“Rolling Collaborative Review” of Covid-19 treatments

BAMLANIVIMAB (LY-COV555) FOR THE TREATMENT OF COVID-19

Project ID: RCR17
Monitoring Report

Version 3.0, February 2021

Template version November 2020
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<thead>
<tr>
<th>Version</th>
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<td>V 1.0</td>
<td>15/12/2020</td>
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<tr>
<td>Chapter 3</td>
<td>• New regulatory data added</td>
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<td></td>
<td>• 1 new publication on RCT with phase 2 final results in outpatient setting was added</td>
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<tr>
<td>Chapter 4</td>
<td>• 1 new ongoing RCT was found (in hospitalised patients)</td>
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<tr>
<td></td>
<td>• Summary text changed and Summary of findings table was added related to new published RCT with phase 2 final results in outpatient setting</td>
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<td>• New search strategy for observational studies added</td>
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<td>Zorginstituut Nederland (ZIN), Netherlands</td>
<td>Coordination of RCR</td>
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<tr>
<td>Austrian Institute for Health Technology Assessment (AIHTA), Austria</td>
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Conflict of interest

All authors and co-authors involved in the production of this living document 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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<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>AE</td>
<td>Adverse Event</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence Interval</td>
</tr>
<tr>
<td>DOI</td>
<td>Declaration of interest</td>
</tr>
<tr>
<td>ED</td>
<td>Emergency Department</td>
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<tr>
<td>EUA</td>
<td>Emergency Use Authorization</td>
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<tr>
<td>EUnetHTA</td>
<td>European Network of Health Technology Assessment</td>
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<tr>
<td>GRADE</td>
<td>Grading of Recommendations, Assessment, Development and Evaluation</td>
</tr>
<tr>
<td>HR</td>
<td>Hazard Ratio</td>
</tr>
<tr>
<td>ICD</td>
<td>International Classification of Diseases</td>
</tr>
<tr>
<td>MD</td>
<td>Mean Difference</td>
</tr>
<tr>
<td>MeSH</td>
<td>Medical Subject Headings</td>
</tr>
<tr>
<td>NA</td>
<td>Not applicable</td>
</tr>
<tr>
<td>NR</td>
<td>Not reported</td>
</tr>
<tr>
<td>nRCT</td>
<td>Non-Randomized Controlled Trial</td>
</tr>
<tr>
<td>OR</td>
<td>Odds Ratio</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomized Controlled Trial</td>
</tr>
<tr>
<td>RCR</td>
<td>Rolling Collaborative Review</td>
</tr>
<tr>
<td>REA</td>
<td>Relative Effectiveness Assessment</td>
</tr>
<tr>
<td>RR</td>
<td>Relative Risk</td>
</tr>
<tr>
<td>SAE</td>
<td>Serious Adverse Event</td>
</tr>
<tr>
<td>SD</td>
<td>Standard Deviation</td>
</tr>
<tr>
<td>SMD</td>
<td>Standardized Mean Difference</td>
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<tr>
<td>WP4</td>
<td>Work Package 4</td>
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1 OBJECTIVE

The aim of this EUnetHTA Rolling Collaborative Review is

- to inform health policy at the national/regional and at the European level at an early stage in the life-cycle of therapies which interventions are currently undergoing clinical trials,
- to monitor (ongoing studies and their results) permanently - in the format of a Living Document - potential therapies against covid-19,
- to present comparative data on effectiveness and safety of potential therapies and
- to support preparations for an evidence-based purchasing of regional/ national health politicians, if necessary.

To avoid redundancies and duplication, the EUnetHTA Rolling Collaborative Review will reuse sources from international initiatives to collect information and data on Covid-19 treatments.

The scope of the Rolling Collaborative Review is of descriptive nature. These EUnetHTA Rolling Collaborative Reviews are not meant to substitute a joint Relative Effectiveness Assessment (REA) adhering to the agreed procedures and aiming at critical appraisal of the clinical evidence based on the Submission Dossier submitted by the (prospective) Marketing Authorization Holder (MAH).

2 METHODS

This Rolling Collaborative Review is prepared according to the project plan (“Rolling Collaborative Review (RCR) on Covid-19 treatments: Project description and planning”, published on the EUnetHTA website) and will be updated monthly. Monthly updates are published on the EUnetHTA Covid-19 Website (https://eunethta.eu/covid-19-treatment/) and on the EUnetHTA Rolling Collaborative Review Sharepoint page each 15th of the month.

2.1 Scope

<table>
<thead>
<tr>
<th>Description</th>
<th>Project Scope</th>
</tr>
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</table>
| Population          | Disease
|                     | **ICD-Codes** ([https://www.who.int/classifications/icd/covid19/en](https://www.who.int/classifications/icd/covid19/en))
|                     | - 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                                                                                                                                                                                                                                                                                                        |
|                     | • Asymptomatic or pre-symptomatic Infection: Individuals who test positive for SARS-CoV-2 by virologic testing using a molecular diagnostic (e.g., polymerase chain reaction) or antigen test, but have no symptoms.                                                                               |
- 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 (SpO2) ≥94% on room air at sea level.
- Severe Illness: Individuals who have respiratory frequency >30 breaths per minute, SpO2 <94% on room air at sea level, ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO2/FiO2) <300 mmHg, or lung infiltrates >50%.
- Critical Illness: Individuals who have respiratory failure, septic shock, and/or multiple organ dysfunction.

**Intervention**
Bamlanivimab is neutralizing monoclonal antibody.

**Comparison**
Any active treatment, placebo, or standard of care.

**Rationale:** Since there is no gold standard treatment any comparator is acceptable as well as the above listed interventions.

**Outcomes**

Main outcome:
- All-cause Mortality (Survival)

Additional Outcomes:
- Efficacy:
  - Length of hospital stay,
  - Viral burden (2019-nCoV RT-PCR negativity),
  - Clinical progression (WHO Clinical Progression Scale measured daily over the course of the study),
  - Rates of hospitalization and of patients entering ICU,
  - Duration of mechanical ventilation,
  - Quality of life.
- Safety:
  - Adverse events (AE),
  - Severe adverse events (SAE),
  - Withdrawals due to AEs,
  - Most frequent AEs,
  - Most frequent SAEs.

**Rationale:** We will give priority according to the Core Outcome Set for Clinical Trials on Coronavirus Disease 2019 (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7102592/pdf/main.pdf) 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.

**Study design**
Efficacy: randomised controlled trials (RCT)
Safety: observational studies (comparative or single-arm prospective studies and registries)

## 2.2 Sources of information

According to the project plan, this Rolling Collaborative Review is based on three main sources of information, as described below:
1. Summary of findings (SoF) table for published RCTs related to effectiveness and safety:

This table is based on the living systematic review and Network Meta-Analysis (NMA) created by the partnering institute of DEPlazio: find the PROSPERO protocol here. DEPlazio provides updates for the SoF table on a monthly basis to the EUnetHTA partners authoring the respective Rolling CR documents who are integrating this information accordingly.

The literature search is conducted in the following databases:
- PubMed
- MEDLINE, accessed via OVID
- Embase, accessed via OVID

<table>
<thead>
<tr>
<th>Population</th>
<th>People affected by COVID-19, as defined by the authors of the studies. No limits in terms of gender or ethnicity. SARS-CoV-2 is a novel coronavirus causing a respiratory illness termed Covid-19. It started spreading in December 2019, and was declared a pandemic by the World Health Organisation on 11th March 2020. The full spectrum of Covid-19 ranges from mild, self-limiting respiratory tract illness to severe progressive pneumonia, multi-organ failure, and death.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>Interventions for the treatment of people affected by COVID-19, including pharmacological interventions (e.g. antibiotics, antibodies, antimalarial, antiviral, antiretroviral, immune-suppressors/modulators, kinase inhibitors) and their combinations.</td>
</tr>
<tr>
<td>Comparison</td>
<td>Any active treatment, placebo, or standard of care.</td>
</tr>
<tr>
<td>Outcomes</td>
<td>All-cause mortality Additional outcomes: Length of hospital stay, 2019-nCoV RT-PCR negativity, PaO2/FiO2, Duration of mechanical ventilation, radiological imaging, Adverse events, Severe adverse events.</td>
</tr>
<tr>
<td>Study design</td>
<td>Randomised controlled trials (RCT); no restriction on language of publication</td>
</tr>
</tbody>
</table>

To identify preprints of preliminary reports of work that have not been peer-reviewed, the following sources are searched:
- medRxiv Health Sciences
- bioRxiv Biology

In addition to the sources and strategies described above, registers of ongoing studies are screened. Key conferences and conference proceedings are considered. Table 6-1 describes in detail the sources searched, the search terms used and the dates at which the searches are executed.

Data extraction, Risk of bias assessment, data synthesis:
Two reviewers from DEPlazio are screening search results, assessing full texts of studies and extract study characteristics and outcome data according to pre-defined criteria. The process of study selection is depicted as a flow diagram in Appendix Figure 6-1.

Risk of bias is assessed using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions [1].

Dichotomous outcomes are analysed by calculating the relative risk (RR) for each trial with the uncertainty in each result being expressed by its 95% confidence interval (CI). Continuous outcomes are analysed by calculating the mean difference (MD) with the relative 95% CI when the study used the same instruments for assessing the outcome.
The standardised mean difference (SMD) is applied when studies used different instruments. Pairwise meta-analyses is performed for primary and secondary outcomes using a random-effects model in RevMan for every treatment comparison [2]. Network meta-analysis (NMA) is performed for the primary outcome. For rating the certainty of the evidence, the GRADE approach is being used [3].

- Sources: [http://deplazio.net/farmacicovid/index.html](http://deplazio.net/farmacicovid/index.html) for SoF (or [https://covid-nma.com/](https://covid-nma.com/))

2. **Table(s) on published (peer reviewed) observational studies for safety results:**

The literature search is conducted on a monthly basis.
The sources and search methods are described in more detail in Table 6-2.

<table>
<thead>
<tr>
<th>Population</th>
<th>See project Scope</th>
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<tbody>
<tr>
<td>Intervention</td>
<td>Bamlanivimab is neutralizing monoclonal antibody.</td>
</tr>
<tr>
<td>Comparison</td>
<td>Any active treatment, placebo, or standard of care.</td>
</tr>
<tr>
<td>Outcomes</td>
<td>See project Scope</td>
</tr>
<tr>
<td>Study design</td>
<td>Inclusion criteria: Prospective non-randomised controlled trials, prospective case series (i.e. comparative or single-arm prospective studies), registries Exclusion criteria: retrospective studies, case studies/ case reports, observational studies that do not report safety data</td>
</tr>
</tbody>
</table>

Two researchers from NIPHNO carry out title and abstract screening and assess the full texts of all potentially eligible studies. The study selection process is depicted in a flow diagram (Appendix Figure 6-2).

One researcher of AIHTA extracts the data and assesses the risk of bias using Robins-I ([https://training.cochrane.org/handbook/current/chapter-25](https://training.cochrane.org/handbook/current/chapter-25)).

Results are presented in tabular form for all included studies.

3. **Table(s) on ongoing trials:**

The following clinical trial registries are searched on a monthly basis:

- ClinicalTrials.gov: [https://clinicaltrials.gov/](https://clinicaltrials.gov/)
- ISRCTN: [https://www.isrctn.com/](https://www.isrctn.com/)
- European Clinical Trials Registry: [https://www.clinicaltrialsregister.eu/](https://www.clinicaltrialsregister.eu/)

Inclusion criteria: Randomised controlled trials, Controlled trials

One researcher of AIHTA is searching and extracting the data for the eligible studies. At the drafting stage of each update, the author team verifies whether the status of previously identified studies has changed. This is done by verifying the date of the last update posted in the trial registers. In addition, trial register IDs of all previously identified studies are entered in both PubMed and Google (google.com) to verify if previously identified studies have been published since the last update. In Google, the first 10 hits are screened for this purpose.

Search methods are described in more detail in Table 6-3.

Data are presented in tabular form.
3 ABOUT THE TREATMENT

3.1 Mode of Action

Neutralizing monoclonal antibodies to SARS-CoV-2 have the potential to be used for both prevention and treatment of infection. They can help to guide vaccine design and development. The main target of SARS-CoV-2 neutralizing monoclonal antibodies is the surface spike glycoprotein that mediates viral entry into host cells. Some products will include a combination of 2 monoclonal antibodies targeting different sites on the spike protein. Due to the long half-life of most monoclonal antibodies (approximately 3 weeks for IgG1), a single infusion should be sufficient. A potential limitation of monoclonal antibodies for treatment of COVID-19 is the unknown bioavailability of passively infused IgG in tissues affected by the disease, especially the lungs, which serve as a key target of SARS-CoV-2 infection. Due to the effect of viral diversity, it will be important to monitor the emergence of resistant viral mutations under selective pressure of monoclonal antibody treatment [4, 5].

Bamlanivimab (previously LY-CoV555 or LY3819253) 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.

3.2 Regulatory Status

Bamlanivimab is not authorised in Covid-19 patients (EMA, FDA).

On November 9, 2020, the U.S. Food and Drug Administration issued an Emergency Use Authorization (EUA) for the investigational monoclonal antibody therapy bamlanivimab (previously LY-CoV555) for the treatment of mild-to-moderate COVID-19 in adult and pediatric patients. Bamlanivimab is authorised for patients with positive results of direct SARS-CoV-2 viral testing who are 12 years of age and older, weighing at least 40 kilograms (about 88 pounds), and who are at high risk for progressing to severe COVID-19 and/or hospitalisation. This includes those who are 65 years of age or older, or who have certain chronic medical conditions, [https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-monoclonal-antibody-treatment-covid-19](https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-monoclonal-antibody-treatment-covid-19).

High risk is defined as patients who meet at least one of the following criteria: have a body mass index (BMI) ≥35, chronic kidney disease, diabetes, immunosuppressive disease (immunocompromised), are currently receiving immunosuppressive treatment, are ≥65 years of age, are ≥55 years of age AND have cardiovascular disease or hypertension or chronic obstructive pulmonary disease/other chronic respiratory disease, are 12 – 17 years of age AND have a BMI ≥85th percentile for their age and gender based on CDC growth charts, or sickle cell disease or congenital or acquired heart disease or neurodevelopmental disorders (e.g. cerebral palsy) or a medical-related technological dependence (e.g. tracheostomy, gastrostomy, or positive pressure ventilation (not related to COVID-19), or asthma, reactive airway or other chronic respiratory disease that requires daily medication for control.

The authorised dosage for bamlanivimab is a single intravenous (IV) infusion of 700 mg administered as soon as possible after positive results of direct SARS-CoV-2 viral testing and within 10 days of symptom onset.

Bamlanivimab is not authorised for patients who are hospitalised due to COVID-19 or require oxygen therapy due to COVID-19. A benefit of bamlanivimab treatment has not been shown in patients hospitalised due to COVID-19. Monoclonal antibodies, such as bamlanivimab, may be associated with worse clinical outcomes when administered to hospitalised patients with COVID-19 requiring high flow oxygen or mechanical ventilation [6].

On February 9, 2021, the FDA issued an EUA for bamlanivimab and etesevimab administered together for the treatment of mild to moderate COVID-19 in adults and pediatric patients (12 years of age or older, weighing at least 40 kilograms [about 88 pounds]) who test positive for SARS-CoV-2 and who are at high risk for progressing to severe COVID-19. The authorized use includes treatment for those who are 65 years of age or older or who have certain chronic medical conditions.
In a clinical trial of patients with COVID-19 at high risk for disease progression, a single intravenous infusion of bamlanivimab and etesevimab administered together significantly reduced COVID-19-related hospitalisation and death during 29 days of follow-up compared to placebo. The safety and effectiveness of this investigational therapy for use in the treatment of COVID-19 continue to be evaluated.

Bamlanivimab and etesevimab are not authorized for patients who are hospitalised due to COVID-19 or require oxygen therapy due to COVID-19. Treatment with bamlanivimab and etesevimab has not been studied in patients hospitalised due to COVID-19. Monoclonal antibodies, such as bamlanivimab and etesevimab, may be associated with worse clinical outcomes when administered to hospitalised patients with COVID-19 requiring high flow oxygen or mechanical ventilation, https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-monoclonal-antibodies-treatment-covid-19-0.

On February 4, 2021, the EMA stated that the CHMP is reviewing available data on the use of monoclonal antibodies, as two separate reviews; one for the casirivimab/imdevimab combination and another for bamlanivimab/etesevimab, 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. The Committee will also look at the use of bamlanivimab alone based on a study which indicated that bamlanivimab monotherapy can reduce viral load and provide clinical benefit [7].

**US COVID-19 Treatment Guidelines**

The US COVID-19 Treatment Guidelines Panel issued new recommendations on pharmacological treatment for patients with COVID-19 (as of December 3, 2020) [8].

At this time, there are insufficient data to recommend either for or against the use of bamlanivimab for the treatment of outpatients with mild to moderate COVID-19. Bamlanivimab should not be considered the standard of care for the treatment of patients with COVID-19. Patients who are hospitalised for COVID-19 should not receive bamlanivimab outside of a clinical trial. There are currently no comparative data to determine whether there are differences in clinical efficacy or safety between casirivimab plus imdevimab and bamlanivimab.

### 3.3 Level of Evidence

**Outpatient**

**Final analysis of the phase 2 portion of the BLAZE-1 clinical trial**

Final results of the phase 2 portion of BLAZE-1, randomised, double-blind, placebo-controlled trial (NCT04427501), were published by Gottlieb et al. 2021 [9].

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 endpoint was change in SARS-CoV-2 log viral load at day 11 (±4 days). Nine pre-specified secondary outcome measures were evaluated 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).
Effectiveness

Among the 577 patients who were randomized and received an infusion, 533 (92.4%) completed the efficacy evaluation period (day 29). 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.

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. The proportion of patients with COVID-19–related hospitalisations or ED visits was 5.8% (9 events) for placebo, 1.0% (1 event) for 700mg, 1.9% (2 events) for 2800 mg, 2.0% (2 events) for 7000 mg, and 0.9% (1 event) for combination treatment. The proportion of patients with COVID-19–related hospitalisations or emergency department 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.

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.

Data on high certainty of evidence, related to effectiveness and safety of bamlanivimab monotherapy and bamlanivimab + etesevimab compared to placebo and each other, reported in this RCT, prepared by Cruciani et al. [10-13], can be found in the Summary of Findings Table 4-1 and Table 4-2. Study characteristics can be found in Table 4-4.

On January 26, 2021 Eli Lilly and Company announced unpublished results from the phase 3 BLAZE-1 RCT on the combination therapy arms that enrolled mild to moderate, recently diagnosed COVID-19 patients who are at high risk for progressing to severe COVID-19 and/or hospitalization, studying bamlanivimab 2800 mg plus etesevimab 2800 mg versus placebo. The primary outcome measure for the phase 3 portion of the BLAZE-1 trial was the percentage of participants who experience COVID-related hospitalizations 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-CoV2 viral load on day 7, time to sustained symptom resolution, and COVID-related hospitalization, 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. Bamlanivimab (LY-CoV555) 2800 mg and etesevimab (LY-CoV016) 2800 mg together significantly reduced COVID-19-related hospitalisations and deaths (collectively, "events") in high-risk patients recently diagnosed with COVID-19. Across 1,035 patients, there were 11 events (2.1 %) in patients taking therapy and 36 events (7.0 %) in patients taking placebo, representing a 70 % risk reduction (p=0.0004). There were 10 deaths in total, all of which occurred in patients taking placebo, and no deaths in patients taking bamlanivimab and etesevimab together. Bamlanivimab and etesevimab together also demonstrated statistically significant improvements on all key secondary endpoints, providing strong 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
phase 1, phase 2 and phase 3 trials evaluating these antibodies. Serious adverse events were reported at a similar frequency in the bamlanivimab and etesevimab together and placebo groups.

Additionally, initial results from the ongoing BLAZE-4 trial (NCT04634409) provide viral load and pharmacodynamic/pharmacokinetic data which demonstrated that lower doses, including bamlanivimab 700 mg and etesevimab 1400 mg together, are similar to bamlanivimab 2800 mg and etesevimab 2800 mg together.

Lilly plans to explore even lower doses of bamlanivimab and etesevimab together, as lower doses can maximize available supply to treat more patients, allow potential for subcutaneous dosing, and potentially reduce the burden on the healthcare system and patients through reduced infusion times [14].

On 27 January 2021, Eli Lilly and Company, Vir Biotechnology, Inc. and Glaxo Smith Kline plc announced a collaboration to evaluate a combination of two COVID-19 therapies in low-risk patients with mild to moderate COVID-19. Lilly has expanded its ongoing BLAZE-4 trial to evaluate the administration of bamlanivimab (LY-CoV555) 700mg with VIR-7831 (also known as GSK4182136) 500mg, two neutralizing antibodies that bind to different epitopes of the SARS-CoV-2 spike protein. VIR-7831 is a dual-action monoclonal antibody that was selected for clinical development based on its potential to both block viral entry into healthy cells and clear infected cells, as well as its potential to provide a high barrier to resistance [15].

Hospitalised patients

On October 26, 2020, the National Institute of Health (NIH) announced that the bamlanivimab (LY-CoV555) sub-study of the ACTIV-3 trial for the treatment of COVID-19 would no longer be recruiting patients due to a low likelihood of efficacy. The ACTIV-3 trial (NCT04501978) is a multi-centre, randomised, double-blind, placebo-controlled, phase III trial with an adaptive design to evaluate different therapeutic agents (in addition to the standard of care, including remdesivir), for the treatment of COVID-19 in hospitalised patients [16].

Lundgren et al. 2020 (ACTIV-3/TICO LY-CoV555 Study group) published preliminary negative results from the above mentioned RCT (NCT04501978), comparing LY-CoV555 with placebo in hospitalised patients who had Covid-19 without end-organ failure [17]. 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 enrolment for futility after 314 patients (163 in the LY-CoV555 group and 151 in the placebo group) had undergone randomization and infusion.

Monoclonal antibody LY-CoV555, when co-administered with remdesivir, did not demonstrate efficacy among hospitalised patients who had Covid-19 without end-organ failure. Across the seven categories, the odds ratio of being in a more favourable category in the LY-CoV555 group than in the placebo group was 0.85 (95% confidence interval [CI], 0.56 to 1.29; p=0.45). The percentage of patients with the primary safety outcome (a composite of death, serious adverse events, or clinical grade 3 or 4 adverse events through day 5) was similar in the LY-CoV555 group and the placebo group (19% and 14%, respectively; odds ratio, 1.56; 95% CI, 0.78 to 3.10; p=0.20). The rate ratio for a sustained recovery was 1.06 (95% CI, 0.77 to 1.47).

Data on high certainty of evidence, related to effectiveness and safety of bamlanivimab reported in this one RCT mentioned above, prepared by Cruciani et al. [18], can be found in the Summary of Findings Table 4-3. Study characteristics can be found in Table 4-4.
4 SUMMARY

4.1 Effectiveness and Safety evidence from RCTs

Effectiveness

Outcome: All-cause mortality

Outpatient:

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.

Hospitalised patients:

According to the results of one RCT, bamlanivimab does not reduce mortality (high certainty of evidence); RR 1.67 (0.57 to 4.88), absolute effect (95% CI) 21 more per 1.000 (from 14 fewer to 124 more).

Outcome: COVID-19 related hospitalisation

Outpatient:

Bamlanivimab monotherapy vs placebo

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, and 5.8% (9 events/156 patients) in the placebo group. Change from baseline to day 29 vs placebo was not statistically significant.

Bamlanivimab + etesevimab vs placebo

The proportion of patients with COVID-19–related hospitalizations or emergency department visits at day 29 was 0.9% (1 event/112 patients) in the combination therapy group; change from baseline to day 29 vs placebo was statistically significant in favour of combination therapy: −4.9% (95% CI, −8.9% to −0.8%; p=0.049).

Outcome: Symptom score

Outpatient:

Bamlanivimab monotherapy vs placebo

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).

Bamlanivimab + etesevimab vs placebo

The change in mean total symptom score from baseline to day 11 was statistically significantly different for the combination group (mean difference, −0.60 [95% CI, −1.18 to −0.03]; p=0.04).
**Outcome: Number of patients discharged**

**Hospitalised patients:**

According to the results of one RCT, bamlanivimab does not increase the Number of patients discharged (high certainty of evidence); RR 0.98 (0.89 to 1.07), absolute effect (95% CI) 17 fewer per 1.000 (from 95 fewer to 61 more), compared to standard treatment/placebo.

**Outcome: Viral clearance**

**Outpatient:**

Bamlanivimab monotherapy vs placebo

Compared to placebo, bamlanivimab does not 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 monotherapy vs Bamlanivimab + etesevimab

Compared to bamlanivimab + etesevimab combination, bamlanivimab does not 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 + etesevimab 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).

**Safety**

**Outcome: Number of patients with adverse events**

**Outpatient:**

Bamlanivimab 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 0.90 (0.65 to 1.25), absolute effect (95% CI) 27 fewer per 1.000 (from 94 fewer to 67 more).

Bamlanivimab monotherapy vs Bamlanivimab + etesevimab

According to the results of one RCT, in outpatients with recently diagnosed mild or moderate Covid-19, bamlanivimab compared to bamlanivimab + etesevimab combination treatment does not increase the number of patients with adverse events (high certainty of evidence); RR 1.43 (0.91 to 2.25), absolute effect (95% CI) 73 more per 1.000 (from 15 fewer to 212 more).

Bamlanivimab + etesevimab 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).
Hospitalised patients:

Bamlanivimab monotherapy vs Standard care/Placebo

According to the results of one RCT [17] bamlanivimab, compared to standard care/placebo, does not reduce the number of patients with AEs (high certainty of evidence); RR 1.27 (0.82 to 1.99), absolute effect (95% CI) 46 more per 1.000 (from 31 fewer to 170 more).

Outcome: Number of patients with serious adverse events

Outpatient:

Bamlanivimab 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 serious adverse events (high certainty of evidence); RR 0.17 (0.01 to 4.12), absolute effect (95% CI) 5 fewer per 1.000 (from 6 fewer to 20 more).

Bamlanivimab monotherapy vs Bamlanivimab + etesevimab

According to the results of one RCT, in outpatients with recently diagnosed mild or moderate Covid-19, bamlanivimab compared to bamlanivimab + etesevimab does not increase the number of patients with serious adverse events (high certainty of evidence); RR 0.12 (0.00 to 2.96), absolute effect (95% CI) 8 fewer per 1.000 (from -- fewer to 17 more).

Bamlanivimab + etesevimab 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 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) 0 fewer per 1.000 (from 103 fewer to 140 more).

Hospitalised patients:

Bamlanivimab monotherapy vs Standard care/Placebo

According to the results of one RCT [17] bamlanivimab compared to standard care/placebo does not increase the number of patients with SAEs (high certainty of evidence); RR 0.93 (0.27 to 3.15), absolute effect (95% CI) 2 fewer per 1.000 (from 23 fewer to 68 more).

4.2 Safety evidence from observational studies

No publications related to prospective observational studies of bamlanivimab treatment in COVID-19 patients were found.

4.3 Ongoing studies

There are five registered ongoing RCTs (three in ambulatory mild to moderate patients, and two in hospitalised patients), and one nRCT (in ambulatory mild to moderate patients), evaluating the treatment with bamlanivimab alone or in combination with another monoclonal antibody, in Covid-19 patients, in ClinicalTrials.gov and EUdraCT registers (details listed in Table 4-5).

Two studies, one phase 3 study for the prevention of COVID-19 in residents and staff at long-term care facilities (NCT04497987, BLAZE-2) and one single group assignment phase 4 study (NCT04656691,
UNITED) evaluating at-home infusion of bamlanivimab in patients with mild to moderate COVID-19, are not listed here.

### 4.4 Scientific conclusion about status of evidence generation

Based on the final results of the phase 2 portion of one RCT in **outpatients** with recently diagnosed mild or moderate Covid-19, no deaths occurred in bamlanivimab, bamlanivimab + etesevimab combination and placebo groups (high certainty of evidence).

Bamlanivimab + etesevimab treatment compared to placebo significantly reduces Covid-19–related hospitalisation or visit to an emergency department at day 29, but bamlanivimab monotherapy does not.

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

Bamlanivimab and bamlanivimab + etesevimab treatment compared to placebo does not increase the number of patients with adverse events or the number of serious adverse events (high certainty of evidence). The same is true for bamlanivimab compared to bamlanivimab + etesevimab treatment.

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

Based on the interim results from one RCT with high certainty of evidence, in **hospitalised** patients, bamlanivimab compared to standard treatment does not reduce all-cause mortality, does not increase the number of patients with AEs and SAEs, and does not increase the number of patients discharged.

Further RCTs examining bamlanivimab alone or in combination with etesevimab for the treatment of COVID-19 patients (outpatients or hospitalised) 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.

On November 9, 2020, the **U.S. Food and Drug Administration** issued an Emergency Use Authorization (EUA) for the investigational monoclonal antibody therapy bamlanivimab for the treatment of **mild-to-moderate COVID-19** in adult and pediatric patients, who are at high risk for progressing to severe COVID-19 and/or hospitalisation.

On February 9, 2021, the FDA issued an **EUA** for bamlanivimab and etesevimab administered **together** for the treatment of **mild to moderate COVID-19** in adults and pediatric patients (12 years of age or older weighing at least 40 kilograms [about 88 pounds]) who test positive for SARS-CoV-2 and who are at high risk for progressing to severe COVID-19. The authorized use includes treatment for those who are 65 years of age or older or who have certain chronic medical conditions.
## Table 4-1 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

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Anticipated absolute effects (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>Number of participants (studies)</th>
<th>Certainty of evidence</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Risk with Placebo</td>
<td>Risk with Bamlanivimab (previously neutralizing antibody LY-CoV555)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>No deaths occurred</td>
<td>No deaths occurred</td>
<td>No deaths occurred</td>
<td>No deaths occurred</td>
<td>⬤批示HIGH</td>
</tr>
<tr>
<td>Number of patients with any adverse events</td>
<td>269 per 1000</td>
<td>242 per 1000</td>
<td>RR 0.90 (0.65 to 1.25)</td>
<td>465 (1 RCT) a</td>
<td>⬤批示HIGH</td>
</tr>
<tr>
<td></td>
<td>170 per 1000</td>
<td>243 per 1000</td>
<td>RR 1.43 (0.91 to 2.25)</td>
<td>421 (1 RCT) a</td>
<td>⬤批示HIGH</td>
</tr>
<tr>
<td>Number of patients with serious adverse events</td>
<td>60 per 1000</td>
<td>10 per 1000</td>
<td>RR 0.17 (0.01 to 4.12)</td>
<td>465 (1 RCT) a</td>
<td>⬤批示HIGH</td>
</tr>
</tbody>
</table>
## Outcome

<table>
<thead>
<tr>
<th></th>
<th>Anticipated absolute effects (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>Number of participants (studies)</th>
<th>Certainty of evidence</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Risk with Placebo</strong></td>
<td>90 per 1000</td>
<td><strong>RR 0.12</strong> (0.00 to 2.96)</td>
<td>421 (1 RCT)</td>
<td>⬤⬤⬤⬤ HIGH</td>
<td>8 fewer per 1.000 (from -- to 17 more)</td>
</tr>
<tr>
<td><strong>Risk with Bamlanivimab</strong></td>
<td>11 per 1000</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Risk with Bamlanivimab + etesevimab</strong></td>
<td>11 per 1000</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>(previously neutralizing antibody LY-CoV555)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>SARS-CoV-2 clearance</strong></td>
<td>368 per 1000</td>
<td><strong>RR 1.06</strong> (0.83 to 1.37)</td>
<td>461 (1 RCT)</td>
<td>⬤⬤⬤⬤ HIGH</td>
<td>Absolute effect (95% CI) 22 more per 1.000 (from 63 fewer to 136 more)</td>
</tr>
<tr>
<td></td>
<td>390 per 1000</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>367 per 1000</strong></td>
<td>392 per 1000</td>
<td><strong>RR 1.07</strong> (0.80 to 1.42)</td>
<td>418 (1 RCT)</td>
<td>⬤⬤⬤⬤ HIGH</td>
<td>Absolute effect (95% CI) 26 more per 1.000 (from 73 fewer to 154 more)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>SARS-CoV-2 clearance</strong></td>
<td>367 per 1000</td>
<td>392 per 1000</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Source:** [10, 11]

[A9] Abbreviations: CI=Confidence interval; RR=Risk ratio
Table 4-2 Summary of findings (SoF) table for published RCTs related to effectiveness and safety of bamlanivimab + etesevimab combination compared to placebo – OUTPATIENT

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Anticipated absolute effects (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>Number of participants (studies)</th>
<th>Certainty of evidence</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Risk with Placebo</td>
<td>Risk with Bamlanivimab + Etesevimab</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>No deaths occurred</td>
<td>No deaths occurred</td>
<td>No deaths occurred</td>
<td>⬤⬤⬤⬤ HIGH</td>
<td>No deaths occurred</td>
</tr>
<tr>
<td>Number of patients with any adverse events</td>
<td>269 per 1000</td>
<td>170 per 1000</td>
<td>RR 0.63 (0.39 to 1.02)</td>
<td>268 (1 RCT) a</td>
<td>Absolute effect (95% CI) 100 fewer per 1.000 (from 164 fewer to 5 more)</td>
</tr>
<tr>
<td>Number of patients with serious adverse events</td>
<td>60 per 1000</td>
<td>83 per 1000</td>
<td>RR 1.39 (0.09 to 22.03)</td>
<td>268 (1 RCT) a</td>
<td>Absolute effect (95% CI) 2 more per 1.000 (from 6 fewer to 135 more)</td>
</tr>
<tr>
<td>SARS-CoV-2 clearance</td>
<td>368 per 1000</td>
<td>368 per 1000</td>
<td>RR 1.00 (0.72 to 1.38)</td>
<td>261 (1 RCT) a</td>
<td>Absolute effect (95% CI) 0 fewer per 1.000 (from 103 fewer to 140 more)</td>
</tr>
</tbody>
</table>

Source: [12]  
[9]  
Abbreviations: CI=Confidence interval; RR=Risk ratio
### Table 4-3 Summary of findings (SoF) table for published RCTs related to effectiveness and safety of bamlanivimab compared to standard treatment/placebo—HOSPITALISED

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Anticipated absolute effects (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>Number of participants (studies)</th>
<th>Certainty of evidence</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Risk with Standard treatment/Placebo</td>
<td>Risk with Bamlanivimab (previously neutralizing antibody LY-CoV555)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>32 per 1000</td>
<td>53 per 1000</td>
<td>RR 1.67 (0.57 to 4.88)</td>
<td>326 (1 RCT) a</td>
<td>☒☒☒☒ HIGH</td>
</tr>
<tr>
<td>Number of patients with adverse events</td>
<td>172 per 1000</td>
<td>219 per 1000</td>
<td>RR 1.27 (0.82 to 1.99)</td>
<td>326 (1 RCT) a</td>
<td>☒☒☒☒ HIGH</td>
</tr>
<tr>
<td>Number of patients with serious adverse events</td>
<td>32 per 1000</td>
<td>30 per 1000</td>
<td>RR 0.93 (0.27 to 3.15)</td>
<td>326 (1 RCT) a</td>
<td>☒☒☒☒ HIGH</td>
</tr>
<tr>
<td>Number of patients discharged</td>
<td>866 per 1000</td>
<td>846 per 1000</td>
<td>RR 0.98 (0.89 to 1.07)</td>
<td>326 (1 RCT) a</td>
<td>☒☒☒☒ HIGH</td>
</tr>
</tbody>
</table>

Source: [13, 18]

a [17]

**Abbreviations:** CI=Confidence interval; RR=Risk ratio
### Table 4-4 Study characteristics of included RCTs

<table>
<thead>
<tr>
<th>Author, year, reference number/Study name/Study ID</th>
<th>Gottlieb et al. 2021 [9], BLAZE-1, NCT04427501</th>
<th>Lundgren et al. 2020 [17] (ACTIV-3/TICO LY-CoV555 Study group), NCT04501978, preliminary results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study design, study phase</td>
<td>RCT, phase 2/3</td>
<td>RCT, phase 3</td>
</tr>
<tr>
<td>Centres (single centre or multicentre), country, setting</td>
<td>Multicentre, US, Outpatients</td>
<td>Multicentre (US, Denmark and Singapore), Hospitalised</td>
</tr>
<tr>
<td>Patient population (number of included patients/ Mean age and sex/ Disease severity*)</td>
<td>Mixed (mild to moderate), 592 randomized; mean age, 44.7 [SD, 15.7] years; 315 [54.6%] women; 449 patients (77.8%): Mild</td>
<td>Mixed (moderate to severe), 314 patients who received an infusion of LY-CoV555 (163 patients) or placebo (151 patients); 63 vs 59 y; female 40% vs 47%</td>
</tr>
<tr>
<td>Inclusion criteria</td>
<td>Are ≥18 years of age at the time of randomization; 2. currently not hospitalized 3. Have one or more mild or moderate COVID-19 symptoms (FDA resource page [WWW]) i. Fever ii. Cough iii. Sore throat iv. Malaise v. Headache vi. Muscle pain vii. Gastrointestinal symptoms, or viii. Shortness of breath with exertion 4. sample collection for first positive SARS-CoV-2 viral infection determination ≤3 days prior to start of the infusion Sex 5. 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. 6. Understand and agree to comply with planned study procedures 7. Agree to the collection of nasopharyngeal swabs and venous blood Informed Consent 8. 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.</td>
<td>Adult hospitalised patients who had documented SARS-CoV-2 infection and a duration of symptoms attributable to Covid-19 of 12 days or less</td>
</tr>
<tr>
<td>Exclusion criteria</td>
<td>9. SpO2 ≤ 93% on room air at sea level or PaO2/FiO2 &lt; 300, respiratory rate ≥30 per minute, heart rate ≥125 per minute (FDA resource page, WWW) 10. Require mechanical ventilation or anticipated impending need for mechanical ventilation 11. known allergies to any of the components used in the formulation of the interventions 12. hemodynamic instability requiring use of pressors within 24 hours of randomization 13. 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 14. any co-morbidity requiring surgery within within 29 days 15. any serious concomitant systemic disease, condition or disorder that, in the opinion of the investigator, should preclude participation in this study. 16. history of a positive SARS-CoV-2 serology test 17. history of a positive SARS-CoV-2 test prior to the one serving as eligibility for this study 18. received an investigational intervention for SARS-CoV-2 prophylaxis within 30 days before</td>
<td>Patients who had received SARS-CoV-2 intravenous immune globulin, convalescent plasma from a patient who had recovered from Covid-19, or another neutralizing monoclonal antibody against SARS-CoV-2. During stage 1, patients were excluded from the trial if they had end-organ failure (including vasopressor therapy, new renal replacement therapy, or the receipt of invasive mechanical ventilation, extracorporeal membrane oxygenation, or mechanical circulatory support) or certain extrapulmonary complications. For treatments that passed the early futility assessment, subsequent patients would be enrolled according to expanded eligibility criteria, which permit the presence of end-organ failure and extrapulmonary complications.</td>
</tr>
<tr>
<td>Author, year, reference number/Study name/Study ID</td>
<td>Gottlieb et al. 2021 [9], BLAZE-1, NCT04427501</td>
<td>Lundgren et al. 2020 [17] (ACTIV-3/TICO LY-CoV555 Study group), NCT04501978, preliminary results</td>
</tr>
<tr>
<td>---</td>
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</tr>
<tr>
<td>Study design, study phase</td>
<td>RCT, phase 2/3</td>
<td>RCT, phase 3</td>
</tr>
<tr>
<td>Centres (single centre or multicentre), country, setting</td>
<td>Multicentre, US, Outpatients</td>
<td>Multicentre (US, Denmark and Singapore), Hospitalised</td>
</tr>
<tr>
<td>Patient population (number of included patients/ Mean age and sex/ Disease severity*)</td>
<td>Mixed (mild to moderate), 592 randomized; mean age, 44.7 [SD, 15.7] years; 315 [54.6%] women; 449 patients (77.8%): Mild</td>
<td>Mixed (moderate to severe), 314 patients who received an infusion of LY-CoV555 (163 patients) or placebo (151 patients); 63 vs 59 y; female 40% vs 47%</td>
</tr>
<tr>
<td>Intervention (generic drug name and dosage, time frame; number of randomized/ enrolled patients in subgroups - Mild, Moderate, Severe, Critical COVID-19)</td>
<td>Single infusion of bamlanivimab (700mg [n = 101], 2800mg [n = 107], or 7000mg [n = 101]) Combination treatment (2800mg of bamlanivimab and 2800mg of etesevimab [n = 112]) Bamlanivimab n=309 Mild 83 (82.2%); 79 (73.8%); 70 (69.3) Moderate 18 (17.8%); 28 (26.2%); 31 (30.7%) Combination treatment n=112 Mild 92 (82.1%) Moderate 20 (17.9%)</td>
<td>Single intravenous infusion of neutralizing antibody LY-CoV555 (7000 mg) (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)</td>
</tr>
<tr>
<td>Comparator(s) (standard care or generic drug name and dosage, time frame; number</td>
<td>Placebo n=156 Mild 125 (80.1%) Moderate 31 (19.9%)</td>
<td>Placebo (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)</td>
</tr>
<tr>
<td>Author, year, reference number/Study name/Study ID</td>
<td>Gottlieb et al. 2021 [9], BLAZE-1, NCT04427501</td>
<td>Lundgren et al. 2020 [17] (ACTIV-3/TICO LY-CoV555 Study group), NCT04501978, preliminary results</td>
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<td>Study design, study phase</td>
<td>RCT, phase 2/3</td>
<td>RCT, phase 3</td>
</tr>
<tr>
<td>Centres (single centre or multicentre), country, setting</td>
<td>Multicentre, US, Outpatients</td>
<td>Multicentre (US, Denmark and Singapore), Hospitalised</td>
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<tr>
<td>Patient population (number of included patients/ Mean age and sex/ Disease severity*)</td>
<td>Mixed (mild to moderate), 592 randomized; mean age,44.7 [SD, 15.7] years; 315 [54.6%] women); 449 patients (77.8%): Mild</td>
<td>Mixed (moderate to severe), 314 patients who received an infusion of LY-CoV555 (163 patients) or placebo (151 patients); 63 vs 59 y; female 40% vs 47%</td>
</tr>
<tr>
<td>of randomized/enrolled patients in subgroups - Mild, Moderate, Severe, Critical COVID-19</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary Outcome(s)</td>
<td>Change in SARS-CoV-2 log viral load at day 11 (±4 days)</td>
<td>Sustained recovery during a 90-day period</td>
</tr>
<tr>
<td>Patient-relevant secondary outcome(s)</td>
<td>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</td>
<td>A key secondary outcome was death from any cause. Deaths and serious adverse events were assessed during 90 days of follow-up. Data regarding clinical organ failure, serious infections, and clinical adverse events of grade 3 or 4 were collected through day 28. The primary safety outcome was a composite of death, serious adverse events, or grade 3 or 4 adverse events through day 5.</td>
</tr>
<tr>
<td>Follow-up (days, months)</td>
<td>Up to day 29</td>
<td>Up to 90-day period, the median follow-up 31 days</td>
</tr>
<tr>
<td>Sponsor/ lead institution</td>
<td>Eli Lilly</td>
<td>Operation Warp Speed and others</td>
</tr>
<tr>
<td>Trial Identifier/registry ID(s)/contact</td>
<td>NCT04427501, BLAZE-1</td>
<td>NCT04634409, BLAZE-4</td>
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<tr>
<td>--------------------------------------</td>
<td>------------------------</td>
<td>------------------------</td>
</tr>
<tr>
<td>Study design, study phase</td>
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<td>RCT, phase 2</td>
</tr>
<tr>
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<td>Recruiting</td>
</tr>
<tr>
<td>Number of Patients, Disease severity*</td>
<td>1200, Mixed (Mild and Moderate)</td>
<td>500, Mixed (Mild and Moderate)</td>
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<tr>
<td>Setting (hospital, ambulatory...)</td>
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<td>Ambulatory</td>
</tr>
<tr>
<td>Intervention (generic drug name and dosage)</td>
<td>Bamlanivimab alone (LY-CoV555)</td>
<td>Bamlanivimab alone (LY-CoV555)</td>
</tr>
<tr>
<td>Comparator (standard care or generic drug name and dosage)</td>
<td>Placebo</td>
<td>Placebo</td>
</tr>
<tr>
<td>Primary Outcome(s)</td>
<td>Change from Baseline to Day 11 in SARS-CoV-2 Viral Load [Time Frame: 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</td>
<td>Percentage of Participants with SARS-CoV-2 Viral Load Greater than 5.27 [Time Frame: Day 7]</td>
</tr>
<tr>
<td>Trial Identifier/registry ID(s)/contact</td>
<td>Study design, study phase</td>
<td>Recruitment status</td>
</tr>
<tr>
<td>----------------------------------------</td>
<td>--------------------------</td>
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<tr>
<td>NCT04427501, BLAZE-1</td>
<td>RCT, phase 2</td>
<td>Recruiting</td>
</tr>
<tr>
<td>NCT04634409, BLAZE-4</td>
<td>RCT, phase 2</td>
<td>Recruiting</td>
</tr>
<tr>
<td>NCT04501978-ACTIV 3 EudraCT 2020-003278-37</td>
<td>RCT, phase 3</td>
<td>Active, not recruiting</td>
</tr>
<tr>
<td>NCT04518410-ACTIV-2</td>
<td>RCT, phase 2/3</td>
<td>Recruiting</td>
</tr>
<tr>
<td>NCT04701658 (BLAZE-5)</td>
<td>nRCT</td>
<td>Not yet recruiting</td>
</tr>
<tr>
<td>NCT04748588 (CATCO-NOS)</td>
<td>RCT, phase 4</td>
<td>Not yet recruiting</td>
</tr>
</tbody>
</table>
5 REFERENCES


6 APPENDIX

6.1 Search strategy to identify randomised controlled trials

DEPLazio, the Department of Epidemiology of the Regional Health Service Lazio in Rome, Italy is responsible for setting up the search strategy to identify randomised controlled trials (RCTs). DEPLazio performed a search in Medline, PubMed, and Embase, which has been updated weekly from March 2020 (Appendix Table 6-1). DEPLazio searched medRxiv.org (https://www.medrxiv.org/), bioRxiv.org (https://www.biorxiv.org/), and arXiv.org (https://www.arXiv.org/) for preprints of preliminary reports of randomised trials. The Cochrane Covid-19 Study Register (https://covid-19.cochrane.org/), ClinicalTrials.gov (www.clinicaltrials.gov) and World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/en/) were search in addition. Other sources included journal alerts, contact with researchers, websites such as Imperial College, London School of Hygiene and Tropical Medicine, and Eurosurveillance. We applied no restriction on language of publication.

We included randomised controlled trials (RCTs) comparing any pharmacological intervention against another pharmacological intervention or placebo or standard care (SC), for the treatment of individuals with Covid-19. We excluded studies comparing two dosages of the same pharmacological agent. We did not exclude studies on individuals with a comorbid disorder.

Four authors independently screened the references retrieved by the search, selected the studies, and extracted the data, using a predefined data-extraction sheet. The same reviewers discussed any uncertainty regarding study eligibility and data extraction until consensus was reached; conflicts of opinion were resolved with other members of the review team. Two authors independently assessed the risk of bias of the included studies with the Cochrane tool. Three authors used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, to evaluate the strength of evidence.

The methods described above are part of a living review of pharmacological agents for the treatment of Covid-19 conducted by the Department of Epidemiology of the Regional Health Service Lazio, Italy, to inform national regulatory agencies and clinicians, available at https://www.deplazio.net/farmacicovid. The review is registered on Prospero (CRD42020176914).
### Table 6-1 Search strategy to identify randomised controlled studies

<table>
<thead>
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<td>Pubmed</td>
<td>pubmed.ncbi.nlm.nih.gov</td>
<td>1. (((((((“Coronavirus”[Mesh]) OR (coronavirus)[Title/Abstract]) OR coronavirinae)[Title/Abstract]) OR Coronavirus)[Title/Abstract]) OR Coronavirus)[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 COVID19)[Title/Abstract]) OR “SARS-CoV-2”)[Title/Abstract]) OR “SARS-CoV-2”)[Title/Abstract]) OR “SARS-CoV2”)[Title/Abstract]) OR “SARS-CoV-2”)[Title/Abstract]) OR SARS-CoV19)[Title/Abstract]) OR “SARS-CoV-19”)[Title/Abstract]) OR “SARS-CoV-19”)[Title/Abstract]) OR “SARS-CoV-19”)[Title/Abstract]) OR “SARS-CoV-19”)[Title/Abstract]) OR Ncorona)[Title/Abstract]) OR Ncorono)[Title/Abstract]) OR NcovWuhan)[Title/Abstract]) OR NcovHubei)[Title/Abstract]) OR NcovChina)[Title/Abstract]) OR NcovChinese)AND (((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 virinae*)[Title/Abstract])) OR ((((randomized controlled trial)[tiab]) OR (controlled clinical trial)[tiab]) OR (randomized [tiab])) OR (placebo [tiab])) OR (clinical trials as topic [mesh: noexp])) OR (randomly [tiab])) OR (trial [tiab])) NOT (animals [mh]) NOT humans [mh]) AND (2019/10/01:2020[dp])</td>
<td>05/02/2020</td>
</tr>
<tr>
<td>Database</td>
<td>URL</td>
<td>Search line / Search terms</td>
<td>Date of search</td>
</tr>
<tr>
<td>------------</td>
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<td>-------------------------------------------------------------------------------------------</td>
<td>----------------</td>
</tr>
</tbody>
</table>
| Ovid MEDLINE(R) ALL | ovidsp.dc2.ovid.com | 1. exp coronavirus/  
2. ((corona* or corono*) adj1 (virus* or viral* or viinneae*).ti,ab,kw.  
3. (coronavirus* or coronovirus* or coronavirinae* or Coronavirus* or Coronavirus* 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 "SARS-CoV2" or SARS-CoV2 or "SARS-CoV" or SARS-CoV19 or "SARS-Cov-19" or "SARS-Cov-19" or "SARS-CoV" or Ncov or Ncorona* or Ncoron* 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" | 05/02/2020 |
| 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 Coronavirus 2" or "SARS Coronavirus" or "Severe Acute Respiratory Syndrome Coronavirus 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 (blindS3 or maskS3)) or (randomS$ adj (assignS or allocat$ or group or grouped or patients or study or trial or distrib$)) 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" | 05/02/2020 |
6.2 Search strategy to identify observational studies

As of October 2020, NIPHNO is responsible for setting up the search strategy to identify observational studies.

From September to December 2020, we received records that EPPI Centre has screened after searching weekly in Medline and Embase (until beginning of November 2020), from November onwards Microsoft Academics Graph (MAG). We supplemented these studies with a weekly search in Scopus (Elsevier). Detailed descriptions of the EPPI and NIPHNO searches are given at their websites [19, 20]. The retrieved hits were imported to a reference management tool, Endnote (Clarivate Analytics), for deduplication. We then searched the EndNote database using the generic names and synonyms for the included COVID-19 drugs.

From January onwards, an information specialist at NIPHNO has conducted searches in Medline (Ovid), Embase (Ovid) and Scopus (Elsevier) using the search strategy described in table 6.2. To screen the references, two reviewers use a binary machine learning (ML) classifier. References that scored above the identified threshold of 30% certainty to be relevant were retained for screening; while those scoring below this threshold score were set aside.

Prior to using the binary ML classifier score to discard low scoring records, we screened 1028 references manually to train the classifier. The classifier is continuously being updated along with new references being screened. References that have been set aside, can potentially be picked up in a later stage by a new classifier version. For drugs that have less than 5 publications included in the training batch, we combine the classifier with manual text word searches.
### Table 6-2 Search strategy to identify observational studies

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<th>Search terms / Search modality</th>
<th>Date of search</th>
</tr>
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<td>Embase</td>
<td>1974 to 2021</td>
<td>Lines 1 and 2 are copies of Ovid's Expert searches for covid-19 in MEDLINE and Embase</td>
<td>From 1/9/2020 until 3/2/2021 Covering publication dates 01. September 2020</td>
</tr>
<tr>
<td>Ovid Embase (R)</td>
<td>MEDLINE(R) ALL 1946 to 2021</td>
<td>1 (((pneumonia or covid* or coronavirus* or corona virus* or ncov* or 2019-ncov or sars*).mp. or exp pneumonia/) and Wuhan.mp.) or (2019-ncov or ncoiv19 or ncov19 or 2019-novel CoV or sars-cov2 or sars-cov-2 or sarccov2 or sars-cov-2 or Sars-coronavirus2 or Sars-coronavirus-2 or SARS-like coronavirus* or coronavirus-19 or covid19 or covid-19 or covid 2019 or ((novel or new or nouveau) adj2 (CoV or nCoV or covid or coronavirus* or corona virus or pandemi<em>2)) or ((covid or covid19 or covid-19 and pandemic</em>2) or (coronavirus* and pneumonia)).mp. or COVID-19.rx,px,ox,sh. or severe acute respiratory syndrome coronavirus 2.os.) use medall [COVID-19 in MEDLINE]</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 (((pneumonia or covid* or coronavirus* or corona virus* or ncov* or 2019-ncov or sars*).mp. or exp pneumonia/) and Wuhan.mp.) or (coronavirus disease 2019 or 2019-ncov or ncov19 or ncov-19 or 2019-novel CoV or severe acute respiratory syndrome coronavirus 2 or sars-cov2 or sars-cov-2 or sarccov2 or sarccov-2 or Sars-coronavirus2 or Sars-coronavirus-2 or SARS-like coronavirus* or coronavirus-19 or covid19 or covid-19 or covid 2019 or ((novel or new or nouveau) adj2 (CoV or nCoV or covid or coronavirus* or corona virus or pandemi<em>2)) or ((covid or covid19 or covid-19 and pandemic</em>2) or (coronavirus* and pneumonia)).mp. or (coronavirus disease 2019 or severe acute respiratory syndrome coronavirus 2).sh,adj.) use oemezd [COVID-19 in Embase]</td>
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<td>3 (COVID-19 serotherapy/ or Immunization, Passive/ or tocilizumab/ or camostat/ or nafamostat/ or AP301 peptide/ or Interleukin 1 Receptor Antagonist Protein/ or alunacedase alfa/ or darunavir/ or favipiravir/ or sarilumab/ or exp Interferons/ or gimsilumab/ or canakinumab/ or REGN-COV-2/ or bamlanivimab/ or baricitinib/ or molnupiravir/ or Aspirin/ or mavrilimumab/ or exp Vitamin D/dt or Vitamin D Deficiency/dt or Ivermectin/) use medall [MeSH-terms for drugs in MEDLINE]</td>
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<td></td>
<td>5 ((convalescent adj (plasma or sera or serum)) or serotherap* or ((latoxin or hyperimmunoglobulin or hyperimmune globulin or hyperimmune gammaglobulin) adj therap*) or passive</td>
<td></td>
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immunization or (tocilizumab or atilizumab or (MRA adj monoclonal antibody*) or MSB-11456 or MSB11456 or R-1569 or R1569 or RO-4788533 or RO4788533 or Actemra or Roactemra) or (camostat* or FOY-305 or FOY305 or FOY S 980) or (nafamostat or nafamstat or FUT-175 or FUT175) or (solinate or AP301 or AP-301 or (TIP adj peptide)) or (anakinra or ((interleukin 1 or IL1 or IL-1) adj2 (antagonist or block* or inhibitor*)) or IL-1Ra or Kineret) or (alunacedase or APN01 or APN-01 or rhACE2 or recombinant human angiotensin converting enzyme 2 or GSK-2586881 or GSK2586881) or (darunavir or prezista or TMC-114 or TMC114 or UIC-94017 or UIC94017) or (favipiravir or T-705 or T705 or Avigan or Olumiant) or (sarilumab or REGN-88 or REGN88 or SAR-153191 or SAR153191 or Kevzara) or (interferon* or (IFN adj1 (alpha* or beta* or gamma*))) or novafenon or CL-884 or CL884) or (gimsilumab or KIN-1901 or KIN1901 or morab-022 or morab022) or (canakinumab or ACZ-885 or ACZ885 or immunoglobulin G1 or Ilaris) or (REGN-CoV-2 or REGN-CoV2 or antibody cocktail or ((casirivimab or REGN-10933 or REGN10933) and (imdevimab or REGN-10987 or REGN10987))) or (bamlanivimab or LY-CoV555 or LYCoV555 or LY-3819253 or LY3819253) or (baricitinib or LY-3009104 or LY3009104 or INC2-028050 or INC28050 or INC28050 or Olumiant) or (molnupiravir or MK-4482 or MK4482 or EIDD-2801 or EIDD2801) or (aspirin or acetylsalicylic acid) or (mavrilimumab or immunoglobulin G4 or CAM-3001 or CAM3001) or ((vitamin? D? or D?-vitamin?) adj4 (high-dose* or higndose* or supplement*)) or (ivermect* or MK-933 OR MK933)).mp,pt.ot,dy,tn,nm. [other terms (title, abstract, author keywords and more) in MEDLINE and Embase]

6 (202009* or 202010* or 202011 or 202012* or 202101* or 202102*).dt. use medall [time limits in MEDLINE]

7 (202009* or 202010* or 202011 or 202012* or 202101* or 202102*).dc. use oemezd [time limits in Embase]

8 (1 and (3 or 5) and 6) use medall

9 (2 and (4 or 5) and 7) use oemezd
### 6.3 Search strategy to identify ongoing studies

AIHTA is responsible for searching in trial registries to identify ongoing and unpublished studies. The combination of search terms related to COVID-19 and bamlanivimab are described in Appendix Table 6-3.

**Table 6-3 Search strategy to identify ongoing studies**

<table>
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<tr>
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<td><em>Basic search mode</em>&lt;sup&gt;**&lt;/sup&gt;&lt;br&gt;Terms used at Condition or disease:&lt;br&gt;• covid-19&lt;br&gt;Terms used at &quot;other terms&quot;:&lt;br&gt;• LY3819253&lt;br&gt; • LY-CoV555</td>
<td>11/02/2021</td>
<td>6 1 new</td>
</tr>
<tr>
<td>ISRCTN</td>
<td><a href="https://www.isrctn.com/">https://www.isrctn.com/</a></td>
<td>Basic search mode&lt;br&gt;Search terms:&lt;br&gt;1. covid-19 and bamlanivimab&lt;br&gt;2. covid-19 and LY-CoV555&lt;br&gt;3. covid-19 and LY3819253&lt;br&gt;4. SARS-CoV-2 and bamlanivimab&lt;br&gt;5. SARS-CoV-2 and SARS-CoV-2&lt;br&gt;6. SARS-CoV-2 and LY3819253</td>
<td>11/02/2021</td>
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<td>European Clinical Trials Registry</td>
<td><a href="https://www.clinicaltrialsregister.eu/">https://www.clinicaltrialsregister.eu/</a></td>
<td>Basic search mode&lt;br&gt;Search terms:&lt;br&gt;1. covid-19 and bamlanivimab&lt;br&gt;2. covid-19 and LY-CoV555&lt;br&gt;3. covid-19 and LY3819253&lt;br&gt;4. SARS-CoV-2 and bamlanivimab&lt;br&gt;5. SARS-CoV-2 and LY-CoV555&lt;br&gt;6. SARS-CoV-2 and LY3819253</td>
<td>11/02/2021</td>
<td>1 0 new</td>
</tr>
</tbody>
</table>

* In Basic Search mode, one term was added to the field “condition or disease” and one term in the field “other terms”.

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6.4 Flow diagrams

9714 records identified through database search: Medline, PubMED, EMBASE, LOVE platform

40 records identified through other sources, including Cochrane Covid-19 study register, international trial registries, medRxiv, bioRxiv, arXiv, EuropePMC preprint server, and industry websites

6471 excluded
- 4320 because of title and abstract
- 3151 excluded because study duplicate

92 full-text articles assessed for eligibility

11 excluded
- 3 comparison not fulfilling eligibility criteria
- 5 population not fulfilling eligibility criteria
- 2 outcomes not fulfilling eligibility criteria
- 1 no useful data

9714 records identified through database search: Medline, PubMED, EMBASE, LOVE platform

10 excluded
- 3 study design not fulfilling eligibility criteria
- 2 intervention not fulfilling eligibility criteria
- 1 comparison not fulfilling eligibility criteria
- 4 outcomes not fulfilling eligibility criteria

81 published studies selected for inclusion

30 preprint selected for inclusion

111 randomised controlled trials included in quantitative synthesis*
- 1 RCT comparing bamlanivimab monotherapy and bamlanivimab + etesevimab with placebo (outpatients)
- 1 RCT comparing bamlanivimab with placebo (hospitalised)
- 109 RCTs comparing other active substances not relevant to this report with control*

Appendix Figure 6-1. Flow diagram depicting the selection process of RCTs

RCT = randomised controlled trial;
* The selection process was part of an external project, see https://www.deplazio.net/farmacicovid and Prospero ID CRD42020176914
Appendix Figure 6-2. Flow diagram depicting the selection process of observational studies

** studies evaluating active substances relevant to other EUnetHTA rolling collaborative reviews