Tixagevimab/cilgavimab (COVID-19) –

Benefit assessment according to §35a SGB V[1]

EXTRACT

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Patient and family involvement

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

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Part I: Benefit assessment

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

I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
COVID-19	Coronavirus Disease 2019
COVRIIN	Fachgruppe Intensivmedizin, Infektiologie und Notfallmedizin (Expert Working Group Intensive Care, Infectiology and Emergency Medicine)
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
PCR	polymerase chain reaction
RCT	randomized controlled trial
RKI	Robert Koch Institute
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics
STIKO	Ständige Impfkommission (Standing Committee on Vaccination)
WHO	World Health Organization

I 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 tixagevimab/cilgavimab. 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 17 October 2022.

Research question

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

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

Table 2: Research question for the benefit assessment of tixagevimab/cilgavimab

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

a. Presented is the ACT specified by the G-BA.
b. In case of a positive rapid antigen test, the diagnosis of SARS-CoV-2 infection should be confirmed by a PCR test, especially if the results have therapeutic consequences.
c. It is recommended that relevant SARS-CoV-2 mutation variants (e.g. variants of concern [VOC]) are also taken into account when recording and interpreting the results on efficacy.
d. Recently, the intravenous drugs casirivimab/imdevimab, regdanvimab, remdesivir, and sotrovimab have been approved for the treatment of COVID-19 patients who do not require supplemental oxygen and are at increased risk of progressing to severe COVID-19. The clinical significance of these therapy options cannot be assessed at the present time.
e. In case of disease progression and patient hospitalization, additional therapies must be considered; these include both drug-based therapies (e.g. dexamethasone; anticoagulants / thrombosis prevention, antibiotics) and non-drug-based therapies (e.g. oxygen therapy, type of ventilation, balanced fluid therapy).

ACT: appropriate comparator therapy; COVID-19: Coronavirus Disease 2019; G-BA: Federal Joint Committee; PCR: polymerase chain reaction; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; VOC: variants of concern

The company followed the G-BA's ACT.

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

Neutralizing activity against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus variants

According to the Summary of Product Characteristics (SPC), tixagevimab/cilgavimab has decreased *in vitro* neutralization activity against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) Omicron variants BA.1, BA.1.1, BA.4, and BA.5. According to the SPC, however, the clinical relevance of this decreased *in vitro* neutralization activity of tixagevimab/cilgavimab against these variants is unknown.

The Intensive Care, Infectiology and Emergency Medicine (COVRIIN) expert group at the Robert Koch Institute (RKI) recommends taking into account the current epidemiological situation and neutralizing activity against individual virus variants when selecting monoclonal antibodies for treatment or prophylaxis. For the virus variants Omicron BA.1, BA.4, and BA.5, the expert group reports moderately to substantially decreased *in vitro* neutralization activity of tixagevimab/cilgavimab and therefore deems reduced efficacy against these variants to be probable. Against the newly arisen BA.5 subline BQ1.1, in contrast, the expert group reports no *in vitro* neutralization activity.

Study pool and study design

The TACKLE study is used to assess the added benefit of tixagevimab/cilgavimab in comparison with therapy of the physician's choice. The TACKLE study is an ongoing, double-blind randomized controlled trial (RCT) comparing treatment with tixagevimab/cilgavimab versus placebo in adult patients in early stage COVID-19. The study enrolled symptomatic patients with SARS-CoV-2 infection confirmed by polymerase chain reaction (PCR) ≤ 3 days before study start. Symptom onset had to have occurred ≤ 7 days before study inclusion and persist within 24 hours prior to study start. At the time of study inclusion, patients were to be not hospitalized and not require supplemental oxygen (oxygen saturation ≥ 92% on room air). At least 60% of participants were to be at high risk of progressing to severe COVID-19. Furthermore, patients who had received at least 1 vaccination against SARS-CoV-2 were excluded from the study. Consequently, the TACKLE study investigated only unvaccinated patients.

A total of 910 patients were randomized at a 1:1 ratio.

Tixagevimab/cilgavimab was administered in line with the SPC in the TACKLE study.

The study's primary outcome is the combined outcome of severe COVID-19 or death for any cause by Day 29. Patient-relevant secondary outcomes were morbidity outcomes and adverse events (AEs).

According to the study protocol, the follow-up observation period was 29 or 169 days, depending on the outcome. AE outcomes were further observed until Day 457.

Subpopulation presented by the company

The company presents the results of a prespecified subpopulation of participants who received the study medication in line with the SPC within 7 days after the onset of COVID-19 symptoms and were not hospitalized at baseline. This population comprises a total of 834 patients, 413 of whom were treated with tixagevimab/cilgavimab and 421 with placebo.

The subpopulation submitted by the company does not fully correspond to the present research question. Firstly, about 10% of included participants were at low risk of progressing to severe disease. These patients therefore do not fall under the present research question. For the present research question, an analysis of the subpopulation at high risk of progressing to severe disease would be more suitable. However, the results of the subgroup analyses presented in the dossier show that the participants in the subpopulation presented by the company who are at low risk of progressing to severe disease do not have a relevant effect on results.

Furthermore, participants who were hospitalized at baseline for isolation purposes (< 8% of the study population) do not fall under the subpopulation submitted by the company. For these participants, the company assumes that the study results may be potentially biased due to the medical treatment of COVID-19 changing over the course of the study. On 5 July 2021, Amendment 6 of the study protocol therefore excluded these patients from the analysis population.

Overall, the relevance of the subpopulation submitted by the company is not called into question, and the results are used for the benefit assessment.

Implementation of the appropriate comparator therapy

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

Overall, the TACKLE study's concomitant treatment with anti-inflammatory and analgesic drugs represents a sufficient implementation of the ACT. For early-phase COVID-19 in patients who are at increased risk of progressing to severe disease, the guideline recommends further specific antiviral substances which were disallowed or not used in the study. However, the guidelines issue only a mild or open recommendation for specific risk groups for these treatment options. In addition, the treatment of patients with COVID-19 can be safely

assumed to have continuously changed over the course of the pandemic, particularly in light of increasing SARS-CoV-2 immunocompetence due to vaccinations and prior virus exposure as well as the evolution of new virus variants with potentially differing pathogenicity. Overall, the fact that the TACKLE study did not use specific antiviral substances is therefore of no consequence for the present benefit assessment.

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

As described above, the TACKLE study enrolled only unvaccinated patients. At the time of the benefit assessment, however, vaccinations and potential prior exposure to the virus have resulted in a large proportion of the population already being completely immunized according to the definition of the Standing Committee on Vaccination (STIKO), thereby reducing the risk for severe COVID-19. Accordingly, these patients do not fall under the present therapeutic indication, because they are not at increased risk of progressing to severe disease. However, patients with incomplete immunization or with a relevant risk of an insufficient vaccination response according to the STIKO definition may still be at increased risk of progressing to severe disease. According to COVRIIN, the same applies to patients exhibiting complex risk factors despite being immunocompetent and fully vaccinated. The studies submitted for the benefit assessment excluded patients who exhibited an inadequate vaccine response and are therefore not fully immunized. Likewise excluded were patients who, despite being immunocompetent and fully vaccinated, had complex risk factors resulting in an increased risk of progressing to severe disease. It is plausible to transfer evidence from the unvaccinated TACKLE participants to patient groups who do not achieve complete immunization despite being vaccinated and who are at increased risk of progressing to severe disease. Nevertheless, it remains unclear whether the effects observed in unvaccinated patients are fully transferable to these patient groups. This issue has been taken into account in the assessment of the certainty of conclusions.

About 14% of TACKLE participants had a positive serum status for SARS-CoV-2 at baseline. The study documents show that among the participants with a positive serum status at study start, only 1 person in the control arm had been previously diagnosed with COVID-19 disease. It remains unclear whether the included patients with positive serostatus are comparable to those recovered from symptomatic COVID-19, who, in the current health care context, represent a large percentage of the population in the present therapeutic indication.

The company's Module 4 A does not provide any information on the viral variant present in TACKLE participants. However, the documents on the TACKLE study show that only about 38% of patients for whom sequencing data were available were infected with the Alpha variant. Other frequently confirmed variants were B.1.1.519 (19%), Gamma (12%), and Delta (10%). The currently predominant SARS-CoV variant, Omicron, was not found among the study participants. According to the SPC, tixagevimab/cilgavimab exhibits *in vitro* antiviral activity

against the Omicron variant BA.2, while Omicron variants BA.1, BA.1.1, BA.4, and BA.5 exhibit reduced sensitivity to tixagevimab/cilgavimab. However, no *in vitro* neutralization activity has been found against the recently emerged BA.5 subline BQ.1.1. On the basis of the TACKLE study, conclusions on added benefit can be drawn only for patients who are infected with a virus variant for which tixagevimab/cilgavimab has sufficient neutralization activity.

In summary, on the basis of the TACKLE study, conclusions on added benefit can be drawn for patients who have not yet been vaccinated against COVID-19 or who are not fully immunized against COVID-19, or who, despite being immunocompetent and fully vaccinated, still are at increased risk of progressing to severe COVID-19 due to complex risk factors. Patients with complete immunization are not comprised by the present therapeutic indication and are therefore not subject of the present benefit assessment. In addition, conclusions on added benefit are only possible for patients who are infected with a virus variant for which there is sufficient neutralization activity.

Further limitation of the study population

According to the study protocol, only adult patients were to be included in the TACKLE study. The company does not submit any data on children and adolescents, nor did it supply an adequate justification of transferability to adolescents aged 12 years and older. The available data allow drawing a conclusion on added benefit only for adults with COVID-19.

Risk of bias and assessment of the certainty of conclusions

The risk of bias is rated as low for the results of all-cause mortality, the morbidity outcomes, and the outcome of discontinuation due to AEs. The risk of bias for the results of the outcome of serious adverse events (SAEs) was rated as high. The analyses disregard the events which the company classified as disease related. However, due to the broad range of COVID-19 symptoms, other events which may be either side effects or symptoms of the underlying disease may have plausibly been recorded.

As described above, it is possible to transfer evidence from the unvaccinated patients included in the TACKLE study to patient groups who do not achieve complete immunization despite being vaccinated or who have complex risk factors despite being immunocompetent and fully vaccinated. Nevertheless, it remains unclear whether the effects observed in unvaccinated patients are fully transferable to these patient groups. Overall, this reduces the certainty of conclusions of the study results for the present research question. Based on the TACKLE study, at most hints, e.g. of an added benefit, can be determined for all outcomes presented.

Results

Mortality

All-cause mortality

There was no statistically significant difference between treatment groups for the outcome of all-cause mortality. This results in no hint of added benefit of tixagevimab/cilgavimab in comparison with treatment of physician's choice; an added benefit is therefore not proven.

Morbidity

Severe COVID-19

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

ICU admission for any cause

No statistically significant difference between treatment groups was shown for the outcome of ICU admission for any cause. This results in no hint of added benefit of tixagevimab/cilgavimab in comparison with treatment of physician's choice; an added benefit is therefore not proven.

Return to normal health

There was no statistically significant difference between treatment groups for the outcome of return to normal health. This results in no hint of added benefit of tixagevimab/cilgavimab in comparison with treatment of physician's choice; an added benefit is therefore not proven.

COVID-19 symptoms

No suitable data were available for the outcome of COVID-19 symptoms. This results in no hint of added benefit of tixagevimab/cilgavimab in comparison with treatment of physician's choice; an added benefit is therefore not proven.

Health-related quality of life

Health-related quality of life outcomes were not recorded in the included study. This results in no hint of added benefit of tixagevimab/cilgavimab in comparison with treatment of physician's choice; an added benefit is therefore not proven.

Side effects

SAEs

For the outcome of SAEs, no statistically significant difference between treatment groups was found. This results in no hint of greater or lesser harm from tixagevimab/cilgavimab in

comparison with treatment of physician's choice; greater or lesser harm is therefore not proven.

Severe AEs

No suitable data are available for the outcome of severe AEs. This results in no hint of greater or lesser harm from tixagevimab/cilgavimab in comparison with treatment of physician's choice; greater or lesser harm is therefore not proven.

Discontinuation due to AEs

No events occurred in the outcome of discontinuation due to AEs. This results in no hint of greater or lesser harm from tixagevimab/cilgavimab in comparison with treatment of physician's choice; greater or lesser harm is therefore not proven.

Specific AEs

Hypersensitivity reactions and injection site reactions

For the outcome of hypersensitivity reactions and injection site reactions, no suitable data are available. This results in no hint of greater or lesser harm from tixagevimab/cilgavimab in comparison with treatment of physician's choice; greater or lesser harm is therefore not proven.

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

On the basis of the results presented, the probability and extent of added benefit of the drug tixagevimab/cilgavimab compared with the ACT is assessed as follows:

As already described, the following conclusion on added benefit applies exclusively to adult patients who have not yet received a vaccination against COVID-19 or who are not fully immunized against COVID-19 or who have complex risk factors despite being immunocompetent and fully vaccinated. Fully immunized patients do not fall under the present therapeutic indication because they are not at increased risk of progressing to severe COVID-19.

[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].

In addition, the conclusion on added benefit relates only to patients who are infected with a virus variant for which there is sufficient neutralization activity. According to the SPC, tixagevimab/cilgavimab has reduced *in vitro* neutralization activity against the SARS-CoV-2 Omicron variants BA.1, BA1.1, BA.4, and BA.5. It remains unclear whether the effects observed in the TACKLE study are transferable to patients infected with the virus variants BA.5 or a BA.5 subline, which were circulating at the time of the benefit assessment.

No data are available for adolescents aged 12 to < 18 years and weighing at least 40 kg who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19. For this age group, this results in no proof of added benefit of tixagevimab/cilgavimab.

Overall, there is only 1 favourable effect of tixagevimab/cilgavimab in comparison with treatment of physician's choice for adults with COVID-19 who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19: There is a hint of considerable added benefit for the outcome of severe COVID-19.

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

Table 3 presents a summary of the probability and extent of added benefit of tixagevimab/cilgavimab.

Table 3: Tixagevimab/cilgavimab – probability and extent of added benefit

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

a. Presented is the ACT specified by the G-BA.
b. In case of a positive rapid antigen test, the diagnosis of SARS-CoV-2 infection should be confirmed by a PCR test, especially if the results have therapeutic consequences.
c. It is recommended that relevant SARS-CoV-2 mutation variants (e.g. variants of concern [VOC]) are also taken into account when recording and interpreting the results on efficacy.
d. Recently, the intravenous drugs casirivimab/imdevimab, regdanvimab, remdesivir, and sotrovimab have been approved for the treatment of COVID-19 patients who do not require supplemental oxygen and are at increased risk of progressing to severe COVID-19. The clinical significance of these therapy options cannot be assessed at the present time.
e. In case of disease progression and patient hospitalization, further drug therapies (e.g. dexamethasone; anticoagulation / thrombosis prophylaxis, antibiotics) as well as non-drug therapies (e.g. oxygen therapy, type of ventilation, balanced fluid therapy) must be considered.
f. The conclusion on added benefit applies only to patients who are infected with a virus variant for which there is sufficient neutralization activity. According to the SPC, tixagevimab/cilgavimab has decreased neutralization activity against the SARS-CoV-2 Omicron variants BA.4 and BA.5. It remains unclear whether the effects observed in the TACKLE study are transferable to patients infected with the virus variants BA.5 or a BA.5 subline, which are circulating at the time of the benefit assessment.

ACT: appropriate comparator therapy; COVID-19: Coronavirus Disease 2019; G-BA: Federal Joint Committee; PCR: polymerase chain reaction; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; VOC: variants of concern

The approach for deriving an overall conclusion on added benefit constitutes a proposal by IQWiG. The G-BA decides on the added benefit.

I 2 Research question

The aim of the present report is to assess the added benefit of tixagevimab/cilgavimab in comparison with the ACT in adults and adolescents (aged 12 years and older and weighing at least 40 kg) with COVID-19 who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19.

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

Table 4: Research question for the benefit assessment of tixagevimab/cilgavimab

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

a. Presented is the ACT specified by the G-BA.
b. In case of a positive rapid antigen test, the diagnosis of SARS-CoV-2 infection should be confirmed by a PCR test, especially if the results have therapeutic consequences.
c. It is recommended that relevant SARS-CoV-2 mutation variants (e.g. VOCs) are also taken into account when recording and interpreting the results on efficacy.
d. Recently, the intravenous drugs casirivimab/imdevimab, regdanvimab, remdesivir, and sotrovimab have been approved for the treatment of COVID-19 patients who do not require supplemental oxygen and are at increased risk of progressing to severe COVID-19. The clinical significance of these therapy options cannot be assessed at the present time.
e. In case of disease progression and patient hospitalization, further drug therapies (e.g. dexamethasone; anticoagulation / thrombosis prophylaxis, antibiotics) as well as non-drug therapies (e.g. oxygen therapy, type of ventilation, balanced fluid therapy) must be considered.

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

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

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

Neutralizing activity against SARS-CoV-2 virus variants

According to the SPC [3], tixagevimab/cilgavimab has decreased *in vitro* neutralization activity against the SARS-CoV-2 Omicron variants BA.1, BA.1.1, BA.4, and BA.5. According to the SPC, however, the clinical relevance of the decreased *in vitro* neutralization activity of tixagevimab/cilgavimab against these variants is unknown.

The COVRIIN expert group at the RKI recommends taking into account the current epidemiological situation and neutralizing activity against individual virus variants when selecting monoclonal antibodies for treatment or prophylaxis. For the virus variants Omicron

BA.1, BA.4, and BA.5, the expert group states that the *in vitro* neutralization activity of tixagevimab/cilgavimab is moderately to substantially reduced and presumes the efficacy against these variants to be likely reduced [4]. However, no neutralization activity is reportedly found *in vitro* against the recently emerged BA.5 subline BQ.1.1 [4].

I 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 tixagevimab/cilgavimab (status: 22 September 2022)
- bibliographical literature search on tixagevimab/cilgavimab (last search on 22 September 2022)
- search in trial registries / trial results databases for studies on tixagevimab/cilgavimab (last search on 22 September 2022)
- search on the G-BA website for tixagevimab/cilgavimab (last search on 22 September 2022)

To check the completeness of the study pool:

- search in trial registries for studies on tixagevimab / cilgavimab (last search on 7 November 2022); for search strategies, see I Appendix A of the full dossier assessment

The check did not identify any additional relevant study.

Concurring with the company, the TACKLE study is included in the present benefit assessment.

Furthermore, the ACTIV-2 study is potentially relevant for the assessment but was presented only as supplementary information by the company and was disregarded in the benefit assessment. This approach is appropriate as justified below.

ACTIV-2 study was disregarded in the benefit assessment

The ACTIV-2 study is a placebo-controlled, double-blind, adaptive, randomized phase 2/3 platform study comparing several investigational products versus placebo in patients with COVID-19; the study investigated, for instance, the comparison of tixagevimab/cilgavimab versus placebo. The study included symptomatic patients with SARS-CoV-2 infection confirmed by means of molecular diagnostics ≤ 10 days prior to study start. Symptoms had to have started ≤ 7 days before enrolment and persist 24 hours before study start. The subpopulation submitted by the company (patients at high risk of progressing to severe COVID-19) comprises a total of 66 patients, of which 33 patients were treated with tixagevimab/cilgavimab and 33 with placebo.

The company presents the ACTIV-2 study only as supplementary information, disregarding it in its derivation of added benefit. It justifies this approach by citing low patient numbers and few events in the observed outcomes. In comparison with the much larger TACKLE study,

which the company included in its benefit assessment, the ACTIV-2 study reportedly has only minor impact on the respective effect estimator of a metaanalysis.

Irrespective of the company's approach, the dossier lacks any information on concomitant therapies administered to participants during the study. Hence, it cannot be determined to what extent the ACT, i.e. therapy according to physician's choice, was implemented in the ACTIV-2 study. Furthermore, the dossier contains little information on the data cutoff used. The company's dossier does not show whether the data cutoff was planned or whether patients completed the prespecified observation periods. For these reasons, the relevance of the ACTIV-2 study in the present benefit assessment cannot be evaluated with sufficient certainty.

Irrespective of the points listed above, the relevant patient population of the ACTIV-2 study (N = 66) equals less than 8% of the population of the TACKLE study which was included in the benefit assessment (N = 834). Concurring with the company, potential results from the ACTIV-2 study would therefore presumably not impact the result of the benefit assessment in a relevant manner. The exclusion of the ACTIV-2 study from the present benefit assessment is therefore without consequence for the conclusion.

I 3.1 Studies included

The studies listed in the following table were included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: tixagevimab/cilgavimab versus placebo

Study	Study category			Available sources		
	Approval study for 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 and other sources[c] (yes/no [citation])
Study D8851C0 (TACKLE[d])	Yes	Yes	No	Yes [5]	Yes [6-8]	Yes [9,10]

a. Study for which the company was sponsor.
b. References of the trial registry entries and, if available, of the reports on study design and/or results listed in the trial registries.
c. Other sources: documents from the search on the G-BA website and other publicly available sources.
d. In the following tables, the study is referred to by this acronym.

CSR: clinical study report; G-BA: Federal Joint Committee; RCT: randomized controlled trial

I 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: tixagevimab/cilgavimab 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]
TACKLE	RCT, double-blind[b], parallel	Non-hospitalized[c] adults (≥ 18 years) with acute COVID-19[d] ▪ WHO score of the clinical progression scale for COVID-19 of > 1 and < 4[e] ▪ Mild to moderate COVID-19 symptoms ≤ 7 days prior to administration of the study medication[f] ▪ Symptoms within 24 hours prior to study start[g] ▪ Oxygen saturation ≥ 92% measured at rest within 24 hours prior to Day 1[e]	Tixagevimab/cilgavimab (N = 456) Placebo (N = 454) Relevant subpopulation[h]: tixagevimab/cilgavimab (n = 413) Placebo (n = 421)	Screening: < 1 day Treatment: 1 day Observation: 457 days maximum	95 study centres in Argentina, Brazil, Czech Republic, Germany, Great Britain, Hungary, Italy, Japan, Mexico, Poland, Russia, Spain, Ukraine, United States 01/2021–ongoing Data cutoffs: ▪ 1st data cutoff: 21 August 2021 (primary data cutoff)[i] ▪ 2nd data cutoff: 14 January 2022[j]	Primary: composite outcome of severe COVID-19 or death from any cause up to Day 29 Secondary: morbidity, AEs

Table 6: Characteristics of the included study – RCT, direct comparison: tixagevimab/cilgavimab 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. It was possible to receive a COVID-19 vaccination 30 days after receipt of the study medication, if desired. If so, unblinding via the study's unblinding procedure was allowed. Patients who were unblinded in order to be vaccinated were to remain in the study after unblinding.
c. As per local guidelines, patients in Japan and Russia were allowed to be hospitalized at study start for observational purposes.
d. Documented positive SARS-CoV-2 PCR test from a sample which was taken ≤ 3 days prior to study enrolment.
e. Patients with a score < 4 on the COVID-19 WHO Clinical Progression Scale do not require supplemental oxygen. Any patients who received long-term supplemental oxygen therapy due to chronic pulmonary disease were nevertheless eligible for study inclusion.
f. Mild to moderate symptoms include: subjective fever or feeling feverish, cough, shortness of breath or difficulty breathing at rest or during activity, sore throat, body aches or muscle pain/soreness, fatigue, headache, chills, nasal obstruction or stuffy nose, runny nose, new loss of taste or smell, nausea or vomiting, diarrhoea, documented body temperature > 37.8°C, new confusion (only in participants ≥ 60 years), appetite loss or reduced food intake (only in participants aged ≥ 60 years), increased need for supplemental oxygen (only for participants who received supplemental oxygen at the start of treatment).
g. Symptoms within 24 hours prior to study start: cough, sore throat, shortness of breath or difficulty breathing at rest or during activity, body aches or muscle pain/soreness, fatigue, headache, chills, nasal obstruction or stuffy nose, runny nose, nausea or vomiting, diarrhoea, new loss of taste or smell.
h. Prespecified subpopulation which received the investigational product ≤ 7 days after symptom onset and had not been hospitalized for isolation at study start (≤ Day 1).
i. Interim analysis 30 days after the occurrence of 43 primary outcome events.
j. Data cutoff at which all randomized patients had been observed up to Day 169.

AE: adverse event; CLIA: Clinical Laboratory Improvement Amendments; COVID-19: Coronavirus Disease 2019; DAIDS: Division of Acquired Immunodeficiency Syndrome; i.m.: intramuscular; n: relevant subpopulation; N: number of randomized patients; PCR: polymerase chain reaction; RCT: randomized controlled trial; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus Type 2; WHO: World Health Organization

Table 7: Characteristics of the intervention – RCT, direct comparison: tixagevimab/cilgavimab versus placebo

Study	Intervention	Comparison
TACKLE	Tixagevimab 300 mg, i.m. + Cilgavimab 300 mg, i. m., once on Day 1 as 2 separate consecutive injections	Placebo i.m. Once on Day 1 in the form of 2 separate consecutive injections
	Permitted concomitant treatment ▪ Additional standard therapy according to local guidelines for the treatment of COVID-19 ▪ Other therapies as required **Prohibited prior and concomitant treatment** ▪ Vaccinations of any kind during the study[b] ▪ COVID-19 convalescent plasma ▪ Systemic steroids (e.g. prednisone, dexamethasone) or inhaled steroids ≤ 30 days prior to study start[c] ▪ Mechanical ventilation ▪ Any investigational products < 90 days or 5 half-lives (whichever was longer) before randomization ▪ HIV protease inhibitors during the study[c] ▪ Hydroxychloroquine during the study[c] ▪ Chloroquine and ivermectin during the study[d] ▪ Surgical procedures ≤ 7 days before study start	

a. In the form of constant-dose therapy which started 30 days prior to study start.
b. Vaccinations, including against SARS-CoV-2, were allowed from 30 days after administration of the study medication. The administration of influenza vaccinations was allowed at any time.
c. At constant dosage for the treatment of a disease with onset before study enrolment.
d. Allowed for the treatment of parasite infection.

COVID-19: Coronavirus Disease 2019; HIV: human immunodeficiency virus; i.m.: intramuscular; RCT: randomized controlled trial; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus type 2

The TACKLE study is an ongoing, double-blind RCT comparing tixagevimab/cilgavimab treatment versus placebo in adult patients in early-stage COVID-19. The study enrolled symptomatic patients with SARS-CoV-2 infection confirmed by PCR test ≤ 3 days before study start. Symptoms had to have started ≤ 7 days before enrolment and persist within 24 hours before study start. At the time of study inclusion, patients were to be not hospitalized and not require supplemental oxygen (oxygen saturation ≥ 92% on room air). At least 60% of participants were to be at high risk of progressing to severe COVID-19. The study defined high risk of progressing to severe disease via the risk factors of age ≥ 65 years, cancer, chronic lung disease / asthma, obesity, hypertension, cardiovascular disease, diabetes, chronic kidney disease, weakened immune system (due to organ transplantation, blood or bone marrow transplantation, immune defects, human immunodeficiency virus [HIV], use of corticosteroids or other immunosuppressant medications), chronic liver disease, sickle cell anaemia, and smoking. Overall, these criteria are appropriate for assessing the risk of progressing to severe

disease [11]. Furthermore, patients who had received at least 1 vaccination against SARS-CoV-2 were excluded from the study. Consequently, the TACKLE study investigated only unvaccinated patients.

A total of 910 patients were randomized at a 1:1 ratio. Randomization was stratified by risk of progressing to severe disease (high versus low risk) and time since symptom onset (≤ 5 versus > 5 days). About 90% of patients were at high risk of progressing to severe disease as per the above-listed criteria.

In the TACKLE study, tixagevimab/cilgavimab was administered in line with the SPC [3].

The study's primary outcome is the combined outcome of severe COVID-19 or death for any cause by Day 29. Patient-relevant secondary outcomes were morbidity outcomes and AEs.

According to the study protocol, the follow-up observation period was 29 or 169 days, depending on the outcome. AE outcomes were further observed until Day 457.

As per study protocol, an interim analysis was conducted 30 days after the occurrence of 43 primary outcome events. This 1st data cutoff took place on 21 August 2021. The 2nd cutoff dated 14 January 2022 comprises the observations of all randomized patients up to Day 169. Analyses of the 2nd data cutoff were used for the present benefit assessment.

Subpopulation presented by the company

The company presents the results of a prespecified subpopulation of participants who received the study medication in line with the SPC within 7 days after the onset of COVID-19 symptoms and were not hospitalized at baseline. This population comprises a total of 834 patients, 413 of whom were treated with tixagevimab/cilgavimab and 421 with placebo.

The subpopulation submitted by the company does not fully correspond to the present research question. Firstly, about 10% of the patients in this subpopulation were at low risk of progressing to severe disease (see Table 9). These patients therefore do not fall under the present research question. For the present research question, an analysis of the subpopulation at high risk of developing severe disease would be more suitable. However, the results of the subgroup analyses presented in the dossier show that the participants in the subpopulation presented by the company who are at low risk of progressing to severe disease do not have a relevant effect on results. Furthermore, the subpopulation submitted by the company excluded any participants who were hospitalized at baseline for isolation purposes (< 8% of the study population). For these participants, the company assumes that the study results may be potentially biased due to the medical treatment of COVID-19 changing over the course of the study. On 5 July 2021, Amendment 6 of the study protocol therefore excluded these patients from the analysis population.

Overall, the relevance of the subpopulation submitted by the company is not called into question, and the results are used for the benefit assessment.

Implementation of the appropriate comparator therapy

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

According to the current assessment of the COVRIIN Expert Group at the RKI (status: 22 November 2022), besides tixagevimab/cilgavimab, another monoclonal antibody by name of sotrovimab and the virustatic drugs nirmatrelvir/ritonavir, molnupiravir, and remdesivir are available as antiviral therapy in early-phase COVID-19 in patients with risk factors for progressing to severe disease [4]. At the time of the benefit assessment, molnupiravir is not approved for the present therapeutic indication. The recommendations of the COVRIIN Expert Group essentially correspond to the recommendations of the guidelines current at the time of the benefit assessment (S3 guideline on inpatient therapy for patients with COVID-19 [status: 12 September 2022] and the guideline of the German College of General Practitioners and Family Physicians (DEGAM) [status: 4 February 2022] [12]). However, the guidelines issue merely a weak or open recommendation for these substances for specific risk groups. This is justified in particular by the evolution of new virus variants with potentially changed pathogenicity and the population's increased immunocompetence, which is promoted in particular by vaccination and prior virus exposure. Overall, according to information provided in the S3 guideline [13], it is therefore difficult to quantify the current risk of requiring inpatient or outpatient therapy, experiencing longer-term limitations of quality of life, or dying due to SARS-CoV-2 infection. The suitable treatment should be selected on a case-by-case basis, taking into account individualized risk profile, immunization status, comorbidities, availability, and contraindications. This is also reflected in the assessment by the more recent (22 November 2022) assessment by the COVRIIN expert group, whose proposals for the selection of antiviral therapy not only includes the immunization status but also the neutralization activity against currently prevailing viral variants [4,14].

Administered concomitant therapies

In the TACKLE study, COVID-19 therapy was to be administered according to local standards. However, there were limitations. The study did not allow the use of convalescent COVID-19 plasma against SARS-CoV-2. Also not allowed was the use of hydroxychloroquine or

chloroquine. Further, some of the monoclonal antibodies or antiviral drugs against COVID-19 were not yet available at the time the study was conducted.

Beyond that, there were no further restrictions or specific requirements for the concomitant treatment.

Data on the concomitant therapies administered in the TACKLE study, which were received by ≥ 5% of the patients in at least one study arm, are listed in Table 8.

Table 8: Information on concomitant therapies (≥ 5% of the patients in ≥ 1 treatment arm) – RCT, direct comparison: tixagevimab/cilgavimab versus placebo (TACKLE study) (multipage table)

Study **Drug class** **Drug**	**Patients with subsequent therapy n (%)** **Tixagevimab/cilgavimab** **N = 413**	 **Placebo** **N = 421**
TACKLE[a]		
Total	351 (85.0)	362 (86.0)
ACE inhibitors, pure	44 (10.7)	32 (7.6)
Enalapril	21 (5.1)	15 (3.6)
Sympathomimetics in combination with glucocorticoids (except anticholinergics)	21 (5.1)	18 (4.3)
Angiotensin II receptor antagonists	51 (12.3)	53 (12.6)
Losartan	31 (7.5)	24 (5.7)
Anilide	143 (34.6)	142 (33.7)
Paracetamol	140 (33.9)	142 (33.7)
Beta-adrenoreceptor antagonists, selective	29 (7.0)	31 (7.4)
Biguanides	36 (8.7)	46 (10.9)
Metformin	33 (8.0)	43 (10.2)
Dihydropyridine derivatives	16 (3.9)	22 (5.2)
Direct factor-Xa inhibitors	18 (4.4)	29 (6.9)
Glucocorticoids	41 (9.9)	71 (16.9)
Dexamethasone	17 (4.1)	42 (10.0)
Heparin group	32 (7.7)	43 (10.2)
Enoxaparin	22 (5.3)	28 (6.7)
HMG-CoA reductase inhibitors	36 (8.7)	38 (9.0)
Macrolides	33 (8.0)	33 (7.8)
Azithromycin	17 (4.1)	22 (5.2)
Mucolytics	27 (6.5)	32 (7.6)
Natural and semisynthetic oestrogens, pure	26 (6.3)	28 (6.7)
Other antihistamines for systemic use	17 (4.1)	27 (6.4)
Other viral vaccines	25 (6.1)	56 (13.3)
Vaxzevria	9 (2.2)	23 (5.5)

Table 8: Information on concomitant therapies (≥ 5% of the patients in ≥ 1 treatment arm) – RCT, direct comparison: tixagevimab/cilgavimab versus placebo (TACKLE study) (multipage table)

Study	**Patients with subsequent therapy n (%)**	
Drug class **Drug**	**Tixagevimab/cilgavimab** **N = 413**	**Placebo** **N = 421**
Tozinameran	6 (1.5)	23 (5.5)
Platelet aggregation inhibitors, excluding heparin	33 (8.0)	41 (9.7)
Acetylsalicylic acid	27 (6.5)	37 (8.8)
Progestogens	29 (7.0)	37 (8.8)
Propionic acid derivatives	68 (16.5)	70 (16.6)
Ibuprofen	54 (13.1)	56 (13.3)
Proton pump inhibitors	38 (9.2)	40 (9.5)
Omeprazole	25 (6.1)	25 (5.9)
Selective beta$_2$-adrenoceptor agonists	41 (9.9)	39 (9.3)
Salbutamol	33 (8.0)	24 (5.7)
Thyroid hormones	24 (5.8)	19 (4.5)
Oxygen	18 (4.4)	45 (10.7)
Vitamin D and analogues	52 (12.6)	57 (13.5)
Vitamin D NOS	28 (6.8)	33 (7.8)
Colecalciferol	21 (5.1)	23 (5.5)

a. Data are based on information on the 1st data cutoff (21 August 2021). Data on the 2nd data cutoff were not available for the benefit assessment.

n: number of patients with subsequent therapy; N: number of analysed patients; RCT: randomized controlled trial

As concomitant therapies for the treatment of COVID-19, the TACKLE study administered, in particular, anti-inflammatory and analgesic drugs. The frequency of administration of these drugs was about equal in both study arms. Other concomitant therapies frequently used in the study reflect the underlying illnesses of the enrolled patients with risk factors for progression to severe disease.

Overall, the TACKLE study's concomitant treatment with anti-inflammatory and analgesic drugs represents a sufficient implementation of the ACT. For early-phase COVID-19 in patients who are at increased risk of progressing to severe disease, the guideline recommends further specific antiviral substances which were not allowed or not used in the study. As described above, however, guidelines give these therapy options merely a weak or open recommendation for special risk groups. In addition, the treatment of patients with COVID-19 can be safely assumed to have continuously changed over the course of the pandemic, particularly in light of increasing SARS-CoV-2 immunocompetence due to vaccinations and prior virus exposure as well as the evolution of new virus variants with potentially differing

pathogenicity. Overall, the fact that the TACKLE study did not use specific antiviral substances is therefore of no consequence for the present benefit assessment.

Table 9 shows the characteristics of the patients in the studies included.

Table 9: Characteristics of the study population as well as study/therapy discontinuation – RCT, direct comparison: tixagevimab/cilgavimab versus placebo (multipage table)

Study	**TACKLE**	
Characteristic **Category**	**Tixagevimab/cilgavimab**	**Placebo**
	N[a] = 413	**N[a] = 421**
Age [years], mean (SD)	46 (15)	46 (15)
Age [years], n (%)		
< 65 years	364 (88)	369 (88)
≥ 65 years	49 (12)	52 (12)
Sex [f/m], %	55/45	49/51
Geographical region, n (%)		
United States	63 (15)	37 (9)
Latin America	171 (41)	204 (48)
Asia	6 (1)	3 (1)
Europe	173 (42)	177 (42)
WHO score on the clinical progression scale for COVID-19, n (%)		
2	376 (91)	379 (90)
3	37 (9)	42 (10)
Serum status regarding SARS-CoV-2, n (%)		
positive	52 (13)	62 (15)
negative	353 (85)	351 (83)
no data	8 (2)	8 (2)
Time since initial onset of symptoms [days]		
mean (SD)	4.8 (1.6)	4.9 (1.6)
Time since initial onset of symptoms, n (%)		
≤ 5 days	255 (62)	253 (60)
> 5 days	158 (38)	168 (40)
Risk factors for a severe course of COVID-19[b], n (%)		
high	370 (90)	377 (90)
low	43 (10)	44 (10)
Smoking status, n (%)		
current smoker	88 (21)	88 (21)
ex-smoker	77 (19)	86 (20)
never smoker	248 (60)	247 (59)
BMI [kg/m²], mean (SD)	29 (6)	29 (7)

Table 9: Characteristics of the study population as well as study/therapy discontinuation – RCT, direct comparison: tixagevimab/cilgavimab versus placebo (multipage table)

Study	**TACKLE**	
Characteristic **Category**	**Tixagevimab/cilgavimab**	**Placebo**
	N[a] = 413	**N[a] = 421**
COVID-19 comorbidities, n (%)		
no comorbidities	47 (11)	50 (12)
≥ 1 comorbidity	366 (89)	371 (88)
cancer	16 (4)	13 (3)
chronic lung disease / asthma	55 (13)	48 (11)
obesity	185 (45)	179 (43)
hypertension	118 (29)	108 (26)
cardiovascular disease	37 (9)	35 (8)
diabetes	44 (11)	51 (12)
chronic kidney disease	9 (2)	6 (1)
compromised immune system	21 (5)	23 (5)
chronic liver disease	4 (1)	9 (2)
Treatment discontinuation, n (%)	ND	ND
Study discontinuation, n (%)	ND[c]	ND[c]

a. Number of participants who received the study medication within 7 days after the occurrence of the first COVID-19 symptoms and were not hospitalized at baseline. Values which are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b. Patients are at high risk of progressing to severe COVID-19 if at least 1 of the following criteria applies: age ≥ 65 years, cancer, chronic lung disease / asthma, obesity, hypertension, cardiovascular disease, diabetes, chronic kidney disease, weakened immune system (due to organ transplantation, blood or bone marrow transplantation, immune defects, HIV, use of corticosteroids or other immunosuppressants), chronic liver disease, sickle cell anaemia, smoking.
c. Information on the most frequent reasons for discontinuation are available only for all randomized patients (456 vs. 454). Out of these patients, 23 (intervention arm) versus 34 (control arm) dropped out of the study. Common reasons for study dropout in the intervention vs. the control arm were withdrawal of consent (2.6% vs. 3.5%), death (1.5% vs. 1.3%), and loss to follow-up (0.7% vs. 1.7%).

BMI: body mass index; COVID-19: Coronavirus Disease 2019; f: female; HIV: human immunodeficiency virus; i.m.: intramuscular; m: male; n: number of patients in the category; N: number of included patients; ND: no data; RCT: randomized controlled trial SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus Type 2; SD: standard deviation

Patient characteristics are largely balanced between the TACKLE study arms.

The mean patient age at enrolment in the TACKLE study was about 46 years. The proportion of women in the study population was about half. About 60% of patients had symptoms ≤ 5 days before the start of the study. In the included patients, the most common risk factors for severe COVID-19 were obesity (44%), followed by smoking (current and past) (about 40%) and hypertension (27%).

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

As described above, the TACKLE study enrolled only unvaccinated patients. At the time of the benefit assessment, however, a large percentage of the population has already achieved complete immunization according to the definition of the STIKO [15] due to vaccinations and possibly previous exposure to the virus; this reduces the risk of progression to severe COVID-19. Accordingly, these patients do not fall under the present therapeutic indication, because they are not at increased risk of progressing to severe disease. Patients with incomplete immunization or those at relevant risk of inadequate vaccine response as defined by the STIKO [15], however, might continue to be at risk of the disease becoming severe. According to COVRIIN, the same applies to patients who have complex risk factors despite being immunocompetent and fully vaccinated [4]. Patients who exhibited an inadequate vaccine response and are therefore not fully immunized were excluded from the study available for the benefit assessment. Likewise excluded were patients who, despite being immunocompetent and fully vaccinated, had complex risk factors resulting in an increased risk of progressing to severe disease. It is plausible to transfer evidence from the unvaccinated TACKLE participants to patient groups who do not achieve complete immunization despite being vaccinated and who are at increased risk of progressing to severe disease. Nevertheless, it remains unclear whether the effects observed in unvaccinated patients are fully transferable to these patient groups. This issue has been taken into account in the assessment of the certainty of conclusions (see Section I 4.2).

About 14% of TACKLE participants had a positive serum status for SARS-CoV-2 at baseline. The study documents show that, among the patients for whom a positive serum status was available at study start, only 1 person in the control arm had been previously diagnosed with COVID-19. It remains unclear whether the included patients with positive serostatus are comparable to those recovered from symptomatic COVID-19, who currently represent a large percentage of the population in the present therapeutic indication.

The company's Module 4A did not provide any information on the viral variant present in TACKLE participants. However, the documents on the TACKLE study show that only about 38% of patients for whom sequencing data were available were infected with the Alpha variant. Other frequently confirmed variants were B.1.1.519 (19%), Gamma (12%), and Delta (10%). The currently predominant SARS-CoV variant, Omicron, was not found among the study participants. According to the SPC, tixagevimab/cilgavimab exhibits *in vitro* antiviral activity against the Omicron variant BA.2, while Omicron variants BA.1, BA.1.1, BA.4, and BA.5 exhibit reduced sensitivity to tixagevimab/cilgavimab [3]. However, according to the COVRIIN expert group, no neutralization activity has been found *in vitro* against the new BA.5 subline BQ.1.1 [4]. On the basis of the TACKLE study, conclusions on added benefit can be drawn only for patients who are infected with a virus variant for which tixagevimab/cilgavimab has sufficient neutralization activity.

In summary, on the basis of the TACKLE study, conclusions on added benefit can be drawn for patients who have not yet been vaccinated against COVID-19 or who are not fully immunized against COVID-19, or who, despite being immunocompetent and fully vaccinated, still are at increased risk of progressing to severe COVID-19 due to complex risk factors. Patients with complete immunization are not comprised by the present therapeutic indication and are therefore not subject of the present benefit assessment. In addition, conclusions on added benefit can be drawn only on patients who are infected with a virus variant for which there is sufficient neutralization activity.

Further limitation of the study population

According to the study protocol, only adult patients were to be included in the TACKLE study. The company did not submit any data on children and adolescents, nor did it supply an adequate justification of transferability to adolescents aged 12 years and older. The available data allow drawing a conclusion on added benefit only for adults with COVID-19.

Risk of bias across outcomes (study level)

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

Table 10: Risk of bias across outcomes (study level) – RCT, direct comparison: tixagevimab/cilgavimab versus placebo

Study	Adequate random sequence generation	Allocation concealment	Blinding		Nonselective reporting	No additional aspects	Risk of bias at study level
			Patients	Treatment providers			
TACKLE	Yes	Yes	Yes	Yes	Yes	Yes	Low
RCT: randomized controlled trial							

The risk of bias across outcomes was rated as low for the TACKLE study.

Transferability of the study results to the German health care context

The company assumes that the results of the TACKLE study can be adequately transferred to the German health care context because the study population is comparable to the risk groups for severe disease defined by the RKI in the German health care context, including older persons, (severely) obese patients, and patients with certain pre-existing conditions of the cardiovascular system, the lungs or kidneys, or with diabetes mellitus. Furthermore, the company reports that neither the mechanism of action nor the dose-effect relationship of tixagevimab/cilgavimab differ between adults and adolescents, and it therefore deems the

results for adult patients from the studies presented by the company to be transferable to patients aged 12 years and older and weighing at least 40 kg.

The company reports that at present, the context of SARS-CoV-2 already differs from the time the study was conducted. It explains that while further changes in the disease are expected, tixagevimab/cilgavimab continues to be effective against the currently predominant sublines of the Omicron variant. As already described in Section I 3.2, this assessment by the company departs from the information provided in the SPC and by the COVRIIN expert group.

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

I 4 Results on added benefit

I 4.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment:

- Mortality
  - all-cause mortality
- Morbidity
  - severe COVID-19
  - ICU admission for any cause
  - return to normal health
  - COVID-19 symptoms
- Health-related quality of life
- Side effects
  - SAEs
  - severe AEs
  - discontinuation due to AEs
  - hypersensitivity reactions and injection site reactions
  - further specific AEs, if any

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

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

Table 11: Matrix of outcomes – RCT, direct comparison: tixagevimab/cilgavimab versus placebo

Study	Outcomes										
	All-cause mortality[a]	Severe COVID-19[b]	ICU admission for any cause	Return to normal health	COVID-19 symptoms	Health-related quality of life	SAEs[c]	Severe AEs[c]	Discontinuation due to AEs	Hypersensitivity reactions and injection site reactions	Further specific AEs
TACKLE	Yes	Yes	Yes	Yes	No[d]	No[e]	Yes	No[d]	Yes	No[d]	No[f]

a. Death from any cause up to and including Day 169.
b. Severe COVID-19 was defined as the occurrence of pneumonia, hypoxaemia, or a score ≥ 5 on the WHO Clinical Progression Scale for COVID-19 up to and including Day 29.
c. Total rate without events rated by the company as being disease-related (defined as PT COVID-19, COVID-19 pneumonia, asymptomatic SARS-CoV-2 infection, post-acute COVID-19 syndrome).
d. No suitable data available; see body of text below for reasons.
e. Outcome not recorded.
f. No specific AEs were identified based on the AEs occurring in the relevant studies.

AE: adverse event; COVID-19: Coronavirus Disease 2019; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SARS-CoV-2: severe acute respiratory syndrome coronavirus type 2; WHO: World Health Organization

Morbidity

Severe COVID-19

In the TACKLE study, the outcome of severe COVID-19 is operationalized as the occurrence of at least 1 of the following events up to Day 29:

- pneumonia (fever, cough, tachypnoea or dyspnoea and lung infiltrates)
- hypoxaemia (oxygen saturation < 90% in room air and/or severe shortness of breath)
- score of 5 or higher on the World Health Organization (WHO) Clinical Progression Scale for COVID-19 [16]

Since they correspond to severe symptoms, the events included in the outcome are suitable for adequately depicting severe COVID-19. A WHO score of 5 or higher additionally means that patients are hospitalized and require oxygen therapy. Furthermore, the results of this operationalization are comparable to the results of the survey of severe COVID-19, operationalized as hospitalization due to COVID-19 (presented as supplementary information). Therefore, the results of this operationalization were used for the benefit assessment.

Further morbidity outcomes

Module 4 of the company's dossier presents analyses of additional outcomes which the company deems to reflect progression of disease. They include hospitalization for any cause as well as the outcome of respiratory insufficiency. These outcomes are already reflected by the outcome of severe COVID-19 and are therefore disregarded for the benefit assessment; the results are presented as supplementary information in Table 13. The present benefit assessment uses ICU admission for any cause up to Day 29 as a further morbidity outcome because it represents further disease progression. The additionally available results on this outcome at Day 169 are not presented as supplementary information because the results for Days 29 and 169 are nearly identical.

Return to normal health

In the TACKLE study, the outcome of return to normal health was to be surveyed daily from Day 1 up to and including Day 29 using patients' binary rating (yes/no) of the previous 24-hour period. In the TACKLE study, time to return to usual health was operationalized as the number of days until patients believed that they had regained their usual health status. The results of the data cutoff were used for the present benefit assessment.

COVID-19 symptoms

TACKLE participants recorded their body temperature and the following COVID-19 symptoms daily for 28 days:

- shortness of breath
- difficulty breathing
- chills
- cough
- fatigue
- muscle pain
- body aches
- headache
- loss of taste
- loss of smell
- sore throat
- stuffy nose
- runny nose

- nausea
- vomiting
- diarrhoea

The severity of each of these symptoms was rated on a scale of 0 to 4 (0: not present; 1: mild; 2: moderate; 3: severe; 4: hospitalized). The company presents, firstly, the analyses of the mean differences of each symptom, and secondly, responder analyses on the percentage of patients with deterioration in at least 1 of these symptoms by ≥ 1 within 28 days. The analyses presented by the company cannot be reasonably interpreted, because no conclusions can be drawn about patients' symptom burden. This applies to both the analysis of individual symptoms and to the presented responder analysis. For instance, the responder analysis takes into account only events where existing symptoms deteriorated, but not improved symptoms or those with new onset. Relevant for the benefit assessment would be, for instance, analyses of alleviation of all symptoms so that an overall conclusion can be drawn about the number of patients whose symptoms have become mild or have completely resolved (see, e.g. dossier assessment A22-64 on nirmatrelvir/ritonavir [17]). The analyses presented by the company are therefore disregarded in the benefit assessment.

Side effects

Severe AEs

In the TACKLE study, the severity of AEs was assessed based on categories defined by the company rather than an established classification. This is not an adequate operationalization of the degree of severity and is disregarded in the benefit assessment.

Hypersensitivity reactions and injection site reactions

While the TACKLE study surveyed hypersensitivity reactions and injection site reactions, it did not use any prespecified criteria to do so. Furthermore, it remains unclear which events were included in the analyses presented by the company. Therefore, the outcome analyses presented by the company are disregarded for the benefit assessment.

I 4.2 Risk of bias

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

Table 12: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: tixagevimab/cilgavimab versus placebo

Study	Study level	Outcomes										
		All-cause mortality[a]	Severe COVID-19[b]	ICU admission for any cause	Return to normal health	COVID-19 symptoms	Health-related quality of life	SAEs[c]	Severe AEs[c]	Discontinuation due to AEs	Hypersensitivity reactions and injection site reactions	Specific AEs
TACKLE	L	L	L	L	L	-[d]	-[e]	H[f]	-[d]	L	-[d]	-

a. Death from any cause up to and including Day 169.
b. Severe COVID-19 was defined as the occurrence of pneumonia, hypoxaemia, or a score ≥ 5 on the WHO Clinical Progression Scale for COVID-19.
c. Total rate without events rated by the company as being disease-related (defined as PT COVID-19, COVID-19 pneumonia, asymptomatic SARS-CoV-2 infection, post-acute COVID-19 syndrome).
d. No suitable data available; for the reasoning, see Section 2.4.4.1 of the full dossier assessment.
e. Outcome not recorded.
f. The analyses do not take into account the events which were classified as disease-related by the company. However, due to the wide range of COVID-19 symptoms, it is plausible that other events are included which may be either side effects or symptoms of the underlying disease.

AE: adverse event; COVID-19: Coronavirus Disease 2019; H: high; L: low; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus Type 2

The risk of bias is rated as low for the results of all-cause mortality, the morbidity outcomes, and the outcome of discontinuation due to AEs. The risk of bias of the results on the outcome of SAEs was rated as high. The analyses disregard the events which the company classified as disease related. However, due to the broad range of COVID-19 symptoms, other events which may be either side effects or symptoms of the underlying disease may have plausibly been recorded.

Summary assessment of the certainty of conclusions

For patients between 12 and 18 years of age and weighing at least 40 kg who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19, no conclusions can be drawn on the basis of the available analyses of the TACKLE study (see Section I 3.2). The following evaluation of the certainty of results therefore applies exclusively to adult patients ≥ 18 years of age. In addition, the assessment refers to patients who have not yet been vaccinated against SARS-CoV-2 or who are not fully immunized against SARS-CoV-2, or who, due to complex risk factors, remain at increased risk of progressing to severe COVID-19 despite being immunocompetent and fully vaccinated. Patients with

complete immunization are not comprised by the present therapeutic indication and are therefore not subject of the present benefit assessment. Furthermore, conclusions on added benefit can be drawn only on patients who are infected with a virus variant for which there is sufficient neutralization activity.

As described in Section I 3.2, it is possible to transfer evidence from the unvaccinated patients included in the TACKLE study to patient groups who do not achieve complete immunization despite vaccination or who have complex risk factors despite immunocompetence and complete vaccination. Nevertheless, it remains unclear whether the effects observed in unvaccinated patients are fully transferable to these patient groups.

Overall, this reduces the certainty of conclusions of the study results for the present research question. Based on the TACKLE study, at most hints, e.g. of an added benefit, can be determined for all outcomes presented.

I 4.3 Results

Table 13 and Table 14 summarize the results of the comparison of tixagevimab/cilgavimab versus placebo in patients with COVID-19 who do not require supplemental oxygen and who are at increased risk for progressing to severe COVID-19. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier.

Tables on common AEs and common SAEs are presented in I Appendix B of the full dossier assessment. Kaplan-Meier curves on the presented time-to-event analyses can be found in I Appendix C of the full dossier assessment.

Table 13: Results (mortality, morbidity, side effects) – RCT, direct comparison: tixagevimab/cilgavimab versus placebo (multipage table)

Study Outcome category	Tixagevimab/cilgavimab		Placebo		Tixagevimab/cilgavimab vs. placebo
Outcome Time point	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value[a]
TACKLE					
Mortality					
All-cause mortality					
until Day 169	399	4 (1.0)	407	6 (1.5)	0.68 [0.19; 2.39]; 0.547
Morbidity					
Severe COVID-19[b]					
until Day 29	410	16 (3.9)	419	37 (8.8)	0.44 [0.25; 0.78]; 0.005
Severe respiratory insufficiency (presented as supplementary information)[c]					
until Day 29	*413*	*3 (0.7)*	*421*	*11 (2.6)*	*0.28 [0.08; 0.996]; 0.049*
ICU admission for any cause					
until Day 29	413	6 (1.5)	421	11 (2.6)	0.56 [0.21; 1.48]; 0.240
Severe COVID-19 (hospitalization, presented as supplementary information)[d]					
until Day 29	*413*	*17 (4.1)*	*421*	*40 (9.5)*	-
until Day 169	*413*	*17 (4.1)*	*421*	*40 (9.5)*	*0.43 [0.25; 0.75]; 0.003*
Hospitalization for any cause (supplementary information)					
until Day 169	*413*	*28 (6.8)*	*421*	*48 (11.4)*	*0.59 [0.38; 0.93]; 0.022*
COVID-19 symptoms	No suitable data				
Health-related quality of life	Outcome not recorded				
Side effects					
AEs (supplementary information)[e]	413	136 (32.9)	421	147 (34.9)	-
SAEs[e]	413	13 (3.1)	421	13 (3.1)	1.03 [0.48; 2.19]; 0.947
Severe AEs[e]	No suitable data				
Discontinuation due to AEs[f]	413	0 (0)	421	0 (0)	-
Hypersensitivity reactions and injection site reactions	No suitable data				

a. CMH method stratified by time since symptom onset (≤ 5 days vs. > 5 days) and risk of progressing to severe COVID-19 (high vs. low).
b. Operationalized as the occurrence of pneumonia (fever, cough, tachypnoea or dyspnoea, and lung infiltrates), hypoxaemia (oxygen saturation < 90% in room air and/or severe shortness of breath), or a score of 5 or higher on the WHO Clinical Progression Scale for COVID-19.
c. Defined as need for mechanical ventilation, ECMO, noninvasive ventilation or oxygen therapy via a high-flow nasal cannula.
d. Operationalized as hospitalization for COVID-19.
e. Overall rate excluding events classified by the company as disease-related (see Table 11 for details).
f. Presentation of treatment discontinuations due to AEs; in Module 4 A, the company presented results on study discontinuations due to AEs for the TACKLE study (3 [0.7%] vs. 7 [1.7%]).

Table 13: Results (mortality, morbidity, side effects) – RCT, direct comparison: tixagevimab/cilgavimab versus placebo (multipage table)

Study Outcome category	Tixagevimab/cilgavimab		Placebo		Tixagevimab/cilgavimab vs. placebo
Outcome Time point	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value[a]
AE: adverse event; CI: confidence interval; CMH: Cochran-Mantel-Haenszel; COVID-19: Coronavirus Disease 2019; n: number of patients with (at least 1) event; N: number of analysed patients; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event					

Table 14: Results (morbidity, time to event) – RCT, direct comparison: tixagevimab/cilgavimab versus placebo

Study Outcome category	Tixagevimab/cilgavimab		Placebo		Tixagevimab/cilgavimab vs. placebo
Outcome Study	N	Median time to event in days [95% CI] Patients with event n (%)	N	Median time to event in days [95% CI] Patients with event n (%)	HR [95% CI]; p-value[a]
TACKLE					
Morbidity					
Return to normal health					
until Day 29	413	29 [27; 29] 270 (65.4)	421	29 [NC; NC] 266 (63.2)	1.12 [0.95; 1.33]; 0.190
a. Cox model, stratified by time since symptom onset (≤ 5 days vs. > 5 days) and risk of progressing to severe COVID-19 (high vs. low). CI: confidence interval; HR: hazard ratio; N: number of analysed patients; n: number of patients with event; NC: not calculable; RCT: randomized controlled trial					

Based on the available information, at most hints, e.g. of an added benefit, can be determined for all outcomes (see Section I 4.2).

Mortality

All-cause mortality

There was no statistically significant difference between treatment groups for the outcome of all-cause mortality. This results in no hint of added benefit of tixagevimab/cilgavimab in comparison with treatment of physician's choice; an added benefit is therefore not proven.

Morbidity

Severe COVID-19

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

ICU admission for any cause

No statistically significant difference between treatment groups was shown for the outcome of ICU admission for any cause. This results in no hint of added benefit of tixagevimab/cilgavimab in comparison with treatment of physician's choice; an added benefit is therefore not proven.

Return to normal health

There was no statistically significant difference between treatment groups for the outcome of return to normal health. This results in no hint of added benefit of tixagevimab/cilgavimab in comparison with treatment of physician's choice; an added benefit is therefore not proven.

COVID 19 symptoms

No suitable data were available for the outcome of COVID-19 symptoms. This results in no hint of added benefit of tixagevimab/cilgavimab in comparison with treatment of physician's choice; an added benefit is therefore not proven.

Health-related quality of life

Health-related quality of life outcomes were not recorded in the included study. This results in no hint of added benefit of tixagevimab/cilgavimab in comparison with treatment of physician's choice; an added benefit is therefore not proven.

Side effects

SAEs

For the outcome of SAEs, no statistically significant difference between treatment groups was found. This results in no hint of greater or lesser harm from tixagevimab/cilgavimab in comparison with treatment of physician's choice; greater or lesser harm is therefore not proven.

Severe AEs

No suitable data are available for the outcome of severe AEs. This results in no hint of greater or lesser harm from tixagevimab/cilgavimab in comparison with treatment of physician's choice; greater or lesser harm is therefore not proven.

Discontinuation due to AEs

No events occurred in the outcome of discontinuation due to AEs. This results in no hint of greater or lesser harm from tixagevimab/cilgavimab in comparison with treatment of physician's choice; greater or lesser harm is therefore not proven.

Specific AEs

Hypersensitivity reactions and injection site reactions

For the outcome of hypersensitivity reactions and injection site reactions, no suitable data are available. This results in no hint of greater or lesser harm from tixagevimab/cilgavimab in comparison with treatment of physician's choice; greater or lesser harm is therefore not proven.

I 4.4 Subgroups and other effect modifiers

The present benefit assessment accounts for the following subgroup characteristics:

- age (< 65 years versus ≥ 65 years)
- sex (male versus female)

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

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

Using the methods described above, the available subgroup results do not reveal any effect modifications.

I 5 Probability and extent of added benefit

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

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

I 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 I 4 (see Table 15).

Determination of the outcome category for symptom outcomes

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

Severe COVID-19

Events included in the outcome of severe COVID-19 (see Section I 4.1) are to be deemed serious or severe. Therefore, the outcome of severe COVID-19 was assigned to the outcome category of serious/severe symptoms / late complications.

Table 15: Extent of added benefit at outcome level: tixagevimab/cilgavimab versus placebo

Outcome category **Outcome**	**Tixagevimab/cilgavimab vs. placebo** **Proportion of events (%)** **Effect estimation [95% CI];** **p-value** **Probability[a]**	**Derivation of extent[b]**
Mortality		
All-cause mortality	1.0% vs. 1.5% RR: 0.68 [0.19; 2.39] p = 0.547	Lesser/added benefit not proven
Morbidity		
Severe COVID-19	3.9% vs. 8.8% RR: 0.44 [0.25; 0.78] p = 0.005 Probability: hint	Outcome category: serious/severe symptoms / late complications $0.75 \leq CI_u < 0.90$ Added benefit, extent: considerable
ICU admission for any cause	1.5% vs. 2.6% RR: 0.56 [0.21; 1.48] p = 0.240	Lesser/added benefit not proven
Return to normal health	Median time to event (days): 29 vs. 29 HR: 1.12 [0.95; 1.33] p = 0.190	Lesser/added benefit not proven
COVID-19 symptoms	No suitable data	Lesser/added benefit not proven
Health-related quality of life		
-	No outcomes of this category recorded	Lesser/added benefit not proven
Side effects		
SAEs	3.1% vs. 3.1% RR: 1.03 [0.48; 2.19] p = 0.947	Greater/lesser harm not proven
Severe AEs	No suitable data	Greater/lesser harm not proven
Discontinuation due to AEs	0% vs. 0% RR: –	Greater/lesser harm not proven
Hypersensitivity reactions and injection site reactions	No suitable data	Greater/lesser harm not proven

a. Probability provided if statistically significant differences are present.
b. Depending on the outcome category, the effect size is estimated using different limits based on the upper limit of the confidence interval (CI_u).

AE: adverse event; COVID-19: Coronavirus Disease 2019; CI: confidence interval; CI_u: upper limit of confidence interval; HR: hazard ratio; RR: relative risk; SAE: serious adverse event

I 5.2 Overall conclusion on added benefit

Table 16 summarizes the results included in the overall conclusion on the extent of added benefit.

Table 16: Favourable and unfavourable effects from the assessment of tixagevimab/cilgavimab compared with treatment of physician's choice

Favourable effects	**Unfavourable effects**
Serious/severe symptoms / late complications ▪ Severe COVID-19: hint of an added benefit – extent: considerable	–
No usable data are available for the outcome of health-related quality of life. These effects apply only to patients who have not yet been vaccinated against SARS-CoV-2 or who are not fully immunized against SARS-CoV-2, or who have complex risk factors despite being immunocompetent and fully vaccinated.	
COVID-19: Coronavirus Disease 2019; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2	

As described in Section I 3.2, the following conclusion on added benefit applies exclusively to adult patients who have not yet received a vaccination against COVID-19 or who are not fully immunized against COVID-19 or who have complex risk factors despite being immunocompetent and fully vaccinated. Fully immunized patients do not fall under the present therapeutic indication because they are not at increased risk of progressing to severe COVID-19.

In addition, the conclusion on added benefit relates only to patients who are infected with a virus variant for which there is sufficient neutralization activity. According to the SPC [3], tixagevimab/cilgavimab has decreased *in vitro* neutralization activity against the SARS-CoV-2 Omicron variants BA.1, BA.1.1, BA.4, and BA.5. It remains unclear whether the effects observed in the TACKLE study are transferable to patients infected with the virus variants BA.5 or a BA.5 subline, which were circulating at the time of the benefit assessment.

No data are available for adolescents aged 12 to < 18 years and weighing at least 40 kg who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19. For this age group, this results in no proof of added benefit of tixagevimab/cilgavimab.

Overall, there is only 1 favourable effect of tixagevimab/cilgavimab in comparison with treatment of physician's choice for adults with COVID-19 who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19: There is a hint of considerable added benefit for the outcome of severe COVID-19.

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

Table 17: Tixagevimab/cilgavimab – probability and extent of added benefit

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

a. Presented is the ACT specified by the G-BA.
b. In case of a positive rapid antigen test, the diagnosis of SARS-CoV-2 infection should be confirmed by a PCR test, especially if the results have therapeutic consequences.
c. It is recommended that relevant SARS-CoV-2 mutation variants (e.g. VOCs) are also taken into account when recording and interpreting the results on efficacy.
d. Recently, the intravenous drugs casirivimab/imdevimab, regdanvimab, remdesivir, and sotrovimab have been approved for the treatment of COVID-19 patients who do not require supplemental oxygen and are at increased risk of progressing to severe COVID-19. The clinical significance of these therapy options cannot be assessed at the present time.
e. In case of disease progression and patient hospitalization, further drug therapies (e.g. dexamethasone; anticoagulation / thrombosis prophylaxis, antibiotics) as well as non-drug therapies (e.g. oxygen therapy, type of ventilation, balanced fluid therapy) must be considered.
f. The conclusion on added benefit applies only to patients who are infected with a virus variant for which there is sufficient neutralization activity. According to the SPC [3], tixagevimab/cilgavimab has decreased neutralization activity against the SARS-CoV-2 Omicron variants BA.4 and BA.5. It remains unclear whether the effects observed in the TACKLE study are transferable to patients infected with the virus variants BA.5 or a BA.5 subline, which are circulating at the time of the benefit assessment.

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

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

The approach for deriving an overall conclusion on added benefit constitutes a proposal by IQWiG. The G-BA decides on the added benefit.

I 6 References for English extract

Please see full dossier assessment for full reference list.

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

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The full report (German version) is published under https://www.iqwig.de/en/projects/a22-111.html.