EUnetHTA Joint Action 3 WP4

Rapid Collaborative Review

BAMLANIVIMAB MONOTHERAPY AND BAMLANIVIMAB PLUS ETESEVIMAB COMBINATION FOR THE TREATMENT OF COVID-19

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This Rapid Collaborative Review was published before the compounds under review are granted Marketing Authorisation by the European Medicines Agency (EMA). At time of publication, to the best of the knowledge of EUnetHTA, the EMA Rolling Review is still ongoing. Under Article 5(3)[1] the EMA has issued an advice on the use of the compound in European Member States. Therefore, EUnetHTA has decided to publish the Rapid Collaborative Review to support the Member States in potential HTA activities on this compound. However, when Marketing Authorisation is granted, this Rapid Collaborative Review needs to be read with caution as the indication used in this report may be different from the indication approved by EMA. The authors of this report reserve the right to edit the report at a later point in time if necessary.

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Conflict of interest

All authors, co-authors, dedicated reviewers, external experts (patients or patient representatives) involved in the production of this assessment have declared they have no conflicts of interest in relation to the technology and comparator(s) assessed according to the EUnetHTA declaration of interest (DOI) form. Conflict of Interest was evaluated following the EUnetHTA Procedure Guidance for handling DOI form (https://eunethta.eu/doi).

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[1] https://www.ema.europa.eu/en/documents/referral/eli-lilly-company-limited-antibody-combination-bamlanivimab/etesevimab-covid19-article-53-procedure-conditions-use-conditions-distribution-patients-targeted_en.pdf

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LIST OF ABBREVIATIONS

2019-nCoV	2019 novel coronavirus
AE	Adverse events
ARDS	Acute Respiratory Distress Syndrome
BAM	Bamlanivimab
BMI	Body Mass Index
CDSR	Cochrane Database of Systematic Reviews
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CMA	Conditional Marketing Authorization
COPD	Chronic Obstructive Pulmonary Disorder
CSR	Clinical Study Reports
CT	Cycle Threshold
CV	Cardiovascular
DOI	Declaration of Interest
DR	Dedicated Reviewers
COVID-19	Coronavirus Disease 2019
ECDC	European Centre for Disease Prevention and Control
ECMO	Extracorporeal membrane oxygenation
ED	Emergency Department
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
EUA	Emergency Use Authorization
EEA	European Economic Area
EUnetHTA	European Network of Health Technology Assessment
EuroMOMO	European Mortality Monitoring
HRQoL	Health-related quality of life
HTA	Health Technology Assessment
HTAi	Health Technology Assessment international
ICD-codes	Classification of Disease Codes
ICU	Intensive Care Unit
PICO	Population, intervention, control, outcome
MAH	Marketing Authorisation Holder
MEDLINE	Medical Literature Analysis and Retrieval System Online
PaO2/FiO2	Ratio of arterial partial pressure of oxygen to fraction of inspired oxygen
PBO	Placebo
PICO	Population, intervention, control, outcome
PTJA	Pharmaceutical Joint Assessment
RCT	Randomized Controlled Trial
REA	Relative Effectiveness Assessment
RoB	Risk of Bias
RR	Relative risk
SAE	Serious adverse event
SARS-CoV	Severe Acute Respiratory Syndrome Coronavirus
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SLR	Systematic Literature Review
SpO2	Oxygen saturation
SR	Systematic review
TEAE	Treatment-Emergent Adverse Event
VOC	Variant of Concern
VOI	Variants of Interest
WHO	World Health Organization
WP4	Work Package 4

1 INTRODUCTION

In 2020, EUnetHTA prioritized its activities around Coronavirus disease 2019 (COVID-19) to respond to the public health emergency.

In terms of COVID-19 products, EUnetHTA is producing 'Rapid Collaborative Reviews' for diagnostic testing as well as for therapeutic treatments and 'Rolling Collaborative Reviews' for therapeutic treatments. These are evidence-based reports with a timely synthesis of available evidence on the comparative effectiveness and safety of health technologies (diagnostic, therapeutic, etc.) for the management of the current pandemic, with continuous updates as research evolves[2].

1.1 Overview of the disease: COVID-19

A novel coronavirus, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), was first identified in December of 2019 in Wuhan, China as causing a respiratory illness designated as Coronavirus disease 2019, or COVID-19. On 30 January 2020, the International Health Regulations Emergency Committee of the WHO declared the COVID-19 outbreak a public health emergency of international concern. Since then, there has been rapid spread of the virus, leading to a global pandemic of COVID-19. As of May 6, 2021, more than 153 million cases of COVID-19—caused by SARS-CoV-2 infection—have been reported globally, including more than 3,2 million deaths. According to current evidence, SARS-CoV-2 is primarily transmitted between people through respiratory droplets and contact routes. Human-to-human transmission is occurring extensively. Precautions to prevent human-to-human transmission are appropriate for both suspected and confirmed cases. The estimated incubation period for COVID-19 is up to 14 days from the time of exposure, with a median incubation period of 4 to 5 days. Individuals of all ages are at risk for infection and severe disease. The probability of serious COVID-19 disease is higher in people aged ≥60 years, those living in a nursing home or long-term care facility, and those with chronic medical conditions [1], [2]. FDA defines groups of individuals (adults and pediatric patients age 12-17 years and weighing at least 40 kg) having high risk for progression to severe COVID-19 and/or hospitalisation as patients who meet at least one of the following criteria: older age (for example age ≥65 years of age); obesity or being overweight (for example, adults with BMI >25 kg/m2, or if age 12-17, have BMI ≥85th percentile for their age and gender based on CDC growth charts; pregnancy; chronic kidney disease; diabetes; immunosuppressive disease or immunosuppressive treatment; cardiovascular disease (including congenital heart disease) or hypertension; chronic lung diseases (for example, chronic obstructive pulmonary disease, asthma [moderate-to-severe], interstitial lung disease, cystic fibrosis and pulmonary hypertension); sickle cell disease; neurodevelopmental disorders (for example, cerebral palsy) or other conditions that confer medical complexity (for example, genetic or metabolic syndromes and severe congenital anomalies); having a medical-related technological dependence (for example, tracheostomy, gastrostomy, or positive pressure ventilation (not related to COVID-19)). Other medical conditions or factors (for example, race or ethnicity) may also place individual patients at high risk for progression to severe COVID-19 and authorization of bamlanivimab and etesevimab under the EUA is not limited to the medical conditions or factors listed above. As defined by EMA, risk factors may include but are not limited to: advanced age; obesity; cardiovascular disease, including hypertension; chronic lung disease, including asthma; type 1 or type 2 diabetes mellitus; chronic kidney disease, including those on dialysis; chronic liver disease; immunosuppressed, based on prescriber's assessment [3], [4], [5], [6], [7].

SARS-CoV-2 Variants of Concern

The data on the emergence, spread, and clinical relevance of these new variants is rapidly evolving; this is especially true for research on how variants might affect transmission rates, disease progression, vaccine development, and the efficacy of current therapeutics [2]. Since December 2020, several SARS-CoV-2 variants of concern have been identified. The B.1.1.7 variant first seen in the United Kingdom is more infectious than earlier variants and may be more virulent. It has become the predominant variant in the United Kingdom, and it continues to spread across the globe, including throughout many regions of the United States. The B.1.351 variant that was originally identified in South Africa is now the

[2] https://eunethta.eu/services/COVID-19/

predominant variant in that region and has spread to many other countries, including the United States. The P.1 variant was originally identified in Manaus, Brazil, and has now been identified in the United States. Other variants that have emerged in the United States are receiving attention, such as the B.1.427/B.1.429 variants that are circulating throughout California and the B.1.526 variant reported in New York [2].

First reported in India in December 2020, SARS-CoV-2 lineages **B.1.617.1**, **B.1.617.2** and **B.1.617.3** have been increasingly detected in other countries. In the EU/EEA there are indications that the frequency of detection of both lineages B.1.617.1 and B.1.617.2 is increasing. Currently described lineages B.1.617.1, B.1.617.2 and B.1.617.3 have distinct mutation profiles and warrant individual assessment. Given the still very limited available data with respect to their transmissibility, disease severity and immune escape potential relative to other co-circulating SARS-CoV-2 variants in the EU/EEA, the full impact of these lineages on public health is not yet possible to assess [8].

At the 24th of May 2021, ECDC lists **B.1.1.7, B.1.351, P.1 and B.1.617.2** as variants of concern. ECDC maintains its assessment of B.1.617.1, B.1.617.3 and several other lineages as **variants of interest** and will continue to actively monitor the situation [8], [9].

European Centre for Disease Prevention and Control (ECDC) data

As of May 14, 2021 in the EU/EEA 31 545 500 cases and 703 975 deaths have been reported [10].

ECDC collected data from official national sources for 30 countries showed that as of May 9, 2021 the 14-day COVID-19 death rate for the EU/EEA was 55.6 (country range: 0.0-193.7) per million persons. The rate has been decreasing for two weeks. Among 22 countries with high 14-day COVID-19 death rates (at least 10 per million), increases were observed in three countries (Cyprus, Latvia and the Netherlands). Stable or decreasing trends in death rates of 1–7 weeks' duration were observed in 19 countries (Austria, Belgium, Bulgaria, Croatia, Czechia, Estonia, France, Germany, Greece, Hungary, Italy, Liechtenstein, Lithuania, Luxembourg, Poland, Romania, Slovakia, Slovenia and Spain) [11].

Regarding hospitalisation and ICU, pooled data from 25 countries for week 18 of 2021 show that the rate of hospitalised patients due to COVID-19 was 8.1 patients per 100 000 persons. According to weekly hospital admissions data pooled from 20 countries, new admissions were 7.2 per 100 000 population. Pooled data from 19 countries for week 18 in 2021 show that there were 1.8 patients per 100 000 population in ICU due to COVID-19. Pooled weekly ICU admissions based on data from 14 countries show that there were 2.0 new admissions per 100 000 population [11].

Regarding variants of concern, among the 14 countries with the recommended level of 10% or 500 sequences reported per week in the period from 19 April to 2 May 2021, 12 had a valid denominator. The median (range) of the variants of concern (VOC) reported in all samples sequenced in the period in these 12 countries was 92.4% (80.7–98.2%) for B.1.1.7, 0.7% (0.0–8.9%) for B.1.351, 0.1% (0.0–6.7%) for P.1 and 0.0% (0.0–0.6%) for B.1.1.7+E484K. The median (range) of the variants of interest (VOI) reported in all samples sequenced in the period in these 12 countries was 0.0% (0.0–2.5%) for B.1.617, 0.0% (0.0–2.2%) for B.1.525, 0.0% (0.0–0.1%) for B.1.620 and 0.0% (0.0–0.0%) for B.1.621 [11].

1.1.1 Clinical symptoms and disease severity

Adults with COVID-19 can be grouped into the following severity of illness categories, although the criteria in each category may overlap or vary across guidelines and clinical trials [1], [2]. Clinical symptoms and COVID-19 severity of illness categories are presented in Table 1.1.

Table 1.1. COVID-19 severity of illness categories

WHO definitions of disease severity for COVID-19	NIH COVID-19 Treatment Guidelines (last update April 21, 2020)
***Non-severe COVID-19**:* Defined as absence of any signs of severe or critical COVID-19.	***Asymptomatic or Presymptomatic Infection**:* Individuals who test positive for SARS-CoV-2 using a virologic test (i.e., a nucleic acid amplification test or an antigen test), but who have no symptoms that are consistent with COVID-19.
	***Mild Illness**:* Individuals who have any of the various signs and symptoms of COVID-19 (e.g., fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhoea, loss of taste and smell) but who do not have shortness of breath, dyspnoea, or abnormal chest imaging.
	***Moderate Illness**:* Individuals who show evidence of lower respiratory disease during clinical assessment or imaging and who have saturation of oxygen (SpO_2) ≥94% on room air at sea level.
***Severe COVID-19**:* Defined by any of: - Oxygen saturation <90% on room air[a] - Respiratory rate >30 breaths per minute in adults and children >5years old, ≥60 breaths/min in children <2 months old, ≥50 in children 2-11 months old, and ≥40 in children 1-5 years old - Signs of severe respiratory distress (accessory muscle use, inability to complete full sentences, and, in children, very severe chest wall indrawing, grunting, central cyanosis, or presence of any other general danger signs).	***Severe Illness**:* Individuals who have SpO_2 <94% on room air at sea level, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2) <300 mmHg, respiratory frequency >30 breaths per minute, or lung infiltrates >50%.
***Critical COVID-19**:* Defined by the criteria for acute respiratory distress syndrome (ARDS), sepsis, septic shock, or other conditions that would normally require the provision of life sustaining therapies such as mechanical ventilation (invasive or non-invasive) or vasopressor therapy.	***Critical Illness**:* Individuals who have respiratory failure, septic shock, and/or multiple organ dysfunction.

[a] Caution: The panel noted that the oxygen saturation threshold of 90% to define severe COVID-19 was arbitrary and should be interpreted cautiously when used for determining which patients should be offered systemic corticosteroids. For example, clinicians must use their judgment to determine whether a low oxygen saturation is a sign of severity or is normal for a given patient with chronic lung disease. Similarly, a saturation >90-94% on room air may be abnormal if the clinician suspects that this number is on a downward trend. Generally, if there is any doubt, the panel suggested erring on the side of considering the illness as severe.
Abbreviations: ARDS=acute respiratory distress syndrome; SARS-CoV-2=Severe Acute Respiratory Syndrome Coronavirus 2; SpO_2=oxygen saturation; PaO2/FiO_2=ratio of arterial partial pressure of oxygen to fraction of inspired oxygen.
Source: [1], [2].

COVID-19 is primarily a pulmonary disease, but emerging data suggest that it also leads to cardiac, dermatologic, hematologic, hepatic, neurologic, renal, and other complications. Thromboembolic events also occur in patients with COVID-19, with the highest risk occurring in critically ill patients. SARS-CoV-2 infection has been associated with a potentially severe inflammatory syndrome in children (multisystem inflammatory syndrome in children, or MIS-C).

The spectrum of illness can range from asymptomatic infection to severe pneumonia with acute respiratory distress syndrome and death. Around 70% of patients experienced fever, cough, or shortness of breath, 36% had muscle aches, and 34% reported headaches. Other reported symptoms have included, but are not limited to, diarrhea, dizziness, rhinorrhea, anosmia, dysgeusia, sore throat, abdominal pain, anorexia, and vomiting [2]. Patients admitted to hospital with COVID-19 typically report symptoms onset three to five days after exposure (fatigue, chills), progressing to fever and dry cough 48 hours later. Transition to severe disease with hypoxaemia can occur five to seven days into the symptomatic illness, about 8-14 days after original exposure. Recently, the 4C Mortality Score was developed and validated, categorising patients as being at low, intermediate, high, or very high risk of death, to directly inform clinical decision making. The score can be used to stratify patients admitted to hospital with COVID-19 into different management groups [12]. The understanding of the mid- and long-

term sequelae of COVID-19 is increasing. This new condition which has been described as post-COVID syndrome or long COVID still lacks a worldwide consensus on terminology and clinical definition. The post-intensive care syndrome (PICS) has been well described in other critically ill patients and it also seems to occurs in COVID-19 patients. Non-hospitalised patients (or those with mild and moderate COVID-19) and children are also reporting persisting clustering of symptoms and mid- and long-term sequalae [2], [13].

1.2 Current clinical management

Pharmacological treatment options for COVID-19 are limited while multiple trials are ongoing to assess the efficacy of available medicines to manage the disease. EUnetHTA Rolling Collaborative Reviews present the comparative data on effectiveness and safety of potential therapies for COVID-19, and are updated on a monthly basis [14]. Neutralizing monoclonal antibodies to SARS-CoV-2 have the potential to be used for both prevention and treatment of infection. They may help to guide vaccine design and development as well. The main target of SARS-CoV-2 neutralizing monoclonal antibodies is the surface spike glycoprotein that mediates viral entry into host cells [15]. Standard of care, can vary according to country and currently is guided by disease severity. According to WHO guideline [1] symptomatic treatment is recommended for management of mild COVID-19, such as antipyretics for fever and pain, adequate nutrition and appropriate rehydration. WHO recommends that antibiotic therapy or prophylaxis should not be used in patients with mild COVID-19. Patients with moderate COVID-19 disease may present to an emergency unit or primary care/outpatient department, or be encountered during community outreach activities, such as home visits or by telemedicine. WHO recommends for patients with suspected or confirmed moderate COVID-19, that antibiotics should not be prescribed unless there is clinical suspicion of a bacterial infection. Close monitoring of patients for signs or symptoms of disease progression is recommended.

A summary of outpatient management as recommended by US COVID-19 Treatment Guidelines (updated April 21, 2021) is described in Box 1, with further details in Appendix 1 [2]:

Box 1: Outpatient management as recommended by US COVID-19 treatment guidelines

Outpatient management of acute COVID-19 should include providing supportive care, taking steps to reduce the risk of SARS-CoV-2 transmission (including isolating the patient), and advising patients on when to contact a health care provider and seek an in-person evaluation **(AIII)**. Patients with symptoms of COVID-19 should be triaged, when possible, via telehealth visits before receiving in-person care. Patients with dyspnea should be referred for an in-person evaluation by a health care provider and should be followed closely during the initial days after the onset of dyspnea to assess for worsening respiratory status **(AIII)**. Management plans should be based on a patient's vital signs, physical exam findings, risk factors for progression to severe illness, and the availability of health care resources **(AIII)**.

Specific therapy for outpatients with mild to moderate COVID-19

The COVID-19 Treatment Guidelines Panel recommends using one of the following combination anti-SARS-CoV-2 monoclonal antibodies to treat outpatients with mild to moderate COVID-19 who are at high risk of clinical progression, as defined by the Emergency Use Authorization criteria (treatments are listed in alphabetical order): Bamlanivimab 700 mg plus etesevimab 1,400 mg **(AIIa)**; *or* Casirivimab 1,200 mg plus imdevimab 1,200 mg **(AIIa)**.

The Panel recommends against the use of anti-SARS-CoV-2 monoclonal antibodies for patients who are hospitalized because of COVID-19, except in a clinical trial (**AIIa**). However, their use should be considered for persons with mild to moderate COVID-19 who are hospitalized for a reason other than COVID-19 but who otherwise meet the EUA criteria. There are currently no comparative data to determine whether there are differences in clinical efficacy or safety between casirivimab plus imdevimab and bamlanivimab. The Panel recommends against the use of chloroquine or hydroxychloroquine with or without azithromycin **(AI)**. The Panel recommends against the use of dexamethasone or other systemic glucocorticoids in outpatients in the absence of another indication **(AIII)**. The Panel recommends against the use of antibacterial therapy (e.g., azithromycin, doxycycline) in the absence of another indication **(AIII)**. Health care providers should provide information about ongoing clinical trials of investigational therapies to eligible outpatients with COVID.

Rating of Recommendations: A = Strong; B = Moderate; C = Optional
Rating of Evidence: I = One or more randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion

1.3 Features of the intervention:

1.3.1 Mode of Action and intended use

Bamlanivimab (LY-CoV555) is a neutralizing IgG1 monoclonal antibody (mAb) directed against the spike protein of SARS-CoV-2. It is designed to block viral attachment and entry into human cells, thus neutralizing the virus, potentially preventing and treating COVID-19.

Etesevimab (LY-CoV016, also known as JS016) is a recombinant fully human monoclonal neutralizing antibody, which specifically binds to the SARS-CoV-2 surface spike protein receptor binding domain with high affinity and can effectively block the binding of the virus to the ACE2 host cell surface receptor.

On March 5, 2021, the EMA stated that the CHMP has completed its review under Article 5(3) started in February 2021 to provide a harmonised scientific opinion at EU level to support national decision making on the possible use of the antibodies before a formal authorisation is issued. EMA concluded that bamlanivimab monotherapy and bamlanivimab and etesevimab combination can be used together to treat confirmed COVID-19 in patients who do not require supplemental oxygen and who are at high risk of their COVID-19 disease becoming severe. Risk factors may include but are not limited to: advanced age; obesity; cardiovascular disease, including hypertension; chronic lung disease, including asthma; type 1 or type 2 diabetes mellitus; chronic kidney disease, including those on dialysis; chronic liver disease; or being immunosuppressed, based on prescriber's assessment [3], [4].

The recommended dose for bamlanivimab in adults and paediatric patients (12 years of age and older weighing at least 40 kg) is a single infusion of 700 mg administered as soon as possible after testing positive for SARS-CoV-2 and within 10 days of symptom onset.
The recommended dose for bamlanivimab and etesevimab in adults and paediatric patients (12 years of age and older weighing at least 40 kg) is a single infusion of 700 mg bamlanivimab and 1,400 mg etesevimab administered as soon as possible after testing positive for SARS-CoV-2 and within 10 days of symptom onset.

Bamlanivimab and etesevimab may only be administered in settings in which health care providers have immediate access to medications to treat a severe infusion reaction, such as anaphylaxis. Contraindication is hypersensitivity to bamlanivimab and etesevimab or to any of the excipients (L-histidine, L-histidine hydrochloride monohydrate, sodium chloride, sucrose, polysorbate 80, water for injection) [4].

On March 11, 2021 EMA's CHMP has started a 'rolling review' of data on the antibodies bamlanivimab and etesemivab to be used in combination for the treatment of COVID-19. The review will also look at bamlanivimab used alone. The rolling review will continue until enough evidence is available to support formal marketing authorisation applications [7].

1.3.2 New SARS-CoV-2 Variants

Bamlanivimab monotherapy

In the revision of the FDA fact sheet related to bamlanivimab monotherapy and new variants, published on March 2021, there is a potential risk of treatment failure due to the development of viral SARS-CoV-2 variants that are resistant to bamlanivimab [5]. On April 16, 2021 FDA revoked Emergency Use Authorization (EUA) for the investigational monoclonal antibody therapy bamlanivimab (previously LY-CoV555), when administered alone, for the treatment of mild-to-moderate COVID-19 in adult and pediatric patients. Based on its ongoing analysis of emerging scientific data, specifically the sustained increase of SARS-CoV-2 viral variants that are resistant to bamlanivimab alone resulting in the increased risk for treatment failure, the FDA has determined that the known and potential benefits of bamlanivimab, when administered alone, no longer outweigh the known and potential risks for its authorized use [16]. At the time of publication of this rapid review, EMA had not made a similar announcement related to bamlanivimab monotherapy for the EU setting.

Non-clinical studies using serial passage of SARS-CoV-2 and directed evolution of the spike protein identified amino acid substitutions E484D/K/Q, F490S, Q493R and S494P, in the spike protein receptor binding domain. These substitutions conferred reduced susceptibility to bamlanivimab as determined in neutralization assays using SARS-CoV-2 (F490S and S494P: >485-fold and >71-fold reduction,

respectively), vesicular stomatitis virus-based pseudovirus expressing spike protein with variant substitutions (all variants >100-fold reduction), and spike protein binding assessment if pseudovirus assessment was unsuccessful (E484D) [5].

Evaluation of susceptibility of variants identified through global surveillance and in subjects treated with bamlanivimab is ongoing. Pseudovirus harboring the E484K substitution had reduced susceptibility to bamlanivimab; this substitution is found in several lineages, including B.1.351 (South Africa origin), P.1 (Brazil origin) and B.1.526 (New York origin). In addition, pseudoviruses with the spike protein and concurrent spike substitutions present in the South African B.1.351 origin variant lineage (K417N + E484K + N501Y), and the Brazil origin P.1 variant lineage (K417T + E484K + N501Y) exhibited reduced susceptibility to bamlanivimab. Pseudovirus harboring the L452R and the spike protein from the California origin variant lineage B.1.427/B.1.429 exhibited reduced susceptibility to bamlanivimab. Bamlanivimab retained activity against pseudovirus expressing del69-70 + N501Y spike substitutions found in the UK origin B.1.1.7 variant lineage (Table 1.2) [5].

Table 1.2. Pseudovirus neutralization data for SARS-CoV-2 variant substitutions with bamlanivimab alone

Lineage with Spike Protein Substitution	Key substitutions tested [a]	Fold reduction in susceptibility
B.1.1.7 (UK origin)	N501Y	no change [b]
B.1.351 (South Africa origin)	E484K	>2,360 [c]
P.1 (Brazil origin)	E484K	>2,360 [c]
B.1.427/B.1.429 (California origin)	L452R	>1,020 [c]
B.1.526 (New York origin) [d]	E484K	>2,360 [c]

Source: [5]
[a] For variants with more than one substitution of concern, only the one with the greatest impact on activity is listed.
[b] No change: <5-fold reduction in susceptibility
[c] No activity was observed at the highest concentration tested. Bamlanivimab alone is unlikely to be active against variants from this lineage.
[d] Not all isolates of the New York lineage harbor the E484K substitution (as of February 2021).

Bamlanivimab plus etesevimab combination

In the FDA revision published on May 2021, related to bamlanivimab plus etesevimab combination and new variants, resistant variants were identified using directed evolution of the spike protein and serial passage in cell culture of SARS-CoV-2 in the presence of bamlanivimab or etesevimab individually. Resistant variants were not identified when bamlanivimab and etesevimab were tested together using the same methodology [6].

Bamlanivimab alone and bamlanivimab and etesevimab together retained activity against a SARS-CoV-2 B.1.1.7 lineage (UK origin) virus and related pseudotyped VLPs expressing del69-70 + N501Y found in the B.1.1.7 variant. Pseudotyped VLPs expressing spike protein from the B.1.351 lineage (South Africa origin) or substitutions K417N + E484K + N501Y found in this lineage had reduced susceptibility to bamlanivimab and etesevimab together of 215-fold or >45-fold, respectively, and pseudotyped VLPs expressing spike protein from the P.1 lineage (Brazil origin) or K417T + E484K + N501Y found in the P.1 lineage had reduced susceptibility to bamlanivimab and etesevimab together of >46-fold or >511-fold, respectively. Pseudotyped VLPs expressing spike protein from the B.1.427/B.1.429 lineages (California origin) or the L452R substitution found in this lineage, maintained activity for etesevimab but showed reduced susceptibility to bamlanivimab and etesevimab together of 9-fold or 15-fold, respectively (Table 1.3). Due to the lack of pseudotyped VLP neutralization activity of both bamlanivimab and etesevimab against the substitutions in B.1.351 (South Africa origin) and P.1 (Brazil origin), it is unlikely that bamlanivimab and etesevimab together will be active against these variants. It is unclear how small reductions in susceptibility to bamlanivimab and etesevimab seen in authentic or recombinant SARS-CoV-2 or pseudotyped VLP assays correlate with clinical outcomes. Genotypic and phenotypic

testing are ongoing to monitor for potential bamlanivimaband etesevimab-resistance associated spike variations in clinical trials [6].

Table 1.3. Pseudovirus neutralization data for SARS-CoV-2 variant substitutions with bamlanivimab plus etesevimab together (1:2 molar ratio)

Lineage with Spike Protein Substitution	Key substitutions tested [a]	Fold reduction in susceptibility
B.1.1.7 (UK origin)	N501Y	no change [b]
B.1.351 (South Africa origin)	K417N + E484K + N501Y	215[c]
P.1 (Brazil origin)	K417N + E484K + N501Y	> 46 [c]
B.1.427/B.1.429 (California origin)	L452R	9 [d]
B.1.526 (New York origin) [e]	E484K	31

Source: [6]
[a] For variants with more than one substitution of concern, only the substitution(s) with the greatest impact on activity is(are) listed. For B.1.351, P.1 and B.1.427/B.1.429, spike variants reflective of the consensus sequence for the lineage were tested.
[b] No change: <5-fold reduction in susceptibility
[c] Bamlanivimab and etesevimab together are unlikely to be active against variants from this lineage. No activity observed at the highest concentration tested for the P.1 variant.
[d] Etesevimab retains activity against this variant.
[e] Isolates of the B.1.526 lineage harbor several spike protein amino acid substitutions, and not all isolates contain the E484K substitution (as of February 2021). This assay was conducted using pseudotyped VLPs with the E484K substitution only.

2 OBJECTIVE AND SCOPE

The aim of this EUnetHTA Rapid Collaborative Review is to summarize the best publicly available scientific evidence on the clinical effectiveness and safety of bamlanivimab monotherapy and bamlanivimab plus etesevimab combination treatment in the target patient populations with relevant comparators and next, to support the local productions of national/regional HTA reports based on this review. The target patient populations and relevant comparators (based on the requirements of EUnetHTA Partners) are defined in the project scope in Table 2.1.

Table 2.1: Assessment scope: relevant PICO(s) identified for the rapid review

Description	Assessment scope
PICO	
Population	**Target population: patients with mild or moderate COVID-19 who are at high risk of progressing to severe COVID-19** [a] • *Mild Illness*: Individuals who have any of the various signs and symptoms of COVID 19 (e.g., fever, cough, sore throat, malaise, headache, muscle pain) without shortness of breath, dyspnoea, or abnormal chest imaging; • *Moderate Illness*: Individuals who have evidence of lower respiratory disease by clinical assessment or imaging and a saturation of oxygen (SpO_2) ≥94% on room air at sea level [1], [2]. **Disease** SARS-CoV-2 is a novel coronavirus causing a respiratory illness termed COVID-19. The full spectrum of COVID-19 ranges from mild, self-limiting respiratory tract illness to severe progressive pneumonia, multi-organ failure, and death. **ICD-Codes** [17] An emergency ICD-10 code of 'U07.1 COVID-19, virus identified' is assigned to a disease diagnosis of COVID-19 confirmed by laboratory testing. An emergency ICD-10 code of 'U07.2 COVID-19, virus not identified' is assigned to a clinical or epidemiological diagnosis of COVID-19 where laboratory confirmation is inconclusive or not available. Both U07.1 and U07.2 may be used for mortality coding as cause of death. See the International guidelines for certification and classification (coding) of COVID-19 as cause of death following the link below. In ICD-11, the code for the confirmed diagnosis of COVID-19 is RA01.0 and the code for the clinical diagnosis (suspected or probable) of COVID-19 is RA01.1. **MeSH-terms:** COVID-19; Coronavirus Disease 2019; 2019 novel coronavirus disease; COVID19; COVID-19 pandemic; SARS-CoV-2 infection; COVID-19 virus disease; 2019 novel coronavirus infection; 2019-nCoV infection; coronavirus disease 2019; coronavirus disease-19; 2019-nCoV disease; COVID-19 virus infection.
Intervention	1. Bamlanivimab monotherapy 2. Bamlanivimab + etesevimab combination **More information:** for the treatment of confirmed COVID-19 in patients aged 12 years and older that do not require supplemental oxygen for COVID-19 and who are at high risk of progressing to severe COVID-19; The authorised dosage for bamlanivimab is a single intravenous (IV) infusion of 700 mg. The authorised dosage is 700 milligrams bamlanivimab and 1400 milligrams etesevimab administered together [3], [4], [7].
Comparison	Active pharmacological treatment (approved pharmaceuticals for COVID-19 or investigational pharmaceuticals) [b], or Standard of care/usual care. **Rationale**: at the time of the publication of this report, no agreement was reached by the scientific community on standard treatment for mild/moderate COVID-19 or the relevance of the type of head-to-head comparisons

Outcomes	**Effectiveness** (short-term up to 1 month; long term up to 3-6 months) • All-cause mortality • Number of patients with ≥1 COVID-19 related medically attended visit (emergency room visits, urgent care visits, or telehealth/physician office visits) • Number of patients with COVID-19 related hospitalisation • Viral negative conversion (D7) • Clinical improvement defined as a hospital discharge or improvement on the scale used by trialists to evaluate clinical progression and recovery • WHO Clinical Progression Score level 7 or above (i.e., Mechanical ventilation +/- additional organ support (ECMO, vasopressors or dialysis) OR death • Number of patients admitted to an intensive care unit (ICU) • Number of patients requiring supplemental oxygen • Number of patients requiring mechanical ventilation • Length of hospital stay • Pulmonary function • Health-related Quality of life • Time to clinical improvement • Time to WHO Clinical Progression Score level 7 or above • Time to death • Time to viral negative conversion • Duration of mechanical ventilation • Duration of supplemental oxygen therapy • Time to ICU admission • Kinetic of viral load (D1, D7, D14, D30...) • Efficacy depending on SARS-CoV-2 variants • Resistance **Safety** (short-term up to 1 month; long term up to 3-6 months) • Number of patients with one or more Adverse events (AE); • Number of patients with one or more Serious adverse events (SAE); • Number of deaths attributable to SAE; • Number of withdrawals due to AEs; • Description of most frequent AEs; • Description of most frequent SAEs. If possible: subgroup analysis according to disease severity and according to risk factors for severe disease. **Rationale:** priority will be given on outcomes according to the Core Outcome Set for Clinical Trials on Coronavirus Disease 2019 [18] and a minimal common outcome measure set for COVID-19 clinical research from the WHO Working Group on the Clinical Characterisation and Management of COVID-19 infection [19].
Study design	Randomised controlled trials (RCTs)

[a] EMA recommended indication: for the treatment of confirmed COVID-19 in patients aged 12 years and older that do not require supplemental oxygen for COVID-19 and who are at high risk of progressing to severe COVID-19. Risk factors may include but are not limited to: advanced age; obesity; cardiovascular disease, including hypertension; chronic lung disease, including asthma; type 1 or type 2 diabetes mellitus; chronic kidney disease, including those on dialysis; chronic liver disease; immunosuppressed, based on prescriber's assessment.
[b] Approved or conditionally approved COVID-19 pharmaceutical: EUA in US: REGN-COV2; other investigational neutralising monoclonal antibodies (for example VIR-7831, regdanvimab) or their combinations; convalescent plasma; polyclonal antibodies
Abbreviations: 2019-nCoV=2019 novel coronavirus; AE=adverse events; ECMO=Extracorporeal membrane oxygenation; EMA=European Medicines Agency; EUA=Emergency Use Authorization; ICD-Codes=Classification of Disease Codes; ICU=Intensive Care Unit; RCT=randomized controlled trial; SAE=serious adverse events; SARS-COV-2=severe acute respiratory syndrome coronavirus 2; IV=intravenous, SpO_2=peripheral oxygen saturation

3 METHODS

3.1 Data sources and searches

To avoid redundancies and duplication, this RCR reused data relevant to our PICO from two already published living systematic reviews/meta-analysis (SRs/MA) sources from international initiatives [20], [21], [22], [23]. The data were included according to the methodology suggested by Whitlock 2008 [24] and Robinson 2014 [25] on how to integrate existing SRs into new SRs. As described by Robinson et al., four different approaches could be followed: 1) use the existing SR(s)' list of included studies as a quality check for our literature search and screening strategy (Scan References), 2) use the existing SR(s) to completely or partially provide the body of included studies for one or more research questions of our assessment ("Use Existing Search"), 3) use the data abstraction, risk of bias assessments, and/or analyses from existing SRs for one or more research questions of our assessment ("Use Data Abstraction/Syntheses") and 4) use the existing SR(s), including conclusions, to fully or partially answer one or more research questions of our REA ("Use Complete Review"). Approach number 3 was followed for this report.

Literature search was used from the EUnetHTA Rolling Collaborative Reviews, updated on May 3, 2021, to find possible RCTs related to bamlanivimab monotherapy and in combination with etesevimab in non-hospitalised patients with COVID-19 [26], [27]. Details can be found in Table A1, Appendix 2. References were included or excluded according to the Population-Intervention-Control-Outcome (PICO)-scheme and presented according to the PRISMA Statement [28].

A separate Guideline (GL) search (G-I-N, TRIP-Database and hand search) was performed as well, on May 7, 2021. Only living clinical guidelines, with regular and the most recent updates, were considered in this report.

As stated above, quantitative syntheses (using pairwise meta-analyses) from existing living SRs/MA were presented in the Result section if available for outcomes of interest to this report [20], [21], [22] [23]. According to published protocols of living SRs/MAs, pairwise meta-analysis was performed for primary and secondary outcomes using random-effects models to incorporate the anticipated clinical and methodological heterogeneity across [20], [21], [22], [23]. Analyses related to two clinical outcomes (Time-weighted average change from baseline in viral load through day 7 and Proportion of patients with COVID-19–related hospitalisations or emergency department visits at day 29 were performed by authors of this RCR. These analyses incorporated additional outcome data on the outcome time-weighted average change from baseline in viral load that was provided by Eli-Lily.

A teleconference with Manufacturer was performed on April 20, 2021, to discuss PICO and some missing data that could be shared and used in this report.

3.2 Risk of bias

Risk of bias assessment related to 1 RCT (phase 1-2 portion) on bamlanivimab monotherapy and in combination with etesevimab was reused from one living SR/MA source [23]. Each study was presented with the Cochrane Risk of bias 2 (RoB 2) tool for RCTs [29]. The Cochrane RoB 2 tool is structured into 5 domains: 1) risk of bias arising from the randomization process, 2) risk of bias due to deviations from intended interventions, 3) risk of bias due to missing outcome data, 4) risk of bias in measurement of the outcome, 5) risk of bias in selection of the reported result. Within each domain, a series of 'signalling questions' elicit information relevant to risk of bias assessment. The response options to the signalling questions are: "Yes", "Probably yes", "Probably no", "No" and "No information". A risk of bias judgement arising from each domain is generated by an algorithm, based on answers to the signalling questions. The automated judgement can be overruled if indicated. Judgement can be "Low", "Some concerns" or "High" risk of bias. Overall risk of bias will be considered as "low risk of bias" if all domains are at low risk, "some concerns" if at least one domain is some concern and no domain is of high risk of bias, and "high risk of bias" if there is at least one domain at high risk, or several domains with some concerns.

3.3 Certainty of evidence

Certainty of evidence related to further clinical outcomes: “All-cause mortality”, “Adverse events” “Serious adverse events” and “SARS-COV2 clearance” was reused from two different sources: two already published living systematic reviews/meta-analysis (SRs/MA) sources from international initiatives [20], [21], [22], [23]. Certainty of evidence related to two clinical outcomes (“Symptom score at day 11 and day 22”” and “Proportion of patients with COVID-19–related hospitalisations or emergency department visits at day 29” was performed by the authors of this RCR.
For rating the certainty of the evidence, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) is being presented [20], [21], [22], [30]. The GRADE approach specifies four levels of certainty: “High”, further research is very unlikely to change our confidence in the estimate of effect; “Moderate”, further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimates; “Low”, further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; “Very low”, we are very uncertain about the estimate.

3.4 Ongoing studies

The following clinical trial registries were searched for ongoing RCTs on bamlanivimab monotherapy and bamlanivimab plus etesevimab combination in COVID-19 in May 2021: ClinicalTrials.gov[3], ISRCTN[4] and European Clinical Trials Registry[5].

3.5 Patient Involvement

As patient involvement is recognised as important at different levels of HTA process, an open call for patient input was published on the EUnetHTA website from March 4, 2021 to March 15, 2021. This open call with on-line questionnaire asked patient organisations and individual patient or caregiver to provide answers to the questions from a patient and/or caregiver perspective and experiences. The open call used by EUnetHTA asks general questions related to the impact of COVID-19; experience with currently available therapies; expectations of/requirements for a new medicine for COVID-19 patients, and additional information which the patient believed would be helpful to the HTA researchers. The questions were based on the Health Technology Assessment International questionnaire template; more information on the development of this template is available on the https://htai.org/ website.

[3] https://clinicaltrials.gov/

[4] https://www.isrctn.com/

[5] https://www.clinicaltrialsregister.eu/

4 RESULTS

4.1 Information retrieval/Existing Evidence

As of May 3, 2021, only one scientific publication relevant to our PICO, related to final results of an RCT in outpatient setting was found. Final results of the phase 2 portion of BLAZE-1, randomised, double-blind, placebo-controlled trial (NCT04427501) were published by Gottlieb et al. 2021 [31]. One RCT was excluded from our analysis as the study population consisted of a mixture of hospitalised COVID-19 patients with moderate to severe COVID-19 (ACTIV-3/TICO LY-CoV555 Study group, NCT04501978) [32]. In latter trial, Lundgren and colleagues compared bamlanivimab monotherapy (LY-CoV555) with placebo, and the data and safety monitoring board recommended stopping enrolment for futility after 314 patients had undergone randomization and infusion.

Flow diagram depicting the selection process of RCTs can be found in Figure A1, Appendix 2.

The BLAZE-1 study is a randomized phase 2/3 trial at 49 US centers including ambulatory patients (n = 613) who tested positive for SARS-CoV-2 infection and had 1 or more mild to moderate COVID-19 symptoms. Patients who received bamlanivimab (LY-CoV555) monotherapy or placebo were enrolled first, followed by patients who received bamlanivimab (LY-CoV555) and etesevimab (LY-CoV016) combination or placebo. Patients were randomized to receive a single infusion of bamlanivimab (700 mg [n=101], 2800 mg [n=107], or 7000 mg [n=101]), the combination treatment (2800mg of bamlanivimab and 2800 mg of etesevimab [n=112]), or placebo (n=156). The primary end point was change in SARS-CoV-2 log viral load at day 11 (±4 days). Nine prespecified secondary outcome measures were evaluated with comparisons between each treatment group and placebo, and included 3 other measures of viral load (time to viral clearance; proportion of patients with viral clearance at days 7, 11, 15, and 22; and viral load area under the curve at day 29), 5 on symptoms (change in symptom score at days 7, 11, 15, and 22; time to symptom improvement; time to symptom resolution; and the proportion of patients showing symptom improvement or resolution at days 7, 11, 15, and 22), and 1 measure of clinical outcome (the proportion of patients with a COVID-19–related hospitalisation, an emergency department (ED) visit, or death at day 29). A questionnaire was used to assess symptom severity. The total symptom score (range, 0-24) was achieved by rating 8 symptom domains (cough, shortness of breath, feeling feverish, fatigue, body aches and pain, sore throat, chills, headache) from none or absent (score of 0) to severe (score of 3) and combining them to provide an overall score (excluding loss of appetite, taste, and smell). Related to exploratory outcomes, the total symptom score AUC from day 0 to day 11 and from day 0 to day 29 were analysed using a linear model; nasopharyngeal samples were obtained at study enrolment (baseline sample), and then subsequent sampling was done at days 3, 7, 11, 15, 22, and 29, to assess the prevalence of resistance variants. A sample size of 100 participants per group was estimated to provide 91% power to test the superiority of bamlanivimab monotherapy or the bamlanivimab and etesevimab combination treatment vs placebo for the effect on viral load, as measured by change from baseline to day 11 (±4 days) at the 2-sided α level of .05. A post hoc analysis was performed evaluating COVID-19–related deterioration for patients aged 65 years or older or those with a body mass index (BMI; calculated as weight in kilograms divided by height in meters squared) of 35 or greater. COVID-19–related deterioration was defined as a patient experiencing a COVID-19–related hospitalization, an emergency department visit, or death.

The mean age of patients was 44.7 years (SD, 15.7 years). A total of 315 patients (54.6%) were female, 245 patients (42.5%) identified as Hispanic, and 387 patients (67.1%) had at least 1 risk factor for severe COVID-19 (aged ≥55 years, BMI ≥30, or ≥1 relevant comorbidity such as hypertension). Patients were randomized and received study infusions within a median of 4 days of symptom onset. At the time of randomization, 449 patients (77.8%) had mild symptoms. On the day of the infusion, the observed mean polymerase chain reaction cycle threshold value (a measure of viral load) was 23.7 (SD, 7.4), demonstrating a high viral burden in the population. There were 533 patients (92.4%) who completed the efficacy evaluation period (day 29).

Main characteristics of this RCT abstracted from the scientific publication can be found in Table A2, Appendix 3.

4.2 Risk of bias/Quality of evidence

According to COVID-NMA, overall **Risk of Bias** for this RCT is judged as “some concerns”, due to missing outcome data on the outcome Incidence of viral negative conversion at day 7 [23].

Certainty of evidence as assessed by DePlazio is graded as “high” for the outcomes: All-cause mortality, SARS-CoV-2 clearance and Number of patients with adverse events. For the outcome: Number of patients with serious adverse events, certainty of evidence is graded as “moderate” presented [20], [21], [22]. For the outcome: COVID-19–related hospitalisations or ED visits at day 29 (bamlanivimab monotherapy vs placebo and bamlanivimab plus etesevimab combination vs placebo), certainty of evidence is graded as “high”, and as “moderate” for the bamlanivimab monotherapy vs bamlanivimab plus etesevimab combination, by the authors of this report. The certainty of the evidence on the outcome Symptom score was judged moderate to high, depending on the timepoint and comparison considered. Details can be found in Table A3, Table A4 and Table A5 in Appendix 3.

4.3 Results on clinical effectiveness and safety

4.3.1 Published results

Original publication by the trial authors (phase 2 portion of BLAZE-1 trial)

In this section we describe and quote the published final results of phase phase 2 portion of RCT BLAZE-1, on bamlanivimab monotherapy (700 mg, 2800 mg, or 7000 mg), and the combination treatment (2800mg of bamlanivimab and 2800 mg of etesevimab) when compared to placebo, in outpatient setting on mild to moderate COVID-19 [31], as abstracted from the original publication.

Gottlieb and colleagues randomised 592 patients of whom 577 patients received the intervention as randomised. A total of 533 (92.4%) completed the efficacy evaluation period (day 29), whereas 570 patients contributed to the efficacy analysis population and 546 contributed to the primary analysis of the trial authors [31]. The baseline demographics and disease characteristics were well balanced across bamlanivimab and placebo treatment groups:
43.6% patients in the placebo group, 33.9% in the combination group and 45.5% patients in bamlanivimab monotherapy group were high risk patients for severe COVID-19 [33]. Details can be found in Table A6 in Appendix 3.

Effectiveness

There were no deaths caused by COVID-19.

The change in log viral load from baseline at day 11 was not significantly different for the bamlanivimab monotherapy groups compared with the placebo group, but was significantly different for the bamlanivimab and etesevimab combination therapy group compared with the placebo group: 0.09 (95%CI, –0.35 to 0.52; p=0.69) for 700 mg, –0.27 (95%CI, –0.71 to 0.16; p=0.21) for 2800 mg, 0.31 (95%CI, –0.13 to 0.76; p=0.16) for 7000 mg, and –0.57 (95%CI, –1.00 to –0.14; p=0.01) for combination treatment.

Secondary outcomes

The trial authors reported that among the secondary outcome measures, differences between each treatment group vs the placebo group were statistically significant for 10 of 84 endpoints. There were no consistent differences between the monotherapy groups or the combination therapy group vs placebo for the other measures of viral load or clinical symptom scores.

Outcomes: Change in mean total symptom score; Change in symptom improvement; Change in symptom resolution

Compared with the placebo group, the change in mean total symptom score from baseline to day 11 was statistically significantly different for the 700 mg monotherapy group (mean difference, –0.78 [95% CI, –1.37 to –0.20]; p=0.009) and for the combination group (mean difference, –0.60 [95% CI, –1.18 to

–0.03]; p=0.04), but the change was not significantly different for the 2800 mg monotherapy group (mean difference, –0.32 [95% CI, –0.91 to 0.26]; p=0.27) or for the 7000 mg group (mean difference, –0.45 [95% CI, –1.04 to 0.13]; p=0.13).

Compared with the placebo group, the change in symptom improvement from baseline to day 11 was statistically significantly different for the 700 mg group (difference, 16.0% [95% CI, 3.6% to 28.4%]; p=0.02) and the 7000 mg group (difference, 15.0% [95% CI, 2.6% to 27.4%]; p=0.02), but the change was not significant for the 2800 mg group (difference, 1.4% [95% CI, –10.8% to 13.7%]; p=0.90) and the combination treatment group (difference, 9.8% [95% CI, –2.5% to 22.0%]; p=0.13).

Compared with the placebo group, the change in symptom resolution from baseline to day 11 was statistically significantly different for the 700 mg group (difference, 13.7% [95% CI, 1.2% to 26.1%]; p=0.04), but the change was not significant for the 2800 mg group (difference, 3.3% [95% CI, –8.7% to 15.4%]; p=0.61), the 7000 mg group (difference, 6.7% [95% CI, –5.6% to 19.1%]; p=0.30), or the combination group (difference, 9.0% [95% CI, –3.1% to 21.1%]; p=0.16).

Outcome: COVID-19–related hospitalisations or ED visits at day 29

The proportion of patients with COVID-19–related hospitalisations or ED visits was numerically lower for the monotherapy groups and the combination therapy group compared with the placebo group, but the difference was only significant for the combination group. The proportion of patients with COVID-19–related hospitalizations or emergency department visits at day 29 was 1.0% (1 event/101 patients) in the 700 mg group, 1.9% (2 events/107 patients) in the 2800 mg group, 2.0% (2 events/101 patients) in the 7000 mg group, 0.9% (1 event/112 patients) in the combination therapy group, and 5.8% (9 events/156 patients) in the placebo group. The difference vs placebo was –4.8% (95% CI, –8.9% to –0.6%; p=0.09) for the 700 mg group, –3.9% (95% CI, –8.4% to 0.6%; p=0.21) for the 2800 mg group, –3.8% (95% CI, –8.3% to –0.8%; p=0.21) for the 7000 mg group, and –4.9% (95% CI, –8.9% to –0.8%; p=0.049) for the combination group.

Post hoc analyses

A smaller percentage of bamlanivimab-treated participants who were at a higher risk of hospitalisation (i.e. ≥65 years or BMI ≥35) progressed to COVID 19-related hospitalisations or emergency room visits compared with placebo.

Among patients aged 65 years or older or with a BMI of 35 or greater, those who received bamlanivimab monotherapy had a lower hospitalisation rate (2.7%;1/37 patients in the 700 mg group and a difference of –10.8% (95% CI, –21.4% to –0.1%); those who received combination therapy had a lower hospitalisation rate (0%; 0/31 patients in the bamlanivimab and etesevimab group and a difference of –13.5% (95% CI, –22.7% to –4.2%); p=0.04) compared with those who received placebo (13.5%;[7/52 patients). Only 1 patient in the study (in the placebo group) was admitted to the intensive care unit. Details can be found in Table A7 in Appendix 3.

Exploratory outcomes

Total symptom score AUC from baseline to day 11 was assessed in an exploratory analysis. Compared with placebo, the difference in mean change in total symptom score AUC from baseline to day 11 was –8.28 (95% CI, –14.04 to –2.53; p=0.005) for the 700 mg group, –6.59 (95% CI, –12.46 to –0.72; p=0.03) for the 2800 mg group, –8.09 (95% CI, –14.05 to –2.13; p=0.008) for the 7000 mg group, and –8.63 (95% CI, –14.39 to –2.88; p=0.003) for the combination therapy group.

In an exploratory analysis to assess the ability of bamlanivimab and etesevimab to reduce the levels of treatment-emergent bamlanivimab-resistant variants, the frequency of these variants in baseline samples across cohorts in the study population was low (0.4% [2/523 patients]) and is similar to the global prevalence of these variants. Putative treatment-emergent bamlanivimab-resistant variants were detected in 7.1% of patients (7/98) in the 700 mg group, in 9.8% of patients (10/102) in the 2800 mg group, in 11.3% of patients (11/97) in the 7000 mg group, in 1% of patients (1/102) in the bamlanivimab and etesevimab combination group, and in 4.8% of patients (7/145) in the placebo group. Details can be found in Table A7 in Appendix 3.

Safety

Serious adverse events unrelated to SARS-CoV-2 infection or considered related to the study drug by the investigator occurred in 0% (0/309) of patients in the bamlanivimab monotherapy groups, in 0.9% (1/112) of patients in the bamlanivimab and etesevimab combination group, and in 0.6% (1/156) of patients in the placebo group. The serious adverse event observed in the combination group was a urinary tract infection that was deemed unrelated to the study drug. The serious adverse event observed in the placebo group was upper abdominal pain and was deemed unrelated to the study drug.

The most frequently reported adverse events were nausea (3.0% for the 700 mg group, 3.7% for the 2800 mg group, 5.0% for the 7000 mg group, 3.6% for the combination therapy group, and 3.8% for the placebo group) and diarrhoea (1.0%, 1.9%, 5.9%, 0.9%, and 4.5%, respectively).
Immediate hypersensitivity reactions that could have been infusion-related were reported in 9 patients (6 in the bamlanivimab monotherapy groups, 2 in the bamlanivimab and etesevimab group, and 1 in the placebo group). Most reactions occurred during infusion and were reported as mild in severity and not dose related. There were no changes in vital signs and symptoms included pruritus, flushing, rash, and facial swelling. No deaths occurred during the study treatment. There have been no discontinuations due to AEs.

Living Systematic Reviews with Meta-Analyses (MAs) related to above mentioned published phase 2 results from BLAZE-1 trial

In this section we describe GRADE assessments of the certainty of the evidence as summarized in two Living Systematic Reviews with Meta-Analyses (MAs) related to the single published RCT mentioned in the previous section. The GRADE-assessments are used to describe observed effects. In line with the assessments of these evidence synthesis reports, bamlanivimab monotherapy was compared with placebo, but also with bamlanivimab combination therapy.

As mentioned in section 4.2, the certainty of evidence, related to effectiveness and safety of bamlanivimab monotherapy (all doses, and each separate doses) and bamlanivimab 2800 mg + etesevimab 2800 mg compared to placebo and each other, was judged to be of high and moderate. Details on the GRADE-assessment prepared by Cruciani et al. [21], [22] can be found in the Summary of Findings tables and GRADE tables (Table 4.1, Table 4.2 and Table A4 and Table A5 in Appendix 3).

The review authors Cruciani and colleagues deemed the certainty on mortality high, although no deaths were reported so that estimates of effect could not be calculated.

The certainty of evidence was high for bamlanivimab 700 mg monotherapy treatment compared to placebo on the outcome COVID-19–related hospitalisation or visit to an emergency department at day 29 (high certainty of evidence). When compared to placebo, both bamlanivimab 700 mg monotherapy as bamlanivimab + etesevimab combination treatment reduce COVID-19–related hospitalisation or visit to an emergency department at day 29 (high certainty of evidence).

The living systematic reviews did not address the outcome on symptom scores. The authors of this report deemed certainty to be moderate so that the change in mean total symptom score from baseline to day 22 probably slightly favours the 700 mg monotherapy group and for the bamlanivimab + etesevimab combination group when compared to placebo.

Bamlanivimab 700 mg monotherapy or bamlanivimab + etesevimab treatment, compared to placebo, does not importantly accelerate the natural decline in viral load over time (high certainty of evidence). The same is true for bamlanivimab compared to bamlanivimab + etesevimab treatment.

Bamlanivimab 700 mg and bamlanivimab + etesevimab combination treatment compared to placebo does not increase number of patients with adverse events (high certainty of evidence) and probably does not increase number number of serious adverse events (moderate certainty of evidence).
bamlanivimab compared to bamlanivimab + etesevimab combination treatment increases the number of patients with adverse events (high certainty of evidence).

OUTPATIENT: Bamlanivimab monotherapy (700 mg) compared to placebo and bamlanivimab + etesevimab combination

Table 4.1. Summary of findings table for published RCT related to effectiveness and safety of bamlanivimab monotherapy (700 mg) compared to placebo and bamlanivimab (2800 mg) + etesevimab (2800 mg) combination treatment – OUTPATIENT

Patient or population: Mild/Moderate COVID-19
Setting: Outpatient
Intervention: Bamlanivimab monotherapy 700 mg
Comparison: Placebo and Bamlanivimab 2800 mg plus etesevimab 2800 mg

Outcome	Anticipated absolute effects (95% CI) [a]		Relative effect (95% CI)	Number of participants (studies)	Certainty of evidence	Comments
	Risk with Placebo **Risk with Bamlanivimab + etesevimab**	**Risk with Bamlanivimab** (previously neutralizing antibody LY-CoV555)				
All-cause mortality						
vs Placebo	No deaths occurred	No deaths occurred	No deaths occurred	465 (1 RCT) [b]	⊕⊕⊕⊕ HIGH	No deaths occurred
vs Bamlanivimab + etesevimab	No deaths occurred	No deaths occurred	No deaths occurred	465 (1 RCT) [b]	⊕⊕⊕⊕ HIGH	No deaths occurred
COVID-19 related hospitalisation or emergency department visit at day 29 [d]						
vs Placebo	58 per 1000	10 per 1000 (1 to 77)	RR 0.17 (0.02 to 1.33)	257 (1 RCT) [b]	⊕⊕⊕⊕ HIGH	Absolute effect (95% CI) 48 fewer per 1000 (from 57 fewer to 19 more)
vs Bamlanivimab + etesevimab	9 per 1000	10 per 1000 (1 to 156)	RR 1.11 (0.07 to 17.50)	213 (1 RCT) [b]	⊕⊕⊕◯ MODERATE [c]	Absolute effect (95% CI) 1 more per 1000 (from 8 fewer to 147 more)
Symptom score at day 11 [d]						
vs Placebo	Mean 1.88 (SD 2.50)	Mean 1.06 (SD 1.58)	MD -0.78 (-1.37 to -0.20) p=0.009 [e]	228 (1 RCT) [b]	⊕⊕⊕⊕ HIGH	
vs Bamlanivimab + etesevimab	Mean 1.28 (SD 2.48)	Mean 1.06 (SD 1.58)	-0.22 (-0.81 to 0.37) [f]	189 (1 RCT) [b]	⊕⊕⊕◯ MODERATE [c]	
Symptom score at day 22 [d]						
vs Placebo	Mean 0.77 (SD 1.67)	Mean 0.46 (SD 1.16)	Mean difference -0.17 (-0.60 to 0.25) p=0.42 [e]	215 (1 RCT) [b]	⊕⊕⊕◯ MODERATE [c]	

Outcome	Anticipated absolute effects (95% CI) [a]		Relative effect (95% CI)	Number of participants (studies)	Certainty of evidence	Comments
	Risk with Placebo Risk with Bamlanivimab + etesevimab	Risk with Bamlanivimab (previously neutralizing antibody LY-CoV555)				
vs Bamlanivimab + etesevimab	Mean 0.76 (SD 2.00)	Mean 0.46 (SD 1.16)	-0.30 (-0.77 to 0.17) [f]	182 (1 RCT) [b]	⊕⊕⊕◯ MODERATE [c]	
SARS-CoV-2 clearance at day 22 [d]						
vs Placebo	368 per 1000	405 per 1000	RR 1.10 (0.80 to 1.51)	253 (1 RCT) [b]	⊕⊕⊕⊕ HIGH	Absolute effect (95% CI) 37 more per 1.000 (from 74 fewer to 188 more)
vs Bamlanivimab + etesevimab	367 per 1000	407 per 1000	RR 1.11 (0.79 to 1.56)	210 (1 RCT) [b]	⊕⊕⊕⊕ HIGH	Absolute effect (95% CI) 40 more per 1.000 (from 77 fewer to 206 more)
Number of patients with any adverse events						
vs Placebo	269 per 1000	266 per 1000	RR 0.99 (0.66 to 1.50)	257 (1 RCT) [b]	⊕⊕⊕⊕ HIGH	Absolute effect (95% CI) 3 fewer per 1.000 (from 92 fewer to 135 more)
vs Bamlanivimab + etesevimab	170 per 1000	269 per 1000	RR 1.58 (0.94 to 2.65)	213 (1 RCT) [b]	⊕⊕⊕⊕ HIGH	Absolute effect (95% CI) 98 more per 1.000 (from 10 fewer to 280 more)
Number of patients with serious adverse events						
vs Placebo	60 per 1000	31 per 1000	RR 0.51 (0.02 to 12.47)	257 (1 RCT) [b]	⊕⊕⊕◯ MODERATE [c]	Absolute effect (95% CI) 3 fewer per 1.000 (from 6 fewer to 74 more)
vs Bamlanivimab + etesevimab	90 per 1000	33 per 1000	RR 0.37 (0.02 to 8.96)	213 (1 RCT) [b]	⊕⊕⊕◯ MODERATE [c]	Absolute effect (95% CI) 6 fewer per 1.000 (from 9 fewer to 71 more)

Source: [21]
Explanations: [a] The risk in the intervention group is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI); [b] [31] [c] Downgraded of one level for wide CI; [d] Authors of current rapid review; ; [e] mean and SD refer to change from baseline values as reported by the trial authors, the mean difference refers to between group differences in change from baseline as reported by the trial authors; [f] Not reported by the trial authors but calculated by the authors of this rapid report, using the reported trial arm mean changes from baseline with standard deviations and group size in Cochrane Review Manager 5.3 software

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect
Abbreviations: CI=confidence interval; RR=risk ratio; SAE=serious adverse event; AE=adverse event; RCT=randomised controlled trial; g=gram; MD=mean difference

OUTPATIENT: Bamlanivimab + etesevimab combination vs placebo

Table 4.2. Summary of findings table for published RCTs related to effectiveness and safety of bamlanivimab (2800 mg) + etesevimab (2800 mg) combination compared to placebo – OUTPATIENT

Patient or population: Mild/Moderate COVID-19
Setting: Outpatient
Intervention: Bamlanivimab plus etesevimab
Comparison: Placebo

Outcome	Anticipated absolute effects (95% CI) [a]		Relative effect (95% CI)	Number of participants (studies)	Certainty of evidence	Comments
	Risk with Placebo	Risk with Bamlanivimab + etesevimab				
All-cause mortality	No deaths occured	No deaths occured	No deaths occured	268 (1 RCT) [b]	⨁⨁⨁⨁ HIGH	No deaths occurred
COVID-19 related hospitalisation or emergency department visit at day 29 [d]	58 per 1000	9 per 1000 (1 to 69)	RR 0.15 (0.02 to 1.20)	268 (1 RCT) [b]	⨁⨁⨁⨁ HIGH	Absolute effect (95% CI) 49 fewer per 1000 (from 57 fewer to 12 more)
Symptom score at day 11 [d]	Mean 1.88 (SD 2.50)	Mean 1.28 (SD 2.48)	Mean difference -0.60 (-1.18 to -0.03) p=0.04	229 (1 RCT) [b]	⨁⨁⨁◯ MODERATE [c]	
Symptom score at day 22 [d]	Mean 0.77 (SD 1.67)	Mean 0.76 (SD 2.00)	Mean difference 0.03 (-0.38 to 0.44)	261 (1 RCT) [b]	⨁⨁⨁◯ MODERATE [c]	
SARS-CoV-2 clearance at day 22 [d]	368 per 1000	368 per 1000	RR 1.00 (0.72 to 1.38)	261 (1 RCT) [b]	⨁⨁⨁⨁ HIGH	Absolute effect (95% CI) 0 fewer per 1.000 (from 103 fewer to 140 more)
Number of patients with any adverse events	269 per 1000	170 per 1000	RR 0.63 (0.39 to 1.02)	268 (1 RCT) [b]	⨁⨁⨁⨁ HIGH	Absolute effect (95% CI) 100 fewer per 1.000 (from 164 fewer to 5 more)
Number of patients with serious adverse events	60 per 1000	83 per 1000	RR 1.39 (0.09 to 22.03)	268 (1 RCT) [b]	⨁⨁⨁◯ MODERATE [c]	Absolute effect (95% CI)

Outcome	Anticipated absolute effects (95% CI) [a]		Relative effect (95% CI)	Number of participants (studies)	Certainty of evidence	Comments
	Risk with Placebo	Risk with Bamlanivimab + etesevimab				
						2 more per 1.000 (from 6 fewer to 135 more)

Source: [22]
Explanations: [a] The risk in the intervention group is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI);
[b] [31];
[c] Downgraded of one level for wide CI, including the possibility of trivial or harmful effects;
[d] Authors of current rapid review;
[e] mean and SD refer to change from baseline values as reported by the trial authors, the mean difference refers to between group differences in change from baseline as reported by the trial authors
GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect
Abbreviations: CI=confidence interval; RR=risk ratio; SAE=serious adverse event; AE=adverse event; RCT=randomised controlled trial; SD=standard deviation

4.3.2 Unpublished results announced by Eli Lilly and Company and presented in conference abstracts related to phase 3 portion of BLAZE-1 trial

In this section we describe outcome data as released by Eli-Lilly in press conferences on January 21, 2021 [34] and March 20, 2021 [35], which was also presented in a conference abstract [36]. Eli-Lilly provided additional outcome data that was presented at a conference [33]. Data from FDA revised fact sheet in May 2021 was used as well [6]. No GRADE-assessment of ROB assessment was performed, as the current format doesn't allow that.

In the phase 3 portion of BLAZE-1, the combination therapy arms enrolled mild to moderate, recently diagnosed COVID-19 patients who are at high risk for progressing to severe COVID-19 and/or hospitalisation, studying bamlanivimab 2800 mg plus etesevimab 2800 mg (n=518) versus placebo (n=517), and bamlanivimab 700 mg plus etesevimab 1400 mg (n=511) versus placebo (258). The primary outcome measure for the phase 3 portion of the BLAZE-1 trial was the percentage of participants who experience COVID-related hospitalisations or death from any cause by day 29. The key secondary endpoints were change from baseline to day 7 in SARS-CoV-2 viral load, persistently high SARS-CoV-2 viral load on day 7, time to sustained symptom resolution, and COVID-related hospitalisation, ER visit or death from any cause from baseline by day 29. Additional endpoints include change from baseline in viral load at other time points, symptom improvement, symptom resolution, as well as safety. The study is ongoing with additional treatment arms.

In trial arm **bamlanivimab 2800 mg plus etesevimab 2800 mg** the baseline demographics and disease characteristics were well balanced across treatment groups (Table 4.3).

Table 4.3. BLAZE-1 phase 3 arm bamlanivimab 2800 mg plus etesevimab 2800 mg: baseline demographics and disease characteristics

Baseline characteristics	Placebo (n=517)	Bamlanivimab 2800 mg + Etesevimab 2800 mg (n=518)
Female†	50%	54%
Hispanic or Latino	30%	29%
Black or African American	8%	9%
Age (median)	56	57
Age ≥ 65	30%	32%
Age 12-17 years	1.4%	0.8%
Body-mass index (mean)	33	34
Mild COVID-19	78%	77%
Moderate COVID-19	22%	23%
Duration of symptoms (days, mean)	4.2	4.1
Viral load (mean, CT value, efficacy population)	24.0	24.0

† Limitation: Data not gender-stratified; Abbreviations: CT=cycle threshold

In trial arm **bamlanivimab 700 mg plus etesevimab 1400 mg** the majority (99.2%) of the patients enrolled in these dose arms met the criteria for high-risk adults (≥18 years of age) that included at least one of the following: age ≥65 years, BMI ≥35, chronic kidney disease, diabetes, immunosuppressive disease, immunosuppressant treatment, or age ≥55 years with cardiovascular disease, hypertension, chronic pulmonary disease or other chronic respiratory disease. Participants ages 12-17 were also

enrolled in the trial (10 patients, 2.0% were treated with bamlanivimab and etesevimab and 13 patients,1.7% were treated with placebo), and met high-risk criteria as defined in the trial protocol.

The baseline demographics and disease characteristics were well balanced across treatment groups: median age was 56 years (with 30% of subjects aged 65 or older); 53% of subjects were female, 87% were White, 27% were Hispanic or Latino, and 8% were Black or African American. Subjects had mild (76%) to moderate (24%) COVID-19; the mean duration of symptoms was 4 days; mean viral load by cycle threshold (CT) was 24.33 at baseline [6].

Effectiveness

Outcome: COVID-related hospitalisations or death from any cause by day 29

Trial arm: bamlanivimab 2800 mg plus etesevimab 2800 mg

Bamlanivimab (LY-CoV555) 2800 mg and etesevimab (LY-CoV016) 2800 mg together significantly reduced COVID-19-related hospitalisations and deaths in high-risk patients recently diagnosed with COVID-19. Across 1035 patients (therapy: n=518; placebo n=517), there were 11 events (2.1 percent) in patients taking therapy and 36 events (7.0 percent) in patients taking placebo, representing a 70 percent risk reduction (unadjusted RR from own calculations 0.3; 95% CI 0.16 to 0.59). There were 10 deaths total, all of which occurred in patients taking placebo, and no deaths in patients taking bamlanivimab and etesevimab together (unadjusted RR from own calculations 0.05; 95% CI 0.00 to 0.81).

Trial arm: bamlanivimab 700 mg plus etesevimab 1400 mg

In 769 high-risk patients, aged 12 and older with mild to moderate COVID-19**,** recently diagnosed with COVID-19 (therapy: n=511; placebo: n=258), bamlanivimab (LY-CoV555) 700 mg and etesevimab (LY-CoV016) 1400 mg together significantly reduced COVID-19 related hospitalisations and deaths ("events"). There were four events in patients taking bamlanivimab with etesevimab (0,8%) and 15 events in patients taking placebo (6%), representing an 87 percent risk reduction (p<0.0001). The unadjusted RR from own calculations was 0.13 (95% CI 0.05 to 0.40).

Secondary outcomes

Trial arm: bamlanivimab 2800 mg plus etesevimab 2800 mg

Bamlanivimab and etesevimab together also demonstrated statistically significant improvements on all key secondary endpoints, providing evidence that the therapy reduced viral load and accelerated symptom resolution [36]. A greater reduction in log10 viral load from baseline at Day 7 of 1.20 was observed in patients who received bamlanivimab plus etesevimab compared to placebo (MD -1.20; 95% CI -1.46 to -0.94]; p<0.00000001). At each of the time points measured, at day 3, day 5, day 7 and day 11, statistically significant differences were found (p<0.01; Table 4.4). The median time to sustained symptom resolution was 8 days in those who received the combination treatment (95% CI 7.0 to 8.0) and 9 days in those who received placebo (95% CI 8.0 to 10.0; p=0.007).

Table 4.4. BLAZE-1 phase 3: Mean Viral load

	Placebo	Bamlanivimab 2800 mg + Etesevimab 2800 mg	p value
Day 1	6.52	6.51	-
Day 3	5.74	5.04	<0.001
Day 5	4.68	3.85	<0.001
Day 7	4.05	2.87	<0.001
Day 11	2.69	2.21	<0.001

Trial arm: bamlanivimab 700 mg plus etesevimab 1400 mg

Bamlanivimab and etesevimab together also demonstrated statistically significant improvements on key secondary endpoints.

There were four deaths in total, all of which were deemed related to COVID-19 and all of which occurred in patients taking placebo.

The median time to sustained symptom resolution as recorded in a trial specific daily symptom diary was 8 days for subjects treated with bamlanivimab 700 mg and etesevimab 1400 mg together as compared with 10 days for subjects treated with placebo (p=0.009). Symptoms assessed were cough, shortness of breath, feeling feverish, fatigue, body aches and pains, sore throat, chills, and headache. Sustained symptom resolution was defined as absence of any of these symptoms, except for allowance of mild fatigue and cough, in two consecutive assessments [6].

Across the two phase 3 cohorts of the study that have been analysed to date, no deaths occurred in patients receiving treatment with bamlanivimab and etesevimab together, and 14 deaths occurred in patients receiving placebo, 13 of which were deemed COVID-19 related.

Safety

Trial arm: bamlanivimab 2800 mg plus etesevimab 2800 mg

Serious adverse events were reported in 7 out of 518 at in the bamlanivimab and etesevimab groups and in 5 out of 517 in the placebo groups (unadjusted RR from own calculations 1.40; 95% CI 0.45 to 4.37). Adverse events occurred in 13.3% of subjects who received 2800 mg of bamlanivimab and 2800 mg etesevimab together, and in 11.6% of placebo-treated subjects (unadjusted RR from own calculations 1.15; 95% CI 0.83 to 1.59). The most common adverse events were nausea, dizziness, and rash. These events each occurred in 1% of subjects treated with bamlanivimab and etesevimab and in 1% of placebo subjects (Table 4.5).

Table 4.5. BLAZE-1 phase 3: Summary of Adverse events (Safety population)

N (%)	**Placebo** (n=517)	**Bamlanivimab 2800 mg + Etesevimab 2800 mg** (n=518)
TEAEs	60 (11.6)	69 (13.3)
TEAEs by severity		
Mild	35 (6.8)	37 (7.1)
Moderate	20 (3.9)	24 (4.6)
Severe	5 (1.0)	7 (1.4)
Deaths	1 (0.2)	0
SAEs	5 (1.0)	7 (1.4)

Study-specific clinical events related to COVID-19 including deaths are reported separately and not as Adverse Events; Abbreviations: SAE=Serious Adverse Event; TEAE=Treatment-Emergent Adverse Event; **Source**: [33]

Trial arm: bamlanivimab 700 mg plus etesevimab 1400 mg

In this data set, the safety profile of bamlanivimab and etesevimab together was consistent with observations from other phase 1, phase 2 and phase 3 trials evaluating these antibodies.

4.4 Ongoing trials

Currently, there are seven registered ongoing clinical trials evaluating bamlanivimab alone or in combination with another monoclonal antibody treatment in COVID-19 patients, in ClinicalTrials.gov, ISRCTN and EUdraCT registers related to outpatient setting: five registered ongoing RCTs and two nRCTs. Details can be found in Table A7 in Appendix 3.

One phase 3 study for the prevention of COVID-19 in residents and staff at long-term care facilities (NCT04497987, BLAZE-2) is not listed here, as prevention trial, not relevant for our assessment.

4.5 Patient involvement

One patient organisation (International Council of The Patient Ombudsman from Croatia), two individual adult patients and one informal caregiver (related to child care) contributed to the open call for patient input, published on the EUnetHTA website from 04 to 15 March 2021.

The summary of the most important answers related to the different questions on the impact of COVID-19 condition; experience with currently available therapies; expectations of/requirements for a new medicine for COVID-19 patients, and additional information which the patient believed would be helpful to the HTA researchers are provided below.

The impact of COVID-19 condition (on patients' quality of life and carers/unpaid caregivers)

One patient organisation stated that patients faced too many sources of information related to COVID-19, so for them it was not possible to distinguish between evidence base information and fake news. There was an express loss of confidence in authority and fear to seek help in healthcare. The hospital lockdown due to the COVID-19 pandemic brings limited access to healthcare and presents a big problem where patient rights were violated. The majority of them are patients with the oncological disease, following patient with another chronic diseases, such as asthma, diabetes or multiple sclerosis, with complications. The patient organisation pointed out that the biggest challenges of COVID-19 episodes are to ensure the protection of the patient's rights, the safety in the hospitals and to guarantee the full access to healthcare.

The informal caregiver found it detrimental not to have access to hospital (because level of saturation was the only element taken into consideration at that time in November 2020) and access to care that his/her child should have received (at least access to a qualified monitoring of child's condition).

The patient organisation stated that quality of life is impacted severely in both mental and physical domains. Challenges pointed as important are needs to provide support for the patients and to courage them to be responsible but live "normal", especially without fear to go in the hospitals for preventive measures and follow up.

According to replies of individual patients and informal caregiver, quality of life was impacted in the acute COVID-19 phase but also after, because they experience prolonged illness, so some serious symptoms had not finished yet. For example, at the time of the survey, the child has not been going to school on a regular basis for more than 4 months and still did not, as the child cannot walk and experiences extreme fatigue and brain fog. The child's life has not back to normal. All participants stated that quality of life is highly affected in all aspects and for the whole family.

According to the impact on carers/unpaid care-givers, the patient organisation stated that the problems are most visible in the gynaecology departments, where fathers currently were not allowed to be with their wives during labour. The problems are also visible in the elderly homes, with limited visits. Many persons die without possibility to say goodbye.

The informal caregiver pointed at the extremely difficult and stressful acute phase of COVID-19, even though they were checking the saturation with an oximeter at home during the initial period of infection. Today's knowledge is limited and it is perfectly understandable, but doctors should be able to hear and consider what the patient experience is.

Experience with currently available therapies for COVID-19

According to replies of individual patients and informal caregiver, none of patients received specific COVID-19 treatment (only symptomatic treatment); one adult patient needed hospitalisation due to respiratory problems. They have no experience or did not hear about possible specific treatment options.

Expectations of/requirements for a new medicine for COVID-19 patients

Related to expectation of/requirements for a new medicine for COVID-19 patients, the patient organisation stated that a new medicine could also activates and provide telemedicine health care, and email correspondence with doctors and patients as well, instead of on-site visits and care. Informal caregiver pointed out that health authorities should consider that children/teenagers should be involved in research and development of specific COVID-19 treatment. Guidelines for general practitioners should better address this situation.

5 DISCUSSION

Evidence on effectiveness and safety of bamlanivimab monotherapy and in combination with etesevimab comes from one scientific publication related to final results of phase 2 portion of BLAZE-1 RCT, on bamlanivimab monotherapy (700 mg, 2800 mg, or 7000 mg), and the combination treatment (2800mg of bamlanivimab and 2800 mg of etesevimab), in mild to moderate COVID-19 (outpatient setting) [31], as well as from unpublished results from phase 3 portion of BLAZE-1 RCT related to bamlanivimab 2800 mg plus etesevimab 2800 mg arm, and bamlanivimab 700 mg and etesevimab 1400 mg arm, in high-risk patients with mild to moderate COVID-19 [6], [34], [35].

One RCT was excluded from our analysis due to mixed COVID-19 patient (hospitalised moderate to severe COVID-19) published by Lundgren et al. 2020 (ACTIV-3/TICO LY-CoV555 Study group). They published preliminary negative results from RCT (NCT04501978) compared bamlanivimab monotherapy (LY-CoV555) with placebo in hospitalised patients with moderate and severe COVID-19: in addition, all the patients received high-quality supportive care as background therapy, including the antiviral drug remdesivir (95% of patients) and, when indicated, supplemental oxygen and glucocorticoids. The data and safety monitoring board recommended stopping enrollment for futility after 314 patients (163 in the LY-CoV555 group and 151 in the placebo group) had undergone randomization and infusion [32].

No head-to-head trials comparing bamlanivimab monotherapy or bamlanivimab plus etesevimab combination treatment with other neutralising monoclonal antibodies were published yet.

The main limitation of phase 2 portion of BLAZE-1 trial is that only the post hoc analyses were performed in small samle size of high-risk patients (i.e., ≥65 years or BMI ≥35), the most important group of COVID-19 patients according to the current indication of regulatory agencies in US and EU.

Related to bamlanivimab monotherapy, on April 16, 2021 FDA revoked Emergency Use Authorization (EUA) for the investigational monoclonal antibody therapy bamlanivimab (previously LY-CoV555), when administered alone, for the treatment of mild-to-moderate COVID-19 in adult and pediatric patients. Based on its ongoing analysis of emerging scientific data, specifically the sustained increase of SARS-CoV-2 viral variants that are resistant to bamlanivimab alone resulting in the increased risk for treatment failure, the FDA has determined that the known and potential benefits of bamlanivimab, when administered alone, no longer outweigh the known and potential risks for its authorized use [16].
At the time of publication of this rapid review no such announcement found related to bamlanivimab monotherapy in EU by EMA.

Unpublished results from phase 3 BLAZE-1 RCT related to bamlanivimab 2800 mg plus etesevimab 2800 mg arm, and bamlanivimab 700 mg and etesevimab 1400 mg arm, in high-risk patients with mild to moderate COVID-19 showed positive important clinical outcomes results: such combination therapy significantly reduced COVID-19 related hospitalisations and deaths and demonstrated statistically significant improvements on key secondary endpoints providing evidence that the therapy reduced viral load and accelerated symptom resolution. The main limitation is that no GRADE-assessment of ROB assessment was performed by the authors of this rapid review because no full scientific publications appear yet.

On March 29, 2021 Eli Lilly and Company, Vir Biotechnology, Inc. and GlaxoSmithKline plc announced data from the expanded phase 2 BLAZE-4 trial studying low-risk adult patients with mild to moderate COVID-19. These data are not included in results section of our report. Results showed that investigational bamlanivimab (LY-CoV555) 700 mg co-administered with VIR-7831 (also known as GSK4182136) 500 mg demonstrated a 70 percent ($p<0.001$) relative reduction in persistently high viral load (> 5.27; cycle threshold value < 27.5) at day 7 compared to placebo, meeting the primary endpoint. Bamlanivimab administered with VIR-7831 demonstrated a statistically significant reduction compared to placebo in the key virologic secondary endpoints of mean change from baseline to days 3, 5 and 7 in SARS-CoV-2 viral load. There were no events for the secondary endpoint of COVID-19 related hospitalization or death by day 29 in either study arm. One patient (in the treatment arm) visited the emergency room for COVID-19 related symptoms. No serious adverse events were seen with co-administration of bamlanivimab and VIR-7831. Bamlanivimab and VIR-7831 bind to different regions of the spike protein of SARS-CoV-2. Preclinical data suggest the administration of these two

investigational antibodies together may provide protection against current variants of SARS-CoV-2 that are resistant to bamlanivimab [37].

Uncertainties for bamlanivimab monotherapy and in combination with etesevimab are related to effects on further outcomes of interest, particularly those related to hospitalisation that impact resource allocation (for example, the need for mechanical ventilation, duration of mechanical ventilation, and duration of hospitalisation). Further short-term outcomes related to hospitalisation are lacking also: Number of patients with COVID-19 related hospitalisation; Number of patients admitted to an intensive care unit; Number of patients requiring supplemental oxygen; Pulmonary function; Health-related Quality of life; Clinical improvement defined as a hospital discharge or improvement on the scale used by trialists to evaluate clinical progression and recovery; WHO Clinical Progression Score level 7 or above (i.e., Mechanical ventilation +/- additional organ support (ECMO, vasopressors or dialysis) or death; Time to clinical improvement; Time to WHO Clinical Progression Score level 7 or above; Time to death; Time to viral negative conversion; Duration of supplemental oxygen therapy; Time to ICU admission; Kinetic of viral load; Efficacity depending on SARS-CoV-2 variants and Resistance.

Long term outcomes (such as 6 months endpoint) examining mortality or long-term quality of life; long term safety; patient-reported outcomes such as symptom burden; outcomes when used in combination with other neutralising antibodies and published RCTs with high certainty of evidence are lacking as well. The applicability of these results in specific subgroups, such as children and older adults, pregnant or lactating women is currently uncertain also.

There are several registered ongoing clinical trials evaluating bamlanivimab monotherapy and in combination with etesevimab treatment, compared to standard treatment or other investigational neutralising monoclonal antibodies in outpatient settings. The availability of full clinical study reports for completed trials to allow open and robust scrutiny of the trials is needed as well.

HTA doers recognise that patients and those who support them have unique knowledge about what it is like to live with a specific disease or medical condition. Patients can help to understand unique perspectives by presenting patients' and carers/care-givers' views and experiences. Patients can describe advantages and disadvantages of health interventions based on patients' experiences and values concerning a new intervention [38]. Related to received patient input on issues asked on COVID-19, one patient organisation, two individual patients and one informal caregiver stressed negative impact on quality of life (individually as well as the whole family), burden on carers/unpaid caregivers and negative impact on access and quality of health care. They pointed prolonged symptoms also, known as post-acu COVID-19 ("long covid"). Literature data showed that post-acute COVID-19 ("long covid") seems to be a multisystem disease, sometimes occurring after a relatively mild acute illness. Clinical management requires a whole-patient perspective. Such patients can be divided into those who may have serious sequelae (such as thromboembolic complications) and those with a non-specific clinical picture, often dominated by fatigue and breathlessness. Post-acute COVID-19 symptoms vary widely. Even so-called mild COVID-19 may be associated with long term symptoms, most commonly cough, low grade fever, and fatigue, all of which may relapse and remit. Other reported symptoms include shortness of breath, chest pain, headaches, neurocognitive difficulties, muscle pains and weakness, gastrointestinal upset, rashes, metabolic disruption (such as poor control of diabetes), thromboembolic conditions, and depression and other mental health conditions. Skin rashes can take many forms including vesicular, maculopapular, urticarial, or chilblain-like lesions on the extremities (so called covid toe) [13].

6 SUMMARY OF CLINICAL EFFECTIVENESS AND SAFETY WITH CONCLUSION

A summary of the effectiveness and safety evidence from one published phase 2 BLAZE-1 RCT (related to bamlanivimab 700 mg monotherapy and bamlanivimab 2800 mg plus etesevimab 2800 mg combination therapy) in outpatients with recently diagnosed mild or moderate COVID-19, as well as from unpublished results from phase 3 BLAZE-1 RCT related to bamlanivimab 2800 mg plus etesevimab 2800 mg arm, and bamlanivimab 700 mg and etesevimab 1400 mg arm, in high-risk patients with mild to moderate COVID-19 can be found below.

6.1 Clinical effectiveness

Outcome: All-cause mortality

Published results:

No deaths occurred in bamlanivimab, bamlanivimab + etesevimab combination and placebo groups of outpatients with recently diagnosed mild or moderate COVID-19, according to the results of one RCT with high certainty of evidence.

Unpublished results:

Across the two phase 3 cohorts of the study that have been analysed to date, there were no deaths in patients receiving treatment with bamlanivimab and etesevimab together, while 14 deaths occurred in patients receiving placebo, 13 of which were deemed COVID-19 related.

Outcome: COVID-19 related hospitalisation or emergency department visit at day 29

Published results:

- Bamlanivimab 700 mg monotherapy vs placebo

Bamlanivimab 700 mg monotherapy treatment compared to placebo reduces COVID-19 related hospitalisation or visit to an emergency department at day 29; RR 0.17 (95% CI 0.02 to 1.33), 48 fewer per 1000 (from 57 fewer to 19 more), however the 95% confidence interval includes the possibility of both increased and reduced hospitalisations and emergency department visits (high certainty of evidence).

- Bamlanivimab 700 mg monotherapy vs Bamlanivimab 2800 mg + etesevimab 2800 mg

Compared to bamlanivimab + etesevimab combination, bamlanivimab probably doses not reduce COVID-19 related hospitalisation or visit to an emergency department at day 29; RR 1.11 (95% CI 0.07 to 17.50), 1 more per 1000 (from 8 fewer to 147 more) (moderate certainty of evidence).

- Bamlanivimab 2800 mg + etesevimab 2800 mg vs placebo

Bamlanivimab + etesevimab combination treatment compared to placebo reduces COVID-19 related hospitalisation or visit to an emergency department at day 29 but the 95% confidence interval includes the possibility of both increased and reduced hospitalisations or emergency department visits; RR 0.15 (95% CI 0.02 to 1.20), 49 fewer per 1000 (from 57 fewer to 12 more) (high certainty of evidence).

Unpublished results

Outcome: COVID-19-related hospitalisations and deaths by day 29

- Bamlanivimab 2800 mg + etesevimab 2800 mg vs placebo

Bamlanivimab 2800 mg and etesevimab 2800 mg together significantly reduced COVID-19-related hospitalisations and deaths in high-risk patients recently diagnosed with COVID-19: there were 11 events (2.1 percent) in patients taking therapy and 36 events (7.0 percent) in patients taking placebo, representing a 70 percent risk reduction (unadjusted RR from own calculations 0.3; 95% CI 0.16 to 0.59).

- Bamlanivimab 700 mg + etesevimab 1400 mg vs placebo

Bamlanivimab 700 mg and etesevimab 1400 mg together significantly reduced COVID-19 related hospitalisations and deaths: there were four events in patients taking bamlanivimab with etesevimab and 15 events in patients taking placebo, representing an 87 percent risk reduction (unadjusted RR from own calculations was 0.13, 95% CI 0.05 to 0.40).

Outcome: Symptom score

Published results:

- Bamlanivimab 700 mg monotherapy vs placebo

Compared to placebo, the change in mean total symptom score from baseline to day 22 is probably slightly favouring the 700 mg monotherapy group (mean difference, –0.17, 95%CI, –0.60 to –0.25; p=0.42, moderate certainty of evidence). The change in mean total symptom score from baseline to day 11 was higher in the 700 mg monotherapy group (mean difference, –0.78, 95%CI, –1.37 to –0.20; p=0.009, high certainty of evidence).

- Bamlanivimab 2800 mg + etesevimab 2800 mg vs placebo

Compared to placebo, the change in mean total symptom score from baseline to day 22 is similar in the combination group (mean difference, 0.03, 95%CI, –0.38 to 0.44; p=0.89, moderate certainty of evidence). The change in mean total symptom score from baseline to day 11 was favouring the combination group over placebo (mean difference, –0.60, 95% CI, –1.18 to –0.03; p=0.04, moderate certainty of evidence).

Unpublished results:

- Bamlanivimab 2800 mg + etesevimab 2800 mg vs placebo and Bamlanivimab 700 mg + etesevimab 1400 mg vs placebo

Bamlanivimab and etesevimab together demonstrated statistically significant accelerated symptom resolution.

Outcome: Viral clearance

Published results:

- Bamlanivimab 700 mg monotherapy vs placebo

Compared to placebo, bamlanivimab does not importantly accelerate the natural decline in viral load over time; RR 1.06 (95% CI 0.83 to 1.37), 22 more per 1.000 (from 63 fewer to 136 more) (high certainty of evidence).

- Bamlanivimab 700 mg monotherapy vs Bamlanivimab 2800 mg + etesevimab 2800 mg

Compared to bamlanivimab + etesevimab combination, bamlanivimab does not importantly accelerate the natural decline in viral load over time; RR 1.07 (95% CI 0.80 to 1.42), 26 more per 1.000 (from 73 fewer to 154 more) (high certainty of evidence).

- Bamlanivimab 2800 mg + etesevimab 2800 mg vs placebo

Comparing to placebo, bamlanivimab + etesevimab combination does not accelerate the natural decline in viral load over time; RR 1.00 (95% CI 0.72 to 1.38), 0 fewer per 1.000 (from 103 fewer to 140 more) (high certainty of evidence).

Unpublished results:

- Bamlanivimab 2800 mg + etesevimab 2800 mg vs placebo and Bamlanivimab 700 mg + etesevimab 1400 mg vs placebo

Bamlanivimab and etesevimab together demonstrated statistically significant reduced viral load.

6.2 Safety

Outcome: Number of patients with adverse events

Published results:

- Bamlanivimab 700 mg monotherapy vs placebo

According to the results of one RCT, in outpatients with recently diagnosed mild or moderate COVID-19, bamlanivimab compared to placebo does not increase the number of patients with adverse events (high certainty of evidence); RR 0.99 (0.66 to 1.50), absolute effect (95% CI) 3 fewer per 1.000 (from 92 fewer to 135 more).

- Bamlanivimab 700 mg monotherapy vs Bamlanivimab 2800 mg + etesevimab 2800 mg

According to the results of one RCT, in outpatients with recently diagnosed mild or moderate COVID-19, bamlanivimab compared to bamlanivimab + etesevimab combination treatment increases the number of patients with adverse events (high certainty of evidence); RR 1.58 (0.94 to 2.65), absolute effect (95% CI) 98 more per 1.000 (from 10 fewer to 280 more).

- Bamlanivimab 2800 mg + etesevimab 2800 mg vs placebo

According to the results of one RCT, in outpatients with recently diagnosed mild or moderate COVID-19, bamlanivimab + etesevimab combination, compared to placebo, does not increase the number of patients with adverse events (high certainty of evidence); RR 0.63 (0.39 to 1.02), absolute effect (95% CI) 100 fewer per 1.000 (from 164 fewer to 5 more).

Unpublished results:

- Bamlanivimab 2800 mg + etesevimab 2800 mg vs placebo

In the group of bamlanivimab 2800 mg and etesevimab 2800 mg together, unadjusted RR from own calculations is 1.15; 95% CI 0.83 to 1.59.

- Bamlanivimab 700 mg + etesevimab 1400 mg vs placebo

The safety profile of bamlanivimab 700 mg and etesevimab 1400 mg together was consistent with observations from phase 1 and phase 2 trials related to these antibodies.

Outcome: Number of patients with serious adverse events

Published results:

- Bamlanivimab 700 mg monotherapy vs placebo

According to the results of one RCT, in outpatients with recently diagnosed mild or moderate COVID-19, bamlanivimab, compared to placebo, probably does not increase the number of patients with serious

adverse events (moderate certainty of evidence); RR 0.51 (0.02 to 12.47), absolute effect (95% CI) 3 fewer per 1.000 (from 6 fewer to 74 more).

- Bamlanivimab 700 mg monotherapy vs Bamlanivimab 2800 mg + etesevimab 2800 mg

According to the results of one RCT, in outpatients with recently diagnosed mild or moderate COVID-19, bamlanivimab compared to bamlanivimab + etesevimab probably does not increase the number of patients with serious adverse events (moderate certainty of evidence); RR 0.37 (0.02 to 8.96), absolute effect (95% CI) 6 fewer per 1.000 (from 9 fewer to 71 more).

- Bamlanivimab 2800 mg + etesevimab 2800 mg vs placebo

According to the results of one RCT, in outpatients with recently diagnosed mild or moderate COVID-19, bamlanivimab + etesevimab combination, compared to placebo, probably does not importantly increase the number of patients with serious adverse events (moderate certainty of evidence); RR 1.39 (0.09 to 22.03), absolute effect (95% CI) 2 more per 1.000 (from 6 fewer to 135 more).

Unpublished results:

- Bamlanivimab 2800 mg + etesevimab 2800 mg vs placebo

In the group of bamlanivimab 2800 mg and etesevimab 2800 mg together, unadjusted RR from own calculations is 1.40; 95% CI 0.45 to 4.37.

- Bamlanivimab 700 mg + etesevimab 1400 mg vs placebo

The safety profile of bamlanivimab 700 mg and etesevimab 1400 mg together was consistent with observations from phase 1 and phase 2 trials related to these antibodies.

6.3 Scientific conclusion

Based on published final results of the phase 2 portion of BLAZE-1 RCT in outpatients with recently diagnosed mild or moderate COVID-19 (related to bamlanivimab 700 mg monotherapy and bamlanivimab 2800 mg plus etesevimab 2800 mg combination therapy), and as summarized in two Living Systematic Reviews with Meta-Analyses (MAs), no deaths occurred in bamlanivimab, bamlanivimab + etesevimab combination and placebo groups (high certainty of evidence).

Bamlanivimab monotherapy and bamlanivimab + etesevimab treatment compared to placebo reduces COVID-19–related hospitalisation or visit to an emergency department at day 29.

The change in mean total symptom score from baseline to day 11 was favouring the 700 mg monotherapy group and the bamlanivimab + etesevimab combination group.

Bamlanivimab monotherapy or bamlanivimab + etesevimab treatment, compared to placebo, does not importantly accelerate the natural decline in viral load over time (high certainty of evidence). The same is true for bamlanivimab compared to bamlanivimab + etesevimab treatment.

Bamlanivimab and bamlanivimab + etesevimab treatment compared to placebo does not increase the number of patients with adverse events (high certainty of evidence) and probably does not increase the number of serious adverse events (moderate certainty of evidence). Bamlanivimab compared to bamlanivimab + etesevimab treatment increases the risk of adverse events but does not importantly affect the risk of serious adverse events.

Unpublished results from phase 3 BLAZE-1 RCT related to bamlanivimab 2800 mg plus etesevimab 2800 mg arm, and bamlanivimab 700 mg and etesevimab 1400 mg arm, in high-risk patients with mild to moderate COVID-19 showed that such combination therapy significantly reduced COVID-19 related hospitalisations and deaths and demonstrated statistically significant improvements on key secondary endpoints providing evidence that the therapy reduced viral load and accelerated symptom resolution. The safety profile of bamlanivimab and etesevimab together was consistent with observations from

other trial phases evaluating these antibodies. Serious adverse events were reported at a similar frequency in the bamlanivimab and etesevimab together and placebo groups.

All unpublished results however have to be interpreted with care, until peer-reviewed reports are available. Genotypic and phenotypic testing are ongoing to monitor for potential bamlanivimab and etesevimab-resistance associated spike variations in clinical trials.

Further RCTs examining bamlanivimab alone or in combination with etesevimab or other neutralising monoclonal antibody for the treatment of COVID-19 patients in outpatient setting are under way.

Published, peer-reviewed, high-quality evidence on final results from ongoing RCTs are needed to further assess effectiveness and safety of bamlanivimab alone or in combination with etesevimab in COVID-19 patients. Updates of this document are indicated once new evidence becomes available.

In the EU, there are no authorised treatments yet for individuals with mild to moderate COVID-19 early in the disease course. On March 5, 2021 EMA stated that the CHMP has completed its review started in February 2021 to provide a harmonised scientific opinion at EU level to support national decision making on the possible use of the antibodies before a formal authorisation is issued. EMA concluded that bamlanivimab monotherapy and bamlanivimab and etesevimab combination can be used together to treat confirmed COVID-19 in patients who do not require supplemental oxygen and who are at high risk of their COVID-19 disease becoming severe. On March 11, 2021 EMA's CHMP has started a 'rolling review' of data on the antibodies bamlanivimab and etesemivab to be used in combination for the treatment of COVID-19. The review will also look at bamlanivimab used alone. The rolling review will continue until enough evidence is available to support formal marketing authorisation applications. The same is true for other neutralising monoclonal antibodies like REGN-COV2 and regdanvimab monotherapy.

Related to bamlanivimab monotherapy, on April 16, 2021 FDA revoked Emergency Use Authorization for the bamlanivimab, when administered alone, for the treatment of mild-to-moderate COVID-19 in adult and pediatric patients due to the sustained increase of SARS-CoV-2 viral variants that are resistant to bamlanivimab alone resulting in the increased risk for treatment failure. At the time of publication of this rapid review, EMA had not made a similar announcement related to bamlanivimab monotherapy for the European context.

Patient organisation/individual patients/informal caregiver stressed negative impact of COVID-19 on quality of life, burden on carers/unpaid caregivers and negative impact on access and quality of health care. They all pointed at the burden of prolonged symptoms, currently known as post-acute COVID-19 ("long covid").

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APPENDIX 1 : CLINICAL GUIDELINES FOR MANAGEMENT

Box A1. Summary of the current therapeutic management of patients with COVID-19

NIH COVID-19 treatment guidelines: Pharmacological management of patients with COVID-19 based on disease severity [2]

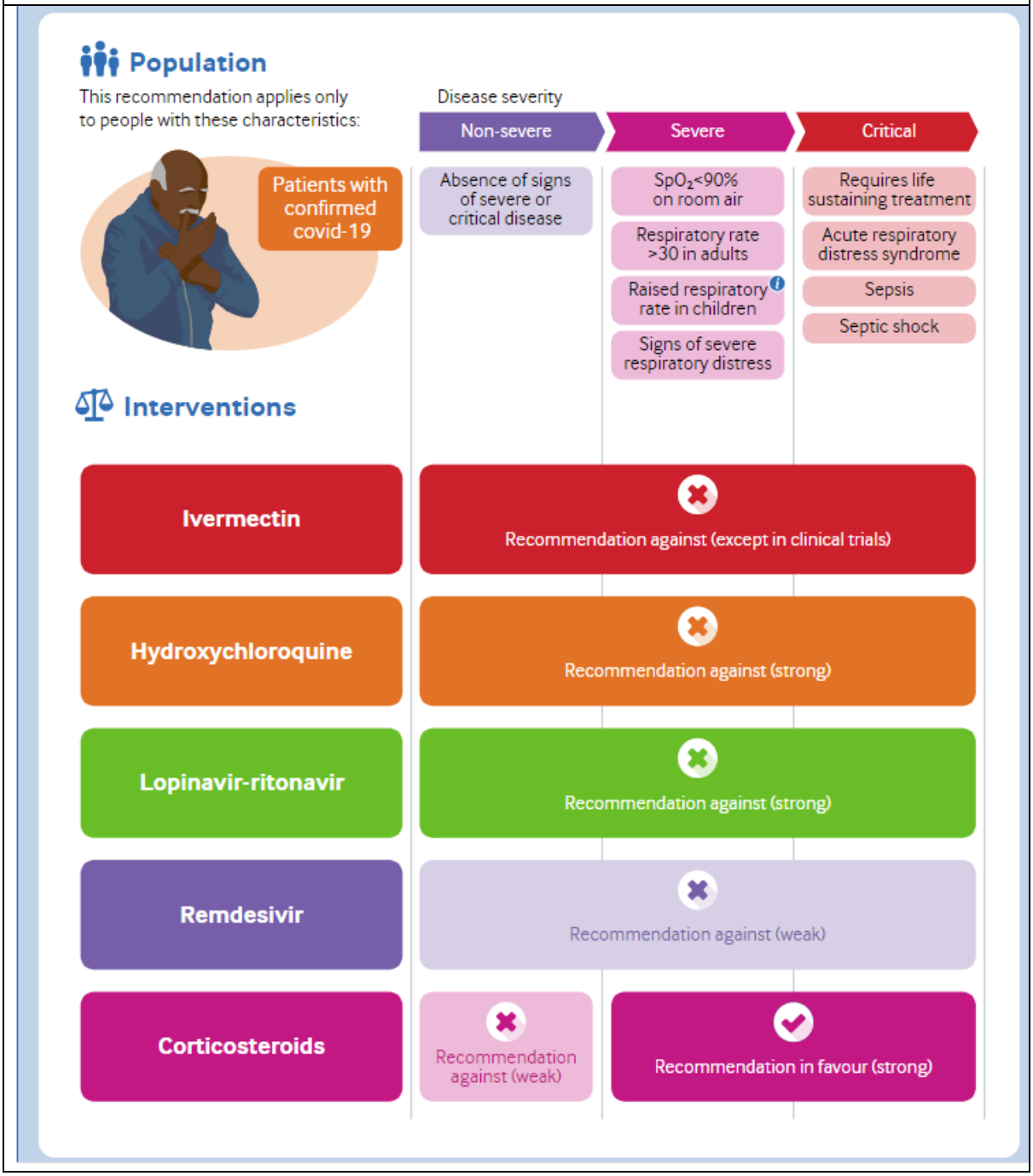
DISEASE SEVERITY	PANEL'S RECOMMENDATIONS
Not Hospitalized, Mild to Moderate COVID-19	For patients who are not at high risk for disease progression, provide supportive care and symptomatic management **(AIII)**. For patients who are at high risk of disease progression (as defined by the FDA EUA criteria for treatment with anti-SARS-CoV-2 monoclonal antibodies), use one of the following combinations: • **Bamlanivimab plus etesevimab (AIIa)** • **Casirivimab plus imdevimab (AIIa)**
Hospitalized but Does Not Require Supplemental Oxygen	There are insufficient data to recommend either for or against the routine use of remdesivir. For patients at high risk of disease progression, the use of remdesivir may be appropriate.
Hospitalized and Requires Supplemental Oxygen	Use one of the following options: • **Remdesivir**[a,b] (e.g., for patients who require minimal supplemental oxygen) **(BIIa)** • **Dexamethasone**[c] **plus remdesivir**[a,b] (e.g., for patients who require increasing amounts of supplemental oxygen) **(BIII)**[d,e] • **Dexamethasone**[c] (e.g., when combination therapy with remdesivir cannot be used or is not available) **(BI)**
Hospitalized and Requires Oxygen Delivery Through a High-Flow Device or Noninvasive Ventilation	Use one of the following options: • **Dexamethasone**[c] **(AI)**[e] • **Dexamethasone**[c] **plus remdesivir**[a,b] **(BIII)**[d,e] For patients who were recently hospitalized[f] with rapidly increasing oxygen needs and systemic inflammation: • Add **tocilizumab**[g] to one of the two options above **(BIIa)**
Hospitalized and Requires Invasive Mechanical Ventilation or ECMO	• **Dexamethasone**[c] **(AI)**[h] For patients who are within 24 hours of admission to the ICU: • **Dexamethasone**[c] **plus tocilizumab**[g] **(BIIa)**

Rating of Recommendations: A = Strong; B = Moderate; C = Optional
Rating of Evidence: I = One or more randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion

[a] The remdesivir dose is 200 mg IV for one dose, followed by remdesivir 100 mg IV once daily for 4 days or until hospital discharge (unless the patient is in a health care setting that can provide acute care that is similar to inpatient hospital care). Treatment duration may be extended to up to 10 days if there is no substantial clinical improvement by Day 5.
[b] For patients who are receiving remdesivir but progress to requiring oxygen through a high-flow device, noninvasive ventilation, invasive mechanical ventilation, or ECMO, remdesivir should be continued until the treatment course is completed.
[c] The dexamethasone dose is 6 mg IV or PO once daily for 10 days or until hospital discharge. If dexamethasone is not available, equivalent doses of other corticosteroids (e.g., prednisone, methylprednisolone, hydrocortisone) may be used. See the Corticosteroids section for more information.
[d] The combination of dexamethasone and remdesivir has not been studied in clinical trials.
[e] In the rare circumstances where corticosteroids cannot be used, **baricitinib plus remdesivir** can be used **(BIIa)**. The FDA has issued an EUA for baricitinib use in combination with remdesivir. The dose for baricitinib is 4 mg PO once daily for 14 days or until hospital discharge.
[f] For example, within 3 days of hospital admission. See the Interleukin-6 Inhibitors section for more information.
[g] The tocilizumab dose is 8 mg/kg of actual body weight (up to 800 mg) administered as a single IV dose. Tocilizumab should not be combined with baricitinib and should be avoided in certain groups of patients who are at increased risk for complications. See the Interleukin-6 Inhibitors section for more information.
[h] The combination of **dexamethasone plus remdesivir** may be considered for patients who have recently been intubated **(CIII)**. The Panel **recommends against** the use of remdesivir monotherapy in these patients.

Key: ECMO = extracorporeal membrane oxygenation; EUA = Emergency Use Authorization; FDA = Food and Drug Administration; ICU = intensive care unit; IV = intravenous; the Panel = the COVID-19 Treatment Guidelines Panel; PO = orally

A living WHO guideline on drugs for COVID-19, Visual summary of recommendation [1], [39]



APPENDIX 2: LITERATURE SEARCH AND FLOW-DIAGRAMS FOR RCTS

Table A1. Search strategy to identify randomised controlled studies

Database	URL	Search line / Search terms	Date of search
Pubmed	pubmed.ncbi.nlm.nih.gov	1. (((((((("Coronavirus"[Mesh]) OR (coronavirus*[Title/Abstract] OR coronovirus*[Title/Abstract] OR coronavirinae*[Title/Abstract] OR Coronavirus*[Title/Abstract] OR Coronovirus*[Title/Abstract] OR Wuhan*[Title/Abstract] OR Hubei*[Title/Abstract] OR Huanan[Title/Abstract] OR "2019-nCoV"[Title/Abstract] OR 2019nCoV[Title/Abstract] OR nCoV2019[Title/Abstract] OR "nCoV-2019"[Title/Abstract] OR "COVID-19"[Title/Abstract] OR COVID19[Title/Abstract] OR "CORVID-19"[Title/Abstract] OR CORVID19[Title/Abstract] OR "WN-CoV"[Title/Abstract] OR WNCoV[Title/Abstract] OR "HCoV-19"[Title/Abstract] OR HCoV19[Title/Abstract] OR CoV[Title/Abstract] OR "2019 novel*"[Title/Abstract] OR Ncov[Title/Abstract] OR "n-cov"[Title/Abstract] OR "SARS-CoV-2"[Title/Abstract] OR "SARSCoV-2"[Title/Abstract] OR "SARSCoV2"[Title/Abstract] OR "SARS-CoV2"[Title/Abstract] OR SARSCov19[Title/Abstract] OR "SARS-Cov19"[Title/Abstract] OR "SARSCov-19"[Title/Abstract] OR "SARS-Cov-19"[Title/Abstract] OR Ncovor[Title/Abstract] OR Ncorona*[Title/Abstract] OR Ncorono*[Title/Abstract] OR NcovWuhan*[Title/Abstract] OR NcovHubei*[Title/Abstract] OR NcovChina*[Title/Abstract] OR NcovChinese*[Title/Abstract])) OR ((((respiratory*[Title/Abstract] AND (symptom*[Title/Abstract] OR disease*[Title/Abstract] OR illness*[Title/Abstract] OR condition*))[Title/Abstract] OR "seafood market*"[Title/Abstract] OR "food market*")[Title/Abstract] AND (Wuhan*[Title/Abstract] OR Hubei*[Title/Abstract] OR China*[Title/Abstract] OR Chinese*[Title/Abstract] OR Huanan*))[Title/Abstract])) OR ("severe acute respiratory syndrome*")) OR ((corona*[Title/Abstract] OR corono*)[Title/Abstract] AND (virus*[Title/Abstract] OR viral*[Title/Abstract] OR virinae*)[Title/Abstract])) AND (((((((randomized controlled trial [12]) OR (controlled clinical trial [12])) OR (randomized [tiab])) OR (placebo [tiab])) OR (clinical trials as topic [mesh: noexp])) OR (randomly [tiab])) OR (trial [ti]))) NOT (animals [mh] NOT humans [mh]) AND (2019/10/01:2020[dp])	03/05/2021

Database	URL	Search line / Search terms	Date of search
Ovid MEDLINE(R) ALL)	ovidsp.dc2.ovid.com	1. exp coronavirus/ 2. ((corona* or corono*) adj1 (virus* or viral* or virinae*)).ti,ab,kw. 3. (coronavirus* or coronovirus* or coronavirinae* or Coronavirus* or Coronovirus* or Wuhan* or Hubei* or Huanan or "2019-nCoV" or 2019nCoV or nCoV2019 or "nCoV-2019" or "COVID-19" or COVID19 or "CORVID-19" or CORVID19 or "WN-CoV" or WNCoV or "HCoV-19" or HCoV19 or CoV or "2019 novel*" or Ncov or "n-cov" or "SARS-CoV-2" or "SARSCoV-2" or "SARSCoV2" or "SARS-CoV2" or SARSCov19 or "SARS-Cov19" or "SARSCov-19" or "SARS-Cov-19" or Ncovor or Ncorona* or Ncorono* or NcovWuhan* or NcovHubei* or NcovChina* or NcovChinese*).ti,ab,kw. 4. (((respiratory* adj2 (symptom* or disease* or illness* or condition*)) or "seafood market*" or "food market*") adj10 (Wuhan* or Hubei* or China* or Chinese* or Huanan*)).ti,ab,kw. 5. ((outbreak* or wildlife* or pandemic* or epidemic*) adj1 (China* or Chinese* or Huanan*)).ti,ab,kw. 6. "severe acute respiratory syndrome*".ti,ab,kw. 7. or/1-6 8. randomized controlled trial.pt. 9. controlled clinical trial.pt. 10. random*.ab. 11. placebo.ab. 12. clinical trials as topic.sh. 13. random allocation.sh. 14. trial.ti. 15. or/8-14 16. exp animals/ not humans.sh. 17. 15 not 16 18. 7 and 17 19. limit 18 to yr="2019 -Current"	03/05/2021
OVID EMBASE	ovidsp.dc2.ovid.com	1. exp Coronavirinae/ or exp Coronavirus/ 2. exp Coronavirus infection/ 3. ((("Corona virinae" or "corona virus" or Coronavirinae or coronavirus or COVID or nCoV) adj4 ("19" or "2019" or novel or new)) or (("Corona virinae" or "corona virus" or Coronavirinae or coronavirus or COVID or nCoV) and (wuhan or china or chinese)) or "Corona virinae19" or "Corona virinae2019" or "corona virus19" or "corona virus2019" or Coronavirinae19 or Coronavirinae2019 or coronavirus19 or coronavirus2019 or COVID19 or COVID2019 or nCOV19 or nCOV2019 or "SARS Corona virus 2" or "SARS Coronavirus 2" or "SARS-COV-2" or "Severe Acute Respiratory Syndrome Corona virus 2" or "Severe Acute Respiratory Syndrome Coronavirus 2").ti,ab,kw. 4. or/1-3 5. Clinical-Trial/ or Randomized-Controlled-Trial/ or Randomization/ or Single-Blind-Procedure/ or Double-Blind-Procedure/ or Crossover-Procedure/ or Prospective-Study/ or Placebo/ 6. (((clinical or control or controlled) adj (study or trial)) or ((single or double or triple) adj (blind$3 or mask$3)) or (random$ adj (assign$ or allocat$ or group or grouped or patients or study or trial or distribut$)) or (crossover adj (design or study or trial)) or placebo or placebos).ti,ab. 7. 5 or 6 8. 4 and 7 9. limit 8 to yr="2019 -Current"	03/05/2021

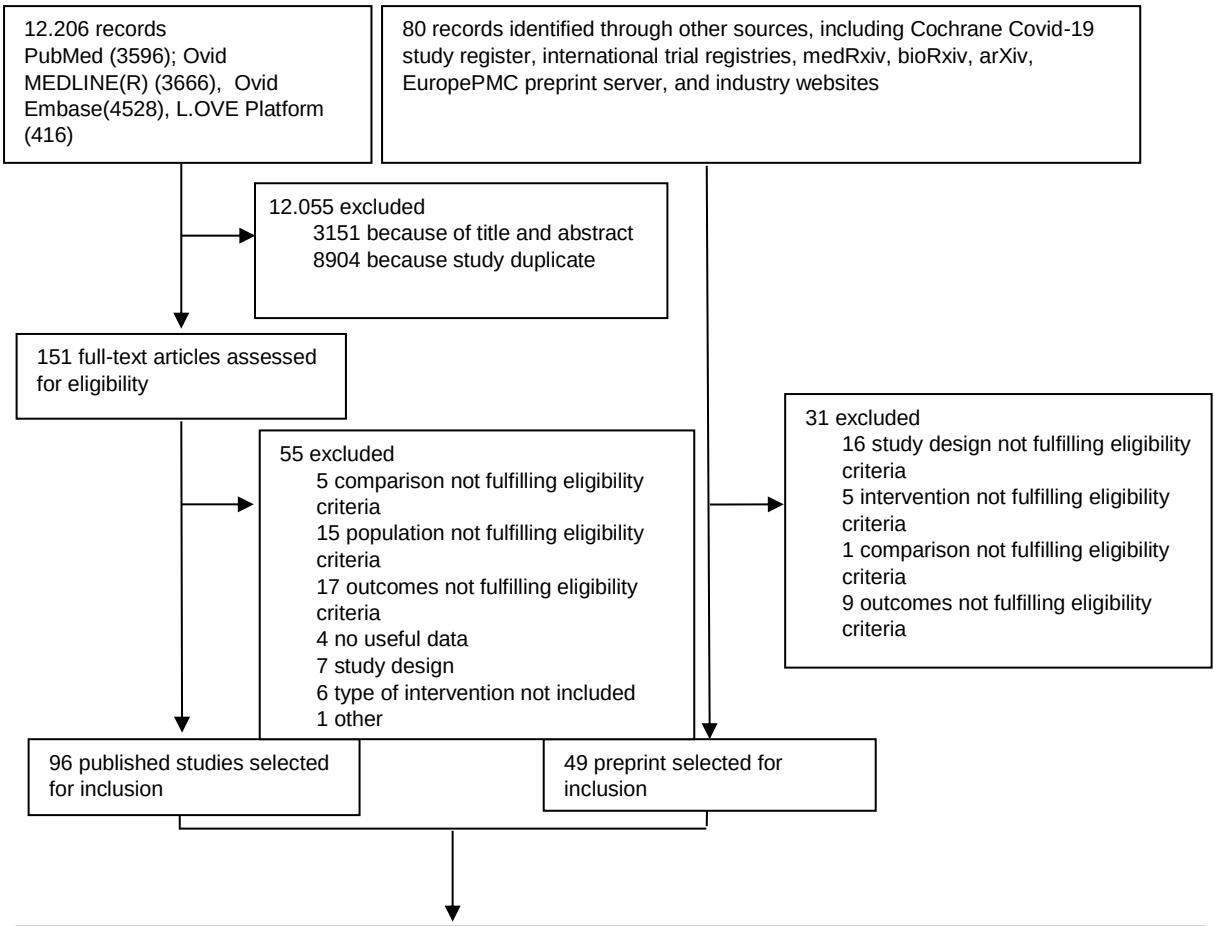


Figure A1. Flow diagram depicting the selection process of RCTs

* The selection process was part of an external project, see https://www.deplazio.net/farmacicovid and Prospero ID CRD42020176914.
Abbreviation: RCT = randomised controlled trial;

APPENDIX 3: TABLES RELATED TO TRIAL CHARACTERISTICS, RISK OF BIAS, CERTAINTY OF EVIDENCE, EFFECTIVENESS OUTCOMES AND ONGOING TRIALS

In this appendix, additional tables related to trial characteristics, risk of bias, certainty of evidence, effectiveness outcomes, and ongoing trials are provided.

Table A2. Study characteristics of included RCT retrieved from scientific publication

Author, year, reference number/Study name/Study ID	Gottlieb et al. 2021 [31] BLAZE-1, NCT04427501
Study design, study phase	5-arm placebo controlled RCT with parallel group assignment, phase 2/3; Centrally randomized to study intervention using an Interactive Web Response System (IWRS); Blinding of participants, investigators and sponsor study team
Centres (single centre or multicentre), country, setting	Multicentre, US, Outpatients
Patient population (number of included patients/ Mean age and sex/ Disease severity*)	Mild to moderate COVID-19, 592 randomized; Mean age,44.7 [SD, 15.7] years; 315 [54.6%] women); 449 patients (77.8%); Mild COVID-19 387 (67.1%) with at least one risk factor for severe COVID-19 (aged ≥55 years, BMI ≥30, or ≥1 relevant comorbidity such as hypertension)
Inclusion criteria	Are ≥18 years of age at the time of randomization; Not hospitalized; Have one or more mild or moderate COVID-19 symptoms i. Fever ii. Cough iii. Sore throat iv. Malaise v. Headache vi. Muscle pain vii. Gastrointestinal symptoms, or viii. Shortness of breath with exertion; Sample collection for first positive SARS-CoV-2 viral infection determination ≤3 days prior to start of the infusion; Sex men or non-pregnant women Reproductive and Contraceptive agreements. Contraceptive use by men or women should be consistent with local regulations for those participating in clinical studies; Understand and agree to comply with planned study procedures; Agree to the collection of nasopharyngeal swabs and venous blood; Informed Consent - The participant or legally authorized representative give signed informed consent which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.
Exclusion criteria	SpO2 ≤ 93% on room air at sea level or PaO2/FiO2 < 300, respiratory rate ≥30 per minute, heart rate ≥125 per minute; Require mechanical ventilation or anticipated impending need for mechanical ventilation; known allergies to any of the components used in the formulation of the interventions; hemodynamic instability requiring use of pressors within 24 hours of randomization; Suspected or proven serious, active bacterial, fungal, viral, or other infection (besides COVID-19) that in the opinion of the investigator could constitute a risk when taking intervention; any co-morbidity requiring surgery within < 7 days, or that is considered life-threatening within 29 days; any serious concomitant systemic disease, condition or disorder that, in the opinion of the investigator, should preclude participation in this study; history of a positive SARS-CoV-2 serology test; history of a positive SARS-CoV-2 test prior to the one serving as eligibility for this study; received an investigational intervention for SARS-CoV-2 prophylaxis within 30 days before dosing; received treatment with a SARS-CoV-2 specific monoclonal antibody; history of convalescent COVID-19 plasma treatment; participated in a previous SARS-CoV-2 vaccine study; participated, within the last 30 days, in a clinical study involving an investigational intervention. If the previous investigational intervention has a long half-life, 5 half-lives or 30 days, whichever is longer, should have passed; concurrently enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study; pregnant or breast feeding; Are investigator site personnel directly affiliated with this study.
Intervention (generic drug name and dosage, time frame; number of randomized/ enrolled patients in subgroups - Mild, Moderate, Severe, Critical COVID-19)	Trial arm 1: single infusion of bamlanivimab 700mg; n = 101 Trial arm 2: single infusion of bamlanivimab 2800mg; n = 107 Trial arm 3: single infusion of bamlanivimab 7000mg; n = 101 Disease severity in trial arms 1-3 Mild 83 (82.2%); 79 (73.8%); 70 (69.3) Moderate 18 (17.8%); 28 (26.2%); 31 (30.7%) Trial arm 4: combination treatment with 2800mg of bamlanivimab and 2800mg of etesevimab; n = 112 Disease severity in trial arm 4: Mild 92 (82.1%) Moderate 20 (17.9%) Concomitant treatments: standard of care as defined by local centres

	Prior treatment: convalescent COVID-19 plasma treatment is not allowed, other prior treatments are allowed and recorded
Comparator(s) (standard care or generic drug name and dosage, time frame; number of randomized/ enrolled patients in subgroups - Mild, Moderate, Severe, Critical COVID-19)	Trial arm 5: single infusion of 0.9% sodium chloride solution (placebo) n=156 Disease severity in trial arm 5: Mild 125 (80.1%) Moderate 31 (19.9%) Concomitant treatments: see above Prior treatment: see above
Primary Outcome(s)	According to the published report by Gottlieb [31] and the final protocol: Change in SARS-CoV-2 log viral load at day 11 (±4 days) According to clinicaltrials.gov: Percentage of Participants Who Experience COVID-Related Hospitalization or Death from Any Cause [Time Frame: Baseline through Day 29]; Change from Baseline to Day 11 in SARS-CoV-2 Viral Load [Time Frame: Baseline, Day 11]; Percentage of Participants with SARS-CoV-2 Viral Load Greater than a Prespecified Threshold [Time Frame: Day 7]; Pharmacokinetics (PK): Area Under the Concentration-time Curve from 0 to Infinity (AUC0-inf) for both LY3819253 and LY3832479 [Time Frame: Baseline through Day 85]; Percentage of Participants who Experience a Serious Adverse Event(s) SAE(s) [Time Frame: Baseline through Day 85]
Patient-relevant secondary outcome(s)	According to the published report by Gottlieb [31] and the final protocol: Nine prespecified secondary outcome measures: with comparisons between each treatment group and placebo, and included 3 other measures of viral load, 5 on symptoms, and 1 measure of clinical outcome (the proportion of patients with a COVID-19–related hospitalization, an emergency department [ED] visit, or death at day 29); AEs, SAEs
Follow-up (days, months)	Up to day 29
Sponsor/ lead institution	Eli Lilly

RISK OF BIAS 2 (RoB2) Table

Table A3. Risk of bias assessed with the Cochrane risk of bias 2 tool

Studies	Randomisation process	Deviations from the intended interventions	Missing outcomes	Measurement of the outcome	Selection of reported results	Overall bias
Gottlieb R, BLAZE-1, 2021 [31]	Low a	Low b	Some concerns c	Low d	Low e	Some concerns

Source: adapted from https://covid-nma.com [23]

a Quote: "All participants were centrally randomized to each study intervention using an interactive web response system. Before the study was initiated, the log-in information and directions for the interactive web response system was provided to each of the 49 US study sites." Comment: Allocation sequence random. Allocation sequence concealed. Imbalances in baseline characteristics appear to be compatible with chance b Quote: "double-blind, placebo-controlled"; "Double-blind. Neither participants, nor investigators, nor the sponsor study team will be aware of treatment assignments prior to the final data base locks at the conclusion of the study.' Comment: Blinded study (participants, personnel/carers). Data for the safety outcomes were analyzed using intention-to-treat analysis. This method was considered appropriate to estimate the effect of assignment to intervention. Participants were analyzed according to their randomized groups for the viral negative conversion outcome. Of note, 10 vs 9 vs 7 participants were excluded from the analysis post-randomization for reasons likely related to missing data. This method was considered appropriate to estimate the effect of assignment to intervention for this outcome. Risk assessed to be low for outcomes: Mortality (D28). Incidence of viral negative conversion (D7). Adverse events. Serious adverse events. c Comment: 592 patients randomized; 577 patients analyzed for mortality, adverse events and serious adverse events; 544 for viral clearance. Data available for all or nearly all participants in the safety population. Risk assessed to be low for outcomes: Mortality (D28). Adverse events. Serious adverse events. For viral negative conversion (D7), data were not available for all or nearly all participants. No evidence that the result is not biased. Reasons for missing data unknown, hence no information on whether missingness could depend on its true value, but it is not considered likely to be related to the true value of the outcome as only 15 people in this population of outpatients with mild COVID-19 reported hospitalization or an ER visit, in which symptoms improved for the majority. Missing data were balanced among arms. Risk assessed to be some concerns for the outcome: Incidence of viral negative conversion (D7). d Quote: "Neither participants, nor investigators, nor the sponsor study team will be aware of treatment assignments prior to the final data base locks at the conclusion of the study."; double-blind, placebo-controlled"
Comment: Method of measuring the outcome probably appropriate. Measurement or ascertainment of outcome probably does not differ between groups. Blinded study (outcome assessor).
Risk assessed to be low for the outcomes: Mortality (D28). Incidence of viral negative conversion (D7). Adverse events. Serious adverse events. e Comment: The protocol, statistical analysis plan and trial registry were available. Results were not selected from multiple outcome measurements or analyses of the data. Trial analyzed as pre-specified.
Risk assessed to be low for the outcomes: Mortality (D28). Incidence of viral negative conversion (D7). Adverse events. Serious adverse events.

CERTAINTY OF EVIDENCE

Table A4. GRADE evidence

Author(s): Cruciani F, De Crescenzo F, Vecchi S, Saulle R, Mitrova Z, Amato L, Davoli M. [21]
Question: Should **LY-CoV555 antibody compared to Placebo** be used for COVID-19 patients?
Setting: **Outpatient**

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**LY-CoV555 antibody**	**Placebo**	**Relative (95% CI)**	**Absolute (95% CI)**	
All-cause mortality (all doses)											
1 [31]	randomised trials	not serious	not serious	not serious	not serious	none	No deaths reported				⊕⊕⊕⊕ HIGH
All-cause mortality (700 mg)											
1 [31]	randomised trials	not serious	not serious	not serious	not serious	none	No deaths reported				⊕⊕⊕⊕ HIGH
All-cause mortality (2800 mg)											
1 [31]	randomised trials	not serious	not serious	not serious	not serious	none	No deaths reported				⊕⊕⊕⊕ HIGH
All-cause mortality (7000 mg)											
1 [31]	randomised trials	not serious	not serious	not serious	not serious	none	No deaths reported				⊕⊕⊕⊕ HIGH
Number of patients with any adverse events (all doses)											
1 [31]	randomised trials	not serious	not serious	not serious	not serious	none	75/309 (24.3%)	42/156 (26.9%)	RR 0.90 (0.65 to 1.25)	**27 fewer per 1.000** (from 94 fewer to 67 more)	⊕⊕⊕⊕ HIGH
Number of patients with any adverse events (700 mg)											

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LY-CoV555 antibody	Placebo	Relative (95% CI)	Absolute (95% CI)	
1 [31]	randomised trials	not serious	not serious	not serious	not serious	none	27/101 (26.7%)	42/156 (26.9%)	RR 0.99 (0.66 to 1.50)	**3 fewer per 1.000** (from 92 fewer to 135 more)	⊕⊕⊕⊕ HIGH
Number of patients with any adverse events (2800 mg)											
1 [31]	randomised trials	not serious	not serious	not serious	not serious	none	26/107 (24.3%)	42/156 (26.9%)	RR 0.90 (0.59 to 1.38)	**27 fewer per 1.000** (from 110 fewer to 102 more)	⊕⊕⊕⊕ HIGH
Number of patients with any adverse events (7000 mg)											
1 [31]	randomised trials	not serious	not serious	not serious	not serious	none	22/101 (21.8%)	42/156 (26.9%)	RR 0.81 (0.52 to 1.27)	**51 fewer per 1.000** (from 129 fewer to 73 more)	⊕⊕⊕⊕ HIGH
Number of patients with serious adverse events (all doses)											
1 [31]	randomised trials	not serious	not serious	not serious	not serious	none	0/309 (0.0%)	1/156 (0.6%)	RR 0.17 (0.01 to 4.12)	**5 fewer per 1.000** (from 6 fewer to 20 more)	⊕⊕⊕⊕ HIGH
Number of patients with serious adverse events (700 mg)											

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LY-CoV555 antibody	Placebo	Relative (95% CI)	Absolute (95% CI)	
1 [31]	randomised trials	not serious	not serious	not serious	serious [a]	none	0/101 (0.0%)	1/156 (0.6%)	RR 0.51 (0.02 to 12.47)	**3 fewer per 1.000** (from 6 fewer to 74 more)	⊕⊕⊕◯ MODERATE
Number of patients with serious adverse events (2800 mg)											
1 [31]	randomised trials	not serious	not serious	not serious	serious [a]	none	0/107 (0.0%)	1/156 (0.6%)	RR 0.48 (0.02 to 11.78)	**3 fewer per 1.000** (from 6 fewer to 69 more)	⊕⊕⊕◯ MODERATE
Number of patients with serious adverse events (7000 mg)											
1 [31]	randomised trials	not serious	not serious	not serious	serious [a]	none	0/101 (0.0%)	1/156 (0.6%)	RR 0.51 (0.02 to 12.47)	**3 fewer per 1.000** (from 6 fewer to 74 more)	⊕⊕⊕◯ MODERATE
SARS-CoV-2 clearance (all doses)											
1 [31]	randomised trials	not serious	not serious	not serious	not serious	none	121/309 (39.2%)	56/152 (36.8%)	RR 1.06 (0.83 to 1.37)	**22 more per 1.000** (from 63 fewer to 136 more)	⊕⊕⊕⊕ HIGH
SARS-CoV-2 clearance (700 mg)											

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LY-CoV555 antibody	Placebo	Relative (95% CI)	Absolute (95% CI)	
1 [31]	randomised trials	not serious	not serious	not serious	not serious	none	41/101 (40.6%)	56/152 (36.8%)	RR 1.10 (0.80 to 1.51)	**37 more per 1.000** (from 74 fewer to 188 more)	⊕⊕⊕⊕ HIGH
SARS-CoV-2 clearance (2800 mg)											
1 [31]	randomised trials	not serious	not serious	not serious	not serious	none	43/107 (40.2%)	56/152 (36.8%)	RR 1.09 (0.80 to 1.49)	**33 more per 1.000** (from 74 fewer to 181 more)	⊕⊕⊕⊕ HIGH
SARS-CoV-2 clearance (7000 mg)											
1 [31]	randomised trials	not serious	not serious	not serious	not serious	none	37/101 (36.6%)	56/152 (36.8%)	RR 0.99 (0.71 to 1.38)	**4 fewer per 1.000** (from 107 fewer to 140 more)	⊕⊕⊕⊕ HIGH

Source: [31]
[a] Downgraded of one level for wide CI

Author(s): Cruciani F, De Crescenzo F, Vecchi S, Saulle R, Mitrova Z, Amato L, Davoli M. [21]
Question: Should **LY-CoV555 antibody compared to LY-CoV555 antibody + Etesevimab** be used for COVID-19 patients?
Setting: **Outpatient**

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LY-CoV555 antibody	LY-CoV555 antibody + Etesevimab	Relative (95% CI)	Absolute (95% CI)	
All-cause mortality (all doses)											
1 [31]	randomised trials	not serious	not serious	not serious	not serious	none	No deaths reported				⨁⨁⨁⨁ HIGH
All-cause mortality (700 mg)											
1 [31]	randomised trials	not serious	not serious	not serious	not serious	none	No deaths reported				⨁⨁⨁⨁ HIGH
All-cause mortality (2800 mg)											
1 [31]	randomised trials	not serious	not serious	not serious	not serious	none	No deaths reported				⨁⨁⨁⨁ HIGH
All-cause mortality (7000 mg)											
1 [31]	randomised trials	not serious	not serious	not serious	not serious	none	No deaths reported				⨁⨁⨁⨁ HIGH
Number of patients with any adverse events (all doses)											
1 [31]	randomised trials	not serious	not serious	not serious	not serious	none	75/309 (24.3%)	19/112 (17.0%)	RR 1.43 (0.91 to 2.25)	**73 more per 1.000** (from 15 fewer to 212 more)	⨁⨁⨁⨁ HIGH
Number of patients with any adverse events (700 mg)											
1 [31]	randomised trials	not serious	not serious	not serious	not serious	none	27/101 (26.7%)	19/112 (17.0%)	RR 1.58 (0.94 to 2.65)	**98 more per 1.000** (from 10 fewer to 280 more)	⨁⨁⨁⨁ HIGH
Number of patients with any adverse events (2800 mg)											

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LY-CoV555 antibody	LY-CoV555 antibody + Etesevimab	Relative (95% CI)	Absolute (95% CI)	
1 [31]	randomised trials	not serious	not serious	not serious	not serious	none	26/107 (24.3%)	19/112 (17.0%)	RR 1.43 (0.84 to 2.43)	**73 more per 1.000** (from 27 fewer to 243 more)	⨁⨁⨁⨁ HIGH
Number of patients with any adverse events (7000 mg)											
1 [31]	randomised trials	not serious	not serious	not serious	not serious	none	22/101 (21.8%)	19/112 (17.0%)	RR 1.28 (0.74 to 2.23)	**48 more per 1.000** (from 44 fewer to 209 more)	⨁⨁⨁⨁ HIGH
Number of patients with serious adverse events (all doses)											
1 [31]	randomised trials	not serious	not serious	not serious	not serious	none	0/309 (0.0%)	1/112 (0.9%)	RR 0.12 (0.00 to 2.96)	**8 fewer per 1.000** (from -- to 17 more)	⨁⨁⨁⨁ HIGH
Number of patients with serious adverse events (700 mg)											
1 [31]	randomised trials	not serious	not serious	not serious	serious [a]	none	0/101 (0.0%)	1/112 (0.9%)	RR 0.37 (0.02 to 8.96)	**6 fewer per 1.000** (from 9 fewer to 71 more)	⨁⨁⨁◯ MODERATE
Number of patients with serious adverse events (2800 mg)											
1 [31]	randomised trials	not serious	not serious	not serious	serious [a]	none	0/107 (0.0%)	1/112 (0.9%)	RR 0.35 (0.01 to 8.47)	**6 fewer per 1.000** (from 9 fewer to 67 more)	⨁⨁⨁◯ MODERATE
Number of patients with serious adverse events (7000 mg)											
1 [31]	randomised trials	not serious	not serious	not serious	serious [a]	none	0/101 (0.0%)	1/112 (0.9%)	RR 0.37 (0.02 to 8.96)	**6 fewer per 1.000** (from 9 fewer to 71 more)	⨁⨁⨁◯ MODERATE

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LY-CoV555 antibody	LY-CoV555 antibody + Etesevimab	Relative (95% CI)	Absolute (95% CI)	
SARS-CoV-2 clearance (all doses)											
1 [31]	randomised trials	not serious	not serious	not serious	not serious	none	121/309 (39.2%)	40/109 (36.7%)	RR 1.07 (0.80 to 1.42)	**26 more per 1.000** (from 73 fewer to 154 more)	⊕⊕⊕⊕ HIGH
SARS-CoV-2 clearance (700 mg)											
1 [31]	randomised trials	not serious	not serious	not serious	not serious	none	41/101 (40.6%)	40/109 (36.7%)	RR 1.11 (0.79 to 1.56)	**40 more per 1.000** (from 77 fewer to 206 more)	⊕⊕⊕⊕ HIGH
SARS-CoV-2 clearance (2800 mg)											
1 [31]	randomised trials	not serious	not serious	not serious	not serious	none	43/107 (40.2%)	40/109 (36.7%)	RR 1.10 (0.78 to 1.54)	**37 more per 1.000** (from 81 fewer to 198 more)	⊕⊕⊕⊕ HIGH
SARS-CoV-2 clearance (7000 mg)											
1 [31]	randomised trials	not serious	not serious	not serious	not serious	none	37/101 (36.6%)	40/109 (36.7%)	RR 1.00 (0.70 to 1.42)	**0 fewer per 1.000** (from 110 fewer to 154 more)	

Source: [31]
[a] Downgraded of one level for wide CI

Author(s): Cruciani F, De Crescenzo F, Vecchi S, Saulle R, Mitrova Z, Amato L, Davoli M. [22]
Question: Should **LY-CoV555 antibody+ Etesevimab** compared to **Placebo** be used for COVID-19 patients?
Setting: **Outpatient**

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Combination LY-CoV555+Etesevimab**	**Placebo**	**Relative (95% CI)**	**Absolute (95% CI)**	
All-cause mortality											
1 [31]	randomised trials	not serious	not serious	not serious	not serious	none	Non sono stati segnalati decessi				⊕⊕⊕⊕ HIGH
Number of patients with any adverse event											
1 [31]	randomised trials	not serious	not serious	not serious	not serious	none	19/112 (17.0%)	42/156 (26.9%)	RR 0.63 (0.39 to 1.02)	**100 fewer per 1.000** (from 164 fewer to 5 more)	⊕⊕⊕⊕ HIGH
Number of patients with serious adverse events											
1 [31]	randomised trials	not serious	not serious	not serious	serious [a]	none	1/112 (0.9%)	1/156 (0.6%)	RR 1.39 (0.09 to 22.03)	**2 more per 1.000** (from 6 fewer to 135 more)	⊕⊕⊕◯ MODERATE
SARS-CoV-2 clearance											
1 [31]	randomised trials	not serious	not serious	not serious	not serious	none	40/109 (36.7%)	56/152 (36.8%)	RR 1.00 (0.72 to 1.38)	**0 fewer per 1.000** (from 103 fewer to 140 more)	⊕⊕⊕⊕ HIGH

Source: [31]
[a] Downgraded of one level for wide CI

EFFECTIVENESS RESULTS

OUTPATIENT: Bamlanivimab monotherapy (all doses) compared to placebo and bamlanivimab + etesevimab combination

Table A5. Summary of findings (SoF) table for published RCTs related to effectiveness and safety of bamlanivimab monotherapy (all doses) compared to placebo and bamlanivimab+etesevimab combination treatment – OUTPATIENT

Patient or population: Mild/Moderate COVID-19
Setting: Outpatient
Intervention: Bamlanivimab monotherapy
Comparison: Placebo and Bamlanivimab plus etesevimab

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of evidence	Comments
	Risk with Placebo **Risk with Bamlanivimab + etesevimab**	**Risk with Bamlanivimab** (previously neutralizing antibody LY-CoV555)				
All-cause mortality						
vs Placebo	No deaths occurred	No deaths occurred	No deaths occurred	465 (1 RCT) [a]	⊕⊕⊕⊕ HIGH	No deaths occurred
vs Bamlanivimab + etesevimab	No deaths occurred	No deaths occurred	No deaths occurred	465 (1 RCT) [a]	⊕⊕⊕⊕ HIGH	No deaths occurred
COVID-19 related hospitalisation or ED visits at day 29 [b]						
vs Placebo	58 per 1000	16 per 1000 (6 to 47	**RR 0.28** (0.10 to 0.82)	465 (1 RCT) [a]	⊕⊕⊕⊕ HIGH	**Absolute effect (95% CI)** 42 fewer per 1000 (from 52 fewer to 10 fewer)
vs Bamlanivimab + etesevimab	9 per 1000	16 per 1000 (2 to 137)	**RR 1.81** (0.21 to 15.34)	421 (1 RCT) [a]	⊕⊕⊕◯ MODERATE [c]	**Absolute effect (95% CI)** 7 more per 1000 (from 7 fewer to 128 more)
SARS-CoV-2 clearance						
	368 per 1000	390 per 1000	**RR 1.06** (0.83 to 1.37)	461 (1 RCT) [a]	⊕⊕⊕⊕ HIGH	**Absolute effect (95% CI)**

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of evidence	Comments
	Risk with Placebo **Risk with Bamlanivimab + etesevimab**	**Risk with Bamlanivimab** (previously neutralizing antibody LY-CoV555)				
						22 more per 1.000 (from 63 fewer to 136 more)
	367 per 1000	392 per 1000	**RR 1.07** (0.80 to 1.42)	418 (1 RCT) [a]	⊕⊕⊕⊕ HIGH	**Absolute effect (95% CI)** **26 more per 1.000** (from 73 fewer to 154 more)
Number of patients with any adverse events						
	269 per 1000	242 per 1000	**RR 0.90** (0.65 to 1.25)	465 (1 RCT) [a]	⊕⊕⊕⊕ HIGH	**Absolute effect (95% CI)** **27 fewer per 1.000** (from 94 fewer to 67 more)
	170 per 1000	243 per 1000	**RR 1.43** (0.91 to 2.25)	421 (1 RCT) [a]	⊕⊕⊕⊕ HIGH	**Absolute effect (95% CI)** **73 more per 1.000** (from 15 fewer to 212 more)
Number of patients with serious adverse events						
	60 per 1000	10 per 1000	**RR 0.17** (0.01 to 4.12)	465 (1 RCT) [a]	⊕⊕⊕⊕ HIGH	**Absolute effect (95% CI)** **5 fewer per 1.000** (from 6 fewer to 20 more)

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of evidence	Comments
	Risk with Placebo **Risk with Bamlanivimab + etesevimab**	**Risk with Bamlanivimab** (previously neutralizing antibody LY-CoV555)				
	90 per 1000	11 per 1000	**RR 0.12** (0.00 to 2.96)	421 (1 RCT) [a]	⨁⨁⨁⨁ HIGH	**8 fewer per 1.000** (from -- to 17 more)

Source: [21]
Explanations: [a] [31]; [b] Authors of current rapid review; [c] Downgraded of one level for wide CI
GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect
Abbreviations: CI=Confidence interval; RR=Risk ratio

Table A6. Summary of patients in the phase 2 BLAZE-1 trial at high risk for severe COVID-19 illness, as delineated in the bamlanivimab and etesevimab Fact Sheet for healthcare providers – BLAZE 1, phase 2

n (%)	PBO (N=156)	BAM + ETE Combo[a] (N=112)	BAM 700 mg (N=101)
High risk for severe COVID-19 Illness[b]	68 (43.6)	38 (33.9)	46 (45.5)
BMI[c]			
≥35	34 (21.8)	21 (18.8)	28 (27.7)
<35	122 (78.2)	91 (81.3)	73 (72.3)
Chronic kidney disease[d]	0	0	1 (1.0)
Diabetes	18 (11.5)	10 (8.9)	6 (5.9)
Immunosuppressive disease[e]	0	2 (1.8)	1 (1.0)
Immunosuppressive treatment [f]	3 (1.9)	5 (4.5)	1 (1.0)
Age category			
≥65	23 (14.7)	13 (11.6)	11 (10.9)
<65	133 (85.3)	99 (88.4)	90 (89.1)
Age ≥55 with CV disease	3 (1.9)	0	7 (6.9)
Age ≥55 with hypertension	31 (19.9)	15 (13.4)	17 (16.8)
Age ≥55 with COPD	3 (1.9)	3 (2.7)	5 (5.0)

Source: [33]
Explanations: [a] BAM + ETE Combo includes data from the 2800-mg BAM + 2800-mg ETE treatment arm.; [b] High risk as defined in the Bamlanivimab Fact Sheet for Healthcare Providers; [c] The BMI is the weight in kilograms divided by the square of the height in meters.; [d] Based on patient self-report, not laboratory values or creatinine clearance.; [e] Per the CDC, immunosuppressive diseases included the following: having a solid organ transplant, blood, or bone marrow transplant; HIV with a low CD4 cell count or not on HIV treatment, and immune deficiencies, including primary immunodeficiency.; [f] Immunosuppressive treatments were not defined in the BLAZE-1 protocol and categorization as such was left to the interpretation of the investigator.
Abbreviations: BAM = bamlanivimab; BMI = body mass index; COPD = chronic obstructive pulmonary disorder; COVID-19 = coronavirus disease 2019; CT = cycle threshold; CV = cardiovascular; ETE = etesevimab; PBO = placebo.

Table A7. Outcomes for post hoc and exploratory analyses in phase 2 BLAZE-1 trial

	Bamlanivimab 700mg	Bamlanivimab 2800mg	Bamlanivimab 7000mg	Bamlanivimab + Etesevimab	Placebo
***Post Hoc* Analyses**					
COVID-Related Hospitalization or Emergency Room Events at Day 29 in high-risk patients[a]					
Number of patients, N	37	30	34	31	52
Events, (%)	1 (2.7)	1 (3.3)	2 (5.9)	0 (0.0)	7 (13.5)
vs Placebo, difference (95% CI)	-10.8 (-21.4, -0.1)	-10.1 (-21.4, 1.2)	-7.6 (-19.8, 4.6)	-13.5 (-22.7, -4.2)	
P value	0.13	0.25	0.31	0.042	
Exploratory Outcomes					
Virological Measures					
SARS-CoV-2 Viral Load Change from Baseline at Day 3					
Number of patients, n/N	96/101	98/107	93/101	96/109	141/152
Viral load at Day 3, mean (SD)	5.00 (1.79)	4.71 (2.31)	5.02 (1.77)	4.83 (2.08)	5.24 (2.55)
Viral load change from baseline at Day 3 vs Placebo, difference (95% CI)	-0.23 (-0.67, 0.20)	-0.43 (-0.87, -0.00)	-0.31 (-0.75, 0.13)	-0.55 (-0.99, -0.11)	
P value	0.30	0.05	0.17	0.013	
SARS-CoV-2 Viral Load Change from Baseline at Day 7					
Number of patients, n/N	98/101	101/107	95/101	95/109	142/152

Viral load at Day 7, mean (SD)	3.42 (1.81)	3.23 (1.81)	3.45 (1.94)	2.80 (1.81)	3.74 (2.07)
Viral load change from baseline at Day 7 vs Placebo, difference (95% CI)	-0.26 (-0.70, 0.19)	-0.40 (-0.84, 0.04)	-0.29 (-0.74, 0.15)	-1.12 (-1.57, -0.67)	
P value	0.26	0.07	0.20	<0.001	
SARS-CoV-2 Viral Load Change from Baseline AUC (Days 0-11)					
Number of patients, n/N	91/101	99/107	90/101	99/109	132/152
Viral Load AUC (Days 0-11) AUC, mean (SD)	42.93 (14.55)	39.82 (17.34)	42.22 (15.95)	38.14 (16.01)	42.84 (19.51)
vs Placebo, difference (95% CI)	-0.50 (-3.82 2.82)	-2.39 (-5.63, 0.85)	-1.67 (-5.00, 1.67)	-6.51 (-9.76, -3.27)	
P value	0.77	0.15	0.33	<0.001	
Clinical Measures					
Total Symptom Score AUC (Days 0-11)					
Number of patients, n/N	80/101	74/107	71/101	80/109	99/152
Total Symptom Score AUC (Days 0-11), mean (SD)	23.54 (20.42)	27.43 (24.54)	29.39 (28.16)	23.40 (18.41)	34.32 (25.59)
vs Placebo, difference (95% CI)	-8.28 (-14.04, -2.53)	-6.59 (-12.46, -0.72)	-8.09 (-14.05, -2.13)	-8.63 (-14.39, -2.88)	
P value	0.005	0.028	0.008	0.003	
Total Symptom Score AUC (Days 0-29)					
Number of patients, n/N	65/101	59/107	54/101	77/109	84/152
Total Symptom Score AUC (Days 0-29), mean (SD)	38.52 (47.77)	39.86 (42.04)	46.49 (58.37)	40.35 (57.11)	50.19 (44.84)
vs Placebo, difference (95% CI)	-6.95 (-21.44, 7.54)	-11.80 (-26.67, 3.07)	-5.27 (-20.54, 9.99)	-5.95 (-19.78, 7.88)	
P value	0.35	0.12	0.50	0.40	

Viral Resistance Measures					
Patients with Treatment-Emergent Bamlanivimab Resistance Variants[b]					
P value	0.26	0.07	0.20	<0.001	
Number of patients, N	98	102	97	102	145
Any occurrence; n, (%)	7 (7.1)	10 (9.8)	11 (11.3)	1 (1.0)	7 (4.8)
Multiple occurrences; n, (%)	4 (4.1)	6 (5.9)	7 (7.2)	0 (0.0)	0 (0.0)

N, number of patients in the analysis population; n, number of patients in the specified category.
[a] ≥65 years of age or with BMI ≥35.
[b] Treatment emergent variants were determined by comparing the sequencing results from the study participant's baseline sample to those obtained from that participant post-treatment. Analysis was then focused on variants that were phenotypically confirmed to be resistant to bamlanivimab (E484K; E484Q; F490S and S494P) and occurred a ≥15% variant allele frequency.

Source: [31] Supplemental Online content

Table A8. Ongoing treatment studies related to bamlanivimab monotherapy, bamlanivimab plus etesevimab combination or bamlanivimab with other neutralising monoclonal antibody

Trial Identifier/registry ID(s)/contact	**NCT04427501, BLAZE-1**	**NCT04634409, BLAZE-4**	**NCT04518410-ACTIV-2**	**NCT04701658, BLAZE-5**	**NCT04840459**	**NCT04796402, B-EPIC**	**NCT04790786, OPTIMISE-C19**
Study design, study phase	RCT, phase 2 and 3 (high risk)	RCT, phase 2	RCT, phase 2/3	nRCT, phase 2	nRCT, phase 2	RCT, phase 4	RCT, phase 3
Recruitment status	Recruiting	Recruiting	Recruiting	Recruiting	Recruiting	Not yet recruiting	Recruiting
Number of Patients, Disease severity*	3160, Mild and Moderate; in phase 3 at high risk to progression to severe or hospitalisation	1416, Mild and Moderate	2000, Mild and Moderate	3000, Mild and Moderate	1000, Mild and Moderate	576, Mild and Moderate, high-risk	5000, Mild and Moderate
Setting (hospital, ambulatory,)	Ambulatory	Ambulatory	Ambulatory	Ambulatory	Ambulatory	Ambulatory	Ambulatory
Intervention (generic drug name and dosage)	Phase 2: Bamlanivimab (BAM) alone 700,1400, 2800 mg Bamlanivimab plus etesevimab (ETE): 2800/2800 Phase 3: BAM+ETE 2800/2800, BAM+ETE 700/1400	Bamlanivimab alone Bamlanivimab plus etesevimab Bamlanivimab 700mg with VIR-7831 500mg	Bamlanivimab	Bamlanivimab	Bamlanivimab alone REGN-COV2	Bamlanivimab 700mg IV x1	Bamlanivimab alone Bamlanivimab plus etesevimab REGN-COV2
Comparator (standard care or generic drug name and dosage)	Placebo	Placebo	Placebo	Standard of care	Head to head comparison	Standard of care	Head to head comparisons
Primary Outcome(s)	Change from Baseline to Day 11 in SARS-CoV-2 Viral Load [Time Frame:	Percentage of Participants with SARS-CoV-2 Viral Load Greater than	Duration of COVID-19 symptoms (Phase 2) [Time Frame: Up	Percentage of Participants who Experience COVID-19 Related Hospitalisation or	Minimize and/or eliminate the number of patients with mild to moderate COVID-19 who are at high risk for	Any incidence of admission to hospital for >24 hours in the 28 days following first positive test for SARS-	Alive and free from hospitalization [Time Frame: 28 days after initial participation]

	Baseline, Day 11]; Percentage of participants who experience COVID-Related Hospitalization or Death; Percentage of participants with SARS-CoV-2 Viral Load greater than a prespecified threshold	5.27 [Time Frame: Day 7]	to Day 28]; Post-treatment presence of SARS-CoV-2 RNA at Day 3; at Day 7; at day 14; at day 21; at day 28; Incidence of new adverse event (AE) ≥ Grade 3 (Phase 2); Cumulative incidence of death from any cause or hospitalization (Phase 3); Proportion of participants with new adverse event (AE) ≥ Grade 3 (Phase 3)	Death [Time Frame: Baseline through Day 29]	progressing to severe COVID-19 and/or hospitalization. [Time Frame: two weeks]	CoV2. [Time Frame: 0 - 28 days following first positive test for COVID 19]	
Sponsor/ lead institution, country (also, country of recruitment if different)	Eli Lilly and Company, Puerto Rico, United States	Eli Lilly and Company, Puerto Rico, United States	National Institute of Allergy and Infectious Diseases (NIAID), Eli Lilly and Company, Puerto Rico, United States	Eli Lilly and Company	DHR Health Institute for Research and Development, US	Fraser Health, British Columbia	University of Pittsburgh, US

Source: [26] [33] [40]

APPENDIX 4: EVIDENCE GAPS

Table A9. Evidence gaps

Additional evidence generation needs (to be published) **Research question: What is the relative clinical effectiveness and safety of bamlanivimab alone or in combination therapy, compared with other interventions, in high-risk mild to moderate COVID-19 patients?**	
Population	For subgroups: children, immunocompromised patients, older patients, pregnant or lactating women
Intervention	Direct comparison with other investigational neutralising antibodies; combination therapy;
Comparator	REGN-COV2 or other investigational neutralising antibodies as combination therapy or other investigational COVID-19 pharmaceuticals
Outcome(s)	Related to hospitalisation: Number of patients with COVID-19 related hospitalisation; Number of patients admitted to an intensive care unit (ICU); Number of patients requiring supplemental oxygen; Number of patients requiring mechanical ventilation; Length of hospital stay; Pulmonary function; Health-related Quality of life; Clinical improvement defined as a hospital discharge or improvement on the scale used by trialists to evaluate clinical progression and recovery; WHO Clinical Progression Score level 7 or above (i.e., Mechanical ventilation +/- additional organ support (ECMO, vasopressors or dialysis) OR death; Time to clinical improvement; Time to WHO Clinical Progression Score level 7 or above; Time to death; Time to viral negative conversion; Duration of mechanical ventilation; Duration of supplemental oxygen therapy; Time to ICU admission; Kinetic of viral load (D1, D7, D14, D30...); Efficacity depending on SARS-CoV-2 variants; Resistance. Long term outcomes (such as 6 months endpoint) examining mortality or long-term quality of life; long term safety; lung function; patient-reported outcomes such as symptom burden; RCTs with high certainty of evidence provided are lacking as well.
Time stamp	Short-term (28 days) and long-term (up to 6 months)
Study design	RCTs with high certainty of evidence provided; The availability of full clinical study reports for completed trials to allow open and robust scrutiny of the trials is needed.

APPENDIX 5: PROJECT ORGANISATION

Participants

Table A10. Project participants and stakeholders

Role in the project	Agency	Country	Distribution of work
Assessment Team			
Author	Austrian Institute for Health Technology Assessment (AIHTA)	Austria	Author will draft the report. Author will review and comment the sections drafted by the co-author. All important milestones will be discussed in advance with the co-author.
Co-Author	Swiss Network for Health Technology Assessment (SNHTA)	Switzerland	Co-author will support drafting the report. Co-author will review and comment on all parts of the report.
Dedicated Reviewer	State Institute for Drug Control (SUKL)	Czech Republic	Review of first draft
Dedicated Reviewer	Evaluation Unit of the Canary Islands Health Service/ Canary Islands Health Research Institute Foundation (SESCS/FIISC)	Spain	Review of first draft
Contributors			
Project Manager	Zorginstituut Nederland (ZIN)	Netherlands	Coordination between involved parties throughout the assessment period

Project stakeholder	Organisation	Role in the project
pMAH	Eli-Lilly	Submitted data; Fact check of draft Rapid Collaborative Review.

Milestones and deliverables

Table A11. Milestones and deliverables

Task	Start	End
Call for Collaboration	17-02-2021	25-02-2021
Scoping PICO and development of first draft RCR	08-03-2021	09-04-2021
PICO survey – request relevant PICO from Member States	04-03-2021	15-03-2021
Collect patient input	04-03-2021	15-03-2021
Adapt draft RCR based on PICO survey	25-03-2021	09-04-2021
Review of the first draft RCR	12-04-2021	16-04-2021
Development of second draft RCR & answers to DR comments	19-04-2021	26-04-2021
TC with the whole assessment team	19-04-2021	
TC with Manufacturer	20-04-2021	
Additional information	20-04-2021	11-05-2021
Finalise RCR for DRs	18-05-2021	
DRs review of the 2nd draft and fact check	19-05-2021	21-05-2021
Response on DR comments	24-05-2021	25-05-2021
Finalise RCR	26-05-2021	
Publish RCR	31-05-2021	