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Casirivimab/imdevimab (post-exposure prophylaxis 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 (Postexpositions-prophylaxe von COVID-19) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 12 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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Patient and family involvement

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

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[2] Table numbers start with “2” as numbering follows that of the full dossier assessment.

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
CDC	Centers for Disease Control and Prevention
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
EAP	efficacy assessment period
FAS	full analysis set
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
PEI	Paul Ehrlich Institute
PEP	post-exposure prophylaxis
RCT	randomized controlled trial
RKI	Robert Koch Institute
RT-qPCR	reverse transcriptase quantitative polymerase chain reaction
SAE	serious adverse event
SAF	safety analysis set
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus Type 2
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics
STIKO	Ständige Impfkommission (Germany’s Standing Committee on Vaccinations)

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (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) for post-exposure prophylaxis (PEP) of Coronavirus Disease 2019 (COVID-19) in adult and adolescent patients aged 12 years and older with a body weight of at least 40 kg.

Casirivimab/imdevimab is also approved for pre-exposure prophylaxis, but this therapeutic indication is not the subject of the present benefit assessment.

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]
PEP for COVID-19 in adults and adolescents aged 12 years and older and with a body weight of at least 40 kg[b, c]	Watchful waiting[d]

a. Presented is the ACT specified by the G-BA.
b. 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.
c. The G-BA assumes that study participants in all study arms observe the generally recognized hygiene rules (e.g. social distancing, hygiene measures, face masks) for reducing the risk of infection. In cases where medical reasons (e.g. dementia) preclude compliance with established hygiene rules, this must be documented.
d. As soon as the disease becomes symptomatic, treatment according to current medical knowledge is indicated.

ACT: appropriate comparator therapy; COVID-19: Coronavirus Disease 2019; G-BA: Federal Joint Committee; PEP: post-exposure prophylaxis; 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 SARS-CoV-2 viruses, including regional or geographical differences and available information on casirivimab/imdevimab susceptibility patterns. In addition, the SPC specifies that, if 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. For the present benefit assessment, it is therefore assumed that the therapeutic indication excludes any individuals who have come into contact with a SARS-CoV-2 virus variant for which neutralizing activity is inadequate, 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 surmises that casirivimab/imdevimab is 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 benefit assessment used the R10933-10987-COV-2069 study (hereinafter referred to as COV-2069 study). The COV-2069 study is a double-blind randomized controlled trial (RCT) comparing casirivimab/imdevimab versus placebo. The study enrolled adults, adolescents, and children after contact with an individual with SARS-CoV-2 infection.

The COV-2069 study investigated asymptomatic adults, adolescents, and children who have been in contact with a SARS-CoV-2 infected person (hereinafter referred to as "index case") living in their own household. The index case had to have tested positive for SARS-CoV-2. The contact person had to be included in the study within 96 hours after the sample was taken for diagnostic testing of the index case.

At baseline, the contact persons' serostatus was determined regarding SARS-CoV-2 antibodies. However, contact persons were included irrespective of test results; consequently, both the individuals with negative and those with positive serostatus were enrolled in the study. In contrast, individuals testing positive for SARS-CoV-2 in reverse transcriptase quantitative polymerase chain reaction (RT-qPCR) or those with a (self-reported) positive SARS-CoV-2 serology test at any point before enrolment were excluded from the COV-2069 study. Individuals who, in the investigator's opinion, had respiratory disease with signs/symptoms of SARS-CoV-2 infection in the 6 months preceding enrolment were likewise excluded.

Furthermore, individuals who had received at least 1 dose of a SARS-CoV-2 vaccine, whether under investigation or approved, were likewise excluded from participation. Consequently, the study investigated only individuals not protected by vaccination.

A total of 3298 adults, adolescents, and children were included and randomized in a 1:1 ratio to treatment with casirivimab/imdevimab or placebo. For adults and adolescents, randomization was stratified by study centre, test result of the local diagnostic test for SARS-CoV-2, and age group (≥ 12 to < 18 years, ≥ 18 to < 50 years, or ≥ 50 years). To avoid delays, randomization was stratified by the results of local diagnostic testing. The results from an RT-qPCR assay which was performed by the central laboratory and additionally carried out at baseline were used to allocate individuals to study cohorts. Depending on the RT-qPCR assay results and age, individuals were allocated to the following cohorts in accordance with the study protocol:

- Cohort A: SARS-CoV-2 RT-qPCR negative at baseline; ≥ 12 years
- Cohort A1: SARS-CoV-2 RT-qPCR negative at baseline; < 12 years
- Cohort B: SARS-CoV-2 RT-qPCR positive at baseline; ≥ 12 years
- Cohort B1: SARS-CoV-2 RT-qPCR positive at baseline; < 12 years

Individuals with undetermined SARS-CoV-2 infection status were allocated to another, separate cohort. According to the study protocol, individuals were also to be analysed separately by serostatus (positive or negative).

Being made up of children < 12 years, Cohorts A1 and B1 comprised individuals for whom casirivimab/imdevimab is not approved; consequently, these cohorts are irrelevant for the present benefit assessment.

In Module 4 A of its dossier, the company presents only separate analyses of cohort A and cohort B. Each of the analyses included all individuals, irrespective of serostatus. For a qualitative analysis of the 2 cohorts' results regarding the determinative morbidity outcome, a joint evaluation of Cohorts A and B is deemed inappropriate. In the present benefit assessment, Cohort A (SARS-CoV-2 RT-qPCR negative at baseline) and Cohort B (SARS-CoV-2 RT qPCR positive at baseline) are analysed separately.

Casirivimab/imdevimab was administered as a single subcutaneous dose on Day 1 of the study, in line with the SPC. The COV-2069 study did not investigate administration via infusion, which the SPC also allows. Individuals in the comparator arm received a placebo.

Outcomes of the morbidity category were observed for 28 days (efficacy assessment period [EAP]). Furthermore, adverse events (AEs) were followed up until the last study visit on Day 225. Individuals who tested positive for SARS-CoV-2 in RT-qPCR within the EAP were observed for outcomes of the morbidity category until they had 2 negative RT-qPCR tests or until resolution of COVID-19 symptoms, whichever was later, even if this occurred during the follow-up observation phase (after Day 29).

For Cohort A, the study's primary outcome was the proportion of participants with symptomatic SARS-CoV-2 infection; for Cohort B, it was the proportion of participants who develop symptomatic SARS-CoV-2 infection 14 days after a positive RT-qPCR test. Patient-relevant secondary outcomes were outcomes on morbidity and AEs.

Implementation of the ACT

The G-BA specified watchful waiting as the ACT.

The COV-2069 study operationalized watchful waiting as a follow-up observation strategy. In addition, a placebo was administered in the comparator arm to ensure blinding. According to the study protocol, follow-up observation comprised, up to Day 29, weekly RT-qPCR tests for SARS-CoV-2, the recording of AEs, and in case of a positive RT-qPCR test, the survey of hospitalizations, emergency room visits, or urgent care visits for COVID-19. The dossier does not show whether, as part of their study participation, individuals were made aware of preventive measures, e.g. mask use within the household or spatial isolation, in order to reduce the risk of SARS-CoV-2 infection. The dossier likewise provides no information as to whether a mask was worn in the household during the study or whether any other preventive measures were taken. For the purposes of this benefit assessment, however, the implementation of preventive measures in the COV-2069 study is assumed to reflect the context of care. Therefore, the missing information has no consequence for the present benefit assessment.

In case of symptomatic COVID-19, the study allowed the initiation of treatment according to local guidelines at the treating physician's discretion. The study protocol did not restrict the drugs to be used in symptomatic patients.

In summary, the ACT was adequately implemented in the COV-2069 study.

Data cut-offs

The COV-2069 study has already been completed. Three data cut-offs were implemented:

- 1st data cut-off dated 11 March 2021 (primary analysis): predefined for all study participants who were randomized by 28 January 2021 and fully completed the EAP
- 2nd data cut-off dated 1 July 2021: data cut-off upon request by the Food and Drug Administration (FDA)
- 3rd data cut-off dated 4 October 2021 (final analysis): planned to occur when the last study participant has completed the study

Module 4 A of the company's dossier presents an analysis of the results from the 2nd data cut-off. The company reports that access to data for the final analysis was delayed and that the results of the 3rd data cut-off are therefore made available together with the comments. The study report on the 3rd data cut-off has already been presented in the company's dossier. At the time of the 2nd data cut-off, more than 99% of study participants had completed the EAP, and no additional participants were included by the 3rd data cut-off. Moreover, the occurred AEs

did not substantially differ between the analyses of the 2nd and 3rd data cut-offs. Hence, the 3rd data cut-off does not provide any relevant additional information when compared with the 2nd data cut-off. The present benefit assessment therefore uses the results from the 2nd data cut-off (1 July 2021) presented by the company in Module 4 A.

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

As described above, adults and adolescents who had received at least 1 vaccination against SARS-CoV-2 were excluded from the COV-2069 study. At the time of the benefit assessment, however, a large percentage of the population has already been completely immunized as defined by Germany's Standing Committee on Vaccinations (STIKO) through vaccinations and potential prior virus exposure, thereby reducing the risk of SARS-CoV-2 infection and/or of COVID-19 becoming symptomatic. Additionally, complete vaccination protection leads to an altered immune response after contact with SARS-CoV-2. Depending on the virus variant, it can be safely assumed that people who are completely immunized possibly exhibit no detectable infection or a milder course of COVID-19. Incompletely immunized individuals or those at relevant risk of inadequate vaccine response as defined by STIKO, however, continue to be at risk of SARS-CoV-2 infection and/or a symptomatic course of COVID-19, and this risk is comparable to the risk of unvaccinated people. Individuals who exhibited inadequate vaccine response and are therefore not completely immunized were excluded from the COV-2069 study. Likewise excluded were people at relevant risk of inadequate vaccine response. However, evidence can be transferred from unvaccinated individuals who were included in the COV-2069 study to groups who failed to achieve complete immunization despite being vaccinated. Whether the effects observed in unvaccinated individuals are fully transferable to these groups nevertheless remains unclear. This issue has been taken into account in the assessment of the certainty of conclusions. On the basis of the COV-2069 study, no conclusions on added benefit can be drawn on incompletely immunized adults and adolescents.

Furthermore, the COV-2069 study excluded individuals who tested positive for SARS-CoV-2 in RT-qPCR or in serology testing for SARS-CoV-2 at any time prior to study inclusion or who, in the investigator's opinion, had a respiratory disease with signs/symptoms of SARS-CoV-2 infection in the 6 months preceding study inclusion. Despite these limitations imposed by the inclusion criteria, about one-fourth of the individuals included in the study had a positive serostatus at baseline. Since the study population was to exclude recovered patients, those included in the COV-2069 study can be safely assumed to have had an asymptomatic infection. Therefore, it remains unclear whether the participants with positive serostatus are comparable to patients who have recovered from symptomatic COVID-19 infection, which, at the current time, represent the majority of the population in the present therapeutic indication.

According to the casirivimab/imdevimab 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. For the purposes of the present benefit assessment, the therapeutic indication is therefore assumed to exclude any individuals

who have come into contact with a SARS-CoV-2 virus variant for which neutralizing activity is inadequate, 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 SARS-CoV-2 virus variant adult and adolescent COV-2069 study participants were infected and for how many participants a virus genotype was even available. Because the study was conducted in an earlier wave of the pandemic (07/2020 to 10/2021), it can be safely assumed that the majority of adults and adolescents included in the study were infected with virus variants which circulated prior to the spread of the omicron variant, which predominates at the time of the benefit assessment. In vitro neutralization assays show that the neutralizing activity of casirivimab/imdevimab is markedly reduced against the omicron virus variant, therefore suggesting lower effectiveness. Using casirivimab/imdevimab for preventing infection with the omicron variant is therefore not recommended.

In summary, on the basis of the COV-2069 study, conclusions can be drawn for adults and adolescents who have not yet been vaccinated against SARS-CoV-2 or who are not completely immunized against SARS-CoV-2. On the basis of the COV-2069 study, no conclusions on added benefit can be drawn on incompletely immunized adults and adolescents. In addition, the present therapeutic indication does not cover adults and adolescents who have come into contact with a SARS-CoV-2 virus variant for which neutralizing activity is inadequate, either demonstrably so or as expected based on the current pandemic activity; consequently, these individuals are not the subject of the present benefit assessment.

Risk of bias and assessment of the certainty of conclusions

The risk of bias across outcomes and the risk of bias on the outcome level were rated as low for the results of the COV-2069 study.

As described above, evidence can be transferred from unvaccinated persons included in the COV-2069 study to groups of individuals who do not achieve complete immunization despite being vaccinated. Nevertheless, it remains unclear whether the effects observed in unvaccinated persons are fully transferable to these groups. Overall, the certainty of conclusions of the study results for the present research question is therefore reduced. Based on the COV-2069 study, at most hints, e.g. of an added benefit, can be derived for all outcomes presented.

Results

Mortality

All-cause mortality

For Cohort A of the COV-2069 study, no statistically significant difference between treatment groups was found for the outcome of all-cause mortality. For the outcome of all-cause mortality, this results in no hint of added benefit of casirivimab/imdevimab in comparison with watchful waiting for adults and adolescents tested negative for SARS-CoV-2 in RT-qPCR; an added benefit is therefore not proven.

No deaths occurred in the COV-2069 Cohort B. For the outcome of all-cause mortality, this results in no hint of added benefit of casirivimab/imdevimab in comparison with watchful waiting for adults and adolescents tested positive for SARS-CoV-2 in RT-qPCR; an added benefit is therefore not proven.

Morbidity

Symptomatic SARS-CoV-2 infection (broad definition)

In both Cohort A and Cohort B of the COV-2069 study, there was a statistically significant difference between treatment groups in favour of casirivimab/imdevimab for the outcome of symptomatic SARS-CoV-2 infection (broad definition). For Cohort A, this favourable effect was also found in the proportion of participants testing positive for SARS-CoV-2 in RT-qPCR, irrespective of symptoms, which was presented as supplementary information. For this outcome, this results in a hint of added benefit of casirivimab/imdevimab in comparison with watchful waiting for both adults and adolescents tested positive for SARS-CoV-2 in RT-qPCR and for those tested negative. For both groups, substantial heterogeneity of effects was found in the interaction test ($p_{Int} < 0.05$). Moreover, the extent of added benefit differs. The results on symptomatic SARS-CoV-2 infection, surveyed using the definition from the Centers for Disease Control and Prevention (CDC), are comparable with the results based on the broad definition.

Hospitalization for COVID-19

For Cohort A of the COV-2069 study, no statistically significant difference between treatment arms was found for the outcome of hospitalization for COVID-19. Regarding the outcome of hospitalization for COVID-19, this results in no hint of added benefit of casirivimab/imdevimab in comparison with watchful waiting for adults and adolescents tested negative for SARS-CoV-2; an added benefit is therefore not proven.

For the outcome of hospitalization for COVID-19, a statistically significant difference between treatment groups was found in favour of casirivimab/imdevimab in Cohort B of the COV-2069 study. Regarding this outcome, this results in a hint of added benefit of casirivimab/imdevimab in comparison with watchful waiting for adults and adolescents tested positive for SARS-CoV-2 in RT-qPCR.

Health-related quality of life

The included study did not record any outcomes on health-related quality of life.

Side effects

Serious AEs (SAEs) and severe AEs

In the survey of SAEs and severe AEs, the COV-2069 study included disease-related events. For these outcomes, Module 4 A 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 of SAEs and severe AEs are

unusable for assessing the side effects of casirivimab/imdevimab. Given the small percentage of COV-2069 participants in Cohort A and Cohort B who had 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 on the basis of the results on common SAEs and common severe AEs. For the outcomes of SAEs and severe AEs, there is no hint of greater or lesser harm from casirivimab/imdevimab in comparison with watchful waiting for adults and adolescents tested positive or negative for SARS-CoV-2 in RT-qPCR; greater or lesser harm is therefore not proven for either of them.

Discontinuation due to AEs

In the course of the COV-2069 study, neither Cohort A nor Cohort B had any discontinuations due to AEs. This results in no hint of greater or lesser harm from casirivimab/imdevimab in comparison with watchful waiting for adults and adolescents tested positive or negative for SARS-CoV-2 in RT-qPCR; greater or lesser harm is therefore not proven for either of them.

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 described, for adults and adolescents 12 years and older with a minimum body weight of 40 kg, the added benefit of casirivimab/imdevimab is derived separately for those testing negative versus positive for SARS-CoV-2 in RT-qPCR. In addition, the present therapeutic indication does not cover adults and adolescents who have come into contact with a SARS-CoV-2 virus variant for which neutralizing activity is inadequate, either demonstrably so or as expected based on the current pandemic activity; consequently, these individuals are not the subject of the present benefit assessment. Moreover, the following conclusions on added benefit apply only to adults and adolescents who have not yet been vaccinated against SARS-CoV-2 or who are not completely immunized against SARS-CoV-2. No data are available for adults and adolescents who are completely immunized against SARS-CoV-2. For this group, there is therefore no proof of added benefit of casirivimab/imdevimab.

[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].

Adults and adolescents 12 years of age and older weighing at least 40 kg testing negative for SARS-CoV-2 in RT-qPCR

Overall, only a favourable effect of casirivimab/imdevimab was found for the study population in Cohort A. For the outcome of symptomatic SARS-CoV-2 infection, this results in a hint of considerable added benefit. For some outcomes in the side effects category, no usable data are available. However, the available information does not suggest any unfavourable effects to an extent that might call an added benefit into question.

In summary, for adults and adolescents 12 years of age and older weighing at least 40 kg who have tested negative for SARS-CoV-2 in RT-qPCR, there is a hint of considerable added benefit of casirivimab/imdevimab in comparison with the ACT of watchful waiting for PEP of COVID-19.

Adults and adolescents 12 years of age and older weighing at least 40 kg who have tested positive for SARS-CoV-2 in RT-qPCR

Overall, only favourable effects of casirivimab/imdevimab were found for the study population in Cohort B. For each of the outcomes of symptomatic SARS-CoV-2 infection and hospitalization for COVID-19, there is a hint of minor added benefit. For some outcomes in the side effects category, no usable data are available. However, the available information does not suggest any unfavourable effects to an extent that might call an added benefit into question.

In summary, for adults and adolescents 12 years of age and older weighing at least 40 kg who have tested positive for SARS-CoV-2 in RT-qPCR, there is a hint of minor added benefit of casirivimab/imdevimab in comparison with the ACT of watchful waiting in the PEP of COVID-19.

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**
PEP of COVID-19 in adults and adolescents aged 12 years and older and with a body weight of at least 40 kg[b,c]	Watchful waiting[d]	Adults and adolescents without complete immunization[e] ▪ Negative for SARS-CoV-2 in RT-qPCR: hint of considerable added benefit ▪ Positive for SARS-CoV-2 in RT-qPCR: hint of minor added benefit
		Adults and adolescents who are completely immunized[f] ▪ Added benefit not proven

a. Presented is the respective ACT specified by the G-BA.
b. 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.
c. The G-BA assumes that study participants in all study arms observe the generally recognized hygiene rules (e.g. social distancing, hygiene measures, face masks) for reducing the risk of infection. In cases where medical reasons (e.g. dementia) preclude compliance with established hygiene rules, this must be documented.
d. As soon as the disease becomes symptomatic, treatment according to current medical knowledge is indicated.
e. Not vaccinated against SARS-CoV-2 or not completely immunized against SARS-CoV-2 according to STIKO recommendations.
f. Completely immunized against SARS-CoV-2 in accordance with STIKO recommendations.

ACT: appropriate comparator therapy; COVID-19: Coronavirus Disease 2019; G-BA: Federal Joint Committee; RT-qPCR: reverse transcriptase quantitative polymerase chain reaction; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus Type 2; STIKO: Germany's Standing Committee on Vaccinations

The approach for the derivation of an overall conclusion on the added benefit constitutes 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 for PEP of COVID-19 in adult and adolescent patients aged 12 years and older with a body weight of at least 40 kg.

Casirivimab/imdevimab is also approved for pre-exposure prophylaxis, but this therapeutic indication is not the subject of the present benefit assessment.

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

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

Therapeutic indication	**ACT[a]**
PEP of COVID-19 in adults and adolescents aged 12 years and older and with a body weight of at least 40 kg[b, c]	Watchful waiting[d]

a. Presented is the ACT specified by the G-BA.
b. 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].
c. The G-BA assumes that study participants in all study arms observe the generally recognized hygiene rules (e.g. social distancing, hygiene measures, face masks) for reducing the risk of infection. In cases where medical reasons (e.g. dementia) preclude compliance with established hygiene rules, this must be documented.
d. As soon as the disease becomes symptomatic, treatment according to current medical knowledge is indicated.

ACT: appropriate comparator therapy; COVID-19: Coronavirus Disease 2019; G-BA: Federal Joint Committee

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 [3], decisions regarding the use of casirivimab/imdevimab should take into account what is known about the characteristics of the circulating SARS-CoV-2 viruses, including regional or geographical differences and available information on casirivimab/imdevimab susceptibility patterns. In addition, the SPC specifies that, if 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. For the purposes of the present benefit assessment, the therapeutic indication is therefore assumed to exclude any individuals who have come into contact with a SARS-CoV-2 virus variant for which neutralizing activity is inadequate, 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 surmises that casirivimab/imdevimab is 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

Alongside the study included by the company, R10933-10987-COV-2069 (hereinafter referred to as the COV-2069 study), the R10933-10987-COV-20145 study was identified (hereinafter referred to as the COV-20145 study) [6]. The company's dossier presents no analyses of this study. The study enrolled a small number of participants who are potentially relevant for the present benefit assessment (11 asymptomatic patients who received casirivimab/imdevimab intravenously and 12 asymptomatic patients who received casirivimab/imdevimab subcutaneously). Due to the low numbers of cases compared with the COV-2069 study, however, the COV-2069 study presumably has no relevant influence on results. Therefore, the company's exclusion of this study remains without consequence for the present benefit assessment.

2.3.1 Studies included

The study presented 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-2069 (COV-2069[c])	Yes	Yes	No	Yes [7-9]	Yes [10]	Yes [11,12]

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 COV-2069 study was used for the benefit assessment. The company's exclusion of the COV-20145 study remains without consequences for the present benefit assessment (see Section 2.3.1).

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, 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[a]
COV-2069	RCT, double-blind, parallel-group	Unvaccinated adults, adolescents, and children: ▪ asymptomatic household contacts of an individual infected with SARS-CoV-2 (index case)[b] ▪ not hospitalized and no hospitalization (> 24 h) within 30 days prior to study inclusion ▪ no history of positive SARS-CoV-2 test (self-reported) ▪ no respiratory disease with signs/symptoms deemed by the investigator to be indicative of SARS-CoV-2 infection in the 6 months preceding enrolment	Total study population[c]: ▪ casirivimab/imdevimab (N = 1641) ▪ placebo (N = 1657) Cohort A (SARS-CoV-2 negative at baseline, ≥ 12 years)[d]: ▪ casirivimab/imdevimab (N = 1439) ▪ placebo (N = 1428) Cohort A (SARS-CoV-2 negative at baseline, < 12 years)[e]: ▪ casirivimab/imdevimab (N = 0) ▪ placebo (N = 1) Cohort B (SARS-CoV-2 positive at baseline, ≥ 12 years)[f]: ▪ casirivimab/imdevimab (N = 165) ▪ placebo (N = 171) Cohort B1 (SARS-CoV-2 positive at baseline, < 12 years)[e]: ▪ casirivimab/imdevimab (N = 0) ▪ placebo (N = 0)	Screening including treatment[g]: 1 day Observation[h] 225 days	112 study centres in the Republic of Moldova, Romania, United States 07/2020–10/2021 Data cut-offs ▪ 11 March 2021 (primary analysis)[i] ▪ 1 July 2021[j] ▪ 4 October 2021 (final analysis)[k]	Primary: ▪ Cohort A: proportion of participants with symptomatic SARS-CoV-2 infection, broad term[l] ▪ Cohort B: proportion of participants who develop symptomatic SARS-CoV-2 infection (broad term) 14 days after a positive RT-qPCR test Secondary: all-cause mortality, morbidity, AEs

Table 6: Characteristics of the included study – RCT, 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[a]

a. 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.
b. Randomization had to occur within 96 hours after the SARS-CoV-2-positive sample was taken from the index case.
c. A total of 3298 individuals were randomized. According to the study protocol, participants were allocated to cohorts based on both the results of the central laboratory's RT-qPCR results at baseline and participant age: Cohort A (SARS-CoV-2 negative at baseline; ≥ 12 years; N = 2871), Cohort A1 (SARS-CoV-2 negative at baseline; < 12 years; N = 1), Cohort B (SARS-CoV-2 positive at baseline; ≥ 12 years; N = 339), Cohort B1 (SARS-CoV-2 positive at baseline; < 12 years; N = 0). Participants with undetermined SARS-CoV-2 infection status (N = 87) were allocated to a separate cohort. In Module 4 A of its dossier, the company presents only separate analyses of Cohort A and Cohort B.
d. The first 554 participants allocated to Cohort A were included in a planned descriptive analysis to verify the assumptions for sample size planning (administrative assessment). These participants are included in the analyses of AEs (SAF, casirivimab/imdevimab: N = 1439; placebo: N = 1428), but not in the analyses of further outcomes (FAS, casirivimab/imdevimab: N = 1174; placebo: N = 1143). The analyses of AEs excluded 4 participants who received no treatment.
e. Cohort A1 and Cohort B1 are irrelevant for the present benefit assessment and not presented in the tables below.
f. The analyses of AEs disregarded 1 participant who did not receive any treatment (SAF, casirivimab/imdevimab: N = 165; placebo: N = 170); the analyses of other outcomes took into account this participant (FAS, casirivimab/imdevimab: N = 165; placebo: N = 171). Three participants in Cohort B were not treated due to the presence of symptoms and were excluded from the analyses.
g. According to the study protocol, screening and randomization were to take place on the same day. The study medication was administered after completion of the examinations at study inclusion.
h. Observation consists of a 28-day phase for outcomes of the morbidity category (EAP), followed by a 197-day follow-up for AEs.
i. Predefined for all study participants randomized by 28 January 2021 who fully completed EAP.
j. Data cut-off upon FDA request.
k. Data cut-off planned to occur when the last study participant has completed the study.
l. For the outcome of symptomatic SARS-CoV-2 infection, the company presented 3 different operationalizations which are based on different criteria for the presence of symptoms (broad term, strict term, and CDC definition; also see Section 2.4.1).

AE: adverse events; CDC: Centers for Disease Control and Prevention; EAP: efficacy assessment period; FAS: full analysis set; FDA: Food and Drug Administration; N: number of randomized study participants; RCT: randomized controlled trial; RT-qPCR: reverse transcriptase quantitative polymerase chain reaction; SAF: safety analysis set; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus Type 2

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

Study	Intervention	Comparison
COV-2069	Casirivimab/imdevimab 1200 mg (600 mg / 600 mg), s.c., single dose on Day 1[a]	Placebo s.c., single dose on Day 1[a]
	Dose adjustments were not allowed.	
	Prohibited prior and concomitant treatment[b] ▪ SARS-CoV-2 vaccines, whether in clinical testing or approved[c] ▪ Passive antibodies for SARS-CoV-2 prophylaxis, whether in clinical testing or approved ▪ Hydroxychloroquine/chloroquine for the prophylaxis or treatment of COVID-19 ▪ ≤ 60 days prior to screening and during the study: remdesivir or antiviral drugs against SARS	

a. The study medication had to be administered within 96 hours after the sample was taken for diagnostic testing of the index case.
b. Applies only to prophylactic use in individuals not infected with SARS-CoV-2 or asymptomatic individuals infected with SARS-CoV-2; treatment according to the applicable local standard was allowed for individuals with symptomatic SARS-CoV-2 infection.
c. Approved SARS-CoV-2 vaccines were allowed in the follow-up observation phase (disallowed during EAP).

COVID-19: Coronavirus Disease 2019; EAP: efficacy assessment period; RCT: randomized controlled trial; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus Type 2; s.c.: subcutaneous

The COV-2069 study is a randomized, double-blind RCT comparing casirivimab/imdevimab versus placebo. The study enrolled adults, adolescents, and children who have had contact with an individual infected with SARS-CoV2. The study investigated asymptomatic adults, adolescents, and children with a household contact infected with SARS-CoV-2 (hereinafter referred to as "index case"). The index case had to have tested positive for SARS-CoV-2 but was not included in the study. The contact person had to be included in the study within 96 hours after the sample was taken for diagnostic testing of the index case. In addition, the contact person had to live in the same household as the index patient until at least Day 29 of the study. Hence, the study did not include hospitalized persons and investigated only the outpatient use of casirivimab/imdevimab for PEP. Contact persons other than household contacts were not investigated in the study.

At baseline, the contact persons' serostatus was determined regarding SARS-CoV-2 antibodies. However, contact persons were included irrespective of test results; consequently, both individuals with negative and those with positive serostatus were enrolled in the study. In contrast, individuals testing positive for SARS-CoV-2 in RT-qPCR or those with a (self-reported) positive SARS-CoV-2 serology test at any point before enrolment were excluded from the COV-2069 study. Individuals who, in the investigator's opinion, had respiratory disease with signs/symptoms of SARS-CoV-2 infection in the 6 months preceding enrolment were likewise excluded. Furthermore, individuals who had received at least 1 dose of a SARS-CoV-2 vaccine, whether under investigation or approved, were likewise excluded from participation. Consequently, the study investigated only individuals not protected by vaccination.

A total of 3298 adults, adolescents, and children were included and randomized in a 1:1 ratio to treatment with casirivimab/imdevimab or placebo. For adults and adolescents, randomization was stratified by study centre, test result of the local diagnostic test for SARS-CoV-2, and age group (≥ 12 to < 18 years, ≥ 18 to < 50 years, or ≥ 50 years). To avoid delays, randomization was stratified by the results of local diagnostic testing. The results from an RT-qPCR assay which was performed by the central laboratory and additionally carried out at baseline were used to allocate individuals to study cohorts. Depending on the RT-qPCR assay results and age, individuals were allocated to the following cohorts in accordance with the study protocol:

- Cohort A: SARS-CoV-2 RT-qPCR negative at baseline; ≥ 12 years
- Cohort A1: SARS-CoV-2 RT-qPCR negative at baseline; < 12 years
- Cohort B: SARS-CoV-2 RT-qPCR positive at baseline; ≥ 12 years
- Cohort B1: SARS-CoV-2 RT-qPCR positive at baseline; < 12 years

Individuals with undetermined SARS-CoV-2 infection status were allocated to another, separate cohort. According to the study protocol, individuals were additionally to be analysed separately by serostatus (positive or negative).

By consisting of children < 12 years, Cohorts A1 and B1 comprised individuals for whom casirivimab/imdevimab is not approved; consequently, these cohorts are irrelevant for the present benefit assessment.

In Module 4 A of its dossier, the company presents only separate analyses of Cohort A and Cohort B. The analyses of each cohort included all allocated individuals irrespective of serostatus. A joint analysis of Cohorts A and B is not deemed meaningful for a qualitative analysis of the results of the determinative morbidity outcome for the 2 cohorts (see Section 2.4.3 for a detailed explanation). For the present benefit assessment, the analyses of Cohort A (SARS-CoV-2 RT-qPCR negative at baseline) and Cohort B (SARS-CoV-2 RT-qPCR positive at baseline) are therefore analysed separately.

The study protocol specified an interim analysis for verifying the assumptions made for sample size planning (administrative assessment). This descriptive analysis was based on the first 554 participants included in Cohort A. Study staff and study participants remained blinded during this analysis. However, the sponsor (statistics and analysis team) was unblinded. To preserve the integrity of the ongoing study, the company reports that study participants included in the administrative assessment were excluded from further analyses of morbidity outcomes, but they remained part of the population for the analysis of AEs. For Cohort A, this results in an analysis population for the morbidity outcomes (full analysis set [FAS], casirivimab/imdevimab: N = 1174; placebo: N = 1143), as well as an analysis population for AEs (safety analysis set [SAF], casirivimab/imdevimab: N = 1439; placebo: N = 1428). In principle, the data of the study participants investigated in the administrative assessment are also relevant for the morbidity outcomes in the benefit assessment. However, the company's

approach presumably does not lead to systematic bias, since both treatment arms are equally affected. For the present benefit assessment, the company's approach therefore remains without consequence. This benefit assessment uses the analyses presented by the company for Cohort A on the basis of the FAS or SAF for the various outcome categories.

Casirivimab/imdevimab was administered subcutaneously as a single dose on Day 1 of the study in line with the SPC [3]. Administration via infusion, which the SPC also allows, was not investigated in the COV-2069 study [3]. Individuals in the comparator arm received a corresponding placebo.

Outcomes of the morbidity category were observed for 28 days (EAP). Furthermore, AEs were followed up until the last study visit on Day 225. Individuals who tested positive for SARS-CoV-2 in RT-qPCR within the EAP were observed for outcomes of the morbidity category until they had 2 negative RT-qPCR tests or until resolution of COVID-19 symptoms, whichever was later, even if this occurred during the follow-up observation phase (after Day 29).

For Cohort A, the study's primary outcome was the proportion of participants who have a symptomatic SARS-CoV-2 infection; for Cohort B, it was the proportion of participants who develop symptomatic SARS-CoV-2 infection within 14 days of a positive RT-qPCR. For the definition of symptomatic SARS-CoV-2 infection, the broad term was used in each case (see Section 2.4.1). Patient-relevant secondary outcomes were outcomes on morbidity and AEs.

Implementation of the ACT

The G-BA specified watchful waiting as the ACT.

The COV-2069 study operationalized watchful waiting as a follow-up observation strategy. In addition, a placebo was administered in the comparator arm to ensure blinding. According to the study protocol, follow-up observation comprised, until Day 29, weekly RT-qPCR tests for SARS-CoV-2, the recording of AEs, and in case of a positive RT-qPCR test, the survey of hospitalizations, emergency room visits, or urgent care centre visits for COVID-19. The dossier does not show whether, as part of their study participation, participants were made aware of preventive measures, such as wearing a mask within their household or spatial isolation in order to reduce the risk of SARS-CoV-2 infection. The dossier likewise provides no information as to whether a mask was worn in the household during the study or whether any other preventive measures were taken. For this benefit assessment, however, the implementation of preventive measures in the COV-2069 study is assumed to adequately reflect the context of care. Therefore, the missing information is of no consequence for the present benefit assessment.

In case of symptomatic COVID-19, the study allowed the initiation of treatment according to local guidelines at the treating physician's discretion. The study protocol did not restrict the drugs to be used in symptomatic patients. The concomitant medications most frequently administered in the COV-2069 study are presented in Appendix B of the full dossier assessment. Generally, about half of the study participants received concomitant medication

over the course of the entire study. The concomitant medications primarily reflect the therapies of the various underlying illnesses of the included study participants and are comparable between the 2 study arms and cohorts. Furthermore, anti-inflammatory and pain-relieving drugs are administered as possible concomitant therapies of symptomatic COVID-19.

In summary, the ACT was adequately implemented in the COV-2069 study.

Data cut-offs

The COV-2069 study has already been completed. After the administrative assessment, there were 3 data cut-offs:

- 1st data cut-off dated 11 March 2021 (primary analysis): predefined for all study participants who had been randomized by 28 January 2021 and fully completed EAP.
- 2nd data cut-off dated 1 July 2021: data cut-off requested by the FDA
- 3rd data cut-off dated 4 October 2021 (final analysis): planned to occur when the last study participant has completed the study

Module 4 A of the company's dossier presents an analysis of results for the 2nd data cut-off. The company reports that access to data for the final analysis was delayed and that the results of the 3rd data cut-off are therefore made available together with the comments. The study report on the 3rd data cut-off has already been presented in the company's dossier. At the time of the 2nd data cut-off, more than 99% of study participants had completed EAP, and no additional participants had been included by the 3rd data cut-off. In addition, the occurred AEs showed no substantial differences between the analyses of the 2nd and 3rd data cut-offs. Hence, the 3rd data cut-off does not provide any relevant additional information when compared with the 2nd data cut-off. This benefit assessment therefore uses the results from the 2nd data cut-off (1 July 2021) presented by the company in Module 4 A.

Characteristics of the study population

Table 8 characterizes the adults and adolescents in the included study.

Table 8: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: casirivimab/imdevimab versus placebo (multipage table)

Study Characteristic Category	Cohort A (Negative SARS-CoV-2 RT-qPCR test at baseline)		Cohort B (Positive SARS-CoV-2 RT-qPCR test at baseline)	
	Casirivimab/ imdevimab N[a] = 1174	Placebo N[a] = 1143	Casirivimab/ imdevimab N[a] = 165	Placebo N[a] = 171
COV-2069				
Age [years], mean (SD)	42 (16)	42 (16)	39 (18)	42 (18)
Age group [years], n (%)				
12–17	52 (4)	47 (4)	23 (14)	20 (12)
18–49	711 (61)	692 (61)	87 (53)	91 (53)
≥ 50	411 (35)	404 (35)	55 (33)	60 (35)
Sex [f/m], %	54/46	51/49	48/52	56/44
Country, n (%)				
United States	1087 (93)	1061 (93)	147 (89)	151 (88)
Countries other than USA[b]	87 (7)	82 (7)	18 (11)	20 (12)
Body weight [kg], mean (SD)	81.3 (19.5)	81.9 (19.9)	82.8 (21.7)	78.8 (19.5)
Number of households[c] with given number of study participants in the same household, n (%)				
1 participant in the household	671 (64.5)	682 (66.5)	104 (65.8)	107 (64.8)
2 participants in the same household	252 (24.2)	238 (23.2)	33 (20.9)	41 (24.8)
3 participants in the same household	80 (7.7)	70 (6.8)	11 (7.0)	10 (6.1)
4 participants in the same household	22 (2.1)	22 (2.1)	7 (4.4)	4 (2.4)
> 4 participants in the same household	15 (1.4)	14 (1.4)	3 (1.9)	3 (1.8)
Household size, n (%)				
2 persons	446 (38.0)	413 (36.1)	66 (40.0)	75 (43.9)
> 2 persons	728 (62.0)	729 (63.8)	99 (60.0)	96 (56.1)
Others/unclear	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
Risk factor[d], n (%)				
Yes	315 (26.8)	307 (26.9)	45 (27.3)	54 (31.6)
No	859 (73.2)	836 (73.1)	120 (72.7)	117 (68.4)
Serostatus[e], n (%)				
Seropositive	276 (23.5)	251 (22.0)	49 (29.7)	43 (25.1)
Seronegative	841 (71.6)	842 (73.7)	108 (65.5)	114 (66.7)
Others/unclear	57 (4.9)	50 (4.4)	8 (4.8)	14 (8.2)

Table 8: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: casirivimab/imdevimab versus placebo (multipage table)

Study Characteristic Category	Cohort A (Negative SARS-CoV-2 RT-qPCR test at baseline)		Cohort B (Positive SARS-CoV-2 RT-qPCR test at baseline)	
	Casirivimab/ imdevimab Na = 1174	Placebo Na = 1143	Casirivimab/ imdevimab Na = 165	Placebo Na = 171
At baseline, no household members wore a mask, n (%)				
Yes	638 (54.3)	567 (49.6)	86 (52.1)	88 (51.5)
No	528 (45.0)	566 (49.5)	76 (46.1)	79 (46.2)
Unknown or not reported[f]	8 (0.7)	10 (0.9)	3 (1.8)	4 (2.3)
Shared bedroom with contact person at baseline				
Yes	353 (30.1)	355 (31.3)	69 (41.8)	78 (45.6)
No	816 (69.5)	777 (68.0)	94 (57.0)	88 (51.5)
Unknown or not reported[f]	5 (0.4)	11 (1.0)	2 (1.2)	5 (2.9)
Treatment discontinuation, n (%)	0 (0)	0 (0)	0 (0)	0 (0)
Study discontinuation, n (%)[g]	6 (0.5)	4 (0.3)	0 (0)	2 (1.1)

a. Number of randomized persons in the FAS population. Values based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b. One study centre each in Romania and the Republic of Moldova.
c. Total number of households in Cohort A: intervention arm N = 1040; control arm N = 1026; in cohort B: intervention arm N = 158; control arm N = 165.
d. "Yes" if at least 1 of the following risk factors is met: ≥ 65 years of age, BMI ≥ 35 kg/m², chronic kidney disease, diabetes, immunosuppressive disorder, immunosuppressant treatment, ≥ 55 years of age with heart disease, blood pressure, or chronic obstructive pulmonary disease.
e. Three antibody tests were used for serological testing: EuroImmun anti-S IgA, EuroImmun anti-S IgG, and Abbott anti-N IgG (Architect). Seronegative is defined as all available test results being negative. Seropositive is defined as 1 or more available test results being positive. Other/unclear is defined as the serostatus being neither positive nor negative (e.g. borderline result) or unknown. No data are available on the thresholds used to define when an individual was rated as seropositive.
f. IQWiG calculation.
g. Based on EAP.

BMI: body mass index; EAP: efficacy assessment period; f: female; FAS: full analysis set; m: male; n: number of persons in the category; N: number of randomized persons in the FAS populations; RCT: randomized controlled trial; RT-qPCR: reverse transcriptase quantitative polymerase chain reaction; SD: standard deviation

The characteristics of study participants are sufficiently comparable between treatment arms and between Cohorts A and B. The mean age of participants was about 42 years, and the sex distribution was nearly balanced. The majority of study participants were included in the United States. About one-fourth of the investigated individuals were seropositive for SARS-CoV-2 at baseline. In about one-third of households, more than 1 person participated in the study. About 40% of households consisted of 2 members, i.e. only the index case and the study participant.

In about half of households, no mask was worn at baseline, and about 30% to 40% of study participants shared a bedroom with the index case. Hence, the established hygiene rules were implemented in only some of the households at the start of the COV-2069 study.

None of the study arms had any cases of premature treatment discontinuation. There were sporadic cases of study discontinuation during EAP.

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

As described above, adults and adolescents who had received at least 1 vaccination against SARS-CoV-2 were excluded from the COV-2069 study. At the time of the benefit assessment, however, a large proportion of the population has already been completely immunized as defined by the STIKO [13] through vaccinations and potential prior virus exposure, thereby reducing the risk of SARS-CoV-2 infection and/or of COVID-19 becoming symptomatic. Additionally, complete vaccination protection leads to an altered immune response after contact with SARS-CoV-2. Depending on the virus variant, it can be safely assumed that people who are completely immunized possibly exhibit no detectable infection or a milder course of COVID-19 [13,14]. Incompletely immunized individuals or those at relevant risk of inadequate vaccine response as defined by STIKO [13], however, continue to be at a risk of infection with SARS-CoV-2 and/or of a symptomatic course of COVID-19, with the risk being comparable to unvaccinated people. Individuals who exhibited inadequate vaccine response and are therefore not completely immunized were excluded from the COV-2069 study. Likewise excluded were people at relevant risk of inadequate vaccine response. However, evidence can be transferred from unvaccinated individuals who were included in the COV-2069 study to groups who failed to achieve complete immunization despite being vaccinated. Nevertheless, it remains unclear whether the effects observed in unvaccinated individuals are fully transferable to these groups. This issue has been taken into account in the assessment of the certainty of conclusions (see Section 2.4.2). On the basis of the COV-2069 study, no conclusions on added benefit can be drawn on incompletely immunized adults and adolescents.

Furthermore, the COV-2069 study excluded individuals who were positive for SARS-CoV-2 in RT-qPCR or had a positive SARS-CoV-2 serology test at any time prior to study inclusion or who, in the investigator's opinion, had a respiratory disease with signs/symptoms of SARS-CoV-2 infection in the 6 months preceding study inclusion. Despite these limitations imposed by the inclusion criteria, about one-fourth of the individuals included in the study had a positive serostatus at baseline. Since the study population was to exclude recovered patients, those included in the COV-2069 study can be safely assumed to have had an asymptomatic infection. Therefore, it remains unclear whether the participants with positive serostatus are comparable to patients who have recovered from symptomatic COVID-19 infection, which, at the current time, represent the majority of the population in the present therapeutic indication.

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]. For the purposes of the present benefit assessment, the therapeutic indication is therefore assumed to exclude any individuals who have come into contact with a SARS-CoV-2 virus variant for which neutralizing activity is inadequate, either demonstrably so or as expected based on the current pandemic situation. (For a detailed description, see Section 2.2). Based on the information provided in the dossier, it remains unclear with which SARS-CoV2 virus variant adult and adolescent COV-2069 study participants were infected and for how many a virus genotype was even available. Because the study was conducted in an earlier wave of the pandemic (07/2020 to 10/2021), it can be safely assumed that the majority of adults and adolescents included in the study were infected with virus variants which circulated prior to the spread of the omicron variant, which predominates at the time of the benefit assessment. In vitro neutralization assays show that the neutralizing activity of casirivimab/imdevimab is markedly reduced against the omicron virus variant, therefore suggesting lower effectiveness. Hence, casirivimab/imdevimab is not recommended for prophylaxis in the presence of the omicron variant [4,5].

In summary, on the basis of the COV-2069 study, conclusions can be drawn for adults and adolescents who have not yet been vaccinated against SARS-CoV-2 or who are not completely immunized against SARS-CoV-2. On the basis of the COV-2069 study, no conclusions on added benefit can be drawn on incompletely immunized adults and adolescents. In addition, the present therapeutic indication does not cover adults and adolescents who have come into contact with a SARS-CoV-2 virus variant for which neutralizing activity is inadequate, either demonstrably so or as expected based on the current pandemic activity; consequently, these individuals are not the subject of the present benefit assessment.

Risk of bias across outcomes (study level)

Table 9 shows the risk of bias across outcomes (risk of bias at study level).

Table 9: Risk of bias across outcomes (study level) – RCT, 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-2069	Yes	Yes	Yes	Yes	Yes	Yes	Low
RCT: randomized controlled trial							

The risk of bias across outcomes for the COV-2069 study is rated as low.

Transferability to the German health care context

The company deems the results of the COV-2069 study to be transferable to the German health care context because of the comparability in patient characteristics between the study population and the German population susceptible for SARS-CoV-2 infection. The company argues that they are comparable based on the study predominantly including participants of White ancestry, the sex ratio being balanced, and a broad range of ages being included.

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) 1. casirivimab/imdevimab neutralizes a virus variant and
2) 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 [3,4,15]. In summary, the company deems the COV-2069 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 considered in the assessment:

- Mortality
  - all-cause mortality
- Morbidity
  - symptomatic SARS-CoV-2 infection
  - hospitalization for COVID-19
- 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
- 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 A).

Table 10 shows the outcomes for which data were available in the included study.

Table 10: Matrix of outcomes – RCT, direct comparison: casirivimab/imdevimab versus placebo

Study	Outcomes							
	All-cause mortality[a]	Symptomatic SARS-CoV-2 infection[b]	Hospitalization for COVID-19[c]	Health-related quality of life	SAEs	Severe AEs[d]	Discontinuation due to AEs	Specific AEs
COV-2069	Yes	Yes	Yes	No[e]	No[f]	No[f]	Yes[g]	No[h]

a. Death for any cause up to and including Day 225.
b. Symptomatic SARS-CoV-2 infection is defined as a positive RT-qPCR test from the central laboratory in conjunction with the occurrence of COVID-19 symptoms within ± 14 days of a positive test during EAP. For Cohort B, the positive test might have been available already at baseline, or another positive test might have been taken within the EAP.
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. Outcome not recorded.
f. The analyses are unusable because the company does not present any definition of the events it deemed disease-related and excluded from the analyses (see text below).
g. No AEs leading to discontinuation occurred.
h. No specific AEs were identified based on the AEs occurring in the relevant study.

AE: adverse event; COVID-19: Coronavirus Disease 2019; CTCAE: Common Terminology Criteria for Adverse Events; EAP: efficacy assessment period; RCT: randomized controlled trial; SAE: serious adverse event; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus Type 2

Morbidity

Symptomatic SARS-CoV-2 infection

The study protocol defined symptomatic SARS-CoV-2 infection as a positive RT-qPCR test for SARS-CoV-2 from the central laboratory within the EAP in conjunction with the occurrence of symptoms within ± 14 days of the positive test result. Symptoms developing outside the EAP were acceptable. For symptomatic SARS-CoV2 infection, the company presented 3 different operationalizations based on different criteria for the presence of symptoms:

- broad definition
- strict definition
- CDC definition

Appendix C of the full dossier assessment presents in detail the criteria for the respective definitions. For the present benefit assessment, symptomatic SARS-CoV-2 infection is operationalized using the broad definition. This operationalization comprises a larger number of potential COVID-19 symptoms and therefore better depicts the variable clinical picture of COVID-19. The broad definition also corresponds to the primary definition used in the study protocol. According to the company, the CDC definition was added to ensure comparability with other studies in the same therapeutic indication. In this benefit assessment, this operationalization is presented as supplementary information. The results of the CDC definition and the broad definition are comparable for the outcome of symptomatic SARS-CoV-2 infection (see Table 12).

In addition, SARS-CoV-2 infection confirmed by RT-qPCR, irrespective of symptoms, is presented as supplementary information because this operationalization provides information beyond symptomatic SARS-CoV-2 infection for the present therapeutic indication of PEP of COVID-19.

Hospitalization for COVID-19 / for any cause

Regarding hospitalization for COVID-19, the company's dossier presents analyses of the proportion of individuals with event, which is based on confirmation of SARS-CoV-2 infection by RT-qPCR within the EAP. The study documents and Module 4 A 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. In addition, on the basis of information on the length of stay in the hospital or intensive care unit for COVID-19, as presented in Module 4 A of the company's dossier, the majority of events can be safely assumed to not have been short-term hospitalizations.

Number of days with missed daily duties

In Module 4 A of the dossier, the company presents analyses on the number of days with daily duties missed due to COVID-19. According to the study protocol, daily duties included work (for those in the labour force), school, day care, or family duties/responsibilities (child care or care for elderly people). For the present therapeutic indication of PEP, the primary treatment goal is to prevent symptomatic SARS-CoV-2 infection. The duration of symptoms and the associated number of daily duties missed additionally do not provide any reliable information as to the extent of restrictions suffered by study participants due to the infection. For instance, the analyses presented by the company reflect only daily duties, rather than all activities of daily living. The analyses disregard study participants who do not have any daily duties but were unable to pursue other activities. It remains unclear how many study participants pursued daily duties and how many did not. Additionally, it remains unclear to what extent some study participants may have been restricted in their activities – at least temporarily – not due to symptoms, but only due to a positive SARS-CoV-2 PCR test and the associated quarantine rules. The analyses presented by the company are therefore irrelevant for this benefit assessment.

Side effects

SAEs and severe AEs

The COV-2069 study's survey of SAEs and severe AEs recorded both treatment-related AEs and events to be allocated to the symptoms of COVID. For the outcomes of SAEs and severe AEs, Module 4 A of the company's dossier does present analyses excluding disease-related events. However, the company did not define which events it deemed disease-related and 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 available analyses on the outcomes of SAEs and severe AEs are therefore unusable for the present benefit assessment.

2.4.2 Risk of bias

Table 11 describes the risk of bias for the results of the relevant outcomes.

Table 11: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: casirivimab/imdevimab versus placebo

Study	Study level	Outcomes							
		All-cause mortality[a]	Symptomatic SARS-CoV-2 infection[b]	Hospitalization for COVID-19[c]	Health-related quality of life	SAEs	Severe AEs[d]	Discontinuation due to AEs	Specific AEs
COV-2069									
Cohort A (negative SARS-CoV-2 RT-qPCR test at baseline)	L	L	L	L	–[e]	–[f]	–[f]	L[g]	–
Cohort B (positive SARS-CoV-2 RT-qPCR test at baseline)	L	L	L	L	–[e]	–[f]	–[f]	L[g]	–

a. Death for any cause up to and including Day 225.
b. Symptomatic SARS-CoV-2 infection is defined as a positive RT-qPCR test from the central laboratory in conjunction with the occurrence of COVID-19 symptoms within ± 14 days of a positive test during EAP. For Cohort B, the positive test could either be available already at baseline, or another positive test might have been taken within the EAP.
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. Outcome not recorded.
f. The company did not provide any information regarding which events it deemed disease-related (see Section 2.4.1).
g. No AEs leading to discontinuation occurred.

AE: adverse event; COVID-19: Coronavirus Disease 2019; CTCAE: Common Terminology Criteria for Adverse Events; EAP: efficacy assessment period; H: high; L: low; RCT: randomized controlled trial; SAE: serious adverse event; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus Type 2

The risk of bias for the results of all outcomes included in the benefit assessment was rated as low.

Summary assessment of the certainty of conclusions

As described above, the COV-2069 study presents only data on adults and adolescents who have not yet been vaccinated against SARS-CoV-2. However, the effects are assumed to be transferable to individuals not completely immunized against SARS-CoV-2. No conclusions can be drawn on completely immunized persons (also see Section 2.3.2). The following estimate of the certainty of conclusions therefore applies only to adults and adolescents who

have not yet been vaccinated against SARS-CoV-2 or who are not completely immunized against SARS-CoV-2. The present therapeutic indication does not cover individuals who have come into contact with a SARS-CoV-2 virus variant for which neutralizing activity is inadequate, either demonstrably so or as expected based on the current pandemic activity; consequently, these individuals are not subject of the present benefit assessment.

As described in Section 2.3.2, evidence can be transferred from unvaccinated individuals included in the COV-2069 study to groups who do not achieve complete immunization despite being vaccinated. Whether the effects observed in unvaccinated individuals are fully transferable to these groups nevertheless remains unclear. Overall, this reduces the certainty of conclusions of the study results for the present research question. Based on the COV-2069 study, at most hints, e.g. of an added benefit, can be derived for all outcomes presented.

2.4.3 Results

Table 12 summarizes the results of the comparison of casirivimab/imdevimab with placebo for the PEP of COVID-19 in adults and adolescents 12 years of age or older with a minimum body weight of 40 kg. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier.

Appendix D of the full dossier assessment presents the results on common AEs, SAEs, and severe AEs not excluding disease-related events. The outcome of discontinuation due to AEs is not presented because in Cohorts A and B of the COV-2069 study, no events leading to discontinuation occurred.

Table 12: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: casirivimab/imdevimab versus placebo (multipage table)

Study Outcome category Outcome Study	Casirivimab/ imdevimab		Placebo		Casirivimab/imdevimab vs. placebo
	N	Individuals with event n (%)	N	Individuals with event n (%)	RR [95% CI]; p-value[a]
COV-2069 (data cut-off 1 July 2021)					
Mortality					
All-cause mortality (up to Day 225)					
Cohort A (negative SARS-CoV-2 RT-qPCR test at baseline)	1174	3 (0.3)	1143	1 (0.1)	2.92 [0.30; 28.04]; 0.530
Cohort B (Positive SARS-CoV-2 RT-qPCR test at baseline)	165	0 (0)	171	0 (0)	–
Morbidity					
Symptomatic SARS-CoV-2 infection (broad definition)					
Cohort A (negative SARS-CoV-2 RT-qPCR test at baseline)	1174	15 (1.3)	1143	78 (6.8)	0.19 [0.11; 0.32]; < 0.001
Cohort B (Positive SARS-CoV-2 RT-qPCR test at baseline)	165	35 (21.2)	171	59 (34.5)	0.61 [0.43; 0.88]; 0.007
Symptomatic SARS-CoV-2 infection (CDC definition; presented as supplementary information)					
Cohort A (Negative SARS-CoV-2 RT-qPCR test at baseline)	*1174*	*9 (0.8)*	*1143*	*61 (5.3)*	*0.14 [0.07; 0.29]; < 0.001*
Cohort B (Positive SARS-CoV-2 RT-qPCR test at baseline)	*165*	*32 (19.4)*	*171*	*55 (32.2)*	*0.60 [0.41; 0.88]; 0.009*
Positive SARS-CoV-2 RT qPCR test irrespective of symptoms (presented as supplementary information)					
Cohort A (Negative SARS-CoV-2 RT-qPCR test at baseline)	*1174*	*56 (4.8)*	*1143*	*145 (12.7)*	*0.38 [0.28; 0.51]; < 0.001*
Cohort B (Positive SARS-CoV-2 RT-qPCR test at baseline)	*Not applicable*				
Hospitalization for COVID-19 (up to Day 29)					
Cohort A (Negative SARS-CoV-2 RT-qPCR test at baseline)	1174	0 (0)	1143	1 (0.1)	0.32 [0.01; 7.96][b]; 0.369
Cohort B (Positive SARS-CoV-2 RT-qPCR test at baseline)	165	0 (0)	171	4 (2.3)	-[c] 0.049
Health-related quality of life	Outcome not recorded				

Table 12: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: casirivimab/imdevimab versus placebo (multipage table)

Study Outcome category Outcome Study	Casirivimab/ imdevimab		Placebo		Casirivimab/imdevimab vs. placebo
	N	Individuals with event n (%)	N	Individuals with event n (%)	RR [95% CI]; p-value[a]
Side effects					
AEs (supplementary information)				*No usable data*[d]	
SAEs				No usable data[d]	
Severe AEs[e]				No usable data[d]	
Discontinuation due to AEs					
Cohort A (Negative SARS-CoV-2 RT-qPCR test at baseline)	1439	0	1428	0	–
Cohort B (Positive SARS-CoV-2 RT-qPCR test at baseline)	165	0	170	0	–

a. Institute's calculation (unconditional exact test [CSZ method according to [16]]).
b. Institute's calculation, asymptotic.
c. Discrepancy between p-value (exact) and CI (asymptotic) due to different calculation methods; effect estimation and CI not presented for lack of informative value.
d. The company did not provide any definition of the events it deemed disease-related (see Section 2.4.1).
e. Severe AEs are operationalized as CTCAE grade ≥ 3.

AE: adverse event; CI: confidence interval; CSZ: convexity, symmetry, z-score; CTCAE: Common Terminology Criteria for Adverse Events; n: number of persons with (at least 1) event; N: number of analysed persons; RCT: randomized controlled trial; RR: relative risk; RT-qPCR: reverse transcriptase quantitative polymerase chain reaction; SAE: serious adverse event; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus Type 2

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

For the present benefit assessment, the analyses of Cohort A (negative SARS-CoV-2 RT-qPCR test at baseline) and Cohort B (positive SARS-CoV-2 RT-qPCR test at baseline) are analysed separately. Joint evaluation of Cohorts A and B is not deemed meaningful for a qualitative analysis of the results of these cohorts. For the determinative outcome of symptomatic SARS-CoV-2 infection, the interaction test shows substantial heterogeneity of effects ($p_{Int} < 0.05$). Hence, for adults and adolescents 12 years and older with a minimum body weight of 40 kg, the evaluation and derivation of added benefit are performed separately for those testing positive versus negative for SARS-CoV-2 in RT-qPCR.

Mortality

All-cause mortality

For Cohort A of the COV-2069 study, no statistically significant difference between treatment groups was found for the outcome of all-cause mortality. For the outcome of all-cause mortality, this results in no hint of added benefit of casirivimab/imdevimab in comparison with watchful waiting for adults and adolescents tested negative for SARS-CoV-2 in RT-qPCR; an added benefit is therefore not proven.

No deaths occurred in COV-2069 Cohort B. For the outcome of all-cause mortality, this results in no hint of added benefit of casirivimab/imdevimab in comparison with watchful waiting for adults and adolescents tested positive for SARS-CoV-2 in RT-qPCR; an added benefit is therefore not proven.

Morbidity

Symptomatic SARS-CoV-2 infection (broad definition)

In both Cohort A and Cohort B of the COV-2069 study, there was a statistically significant difference between treatment groups in favour of casirivimab/imdevimab for the outcome of symptomatic SARS-CoV-2 infection (broad definition). For Cohort A, this favourable effect was also found in the proportion of participants testing positive for SARS-CoV-2 in RT-qPCR, irrespective of symptoms, and is presented as supplementary information. For this outcome, this results in a hint of added benefit of casirivimab/imdevimab in comparison with watchful waiting for both adults and adolescents tested positive for SARS-CoV-2 in RT-qPCR and for those tested negative. For both groups, substantial heterogeneity of effects was found in the interaction test ($p_{Int} < 0.05$). In addition, the extent of added benefit differs (see Section 2.5.1). The results on symptomatic SARS-CoV-2 infection, surveyed using the CDC definition, are comparable with the results for the broad definition.

Hospitalization for COVID-19

For Cohort A of the COV-2069 study, no statistically significant difference between treatment arms was found for the outcome of hospitalization for COVID-19. Regarding the outcome of hospitalization for COVID-19, this results in no hint of added benefit of casirivimab/imdevimab in comparison with watchful waiting for adults and adolescents tested negative for SARS-CoV-2; an added benefit is therefore not proven.

For the outcome of hospitalization for COVID-19, a statistically significant difference between treatment groups was found in favour of casirivimab/imdevimab in Cohort B of the COV-2069 study. Regarding this outcome, this results in a hint of added benefit of casirivimab/imdevimab in comparison with watchful waiting for adults and adolescents tested positive for SARS-CoV-2 in RT-qPCR.

Health-related quality of life

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

Side effects

SAEs and severe AEs

In the survey of SAEs and severe AEs, the COV-2069 study included disease-related events. For these outcomes, Module 4 A 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 of SAEs and severe AEs are unusable for assessing the side effects of casirivimab/imdevimab. Given the small proportion of participants with an event in Cohort A and Cohort B of the COV-2069 study, 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 common severe AEs (see Appendix D of the full dossier assessment). For the outcomes of SAEs and severe AEs, there is no hint of greater or lesser harm from casirivimab/imdevimab in comparison with watchful waiting for adults and adolescents tested positive or negative for SARS-CoV-2 in RT-qPCR; greater or lesser harm is therefore not proven for either of them.

Discontinuation due to AEs

In the course of the COV-2069 study, neither Cohort A nor Cohort B had any discontinuations due to AEs. This results in no hint of greater or lesser harm from casirivimab/imdevimab in comparison with watchful waiting for adults and adolescents tested positive or negative for SARS-CoV-2 in RT-qPCR; greater or lesser harm is therefore not proven for either of them.

2.4.4 Subgroups and other effect modifiers

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

- age (12 to 17 years versus 18 to 49 years versus > 50 years)
- sex (female versus male)

Subgroup analyses by age and sex were predefined for the study's primary outcome. The company submitted subgroup analyses 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.

Using the methods described above, the available subgroup results did not show any effect modifications.

2.5 Probability and extent of added benefit

Probability and extent of the added benefit per subpopulation 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 the added benefit based on the aggregation of conclusions derived at outcome level is 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 is estimated from the results presented in Section 2.4 (see Table 13).

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.

Symptomatic SARS-CoV-2 infection

The company's dossier did not provide any information on the assessment of severity of the events which occurred. Few patients in the COV-2069 study were hospitalized for COVID-19. Therefore, the events included in the outcome of symptomatic SARS-CoV-2 infection presumably tend to be non-serious/non-severe. Therefore, the outcome was assigned to the outcome category of non-serious/non-severe symptoms / late complications.

Hospitalization for COVID-19

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

Table 13: Extent of added benefit at outcome level: casirivimab/imdevimab versus watchful waiting (multipage table)

Outcome category **Outcome**	**Casirivimab/imdevimab vs. placebo** **Proportion of events (%)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
All-cause mortality		
Cohort A (Negative SARS-CoV-2 RT-qPCR test at baseline)	0.3% vs. 0.1% RR: 2.92 [0.30; 28.04] p = 0.530	Lesser/added benefit not proven
Cohort B (Positive SARS-CoV-2 RT-qPCR test at baseline)	0% vs. 0% RR: –	Lesser/added benefit not proven
Morbidity		
Symptomatic SARS-CoV-2 infection (broad definition)		
Cohort A (Negative SARS-CoV-2 RT-qPCR test at baseline)	1.3% vs. 6.8% RR: 0.19 [0.11; 0.32] p < 0.001 Probability: hint	Outcome category: non-serious/non-severe symptoms / late complications $CI_u < 0.80$ Added benefit; extent: considerable
Cohort B (Positive SARS-CoV-2 RT-qPCR test at baseline)	21.2% vs. 34.5% RR: 0.61 [0.43; 0.88] p = 0.007 Probability: hint	Outcome category: non-serious/non-severe symptoms / late complications $0.80 \leq CI_u < 0.90$ Added benefit; extent: minor
Hospitalization for COVID-19		
Cohort A (Negative SARS-CoV-2 RT-qPCR test at baseline)	0% vs. 0.1% RR: 0.32 [0.01; 7.96] p = 0.369	Lesser/added benefit not proven
Cohort B (Positive SARS-CoV-2 RT-qPCR test at baseline)	0% vs. 2.3% RR: –[c] p = 0.049 Probability: hint	Outcome category: serious/severe symptoms / late complications Added benefit; extent: minor[d]
Health-related quality of life		
–	Outcomes from this category were not recorded	Lesser/added benefit not proven
Side effects		
SAEs	Data not evaluable[c]	Greater/lesser harm not proven
Severe AEs	Data not evaluable[c]	Greater/lesser harm not proven
Discontinuation due to AEs		
Cohort A (Negative SARS-CoV-2 RT-qPCR test at baseline)	0% vs. 0% RR: –	Greater/lesser harm not proven

Table 13: Extent of added benefit at outcome level: casirivimab/imdevimab versus watchful waiting (multipage table)

Outcome category **Outcome**	**Casirivimab/imdevimab vs. placebo** **Proportion of events (%)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Cohort B (Positive SARS-CoV-2 RT-qPCR test at baseline)	0% vs. 0% RR: –	Greater/lesser harm not proven

a. Probability provided if there is a statistically significant and relevant effect.
b. Depending on the outcome category, estimations of effect size are made with different limits based on the upper limit of the confidence interval (CI_u).
c. Discrepancy between p-value (exact) and CI (asymptotic) due to different calculation methods; effect estimation and CI not presented, because not informative.
d. The result of the statistical test is determinative for the derivation of added benefit. Due to the size of the p-value, extent is rated as minor.

AE: adverse event; CI: confidence interval; CI_u: upper limit of CI; COVID-19: Coronavirus Disease-2019; RR: relative risk; RT-qPCR: reverse transcriptase quantitative polymerase chain reaction; SAE: serious adverse event; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus Type 2

2.5.2 Overall conclusion on added benefit

Table 14 summarizes the results taken into account in the overall conclusion on the extent of added benefit.

Table 14: Favourable and unfavourable effects from the assessment of casirivimab/imdevimab in comparison with watchful waiting

Favourable effects	Unfavourable effects
(Negative SARS-CoV-2 RT-qPCR test at baseline)	
Non-serious/non-severe symptoms / late complications ▪ Symptomatic SARS-CoV-2 infection (broad definition): hint of added benefit – extent: considerable	–
No data were available for outcomes on health-related quality of life. For the outcomes of SAEs and severe AEs, no usable data were available. Effects apply only to individuals who have not yet been vaccinated against SARS-CoV-2 or who are not completely immunized against SARS-CoV-2.	
Cohort B (positive SARS-CoV-2 RT-qPCR test at baseline)	
Serious/severe symptoms / late complications Hospitalization for COVID-19 ▪ Hospitalization for COVID-19: hint of an added benefit – extent: minor	–
Non-serious/non-severe symptoms / late complications ▪ Symptomatic SARS-CoV-2 infection (broad definition): hint of added benefit – extent: minor	–
No data were available for outcomes on health-related quality of life. For the outcomes of SAEs and severe AEs, no usable data were available. Effects apply only to individuals who have not yet been vaccinated against SARS-CoV-2 or who are not completely immunized against SARS-CoV-2. AE: adverse event; COVID-19: Coronavirus Disease 2019; RT-qPCR: reverse transcriptase quantitative polymerase chain reaction; SAE: serious adverse event; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus Type 2	

As described in Section 2.4.3, for adults and adolescents 12 years and older with a minimum body weight of 40 kg, the added benefit of casirivimab/imdevimab is derived separately for those testing negative versus positive for SARS-CoV-2 in RT-qPCR. In addition, the present therapeutic indication does not cover adults and adolescents who have come into contact with a SARS-CoV-2 virus variant for which neutralizing activity is inadequate, either demonstrably so or as expected based on the current pandemic activity; consequently, these individuals are not the subject of the present benefit assessment. Moreover, the following conclusions on added benefit apply only to adults and adolescents who have not yet been vaccinated against SARS-CoV-2 or who are not completely immunized against SARS-CoV-2. No data are available for adults and adolescents who are completely immunized against SARS-CoV-2. For this group, there is therefore no proof of added benefit of casirivimab/imdevimab.

Adults and adolescents 12 years of age and older weighing at least 40 kg testing negative for SARS-CoV-2 in RT-qPCR

Overall, only a favourable effect of casirivimab/imdevimab was found for the study population in Cohort A. For the outcome of symptomatic SARS-CoV-2 infection, this results in a hint of considerable added benefit. For some outcomes in the side effects category, no usable data are

available. However, the available information does not suggest any unfavourable effects to an extent that could call the favourable effect into question.

In summary, for adults and adolescents 12 years of age and older weighing at least 40 kg who have tested negative for SARS-CoV-2 in RT-qPCR, there is a hint of considerable added benefit of casirivimab/imdevimab in comparison with the ACT of watchful waiting for PEP of COVID-19.

Adults and adolescents 12 years of age and older weighing at least 40 kg who have tested positive for SARS-CoV-2 in RT-qPCR

Overall, only favourable effects of casirivimab/imdevimab were found for the study population in Cohort B. For each of the outcomes of symptomatic SARS-CoV-2 infection and hospitalization for COVID-19, there is a hint of minor added benefit. For some outcomes in the side effects category, no usable data are available. However, the available information does not suggest any unfavourable effects to an extent that could call the favourable effects into question.

In summary, for adults and adolescents 12 years of age and older weighing at least 40 kg who have tested positive for SARS-CoV-2 in RT-qPCR, there is a hint of minor added benefit of casirivimab/imdevimab in comparison with the ACT of watchful waiting in the PEP of COVID-19.

Table 15 summarizes the result of the assessment of added benefit of casirivimab/imdevimab in comparison with the ACT.

Table 15: Casirivimab/imdevimab – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
PEP of COVID-19 in adults and adolescents aged 12 years and older and with a body weight of at least 40 kg[b,c]	Watchful waiting[d]	Adults and adolescents without complete immunization[e] ▪ Negative for SARS-CoV-2 in RT-qPCR: hint of considerable added benefit ▪ Positive for SARS-CoV-2 in RT-qPCR: hint of minor added benefit
		Adults and adolescents who are completely immunized[f] ▪ Added benefit not proven

a. Presented is the respective ACT specified by the G-BA.
b. 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].
c. The G-BA assumes that study participants in all study arms observe the generally recognized hygiene rules (e.g. social distancing, hygiene measures, face masks) for reducing the risk of infection. In cases where medical reasons (e.g. dementia) preclude compliance with established hygiene rules, this must be documented.
d. As soon as the disease becomes symptomatic, treatment according to current medical knowledge is indicated.
e. No vaccination against SARS-CoV-2 or no complete immunization against SARS-CoV-2 according to STIKO recommendations [13].
f. Complete immunization against SARS-CoV-2 in accordance with STIKO recommendations [13].

ACT: appropriate comparator therapy; COVID-19: Coronavirus Disease 2019; G-BA: Federal Joint Committee; RT-qPCR: reverse transcriptase quantitative polymerase chain reaction; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus Type 2; STIKO: Germany's Standing Committee on Vaccinations

The assessment described above deviates from the company's assessment, which derived proof of considerable added benefit for the entire population of the present therapeutic indication, irrespective of immunization status or the presence of a positive or negative RT-qPCR test for SARS-CoV-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.

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.

1. Institute for Quality and Efficiency in Health Care. General Methods; Version 6.1 [online]. 2022 [Accessed: 17.08.2022]. URL: https://www.iqwig.de/methoden/general-methods_version-6-1.pdf.

2. Skipka G, Wieseler B, Kaiser T et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. Biom J 2016; 58(1): 43-58. https://dx.doi.org/10.1002/bimj.201300274.

3. Roche Registration. Fachinformation Ronapreve 300 mg + 300 mg Injektions-/Infusionslösung. Stand März 2022. 2022.

4. Paul Ehrlich Institut. Information für Angehörige aus Gesundheitsberufen. Casirivimab/Imdevimab (Ronapreve) 120 mg/ml Injektions-/ Infusionslösung. Stark verminderte Neutralisierungseigenschaften des Volllängen Spike-Proteins der Omikron-Variante durch die Antikörperkombination Casivimab/Imdevimab [online]. 2022 [Accessed: 11.03.2022]. URL: https://www.pei.de/SharedDocs/Downloads/DE/newsroom/dossiers/ronapreve-neutralisationsdaten-omikron.pdf?__blob=publicationFile&v=9.

5. Fachgruppe COVRIIN am Robert-Koch-Institut. Möglicher Einsatz der neutralisierenden monoklonalen Antikörper in Abhängigkeit von der diagnostizierten SARS-CoV-2-Virusvariante [online]. 2022 [Accessed: 30.06.2022]. URL: https://www.rki.de/DE/Content/InfAZ/N/Neuartiges_Coronavirus/COVRIIN_Dok/Monoklonale_AK.pdf?__blob=publicationFile.

6. Regeneron Pharmaceuticals. COVID-19 Study Assessing the Virologic Efficacy of REGN10933+REGN10987 Across Different Dose Regimens in Adult Outpatients With SARS-CoV-2 Infection [online]. 2022 [Accessed: 02.05.2022]. URL: https://clinicaltrials.gov/ct2/show/NCT04666441.

7. Regeneron Pharmaceuticals. A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study Assessing the Efficacy and Safety of Anti-Spike SARS-CoV-2 Monoclonal Antibodies in Preventing SARS-CoV-2 Infection in Household Contacts of Individuals Infected With SARS-CoV-2; study R10933-10987-COV-2069; Clinical Study Report Addendum; 2nd Data Cut-Off [unpublished]. 2021.

8. Regeneron Pharmaceuticals. A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study Assessing the Efficacy and Safety of Anti-Spike SARS-CoV-2 Monoclonal Antibodies in Preventing SARS-CoV-2 Infection in Household Contacts of Individuals Infected With SARS-CoV-2; study R10933-10987-COV-2069; Clinical Study Report Addendum 2; 3rd Data Cut-Off [unpublished]. 2021.

9. Regeneron Pharmaceuticals. A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study Assessing the Efficacy and Safety of Anti-Spike SARS-CoV-2 Monoclonal Antibodies in Preventing SARS-CoV-2 Infection in Household Contacts of Individuals Infected With SARS-CoV-2; study R10933-10987-COV-2069; Clinical Study Report [unpublished]. 2021.

10. Regeneron Pharmaceuticals. COVID-19 Study Assessing the Efficacy and Safety of Anti-Spike SARS CoV-2 Monoclonal Antibodies for Prevention of SARS CoV-2 Infection Asymptomatic in Healthy Adults and Adolescents Who Are Household Contacts to an Individual With a Positive SARS-CoV-2 RT-PCR Assay [online]. 2021 [Accessed: 05.02.2022]. URL: https://clinicaltrials.gov/ct2/show/NCT04452318.

11. O'Brien MP, Forleo-Neto E, Musser BJ et al. Subcutaneous REGEN-COV Antibody Combination to Prevent Covid-19. N Engl J Med 2021; 385(13): 1184-1195. https://dx.doi.org/10.1056/NEJMoa2109682.

12. O'Brien MP, Forleo-Neto E, Sarkar N et al. Effect of Subcutaneous Casirivimab and Imdevimab Antibody Combination vs Placebo on Development of Symptomatic COVID-19 in Early Asymptomatic SARS-CoV-2 Infection: A Randomized Clinical Trial. JAMA 2022; 327(5): 432-441. https://dx.doi.org/10.1001/jama.2021.24939.

13. Robert Koch Institut. Epidemiologisches Bulletin 21/2022 [online]. 2022 [Accessed: 01.07.2022]. URL: https://www.rki.de/DE/Content/Infekt/EpidBull/Archiv/2022/Ausgaben/21_22.pdf?__blob=publicationFile.

14. Danza P, Koo TH, Haddix M et al. SARS-CoV-2 Infection and Hospitalization Among Adults Aged >/=18 Years, by Vaccination Status, Before and During SARS-CoV-2 B.1.1.529 (Omicron) Variant Predominance - Los Angeles County, California, November 7, 2021-January 8, 2022. MMWR Morb Mortal Wkly Rep 2022; 71(5): 177-181. https://dx.doi.org/10.15585/mmwr.mm7105e1.

15. Fachgruppe COVRIIN beim Robert-Koch-Institut. Medikamentöse Therapie bei COVID-19 mit Bewertung durch die Fachgruppe COVRIIN beim Robert Koch-Institut [online]. 2022 [Accessed: 22.04.2022]. URL: https://www.rki.de/DE/Content/InfAZ/N/Neuartiges_Coronavirus/COVRIIN_Dok/Therapieuebersicht.pdf?__blob=publicationFile.

16. Martín Andrés A, Silva Mato A. Choosing the optimal unconditioned test for comparing two independent proportions. Computat Stat Data Anal 1994; 17(5): 555-574. https://dx.doi.org/10.1016/0167-9473(94)90148-1.

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