EUnetHTA Joint Action 3 WP4

"Rolling Collaborative Review" of Covid-19 treatments

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

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Monitoring Report

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V 1.0	**15/12/2020**	First version
V 1.1	**12/01/2021**	Literature searches, Literature screening, Data extraction
V 1.2	**15/01/2021**	Data extraction and analysis complete
V 1.3	**18/01/2021**	Check of data extraction and analysis
V 2.0	**20/01/2021**	Second version

Major changes from previous version

Chapter, page no.	Major changes from version 1.0
Chapter 3, p.11 p. 13	• US COVID-19 Treatment Guidelines recommendations are added • 1 new publication on RCT in hospitalised patients was added
Chapter 4, p.15 p.16	• 1 new ongoing nRCT was found (in ambulatory mild to moderate patients) • Summary of findings table was added related to new published RCT in hospitalised patients

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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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LIST OF ABBREVIATIONS

AE	Adverse Event
CI	Confidence Interval
DOI	Declaration of interest
EUnetHTA	European Network of Health Technology Assessment
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HR	Hazard Ratio
ICD	International Classification of Diseases
MD	Mean Difference
MeSH	Medical Subject Headings
NA	Not applicable
NR	Not reported
nRCT	Non-Randomized Controlled Trial
OR	Odds Ratio
RCT	Randomized Controlled Trial
RCR	Rolling Collaborative Review
REA	Relative Effectiveness Assessment
RR	Relative Risk
SAE	Serious Adverse Event
SD	Standard Deviation
SMD	Standardized Mean Difference
WP4	Work Package 4

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/services/covid-19/) and on the EUnetHTA Rolling Collaborative Review Sharepoint page each 15th of the month.

2.1 Scope

Table 2-1 Scope of the RCR

Description	Project Scope
Population	**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** (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 **Target population** (https://www.covid19treatmentguidelines.nih.gov/overview/management-of-covid-19/) • 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	<u>Main outcome:</u> • All-cause Mortality (Survival) <u>Additional Outcomes:</u> 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.pdfc) 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:

- Cochrane Central Register of Controlled Trials (CENTRAL), in the Cochrane Library
- MEDLINE, accessed via OVID
- Embase, accessed via OVID

Population	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.
Intervention	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.
Comparison	Any active treatment, placebo, or standard of care.
Outcomes	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.
Study design	Randomised controlled trials (RCT); no restriction on language of publication

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 for SoF (or 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 using the following sources:

- https://www.fhi.no/en/qk/systematic-reviews-hta/map/

Search methods are described in more detail in Table 6-2.

Population	See project Scope
Intervention	Bamlanivimab is neutralizing monoclonal antibody.
Comparison	Any active treatment, placebo, or standard of care.
Outcomes	See project Scope
Study design	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

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).

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/
- ISRCTN: https://www.isrctn.com/
- European Clinical Trials Registry: 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 as well. 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 of a combination of 2 monoclonal antibodies targeting different sites on the spike protein. Due to 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 for 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.

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 SARSCoV-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].

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) [7].

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

Results of a **preplanned interim analysis** of the **bamlanivimab monotherapy** arms of the BLAZE-1, randomised, double-blind, placebo-controlled trial **(NCT04427501)** were published by Chen et al. 2020 [8]. This is an ongoing phase 2 trial involving **outpatients** with recently diagnosed **mild or moderate Covid-19,** with an anticipated study completion date of January 15, 2021.

After undergoing randomisation, patients received an infusion of LY-CoV555 or placebo within a median of 4 days after the onset of symptoms; at the time of randomisation, more than 80% of the patients had only mild symptoms. 452 patients received a single intravenous infusion of neutralizing antibody LY-CoV555 in one of three doses (700 mg, 2800 mg, or 7000 mg) or placebo and evaluated the quantitative virologic end points and clinical outcomes. The primary outcome was the change from baseline in the viral load at day 11.

Effectiveness

One of three doses of neutralizing antibody LY-CoV555 appeared to accelerate the natural decline in viral load over time, whereas the other doses had not by day 11: 2800-mg dose of LYCoV555, the difference from placebo in the decrease from baseline was -0.53 (95% confidence interval [CI], -0.98 to -0.08; p=0.02. Smaller differences from placebo in the change from baseline were observed among the patients who received the 700-mg dose (−0.20; 95% CI, −0.66 to 0.25; p=0.38) or the 7000-mg dose (0.09; 95% CI, −0.37 to 0.55; p=0.70). On days 2 to 6, the patients who received LY-CoV555 had a slightly lower severity of symptoms than those who received placebo: with values of −0.79 (95% CI, −1.35 to −0.24) on day 2, −0.57 (95% CI, −1.12 to −0.01) on day 3, −1.04 (95% CI, −1.60 to −0.49) on day 4, −0.73 (95% CI, −1.28 to −0.17) on day 5, and −0.79 (95% CI, −1.35 to −0.23) on day 6. The percentage of patients who had a Covid-19–related hospitalisation or visit to an emergency department was 1.6% (5 of 309 patients) in the LY-CoV555 group and 6.3% (9 of 143 patients) in the placebo group. In a post hoc analysis that was focused on high-risk subgroups (an age of ≥65 years or a BMI of ≥35), the percentage of hospitalisation was 4.2% (4 of 95) in the LY-CoV555 group and 14.6% (7 of 48) in the placebo group. Only 1 patient in the trial (in the placebo group) was admitted to an intensive care unit.

Safety

The safety outcomes were similar in intervention and placebo groups. Serious adverse events occurred in none of the 309 patients in LY-CoV555 group and in 0.7% (1 of 143 patients) in the placebo group.

The percentage of patients who had an adverse event during treatment was 22.3% (69 of 309) in the LY-CoV555 group and 24.5% (35 of 143) in the placebo group. The most frequently reported adverse event in the LY-CoV555 group was nausea (3.9%), whereas diarrhoea (4.9%) was the most frequent adverse event in the placebo group. Infusion-related reactions were reported in 2.3% of the patients (7 of 309) in the LY-CoV555 group and in 1.4% (2 of 143) in the placebo group. Most of these events — which included pruritus, flushing, rash, and facial swelling — occurred during the infusion and were reported as mild in severity. No changes in vital signs were noted during these reactions, and the infusions were completed in all instances. In some patients, antihistamines were administered to help resolve symptoms.

Data on high certainty of evidence, related to effectiveness and safety of bamlanivimab reported in this one RCT, prepared by Cruciani et al. [9], can be found in the Summary of Findings Table 4-1. Study characteristics can be found in Table 4-3.

On October 7, 2020 Eli Lilly and Company announced **unpublished results** from an interim analysis from 268 mild or moderate COVID-19 patients who participated in the **combination bamlanivimab (LY-CoV555) and etesevimab (LY-CoV016)** arm and the placebo arm of the BLAZE-1 clinical trial. Such combination therapy reduced viral load, symptoms and COVID-related hospitalization and ER visits. The combination cohort enrolled recently diagnosed patients with mild-to-moderate COVID-19, who were assigned to 2800 mg of each antibody (n=112) or placebo (n=156). The combination therapy significantly reduced viral load at day 11 (p=0.011), meeting the primary endpoint of the study. The combination therapy also met prespecified clinical endpoints, including the time-weighted average change from baseline in total symptom score from day 1 to 11 (p=0.009). The rate of COVID-related hospitalization and ER visits was lower for patients treated with combination therapy (0.9 percent) versus placebo (5.8 percent), a relative risk reduction of 84.5 percent (p=0.049). Combination therapy has been generally well tolerated with no drug-related serious adverse events [5].

Hospitalised patients

On October 26, 2020**,** the National Institute of Health (NIH) **announced** that bamlanivimab (LY-CoV555) substudy 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** [10].

Lundgren et al. 2020 (**ACTIV-3/TICO** LY-CoV555 Study group) published **preliminary** negative results from above mentioned RCT (**NCT04501978**) compared LY-CoV555 with placebo in **hospitalised patients** who had Covid-19 without end-organ failure [11]. 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.
Monoclonal antibody LY-CoV555, when coadministered 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 favorable 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. [9], can be found in the Summary of Findings Table 4-2. Study characteristics can be found in Table 4-3.

4 SUMMARY

4.1 Effectiveness and Safety evidence from RCTs

Effectiveness

Outcome: Viral clearance

2800-mg dose of neutralizing antibody LY-CoV555 statistically significant accelerated the natural decline in viral load over time; difference -0.53 (95% CI -0.98 to -0.08); p=0.02.

Outcome: COVID-19 related hospitalisation

The percentage of patients who had a Covid-19–related hospitalisation or visit to an emergency department was 1.6% in the LY-CoV555 group and 6.3% in the placebo group. In a post hoc analysis focused on high-risk subgroups (an age of ≥65 years or a BMI of ≥35), the percentage of hospitalisation was 4.2% in the LY-CoV555 group and 14.6% in the placebo group. P value was not reported.

Outcome: Symptom score

On days 2 to 6, the patients who received LY-CoV555 had a slightly lower severity of symptoms than those who received placebo.

Outcome: All-cause mortality

No deaths occurred in bamlanivimab and placebo group of outpatients with recently diagnosed mild or moderate Covid-19, according to the results of one RCT [8] with high certainty of evidence.

Hospitalised patients: According to the results of one RCT [11], 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: Number of patients discharged

Hospitalised patients: According to the results of one RCT [11], 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).

Safety

Outcome: Number of patients with adverse events

According to the results of one RCT [8], in outpatients with recently diagnosed mild or moderate Covid-19, bamlanivimab does not increase number of patients with adverse events (high certainty of evidence); RR 0.91 (0.64 to 1.30), absolute effect (95% CI) 22 fewer per 1.000 (from 88 fewer to 73 more).

Hospitalised patients: According to the results of one RCT [11], bamlanivimab does not reduce 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

According to the results of one RCT [8], in outpatients with recently diagnosed mild or moderate Covid-19, bamlanivimab does not increase number of patients with serious adverse events (high certainty of evidence); RR 0.15 (0.01 to 3.78), absolute effect (95% CI) 6 fewer per 1.000 (from 7 fewer to 19 more).

Hospitalised patients: According to the results of one RCT [11], bamlanivimab does not reduce 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 four registered ongoing RCTs (three in ambulatory mild to moderate patients, and one in hospitalised patients), and one nRCT (in ambulatory mild to moderate patients), evaluating 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 4-4).

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 interim results from one RCT, in **outpatients** with recently diagnosed mild or moderate Covid-19, bamlanivimab 2800-mg dose treatment significantly reduced SARS-COV2 viral load. Bamlanivimab reduced Covid-19–related hospitalisation or visit to an emergency department with the most pronounced effects observed in high-risk cohorts and lowered symptom burden from day to day 6 (but most participants in both groups had fully recovered or had only mild symptoms by day 11). No deaths occurred during the trial. Bamlanivimab does not increase number of patients with adverse events or number of serious adverse events.

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

Further RCTs examining bamlanivimab 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 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.

Table 4-1 Summary of findings (SoF) table for published RCTs related to effectiveness and safety of bamlanivimab - Outpatients

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of evidence	Comments
	Risk with Placebo	Risk with Bamlanivimab (previously neutralizing antibody LY-CoV555)				
All-cause mortality	No deaths occured	No deaths occured	No deaths occured	452 (1 RCT) [a]	⊕⊕⊕⊕ HIGH	No deaths occurred
Number of patients with adverse events	245 per 1000	223 per 1000	**RR 0.91** (0.64 to 1.30)	452 (1 RCT) [a]	⊕⊕⊕⊕ HIGH	**Absolute effect (95% CI) 22 fewer per 1.000** (from 88 fewer to 73 more)
Number of patients with serious adverse events	70 per 1000	10.5 per 1000	**RR 0.15** (0.01 to 3.78)	452 (1 RCT) [a]	⊕⊕⊕⊕ HIGH	**Absolute effect (95% CI) 6 fewer per 1.000** (from 7 fewer to 19 more)

Source: [9]
[a] [8]
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 – Hospitalised patients

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of evidence	Comments
	Risk with Placebo	Risk with Bamlanivimab (previously neutralizing antibody LY-CoV555)				
All-cause mortality	32 per 1000	53 per 1000	**RR 1.67** (0.57 to 4.88)	326 (1 RCT) [a]	⊕⊕⊕⊕ HIGH	**Absolute effect (95% CI) 21 more per 1.000** (from 14 fewer to 124 more)
Number of patients with adverse events	172 per 1000	219 per 1000	**RR 1.27** (0.82 to 1.99)	326 (1 RCT) [a]	⊕⊕⊕⊕ HIGH	**Absolute effect (95% CI) 46 more per 1.000** (from 31 fewer to 170 more)
Number of patients with	32 per 1000	30 per 1000	**RR 0.93** (0.27 to 3.15)	326 (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 (previously neutralizing antibody LY-CoV555)				
serious adverse events						**2 fewer per 1.000** (from 23 fewer to 68 more)
Number of patients discharged	866 per 1000	846 per 1000	**RR 0.98** (0.89 to 1.07)	326 (1 RCT) [a]	⊕⊕⊕⊕ HIGH	**Absolute effect (95% CI) 17 fewer per 1.000** (from 95 fewer to 61 more)

Source: [9]
[a] [11]
Abbreviations: CI=Confidence interval; RR=Risk ratio

Table 4-3 Study characteristics of included RCTs

Author, year, reference number/Study name/Study ID	Chen P et al. 2020 [8], BLAZE-1, NCT04427501, Interim analysis	Lundgren et al. 2020 [11] (ACTIV-3/TICO LY-CoV555 Study group), NCT04501978, preliminary results
Study design, study phase	RCT, phase 2	RCT, phase 3
Centres (single centre or multicentre), country, setting	Multicentre, US, Outpatients	Multicentre (US, Denmark and Singapore), Hospitalised
Patient population (number of included patients/ Mean age and sex/ Disease severity*)	Mixed (mild to moderate), 467 randomized (452 in the primary analysis); 45y vs 46y; female 55.3% vs 54.5%	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%
Inclusion criteria	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	Adult hospitalised patients who had documented SARS-CoV-2 infection and a duration of symptoms attributable to Covid-19 of 12 days or less

Author, year, reference number/Study name/Study ID	Chen P et al. 2020 [8], BLAZE-1, NCT04427501, Interim analysis	Lundgren et al. 2020 [11] (ACTIV-3/TICO LY-CoV555 Study group), NCT04501978, preliminary results
Study design, study phase	RCT, phase 2	RCT, phase 3
Centres (single centre or multicentre), country, setting	Multicentre, US, Outpatients	Multicentre (US, Denmark and Singapore), Hospitalised
Patient population (number of included patients/ Mean age and sex/ Disease severity*)	Mixed (mild to moderate), 467 randomized (452 in the primary analysis); 45y vs 46y; female 55.3% vs 54.5%	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%
	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.	
Exclusion criteria	9. SpO2 ≤ 93% on room air at sea level or PaO2/FiO2 < 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 dosing 19. received treatment with a SARS-CoV-2 specific monoclonal antibody 20. history of convalescent COVID-19 plasma treatment 21. participated in a previous SARS-CoV-2 vaccine study 22. 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. 23. concurrently enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study 24. pregnant or breast feeding 25. Are investigator site personnel directly affiliated with this study.	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.

Author, year, reference number/Study name/Study ID	Chen P et al. 2020 [8], BLAZE-1, NCT04427501, Interim analysis	Lundgren et al. 2020 [11] (ACTIV-3/TICO LY-CoV555 Study group), NCT04501978, preliminary results
Study design, study phase	RCT, phase 2	RCT, phase 3
Centres (single centre or multicentre), country, setting	Multicentre, US, Outpatients	Multicentre (US, Denmark and Singapore), Hospitalised
Patient population (number of included patients/ Mean age and sex/ Disease severity*)	Mixed (mild to moderate), 467 randomized (452 in the primary analysis); 45y vs 46y; female 55.3% vs 54.5%	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%
Intervention (generic drug name and dosage, time frame; number of randomized/ enrolled patients in subgroups - Mild, Moderate, Severe, Critical COVID-19)	Single intravenous infusion of neutralizing antibody LY-CoV555 in one of three doses (700 mg, 2800 mg, or 7000 mg) n=309 Mild 232 (75.1%) Moderate 77 (24.9%)	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)
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)	Placebo n=143 Mild 113 (79.9%) Moderate 30 (21.0%)	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)

Author, year, reference number/Study name/Study ID	Chen P et al. 2020 [8], BLAZE-1, NCT04427501, Interim analysis	Lundgren et al. 2020 [11] (ACTIV-3/TICO LY-CoV555 Study group), NCT04501978, preliminary results
Study design, study phase	RCT, phase 2	RCT, phase 3
Centres (single centre or multicentre), country, setting	Multicentre, US, Outpatients	Multicentre (US, Denmark and Singapore), Hospitalised
Patient population (number of included patients/ Mean age and sex/ Disease severity*)	Mixed (mild to moderate), 467 randomized (452 in the primary analysis); 45y vs 46y; female 55.3% vs 54.5%	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%
Primary Outcome(s)	Change from baseline in the viral load at day 11	Sustained recovery during a 90-day period
Patient-relevant secondary outcome(s)	Safety assessments, symptom burden as reported by the patient on a questionnaire, and clinical outcomes. The major clinical outcome was defined as Covid-19–related in-patient hospitalization, a visit to the emergency department, or death. No deaths were reported, and since most emergency department visits resulted in hospital admissions, we refer to a composite of emergency department visits and in-patient hospitalizations simply as hospitalizations (this report includes an analysis of the primary outcome as well as safety and adverse-event data, information regarding symptoms, and clinical outcomes).	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.
Follow-up (days, months)	Up to day 29	Up to 90-day period, the median follow-up 31 days
Sponsor/ lead institution	Eli Lilly	Operation Warp Speed and others

Table 4-4 Ongoing trials of single agent bamlanivimab (LY-CoV555) or in combination with etesevimab (LY-CoV016)

Trial Identifier/registry ID(s)/contact	**NCT04427501, BLAZE-1**	**NCT04634409, BLAZE-4**	**NCT04501978-ACTIV 3 EudraCT 2020-003278-37**	**NCT04518410-ACTIV-2**	**NCT04701658 (BLAZE-5)**
Study design, study phase	RCT, phase 2	RCT, phase 2	RCT, phase 3	RCT, phase 2/3	nRCT
Recruitment status	Recruiting	Recruiting	Active, not recruiting	Recruiting	Not yet recruiting
Number of Patients, Disease severity*	1200, Mixed (Mild and Moderate)	500, Mixed (Mild and Moderate)	10000, hospitalised mixed	2000, Mixed (Mild and Moderate)	3000, Mixed (Mild and Moderate)
Setting (hospital, ambulatory...)	Ambulatory	Ambulatory	Hospitalised	Ambulatory	Ambulatory
Intervention (generic drug name and dosage)	Bamlanivimab alone (LY-CoV555) Bamlanivimab plus LY-CoV016	Bamlanivimab alone (LY-CoV555) Bamlanivimab plus LY-CoV016	Bamlanivimab alone (LY-CoV555) Remdesivir alone	Bamlanivimab (LY-CoV555)	Bamlanivimab (LY-CoV555)
Comparator (standard care or generic drug name and dosage)	Placebo	Placebo	Placebo + Standard of care	Placebo	Standard of care
Primary Outcome(s)	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	Percentage of Participants with SARS-CoV-2 Viral Load Greater than 5.27 [Time Frame: Day 7]		Duration of COVID-19 symptoms (Phase 2) [Time Frame: Up 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)	Percentage of Participants who Experience COVID-19 Related Hospitalisation or Death [Time Frame: Baseline through Day 29]
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), Denmark, Singapore, Spain, United States	National Institute of Allergy and Infectious Diseases (NIAID), Eli Lilly and Company, Puerto Rico, United States	Eli Lilly and Company

5 REFERENCES

1. Higgins JPT TJ, Chandler J, Cumpston M, Li T, Page MJ,, (editors) WV. Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019). Cochrane, 2019.

2. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986;7(3):177-88.

3. Balshem H, Helfand M, Schünemann HJ, Oxman AD, Kunz R, Brozek J, et al. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol. 2011;64(4):401-6.

4. Marovich M, Mascola JR, Cohen MS. Monoclonal Antibodies for Prevention and Treatment of COVID-19. Jama. 2020;324(2):131-2.

5. AIHTA. Policy Brief Nr.: 002_V8 2020: Covid-19, HSS/ Horizon Scanning, Living Document November 2020, Part 1. . 2020.

6. (FDA). Fact Sheet for Health Care Providers: Emergency Use Authorization (EUA) of Bamlanivimab (fda.gov) 2020 [cited 2020 08-12-2020]. Available from: https://www.fda.gov/media/143603/download.

7. (NIH). COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines 2020 [15/01/2021]. Available from: https://www.covid19treatmentguidelines.nih.gov/.

8. Chen P, Nirula A, Heller B, Gottlieb RL, Boscia J, Morris J, et al. SARS-CoV-2 Neutralizing Antibody LY-CoV555 in Outpatients with Covid-19. New England Journal of Medicine. 2020.

9. Cruciani F DCF, Vecchi S., Saulle R., Mitrova Z., Amato L., Davoli M. . GRADE Table. LY-CoV555 antibody vs Placebo Treatment for COVID-19. . 2020.

10. (NIH). Statement—NIH-Sponsored ACTIV-3 Trial Closes LY-CoV555 Sub-Study 2020 [11/12/2020]. Available from: https://www.niaid.nih.gov/news-events/statement-nih-sponsored-activ-3-trial-closes-ly-cov555-sub-study.

11. Lundgren JD, Grund B, Barkauskas CE, Holland TL, Gottlieb RL, Sandkovsky U, et al. A Neutralizing Monoclonal Antibody for Hospitalized Patients with Covid-19. N Engl J Med. 2020.

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 6-2). 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

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 [1]) OR (controlled clinical trial [1])) 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])	30/12/2020

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"	30/12/2020
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 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"	30/12/2020

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. We receive studies that EPPI Centre has screened after searching weekly in Medline and Embase. We supplement these studies with a weekly search in Scopus. The retrieved hits were imported into an Endnote database and combined with generic names of the 20 included COVID-19 drugs.

Table 6-2 Search strategy to identify observational studies

Database	URL	Search terms / Search modality	Date of search
OVID Medline	Imported from EPPI Centre	1 exp Coronavirus/ 2 exp Coronavirus Infections/ 3 (coronavirus* or corona virus* or OC43 or NL63 or 229E or HKU1 or HCoV* or ncov* or covid* or sars-cov* or sarscov* or Sars-coronavirus* or Severe Acute Respiratory Syndrome Coronavirus*).mp. 4 (or/1-3) and ((20191* or 202*).dp. or 20190101:20301231.(ep).) 5 4 not (SARS or SARS-CoV or MERS or MERS-CoV or Middle East respiratory syndrome or camel* or dromedar* or equine or coronary or coronal or covidence* or covidien or influenza virus or HIV or bovine or calves or TGEV or feline or porcine or BCoV or PED or PEDV or PDCoV or FIPV or FCoV or SADS-CoV or canine or CCov or zoonotic or avian influenza or H1N1 or H5N1 or H5N6 or IBV or murine corona*).mp. 6 ((pneumonia or covid* or coronavirus* or corona virus* or ncov* or 2019-ncov or sars*).mp. or exp pneumonia/) and Wuhan.mp. 7 (2019-ncov or ncov19 or ncov-19 or 2019-novel CoV or sars-cov2 or sars-cov-2 or sarscov2 or sarscov-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 on nCoV or covid or coronavirus* or corona virus or Pandemi*2)) or ((covid or covid19 or covid-19) and pandemic*2) or (coronavirus* and pneumonia)).mp. 8 COVID-19.rx,px,ox. or severe acute respiratory syndrome coronavirus 2.os. 9 ("32240632" or "32236488" or "32268021" or "32267941" or "32169616" or "32267649" or "32267499" or "32267344" or "32248853" or "32246156" or "32243118" or "32240583" or "32237674" or "32234725" or "32173381" or "32227595" or "32185863" or "32221979" or "32213260" or "32205350" or "32202721" or "32197097" or "32196032" or "32188729" or "32176889" or "32088947" or "32277065" or "32273472" or "32273444" or "32145185" or "31917786" or "32267384" or "32265186" or "32253187" or "32265567" or "32231286" or "32105468" or "32179788" or "32152361" or "32152148" or "32140676" or "32053580" or "32029604" or "32127714" or "32047315" or "32020111" or "32267950" or "32249952" or "32172715").ui. 10 or/6-9 11 5 or 10	1/12/2020 until 04/01/2021 And from 1/09/2020 until 04/01/2021 for the new compounds Vitamin D, Aspirin and Mavrilimumab
OVID EMBASE		1 exp Coronavirus Infections/ 2 exp coronavirinae/ 3 (coronavirus* or corona virus* or OC43 or NL63 or 229E or HKU1 or HCoV* or ncov* or covid* or sars-cov* or sarscov* or Sars-coronavirus* or Severe Acute Respiratory Syndrome Coronavirus*).mp. 4 or/1-3 5 4 not (SARS or SARS-CoV or MERS or MERS-CoV or Middle East respiratory syndrome or camel* or dromedar* or equine or coronary or coronal or covidence* or covidien or influenza virus or HIV or bovine or calves or TGEV or feline or porcine or BCoV or PED or PEDV or PDCoV or FIPV or FCoV or SADS-CoV or canine or CCov or zoonotic or avian influenza or H1N1 or H5N1 or H5N6 or IBV or murine corona*).mp.	1/12/2020 until 04/01/2021 And from 1/09/2020 until 04/01/2021 for the new compounds Vitamin D, Aspirin and Mavrilimumab

		6 ((pneumonia or covid* or coronavirus* or corona virus* or ncov* or 2019-ncov or sars*).mp. or exp pneumonia/) and Wuhan.mp. 7 (2019-ncov or ncov19 or ncov-19 or 2019-novel CoV or sars-cov2 or sars-cov-2 or sarscov2 or sarscov-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 on nCoV or covid or coronavirus* or corona virus or Pandemi*2)) or ((covid or covid19 or covid-19) and pandemic*2) or (coronavirus* and pneumonia)).mp. 8 6 or 7 9 5 or 8	
Scopus		TITLE-ABS-KEY(((pneumonia OR covid* OR coronavirus* OR "corona virus*" OR ncov* OR 2019-ncov OR sars*) AND Wuhan) OR 2019-ncov OR ncov19 OR ncov-19 OR "2019-novel CoV" OR sars-cov2 OR sars-cov-2 OR sarscov2 OR sarscov-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) W/1 (CoV OR nCoV OR covid OR coronavirus* OR "corona virus*" OR pandemi*)) OR ((covid OR covid19 OR covid-19) AND pandemic*) OR ((coronavirus* OR "corona virus*") AND pneumonia)) AND ORIG-LOAD-DATE > 20200920[date changes from week to week] AND ORIG-LOAD-DATE < 20200928 [date changes from week to week] AND NOT INDEX(medline)	1/12/2020 until 04/01/2021 And from 1/09/2020 until 04/01/2021 for the new compounds Vitamin D, Aspirin and Mavrilimumab

6.3 Search strategy to identify ongoing studies

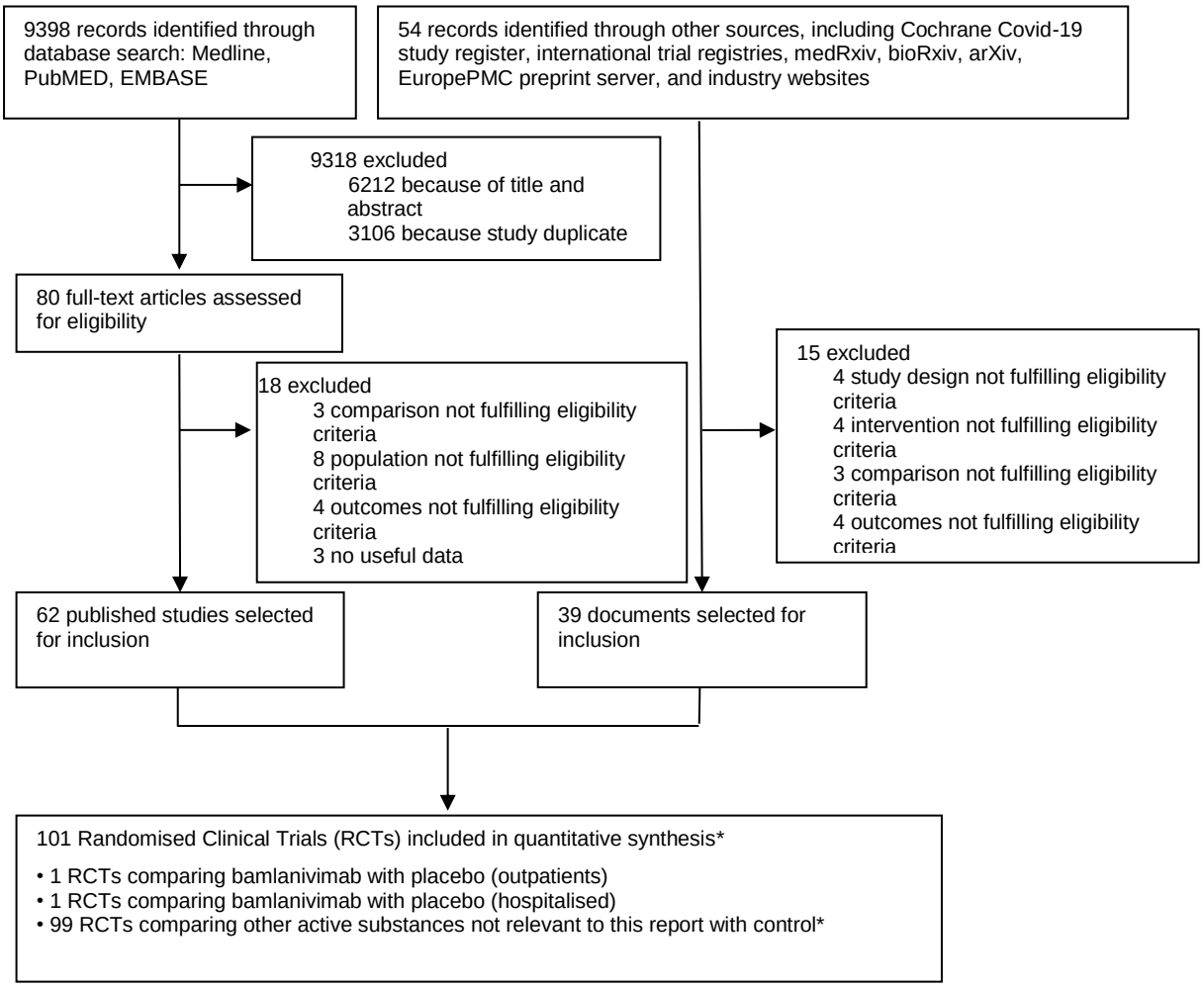
AIHTA is responsible for searching in trial registries to identify ongoing and unpublished studies. The combination of search terms related to COVID-19 and bamlanivimab are described in Appendix Table 6-3.

Table 6-3 Search strategy to identify ongoing studies

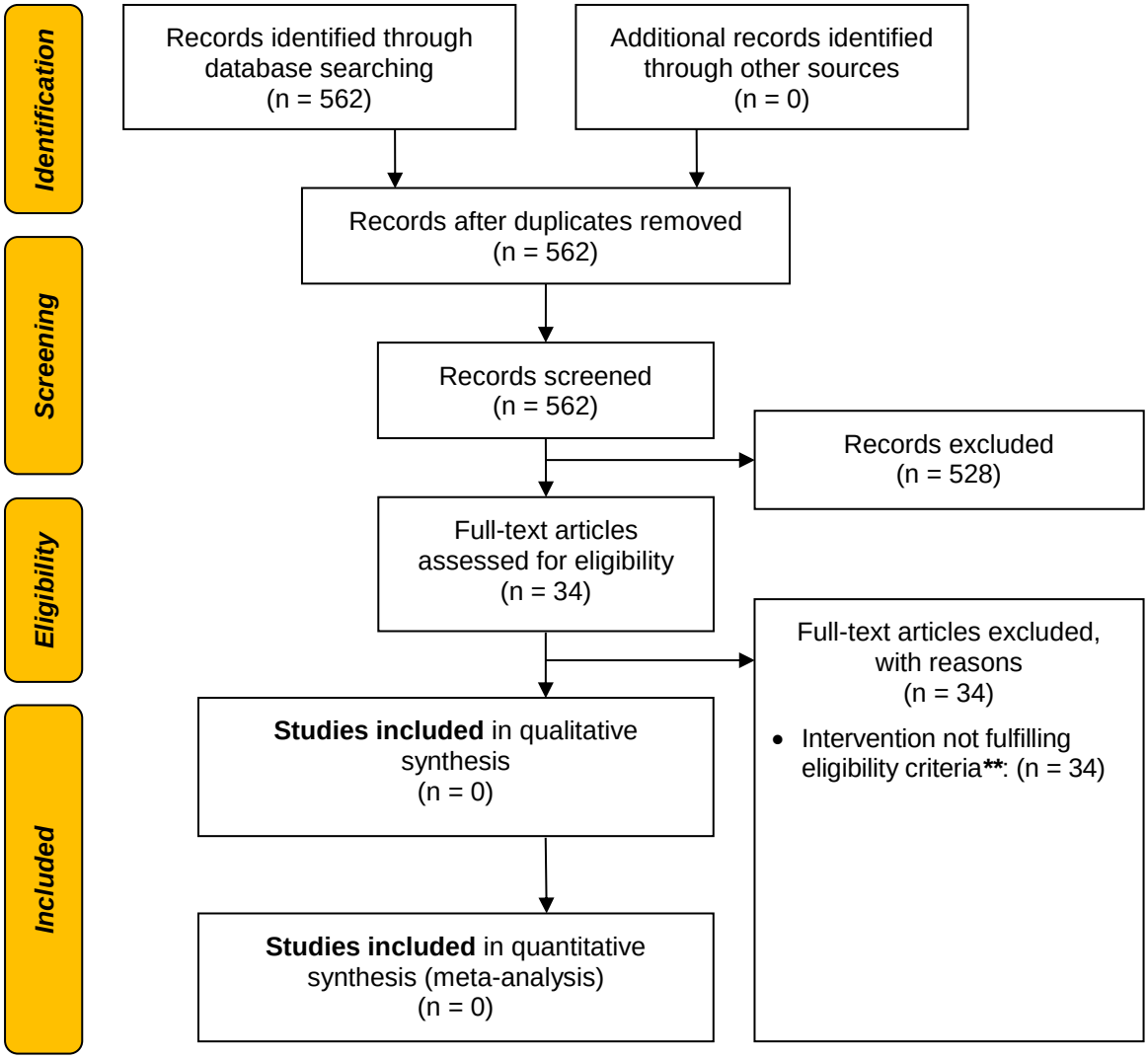
Database	URL	Search line / search terms	Date of search	Hits retrieved
ClinicalTrials.gov	https://clinicaltrials.gov/	"Basic search mode*" Terms used at Condition or disease: • covid-19 Terms used at "other terms": • LY3819253 • LY-CoV555	08/12/2020	5 1 new
ISRCTN	https://www.isrctn.com/	Basic search mode Search terms: 1. covid-19 and bamlanivimab 2. covid-19 and LY-CoV555 3. covid-19 and LY3819253 4. SARS-CoV-2 and bamlanivimab 5. SARS-CoV-2 and SARS-CoV-2 6. SARS-CoV-2 and LY3819253	08/12/2020	0
European Clinical Trials Registry	https://www.clinicaltrialsregister.eu/	Basic search mode Search terms: 1. covid-19 and bamlanivimab 2. covid-19 and LY-CoV555 3. covid-19 and LY3819253 4. SARS-CoV-2 and bamlanivimab 5. SARS-CoV-2 and LY-CoV555 6. SARS-CoV-2 and LY3819253	08/12/2020	1 0 new

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

6.4 Flow diagrams



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