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Nirmatrelvir/ritonavir (COVID-19) –

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

Extract

[1] Translation of Sections I 1 to I 5 of the dossier assessment *Nirmatrelvir/Ritonavir (COVID-19) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 29 September 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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IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

Patient and family involvement

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

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Part I: Benefit assessment

I Table of contents

Page

I List of tables I.3
I List of abbreviations I.4
I 1 Executive summary of the benefit assessment I.1
I 2 Research question I.8
I 3 Information retrieval and study pool I.9
I 3.1 Studies included I.9
I 3.2 Study characteristics I.9
I 4 Results on added benefit I.22
I 4.1 Outcomes included I.22
I 4.2 Risk of bias I.26
I 4.3 Results I.27
I 4.4 Subgroups and other effect modifiers I.30
I 5 Probability and extent of added benefit I.32
I 5.1 Assessment of added benefit at outcome level I.32
I 5.2 Overall conclusion on added benefit I.34
References for English extract I.36

I List of tables[2]

Page

Table 2: Research question of the benefit assessment of nirmatrelvir/ritonavir I.1
Table 3: Nirmatrelvir/ritonavir – probability and extent of added benefit.....I.7
Table 4: Research question of the benefit assessment of nirmatrelvir/ritonavir I.8
Table 5: Study pool – RCT, direct comparison: nirmatrelvir/ritonavir vs. placebo.....I.9
Table 6: Characteristics of the study included – RCT, direct comparison: nirmatrelvir/ritonavir vs. placebo I.10
Table 7: Characteristics of the intervention – RCT, direct comparison: nirmatrelvir/ritonavir vs. placebo I.12
Table 8: Information on concomitant therapies (≥ 2% of the patients in ≥ 1 treatment arm) – RCT, direct comparison: nirmatrelvir/ritonavir vs. placebo (total population).....I.15
Table 9: Characteristics of the study population as well as study/therapy discontinuation – RCT, direct comparison: nirmatrelvir/ritonavir vs. placebo.....I.17
Table 10: Risk of bias across outcomes (study level) – RCT, direct comparison: nirmatrelvir/ritonavir vs. placebo I.20
Table 11: Matrix of outcomes – RCT, direct comparison: nirmatrelvir/ritonavir vs. placebo.....I.23
Table 12: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: nirmatrelvir/ritonavir vs. placebo.....I.26
Table 13: Results (outcome categories, dichotomous) – RCT, direct comparison: nirmatrelvir/ritonavir vs. placebo I.28
Table 14: Results (outcome categories, time to event) – RCT, direct comparison: nirmatrelvir/ritonavir vs. placebo I.29
Table 15: Extent of added benefit at outcome level: nirmatrelvir/ritonavir vs. placebo.....I.33
Table 16: Positive and negative effects from the assessment of nirmatrelvir/ritonavir compared with treatment of physician's choice I.34
Table 17: Nirmatrelvir/ritonavir – probability and extent of added benefit.....I.35

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

I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
BMI	body mass index
COVID-19	coronavirus disease 2019
COVRIIN	Fachgruppe Intensivmedizin, Infektiologie und Notfallmedizin (Expert Group on Intensive Care, Infectious Diseases and Emergency Medicine)
CTCAE	Common Terminology Criteria for Adverse Events
CYP3A4	cytochrome P450 3A4
DAIDS	Division of Acquired Immunodeficiency Syndrome
DEGAM	Deutsche Gesellschaft für Allgemeinmedizin und Familienmedizin (German College of General Practitioners and Family Physicians)
EMA	European Medicines Agency
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
GIQ	Global Impression Questions
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
PCR	polymerase chain reaction
RCT	randomized controlled trial
RKI	Robert Koch Institute
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SGB	Sozialgesetzbuch (Social Code Book)
STIKO	Ständige Impfkommission (Standing Committee on Vaccination)
VAS	visual analogue scale
WPAI	Work Productivity and Activity Impairment

I 1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug nirmatrelvir/ritonavir. 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 29 June 2022.

Research question

The aim of this report is to assess the added benefit of nirmatrelvir/ritonavir 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 who are at increased risk for progressing to severe COVID-19.

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

Table 2: Research question of the benefit assessment of nirmatrelvir/ritonavir

Therapeutic indication	**ACT[a]**
Adults with COVID-19[b] who do not require supplemental oxygen and who are at increased risk for progressing to severe COVID-19[c]	Treatment of physician's choice[d]
a. Presented is the respective 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 on efficacy. d. Specific therapeutic measures are usually not required for mildly to moderately symptomatic COVID-19. 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. Recently, the drugs casirivimab/imdevimab, remdesivir, 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 for severe COVID-19. The drug molnupiravir has not yet been approved in the EU, but can be used for the treatment of COVID-19 in adults who do not require supplemental oxygen and who are at increased risk for progressing to severe COVID-19, based on the General Administrative Act on the purchase and use of monoclonal antibodies and on the purchase and dispensing of antiviral oral drugs against COVID-19 issued by the Federal Ministry of Health on 25 March 2022. The clinical significance of these therapy options cannot be assessed at the present time. If the disease progresses and the patient is hospitalized, further drug therapies (e.g. dexamethasone, remdesivir, anticoagulation/thrombosis prophylaxis, antibiotics) as well as non-drug therapies (e.g. oxygen support, type of ventilation, balanced fluid therapy) must be considered. COVID-19: coronavirus disease 2019; G-BA: Federal Joint Committee; PCR: polymerase chain reaction; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; VOC: variants of concern	

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

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

Study pool and study design

Study C4671005 (hereafter referred to as the EPIC-HR study) is used for the benefit assessment. The EPIC-HR study is a placebo-controlled, double-blind, randomized phase 2/3 study on nirmatrelvir/ritonavir. The study included non-hospitalized, symptomatic patients in the early phase of COVID-19 who had ≥ 1 risk factor for severe COVID-19. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection had to be determined by polymerase chain reaction (PCR) ≤ 5 days prior to randomization.

According to the inclusion criteria, patients were not allowed to be receiving supplemental oxygen at the time of study inclusion (oxygen saturation of ≥ 92% on room air), and there was no anticipated need for hospitalization within 48 hours after randomization. Patients who were hospitalized at the time of study inclusion were excluded from the study. Accordingly, only outpatient treatment with nirmatrelvir/ritonavir was investigated in the study. Patients who had received any dose of a COVID-19 vaccine were also excluded from the study. Thus, only unvaccinated patients were considered in the EPIC-HR study.

A total of 2246 patients were allocated in a 1:1 ratio to treatment with nirmatrelvir/ritonavir (N = 1120) or to the placebo group (N = 1126).

Treatment with nirmatrelvir/ritonavir was in compliance with the approval.

Primary outcome of the study was the composite outcome of COVID-19-related hospitalization or death from any cause until day 28. Patient-relevant secondary outcomes were all-cause mortality, outcomes on morbidity and adverse events (AEs). According to the planning of the study, outcome-specific follow-up was up to 24 weeks.

Relevant subpopulation

The EPIC-HR study included patients with ≥ 1 risk factor for severe COVID-19. However, the risk factors defined in the inclusion criteria did not fully correspond to the risk factors defined by the Robert Koch Institute (RKI). Consequently, an RKI-compliant subpopulation of the EPIC-HR study is used for the benefit assessment. Patients in this subpopulation had to have at least one specific pre-existing condition (e.g. immunosuppressive disease or cardiovascular disease) or the use of immune-weakening medications, or be ≥ 60 years of age, or have a body mass index (BMI) of ≥ 30, or smoke. The relevant subpopulation consists of a total of 1908 patients, 944 of whom were treated with nirmatrelvir/ritonavir and 964 with placebo.

Implementation of the appropriate comparator therapy

The G-BA specified treatment of physician's choice as ACT. Mildly to moderately symptomatic COVID-19 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, remdesivir, anticoagulation/ thrombosis prophylaxis, antibiotics) as well as non-drug therapies (oxygen support, balanced fluid therapy) must be considered.

Overall, concomitant treatment with anti-inflammatory and analgesic drugs in the EPIC-HR study is a sufficient implementation of the ACT. According to the guideline, there are also recommendations for other specific antiviral substances for the early phase of COVID-19 in patients who are at increased risk for severe disease, which were not used 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 used in the EPIC-HR study therefore has no consequence for the present benefit assessment.

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

As described above, patients who had received any dose of a COVID-19 vaccine were excluded from the EPIC-HR study. At the time of the benefit assessment, however, due to vaccinations and possibly previous exposure to the virus, a large proportion of the population already has complete immunization according to the definition of the Standing Committee on Vaccination (STIKO), which reduces the risk for severe COVID-19. Accordingly, these patients are not covered by the present therapeutic indication, as they are not at increased risk for severe disease. However, patients with incomplete immunization or with a relevant risk of an insufficient vaccination response according to the STIKO definition may still be at increased risk for severe disease. According to information from the Expert Group on Intensive Care, Infectious Diseases and Emergency Medicine (COVRIIN), the same applies to patients who have complex risk factors despite immunocompetence and complete vaccination. However, only a few patients with complex risk factors were included in the EPIC-HR study. The small proportion of patients with complex risk factors in the study population can be attributed, among other things, to the interaction potential of nirmatrelvir/ritonavir. Thus, cytochrome P450 3A4 (CYP3A4) inducers and drugs that are highly dependent on CYP3A for clearance are contraindicated when administering nirmatrelvir/ritonavir. This means that particularly older, multimorbid patients, who are taking drugs with interaction potential for their pre-existing conditions, are excluded from treatment with nirmatrelvir/ritonavir.

Patients who do not show a sufficient vaccination response and are therefore not fully immunized were not included in the EPIC-HR study. Also not included were patients who, despite immunocompetence and complete vaccination, had complex risk factors resulting in an increased risk for severe disease.

An evidence transfer from the unvaccinated patients in the EPIC-HR study to patient groups who do not achieve complete immunization despite vaccination and who are at increased risk for severe disease is nevertheless plausible. However, it remains unclear whether the effects observed in the unvaccinated patients can be transferred to these patient groups without limitation. This issue has been taken into account in the assessment of the certainty of conclusions.

In addition, patients with a prior confirmed SARS-CoV-2 infection, as determined by a molecular test, were excluded from the EPIC-HR study. However, about half of the patients included in the study had a positive serostatus at baseline despite these limitations according to the inclusion criteria. It is not clear from the available data whether the previous infection in these patients was asymptomatic. It remains unclear whether the included patients with positive serostatus are comparable to those recovered from symptomatic COVID-19 disease, who, in the current health care context, represent a large proportion of the population of the present therapeutic indication.

In Module 4 A, the company did not provide any information on which viral variant is present in the included patients. The assessment report of the European Medicines Agency (EMA) shows that about 99% of the patients were infected with the Delta variant, however. According to the Summary of Product Characteristics (SPC), nirmatrelvir/ritonavir also shows antiviral in vitro activity against the Omicron variant (B.1.1.529). Therefore, it can be assumed that the effects observed in the study are transferable to the Omicron variants circulating at the time of the benefit assessment.

In summary, on the basis of the EPIC-HR study, conclusions on the added benefit are possible for patients who have not yet had a vaccination against COVID-19 or who are not fully immunized against COVID-19, or who, despite immunocompetence and complete vaccination, still are at increased risk for severe COVID-19 due to complex risk factors. Patients with complete immunization are not comprised by the present therapeutic indication and are therefore not covered by the present benefit assessment. In addition, conclusions on the added benefit are only possible for patients who are infected with a viral variant for which there is sufficient antiviral activity.

Risk of bias and assessment of the certainty of conclusions

The risk of bias across outcomes for the EPIC-HR study is rated as low. The outcome-specific risk bias is rated as low for the results on all usable outcomes, except COVID-19 symptom relief until day 28. For the results of the outcome of COVID-19 symptom relief until day 28, it is estimated to be high due to the relevant decreasing response rate of questionnaires over the course of the study.

As described above, it is possible to transfer evidence from the unvaccinated patients included in the EPIC-HR study to patient groups who do not achieve complete immunization despite vaccination or who have complex risk factors despite immunocompetence and complete

vaccination. However, it remains unclear whether the effects observed in the unvaccinated patients can be transferred to these patient groups without limitation. Overall, the certainty of conclusions of the study results for the present research question is therefore reduced. Based on the EPIC-HR study, at most hints, e.g. of an added benefit, can be determined for all outcomes presented.

Results

Mortality

All-cause mortality

A statistically significant difference between treatment groups in favour of nirmatrelvir/ ritonavir was shown for the outcome of all-cause mortality. This results in a hint of added benefit of nirmatrelvir/ritonavir in comparison with treatment of physician's choice.

Morbidity

Severe COVID-19

A statistically significant difference between treatment groups in favour of nirmatrelvir/ritonavir was shown for the outcome of severe COVID-19. This results in a hint of added benefit of nirmatrelvir/ritonavir in comparison with treatment of physician's choice.

Need for intensive medical care due to any cause

A statistically significant difference between treatment groups in favour of nirmatrelvir/ritonavir was shown for the outcome of need for intensive medical care due to any cause. This results in a hint of added benefit of nirmatrelvir/ritonavir in comparison with treatment of physician's choice.

COVID-19 symptom relief until day 28

A statistically significant difference between treatment groups in favour of nirmatrelvir/ ritonavir was shown for the outcome of COVID-19 symptom relief until day 28. This results in a hint of added benefit of nirmatrelvir/ritonavir in comparison with treatment of physician's choice.

COVID-19 symptoms at week 24

No statistically significant difference between treatment groups was shown for the outcome of COVID-19 symptoms at week 24. This results in no hint of added benefit of nirmatrelvir/ ritonavir in comparison with treatment of physician's choice; an added benefit is therefore not proven.

Activity impairment (Work Productivity and Activity Impairment [WPAI]-COVID-19), health status (EQ-5D visual analogue scale [VAS])

There are no usable data for the outcomes of activity impairment recorded with the WPAI-COVID-19, and health status recorded with the EQ-5D VAS. For these outcomes, this results

in no hint of added benefit of nirmatrelvir/ritonavir in comparison with treatment of physician's choice for either of them; an added benefit is therefore not proven.

Health-related quality of life

Health-related quality of life outcomes were not recorded in the included study.

Side effects

Serious AEs (SAEs), severe AEs, and discontinuation due to AEs

The recording of SAEs, severe AEs, and discontinuations due to AEs also included disease-related events to a large extent. Although the company presented analyses for these outcomes without disease-related events in Module 4 A, it did not specify which events were classified as disease-related and were therefore not taken into account in the analyses. As a result, the overall rates on SAEs, severe AEs, and discontinuations due to AEs are not usable for the assessment of the side effects of nirmatrelvir/ritonavir. However, based on the results on common SAEs, severe AEs, and discontinuations due to AEs, it is not expected that there are negative effects of nirmatrelvir/ritonavir to an extent that may call the added benefit of nirmatrelvir/ritonavir into question. In each case, this results in no hint of greater or lesser harm from nirmatrelvir/ritonavir in comparison with treatment of physician's choice for the outcomes of the category of side effects; greater or lesser harm is therefore not proven.

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

On the basis of the results presented, the probability and extent of added benefit of the drug nirmatrelvir/ritonavir in comparison with the ACT are assessed as follows:

As described, the following conclusion on the added benefit applies exclusively to adult patients who have not yet received a vaccination against COVID-19 or who are not fully immunized against COVID-19 or who have complex risk factors despite immunocompetence and complete vaccination. Patients with complete immunization are not covered by the present therapeutic indication, as they are not at increased risk for severe COVID-19.

Overall, there are only positive effects of nirmatrelvir/ritonavir in comparison with treatment of physician's choice for adults with COVID-19 who do not require supplemental oxygen and who are at increased risk for severe COVID-19. For the outcomes of all-cause mortality and severe COVID-19, there is a hint of major added benefit. For the outcomes of need for intensive

[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].

medical care due to any cause and COVID-19 symptom relief until day 28, there is a hint of minor added benefit. No usable data are available for side effects. However, based on the available information, no negative effects to an extent that may call an added benefit into question are expected.

In summary, there is a hint of a major added benefit of nirmatrelvir/ritonavir compared with the ACT of treatment of physician's choice for adults with COVID-19 who do not require supplemental oxygen and who are at increased risk for progressing to severe COVID-19.

Table 3 shows a summary of probability and extent of the added benefit of nirmatrelvir/ritonavir.

Table 3: Nirmatrelvir/ritonavir – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adults with COVID-19[b] who do not require supplemental oxygen and who are at increased risk for progressing to severe COVID-19[c]	Treatment of physician's choice[e]	Hint of major added benefit

a. Presented is the respective 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 on efficacy.
d. Patients with complete immunization are not comprised by the therapeutic indication (see Section I 3.2 for details).
e. Specific therapeutic measures are usually not required for mildly to moderately symptomatic COVID-19. 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.
Recently, the drugs casirivimab/imdevimab, remdesivir, 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 for severe COVID-19. The drug molnupiravir has not yet been approved in the EU, but can be used for the treatment of COVID-19 in adults who do not require supplemental oxygen and who are at increased risk for progressing to severe COVID-19, based on the General Administrative Act on the purchase and use of monoclonal antibodies and on the purchase and dispensing of antiviral oral drugs against COVID-19 issued by the Federal Ministry of Health on 25 March 2022. The clinical significance of these therapy options cannot be assessed at the present time.
If the disease progresses and the patient is hospitalized, further drug therapies (e.g. dexamethasone, remdesivir, anticoagulation/thrombosis prophylaxis, antibiotics) as well as non-drug therapies (e.g. oxygen support, type of ventilation, balanced fluid therapy) must be considered.

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

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

I 2 Research question

The aim of this report is to assess the added benefit of nirmatrelvir/ritonavir in comparison with the ACT for the treatment of COVID-19 in adults who do not require supplemental oxygen and who are at increased risk for progressing to severe COVID-19.

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

Table 4: Research question of the benefit assessment of nirmatrelvir/ritonavir

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

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 on efficacy.
d. Specific therapeutic measures are usually not required for mildly to moderately symptomatic COVID-19. 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.
Recently, the drugs casirivimab/imdevimab, remdesivir, 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 for severe COVID-19. The drug molnupiravir has not yet been approved in the EU, but can be used for the treatment of COVID-19 in adults who do not require supplemental oxygen and who are at increased risk for progressing to severe COVID-19, based on the General Administrative Act on the purchase and use of monoclonal antibodies and on the purchase and dispensing of antiviral oral drugs against COVID-19 issued by the Federal Ministry of Health on 25 March 2022. The clinical significance of these therapy options cannot be assessed at the present time.
If the disease progresses and the patient is hospitalized, further drug therapies (e.g. dexamethasone, remdesivir, anticoagulation/thrombosis prophylaxis, antibiotics) as well as non-drug therapies (e.g. oxygen support, type of ventilation, balanced fluid therapy) must be considered.

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

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

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

I 3 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on nirmatrelvir/ritonavir (status: 20 May 2022)
- bibliographical literature search on nirmatrelvir/ritonavir (last search on 29 April 2022)
- search in trial registries/trial results databases for studies on nirmatrelvir/ritonavir (last search on 13 April 2022)
- search on the G-BA website for nirmatrelvir/ritonavir (last search on 13 April 2022)

To check the completeness of the study pool:

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

The check did not identify any additional relevant studies.

I 3.1 Studies included

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

Table 5: Study pool – RCT, direct comparison: nirmatrelvir/ritonavir vs. placebo

Study	Study category			Available sources		
	Approval study for the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication and other sources[c] (yes/no [citation])
C4671005 (EPIC-HR[d])	Yes	Yes	No	Yes [3,4]	Yes [5-7]	Yes [8,9]

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

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

Study C4671005 (hereafter referred to as the EPIC-HR study) is used for the benefit assessment. This concurs with the company's study pool.

I 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: nirmatrelvir/ritonavir vs. placebo (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
EPIC-HR	RCT, double-blind, parallel	Adult patients (≥ 18 years) with confirmed COVID-19[b] ▪ with ≥ 1 risk factor for severe disease[c] ▪ initial onset of symptoms[d] ≤ 5 days prior to randomization and at least 1 symptom on the day of randomization ▪ no need for hospitalization (acute care ≥ 24 hours) within 48 hours after randomization (in the opinion of the investigator) ▪ oxygen saturation of ≥ 92% on room air	▪ Nirmatrelvir/ritonavir (N = 1120)[e] ▪ Placebo (N = 1126)[e] Relevant subpopulation thereof: RKI-mITT2 population[f] ▪ nirmatrelvir/ritonavir (n = 944) ▪ placebo (n = 964)	▪ Screening: 48 hours ▪ Treatment: 5 to 6 days ▪ Observation: 24 weeks	343 study centres in Argentina, Brazil, Bulgaria, Colombia, Czech Republic, Hungary, India, Japan, Malaysia, Mexico, Poland, Puerto Rico, Russia, South Africa, South Korea, Spain, Taiwan, Thailand, Turkey, Ukraine, USA 7/2021–4/2022 ▪ Primary data cut-off: 11 December 2021 ▪ End of study (long-term follow-up analysis): 29 April 2022	Primary: composite outcome of COVID-19-related hospitalization or death from any cause until day 28 Secondary: mortality, morbidity, AEs

a. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes include only information on relevant available outcomes for this benefit assessment.
b. Confirmed SARS-CoV-2 infection as determined by RT-PCR in any specimen

collected within 5 days prior to randomization. Patients with any prior confirmed SARS-CoV-2 infection, as determined by a molecular test (antigen or nucleic acid) from any specimen collection, were excluded.
c. Risk factors were either ≥ 60 years of age, BMI > 25, current smoker, immunosuppressive disease or therapy, use of immune-weakening medications, chronic lung disease, hypertension, cardiovascular disease, type 1 or type 2 diabetes mellitus, chronic kidney disease, sickle cell disease, neurodevelopmental disorders (e.g. Down syndrome), active cancer, including types of cancer requiring treatment, or medical-related technological dependence (e.g. CPAP [not related to COVID-19]).
d. Cough, shortness of breath, fever, chills, fatigue, muscle or body aches, diarrhoea, vomiting, nausea, headache, sore throat, stuffy or runny nose.
e. 11 vs. 11 patients (intervention vs. control arm) did not receive any treatment.
f. The EPIC-HR study included patients with BMI ≥ 25 as risk factor for severe COVID-19. The RKI specifies a threshold value of > 30 for the BMI as a risk factor. The benefit assessment uses a subpopulation (RKI-mITT2) with BMI ≥ 30 as a risk factor for severe COVID-19 (see Section I 3.2). Patients with BMI < 30 who had at least one other risk factor are included in this subpopulation.

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

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
AE: adverse event; BMI: body mass index; COVID-19: coronavirus disease 2019; CPAP: continuous positive airway pressure; mITT: modified intention to treat; n: relevant subpopulation; N: number of randomized patients; RCT: randomized controlled trial; RKI: Robert Koch Institute; RT-PCR: reverse transcriptase polymerase chain reaction; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2						

Table 7: Characteristics of the intervention – RCT, direct comparison: nirmatrelvir/ritonavir vs. placebo

Study	Intervention	Comparison
EPIC-HR	Nirmatrelvir/ritonavir orally, every 12 hours for 5 days[a, b] ▪ nirmatrelvir 300 mg (2 tablets) + ▪ ritonavir 100 mg (1 capsule)	Placebo for nirmatrelvir/ritonavir orally, every 12 hours for 5 days[a, b]
	▪ Dose adjustments were not allowed[c]	
	Permitted concomitant treatment ▪ additional standard therapy according to local guidelines for the treatment of COVID-19 **Prohibited prior and concomitant treatment** ▪ COVID-19 vaccinations[d], convalescent COVID-19 plasma ▪ strong CYP3A4 inducers from 28 days before the first dose of the study medication ▪ medications that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations may be associated with serious and/or life-threatening events during treatment (from 24 hours before the first dose of the study medication up to 4 days after the last dose of the study medication)	

a. The second dose could be taken between 4 and 12 hours after the first dose. The remaining doses had to be taken every 12 hours (±30 minutes).
b. If a dose was missed, it had to be taken as soon as possible, but no later than 4 hours before the next scheduled dose. The next dose of study drug was not to be doubled up in order to make up the missed dose. Dosing was to be stopped at the end of the

treatment period (10 doses total).
c. Discontinuation of study treatment if eGFR was < 45 mL/min/1.73m².
d. COVID-19 vaccinations were permitted after the day 34 visit.

COVID-19: coronavirus disease 2019; CYP3A4: cytochrome P450 3A4; eGFR: estimated glomerular filtration rate; RCT: randomized controlled trial

The EPIC-HR study is a placebo-controlled, double-blind, randomized phase 2/3 study on nirmatrelvir/ritonavir. The study included non-hospitalized, symptomatic patients in the early phase of COVID-19 who had ≥ 1 risk factor for severe COVID-19. SARS-CoV-2 infection had to be determined by PCR ≤ 5 days prior to randomization.

According to the inclusion criteria, patients were not allowed to be receiving supplemental oxygen at the time of study inclusion (oxygen saturation of ≥ 92% on room air), and there was no anticipated need for hospitalization within 48 hours after randomization. Patients who were hospitalized at the time of study inclusion were excluded from the study. Accordingly, only outpatient treatment with nirmatrelvir/ritonavir was investigated in the study. Patients who had received any dose of a COVID-19 vaccine were also excluded from the study. Thus, only unvaccinated patients were considered in the EPIC-HR study.

A total of 2246 patients were allocated in a 1:1 ratio to treatment with nirmatrelvir/ritonavir (N = 1120) or to the placebo group (N = 1126). Randomization was stratified by region and by treatment or planned treatment with monoclonal antibodies against COVID-19.

Treatment with nirmatrelvir/ritonavir was in compliance with the approval [10].

Primary outcome of the study was the composite outcome of COVID-19-related hospitalization or death from any cause until day 28. Patient-relevant secondary outcomes were all-cause mortality, outcomes on morbidity and AEs.

Follow-up observation of all-cause mortality, the patient-reported outcomes of WPAI-COVID-19 and EQ-5D, and AEs was until week 24. COVID-19 symptoms were recorded daily until day 28, and concluding at week 24.

Relevant subpopulation

The EPIC-HR study included patients with ≥ 1 risk factor for severe COVID-19. However, the risk factors defined in the inclusion criteria did not fully correspond to the risk factors defined by the RKI. Inclusion criteria in the EPIC-HR study with regard to the risk for severe COVID-19 were the presence of specific pre-existing conditions (e.g. immunosuppressive disease or cardiovascular disease), the use of immune-weakening medications, an age of ≥ 60 years, smoking, or a BMI of ≥ 25. However, the BMI threshold does not correspond to the threshold defined by the RKI above which an increased risk for severe COVID-19 can be assumed. The RKI considers there to be an increased risk for severe COVID-19 only with a BMI of > 30 [11]. Based on this, the company formed the RKI-modified intention to treat 2 (RKI-mITT2) population for the present benefit assessment. This population excludes patients who had a BMI of ≥ 25 and < 30 as the only risk factor for severe COVID-19 at study inclusion. Thus, a BMI of ≥ 30 is defined as a risk factor for the present RKI-mITT2 population. However, this also does not correspond exactly to the specification by the RKI, which defines a BMI of > 30 as a risk factor for severe COVID-19. Despite this deviation, the RKI-mITT2 population is used for the benefit assessment of nirmatrelvir/ritonavir. This population consists of a total of 1908 patients, 944 of whom were treated with nirmatrelvir/ritonavir and 964 with placebo.

Implementation of the appropriate comparator therapy

The G-BA specified treatment of physician's choice as ACT. Mildly to moderately symptomatic COVID-19 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, remdesivir, anticoagulation/thrombosis prophylaxis, antibiotics) as well as non-drug therapies (oxygen support, balanced fluid therapy) must be considered.

According to the current assessment of the COVRIIN Expert Group at the RKI (status: 5 July 2022), besides nirmatrelvir/ritonavir, the virostatic drugs molnupiravir and remdesivir as well as the neutralizing monoclonal antibodies sotrovimab and tixagevimab/cilgavimab are available as antiviral therapy in the early phase of COVID-19 in patients with risk factors for severe disease [12]. At the time of the benefit assessment, molnupiravir and tixagevimab/cilgavimab

are not approved for the present therapeutic indication. The recommendations of the COVRIIN Expert Group essentially correspond to the recommendations of the guidelines that are current at the time of the benefit assessment (S3 guideline on inpatient therapy for patients with COVID-19 [status: 28 February 2022] [13] and guideline of the German College of General Practitioners and Family Physicians (DEGAM) [status: 4 February 2022] [14]). 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. 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, is thus difficult to quantify, according to the S3 guideline [13]. According to the guidelines, the selection of the appropriate therapy should be a case-by-case decision, taking into account individual risk profile, immunization status, comorbidities, availability and contraindications. This is also reflected in the assessment of the COVRIIN Expert Group with more recent status (5 July 2022), which, in addition to the immunization status, also includes the neutralization activity against the currently prevailing viral variants in the suggestions for the selection of antiviral therapy [12,15].

Concomitant therapies administered in the EPIC-HR study

In the EPIC-HR study, COVID-19 therapy was to be administered according to local standards. However, there were limitations. The use of convalescent COVID-19 plasma against SARS-CoV-2 was not allowed. Similarly, the use of strong CYP3A4 inducers and of drugs that are highly dependent on CYP3A for clearance was not allowed. In addition, some of the monoclonal antibodies or antiviral drugs for the treatment of COVID-19 were not yet available at the time the study was conducted [16].

Beyond that, there were no further restrictions or specific requirements for the concomitant treatment in both the intervention and the control arm.

Data on the concomitant therapies received by ≥ 2% of the patients in at least one study arm are listed in Table 8.

Table 8: Information on concomitant therapies (≥ 2% of the patients in ≥ 1 treatment arm) – RCT, direct comparison: nirmatrelvir/ritonavir vs. placebo (total population) (multipage table)

Study Drug Non-drug treatment	Patients with concomitant therapy n (%) Nirmatrelvir/ritonavir N = 1109[a]	 Placebo N = 1115[a]
EPIC-HR		
Total	854 (77.0)	868 (77.8)
Enalapril	33 (3.0)	30 (2.7)
Lisinopril	72 (6.5)	59 (5.3)
Losartan	41 (3.7)	42 (3.8)
Ascorbic acid	160 (14.4)	167 (15.0)
Acetylsalicylic acid	141 (12.7)	136 (12.2)
Paracetamol	302 (27.2)	292 (26.2)
Azithromycin	47 (4.2)	49 (4.4)
Dexamethasone	23 (2.1)	59 (5.3)
Doxycycline	15 (1.4)	22 (2.0)
Ibuprofen	83 (7.5)	100 (9.0)
Methylprednisolone	19 (1.7)	32 (2.9)
Levofloxacin	57 (5.1)	55 (4.9)
Prednisone	21 (1.9)	23 (2.1)
Cetirizine dihydrochloride	15 (1.4)	27 (2.4)
Loratadine	22 (2.0)	22 (2.0)
Clopidogrel	30 (2.7)	32 (2.9)
Enoxaparin sodium	24 (2.2)	35 (3.1)
Hydroxytyrosol; nattokinase	8 (0.7)	23 (2.1)
Favipiravir	27 (2.4)	34 (3.0)
Bisoprolol	18 (1.6)	25 (2.2)
Bisoprolol fumarate	23 (2.1)	31 (2.8)
Sodium chloride	10 (0.9)	31 (2.8)
Zinc	31 (2.8)	18 (1.6)
Amlodipine	41 (3.7)	41 (3.7)
Dextromethorphan	26 (2.3)	37 (3.3)
Hydrochlorothiazide	16 (1.4)	32 (2.9)
Famotidine	62 (5.6)	67 (6.0)
Omeprazole	22 (2.0)	34 (3.0)
Pantoprazole	27 (2.4)	29 (2.6)
Salbutamol	37 (3.3)	39 (3.5)
Metformin	81 (7.3)	82 (7.4)
Metformin hydrochloride	23 (2.1)	22 (2.0)
Colecalciferol	35 (3.2)	33 (3.0)
Vitamin D	24 (2.2)	19 (1.7)
Non-drug treatment		
Need for supplemental oxygen	10 (0.9[b])	54 (4.8[b])

Table 8: Information on concomitant therapies (≥ 2% of the patients in ≥ 1 treatment arm) – RCT, direct comparison: nirmatrelvir/ritonavir vs. placebo (total population) (multipage table)

Study	Patients with concomitant therapy n (%)	
Drug Non-drug treatment	Nirmatrelvir/ritonavir N = 1109[a]	Placebo N = 1115[a]

a. Number of patients who received at least one dose of the study medication. No data on concomitant medication are available for the relevant subpopulation (RKI-mITT2 population).
b. Institute's calculation.

mITT: modified intention to treat; n: number of patients with subsequent therapy; N: number of analysed patients; RCT: randomized controlled trial; RKI: Robert Koch Institute

As concomitant therapies for the treatment of COVID-19, anti-inflammatory and analgesic drugs in particular were administered in the EPIC-HR study. Frequency of administration of these drugs was about equal in both study arms. Specific therapeutic measures, such as dexamethasone or oxygen support, were only used in a small proportion of patients during the course of the study. However, these therapies are also only recommended in later phases of the disease. Both therapies were used more frequently in the control arm (dexamethasone: 2.1% [nirmatrelvir/ritonavir] versus 5.3% [placebo]; oxygen support 0.9% [nirmatrelvir/ritonavir] versus 4.8% [placebo]).

Overall, concomitant treatment with anti-inflammatory and analgesic drugs in the EPIC-HR study is a sufficient implementation of the ACT. According to the guideline, there are also recommendations for other specific antiviral substances for the early phase of COVID-19 in patients who are at increased risk for severe disease, which were not used in the study. As described above, however, according to the guidelines, these therapy options are only given a weak or open recommendation for special risk groups. In addition, it can be assumed that the treatment of patients with COVID-19 will constantly change 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 used in the EPIC-HR study therefore has no consequence for the present benefit assessment.

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

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

Study **Characteristic** **Category**	**Nirmatrelvir/ritonavir** **N[a] = 944**	**Placebo** **N[a] = 964**
EPIC-HR		
Age [years], mean (SD)	47 (16)	48 (15)
Age [years], n (%)		
18 to 44	423 (45)	396 (41)
45 to 59	296 (31)	309 (32)
60 to 64	85 (9)	111 (12)
≥ 65	140 (15)[b]	148 (15)[b]
Sex [F/M], %	50/50	47/53
Region, n (%)		
United States	387 (41)	395 (41)
Europe	322 (34)	321 (33)
India	74 (8)	78 (8)
Rest of the world	161 (17)	170 (18)
Time since initial onset of symptoms, n (%)		
≤ 3 days	637 (67)	632 (66)
> 3 days	307 (33)	332 (34)
Number of risk factors for severe COVID-19, n (%)		
1	483 (51)	476 (49)
2	261 (28)	286 (30)
3	143 (15)	134 (14)
4	49 (5)	51 (5)
> 4	8 (1)	17 (2)
Risk factors, n (%)		
Smoking	423 (45)	442 (46)
BMI ≥ 30 kg/m²	403 (43)[b]	415 (43)[b]
Hypertension	358 (38)	375 (39)
Age ≥ 60 years	225 (24)[b]	259 (27)[b]
Diabetes mellitus	135 (14)	137 (14)
Chronic lung disorder	62 (7)	39 (4)
Cardiovascular disease	42 (4)	49 (5)
Chronic kidney disease	6 (1)	8 (1)
Immunosuppressive disease or immunosuppressive therapy	6 (1)	7 (1)
Cancer	5 (1)	6 (1)
Medical-related technological dependence	4 (< 1)	3 (< 1)
Neurodevelopmental disorder	2 (< 1)	1 (< 1)
HIV infection	0 (0)	1 (< 1)
Sickle cell anaemia	0 (0)	0 (0)

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

Study Characteristic Category	Nirmatrelvir/ritonavir N[a] = 944	Placebo N[a] = 964
COVID-19 mAb treatment, n (%)	60 (6)	60 (6)
Serological status, n (%)		
Negative	439 (47)	457 (47)
Positive	494 (52)	495 (51)
Unclear	11 (1)	12 (1)
Treatment discontinuation, n (%)[c]	47 (5)	67 (7)
Study discontinuation, n (%)[d]	53 (6)	71 (7)

a. Number of randomized patients in the RKI-mITT2 population.
b. Institute's calculation.
c. Common reasons for treatment discontinuation in the intervention vs. control arm were: withdrawal of consent (2.6% vs. 2.4%) and AEs (1.8% vs. 4.3%).
d. Common reasons for study discontinuation in the intervention vs. control arm were: withdrawal of consent (3.8% vs. 4.1%) and lost to follow-up (1.4% vs. 1.7%).

AE: adverse event; BMI: body mass index; COVID-19: coronavirus disease 2019; F: female; HIV: human immunodeficiency virus; M: male; mAb: monoclonal antibody; mITT: modified intention to treat; n: number of patients in the category; N: number of randomized patients in the RKI-mITT2 subpopulation; RCT: randomized controlled trial; RKI: Robert Koch Institute; SD: standard deviation

Patient characteristics were largely balanced between the treatment arms. The mean age of the patients was about 48 years. The proportion of women in the study population was about half. About 66% of the patients had symptoms ≤ 3 days before the start of the study. The most common risk factor for severe COVID-19 in the included patients was smoking (45%), followed by BMI ≥ 30 (43%), hypertension (38%), and age (25%). Half of the patients had one risk factor.

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

As described above, patients who had received any dose of a COVID-19 vaccine were excluded from the EPIC-HR study. At the time of the benefit assessment, however, due to vaccinations and possibly previous exposure to the virus, a large proportion of the population already has complete immunization according to the STIKO definition [17], which reduces the risk for severe COVID-19. Accordingly, these patients are not covered by the present therapeutic indication, as they are not at increased risk for severe disease. However, patients with incomplete immunization or with a relevant risk of an insufficient vaccination response according to the STIKO definition [17] may still be at increased risk for severe disease. According to the COVRIIN Expert Group, the same applies to patients who have complex risk factors despite immunocompetence and complete vaccination [12]. However, only a few patients with complex risk factors were included in the EPIC-HR study. Only very few patients had an immunosuppressive disease or immunosuppressive therapy (1%) or cancer (1%). Only 15% of the patients were ≥ 65 years old. The most common risk factors were smoking, elevated

BMI and hypertension (see Table 9), with about half of the patients having only one risk factor for severe COVID-19. The small proportion of patients with complex risk factors in the study population can be attributed, among other things, to the interaction potential of nirmatrelvir/ritonavir. Thus, CYP3A4 inducers and drugs that are highly dependent on CYP3A for clearance are contraindicated when administering nirmatrelvir/ritonavir. This means that particularly older, multimorbid patients, who are taking drugs with interaction potential for their pre-existing conditions, are excluded from treatment with nirmatrelvir/ritonavir. Concomitant administration of nirmatrelvir/ritonavir is strongly discouraged in patients treated with the statins or lipid-lowering drugs simvastatin, lovastatin or lomitapide, for example. Administration of certain anticoagulants (e.g. rivaroxaban, edoxaban, apixaban, dabigatran) is also contraindicated [16].

Patients who do not show a sufficient vaccination response and are therefore not fully immunized were also not included in the EPIC-HR study. Also not included were patients who, despite immunocompetence and complete vaccination, had complex risk factors resulting in an increased risk for severe disease.

An evidence transfer from the unvaccinated patients in the EPIC-HR study to patient groups who do not achieve complete immunization despite vaccination and who are at increased risk for severe disease is nevertheless plausible. However, it remains unclear whether the effects observed in the unvaccinated patients can be transferred to these patient groups without limitation. This issue has been taken into account in the assessment of the certainty of conclusions (see Section I 4.2).

In addition, patients with a prior confirmed SARS-CoV-2 infection, as determined by a molecular test, were excluded from the EPIC-HR study. However, about half of the patients included in the study had a positive serostatus at baseline despite these limitations according to the inclusion criteria. It is not clear from the available data whether the previous infection in these patients was asymptomatic. It remains unclear whether the included patients with positive serostatus are comparable to those recovered from symptomatic COVID-19 disease, who, in the current health care context, represent a large proportion of the population of the present therapeutic indication.

In Module 4 A, the company did not provide any information on the viral variant present in the included patients. The EMA assessment report shows that about 99% of the patients were infected with the Delta variant, however. According to the SPC [10], nirmatrelvir/ritonavir also shows antiviral in vitro activity against the Omicron variant (B.1.1.529). Therefore, it can be assumed that the effects observed in the study are transferable to the Omicron variants circulating at the time of the benefit assessment.

In summary, on the basis of the EPIC-HR study, conclusions on the added benefit are possible for patients who have not yet had a vaccination against COVID-19 or who are not fully immunized against COVID-19, or who, despite immunocompetence and complete vaccination,

still are at increased risk for severe COVID-19 due to complex risk factors. Patients with complete immunization are not comprised by the present therapeutic indication and are therefore not covered by the present benefit assessment. In addition, conclusions on the added benefit are only possible for patients who are infected with a viral variant for which there is sufficient antiviral activity.

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: nirmatrelvir/ritonavir vs. placebo

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

The risk of bias across outcomes for the EPIC-HR study is rated as low.

Transferability of the study results to the German health care context

The company assumed that the results of the EPCI-HR study can be transferred very well to the German health care context. It justified this with the fact that the median age of disease onset of the patients in the mITT2 population of 47 to 49 years corresponds to the median age of disease onset in Germany in the course of a week. According to the company, the distribution of women and men was even across both study arms and the majority of patients included were of Caucasian family origin.

Furthermore, the company described that the patients included in the EPIC-HR study had at least one risk factor for severe COVID-19 and thus represented patients for whom nirmatrelvir/ritonavir is approved. The patients were treated in compliance with the SPC of nirmatrelvir/ritonavir with regard to dosage and start of treatment, the company added,

and the virological diagnostics in the EPIC-HR study for the detection of an infection with SARS-CoV-2, which preferably consists of RT-PCR or alternatively other molecular antigen tests, complied with the recommendations of the RKI. Besides, all patients could receive standard treatment in addition to the investigational medication. This included any therapy that is approved and used as indicated by the regulatory authorities or recommended by scientific bodies. Thus, the concomitant medication that was permitted for the study population of the

EPIC-HR study according to the study protocol corresponded to the therapy options in everyday German health care, according to the company, and

in the overall view, it was shown that the design of the EPIC-HR study was transferable to everyday health care in Germany and that its results could therefore be used for the added benefit assessment.

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

I 4 Results on added benefit

I 4.1 Outcomes included

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

- Mortality
  - all-cause mortality
- Morbidity
  - severe COVID-19
  - need for intensive medical care due to any cause
  - COVID-19 symptom relief until day 28
  - COVID-19 symptoms at week 24
  - activity impairment (WPAI-COVID-19)
  - health status (EQ-5D VAS)
- Health-related quality of life
- Side effects
  - serious AEs (SAEs)
  - severe AEs (Division of Acquired Immunodeficiency Syndrome [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 the outcomes for which data were available in the included study.

Table 11: Matrix of outcomes – RCT, direct comparison: nirmatrelvir/ritonavir vs. placebo

Study	Outcomes											
	All-cause mortality	Severe COVID-19[a]	Need for intensive medical care due to any cause	COVID-19 symptom relief until day 28[b]	COVID-19 symptoms at week 24[c]	Activity impairment (WPAI-COVID-19)	Health status (EQ-5D VAS)	Health-related quality of life	SAEs	Severe AEs[d]	Discontinuation due to AEs	Specific AEs
EPIC-HR	Yes	Yes	Yes	Yes	Yes	No[e]	No[e]	No[f]	No[g]	No[g]	No[g]	No[h]

a. Operationalized as COVID-19-related hospitalization (acute care > 24 hours).
b. Symptoms analysed: myalgia, shortness of breath or difficulty breathing, chills, cough, diarrhoea, feeling hot or feverish (subjective fever), headache, nausea, stuffy or runny nose, sore throat, vomiting, fatigue, loss of smell and loss of taste.
c. In addition to the COVID-19 symptoms until day 28, the symptoms of difficulty concentrating, sleep disorders, palpitations and other symptoms were analysed at week 24.
d. Severe AEs are operationalized as DAIDS grade ≥ 3.
e. No usable data due to insufficient response rates.
f. Outcome not recorded.
g. No usable data available; the company did not provide any information on which events it classified as disease-related (for explanation see text below).
h. No specific AEs were identified based on the AEs that occurred in the relevant study.

AE: adverse event; COVID-19: coronavirus disease 2019; DAIDS: Division of Acquired Immunodeficiency Syndrome; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; WPAI: Work Productivity and Activity Impairment

Morbidity

Severe COVID-19

Severe COVID-19 was operationalized as > 24 hours of acute care in a hospital or similar acute care facility. It is not clear from the study documents and the information provided by the company in Module 4 A under which conditions COVID-19-related hospitalization occurred.

The present benefit assessment uses the outcome of severe COVID-19, operationalized as COVID-19-related hospitalization. It is assumed that hospitalization was at the discretion of the attending physician. Based on the data on the proportion of patients requiring supplemental oxygen (see Table 8), it is also assumed that COVID-19-related hospitalization is a sufficient approximation of the occurrence of severe disease. Data on hospitalization due to any cause are not available in the dossier.

COVID-19 symptoms

For the EPIC-HR study, patients recorded the following 14 COVID-19 symptoms daily for 28 days using a digital patient diary:

- myalgia
- shortness of breath or difficulty breathing
- chills
- cough
- diarrhoea
- feeling hot or feverish (subjective fever)
- headache
- nausea
- stuffy or runny nose
- sore throat
- vomiting
- fatigue
- loss of smell
- loss of taste

In the recording of symptoms, symptom severity was rated on a 4-point Likert scale in which 0 was reported if no symptoms were present; 1 if mild; 2 if moderate; and 3 if severe. In deviation from this, the symptoms of vomiting and diarrhoea were each rated on a 4-point frequency scale where 0 was reported for no occurrence, 1 for 1 to 2 times, 2 for 3 to 4 times, and 3 for 5 or greater. The symptoms of loss of smell and loss of taste were each rated on a 3-point Likert scale where 0 was reported if the sense of smell/taste was the same as usual, 1 if the sense of smell/taste was less than usual, and 2 for no sense of smell/taste.

According to the planning of the study, the analysis of 11 of these symptoms (excluding fatigue, loss of smell and loss of taste) was prespecified. In addition to these analyses, the company also presented analyses of all 14 COVID-19 symptoms recorded until day 28 in Module 4 A. As the 3 additional symptoms are characteristic COVID-19 symptoms, relief of all 14 COVID-19 symptoms is used for the benefit assessment. The company presented both analyses of the time to relief of each individual COVID-19 symptom recorded and analyses of the time to relief of all symptoms in total. The time to relief of all symptoms is used for the present benefit assessment.

COVID-19 symptom relief was operationalized as the event occurring on the first of 4 consecutive days on which all symptoms classified as moderate (2) or severe (3) at study entry

were classified as mild (1) or absent (0), and all symptoms classified as mild (1) or absent (0) at study entry were classified as absent (0). The first day of the period of 4 consecutive days was considered the time of the event.

In addition, COVID-19 symptoms were recorded by telephone at the end of the study after 24 weeks. In this recording, concentration difficulties, sleep disorders, palpitations and other symptoms were analysed in addition to the 14 symptoms already described. However, there is no information on how precisely symptoms that are supposed to be related to COVID-19 were queried after 24 weeks. Information, e.g. on the wording of the query, is not provided by the company in its dossier. The outcome of COVID-19 symptoms at week 24 is nevertheless used for the benefit assessment.

Activity impairment (WPAI-COVID-19) and health status (EQ-5D VAS)

The outcomes on activity impairment recorded by question 6 of the WPAI-COVID-19 and on health status recorded by the EQ-5D VAS are patient-relevant and are used for the benefit assessment. Health status recorded by the EQ-5D VAS was to be recorded on day 1, day 5, day 14, day 34 and as part of the follow-up at week 12 and week 24. The outcome of activity impairment (WPAI-COVID-19) was recorded on day 5 and day 14 and at week 12 and week 24.

For both outcomes, the response rates at the beginning of the survey were very low (about 3% each). Although the response rates increased at later documentation times, they remained at a low level of less than 45% in each case. Consequently, only very few patients were included in the analyses, so that no usable data are available for the benefit assessment.

Global Impression Questions (GIQ)

The company described in Module 4 A that the GIQ consists of 3 questions, which allow a patient-reported global assessment of symptoms and quality of life. The validity of this instrument cannot be conclusively assessed on the basis of the available information. Thus, neither the wording of the individual questions is available, nor is there any information about the scales used. Analyses of the GIQ are therefore not used for the benefit assessment.

Side effects

In addition to therapy-related AEs, events that can be assigned to the symptoms of the disease were obviously recorded as AEs. In Module 4 A, the company presented analyses with the exclusion of disease-related events. However, it did not provide any information on which events were classified as disease-related and accordingly not taken into account in the analyses. An adequate assessment of side effects would require an analysis of the overall rates of SAEs and severe AEs without disease-related events. On the basis of the available data, it remains unclear whether events that can be assigned to the symptoms of the underlying disease were excluded from the analyses. The overall rates of SAEs, severe AEs and discontinuation due to AEs are therefore not usable for the present benefit assessment.

I 4.2 Risk of bias

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

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

Study		Outcomes											
	Study level	All-cause mortality	Severe COVID-19[a]	Need for intensive medical care due to any cause	COVID-19 symptom relief until day 28[b]	COVID-19 symptoms at week 24[c]	Activity impairment (WPAI-COVID-19)	Health status (EQ-5D VAS)	Health-related quality of life	SAEs	Severe AEs[d]	Discontinuation due to AEs	Specific AEs
EPIC-HR	L	L	L	L	H[e]	L	-[f]	-[f]	-[g]	-[h]	-[h]	-[h]	-[i]

a. Operationalized as COVID-19-related hospitalization (acute care > 24 hours).
b. Symptoms analysed: myalgia, shortness of breath or difficulty breathing, chills, cough, diarrhoea, feeling hot or feverish (subjective fever), headache, nausea, stuffy or runny nose, sore throat, vomiting, fatigue, loss of smell and loss of taste.
c. In addition to the COVID-19 symptoms until day 28, the symptoms of difficulty concentrating, sleep disorders, palpitations and other symptoms were analysed at week 24.
d. Severe AEs are operationalized as DAIDS grade ≥ 3.
e. Decreasing response to questionnaire over the course of the study.
f. Insufficient response rates.
g. Not recorded.
h. No usable data available; the company did not provide any information on which events it classified as disease-related (for explanation see text below).
i. No specific AEs were identified based on the AEs that occurred in the relevant study.

AE: adverse event; COVID-19: coronavirus disease 2019; DAIDS: Division of Acquired Immunodeficiency Syndrome; H: high; L: low; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; WPAI: Work Productivity and Activity Impairment

The risk bias is rated as low for the results on all usable outcomes, except COVID-19 symptom relief until day 28. For the results of the outcome of COVID-19 symptom relief until day 28, it is estimated to be high due to the relevant decreasing response rate of questionnaires over the course of the study.

Summary assessment of the certainty of conclusions

As described in Section I 3.2, the following assessment of the certainty of conclusions applies to patients who have not yet had a vaccination against COVID-19 or who are not fully immunized against COVID-19, or who, despite immunocompetence and complete vaccination, still are at increased risk for severe COVID-19 due to complex risk factors. Patients with

complete immunization are not comprised by the present therapeutic indication and are therefore not covered by the present benefit assessment. Furthermore, conclusions on the added benefit are only possible for patients who are infected with a viral variant for which there is sufficient antiviral activity.

As described in Section I 3.2, it is possible to transfer evidence from the unvaccinated patients included in the EPIC-HR study to patient groups who do not achieve complete immunization despite vaccination or who have complex risk factors despite immunocompetence and complete vaccination. However, it remains unclear whether the effects observed in the unvaccinated patients can be transferred to these patient groups without limitation. Overall, the certainty of conclusions of the study results for the present research question is therefore reduced. Based on the EPIC-HR study, at most hints, e.g. of an added benefit, can be determined for all outcomes presented.

I 4.3 Results

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

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

Table 13: Results (outcome categories, dichotomous) – RCT, direct comparison: nirmatrelvir/ritonavir vs. placebo

Study Outcome category Outcome	Nirmatrelvir/ritonavir		Placebo		Nirmatrelvir/ritonavir vs. placebo
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value
EPIC-HR					
Mortality					
All-cause mortality	944	0 (0)	964	15 (1.6)	0.03 [0.00; 0.55]; 0.017
Morbidity					
Severe COVID-19	944	10 (1.1)	964	60 (6.2)	0.17 [0.09; 0.33]; < 0.001[a]
Need for intensive medical care due to any cause	944	0 (0)	964	9 (0.9)	0.05 [0.00; 0.92]; 0.044
COVID-19 symptoms at week 24	944	37 (3.9)	964	34 (3.5)	1.11 [0.70; 1.76]; 0.651
Activity impairment (WPAI)	No usable data[b]				
Health status (EQ-5D VAS)	No usable data[b]				
Health-related quality of life	Outcome not recorded				
Side effects					
AEs (supplementary information)	No usable data[c]				
SAEs	No usable data[c]				
Severe AEs[d]	No usable data[c]				
Discontinuation due to AEs	No usable data[c]				

a. Institute's calculation of RR, CI (unconditional exact test, CSZ method according to [18]).
b. No usable data due to insufficient response rates.
c. The company did not provide any information on which events it classified as disease-related (see Section I 4.1).
Overall rates without disease-related events reported by the company: SAEs: 6 (0.6%) [nirmatrelvir/ritonavir] vs. 8 (0.8%) [placebo]; severe AEs: 21 (2.2%) [nirmatrelvir/ritonavir] vs. 26 (2.7%) [placebo]; discontinuation due to AEs: 11 (1.2%) [nirmatrelvir/ritonavir] vs. 14 (1.5%) [placebo].
d. Severe AEs are operationalized as DAIDS grade ≥ 3.

AE: adverse event; CI: confidence interval; CSZ: convexity, symmetry, z-score; COVID-19: coronavirus disease 2019; DAIDS: Division of Acquired Immunodeficiency Syndrome; n: number of patients with (at least one) event; N: number of analysed patients; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; VAS: visual analogue scale; WPAI: Work Productivity and Activity Impairment

Table 14: Results (outcome categories, time to event) – RCT, direct comparison: nirmatrelvir/ritonavir vs. placebo

Study Outcome category Outcome	Nirmatrelvir/ritonavir N	Nirmatrelvir/ritonavir Median time to event in days [95% CI] Patients with event n (%)	Placebo N	Placebo Median time to event in days [95% CI] Patients with event n (%)	Nirmatrelvir/ritonavir vs. placebo HR [95% CI]; p-value[a]
EPIC-HR					
Morbidity					
COVID-19 symptom relief until day 28	928	16 [15; 17] 588 (63.4)	955	20 [19; 22] 522 (54.7)	1.30 [1.16; 1.47]; < 0.001

a. HR, CI and p-value: Cox proportional hazards model adjusted for treatment, baseline viral load, baseline serology status, region, treatment or planned treatment with monoclonal antibodies against COVID-19 at study start, time between onset of symptoms and administration of first dose (≤ 3 days, > 3 days) and the interaction between treatment and covariables.

CI: confidence interval; COVID-19: coronavirus disease 2019; HR: hazard ratio; n: number of patients with event; N: number of analysed patients; RCT: randomized controlled trial

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

Mortality

All-cause mortality

A statistically significant difference between treatment groups in favour of nirmatrelvir/ ritonavir was shown for the outcome of all-cause mortality. This results in a hint of added benefit of nirmatrelvir/ritonavir in comparison with treatment of physician's choice.

Morbidity

Severe COVID-19

A statistically significant difference between treatment groups in favour of nirmatrelvir/ ritonavir was shown for the outcome of severe COVID-19. This results in a hint of added benefit of nirmatrelvir/ritonavir in comparison with treatment of physician's choice.

Need for intensive medical care due to any cause

A statistically significant difference between treatment groups in favour of nirmatrelvir/ritonavir was shown for the outcome of need for intensive medical care due to any cause. This results in a hint of added benefit of nirmatrelvir/ritonavir in comparison with treatment of physician's choice.

COVID-19 symptom relief until day 28

A statistically significant difference between treatment groups in favour of nirmatrelvir/ ritonavir was shown for the outcome of COVID-19 symptom relief until day 28. This results in a hint of added benefit of nirmatrelvir/ritonavir in comparison with treatment of physician's choice.

COVID-19 symptoms at week 24

No statistically significant difference between treatment groups was shown for the outcome of COVID-19 symptoms at week 24. This results in no hint of added benefit of nirmatrelvir/ ritonavir in comparison with treatment of physician's choice; an added benefit is therefore not proven.

Activity impairment (WPAI-COVID-19), health status (EQ-5D VAS)

There are no usable data for the outcomes of activity impairment recorded with the WPAI-COVID-19, and health status recorded with the EQ-5D VAS (see Section I 4.1). For these outcomes, this results in no hint of added benefit of nirmatrelvir/ritonavir in comparison with treatment of physician's choice for either of them; an added benefit is therefore not proven.

Health-related quality of life

Health-related quality of life outcomes were not recorded in the included study.

Side effects

SAEs, severe AEs and discontinuation due to AEs

The recording of SAEs, severe AEs, and discontinuations due to AEs also included disease-related events to a large extent. Although the company presented analyses for these outcomes without disease-related events in Module 4 A, it did not specify which events were classified as disease-related and were therefore not taken into account in the analyses. As a result, the overall rates on SAEs, severe AEs, and discontinuations due to AEs are not usable for the assessment of the side effects of nirmatrelvir/ritonavir. However, based on the results on common SAEs, severe AEs, and discontinuations due to AEs (see I Appendix B of the full dossier assessment), it is not expected that there are negative effects of nirmatrelvir/ritonavir to an extent that may call the added benefit of nirmatrelvir/ritonavir into question. In each case, this results in no hint of greater or lesser harm from nirmatrelvir/ritonavir in comparison with treatment of physician's choice for the outcomes of the category of side effects; greater or lesser harm is therefore not proven.

I 4.4 Subgroups and other effect modifiers

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

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

The company did not provide any subgroup analyses for the outcomes of need for intensive care due to any cause and COVID-19 symptoms at week 24.

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 one subgroup.

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

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

I 5 Probability and extent of added benefit

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

I 5.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level is estimated from the results presented in Chapter I 4 (see Table 15).

Determination of the outcome category for symptom outcomes

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

Severe COVID-19, need for intensive medical care due to any cause

Events that require inpatient treatment are considered severe or serious. Therefore, the outcomes of severe COVID-19 and need for intensive care due to any cause are assigned to the outcome category of serious/severe symptoms/late complications.

COVID-19 symptom relief until day 28

The severity of the COVID-19 symptoms surveyed at the beginning of the EPIC-HR study is considered to be overall non-severe or non-serious. Thus, the majority of patients reported only mild or moderate symptoms at baseline (58% [nirmatrelvir/ritonavir] versus 61% [placebo]). Therefore, the outcome of COVID-19 symptom relief until day 28 is assigned to the outcome category of non-serious/non-severe symptoms/late complications.

Table 15: Extent of added benefit at outcome level: nirmatrelvir/ritonavir vs. placebo

Outcome category **Outcome**	**Nirmatrelvir/ritonavir vs. placebo** **Median time to event (days) or proportion of events (%)** **Effect estimation [95% CI]; p-value** **Probability[a]**	**Derivation of extent[b]**
Mortality		
All-cause mortality	0% vs. 1.6% RR: 0.03 [0.00; 0.55] p = 0.017 probability: "hint"	Outcome category: mortality $CI_u < 0.85$ added benefit, extent: "major"
Morbidity		
Severe COVID-19	1.1% vs. 6.2% RR: 0.17 [0.09; 0.33] p < 0.001 probability: "hint"	Outcome category: serious/severe symptoms/late complications $CI_u < 0.75$, risk ≥ 5% added benefit, extent: "major"
Need for intensive medical care due to any cause	0% vs. 0.9% RR: 0.05 [0.00; 0.92] p = 0.044 probability: "hint"	Outcome category: serious/severe symptoms/late complications $0.90 \leq CI_u < 1.00$ added benefit, extent: "minor"
COVID-19 symptom relief until day 28	16 vs. 20 days HR: 1.30 [1.16; 1.47] HR: 0.77 [0.68; 0.86][c] p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications $0.80 \leq CI_u < 0.90$ added benefit, extent: "minor"
COVID-19 symptoms at week 24	3.9% vs. 3.5% RR: 1.11 [0.70; 1.76] p = 0.651	Lesser benefit/added benefit not proven
Activity impairment (WPAI)	No usable data	Lesser benefit/added benefit not proven
Health status (EQ-5D VAS)	No usable data	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	No usable data	Greater/lesser harm not proven
Severe AEs		
Discontinuation due to AEs		

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. Institute's calculation; inverse direction of effect to enable use of limits to derive the extent of the added benefit.

AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; COVID-19: coronavirus disease 2019; HR: hazard ratio; RR: relative risk; SAE: serious adverse event; VAS: visual analogue scale; WPAI: Work Productivity and Activity Impairment

I 5.2 Overall conclusion on added benefit

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

Table 16: Positive and negative effects from the assessment of nirmatrelvir/ritonavir compared with treatment of physician's choice

Positive effects	**Negative effects**
Mortality ▪ All-cause mortality: hint of an added benefit – extent: "major"	–
Serious/severe symptoms/late complications ▪ Severe COVID-19: hint of an added benefit – extent: "major" ▪ Need for intensive care due to any cause: hint of an added benefit – extent: "minor"	–
Non-serious/non-severe symptoms/late complications ▪ COVID-19 symptom relief until day 28: hint of an added benefit – extent: "minor"	–
No usable data are available for the outcomes on health-related quality of life and on side effects. Effects apply exclusively to patients who have not yet received a vaccination against COVID-19 or who are not fully immunized against COVID-19 or who have complex risk factors despite immunocompetence and complete vaccination.	
COVID-19: coronavirus disease 2019	

As described in Section I 3.2, the following conclusion on the added benefit applies exclusively to adult patients who have not yet received a vaccination against COVID-19 or who are not fully immunized against COVID-19 or who have complex risk factors despite immunocompetence and complete vaccination. Patients with complete immunization are not covered by the present therapeutic indication, as they are not at increased risk for severe COVID-19.

Overall, there are only positive effects of nirmatrelvir/ritonavir in comparison with treatment of physician's choice for adults with COVID-19 who do not require supplemental oxygen and who are at increased risk for severe COVID-19. For the outcomes of all-cause mortality and severe COVID-19, there is a hint of major added benefit. For the outcomes of need for intensive medical care due to any cause and COVID-19 symptom relief until day 28, there is a hint of minor added benefit. No usable data are available for side effects. However, based on the available information, no negative effects to an extent that may call an added benefit into question are expected.

In summary, there is a hint of a major added benefit of nirmatrelvir/ritonavir compared with the ACT of treatment of physician's choice for adults with COVID-19 who do not require supplemental oxygen and who are at increased risk for progressing to severe COVID-19.

Table 17 summarizes the result of the assessment of added benefit of nirmatrelvir/ritonavir in comparison with the ACT.

Table 17: Nirmatrelvir/ritonavir – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adults with COVID-19[b] who do not require supplemental oxygen and who are at increased risk for progressing to severe COVID-19[c]	Treatment of physician's choice[e]	Hint of major added benefit

a. Presented is the respective 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 on efficacy.
d. Patients with complete immunization are not comprised by the therapeutic indication (see Section I 3.2 for details).
e. Specific therapeutic measures are usually not required for mildly to moderately symptomatic COVID-19. 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.
Recently, the drugs casirivimab/imdevimab, remdesivir, 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 for severe COVID-19. The drug molnupiravir has not yet been approved in the EU, but can be used for the treatment of COVID-19 in adults who do not require supplemental oxygen and who are at increased risk for progressing to severe COVID-19, based on the General Administrative Act on the purchase and use of monoclonal antibodies and on the purchase and dispensing of antiviral oral drugs against COVID-19 issued by the Federal Ministry of Health on 25 March 2022. The clinical significance of these therapy options cannot be assessed at the present time.
If the disease progresses and the patient is hospitalized, further drug therapies (e.g. dexamethasone, remdesivir, anticoagulation/thrombosis prophylaxis, antibiotics) as well as non-drug therapies (e.g. oxygen support, type of ventilation, balanced fluid therapy) must be considered.

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

The above assessment differs from that of the company, which derived proof of considerable added benefit of nirmatrelvir/ritonavir in comparison with treatment of physician's choice in adults with COVID-19 who do not require supplemental oxygen and who are at increased risk for progressing to severe COVID-19.

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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