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Casirivimab/imdevimab (treatment of COVID-19) –

Benefit assessment according to §35a Social Code Book V[1]

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Casirivimab/Imdevimab (Behandlung von COVID-19) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 13 July 2022). Please note: This document was translated by an external translator and is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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Address of publisher
Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Im Mediapark 8
50670 Köln
Germany

Phone: +49 221 35685-0
Fax: +49 221 35685-1
E-mail: berichte@iqwig.de
Internet: www.iqwig.de

Medical and scientific advice

- Michael Freitag, Division of General Practice/Family Medicine, Department of Health Services Research, Carl von Ossietzky University of Oldenburg, Germany

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Patient and family involvement

No feedback was received in the framework of the present dossier assessment.

IQWiG employees involved in the dossier assessment

- Christian Siebel
- Nadia Abu Rajab
- Kirsten Janke
- Marco Knelangen
- Stefan Kobza
- Jona Lilienthal
- Sabine Ostlender
- Volker Vervölgyi

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
COVID-19	Coronavirus Disease 2019
COVRIIN	Fachgruppe Intensivmedizin, Infektiologie und Notfallmedizin (Division of Intensive Care Medicine, Infectious Diseases and Emergency Medicine)
CTCAE	Common Terminology Criteria for Adverse Events
DEGAM	Deutsche Gesellschaft für Allgemeinmedizin und Familienmedizin (German College of General Practitioners and Family Physicians)
EQ-5D	European Quality of Life Questionnaire – 5 Dimensions
FAS	full analysis set
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
ICU	intensive care unit
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
PEI	Paul Ehrlich Institute
RKI	Robert Koch Institute
RT-qPCR	reverse transcriptase quantitative polymerase chain reaction
SAE	serious adverse event
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus Type 2
SE-C19	Symptoms Evolution of COVID-19
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics
STIKO	Ständige Impfkommission (German Standing Committee on Vaccination)
VAS	visual analogue scale

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code SGB V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug combination casirivimab/imdevimab. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 19 April 2022.

Research question

The aim of the present report is to assess the added benefit of casirivimab/imdevimab in comparison with the appropriate comparator therapy (ACT) in adults and adolescents from 12 years of age and weighing at least 40 kg with Coronavirus Disease 2019 (COVID-19) who do not require supplemental oxygen and who are at increased risk of their disease becoming severe.

The research question presented in Table 2 is derived from the ACT specified by the G-BA.

Table 2: Research question of the benefit assessment of casirivimab/imdevimab

Therapeutic indication	**ACT[a]**
Adults and adolescents from 12 years of age and weighing at least 40 kg with COVID-19[b] who do not require supplemental oxygen and who are at increased risk of their disease becoming severe[c, d]	Treatment of physician's choice[e]

a. Presented is the ACT specified by the G-BA.
b. In case of a positive rapid antigen test, the diagnosis of SARS-CoV-2 infection should be confirmed by a PCR test, especially if the results have therapeutic consequences.
c. In the recording and interpretation of effectiveness results, it is recommended for relevant SARS-CoV-2 mutation variants (e.g. variants of concern) to be taken into account.
d. According to the SPC, decisions regarding the use of casirivimab/imdevimab should take into consideration what is known about the characteristics of the circulating SARS-CoV-2 viruses, including regional or geographic differences and available information on casirivimab/imdevimab susceptibility patterns.
e. Specific therapeutic measures are usually not required for mildly to moderately symptomatic COVID-19 disease. Depending on the severity of disease, the treatment at physician's choice of non-hospitalized patients, if indicated, should primarily be chosen from symptomatic drug therapies (e.g. analgesics, antipyretics, thrombosis prophylaxis). If the disease progresses and the patient is hospitalized, further drug therapies (e.g. dexamethasone; anticoagulation/thrombosis prophylaxis, antibiotics) as well as non-drug therapies (e.g. oxygen supply, type of ventilation, balanced fluid therapy) must be considered.

ACT: appropriate comparator therapy; COVID-19: Coronavirus Disease 2019; G-BA: Federal Joint Committee; PCR: polymerase chain reaction; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus Type 2; SPC: Summary of Product Characteristics

The company followed the G-BA's specification of the ACT.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier.

Neutralizing activity against Severe Acute Respiratory Syndrome Coronavirus Type 2 (SARS-CoV-2) virus variants

According to the Summary of Product Characteristics (SPC), decisions regarding the use of casirivimab/imdevimab should take into account what is known about the characteristics of the circulating Severe Acute Respiratory Syndrome Coronavirus Type 2 (SARS-CoV-2) viruses, including regional or geographical differences and available information on casirivimab/imdevimab susceptibility patterns. In addition, the SPC specifies that, when molecular testing or sequencing data are available, they should be taken into account when selecting the antiviral therapy to rule out use against SARS-CoV-2 variants shown to have reduced susceptibility to casirivimab/imdevimab. This benefit assessment therefore assumes that the present therapeutic indication excludes patients infected with a virus variant for which neutralizing activity is insufficient – either demonstrably so or as expected based on the current pandemic situation.

The Paul Ehrlich Institute (PEI) and the Robert Koch Institute's (RKI) Division of Intensive Care Medicine, Infectious Diseases and Emergency Medicine (COVRIIN) recommend taking into account the current epidemiological situation and neutralizing activity against individual virus variants when selecting monoclonal antibodies for treatment or prophylaxis. Where a mutation analysis is not yet available, treatment should be selected based on the current epidemiological situation to avoid delaying treatment initiation. The present benefit assessment therefore is predicated on casirivimab/imdevimab being typically used only if sufficient neutralizing activity is assumed for the predominant virus variant. Because of its lack of effectiveness against the omicron variant, the use of casirivimab/imdevimab is currently not recommended.

Study pool and study design

The R10933-10987-COV-2067 study (hereinafter referred to as the COV-2067 study) was used for the benefit assessment. The COV-2067 study is an adaptive, placebo-controlled double-blind, randomized, phase 1–3 study on the treatment with casirivimab/imdevimab in patients with COVID-19. The study enrolled only outpatients with early-stage COVID-19 who did not require any supplemental oxygen therapy. Depending on study phase and cohort, both symptomatic and asymptomatic patients were enrolled, as were both patients with at least 1 risk factor or no risk factors for COVID-19 becoming severe.

The study was conducted using a master protocol governing phases 1, 2, and 3. The study's phase 1 enrolled adult patients symptomatic for COVID-19 and randomly allocated them in a 1:1:1 ratio to receive a single dose of 2400 mg casirivimab/imdevimab, 8000 mg casirivimab/imdevimab, or placebo. Phase 2 enrolled both symptomatic and asymptomatic adult patients in 2 separate cohorts. In both of these cohorts, patients were randomly allocated in a 1:1:1 ratio to a single intravenous infusion of 2400 mg casirivimab/imdevimab, 8000 mg casirivimab/imdevimab, or placebo.

At the beginning of phase 3, adult patients were first allocated to the respective study arms in accordance with the phase 2 randomization system. Protocol amendment 6 dated 14 November 2020 modified the phase 3 study design on the basis of the data collected in phases 1 and 2. Patients were now placed in 1 of 2 cohorts. Adult patients were put in cohort 1. Patients < 18 years of age were placed in cohort 2. Patients who were pregnant at the time of randomization were allocated to either cohort 1 or 2 based on age. Starting from protocol amendment 7 dated 18 December 2020, pregnant people were placed in a separate cohort 3. Likewise, protocol amendment 6 closed the 8000 mg study arm and introduced and a new study arm with 1200 mg casirivimab/imdevimab. Starting from protocol amendment 8 dated 12 March 2021, no patients were randomized to the placebo arm any longer. In phase 3, casirivimab/imdevimab was administered once intravenously on Day 1, followed by a 169-day follow-up observation phase.

Starting from protocol amendment 6, the study excluded patients with an antigen test or molecular diagnostic test positive for SARS-CoV-2 from a sample taken > 72 hours prior to randomization as well as patients with a known history of a positive serological SARS-CoV-2. The study also excluded patients with a history of hospitalization for COVID-19. In addition, patients who had received at least 1 vaccination against SARS-CoV-2 were excluded from the study.

Patients included in cohort 1 had to have symptoms consistent with COVID-19, with symptom onset ≤ 7 days prior to randomization, and exhibit ≥ 1 risk factor for severe disease. Under protocol amendments 6 and 7, a total of 4046 patients were randomized in a 1:1:1 ratio to 1200 mg casirivimab/imdevimab (N = 1347), 2400 mg casirivimab/imdevimab (N = 1350), or placebo (N = 1349) in cohort 1. Randomization was stratified by country, with centres in the United States, Mexico, and Romania participating according to the study protocol. For cohort 1, the primary outcome is the combined outcome of hospitalization for COVID-19 or death due to any cause by Day 29. Patient-relevant secondary outcomes are all-cause mortality as well as outcomes on morbidity and adverse events (AEs). These outcomes were to be observed until Day 29. The observation duration for all-cause mortality and AEs, in contrast, was 169 days.

According to protocol amendment 6, both symptomatic and asymptomatic patients were eligible for inclusion in cohort 2. Patients had to either exhibit ≥ 1 risk factor for COVID-19 becoming severe or live with a person with a risk factor. From protocol amendment 7, enrolment was limited to symptomatic patients exhibiting ≥ 1 risk factor for their disease becoming severe. Like in cohort 1, patients were randomized to 1 of the 3 study arms (1200 mg casirivimab/imdevimab, 2400 mg casirivimab/imdevimab, or placebo), but the casirivimab/imdevimab dose was adjusted based on bodyweight.

Pregnant patients included in cohort 3 were randomly allocated in a 1:1 ratio to the 1200 mg study arm or the 2400 mg study arm. None of them were randomized to placebo. As described for cohort 2, cohort 3 patients who were < 18 years old also received a weight-adjusted casirivimab/imdevimab dose. Patients had to be symptomatic. The study protocol did not

provide for the presence of additional risk factors other than pregnancy. For the present benefit assessment, the company presented no data on cohorts 2 and 3.

In all study cohorts, casirivimab/imdevimab was administered as a single intravenous infusion. Treatment was largely in accordance with the SPC, but with a longer infusion duration. The SPC additionally allows subcutaneous injection, but this administration route was not investigated in the study.

Study phases and cohorts relevant for the benefit assessment

The data surveyed in phases 1 and 2 as well as data from phase 3 prior to protocol amendment 6 are irrelevant for the benefit assessment because of deviations from the SPC with regard to the administered casirivimab/imdevimab dose. Data relevant for the benefit assessment are from patients in phase 3 who were allocated to the study arms 1200 mg casirivimab/imdevimab or placebo under protocol amendments 6 and 7. For cohort 1, the company submitted data on this patient population in the dossier's Module 4 B.

Cohort 2 includes a subpopulation which would, in principle, be relevant for the benefit assessment: patients between 12 and < 18 years of age weighing at least 40 kg who exhibit symptoms of COVID-19 as well as ≥ 1 risk factor for their disease becoming severe. As described above, however, the dossier does not present any data for the cohort 2 subpopulation which is relevant for this benefit assessment. Therefore, the available data allow drawing a conclusion on added benefit only for adults with COVID-19. Data on cohort 3 are irrelevant for the present benefit assessment because all patients in this cohort were treated with casirivimab/imdevimab, and none were randomized to placebo. On the basis of the data on this cohort's pregnant patients, it is therefore impossible to draw a comparison with the ACT.

Implementation of the ACT

The G-BA specified treatment of physician's choice as the ACT. Mildly to moderately symptomatic COVID-19 usually requires no specific therapeutic measures. Depending on the severity of disease, the treatment of physician's choice of non-hospitalized patients, if indicated, should primarily be chosen from symptomatic drug therapies (e.g. analgesics, antipyretics, thrombosis prophylaxis). If the disease progresses and the patient is hospitalized, further drug therapies (e.g. dexamethasone, anticoagulation / thrombosis prophylaxis, antibiotics) and non-drug therapies (oxygen supply, type of ventilation, balanced fluid therapy) must be included.

Overall, the concomitant treatment with anti-inflammatory and analgesic drugs used in the COV-2067 study represents a sufficient implementation of the ACT. While the guideline recommends specific antiviral substances for early-phase COVID-19 in patients at increased risk of their disease becoming severe, the study disallowed these substances. However, the guidelines issue only a mild or open recommendation for specific risk groups for these treatment options. In addition, the treatment of patients with COVID-19 can be safely assumed to have continuously changed over the course of the pandemic, particularly in light of increasing SARS-CoV-2 immunocompetence due to vaccinations and prior virus exposure as well as the

evolution of new virus variants with potentially differing pathogenicity. Overall, the fact that the COV-2067 study disallowed specific antiviral substances therefore remains without consequence for the present benefit assessment.

Limitations of the study population in comparison with the current pandemic situation

As described above, patients with at least 1 vaccination against SARS-CoV-2 were excluded from phase 3 of the COV-2067 study. At the time the benefit is assessed, however, a large percentage of the population already exhibits complete immunization on the basis of vaccinations and potential prior virus exposure, thereby reducing the risk of COVID-19 becoming severe. Since they are not at increased risk of COVID-19 becoming severe, these patients are therefore excluded from the present therapeutic indication Patients with incomplete immunisation or at relevant risk of inadequate vaccine response as defined by the German Standing Committee on Vaccination (STIKO), however, possibly continue to be at risk of their disease becoming severe. According to COVRIIN, the same applies to patients exhibiting complex risk factors despite being immunocompetent and fully vaccinated. The COV-2067 study excluded patients who exhibited an inadequate vaccine response and were therefore not fully immunized. Likewise excluded were patients who, despite being immunocompetent and fully vaccinated, exhibited complex risk factors which result in an increased risk of their disease becoming severe. However, it is possible to transfer evidence from the unvaccinated patients in the COV-2067 study to patient groups which do not achieve complete immunization despite being vaccinated and who are at increased risk of their disease becoming severe. Nevertheless, it remains unclear whether the effects observed in unvaccinated patients are fully transferable to these patient groups. This issue has been taken into account in the assessment of the certainty of conclusions.

Furthermore, phase 3 of the COV-2067 study excluded patients with known positive serological SARS-CoV-2 test as well as patients with positive SARS-CoV-2 antigen test or molecular diagnostic test from a sample taken > 72 hours prior to randomization. Despite these limitations posed by inclusion criteria, about one fourth of the patients included in the study had a positive serostatus at baseline. Since the study population was to exclude recovered patients, those included in the COV-2067 study can be safely assumed to have had an asymptomatic infection. Therefore, it remains unclear whether the included patients with positive serostatus are comparable to patients who have recovered from symptomatic COVID-19 infection, which represent the majority of the population in the present therapeutic indication at the current time.

According to the SPC, decisions regarding the use of casirivimab/imdevimab should take into account what is known about the characteristics of circulating SARS-CoV-2 viruses, including regional or geographic differences and available information on casirivimab/imdevimab susceptibility patterns. This benefit assessment therefore assumes that the therapeutic indication excludes patients who are infected with a virus variant for which there is insufficient neutralizing activity – either demonstrably so or as expected based on the current pandemic situation. Based on the information provided in the dossier, it remains unclear with which virus variant COV-2067 study participants were infected and for how many patients a virus genotype

was even available. However, the omicron variant did not yet exist at the time the study population analysed in this benefit assessment (patients in cohort 1 from protocol amendment 6 to protocol amendment 8 [11/2020 to 02/2021]) was included. In vitro neutralization assays show that the neutralizing activity of casirivimab/imdevimab is markedly reduced against the omicron virus variant, which predominated at the time of the benefit assessment, therefore suggesting lower effectiveness. In case of the omicron variant, using casirivimab/imdevimab for the treatment of COVID-19 infection is therefore not recommended.

In summary, on the basis of the COV-2067 study, conclusions on added benefit can be drawn for patients who have not yet been vaccinated against SARS-CoV-2, who are not fully immunized against SARS-CoV-2, or who, due to complex risk factors, remain at increased risk of COVID-19 becoming severe despite being immunocompetent and fully vaccinated. The present therapeutic indication excludes patients who are fully immunized as well as patients who are infected with a virus variant for which neutralization activity is inadequate, either demonstrably so or as expected due to the current pandemic activity; therefore, said patients are not subject of the present benefit assessment.

Risk of bias and assessment of the certainty of conclusions

The risk of bias across outcomes was rated as low for the results of phase 3 of the COV-2067 study. The risk of bias on the outcome level is deemed low for the results of all outcomes except abatement of COVID-19 symptoms.

As described above, evidence can be transferred from unvaccinated patients included in the COV-2067 study to patient groups who do not reach full immunization despite vaccination or who have complex risk factors despite being immunocompetent and fully vaccinated. Nevertheless, it remains unclear whether the effects observed in unvaccinated patients are fully transferable to these patient groups. Overall, the certainty of conclusions of the study results for the present research question is therefore reduced. Based on the COV-2067 study, at most hints, e.g. of an added benefit, can be derived for all outcomes presented.

Results

Mortality

All-cause mortality

For the outcome of all-cause mortality, a statistically significant difference between treatment groups was found in favour of casirivimab/imdevimab. This results in a hint of added benefit of casirivimab/imdevimab in comparison with treatment of physician’s choice.

Morbidity

Hospitalization for COVID-19

For the outcome of hospitalization for COVID-19, a statistically significant difference between treatment groups was found in favour of casirivimab/imdevimab. This results in a hint of added benefit of casirivimab/imdevimab in comparison with treatment of physician’s choice.

Admission to intensive care unit due to COVID-19

No statistically significant difference between treatment groups was shown for the outcome of intensive care (ICU) admission due to COVID-19. This results in no hint of an added benefit of casirivimab/imdevimab in comparison with treatment of physician's choice; an added benefit is therefore not proven.

Abatement of COVID-19 symptoms (Symptoms Evolution of COVID-19 [SE-C19])

A statistically significant difference between treatment groups was found in favour of casirivimab/imdevimab for the outcome of abatement of COVID-19 symptoms, surveyed with SE-C19. However, an effect modification by the characteristic of age was found. For patients 18 to 64 years of age, this results in no hint of an added benefit of casirivimab/imdevimab in comparison with treatment of physician's choice; an added benefit is therefore not proven. For patients ≥ 65 years of age, in contrast, this results in a hint of added benefit of casirivimab/imdevimab in comparison with treatment of physician's choice.

Return to normal health, return to normal activities, and health status (European Quality of Life Questionnaire – 5 Dimensions [EQ-5D] visual analogue scale [VAS])

No usable data are available for the outcomes of return to normal health, return to normal activities, and health status as surveyed using EQ-5D VAS. For each of these outcomes, this results in no hint of an added benefit of casirivimab/imdevimab in comparison with treatment of physician's choice; an added benefit is therefore not proven.

Health-related quality of life

Outcomes on health-related quality of life were not recorded in the included study.

Side effects

Serious adverse events (SAEs), severe AEs, discontinuation due to AEs, and infusion-related reactions

No usable data are available for outcomes in the side effects category. In the survey of SAEs and severe AEs, the COV-2067 study included disease-related events. For these outcomes, Module 4 B of the company's dossier presents analyses excluding disease-related events, but it remains unclear which events the company deemed disease-related and therefore disregarded in the analyses. As a result, the total rates for SAEs and severe AEs are unusable for assessing the side effects of casirivimab/imdevimab. Further, the study failed to systematically survey discontinuation due to AEs. The COV-2067 study's results on infusion-related reactions are unusable due to (a) uncertainties regarding its operationalization and (b) an extended infusion duration. All things considered, no usable data are therefore available for assessing the side effects of casirivimab/imdevimab. Given the small percentage of patients with an event, however, no unfavourable effects of casirivimab/imdevimab of an extent which could call into question the added benefit of casirivimab/imdevimab are expected based on the results on common SAEs and severe AEs. For the side effects outcomes, this results in no hint of greater

or lesser harm from casirivimab/imdevimab in comparison with treatment of physician's choice; greater or lesser harm is therefore not proven.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

On the basis of the results presented, the probability and extent of added benefit of the drug combination of casirivimab/imdevimab in comparison with the ACT are assessed as follows:

As discussed, the below conclusion on added benefit applies only to adult patients who have not yet received any vaccination against SARS-CoV-2 or who are not fully immunized against SARS-CoV-2 or who have complex risk factors despite being immunocompetent and fully vaccinated. Patients who are completely immunized are excluded from the present benefit assessment because they are not at increased risk of COVID-19 becoming severe. In addition, the present therapeutic indication does not cover patients who are infected with a virus variant for which neutralizing activity is inadequate, either demonstrably so or as expected based on the current pandemic activity; consequently, these patients are not subject of the present benefit assessment.

No data are available for adolescents 12 to < 18 years of age weighing at least 40 kg who do not require supplemental oxygen and who are at increased risk of COVID-19 becoming severe. For this age group, there is therefore no proof of added benefit of casirivimab/imdevimab.

Overall, for adults with COVID-19 infection who do not require supplemental oxygen and who are at increased risk of COVID-19 becoming severe, only favourable effects of casirivimab/imdevimab were found in comparison with treatment of physician's choice. For the outcome of overall survival, there is a hint of a non-quantifiable added benefit. A hint of considerable added benefit was found for each of the outcomes of hospitalization for COVID-19 and abatement of COVID-19 symptoms (in older patients). For side effects, no usable data were available. However, the obtainable information does not suggest any unfavourable effects of an extent that might call the added benefit into question.

In summary, for adults with COVID-19 infection who do not require supplemental oxygen and who are at increased risk of COVID-19 becoming severe, there is a hint of considerable added benefit of casirivimab/imdevimab in comparison with treatment of physician's choice.

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) "proof", (2) "indication", (3) "hint", or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

Table 3 shows a summary of the probability and extent of added benefit of casirivimab/imdevimab.

Table 3: Casirivimab/imdevimab – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adults and adolescents from 12 years of age and weighing at least 40 kg with COVID-19[b] who do not require supplemental oxygen and who are at increased risk of COVID-19 becoming severe[c,d,e]	Treatment of physician's choice[f]	Patients ≥ 18 years: ▪ Hint of considerable added benefit
		Patients ≥ 12 to < 18 years of age: ▪ Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. In case of a positive rapid antigen test, the diagnosis of SARS-CoV-2 infection should be confirmed by a PCR test, especially if the results have therapeutic consequences.
c. In the recording and interpretation of effectiveness results, it is recommended for relevant SARS-CoV-2 mutation variants (e.g. variants of concern) to be taken into account.
d. According to the SPC, decisions regarding the use of casirivimab/imdevimab should take into consideration what is known about the characteristics of the circulating SARS-CoV-2 viruses, including regional or geographic differences and available information on casirivimab/imdevimab susceptibility patterns.
e. Patients who are completely immunized are excluded from the therapeutic indication.
f. Specific therapeutic measures are usually not required for mildly to moderately symptomatic COVID-19. Depending on the severity of disease, the treatment of physician's choice of non-hospitalized patients, if indicated, should primarily be chosen from symptomatic drug therapies (e.g. analgesics, antipyretics, thrombosis prophylaxis). If the disease progresses and the patient is hospitalized, further drug therapies (e.g. dexamethasone; anticoagulation/thrombosis prophylaxis, antibiotics) as well as non-drug therapies (e.g. oxygen supply, type of ventilation, balanced fluid therapy) must be considered.

ACT: appropriate comparator therapy; COVID-19: Coronavirus Disease 2019; G-BA: Federal Joint Committee; PCR: polymerase chain reaction; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus Type 2

The approach for the derivation of an overall conclusion on the added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

2.2 Research question

The aim of the present report is to assess the added benefit of casirivimab/imdevimab in comparison with the ACT in adults and adolescents from 12 years of age and weighing at least 40 kg with COVID-19 who do not require supplemental oxygen and who are at increased risk of their disease becoming severe.

The research question presented in Table 4 is derived from the ACT specified by the G-BA.

Table 4: Research question of the benefit assessment of casirivimab/imdevimab

Therapeutic indication	**ACT[a]**
Adults and adolescents from 12 years of age and weighing at least 40 kg with COVID-19[b] who do not require supplemental oxygen and who are at increased risk of their disease becoming severe[c, d]	Treatment of physician's choice[e]
a. Presented is the ACT specified by the G-BA. b. In case of a positive rapid antigen test, the diagnosis of SARS-CoV-2 infection should be confirmed by a PCR test, especially if the results have therapeutic consequences. c. In the recording and interpretation of effectiveness results, it is recommended for relevant SARS-CoV-2 mutation variants (e.g. variants of concern) to be taken into account. d. According to the SPC, decisions regarding the use of casirivimab/imdevimab should take into account what is known about the characteristics of circulating SARS-CoV-2 viruses, including regional or geographic differences and the available information on casirivimab/imdevimab susceptibility patterns [3]. e. Specific therapeutic measures are usually not required for mildly to moderately symptomatic COVID-19 disease. Depending on the severity of disease, the treatment of physician's choice of non-hospitalized patients, if indicated, should primarily be chosen from symptomatic drug therapies (e.g. analgesics, antipyretics, thrombosis prophylaxis). If the disease progresses and the patient is hospitalized, further drug therapies (e.g. dexamethasone; anticoagulation/thrombosis prophylaxis, antibiotics) as well as non-drug therapies (e.g. oxygen supply, type of ventilation, balanced fluid therapy) must be considered. ACT: appropriate comparator therapy; COVID-19: Coronavirus Disease 2019; G-BA: Federal Joint Committee; PCR: polymerase chain reaction; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus Type 2	

The company followed the G-BA's specification of the ACT.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier.

Neutralizing activity against SARS-CoV-2 virus variants

According to the SPC, decisions regarding the use of casirivimab/imdevimab should be informed by what is known about the characteristics of the circulating SARS-CoV-2 viruses, including regional or geographic differences and available information on casirivimab/ imdevimab susceptibility patterns [3]. In addition, the SPC specifies that, when molecular testing or sequencing data are available, they should be taken into account when selecting the antiviral therapy to rule out use against SARS-CoV-2 variants shown to have reduced susceptibility to casirivimab/imdevimab. This benefit assessment therefore assumes that the present therapeutic indication does not cover patients who are infected with a virus variant for

which neutralizing activity is insufficient – either demonstrably so or as expected based on the current pandemic situation.

The PEI and the RKI's COVRIIN division likewise recommend taking into account the current epidemiological situation and neutralizing activity against the individual virus variants when choosing monoclonal antibodies for treatment or prophylaxis [4,5]. Where a mutation analysis is not yet available, treatment should be selected based on the current epidemiological situation to avoid delaying treatment initiation. The present benefit assessment therefore is predicated on casirivimab/imdevimab being typically used only if sufficient neutralizing activity is assumed for the predominant virus variant. Because of its lack of effectiveness against the omicron variant, the use of casirivimab/imdevimab is currently not recommended.

2.3 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on casirivimab/imdevimab (status: 15 February 2022)
- bibliographical literature search on casirivimab/imdevimab (last search on 15 February 2022)
- search in trial registries / trial results databases for studies on casirivimab/imdevimab (last search on 15 February 2022)
- search on the G-BA website for casirivimab/imdevimab (last search on 15 February 2022)

To check the completeness of the study pool:

- search in trial registries for studies on casirivimab/imdevimab (last search on 27 April 2022); for search strategies, see Appendix A of the full dossier assessment

The check did not identify any additional relevant study.

2.3.1 Studies included

The study listed in the following table was included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: casirivimab/imdevimab versus placebo

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication (yes/no [citation])
R10933-10987-COV-2067 (COV-2067[c])	Yes	Yes	No	Yes [6,7]	Yes [8,9]	Yes [10,11]

a. Study for which the company was sponsor.
b. Citation of the trial registry entries and, if available, of the reports on study design and/or results listed in the trial registries.
c. In the tables below, the study will be referred to using this acronym.

CSR: clinical study report; RCT: randomized controlled trial

The R10933-10987-COV-2067 study (hereinafter referred to as COV-2067 study) was used for the benefit assessment. This concurs with the company's study pool.

2.3.2 Study characteristics

Table 6 and Table 7 describe the study used for the benefit assessment.

Table 6: Characteristics of the included study – RCT[a], direct comparison: casirivimab/imdevimab versus placebo (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[b]
COV-2067	RCT, double-blind, parallel	Non-hospitalized patients with confirmed COVID-19 infection[c] ▫ Cohort 1: ≥ 18 years ▫ Cohort 2[d, e] < 18 years ▫ Cohort 3[e, f]: pregnant ▪ With COVID-19 symptoms[g] with an onset ≤ 7 days before randomization[h] ▪ With ≥ 1 risk factor for COVID-19 becoming severe[i] ▪ Oxygen saturation ≥ 93% on room air ▪ Not hospitalized due to COVID-19 prior to randomization	Cohort 1[j]: ▪ Casirivimab/imdevimab 1200 mg (N = 1347) ▪ Casirivimab/imdevimab 2400 mg (N = 1350)[k] ▪ Placebo (N = 1349)[l]	Screening: ≤ 2 days Treatment: 1 day Observation: 169 days	95 centres in Mexico, Romania, United States 06/2020 – ongoing Data cut-offs: ▪ 18/02/2021 (interim analysis) ▪ 19/08/2021 (final analysis)	Primary: combined outcome of hospitalization due to COVID-19 or death due to any cause up to Day 29 Secondary: all-cause mortality, morbidity, AEs

Table 6: Characteristics of the included study – RCT[a], direct comparison: casirivimab/imdevimab versus placebo (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[b]

a. The COV-2067 study is an adaptive phase 1–3 study; presented is phase 3 of the study from protocol amendment 6 (14 November 2020), which is the phase relevant for the benefit assessment.
b. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes include only information on relevant available outcomes for this benefit assessment.
c. SARS-CoV-2 infection had to be confirmed by an antigen test, RT-qPCR test, or other molecular biological test from a sample taken ≤ 72 hours prior to randomization. From protocol amendment 6 onward, the study excluded patients with a positive SARS-CoV-2 antigen test or molecular diagnostic test from a sample taken > 72 hours prior to randomization as well as patients with a known history of positive serological SARS-CoV-2 test.
d. The study enrolled patients < 18 years of age only starting from protocol amendment 6 (only in countries where local law allowed doing so).
e. For the present benefit assessment, no analyses of cohorts 2 and 3 are available. These cohorts are disregarded in the following tables. Cohort 2 comprises a subpopulation relevant for the benefit assessment, while cohort 3 is irrelevant for the benefit assessment (see below for an explanation).
f. The study enrolled pregnant patients starting from protocol amendment 6, allocating them to cohort 1 or 2 based on their age. From protocol amendment 7 (18 December 2020), these patients were allocated to a separate cohort (cohort 3).
g. According to the opinion of the investigator.
h. Under protocol amendment 6, cohort 2 also included patients < 18 years who were asymptomatic at enrolment.
i. The risk factors applied only to cohorts 1 and 2 and were the following: age ≥ 50 years, obesity, cardiovascular disease including hypertension, chronic pulmonary disease including asthma, type 1 or type 2 diabetes mellitus, chronic kidney disease including dialysis, chronic liver disease, pregnancy (only under protocol amendment 6 due to a separate cohort for pregnant patients being used thereafter), immunosuppression; additionally, for cohort 2 only, starting from protocol amendment 7: any genetic underlying disorder, neurological disorder, metabolic disorder, or congenital heart disease which was deemed by the investigator to be a risk factor for the disease becoming severe. Under protocol amendment 6, the study also enrolled patients < 18 years of age who did not have any risk factors for the disease becoming severe but were living with a person with risk factor.
j. Only cohort 1 presented since no data were yet available for cohorts 2 and 3. For cohort 1, analyses are available on different analysis populations (see below for an explanation).
k. Arm is irrelevant for the assessment and is no longer presented in the following tables.
l. Figure based on patients in the placebo arm who were enrolled at the same time as patients in the 1200 mg study arm.

AE: adverse event; COVID-19: Coronavirus Disease 2019; N: number of randomized patients; RCT: randomized controlled trial; RT-qPCR: reverse transcriptase quantitative polymerase chain reaction; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus type 2

Table 7: Characteristics of the intervention – RCT[a], direct comparison: casirivimab/imdevimab versus placebo

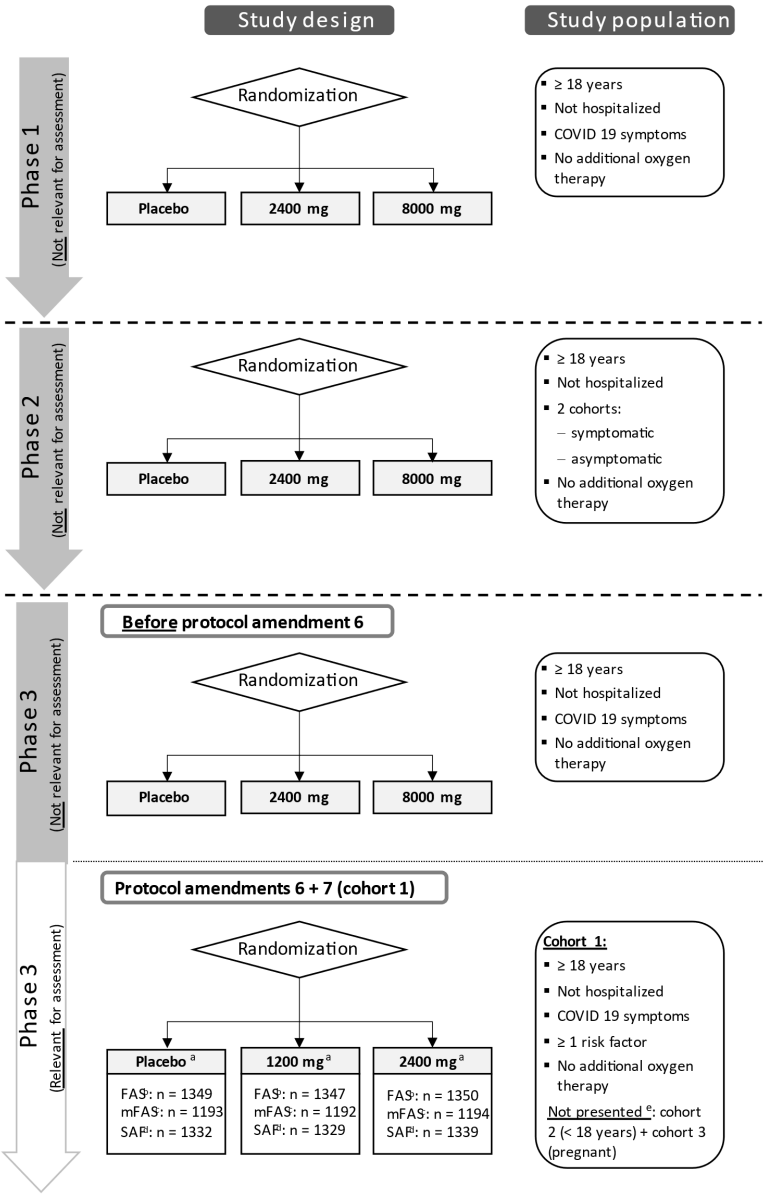
Study	Intervention	Comparison
COV-2067	Casirivimab/imdevimab 1200 mg (600 mg/600 mg), i.v., single dose on Day 1	Placebo i.v., single dose on Day 1
	For the single dose, no dose adjustments were allowed. In case of infusion reactions, dose interruptions were allowed; afterwards, continuing the infusion at 50% of the original infusion rate was allowed. The infusion was discontinued in the presence of anaphylaxis, laryngeal or pharyngeal oedema, severe bronchospasm, chest pain, seizure, severe hypotension, neurological symptoms as well as symptoms which, in the investigator's opinion, require doing so.	
	Prohibited prior and concomitant treatment ▪ ≤ 30 days[b] before screening: COVID-19 convalescent plasma[c], monoclonal antibodies against SARS-CoV-2[c], intravenous immunoglobulins[c], systemic corticosteroids, or any authorized, approved, or investigational COVID-19 treatment ▪ SARS-CoV-2 or COVID-19 vaccines [d]	

a. The COV-2067 study is an adaptive phase 1–3 study; presented is phase 3 of the study from protocol amendment 6 (14 November 2020), which is the phase relevant for the benefit assessment.
b. Or ≤ 5 half-lives, whichever is longer.
c. In studies assessing these investigational products, this period was ≤ 3 months before screening or ≤ 5 half-lives of the product.
d. From protocol amendment 7 (18 December 2020), SARS-CoV-2 vaccination was allowed from 90 days after administration of the study medication.

COVID-19: Coronavirus Disease 2019; i.v.: intravenous; RCT: randomized controlled trial; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus Type 2

The COV-2067 study is an adaptive, placebo-controlled double-blind, randomized, phase 1–3 study on the treatment with casirivimab/imdevimab in patients with COVID-19. The study included only outpatients with early-stage COVID-19 who did not require any supplemental oxygen therapy (oxygen saturation ≥ 93% on room air). Depending on study phase and cohort, both symptomatic and asymptomatic patients were enrolled, as were both patients with at least 1 risk factor or no risk factors for COVID-19 becoming severe. The SARS-CoV-2 infection was detected via an antigen test, reverse transcriptase quantitative polymerase chain reaction (RT-qPCR) test, or another molecular diagnostic test from a sample collected ≤ 72 hours before randomization.

The study was conducted using a master protocol governing phases 1, 2, and 3. In the course of the study, the master protocol was modified multiple times with regard to the dosage used and inclusion and exclusion criteria, some of which differed between study phases. Figure 1 graphically presents the individual study phases with the patients investigated and doses applied.



a. The placebo arm was closed as of protocol amendment 8 (12 March 2021). Patients who were included under amendment 8 or later are irrelevant for this benefit assessment and are not presented.
b. The FAS population comprises all randomized patients.
c. The mFAS population comprises all patients from the FAS population who have a positive RT-qPCR test for SARS-CoV-2 from a nasopharyngeal swab confirmed by the central laboratory at baseline. For this analysed population, the dossier presents evaluations on the outcomes of the mortality and morbidity categories.
d. The SAF population comprises all randomized patients who received the study medication. For this analysed population, the dossier presents analyses on the outcomes of the side effects category.
e. For cohorts 2 and 3, no data are available at the time of this benefit assessment.
COVID-19: Coronavirus Disease 2019; FAS: full analysis set; mFAS: modified full analysis set; n: number of patients in the analysed population; RT-qPCR: reverse transcriptase quantitative polymerase chain reaction; SAF: safety analysis set; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus Type 2

Figure 1: Graphic presentation of the COV-2067 study design

The study's phase 1 enrolled adult patients symptomatic for COVID-19 randomly allocated them in a 1:1:1 ratio to a single intravenous dose of 2400 mg casirivimab/imdevimab, 8000 mg casirivimab/imdevimab, or placebo. Phase 2 enrolled both symptomatic and asymptomatic adult patients in 2 separate cohorts. In both cohorts, patients were randomly allocated in a 1:1:1 ratio to a single intravenous dose of 2400 mg casirivimab/imdevimab, 8000 mg casirivimab/imdevimab, or placebo. In phases 1 and 2, the study duration was 29 days.

At the beginning of phase 3, adult patients were first allocated to the respective study arms in accordance with the phase 2 randomization scheme. Protocol amendment 6 dated 14 November 2020 modified the phase 3 study design on the basis of the data collected in phases 1 and 2. Patients were now placed in 1 of 2 cohorts. Adult patients were put in cohort 1. Patients < 18 years of age were placed in cohort 2. Patients who were pregnant at the time of randomization were allocated to either cohort 1 or 2 based on age. Starting from protocol amendment 7 dated 18 December 2020, pregnant people were placed in a separate cohort 3. With protocol amendment 6, the 8000 mg study arm was closed, and a new study arm with 1200 mg casirivimab/imdevimab was introduced. Starting from protocol amendment 8 dated 12 March 2021, upon recommendation by the Independent Data Monitoring Committee (IDMC), patients were no longer randomized to the placebo arm. In phase 3, casirivimab/imdevimab was administered once intravenously on Day 1, followed by a 169-day follow-up observation phase.

Starting from protocol amendment 6, the study excluded patients with an antigen test or molecular diagnostic test positive for SARS-CoV-2 from a sample taken > 72 hours prior to randomization as well as patients with a known history of a positive serological SARS-CoV-2. The study also excluded patients with a history of hospitalization for COVID-19. In addition, patients who had received at least 1 vaccination against SARS-CoV-2 were excluded from the study. Starting from protocol amendment 7, however, vaccination was allowed from 90 days after administration of the study medication.

Patients included in cohort 1 had to have symptoms consistent with COVID-19, with an onset ≤ 7 days before randomization and ≥ 1 risk factor for the disease becoming severe. Under protocol amendments 6 and 7, a total of 4046 patients were randomized in a 1:1:1 ratio to 1200 mg casirivimab/imdevimab (N = 1347), 2400 mg casirivimab/imdevimab (N = 1350), or placebo (N = 1349) in cohort 1. Randomization was stratified by country, with centres in the United States, Mexico, and Romania participating according to the study protocol. However, cohort 1 was recruited predominantly in study centres in the United States. For cohort 1, the primary outcome is the combined outcome of hospitalization for COVID-19 or death due to any cause by Day 29. Patient-relevant secondary outcomes are all-cause mortality as well as outcomes on morbidity and AEs. These outcomes were to be observed until Day 29. The observation duration for all-cause mortality and AEs, in contrast, was 169 days.

According to protocol amendment 6, both symptomatic and asymptomatic patients were eligible for inclusion in cohort 2. Patients had to either exhibit ≥ 1 risk factor for COVID-19

becoming severe or live with a person with a risk factor. From protocol amendment 7, enrolment was limited to symptomatic patients exhibiting ≥ 1 risk factor for their disease becoming severe. Like in cohort 1, patients were randomized to 1 of the 3 study arms (1200 mg casirivimab/imdevimab, 2400 mg casirivimab/imdevimab, or placebo), but the casirivimab/imdevimab dose was adjusted based on bodyweight. Patients ≥ 40 kg body weight received the same casirivimab/imdevimab dose as adults in cohort 1 (either 1200 mg or 2400 mg). Patients < 40 kg received a reduced weight-adjusted dose.

Pregnant patients included in cohort 3 were randomly allocated in a 1:1 ratio to the 1200 mg study arm or the 2400 mg study arm. None of them were randomized to placebo. As described for cohort 2, cohort 3 patients who were < 18 years old also received a weight-adjusted casirivimab/imdevimab dose. Patients had to be symptomatic. The study protocol did not provide for the presence of additional risk factors other than pregnancy. For the present benefit assessment, the company presented no data on cohorts 2 and 3.

In all study cohorts, casirivimab/imdevimab was administered as a single intravenous infusion. Treatment was largely in accordance with the SPC [3], with the infusion being administered for a longer period than specified in the SPC of 20 to 30 minutes (median duration of casirivimab/imdevimab infusion is 60 minutes [1st quartile to 3rd quartile: 60 to 67 minutes]). The SPC additionally allows subcutaneous injection, but this administration route was not investigated in the study. However, subcutaneous administration is recommended only where intravenous administration is impossible and would lead to a delay in treatment.

Study phases and cohorts relevant for the benefit assessment

The data surveyed in phases 1 and 2 as well as data from phase 3 prior to protocol amendment 6 are irrelevant for the benefit assessment due to deviations from the SPC regarding the administered casirivimab/imdevimab dose [3]. The dose specified in the SPC of 1200 mg casirivimab/imdevimab was used only in phase 3, starting from protocol amendment 6. From protocol amendment 8, patients were no longer randomized to placebo, but exclusively to 2 different dosages of casirivimab/imdevimab. Data relevant for the benefit assessment are those on patients from study phase 3 who were allocated to either 1200 mg casirivimab/imdevimab or to placebo under protocol amendment 6 and 7. For cohort 1, the company submitted data on this patient population in the dossier's Module 4 B.

Cohort 2 includes a subpopulation which would in principle be relevant for the benefit assessment: patients between 12 and < 18 years of age weighing at least 40 kg who exhibit symptoms of COVID-19 as well as ≥ 1 risk factor for their disease becoming severe. Patients weighing < 40kg, in contrast, received a weight-adjusted dose which differed from SPC specifications. As described above, however, the dossier does not present any data for the cohort 2 subpopulation which is relevant for this benefit assessment. Therefore, the available data allow drawing a conclusion on added benefit only for adults with COVID-19. Data on cohort 3 are irrelevant for the present benefit assessment because all patients in this cohort were treated with casirivimab/imdevimab, and none were randomized to placebo. On the basis of the

data on this cohort's pregnant patients, it is therefore impossible to draw a comparison with the ACT.

Analysis population

At the time the present benefit assessment is conducted, 2 data cut-offs are available for the COV-2067 study which comprise analyses of the patients of cohort 1 who were recruited into study phase 3 under protocol amendment 6 or later and were treated with the 1200-mg dose of casirivimab/imdevimab or received placebo. The 1st data cut-off from 18 February 2021 comprises an interim analysis of all patients randomized by 17 January 2021. The 2nd data cut-off from 19 August 2021 comprises all patients in cohort 1 who were randomized by 24 February 2021 under protocol amendments 6 and 7, including the 169-day follow-up observation. The present benefit assessment uses this 19 August 2021 data cut-off, which represents the final analysis of patients in cohort 1 who were treated with the 1200-mg dose of casirivimab/imdevimab.

For the 2nd data cut-off dated 19 August 2021, the company's dossier presents only analyses based on the modified full analysis set (mFAS) population of cohort 1 (N = 1192 in the casirivimab/imdevimab arm and N = 1193 in the placebo arm) for mortality and morbidity outcomes. In comparison with the full analysis set (FAS) population, which represents all patients randomized in cohort 1, the mFAS population comprises only patients who had a positive SARS-CoV-2 RT-qPCR test from a nasopharyngeal swab confirmed by the central laboratory at baseline. Hence, the analyses disregarded any patients included in the study based on positive SARS-CoV-2 results from a different test method whose results were not confirmed at study start by testing at the central laboratory. According to the recommendations by the German College of General Practitioners and Family Physicians (DEGAM S2e guideline dated 4 February 2022), however, starting treatment on the basis of symptoms and a positive antigen rapid test is permissible in case of exhausted PCR test capacities [12]. Against this background, analyses of the FAS population would generally be relevant for the present benefit assessment. Since the mFAS population makes up > 80% of the FAS population, the analyses presented by the company on the basis of the mFAS population for the outcomes of the mortality and morbidities categories are nevertheless usable despite the restriction to patients with a positive SARS-CoV-2 RT-qPCR test confirmed by the central laboratory.

On the other hand, the analyses presented in the company's dossier from the 2nd data cut-off of 19 August 2021 for outcomes of the side effects category are based on the safety analysis set (SAF) population, which also includes patients in whom SARS-CoV-2 infection was not confirmed at baseline by an RT-qPCR test performed in the central laboratory (N = 1329 in the casirivimab/imdevimab arm and N = 1332 in the placebo arm). Additionally, unlike the FAS population, the SAF population takes into account only patients who received the study medication. Since the mFAS population makes up > 80% of the SAF population in both study arms, the discrepancy between the analysis populations remains without consequence for the benefit assessment.

Implementation of the ACT

The G-BA specified treatment of physician's choice as ACT. Mildly to moderately symptomatic COVID-19 usually requires no specific therapeutic measures. Depending on the severity of disease, symptomatic drug therapies (e.g. analgesics, antipyretics, thrombosis prophylaxis) should therefore primarily be taken into account in the treatment of physician's choice of non-hospitalized patients, if indicated. If the disease progresses and the patient is hospitalized, further drug therapies (e.g. dexamethasone, anticoagulation / thrombosis prophylaxis, antibiotics) and non-drug therapies (oxygen supply, type of ventilation, balanced fluid therapy) must be included.

According to the current evaluation by the RKI's COVRIIN department (as of 3 May 2022), in addition to casirivimab/imdevimab, the virostatics nirmatrelvir/ritonavir, molnupiravir and remdesivir as well as the neutralizing monoclonal antibody sotrovimab are available as antiviral therapy of early COVID-19 in patients with risk factors for the disease becoming severe [13]. At the time of the benefit assessment, molnupiravir has not been approved. The COVRIIN recommendations largely overlap with the recommendations by the current guidelines at the time of the benefit assessment (S3 guideline on inpatient therapy of patients with COVID-19 [as of 28 February 2022] and DEGAM guideline [as of 4 February 2022] [12,14]). However, the guidelines issue merely a weak or open recommendation for these substances for specific risk groups. This is justified in particular by the evolution of new virus variants with potentially changed pathogenicity and the population's increased immunocompetence, promoted in particular by vaccination and prior virus exposure. Overall, according to information provided in the S3 guideline [14], it is therefore difficult to quantify the current risk of requiring inpatient or outpatient therapy, experiencing longer-term limitations of quality of life, or dying due to SARS-CoV-2 infection. The suitable treatment should be selected on a case-by-case basis, taking into account individualized risk profile, immunization status, comorbidities, availability, and contraindications.

Administered concomitant therapies in the COV-2067 study

The COV-2067 study disallows the use of COVID-19 convalescent plasma, monoclonal antibodies against SARS-CoV-2, intravenously administered immunoglobulins, systemic corticosteroids, or any approved, authorized, or investigational COVID-19 treatment. Accordingly, the use of other antiviral drugs for treating COVID-19 is likewise disallowed. Further, some of the monoclonal antibodies or antiviral drugs against COVID-19 were not yet available at the time the study was conducted. No other limitations or concrete specifications existed for concomitant treatment in the intervention arm or the control arm. For treatment of disease progression during the study, the study protocol likewise provided no limitations or specifications regarding the use of drug or non-drug therapies. In these cases, COVID-19 therapy was to follow local standards.

Table 8 lists information on the concomitant therapies received by ≥ 2% of patients in at least 1 study arm of cohort 1 (protocol amendment 6 or later) up to Day 29.

Table 8: Information on concomitant therapies up to Day 29 (≥ 2% of patients in ≥ 1 study arm) – RCT[a], direct comparison: casirivimab/imdevimab versus placebo (multipage table)

Study Drug class[b] Drug	Patients with concomitant therapy n (%)	
	Casirivimab/imdevimab N = 1192	Placebo N = 1193
COV-2067 (phase 3, cohort 1)		
Total	789 (66.2)	786 (65.9)
Analgesics	300 (25.2)	290 (24.3)
Paracetamol	251 (21.1)	245 (20.5)
Drugs with effect on the renin-angiotensin system	248 (20.8)	233 (19.5)
Lisinopril	100 (8.4)	99 (8.3)
Losartan	61 (5.1)	81 (6.8)
Drugs against obstructive airway disease	130 (10.9)	152 (12.7)
Salbutamol	83 (7.0)	99 (8.3)
Antiphlogistic and antirheumatic agents	130 (10.9)	139 (11.7)
Ibuprofen	92 (7.7)	107 (9.0)
Agents influencing lipid metabolism	136 (11.4)	100 (8.4)
Atorvastatin	56 (4.7)	31 (2.6)
Antithrombotic agents	100 (8.4)	110 (9.2)
Acetylsalicylic acid	82 (6.9)	83 (7.0)
Antibiotics for systemic use	92 (7.7)	94 (7.9)
Azithromycin	61 (5.1)	54 (4.5)
Vitamins	90 (7.6)	95 (8.0)
Vitamin D, unspecified	34 (2.9)	36 (3.0)
Ascorbic acid	50 (4.2)	48 (4.0)
Vitamins, unspecified	25 (2.1)	18 (1.5)
Antidiabetics	87 (7.3)	91 (7.6)
Metformin	66 (5.5)	65 (5.4)
Beta-adrenoreceptor antagonists	69 (5.8)	69 (5.8)
Metoprolol	28 (2.3)	29 (2.4)
Calcium channel blockers	74 (6.2)	59 (4.9)
Amlodipine	60 (5.0)	43 (3.6)
Diuretics	64 (5.4)	69 (5.8)
Hydrochlorothiazide	46 (3.9)	48 (4.0)
Drugs for acid-related disorders	53 (4.4)	67 (5.6)
Omeprazole	20 (1.7)	38 (3.2)
Psychoanaleptics	65 (5.5)	54 (4.5)
Psycholeptics	58 (4.9)	54 (4.5)
Cough and cold medicines	43 (3.6)	55 (4.6)
Thyroid therapy	54 (4.5)	44 (3.7)
Levothyroxine	30 (2.5)	26 (2.2)
Minerals	45 (3.8)	45 (3.8)
Zinc	31 (2.6)	26 (2.2)

Table 8: Information on concomitant therapies up to Day 29 (≥ 2% of patients in ≥ 1 study arm) – RCT[a], direct comparison: casirivimab/imdevimab versus placebo (multipage table)

Study Drug class[b] Drug	Patients with concomitant therapy n (%) Casirivimab/imdevimab N = 1192	 Placebo N = 1193
Corticosteroids for systemic use	29 (2.4)	60 (5.0)
Dexamethasone	8 (0.7)	39 (3.3)
Antihistamines for systemic use	44 (3.7)	34 (2.8)
Antiviral agents for systemic application	22 (1.8)	40 (3.4)
Sexual hormones and modulators of the genital system	25 (2.1)	29 (2.4)
All other therapeutic agents	10 (0.8)	33 (2.8)
Oxygen	8 (0.7)	32 (2.7)

a. The COV-2067 study is an adaptive phase 1–3 study; presented is the study's phase 3 starting from protocol amendment 6 (14 November 2020), which is the phase relevant for the benefit assessment.
b. ATC level 2.

ATC: Anatomic Therapeutic Chemical classification system for active ingredients and drugs; mFAS: modified full analysis set; n: number of patients with at least 1 concomitant therapy; N: number of randomized patients of the mFAS population; RCT: randomized controlled trial

As concomitant therapies for COVID-19, particularly antiinflammatory agents and analgesics were administered in the COV-2067 study. They were administered at about equal frequencies in the 2 study arms. A small percentage of patients received specific therapeutic measures including systemic corticosteroids such as dexamethasone, remdesivir, or supplemental oxygen. However, these therapies are recommended only in later phases of COVID-19. There was a trend toward more common use in the control arm (dexamethasone: 8 versus 39 patients in the intervention versus control arm; remdesivir: 2 versus 18 patients in the intervention versus control arm; supplemental oxygen: 8 versus 32 patients in the intervention versus control arm). According to the study protocol, no monoclonal antibodies or other antiviral drugs against SARS-CoV-2 were used. Other concomitant therapies frequently used in the study reflect the underlying illnesses of the enrolled patients with risk factors for the disease becoming severe.

Overall, concomitant treatment with anti-inflammatory and analgesic drugs in the COV-2067 study is a sufficient implementation of the ACT. While the guideline recommends specific antiviral substances for early-phase COVID-19 in patients at increased risk of their disease becoming severe, the study disallowed these substances. As described above, however, according to guidelines, these treatment options are merely given a weak or open recommendation for specific risk groups. In addition, the treatment of patients with COVID-19 can be safely assumed to have continuously changed over the course of the pandemic, particularly in light of increasing SARS-CoV-2 immunocompetence due to vaccinations and prior virus exposure as well as the evolution of new virus variants with potentially differing pathogenicity. Overall, the fact that the COV-2067 study disallowed specific antiviral substances therefore remains without consequence for the present benefit assessment.

Patient characteristics

Table 9 shows the patient characteristics of the included study.

Table 9: Characteristics of the study population as well as study/treatment discontinuation – RCT[a], direct comparison: casirivimab/imdevimab versus placebo (multipage table)

Study Characteristic Category	Casirivimab/imdevimab N = 1192	Placebo N = 1193
COV-2067 (phase 3, cohort 1)		
Age [years], mean (SD)	48 (15)	47 (15)
Age [years], n (%)		
18 to 64	1043 (88)	1051 (88)
65 to 74	100 (8)	108 (9)
≥ 75	49 (4)	34 (3)
Sex [f/m], %	51/49	51/49
Country, n (%)		
United States	1116 (94)	1112 (93)
Mexico	76 (6)	81 (7)
Body weight [kg], mean (SD)	90.6 (23.0)	89.8 (22.6)
Viral load at start of study, n (%)[b]		
≤ 10^5 copies/mL	260 (22)	242 (20)
> 10^5 to 10^6 copies/mL	158 (13)	183 (15)
> 10^6 to 10^7 copies/mL	183 (15)	205 (17)
> 10^7 copies/mL	590 (49)	561 (47)
Unknown	1 (< 1)	2 (< 1)
Serostatus at start of study, n (%)		
Negative	798 (67)	813 (68)
Positive	311 (26)	284 (24)
Others/unclear[c]	83 (7)	96 (8)
Symptom duration prior to randomization [days], median [Q1; Q3]	3 [2; 5]	3 [2; 5]
Risk factors for COVID-19 becoming severe, n (%)		
Age ≥ 50 years	594 (50)	565 (47)
Obesity (BMI ≥ 30)	687 (58)	705 (59)
Cardiovascular disease	439 (37)	418 (35)
Chronic pulmonary disease	200 (17)	209 (18)
Diabetes mellitus	144 (12)	153 (13)
Chronic kidney disease	11 (1)	9 (1)
Chronic liver disease	8 (1)	5 (< 1)
Immunosuppression	32 (3)	17 (1)

Table 9: Characteristics of the study population as well as study/treatment discontinuation – RCT[a], direct comparison: casirivimab/imdevimab versus placebo (multipage table)

Study Characteristic Category	Casirivimab/imdevimab N = 1192	Placebo N = 1193
Treatment discontinuation, n (%)	ND	ND
Study discontinuation, n (%)[d]	55 (5)	63 (5)

a. The COV-2067 study is an adaptive phase 1–3 study; presented is the study's phase 3 starting from protocol amendment 6 (14 November 2020), which is the phase relevant for the benefit assessment.
b. Viral load in nasopharyngeal swabs.
c. Serostatus is rated "other/unclear" if it is neither positive nor negative (e.g. borderline result) or unknown.
d. Common reasons for study discontinuation in the intervention versus control arms: loss to follow-up (2.3% vs. 2.5%) or patient decision (2.1% vs. 2.0%).

BMI: body mass index; COVID-19: Coronavirus Disease 2019; f: female; m: male; mFAS: modified full analysis set; n: number of patients in the category; N: number of randomized patients of the mFAS population; ND: no data; Q1; 1st quartile; Q3: 3rd quartile; RCT: randomized controlled trial; SD: standard deviation

The patient characteristics were largely comparable between the 2 study arms. The average patient age was about 48 years. The sex ratio was nearly balanced between the study arms. In both study arms, nearly half of the patients exhibited a high viral load (> 10^7 copies/mL) at baseline. About a quarter of patients in both study arms had a positive serostatus at baseline. In both study arms, the median time of COVID-19 symptom onset was 3 days before randomization. The most common risk factors were age ≥ 50 years, obesity, cardiovascular disease, chronic pulmonary disease, and diabetes mellitus. The study was conducted predominantly in the United States, with only a small percentage of patients being enrolled in centres outside the United States.

Limitations of the study population in comparison with the current pandemic situation

As described above, patients with at least 1 vaccination against SARS-CoV-2 were excluded from phase 3 of the COV-2067 study. At the time of the benefit assessment, however, a large percentage of the population has already been completely immunized as defined by the STIKO [15] through vaccinations and potential prior virus exposure, which reduces the risk of COVID-19 becoming severe. Since they are not at increased risk of COVID-19 becoming severe, these patients are therefore excluded from the present therapeutic indication Patients with incomplete immunisation or those at relevant risk of inadequate vaccine response as defined by the STIKO [15], however, might continue to be at risk of the disease becoming severe. According to COVRIIN, the same applies to patients who have complex risk factors despite being immunocompetent and fully vaccinated [13]. Patients who exhibited inadequate vaccine response and are therefore not completely immunized were excluded from the COV-2067 study. Likewise excluded were patients who, despite being immunocompetent and fully vaccinated, had complex risk factors which put them at increased risk for their disease becoming severe. However, it is possible to transfer evidence from the unvaccinated patients in the COV-2067 study to patient groups which do not achieve complete immunization despite

being vaccinated and who are at increased risk of their disease becoming severe. Nevertheless, it remains unclear whether the effects observed in unvaccinated patients are fully transferable to these patient groups. This issue has been taken into account in the assessment of the certainty of conclusions (see Section 2.4.2).

Furthermore, phase 3 of the COV-2067 study excluded patients with known positive serological SARS-CoV-2 test as well as patients with positive SARS-CoV-2 antigen test or molecular diagnostic test from a sample taken > 72 hours prior to randomization. Despite these limitations posed by inclusion criteria, about one-fourth of the patients included in the study had a positive serostatus at baseline. Since the study population was to exclude recovered patients, those included in the COV-2067 study can be safely assumed to have had an asymptomatic infection. Therefore, it remains unclear whether the included patients with positive serostatus are comparable to patients who have recovered from symptomatic COVID-19 infection, which represent the majority of the population in the present therapeutic indication at the current time.

According to the SPC, decisions regarding the use of casirivimab/imdevimab should be informed by what is known about the characteristics of the circulating SARS-CoV-2 viruses, including regional or geographic differences and available information on casirivimab/imdevimab susceptibility patterns [3]. In the present benefit assessment, it is therefore assumed that the present therapeutic indication excludes patients who are infected with a virus variant for which neutralizing activity is insufficient – either demonstrably so or as expected based on the current pandemic situation (see Section 2.2 for a detailed discussion). Based on the information provided in the dossier, it remains unclear with which virus variant COV-2067 study participants were infected and for how many patients a virus genotype was even available. However, the omicron variant did not yet exist at the time the study population analysed in this benefit assessment (patients in cohort 1 from protocol amendment 6 to protocol amendment 8 [11/2020 to 02/2021]) was included. In vitro neutralization assays show that the neutralizing activity of casirivimab/imdevimab is markedly reduced against the omicron virus variant, which predominated at the time of the benefit assessment, therefore suggesting lower effectiveness. Hence, casirivimab/imdevimab is not recommended for the treatment of COVID-19 infection in the presence of the omicron variant [4,5].

In summary, on the basis of the COV-2067 study, conclusions on added benefit can be drawn for patients who are unvaccinated against SARS-CoV-2, who are not fully immunized against SARS-CoV-2, or who despite being immunocompetent and fully vaccinated, remain at increased risk of COVID-19 becoming severe due to complex risk factors. The present therapeutic indication excludes patients who are fully immunized as well as patients who are infected with a virus variant for which neutralization activity is inadequate, either demonstrably so or as expected due to the current pandemic activity; therefore, said patients are not subject of the present benefit assessment.

Risk of bias across outcomes (study level)

Table 10 shows the risk of bias across outcomes (risk of bias at study level).

Table 10: Risk of bias across outcomes (study level) – RCT[a], direct comparison: casirivimab/imdevimab versus placebo

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
COV-2067	Yes	Yes	Yes	Yes	Yes	Yes	Low

a. The COV-2067 study is an adaptive phase 1–3 study; presented is phase 3 of the study from protocol amendment 6 (14 November 2020), which is the phase relevant for the benefit assessment.

RCT: randomized controlled trial

The risk of bias across outcomes was rated as low for the results of the COV-2067 study's phase 3.

Transferability to the German health care context

The company deems the results of the COV-2067 study to be transferable to the German health care context based on the comparability between the patient characteristics of the study population and the SARS-CoV-2-infected German population. The company argues that SARS-CoV-2 infects all age groups equally, and women and men are affected by SARS-CoV-2 infection at about equal rates. From the company's perspective, the study population adequately covers the age groups and sex ratios. The company further deems the relevant therapeutic indication to be patients with risk factors for COVID-19 becoming severe. In the company's opinion, the population included in the COV-2067 study is congruent with the population at increased risk of the disease becoming severe in the German healthcare context as defined by the RKI. The company further argues that the risk factor distribution in the COV-2067 study corresponds to the distribution of said risk factors in the German overall population.

Regarding the transferability of results taking into account the currently predominant virus variant, the company suggests an approach based on the virus variant (and the respective neutralizing ability of casirivimab/imdevimab) and its treatment. From the company's perspective, this results in 2 case constellations:

1) casirivimab/imdevimab neutralizes a virus variant and
2) casirivimab/imdevimab does not neutralize a virus variant, e.g. omicron.

According to the company, casirivimab/imdevimab can be used in the 1st case, while it is not used in the 2nd case, in accordance with the COVRIIN comments in the treatment recommendations, the PEI comments, and the notes found in the SPC [3,4,16]. In summary, the company deems the COV-2067 study data to always be transferable to the German healthcare

system, but the number of persons benefiting continuously changes over the course of the pandemic, taking into account the predominant virus variant.

The company did not provide any further information on the transferability of the study results to the German health care context.

The overall limited transferability to the current pandemic situation in Germany is discussed in detail in the previous section.

2.4 Results on added benefit

2.4.1 Outcomes included

The following patient-relevant outcomes were to be taken into account in the assessment:

- Mortality
  - all-cause mortality
- Morbidity
  - hospitalization for COVID-19
  - admission to intensive care unit due to COVID-19
  - abatement of COVID-19 symptoms (SE-C19)
  - return to normal health
  - return to normal activities
  - health status (EQ-5D VAS)
- Health-related quality of life
- Side effects
  - SAEs
  - severe AEs (operationalized as Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3)
  - discontinuation due to AEs
  - infusion-related reactions
  - further specific AEs, if any

The choice of patient-relevant outcomes deviates from that made by the company, which used further outcomes in the dossier (Module 4 B).

Table 11 shows for which outcomes data were available in the included study.

Table 11: Characteristics of the intervention – RCT[a], direct comparison: casirivimab/imdevimab versus placebo

Study	Outcomes												
	All-cause mortality[b]	Hospitalization for COVID-19[c]	Admission to intensive care unit due to COVID-19	Abatement of COVID-19 symptoms (SE-C19)	Return to normal health	Return to normal activities	Health status (EQ-5D VAS)	Health-related quality of life	SAEs	Severe AEs[d]	Discontinuation due to AEs	Infusion-related reactions	Further specific AEs
COV-2067	Yes	Yes	Yes	Yes	No[e]	No[e]	No[e]	No[f]	No[g]	No[g]	No[h]	No[i]	No[j]

a. The COV-2067 study is an adaptive phase 1–3 study; presented is phase 3 of the study from protocol amendment 6 (14 November 2020), which is the phase relevant for the benefit assessment.
b. Death due to any cause up to and including Day 169.
c. The company did not provide any additional information on the operationalization (e.g. regarding a minimum time).
d. Severe AEs are operationalized as CTCAE grade ≥ 3.
e. No usable data available due to the return rates being generally low and fluctuating strongly across the observation period (see text below for an explanation).
f. Outcome not recorded.
g. The company did not provide any information as to which events it classified as disease-related (see below for an explanation).
h. Discontinuation due to AEs was not systematically surveyed in the COV-2067 study.
i. No usable data available because it remains unclear how infusion-related reactions were surveyed in the study (see below for explanation).
j. No other specific AEs were identified based on the SAEs or severe AEs occurring in the relevant study. AEs were not systematically surveyed in the relevant study; selecting specific AEs on the basis of the AEs which occurred is therefore impossible.

AE: adverse event; COVID-19: Coronavirus Disease 2019; CTCAE: Common Terminology Criteria for Adverse Events; RCT: randomized controlled trial; SAE: serious adverse event; SE-C19: Symptoms Evolution of COVID-19; VAS: visual analogue scale

Morbidity

Hospitalization for COVID-19 / for any cause

Regarding hospitalization for COVID-19, the company's dossier presents analyses of the percentage of patients with an event up to and including Day 29. The study documents and Module 4 B of the company's dossier do not show under which conditions patients were hospitalized for COVID-19. In addition, it remains unclear whether the hospitalization was associated with a minimum length of stay, e.g. 24 hours. The dossier does not provide information on hospitalization for any cause.

Hospitalization for COVID-19 was used in the present benefit assessment. Hospitalization is assumed to have occurred upon the treating physician's discretion. On the basis of the

information provided on the percentage of patients requiring supplemental oxygen due to COVID-19, hospitalization for COVID-19 is additionally assumed to represent a sufficient approximation of the occurrence of severe courses of disease.

Abatement of COVID-19 symptoms (surveyed with SE-C19)

The COV-2067 study surveyed COVID-19 symptoms using the SE-C19 questionnaire. The SE-C19 has been validated by the company for surveying symptoms in outpatients with COVID-19 [17-19]. The survey comprised the 19 symptoms of fever, sore throat, cough, shortness of breath or difficulty breathing, chills, nausea, diarrhoea, headache, red or water eyes, body and muscle aches, loss of taste or smell, fatigue, loss of appetite, dizziness, pressure or tight chest, chest pain, stomach ache, runny nose, and sputum/phlegm. In the COV-2067 study, COVID-19 symptoms were rated by patients and recorded in an electronic diary every day for the previous 24 hours, from Day 1 up to and including Day 29. The severity of symptoms was rated on a 3-point scale (0: none; 1: mild/moderate; 2: severe). The company's dossier presents analyses for time to symptom abatement. For most symptoms, abatement was defined as a score of 0 on the severity scale. Only for the symptoms of headache, fatigue, and cough was a score of 1 allowed. Patients who had a combined raw score ≤ 3 across all symptoms (e.g. a score of 1 for 3 symptoms) were censored. Return rates were typically above 70% throughout the observation period. In departure from this trend, the return rate on Day 29 was < 50% in both study arms. However, the questionnaire was surveyed daily, with return rates being adequate at > 70% up to and including Day 27, and even on Day 28, about 69% of patients had answered the questionnaire. The analyses presented by the company on time to symptom abatement, surveyed using SE-C19, were therefore included in the present benefit assessment despite the low return rate on Day 29.

Return to normal health, return to normal activities, and health status (EQ-5D VAS)

In the COV-2067 study, the outcomes of return to normal health and return to normal activities were to be surveyed daily from Day 1 up to and including Day 29 using patients' binary rating (yes/no) of the previous 24-hour period. Furthermore, health status, surveyed with EQ-5D VAS, was to be rated by patients daily from Day 1 to Day 29 as well as on Days 60, 90, 120, and 169. However, the 2 questionnaires as well as the EQ-5D VAS were available to the study centres only after a delay, which resulted in some included patients not being surveyed. This particularly applies to the survey by means of EQ-5D VAS. Over the course of the study, return rates for all 3 instruments markedly decreased at an early time. Furthermore, return rates fluctuated substantially over the course of the study. Higher return rates (> 40%) were reached only on days where a swab was to be taken for the RT-qPCR assay. The analyses presented by the company for the 3 instruments are unusable for the benefit assessment because of return rates being generally low and fluctuating over the course of the study.

Further morbidity outcomes

According to details in the study protocol, the COV-2067 study surveyed further patient-reported outcomes (Patient Global Impression of Change [PGIC], Patient Global Impression of

Severity [PGIS], and Work Productivity and Activity Impairment and Classroom Impairment Questions [WPAI+CIQ]). Irrespective of the evaluation of the employed instruments' validity in the present indication, the study documents present no analyses on these patient-reported outcomes. Module 4 B of the company's dossier likewise presents no analyses. Hence, no results on these outcomes are available for this benefit assessment.

Further morbidity outcomes surveyed in the COV-2067 study were admission to an intensive care unit due to COVID-19, emergency room visit due to COVID-19, need for supplemental oxygen due to COVID-19, and need for mechanical ventilation due to COVID-19. The study protocol did not operationalize these outcomes in further detail. For example, it did not differentiate between types of oxygen administration or ventilation methods. In addition, it is safe to assume that some individual events were recorded as several of the listed outcomes. As another morbidity outcome, the present benefit assessment uses ICU admission due to COVID-19 alongside hospitalization for COVID-19 because the former outcome represents further progression of disease. The outcome of emergency room visit due to COVID-19 was disregarded in this benefit assessment because the majority of emergency room visits is presumed to have already been recorded through the outcome of hospitalization for COVID-19. The outcomes of need for supplemental oxygen due to COVID-19 and need for mechanical ventilation due to COVID-19 are presented as supplementary information in Appendix D of the full dossier assessment.

Side effects

Discontinuation due to AEs and specific AEs

AEs and discontinuation due to AEs were not systematically surveyed in the COV-2067 study. The total rate of discontinuation due to AEs is therefore unusable for the benefit assessment. Furthermore, it was impossible to select specific AEs from the available data on AEs.

SAEs and severe AEs

In principle, the COV-2067 study systematically surveyed SAEs and severe AEs. However, the survey of SAEs and severe AEs recorded both treatment-related AEs and events to be allocated to the symptoms of disease. Module 4 B of the company's dossier does present analyses excluding disease-related events. However, the company did not define which events were deemed disease-related and were therefore disregarded in the analyses. To allow an adequate assessment of side effects, the overall rates of SAEs and severe AEs must be analysed excluding disease-related events. On the basis of the available information, it remains unclear whether all events to be allocated to symptoms of the underlying disease were in fact excluded from the analyses. The total rates of SAEs and severe AEs are therefore unusable for the present benefit assessment.

Infusion-related reactions

The COV-2067 study systematically surveyed infusion-related reactions. However, no details are available on the operationalization of the outcome. Furthermore, the infusion duration used

in the study departs from the SPC. According to the SPC, the infusion must be administered for 20 to 30 minutes [3], while in the study, the median infusion duration for casirivimab/imdevimab was 60 minutes (1st quartile to 3rd quartile: 60 to 67 minutes). The extent to which the longer infusion duration might affect the rate of infusion-related reactions remains unclear. Due to the described uncertainties, no usable data on infusion-related reactions are available for the present benefit assessment.

2.4.2 Risk of bias

Table 12 shows the risk of bias for the results of the relevant outcomes.

Table 12: Risk of bias across outcomes and outcome-specific risk of bias – RCT[a], direct comparison: casirivimab/imdevimab versus placebo

Study	Study level	Outcomes												
		All-cause mortality[b]	Hospitalization for COVID-19[c]	Admission to intensive care unit due to COVID-19	Abatement of COVID-19 symptoms (SE-C19)	Return to normal health	Return to normal activities	Health status (EQ-5D VAS)	Health-related quality of life	SAEs	Severe AEs[d]	Discontinuation due to AEs	Infusion-related reactions	Further specific AEs
COV-2067	L	L	L	L	H[e]	-[f]	-[f]	-[f]	-[g]	-[h]	-[h]	-[i]	-[j]	-[k]

a. The COV-2067 study is an adaptive phase 1–3 study; presented is phase 3 of the study from protocol amendment 6 (14 November 2020), which is the phase relevant for the benefit assessment.
b. Death due to any cause up to and including Day 169.
c. The company did not provide any additional information on the operationalization (e.g. regarding a minimum time).
d. Severe AEs are operationalized as CTCAE grade ≥ 3.
e. Decreasing questionnaire response rate over the course of the study.
f. No usable data due to the return rates being generally low and fluctuating substantially across the observation period (see Section 2.4.1).
g. Outcome not surveyed.
h. The company did not provide any information regarding which events it deemed disease-related (see Section 2.4.1).
i. Discontinuation due to AEs was not systematically surveyed in the COV-2067 study.
j. No usable data available since it remains unclear how infusion-related reactions were surveyed in the study (see Section 2.4.1).
k. No further specific AEs were identified based on the SAEs or severe AEs which occurred in the relevant study. AEs were not systematically surveyed in the relevant study; selecting specific AEs on the basis of the AEs which occurred is therefore impossible.

AE: adverse event; COVID-19: Coronavirus Disease 2019; CTCAE: Common Terminology Criteria for Adverse Events; H: high; L: low; RCT: randomized controlled trial; SAE: serious adverse event; SE-C19: Symptoms Evolution of COVID-19; VAS: visual analogue scale

The risk of bias is deemed low for the results of all outcomes except for abatement of COVID-19 symptoms. For the outcome of abatement of COVID-19 symptoms, the risk of bias is deemed high because of the questionnaire's return rate decreasing over the course of the study.

Summary assessment of the certainty of conclusions

For patients 12 to < 18 years of age and weighing at least 40 kg with COVID-19 who do not require supplemental oxygen therapy and who are at increased risk of their disease becoming severe, no conclusions can be drawn on the basis of the available analyses of the COV-2067 study (see Section 2.3.2). The following evaluation of the certainty of results therefore exclusively applies to adult patients ≥ 18 years of age for whom data are available from the COV-2067 study. In addition, as described in Section 2.3.2, the evaluation is based on patients who have not yet been vaccinated against SARS-CoV-2 or who, despite being immunocompetent and fully vaccinated, remain at increased risk of COVID-19 becoming severe due to complex risk factors. The present therapeutic indication excludes patients who are fully immunized as well as patients who are infected with a virus variant for which neutralization activity is inadequate, either demonstrably so or as expected due to the current pandemic activity; therefore, said patients are not subject of the present benefit assessment.

As described in Section 2.3.2, evidence can be transferred from the unvaccinated patients included in the COV-2067 study to patient groups who do not reach complete immunization despite being vaccinated or who have complex risk factors despite being immunocompetent and fully vaccinated. However, it remains unclear whether the observed effects in unvaccinated patients are fully transferable to the above patient groups. Overall, the certainty of conclusions of the study results for the present research question is therefore reduced. Based on the COV-2067 study, at most hints, e.g. of an added benefit, can be derived for all outcomes presented.

2.4.3 Results

Table 13 and Table 14 summarize the results for the comparison of casirivimab/imdevimab versus placebo in patients with COVID-19 who do not require any supplemental oxygen therapy and who are at increased risk of COVID-19 becoming severe. Where necessary, IQWiG calculations are provided to supplement the data from the company's dossier.

Kaplan-Meier curves on the presented time-to-event analyses can be found in Appendix B of the full dossier assessment. Appendix C of the full dossier assessment presents tables on common SAEs and common severe AEs not excluding disease-related events. Supplementary results on the morbidity outcomes of need for supplemental oxygen and need for mechanical ventilation are presented in Appendix D of the full dossier assessment.

Table 13: Results (mortality, morbidity, health-related quality of life, side effects, dichotomous) – RCT[a], direct comparison: casirivimab/imdevimab versus placebo

Study Outcome category Outcome	Casirivimab/ imdevimab		Placebo		Casirivimab/imdevimab vs. placebo
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value[b]
COV-2067 (phase 3, cohort 1)					
Mortality (up to Day 169)					
All-cause mortality	1192	1 (0.1)	1193	7 (0.6)	0.14 [0.02; 1.16]; 0.035[c]
Morbidity (up to Day 29)					
Hospitalization for COVID-19	1192	11 (0.9)	1193	40 (3.4)	0.28 [0.14; 0.53]; < 0.001
Admission to intensive care unit due to COVID-19	1192	3 (0.3)	1193	9 (0.8)	0.33 [0.09; 1.23]; 0.086
Health-related quality of life	Outcome not recorded				
Side effects					
AEs (supplementary information)	No usable data[d]				
SAEs	No usable data[e]				
Severe AEs[f]	No usable data[e]				
Discontinuation due to AEs	No usable data[d]				
Infusion-related reactions	No usable data[g]				
Further specific AEs	No usable data[h]				

a. The COV-2067 study is an adaptive phase 1–3 study; presented is phase 3 of the study from protocol amendment 6 (14 November 2020), which is the phase relevant for the benefit assessment.
b. IQWiG calculation, unconditional exact test (CSZ method according to [20]).
c. Discrepancy between p-value (exact) and CI (asymptotic) due to different calculation methods.
d. Not systematically surveyed in the study (see Section 2.4.1).
e. The company did not provide any information on which events it deemed disease-related (see Section 2.4.1).
f. Operationalized as CTCAE grade ≥ 3.
g. No usable data available because it remains unclear how infusion-related reactions were surveyed in the study (see Section 2.4.1).
h. No further specific AEs were identified based on the SAEs or severe AEs occurring in the relevant study. AEs were not systematically surveyed in the relevant study; selecting specific AEs on the basis of the AEs which occurred is therefore impossible.

AE: adverse event; CI: confidence interval; COVID-19: Coronavirus Disease 2019; CSZ: convexity, symmetry, z score; CTCAE: Common Terminology Criteria for Adverse Events; mFAS: modified full analysis set; n: number of patients with (at least 1) event; N: number of randomized patients from the mFAS population; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event

Table 14: Results (morbidity, time to event) – RCT[a], direct comparison: casirivimab/imdevimab versus placebo

Study Outcome category Outcome	Casirivimab/ imdevimab		Placebo		Casirivimab/imdevimab vs. placebo
	N	Median time to event in days [95% CI] Patients with event n (%)	N	Median time to event in days [95% CI] Patients with event n (%)	HR [95% CI]; p-value[b]
COV-2067 (phase 3, cohort 1)					
Morbidity (at Day 29)					
Abatement of COVID-19 symptoms (SE-C19)[c]	1192	10.0 [9.0; 11.0][d] 683 (57.3)	1193	13.0 [12.0; 15.0][d] 591 (49.5)	1.27 [1.14; 1.42]; < 0.001
Return to normal health				No usable data[e]	
Return to normal activities				No usable data[e]	
Health status (EQ-5D VAS)				No usable data[e]	

a. The COV-2067 study is an adaptive phase 1–3 study; presented is the study's phase 3 starting from protocol amendment 6 (14 November 2020), which is the phase relevant for the benefit assessment.
b. Effect and CI: Cox proportional hazards model with treatment and country as fixed effects; p-value: log-rank test, stratified by country.
c. Patients with a summary raw score ≤ 3 across all symptoms at baseline were censored (see Section 2.4.1 for an explanation).
d. Discrepancy between the dossier's Module 4 B and Module 5. The presented data are taken from the study report.
e. Inadequate return rates (see Section 2.4.1 for reasoning).

CI: confidence interval; COVID-19: Coronavirus Disease 2019; HR: hazard ratio; mFAS: modified full analysis set; n: number of patients with event; N: number of randomized patients of the mFAS population; RCT: randomized controlled trial; SE-C19: Symptoms Evolution of COVID-19; VAS: visual analogue scale

Based on the available information, at most hints, e.g. of an added benefit, can be determined for all outcomes (see Section 2.4.2).

Mortality

All-cause mortality

For the outcome of all-cause mortality, a statistically significant difference between treatment groups was found in favour of casirivimab/imdevimab. This results in a hint of added benefit of casirivimab/imdevimab in comparison with treatment of physician's choice.

Morbidity

Hospitalization for COVID-19

For the outcome of hospitalization for COVID-19, a statistically significant difference between treatment groups was found in favour of casirivimab/imdevimab. This results in a hint of added benefit of casirivimab/imdevimab in comparison with treatment of physician's choice.

Admission to intensive care unit due to COVID-19

No statistically significant difference between treatment groups was shown for the outcome of ICU admission due to COVID-19. This results in no hint of an added benefit of casirivimab/imdevimab in comparison with treatment of physician's choice; an added benefit is therefore not proven.

Abatement of COVID-19 symptoms (SE-C19)

A statistically significant difference between treatment groups was found in favour of casirivimab/imdevimab for the outcome of abatement of COVID-19 symptoms, surveyed with SE-C19. There is an effect modification by the characteristic of age, however. For patients 18 to 64 years of age, this results in no hint of an added benefit of casirivimab/imdevimab in comparison with treatment of physician's choice; an added benefit is therefore not proven. For patients ≥ 65 years of age, in contrast, this results in a hint of added benefit of casirivimab/ imdevimab in comparison with treatment of physician's choice (see Section 2.4.4).

Return to normal health, return to normal activities, and health status (EQ-5D VAS)

No usable data are available for the outcomes of return to normal health, return to normal activities, and health status as surveyed using EQ-5D VAS (see Section 2.4.1). For each of these outcomes, this results in no hint of an added benefit of casirivimab/imdevimab in comparison with treatment of physician's choice; an added benefit is therefore not proven.

Health-related quality of life

Outcomes on health-related quality of life were not recorded in the included study.

Side effects

SAEs, severe AEs, discontinuation due to AEs, and infusion-related reactions

No usable data were available for side effects outcomes (see Section 2.4.1). In the survey of SAEs and severe AEs, the COV-2067 study included disease-related events. For these outcomes, Module 4 B of the company's dossier presents analyses excluding disease-related events, but it remains unclear which events the company deemed disease-related and therefore disregarded in the analyses. As a result, the total rates for SAEs and severe AEs are unusable for assessing the side effects of casirivimab/imdevimab. Further, the study failed to systematically survey discontinuation due to AEs. The COV-2067 study's results on infusion-related reactions are unusable due to (a) uncertainties regarding its operationalization and (b) an extended infusion duration. All things considered, no usable data are therefore available for assessing the side effects of casirivimab/imdevimab. Based on the results on common SAEs and severe AEs (see Appendix C of the full dossier assessment) and in view of the low percentage of patients with an event, however, no unfavourable effects of casirivimab/imdevimab of an extent which could call into question the added benefit of casirivimab/imdevimab are expected. For the side effects outcomes, this results in no hint of greater or lesser harm from casirivimab/imdevimab in comparison with treatment of physician's choice; greater or lesser harm is therefore not proven.

2.4.4 Subgroups and other effect modifiers

The following subgroup characteristics are relevant for the present benefit assessment:

- age (18 to 64 years versus 65 to 74 years versus > 74 years)
- sex (women versus men)

The company submitted subgroup analyses by age and sex for all outcomes listed in the dossier.

Interaction tests are performed if at least 10 patients per subgroup are included in the analysis. Moreover, for binary data, there had to be at least 10 events in at least 1 subgroup.

Only the results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup results are presented only if there is a statistically significant and relevant effect in at least 1 subgroup.

Table 15 summarizes the subgroup results for the comparison of casirivimab/imdevimab versus placebo in patients with COVID-19 who do not require any supplemental oxygen therapy and who are at increased risk of COVID-19 becoming severe. Where necessary, IQWiG calculations are provided to supplement the data from the company's dossier.

Kaplan-Meier curves on the presented time-to-event analyses can be found in Appendix B of the full dossier assessment.

Table 15: Subgroups (morbidity, time to event) – RCT[a], direct comparison: casirivimab/imdevimab versus placebo

Study Outcome Characteristic Subgroup	Casirivimab/ imdevimab N	Median time to event in days [95% CI] Patients with event n (%)	Placebo N	Median time to event in days [95% CI] Patients with event n (%)	Casirivimab/imdevimab vs. placebo HR [95% CI][b]	p-value[c]
COV-2067 (phase 3, cohort 1)						
Morbidity						
Abatement of COVID-19 symptoms (SE-C19)[d]						
Age						
18 to 64 years	1043	11 [10; 12] 616 (59.1)	1051	14 [13; 15] 547 (52.0)	1.21 [1.08; 1.35]	< 0.001
≥ 65[e] years	149	ND 67 (45.0)[f]	142	ND 44 (31.0)[f]	1.95 [1.33; 2.86][g]	< 0.001[g]
65 to 74 years	*100*	*10 [9; 15]* *48 (48.0)*	*108*	*27 [17; NC]* *34 (31.5)*	*2.07 [1.33; 3.23]*	*< 0.001*
≥ 75 years	*49*	*13 [6; 21]* *19 (38.8)*	*34*	*26 [7; NC]* *10 (29.4)*	*1.62 [0.75; 3.49]*	*0.207*
Total					Interaction[h]:	0.019

a. The COV-2067 study is an adaptive phase 1–3 study; presented is the study's phase 3 starting from protocol amendment 6 (14 November 2020), which is the phase relevant for the benefit assessment.
b. Unstratified Cox proportional hazards model.
c. Unstratified log-rank test.
d. Patients with a summary raw score ≤ 3 across all symptoms at baseline were censored (see Section 2.4.1 for an explanation).
e. Summary of the subgroups of 65 to 74 years and ≥ 75 years.
f. IQWiG calculation.
g. IQWiG calculation: metaanalytical summary of subgroup results for age groups 65 to 74 years and ≥ 75 years (model with fixed effect).
h. IQWiG calculation: p-value from Q test for heterogeneity, based on the 2 subgroups 18 to 64 years and ≥ 65 years.

CI: confidence interval; COVID-19: Coronavirus Disease 2019; HR: hazard ratio; mFAS: modified full analysis set; n: number of patients with event; N: number of randomized patients of the mFAS population; NC: not calculable; RCT: randomized controlled trial; SE-C19: Symptoms Evolution of COVID-19

Morbidity

Abatement of COVID-19 symptoms (SE-C19)

For the outcome of abatement of COVID-19 symptoms, there was an effect modification by the characteristic of age. Given the homogeneity of the adjacent subgroups, the subgroups of 65 to 74 years and ≥ 75 years were metaanalytically combined using a model with fixed effect (see Appendix E of the full dossier assessment). Below, the derivation of added benefit for the outcome of abatement of COVID-19 symptoms is based on the results of IQWiG calculations.

For each of the subgroups of 18 to 65 years and ≥ 65 years of age, there is a statistically significant difference between treatment arms in favour of casirivimab/imdevimab. However, for this outcome of the non-serious/non-severe symptoms / late complications category, the extent of the effect in the age group 18 to 64 years was no more than marginal. For patients 18 to 64 years of age, this results in no hint of an added benefit of casirivimab/imdevimab in comparison with treatment of physician's choice; an added benefit is therefore not proven. For patients ≥ 65 years of age, in contrast, this results in a hint of added benefit of casirivimab/imdevimab in comparison with treatment of physician's choice.

2.5 Probability and extent of added benefit

The probability and extent of added benefit at outcome level are derived below, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the IQWiG General Methods [1].

The approach for deriving an overall conclusion on added benefit based on the aggregation of conclusions derived at outcome level constitutes a proposal by IQWiG. The G-BA decides on the added benefit.

2.5.1 Assessment of the added benefit at outcome level

The extent of the respective added benefit at outcome level was estimated from the results presented in Section 2.4 (see Table 16).

Determination of the outcome category for the outcomes on morbidity

For the symptoms outcomes below, it cannot be inferred from the dossier whether they are serious/severe or non-serious/non-severe. The classification for these outcomes is justified.

Hospitalization for COVID-19

Events which require inpatient treatment are considered severe or serious. Therefore, the outcome of hospitalization for COVID-19 was assigned to the outcome category of serious/severe symptoms / late complications.

Abatement of COVID-19 symptoms

On the basis of the included population not requiring supplemental oxygen therapy, the symptoms surveyed via SE-C19 at the start of the COV-2067 study are to be deemed non-severe or non-serious. Consistent with this classification, the median patient-rated severity levels at baseline were mild for 2 symptoms and moderate for 2 others, while none of the symptoms were rated as severe. Therefore, the outcome of abatement of COVID-19 symptoms was assigned to the outcome category of non-serious/non-severe symptoms / late complications.

Table 16: Extent of added benefit at outcome level: casirivimab/imdevimab versus treatment of physician's choice (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Casirivimab/imdevimab vs. placebo** **Median time to event (days) or event rate (%)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
All-cause mortality	0.1% vs. 0.6% RR: 0.14 [0.02; 1.16]; p = 0.035 Probability: hint	Outcome category: mortality Added benefit[c]; extent: non-quantifiable
Morbidity		
Hospitalization for COVID-19	0.9% vs. 3.4% RR: 0.28 [0.14; 0.53]; p < 0.001 Probability: hint	Outcome category: serious/severe symptoms / late complications $CI_u < 0.75$, risk < 5% Added benefit; extent: considerable
Admission to intensive care unit due to COVID-19	0.3% vs. 0.8% RR: 0.33 [0.09; 1.23]; p = 0.086	Lesser/added benefit not proven
Abatement of COVID-19 symptoms (SE-C19)		
Age		
18 to 64 years	11 vs. 14 days HR: 1.21 [1.08; 1.35] HR: 0.83 [0.74; 0.93][d]; p < 0.001 Probability: hint	Outcome category: non-serious/non-severe symptoms / late complications $0.90 \leq CI_u < 1.00$ Lesser/added benefit not proven[e]
≥ 65 years	ND vs. ND HR: 1.95 [1.33; 2.86] HR: 0.51 [0.35; 0.75][d]; p < 0.001 Probability: hint	Outcome category: non-serious/non-severe symptoms / late complications $CI_u < 0.80$ Added benefit; extent: considerable
Return to normal health	No usable data	Lesser/added benefit not proven
Return to normal activities	No usable data	Lesser/added benefit not proven
Health status (EQ-5D VAS)	No usable data	Lesser/added benefit not proven
Health-related quality of life		
-	Outcomes from this category were not recorded	Lesser/added benefit not proven
Side effects		
SAEs	No usable data	Greater/lesser harm not proven
Severe AEs	No usable data	Greater/lesser harm not proven

Table 16: Extent of added benefit at outcome level: casirivimab/imdevimab versus treatment of physician's choice (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Casirivimab/imdevimab vs. placebo** **Median time to event (days) or event rate (%)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Discontinuation due to AEs	No usable data	Greater/lesser harm not proven
Infusion-related reactions	No usable data	Greater/lesser harm not proven
Further specific AEs	No usable data	Greater/lesser harm not proven

a. Probability provided if there is a statistically significant and relevant effect.
b. Depending on the outcome category, the effect size is estimated using different limits based on the upper limit of the confidence interval (CI_u).
c. The result of the statistical test is determinative for deriving added benefit.
d. IQWiG calculation; reversed direction of effect to enable use of limits to derive the extent of the added benefit.
e. The extent of the effect in this non-serious/non-severe outcome was no more than marginal.

AE: adverse event; CI: confidence interval; CI_u: upper limit of CI; COVID-19: Coronavirus Disease 2019; HR: hazard ratio; ND: no data; RR: relative risk; SAE: serious adverse event; SE-C19: Symptoms Evolution of COVID-19; VAS: visual analogue scale

2.5.2 Overall conclusion on added benefit

Table 17 summarizes the results taken into account in the overall conclusion on the extent of added benefit.

Table 17: Favourable and unfavourable effects from the assessment of casirivimab/imdevimab compared with treatment according to the physician's choice

Favourable effects	**Unfavourable effects**
Mortality ▪ All-cause mortality: hint of an added benefit – extent: non-quantifiable	–
Serious/severe symptoms / late complications ▪ Hospitalization due to COVID-19: hint of an added benefit – extent: considerable	–
Non-serious/non-severe symptoms / late complications ▪ Abatement of COVID-19 symptoms ▫ Age ≥ 65 years: hint of added benefit – extent: considerable	–
No usable data are available for outcomes on health-related quality of life or side effects. These effects apply only to patients who have not yet been vaccinated against SARS-CoV-2 or who are not completely immunized against SARS-CoV-2 or who have complex risk factors despite being immunocompetent and fully vaccinated.	
COVID-19: Coronavirus Disease 2019; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus Type 2	

As described in Section 2.3.2, the following conclusion on added benefit applies only to adult patients who have not yet been vaccinated against SARS-CoV-2 or who are not completely immunized against SARS-CoV-2 or who have complex risk factors despite being immunocompetent and fully vaccinated. Patients who are completely immunized are excluded from the present benefit assessment because they are not at increased risk of COVID-19 becoming severe. In addition, the present therapeutic indication does not cover patients who are infected with a virus variant for which neutralizing activity is inadequate, either demonstrably so or as expected based on the current pandemic activity; consequently, these patients are not subject of the present benefit assessment.

No data are available for adolescents 12 to < 18 years of age weighing at least 40 kg who do not require supplemental oxygen and who are at increased risk of COVID-19 becoming severe. For this age group, there is therefore no proof of added benefit of casirivimab/imdevimab.

Overall, for adults with COVID-19 infection who do not require supplemental oxygen and who are at increased risk of COVID-19 becoming severe, only favourable effects of casirivimab/imdevimab were found in comparison with treatment of physician's choice. For the outcome of overall survival, there is a hint of a non-quantifiable added benefit. A hint of considerable added benefit was found for each of the outcomes of hospitalization for COVID-19 and abatement of COVID-19 symptoms (in older patients). For side effects, no usable data were available. However, the available information does not suggest any unfavourable effects to an extent that could call an added benefit into question.

In summary, for adults with COVID-19 infection who do not require supplemental oxygen and who are at increased risk of COVID-19 becoming severe, there is a hint of considerable added benefit of casirivimab/imdevimab in comparison with treatment of physician's choice.

Table 18 summarizes the result of the assessment of added benefit of casirivimab/imdevimab in comparison with the ACT.

Table 18: Casirivimab/imdevimab – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adults and adolescents from 12 years of age and weighing at least 40 kilograms with COVID-19[b] who do not require supplemental oxygen and who are at increased risk of COVID-19 becoming severe[c, d,e]	Treatment of physician's choice[f]	Patients ≥ 18 years: ▪ Hint of considerable added benefit
		Patients ≥ 12 to < 18 years of age: ▪ Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. In case of a positive rapid antigen test, the diagnosis of SARS-CoV-2 should be confirmed by a PCR test, especially if the results have therapeutic consequences.
c. In the recording and interpretation of effectiveness results, it is recommended for relevant SARS-CoV-2 mutation variants (e.g. variants of concern) to be taken into account.
d. According to the SPC, decisions regarding the use of casirivimab/imdevimab should take into account what is known about the characteristics of circulating SARS-CoV-2 viruses, including regional or geographic differences and the available information on casirivimab/imdevimab susceptibility patterns [3].
e. Patients with complete immunization are not included in the therapeutic indication (see Section 2.3.2 for an explanation).
f. Specific therapeutic measures are usually not required for mildly to moderately symptomatic COVID-19 disease. Depending on the severity of disease, the treatment of physician's choice of non-hospitalized patients, if indicated, should primarily be chosen from symptomatic drug therapies (e.g. analgesics, antipyretics, thrombosis prophylaxis). If the disease progresses and the patient is hospitalized, further drug therapies (e.g. dexamethasone; anticoagulation/thrombosis prophylaxis, antibiotics) as well as non-drug therapies (e.g. oxygen supply, type of ventilation, balanced fluid therapy) must be considered.

COVID-19: Coronavirus Disease 2019; G-BA: Federal Joint Committee; PCR: polymerase chain reaction; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus Type 2

The assessment described above deviates from that by the company, which derived proof of major added benefit for all patients in the present therapeutic indication, regardless of age.

The approach for the derivation of an overall conclusion on the added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

References for English extract

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

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