IQWiG Reports – Commission No. A22-56

Sotrovimab (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 *Sotrovimab (COVID-19) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 11 August 2022). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher
Institute for Quality and Efficiency in Health Care

Topic
Sotrovimab (COVID-19) – Benefit assessment according to §35a Social Code Book V

Commissioning agency
Federal Joint Committee

Commission awarded on
13 May 2022

Internal Commission No.
A22-56

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

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

Medical and scientific advice

- Manfred Gogol, Hannover Medical School, Clinic for Trauma Surgery, Geriatric Trauma Centre, Germany

IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

Patient and family involvement

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

IQWiG employees involved in the dossier assessment

- Can Ünal
- Nadia Abu Rajab
- Lars Beckmann
- Tatjana Hermanns
- Kirsten Janke
- Michaela Florina Kerekes
- Stefan Kobza
- Volker Vervölgyi

Keywords: Sotrovimab, COVID-19, Benefit Assessment, NCT04545060

Table of contents

List of tables[2]

Page

[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
CI	confidence interval
COVID-19	coronavirus disease 2019
COVRIIN	Fachgruppe Intensivmedizin, Infektiologie und Notfallmedizin (Expert Group on Intensive Care, Infectious Diseases and Emergency Medicine)
DAIDS	Division of Acquired Immunodeficiency Syndrome
DEGAM	Deutsche Gesellschaft für Allgemeinmedizin und Familienmedizin (German College of General Practitioners and Family Physicians)
ECMO	extracorporeal membrane oxygenation
EMA	European Medicines Agency
FLU-PRO	Influenza Patient-Reported Outcome
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HR	hazard ratio
IDMC	independent data monitoring committee
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MedDRA	Medical Dictionary for Regulatory Activities
PT	Preferred Term
RCT	randomized controlled trial
RKI	Robert Koch Institute
RR	relative risk
RT-PCR	reverse transcriptase polymerase chain reaction
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SF-12	Short Form 12 Health Survey
SF-36	Short Form 36 Health Survey
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics
STIKO	Ständige Impfkommission (Standing Committee on Vaccination)
VOC	variant of concern
VOI	variant of interest
WPAI	Work Productivity and Activity Impairment

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 sotrovimab. 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 13 May 2022.

Research question

The aim of the present report is to assess the added benefit of sotrovimab in comparison with the appropriate comparator therapy (ACT) for the treatment of coronavirus disease 2019 (COVID-19) in adults and adolescents aged 12 years and over and weighing at least 40 kg who do not require oxygen supplementation and who are at increased risk of progressing to severe COVID-19.

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

Table 2: Research question of the benefit assessment of sotrovimab

Therapeutic indication	**ACT**[a]
Adults and adolescents aged 12 years and over and weighing at least 40 kg with COVID-19[b] who do not require oxygen supplementation 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. so-called variants of concern [VOC]) are also taken into account when recording and interpreting the results on efficacy. d. Depending on the severity of disease, both drug therapies (e.g. analgesics, antipyretics, dexamethasone, anticoagulation/thrombosis prophylaxis, antibiotics, remdesivir, baricitinib, tocilizumab, nirmatrelvir/ritonavir, molnupiravir) and non-drug therapies (e.g. oxygen support, type of ventilation, balanced fluid therapy) should be taken into account in the treatment of physician's choice, if indicated. e. Recently, the intravenous drugs casirivimab/imdevimab, regdanvimab and remdesivir have been approved for the treatment of COVID-19 patients who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19. The clinical significance of these therapy options cannot be assessed at the present time. 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 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 Summary of Product Characteristics (SPC), sotrovimab has decreased *in vitro* neutralization activity against the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) Omicron variants BA.2, BA.2.12.1, BA.4 and BA.5 circulating at the time of the present benefit assessment. However, the clinical relevance of the decreased *in vitro* neutralization of sotrovimab against these variants is not known, according to the SPC.

The Robert Koch Institute's (RKI) Expert Group on Intensive Care, Infectious Diseases and Emergency Medicine (COVRIIN) 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.2, BA.4 and BA.5, the expert group states that there is a marked decrease in *in vitro* neutralization activity of sotrovimab and assumes a probably reduced efficacy against these variants.

Study pool and study design

The benefit assessment uses the VIR-7831-5001/214367 study (hereinafter referred to as "COMET-ICE study"). The COMET-ICE study is a placebo-controlled, double-blind, randomized study on the outpatient treatment with sotrovimab in adult patients with early-stage COVID-19. The study included symptomatic patients with confirmed SARS-CoV-2 infection detected by reverse transcriptase polymerase chain reaction (RT-PCR) test or antigen test ≤ 7 days prior to screening. Onset of symptoms had to be ≤ 5 days before study inclusion. Furthermore, COVID-19 patients had to have at least one pre-existing risk factor for disease progression up to hospitalization or they had to be ≥ 55 years old. However, patients with severe immunosuppression or immunosuppressive therapy including cancer treatment were excluded from the study. In the study, only outpatient treatment with sotrovimab was investigated. In addition, the COMET-ICE study only looked at patients who had not been vaccinated against SARS-CoV-2.

The COMET-ICE study has several phases: In the first study phase (lead-in phase), a total of 21 patients were included and randomized at a 1:1 ratio to the intervention arm and the control arm. After the first 15 days, adverse events (AEs) were assessed by an independent data monitoring committee (IDMC). Subsequently, the second study phase (expansion phase) was initiated, where additional patients were enrolled. Across both phases, a total of 1057 patients were randomly allocated in a 1:1 ratio to treatment with sotrovimab or placebo.

Sotrovimab was administered as a single intravenous infusion in the COMET-ICE study. Treatment was largely in compliance with the SPC, but with a longer infusion duration.

The primary outcome of the study was the composite outcome of hospitalization due to any cause or death due to any cause by day 29. Patient-relevant secondary outcomes were all-cause mortality as well as outcomes on morbidity, health-related quality of life, and AEs. According to the planning of the study, outcome-specific follow-up was up to 24 weeks.

On the recommendation of the IDMC, recruitment of new patients was terminated in the expansion phase on the basis of a prespecified interim analysis, as criteria for proof of efficacy prespecified according to the planning of the study were met. All included patients randomized until the time of this analysis were observed until week 24.

Implementation of the appropriate comparator therapy

The G-BA specified treatment of physician's choice as ACT. Depending on the severity of disease, both drug therapies (e.g. analgesics, antipyretics, dexamethasone, anticoagulation/ thrombosis prophylaxis, antibiotics, remdesivir, baricitinib, tocilizumab, nirmatrelvir/ritonavir, molnupiravir) and non-drug therapies (e.g. oxygen support, type of ventilation, balanced fluid therapy) should be taken into account in the treatment of physician's choice, if indicated. Some of the specific therapeutic measures are not usually necessary in mildly to moderately symptomatic disease, but may only be necessary if the disease progresses and the patient is hospitalized.

Overall, concomitant treatment with anti-inflammatory and analgesic drugs in the COMET-ICE study is 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. However, the guidelines issue only a weak or open recommendation for specific risk groups for these treatment options. In addition, it can be assumed that the treatment of patients with COVID-19 will constantly change over the course of the pandemic, particularly in light of increasing SARS-CoV-2 immunocompetence due to vaccinations and prior virus exposures as well as the emergence of new virus variants with potentially altered pathogenicity. Overall, the fact that specific antiviral substances were not allowed or not used in the COMET-ICE study therefore has no consequence for the present benefit assessment.

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

As described above, patients who had received at least one vaccination against SARS-CoV-2 were excluded from the COMET-ICE study. At the time of the benefit assessment, however, due to vaccinations and possibly previous exposure to the virus, a large proportion of the population already has complete immunization according to the definition of the Standing Committee on Vaccination (STIKO), which reduces the risk for severe COVID-19. Accordingly, these patients are not covered by the present therapeutic indication, as they are not at increased risk for 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 for severe disease. According to COVRIIN, the same applies to patients exhibiting complex risk factors despite being immunocompetent and fully vaccinated. Patients who exhibited inadequate vaccine response and are therefore not fully immunized were excluded from the COMET-ICE study. Likewise excluded were patients who, despite being immunocompetent and fully vaccinated, had complex risk factors resulting in an increased risk for severe disease. It is plausible to transfer evidence from the unvaccinated patients in the

COMET-ICE study to patient groups who do not achieve complete immunization despite being vaccinated and who are 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.

In addition, Module 4 A of the dossier provides no information on the serostatus of the patients at the time of study inclusion. Although the European Medicines Agency (EMA) assessment report provides information on the serostatus of some of the patients included, it does not indicate whether their previous infection was symptomatic. Therefore, it remains unclear whether these patients are comparable to patients who have recovered from symptomatic COVID-19 infection, which represent the majority of the population in the present therapeutic indication at the current time.

According to information in Module 4 A, information on the virus variant present at the start of the study and/or during the study was available from sequencing for some of the patients included. The majority of the study participants were infected with the wild type virus. A variant of concern (VOC) or a variant of interest (VOI) was detected in about 22% of patients, with the Alpha variant (B.1.1.7) and the Epsilon variant (B.1.427/B.1.429) being the most common. In accordance with the infection situation at the time the study was conducted, neither the Delta nor the Omicron variant was detected in the study participants examined. According to the SPC and the current assessment of the COVRIIN expert group, sotrovimab has decreased *in vitro* neutralization activity against the Omicron variants BA.2, BA.2.12.1, BA.4 and BA.5 circulating in Germany at the time of the benefit assessment. The COMET-ICE study investigated only patients infected with virus variants for which there was sufficient neutralization activity. It remains unclear whether the observed effects are transferable to patients infected with the virus variants Omicron BA.2, BA.2.12.1, BA.4 or BA.5 circulating at the time of the benefit assessment. On the basis of the COMET-ICE study, conclusions on the added benefit are only possible for patients who are infected with a virus variant for which there is sufficient neutralization activity.

In summary, on the basis of the COMET-ICE study, conclusions on added benefit can be drawn for 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 covered by the present benefit assessment. In addition, conclusions on the 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 planning of the study, only adult patients were to be included in the COMET-ICE study. However, there were isolated protocol violations, leading to the inclusion

of some adolescents (2 adolescents in the intervention arm and 4 in the control arm). Nonetheless, 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 across outcomes for the COMET-ICE study is rated as low. The outcome-specific risk of bias is rated as low for the results of all outcomes except for the outcomes of serious AEs (SAEs) and severe AEs. The analyses on SAEs and severe AEs do not take into account the events that 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 that can be both side effects and symptoms of the underlying disease. For the outcomes on infusion-related reactions (operationalized via AEs and SAEs), the certainty of results is limited despite a low risk of bias.

As described above, it is possible to transfer evidence from the unvaccinated patients included in the COMET-ICE 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, the certainty of conclusions of the study results for the present research question is therefore reduced. Based on the COMET-ICE study, at most hints, e.g. of an added benefit, can be determined for all outcomes presented.

Results

Mortality

All-cause mortality

For the outcome of all-cause mortality, there is a statistically significant difference between treatment groups in favour of sotrovimab. This results in a hint of added benefit of sotrovimab in comparison with treatment of physician’s choice.

Morbidity

Development of severe and/or critical respiratory COVID-19

For the outcome of severe and/or critical respiratory COVID-19, there is a statistically significant difference between treatment groups in favour of sotrovimab. This results in a hint of added benefit of sotrovimab in comparison with treatment of physician’s choice.

Hospitalization of any duration due to non-respiratory complications of COVID-19

For the outcome of hospitalization of any duration due to non-respiratory complications of COVID-19, there is no statistically significant difference between treatment groups. This results in no hint of added benefit of sotrovimab in comparison with treatment of physician’s choice; an added benefit is therefore not proven.

Admission to intensive care unit due to any cause

For the outcome of intensive care unit (ICU) admission due to any cause, there is a statistically significant difference between treatment groups in favour of sotrovimab. This results in a hint of added benefit of sotrovimab in comparison with treatment of physician's choice.

Health-related quality of life

There are no usable data for health-related quality of life, recorded with Short Form 12 Health Survey (SF-12). This results in no hint of added benefit of sotrovimab in comparison with treatment of physician's choice for health-related quality of life; an added benefit is therefore not proven.

Side effects

SAEs, severe AEs and infusion-related reactions (AEs)

For the outcomes of SAEs, severe AEs and infusion-related reactions (AEs), there is no statistically significant difference between treatment groups. In each case, this results in no hint of greater or lesser harm from sotrovimab in comparison with treatment of physician's choice; greater or lesser harm is therefore not proven.

Discontinuation due to AEs and infusion-related reactions (SAEs)

There were no events in the outcomes of discontinuation due to AEs and infusion-related reactions (SAEs). In each case, this results in no hint of greater or lesser harm from sotrovimab 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 sotrovimab in comparison with the ACT are assessed as follows:

As discussed, the below conclusion on added benefit applies only to adult patients who have not yet received any vaccination against SARS-CoV-2 or who are not fully immunized against SARS-CoV-2, or who have complex risk factors despite being immunocompetent and fully vaccinated. Patients with complete immunization are not covered by the present therapeutic indication, as 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, sotrovimab has decreased *in vitro* neutralization activity against the SARS-CoV-2 Omicron variants BA.2, BA.2.12.1, BA.4 and BA.5. It remains unclear whether the effects observed in the COMET-ICE study are transferable to patients infected with the virus variants BA.2, BA.2.12.1, BA.4 or BA.5 circulating at the time of the benefit assessment.

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

Overall, for adults with COVID-19 infection who do not require oxygen supplementation and who are at increased risk of progressing to severe COVID-19, there are only positive effects of sotrovimab in comparison with treatment of physician's choice. For the outcomes of all-cause mortality and ICU admission due to any cause, there is a hint of a minor added benefit. For the outcome of development of severe and/or critical respiratory COVID-19, there is a hint of considerable added benefit.

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

Table 3 shows a summary of the probability and extent of added benefit of sotrovimab.

Table 3: Sotrovimab – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adults and adolescents aged 12 years and over and weighing at least 40 kg with COVID-19[b] who do not require oxygen supplementation and who are at increased risk of progressing to severe COVID-19[c, d]	Treatment of physician's choice[e, f]	Patients ≥ 18 years: ▪ hint of considerable added benefit[g]
		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. so-called variants of concern [VOC]) are also taken into account when recording and interpreting the results on efficacy.
d. Patients with complete immunization are not comprised by the therapeutic indication.
e. Depending on the severity of disease, both drug therapies (e.g. analgesics, antipyretics, dexamethasone, anticoagulation/thrombosis prophylaxis, antibiotics, remdesivir, baricitinib, tocilizumab, nirmatrelvir/ritonavir, molnupiravir) and non-drug therapies (e.g. oxygen support, type of ventilation, balanced fluid therapy) should be taken into account in the treatment of physician's choice, if indicated.
f. Recently, the intravenous drugs casirivimab/imdevimab, regdanvimab and remdesivir have been approved for the treatment of COVID-19 patients who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19. The clinical significance of these therapy options cannot be assessed at the present time.
g. 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, sotrovimab has decreased *in vitro* neutralization activity against the SARS-CoV-2 Omicron variants BA.2, BA.2.12.1, BA.4 and BA.5. It remains unclear whether the effects observed in the COMET-ICE study are transferable to patients infected with the virus variants BA.2, BA.2.12.1, BA.4 or BA.5 circulating at the time of the benefit assessment.

COVID-19: coronavirus disease 2019; G-BA: Federal Joint Committee; PCR: polymerase chain reaction; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

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

2.2 Research question

The aim of the present report is to assess the added benefit of sotrovimab in comparison with the ACT for the treatment of COVID-19 in adults and adolescents aged 12 years and over and weighing at least 40 kg who do not require oxygen supplementation 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 of the benefit assessment of sotrovimab

Therapeutic indication	**ACT[a]**
Adults and adolescents aged 12 years and over and weighing at least 40 kg with COVID-19[b] who do not require oxygen supplementation 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. so-called variants of concern [VOC]) are also taken into account when recording and interpreting the results on efficacy. d. Depending on the severity of disease, both drug therapies (e.g. analgesics, antipyretics, dexamethasone, anticoagulation/thrombosis prophylaxis, antibiotics, remdesivir, baricitinib, tocilizumab, nirmatrelvir/ritonavir, molnupiravir) and non-drug therapies (e.g. oxygen support, type of ventilation, balanced fluid therapy) should be taken into account in the treatment of physician's choice, if indicated. e. Recently, the intravenous drugs casirivimab/imdevimab, regdanvimab and remdesivir have been approved for the treatment of COVID-19 patients who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19. The clinical significance of these therapy options cannot be assessed at the present time. 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 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], sotrovimab has decreased *in vitro* neutralization activity against the SARS-CoV-2 Omicron variants BA.2, BA.2.12.1, BA.4 and BA.5 circulating at the time of the present benefit assessment [4]. However, the clinical relevance of the decreased *in vitro* neutralization of sotrovimab against these variants is not known, according to the SPC.

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.2, BA.4 and BA.5, the expert group states that there is a marked decrease in *in vitro*

neutralization activity of sotrovimab and assumes a probably reduced efficacy against these variants [5,6].

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 sotrovimab (status: 17 February 2022)
- bibliographical literature search on sotrovimab (last search on 17 February 2022)
- search in trial registries/trial results databases for studies on sotrovimab (last search on 17 February 2022)
- search on the G-BA website for sotrovimab (last search on 17 February 2022)

To check the completeness of the study pool:

- search in trial registries for studies on sotrovimab (last search on 30 May 2022); for search strategies, see Appendix A of the full dossier assessment

The check did not identify any additional relevant study.

2.3.1 Studies included

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

Table 5: Study pool – RCT, direct comparison: sotrovimab vs. 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 and other sources[c] (yes/no [citation])
VIR-7831-5001/214367 (COMET-ICE[d])	Yes	Yes	No	Yes [7-9]	Yes [10,11]	Yes [12,13]

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. 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

The benefit assessment uses the VIR-7831-5001/214367 study (hereinafter referred to as "COMET-ICE study"). This concurs with the company's study pool.

2.3.2 Study characteristics

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

Table 6: Characteristics of the included study – RCT, direct comparison: sotrovimab vs. placebo (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
COMET-ICE	RCT[b], double-blind, parallel	Non-hospitalized adults (≥ 18 years) with confirmed COVID-19[c] ▫ with ≥ 1 pre-existing risk factor[d] or ▫ ≥ 55 years old, irrespective of risk factors ▪ ≥ 1 COVID-19 symptoms ≤ 5 days before randomization ▪ oxygen saturation ≥ 94% on room air ▪ without need for hospitalization in the first 24 h after randomization	Sotrovimab (N = 528) Placebo (N = 529)[f]	Screening: < 1 day Treatment: 1 day Observation[g]: up to 24 weeks	57 centres in: Brazil, Canada, Peru, Spain, USA 8/2020–9/2021[h] Data cut-offs: ▪ First data cut-off: 4 March 2021 (interim analysis)[i] ▪ Second data cut-off: 27 April 2021 (primary analysis)[j] ▪ Third data cut-off: 4 February 2022 (final safety analysis)[k]	Primary: composite outcome of hospitalization > 24 h or death from any cause until day 29 Secondary: all-cause mortality, morbidity, health-related quality of life, AEs

Table 6: Characteristics of the included study – RCT, direct comparison: sotrovimab vs. 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. The study comprises several phases: a lead-in phase for the first-in-human assessment, which included 21 patients, and an expansion phase, in which further patients were recruited. According to the planning of the study, patients from the lead-in phase were taken into account in the analyses of the expansion phase.
c. SARS-CoV-2 infection had to be confirmed ≤ 7 days prior to screening by either nucleic acid detection (e.g. RT-PCR) or antigen testing. Patients with a negative test prior to screening, who were tested again at screening and were positive for SARS-CoV-2 could be included as long as they had had symptoms ≤ 5 days.
d. Risk factors were diabetes requiring medication, obesity (from amendment 1 BMI > 35 kg/m², originally > 30 kg/m²), chronic kidney disease (eGFR < 60 mL/min/1.73 m²), heart failure (NYHA class II or more), COPD, or moderate to severe asthma.
e. E.g. fever, chills, cough, sore throat, malaise, headache, joint or muscle pain, change in smell or taste, vomiting, diarrhoea, shortness of breath on exertion.
f. One participant in the placebo arm received sotrovimab. This participant was assigned to the placebo arm for the analyses on benefit outcomes, and to the sotrovimab arm for the analyses on AEs.
g. The maximum observation period is indicated. COVID-19-related symptoms by FLU-PRO Plus and AEs were recorded until week 12, SAEs were recorded until week 24. Other outcomes were observed at least 28 days after dosing.
h. Time of the last visit of the last patient.
i. Prespecified interim analysis when 41% of planned patients had their visit on day 29; on the recommendation of the IDMC, recruitment of new patients was terminated, as criteria for proof of efficacy prespecified according to the planning of the study were met. All patients randomized until the time of this analysis were observed until week 24 or their premature study termination.
j. Data cut-off, at which all randomized patients were observed until day 29.
k. Data cut-off, at which all randomized patients were observed until week 24.

AE: adverse event; BMI: body mass index; COPD: chronic obstructive pulmonary disease; COVID-19: coronavirus disease 2019; eGFR: estimated glomerular filtration rate; FLU-PRO Plus: Influenza Patient-Reported Outcome Questionnaire Plus; IDMC: Independent Data Monitoring Committee, N: number of randomized patients; NYHA: New York Heart Association; RCT: randomized controlled trial; RT-PCR: reverse transcriptase polymerase chain reaction; SAE: serious adverse event; SARS-CoV-2 severe acute respiratory syndrome coronavirus 2

Table 7: Characteristics of the intervention – RCT, direct comparison: sotrovimab vs. placebo

Study	Intervention	Comparison
COMET-ICE	Sotrovimab IV 500 mg, single-dose on day 1[a]	Placebo IV, single dose on day 1
	For the single dose, no dose adjustments were allowed. Discontinuation of treatment in case of life-threatening infusion-related systemic reactions[b].	
	Prohibited prior and concomitant treatment ▪ any vaccination within 48 h before and 4 weeks after dosing ▪ approved or investigational SARS-CoV-2 vaccines[c] ▪ hydroxychloroquine and chloroquine during the study ▪ convalescent plasma from recovered COVID-19 patients or anti-SARS-CoV-2 monoclonal antibodies < 3 months before study start and during the study	

a. Administered as an infusion over 1 hour; if a patient experienced an infusion-related reaction (grade 2), the infusion was paused and subsequently resumed at a slower pace, and the patient could receive symptomatic treatment.
b. Including severe allergic or hypersensitivity reactions or severe cytokine release syndrome.
c. Vaccination against SARS-CoV-2 was allowed from 4 weeks after dosing.

COVID-19: coronavirus disease 2019; IV: intravenous; RCT: randomized controlled trial; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

The COMET-ICE study is a placebo-controlled, double-blind, randomized study on the outpatient treatment with sotrovimab in adult patients with early-stage COVID-19. The study included symptomatic patients with confirmed SARS-CoV-2 infection detected by RT-PCR test or antigen test ≤ 7 days prior to screening. Onset of symptoms had to be ≤ 5 days before study inclusion. Furthermore, COVID-19 patients had to have at least one pre-existing risk factor for disease progression up to hospitalization or they had to be ≥ 55 years old. However, patients with severe immunosuppression or immunosuppressive therapy including cancer treatment were excluded from the study. The included patients did not require supplemental oxygen at the time of study inclusion (oxygen saturation of ≥ 94% on room air), and there was no anticipated need for hospitalization within 24 h after randomization. Patients who were hospitalized at the time of study inclusion were excluded from the study. Accordingly, only outpatient treatment with sotrovimab was investigated in the study. Patients who had received at least one SARS-CoV-2 vaccination were also excluded from the study. Thus, only unvaccinated patients were considered in the COMET-ICE study.

The COMET-ICE study initially comprised the first-in-human assessment of sotrovimab. Therefore, the study consisted of several phases: In the first study phase (lead-in phase), a total of 21 patients were included and randomized at a 1:1 ratio to the intervention arm and the control arm, stratified by age and duration of COVID-19 symptoms. After the first 15 days, AEs were assessed by an IDMC. Subsequently, the second study phase (expansion phase) was initiated, where additional patients were enrolled. According to the planning of the study, patients of the lead-in phase were taken into account in the analyses of the expansion phase.

The study randomly allocated a total of 1057 patients at a 1:1 ratio to treatment with either sotrovimab (N = 528) or placebo (N = 529). Randomization in the expansion phase was stratified by age, duration of COVID-19 symptoms and region.

Sotrovimab was administered as a single intravenous infusion in the COMET-ICE study. Treatment was largely in compliance with the SPC [3], but the infusion was administered over 1 hour in the study, whereas the SPC recommends 30 minutes.

The primary outcome of the study was the composite outcome of hospitalization due to any cause or death due to any cause by day 29. Patient-relevant secondary outcomes were all-cause mortality as well as outcomes on morbidity, health-related quality of life, and AEs.

According to the planning of the study, outcome-specific follow-up was up to 24 weeks. Health-related quality of life and SAEs were observed until week 24, AEs until week 12. For the other patient-relevant outcomes, the planned follow-up observation is not clear from the study documents. According to the statistical analysis plan, analyses until day 90 were planned for the outcomes of all-cause mortality and ICU admission due to any cause, and analyses until day 29 were planned for the outcomes of development of severe and/or critical respiratory COVID-19 and hospitalization from non-respiratory complications of COVID-19. These analyses were presented by the company in the dossier.

According to the study protocol, an interim analysis was conducted when approximately 41% of the planned 1360 patients (N = 583) had reached observation for the primary outcome until day 29. On the recommendation of the IDMC, recruitment of new patients was terminated on the basis of this analysis, as criteria for proof of efficacy prespecified according to the planning of the study were met. All included patients randomized until the time of this analysis (N = 1057) were observed until week 24. In the dossier, the company presented analyses of 2 data cut-offs conducted after the first data cut-off for the interim analysis. The second data cut-off of 27 April 2021 included observations of all randomized patients until day 29, and the third final data cut-off of 4 February 2022 included observations until week 24. The present benefit assessment uses analyses of the second and/or third data cut-off on an outcome-specific basis.

Implementation of the appropriate comparator therapy

The G-BA specified treatment of physician's choice as ACT. Depending on the severity of disease, both drug therapies (e.g. analgesics, antipyretics, dexamethasone, anticoagulation/ thrombosis prophylaxis, antibiotics, remdesivir, baricitinib, tocilizumab, nirmatrelvir/ritonavir, molnupiravir) and non-drug therapies (e.g. oxygen support, type of ventilation, balanced fluid therapy) should be taken into account in the treatment of physician's choice, if indicated. Some of the specific therapeutic measures are not usually necessary in mildly to moderately symptomatic disease, but may only be necessary if the disease progresses and the patient is hospitalized.

According to the current assessment by the RKI's COVRIIN expert group (as of 5 July 2022), in addition to sotrovimab, the virostatics nirmatrelvir/ritonavir, molnupiravir and remdesivir as well as the antibody combination of tixagevimab/cilgavimab are available as antiviral therapy of early COVID-19 in patients with risk factors for progression to severe disease [6]. At the time of the benefit assessment, molnupiravir and tixagevimab/cilgavimab are not approved for the present therapeutic indication. The COVRIIN recommendations largely overlap with the recommendations by the current guidelines at the time of the benefit assessment (S3 guideline on inpatient therapy of patients with COVID-19 [as of 28 February 2022] and German College of General Practitioners and Family Physicians (DEGAM) guideline [as of 4 February 2022] [14,15]). However, the guidelines issue merely a weak or open recommendation for these substances for specific risk groups. This is justified in particular by the evolution of new virus variants with potentially changed pathogenicity and the population's increased immunocompetence, promoted in particular by vaccination and prior virus exposure. Overall, according to information provided in the S3 guideline [14], it is therefore difficult to quantify the current risk of requiring inpatient or outpatient therapy, experiencing longer-term limitations of quality of life, or dying due to SARS-CoV-2 infection. The suitable treatment should be selected on a case-by-case basis, taking into account individualized risk profile, immunization status, comorbidities, availability, and contraindications. This is also reflected in the assessment of the COVRIIN expert group with more recent status (5 July 2022), which, in addition to the immunization status, also includes the neutralization activity against the currently prevailing viral variants in the suggestions for the selection of antiviral therapy [5,6].

Concomitant therapies administered in the COMET-ICE study

The use of convalescent COVID-19 plasma and anti-SARS-CoV-2 monoclonal antibodies monoclonal antibodies was not allowed in the study. Further, some of the monoclonal antibodies or antiviral drugs against COVID-19 were not yet available at the time the study was conducted. In addition, the use of hydroxychloroquine or chloroquine was not allowed. Beyond this, there were no further restrictions or specific requirements for the concomitant treatment in the intervention or control arm and COVID-19 therapy was to be given according to local standards.

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

Table 8: Information on concomitant therapies up to week 24 (≥ 5% of patients in ≥ 1 study arm) – RCT, direct comparison: sotrovimab vs. placebo

Study Drug	Patients with concomitant therapy n (%)	
	Sotrovimab N = 528	Placebo N = 529
COMET-ICE		
Total	476 (90)	468 (88)
Paracetamol	144 (27)	157 (30)
Metformin	100 (19)	98 (19)
Ascorbic acid	92 (17)	104 (20)
Lisinopril	81 (15)	70 (13)
Salbutamol	66 (13)	81 (15)
Acetylsalicylic acid	58 (11)	71 (13)
Zinc	57 (11)	56 (11)
Vitamin D NOS	60 (11)	52 (10)
Atorvastatin	53 (10)	47 (9)
Hydrochlorothiazide	52 (10)	46 (9)
Ibuprofen	47 (9)	46 (9)
Azithromycin	45 (9)	42 (8)
Losartan	44 (8)	53 (10)
Amlodipine	36 (7)	40 (8)
Omeprazole	34 (6)	47 (9)
Budesonide	32 (6)	47 (9)
Guaifenesin	30 (6)	37 (7)
Levothyroxine	29 (5)	23 (4)
Dexamethasone	27 (5)	36 (7)
Formoterol fumarate	25 (5)	35 (7)
Colecalciferol	22 (4)	46 (9)
Montelukast	22 (4)	34 (6)
Tozinameran (BNT162b2)	21 (4)	28 (5)
Metoprolol	17 (3)	24 (5)
Pantoprazole	13 (2)	24 (5)

n: number of patients with at least one concomitant therapy; N: number of analysed patients; NOS: not otherwise specified; RCT: randomized controlled trial

As concomitant therapies for the treatment of COVID-19, anti-inflammatory and analgesic drugs in particular were administered in the COMET-ICE study. Frequency of administration of these drugs was about equal in both study arms. Specific therapeutic measures, such as dexamethasone, were only used in a small proportion of patients during the course of the study. However, these therapies are also only recommended in later phases of the disease. No monoclonal antibodies or other antiviral drugs against SARS-CoV-2 were used in the study.

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, concomitant treatment with anti-inflammatory and analgesic drugs in the COMET-ICE study is 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, according to the guidelines, these therapy options are only given a weak or open recommendation for special risk groups. In addition, it can be assumed that the treatment of patients with COVID-19 will constantly change over the course of the pandemic, particularly in light of increasing SARS-CoV-2 immunocompetence due to vaccinations and prior virus exposures as well as the emergence of new virus variants with potentially altered pathogenicity. Overall, the fact that specific antiviral substances were not allowed or not used in the COMET-ICE study therefore has no consequence for the present benefit assessment.

Patient characteristics

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

Table 9: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: sotrovimab vs. placebo (multipage table)

Study **Characteristic** **Category**	**Sotrovimab** **N[a] = 528**	**Placebo** **N[a] = 529**
COMET-ICE		
Age [years], mean (SD)	52 (15)	53 (15)
Age [years], n (%)		
≤ 70 years	472 (89)	473 (89)
> 70 years	56 (11)	56 (11)
Sex [F/M], %	57/43	52/48
Region, n (%)		
Europe	14 (3)	15 (3)
North America	503 (95)	502 (95)
South America	11 (2)	12 (2)
Body weight [kg], mean (SD)	89.5 (21.5)	90.1 (21.3)
SARS-CoV-2 viral load at baseline, n (%)[b, c]		
Undetectable	64 (14)	63 (13)
< 2228 copies/mL	34 (7)	33 (7)
≤ 10^5 copies/mL	72 (15)	84 (17)
> 10^5 – ≤ 10^6 copies/mL	64 (14)	58 (12)
> 10^6 – ≤ 10^7 copies/mL	74 (16)	60 (12)
> 10^7 copies/mL	159 (34)	183 (38)
Symptom duration before start of treatment [days]		
≤ 3	314 (59)	310 (59)
4 – 5	213 (40)	219 (41)
> 5	1 (< 1)	0 (0)
Risk factors for COVID-19 progression, n (%)		
Obesity (BMI > 30/m²)	330 (63)	341 (64)
Age ≥ 55 years	243 (46)	256 (48)
Diabetes requiring treatment	119 (23)	109 (21)
Moderate to severe asthma	90 (17)	88 (17)
COPD	34 (6)	27 (5)
Chronic kidney disease	5 (1)	8 (2)
Congestive heart failure	4 (1)	3 (1)
Number of risk factors for COVID-19 progression, n (%)		
0	3 (1)	3 (1)
1	290 (55)	304 (57)
2	178 (34)	153 (29)
3	50 (9)	55 (10)
> 3	7 (1)	14 (3)
Treatment discontinuation, n (%)	ND	ND
Study discontinuation, n (%)[d]	30 (5.7[e])	36 (6.8[e])

Table 9: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: sotrovimab vs. placebo (multipage table)

Study Characteristic Category	Sotrovimab N[a] = 528	Placebo N[a] = 529
a. Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant. b. Viral load in nasal secretions, intervention arm: N = 467, control arm: N = 481. c. Central nasopharyngeal swab. Before logarithmizing, values below the limit of detection (LLD = 1493 copies/mL) were replaced by 0.5*LLD and detectable values below the limit of quantification (LLQ = 2228 copies/mL) by LLQ-0.5*(LLQ-LLD). Percentages are based on the number of values available. d. Common reasons for study discontinuation in the intervention vs. control arm were: patient request (3.2% vs. 4.2%) and lost to follow-up (1.9% vs. 2.5%). e. Institute's calculation. BMI: body mass index; COVID-19: coronavirus disease 2019; F: female; LLD: lower limit of detection; LLQ: lower limit of quantification; M: male; n: number of patients in the category; N: number of randomized (or included) patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation		

Patient characteristics were largely balanced between the treatment arms. The mean age of the patients was about 53 years. At 55%, the percentage of women was slightly higher than that of men. About 60% of the patients in both study arms had symptoms ≤ 3 days before the start of the study. The most common risk factors for progression to severe COVID-19 were obesity (64%), age (47%) and diabetes requiring treatment (22%). About 56% of the patients had one risk factor, and about 43% had ≥ 2 risk factors for progression to severe disease. The study was mainly conducted in study centres in the USA with about 95% patients from North America.

According to the inclusion criteria of the study, the diagnosis of SARS-CoV-2 infection could be made by RT-PCR or antigen test. In 85% of the patients, the diagnosis was made by RT-PCR and in 15% by antigen tests. The infection should ideally be confirmed via PCR testing, particularly if there are therapeutic consequences. However, according to DEGAM, if PCR test capacities are exhausted, therapy can also be started on the basis of symptoms and a positive rapid antigen test [15].

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

As described above, patients who had received at least one vaccination against SARS-CoV-2 were excluded from the COMET-ICE study. At the time of the benefit assessment, however, due to vaccinations and possibly previous exposure to the virus, a large proportion of the population already has complete immunization according to the definition of the STIKO [16], which reduces the risk for severe COVID-19. Accordingly, these patients are not covered by the present therapeutic indication, as they are not at increased risk for severe disease. Patients with incomplete immunization or those at relevant risk of inadequate vaccine response as defined by the STIKO [16], however, might continue to be at increased risk of progressing to severe disease. According to COVRIIN, the same applies to patients who have complex risk factors despite being immunocompetent and fully vaccinated [6]. Patients who exhibited

inadequate vaccine response and are therefore not fully immunized were excluded from the COMET-ICE study. Likewise excluded were patients who, despite being immunocompetent and fully vaccinated, had complex risk factors resulting in an increased risk for severe disease. It is plausible to transfer evidence from the unvaccinated patients in the COMET-ICE study to patient groups who do not achieve complete immunization despite being vaccinated and who are 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 of the results (see Section 2.4.2).

In addition, Module 4 A of the dossier provides no information on the serostatus of the patients at the time of study inclusion. The EMA assessment report [13] shows that the serostatus was determined for 470 patients in the intervention arm and for 472 in the control arm. Of these, 105 (22%) patients in the intervention arm and 97 (21%) patients in the control arm had a positive serostatus. It is not clear from the available data whether the previous infection in these patients was symptomatic. Therefore, it remains unclear whether these patients are comparable to patients who have recovered from symptomatic COVID-19 infection, which represent the majority of the population in the present therapeutic indication at the current time.

According to information in Module 4 A, information on the virus variant present at the start of the study and/or during the study was available from sequencing for 338 patients in the intervention arm and for 358 in the control arm of the study. The majority of the study participants were infected with the wild type virus. A VOC or VOI was detected in 22% of patients in the intervention arm and in 21% in the control arm. Among these, the most common variants were the Alpha variant (B.1.1.7) (10.4% in the intervention arm versus 8.7% in the control arm) and the Epsilon variant (B.1.427/B.1.429) (4.7% in the intervention arm versus 6.2% in the control arm). In accordance with the infection situation at the time the study was conducted, neither the Delta nor the Omicron variant was detected in the study participants examined. According to the SPC [3], sotrovimab has decreased *in vitro* neutralization activity against the Omicron variants BA.2, BA.2.12.1, BA.4 and BA.5 circulating in Germany at the time of the benefit assessment [4]. The COMET-ICE study investigated only patients infected with virus variants for which there was sufficient neutralization activity. It remains unclear whether the observed effects are transferable to patients infected with the virus variants Omicron BA.2, BA.2.12.1, BA.4 or BA.5 circulating at the time of the benefit assessment. On the basis of the COMET-ICE study, conclusions on the added benefit are only possible for patients who are infected with a virus variant for which there is sufficient neutralization activity.

In summary, on the basis of the COMET-ICE study, conclusions on added benefit can be drawn for 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 covered by the present benefit assessment. In addition, conclusions on the

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 planning of the study, only adult patients were to be included in the COMET-ICE study. However, there were isolated protocol violations, leading to the inclusion of some adolescents (2 adolescents in the intervention arm and 4 in the control arm). Nonetheless, 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: sotrovimab vs. 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			
COMET-ICE	Yes	Yes	Yes	Yes	Yes	Yes	Low
RCT: randomized controlled trial							

The risk of bias across outcomes for the COMET-ICE study is rated as low.

Transferability to the German health care context

The company considered the results of the COMET-ICE study to be transferable to the German health care context. It justified this with the comparability of the study population to the risk groups for severe disease defined by the RKI in the German health care context, including older patients, (severely) obese patients or patients with certain pre-existing conditions of the cardiovascular system, the lungs or kidneys, or with diabetes mellitus.

Regarding the transferability of the results of the individual outcomes, the company stated that the intervention in the included study corresponded to the approved therapy and that the study population was covered by the therapeutic indication. Overall, the company therefore assumed that the results of all outcomes presented were transferable to the German health care context.

In its discussion of the transferability of the results, the company did not address differences between the study population and the population in the current German health care context regarding immunization status and the virus variants prevailing at the different time points of

the pandemic. In Module 3 A of the dossier, the company stated that, due to an increasing vaccination rate, it can be assumed that the number of patients who are at increased risk of progressing to severe COVID-19 and who are therefore candidates for sotrovimab will decrease. In Module 2 of the dossier, the company stated with reference to a study by Cathcart et al [17] that current *in vitro* data from pseudovirus and live virus studies showed a preserved efficacy of sotrovimab against a large number of virus variants, including the Omicron BA.1 subvariant, and that there was somewhat reduced efficacy only for the Omicron BA.2 variant on the basis of this study.

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 included in the assessment:

- Mortality
  - all-cause mortality
- Morbidity
  - development of severe and/or critical respiratory COVID-19
  - hospitalization of any duration due to non-respiratory complications of COVID-19
  - ICU admission due to any cause
- Health-related quality of life
  - recorded using the SF-12
- Side effects
  - SAEs
  - severe AEs (Division of Acquired Immunodeficiency Syndrome [DAIDS] grade ≥ 3)
  - discontinuation due to AEs
  - infusion-related reactions
  - further specific AEs, if any

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

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

Table 11: Matrix of outcomes – RCT, direct comparison: sotrovimab vs. placebo

Study	Outcomes										
	All-cause mortality[a]	Development of severe and/or critical respiratory COVID-19[b]	Hospitalization of any duration due to non-respiratory complications of COVID-19[c]	ICU admission due to any cause	Health-related quality of life (SF-12)	SAEs[d]	Severe AEs[d, e]	Discontinuation due to AEs	Infusion-related reactions (AEs)	Infusion-related reactions (SAEs)	Specific AEs
COMET-ICE	Yes	Yes	Yes	Yes	No[f]	Yes	Yes	Yes	Yes	Yes	No[g]

a. Death from any cause up to and including day 90.
b. Severe respiratory COVID-19 was defined as need for supplemental oxygen either by nasal cannula, face mask, high-flow oxygen devices, or non-invasive ventilation. Critical respiratory COVID-19 was defined as need for invasive mechanical ventilation or ECMO.
c. Hospitalization was defined as not due to respiratory complications if no oxygen was supplied at any time during the inpatient stay. Primary causes could be cardiac, renal, neurological and haematological events.
d. Overall rate of events rated by the company as disease-related (defined as PT acute pulmonary oedema, PT acute respiratory distress syndrome, PT hypoxia, PT non-cardiogenic pulmonary oedema, PT pulmonary congestion, PT respiratory failure, PT acute lung injury, PT COVID-19 pneumonia, PT SARS-CoV-2 sepsis, PT SARS-CoV-2 viraemia, PT ageusia, PT anosmia, PT arthralgia, PT chills, PT cough, PT diarrhoea, PT dyspnoea, PT fatigue, PT rhinorrhoea, PT vomiting, PT hyposmia, PT oropharyngeal pain, PT illness).
e. Severe AEs are operationalized as DAIDS grade ≥ 3.
f. No usable data available (see text below for reasoning).
g. No specific AEs were identified based on the AEs occurring in the relevant study.

AE: adverse event; COVID-19: corona virus disease 2019; DAIDS: Division of Acquired Immunodeficiency Syndrome; ECMO: extracorporeal membrane oxygenation; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; SF-12: Short Form 12 Health Survey

Morbidity

Hospitalization of any duration due to non-respiratory complications of COVID-19/hospitalization of any duration or > 24 h due to any cause

In the dossier, the company presented various analyses of hospitalization, each of which was based on a different duration of hospitalization. In addition, the company presented analyses based on type and duration of hospitalization that covered different periods of analyses. The following analyses on hospitalization are available in the dossier:

- hospitalization of any duration due to non-respiratory complications of COVID-19 (day 29)

- hospitalization of any duration due to any cause (day 29 and day 90)
- hospitalization > 24 h due to any cause (day 29)

These analyses show that the criterion of a minimum time of > 24 h was met for a large proportion of the hospitalizations that occurred in the study. They also show that few patients with event were additionally recorded between day 29 and day 90.

Regarding operationalization, the study documents show that hospitalization of any duration due to non-respiratory complications of COVID-19 was primarily for cardiac, renal, neurological or haematological events. Patients who developed severe and/or critical respiratory COVID-19 during the course of the study and were possibly hospitalized for this reason were recorded using a separate outcome according to the planning of the study. Further information on the operationalization of the outcome of hospitalization of any duration due to non-respiratory complications of COVID-19 is not available in the study documents and Module 4 A of the dossier. Hospitalization is assumed to have occurred upon the treating physician's discretion.

In addition to the outcome of development of severe and/or critical respiratory COVID-19, the present benefit assessment uses hospitalization of any duration due to non-respiratory complications of COVID-19 to capture events that represent progression to severe disease. Results on the proportion of patients with hospitalization of any duration or a minimum duration > 24 h due to any cause are presented as supplementary information.

Further morbidity outcomes

In addition to analyses of hospitalization, the company's dossier presented analyses of other outcomes, which the company considered to reflect disease progression, such as visit to an emergency room, admission to an ICU, use of a ventilator, or administration of supplemental oxygen. Analyses for day 29 and/or day 90 are also available for these outcomes. The present benefit assessment uses ICU admission on day 29 as a further morbidity outcome, as this represents a further disease progression. The results on ICU admission on day 90 are not additionally presented as they are identical to the results on day 29.

For the other outcomes presented by the company, it is assumed that the recorded events have already been recorded via the development of severe and/or critical respiratory COVID-19 or hospitalization of any duration due to non-respiratory complications of COVID-19. However, as only analyses for day 29 are available for these outcomes, the results for the outcomes of ventilator use and supplemental oxygen on day 90 are presented as supplementary information in Appendix C. These results are comparable to the results of the outcomes relevant for the benefit assessment.

Patient-reported outcomes in the category of morbidity

In the COMET-ICE study, symptoms were recorded using the COVID-19-adapted Influenza Patient-Reported Outcome (FLU-PRO) Plus questionnaire. In addition, the study used the Work

Productivity and Activity Impairment (WPAI). According to the planning of the study, the patients were to complete the FLU-PRO Plus daily from day 1 to day 21, on day 29, in week 8 and in week 12. For the WPAI, recordings were scheduled on day 1, 15 and 29, and monthly recordings between week 8 and 24. In the dossier, the company presented continuous analyses at different dates of analysis for the 2 instruments and, for the FLU-PRO Plus, also responder analyses and event time analyses for response and sustained (≥ 48 h) symptom alleviation.

However, the dossier shows that the responses for both instruments decreased markedly early on in the course of the study. Already on day 7, the proportion of FLU-PRO Plus questionnaires available for the analyses was around 57%. By day 21, the response rates were around 50%. For the WPAI, questionnaires were available for only 36% of the patients already at baseline. In the dossier, the company did not provide a reason for the low response rates. Irrespective of the validity of the instruments in the present therapeutic indication, the analyses on the FLU-PRO Plus and the WPAI presented by the company are therefore not usable for the benefit assessment due to the low number of responses.

Health-related quality of life

SF-12

In the COMET-ICE study, health-related quality of life was assessed using the SF-12 Hybrid. The dossier shows that this instrument is the SF-12 plus the Short Form 36 Health Survey (SF-36) domains of vitality and physical role functioning. The company did not present the SF-12 Hybrid questionnaire in the dossier, nor did it provide information on the validity of the instrument. However, based on the available information, it is assumed that a validated version of the SF-12 with a corresponding extension was used as SF-12 Hybrid in the study. Irrespective of the validity of the extension, analyses of the SF-12 that would be relevant for the present benefit assessment would in principle be possible under these conditions.

However, the dossier shows that there were very low response rates for the SF-12 Hybrid in the study, which decreased markedly early on in the course of the study. According to the planning of the study, the SF-12 Hybrid was scheduled to be recorded on days 1, 15 and 29, and monthly from week 8 to week 24. At baseline, recordings were available for about 75% of the patients, whereas data were recorded for only about 47% on day 15, and for about 35% in week 24. Regardless of the validity of the SF-12 Hybrid, the analyses of this questionnaire presented by the company are therefore not usable for the present benefit assessment. The company also presented additional responder analyses for the SF-12 Hybrid, for which it imputed missing values as non-responders. This affects about 70% of the patients in the study at week 24.

Side effects

Infusion-related reactions

Infusion-related reactions were recorded in the COMET-ICE study using a prespecified list of Preferred Terms (PTs) from the Medical Dictionary for Regulatory Activities (MedDRA). In addition to PTs on infusion-related reactions, this list also includes PTs on hypersensitivity. In

Module 4 A of the dossier, the company presented analyses based on this list for AEs and SAEs that occurred within the first 24 h after the infusion. The present benefit assessment uses the analyses on AEs and SAEs for the outcome of infusion-related reactions. According to the SPC, the infusion of sotrovimab is to be administered over 30 minutes [3]. In the study, however, the administration was planned over a duration of 1 h. The extent to which the longer infusion duration might affect the rate of infusion-related reactions remains unclear. Whether the study results can be transferred without limitation to the use in clinical practice therefore also remains unclear. This issue has been taken into account in the assessment of the certainty of conclusions of the results (see Section 2.4.2).

2.4.2 Risk of bias

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

Table 12: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: sotrovimab vs. placebo

Study	Outcomes												
	Study level	All-cause mortality[a]	Development of severe and/or critical respiratory COVID-19[b]	Hospitalization of any duration due to non-respiratory complications of COVID-19[c]	ICU admission due to any cause	Health-related quality of life (SF-12)	SAEs[d]	Severe AEs[d, e]	Discontinuation due to AEs	Infusion-related reactions (AEs)	Infusion-related reactions (SAEs)	Specific AEs
COMET-ICE	L	L	L	L	L	–[f]	H[g]	H[g]	L	L[h]	L[h]	–

a. Death from any cause up to and including day 90.
b. Severe respiratory COVID-19 was defined as need for supplemental oxygen either by nasal cannula, face mask, high-flow oxygen devices, or non-invasive ventilation. Critical respiratory COVID-19 was defined as need for invasive mechanical ventilation or ECMO.
c. Hospitalization was defined as not due to respiratory complications if no oxygen was supplied at any time during the inpatient stay. Primary causes could be cardiac, renal, neurological and haematological events.
d. Overall rate of events rated by the company as disease-related (defined as PT acute pulmonary oedema, PT acute respiratory distress syndrome, PT hypoxia, PT non-cardiogenic pulmonary oedema, PT pulmonary congestion, PT respiratory failure, PT acute lung injury, PT COVID-19 pneumonia, PT SARS-CoV-2 sepsis, PT SARS-CoV-2 viraemia, PT ageusia, PT anosmia, PT arthralgia, PT chills, PT cough, PT diarrhoea, PT dyspnoea, PT fatigue, PT rhinorrhoea, PT vomiting, PT hyposmia, PT oropharyngeal pain, PT illness).
e. Severe AEs are operationalized as DAIDS grade ≥ 3.
f. No usable data available; see Section 2.4.1 for the reasoning.
g. The analyses do not take into account the events that 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 that can be both side effects and symptoms of the underlying disease.
h. Despite low risk of bias, a limited certainty of results is assumed for the outcome of infusion-related reactions (see Section 2.4.1).

AE: adverse event; COVID-19: corona virus disease 2019; DAIDS: Division of Acquired Immunodeficiency Syndrome; ECMO: extracorporeal membrane oxygenation; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; SF-12: Short Form 12 Health Survey

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. For the results on the outcomes of SAEs and severe AEs, the risk of bias is rated as high. The analyses do not take into account the events that 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 that can be both side effects and symptoms of the underlying disease. For the outcomes on infusion-related reactions

(operationalized via AEs and SAEs), the certainty of results is limited despite a low risk of bias (see Section 2.4.1).

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 oxygen supplementation 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 COMET-ICE study (see Section 2.3.2). The following assessment of the certainty of conclusions therefore exclusively applies to adult patients ≥ 18 years of age for whom data are available from the COMET-ICE study. In addition, as described in Section 2.3.2, 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 covered by the present benefit assessment. Furthermore, conclusions on the added benefit are only possible for patients who are infected with a virus variant for which there is sufficient neutralization activity.

As described in Section 2.3.2, it is possible to transfer evidence from the unvaccinated patients included in the COMET-ICE 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, the certainty of conclusions of the study results for the present research question is therefore reduced. Based on the COMET-ICE study, at most hints, e.g. of an added benefit, can be determined for all outcomes presented.

2.4.3 Results

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

The company presented results from a Cox proportional hazards analysis for the outcome of all-cause mortality. As no event occurred in the intervention arm, this analysis does not provide an effect estimation for the hazard ratio (HR) and the 95% confidence interval (CI). The company did not provide any information on the methods used to calculate the p-value. Since the documentation time is the same for all patients, the relative risk (RR) effect measure is used for the outcome of mortality. Corresponding calculations have been conducted by the Institute.

Tables on common SAEs and common severe AEs, excluding the events classified by the company as disease-related, are presented in Appendix B of the full dossier assessment.

Supplementary results on the morbidity outcomes of supplemental oxygen and ventilator use are presented in Appendix C of the full dossier assessment.

Table 13: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: sotrovimab versus placebo (multipage table)

Study Outcome category Outcome Time point	Sotrovimab N[a]	Sotrovimab Patients with event n (%)	Placebo N[a]	Placebo Patients with event n (%)	Sotrovimab vs. placebo RR [95% CI]; p-value
COMET-ICE					
Mortality					
All-cause mortality[b]					
Day 90	528	0 (0[c])	529	4 (0.8[c])	–[d]; 0.047[e]
Morbidity					
Development of severe and/or critical respiratory COVID-19[f, g]					
Day 29	528	7 (1.3[c])	529	26 (4.9[c])	0.27 [0.12; 0.62][c]; < 0.001[e]
Category 2[h]	528	7 (1.3[c])	529	12 (2.3[c])	–
Category 3[i]	528	0 (0[c])	529	10 (1.9[c])	–
Category 4[j]	528	0 (0[c])	529	4 (0.8[c])	–
Hospitalization of any duration due to non-respiratory complications of COVID-19[f, g]					
Day 29	528	4 (0.8[c])	529	4 (0.8[c])	1.00 [0.25; 3.99][c]; > 0.999[e]
Hospitalization > 24 h due to any cause (supplementary information)[g]					
Day 29	528	*6 (1.2[c])*	529	*29 (5.5[c])*	*0.21 [0.09; 0.50][c]; < 0.001[e]*
Hospitalization of any duration due to any cause (supplementary information)[g]					
Day 29	528	*7 (1.3[c])*	529	*29 (5.5[c])*	*0.24 [0.11; 0.55][c]; < 0.001[e]*
Day 90	528	*11 (2.1[c])*	529	*31 (6.0[c])*	*0.36 [0.18; 0.70][c]; 0.002[e]*
ICU admission due to any cause[g]					
Day 29	528	0 (0[c])	529	9 (1.7[c])	0.05 [< 0.01; 0.90][c]; 0.003[e]
Health-related quality of life					
SF-12	No usable data				

Table 13: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: sotrovimab versus placebo (multipage table)

Study Outcome category Outcome Time point	Sotrovimab N[a]	 Patients with event n (%)	Placebo N[a]	 Patients with event n (%)	Sotrovimab vs. placebo RR [95% CI]; p-value
Side effects					
AEs (supplementary information)[k]	523	128 (24.5)	526	121 (23.0)	–
SAEs[k]	523	9 (1.7)	526	18 (3.4)	0.50 [0.23; 1.11]; 0.084[e]
Severe AEs[k, l]	523	21 (4.0)	526	28 (5.3)	0.75 [0.43; 1.31]; 0.331[e]
Discontinuation due to AEs[m]	523	0 (0)	526	0 (0)	–
Infusion-related reactions (AEs)	523	7 (1.3)	526	6 (1.1)	1.17 [0.40; 3.47]; 0.846[e]
Infusion-related reactions (SAEs)	523	0 (0)	526	0 (0)	–

a. Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b. In the control arm, one additional death during the course of the study after 90 days was recorded as a fatal SAE. The reason given was completed suicide.
c. Institute's calculation.
d. Discrepancy between p-value (exact) and CI (asymptotic) due to different calculation methods; effect estimation and CI not presented because not informative.
e. Institute's calculation, unconditional exact test, CSZ method according to [18].
f. In Module 4 A, the company presented analyses that counted 2 patients in the placebo arm who died before day 29 as events. It is not clear from the study documents whether these patients had experienced the relevant event before death. The patients were therefore not counted as events for the present benefit assessment.
g. In Module 4 A, the company presented analyses for which the corresponding patients were classified as having an event in the case of missing values. For the present benefit assessment, the Institute conducted calculations without imputation of missing values.
h. Low-flow nasal cannula/face mask.
i. Non-re-breather mask or high-flow nasal cannula/non-invasive ventilation (including continuous positive airway pressure support).
j. Mechanical ventilation/ECMO.
k. Overall rate excluding events classified as disease-related by the company (see Table 11 for details).
l. Operationalized as DAIDS grade ≥ 3.
m. Presentation of discontinuations of therapy due to AEs; in Module 4 A, the company presented results on study discontinuations due to AEs. In the placebo arm of the study, 5 patients discontinued the study due to AEs, with the company classifying the AEs for 2 patients as disease-related.

AE: adverse event; CI: confidence interval; CSZ: convexity, symmetry, z-score; DAIDS: Division of Acquired Immunodeficiency Syndrome; ECMO: extracorporeal membrane oxygenation; n: number of patients with (at least one) event; N: number of analysed patients; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SF-12: Short Form 12 Health Survey

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

Mortality

All-cause mortality

For the outcome of all-cause mortality, there is a statistically significant difference between treatment groups in favour of sotrovimab. This results in a hint of added benefit of sotrovimab in comparison with treatment of physician's choice.

Morbidity

Development of severe and/or critical respiratory COVID-19

Operationalization

The development of severe and/or critical respiratory COVID-19 was operationalized in the COMET-ICE study via the need for supplemental oxygen either by low-flow nasal cannula/face mask (category 2), or by high-flow oxygen devices or non-invasive ventilation (category 3), as well as via mechanical ventilation/extracorporeal membrane oxygenation (ECMO) (category 4) by day 29. Categories 2 and 3 were classified as severe and category 4 as critical. The study documents provided no further definition of the basis for the decision on the type of supplemental oxygen. The decision is assumed to be made by the treating physician.

Results

For the outcome of severe and/or critical respiratory COVID-19, there is a statistically significant difference between treatment groups in favour of sotrovimab. This results in a hint of added benefit of sotrovimab in comparison with treatment of physician's choice.

Hospitalization of any duration due to non-respiratory complications of COVID-19

For the outcome of hospitalization of any duration due to non-respiratory complications of COVID-19, there is no statistically significant difference between treatment groups. This results in no hint of added benefit of sotrovimab in comparison with treatment of physician's choice; an added benefit is therefore not proven.

ICU admission due to any cause

For the outcome of ICU admission due to any cause, there is a statistically significant difference between treatment groups in favour of sotrovimab. This results in a hint of added benefit of sotrovimab in comparison with treatment of physician's choice.

Health-related quality of life

There are no usable data for health-related quality of life, recorded with the SF-12 (see Section 2.3.1 for the reasoning). This results in no hint of added benefit of sotrovimab in comparison with treatment of physician's choice for health-related quality of life; 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 sotrovimab in comparison with treatment of physician's choice; greater or lesser harm is therefore not proven.

Severe AEs

There was no statistically significant difference between treatment groups for the outcome of severe AEs. This results in no hint of greater or lesser harm from sotrovimab 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 sotrovimab in comparison with treatment of physician's choice; greater or lesser harm is therefore not proven.

Specific AEs

Infusion-related reactions (AEs)

No statistically significant difference was found between treatment groups for the outcome of infusion-related reactions (AEs). This results in no hint of greater or lesser harm from sotrovimab in comparison with treatment of physician's choice; greater or lesser harm is therefore not proven.

Infusion-related reactions (SAEs)

No events occurred in the outcome of infusion-related reactions (SAEs). This results in no hint of greater or lesser harm from sotrovimab in comparison with treatment of physician's choice; greater or lesser harm is therefore not proven.

2.4.4 Subgroups and other effect modifiers

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

- age (≤ 70 years versus > 70 years)
- sex (male versus female)

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

Interaction tests are performed if at least 10 patients per subgroup are included in the analysis. For binary data, there must also be at least 10 events in at least one subgroup.

Only results showing 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 one subgroup.

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

2.5 Probability and extent of added benefit

The probability and extent of added benefit at outcome level are derived below, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [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 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 14).

Table 14: Extent of added benefit at outcome level: sotrovimab vs. treatment of physician's choice (multipage table)

Outcome category **Outcome**	**Sotrovimab vs. placebo** **Proportion of events (%)** **Effect estimation [95% CI];** **p-value** **Probability[a]**	**Derivation of extent[b]**
Mortality		
All-cause mortality	0% vs. 0.8% RR: –[c] p = 0.047 Probability: "hint"	Outcome category: mortality Added benefit; extent: "minor"[d]
Morbidity		
Development of severe and/or critical respiratory COVID-19	1.3% vs. 4.9% RR: 0.27 [0.12; 0.62]; p < 0.001 Probability: "hint"	Outcome category: serious/severe symptoms/late complications CI_u < 0.75, risk < 5% Added benefit, extent: "considerable"
Hospitalization of any duration due to non-respiratory complications of COVID-19	0.8% vs. 0.8% RR: 1.00 [0.25; 3.99]; p ≥ 0.999	Lesser benefit/added benefit not proven
ICU admission due to any cause	0% vs. 1.7% RR: 0.05 [< 0.01; 0.904]; p = 0.003 Probability: "hint"	Outcome category: serious/severe symptoms/late complications 0.90 ≤ CI_u < 1.00 added benefit, extent: "minor"

Table 14: Extent of added benefit at outcome level: sotrovimab vs. treatment of physician's choice (multipage table)

Outcome category **Outcome**	**Sotrovimab vs. placebo** **Proportion of events (%)** **Effect estimation [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Health-related quality of life		
SF-12	No usable data	Lesser benefit/added benefit not proven
Side effects		
SAEs	1.7% vs. 3.4% RR: 0.50 [0.23; 1.11]; p = 0.084	Greater/lesser harm not proven
Severe AEs	4.0% vs. 5.3% RR: 0.75 [0.43; 1.31]; p = 0.331	Greater/lesser harm not proven
Discontinuation due to AEs	0% vs. 0% RR: −	Greater/lesser harm not proven
Infusion-related reactions (AEs)	1.3% vs. 1.1% RR: 1.17 [0.40; 3.47]; p = 0.846	Greater/lesser harm not proven
Infusion-related reactions (SAEs)	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, the effect size is estimated using 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 for lack of informative value.
d. The result of the statistical test is determinative for the derivation of added benefit. Its extent is rated as "minor".

AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; COVID-19: coronavirus disease 2019; RR: relative risk; SAE: serious adverse event; SF-12: Short Form (12) Health Survey

2.5.2 Overall conclusion on added benefit

Table 15 summarizes the results taken into account in the overall conclusion on the extent of added benefit.

Table 15: Positive and negative effects from the assessment of sotrovimab compared with treatment of physician's choice

Positive effects	**Negative effects**
Mortality ▪ All-cause mortality: hint of added benefit – extent: "minor"	–
Serious/severe symptoms/late complications ▪ Development of severe and/or critical respiratory COVID-19: hint of added benefit – extent: "considerable" ▪ ICU admission due to any cause: hint of added benefit – extent: "minor"	–
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; ICU: intensive care unit; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2	

As described in Section 2.3.2, the following conclusion on added benefit applies only to adult patients who have not yet been vaccinated against SARS-CoV-2 or who are not fully immunized against SARS-CoV-2, or who have complex risk factors despite being immunocompetent and fully vaccinated. Patients with complete immunization are not covered by the present therapeutic indication, as 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], sotrovimab has decreased *in vitro* neutralization activity against the SARS-CoV-2 Omicron variants BA.2, BA.2.12.1, BA.4 and BA.5. It remains unclear whether the effects observed in the COMET-ICE study are transferable to patients infected with the virus variants BA.2, BA.2.12.1, BA.4 or BA.5 circulating at the time of the benefit assessment.

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

Overall, for adults with COVID-19 infection who do not require oxygen supplementation and who are at increased risk of progressing to severe COVID-19, there are only positive effects of sotrovimab in comparison with treatment of physician's choice. For the outcomes of all-cause mortality and ICU admission due to any cause, there is a hint of a minor added benefit. For the outcome of development of severe and/or critical respiratory COVID-19, there is a hint of considerable added benefit.

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

Table 16 summarizes the result of the assessment of added benefit of sotrovimab in comparison with the ACT.

Table 16: Sotrovimab – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adults and adolescents aged 12 years and over and weighing at least 40 kg with COVID-19[b] who do not require oxygen supplementation and who are at increased risk of progressing to severe COVID-19[c, d]	Treatment of physician's choice[e, f]	Patients ≥ 18 years: ▪ hint of considerable added benefit[g]
		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. so-called variants of concern [VOC]) are also taken into account when recording and interpreting the results on efficacy.
d. Patients with complete immunization are not comprised by the therapeutic indication (see Section 2.3.2. for an explanation).
e. Depending on the severity of disease, both drug therapies (e.g. analgesics, antipyretics, dexamethasone, anticoagulation/thrombosis prophylaxis, antibiotics, remdesivir, baricitinib, tocilizumab, nirmatrelvir/ritonavir, molnupiravir) and non-drug therapies (e.g. oxygen support, type of ventilation, balanced fluid therapy) should be taken into account in the treatment of physician's choice, if indicated.
f. Recently, the intravenous drugs casirivimab/imdevimab, regdanvimab and remdesivir have been approved for the treatment of COVID-19 patients who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19. The clinical significance of these therapy options cannot be assessed at the present time.
g. 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], sotrovimab has decreased *in vitro* neutralization activity against the SARS-CoV-2 Omicron variants BA.2, BA.2.12.1, BA.4 and BA.5. It remains unclear whether the effects observed in the COMET-ICE study are transferable to patients infected with the virus variants BA.2, BA.2.12.1, BA.4 or BA.5 circulating at the time of the benefit assessment.

COVID-19: coronavirus disease 2019; G-BA: Federal Joint Committee; PCR: polymerase chain reaction; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

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

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. GlaxoSmithKline. Xevudy : EPAR - Product Information [online]. 2022 [Accessed: 29.07.2022]. URL: https://www.ema.europa.eu/documents/product-information/xevudy-epar-product-information_de.pdf.

4. Robert Koch-Institut. Anzahl und Anteile von VOC und VOI in Deutschland [online]. 2022 [Accessed: 04.08.2022]. URL: https://www.rki.de/DE/Content/InfAZ/N/Neuartiges_Coronavirus/Daten/VOC_VOI_Tabelle.html.

5. Fachgruppe COVRIIN beim Robert Koch-Institut. Möglicher Einsatz der neutralisierenden monoklonalen Antikörper in Abhängigkeit von der diagnostizierten SARS-CoV-2-Virusvariante [online]. 2022 [Accessed: 11.07.2022]. URL: https://www.rki.de/DE/Content/InfAZ/N/Neuartiges_Coronavirus/COVRIIN_Dok/Monoklonale_AK.pdf?__blob=publicationFile.

6. Fachgruppe COVRIIN beim Robert-Koch-Institut. Antivirale Therapie in der Frühphase einer SARS-CoV-2-Infektion [online]. 2022 [Accessed: 08.07.2022]. URL: https://www.rki.de/DE/Content/InfAZ/N/Neuartiges_Coronavirus/COVRIIN_Dok/Antivirale_Therapie_Fruehphase.pdf?__blob=publicationFile.

7. GlaxoSmithKline. A Phase II/III randomised, multi-center, double-blind, placebo-controlled study to assess the safety and efficacy of monoclonal antibody VIR-7831 for the early treatment of coronavirus disease 2019 (COVID-19) in non-hospitalized patients; Clinical Study Report for the VIR-7831-5001 study (Day 29 analysis) [unpublished]. 2021.

8. GlaxoSmithKline. A Phase II/III randomised, multi-center, double-blind, placebo-controlled study to assess the safety and efficacy of monoclonal antibody VIR-7831 for the early treatment of coronavirus disease 2019 (COVID-19) in non-hospitalized patients; Final Clinical Study Report for the VIR-7831-5001 study (Week 24 analysis) [unpublished]. 2022.

9. GlaxoSmithKline. A Phase II/III randomised, multi-center, double-blind, placebo-controlled study to assess the safety and efficacy of monoclonal antibody VIR-7831 for the early treatment of coronavirus disease 2019 (COVID-19) in non-hospitalized patients; Clinical Study Report (Amendment) for the VIR-7831-5001 study (Day 29 analysis) [unpublished]. 2021.

10. Vir Biotechnology. VIR-7831 for the Early Treatment of COVID-19 in Outpatients (COMET-ICE) [online]. 2021 [Accessed: 01.06.2022]. URL: https://ClinicalTrials.gov/show/NCT04545060.

11. Vir Biotechnology. A Phase II/III Randomized, Multi-center, Double-blind, Placebo-controlled Study to Assess the Safety and Efficacy of Monoclonal Antibody VIR-7831 for the Early Treatment of Coronavirus Disease 2019 (COVID-19) in Nonhospitalized Patients [online]. 2022 [Accessed: 01.06.2022]. URL: https://www.ins.gob.pe/ensayosclinicos/rpec/recuperarECPBNuevoEN.asp?numec=095-20.

12. Gupta A, Gonzalez-Rojas Y, Juarez E et al. Early Treatment for Covid-19 with SARS-CoV-2 Neutralizing Antibody Sotrovimab. N Engl J Med 2021; 385(21): 1941-1950. https://dx.doi.org/10.1056/NEJMoa2107934.

13. European Medicines Agency. Xevudy; CHMP assessment report [online]. 2021 [Accessed: 17.05.2022]. URL: https://www.ema.europa.eu/documents/assessment-report/xevudy-epar-public-assessment-report_en.pdf.

14. Kluge S, Janssens U, Welte T et al. S3-Leitlinie - Empfehlungen zur stationären Therapie von Patienten mit COVID-19 [online]. 2022 [Accessed: 08.07.2022]. URL: https://www.awmf.org/uploads/tx_szleitlinien/113-001LGl_S3_Empfehlungen-zur-stationaeren-Therapie-von-Patienten-mit-COVID-19_2022-03.pdf.

15. Blankenfeld H, Kaduszkiewicz H, Kochen MM et al. SARS-CoV-2/Covid-19-Informationen & Praxishilfen für niedergelassene Hausärztinnen und Hausärzte; S2e-Leitlinie [online]. 2022 [Accessed: 08.07.2022]. URL: https://www.degam.de/files/Inhalte/Leitlinien-Inhalte/Dokumente/DEGAM-S2-Leitlinien/053-054_S2e_SARS-CoV-2%20und%20COVID-19/V22/053-054l_S2e%20Coronavirus_V22_22-02-2022.pdf.

16. Koch J, Vygen-Bonnet S, Bogdan C et al. Wissenschaftliche Begründung zur COVID-19-Impfempfehlung der STIKO für Personen mit durchgemachter SARS-CoV-2-Infektion und bisher unvollständiger Immunität. Epidemiologisches Bulletin 2022; (21): 44-51.

17. Cathcart AL, Havenar-Daughton C, Lempp FA et al. The dual function monoclonal antibodies VIR-7831 and VIR-7832 demonstrate potent in vitro and in vivo activity against SARS-CoV-2. BioRxiv 2022. https://dx.doi.org/10.1101/2021.03.09.434607.

18. 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.

The full report (German version) is published under https://www.iqwig.de/en/projects/a22-56.html.