Tixagevimab/cilgavimab (pre-exposure prophylaxis of COVID-19)

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

EXTRACT

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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

The questionnaire on the disease and its treatment was answered by Gabriele Gründl.

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

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Part I: Benefit assessment

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

I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
BMI	body mass index
COVID-19	coronavirus disease 2019
COVRIIN	Expert Group on Intensive Care, Infectious Diseases and Emergency Medicine
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
GFR	glomerular filtration rate
HIV	human immunodeficiency virus
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
RCT	randomized controlled trial
RKI	Robert Koch Institute
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus Type 2
SGB	Sozialgesetzbuch (Social Code Book)
SHI	statutory health insurance
SPC	Summary of Product Characteristics

I 1 Executive summary of the benefit assessment

Background

In accordance with § 35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug tixagevimab/cilgavimab. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 11 May 2023.

Research question

The aim of the present report is to assess the added benefit of tixagevimab/cilgavimab in comparison with watchful waiting as appropriate comparator therapy (ACT) for pre-exposure prophylaxis of coronavirus disease 2019 (COVID-19) in adults and adolescents aged 12 years and older with a body weight of at least 40 kg.

The present assessment refers exclusively to those persons who, according to §2 of the COVID-19 Prevention Ordinance, are entitled to the provision of prescription drugs with monoclonal antibodies for preventive use to protect against COVID-19 at the expense of the statutory health insurance (SHI). This concerns those persons in whom (1) for medical reasons (e.g. congenital or acquired immunodeficiencies, underlying diseases or immunosuppressive therapies) no or no sufficient immune protection against a COVID-19 disease can be achieved by vaccination, or (2) in whom vaccinations against the Severe Acute Respiratory Syndrome Coronavirus Type 2 (SARS-CoV-2) cannot be carried out due to a contraindication, and who are thus exposed to an increased risk of a severe course of a COVID-19 disease.

The research question presented in Table 2 is derived from the G-BA's specification of the ACT and the information provided in COVID-19 Prevention Ordinance §2.

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

Therapeutic indication	**ACT**[a]
Pre-exposure prophylaxis of COVID-19 in adults and adolescents aged 12 years and older and with a body weight of at least 40 kg[b, c, d, e]	Watchful waiting

a. Presented is the ACT specified by the G-BA.
b. According to § 2 of the COVID-19 Prevention Ordinance, an entitlement to the provision of prescription drugs with monoclonal antibodies for preventive use to protect against COVID-19 at the expense of the SHI only exists for insured persons, if, for medical reasons, no or insufficient immune protection against a COVID-19 disease can be achieved by vaccination, or if protective vaccinations against the SARS-CoV-2 coronavirus cannot be carried out due to a contraindication and they are exposed to an increased risk of a severe course of COVID-19 disease. Medical reasons may include, in particular, congenital or acquired immunodeficiencies, underlying diseases or a relevant impairment of the immune response due to immunosuppressive therapy.
c. It is assumed that the study participants will follow the generally accepted hygiene rules (such as keeping distance, observing hygiene measures, wearing mouth-nose coverings) to reduce the risk of infection in all study arms. In cases where medical reasons (e.g. dementia) preclude compliance with established hygiene rules, this must be documented.
d. It is recommended that relevant SARS-CoV-2 mutation variants (e.g. so-called variants of concern [VOCs]) are also taken into account when recording and interpreting the results on efficacy.
e. As soon as the disease becomes symptomatic, treatment according to current medical knowledge is indicated.

COVID-19: coronavirus disease 2019; G-BA: Federal Joint Committee; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; SHI: Statutory Health Insurance; VOCs: variants of concern

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

Neutralizing activity against SARS-CoV-2 variants

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

The Expert Group on Intensive Care, Infectious Diseases and Emergency Medicine (COVRIIN) at the Robert Koch Institute (RKI) recommends taking into account the current epidemiological situation and neutralizing activity against individual virus variants when selecting monoclonal antibodies for treatment or prophylaxis. For the virus variants Omicron BA.1, BA.4, and BA.5, the expert group reports substantially decreased in vitro neutralization activity of tixagevimab/cilgavimab and therefore deems reduced efficacy against these variants to be probable. Against the newly arisen variants BQ.1/BQ1.1, BA.4.6, BF.7 and XBB in contrast, the expert group reports no in vitro neutralization activity.

Study pool and study design

Evidence provided by the company

Design of the PROVENT study

The PROVENT study is a double-blind randomized controlled trial (RCT) comparing COVID-19 pre-exposure prophylaxis with tixagevimab/cilgavimab versus placebo in adults unvaccinated at baseline who are at increased risk of inadequate vaccination response or SARS-CoV-2 infection according to criteria defined by the company.

An increased risk of inadequate vaccination response was determined in the PROVENT study based on the following criteria: age (≥ 60 years), obesity (body mass index [BMI] ≥ 30), heart failure, chronic obstructive pulmonary disease, chronic kidney disease (glomerular filtration rate [GFR] < 30ml/min/1.73m²), chronic liver disease, immunodeficiency (due to solid organ transplantation, blood or bone marrow transplantation, immunocompromised condition, human immunodeficiency virus [HIV], use of corticosteroids or other immunosuppressive drugs) and intolerance to the vaccine (defined as a history of severe or serious adverse events after receiving an approved vaccine).

Individuals at increased risk of SARS-CoV-2 infection were defined as those at significant risk of exposure to SARS-CoV-2 and COVID-19, based on the available risk assessment at the time of study inclusion, due to their location or living circumstances (e.g. health care workers, including staff in long-term care facilities; workers in industrial plants that have been shown to be at high risk for transmission of SARS-CoV-2; military personnel living or working in confined spaces; students living in student residences; other persons living in similarly confined or high-density environments).

A total of 5254 patients were randomly assigned in a ratio of 2:1 to the treatment arms.

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

The study's primary outcome was the proportion of persons with COVID-19 by Day 183. Patient-relevant secondary outcomes were morbidity outcomes and adverse events (AEs). Results on mortality were not recorded as an independent efficacy outcome. The company presents the mortality based on the results of the AEs leading to death.

The subpopulation presented by the company was unsuitable for the benefit assessment

From the total population of the PROVENT study, the company formed a sub-population of those study participants who, according to the criteria of § 2 of the COVID-19 Prevention Ordinance, are entitled to the provision of prescription drugs with monoclonal antibodies for preventive use to protect against COVID-19 at the expense of the SHI system. However, this subpopulation is not relevant for the present assessment. This is justified below.

According to § 2 of the COVID-19 Prevention Ordinance, persons who are immunodeficient or at increased risk of an inadequate COVID-19 vaccination response as a result of immunosuppressive disease and/or therapy are entitled to care. The company operationalized this population based on the following criteria:

1) Presence of immunosuppressive disease at baseline
2) Treatment with immunosuppressants at baseline
3) Persons with an impaired immune system (due to organ or bone marrow transplantation, primary immunodeficiency, HIV, treatment with corticosteroids or other immunosuppressive drugs) and an increased risk of inadequate vaccination response
4) Contraindication to SARS-CoV-2 vaccines in the presence of at least one risk factor for a severe course of COVID-19

Taking into account the above criteria, the company considered 519 (9.9%) of the 5254 participants of the PROVENT study (tixagevimab/cilgavimab arm: N = 346; placebo arm: N = 173) for the present research question.

The RKI recommends SARS-CoV-2 pre-exposure prophylaxis with tixagevimab/cilgavimab only in justified individual cases. Justified individual cases may be persons with an expected or proven severe limitation of the immune response to COVID-19 vaccination (e.g. individuals following autologous or allogeneic stem cell transplantation prior to immunological reconstitution; under or following treatment with anti-B-cell antibodies if no reconstitution of B-cell capacities has occurred; under CAR T-cell therapy; under severe immunosuppression, e.g. following transplantation of a solid organ or under ongoing chemotherapy; with genetic immunodeficiencies that impair antiviral immunity).

The company's criteria for the formation of the subpopulation essentially correspond to the RKI criteria for a risk of reduced vaccination response and are basically suitable for selecting the population described in § 2 of the COVID-19 Prevention Ordinance. Overall, however, the company provides insufficient information on the characteristics that represent these criteria.

With regard to the company's 1st criterion for the formation of the subpopulation - presence of an immunosuppressive disease - it is clear from the characteristics of the study participants that an underlying immunosuppressive disease was present in approx. 5% of the patients in the subpopulation. However, no information is available on the actual underlying diseases and the severity of the disease. For the 2nd criterion of the company - treatment with immunosuppressants - it is shown that approx. 31% of the subpopulation received treatment with immunosuppressive drugs. Here, too, the company does not provide any information on the immunosuppressive drugs used or their dosages or on the underlying diseases. According to the RKI, underlying immunosuppressive diseases or therapies do not per se lead to a

relevant limitation of the immune response. The degree of immunodeficiency depends on the severity of the disease or the dosage of the immunosuppressive drugs used as well as on patient-specific factors. However, the company presented no suitable information.

According to the RKI, cancer patients undergoing immunosuppressive, antineoplastic treatment also are at increased risk of a relevantly reduced immune response. Approximately 17% of the patients in the subpopulation had cancer at baseline. However, there is a lack of information on the stage of the disease and the therapy used. Therefore, it remains unclear how many study participants with cancer have an increased risk of a severely impaired immune response and thus represent the present research question. Overall, criteria 1 and 2 only apply to an insufficiently large proportion of the subpopulation.

The 3rd criterion - impairment of the immune system combined with an increased risk of inadequate vaccination response - overlaps with the first two criteria. The presence of immune system impairment and/or an increased risk of inadequate vaccination response was defined in the Case Report Form with the following criteria:

- Age (≥ 60 years)
- Obesity (BMI ≥ 30)
- Heart failure, chronic obstructive pulmonary disease, chronic kidney disease, chronic liver disease
- Immunodeficiency due to solid organ transplantation, blood or bone marrow transplantation, immunocompromised condition, HIV, use of corticosteroids or other immunosuppressive drugs

Except for immunodeficiency, the criteria do not correspond to the definition of the RKI and are not suitable to define a relevant immunodeficiency or an increased risk for a relevant limitation of the immune response. The company states that about 95% of the subpopulation have an immunocompromised condition. There is no information on individual criteria that justify the immunocompromised condition. Based on the characteristics of the study participants, as described above, the immunocompromised condition is attributed to an underlying immunosuppressive disease in about 5% and to treatment with immunosuppressive drugs in about 31%. In its criteria, the company did not consider cancer separately. If applicable, these persons are considered via the criterion of immunosuppressive treatment. It is assumed that for the remaining patients in the subpopulation, the presence of immune system impairment or an increased risk of inadequate vaccination response was due to other criteria such as age, obesity or a chronic disease. As these criteria are not suitable to select the population described in § 2 of the COVID-19 Prevention Ordinance, the majority of the subpopulation is not relevant for the present research question.

According to criterion 4, the subpopulation also included patients with a contraindication to SARS-CoV-2 vaccination and concomitant presence of at least one risk factor for a severe course of COVID-19. The company does not provide any information on how many study participants this applies to in the subpopulation. Although it states in Module 4 A that about 2% of the subpopulation are intolerant to a vaccine, it does not provide information on the concomitant risk factors for a severe course of COVID-19.

Overall, the majority of the patients included in the subpopulation do not represent the research question of the present assessment and are not used for the benefit assessment.

Results

Suitable data for the benefit assessment are not available. There is no hint of an added benefit of tixagevimab/cilgavimabin in comparison with the ACT; an added benefit 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 tixagevimab/cilgavimab compared with the ACT is assessed as follows:

The data presented by the company are unsuitable to assess the added benefit of tixagevimab/cilgavimab in comparison with watchful waiting as ACT for pre-exposure prophylaxis of COVID-19 in adults and adolescents aged 12 years and older and with a body weight of at least 40 kg. An added benefit of tixagevimab/cilgavimab is thus not proven.

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

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

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

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Pre-exposure prophylaxis of COVID-19 in adults and adolescents aged 12 years and older and with a body weight of at least 40 kg[b, c, d, e]	Watchful waiting	Added benefit not proven

a: Presented is the ACT specified by the G-BA.
b. According to § 2 of the COVID-19 Prevention Ordinance, an entitlement to the provision of prescription drugs with monoclonal antibodies for preventive use to protect against COVID-19 at the expense of the SHI only exists for insured persons, if, for medical reasons, no or insufficient immune protection against a COVID-19 disease can be achieved by vaccination, or if protective vaccinations against the SARS-CoV-2 coronavirus cannot be carried out due to a contraindication and they are exposed to an increased risk of a severe course of COVID-19 disease. Medical reasons may include, in particular, congenital or acquired immunodeficiencies, underlying diseases or a relevant impairment of the immune response due to immunosuppressive therapy.
c. It is assumed that the study participants will follow the generally accepted hygiene rules (such as keeping distance, observing hygiene measures, wearing mouth-nose coverings) to reduce the risk of infection in all study arms. In cases where medical reasons (e.g. dementia) preclude compliance with established hygiene rules, this must be documented.
d. It is recommended that relevant SARS-CoV-2 mutation variants (e.g. so-called VOCs) are also taken into account when recording and interpreting the results on efficacy.
e. As soon as the disease becomes symptomatic, treatment according to current medical knowledge is indicated.

COVID-19: coronavirus disease 2019; G-BA: Federal Joint Committee; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; VOCs: variants of concern

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

I 2 Research question

The aim of the present report is to assess the added benefit of tixagevimab/cilgavimab in comparison with watchful waiting as ACT for pre-exposure prophylaxis of COVID-19 in adults and adolescents aged 12 years and older with a body weight of at least 40 kg.

The present assessment refers exclusively to those persons who, according to §2 of the COVID-19 Prevention Ordinance [3], are entitled to the provision of prescription drugs with monoclonal antibodies for preventive use to protect against COVID-19 at the expense of the SHI. This concerns those persons in whom (1) for medical reasons (e.g. congenital or acquired immunodeficiencies, underlying diseases or immunosuppressive therapies) no or no sufficient immune protection against a COVID-19 disease can be achieved by vaccination, or (2) in whom vaccinations against the SARS-CoV-2 coronavirus cannot be carried out due to a contraindication, and who are thus exposed to an increased risk of a severe course of a COVID-19 disease.

The research question presented in Table 4 is derived from the G-BA's specification of the ACT and the information provided in COVID-19 Prevention Ordinance §2.

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

Therapeutic indication	**ACT[a]**
Pre-exposure prophylaxis of COVID-19 in adults and adolescents aged 12 years and older and with a body weight of at least 40 kg[b, c, d, e]	Watchful waiting

a. Presented is the ACT specified by the G-BA.
b. According to § 2 of the COVID-19 Prevention Ordinance, an entitlement to the provision of prescription drugs with monoclonal antibodies for preventive use to protect against COVID-19 at the expense of the SHI only exists for insured persons, if, for medical reasons, no or insufficient immune protection against a COVID-19 disease can be achieved by vaccination, or if protective vaccinations against the SARS-CoV-2 coronavirus cannot be carried out due to a contraindication and they are exposed to an increased risk of a severe course of a COVID-19 disease. Medical reasons may include, in particular, congenital or acquired immunodeficiencies, underlying diseases or a relevant impairment of the immune response due to immunosuppressive therapy.
c. It is assumed that the study participants will follow the generally accepted hygiene rules (such as keeping distance, observing hygiene measures, wearing mouth-nose coverings) to reduce the risk of infection in all study arms. In cases where medical reasons (e.g. dementia) preclude compliance with established hygiene rules, this must be documented.
d. It is recommended that relevant SARS-CoV-2 mutation variants (e.g. so-called VOCs) are also taken into account when recording and interpreting the results on efficacy.
e. As soon as the disease becomes symptomatic, treatment according to current medical knowledge is indicated.

COVID-19: coronavirus disease 2019; G-BA: Federal Joint Committee; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; SHI: Statutory Health Insurance; VOCs: 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 presented by the company in the dossier. RCTs are used for the derivation of added benefit. This concurs with the company's inclusion criteria.

Neutralizing activity against SARS-CoV-2 variants

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

The COVRIIN expert group at the RKI recommends taking into account the current epidemiological situation and neutralizing activity against individual virus variants when selecting monoclonal antibodies for treatment or prophylaxis. For the virus variants Omicron BA.1, BA.4, and BA.5, the expert group reports substantially decreased in vitro neutralization activity of tixagevimab/cilgavimab and therefore deems reduced efficacy against these variants to be probable. Against the newly arisen variants BQ.1/BQ1.1, BA.4.6, BF.7 and XBB in contrast, the expert group reports no in vitro neutralization activity [5].

I 3 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on tixagevimab/cilgavimab (status: 30 March 2023)
- bibliographical literature search on tixagevimab/cilgavimab (last search on 23 March 2023)
- search in trial registries/trial results databases for studies on tixagevimab/cilgavimab (last search on 23 March 2023)
- search on the G-BA website for tixagevimab/cilgavimab (last search on 30 March 2023)

To check the completeness of the study pool:

- search in trial registries for studies on tixagevimab/cilgavimab (last search on 26 May 2023); for search strategies, see I Appendix A of the full dossier assessment

No relevant study was identified from the check. In contrast, the company identified the PROVENT study from which it formed a subpopulation, which it presented for the benefit assessment.

Evidence provided by the company

Design of the PROVENT study

The PROVENT study is a double-blind RCT comparing COVID-19 pre-exposure prophylaxis with tixagevimab/cilgavimab versus placebo in adults unvaccinated at baseline who are at increased risk of inadequate vaccination response or SARS-CoV-2 infection according to criteria defined by the company.

An increased risk of inadequate vaccine response was determined in the PROVENT study based on the following criteria: age (≥ 60 years), obesity (BMI ≥ 30), heart failure, chronic obstructive pulmonary disease, chronic kidney disease (GFR < 30ml/min/1.73m²), chronic liver disease, immunodeficiency (due to solid organ transplantation, blood or bone marrow transplantation, immunocompromised condition, HIV, use of corticosteroids or other immunosuppressive drugs) and intolerance to the vaccine (defined as a history of severe or serious adverse events after receiving an approved vaccine).

Individuals at increased risk of SARS-CoV-2 infection were defined as those at significant risk of exposure to SARS-CoV-2 and COVID-19, based on the available risk assessment at the time of study inclusion, due to their location or living circumstances (e.g. health care workers, including staff in long-term care facilities; workers in industrial plants that have been shown

to be at high risk for transmission of SARS-CoV-2; military personnel living or working in confined spaces; students living in dormitories; other persons living in similarly confined or high-density environments).

A total of 5254 patients were randomly assigned in a ratio of 2:1 to the treatment arms. Stratification took place in the cohort of study participants aged 60 years and older by stay in a long-term care facility and in the cohort of persons under 60 years of age by risk of infection with SARS-CoV-2.

Tixagevimab/cilgavimab was administered in line with the SPC in the PROVENT study [4].

The study's primary outcome was the proportion of persons with COVID-19 by Day 183. Patient-relevant secondary outcomes were morbidity outcomes and adverse events (AEs). Results on mortality were not recorded as an independent efficacy outcome. The company presents the mortality based on the results of the AEs leading to death.

For a description of the PROVENT study, see also I Appendix B.

The subpopulation presented by the company was unsuitable for the benefit assessment

From the total population of the PROVENT study, the company formed a sub-population of those study participants who, according to the criteria of § 2 of the COVID-19 Prevention Ordinance, are entitled to the provision of prescription drugs with monoclonal antibodies for preventive use to protect against COVID-19 at the expense of the SHI system. This subpopulation is not relevant for the present assessment. This is justified below.

According to § 2 of the COVID-19 Prevention Ordinance, persons who are immunodeficient or at increased risk of an inadequate COVID-19 vaccination response as a result of immunosuppressive disease and/or treatment, or who cannot be vaccinated against the SARS-CoV-2 coronavirus due to a contraindication and are at increased risk of a severe course of COVID-19 disease, are eligible for care [3]. The company operationalized this population based on the following criteria:

1) Presence of immunosuppressive disease at baseline
2) Treatment with immunosuppressants at baseline
3) Persons with an impaired immune system (due to organ or bone marrow transplantation, primary immunodeficiency, HIV, treatment with corticosteroids or other immunosuppressive drugs) and an increased risk of inadequate vaccination response
4) Contraindication to SARS-CoV-2 vaccines in the presence of at least one risk factor for a severe course of COVID-19

taking into account the above criteria, the company considered 519 (9.9%) of the 5254 participants of the PROVENT study (tixagevimab/cilgavimab arm: N = 346; placebo arm: N = 173) for the present research question.

The RKI recommends SARS-CoV-2 pre-exposure prophylaxis with tixagevimab/cilgavimab only in justified individual cases. Justified individual cases may be persons with an expected or proven severe limitation of the immune response to COVID-19 vaccination (e.g. individuals following autologous or allogeneic stem cell transplantation prior to immunological reconstitution; under or following treatment with anti-B-cell antibodies if no reconstitution of B-cell capacities has occurred; under CAR T-cell therapy; under severe immunosuppression, e.g. following transplantation of a solid organ or under ongoing chemotherapy; with genetic immunodeficiencies that impair antiviral immunity) [6].

The company's criteria for the formation of the subpopulation essentially correspond to the RKI criteria for a risk of reduced vaccination response and are basically suitable for selecting the population described in § 2 of the COVID-19 Prevention Ordinance [6,7]. Overall, however, the company provides insufficient information on the characteristics that represent these criteria.

With regard to the company's 1st criterion for the formation of the subpopulation - presence of an immunosuppressive disease - it is clear from the characteristics of the study participants that an underlying immunosuppressive disease was present in approx. 5% of the patients in the subpopulation. However, no information is available on the actual underlying diseases and the severity of the disease. For the company's 2nd criterion - treatment with immunosuppressants - it is shown that approx. 31% of the subpopulation received treatment with immunosuppressive drugs. Here, too, the company does not provide any information on the immunosuppressive drugs used or their dosages or on the underlying diseases. According to the RKI, underlying immunosuppressive diseases or therapies do not per se lead to a relevant limitation of the immune response. The degree of immunodeficiency depends on the severity of the disease or the dosage of the immunosuppressive drugs used as well as on patient-specific factors [6]. However, the company presented no suitable information.

According to the RKI, cancer patients undergoing immunosuppressive, antineoplastic treatment also are at increased risk of a relevantly reduced immune response. Approximately 17% of the patients in the subpopulation had cancer at baseline (see Table 8 of the full dossier assessment). However, there is a lack of information on the stage of the disease and the therapy used. Therefore, it remains unclear how many study participants with cancer have an increased risk of a severely impaired immune response and thus represent the present research question. Overall, criteria 1 and 2 only apply to an insufficiently large proportion of the subpopulation.

The 3rd criterion - impairment of the immune system combined with an increased risk of inadequate vaccination response - overlaps with the first two criteria. The presence of immune system impairment and/or the increased risk of inadequate vaccination response was defined in the Case Report Form with the following criteria:

- Age (≥ 60 years)
- Obesity (BMI ≥ 30)
- Heart failure, chronic obstructive pulmonary disease, chronic kidney disease, chronic liver disease
- Immunodeficiency due to solid organ transplantation, blood or bone marrow transplantation, immunocompromised condition, HIV, use of corticosteroids or other immunosuppressive drugs

Except for immunodeficiency, the criteria do not correspond to the definition of the RKI and are not suitable to define a relevant immunodeficiency or an increased risk for a relevant limitation of the immune response. The company states that about 95% of the subpopulation have an immunocompromised condition. There is no information on individual criteria that justify the immunocompromised condition. Based on the characteristics of the study participants, as described above, the immunocompromised condition is attributed to an underlying immunosuppressive disease in about 5% and to treatment with immunosuppressive drugs in about 31%. In its criteria, the company did not consider cancer separately. If applicable, these persons are considered via the criterion of immunosuppressive treatment. It is assumed that for the remaining patients in the subpopulation, the presence of immune system impairment or an increased risk of inadequate vaccination response was due to other criteria such as age, obesity or a chronic disease. As these criteria are not suitable to select the population described in § 2 of the COVID-19 Prevention Ordinance, the majority of the subpopulation is not relevant for the present research question.

According to criterion 4, the subpopulation also included patients with a contraindication to SARS-CoV-2 vaccination and concomitant presence of at least one risk factor for a severe course of COVID-19. The company does not provide any information on how many study participants this applies to in the subpopulation. In Module 4 A, it states that about 2% of the subpopulation are intolerant to a vaccine, but it does not provide information on the concomitant risk factors for a severe course of COVID-19.

Overall, the majority of the patients included in the subpopulation do not represent the research question of the present assessment and are not used for the benefit assessment.

I 4 Results on added benefit

There are no suitable data to assess the added benefit of tixagevimab/cilgavimab in comparison with watchful waiting as ACT for pre-exposure prophylaxis of COVID-19 in adults and adolescents aged 12 years and older with a body weight of at least 40 kg. There is no hint of an added benefit of tixagevimab/cilgavimabin in comparison with the ACT; an added benefit is therefore not proven.

I 5 Probability and extent of added benefit

The data presented by the company are unsuitable to assess the added benefit of tixagevimab/cilgavimab in comparison with watchful waiting as ACT for pre-exposure prophylaxis of COVID-19 in adults and adolescents aged 12 years and older with a body weight of at least 40 kg. An added benefit of tixagevimab/cilgavimab is thus not proven.

This deviates from the assessment of the company, which derived an indication of considerable added benefit on the basis of the subpopulation of the PROVENT study formed by the it.

Table 5 summarizes the result of the assessment of added benefit for tixagevimab/cilgavimab in comparison with the ACT.

Table 5: Tixagevimab/cilgavimab – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Pre-exposure prophylaxis of COVID-19 in adults and adolescents aged 12 years and older and with a body weight of at least 40 kg[b, c, d, e]	Watchful waiting	▪ Added benefit not proven

a: Presented is the ACT specified by the G-BA.
b. According to § 2 of the COVID-19 Prevention Ordinance, an entitlement to the provision of prescription drugs with monoclonal antibodies for preventive use to protect against COVID-19 at the expense of the SHI only exists for insured persons, if, for medical reasons, no or insufficient immune protection against a COVID-19 disease can be achieved by vaccination, or if protective vaccinations against the SARS-CoV-2 coronavirus cannot be carried out due to a contraindication and they are exposed to an increased risk of a severe course of a COVID-19 disease. Medical reasons may include, in particular, congenital or acquired immunodeficiencies, underlying diseases or a relevant impairment of the immune response due to immunosuppressive therapy.
c. It is assumed that the study participants will follow the generally accepted hygiene rules (such as keeping distance, observing hygiene measures, wearing mouth-nose coverings) to reduce the risk of infection in all study arms. In cases where medical reasons (e.g. dementia) preclude compliance with established hygiene rules, this must be documented.
d. It is recommended that relevant SARS-CoV-2 mutation variants (e.g. so-called VOCs) are also taken into account when recording and interpreting the results on efficacy.
e. As soon as the disease becomes symptomatic, treatment according to current medical knowledge is indicated.

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

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

I 6 References for English extract

Please see full dossier assessment for full reference list.

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

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