published randomized controlled trials.

PREVIOUS RECOMMENDATION
12 October 2021

We suggest the use of bamlanivimab and etesevimab combination therapy as treatment for mild to moderate, non-hospitalized COVID-19 patients with at least 1 risk factor* for progression to severe disease. *(Low certainty of evidence; Weak recommendation)*

*Risk factors for severe COVID-19: age ≥65 years, body-mass index ≥35kg/m2, 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

Consensus issues
The panel favored the use of bamlanivimab + etesevimab among non-hospitalized COVID-19 patients who are at risk for severe disease, based on the results of 2 randomized controlled trials that showed net potential benefit in terms of COVID-19 related hospitalizations and all-cause mortality, reduction in total symptom score and number of days to symptom resolution, with no significant difference in terms of adverse events. Concern regarding the drug's effectivity against variants was raised by one of the panelists. As of writing, the drug has no emergency use authorization from the Philippine FDA, thus may only be used in the context of clinical trials.

INTRODUCTION

Neutralizing monoclonal antibodies are being studied as a way to boost the immune response to SARS-CoV-2. The investigational neutralizing IgG1 monoclonal antibody bamlanivimab (LY-CoV555; Lilly) was shown to bind to the receptor binding domain of the spike protein of SARS-CoV-2 viruses, which blocks attachment of the virus to the human ACE2 receptor [1]. Etesevimab (LY3832479 or LU-CoV016) is another potent monoclonal antibody that binds to a different epitope of the spike protein of SARS-CoV-2 viruses. Preclinical studies have shown that etesevimab may be able to neutralize even the emerging variants thus, the combination of the two drugs may prove to be an effective treatment against COVID-19 and the predominant variants [2,3].

REVIEW METHODS

An updated systematic search was performed from the date of last search in the initial review 03 September 2022 to 28 October 2022 using Medline, CENTRAL, and Google Scholar 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 bamlanivimab or etesevimab. We also searched COVID-NMA: COVID-19 Open Living Evidence Synthesis to Inform Decision data and searched for ongoing studies in the NIH clinicaltrials.gov and various trial registries. Preprints were also searched using MedRxiv, Chinaxiv, and BioRxiv. Only randomized controlled trials that compared a combination of bamlanivimab and etesevimab against placebo or standard care were included in this review. No limits were placed on age, COVID-19 severity, and dosing.

RESULTS

Four RCTs investigated the efficacy of bamlanivimab in combination with etesevimab compared to placebo in 2,072 patients with confirmed COVID-19. All of the included studies were done in the United States. All studies included non-hospitalized adult patients with confirmed mild to moderate COVID-19 [4-7]. Three studies included pediatric population aged 12-17 years old with at least one risk factor for progression to severe disease (BMI least 85th percentile, sickle cell disease, congenital or acquired heart disease, neurodevelopmental disorders, dependence on a medical-related mechanical device or procedure, respiratory disease; diabetes mellitus immunocompromised condition, and/or immunosuppressive treatment). Three studies included aged 18 years and older with at least one risk factor for severe disease (≥65 years, BMI ≥35, chronic kidney disease, diabetes mellitus, immunocompromised condition, cardiovascular disease, hypertension, chronic respiratory disease, and/or immunosuppressive treatment) [5-7]. One of the studies was a phase 2/3 of the BLAZE-1 trial which determined the efficacy of bamlanivimab monotherapy 700mg, 2,800mg, 7,000mg or bamlanivimab in combination with etesevimab 2,800mg/2,800mg compared to placebo [4]. One study was the phase 3 trial of BLAZE-1 trial which compared the efficacy of bamlanivimab in combination with etesevimab 2,800mg/2,800mg compared to placebo [5]. Two studies presented results of the phase 3 trial of BLAZE-1 trial which compared the efficacy of bamlanivimab in combination with etesevimab 700mg/1400mg compared to placebo [6,7]. Only the results of bamlanivimab in combination with etesevimab compared to placebo were pooled. All studies administered bamlanivimab in combination with etesevimab intravenously as single dose.

The combination of bamlanivimab and etesevimab when compared to placebo showed significant decrease in the primary composite outcome comprised of the need for hospitalization, emergency department visit, and death (RR 0.23; 95% CI 0.14-0.40; I^2=0%; Moderate certainty) [4-6]. The combination of bamlanivimab and etesevimab likewise showed significant decrease in all-cause mortality (RR 0.05; 95% CI 0.01-0.40; I^2=0%; Low certainty) [5-6] need for hospitalization (RR 0.25; 95% CI 0.14-0.43; I^2=0%; Moderate certainty) [4,5,7], duration of hospitalization (MD -5.06 days; 95% CI -7.31 to -2.80 days; I^2=90%; Low certainty) [5,7], and the need for oxygen supplementation (RR 0.06; 95% CI 0.01-0.44; Low certainty) [7]. No significant benefit was found with the use of bamlanivimab and etesevimab when compared to placebo in terms of ICU admission (RR 0.20; 95% CI 0.04-1.10; I^2=0%; Low certainty) [4,7] and need for mechanical ventilation (RR 0.17; 95% CI 0.01-4.13; Low certainty) [7]. In terms of clinical improvement, the combination of bamlanivimab and etesevimab when compared to placebo only showed significant benefit in symptom resolution at day 15 (RR 1.83; 95% CI 1.06-3.17; Low certainty) [4]. However, symptom resolution at day 7 (RR 1.17; 95% CI 0.98-1.40; I^2=0%; Low certainty)[4-6] and day 11 (RR 1.04; 95% CI 0.74-1.45; I^2=62%; Very low certainty [4-6] were inconclusive. The use of bamlanivimab and etesevimab showed significant benefit in the mean reduction in viral load at day 7 (MD -0.48 95% CI -0.73 to -0.23; Moderate certainty) [4] and persistently high viral load at day 7 (RR 0.35; 95% CI 0.29-0.42; I^2=0%; Moderate certainty) [5,6] when compared to placebo. However, the combination of bamlanivimab and etesevimab showed no benefit in the viral clearance at day 7 (RR 1.36; 95% CI 0.89-2.06; I^2=0%; Low certainty) [4-6].

Safety

There was no significant difference in adverse events (RR 0.91; 95% CI 0.64-1.28, I^2=51%; Very low certainty) [4-6] and serious adverse events (RR 1.43, 95% CI 0.59 to 3.46, I^2=0%; Low certainty) [4-6] with the use of bamlanivimab and etesevimab when compared to placebo. The most common adverse events observed were nausea, rash/pruritus [4,5], dizziness [5,6], diarrhea, and hypertension [5], transaminitis, anemia, and arthralgia [6]. The serious adverse event noted in the combination bamlanivimab and etesevimab group for one study was a urinary tract infection, deemed unrelated to COVID-19 by the investigators [4]. Other serious adverse events reported were acute myocardial infarction, angina pectoris, unstable angina, atrial flutter, atrial fibrillation, coronary artery disease, macular edema, intestinal obstruction, diabetic ketoacidosis, hyperglycemia, acute kidney injury and hypoxia [5-6].

The overall certainty of evidence was graded low because of serious imprecision and serious indirectness in three of the critical outcomes (serious adverse event, ICU admission, and all-cause mortality). Evidence was downgraded for serious indirectness due to lack of representativeness of the population in terms of the

current prevailing SARS-CoV-2 variant, the omicron variant. Appraisal of study quality showed low risk of bias. The risk of bias summary is in Appendix 4. The GRADE evidence profile is in Appendix 5.

RECOMMENDATIONS FROM OTHER GROUPS

Group or Agency	Recommendation	Strength of Recommendation / Certainty of Evidence
United States Food and Drug Administration as of 04 May 2022 [11]	Due to the high frequency of the Omicron variant, bamlanivimab and etesevimab are not currently authorized in any U.S. region. Therefore, these drugs may not be administered for treatment or post-exposure prevention of COVID-19 under the Emergency Use Authorization until further notice by the Agency. However, it is the recommendation of the U.S. Government that product be retained in the event that future SARS-CoV-2 variants, which may be susceptible to bamlanivimab and etesevimab, emerge and become prevalent in the United States.	
United States National Institutes of Health as of 28 December 2022 [12]	Because the Omicron VOC is now the dominant variant in the United States, the Panel recommends against using bamlanivimab plus etesevimab.	Strong recommendation, Expert opinion
Infectious Diseases Society of America as of 21 November 2022 [13]	Among ambulatory patients with mild-to-moderate COVID-19 at high risk for progression to severe disease, the IDSA guideline panel suggests treatment with anti-SARS-CoV-2 monoclonal antibodies with activity** against the predominant regional variants* within 7 days of symptom onset rather than no anti-SARS-CoV-2 monoclonal antibodies.	Conditional recommendation, Moderate certainty of evidence
Australian COVID-19 Guidelines as of 19 December 2022 [14]	Do not use bamlanivimab plus etesevimab for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.	
World Health Organization as of 06 October 6, 2022 [15]	No recommendation on the use of bamlanivimab + etesevimab combination in the treatment of COVID-19.	

ONGOING STUDIES AND RESEARCH GAPS

There are currently five ongoing randomized clinical trials on bamlanivimab + etesevimab as treatment for COVID-19. One of the studies is a phase 2 trial with 1,755 participants awaiting published results. Three of the ongoing studies included children and adolescent population. A summary of ongoing trials is presented in Appendix 7.

ADDITIONAL CONSIDERATIONS FOR EVIDENCE TO DECISION (ETD) PHASE

COST

In the United States, the government was cited to have expended about US$210,000,000 for 100,000 doses for bamlanivimab and etesevimab, translating to approximately US$2,100 (₱105,000) per dose [8].

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

At present, there is still no emergency use authorization for bamlanivimab and etesevimab in the Philippines. Because of the predominance of omicron variant which causes several mutation on spike proteins, there have been concerns on the efficacy of antibody therapy of COVID-19 including bamlanivimab and etesevimab. Studies showed that omicron variant can be resistant to this combination [9,10].

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[15] World Health Organization. Therapeutics and COVID-19 Living Guidelines v13.0. Updated January 13, 2023. Available at https://app.magicapp.org/#/guideline/nBkO1E/rec/LwrMyv.

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 (10)				• COVID-19 has affected millions of people worldwide and has caused substantial mortality and morbidity.
Benefits	Large (2)	Moderate (6)	Small (2)	Uncertain		• The combination of bamlanivimab and etesevimab compared to placebo showed significant benefit in primary composite outcome of need for hospitalization, emergency room visit, and death. It also showed significant reduction in the all-cause mortality, need for hospitalization, duration of hospitalization, need for oxygenation, symptom resolution at day 15, and mean reduction in viral load compared to placebo.
Harm	Large (1)	Small (8)	Uncertain (1)			• No significant difference in adverse events (RR 0.91, [0.64-1.287]) and serious adverse events ((RR 1.43, [0.59-3.46]) vs placebo. • Serious adverse events reported were acute myocardial infarction, angina pectoris, unstable angina, atrial flutter, atrial fibrillation, coronary artery disease, macular edema, intestinal obstruction, diabetic ketoacidosis, hyperglycemia, acute kidney injury, and hypoxia.
Certainty of Evidence	High	Moderate (2)	Low (8)	Very low		• Low because of serious imprecision and serious indirectness (population included in the study is not representative of the current predominant Omicron variant) in three critical outcomes (all-cause mortality, serious adverse

							events)).
Balance of effects	Favors drug (9)	Does not favor drug (1)	Uncertain				• There is net potential benefit in terms of COVID-19 related hospitalizations and all-cause mortalities, reduction in total symptom score, and number of days to symptom resolution, with no significant difference in terms of adverse events and serious adverse events. • The studies included may not be reflective of SARSCOV2 infection with omicron variant since the studies are done on January 2, 2021 and earlier. • Because of the predominance of omicron variant which causes several mutation on spike proteins, there have been concerns on the efficacy of antibody therapy of COVID-19 including bamlanivimab and etesevimab. Studies showed that omicron variant can be resistant to this combination (Shah 2021 and Tao 2022)
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	• $2,100 or ₱105,000 for a single course (1 dose bamlanivimab + etesevimab IV)
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 bamlanivimab + etesevimab treatment. • The cost was derived from foreign news websites (Forbes, PMLive).

Cost effectiveness	No included studies (6)	Favors the comparison	Does not favor either the intervention or the comparison (1)	Favors the intervention (3)		• None of the included trials assessed 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)			• There is no emergency use authorization for this drug in our country but this can be use under compassionate special permit.

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 Infections"[Mesh] OR "Coronavirus"[Mesh] OR coronavirus OR novel coronavirus OR NCOV OR "COVID-19" [Supplementary Concept] OR COVID19 OR COVID 19 OR COVID-19 OR "severe acute respiratory syndrome coronavirus 2" [Supplementary Concept] OR severe acute respiratory syndrome coronavirus 2 OR SARS2 OR SARS 2 OR SARS COV2 OR SARS COV 2 OR SARS-COV-2} AND (Bamlanivimab) Filters: from September 1, 2021 to October 27, 2022	October 27, 2022 12:00AM	182	3
CENTRAL	MeSH descriptor: [Coronaviridae Infections] explode all trees OR MeSH descriptor: [Coronavirus] explode all trees 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-2 AND (Bamlanivimab) Filters: from September 3, 2021 to October 27, 2022	October 27, 2022 2:35PM	42	3
Google Scholar	“Bamlanivimab AND etesevimab” AND COVID AND randomized trial Since 2021	October 27, 2022 3:48PM	706	3
COVID-NMA initiative	Bamlanivimab and etesevimab	October 26, 2022 10PM	11	3
ClinicalTrials.gov	COVID19 AND bamlanivimab	October 28, 2022 2:46PM	16	0
Chinese Clinical Trial Registry	Bamlanivimab	October 28, 2022 3:39PM	0	0
EU Clinical Trials Register	Bamlanivimab	October 28, 2022 3:41PM	3	0
Republic of Korea – Clinical Research Information Service	Bamlanivimab	October 28, 2022 4:25PM	0	0
Japan Primary Registries Network/ NIPH	Bamlanivimab	October 27, 2022 3:48PM	0	0

Clinical Trials Search				
CenterWatch	Bamlanivimab	October 28, 2022 4:29PM	2	0
chinaxiv.org	Bamlanivimab	October 28, 2022 4:48PM	0	0
Medrxiv.org	COVID AND bamlanivimab AND etesevimab Filters: September 3, 2021 to October 28, 2022	October 27, 2022 4:55PM	67	1
Biorxiv.org	COVID AND bamlanivimab AND etesevimab Filters: September 3, 2021 to October 28, 2022	October 27, 2022 5:00PM	98	0

Appendix 3: Characteristics of Included Studies

Study ID	Patients (n) & Duration of Follow-Up	Interventions	Outcomes	Study Design
Effect of Bamlanivimab as Monotherapy or in Combination with Etesevimab on Viral Load in Patients with Mild to Moderate COVID-19: A Randomized Clinical Trial BLAZE 1 *Gottlieb et al., USA* Phase 2/3	N=268 Age ≥18 years old Non-hospitalized confirmed COVID-19 patients with mild to moderate symptoms Duration of follow-up: 29 days Enrollment: August 22-September 3, 2020	EXPERIMENTAL: Bamlanivimab 2800mg + Etesevimab 2800mg IV CONTROL: Placebo IV	PRIMARY: Change in SARS-CoV-2 log viral load at day 11 SECONDARY: Time to viral clearance, clinical recovery, COVID-19 related hospitalization or all-cause death, adverse events	Randomized, double-blind, placebo-controlled
Bamlanivimab plus Etesevimab in Mild or Moderate COVID-19 BLAZE-1 *Dougan et al.,2021 USA* Phase 3	N=1,035 Ambulatory confirmed COVID-19 Age 12-17 years and BMI least 85th percentile sickle cell disease congenital or acquired heart disease neurodevelopmental disorders dependence on a medical-related mechanical device or procedure respiratory disease; diabetes mellitus immunocompromised condition immunosuppressive treatment. ≥18 years old age risk factor for severe ≥65 years BMI ≥35 chronic kidney disease	EXPERIMENTAL: Bamlanivimab 2800mg + Etesevimab 2800mg IV Single infusion for 1 hr CONTROL: Placebo IV	PRIMARY: COVID-19 related hospitalization or all-cause death SECONDARY: Time to sustained patient-reported resolution of symptoms, reduction in viral load, time to viral clearance, adverse events	Randomized, double-blind, placebo-controlled

	diabetes mellitus immunocompromised condition cardiovascular disease hypertension chronic respiratory disease immunosuppressive treatment Mild to moderate disease <u>Duration of follow-up:</u> 29 days Enrollment: September 4-December 8, 2020			
New Studies				
A Randomized, Placebo-Controlled Clinical Trial of Bamlanivimab and Etesevimab Together in High-Risk Ambulatory Patients With COVID-19 and Validation of the Prognostic Value of Persistently High Viral Load BLAZE-1 Dougan et al Phase 3	N=769 Ambulatory confirmed COVID-19 Age 12-17 years with risk factor for severe disease ≥18 years old with risk factor for severe disease Mild to moderate disease <u>Duration of follow-up:</u> 29 days Enrollment: December 9 2020-January 2, 2021	EXPERIMENTAL: Bamlanivimab 700mg + Etesevimab 1400mg IV CONTROL: Placebo IV	PRIMARY: COVID-19 related hospitalization or all-cause death SECONDARY: Change in SARSCOV2 viral load from baseline Time to viral clearance Time to symptom improvement and resolution Adverse events	Randomized, double-blind, placebo-controlled

Bamlanivimab and Etesevimab Improve Symptoms and Associated Outcomes in Ambulatory Patients at Increased Risk for Severe Coronavirus Disease 2019: Results From the Placebo-Controlled Double-Blind Phase 3 BLAZE-1 Trial Chen P et al US Phase 3	N=769 Ambulatory confirmed COVID-19 Age 12-17 years with risk factor for severe disease ≥18 years old with risk factor for severe disease Mild to moderate disease <u>Duration of follow-up:</u> 29 days Enrollment: December 9 2020-January 2, 2021	EXPERIMENTAL: Bamlanivimab 700mg + Etesevimab 1400mg IV CONTROL: Placebo IV	Symptom resolution Symptom improvement Time to symptom resolution Mean duration of hospitalization	Randomized, double-blind, placebo-controlled

*for the bamlanivimab + etesevimab + placebo groups only

Appendix 4. Study Appraisal

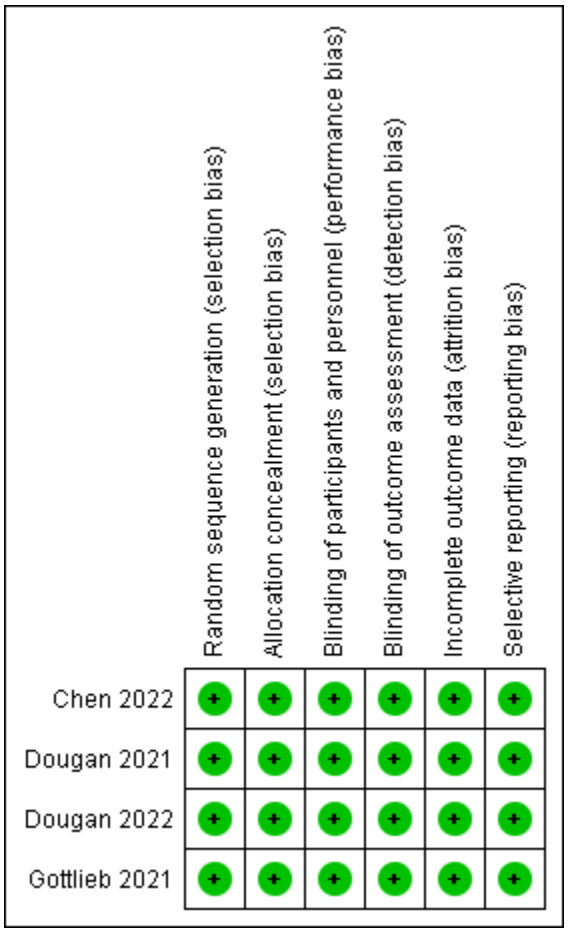

Figure 1. Risk of bias summary

Appendix 5. GRADE Evidence Profile

Author(s): Katherine Ruth Oracion Relato, MD
Question: Bamlanivimab in combination with etesevimab compared to placebo for treatment of COVID-19
Setting: Non-hospitalized
Bibliography: 1. Gottlieb RL, Nirula A, Chen P, et al. Effect of bamlanivimab as monotherapy or in combination with etesevimab on viral load in patients with mild to moderate COVID-19: A randomized clinical trial. JAMA - J Am Med Assoc. [Internet]. 2021;325(7):632-644. Available from: doi:10.1001/jama.2021.02022. Dougan M, Nirula, Azizad M et al. Bamlanivimab plus Etesevimab in Mild or Moderate COVID-19. N Engl J Med. 2021. [Internet]. Available from: doi:10.1056/NEJMoa2102685.3 Dougan M, et. al. A Randomized, Placebo-Controlled Clinical Trial of Bamlanivimab and Etesevimab Together in High-Risk Ambulatory Patients With COVID-19 and Validation of the Prognostic Value of Persistently High Viral Load. CID 2022:75. [Internet]. https://doi.org/10.1093/cid/ciab9124. Chen P, et. al. Bamlanivimab and Etesevimab Improve Symptoms and Associated Outcomes in Ambulatory Patients at Increased Risk for Severe Coronavirus Disease 2019: Results From the Placebo-Controlled Double-Blind Phase 3 BLAZE-1 Trial. OFID. 7 April 2022. [Internet].https://doi.org/10.1093/ofid/ofac172

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bamlanivimab in combination with etesevimab	placebo	Relative (95% CI)	Absolute (95% CI)		
need for hospitalization, emergency visit and deaths												
3	randomised trials	not serious	not serious	serious[a]	not serious	none	16/1141 (1.4%)	60/931 (6.4%)	**RR 0.23** (0.14 to 0.40)	**50 fewer per 1,000** (from 55 fewer to 39 fewer)	⨁⨁⨁◯ Moderate	CRITICAL
Adverse events												
3	randomised trials	not serious	serious[b]	serious[a]	serious[c]	none	134/1141 (11.7%)	127/931 (13.6%)	**RR 0.91** (0.64 to 1.28)	**12 fewer per 1,000** (from 49 fewer to 38 more)	⨁◯◯◯ Very low	CRITICAL
Serious adverse events												
3	randomised trials	not serious	not serious	serious[a]	serious[c]	none	14/1141 (1.2%)	8/931 (0.9%)	**RR 1.43** (0.59 to 3.46)	**4 more per 1,000** (from 4 fewer to 21 more)	⨁⨁◯◯ Low	CRITICAL
All-cause mortality												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bamlanivimab in combination with etesevimab	placebo	Relative (95% CI)	Absolute (95% CI)		
2	randomised trials	not serious	not serious	serious[a]	serious[d]	none	0/1029 (0.0%)	14/775 (1.8%)	**RR 0.05** (0.01 to 0.39)	**17 fewer per 1,000** (from 18 fewer to 11 fewer)	⨁⨁◯◯ Low	CRITICAL
Hospitalization												
3	randomised trials	not serious	not serious	serious[a]	not serious	none	15/1060 (1.4%)	54/827 (6.5%)	**RR 0.25** (0.14 to 0.43)	**49 fewer per 1,000** (from 56 fewer to 37 fewer)	⨁⨁⨁◯ Moderate	CRITICAL
ICU admission												
2	randomised trials	not serious	not serious	serious[a]	serious[c,d]	none	1/542 (0.2%)	5/310 (1.6%)	**RR 0.20** (0.03 to 1.20)	**13 fewer per 1,000** (from 16 fewer to 3 more)	⨁⨁◯◯ Low	CRITICAL
Oxygen supplementation												
1	randomised trials	not serious	not serious	serious[a]	serious[d]	none	1/511 (0.2%)	9/258 (3.5%)	**RR 0.06** (0.01 to 0.44)	**33 fewer per 1,000** (from 35 fewer to 20 fewer)	⨁⨁◯◯ Low	CRITICAL

CI: confidence interval; **MD:** mean difference; **OR:** odds ratio; **RR:** risk ratio; **SMD:** standardised mean difference

Explanations

a. not representative of Omicron variant
b. I2=51%
c. wide confidence interval
d. low event rate

Appendix 6. Forest Plots

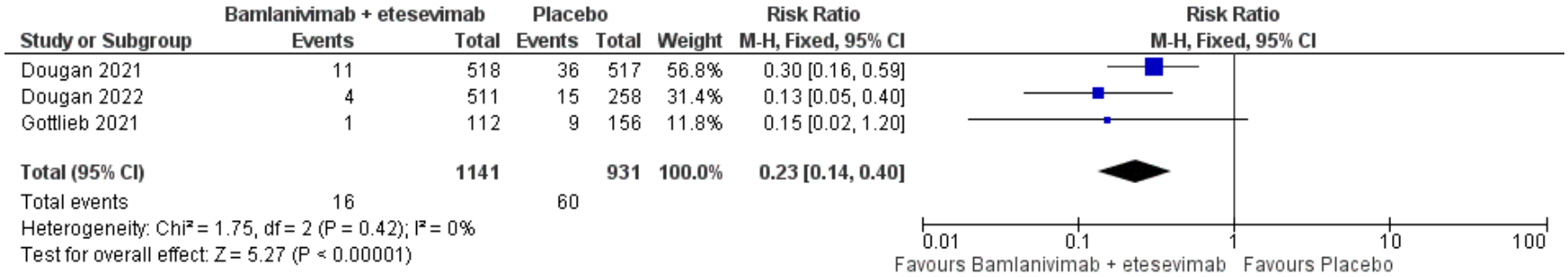

Figure 2. Composite outcomes (need for hospitalizations, emergency room visit and all-cause mortality)

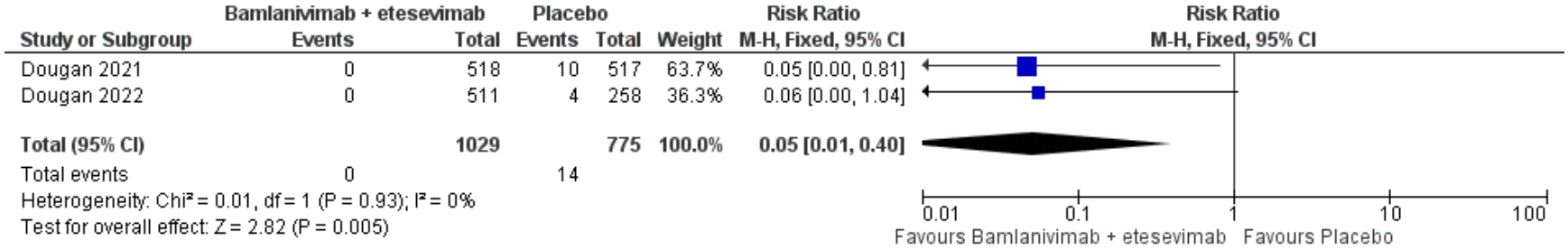

Figure 3. All-cause mortality

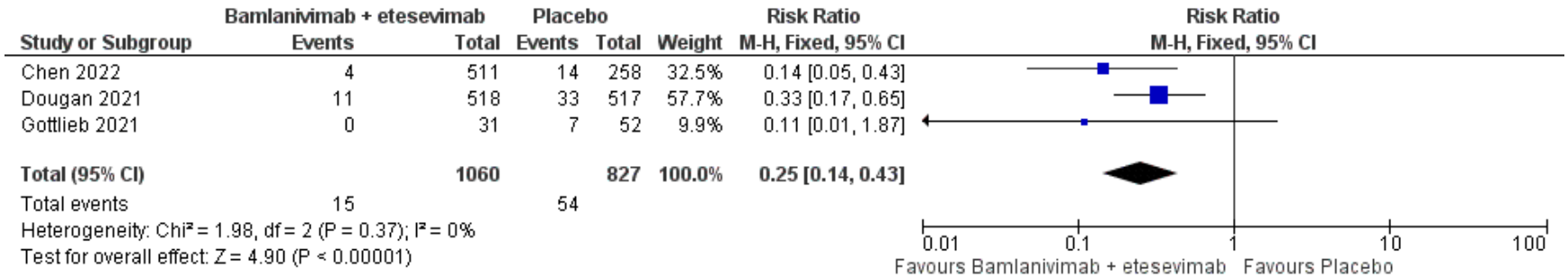

Figure 4. Need for Hospitalization

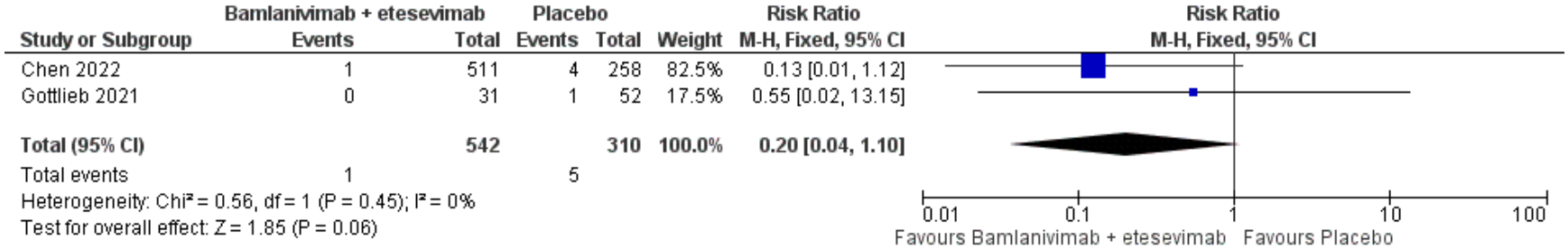

Figure 5. ICU admission

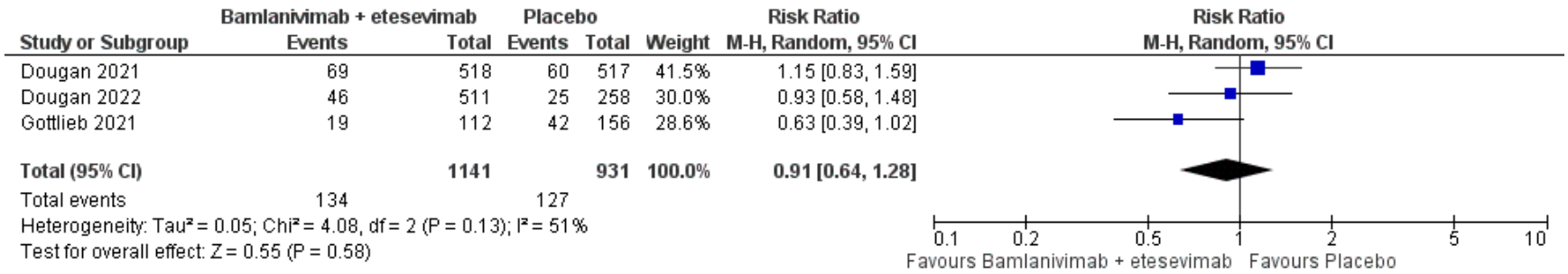

Figure 6. Adverse events

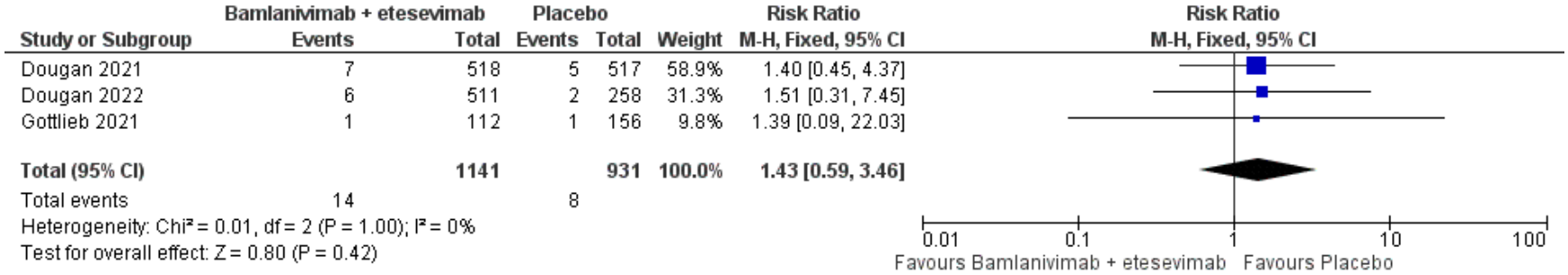

Figure 7. Serious Adverse Events

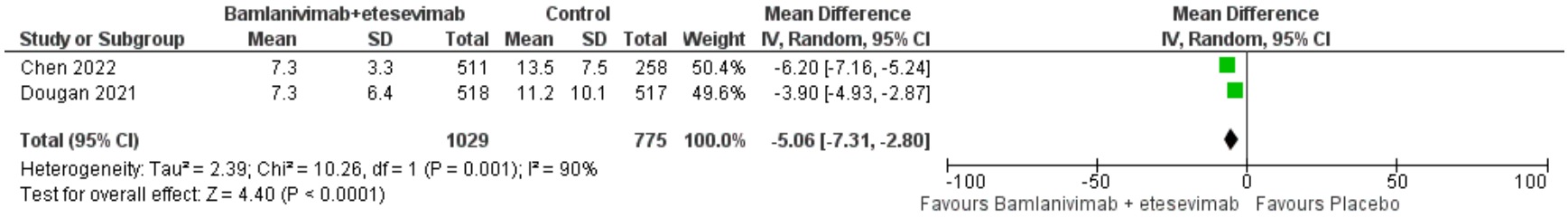

Figure 8. Duration of hospitalization

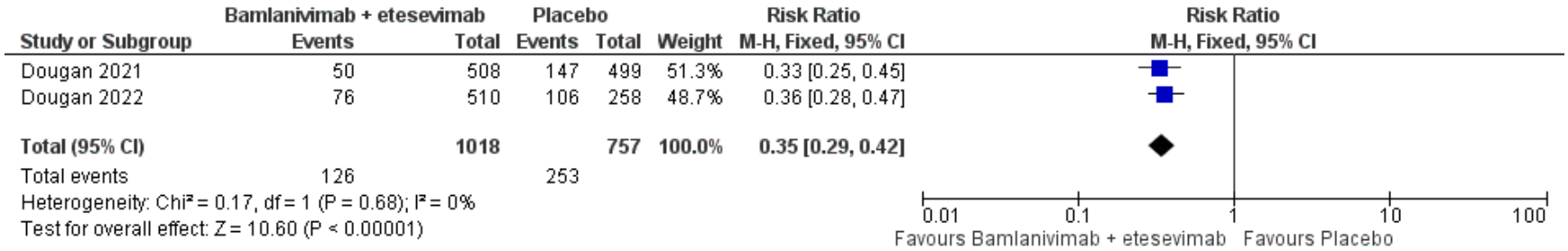

Figure 9. Persistently High Viral Load

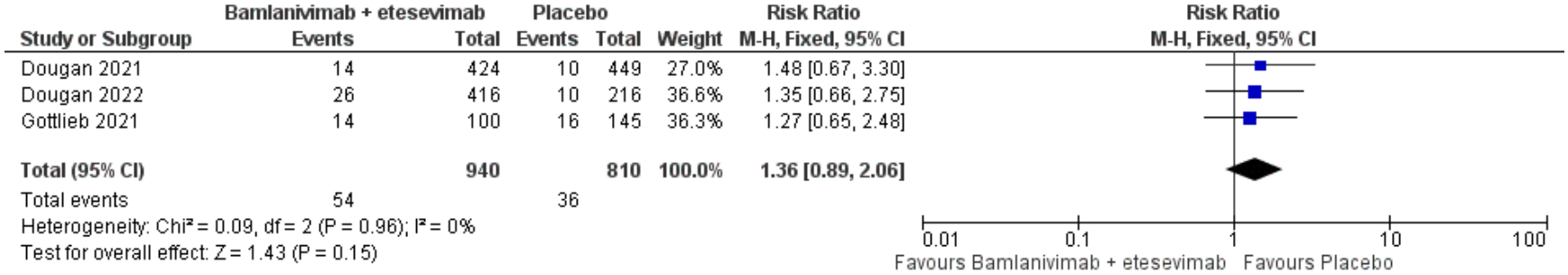

Figure 10. Viral Clearance

Appendix 7. Table of Ongoing Studies

Clinical Trial Identifier/Title	Study Design	Population	Intervention	Outcome	Completion
NCT04427501 A Study of LY3819253 (LY-CoV555) and LY3832479 (LY-CoV016) in Participants With Mild to Moderate COVID-19 Illness (BLAZE-1) Phase 2/3 recruiting	Randomized, double blind, sequential assignment	N=3360 Age 0 years and older including pregnant Confirmed COVID-19, Not hospitalized with mild to moderate symptoms With 1risk for progression to severe disease Exclusion: Previous infection Received SARS-COV2 vaccination	Bamlanivimab vs. bamlanivimab + etesevimab vs. placebo	Percentage of patients who experience COVID-related hospitalization or death from any cause up to 29 days from baseline; change from baseline to day 11 in viral load; adverse events	October 27, 2023
NCT04634409 A Study of Immune System Proteins in Participants With Mild to Moderate COVID-19 Illness BLAZE-4 Phase 2 Completed Awaiting results	Randomized Double blind parallel assignment	N=1755 >12 years old Confirmed COVID-19, Not hospitalized with mild to moderate symptoms Exclusion: Previous infection Received SARS-COV2 vaccination	Bamlanivimab + etesevimab vs. bamlanivimab vs. placebo	Percentage of participants with SARS-CoV-2 viral load greater than 5.27	July 1, 2022
EudraCT 2021-002612-31 Adaptive, randomized, placebo-controlled trial to evaluate the efficacy of monoclonal antibodies in outpatients with mild or moderate COVID-19 Phase 3	Randomized, placebo-controlled trial	N=1260 >50 years old Adult patients with mild confirmed COVID-19 Exclusion: Previous infection Received SARS-COV2 vaccination	Bamlanivimab + etesevimab vs. casirivimab + imdevimab vs. placebo	Prevention of disease progression (need for oxygen therapy supplementation, hospitalization and/or death)	Not mentioned

Ongoing recruitment					
EudraCT 2021-004035-88 A randomized, open-label, active controlled, parallel group, multicenter phase 3 study to evaluate the efficacy and tolerability of bamlanivimab and etesevimab, casirivimab and imdevimab, and sotrovimab versus standard of care in patients with mild to moderate COVID-19 disease (AntiCov) Phase 3 Recruitment may be ongoing or finished	Randomized, open-label, parallel assignment	N=400 >12 years old Patients with mild to moderate confirmed COVID-19 infection Exclusion: Previous infection	Bamlanivimab + etesevimab vs. casirivimab + imdevimab vs. sotrovimab vs. placebo	Prevention of disease progression (hospitalization in intensive care unit, peripheral oxygen saturation ≤92%, oxygen desaturation ≤4%)	Not mentioned
EudraCT 2021-004266-35 A phase 3, multicentre, single-blinded, randomized controlled study to compare the efficacy and safety of Casirivimab and Imdevimab or Bamlanivimab and Etesevimab or Sotrovimab in COVID-19 home patients at high risk of hospitalization. (MAI COVID-19) Phase 3 Ongoing recruitment	Single blinded randomized controlled trial	N= 552 >18 years old Mild to moderate COVID-19 patients at high risk of progression to severe COVID-19 and / or hospitalization Exclusion: Beta and gamma variant SARS COV2 vaccine <15 days	Bamlanivimab + etesevimab vs. casirivimab + imdevimab vs. sotrovimab vs. placebo	Clinical worsening (hospitalization or death day 29) Adverse event	Not mentioned