IQWiG Reports – Commission No. A22-04

Remdesivir (Covid-19, no supplemental oxygen, increased risk of a severe course) –

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

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Remdesivir (COVID-19, ohne zusätzliche Sauerstoffzufuhr, erhöhtes Risiko für schweren Verlauf) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 11 April 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.

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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, Geriatric Trauma Centre, Clinic for Trauma Surgery, Hanover Medical School, 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

The questionnaire on the disease and its treatment was answered by Heidi Hauer and one other person.

IQWiG thanks the respondents for participating in the written exchange about how they experienced the disease and its treatment and about the treatment goals. The respondents were not involved in the actual preparation of the dossier assessment.

IQWiG employees involved in the dossier assessment

- Jana Göbel
- Nadja Abu Rajab
- Lars Beckmann
- Kirsten Janke
- Marco Knelangen
- Stefan Kobza
- Katrin Nink
- Sabine Ostlender

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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
BMI	body mass index
Covid-19	coronavirus disease 2019
DAIDS	Division of Acquired Immunodeficiency Syndrome
EMA	European Medicines Agency
FLU-PRO	Influenza Patient Reported Outcome
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HIV	human immunodeficiency virus
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MedDRA	Medical Dictionary for Regulatory Activities
NIH	National Institutes of Health
PCR	polymerase chain reaction
PT	Preferred Term
RKI	Robert Koch Institute
SAE	serious adverse event
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus Type 2
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics

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 remdesivir. 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 18 January 2022.

Research question

The aim of this report is to assess the added benefit of remdesivir in comparison with the appropriate comparator therapy (ACT) for the treatment of coronavirus disease 2019 (COVID-19) in adults who do not require supplemental oxygen and are at increased risk of developing a severe course of 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 remdesivir

Therapeutic indication	**ACT[a]**
Adults with COVID-19 disease[b] who do not require supplemental oxygen and are at increased risk of developing a severe course of COVID-19[c]	Treatment of physician's choice[d,e]

a. Presentation of the ACT specified by the G-BA.
b. The diagnosis of SARS-CoV-2 infection in the case of a positive rapid antigen test should be confirmed by a PCR test, especially if therapeutic consequences are derived from this.
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.
d. Specific therapeutic measures are usually not required for mildly to moderately symptomatic COVID-19 disease. Depending on the severity of the disease, symptomatic drug therapies (e.g. analgesics, antipyretics, thrombosis prophylaxis) should therefore primarily be taken into account in the treatment of physician's choice of non-hospitalized patients, if indicated. If the disease progresses and the patient is hospitalized, further drug therapies (e.g. dexamethasone; anticoagulation/thrombosis prophylaxis, antibiotics) as well as non-drug therapies (e.g. oxygen supply, type of ventilation, balanced fluid therapy) must be considered.
e. Recently, the drugs casirivimab/imdevimab, regdanvimab and sotrovimab 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 Type 2; VOC: variants of concern

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

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

Results

Study GS9012 will be used to assess the added benefit of remdesivir compared to treatment of physician's choice for the treatment of COVID-19 in adults who do not require supplemental oxygen and are at increased risk of developing a severe course of COVID-19.

Study design

GS9012 is a placebo-controlled double-blind, randomized phase 3 study on the outpatient treatment with remdesivir in patients with early-stage COVID-19 disease. The study included symptomatic patients with confirmed Severe Acute Respiratory Syndrome Coronavirus Type 2 (SARS-CoV-2) infection detected by either polymerase chain reaction (PCR) test or antigen test ≤ 4 days prior to screening. At the time of study inclusion, additional oxygen supply was not allowed to be necessary or expected for the included patients. 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 ≥ 60 years old. Patients with a previous hospitalization (defined as acute care ≥ 24 hours) due to COVID-19 and patients hospitalized at the time of study inclusion were excluded from the study. Accordingly, only outpatient treatment with remdesivir was investigated in the study. Patients who had received at least one SARS-CoV-2 vaccination were also excluded from the study. Consequently, only unvaccinated patients were considered in the GS9012 study.

Overall, 584 patients were randomly assigned to treatment with remdesivir (N = 292) or placebo (N = 292) in a 1:1 ratio, whereby only 279 vs. 283 patients (intervention vs. control arm) received at least one treatment.

For the majority of the intervention group, treatment with remdesivir was performed in accordance with the Summary of Product Characteristics (SPC).

The study was conducted predominantly in study centres in the USA and was terminated before reaching the planned number of sample cases (n = 1264) due to the decrease in new cases, increased availability of monoclonal antibodies as an alternative to placebo and increased vaccination in high-risk patients.

Primary outcomes of the study were the composite outcome of hospitalization due to COVID-19 or death for any reason until day 28 as well as AEs. Patient-relevant secondary outcomes were all-cause mortality as well as outcomes on morbidity. These outcomes were to be observed until day 28.

Implementation of the ACT

The G-BA specified treatment of physician's choice as ACT. Mildly to moderately symptomatic COVID-19 disease usually requires no specific therapeutic measures. Depending on the severity of the disease, symptomatic drug therapies (e.g. analgesics, antipyretics, thrombosis prophylaxis) should therefore primarily be taken into account in the treatment of physician's choice of non-hospitalized patients, if indicated. If the disease progresses and the

patient is hospitalized, further drug therapies (e.g. dexamethasone, anticoagulation/thrombosis prophylaxis, antibiotics) and non-drug therapies (oxygen supply, type of ventilation, balanced fluid therapy) must be included. According to the G-BA, the clinical significance of the monoclonal antibodies casirivimab/imdevimab, regdanvimab and sotrovimab in the present therapeutic indication can currently not be assessed.

Overall, concomitant treatment with anti-inflammatory and analgesic drugs in the GS9012 study is a sufficient implementation of the ACT. According to the guideline, there were also recommendations for specific antiviral substances for the early phase of COVID-19 disease in patients with an increased risk of a severe course, which were not permitted in the study. 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 in the course of the pandemic, especially with the increase in immunocompetence against SARS-CoV-2 due to vaccinations and previous viral exposures, as well as the emergence of new viral variants with potentially altered pathogenicity. Overall, the fact that specific antiviral substances were not allowed in the GS9012 study therefore has no consequence for the present benefit assessment.

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

As described earlier, patients with at least one SARS-CoV-2 vaccination were excluded from the GS9012 study. At the time of the benefit assessment, however, a large proportion of the population already had vaccination protection, which reduces the risk of a severe course of COVID-19 disease. Moreover, the vaccination changes the immune response of the patients. Therefore, an evidence transfer of the available data to vaccinated individuals is not meaningful without additional studies in vaccinated persons. Thus, the study only allows statements on the added benefit for unvaccinated patients.

Furthermore, based on the information in the dossier, it remains unclear with which viral variant the included unvaccinated patients were infected. According to information in the assessment report of the European Medicines Agency (EMA), none of the included patients for whom genotyping was available was infected with the Delta virus variant. The virus variant omikron, which was widely spread at the time of the benefit assessment, was also not yet existent at the time the study was conducted. The risk for a severe course of COVID-19 disease can differ depending on the virus variant with which the patients are infected. According to current information from the Robert Koch Institute (RKI), the renewed increase in hospitalizations during the omikron wave is significantly weaker in relation to the total number of cases than during the first 4 COVID-19 waves. In addition to the effectiveness of the vaccination, this is also attributed to the fundamentally lower disease severity in infections caused by the omikron variant. Moreover, irrespective of the question of how high the risk of hospitalization is in the case of infection with a virus of the omicron variant compared to the alpha or delta variant, it is initially unclear whether remdesivir can inhibit virus replication in the case of infection with the omicron variant to a similar extent as compared to the variant(s) investigated in the study. In this context, the company refers to initial laboratory results that show that remdesivir is also

active against the omikron variant. This is also shown in the recently published data of a Belgian research group. In principle, development of resistance to remdesivir is also conceivable and has also been described in individual cases. However, despite the high number of omikron infections worldwide, no resistance reports are yet available for this variant.

In addition, the dossier provides no information on the serostatus of the unvaccinated patients at the time of study inclusion. Due to the implementation period of the study in an early wave of the pandemic (09/2020 to 05/2021), it can be assumed that the number of seropositive patients was rather low compared to the situation at the time of the benefit assessment. Since the serostatus of the patients has an impact on the risk of a severe course of the COVID-19 disease, it remains unclear whether the effects observed in the GS9012 study can be transferred without restriction to the current situation in Germany with a possibly higher proportion of seropositive patients.

Overall, an evidence transfer from the unvaccinated patients of study GS9012 to unvaccinated patients with an infection with one of the currently known and predominant virus variants is possible in the present situation. However, the uncertainties described regarding the virus variants as well as the changed serostatus in the course of the pandemic are taken into account for the extent of the added benefit.

Risk of bias and assessment of the certainty of conclusions

The risk of bias across outcomes was rated as low for the GS9012 study. Except for the outcomes “serious adverse events (SAEs)” and “severe adverse events (AEs)”, the outcome-specific risk of bias was rated as low.

The available data of study GS9012 permit no conclusions for patients with at least one vaccination against SARS-CoV-2. The following assessment of the certainty of conclusions therefore refers exclusively to the unvaccinated patients included in the study.

For unvaccinated patients, the results of the GS9012 study were transferred to the current situation. However, as described above, there are differences between the study population in the virus variants prevalent at the respective time as well as the serostatus.

Therefore, the extent, e.g. of an added benefit, cannot be quantified for outcomes of the categories of mortality, morbidity and health-related quality of life. On the basis of the available information and because of the high risk of bias, at most hints, e.g. of an added benefit, can be determined for SAEs and severe AEs, and at most indications can be determined for all other outcomes.

Results

Mortality

All-cause mortality

No deaths occurred in the course of the study. This resulted in no hint of an added benefit of remdesivir in comparison with treatment of physician's choice for the outcome "all-cause mortality"; an added benefit is therefore not proven.

Morbidity

Hospitalization for COVID-19

A statistically significant difference between the treatment groups in favour of remdesivir was shown for the outcome "hospitalization for COVID-19". This resulted in an indication of an added benefit of remdesivir in comparison with treatment of physician's choice.

Need for intensive medical care due to any cause

No statistically significant difference between the treatment groups was shown for the outcome "need for intensive medical care due to any cause". This resulted in no hint of an added benefit of remdesivir in comparison with treatment of physician's choice; an added benefit is therefore not proven.

Health-related quality of life

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

Side effects

SAEs and severe AEs (Division of Acquired Immunodeficiency Syndrome [DAIDS] grade ≥ 3)

No statistically significant difference between the treatment groups was shown for the outcomes "SAEs" and "severe AEs". In each case, this resulted in no hint of greater or lesser harm from remdesivir in comparison with treatment of physician's choice; greater or lesser harm is therefore not proven.

Discontinuation due to AEs

There were no discontinuations due to AEs during the course of the study. This resulted in no hint of greater or lesser harm from remdesivir in comparison with treatment of physician's choice for the outcome "discontinuation due to AEs"; greater or lesser harm is therefore not proven.

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

Based on the results presented, probability and extent of the added benefit of the drug remdesivir in comparison with the ACT are assessed as follows:

For the study population, the overall consideration shows a positive effect of remdesivir in comparison with treatment of physician's choice for the outcome "hospitalization for COVID-19".

As described above, the following conclusion on added benefit exclusively applies to unvaccinated patients. No data are available for vaccinated patients and 3r is not possible due to the described differences in immune response depending on vaccination status.

There is an indication of a non-quantifiable added benefit of remdesivir compared to the ACT for unvaccinated adults with COVID-19 disease who do not require supplemental oxygen and are at increased risk of developing a severe course of COVID-19.

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

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

Table 3: Remdesivir – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adults with COVID-19 disease[b] who do not require supplemental oxygen and are at increased risk of developing a severe course of COVID-19[c]	Treatment of physician's choice[d,e]	▪ Vaccinated patients[f]: added benefit not proven ▪ unvaccinated patients[g]: indication of non-quantifiable added benefit

a. Presented is the respective ACT specified by the GBA.
b. The diagnosis of SARS-CoV-2 infection in the case of a positive rapid antigen test should be confirmed by a PCR test, especially if therapeutic consequences are derived from this.
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.
d. Specific therapeutic measures are usually not required for mildly to moderately symptomatic COVID-19 disease. Depending on the severity of the disease, symptomatic drug therapies (e.g. analgesics, antipyretics, thrombosis prophylaxis) should therefore primarily be taken into account in the treatment of physician's choice of non-hospitalized patients, if indicated. If the disease progresses and the patient is hospitalized, further drug therapies (e.g. dexamethasone, anticoagulation/thrombosis prophylaxis, antibiotics) as well as non-drug therapies (e.g. oxygen supply, type of ventilation, balanced fluid therapy) must be considered.
e. Recently, the drugs casirivimab/imdevimab, regdanvimab and sotrovimab 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.
f. At least one SARS-CoV-2 vaccination.
g. No SARS-CoV-2 vaccination.

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

The 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 this report is to assess the added benefit of remdesivir in comparison with the ACT for the treatment of COVID-19 in adults who do not require supplemental oxygen and are at increased risk of developing a severe course of 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 remdesivir

Therapeutic indication	**ACT[a]**
Adults with COVID-19 disease[b] who do not require supplemental oxygen and are at increased risk of developing a severe course of COVID-19[c]	Treatment of physician's choice[d,e]

a. Presentation of the ACT specified by the G-BA.
b. The diagnosis of SARS-CoV-2 infection in the case of a positive rapid antigen test should be confirmed by a PCR test, especially if therapeutic consequences are derived from this.
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.
d. Specific therapeutic measures are usually not required for mildly to moderately symptomatic COVID-19 disease. Depending on the severity of the disease, symptomatic drug therapies (e.g. analgesics, antipyretics, thrombosis prophylaxis) should therefore primarily be taken into account in the treatment of physician's choice of non-hospitalized patients, if indicated. If the disease progresses and the patient is hospitalized, further drug therapies (e.g. dexamethasone, anticoagulation/thrombosis prophylaxis, antibiotics) as well as non-drug therapies (e.g. oxygen supply, type of ventilation, balanced fluid therapy) must be considered.
e. Recently, the drugs casirivimab/imdevimab, regdanvimab and sotrovimab 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 Type 2; VOC: variants of concern

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

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

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 remdesivir (status: 30 December 2021)
- bibliographical literature search on remdesivir (last search on 27 October 2021)
- search in trial registries/trial results databases for studies on remdesivir (last search on 8 November 2021)
- search on the G-BA website for remdesivir (last search on 14 December 2021)

To check the completeness of the study pool:

- search in trial registries for remdesivir (last search on 27 January 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 5 was included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: remdesivir 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)	Clinical study report (CSR) (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication and other sources[c] (yes/no [citation])
GS9012	Yes	Yes	No	Yes [3,4]	Yes [5,6]	Yes [7,8]

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.
G-BA: Federal Joint Committee; RCT: randomized controlled trial

2.3.2 Study characteristics

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

Table 6: Characteristics of the study included – RCT, direct comparison: remdesivir vs. placebo

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
GS9012	RCT, double-blind, parallel	Unvaccinated adolescents[b] or adults with confirmed COVID-19 disease[c] ▫ < 60 years with ≥ 1 pre-existing risk factor[d] for disease progression up to hospitalization or ▫ ≥ 60 years ▪ ≥ 1 COVID-19 symptom[e] ▪ without the need for current or expected oxygen supply ▪ without the need for current hospitalization (acute care 24 ≥ hours[f])	Remdesivir (N = 292)[g] placebo (N = 292)[g]	Screening: ≤ 2 days treatment: 3 days observation: 28 days	64 centres in Denmark, Spain, United Kingdom, USA 09/2020–05/2021[h] data cut-off: ▪ 12 August 2021	Primary: composite outcome of hospitalization due to COVID-19 or death for any reason until day 28, AEs secondary: all-cause mortality, morbidity

a. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes include information only on relevant available outcomes for this benefit assessment.
b. Inclusion of patients ≥ 12 years and < 18 years with a body weight of ≥ 40 kg possible from protocol amendment 1 (11 August 2020).
The SARS-CoV-2 infection had to be confirmed either by nucleic acid detection (e.g. PCR) or an antigen test ≤ 4 days before screening.
d. Risk factors were either chronic pulmonary disease, hypertension, cardiovascular or cerebrovascular disease, diabetes mellitus, obesity (BMI ≥ 30), immunocompromised condition, mild or moderate chronic kidney disease, chronic liver disease, current cancer disease or sickle cell anaemia.
e. For instance fever, cough, fatigue, shortness of breath, sore throat, headache, muscle or joint pain since ≤ 7 days before randomization.
f. The time limitation was introduced with Protocol Amendment 2 (6 November 2020).
g. 13 vs. 9 patients (intervention vs. control arm) did not receive any treatment.
h. The study was terminated prematurely after 584 of the planned 1264 patients had been included, due to the decrease in new cases, increased availability of monoclonal antibodies as an alternative to placebo, and an increased proportion of vaccination in high-risk patients.

AE: adverse event; BMI: body mass index; COVID-19: coronavirus disease 2019; N: number of randomized patients; PCR: polymerase chain reaction; PK: pharmacokinetics; RCT: randomized controlled trial; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus Type 2

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

Study	Intervention	Comparison
GS9012	Remdesivir IV: 200 mg on day 1, followed by 100 mg/day on days 2 and 3[a]	Placebo on days 1-3[a]
	Treatment discontinuation in case of infusion-related systemic reactions ≥ grade 2, infusion-related local reactions ≥ grade 3 or impairment of the liver function[b]	
	Prohibited prior and concomitant treatment ▪ SARS-CoV-2 or COVID-19 vaccines ▪ approved or investigational drugs with actual or potential direct antiviral activity against SARS-CoV-2 including approved HIV protease inhibitors, e.g. lopinavir/ritonavir and interferon[c] ▪ hydroxychloroquine or chloroquine ▪ strong inducers of the P-glycoprotein (e.g. rifampin or herbal drugs)	

a. Administered as an infusion over 30 minutes; to avoid infusion-related reactions, the duration of the infusion could be increased to a maximum of 120 minutes.
b. Treatment was discontinued when the liver function was impaired (ALT or AST ≥ 5-fold ULN or ALT > 3-fold ULN and total bilirubin > 2-fold ULN [confirmed by repeated testing]).
c. Use of these drugs for an approved therapeutic indication other than SARS-CoV-2 infection is not prohibited.

ALT: alanine aminotransferase; AST: aspartate aminotransferase; COVID-19: coronavirus disease 2019; HIV: human immunodeficiency virus; IV: intravenous; RCT: randomized controlled trial; vs.: versus; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus Type 2; ULN: upper limit of normal

GS9012 is a placebo-controlled double-blind, randomized phase 3 study on the outpatient treatment with remdesivir in patients with early-stage COVID-19 disease. The study included symptomatic patients with confirmed SARS-CoV-2 infection detected by PCR test or antigen test ≤ 4 days prior to screening. At the time of study inclusion, additional oxygen supply was not allowed to be necessary or expected for the included patients. 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 ≥ 60 years old. Patients with a previous hospitalization (defined as acute care ≥ 24 hours) due to COVID-19 and patients hospitalized at the time of study inclusion were excluded from the study. Accordingly, only outpatient treatment with remdesivir was investigated in the study. Patients who had received at least one SARS-CoV-2 vaccination were also excluded from the study. Consequently, only unvaccinated patients were considered in the GS9012 study.

Overall, 548 patients were randomly assigned to treatment with remdesivir (N = 292) or placebo (N = 292) in a 1:1 ratio, whereby only 279 vs. 283 patients (intervention vs. control arm) received at least one treatment. Randomization was stratified by accommodation in a nursing facility (yes/no), age (< 60 years versus ≥ 60 years) and region (USA vs. outside the USA).

For the majority of the intervention group, treatment with remdesivir was performed in accordance with the SPC [9]. In principle, treatment should be started within 7 days of the onset of symptoms. However, some patients in the study (about 6%) had symptoms for > 7 days

before the start of treatment (see Table 9). Moreover, remdesivir is only approved for the treatment of adults. However, study GS9012 also included a small number of adolescents (≥ 12 years and < 18 years; body weight ≥ 40 kg) (a total of 8 [1.4%] adolescents, see Table 9). Since the company did not present any analyses for the subpopulation of the study treated in accordance with the SPC, both the adolescents and the patients with symptom onset > 7 days before the start of treatment were included in the present analyses. It is assumed, however, that these deviations in a small number of patients had no relevant influence on the study results.

The study was conducted predominantly in study centres in the USA and was terminated before reaching the planned number of sample cases (n = 1264) due to the decrease in new cases, increased availability of monoclonal antibodies as an alternative to placebo and increased vaccination in high-risk patients.

Primary outcomes of the study were the composite outcome of hospitalization due to COVID-19 or death for any reason until day 28 as well as AEs. Patient-relevant secondary outcomes were all-cause mortality as well as outcomes on morbidity. These outcomes were to be observed until day 28.

Implementation of the ACT

The G-BA specified treatment of physician's choice as ACT. Mildly to moderately symptomatic COVID-19 disease usually requires no specific therapeutic measures. Depending on the severity of the disease, symptomatic drug therapies (e.g. analgesics, antipyretics, thrombosis prophylaxis) should therefore primarily be taken into account in the treatment of physician's choice of non-hospitalized patients, if indicated. If the disease progresses and the patient is hospitalized, further drug therapies (e.g. dexamethasone, anticoagulation/thrombosis prophylaxis, antibiotics) and non-drug therapies (oxygen supply, type of ventilation, balanced fluid therapy) must be included. According to the G-BA, the clinical significance of the monoclonal antibodies casirivimab/imdevimab, regdanvimab and sotrovimab in the present therapeutic indication can currently not be assessed.

According to the guidelines valid at the time of the benefit assessment, apart from symptomatic supportive measures, there are only a few recommendations for therapy in the early phase of COVID-19 disease with a high risk of severe disease progression. According to the S2e guideline of the German Society of General and Family Medicine (Deutschen Gesellschaft für Allgemeinmedizin und Familienmedizin, DEGAM), status 4 February 2022 [10], and the S3 guideline on the inpatient therapy of patients with COVID19, status 28 February 2022 [11], the following antiviral substances are available as therapy options for unvaccinated COVID19 patients with at least one risk factor for a severe course: the SARS-CoV-2 neutralising monoclonal antibody sotrovimab, as well as the drugs nirmatrelvir/ritonavir and molnupiravir. Not all of these options were approved for the treatment of COVID-19 patients in Germany at the time of the benefit assessment, such as molnupiravir. The European approval for nirmatrelvir/ritonavir was granted on 28 January 2022.

However, according to the guidelines, these substances are only given a weak or open recommendation for special risk groups. This is mainly due to the emergence of new virus variants with potentially altered pathogenicity and the increased immunocompetence of the population, which is promoted by vaccination and previous virus exposure. Accordingly, an earlier guideline version of the DEGAM [12] also includes, for example, recommendations on other monoclonal antibodies that are effective against other viral variants apart from omicron. Overall, the current risk of needing inpatient or outpatient treatment for SARS-CoV-2 infection, of experiencing long-term restrictions in quality of life or of dying, as stated in the S3 guideline, is difficult to quantify for the reasons mentioned above [11]. According to the guidelines, the selection of the appropriate therapy should be a case-by-case decision, taking into account individual risk profile, immunisation status, availability and contraindications.

Concomitant therapies administered in the GS9012 study

In the GS9012 study, the use of approved or investigational antiviral drugs against SARS-CoV-2 was not allowed according to the study planning. These drugs included the human immunodeficiency virus (HIV) protease inhibitors such as lopinavir/ritonavir and interferon, among others, which were not allowed to be used for the treatment of COVID-19, as well as other agents such as hydroxychloroquine or chloroquine. Accordingly, the use of monoclonal antibodies against SARS-CoV-2 or other antiviral drugs was also not permitted or the substances were not yet available at the time the study was conducted. Beyond that, there were no further restrictions or specific requirements for the concomitant treatment in both the intervention and the control arm. According to the study design, there were also no restrictions or specifications for the use of drug or non-drug therapies for treatment in the event of disease progression during the course of the study.

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

Table 8: Information on concomitant therapies (≥ 5% of the patients in ≥ 1 study arm) – RCT, direct comparison: remdesivir vs. placebo

Study drug	Patients with concomitant therapy n (%)	
	remdesivir Na = 279	placebo Na = 283
GS9012		
Total	260 (93)	267 (94)
Paracetamol	50 (18)	56 (20)
Ascorbic acid	49 (18)	50 (18)
Acetylsalicylic acid	42 (15)	56 (20)
Salbutamol	41 (15)	44 (16)
Metformin	35 (13)	38 (13)
Colecalciferol	32 (11)	32 (11)
Lisinopril	32 (11)	31 (11)
Ibuprofen	31 (11)	30 (11)
Atorvastatin	28 (10)	28 (10)
Zinc	25 (9)	29 (10)
Vitamin D	23 (8)	28 (10)
Omeprazole	25 (9)	24 (8)
Vitamins	18 (6)	26 (9)
Amlodipine	18 (6)	25 (9)
Losartan	20 (7)	17 (6)
Salbutamol sulfate	17 (6)	19 (7)
Hydrochlorothiazide	15 (5)	19 (7)
Levothyroxine	18 (6)	16 (6)
Ondansetron	17 (6)	15 (5)
Montelukast	16 (6)	14 (5)
Azithromycin	16 (6)	12 (4)
Fluticasone	7 (3)	19 (7)
Simvastatin	13 (5)	13 (5)
Metoprolol	16 (6)	9 (3)
Rosuvastatin	13 (5)	11 (4)
Benzonatate	9 (3)	14 (5)
Zinc sulfate	14 (5)	9 (3)
Atenolol	7 (3)	13 (5)

a. Patients who received at least one dose of the study medication (292 vs. 292 patients were randomized).

n: number of patients with at least 1 concomitant therapy; N: number of patients who received at least one dose of the study medication; RCT: randomized controlled trial

As concomitant therapies for the treatment of COVID-19, anti-inflammatory and analgesic drugs in particular were administered in the GS9012 study. Specific therapeutic measures such as dexamethasone or supplemental oxygen were only used in a few patients during the course

of the study (dexamethasone: 6 vs. 5 patients in the intervention vs. control arm; supplemental oxygen: 1 vs. 5 patients in the intervention vs. control arm, see also Appendix C of the full dossier assessment). However, these therapies are also only recommended in later phases of the COVID-19 disease. According to the study planning, monoclonal antibodies and other antiviral drugs against SARS-CoV-2 were not used.

Overall, concomitant treatment with anti-inflammatory and analgesic drugs in the GS9012 study is a sufficient implementation of the ACT. According to the guideline, there were also recommendations for specific antiviral substances for the early phase of COVID-19 disease in patients with an increased risk of a severe course, which were not permitted 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 in the course of the pandemic, especially with the increase in immunocompetence against SARS-CoV-2 due to vaccinations and previous viral exposures, as well as the emergence of new viral variants with potentially altered pathogenicity. Overall, the fact that specific antiviral substances were not allowed in the GS9012 study therefore has no consequence for the present benefit assessment.

Patient characteristics

Table 9 shows the patient characteristics of the included study.

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

Study characteristic category	Remdesivir N[a] = 279	Placebo N[a] = 283
GS9012		
Age [years], mean (SD)	50 (15)	51 (15)
Age [years], n (%)		
< 18	3 (1)	5 (2)
≥ 18 - < 60	193 (69)	191 (67)
≥ 60	83 (30)	87 (31)
Sex [F/M], %	47/53	49/51
Region, n (%)		
Europe	15 (5)	16 (6)
United States	264 (95)	267 (94)
Symptom duration before start of treatment [days], median [Q1; Q3]	5 [3; 6]	5 [4; 6]
Symptom duration before start of treatment, n (%)		
≤ 7 days	264 (95)	267 (94)
> 7 days	15 (5)	16 (6)
Residents of a nursing facility, n (%)	8 (3)	7 (2)
Risk factors for a severe course of COVID-19, n (%)		
Chronic pulmonary disease	67 (24)	68 (24)
Hypertension	138 (49)	130 (46)
Cardiovascular or cerebrovascular disease	20 (7)	24 (8)
Diabetes mellitus	173 (62)	173 (61)
Overweight (BMI ≥ 30)	154 (56)	156 (55)
Immunocompromised condition	14 (5)	9 (3)
Chronic mild/moderate kidney disease	7 (3)	11 (4)
Chronic liver disease	1 (< 1)	1 (< 1)
Current cancer disease	12 (4)	18 (6)
Sickle cell anaemia	0 (0)	0 (0)
≥ 60 years	83 (30)	87 (31)
Number of risk factors for a severe course of COVID-19, n (%)		
0	3 (1)	5 (2)
1	73 (26)	71 (25)
≥ 2	203 (73)	207 (73)
Positive PCR stage at the start of the study, n (%)	217 (78)	214 (76)
Treatment discontinuation, n (%)[b]	6 (2)	14 (5)
Study discontinuation, n (%)[c]	13 (5)	11 (4)

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

Study characteristic category	Remdesivir N[a] = 279	Placebo N[a] = 283

a. Patients who received at least one dose of the study medication (292 vs. 292 patients were randomized). Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b. Common reasons for treatment discontinuation in the intervention versus the control arm were patient's decision (1.1% vs. 1.8%) and AEs (0.4% vs. 2.1%).
c. Common reasons for study discontinuation in the intervention vs. the control arm were: lost to follow-up (2.5% vs. 0.7%), withdrawal of consent (1.8% vs. 1.4%), AE (0 vs. 1.1%)

AE: adverse event; BMI: body mass index; COVID-19: coronavirus disease 2019; f: female; m: male; n: number of patients in the category; N: number of patients who received at least one dose of the study medication; PCR: polymerase chain reaction; Q1: 1st quartile; Q3: 3rd quartile; RCT: randomized controlled trial; SD: standard deviation

Patient characteristics were largely balanced between the treatment arms. The mean age of the patients was about 50 years. At 52%, the percentage of men was slightly higher than that of women. In the included patients, the median time to symptom onset was 5 days before start of the treatment in both arms of the study. The most common risk factors for a severe course of COVID19 were diabetes mellitus (62%), obesity (55%) and hypertension (48%). The majority of the patients had ≥ 2 risk factors (73%) for a severe course. The study was mainly conducted in study centres in the USA with about 95% American patients. A small proportion of the patients included (3%) were accommodated in care facilities.

The diagnosis of SARS-CoV-2 infection could be made at study inclusion by PCR or antigen test. Information on which test method was used in which proportion of patients is not available. A confirmation of the infection by means of a PCR test should ideally be carried out particularly if therapeutic consequences are to be derived. 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 [10]. For about three quarters of the patients in the study, a positive PCR test was available at the beginning of the study.

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

As described above, patients with at least one SARS-CoV-2 vaccination were excluded from the GS9012 study. At the time of the benefit assessment, however, a large proportion of the population already had vaccination protection, which reduces the risk of a severe course of COVID-19 disease. Moreover, the vaccination changes the immune response of the patients. The immediate virus replication after infection seems to be similar between vaccinated and unvaccinated patients [13]. However, it can be assumed that the immune response is significantly faster in vaccinated patients [14,15], so that it is unclear whether inhibiting the viral replication with remdesivir leads to a noticeable added value in terms of the consequences of the disease in these patients. Therefore, an evidence transfer of the available data to

vaccinated individuals is not meaningful without additional studies in vaccinated persons. Thus, the study only allows statements on the added benefit for unvaccinated patients.

Furthermore, on the basis of the information in the dossier, it remains unclear with which virus variant the included unvaccinated patients were infected and for how many patients a genotyping of the virus was available at all. According to information in the assessment report of the EMA, none of the included patients for whom genotyping was available was infected with the delta virus variant [8]. Due to the implementation period of the study in an early wave of the pandemic (09/2020 to 05/2021), it can be assumed that the majority of the included patients were infected with virus variants circulating before the spread of the delta virus variant. The virus variant omikron, which was widely spread at the time of the benefit assessment, was also not yet existent at the time the study was conducted. The risk for a severe course of COVID-19 disease can differ depending on the virus variant with which the patients are infected. According to current information from the RKI, the renewed increase in hospitalizations during the omikron wave is significantly weaker in relation to the total number of cases than during the first 4 COVID-19 waves. In addition to the effectiveness of the vaccination, this is also attributed to the fundamentally lower disease severity in infections caused by the omikron variant [16].

Moreover, irrespective of the question of how high the risk of hospitalization is in the case of infection with a virus of the omicron variant compared to the alpha or delta variant, it is initially unclear whether remdesivir can inhibit virus replication in the case of infection with the omicron variant to a similar extent as compared to the variant(s) investigated in the study. In this context, the company refers to initial laboratory results that show that remdesivir is also active against the omikron variant (available as preprint version [17]). This is also shown in the recently published data of a Belgian research group [18]. In principle, development of resistance to remdesivir is also conceivable [19] and has also been described in individual cases [20]. However, despite the high number of omikron infections worldwide, no resistance reports are yet available for this variant.

In addition, the dossier provides no information on the serostatus of the unvaccinated patients at the time of study inclusion. Due to the implementation period of the study in an early wave of the pandemic (09/2020 to 05/2021), it can be assumed that the number of seropositive patients was rather low compared to the situation at the time of the benefit assessment. Since the serostatus of the patients has an impact on the risk of a severe course of the COVID-19 disease, it remains unclear whether the effects observed in the GS9012 study can be transferred without restriction to the current situation in Germany with a possibly higher proportion of seropositive patients.

Overall, an evidence transfer from the unvaccinated patients of study GS9012 to unvaccinated patients with an infection with one of the currently known and predominant virus variants is possible in the present situation. However, the uncertainties described regarding the virus

variants as well as the changed serostatus in the course of the pandemic are taken into account for the extent of the added benefit (see Section 2.4.2).

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: remdesivir vs. placebo

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	Absence of other aspects	Risk of bias at study level
			Patients	Treating staff			
GS9012	Yes	Yes	Yes	Yes	Yes	No	Low
RCT: randomized controlled trial							

The risk of bias across outcomes was rated as low for the GS9012 study.

Transferability to the German health care context

The company considers the results of the GS9012 study to be transferable to the German health care context and justifies this with the comparability of the study population and the SARS-CoV-2-infected German population. Thus, the relevant therapeutic indication includes patients who do not require supplementary oxygen supply and have an increased risk of developing a severe course of COVID-19. According to the RKI, groups of people with an increased risk of severe courses in the German health care context include older people, with a steadily increasing risk from around 50 to 60 years of age, and people with particular underlying diseases, such as cardiovascular diseases, diabetes, diseases of the respiratory system, liver, kidney, cancer, obesity or a weakened immune system. From the perspective of the company, these factors correspond to the inclusion criteria of study GS9012. The study was conducted in Denmark, Spain, the United Kingdom and primarily in the USA, i.e. from the point of view of the company in Western industrial nations with highly developed healthcare systems with comparable access to treatments as well as medical and inpatient care as in Germany. In the GS9012 study, the median age was just over 50 years, and more men were included. The median body mass index (BMI) is 31 kg/m^2, most patients had obesity and at least one risk factor for a severe course of COVID-19. In the opinion of the company, this also corresponds to the characteristics of those patients in the German healthcare context for whom remdesivir is approved.

Furthermore, with regard to the transferability of the results of the individual outcomes, the company states that mortality and AEs were recorded objectively or according to predefined

and standardised criteria and independently of the study location.

With regard to the transferability for outcomes on morbidity, the company discusses the specifications of the German S3 guideline in comparison with the guideline of the National Institutes of Health (NIH) applicable in the USA. Overall, the company assumes that the results of all outcomes presented are transferable to the German healthcare context. In its discussion of the transferability of the results, the company does not address differences in vaccination status, serostatus and the virus variants prevailing at the different time points of the pandemic. In Section 4.4.2 in Module 4A of the full dossier assessment, the company only states that laboratory results suggest that remdesivir is also active against the omikron variant.

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

2.4 Results on added benefit

2.4.1 Outcomes included

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

- Mortality
  - all-cause mortality
- Morbidity
  - hospitalization for COVID-19
  - need for intensive medical care due to any cause
- Health-related quality of life
- Side effects
  - serious AEs (SAEs)
  - severe AEs (DAIDS grade ≥ 3)
  - discontinuation due to AEs
  - further specific AEs, if any

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

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

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

Study	Outcomes							
	All-cause mortality	Hospitalization for COVID-19[a]	Need for intensive medical care due to any cause	Health-related quality of life	SAEs[b]	Severe AEs[b,c]	Discontinuation due to AEs[b]	Specific AEs
GS9012	Yes	Yes	Yes	No[d]	Yes	Yes	Yes	No[e]

a. Operationalized as acute care of ≥ 24 hours according to protocol amendment 2 (6 November 2020).
b. Overall rate without events classified as disease-related by the company (defined as PT ageusia, PT hypogeusia, PT dysgeusia, PT anosmia, PT hyposmia, PT fever, PT cough, PT productive cough, PT cough syndrome of the upper respiratory tract, PT acute sinusitis, PT sinusitis, PT sinusitis viral, PT sinus secretion congestion, PT nasopharyngitis, PT pharyngitis, PT viral pharyngitis, PT viral cold, PT rhinitis, PT rhinorrhoea, PT nasal congestion, PT acute respiratory distress syndrome, PT acute respiratory failure, PT alveolar lung disease, PT dyspnoea, PT hypoxia, PT lung infiltration, PT breathing disorder, PT respiratory failure, PT upper respiratory tract infection, PT viral upper respiratory tract infection, PT upper respiratory tract congestion, PT lower respiratory tract infection, PT viral lower respiratory tract infection, PT lower respiratory tract congestion, PT respiratory tract infection, PT viral respiratory tract infection, PT respiratory tract congestion, PT pneumonia, PT viral pneumonia, PT COVID-19, PT COVID-19 pneumonia, PT asymptomatic COVID-19 infection, PT post-acute COVID-19 syndrome, PT SARS-CoV-2 carrier, PT SARS-CoV-2 sepsis, PT SARS-CoV-2 viraemia).
c. Severe AEs are operationalized as DAIDS grade ≥ 3.
d. Outcome not recorded.
e. No specific AEs were identified based on the AEs that occurred in the relevant study.

AE: adverse event; COVID-19: corona virus disease 2019; DAIDS: Division of Acquired Immunodeficiency Syndrome; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus Type 2

Outcomes on morbidity

In study GS9012, the following outcomes on morbidity were recorded: symptoms assessed based on the Influenza Patient Reported Outcome (FLU-PRO) PLUS questionnaire, hospitalization due to COVID-19, hospitalization due to any cause, medical visit, supplemental oxygen requirement, need for intensive care due to any cause, and need for mechanical ventilation.

Symptoms recorded with FLU-PRO Plus

According to the study protocol, the symptoms were to be recorded using the COVID-19-adapted FLU-PRO Plus questionnaire, if this was available. The company only presents results

on the FLU-PRO Plus in Appendix 4-G of Module 4 A of the full dossier assessment and does not use them to derive the added benefit. The company neither presents the questionnaire itself nor information on the validity of the questionnaire in the present indication. In Module 4 A of the dossier, the company states that, according to the study protocol, the first survey should be conducted before the first infusion of the study medication. However, this was only implemented in a small proportion of the included patients (22%). The proportion of patients who completed the questionnaire on day 1 (before or after the first dose) was 59%. It is not clear from the information in the dossier why the proportion of surveys at baseline was so low, although the questionnaire had already been available 1 month after the start of the study according to information in the publication on the study [7]. Due to the lack of information on the validity of the questionnaire and on the reasons for the overall low number of patients with a baseline survey, it is not possible to assess the suitability of the instrument and the usability of the results.

Hospitalization for COVID-19/for any reason

Since amendment 2 of the study protocol (6 November 2020), hospitalization due to COVID-19 was defined as inpatient acute care of ≥ 24 hours. Furthermore, no information is available on the conditions under which a hospitalization due to COVID-19 occurred. In Module 4 A of the dossier, the company describes that hospitalization in the study was at the discretion of the investigator and that no clear criteria for hospitalization were specified in the study. Unlike hospitalization for COVID-19, hospitalization for any cause was not prespecified. Furthermore, it remains unclear whether this was also associated with a minimum time criterion. Hospitalization for COVID-19 was therefore used for the present benefit assessment. Hospitalization for any reason is presented as supplementary information.

Further outcomes on morbidity

Further morbidity outcomes were also not operationalized more precisely in the study protocol. For example, no distinction was made between the type of oxygen supply or the type of ventilation. In addition, it was not further defined when oxygen supply or mechanical ventilation or intensive care was to take place. According to the study design, these outcomes were recorded regardless of whether there was a connection with COVID-19 disease. Moreover, it can be assumed that some events were recorded in several of the outcomes mentioned. In addition to hospitalization due to COVID-19, the need for intensive care for any cause was used as a further morbidity outcome for the present benefit assessment, as admission to an intensive care unit represents a further disease progression. The outcomes “supplemental oxygen requirement” and “mechanical ventilation” are presented as supplementary information in Appendix C of the full dossier assessment.

The outcome “medical visit”, operationalized as personal contact of the patient with medical staff, was not used for the present benefit assessment. This is due to the fact that contact between the patient and medical staff is not necessarily associated with a noticeable worsening of the

patient's symptoms. Moreover, it is assumed that the majority of medical visits were already recorded via the hospitalizations due to COVID-19.

2.4.2 Risk of bias

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

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

Study		Outcomes							
	Study level	All-cause mortality	Hospitalization for COVID-19[a]	Need for intensive medical care due to any cause	Health-related quality of life	SAEs[b]	Severe AEs[b,c]	Discontinuation due to AEs[b]	Specific AEs
GS9012	L	L	L	L	–[d]	H[e]	H[e]	L[f]	–

a. Operationalized as acute care of ≥ 24 hours according to protocol amendment 2 (6 November 2020).
b. Overall rate without events classified as disease-related by the company (defined as PT ageusia, PT hypogeusia, PT dysgeusia, PT anosmia, PT hyposmia, PT fever, PT cough, PT productive cough, PT cough syndrome of the upper respiratory tract, PT acute sinusitis, PT sinusitis, PT sinusitis viral, PT sinus secretion congestion, PT nasopharyngitis, PT pharyngitis, PT viral pharyngitis, PT viral cold, PT rhinitis, PT rhinorrhoea, PT nasal congestion, PT acute respiratory distress syndrome, PT acute respiratory failure, PT alveolar lung disease, PT dyspnoea, PT hypoxia, PT lung infiltration, PT breathing disorder, PT respiratory failure, PT upper respiratory tract infection, PT viral upper respiratory tract infection, PT upper respiratory tract congestion, PT lower respiratory tract infection, PT viral lower respiratory tract infection, PT lower respiratory tract congestion, PT respiratory tract infection, PT viral respiratory tract infection, PT respiratory tract congestion, PT pneumonia, PT viral pneumonia, PT COVID-19, PT COVID-19 pneumonia, PT asymptomatic COVID-19 infection, PT post-acute COVID-19 syndrome, PT SARS-CoV-2 carrier, PT SARS-CoV-2 sepsis, PT SARS-CoV-2 viraemia).
c. Severe AEs are operationalized as DAIDS grade ≥ 3.
d. Outcome not recorded.
e. The assessments 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 cannot be ruled out that other events are included that can be both side effects and symptoms of the underlying disease.
f. There were no AEs that led to discontinuation that were not classified as disease-related by the company.

AE: adverse event; COVID-19: coronavirus disease 2019; DAIDS: Division of Acquired Immunodeficiency Syndrome; H: high; L: low; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus Type 2

The risk of bias for the results of the outcomes of all-cause mortality, hospitalization for COVID-19, need for intensive medical care and discontinuation due to AEs was rated as low. The risk of bias was rated as high for the results of the outcomes “SAEs” and “severe AEs”.

Summary assessment of the certainty of conclusions

The available data of study GS9012 permit no conclusions for patients with at least one vaccination against SARS-CoV-2 (see Section 2.3.2). The following assessment of the certainty of conclusions therefore refers exclusively to the unvaccinated patients included in the study.

For unvaccinated patients, the results of the GS9012 study were transferred to the current situation. However, as described in Section 2.3.2, there were differences between the study population in the virus variants prevalent at the respective time as well as the serostatus.

Therefore, the extent, e.g. of an added benefit, cannot be quantified for outcomes of the categories of mortality, morbidity and health-related quality of life.

2.4.3 Results

Table 13 summarizes the results on the comparison of remdesivir with treatment of physician’s choice in adults with COVID-19 disease who do not require supplemental oxygen and are at increased risk of developing a severe course of COVID-19. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company’s dossier.

Tables on common AEs, common SAEs, common severe AEs and discontinuations due to AEs, including 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 “supplemental oxygen requirement” and “need for mechanical ventilation” 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: remdesivir vs. placebo

Study outcome category outcome	Remdesivir		Placebo		Remdesivir vs. placebo
	N[a]	patients with event n (%)	N[a]	patients with event n (%)	RR [95% CI]; p-value
GS9012					
Mortality					
All-cause mortality	279	0 (0)	283	0 (0)	–
Morbidity					
Hospitalization for COVID-19	279	2 (0.7)	283	15 (5.3)	0.14 [0.03; 0.59]; 0.002[b]
Hospitalization for any reason[c] (supplementary information)	*279*	*5 (1.8)*	*283*	*18 (6.4)*	*0.28 [0.11; 0.75]; 0.006*[b]
Need for intensive medical care due to any cause	279	3 (1.1)	283	3 (1.1)	1.04 [0.21; 5.06]; 0.964[d]
Health-related quality of life	Outcomes from this category were not recorded				
Side effects					
AEs[e] (supplementary information)	279	105 (37.6)	283	112 (39.6)	–
SAEs[e]	279	3 (1.1)	283	6 (2.1)	0.51 [0.13; 2.01]; 0.530[f]
Severe AEs[e, g]	279	8 (2.9)	283	6 (2.1)	1.35 [0.48; 3.85]; 0.601[f]
Discontinuation due to AEs[e, h]	279	0 (0)	283	0 (0)	–

a. Number of patients who received at least one dose of the study medication (292 vs. 292 patients were randomized).
b. Institute's calculation, RR and 95% CI asymptotic; p-value unconditional exact test, (CSZ method according to [21]).
c. In addition to hospitalization due to COVID-19, 3 patients each had an event in both arms (intervention arm: atrial fibrillation, congestive heart failure and atrial fibrillation, angina pectoris; control arm: fracture of a lumbar vertebra and traffic accident, angina pectoris, acute myocardial infarction, see Table S1 in [7]).
d. RR estimated with the Mantel-Haenszel method. 95% CI and p-values were calculated using the normal approximation (Wald test). Stratification factors: Nursing facility residents (yes vs. no), age (< 60 vs. ≥ 60 years) and region (USA vs. non-USA).
e. Overall rate excluding events classified as disease-related by the company (see Table 11 for details).
f. Institute's calculation, unconditional exact test (CSZ method according to [21]).
g. Operationalized as DAIDS grade ≥ 3.
h. The company classified all events leading to discontinuation as disease-related (see Table 24 of the full dossier assessment).

AE: adverse event; COVID-19: coronavirus disease 2019; DAIDS: Division of Acquired Immunodeficiency Syndrome; CI: confidence interval; CSZ: convexity, symmetry, z-score; n: number of patients with (at least 1) event; N: number of patients who received at least one dose of the study medication; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event

On the basis of the available information and because of the high risk of bias, at most hints, e.g. of an added benefit, can be determined for SAEs and severe AEs, and at most indications can be determined for all other outcomes (see Section 2.4.2).

Mortality

All-cause mortality

No deaths occurred in the course of the study. This resulted in no hint of an added benefit of remdesivir in comparison with treatment of physician's choice for the outcome "all-cause mortality"; an added benefit is therefore not proven.

Morbidity

Hospitalization for COVID-19

Operationalization

For its benefit assessment, the company used the time to hospitalization due to COVID-19 until the end of the study (day 28) for the outcome "hospitalization due to COVID-19". In addition, it presented the time to hospitalization due to COVID-19 until day 14. Deviating from the company, the proportion of patients with hospitalization due to COVID-19 until the end of the study is used for the present benefit assessment, as it is relevant for the patients whether hospitalization due to COVID-19 occurs and not at which point in time the hospitalization occurs during the course of the study. Since no events occurred after day 14, the number of patients with events on day 14 is the same as on day 28. Therefore, a supplementary presentation of the results on day 14 is omitted.

Results

A statistically significant difference between the treatment groups in favour of remdesivir was shown for the outcome "hospitalization for COVID-19". This resulted in an indication of an added benefit of remdesivir in comparison with treatment of physician's choice.

Need for intensive medical care due to any cause

No statistically significant difference between the treatment groups was shown for the outcome "need for intensive medical care due to any cause". This resulted in no hint of an added benefit of remdesivir in comparison with treatment of physician's choice; an added benefit is therefore not proven.

Health-related quality of life

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

Side effects

SAEs

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

Severe AEs (DAIDS grade ≥ 3)

Operationalization

In study GS9012, the severity of an AE was recorded according to DAIDS version 2.1 (July 2017) of the National Institute of Allergy and Infectious Diseases [22]. This approach was prespecified according to the study protocol. The classification of the events as ≥ grade 3 is thereby rated as severe AE. Although the DAIDS classification system was developed for recording the severity of AEs in another therapeutic indication (HIV), it can also be used as an operationalization of severe AEs in the present indication. In DAIDS terminology, a specific severity classification is not available for all Preferred Terms (PTs) in the Medical Dictionary for Regulatory Activities (MedDRA). If AEs occur for which the severity is not described by specific criteria in DAIDS, general criteria are used to assess the severity of an AE. Grade 3 is defined by the presence of severe symptoms that limit social and functional activities, with an indication for intervention or hospitalization. This superordinate definition is considered adequate for the operationalization of severe AEs. The analysis presented by the company in Module 4 A of the full dossier assessment for the outcome "overall rate of severe AEs (DAIDS grade ≥ 3)" is therefore used for the present benefit assessment.

Results

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

Discontinuation due to AEs

There were no discontinuations due to AEs during the course of the study. This resulted in no hint of greater or lesser harm from remdesivir in comparison with treatment of physician's choice for the outcome "discontinuation due to AEs"; 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 (< 60 years vs. ≥ 60 years)
- Sex (male versus female)

Subgroup analyses by age and sex were prespecified for the primary outcome of the study. The classification (< 18; ≥ 18 to < 60; ≥ 60 years) was prespecified for the characteristic "age". Due to the small number of 8 patients in the < 18 years group, the subgroups < 18 years and ≥ 18 - < 60 years were combined. The company submitted subgroup analyses for all outcomes listed in the dossier.

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

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 only presented 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 IQWiG General Methods [23].

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

2.5.1 Assessment of the added benefit at outcome level

The extent of the respective added benefit at outcome level was estimated from the results presented in Section 2.4 (see Table 14).

Determination of the outcome category for the outcomes on morbidity

It cannot be inferred from the dossier whether the following symptom outcome is serious/severe or non-serious/non-severe. The classification of this outcome is explained below.

Hospitalization for COVID-19

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

Table 14: Extent of added benefit at outcome level: remdesivir vs. treatment of physician's choice

Outcome category outcome	**Remdesivir vs. placebo proportion of events (%) effect estimation [95% CI]; p-value probability[a]**	**Derivation of extent[b]**
Mortality		
All-cause mortality	0% vs. 0% RR: –	Lesser benefit/added benefit not proven
Morbidity		
Hospitalization for COVID-19	0.7% vs. 5.3% RR: 0.14 [0.03; 0.59]; p = 0.002 probability: "indication"	Outcome category: serious/severe symptoms/late complications added benefit, extent: "non-quantifiable"[c]
Need for intensive medical care due to any cause	1.1% vs. 1.1% RR: 1.04 [0.21; 5.06]; p = 0.964	Lesser benefit/added benefit not proven
Health-related quality of life		
–	Outcomes from this category were not recorded	Lesser benefit/added benefit not proven
Side effects		
SAEs	1.1% vs. 2.1% RR: 0.51 [0.13; 2.01]; p = 0.530	Greater/lesser harm not proven
Severe AEs	2.9% vs. 2.1% RR: 1.35 [0.48; 3.85]; p = 0.601	Greater/lesser harm not proven
Discontinuation due to AEs	0% vs. 0% RR: –	Greater/lesser harm not proven

a. Probability provided if there is a statistically significant and relevant effect.
b. Depending on the outcome category, estimations of effect size are made with different limits based on the upper limit of the confidence interval (CI_u).
c. Due to the unclear serostatus of the patients included in the GS9012 study who were not infected with Omikron (or Delta) but with previous viral variants, and an increasing proportion of seropositive patients in the course of the pandemic, the extent of the added benefit cannot be quantified for this outcome. For explanation, see Section 2.4.2.

AE: adverse event; COVID-19: coronavirus disease 2019; CI: confidence interval; CI_u: upper limit of confidence interval; RR: relative risk; SAE: serious adverse event

2.5.2 Overall conclusion on added benefit

Table 15 summarizes the results considered in the overall conclusion on the extent of added benefit.

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

Positive effects	**Negative effects**
Serious/severe symptoms/late complications ▪ hospitalization for COVID-19: indication of an added benefit – extent: "non-quantifiable"	–
No data were available for outcomes on health-related quality of life. Effects only apply to patients who have not yet received vaccination against SARS-CoV-2	
COVID-19: coronavirus disease 2019; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus Type 2	

For the study population, the overall consideration shows a positive effect of remdesivir in comparison with treatment of physician's choice for the outcome "hospitalization for COVID-19".

As described in Section 2.3.2, the following conclusion on added benefit exclusively applies to unvaccinated patients. No data are available for vaccinated patients and 3r is not possible due to the described differences in immune response depending on vaccination status.

There is an indication of a non-quantifiable added benefit of remdesivir compared to the ACT for unvaccinated adults with COVID-19 disease who do not require supplemental oxygen and are at increased risk of developing a severe course of COVID-19.

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

Table 16: Remdesivir – probability and extent of added benefit

Therapeutic indication	ACT[a]	Probability and extent of added benefit
Adults with COVID-19 disease[b] who do not require supplemental oxygen and are at increased risk of developing a severe course of COVID-19[c]	Treatment of physician's choice[d,e]	▪ Vaccinated patients[f]: added benefit not proven ▪ unvaccinated patients[g]: indication of non-quantifiable added benefit

a. Presented is the respective ACT specified by the GBA.
b. The diagnosis of SARS-CoV-2 infection in the case of a positive rapid antigen test should be confirmed by a PCR test, especially if therapeutic consequences are derived from this.
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.
d. Specific therapeutic measures are usually not required for mildly to moderately symptomatic COVID-19 disease. Depending on the severity of the disease, symptomatic drug therapies (e.g. analgesics, antipyretics, thrombosis prophylaxis) should therefore primarily be taken into account in the treatment of physician's choice of non-hospitalized patients, if indicated. If the disease progresses and the patient is hospitalized, further drug therapies (e.g. dexamethasone; anticoagulation/thrombosis prophylaxis, antibiotics) as well as non-drug therapies (e.g. oxygen supply, type of ventilation, balanced fluid therapy) must be considered.
e. Recently, the drugs casirivimab/imdevimab, regdanvimab and sotrovimab 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.
f. At least one SARS-CoV-2 vaccination.
g. No SARS-CoV-2 vaccination.

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

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

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.

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Please see full dossier assessment for full reference list.

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

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