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Remdesivir (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 *Remdesivir (COVID-19) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 29 June 2021). 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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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.

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

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
ARDS	acute respiratory distress syndrome
CI	confidence interval
COVID-19	Coronavirus disease 2019
ECMO	extracorporeal membrane oxygenation
FiO_2	inspiratory oxygen concentration
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HFO	high-flow oxygen therapy
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
LFO	low-flow oxygen therapy
NIV	non-invasive ventilation
PaO_2	oxygen partial pressure
RR	relative risk
SAE	serious adverse event
SARS-CoV-2	Severe Acute Respiratory Syndrome Corona Virus 2
SGB	Sozialgesetzbuch (Social Code Book)
SaO_2	arterial oxygen saturation
SpO_2	peripheral capillary oxygen saturation
WHO	World Health Organization

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 1 April 2021.

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 COVID-19 in adults and adolescents (aged 12 years and older with body weight at least 40 kg) with pneumonia requiring supplemental oxygen (low-flow oxygen [LFO] or high-flow oxygen [HFO] or other non-invasive ventilation [NIV] at start of treatment).

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

Table 2: Research question of the benefit assessment of remdesivir

Therapeutic indication	ACT[a]
COVID-19 in adults and adolescents (aged 12 years and older with body weight of at least 40 kg) with pneumonia requiring supplemental oxygen (low-flow or high-flow oxygen therapy or other non-invasive ventilation at start of treatment)	Treatment of physician's choice[b]
a. Presentation of the respective ACT specified by the G-BA. b. In the treatment according to physician's choice, both drug (e.g. dexamethasone, anticoagulation/thrombosis prophylaxis, antibiotics) and non-drug therapies (e.g. oxygen supply, type of ventilation, balanced fluid therapy) must be considered. COVID-19: Coronavirus disease 2019; G-BA: Federal Joint Committee	

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

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

Study pool

The study pool for the benefit assessment of remdesivir comprises the studies ACTT-1, CAP-2 and GS5774-A, from each of which subpopulations represent the population relevant to the assessment (patients with low-flow oxygen therapy (LFO) or high-flow oxygen therapy (HFO)/non-invasive ventilation (NIV) at the start of treatment). Moreover, the results were assessed separately according to ventilation status (LFO vs. HFO/NIV) (see below).

The company also used the SOLIDARITY study for the benefit assessment. However, the data from this study are not suitable for the research question of the benefit assessment of remdesivir in the present therapeutic indication. On the one hand, the study results cannot be transferred to German health care options. Moreover, there are no analyses separated by ventilation status for the study, but the present assessment would require such analyses (see below).

Study design

ACTT-1

The ACTT-1 study is a placebo-controlled, double-blind, multicentre randomized parallel-group study on remdesivir. The study included hospitalized adults with confirmed COVID-19 disease with a defined minimum severity of disease (radiologically detectable infiltration of the lung or peripheral capillary oxygen saturation [SpO_2] ≤ 94% at room air or need for oxygen supply or need for mechanical ventilation).

A total of 1062 patients were included and assigned to treatment with remdesivir (N = 541) or to the placebo group (N = 521) in a 1:1 ratio.

In the ACTT-1 study, remdesivir was administered for 10 days in compliance with the approval. Patients in both arms additionally received standard COVID-19 therapy according to local guidelines.

Primary outcome of the study was time to recovery. Patient-relevant secondary outcomes were overall survival, the proportions of recovered patients and adverse events (AEs). These outcomes were to be observed until day 29 after the start of the study.

CAP-2

The CAP-2 study is a placebo-controlled double-blind, randomized parallel-group study on remdesivir. It included hospitalized adults with confirmed COVID-19 disease and pneumonia. Moreover, patients had to have an oxygen saturation of ≤ 94% (arterial oxygen saturation [SaO_2] or SpO_2) or an oxygenation index (ratio of oxygen partial pressure [PaO_2] and inspiratory oxygen concentration [FiO_2]) of < 300 mmHg at hospitalization.

A total of 237 patients were included and assigned to treatment with remdesivir (N = 158) or to the placebo group (N = 79) in a 2:1 ratio.

In the CAP-2 study, remdesivir was administered for 10 days in compliance with the approval. Patients in both arms additionally received standard COVID-19 therapy.

The study was exclusively conducted in 10 centres in Wuhan, China, and was terminated before reaching the planned number of cases (n = 453) due to a decline in new cases.

Primary outcome of the study was time to clinical improvements. Patient-relevant secondary outcomes were overall survival, the proportions of recovered patients and AEs. These outcomes were to be observed until day 28.

GS5774-A

Study GS5774-A is a three-arm, open-label, multicentre, randomized, parallel-group study in which patients were treated with remdesivir for either 5 days or 10 days, or received standard COVID-19 therapy alone. The study included adults with SpO_2 > 94% on room air and radiological evidence of lung infiltration. Mechanical ventilation of the patients was not allowed.

In the GS5774-A study, remdesivir was administered for 5 or up to 10 days in compliance with the approval. As both periods are covered by the approval of remdesivir, the two study arms are described and analysed together below, where possible. Patients in all study arms additionally received standard COVID-19 therapy.

A total of 596 patients were included and randomly assigned to 5-day treatment with remdesivir (N = 199), 10-day treatment with remdesivir (N = 197) or to standard treatment (N = 200) in a 1:1:1 ratio.

Primary outcome of the GS5774-A study was the clinical status at day 11. Patient-relevant secondary outcomes were overall survival, the proportions of recovered patients and AEs. The secondary outcomes were to be observed until day 28 day (± 5 days) after the start of the study.

Implementation of the ACT

The G-BA specified treatment of physician's choice as ACT. Here, both drug (e.g. dexamethasone, anticoagulation/thrombosis prophylaxis, antibiotics) and non-drug therapies (e.g. oxygen supply, type of ventilation, balanced fluid therapy) must be considered.

In all 3 trials, patients in the comparator arm received standard COVID-19 therapy. This standard COVID-19 therapy was defined differently in the study protocols. Based on the available information, it is not possible to assess the extent to which the currently applicable guideline recommendations have been implemented in the studies. Since all studies were conducted at the beginning of the Corona pandemic (study periods 02/2020 to 05/2020), this cannot be assumed, but does not basically challenge the suitability of the studies for the benefit assessment. In general, it can be assumed that the treatment of hospitalized patients with COVID-19 has improved since the beginning of the pandemic. Therefore, the treatment of COVID-19 disease in the studies included can only be transferred to the current care situation to a limited extent. This uncertainty was taken into account in the certainty of conclusions of the results.

Relevant subpopulations and consideration by ventilation status

Only subpopulations of the three included studies ACTT-1, CAP-2 and GS5774-A were relevant for the benefit assessment:

- According to the approval of remdesivir, only patients who needed additional oxygen supply at the start of the study (LFO or HFO/NIV at the start of treatment) were included

for the benefit assessment. For the studies ACTT-1 and GS5774-A, analyses were available for the relevant subpopulation, which make up 59% and 16% of the total population, respectively. Separate analyses for the CAP-2 study are lacking. However, the population of those patients who needed additional oxygen supply (without invasive ventilation) at the start of the study accounts for 98% of the total population, which can therefore be used for the benefit assessment.

- For the outcome "mortality", the meta-analysis of the included studies also shows a clear effect modification for the ventilation status (LFO vs. HFO/NIV), which makes a separate consideration of the patient groups necessary. The company presented such analyses for the studies ACTT-1 and GS5774-A in the form of subgroup analyses. Such subgroup analyses are not available for CAP-2, but the subpopulation of patients with LFO accounts for 83% of the total population, which is why the total population is used for the LFO subpopulation.

Risk of bias and certainty of conclusions

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

Certainty of results for qualitative summary

Although the risk of bias for the results of all outcomes included in the benefit assessment is rated as low, the included studies differ in their certainty of results. The certainty of results in the studies ACTT-1 and GS5774-A was rated as high. There are no separate analyses by ventilation status for the CAP-2 study. However, since 83% of all patients received LFO at the start of the study, the entire study population will be included for the assessment of the LFO subpopulation. Due to the fact that 17% of the patients were thus incorrectly included in the subpopulation (predominantly patients with HFO/NIV), the certainty of results for the analyses of the LFO subpopulation was rated as moderate in this study.

Overall assessment on the certainty of conclusions

Overall, it must be assumed that the results can only be transferred to the current health care situation of hospitalized COVID-19 patients to a limited extent. This resulted in a limited certainty of conclusions for all studies for all outcomes. Hence, at most indications, e.g. of an added benefit, can be derived on the basis of the available data.

Results

Qualitative summary of the results and certainty of conclusions

The analysis was based on quantitative meta-analytical summaries of the study results. If a quantitative summary was not appropriate for an outcome, a qualitative summary was provided. The assessment of the certainty of conclusions and the extent was initially based on the results with high certainty of results. The certainty of conclusions is not called into question by the results with moderate certainty of results.

Mortality

Overall survival

LFO

For the studies with high certainty of results, the meta-analysis shows a statistically significant difference in favour of remdesivir + standard therapy for the outcome "all-cause mortality" for the LFO subpopulation. The addition of CAP-2, the study with moderate certainty of results, yields a heterogeneous data situation. Overall, the qualitative summary resulted in an indication of added benefit from remdesivir + standard therapy in comparison with standard therapy. In the present data situation, the statistically insignificant effect for all-cause mortality in the CAP-2 study is taken into account in the determination of the extent.

HFO/NIV

For the studies with high certainty of results, the meta-analysis shows no statistically significant difference between the treatment groups for the outcome "all-cause mortality" in the HFO/NIV subpopulation. This resulted in no hint of an added benefit of remdesivir + standard therapy in comparison with standard therapy. An added benefit is therefore not proven for the HFO/NIV subpopulation.

Morbidity

Recovery

Patients were defined as recovered when they were discharged from hospital or when they no longer required oxygen (and [for the ACTT-1 and GS5774-A studies] had no need for ongoing medical care).

LFO

- Day 14/15

For the studies with high certainty of results, the meta-analysis shows a statistically significant difference in favour of remdesivir + standard therapy for the outcome "recovery on day 14/15" for the LFO subpopulation. The addition of the CAP-2 study with moderate certainty of results yields a statistically insignificant result with homogeneous data. Therefore, a qualitative summary is also performed in the present data constellation. Due to the discrepancy in terms of statistical significance between the 2 analyses, the result of the studies with high certainty of results is used for the derivation. This resulted in an indication of added benefit of remdesivir + standard therapy in comparison with standard therapy for the outcome "recovery on day 14/15".

- End of study

For the studies with high certainty of results, the meta-analysis shows a statistically significant difference in favour of remdesivir + standard therapy for the outcome "recovery at the end of the study" for the LFO subpopulation. The addition of the CAP-2 study also results in a statistically significant difference between the treatment groups in favour of remdesivir +

standard therapy with homogeneous data, but with a wider confidence interval (CI) (RR: 1.17; 95% CI: [1.01; 1.36]). Therefore, a qualitative summary is also performed in the present data constellation. Overall, this resulted in an indication of an added benefit of remdesivir + standard therapy in comparison with standard therapy.

HFO/NIV

- Day 14/15 and end of study

For the studies with high certainty of results, the meta-analysis shows no statistically significant difference between the treatment groups for the outcome "recovery" in the HFO/NIV subpopulation, neither on day 14/15 nor at the end of the study. This resulted in no hint of an added benefit of remdesivir + standard therapy in comparison with standard therapy. An added benefit is therefore not proven for the HFO/NIV subpopulation.

Health-related quality of life

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

Side effects

In the recording of "serious adverse events (SAEs)" and "discontinuations due to AEs", disease-related events were also recorded to a large extent in the studies. Accordingly, the results of individual frequent AEs (e.g. respiratory failure) show advantages for remdesivir similar to the results on morbidity. As a result, the overall rates on "SAEs" and "discontinuations due to AEs" are not usable for the assessment of the side effects of remdesivir. However, the results on frequent SAEs and discontinuations due to AEs suggest no negative effects of remdesivir to a degree that could call the added benefit of remdesivir into question. For the outcomes "SAEs" and "discontinuation due to AEs", this resulted in no hint of greater or lesser harm from remdesivir + standard therapy in comparison with standard therapy; 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:

[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].

LFO subpopulation

The overall consideration only showed positive effects of remdesivir in comparison with the standard therapy for the subpopulation LFO, both with regard to all-cause mortality and with regard to the outcome "recovery". There were no usable data for the side effects. However, the available information does not suggest any negative effects to an extent that could call an added benefit into question.

In summary, there is an indication of considerable added benefit of remdesivir versus the ACT according to physician's choice for adults with COVID-19 disease with pneumonia requiring LFO therapy at the start of treatment.

HFO/NIV subpopulation

The overall consideration of the results revealed neither positive nor negative effects of remdesivir in comparison with standard therapy in the HFO/NIV subpopulation.

In summary, there is no hint of an added benefit of remdesivir versus the ACT according to physician's choice for adults with COVID-19 disease with pneumonia requiring HFO/NIV at the start of treatment; an added benefit is therefore not proven.

Note on the transferability of the added benefit to adolescents

The subpopulations relevant for the benefit assessment included no adolescents, and the company presented no data on the transfer of the results to adolescents. As there are clearly different mortality risks for COVID-19 depending on age, the results of the benefit assessment observed for adults cannot be transferred to adolescents. There are thus no usable data for adolescents (aged 12 years and older with body weights of at least 40 kg) with pneumonia requiring supplemental oxygen. This resulted in no hint of an added benefit of remdesivir in comparison with the ACT according to physician's choice for these patients; an added benefit is therefore not proven.

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

Table 3: Remdesivir – probability and extent of added benefit

Therapeutic indication	ACT[a]	Probability and extent of added benefit
COVID-19 in adults and adolescents (aged 12 years and older with a body weight of at least 40 kg) with pneumonia requiring supplemental oxygen		
Patients with LFO at start of treatment	Treatment of physician's choice[b]	Adults: ▪ Indication of considerable added benefit[b]
		Adolescents: ▪ Added benefit not proven
Patients with HFO/NIV at the start of treatment		Added benefit not proven

a. Presentation of the respective ACT specified by the G-BA.
b. In the studies ACTT-1, CAP-2 and GS5774-A included in the benefit assessment, the median age of the patients ranged between 52 and 68 years.

COVID-19: coronavirus disease 2019; G-BA: Federal Joint Committee; HFO: high-flow oxygen therapy; LFO: low-flow oxygen therapy; NIV: non-invasive ventilation

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 coronavirus disease 2019 (COVID-19) in adults and adolescents (aged 12 years and older and with a body weight of at least 40 kg) with pneumonia requiring supplemental oxygen (LFO or HFO or other NIV at the start of treatment).

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

Table 4: Research question of the benefit assessment of remdesivir

Therapeutic indication	ACT[a]
COVID-19 in adults and adolescents (aged 12 years and older with a body weight of at least 40 kg) with pneumonia requiring supplemental oxygen (low-flow or high-flow oxygen therapy or other non-invasive ventilation at start of treatment)	Treatment of physician's choice[b]

a. Presentation of the respective ACT specified by the G-BA.
b. In the treatment according to physician's choice, both drug (e.g. dexamethasone, anticoagulation/thrombosis prophylaxis, antibiotics) and non-drug therapies (e.g. oxygen supply, type of ventilation, balanced fluid therapy) must be considered.

COVID-19: Coronavirus disease 2019; G-BA: Federal Joint Committee

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

The assessment was 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: 4 February 2021)
- bibliographical literature search on remdesivir (last search on 4 February 2021)
- search in trial registries/trial results databases for studies on remdesivir (last search on 4 February 2021)
- search on the G-BA website for remdesivir (last search on 4 February 2021)

To check the completeness of the study pool:

- search in trial registries for remdesivir (last search on 15 April 2021), 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 studies listed in the following Table 5 were included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: remdesivir + standard therapy vs. placebo[a] + standard therapy

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[b] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[c] (yes/no [citation])	Publication (yes/no [citation])
CO-US-540-5776 (ACTT-1[d])	Yes	No	Yes[e]	Yes [3]	Yes [4,5]	Yes [6]
CAP-2	No	No	Yes	No	Yes [7]	Yes [8,9]
GS5774-A	No	Yes	No	Yes [10]	Yes [11,12]	Yes [13]

a. No placebo was administered in the GS5774-A study.
b. Study for which the company was sponsor.
c. Citation of the study registry entries and, if available, of the reports on study design and/or results listed in the study registries.
d. In the following tables, the study is referred to with this abbreviated form.
e. The company stated that it had processed the results of the ACTT-1 study in the form of a study report within the framework of the approval process, although it was not the sponsor of the study.

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

The study pool for the benefit assessment of remdesivir comprises the studies ACTT-1, CAP-2 and GS5774-A, from each of which subpopulations represent the population relevant to the

assessment (patients with LFO or HFO/NIV at the start of treatment). Moreover, the results were assessed separately by ventilation status (LFO vs. HFO/NIV). A detailed justification of this approach can be found in Section 2.3.2.

The study pool is only partially consistent with that of the company, which additionally used the SOLIDARITY study [14] for the benefit assessment. However, the data from this study are not suitable for answering the present research question of the benefit assessment of remdesivir. The SOLIDARITY study is described below and the reasons for the exclusion of this study are presented.

SOLIDARITY

The SOLIDARITY study is a randomized, open-label, parallel-group study conducted by the World Health Organization (WHO) with the aim of identifying effective COVID-19 therapeutics. It included hospitalized adults with COVID-19 disease. The study started in March 2020 with the comparison of the drugs hydroxychloroquine, lopinavir/ritonavir, interferon beta-1a and remdesivir versus standard COVID-19 therapy. The study design was adaptive and so new treatment arms could be added or closed again depending on scientific state of knowledge.

With its flexible structure, its size and the simplified study procedures, the design of the SOLIDARITY study addressed the needs in a pandemic situation. However, without further differentiated processing of the data the study is not suitable for the research question of the benefit assessment. The SOLIDARITY study was conducted in 405 centres in 29 countries. These include, for instance, study centres in Egypt, Honduras, India, Indonesia, Lebanon, Pakistan, Peru and the Philippines. Medical care comparable to that available in Germany (e.g. with regard to ventilation and intensive care capacities) is not guaranteed in these countries and the transferability of the study results is therefore not given. Moreover, analyses for the SOLIDARITY study separated by ventilation status (LFO vs. HFO/NIV) are lacking, but such analyses are necessary for the present assessment. Therefore, the SOLIDARITY study is not used for the benefit assessment of remdesivir.

Information on the study characteristics and the results on mortality of the SOLIDARTIY study available for the approval population of remdesivir are presented as supplementary information in Appendix B of the full dossier assessment.

2.3.2 Study characteristics

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

Table 6: Characteristics of the study included – RCT, direct comparison: remdesivir + standard therapy vs. placebo[a] + standard therapy (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[b]
ACTT-1	RCT, double-blind, parallel	Hospitalized adults with symptomatic, laboratory-confirmed COVID-19 disease with ▪ at least one of the following findings: ▫ radiologically detectable infiltration of the lung ▫ $SpO_2 \leq 94\%$ on room air ▫ additional oxygen required ▫ mechanical ventilation required	Remdesivir (N = 541) placebo (N = 521) relevant subpopulation thereof[c]: LFO remdesivir (N = 232) placebo (n = 203) HFO/NIV remdesivir (N = 95) placebo (n = 98)	Screening: 2 days treatment: 10 days observation: 29 days	60 centres in: Denmark, Germany, Greece, Japan, Mexico, Singapore, South Korea, Spain, USA, UK 02/2020–05/2020	Primary: time to recovery based on an 8-point ordinal scale secondary: all-cause mortality, recovery, AEs
CAP-2	RCT, double-blind, parallel	Hospitalized adults with laboratory-confirmed COVID-19 disease with: ▪ radiologically confirmed pneumonia ▪ $SaO_2/SpO_2 \leq 94\%$ on room air or PaO_2/FiO_2 ratio < 300 mmHg on hospital admission	Remdesivir (N = 158) placebo (N = 79[d])	Screening: ND treatment: 10 days observation: 28 days	10 centres in China 02/2020–04/2020[e]	Primary: time to clinical improvement based on a 6-point ordinal scale secondary: all-cause mortality, recovery, AEs

Table 6: Characteristics of the study included – RCT, direct comparison: remdesivir + standard therapy vs. placebo[a] + standard therapy (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[b]
GS5774-A	RCT, open-label, parallel	Hospitalized adolescents[f] and adults with laboratory-confirmed COVID-19 disease with ▪ SpO_2 > 94% on room air at screening ▪ radiological evidence of lung infiltrates ▪ without need for mechanical ventilation	Remdesivir 5 days (N = 199) remdesivir 10 days (N = 197) standard therapy (N = 200) relevant subpopulation thereof[c]: LFO remdesivir 5 days (n = 29) remdesivir 10 days (n = 23) standard therapy (n = 36) HFO/NIV remdesivir 5 days (n = 2) remdesivir 10 days (n = 1) standard therapy (n = 2)	Screening: 2 days treatment: 5 or 10 days observation: 28 days	105 centres in: Germany, France, Hong Kong, Italy, Netherlands, Singapore, Spain, South Korea, Switzerland, Taiwan, USA, United Kingdom 03/2020–4/2020	Primary: clinical status at day 11 based on a 7-point ordinal scale secondary: all-cause mortality, recovery, AEs

a. No placebo was administered in the GS5774-A study.
b. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes only include information on relevant available outcomes for this benefit assessment.
c. Patients who required supplemental oxygen (LFO or HFO/NIV) at the start of the study. The selection corresponds to categories 5 and 6 of the 8-point ordinal scale of the ACTT-1 study, or categories 4 and 3 of the 7-point ordinal scale of the GS5774-A study.
d. One patient withdrew the informed consent after randomization.
e. Due to a decrease in new cases of COVID-19, the study was discontinued prematurely after inclusion of 237 of the planned 453 patients.
f. Patients ≥ 12 years and < 18 years with a body weight of ≥ 40 kg, if locally approved. However, only one patient with these characteristics was included. This individual did not belong to the approval population of remdesivir.

COVID-19: coronavirus disease 2019; FiO_2: inspiratory oxygen concentration; n: relevant subpopulation; HFO: high-flow oxygen therapy; LFO: low-flow oxygen therapy; N: number of randomized patients; NIV: non-invasive ventilation; PaO_2: oxygen partial pressure; RCT: randomized controlled trial; SaO_2: arterial oxygen saturation; SpO_2: peripheral capillary oxygen saturation; AE: adverse event

Table 7: Characteristics of the intervention – RCT, direct comparison: remdesivir + standard therapy vs. placebo[a] + standard therapy

Study	Intervention	Comparison
ACTT-1	Remdesivir IV: 200 mg on day 1, followed by 100 mg/day on days 2-10[b] ± standard therapy	Placebo ± standard therapy
	Dose interruption in case of renal impairment; treatment discontinuation if haemodialysis or haemofiltration was indicated	
	Non-permitted pretreatment ▪ experimental or off-label medication for the treatment of COVID-19 had to be discontinued at the start of the study **permitted concomitant treatment** ▪ NSAIDs or antipyretics (paracetamol not allowed until day 15) ▪ antiviral drugs for concomitant infection (e.g. oseltamivir, lopinavir/ritonavir) ▪ immunosuppressants for concomitant diseases (e.g. hydroxychloroquine for lupus) ▪ treatment with lopinavir/ritonavir, hydroxychloroquine or other drugs (e.g. with effect on the immune response) may be continued if recommended by local guidelines	
CAP-2	Remdesivir IV: 200 mg on day 1, followed by 100 mg/day on days 2-10 ± standard therapy	Placebo ± standard therapy
	Therapy adjustment: ND	
	Non-permitted pretreatment ▪ investigational products for the treatment of COVID-19 within 30 days prior to screening **permitted concomitant treatment** ▪ other treatments including lopinavir/ritonavir, interferon, corticosteroids	
GS5774-A	Remdesivir IV: 200 mg on day 1, followed by 100 mg/day on days 2-10[b] ± Standard therapy	standard therapy
	Interruption/discontinuation of treatment in case of severe or serious AEs, impairment of liver/kidneys	
	Non-permitted concomitant treatment ▪ concurrent or planned concurrent treatment with a drug with actual or potential direct antiviral activity against SARS-CoV-2 ▪ traditional herbal treatments ▪ agents with potential antiviral activity against COVID-19 including approved HIV protease inhibitors such as lopinavir/ritonavir, chloroquine, interferon	

a. No placebo was administered in the GS5774-A study.
b. The maintenance dose was administered for the duration of hospitalization (up to 10 days). If the patient was discharged, no more infusions were administered.

COVID-19: coronavirus disease 2019; IV: intravenous; ND: no data; RCT: randomized controlled trial; NSAID: nonsteroidal anti-inflammatory drug; SARS-CoV-2: Severe Acute Respiratory Syndrome Corona Virus 2

ACTT-1

The ACTT-1 study is a placebo-controlled, double-blind, multicentre randomized parallel-group study on remdesivir. The study included hospitalized adults with confirmed COVID-19 disease with a defined minimum severity of disease (radiologically detectable infiltration of the lung or $SpO_2 \leq 94\%$ at room air or need for oxygen supply or need for mechanical ventilation).

A total of 1062 patients were included and assigned to treatment with remdesivir (N = 541) or to the placebo group (N = 521) in a 1:1 ratio. Randomization was stratified by study centre and disease severity (severe vs. mild/moderate).

In the ACTT-1 study, remdesivir was administered for 10 days in compliance with the approval [15]. Patients in both arms additionally received standard COVID-19 therapy according to local guidelines.

Primary outcome of the study was time to recovery. Patient-relevant secondary outcomes were overall survival, the proportions of recovered patients and AEs. These outcomes were to be observed until day 29 after the start of the study. Treatment could be unblinded before day 29 and patients in the placebo group could then be treated with remdesivir. In this context, 26 patients (5% of the placebo group) switched to treatment with remdesivir during the course of the study.

CAP-2

The CAP-2 study is a placebo-controlled double-blind, randomized parallel-group study on remdesivir. It included hospitalized adults with confirmed COVID-19 disease and pneumonia. Moreover, patients had to have an oxygen saturation of ≤ 94% (SaO_2 or SpO_2) or an oxygenation index (ratio of PaO_2 and FiO_2) of < 300 mmHg at hospitalization.

A total of 237 patients were included and assigned to treatment with remdesivir (N = 158) or to the placebo group (N = 79) in a 2:1 ratio. Randomization was stratified by need for supplemental oxygen supply (no need or LFO vs. HFO/NIV/extracorporeal membrane oxygenation [ECMO]).

In the CAP-2 study, remdesivir was administered for 10 days in compliance with the approval [15]. Patients in both arms additionally received standard COVID-19 therapy.

The study was exclusively conducted in 10 centres in Wuhan, China, and was terminated before reaching the planned number of cases (n = 453) due to a decline in new cases.

Primary outcome of the study was time to clinical improvements. Patient-relevant secondary outcomes were overall survival, the proportions of recovered patients and AEs. These outcomes were to be observed until day 28.

GS5774-A

Study GS5774-A is a three-arm, open-label, multicentre, randomized, parallel-group study in which patients were treated with remdesivir for either 5 days or 10 days, or received standard COVID-19 therapy alone. The study included adults with COVID-19 disease with $SpO_2 > 94\%$ on room air and radiological evidence of lung infiltration. Mechanical ventilation of the patients was not allowed.

In the GS5774-A study, remdesivir was administered for 5 or up to 10 days in compliance with the approval [15]. As both periods are covered by the approval of remdesivir, the two study arms are described and analysed together below, where possible. Patients in all study arms additionally received standard COVID-19 therapy.

A total of 596 patients were included and randomly assigned to 5-day treatment with remdesivir (N = 199), 10-day treatment with remdesivir (N = 197) or to standard treatment (N = 200) without stratification in a 1:1:1 ratio.

Primary outcome of the GS5774-A study was the clinical status at day 11. Patient-relevant secondary outcomes were overall survival, the proportions of recovered patients and AEs. The secondary outcomes were to be observed until day 28 day (± 5 days) after the start of the study.

Implementation of the ACT

The G-BA specified treatment of physician's choice as ACT. Here, both drug (e.g. dexamethasone, anticoagulation/thrombosis prophylaxis, antibiotics) and non-drug therapies (e.g. oxygen supply, type of ventilation, balanced fluid therapy) must be considered. According to the S3 guideline on the inpatient treatment of patients with COVID-19 [16], which was current at the time of the benefit assessment, dexamethasone is the only drug that is both approved and recommended for the treatment of COVID-19. Thus, patients with severe ($SpO_2 < 90\%$, respiratory rate > 30/min) or critical (acute lung failure or acute respiratory distress syndrome [ARDS], sepsis, ventilation, vasopressor administration) COVID-19 disease should be treated with dexamethasone. Although currently not approved for the treatment of COVID-19, the use of tocilizumab in patients with progressively severe COVID-19 disease has also been possible since the last update of the S3 guideline (17 May 2021). However, tocilizumab should not be used in diseases with no or low oxygen demand and in case of ongoing invasive ventilation.

Administered standard therapies in the studies ACTT-1, CAP-2 and GS5774-A

In all 3 trials, patients in the comparator arm received standard COVID-19 therapy. This standard COVID-19 therapy was defined differently in the study protocols. In the ACTT-1 study, the use of drugs specifically aimed at treating COVID-19 disease was only allowed if this was in accordance with local guidelines. In the GS5774-A study, there were no limitations to the treatments in the comparator arm. In the CAP-2 study, the use of lopinavir/ritonavir, interferons and corticosteroids was allowed.

In general, the company provided only very limited information on the implementation of the ACT. Module 4 A, for example, contains no detailed information on the drugs administered or, e.g., on thrombosis prophylaxis. Likewise, there is no information on non-drug interventions such as balanced fluid therapy. The documents available for the included studies show that dexamethasone or other corticosteroids were administered in all 3 studies, albeit to varying extents. For example, 23% of patients in the total population of the ACTT-1 study, 17% in the total population of the GS5774-A study and 66% in the total population of the CAP-2 study were treated with corticosteroids (see Table 8). Information on the subpopulation of patients who corresponded to the approval population of remdesivir is not available for any of the studies, nor is information available on the dosage of the corticosteroids or the time point of use during the course of the disease. For tocilizumab, data are only available for study GS5774-A, in which 2% of the total population was treated with tocilizumab.

Table 8: Selected concomitant therapies– RCT, direct comparison: remdesivir + standard therapy vs. placebo[a] + standard therapy, total population

Study drug	Patients with concomitant therapy n (%)					
	ACTT-1		CAP-2		GS5774-A	
	remdesivir + standard therapy	placebo + standard therapy	remdesivir + standard therapy	placebo + standard therapy	remdesivir + standard therapy	standard therapy
	N = 532	N = 516	N = 158	N = 78	N[b] = 384	N = 200
Antibiotics	420 (79)	443 (86)	142 (90)	73 (94)	76 (20)[c]	62 (31)[c]
Corticosteroids	115 (22)	126 (24)	102 (65)	53 (68)	62 (16)	38 (19)
Hydroxychloroquine	184 (35)	189 (37)	ND	ND	38 (10)	89 (45)
Lopinavir/ritonavir	ND[d]	ND[d]	44 (28)	23 (29)	21 (5)	43 (22)
Interferons	ND[d]	ND[d]	46 (29)	30 (38)	ND	ND
Tocilizumab	ND[e]	ND[e]	ND	ND	2 (1)	10 (5)

a. No placebo was administered in the GS5774-A study.
b. Patients with a treatment duration of 5 days or 10 days; Institute's calculation
c. Azithromycin
d. Only the following data are available: other drugs used for treatment of COVID-19 in the remdesivir or placebo arm: 8 (1.5%) vs. 14 (2.7%); other antiviral drugs: 10 (1.9%) vs. 8 (1.6%).
e. Only general data on the administration of monoclonal antibodies against cytokines are available for the ACTT-1 study (remdesivir arm: 23 [4%] vs. placebo arm: 26 [5%]).

N: number of randomized patients; ND: no data; RCT: randomized controlled trial

Consequences for the benefit assessment

Based on the available information, it is not possible to assess the extent to which the currently applicable guideline recommendations have been implemented in the studies. Since all studies were conducted at the beginning of the Corona pandemic (study periods 02/2020 to 05/2020), this cannot be assumed, but does not basically challenge the suitability of the studies for the benefit assessment. The relevance for the individual subpopulations (LFO vs. HFO/NIV) must also be assumed to differ particularly with regard to the non-guideline-compliant use of corticosteroids. The recommendation of the S3 guideline [16] for the use of dexamethasone is based on the results of the RECOVERY study [17]. This study showed an effect of dexamethasone on mortality, depending on the severity of the COVID-19 disease - measured by the patients' ventilation status. Invasively ventilated patients benefited more (relative risk [RR]: 0.64; [95% CI]: [0.51; 0.81]) than non-invasively ventilated patients with oxygen demand (RR: 0.82; 95% CI: [0.72; 0.94]). However, a numerical disadvantage of dexamethasone on mortality was shown (RR: 1.19; 95% CI: [0.92; 1.55]) for COVID-19 patients who do not need oxygen support. According to these results, all patients covered by the approval of remdesivir would benefit from treatment with dexamethasone. However, within the patient population with oxygen demand, there are no analyses on the subgroups LFO vs. HFO/NIV. The extent to which the efficacy of dexamethasone depends on the severity of the COVID-19 disease thus remains unclear, but seems plausible. These considerations suggest that inadequate treatment with corticosteroids is less significant for patients in the LFO subpopulation and that the effects of inadequate treatment with corticosteroids on the effects of remdesivir are not of material importance, particularly in this subpopulation.

Summary

In general, it can be assumed that the treatment of hospitalized patients with COVID-19 has improved since the beginning of the pandemic. Therefore, the treatment of COVID-19 disease in the included studies conducted at the beginning of the pandemic can only be transferred to the current care situation to a limited extent. This uncertainty was taken into account in the certainty of conclusions of the results (see Section 2.4.2).

Relevant subpopulations and consideration by ventilation status

Only subpopulations of the three included studies ACTT-1, CAP-2 and GS5774-A were relevant for the benefit assessment:

- According to the approval of remdesivir, only patients who needed additional oxygen supply at the start of the study (LFO or HFO/NIV at the start of treatment) were included for the benefit assessment. Moreover, the 3 studies included for the benefit assessment also examined patients without oxygen requirements as well as patients with invasive ventilation at the start of the study. However, for the studies ACTT-1 and GS5774-A, analyses were available for the relevant subpopulation, which make up 59% and 16% of the total population, respectively. Separate analyses for the CAP-2 study are lacking. However, the population of those patients who needed additional oxygen supply (without

invasive ventilation) at the start of the study accounts for 98% of the total population, which can therefore be used for the benefit assessment. This concurs with the company's approach.

- For the outcome "mortality", the meta-analysis of the included studies also shows a clear effect modification for the characteristic "ventilation status (LFO vs. HFO/NIV)" (see Table 13 and Figure 1 in Appendix C of the full dossier assessment), which makes a separate consideration of the patient groups necessary. This approach is substantively supported by the considerations described above on the different relevance of dexamethasone administration in the two subpopulations. The company presented such separate analyses for the studies ACTT-1 and GS5774-A in the form of subgroup analyses. Such subgroup analyses are not available for CAP-2, but the subpopulation of patients with LFO accounts for 83% of the total population, which is why the total population is used for the LFO subpopulation. The related consequences for the certainty of results of the analyses of the CAP-2 study are described in Section 2.4.2.

The approval for remdesivir also includes adolescents aged 12 years and older with a body weight of at least 40 kg [15]. However, the relevant subpopulations included no adolescents. The available data therefore only allow a conclusion on adults with COVID-19 disease.

Patient characteristics

Table 9 shows the characteristics of the patients for the CAP-2 study and the relevant subpopulation of the GS5774-A study. For the ACTT-1 study, data are only available for the total population (these are shown in Table 25 in Appendix D of the full dossier assessment). Data separated by ventilation status are not available for any of the 3 studies.

Table 9: Characteristics of the study populations – RCT, direct comparison: remdesivir + standard therapy vs. placebo[a] + standard therapy, relevant subpopulation (multipage table)

Study characteristic category	ACTT-1[b]		CAP-2[c]		GS5774-A		
	remdesivir + standard therapy	placebo + standard therapy	remdesivir + standard therapy	placebo + standard therapy	remdesivir 5d + standard therapy	remdesivir 10d + standard therapy	standard therapy
	N = 327	N = 301	N = 158	N = 78	N = 31	N = 24	N = 38
Age [years], mean (SD)	ND	ND	66 [57; 73][d]	64 [53; 70][d]	56 (13)	52 (16)	60 (14)
Sex [F/M], %	ND	ND	44/56	35/65	52/48	29/71	34/66
Region, n (%)							
Europe	ND	ND	0 (0)	0 (0)	24 (77)	11 (46)	25 (66)
Rest of the world	ND	ND	158 (100)	78 (100)	7 (23)	13 (54)	13 (34)
Clinical status, n (%)							
Hospitalized, LFO	ND	ND	129 (82)[e]	65 (83)[e]	29 (94)	23 (96)	36 (95)
Hospitalized, HFO/NIV	ND	ND	28 (18)[e]	9 (12)[e]	2 (6)	1 (4)	2 (5)
Symptom duration before start of treatment [days], median [min; max]	ND	ND	11 [9; 12][d]	10 [9; 12][d]	9 [3; 37]	10 [1; 40]	11 [5; 26]
Number of high-risk comorbidities[f]							
0	ND	ND	ND	ND	10 (32)	6 (25)	8 (21)
1	ND	ND	ND	ND	8 (26)	6 (25)	10 (26)
≥ 2	ND	ND	ND	ND	13 (42)	12 (50)	20 (532)
Treatment discontinuation, n (%)	ND	ND	ND[g]	ND[g]	4 (13)	11 (46)	ND
Study discontinuation, n (%)	ND	ND	ND	ND	2 (6)	2 (8)	8 (21)

Table 9: Characteristics of the study populations – RCT, direct comparison: remdesivir + standard therapy vs. placebo[a] + standard therapy, relevant subpopulation (multipage table)

Study characteristic category	ACTT-1[b]		CAP-2[c]		GS5774-A		
	remdesivir + standard therapy	placebo + standard therapy	remdesivir + standard therapy	placebo + standard therapy	remdesivir 5d + standard therapy	remdesivir 10d + standard therapy	standard therapy
	N = 327	N = 301	N = 158	N = 78	N = 31	N = 24	N = 38

a. No placebo was administered in the GS5774-A study.
b. For data on the total population, see Table 21 in Appendix D of the full dossier assessment.
c. Data for the total population, which is used for the benefit assessment as it corresponds to 98% of the approval population.
d. Median [Q1; Q3].
e. One patient in the remdesivir arm and 4 patients in the comparator arm had a clinical status not covered by the approval of remdesivir (LFO, HFO or NIV).
f. The high-risk comorbidities were selected post hoc on the basis of the assessment and information provided by the RKI.
g. In total, 36 patients discontinued treatment in both study arms.

5d: every 5 days; 10d: every 10 days; F: female; HFO: high-flow oxygen therapy; LFO: low-flow oxygen therapy; M: male; max: maximum; min: minimum; n: number of patients in the category; N: number of randomized patients; ND: no data; NIV: non-invasive ventilation; Q1: first quartile; Q3: third quartile; RCT: randomized controlled trial; RKI: Robert Koch Institute; SD: standard deviation

The patient characteristics were essentially balanced, both between the individual study arms and between the relevant subpopulations of the studies. Data for the relevant subpopulation of the ACTT-1 study were lacking, but the patient characteristics of the total population (except for clinical status) were comparable to those of the studies GS5774-A and CAP-2 (see Table 25 in Appendix D of the full dossier assessment). Thus, all studies included predominantly male patients with a mean age between 52 and 66 years. Differences are found in geographical regions where the studies were conducted. The GS5774-A study was mainly conducted in Europe, 80% of the ACTT-1 study was conducted in North America and the CAP-2 study was conducted exclusively in China (Wuhan). In GS5774-A and CAP-2, > 80% of patients were dependent on LFO at baseline. In the ACTT-1 study, this applied to 69% (based on the relevant subpopulation), 31% received HFO/NIV.

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 + standard therapy vs. placeboa + standard therapy

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			
ACTT-1	Yes	Yes	Yes	Yes	Yes	No	Low
CAP-2	Yes	Yes	Yes	Yes	Yes	No	Low
GS5774-A	Yes	Yes	No	No	Yes	No	Low

a. No placebo was administered in the GS5774-A study.
RCT: randomized controlled trial

The risk of bias across outcomes was rated as low for the included studies. This concurs with the company's assessment.

Transferability to the German health care context

The company considers the results of the studies GS5774-A, ACTT-1 and CAP-2 to be transferable to the German health care context and justifies this with the comparability of the study populations and the Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-CoV-2)-infected German population. The relevant therapeutic indication was patients with severe or critical courses of COVID-19 disease. According to the Robert Koch Institute (RKI), risk factors for severe courses are an age of 50 to 60 years and older, male sex, as well as particular

pre-existing conditions, such as diseases of the cardiovascular system, chronic lung, kidney and liver diseases, diabetes mellitus, cancer or a weakened immune system. In the included studies GS5774-A, ACTT-1 and CAP-2, the median age was over 50 years, and in the ACTT-1 and CAP-2 studies even almost 60 years. Moreover, all studies included more men than women. In addition, patients in the studies had high-risk comorbidities. In summary, the company therefore assumes a transferability of the data from the studies GS5774-A, ACTT-1 and CAP-2 to the German health care context.

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

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
  - Recovery on day 14/15 or at the end of the study
- Health-related quality of life
- Side effects
  - SAEs
  - Discontinuation due to AEs
  - Further specific AEs, if any

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

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

Table 11: Matrix of the outcomes – RCT, direct comparison: remdesivir + standard therapy vs. placebo[a] + standard therapy

Study	Outcomes					
	All-cause mortality	Recovery[b]	Health-related quality of life	SAEs	Discontinuation due to AEs	Specific AEs
ACTT-1	Yes	Yes	No[c]	Yes[d]	Yes[d]	No[e]
CAP-2	Yes	Yes	No[c]	Yes[d]	Yes[d]	No[e]
GS5774-A	Yes	Yes	No[c]	Yes[f]	Yes[d]	No[e]

a. No placebo was administered in the GS5774-A study.
b. Recorded using ordinal scales on clinical status; for the exact operationalization see Section 2.4.3.
c. Outcome not recorded.
d. High proportion of disease-related events (e.g. respiratory failure, see Section 2.4.1).
e. A selection of specific AEs was not possible due to lack of complete data on the relevant subpopulations (see Section 2.4.1).
f. In Module 4 A, the company presented overall rates for SAEs without disease-related events only for study GS5774-A, which, however, are not used without corresponding data from the other studies.

AE: adverse event; RCT: randomized controlled trial; SAE: serious adverse event

SAEs, discontinuation due to AEs and specific AEs

In the recording of SAEs and discontinuations due to AEs, events that can be assigned to the symptoms of the disease (e.g. respiratory failure) were obviously recorded to a large extent in addition to treatment-related AEs. The overall rates of SAEs and discontinuations due to SAEs without disease-related events had to be analysed for an adequate assessment of the side effects. The company presented overall rates for SAEs without disease-related events only for study GS5774-A; corresponding analyses for the outcome "discontinuation due to AEs" or for the other studies are not available. For the ACTT-1 study, the access the company has to the study data is unclear in this context. Although, in Module 4 A, the company states having prepared the study report for the ACTT-1 study, it does not show any analyses on the overall rates of SAEs without disease-related events for this study. Overall, the available overall rates on SAEs and discontinuations due to AEs are not usable in the present situation and are therefore not used for the present benefit assessment.

Due to a lack of complete data, a selection of specific AEs from the available data was also impossible: for the ACTT-1 study, both information on common SAEs and discontinuations due to AEs for the relevant subpopulation according to the approval of remdesivir and analyses of common AEs, SAEs and discontinuations due to AEs for the relevant subpopulations separated by ventilation status are missing.

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 + standard therapy vs. placebo[a] + standard therapy

Study	Study level	Outcomes					
		All-cause mortality	Recovery[b]	Health-related quality of life	SAEs	Discontinuation due to AEs	Specific AEs
ACTT-1	L	L	L	–[c]	–[d]	–[d]	–[e]
CAP-2	L	L	L	–[c]	–[d]	–[d]	–[e]
GS5774-A	L	L	L	–[c]	–[f]	–[d]	–[e]

a. No placebo was administered in the GS5774-A study.
b. Recorded using ordinal scales on clinical status; for the exact operationalization see Section 2.4.3.
c. Outcome not recorded.
d. High proportion of disease-related events (e.g. respiratory failure, see Section 2.4.1).
e. A selection of specific AEs was not possible due to lack of complete data on the relevant subpopulations (see Section 2.4.1).
f. In Module 4 A, the company presented overall rates for SAEs without disease-related events only for study GS5774-A, which, however, are not used without corresponding data from the other studies.

AE: adverse event; L: low; RCT: randomized controlled trial; SAE: serious adverse event

The risk of bias for the results of all outcomes included in the benefit assessment was rated as low. This assessment concurs with that of the company.

Certainty of results for qualitative summary

Although the risk of bias for the results of all outcomes included in the benefit assessment is rated as low, the included studies differ in their certainty of results. The certainty of results in the studies ACTT-1 and GS5774-A was rated as high. There are no separate analyses by ventilation status for the CAP-2 study. However, since 83% of all patients received LFO at the start of the study, the entire study population will be included for the assessment of the LFO subpopulation. Due to the fact that 18% of the patients were thus incorrectly included in the subpopulation (predominantly patients with HFO/NIV), the certainty of results for the analyses of the LFO subpopulation was rated as moderate in this study.

Overall assessment on the certainty of conclusions

As described in Section 2.3.2, it must altogether be assumed that the results can only be transferred to the current health care situation of hospitalized COVID-19 patients to a limited

extent. This resulted in a limited certainty of conclusions for all outcomes and all studies. Hence, at most indications, e.g. of an added benefit, can be derived on the basis of the available data.

2.4.3 Results

Table 13 summarizes the results on the comparison of remdesivir + standard therapy with standard therapy in COVID-19 patients with pneumonia who require supplemental oxygen but who are not invasively ventilated. The results are presented separately by ventilation status (LFO vs. HFO/NIV) (see Section 2.3.2). Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier. The two remdesivir arms (5-day and 10-day treatment) of study GS5774-A were combined for the analyses (see also Section 2.3.2). The forest plots of the meta-analyses calculated by the Institute can be found in Appendix C of the full dossier assessment. Tables on common AEs, common SAEs and discontinuations due to AEs are presented in Appendix E of the full dossier assessment.

Table 13: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: remdesivir + standard therapy vs. placebo[a] + standard therapy (multipage table)

Outcome category outcome subpopulation Study	Remdesivir + standard therapy N	 patients with event n (%)	Placebo[a] + standard therapy N	 patients with event n (%)	Remdesivir + standard therapy vs. placebo[a] + standard therapy RR [95% CI]; p-value[b]
Mortality					
All-cause mortality (end of study)					
LFO					
Studies with high certainty of results					
ACTT-1	232	9 (3.9)	203	25 (12.3)	0.32 [0.15; 0.66]; 0.001
GS5774-A[c]	52	0 (0)	36	4 (11.1)	0.08 [< 0.01; 1.40]; 0.016
Total[d]					0.28 [0.14; 0.56]; < 0.001
Study with moderate certainty of results					
CAP-2	158	22 (13.9)	78	10 (12.8)	1.09 [0.54; 2.18]; 0.870
Total (all 3 studies)				Significant heterogeneity:	p = 0.021
HFO/NIV					
Studies with high certainty of results					
ACTT-1	95	19 (20.0)	98	20 (20.4)	0.98 [0.56; 1.72]; 0.997
GS5774-A[c]	3	0 (0)	2	0 (0)	–
Total					0.98 [0.56; 1.72]; 0.997
LFO vs. HFO/NIV				Interaction test	p = 0.006
Morbidity					
Recovery on day 14/15					
LFO					
Studies with high certainty of results					
ACTT-1	232	166 (71,6e)	203	124 (61.1[e])	1.17 [1.02; 1.34]; 0.021
GS5774-A[c]	52	46 (88.5[e])	36	22 (61.1)	1.45 [1.10; 1.91]; 0.003
Total[d]					1.22 [1.08; 1.38]; 0.002
Study with moderate certainty of results					
CAP-2	153	60 (39.2)	78	28 (35.9)	1.09 [0.77; 1.56]; 0.652
Total					Qualitative summary

Table 13: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: remdesivir + standard therapy vs. placebo[a] + standard therapy (multipage table)

Outcome category outcome subpopulation Study	Remdesivir + standard therapy N	 patients with event n (%)	Placebo[a] + standard therapy N	 patients with event n (%)	Remdesivir + standard therapy vs. placebo[a] + standard therapy RR [95% CI]; p-value[b]
HFO/NIV					
Studies with high certainty of results					
ACTT-1	95	40 (42.1[e])	98	33 (33.7[e])	1.25 [0.87; 1.80]; 0.246
GS5774-A[c]	3	0 (0)	2	1 (50.0)	0.25 [0.01; 4.23]; 0.375
Total[d]					1.20 [0.84; 1.72]; 0.319
Recovery at the end of the study					
LFO					
Studies with high certainty of results					
ACTT-1	232	206 (88.8[e])	203	156 (76.8[e])	1.16 [1.06; 1.26]; < 0.001
GS5774-A[c]	52	51 (98.1[c])	36	27 (75.0)	1.31 [1.08; 1.59]; < 0.001
Total[d]					1.18 [1.09; 1.28]; < 0.001
Study with moderate certainty of results					
CAP-2	150	106 (70.7)	77	49 (63.6)	1.11 [0.91; 1.35]; 0.322
Total					Qualitative summary
HFO/NIV					
Studies with high certainty of results					
ACTT-1	95	57 (60.0[e])	98	61 (62.2[e])	0.96 [0.77; 1.21]; 0.808
GS5774-A[c]	3	1 (33.3[c])	2	2 (100)	0.45 [0.12; 1.76]; 0.250
Total[d]					0.94 [0.75; 1.17]; 0.588
Health-related quality of life	Outcomes from this category were not recorded				
Side effects					
AEs (supplementary information)			No usable data[f]		
SAEs			No usable data[f]		
Discontinuation due to AEs			No usable data[f]		

a. No placebo was administered in the GS5774-A study.
b. Institute's calculation, unconditional exact test (CSZ method according to [18]).
c. Joint consideration of the arms for 5-day administration and 10-day administration of remdesivir.
d: Calculated from meta-analysis with fixed effect (Mantel-Haenszel method).
e. Institute's calculation.
f. High proportion of disease-related events (e.g. respiratory failure, see Section 2.4.1).

AE: adverse event; CI: confidence interval; CSZ: convexity, symmetry, z score; HFO: high-flow oxygen therapy; LFO: low-flow oxygen therapy; n: number of patients with (at least one) event; N: number of analysed patients; ND: no data; NIV: non-invasive ventilation; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event

Qualitative summary of the results and certainty of conclusions

The analysis was based on quantitative meta-analytical summaries of the study results. A qualitative summary is performed if a quantitative summary is not appropriate for an outcome due to the small number of studies or the presence of heterogeneity.

In doing so, it is taken into account that results with different qualitative certainty of results are available for the outcomes of the included studies. The procedure is as follows.

The assessment of the certainty of conclusions and the extent was initially based on the results with high certainty of results. The certainty of conclusions is not called into question by the results with moderate certainty of results. The certainty of conclusions can be increased through a joint consideration of the results with high and moderate certainty of results. However, based on the available data, at most hints, e.g. of an added benefit, can be determined for all outcomes due to the limitations in the implementation of the ACT described above (see Section 2.3.2 and Section 2.4.2).

Mortality

All-cause mortality

LFO

For the studies with high certainty of results, the meta-analysis shows a statistically significant difference in favour of remdesivir + standard therapy for the outcome “all-cause mortality” for the LFO subpopulation. The addition of CAP-2, the study with moderate certainty of results, yields a heterogeneous data situation. Overall, the qualitative summary resulted in an indication of added benefit from remdesivir + standard therapy in comparison with standard therapy. In the present data situation, the statistically insignificant effect for all-cause mortality in the CAP-2 study is taken into account in the determination of the extent (see Table 13).

HFO/NIV

For the studies with high certainty of results, the meta-analysis shows no statistically significant difference between the treatment groups for the outcome “all-cause mortality” in the HFO/NIV subpopulation. This resulted in no hint of an added benefit of remdesivir + standard therapy in comparison with standard therapy. An added benefit is therefore not proven for the HFO/NIV subpopulation.

For both subpopulations (LFO and HFO/NIV), this deviates from the assessment of the company, which overall derived proof of an added benefit for remdesivir for the entire approval population.

Morbidity

Recovery

Operationalization

The outcome "recovery" was recorded in all 3 relevant studies via different, but largely congruent ordinal scales on the clinical status of the patients (see Table 33 in Appendix F of the full dossier assessment). Based on this, the outcome "recovery" (referred to as "Genesung" by the company in the German version of this benefit assessment) is operationalized in the studies as follows:

- In the ACTT-1 study, recovery was defined as reaching category 1 to 3 on an 8-point ordinal scale (1: not hospitalized; 2: not hospitalized, activity limitation, oxygen demand at home or both; 3: hospitalized, no need for supplemental oxygen therapy and no need for ongoing medical care).
- In the GS5774-A study, recovery was defined as reaching category 6 or 7 on a 7-point ordinal scale (7: not hospitalized; 6: hospitalized, no need for supplemental oxygen therapy and no need for ongoing medical care).
- For the CAP-2 study, recovery was defined as reaching category 1 or 2 on a 6-point ordinal scale (1: discharge or reaching the discharge criteria; 2: hospitalized, no need for oxygen therapy).

The operationalization of recovery is thus congruent for the studies ACTT-1 and GS5774-A. There is a difference to the CAP-2 study, in which the ordinal scale made no distinction for hospitalized patients without need for oxygen therapy as to whether they have an additional need for ongoing medical care. Accordingly, for the CAP-2 study, all patients were defined as recovered if they no longer had an oxygen requirement. In the studies ACTT-1 and GS5774-A, in contrast, patients without oxygen requirements were only defined as recovered if they also had no need for ongoing medical treatment.

However, since the majority of recovered patients in the studies were no longer hospitalized at the two dates of analyses, the differences in the operationalizations remained without consequences and the results of the three included studies were considered together.

The proportions of recovered patients both at day 14 (CAP-2 and GS5774-A) and day 15 (ACTT-1) and at the end of the study (day 28 [CAP-2 and GS5774-A] and day 29 [ACTT-1]) were considered for the benefit assessment. The corresponding event time analyses from study GS5774-A show consistent results.

LFO

Day 14/15

For the studies with high certainty of results, the meta-analysis shows a statistically significant difference in favour of remdesivir + standard therapy for the outcome "recovery on day 14/15"

for the LFO subpopulation. The addition of the CAP-2 study with moderate certainty of results yields a statistically insignificant result with homogeneous data. Therefore, a qualitative summary is also performed in the present data constellation. Due to the discrepancy in terms of statistical significance between the 2 analyses, the result of the studies with high certainty of results is used for the derivation. This resulted in an indication of added benefit of remdesivir + standard therapy in comparison with standard therapy for the outcome "recovery on day 14/15".

End of study

For the studies with high certainty of results, the meta-analysis shows a statistically significant difference in favour of remdesivir + standard therapy for the outcome "recovery at the end of the study" for the LFO subpopulation. The addition of the CAP-2 study also results in a statistically significant difference between the treatment groups in favour of remdesivir + standard therapy with homogeneous data, but with a wider CI (RR: 1.17; 95% CI: [1.01; 1.36]). Therefore, a qualitative summary is also performed in the present data constellation. Overall, this resulted in an indication of an added benefit of remdesivir + standard therapy in comparison with standard therapy.

HFO/NIV

Day 14/15 and end of study

For the studies with high certainty of results, the meta-analysis shows no statistically significant difference between the treatment groups for the outcome "recovery" in the HFO/NIV subpopulation, neither on day 14/15 nor at the end of the study. This resulted in no hint of an added benefit of remdesivir + standard therapy in comparison with standard therapy. An added benefit is therefore not proven for the HFO/NIV subpopulation.

For both subpopulations, this deviates from the assessment of the company, which summarized the present operationalization (referred to by the company as recovery) together with other operationalizations under the outcome "clinical status" and overall derived proof of an added benefit for remdesivir + standard therapy compared to standard therapy for the entire approval population.

Health-related quality of life

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

Side effects

SAEs and discontinuation due to AEs

In the recording of "SAEs" and "discontinuations due to AEs", disease-related events were also recorded to a large extent in the studies. Accordingly, the results of individual frequent AEs (e.g. respiratory failure) show advantages for remdesivir similar to the results on morbidity. As a result, the overall rates on "SAEs" and "discontinuations due to AEs" are not usable for the assessment of the side effects of remdesivir. However, the results on frequent SAEs and

discontinuations due to AEs (see Appendix E of the full dossier assessment) suggest no negative effects of remdesivir to a degree that could call the added benefit of remdesivir into question. For the outcomes "SAEs" and "discontinuation due to AEs", this resulted in no hint of greater or lesser harm from remdesivir + standard therapy in comparison with standard therapy; greater or lesser harm is therefore not proven.

This deviates from the assessment of the company, which overall derived proof of considerable added benefit of remdesivir + standard therapy in comparison with standard therapy for the outcome category "side effects".

2.4.4 Subgroups and other effect modifiers

No separate subgroup analyses are available for the relevant subpopulations (LFO and HFO/NIV, see Section 2.3.2). However, particularly analyses on the characteristic "age" are very important in the present therapeutic indication, because the mortality risk of COVID-19 patients is known to differ considerably between the different age groups. As the average age of the patients was over 50 years (median: 52 to 68 years) in the included studies, it is unclear what effects remdesivir has in younger and especially in adolescent COVID-19 patients with a significantly lower mortality risk.

2.5 Probability and extent of added benefit

Probability and extent of the added benefit per subpopulation at outcome level are derived below, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *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 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 for the following outcome whether it is serious/severe or non-serious/non-severe. The classification for this outcome is justified.

Recovery on day 14/15 or at the end of the study

Events that require inpatient treatment are considered severe or serious. Since the outcome "recovery" is mainly represented by discharge from inpatient treatment, this outcome is assigned to the outcome category "serious/severe symptoms/late complications".

Table 14: Extent of added benefit at outcome level: remdesivir + standard therapy vs. standard therapy (multipage table)

Outcome category **outcome** **subpopulation**	**Remdesivir vs. standard therapy** **proportion of events (%)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Mortality		
All-cause mortality		
Ventilation status		
LFO	0–13.9% vs. 11.1–12.8%[c] RR: 0.28 [0.14; 0.56]; p < 0.001 probability: "indication"	Added benefit, extent: "considerable"[d]
HFO/NIV	0–20% vs. 0–20.4%[c] RR: 0.98 [0.56; 1.72]; p = 0.997	Lesser benefit/added benefit not proven
Morbidity		
Recovery on day 14/15		
Ventilation status		
LFO	39.2–88.5 % vs. 35.9–61.1 %[c] RR: 1.22 [1.08; 1.38]; RR: 0.82 [0.73; 0.93][e]; p = 0.002 probability: "indication"	Outcome category: serious/severe symptoms/late complications $0.90 \leq CI_u < 1.00$ added benefit, extent: "minor"
HFO/NIV	0–42 % vs. 33.7–50 %[c] RR: 1.20 [0.84; 1.72]; p = 0.319	Lesser benefit/added benefit not proven
Recovery at the end of the study		
Ventilation status		
LFO	70.7–98.1 % vs. 63.6–76.8 %[c] RR: 1.18 [1.09; 1.28][f]; RR: 0.85 [0.78; 0.92][e]; p < 0.001 probability: "indication"	Outcome category: serious/severe symptoms/late complications $0.90 \leq CI_u < 1.00$ added benefit, extent: "minor"
HFO/NIV	33.3–60 % vs. 62.2–100 %[c] RR: 0.94 [0.75; 1.17]; p = 0.588	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	Data not evaluable[c]	Lesser benefit/added benefit not proven
Discontinuation due to AEs		

Table 14: Extent of added benefit at outcome level: remdesivir + standard therapy vs. standard therapy (multipage table)

Outcome category **outcome** **subpopulation**	**Remdesivir vs. standard therapy** **proportion of events (%)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
a. Probability provided if statistically significant differences are present. 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. Minimum and maximum proportions of events. d. Considering only the studies with high certainty of results, there is a major effect. However, in the overall consideration, an added benefit with the extent "considerable" is derived for the outcome "all-cause mortality" in the present data situation since the CAP-2 study revealed no statistically significant effect. e. Institute's calculation; reversed direction of effect to enable use of limits to derive the extent of the added benefit. f. Effect estimation based on studies with high certainty of results. CI: confidence interval; CI_u: upper limit of the confidence interval; HFO: high-flow oxygen therapy; LFO: low-flow oxygen therapy; NIV: non-invasive ventilation; RR: relative risk; SAE: serious adverse event; AE: adverse event		

2.5.2 Overall conclusion on added benefit

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

Table 15: Positive and negative effects from the assessment of remdesivir + standard therapy in comparison with standard therapy

Positive effects	**Negative effects**
LFO subpopulation	
Mortality ▪ indication of an added benefit – extent "considerable" (all-cause mortality):	–
Morbidity ▪ indication of added benefit - extent: low (serious/severe symptoms/late complications: recovery at day 14/15 and recovery at the end of the study)	–
No data were available for outcomes on health-related quality of life. Data on side effects are not interpretable in quantitative terms.	
HFO/NIV subpopulation	
–	–
No data were available for outcomes on health-related quality of life. Data on side effects are not interpretable in quantitative terms	
HFO: high-flow oxygen therapy; LFO: low-flow oxygen therapy; NIV: non-invasive ventilation	

LFO subpopulation

The overall consideration only showed positive effects of remdesivir in comparison with the standard therapy for the subpopulation LFO, both with regard to all-cause mortality and with

regard to the outcome "recovery". There were no usable data for the side effects. However, the available information does not suggest any negative effects to an extent that could call an added benefit into question.

In summary, there is an indication of considerable added benefit of remdesivir versus the ACT according to physician's choice for adults with COVID-19 disease with pneumonia requiring LFO therapy at the start of treatment.

HFO/NIV subpopulation

The overall consideration of the results revealed neither positive nor negative effects of remdesivir in comparison with standard therapy in the HFO/NIV subpopulation.

In summary, there is no hint of an added benefit of remdesivir versus the ACT according to physician's choice for adults with COVID-19 disease with pneumonia requiring HFO/NIV at the start of treatment; an added benefit is therefore not proven.

Note on the transferability of the added benefit to adolescents

The subpopulations relevant for the benefit assessment included no adolescents, and the company presented no data on the transfer of the results to adolescents. As there are clearly different mortality risks for COVID-19 depending on age, the results of the benefit assessment observed for adults cannot be transferred to adolescents. There are thus no usable data for adolescents (aged 12 years and older with body weights of at least 40 kg) with pneumonia requiring supplemental oxygen. This resulted in no hint of an added benefit of remdesivir in comparison with the ACT according to physician's choice for these patients; an added benefit is therefore not proven.

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
COVID-19 in adults and adolescents (aged 12 years and older with a body weight of at least 40 kg) with pneumonia requiring supplemental oxygen		
Patients with LFO at start of treatment	Treatment of physician's choice[b]	Adults: ▪ indication of considerable added benefit[b]
		Adolescents: ▪ added benefit not proven
Patients with HFO/NIV at the start of treatment		Added benefit not proven
a. Presentation of the respective ACT specified by the G-BA. b. In the studies ACTT-1, CAP-2 and GS5774-A included in the benefit assessment, the median age of the patients ranged between 52 and 68 years. ACT: appropriate comparator therapy; COVID-19: coronavirus disease 2019; G-BA: Federal Joint Committee; HFO: high-flow oxygen therapy; LFO: low-flow oxygen therapy; NIV: non-invasive ventilation		

The assessment described above deviates from that of the company, which derived proof of considerable added benefit for the total approval population.

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

References for English extract

Please see full dossier assessment for full reference list.

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

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