HTA Austria
Austrian Institute for
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Kombinationstherapie mit Casirivimab plus Imdevimab (REGN-COV2) bei Covid-19

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Endbericht

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Kombinationstherapie mit Casirivimab plus Imdevimab (REGN-COV2) bei Covid-19

Wien, Mai 2021

This decision support document is based on the EUnetHTA PTRCR19 report 'CASIRIVIMAB AND IMDEVIMAB (REGN-COV2) FOR THE TREATMENT OF COVID-19, adding only a German summary.

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Inhalt

Zusammenfassung der klinischen Wirksamkeit und Sicherheit von Regn-Cov2

Evidenz zu Kombinationstherapie mit Casirivimab plus Imdevimab (REGN-COV2)

Die klinische Evidenz zur Kombinationstherapie mit Casirivimab plus Imdevimab (REGN-COV2) besteht aus einem veröffentlichten RCT mit adaptivem Studiendesign (Teil der Patient*innenpopulation aus Phase 1/ 2) mit vorläufigen Ergebnissen von 275 Patient*innen mit leichter bis mittelschwerer SARS-CoV2-Erkrankung sowie aus dem unveröffentlichten Phase 3 Teil desselben RCT bei 4.567 nicht-hospitalisierten Hochrisiko-Erwachsenen mit leichter bis bis mittelschwerer SARS-CoV2-Erkrankung.

Klinische Wirksamkeit

1 publizierter RCT – Phase 1/2 (Zwischenergebnisse) zu 275 Pts. + unveröffentlichte Daten zu RCT Phase 3 zu 4.567 Pts. leichte/ mittelschwere Erkrankung

In den Zwischenergebnissen des RCTs (Evidenz mit geringer Aussagesicherheit) zur Kombination von Casirivimab und Imdevimab (REGN-COV2) bei 275 nicht-hospitalisierten COVID-19 Patient*innen mit leichter bis mittelschwerer Erkrankung werden keine Todesfälle berichtet wohingegen die Behandlung mit REGN-COV2 sowohl die Viruslast (MD -0,41, 95% CI -0,71 bis -0,10) als auch die Anzahl der Arztbesuche reduzieren konnte (RR 0,51, 95% KI 0,17 bis 1,54). Basierend auf den unveröffentlichten Endergebnissen des Phase 3 Teils desselben RCTs, der mit 4.567 Patient*innen durchgeführt wurde, reduzierte die Kombination aus Casirivimab und Imdevimab (REGN-COV2) das Risiko einer Hospitalisierung oder eines Todes signifikant um 70% (1200 mg intravenös) und 71% (2400 mg intravenös) im Vergleich zu Placebo (RR 0,30, 95% KI 0,13 bis 0,68 für 1200 mg vs. Placebo und RR 0,29, 95% KI 0,17 bis 0,48 für 2400 mg; nach eigenen Berechnungen, unter Verwendung der in der Pressemitteilung präsentierten Rohdaten). REGN-COV2 erreichte alle sekundären Endpunkte, einschließlich der Reduktion der Symptomdauer.

Reduktion der Hospitalisierungen, Arztbesuche

Phase 2 Studie zu unterschiedlichen Dosierungen Reduktion der Viruslast unabhängig von Dosis

Eine begleitende Phase-2 Studie zeigte, dass selbst die niedrigsten getesteten Dosierungen (iv: 300 mg; subkutan: 600 mg) eine signifikante Reduktion der Viruslast über die ersten 7 Studientage aufwiesen, vergleichbar mit den iv Dosen von 2400 mg und 1200 mg, wenngleich diese Ergebnisse ohne weitere numerische Beschreibungen der Effektschätzer und ohne GRADE-Bewertungen schwer zu interpretieren sind.

Sicherheit

keine Aussagen zu Zunahme von AE und/oder SAEs möglich

Hinweis, dass günstiges Sichrheitsprofil

Die Zwischenergebnisse des RCT (Evidenz mit geringer Aussagesicherheit) zur Kombination von Casirivimab und Imdevimab (REGN-COV2) bei 275 nicht-hospitalisierten COVID-19-Patient*innen mit leichter bis mittelschwerer Erkrankung lassen keine Aussage zu, ob REGN-COV2 im Vergleich zu Placebo zu einer Zunahme von unerwünschten Ereignissen (AE) und/oder schweren unerwünschten Ereignissen (SAEs) führt. Das Gleiche gilt für REGN-COV2 in anderen Dosierungen. Auch in den unveröffentlichten Endergebnissen aus dem Phase 3 Teil desselben RCT wurden keine neuen Sicherheitssignale identifiziert. Schwerwiegende unerwünschte Ereignisse standen größtenteils im Zusammenhang mit COVID-19 und traten bei 1,1 % der Patient*innen in der 1200mg Gruppe, bei 1,3 % in der 2400mg Gruppe und bei 4,0 % in der Placebogruppe auf. Es gab 1 Todesfall in der 1200mg Gruppe, 1 Todesfall in der 2400mg Gruppe und 5 Todesfälle in den Placebogruppen (RR

0,31, 95% KI 0,20 bis 0,46 für den Endpunkt SAE und RR 0,28, 95%-KI 0,05 bis 1,42 für den Endpunkt Tod; nach eigenen Berechnungen, die die kombinierten Gruppen von 1200 mg und 2400 mg versus Placebo analysierten). Die berichteten Sicherheitsdaten deuten darauf hin, dass REGN-COV2 ein günstiges Sicherheitsprofil aufweist. Alle unveröffentlichten Ergebnisse müssen jedoch mit Vorsicht interpretiert werden, bis begutachtete Berichte verfügbar sind.

Schlussfolgerung

geringe Evidenz: wenig Informationen

Derzeit (Mai 2021) konnte nur eine wissenschaftliche Publikation identifiziert werden, die sich auf die Zwischenergebnisse des Phase 1/2-Teils eines RCT mit adaptivem Studiendesign zur Kombination von Casirivimab und Imdevimab (REGN-COV2) bei 275 nicht-hospitalisierten Patient*innen mit leichter bis mittelschwerer SARS-CoV2-Erkrankung bezieht. Zusätzlich liegen unveröffentlichte Ergebnisse aus dem Phase 3 Teil desselben RCT, mit 4.567 Patient*innen vor. Beide Studien deuten darauf hin, dass REGN-COV2 Folgebehandlungen reduzieren kann, was vor allem für Patient*innen, die ein hohes Risiko für ein Fortschreiten der Erkrankung haben, von Relevanz ist, und dass REGN-COV2 ein günstiges Sicherheitsprofil aufweist.

Hinweise auf Reduktion von Folgebehandlungen (insb. bei Hochrisiko-Pts von Relevanz) und gutes Sicherheitsprofil

Vorsicht bei unveröffentlichten Daten; keine abschließende Beurteilung möglich

Die unveröffentlichten Ergebnisse müssen jedoch mit Vorsicht interpretiert werden, bis eine begutachtete Publikation verfügbar ist. Eine abschließende Beurteilung ist auf Basis der derzeitigen Datenlage nicht möglich.

keine Zulassung von EMA bislang

In der EU gibt es bislang noch keine zugelassenen Medikamente für Patient*innen mit leichter bis mittelschwerer SARS-CoV2-Erkrankung im Frühstadium der Erkrankung. Am 26. Februar 2021 teilte die European Medicines Agency (EMA) mit, dass der CHMP seine Prüfung abgeschlossen hat und kam zu dem Schluss, dass die Kombinationstherapie REGN-COV2 zur Behandlung von Patient*innen mit bestätigter SARS-CoV2-Erkrankung, die keinen zusätzlichen Sauerstoff benötigen und bei denen ein hohes Risiko für das Fortschreiten zu schwerem Erkrankung besteht, eingesetzt werden kann.

EUnetHTA Joint Action 3 WP4

Rapid Collaborative Review

CASIRIVIMAB AND IMDEVIMAB (REGN-COV2) FOR THE TREATMENT OF COVID-19

Project ID: PTRCR19

Version 1.0, 20 May 2021
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Disclaimer

The content of this Rapid Collaborative Review Report represents a consolidated view based on the consensus within the Authoring Team; it cannot be considered to reflect the views of the European Network for Health Technology Assessment (EUnetHTA), EUnetHTA's participating institutions, the European Commission and/or the Consumers, Health, Agriculture and Food Executive Agency or any other body of the European Union. The European Commission and the Agency do not accept any responsibility for use that may be made of the information it contains.

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

Assessment team

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For further information on the work distribution and further contributors, please see Table A7 in Appendix 5.

Conflict of interest

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

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[1] https://www.ema.europa.eu/en/documents/referral/regn-cov2-antibody-combination-casirivimab/imdevimab-covid19-article-53-procedure-conditions-use-conditions-distribution-patients-targeted_en.pdf

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LIST OF ABBREVIATIONS

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

1 INTRODUCTION

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

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

1.1 Overview of the disease: COVID-19

A novel coronavirus, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), was first identified in December of 2019 in Wuhan, China as causing a respiratory illness designated as Coronavirus disease 2019, or COVID-19. On 30 January 2020, the International Health Regulations Emergency Committee of the WHO declared the COVID-19 outbreak a public health emergency of international concern. Since then, there has been rapid spread of the virus, leading to a global pandemic of COVID-19. As of May 6, 2021, more than 153 million cases of COVID-19—caused by SARS-CoV-2 infection—have been reported globally, including more than 3,2 million deaths. According to current evidence, SARS-CoV-2 is primarily transmitted between people through respiratory droplets and contact routes. Human-to-human transmission is occurring extensively. Precautions to prevent human-to-human transmission are appropriate for both suspected and confirmed cases. The estimated incubation period for COVID-19 is up to 14 days from the time of exposure, with a median incubation period of 4 to 5 days. Individuals of all ages are at risk for infection and severe disease. The probability of serious COVID-19 disease is higher in people aged ≥60 years, those living in a nursing home or long-term care facility, and those with chronic medical conditions [1, 2]. FDA defines groups of individuals (adults and paediatric patients age 12-17 years and weighing at least 40 kg) having high risk for progression to severe COVID-19 and/or hospitalisation as patients who meet at least one of the following criteria: older age (for example age ≥65 years of age); obesity or being overweight (for example, adults with BMI >25 kg/m2, or if age 12-17, have BMI ≥85th percentile for their age and gender based on CDC growth charts; pregnancy; chronic kidney disease; diabetes; immunosuppressive disease or immunosuppressive treatment; cardiovascular disease (including congenital heart disease) or hypertension; chronic lung diseases (for example, chronic obstructive pulmonary disease, asthma [moderate-to-severe], interstitial lung disease, cystic fibrosis and pulmonary hypertension); sickle cell disease; neurodevelopmental disorders (for example, cerebral palsy) or other conditions that confer medical complexity (for example, genetic or metabolic syndromes and severe congenital anomalies); having a medical-related technological dependence (for example, tracheostomy, gastrostomy, or positive pressure ventilation (not related to COVID-19)). Other medical conditions or factors (for example, race or ethnicity) may also place individual patients at high risk for progression to severe COVID-19 and authorization of REGN-COV2 under the EUA is not limited to the medical conditions or factors listed above. As defined by EMA, risk factors may include but are not limited to: advanced age; obesity; cardiovascular disease, including hypertension; chronic lung disease, including asthma; type 1 or type 2 diabetes mellitus; chronic kidney disease, including those on dialysis; chronic liver disease; immunosuppressed, based on prescriber's assessment [3-6].

1.2 SARS-CoV-2 Variants of Concern

Since December 2020, several SARS-CoV-2 variants of concern have been identified. The B.1.1.7 variant first seen in the United Kingdom is more infectious than earlier variants and may be more virulent. It has become the predominant variant in the United Kingdom, and it continues to spread across the globe, including throughout many regions of the United States. The B.1.351 variant that was originally identified in South Africa is now the predominant variant in that region and has spread to many other countries, including the United States. The P.1 variant was originally identified in Manaus, Brazil, and

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

has now been identified in the United States. Other variants that have emerged in the United States are receiving attention, such as the B.1.427/B.1.429 variants that are circulating throughout California and the B.1.526 variant reported in New York. The data on the emergence, spread, and clinical relevance of these new variants is rapidly evolving; this is especially true for research on how variants might affect transmission rates, disease progression, vaccine development, and the efficacy of current therapeutics [1]. Currently in EU, variants of concern are **B.1.1.7, B.1.351** and **P.1.**

First reported in India in December 2020, SARS-CoV-2 lineages **B.1.617.1**, **B.1.617.2** and **B.1.617.3** have been increasingly detected in other countries. In the EU/EEA there are indications that the frequency of detection of both lineages B.1.617.1 and B.1.617.2 is increasing. Currently described lineages B.1.617.1, B.1.617.2 and B.1.617.3 have distinct mutation profiles and warrant individual assessment. Given the still very limited available data with respect to their transmissibility, disease severity and immune escape potential relative to other co-circulating SARS-CoV-2 variants in the EU/EEA, the full impact of these lineages on public health is not yet possible to assess. At this time, ECDC maintains its assessment of B.1.617.1, B.1.617.2 and B.1.617.3 as **variants of interest** and will continue to actively monitor the situation [7].

European Centre for Disease Prevention and Control (ECDC) data

As of May 14, in the EU/EEA 30 983 201 cases and 692 446 deaths have been reported [8].

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

Regarding hospitalisation and ICU, pooled data from 25 countries for week 18 show that there were 8.1 patients per 100 000 population in hospital due to COVID-19. According to weekly hospital admissions data pooled from 20 countries, new admissions were 7.2 per 100 000 population. Pooled data from 19 countries for week 18 show that there were 1.8 patients per 100 000 population in ICU due to COVID-19. Pooled weekly ICU admissions based on data from 14 countries show that there were 2.0 new admissions per 100 000 population [9].

Regarding variants of concern, among the 14 countries with the recommended level of 10% or 500 sequences reported per week in the period from 19 April to 2 May 2021, 12 had a valid denominator. The median (range) of the variants of concern (VOC) reported in all samples sequenced in the period in these 12 countries was 92.4% (80.7–98.2%) for B.1.1.7, 0.7% (0.0–8.9%) for B.1.351, 0.1% (0.0–6.7%) for P.1 and 0.0% (0.0–0.6%) for B.1.1.7+E484K. The median (range) of the variants of interest (VOI) reported in all samples sequenced in the period in these 12 countries was 0.0% (0.0–2.5%) for B.1.617, 0.0% (0.0–2.2%) for B.1.525, 0.0% (0.0–0.1%) for B.1.620 and 0.0% (0.0–0.0%) for B.1.621 [9].

1.1.1. Clinical symptoms and disease severity

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

Table 1-1: COVID-19 severity of illness categories

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

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

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

The spectrum of illness can range from asymptomatic infection to severe pneumonia with acute respiratory distress syndrome and death. Around 70% of patients experienced fever, cough, or shortness of breath, 36% had muscle aches, and 34% reported headaches. Other reported symptoms have included, but are not limited to, diarrhea, dizziness, rhinorrhea, anosmia, dysgeusia, sore throat, abdominal pain, anorexia, and vomiting [1]. Patients admitted to hospital with COVID-19 typically report symptoms onset three to five days after exposure (fatigue, chills), progressing to fever and dry cough 48 hours later. Transition to severe disease with hypoxaemia can occur five to seven days into the symptomatic illness, about 8-14 days after original exposure. Recently, the 4C Mortality Score was developed and validated, categorising patients as being at low, intermediate, high, or very high risk of death, to directly inform clinical decision making, and can be used to stratify patients admitted to hospital with COVID-19 into different management groups [10].

The understanding of the mid- and long-term sequelae of COVID-19 is increasing. This new condition which has been described as post-COVID syndrome or long COVID still lacks a worldwide consensus on terminology and clinical definition. The post-intensive care syndrome (PICS) has been well described in other critically ill patients and it also seems to occurs in COVID-19 patients. Non-hospitalised patients (or those with mild and moderate COVID-19) and children are also reporting persisting clustering of symptoms and mid- and long-term sequalae [1, 11].

1.3 Current clinical management

Pharmacological treatment options for COVID-19 are limited while multiple trials are ongoing to assess the efficacy of available medicines to manage the disease. EUnetHTA Rolling Collaborative Reviews present the comparative data on effectiveness and safety of potential therapies for COVID-19, and are updated on a monthly basis [12]. Neutralizing monoclonal antibodies to SARS-CoV-2 have the potential to be used for both prevention and treatment of infection. They may help to guide vaccine design and development as well. The main target of SARS-CoV-2 neutralizing monoclonal antibodies is the surface spike glycoprotein that mediates viral entry into host cells [13]. Standard of care, can vary according to country and currently is guided by disease severity. According to WHO guideline [2], symptomatic treatment is recommended for management of mild COVID-19, such as antipyretics for fever and pain, adequate nutrition and appropriate rehydration. WHO recommends that antibiotic therapy or prophylaxis should not be used in patients with mild COVID-19. Patients with moderate COVID-19 disease may present to an emergency unit or primary care/outpatient department, or be encountered during community outreach activities, such as home visits or by telemedicine. WHO recommends for patients with suspected or confirmed moderate COVID-19, that antibiotics should not be prescribed unless there is clinical suspicion of a bacterial infection. Also, close monitoring of patients for signs or symptoms of disease progression is recommended. Further details on specific therapy can be found in Box A 1in Appendix 1. Summary of outpatient management recommended by US COVID-19 Treatment Guidelines (updated April 21, 2021), can be found below in Box 1, with further details in Box A 1 in Appendix 1 [1]:

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

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

Specific therapy for outpatients with mild to moderate COVID-19

The COVID-19 Treatment Guidelines Panel recommends using one of the following combination anti-SARS-CoV-2 monoclonal antibodies to treat outpatients with mild to moderate COVID-19 who are at high risk of clinical progression, as defined by the Emergency Use Authorization criteria (treatments are listed in alphabetical order): Bamlanivimab 700 mg plus etesevimab 1,400 mg **(AIIa)**; *or* Casirivimab 1,200 mg plus imdevimab 1,200 mg **(AIIa)**. The Panel recommends against the use of anti-SARS-CoV-2 monoclonal antibodies for patients who are hospitalised because of COVID-19, except in a clinical trial (**AIIa**). However, their use should be considered for persons with mild to moderate COVID-19 who are hospitalised for a reason other than COVID-19 but who otherwise meet the EUA criteria. There are currently no comparative data to determine whether there are differences in clinical efficacy or safety between casirivimab plus imdevimab and bamlanivimab.The Panel recommends against the use of chloroquine or hydroxychloroquine with or without azithromycin **(AI)**. The Panel recommends against the use of dexamethasone or other systemic glucocorticoids in outpatients in the absence of another indication **(AIII)**. The Panel recommends against the use of antibacterial therapy (e.g., azithromycin, doxycycline) in the absence of another indication **(AIII)**. Health care providers should provide information about ongoing clinical trials of investigational therapies to eligible outpatients with COVID.

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

1.4 Features of the intervention:

1.4.1 Mode of Action

Casirivimab and imdevimab (REGN-COV2) are a combination of two monoclonal antibodies (REGN10933 and REGN10987) which bind non-competitively to the critical receptor binding domain of the virus's spike protein, which diminishes the ability of mutant viruses to escape treatment and protects against spike variants that have arisen in the human population.

The U.S. Food and Drug Administration issued an emergency use authorization (EUA) for casirivimab and imdevimab (REGN-COV2) to be administered together for the treatment of mild to moderate COVID-19 in adults and paediatric patients (12 years of age or older weighing at least 40 kilograms [about 88 pounds]) with positive results of direct SARS-CoV-2 viral testing and who are at high risk for progressing to severe COVID-19 and/or hospitalisation.

On February 26, 2021 EMA stated that the CHMP has completed its review 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. Recommended indication is for the treatment of confirmed COVID-19 in patients aged 12 years and older that do not require supplemental oxygen for COVID-19 and who are at high risk of progressing to severe COVID-19.

Risk factors may include but are not limited to: advanced age; obesity; cardiovascular disease, including hypertension; chronic lung disease, including asthma; type 1 or type 2 diabetes mellitus; chronic kidney disease, including those on dialysis; chronic liver disease; or being immunosuppressed, based on prescriber's assessment.

The recommended dose is 1200 mg of casirivimab and 1200 mg of imdevimab administered as a single intravenous infusion. Casirivimab and imdevimab may only be administered in settings in which health care providers have immediate access to medications to treat a severe infusion reaction, such as anaphylaxis. Contraindication is hypersensitivity to casirivimab or imdevimab or to any of the excipients [3-5].

1.4.2 New SARS-CoV-2 Variants and REGN-COV2

On January 27, 2021, Regeneron Pharmaceuticals, Inc. announced that researchers in Columbia University lab and Regeneron scientists have independently confirmed that REGEN-COV™ (casirivimab and imdevimab antibody cocktail) successfully neutralizes the circulating SARS-CoV-2 variants first identified in the UK (B.1.1.7) and South Africa (B.1.351). The announcement was informed by findings from preclinical research [14, 15].

In the FDA new revision related to REGN-COV2 and new variants, published on March 2021, casirivimab and imdevimab individually and together retained neutralization activity against pseudovirus expressing all spike protein substitutions found in the B.1.1.7 lineage (UK origin) and against pseudovirus expressing only N501Y found in B.1.1.7 and other circulating lineages (Table 1-2).

Casivirimab and imdevimab together retained neutralization activity against pseudovirus expressing all spike protein substitutions, or individual substitutions K417N, E484K or N501Y, found in the B.1.1351 lineage (South Africa origin), and against K417T+E484K, found in the P.1 lineage (Brazil origin), although casirivimab alone, but not imdevimab, had reduced activity against pseudovirus expressing K417N or E484K, as indicated above. The E484K substitution is also found in the B.1.526 lineage (New York origin).

Casivirimab and imdevimab, individually and together, retained neutralization activity against the L452R substitution found in the B.1.427/B.1.429 lineages (California origin).

It is not known how pseudovirus data correlate with clinical outcomes [6].

Table 1-2: Pseudovirus neutralization data for SARS-CoV-2 variant substitutions with Casirivimab and Imdevimab together

Lineage with Spike Protein Substitution	Key substitutions tested	Fold reduction in susceptibility
B.1.1.7 (UK origin)	N501Y [a]	no change [c]
B.1.351 (South Africa origin)	K417N, E484K, N501Y [b]	no change [c]
P.1 (Brazil origin)	K417T + E484K	no change [c]
B.1.427/B.1.429 (California origin)	L452R	no change [c]
B.1.526 (New York origin) [d]	E484K	no change [c]

[a] Pseudovirus expressing the entire variant spike protein was tested. The following changes from wild-type spike protein are found in the variant: del69-70, del145, N501Y, A570D, D614G, P681H, T716I, S982A, D1118H. [b] Pseudovirus expressing the entire variant spike protein was tested. The following changes from wild-type spike protein are found in the variant: D80Y, D215Y, del241-243, K417N, E484K, N501Y, D614G, A701V. [c] No change: <2-fold reduction in susceptibility. [d] Not all isolates of the New York lineage harbor the E484K substitution (as of February 2021).
Source: [6]

2 OBJECTIVE AND SCOPE

The aim of this EUnetHTA Rapid Collaborative Review is to summarize the best publicly available scientific evidence on the clinical effectiveness and safety of REGN-COV2 in the target patient populations with relevant comparators and next, to support the local productions of national/regional HTA reports based on this review. The target patient populations and relevant comparators (based on the requirements of EUnetHTA Partners) are defined in the project scope in Table 2-1.

Table 2-1: Assessment scope: relevant PICO(s) identified for the rapid review

PICO	Assessment scope
Population	**Target population: patients with mild or moderate COVID-19 who are at high risk of progressing to severe COVID-19** [a] • *Mild Illness*: Individuals who have any of the various signs and symptoms of COVID 19 (e.g., fever, cough, sore throat, malaise, headache, muscle pain) without shortness of breath, dyspnoea, or abnormal chest imaging; • *Moderate Illness*: Individuals who have evidence of lower respiratory disease by clinical assessment or imaging and a saturation of oxygen (SpO_2) ≥94% on room air at sea level [1, 2]. **Disease** SARS-CoV-2 is a novel coronavirus causing a respiratory illness termed COVID-19. The full spectrum of COVID-19 ranges from mild, self-limiting respiratory tract illness to severe progressive pneumonia, multi-organ failure, and death. **ICD-Codes** [16] An emergency ICD-10 code of 'U07.1 COVID-19, virus identified' is assigned to a disease diagnosis of COVID-19 confirmed by laboratory testing. An emergency ICD-10 code of 'U07.2 COVID-19, virus not identified' is assigned to a clinical or epidemiological diagnosis of COVID-19 where laboratory confirmation is inconclusive or not available. Both U07.1 and U07.2 may be used for mortality coding as cause of death. See the International guidelines for certification and classification (coding) of COVID-19 as cause of death following the link below. In ICD-11, the code for the confirmed diagnosis of COVID-19 is RA01.0 and the code for the clinical diagnosis (suspected or probable) of COVID-19 is RA01.1. **MeSH-terms:** COVID-19; Coronavirus Disease 2019; 2019 novel coronavirus disease; COVID19; COVID-19 pandemic; SARS-CoV-2 infection; COVID-19 virus disease; 2019 novel coronavirus infection; 2019-nCoV infection; coronavirus disease 2019; coronavirus disease-19; 2019-nCoV disease; COVID-19 virus infection.
Intervention	Casirivimab and imdevimab (REGN-COV2): combination of neutralising monoclonal antibodies **More information:** for the treatment of confirmed COVID-19 in patients aged 12 years and older that do not require supplemental oxygen for COVID-19 and who are at high risk of progressing to severe COVID-19; The recommended dose is 1200 mg of casirivimab and 1200 mg of imdevimab administered as a single intravenous infusion [3, 5].
Comparison	Active pharmacological treatment (approved pharmaceuticals for COVID-19 or investigational pharmaceuticals) [b], or Standard of care/usual care. **Rationale**: at the time of the publication of this report, no agreement has been reached by the scientific community on standard treatment for mild/moderate COVID-19 or the relevance of the type of head-to-head comparisons
Outcomes	**Effectiveness** (short-term up to 1 month; long term up to 3-6 months) • All-cause mortality • Number of patients with ≥1 COVID-19 related medically attended visit (emergency room visits, urgent care visits, or telehealth/physician office visits) • Number of patients with COVID-19 related hospitalisation • Viral negative conversion (D7)

	• Clinical improvement defined as a hospital discharge or improvement on the scale used by trialists to evaluate clinical progression and recovery • WHO Clinical Progression Score level 7 or above (i.e., Mechanical ventilation +/- additional organ support (ECMO, vasopressors or dialysis) OR death • Number of patients admitted to an intensive care unit (ICU) • Number of patients requiring supplemental oxygen • Number of patients requiring mechanical ventilation • Length of hospital stay • Pulmonary function • Health-related Quality of life • Time to clinical improvement • Time to WHO Clinical Progression Score level 7 or above • Time to death • Time to viral negative conversion • Duration of mechanical ventilation • Duration of supplemental oxygen therapy • Time to ICU admission • Kinetic of viral load (D1, D7, D14, D30...) • Efficacy depending on SARS-CoV-2 variants • Resistance **Safety** (short-term up to 1 month; long term up to 3-6 months) • Number of patients with one or more Adverse events (AE); • Number of patients with one or more Serious adverse events (SAE); • Number of deaths attributable to SAE; • Number of withdrawals due to AEs; • Description of most frequent AEs; • Description of most frequent SAEs. If possible: subgroup analysis according to disease severity and according to risk factors for severe disease. **Rationale:** priority will be given on outcomes according to the Core Outcome Set for Clinical Trials on Coronavirus Disease 2019 [17] 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 [18].
Study design	Randomised controlled trials (RCTs)

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

3 METHODS

3.1 Data sources and searches

To avoid redundancies and duplication, this RCR reused data relevant to our PICO from two already published living systematic reviews/meta-analysis (SRs/MA) sources from international initiatives [19-22]. The data were included according to the methodology suggested by Whitlock 2008 [23] and Robinson 2014 [24] on how to integrate existing SRs into new SRs. As described by Robinson et al., four different approaches could be followed: 1) use the existing SR(s)' list of included studies as a quality check for our literature search and screening strategy (Scan References), 2) use the existing SR(s) to completely or partially provide the body of included studies for one or more research questions of our assessment ("Use Existing Search"), 3) use the data abstraction, risk of bias assessments, and/or analyses from existing SRs for one or more research questions of our assessment ("Use Data Abstraction/Syntheses") and 4) use the existing SR(s), including conclusions, to fully or partially answer one or more research questions of our REA ("Use Complete Review"). Approach number 3 was followed for this report.

Literature search was used from the EUnetHTA Rolling Collaborative Reviews, updated on May 3, 2021, to find possible RCTs related to REGN-COV2 treatment in non-hospitalised patients with COVID-19 [25, 26]. Details can be found in Table A1, Appendix 2. References were included or excluded according to the Population-Intervention-Control-Outcome (PICO)-scheme and presented according to the PRISMA Statement [27].

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

As stated above, quantitative syntheses (using pairwise meta-analyses) from existing living SRs/MA were presented in the Result section if available for outcomes of interest to this report [19-22]. According to published protocols of living SRs/MAs, pairwise meta-analysis was performed for primary and secondary outcomes using random-effects models to incorporate the anticipated clinical and methodological heterogeneity across [19-22]. Analyses related to two clinical outcomes (Time-weighted average change from baseline in viral load through day 7 and Percentage of patients with one or more medically attended visits through day 29) were performed by authors of this RCR.

3.2 Risk of bias

Risk of bias assessment related to 1 RCT (phase 1-2 portion) on REGN-COV2 was reused from one living SR/MA source [20]. Each study was presented with the Cochrane Risk of bias 2 (RoB 2) tool for randomized controlled trials [28]. The Cochrane RoB 2 tool is structured into 5 domains: 1) risk of bias arising from the randomization process, 2) risk of bias due to deviations from intended interventions, 3) risk of bias due to missing outcome data, 4) risk of bias in measurement of the outcome, 5) risk of bias in selection of the reported result. Within each domain, a series of 'signalling questions' elicit information relevant to risk of bias assessment. The response options to the signalling questions are: "Yes", "Probably yes", "Probably no", "No" and "No information". A risk of bias judgement arising from each domain is generated by an algorithm, based on answers to the signalling questions. The automated judgement can be overruled if indicated. Judgement can be "Low", "Some concerns" or "High" risk of bias. Overall risk of bias will be considered as "low risk of bias" if all domains are at low risk, "some concerns" if at least one domain is some concern and no domain is of high risk of bias, and "high risk of bias" if there is at least one domain at high risk, or several domains with some concerns.

3.3 Certainty of evidence

Certainty of evidence related to further clinical outcomes: "All-cause mortality", "Adverse events" and "Serious adverse events" was reused from two different sources: two already published living systematic reviews/meta-analysis (SRs/MA) sources from international initiatives [19-22]. Certainty of evidence related to two clinical outcomes ("Time-weighted average change from baseline in viral load through day 7" and "Percentage of patients with one or more medically attended visits through day 29") was performed by the authors of this RCR.

For rating the certainty of the evidence, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) is being presented [19-22, 29]. The GRADE approach specifies four levels of certainty: “High”, further research is very unlikely to change our confidence in the estimate of effect; “Moderate”, further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimates; “Low”, further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; “Very low”, we are very uncertain about the estimate.

3.4 Ongoing studies

The following clinical trial registries were searched for ongoing RCTs on REGN-COV2 in COVID-19 in May 2021: ClinicalTrials.gov[3], ISRCTN[4] and European Clinical Trials Registry[5].

3.5 Patient Involvement

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

[3] https://clinicaltrials.gov/

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

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

4 RESULTS

4.1 Information retrieval/Existing Evidence

As of May 3, 2021, only one scientific publication related to interim results of an RCT in outpatient setting was found [30]. A flow diagram depicting the selection process of RCTs can be found in Figure A1, Appendix 2.

Preliminary evidence from this ongoing RCT (NCT04425629) evaluating REGN-COV 2 in 275 non-hospitalised patients with COVID-19 was analysed. These preliminary results, published by Weinreich et al. 2021 [30] are related to phase 1-2 portion of ongoing double-blind, phase 1–3 adaptive RCT on non-hospitalised patients with COVID-19, randomly assigned (1:1:1) to receive placebo (n=93), 2.4 g of REGN-COV2 (n=92), or 8.0 g of REGN-COV2 (n=90) and were prospectively characterized at baseline for endogenous immune response against SARS-CoV-2 (serum antibody–positive or serum antibody–negative). The data cut-off for this interim analysis was September 4, 2020.

Key end points included the time-weighted average change in viral load from baseline (day 1) through day 7 (in patients in the modified full analysis set who were serum antibody–negative at baseline) and the percentage of patients with at least one Covid-19–related medically attended visit through day 29. Medically attended visits could include telemedicine visits, in-person physician visits, urgent care or emergency department visits, and hospitalisation. With respect to safety, the following was collected: adverse events that occurred or worsened during the observation period (grade 3 and 4; phase 1 only), serious adverse events that occurred or worsened during the observation period (phases 1 and 2), and adverse events (AE) of special interest (phases 1 and 2). AE of special interest were grade 2 or higher hypersensitivity or infusion-related reactions. Pharmacokinetic variables included the concentrations of casirivimab and imdevimab in serum over time.

Main characteristics of this ongoing RCT abstracted from the scientific publication can be found in Table A2, Appendix 3. More details of the original and latest version of the protocol (April 5, 2021), registered in ClinicalTrials.gov, is found in Table A5, Appendix 3.

As stated by authors of this scientific publication, a sample of 275 patients (72 in phase 1 and 203 in phase 2) was considered sufficient for the assessment of virologic efficacy, clinical trends, and safety for the purpose of informing subsequent analyses. The full analysis set included the first 275 patients with COVID-19 symptoms who underwent randomisation in the combined phase 1–2 portions of the trial. The modified full analysis set included patients who were confirmed SARS-CoV-2–positive by RT-PCR at baseline. The safety population included all patients who received REGN-COV2 or placebo [30].

4.2 Risk of bias/Quality of evidence

According to COVID-NMA, the overall **Risk of Bias** for this RCT is judged as “low” [20]. **Certainty of evidence** as assessed by DePlazio and authors resulted in the grade “low” for the outcomes: “All-cause mortality”, “Time-weighted average change from baseline in viral load through day 7” and “Percentage of patients with one or more medically attended visits through day 29” and as “very low” for the outcome “Adverse events” and “Serious adverse events” [19, 21, 22]. Details can be found in Table A3 and Table A4 in Appendix 3.

4.3 Results on clinical effectiveness and safety

4.3.1 Published results

Original publication by the trial authors

In this section we describe the published preliminary results of phase 1-2 RCT (NCT04425629) in mild to moderate COVID-19 patients (outpatient setting), as abstracted from the original publication.

In this interim analysis mentioned above [30], out of the 275 patients who underwent randomisation between June 16, 2020, and August 13, 2020, a total of 269 received REGN-COV2 or placebo.

Demographic characteristics, baseline virology and disease characteristics were similar between patients randomised to the REGN-COV2 treatment groups and the placebo group. The median age of the patients in the trial was 44.0 years (32% of patient were over 50 years, and 7% over 65 years), 49% were male, 13% identified as Black or African American, and 56% identified as Hispanic or Latino. Out of 275 patients, 115 (42%) had obesity (defined as a body-mass index of greater than 30). The median number of days of reported Covid-19–related symptoms before randomisation was 3.0. At randomisation, 30 of 275 patients (11%) tested negative for SARS-CoV-2 by qualitative RT-PCR and 17 of 275 (6%) tested positive for SARS-CoV-2 but did not have baseline viral load data; therefore, 228 of the 275 patients (83%) who underwent randomisation made up the modified full analysis set (i.e., those patients who were confirmed SARS-CoV-2–positive by RT-PCR at baseline). At baseline, 123 patients (45%) were serum antibody–positive, 113 (41%) were serum antibody–negative, and 39 (14%) had unknown antibody status.

Effectiveness

The REGN-COV2 antibody cocktail reduced viral load. In the modified full analysis set, the least-squares mean differences from placebo were −0.25 log10 copies per millilitre (95% CI, −0.60 to 0.10) in the low-dose REGN-COV2 group, −0.56 log10 copies per millilitre (95% CI, −0.91 to −0.21) in the high-dose REGN-COV2 group, and −0.41 log10 copies per millilitre (95% CI, −0.71 to −0.10) in the combined REGN-COV2 group (Table 4-1).

In the full analysis set, 6 of 93 patients (6%) in the placebo group and 6 of 182 patients (3%) in the combined REGN-COV2 group had a medically attended visit, a relative difference of approximately 49% (absolute difference vs. placebo, −3 percentage points; 95% CI, −16 to 9) (Table 4-1).

Table 4-1: Effectiveness outcomes: REGN-COV2 vs placebo

End Point	REGN-COV2 2.4 g	REGN-COV2 8 g	REGN-COV2 Combined	Placebo
Time-weighted average change in viral load from day 1 through day 7 (Modified full analysis set*)				
Number of patients	70	73	143	78
Least-squares mean change — log10 copies/ml	−1.60±0.14 (95% CI −1.87 to −1.32)	−1.90 ±0.14 (95% CI −2.18 to −1.62)	−1.74±0.11 (95% CI −1.95 to −1.53)	−1.34±0.13 (95% CI −1.60 to −1.08)
Difference vs. placebo at day 7 — log10 copies/ml / Least-squares mean	−0.25±0.18 (95% CI −0.60 to 0.10)	−0.56±0.18 (95% CI −0.91 to −0.21)	−0.41±0.15 (95% CI −0.71 to −0.10)	
At least one Covid-19–related, medically attended visit within 29 days (Full analysis set***)**				
Number of patients	92	90	182	93
Patients with ≥1 visit within 29 days — no. (%)	3 (3)	3 (3)	6 (3)	6 (6)
Difference vs. placebo — percentage points	-3 (95% CI −18 to 11)	-3 (95% CI −18 to 11)	-3 (95% CI −16 to 9)	

*Modified full analysis set: excluded patients who tested negative for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by qualitative reverse-transcriptase polymerase chain reaction at baseline: ** Confidence intervals for the difference (REGN-COV2 minus placebo) were based on the exact method and were not adjusted for multiplicity: *** Full analysis set: all patients who were randomised
Source: [30]

Safety

Among the 269 patients in the safety population (all patients who received REGN-COV2 or placebo), the percentages of patients with hypersensitivity reactions, infusion-related reactions, and other adverse events were similar in the combined REGN-COV2 dose groups and the placebo group.

An adverse event of special interest was reported in 2 of 93 patients (2%) in the placebo group and in 2 of 176 patients (1%) in the combined REGN-COV2 dose groups. No event led to death nor to withdrawal from the trial (Table 4-2) [30].

Table 4-2: Serious adverse events and Adverse events of special interest in the safety population

Event	REGN-COV2 2.4 g (n=88)	REGN-COV2 8.0 g (n=88)	REGN-COV2 Combined (n=176)	Placebo (n=93)
Any serious adverse event, n (%)	1 (1)	0	1 (1)	2 (2)
Any adverse event of special interest*, n (%)	0	2 (2)	2 (1)	2 (2)
Any serious adverse event of special interest*, n (%)	0	0	0	0
Grade ≥2 infusion-related reaction within 4 days, n (%)	0	2 (2)	2 (1)	1 (1)
Grade ≥2 hypersensitivity reaction within 29 days, n (%)	0	1 (1)	1 (1)	2 (2)
Adverse events that occurred or worsened during the observation period†				
Grade 3 or 4 event, n (%)	1 (1)	0	1 (1)	1 (1)
Event that led to death, n (%)	0	0	0	0
Event that led to withdrawal from the trial, n (%)	0	0	0	0
Event that led to infusion interruption*, n (%)	0	1 (1)	1 (1)	1 (1)

*Events were grade 2 or higher hypersensitivity reactions or infusion-related reactions. † Events listed here were not present at baseline or were an exacerbation of a preexisting condition that occurred during the observation period, which is defined as the time from administration of REGN-COV2 or placebo to the last study visit.
Source: [30]

Outcome data from subgroup analyses in patients with high risk for progression to severe COVID-19 disease were not yet published at the time of writing of this report.

Living Systematic Reviews with Meta-Analyses (MAs) related to above mentioned published phase 1-2 RCT preliminary results
In this section we describe the evidence as summarized in two Living Systematic Reviews with Meta-Analyses (MAs) related to the single published RCT mentioned in the previous section.

No deaths were reported so that estimates of effect could not be calculated (low certainty of evidence).

The REGN-COV2 antibody cocktail may reduce viral load; MD -0.41 (95% CI -0.71 to -0.10), low certainty of evidence, and medically attended visit; RR 0.51 (95% CI 0.17 to 1.54); 32 fewer per 1.000 (from 54 fewer to 35 more); low certainty of evidence (Table 4-3, and Table A4 in Appendix 3).

Whether or not REGN-COV2 increase AE and SAEs in comparison to placebo is uncertain (very low certainty of evidence) (Table 4-3 and Table A4 in Appendix 3). The same is true for REGN-COV2 8 g dose compared to REGN-CoV2 2.4 g dose (Table 4-4, and Table A4 in Appendix 3).

Table 4-3: Summary of findings table for published RCT related to effectiveness and safety of REGN-COV2, any dosages compared to placebo, in COVID-19 patients – OUTPATIENT

Patient or population: Persons with mild COVID-19
Setting: Outpatient
Intervention: REGN-COV2 (2.4 g; 8 g; combined groups of 2.4 g and 8 g)
Comparison: Placebo

Outcome	Anticipated absolute effects a (95% CI)		Relative effect (95% CI)	Absolute effect difference (95% CI)	Number of participants (studies)	Certainty of evidence (GRADE)	Comments
	Risk with Placebo	Risk with REGN-COV2					
All-cause Mortality [b,c] **All doses**	No deaths reported	No deaths reported	Not estimable	Not estimable	275 (1 RCT) [30]	⊕⊕◯◯ LOW	Downgraded of one level for high risk of reporting bias and unclear risk of selection bias Downgraded of one level for small sample size (<200)
2.4 g [b] **(Explanation: in EMA and FDA current indication)**	No deaths reported	No deaths reported	Not estimable	Not estimable	185 (1 RCT) [30]	⊕⊕◯◯ LOW	Downgraded of one level for high risk of reporting bias and unclear risk of selection bias Downgraded of one level for small sample size (<200)
8 g [b] **(Explanation: not in EMA and FDA current indication)**	No deaths reported	No deaths reported	Not estimable	Not estimable	183 (1 RCT) [30]	⊕⊕◯◯ LOW	Downgraded of one level for high risk of reporting bias and unclear risk of selection bias Downgraded of one level for small sample size (<200)
Time-weighted average change in viral load from day 1 through day 7 **All doses [d]**	-1.34 (-1.60 to -1.08) [e]	-1.74 (-1.95 to -1.53) [e]	MD -0.41 (-0.71 to -0.10) [f]	**-**	221 (1 RCT) [30]	⊕⊕◯◯ LOW	Downgraded of one level for high risk of reporting bias and unclear risk of selection bias Downgraded of one level for imprecision, as the upper limit of the confidence interval does not exclude trivial effects
2.4 g [d]	-1.34 (-1.60 to -1.08) [e]	-1.60 (-1.87 to -1.32) [e]	MD -0.25 (-0.60 to -0.10) [f]	-	148 (1 RCT) [30]	⊕⊕◯◯ LOW	Downgraded of one level for high risk of reporting bias and unclear risk of selection bias Downgraded of one level for imprecision, as the upper limit of the confidence interval does not exclude trivial effects

Outcome	Anticipated absolute effects a (95% CI)		Relative effect (95% CI)	Absolute effect difference (95% CI)	Number of participants (studies)	Certainty of evidence (GRADE)	Comments
	Risk with Placebo	Risk with REGN-COV2					
8 g [d]	-1.34 (-1.60 to -1.08) [e]	-1.90 (-2.18 to -1.62)	MD -0.56 (-0.91 to -0.21) [f]	-	151 (1 RCT) [30]	⊕⊕◯◯ LOW	Downgraded of one level for high risk of reporting bias and unclear risk of selection bias Downgraded of one level for imprecision, as the upper limit of the confidence interval does not exclude trivial effects
Number of patients with ≥1 COVID-19 related medically attended visit (telemedicine visits, in-person physician visits, urgent care or emergency department visits, and hospitalization) **All doses** [d]	65 per 1.000	33 per 1.000 (11 to 99)	RR 0.51 (0.17 to 1.54)	32 fewer per 1.000 (from 54 fewer to 35 more)	275 (1 RCT) [30]	⊕⊕◯◯ LOW	Downgraded of one level for high risk of reporting bias and unclear risk of selection bias Downgraded of one level for small sample size (<200)
2.4 g [d]	65 per 1.000	33 per 1.000 (8 to 126)	RR 0.51 (0.13 to 1.96)	32 fewer per 1.000 (from 56 fewer to 62 more)	185 (1 RCT) [30]	⊕⊕◯◯ LOW	Downgraded of one level for high risk of reporting bias and unclear risk of selection bias Downgraded of one level for small sample size (<200)
8 g [d]	65 per 1.000	34 per 1.000 (8 to 129)	RR 0.52 (0.13 to 2.00)	31 fewer per 1.000 (from 56 fewer to 65 more)	183 (1 RCT) [30]	⊕⊕◯◯ LOW	Downgraded of one level for high risk of reporting bias and unclear risk of selection bias Downgraded of one level for small sample size (<200)
Adverse events [b] **All doses**	22 per 1.000	11 per 1.000 (from 2 to 79)	RR 0.53 (0.08 to 3.69)	10 fewer per 1.000 (from 20 fewer to 58 more)	269 (1 RCT) [30]	⊕◯◯◯ VERY LOW	Downgraded of one level for high risk of reporting bias and unclear risk of selection bias Downgraded of two levels for small sample size and wide CI
2.4 g	22 per 1.000	5 per 1.000 (from 0 to 93)	RR 0.21 (0.01 to 4.34)	17 fewer per 1.000	181 (1 RCT) [30]	⊕◯◯◯ VERY LOW	Downgraded of one level for high risk of reporting bias and unclear risk of selection bias

Outcome	Anticipated absolute effects a (95% CI)		Relative effect (95% CI)	Absolute effect difference (95% CI)	Number of participants (studies)	Certainty of evidence (GRADE)	Comments
	Risk with Placebo	Risk with REGN-COV2					
				(from 21 fewer to 72 more)			Downgraded of two levels for small sample size and wide CI
8 g	22 per 1.000	23 per 1.000 (from 3 to 158)	RR 1.06 (0.15 to 7.34)	1 more per 1.000 (from 18 fewer to 136 more)	181 (1 RCT) [30]	⊕◯◯◯ VERY LOW	Downgraded of one level for high risk of reporting bias and unclear risk of selection bias Downgraded of two levels for small sample size and wide CI
Serious adverse events **All doses** [c]	22 per 1.000	6 per 1.000 (from 0 to 62)	RR 0.26 (0.02 to 2.88)	16 fewer per 1.000 (from 21 fewer to 40 more)	269 (1 RCT) [30]	⊕◯◯◯ VERY LOW	Downgraded of one level for high risk of reporting bias and unclear risk of selection bias Downgraded of two levels for small sample size and wide CI
2.4 g [b]	22 per 1.000	11 per 1.000 (from 1 to 123)	RR 0.53 (0.05 to 5.72)	10 fewer per 1.000 (from 20 fewer to 102 more)	181 (1 RCT) [30]	⊕◯◯◯ VERY LOW	Downgraded of one level for high risk of reporting bias and unclear risk of selection bias Downgraded of two levels for small sample size and wide CI
8 g [b]	22 per 1000	5 per 1000 (from 0 to 93)	RR 0.21 (0.01 to 4.34)	17 fewer per 1.000 (from 21 fewer to 72 more)	181 (1 RCT) [30]	⊕◯◯◯ VERY LOW	Downgraded of one level for high risk of reporting bias and unclear risk of selection bias Downgraded of two levels for small sample size and wide CI

Abbreviations: CI=confidence interval; RR=risk ratio; SAE=serious adverse event; AE=adverse event; RCT=randomised controlled trial; g=gram; MD=mean difference

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations:
[a] The risk in the intervention group is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI);
[b] Cruciani F, De Crescenzo F, Vecchi S, Saulle R, Mitrova Z, Amato L, Davoli M. REGN-CoV2 (a cocktail of 2 monoclonal antibodies) any dosages compared to Placebo be used for COVID-19 patients. [21, 22];
[c] covid-nma [20];
[d] Authors of current rapid review
[e] Least squared mean difference from baseline expressed in log10 copies/ml
[f] Least squared between group mean difference, expressed in log10 copies/ml

Table 4-4: Summary of findings table for published RCTs related to effectiveness and safety of REGN-COV2, 8 g compared to REGN-COV2 2.4 g, in COVID-19 patients – OUTPATIENT

Patient or population: Persons with mild COVID-19
Setting: Outpatient
Intervention: REGN-COV 2 8 g
Comparison: REGN-COV2 2.4 g

Outcome	Anticipated absolute effects [a] (95% CI)		Relative effect (95% CI)	Absolute effect difference (95% CI)	Number of participants (studies)	Certainty of evidence (GRADE)	Comments
	Risk with REGN-COV2 2.4 g	Risk with REGN-COV2 8 g					
All-cause Mortality[b]							
8 g vs 2.4 g	No deaths reported	No deaths reported	Not estimable	Not estimable	182 (1 RCT) [30]	⊕⊕◯◯ LOW	Downgraded of one level for high risk of reporting bias and unclear risk of selection bias Downgraded of one level for small sample size (<200)
Adverse events [b]							
8 g vs 2.4 g	0 per 1.000	0 per 1.000 (from 0 to 0)	RR 5.00 (0.24 to 102.67)	0 fewer per 1.000 (from 0 fewer to 0 fewer)	176 (1 RCT) [30]	⊕◯◯◯ VERY LOW	Downgraded of one level for high risk of reporting bias and unclear risk of selection bias Downgraded of two levels for small sample size and wide CI
Serious adverse events[b]							
8 g vs 2.4 g	11 per 1.000	4 per 1000 (from 0 to 92)	RR 0.33 (0.01 to 8.07)	8 fewer per 1.000 (from 11 fewer to 80 more)	176 (1 RCT) [30]	⊕◯◯◯ VERY LOW	Downgraded of one level for high risk of reporting bias and unclear risk of selection bias Downgraded of two levels for small sample size and wide CI

Abbreviations: CI=confidence interval; RR=risk ratio; SAE=serious adverse event; AE=adverse event; RCT=randomised controlled trial; g=gram

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations:

[a] The risk in the intervention group is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI); [b] adapted from Cruciani F, De Crescenzo F, Vecchi S, Saulle R, Mitrova Z, Amato L, Davoli M. Should REGN-CoV2 (a cocktail of 2 monoclonal antibodies) 8 g compared to REGN-CoV2 2.4 g be used for COVID-19 patients? [21]; [c] covid-nma [20]

4.3.2 Unpublished results

In this section we describe unpublished results from the phase 3 portion of the RCT (NCT04425629) in high-risk non-hospitalised COVID-19 patients. All descriptions are from a press release by Regeneron Pharmaceuticals, Inc. on March 23, 2021.

Regeneron Pharmaceuticals, Inc. and Roche announced positive results from the phase 3 portion of above mentioned RCT assessing a REGN-COV2 treatment in COVID-19 infected high-risk non-hospitalised adults (n=4567) [31, 32].

The objective of this confirmatory phase 3 was to prospectively demonstrate clinically significant effect on risk of COVID-19 hospitalisation or all-cause death in high-risk non-hospitalised patients, and confirm safety. The trial also prospectively evaluated potential benefit on symptom duration. The patient population included adult, non-hospitalised patients with COVID-19 with a symptom onset ≤7 days from randomisation. Patients were SARS-CoV-2 confirmed by molecular testing ≤72 hours from randomisation and not on any COVID-19 therapies. The trial design originally compared 8000 mg and 2400 mg versus placebo, and was amended to evaluate 2400 mg and 1200 mg versus placebo.

All patients had at least one risk factor, including obesity (58%), age ≥50 years (51%) and cardiovascular disease, including hypertension (36%). Approximately 35% of patients were Latino/Hispanic, 5% were Black/African American and the median age was 50 years (range: 18-96 years). This phase 3 trial was previously amended to stop enrolment in the placebo group, following a recommendation from the Independent Data Monitoring Committee, which found clear efficacy for both doses.

Effectiveness

The investigational REGEN-COV2 (casirivimab with imdevimab) significantly reduced the risk of hospitalisation or death by 70% (1200 mg intravenous) and 71% (2400 mg intravenous) compared to placebo [31, 32]. From our own calculations, using the raw data presented in the press release, this relates to a relative risk (RR) of 0.30, with a 95% CI from 0.13 to 0.68 for 1200 mg versus placebo and a RR of 0.29 with 95% CI of 0.17 to 0.48 for 2400 mg.

REGEN-COV2 also met all secondary endpoints, including the ability to reduce symptom duration. The between group difference was expressed as a median, which was 4 days in both comparisons. Interquartile ranges were not reported, the p-value was below 0.0001 for both comparisons (Table 4-5).

In addition, a companion phase 2 trial showed that even the lowest doses tested (IV: 300 mg; subcutaneous: 600 mg) had significant viral load reductions over the first 7 study days, comparable to the 2400 mg and 1200 mg IV doses. The press releases did not specify any numerical estimates for this statement.

Table 4-5: Effectiveness results from phase 3 RCT (outpatient)

	REGN-COV2 1200 mg IV (n=736)	**Placebo (n=748)**	**REGN-COV2 2400 mg IV (n=1355)**	**Placebo (n=1341)**
Patients with ≥1 COVID-19 related hospitalisation or death through day 29[1-3]				
Risk reduction	70% (p=0.0024)		71% (p<0.0001)	
Number of patients with events (%)	7 (1)	24 (3.2)	18 (1.3)	62 (4.6)
Time to COVID-19 symptom resolution				
Median reduction (days)	4 (p<0.0001)		4 (p<0.0001)	
Median (days)	10	14	10	14

[1]Based on the modified Full Analysis Set population, which includes all randomized patients with a positive SARS-CoV-2 RT-qPCR test from nasopharyngeal swabs at randomisation and ≥1 risk factor for severe COVID-19.; [2]The formal hierarchical analysis first evaluated the 2,400 mg dose vs. concurrent placebo and then evaluated the 1,200 mg dose vs. concurrent placebo.; [3]Based on phase 1/2 analyses showing that the 8,000 mg and 2,400 mg doses were indistinguishable, the phase 3 protocol was amended to compare the 2,400 mg and 1,200 mg doses vs. placebo, and the 8,000 mg data were converted to a descriptive analysis.
Source: [31, 32]

Safety

A safety assessment conducted on all available patient data up to day 169 identified no new safety signals. Serious adverse events were largely related to COVID-19 and occurred in 1.1% of patients in the 1200 mg group, 1.3% in the 2400 mg group and 4.0% in the placebo group. There was 1 death in the 1200 mg group (n=827), 1 death in the 2400 mg group (n=1849) and 5 deaths in the placebo groups (n=1843) [31, 32]. From our own calculations, analysing the combined groups of 1200 mg and 2400 mg versus placebo, this related to an unadjusted RR of 0.31 with 95% CI of 0.20 to 0.46 for the outcome SAE and 0.28 with 95% CI from 0.05 to 1.42 for the outcome death.

4.4 Ongoing trials

Four ongoing treatment clinical trials (including this one with published preliminary phase 1-2 results and unpublished phase 3 results) evaluating REGN-COV2 treatment in COVID-19 patients in outpatient or hospital setting are currently registered in ClinicalTrials.gov, ISRCTN and EUdraCT registers. Details can be found in Table A5, Appendix 3.

4.5 PATIENT INVOLVEMENT

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

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

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

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

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

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

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

According to the impact on carers/unpaid care-givers, the patient organisation stated that the problems are most visible in the gynaecology departments, where fathers currently were not allowed to be with

their wives during labour. The problems are also visible in the elderly homes, with limited visits. Many persons die without possibility to say goodbye.

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

4.5.2 Experience with currently available therapies for COVID-19

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

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

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

5 DISCUSSION

Evidence on effectiveness and safety of REGN-COV2 versus placebo comes from one ongoing phase 1-2 portion of RCT (NCT04425629) with published preliminary results in 275 non-hospitalised adults with mild to moderate COVID-19 [30]. The most important results for this rapid review, according to the current indication proposed by EMA, from phase 3 portion of the same RCT (NCT04425629) including 4567 mild to moderate COVID-19 with high-risk for progression to severe disease, are still unpublished and recently were released by Manufacturer [31, 32]. No head-to-head trials were published yet.

Results from a companion dose-ranging phase 2 trial (NCT04666441) in 803 outpatient COVID-19 patients, conducted to evaluate the antiviral effect of several different REGN-COV2 doses (IV: 2400 mg, 1200 mg, 600 mg and 300 mg; SC: 1200 mg and 600 mg) were only presented by the Manufacturer in a press release: all tested doses met the primary endpoint, rapidly and significantly reducing patients' viral load (log_{10} copies/mL) compared to placebo ($p<0.001$). Each dose demonstrated similar efficacy, including the lowest doses tested (IV: 300 mg; SC: 600 mg). Based on recently announced results, Manufacturer will share both phase 3 outcomes data and phase 2 virology data with regulatory authorities to discuss next steps, including the possibility of utilizing lower doses and more convenient subcutaneous administration [31, 32].

An important limitation of published interim portion of published RCT is that, although the analyses according to antibody status were prespecified, no formal hypothesis testing was performed to control type I error. As results related to subgroup of patient with high risk are not published, further analysis related to subgroup of patients with high risk for progression to severe COVID-19 was not possible to be provided by authors of this rapid review. The same is true for phase 3 portion of this RCT: the final results in high-risk mild to moderate COVID-19 patients were not yet published, so further meta-analysis, risk of bias and certainty of evidence assessments were not possible to perform.

Uncertainties for REGN-COV2 are related to effects on further outcomes of interest, particularly those related to hospitalisation that impact resource allocation (for example, the need for mechanical ventilation, duration of mechanical ventilation, and duration of hospitalisation). Further short-term outcomes related to hospitalisation are lacking also: Number of patients with COVID-19 related hospitalisation; Number of patients admitted to an intensive care unit; Number of patients requiring supplemental oxygen; Pulmonary function; Health-related Quality of life; Clinical improvement defined as a hospital discharge or improvement on the scale used by trialists to evaluate clinical progression and recovery; WHO Clinical Progression Score level 7 or above (i.e., Mechanical ventilation +/- additional organ support (ECMO, vasopressors or dialysis) or death; Time to clinical improvement; Time to WHO Clinical Progression Score level 7 or above; Time to death; Time to viral negative conversion; Duration of supplemental oxygen therapy; Time to ICU admission; Kinetic of viral load; Efficacity depending on SARS-CoV-2 variants and Resistance.

Long term outcomes (such as 6 months endpoint) examining mortality or long-term quality of life; long term safety; patient-reported outcomes such as symptom burden; outcomes when used in combination with other neutralising antibodies and published RCTs with high certainty of evidence are lacking as well. Uncertainties for REGN-COV2 treatment are also related to dose and route of administration. The applicability of these results in specific subgroups, such as children and older adults, pregnant or lactating women is currently uncertain also.

There are four registered ongoing clinical trials evaluating REGN-COV2 treatment in outpatient and hospital settings. The availability of full clinical study reports for completed trials to allow open and robust scrutiny of the trials is needed as well.

HTA doers recognise that patients and those who support them have unique knowledge about what it is like to live with a specific disease or medical condition. Patients can help to understand unique perspectives by presenting patients' and carers/care-givers' views and experiences. Patients can describe advantages and disadvantages of health interventions based on patients' experiences and values concerning a new intervention [33]. Related to received patient input on issues asked on COVID-19, one patient organisation, two individual patients and one informal caregiver stressed negative impact on quality of life (individually as well as the whole family), burden on carers/unpaid caregivers and negative impact on access and quality of health care. They also pointed at prolonged symptoms,

known as post-acute covid-19 (“long covid”). Literature data showed that post-acute covid-19 (“long covid”) seems to be a multisystem disease, sometimes occurring after a relatively mild acute illness. Clinical management requires a whole-patient perspective. Such patients can be divided into those who may have serious sequelae (such as thromboembolic complications) and those with a non-specific clinical picture, often dominated by fatigue and breathlessness. Post-acute covid-19 symptoms vary widely. Even so-called mild covid-19 may be associated with long term symptoms, most commonly cough, low grade fever, and fatigue, all of which may relapse and remit. Other reported symptoms include shortness of breath, chest pain, headaches, neurocognitive difficulties, muscle pains and weakness, gastrointestinal upset, rashes, metabolic disruption (such as poor control of diabetes), thromboembolic conditions, and depression and other mental health conditions. Skin rashes can take many forms including vesicular, maculopapular, urticarial, or chilblain-like lesions on the extremities (so called covid toe) [11].

6 SUMMARY OF CLINICAL EFFECTIVENESS AND SAFETY WITH CONCLUSION

A summary of the effectiveness and safety evidence from one published RCT (phase 1-2 portion) with preliminary results in 275 mild to moderate COVID-19 patients, as well as from unpublished phase 3 portion of the same RCT in 4567 non-hospitalised, high-risk adults with mild to moderate COVID-19 can be found below.

6.1 Clinical effectiveness

Based on only one scientific publication related to interim results of an RCT on the casirivimab and imdevimab combination (REGN-COV2) in 275 non-hospitalised mild to moderate COVID-19 patients, no deaths were reported. Based on low certainty of evidence, the REGN-COV2 treatment may reduce viral load (MD -0.41,95% CI -0.71 to -0.10) and medically attended visit: RR 0.51, 95% CI 0.17 to 1.54; 32 fewer per 1.000 (from 54 fewer to 35 more).

Based on unpublished final results from phase 3 portion of the same RCT performed on 4567 patients, casirivimab and imdevimab combination (REGN-COV2) significantly reduced the risk of hospitalisation or death by 70% (1200 mg intravenous) and 71% (2400 mg intravenous) compared to placebo. This relates to a relative risk (RR) of 0.30, with a 95% CI from 0.13 to 0.68 for 1200 mg versus placebo and a RR of 0.29 with 95% CI of 0.17 to 0.48 for 2400 mg (according to our own calculations, using the raw data presented in the press release). REGN-COV2 met all secondary endpoints, including the ability to reduce symptom duration.

A companion phase 2 trial showed that even the lowest doses tested (intravenous: 300 mg; subcutaneous: 600 mg) had significant viral load reductions over the first 7 study days, comparable to the 2400 mg and 1200 mg intravenous doses, but latter results are hard to interpret without further numerical descriptions of the estimates and without GRADE-assessments.

6.2 Safety

Based on only one scientific publication related to interim results of phase 1-2 portion RCT on the casirivimab and imdevimab combination (REGN-COV2) in 275 non-hospitalised, mild to moderate COVID-19 patients, whether or not REGN-COV2 increase AE and SAEs in comparison to placebo is uncertain (very low certainty of evidence). The same is true for REGN-COV2 8 g dose compared to REGN-CoV2 2.4 g dose.

Based on unpublished final results from the phase 3 portion of the same RCT, no new safety signals were identified. Serious adverse events were largely related to COVID-19 and occurred in 1.1% of patients in the 1200 mg group, 1.3% in the 2400 mg group and 4.0% in the placebo group. There was 1 death in the 1200 mg group, 1 death in the 2,400 mg group and 5 deaths in the placebo groups. This related to an unadjusted RR of 0.31 with 95% CI of 0.20 to 0.46 for the outcome SAE and 0.28 with 95% CI from 0.05 to 1.42 for the outcome death (according to our own calculations, analysing the combined groups of 1200 mg and 2400 mg versus placebo).

6.3 Scientific conclusion

Currently, only one scientific publication related to interim results phase 1-2 portion of RCT on the casirivimab and imdevimab combination (REGN-COV2) in 275 non-hospitalised mild to moderate COVID-19 patients was found. No deaths were reported. Based on low certainty of evidence, the REGN-COV2 treatment may reduce viral load and medically attended visits.

Based on unpublished results from phase 3 portion of the same RCT, performed in 4567 patients, compared to placebo, casirivimab and imdevimab (REGN-COV2) both doses, 1200 mg and 2400 mg intravenous, significantly reduced the risk of hospitalisation or death by 70% and 71% respectively. REGN-COV2 also met all secondary endpoints, including the ability to reduce symptom duration. The reported safety data indicated that REGN-COV2 has a favourable safety profile. All unpublished results however have to be interpreted with care, until peer-reviewed reports are available.

The safety and effectiveness of REGN-COV2 for the treatment of COVID-19 continues to be evaluated. High quality published evidence from ongoing RCTs in outpatient setting is expected on effectiveness and safety of casirivimab and imdevimab (REGN-COV2) treatment in mild to moderate COVID-19 patients, at high risk of progressing to severe COVID-19. Updates of this document are indicated once new evidence becomes available.

In the EU, there are no authorised treatments yet for individuals with mild to moderate COVID-19 early in the disease course. On February 26, 2021 EMA stated that the CHMP has completed its review to provide a harmonised scientific opinion at EU level to support national decision making on the possible use of the antibodies before a formal authorisation is issued. EMA concluded that the combination (REGN-COV2) can be used for the treatment of confirmed COVID-19 in patients who do not require supplemental oxygen and who are at high risk of progressing to severe COVID-19. The same is true for other neutralising monoclonal antibodies like bamlanivimab monotherapy, bamlanivimab in combination with etesevimab, and regdanvimab monotherapy.

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

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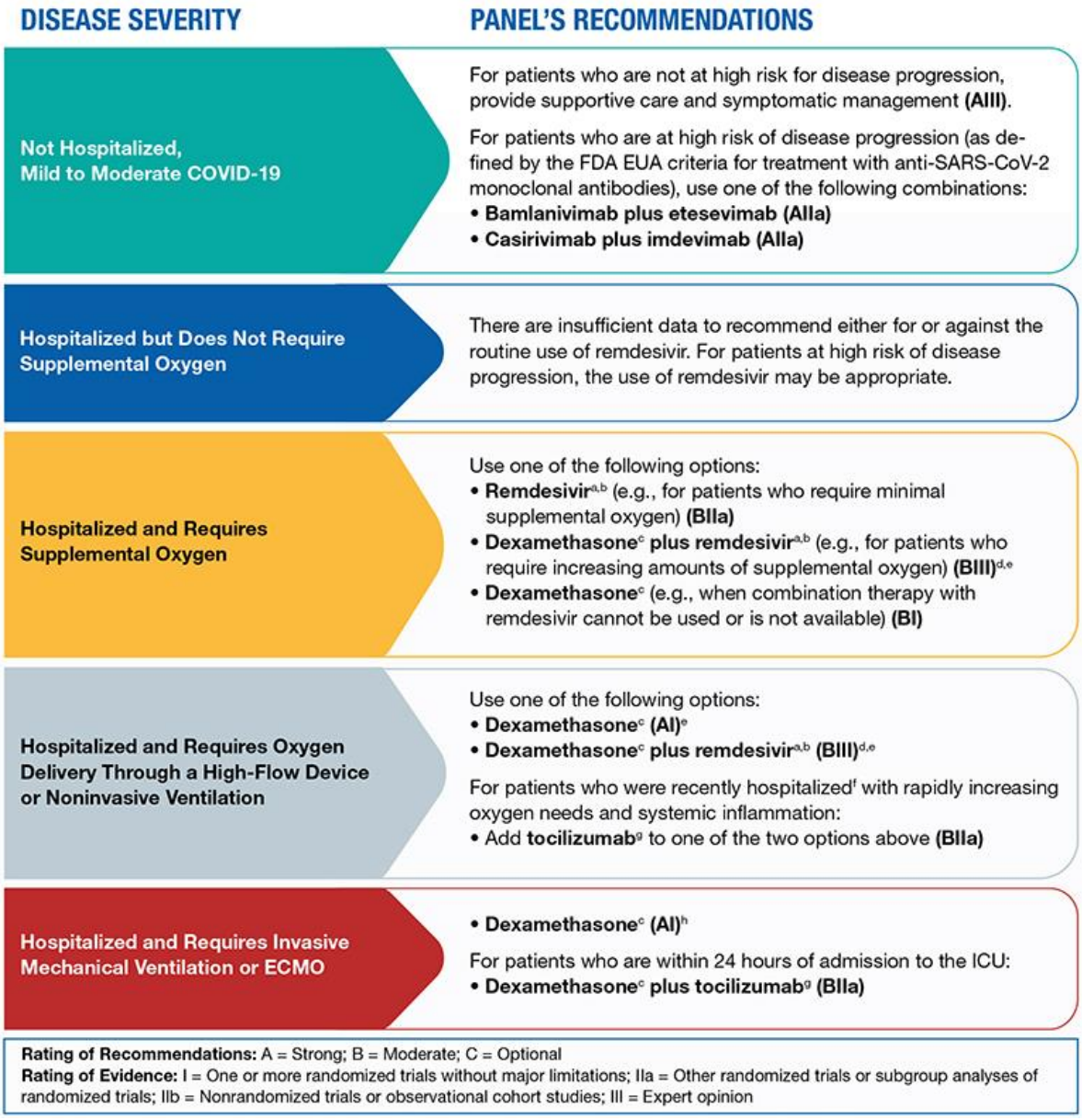
APPENDIX 1: CLINICAL GUIDELINES FOR MANAGEMENT

Box A 1: Summary of the current therapeutic management of patients with COVID-19

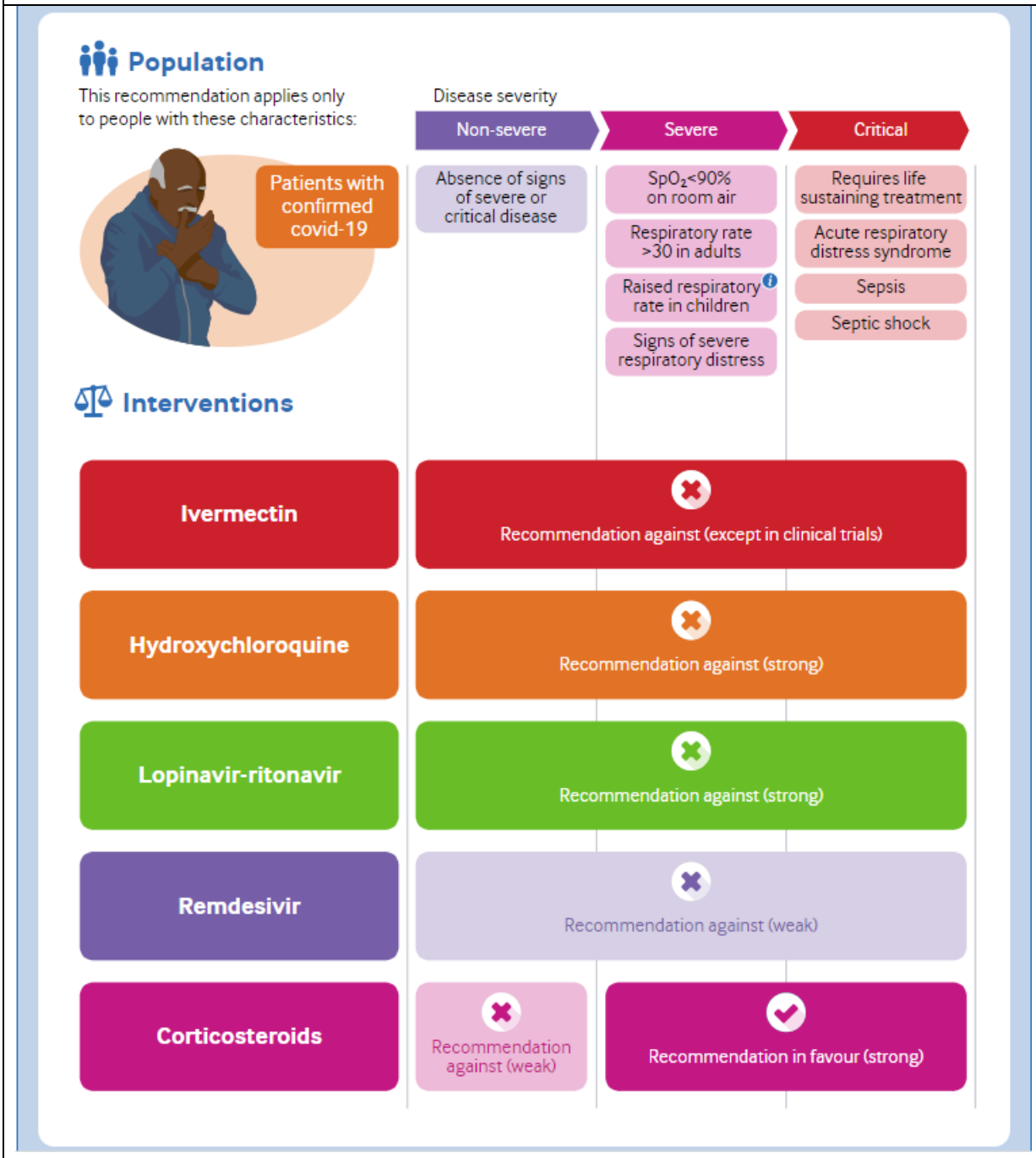
NIH COVID-19 treatment guidelines: Pharmacological management of patients with COVID-19 based on disease severity [1]



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

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

A living WHO guideline on drugs for COVID-19, Visual summary of recommendation [2, 34]



APPENDIX 2: LITERATURE SEARCH AND FLOW-DIAGRAMS FOR RCTS

Table A1: Search strategy to identify randomised controlled studies

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

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

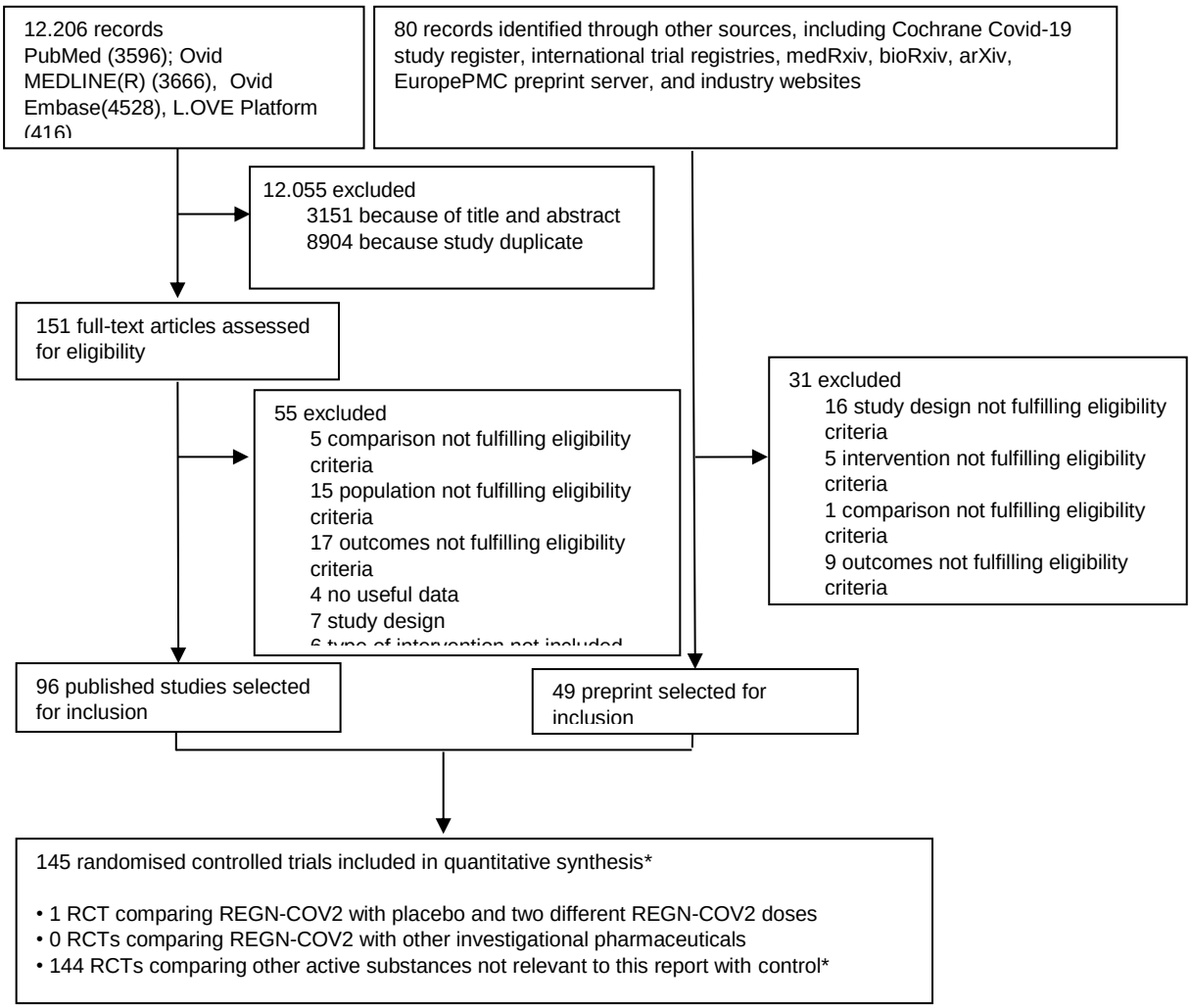


Figure A1: Flow diagram depicting the selection process of RCTs

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

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

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

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

Author, year, reference number/Study name/Study ID	Weinreich et al. [30] NCT04425629
Study design, study phase	RCT, phase 1-2 portion of ongoing double-blind, phase 1–3 trial
Centres (single centre or multicentre), country, setting	Multicenter, non-hospitalised patients
Patient population (number of included patients/ Mean age and sex/ Disease severity*)	275 patients underwent randomization (a total of 269 received REGN-COV2 or placebo / 44.0 years / 49% male
Inclusion criteria	18 years of age or older and nonhospitalized, confirmed SARSCoV-2 infection, with a SARS-CoV-2–positive test result received no more than 72 hours before randomization and symptom onset no more than 7 days before randomization; maintains O2 saturation ≥93% on room air; willing and able to provide informed consent signed by study patient or legally acceptable representative; willing and able to comply with study procedures, including providing samples for viral shedding testing.
Exclusion criteria	Admitted to a hospital prior to randomization, or is hospitalized (inpatient) at randomization, due to Covid-19; participated, or is participating, in a clinical research study evaluating Covid19 convalescent plasma, monoclonal antibodies (mAbs) against SARS-CoV-2, or intravenous immunoglobulin (IVIG) within 3 months or less than 5 half-lives of the investigational product (whichever is longer) prior to the screening visit; Prior, current, or planned future use of any of the following treatments: Covid-19 convalescent plasma, mAbs against SARS-CoV-2, IVIG (any indication), systemic corticosteroids (any indication), or Covid-19 Emergency Use Authorization approved treatments, where prior use is defined as the past 30 days or less than 5 half-lives of the investigational product (whichever is longer) from screening; known allergy or hypersensitivity to components of study drug; n discharged, or is planned to be discharged, to a quarantine center; Pregnant or breastfeeding women; Continued sexual activity in women of childbearing potential (WOCBP) or sexually active men who are unwilling to practice highly effective contraception prior to the initial dose/start of the first treatment, during the study, and for at least 6 months after the last dose
Intervention (generic drug name and dosage, time frame; number of randomized/ enrolled patients in subgroups - Mild, Moderate, Severe, Critical COVID-19)	2.4 g of REGN-COV2, or 8.0 g of REGN-COV2 (90 were assigned to receive high-dose REGN-COV2, 92 to receive low-dose REGN-COV2 / non-hospitalised
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=93) / non-hospitalised
Primary Outcome(s)	Time-weighted average change in the viral load (in log10 copies per millilitre) from baseline (day 1) through day 7, as measured by quantitative reverse-transcriptase–polymerase-chain-reaction (RT-PCR) testing of nasopharyngeal swab samples obtained from serum antibody–negative patients; percentage of patients with at least one Covid-19–related medically attended visit through day 29 in both the serum antibody–negative subgroup and the overall trial population; adverse events that occurred or worsened during the observation period (grade 3 and 4; phase 1 only), serious adverse events that occurred or worsened during the observation period (phases 1 and 2), and the following adverse events of special interest (phases 1 and 2): grade 2 or higher hypersensitivity or infusion-related reactions.

Patient-relevant secondary outcome(s)	Proportion of patients with ≥1 Covid-19 related medically-attended visit through day 29; Proportion of patients with ≥2 Covid-19 related medically-attended visits through day 29; Total number of Covid-19 related medically-attended visits through day 29; Proportion of patients admitted to a hospital due to Covid-19 by day 29; Proportion of patients with ≥1 outpatient or telemedicine visit due to Covid-19 by day 29; Proportion of patients requiring mechanical ventilation due to Covid-19 by day 29; Days of hospitalization due to Covid-19; Proportion of patients with all-cause mortality by day 29; Duration of symptoms consistent with Covid-19.
Follow-up (days, months)	Up to 29 days
Sponsor/ lead institution	Regeneron Pharmaceuticals and the Biomedical and Advanced Research and Development Authority of the Department of Health and Human Services

RISK OF BIAS 2 (RoB2) Table

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

Studies	Randomisation process	Deviations from the intended interventions	Missing outcomes	Measurement of the outcome	Selection of reported results	Overall bias
Weinreich et al [30]	low [a]	Low [b]	Low [c]	Low [d]	Low [e]	Low

[a] Report: "We are conducting an ongoing operationally seamless (continual enrollment), multicenter, randomized, double-blind, placebo-controlled, phase 1–3 clinical trial" Supplementary Appendix: "In the Phase 2 study, randomization was stratified by: Presence/absence of coronavirus disease 2019 (Covid-19) symptoms (i.e., symptomatic versus asymptomatic cohort), Country, Risk factors for hospitalization due to Covid-19 (no risk factors for hospitalization due to Covid-19 versus ≥1 risk factor for hospitalization due to Covid-19)" Protocol: "Patients will be randomized according to a central randomization scheme using an interactive web response system (IWRS)." Comment: Allocation sequence random. Allocation sequence concealed. [b] Quote: "Study patients, the principal investigators, and study site personnel (with the exception of the unblinded pharmacist at each site) will remain blinded to all randomization assignments throughout the study. The Regeneron medical/study director, study monitor, and any other Regeneron and contract research organization (CRO) personnel who are in regular contact with the study site will remain blinded to all patient randomization assignments in all phases of the study." Comment: Blinded study (patients and physicians/carers). Data were analyzed appropriately for the effect of assignment to intervention; participants analyzed according to their randomized assignment. [c] Comment: 275 patients randomized; 269 patients analyzed for safety. Data available for > 95% of population. Risk assessed to be low for the outcomes: Mortality. Serious adverse events. [d] Comment: Methods of measuring the outcomes appropriate. Measurement or ascertainment of outcome does not differ between groups. Blinded study (outcome assessor). Risk assessed to be low for the outcomes: Mortality. Serious adverse events. [e] Comment: The protocol, statistical analysis plan and study registry were available. Results were not selected from multiple outcome measurements or analyses of the data. Trial analyzed as pre-specified. Risk assessed to be low for outcomes: Mortality. Serious adverse events.

Source: adapted from https://covid-nma.com [20]

CERTAINTY OF EVIDENCE

Table A4: GRADE evidence

Author(s): Cruciani F, De Crescenzo F, Vecchi S, Saulle R, Mitrova Z, Amato L, Davoli M.
Question: Should **REGN-CoV2** (a cocktail of 2 monoclonal antibodies) **any dosages compared to Placebo** be used for COVID-19 patients?
Setting: **Outpatient**

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	REGN-CoV2 qualunque dose	Placebo	Relative (95% CI)	Absolute (95% CI)	
All-cause mortality (2.4g)											
1 [1]	randomised trials	serious [a]	not serious	not serious	serious [b]	none	No deaths reported				⊕⊕◯◯ LOW
Number of patients with any adverse event (2.4g)											
1 [1]	randomised trials	serious [a]	not serious	not serious	very serious [c]	none	0/88 (0.0%)	2/93 (2.2%)	**RR 0.21** (0.01 to 4.34)	**17 fewer per 1.000** (from 21 fewer to 72 more)	⊕◯◯◯ VERY LOW
Number of patients with serious adverse events (2.4g)											
1 [1]	randomised trials	serious [a]	not serious	not serious	very serious [c]	none	1/88 (1.1%)	2/93 (2.2%)	**RR 0.53** (0.05 to 5.72)	**10 fewer per 1.000** (from 20 fewer to 102 more)	⊕◯◯◯ VERY LOW
All-cause mortality (8g)											
1 [1]	randomised trials	serious [a]	not serious	not serious	serious [b]	none	No deaths reported				⊕⊕◯◯ LOW
Number of patients with any adverse event (8g)											

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	REGN-CoV2 qualunque dose	Placebo	Relative (95% CI)	Absolute (95% CI)	
1 [1]	randomised trials	serious [a]	not serious	not serious	very serious [c]	none	2/88 (2.3%)	2/93 (2.2%)	**RR 1.06** (0.15 to 7.34)	**1 more per 1.000** (from 18 fewer to 136 more)	⊕◯◯◯ VERY LOW
Number of patients with serious adverse events (8g)											
1 [1]	randomised trials	serious [a]	not serious	not serious	very serious [c]	none	0/88 (0.0%)	2/93 (2.2%)	**RR 0.21** (0.01 to 4.34)	**17 fewer per 1.000** (from 21 fewer to 72 more)	⊕◯◯◯ VERY LOW

Explanations

a. Downgraded of one level for high risk of reporting bias and unclear risk of selection bias
b. Downgraded of one level for small sample size (<200)
c. Downgraded of two levels for small sample size and wide CI

References

1. Weinreich DM, Sivapalasingam S, Norton T, Ali S, Gao H, Bhore R, Musser BJ, et al. REGN-COV2, a Neutralizing Antibody Cocktail, in Outpatients with Covid-19. N Engl J Med. 2021 Jan 21;384(3):238-251. doi: 10.1056/NEJMoa2035002. Epub 2020 Dec 17.

Author(s): Cruciani F, De Crescenzo F, Vecchi S, Saulle R, Mitrova Z, Amato L, Davoli M.
Question: Should **REGN-CoV2** (a cocktail of 2 monoclonal antibodies) **8 g compared to REGN-CoV2 2.4 g** be used for COVID-19 patients?
Setting: **Outpatient**

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	REGN-CoV2 8 g	REGN-CoV2 2.4 g	Relative (95% CI)	Absolute (95% CI)	
All-cause mortality											
1 [1]	randomised trials	serious [a]	not serious	not serious	serious [b]	none	No deaths reported				⊕⊕◯◯ LOW
Number of patients with any adverse event											
1 [1]	randomised trials	serious [a]	not serious	not serious	very serious [c]	none	2/88 (2.3%)	0/88 (0.0%)	**RR 5.00** (0.24 to 102.67)	**0 fewer per 1.000** (from 0 fewer to 0 fewer)	⊕◯◯◯ VERY LOW
Number of patients with serious adverse events											
1 [1]	randomised trials	serious [a]	not serious	not serious	very serious [c]	none	0/88 (0.0%)	1/88 (1.1%)	**RR 0.33** (0.01 to 8.07)	**8 fewer per 1.000** (from 11 fewer to 80 more)	⊕◯◯◯ VERY LOW

Explanations

d. Downgraded of one level for high risk of reporting bias and unclear risk of selection bias
e. Downgraded of one level for small sample size (<200)
f. Downgraded of two levels for small sample size and wide CI

References

1 Weinreich DM, Sivapalasingam S, Norton T, Ali S, Gao H, Bhore R, Musser BJ, et al. REGN-COV2, a Neutralizing Antibody Cocktail, in Outpatients with Covid-19. N Engl J Med. 2021 Jan 21;384(3):238-251. doi: 10.1056/NEJMoa2035002. Epub 2020 Dec 17.

Table A5: Ongoing treatment studies related to REGN-COV2

Trial Identifier/registry ID(s)/contact	NCT04425629 (last update April 5, 2021), EudraCT 2020-003690-21	NCT04426695 EudraCT 2020-002537-15	NCT04381936 RECOVERY EudraCT 2020-001113-21 ISRCTN50189673	NCT04666441
Study design, study phase	RCT, phase 1/2/3 (in phase 3, three cohorts: Cohort 1: ≥18 years old, not pregnant at randomisation; Cohort 2: <18 years old, not pregnant at randomisation; Cohort 3: pregnant at randomisation)	RCT, phase 1/2	RCT, phase 2/3	RCT, phase 2
Recruitment status	Recruiting	Recruiting	Recruiting	Recruiting
Number of Patients, Disease severity*	6420, Mild	2970, Mixed (Severe and Critical): Cohort 1, On Low-Flow Oxygen; Cohort 1A, with COVID-19 symptoms but not requiring supplemental O2; Cohort 2, High O2 no Mechanical ventilation; Cohort 3, on Mechanical ventilation	20000, Mixed	1400; Mixed (mild to moderate)
Setting (hospital, ambulatory,)	Ambulatory	Hospitalised	Hospitalised	Ambulatory
Intervention (generic drug name and dosage)	REGN10933+REGN10987 combination therapy intravenously (IV) single dose High dose Low dose	REGN10933+REGN10987 combination therapy intravenously (IV) single dose	Lopinavir-Ritonavir, Hydroxychloroquine, Corticosteroids, Azithromycin, Colchicine, IV Immunoglobulin (children only), Convalescent plasma, Synthetic neutralizing antibodies (REGN-COV2) single dose of REGN10933 + REGN10987 8 g, Tocilizumab or Aspirin, Colchicine	REGN10933+REGN10987 combination therapy, different intravenously and subcutaneous doses, single dose
Comparator (standard care or generic drug name and dosage)	Placebo IV single dose	Placebo	Standard care	Placebo iv or sc, single dose
Primary Outcome(s)	Proportion of patients with treatment-emergent serious adverse events (SAEs) [Through Day 29]; Proportion of patients with infusion-related reactions	Proportion of patients with treatment-emergent Serious Adverse Events (SAEs) [Through Day 169]; Proportion of patients with infusion-related reactions	All-cause mortality [Within 28 days after randomisation]	Time-weighted average daily change from baseline in viral load (log10 copies/mL), as measured by reverse transcription quantitative polymerase chain reaction

	[Through Day 4]; Proportion of patients with hypersensitivity reactions [through Day 29]; Time-weighted average change from baseline in viral shedding as measured by quantitative reverse transcription quantitative polymerase chain reaction (RT-qPCR) in nasopharyngeal (NP) swab samples up to Day 22; Proportion of patients with at least one (≥1) COVID-19-related hospitalisation or all-cause death [Time Frame: Through Day 29] (original outcome wasProportion of patients with at least one COVID-19 related medically attended visit [Through Day 29]) Concentration of REGN10933 in serum over time [Time Frame: Through Day 29]; Concentration of REGN10987 in serum over time [Time Frame: Through Day 29]	[Through Day 4]; Proportion of patients with hypersensitivity reactions [Through Day 29]; Time-weighted average change from baseline in viral shedding as measured by quantitative reverse transcription polymerase chain reaction (RT-qPCR) in nasopharyngeal (NP) swab samples Baseline up to Day 22]; Proportion of patients with at least 1-point improvement on a 7-Point Ordinal Scale in clinical status [From Day 1 up to Day 29]		(RT-qPCR) in nasopharyngeal (NP) swab samples [Time Frame: Baseline to day 7]
Sponsor/ lead institution, country (also, country of recruitment if different)	Regeneron Pharmaceuticals, Chile, Mexico, Romania, United States	Regeneron Pharmaceuticals, Brazil, Chile, Moldova, Republic of, Romania, United States	University of Oxford United Kingdom	Regeneron Pharmaceuticals, United States

Source: [25, 35]

APPENDIX 4: EVIDENCE GAPS

Table A6: Evidence gaps

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

APPENDIX 5: PROJECT ORGANISATION

Participants

Table A7: Project participants

Role in the project	Agency	Country	Distribution of work
Assessment Team			
Author	Austrian Institute for Health Technology Assessment (AIHTA)	Austria	Author will draft the report. Author will review and comment the sections drafted by the co-author. All important milestones will be discussed in advance with the co-author.
Co-Author	Swiss Network for HTA (SNHTA)	Switzerland	Co-author will support drafting the report. Co-author will review and comment on all parts of the report.
Dedicated Reviewer	UCSC/Gemelli	Italy	Review of first draft
Dedicated Reviewer	GOEG	Austria	Review of first draft
Contributors			
Project Manager	Zorginstituut Nederland (ZIN)	Netherlands	Coordination between involved parties throughout the assessment period

Milestones and deliverables

Table A8: Milestones and deliverables

Task	Start	End
Call for Collaboration	17-02-2021	25-02-2021
Scoping PICO and development of first draft RCR	26-02-2021	03-03-2021
PICO survey – request relevant PICO from Member States	04-03-2021	15-03-2021
Collect patient input	04-03-2021	15-03-2021
Adapt draft RCR based on PICO survey	16-03-2021	02-04-2021
Review of the first draft RCR	06-04-2021	09-04-2021
Development of second draft RCR & answers to DR comments	12-04-2021	19-04-2021
TC with the whole assessment team	12-04-2021	
Additional information	20-04-2021	11-05-2021
Finalise RCR for DRs	11-05-2021	
DRs review of the 2nd draft	12-05-2021	14-05-2021
Response on DR comments	17-05-2021	19-05-2021
Finalise RCR	19-05-2021	
Publish RCR	20-05-2021	